COGNITIVE DECLINE AND
HEALTH RELATED QUALITY OF LIFE
IN ALZHEIMER’S DISEASE

PASCALLE RENÉE BOSBOOM MSc

THIS THESIS IS PRESENTED FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY
OF THE UNIVERSITY OF WESTERN AUSTRALIA

WESTERN AUSTRALIAN CENTRE FOR HEALTH AND AGEING
AND
SCHOOL OF PSYCHIATRY AND CLINICAL NEUROSCIENCES
THE UNIVERSITY OF WESTERN AUSTRALIA

2015
"If I need be--if I really have to--I shall invent a life for myself
from minute to minute and believe in it.

Hidden from the eye of the world.

Like a ship, ... a sailing ship with no wind in its sails.

And then suddenly there is wind, and I set sail again.
And then the world takes me in its grasp again, and I can move again with it.”

From J. Bernlef, “Out of Mind”, 1988

For my parents and grandparents
ABSTRACT

BACKGROUND
Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disease associated with significant disability and burden of care. In the absence of a cure for AD, effective interventions to optimize the health related quality of life (HRQoL) are required. Although the assessment and interpretation of HRQoL ratings are challenging, HRQoL has been recognized as a valuable outcome in AD research. However, knowledge regarding the clinically modifiable factors that drive changes in HRQoL is limited, so that rational evidence-driven interventions are lacking. The assumption that improvements of episodic memory, the prototypical deficit of AD, should lead to better HRQoL is yet to be demonstrated. The impact of progressive cognitive decline on the HRQoL of older adults with AD remains unclear.

AIMS
The body of this research consisted of five inter-related studies designed to address the following aims:
- Study 1: to determine (1) the agreement between community-dwelling people with mild to moderate AD and their family carers HRQoL ratings; (2) whether the instructed perspective of family carer-rated HRQoL (i.e. carer–carer perspective and carer–patient perspective) changes HRQoL outcomes; (3) the factors that independently contribute to self-reported and carer-reported HRQoL ratings (i.e. carer–carer perspective and carer–patient perspective);
- Study 2: to determine (4) whether self-reported and carer-reported HRQoL change over a period of 18 months; (5) the factors that mediate changes in HRQoL ratings by community-dwelling people with AD over a period of 18 months; (6) the factors that mediate changes in HRQoL ratings by family carers over a period of 18 months;
- Study 3: to determine (7) whether the underlying cognitive domains of people with AD remain stable over 18 months compared with controls free of dementia; (8) whether the associations between cognitive domains and carer and self-reported HRQoL ratings remain stable over 18 months;
- Study 4: to determine 9) whether the deterioration of specific cognitive functions commonly associated with AD predict which patients maintain or experience a deterioration of their HRQoL ratings over a period of 18 months.
Study 5: as post-hoc analyses, to determine 10) the prevalence and association of exposure to potentially harmful medication with HRQoL.

METHODS
The research was designed as a longitudinal observational study. We recruited 80 community-dwelling older adults diagnosed with probable AD of mild or moderate severity (NINCDS-ADR criteria) and their family carers, and 75 older adults without a diagnosis of dementia or MCI and their next-of-kin. The primary outcome of interest was HRQoL as measured by the Quality of Life-AD (QoL-AD) (by carer and by self). Specific cognitive functions were assessed with a broad range of well-established neuropsychological measures. Other explanatory variables included demographics, lifestyle, awareness, behavioural and psychological symptoms of dementia, burden-of-care, use of medication, and functionality in daily life. Parametric and non-parametric bi-variate and multi-variate tests were used to test the study hypotheses. Depending on the number of planned comparisons, alpha was set at 1% or 5%.

RESULTS
• Study 1: Mild to moderate community-dwelling people with AD and their carers (with two differently instructed perspectives) agreed within an acceptable range in HRQoL ratings, but their ratings were associated with different factors. HRQoL ratings by carer–carer perspective are inversely associated with the number of medications consumed by the patient, symptoms of anxiety, and living together; while carer–patient perspective is inversely associated with the carers’ age and burden-of-care.
• Study 2: Carer-rated QoL-AD (carer-carer perspective) declined 8.7% (P=0.003) over 18-months, but self-rated QoL-AD remained stable. The final parsimonious model of predictors of changes in QoL-AD self-ratings explained 22.6% of the variance; only changes on Hospital Anxiety and Depression Scale Anxiety retained significance. The final model of predictors of changes in carer-ratings explained 55.0% of the variance: that is, changes on Informant Questionnaire on Cognitive Decline in the Elderly, changes on Hospital Anxiety and Depression Scale Depression, practicing hobbies at 18 months, and number of visit(s) or admission(s) to hospital.
• Study 3: Self-reported QoL-AD scores were not associated with any of the identified cognitive domains at baseline or after 18 months. The structure of the cognitive
domains of people with AD changed between baseline and follow-up, as did the association of these domains with carer-rated HRQoL. The HRQoL scores assigned by the next-of-kin declined alongside a general measure of cognitive function.

- Study 4: Changes in specific cognitive functions were not associated with changes in self-rated or carer-rated HRQoL in AD.
- Study 5: Post-hoc analyses showed that exposure to potentially harmful medications was inversely associated with self-reported HRQoL for people with AD. However, the prevalence of exposure to PHM in our community sample was close to zero.

**CONCLUSIONS**

The studies undertaken for this thesis confirm that HRQoL ratings by patients with AD and their carer as informant are not interchangeable but complementary. HRQoL self-ratings and carer-ratings of community-dwelling people with AD do not decline at same rate over 18 months and changes are associated with different factors. Interventions designed to optimize quality of life of people with AD should consider carefully whose HRQoL ratings they wish to change. HRQoL is not consistently associated with specific cognitive domains in AD, thus cognition enhancing focused therapies may fail to optimize the HRQoL of people with mild to moderate AD living in the community.
ACKNOWLEDGEMENTS

I would like to acknowledge and wholeheartedly thank the people who provided their valuable contributions to this research, and who inspired, guided and supported me in various ways throughout my PhD journey. First and foremost, I would like to thank my supervisor, Winthrop Professor Osvaldo Almeida. I am very grateful to him for offering his academic guidance, expertise, thoughtful perspectives, and ability to challenge, inspire, support and encourage me on all aspects of my project. I sincerely thank all participants for their generous contributions to this research. There would have been no data without the efforts from clinicians and administrative staff of WACHA, Neurosciences Unit, Department of Health, and the contributing Memory Clinics in Perth metropolitan area, for which I am grateful. I wish to acknowledge the people who collaborated: Professor Helman Alfonso, Assoc/Prof Christopher Etherton-Beer, and Ms Joanna Popp. Also my thanks to the support by Ms Cheryl Ackoy, Ms Christianne White and all other colleagues at WACHA and at MindLink Psychology, the next journey has already started. My gratitude goes to my previous supervisors, scholars and colleagues who contributed to the foundations and inspired me to embark on this PhD journey (Professor John Hodges, Professor Cees Jonker), and who provided their valuable time, effort and examination of this thesis (Professor Nancy Pachana, Professor Rudolf Ponds, and Professor Erik Scherder). I am thankful for the funding from WACHA, the University of Western Australia, School of Psychiatry and Clinical Neurosciences (scholarship), by Alzheimer’s Australia (travel grant). Last, but not least, I would like to thank my family, extended family and friends, close by and far away. Especially my husband Martijn, for his manifold support and belief in my PhD commitment, and our children Anouk and Daan, together the equivalent of my quality of life.
TABLE OF CONTENTS

ABSTRACT ........................................................................................................................................... i
ACKNOWLEDGEMENTS .................................................................................................................. v
LIST OF TABLES ................................................................................................................................ xiii
LIST OF FIGURES ........................................................................................................................ xv
LIST OF ABBREVIATIONS ........................................................................................................ xvii
STATEMENT OF CANDIDATE CONTRIBUTION ........................................................................ xxi
PUBLICATIONS ARISEN FROM THIS THESIS ........................................................................... xxv
OUTLINE OF THIS THESIS ........................................................................................................... xxix
  INTRODUCTION TO THESIS BY PUBLICATION .................................................................... xxix
  OVERVIEW OF CHAPTERS, STUDIES AND PUBLICATIONS ................................................ xxix

CHAPTER 1. HEALTH RELATED QUALITY OF LIFE IN ALZHEIMER’S DISEASE - LITERATURE REVIEW .......................................................... 1
  1.1. INTRODUCTION .............................................................................................................. 2
  1.2. THE AGING POPULATION ............................................................................................. 2
    1.2.1. DEMOGRAPHICS: THE CHANGING AGE PROFILE ..................................................... 2
    1.2.2. AGE-RELATED CHRONIC DISEASES ......................................................................... 4
    1.2.3. THE EPIDEMIOLOGY OF DEMENTIA ....................................................................... 6
  1.3. HRQoL AS OUTCOME MEASURE IN DEMENTIA ............................................................... 7
    1.3.1. THE CONCEPTS QoL AND HRQoL ......................................................................... 7
    1.3.2. RELEVANCE IN HRQoL AS OUTCOME MEASURE .................................................. 8
    1.3.3. FACTORS ASSOCIATED WITH QoL AT OLDER AGE ............................................. 9
    1.3.4. A MODEL FOR HRQoL IN DEMENTIA ..................................................................... 11
  1.4. DEMENTIA OF THE ALZHEIMER’S DISEASE (AD) TYPE .................................................... 13
    1.4.1. DIAGNOSIS OF AD ............................................................................................ 13
    1.4.2. NEUROPATHOLOGY ............................................................................................. 16
    1.4.3. PREVALENCE ....................................................................................................... 18
    1.4.4. ASSOCIATED FACTORS ....................................................................................... 19
    1.4.5. COGNITIVE DECLINE .......................................................................................... 20
      1.4.5.1. NEUROPSYCHOLOGICAL PROFILE OF AD ................................................... 20
      1.4.5.2. STAGES OF PROGRESSIVE DETERIORATION ................................................. 21
      1.4.5.3. EPISODIC MEMORY ........................................................................................ 23
1.4.5.4. EXECUTIVE FUNCTIONING, WORKING MEMORY AND ATTENTION ...... 24
1.4.5.5. VISUOSPATIAL ABILITIES ................................................................. 26
1.4.5.6. LANGUAGE & SEMANTIC KNOWLEDGE ........................................ 27
1.4.6. OTHER CLINICAL CHARACTERISTICS ............................................... 27
1.4.6.1. DEPENDENCE IN ACTIVITIES OF DAILY LIVING ...................... 27
1.4.6.2. BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA ...... 29
1.4.6.3. LOSS OF AWARENESS ..................................................................... 30
1.4.7. INTERVENTIONS .................................................................................. 32
1.4.7.1. PHARMACOLOGICAL INTERVENTIONS .................................... 33
1.4.7.2. FROM MEDICAL MODEL TO BIOPSYCHOSOCIAL FRAMEWORK .... 34
1.4.7.3. VIEWS ON FUTURE DIRECTIONS OF INTERVENTIONS FOR AD .... 36
1.5. CHALLENGES IN ASSESSMENT & INTERPRETATION OF HRQoL IN AD ........ 38
1.5.1. ASSESSING HRQoL IN PEOPLE WITH COGNITIVE IMPAIRMENT, THE CARDINAL FEATURE OF AD ................................................................. 39
1.5.2. AVAILABLE INSTRUMENTS TO ASSESS HRQoL IN DEMENTIA ..... 42
1.5.3. DIFFERENCES BETWEEN SELF AND CARER-REPORTED HRQoL RATINGS 45
1.5.4. THE DISABILITY PARADOX AND THE RESPONSE SHIFT THEORY: HIGH QoL AGAINST ALL ODDS? .................................................................................. 46
1.5.5. A CONCEPTUAL FRAMEWORK FOR MULTIPLE PROXY PERSPECTIVES .... 50
1.5.6. HRQoL IN AD AT DIFFERENT STAGES ............................................ 53
1.5.7. IS THERE EVIDENCE FOR EFFECTIVENESS OF PHARMACOLOGICAL AND NON-PHARMACOLOGICAL INTERVENTIONS TO IMPROVE HRQoL IN AD? .... 54
1.5.8. SUMMARY OF THE CHALLENGES ...................................................... 56
1.6. WHAT DRIVES HRQoL IN AD? ............................................................... 57
1.6.1. AVAILABLE CROSS-SECTIONAL STUDIES ........................................ 57
1.6.1.1. FACTORS ASSOCIATED WITH SELF-REPORTED HRQoL RATINGS .... 63
1.6.1.2. FACTORS ASSOCIATED WITH CARER-REPORTED HRQoL RATINGS ... 65
1.6.2. PREDICTORS OF CHANGE IN HRQoL IN AD .................................... 66
1.6.2.1. AVAILABLE LONGITUDINAL STUDIES ........................................ 67
1.6.2.2. IMPACT OF CHANGES IN COGNITIVE FUNCTIONS ON HRQoL OVER TIME ............................................................................................................ 72
1.7. KEY ISSUES – THE RATIONALE FOR THIS THESIS .................................. 75

CHAPTER 2. AIMS, HYPOTHESES AND GENERAL METHODOLOGY .......... 79
2.1. INTRODUCTION ........................................................................................ 80
2.2. AIMS OF THESIS ................................................................................................... 80
2.3. HYPOTHESES ...................................................................................................... 81
2.4. CREATIVE COMPONENT .................................................................................... 82
2.5. SIGNIFICANCE .................................................................................................... 83
2.6. RESEARCH DESIGN ............................................................................................ 84
2.7. PARTICIPANTS .................................................................................................... 84
2.7.1. RECRUITMENT ............................................................................................. 84
2.7.2. INCLUSION CRITERIA .................................................................................. 85
2.7.3. EXCLUSION CRITERIA ............................................................................... 85
2.8. MEASURES ......................................................................................................... 85
2.8.1. HEALTH RELATED QUALITY OF LIFE .......................................................... 85
2.8.2. COGNITIVE EXPLANATORY MEASURES......................................................... 86
2.8.2.1. GLOBAL COGNITIVE MEASURE ........................................................... 86
2.8.2.2. SPECIFIC NEUROPSYCHOLOGICAL MEASURES ....................................... 86
2.8.3. OTHER STUDY MEASURES ........................................................................... 87
2.9. DATA COLLECTION ............................................................................................ 90
2.10. STATISTICAL ANALYSES .............................................................................. 90
2.11. SAMPLE SIZE AND POWER CONSIDERATIONS .................................................. 90
2.12. ETHICAL APPROVAL ....................................................................................... 91

CHAPTER 3. DIFFERENT FACTORS ASSOCIATED WITH COMPLEMENTARY HRQOL RATINGS BY PEOPLE WITH AD AND FAMILY CARERS 93

3.1. ABSTRACT .......................................................................................................... 94
3.2. INTRODUCTION ................................................................................................... 94
3.3. METHODS ........................................................................................................... 96
3.4. RESULTS ............................................................................................................ 101
3.4.1. AGREEMENT BETWEEN PARTICIPANTS AND CARERS ON HRQoL RATINGS 101
3.4.2. FACTORS ASSOCIATED WITH HRQoL RATINGS ....................................... 104
3.4.2.1. UNIVARIATE ANALYSES ................................................................ 104
3.4.2.2. MULTIVARIATE ANALYSES ........................................................... 104
3.5. DISCUSSION ..................................................................................................... 107

CHAPTER 4. DETERMINING THE PREDICTORS OF CHANGE IN HRQOL SELF-RATINGS AND CARER-RATINGS FOR COMMUNITY-DWELLING PEOPLE WITH AD .......................................................... 113
4.1. ABSTRACT ......................................................................................................... 114
4.2. INTRODUCTION .............................................................................................. 114
4.3. METHODS ........................................................................................................ 117
4.4. RESULTS ........................................................................................................... 121
  4.4.1. PARTICIPANTS WITH AD AND CARERS AT BASELINE ......................... 121
  4.4.2. CLINICAL CHARACTERISTICS AT BASELINE AND 18-MONTH FOLLOW-UP .. 123
  4.4.3. QoL-AD RATINGS ................................................................................ 125
  4.4.4. FACTORS ASSOCIATED WITH CHANGES IN HRQoL-RATINGS .......... 125
    4.4.4.1. UNIVARIATE ANALYSES ............................................................... 125
    4.4.4.2. MULTIVARIATE ANALYSES ........................................................... 126
  4.4.5. POST-HOC ANALYSES ........................................................................... 127
4.5. DISCUSSION ................................................................................................... 128

CHAPTER 5. STABILITY OF THE ASSOCIATION BETWEEN COGNITIVE
  DOMAINS AND HRQOL RATINGS IN AD................................. 133
5.1. ABSTRACT ......................................................................................................... 134
5.2. INTRODUCTION .............................................................................................. 134
5.3. METHODS ........................................................................................................ 137
5.4. RESULTS ........................................................................................................... 144
  5.4.1. CHARACTERISTICS AT BASELINE AND 18-MONTHS FOLLOW-UP.......... 144
  5.4.2. COMPARISON RAW SCORES ON COGNITIVE AND HRQoL MEASURES .... 145
  5.4.3. EXPLORATIVE FACTOR ANALYSES (STUDY AIM I) .............................. 145
    5.4.3.1. MODEL I: AD TOTAL GROUP AT BASELINE (N= 80) ...................... 146
    5.4.3.2. MODEL 2: AD DROPOUTS AT BASELINE (N= 33) .......................... 146
    5.4.3.3. MODEL 3: AD COMPLETERS AT BASELINE (N= 47) .................... 148
    5.4.3.4. MODEL 4: AD COMPLETERS AT FOLLOW-UP (N= 47) ............... 148
    5.4.3.5. MODEL 5 & 6: CONTROLS AT BASELINE & FOLLOW-UP (N= 61) .. 149
  5.4.4. ASSOCIATIONS BETWEEN IDENTIFIED COGNITIVE FACTORS AND
    HRQoL ACROSS GROUPS AND TWO POINTS IN TIME (STUDY AIM II) ....... 149
5.5. DISCUSSION ................................................................................................... 152

CHAPTER 6. DO CHANGES IN COGNITIVE FUNCTIONS PREDICT CHANGES
  IN HRQoL IN PEOPLE WITH AD LIVING IN THE COMMUNITY? ...
.......................................................... 157
6.1. ABSTRACT ................................................................................................... 158
6.2. INTRODUCTION ..................................................................................................158
6.3. METHODS ..........................................................................................................159
6.4. RESULTS ............................................................................................................165
  6.4.1. PARTICIPANTS ..........................................................................................165
  6.4.2. CHANGES IN HRQoL OVER 18 MONTHS ...................................................165
  6.4.3. CHANGES IN COGNITION OVER 18 MONTHS ...............................................165
  6.4.4. COGNITIVE MEASURES AND THEIR ASSOCIATIONS WITH HRQoL AFTER
         18 MONTHS. ..............................................................................................166
  6.4.5. POST-HOC ANALYSES ................................................................................169
6.5. DISCUSSION .......................................................................................................169

CHAPTER 7. HRQoL AND THE USE OF POTENTIALLY HARMFUL MEDICATIONS
            AMONG PEOPLE WITH DEMENTIA LIVING IN RESIDENTIAL AGED
            CARE FACILITIES………………173
  7.1. ABSTRACT .........................................................................................................174
  7.2. INTRODUCTION ..................................................................................................174
  7.3. METHODS ..........................................................................................................176
  7.4. RESULTS ............................................................................................................180
    7.4.1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS.........................180
    7.4.2. PREVALENCE OF PHM USE ..............................................................180
    7.4.3. ASSOCIATION OF PHM WITH HRQoL ..............................................183
  7.5. DISCUSSION .......................................................................................................183
  7.6. NOTE – PREVALENCE OF PHM USE IN OUR COMMUNITY SAMPLE ..............185

CHAPTER 8. GENERAL DISCUSSION .....................................................................187
  8.1. INTRODUCTION ..................................................................................................188
  8.2. SUMMARY OF FINDINGS .....................................................................................188
  8.3. CONCLUSIONS REGARDING ORIGINAL STUDY HYPOTHESES .........................190
  8.4. LIMITATIONS AND STRENGTHS .........................................................................192
  8.5. IMPLICATIONS OF THE FINDINGS ......................................................................195
    8.5.1. WHAT ARE THE IMPLICATIONS OF THE FINDINGS FOR ASSESSING AND
           INTERPRETING HRQoL IN PEOPLE WITH AD? ........................................195
    8.5.2. WHAT ARE THE IMPLICATIONS OF THE FINDINGS FOR INTERVENTIONS
           TO ENHANCE HRQoL IN AD? ....................................................................196
    8.5.3. WHAT ARE THE IMPLICATIONS TO JONKER ET AL.’S MODEL? .................197
8.6. THESIS RESULTS IN CONTEXT OF ADVANCEMENT IN THE FIELD AND FUTURE DIRECTIONS ........................................................................................................................................................................ 197

BIBLIOGRAPHY ......................................................................................................................................................................................... 207

APPENDICES

A. PEER REVIEWED PUBLICATIONS RELATED TO THIS THESIS
   1. BEER, BOSBOOM, ALMEIDA, FLICKER (2009) ............................................
   2. BOSBOOM ET AL. (2010) ........................................................................
   3. BOSBOOM, ALFONSO, EATON, ALMEIDA (2012) .................................
   4. BOSBOOM, ALFONSO, ALMEIDA, BEER (2012) ......................................
   5. BOSBOOM, ALFONSO, ALMEIDA (2013) ............................................... 
   6. BOSBOOM & ALMEIDA (2014) ..............................................................
   7. BOSBOOM & ALMEIDA (2014) ..............................................................

B. DOCUMENTS RELATED TO RECRUITMENT
   1. EXAMPLE RECRUITMENT LETTER ...........................................................
   2. INFORMATION SHEET QOLCOG STUDY ..............................................
   3. MEDIA STATEMENT NEW STUDY ...........................................................
   4. BROCHURE QOLCOG STUDY ............................................................... 
   5. PHONE SCREENING MANUAL ..............................................................
   6. RECRUITMENT CHECKLISTS .................................................................
   7. TELEPHONE INTERVIEW FOR COGNITIVE SCREENING ......................
   8. EXAMPLE CONFIRMATION LETTERS TO PARTICIPANT AND INFORMANT ...
   9. FLOWCHART PARTICIPANTS STUDY I FROM RECRUITMENT SOURCES ....
  10. FLOWCHART PARTICIPANTS STUDY I AND II ........................................

C. DOCUMENTS RELATED TO ASSESSMENT
   1. CHECKLIST AND ORDER OF ASSESSMENT .......................................... 
   2. MANUAL ASSESSMENT INSTRUCTIONS ..............................................
   3. CONSENT FORMS ..................................................................................
   4. QUESTIONNAIRES ..................................................................................
   5. QoL-AD - PATIENT & TWO CARER VERSIONS ......................................
   6. NEUROPSYCHOLOGICAL TESTS PROTOCOLS ......................................

D. OTHER DOCUMENTS
   1. CO-AUTHORED PEER-REVIEWED PUBLICATIONS PRIOR TO THESIS .......
   2. QoL-AD - ORIGINAL SELF AND CARER VERSIONS .................................
   3. PROTOCOL OF THE DIRECT STUDY ....................................................
   4. ALZHEIMER’S AUSTRALIA ANNUAL REPORT - TRAVEL GRANT ..........
   5. MEDIA ..................................................................................................
# LIST OF TABLES

| Table 1.1. | Criteria for All-Cause Dementia (McKhann et al., 2011). | p. 15 |
| Table 1.2. | Criteria for Probable Alzheimer's disease (McKhann et al., 2011). | p. 16 |
| Table 1.3. | Areas to consider in formulating comprehensive assessments and interventions for people with AD and their carers applying a biopsychosocial framework (modified from Clare, 2008). | p. 34 |
| Table 1.4. | Characteristics of dementia HRQoL scales (modified version from Ready & Ott, 2003). | p. 43 |
| Table 1.5. | Dementia-specific HRQoL instruments included in each of the eight reviews identified in review by Perales et al., 2013. | p. 44 |
| Table 1.6. | Overview characteristics cross-sectional studies related to or focused on factors associated with QoL or HRQoL ratings in dementia or Alzheimer's disease (before January 2006). | p. 59 |
| Table 1.7. | Overview characteristics longitudinal observational studies in predictors of change of HRQoL ratings in dementia (until January 2007). | p. 70 |
| Table 3.1. | Characteristics of the AD patients and their carers. | p. 102 |
| Table 3.2. | Univariate analyses of independent associations between QoL ratings and exposure factors. | p. 105 |
| Table 3.3. | Final predictive models of three different views on QoL ratings based on stepwise backwards regression analyses. | p. 106 |
| Table 3.4. | Post-hoc model of difference between self-reported and carer-carer reported QoL ratings based on stepwise backwards regression analyses (parsimonious model). | p. 107 |
| Table 4.1. | Comparison of the clinical characteristics of participants with AD at baseline and 18-month follow up assessments (n = 47). | p. 123 |
| Table 4.2. | Univariate associations between change over time in HRQoL ratings and change over time of exposure factors (n = 47). | p. 125 |
| Table 4.3. | Final predictive models of change over time in QoL-AD self-ratings and carer-ratings based on stepwise backwards regression analyses. | p. 126 |
Table 5.1. Results of Explorative Factor Analyses of neuropsychological variables from participants at baseline and at 18-month follow-up.

Table 5.2. Regression analyses (crude and adjusted) of the QoL-AD with global cognition and identified cognitive factors.

Table 6.1. Comparison of raw scores on cognitive tests by participants with Alzheimer’s disease at baseline and 18-months follow-up, separately for subgroups of self-reported or carer-reported stable/increased or declined QoL-AD ratings.

Table 6.2. Odds ratio (95% CI) of stable or higher QoL-AD ratings (i.e. %MaxSc) per standardized change in cognitive scores over 18-months.

Table 7.1. Demographic and clinical characteristics of the participants (PWD living in RACFs) and the prevalence of use of PHM.

Table 7.2. Differences in self-reported QoL-AD ratings (i.e. %MaxSc on the QoL-AD) according to exposure to PHM.

Table 7.3. Odds ratios (95% CI) of self-reported QoL-AD ratings (i.e. %MaxSc on the QoL-AD) according to exposure to PHM.

Table 8.1. Overview characteristics of longitudinal observational studies in predictors of change of HRQoL ratings in dementia (until July 2014).
LIST OF FIGURES

Figure 1.1. The percentage of the world's population that will be over 65 between 1950-2050 (adapted from the UN World Population Prospect, 2008).

Figure 1.2. Australian Population Growth Indices by age group (adapted from: Report Australia’s Demographic Challenges, 2004).

Figure 1.3. Number of publications on ‘quality of life’ in PubMed (as per 22-06-2014).

Figure 1.4. Hierarchic relationships between QoL dimensions in dementia (modified from Jonker et al., 2004).

Figure 1.5. Model of the clinical trajectory of Alzheimer's disease (modified from Sperling et al., 2011).

Figure 1.6. The annual incidence rate (per 100 person-years) for Alzheimer disease (modified from Mayeux & Stern, 2012).

Figure 1.7. Number of publications on ‘quality of life in dementia’ and ‘quality of life in Alzheimer’s disease’ in PubMed (as per 22-06-2014).

Figure 1.8. Response shift model (modified from Sprangers & Schwartz 1999).

Figure 1.9. Conceptualized interrelationship between patient and proxy assessments of HRQL (modified from Pickard & Knight, 2005).

Figure 3.1a. Bland-Altman plot for agreement on the QoL-AD total score between AD patients and carer with carer–carer perspective.

Figure 3.1b. Bland-Altman plot for agreement on the QoL-AD total score between AD patients and carer with carer–patient perspective.

Figure 4.1. Flow of participants during the 18 months of follow-up of the older adults diagnosed with Alzheimer’s disease. Assessments took place at baseline and after 18 months.

Figure 4.2. Box plot showing the change of QoL-AD according to the ratings of participants with AD and their carers, i.e. at baseline and at 18 months assessments.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABS</td>
<td>Australian Bureau of Statistics</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>ADL</td>
<td>Activities of daily living</td>
</tr>
<tr>
<td>ApoE</td>
<td>Apolipoprotein E</td>
</tr>
<tr>
<td>AQ</td>
<td>Anosognosia Questionnaire</td>
</tr>
<tr>
<td>BADL</td>
<td>Basic activities of daily living</td>
</tr>
<tr>
<td>BL</td>
<td>Baseline assessment</td>
</tr>
<tr>
<td>BNT30</td>
<td>Boston Naming Test 30 items version</td>
</tr>
<tr>
<td>BPSD</td>
<td>Behavioural and Psychological Symptoms of Dementia</td>
</tr>
<tr>
<td>CAMCOG-R</td>
<td>Cambridge Cognitive Examination of the Elderly Revised</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>CVLT-II</td>
<td>California Verbal Learning Test, 2nd edition</td>
</tr>
<tr>
<td>DBI</td>
<td>Drug Burden Index</td>
</tr>
<tr>
<td>DIRECT</td>
<td>Dementia in residential care: education intervention trial</td>
</tr>
<tr>
<td>D-KEFS</td>
<td>Delis – Kaplan Executive Functioning System</td>
</tr>
<tr>
<td>DS bwd</td>
<td>Digit Span backward</td>
</tr>
<tr>
<td>DS fwd</td>
<td>Digit Span forward</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 5th edition</td>
</tr>
<tr>
<td>FU</td>
<td>Follow up</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>GRAD</td>
<td>Guidelines for the Rating of Awareness Deficits</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health Related Quality of Life</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>IADL</td>
<td>Instrumental activities of daily living</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>IQCODE</td>
<td>Informant Questionnaire on Cognitive Decline in Elderly</td>
</tr>
<tr>
<td>Ldcr</td>
<td>Long delay cued recall</td>
</tr>
<tr>
<td>Ldfr</td>
<td>Long delay free recall</td>
</tr>
<tr>
<td>Lgst</td>
<td>Longest</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination</td>
</tr>
<tr>
<td>NAB</td>
<td>Neuropsychological Assessment Battery</td>
</tr>
<tr>
<td>NPI</td>
<td>Neuropsychiatric Inventory</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PHM</td>
<td>Potentially harmful medication</td>
</tr>
<tr>
<td>PIM</td>
<td>Potentially inappropriate medication</td>
</tr>
<tr>
<td>PrPr</td>
<td>Proxy-Proxy perspective</td>
</tr>
<tr>
<td>PrPt</td>
<td>Proxy-Patient perspective</td>
</tr>
<tr>
<td>Pt</td>
<td>Patient</td>
</tr>
<tr>
<td>PWD</td>
<td>People with dementia</td>
</tr>
<tr>
<td>PWD-C</td>
<td>People with dementia in community</td>
</tr>
<tr>
<td>PWD-RCF</td>
<td>People with dementia in residential care facility</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>QoL-AD</td>
<td>Quality of Life – Alzheimer’s disease</td>
</tr>
<tr>
<td>RACF</td>
<td>Residential Aged Care Facility</td>
</tr>
<tr>
<td>RCF</td>
<td>Residential Care Facility</td>
</tr>
<tr>
<td>RCFT</td>
<td>Rey Complex Figure Test</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>Sdfr</td>
<td>Short delay free recall</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>TMT</td>
<td>Trail Making Test (D-KEFS)</td>
</tr>
<tr>
<td>Ts</td>
<td>Total score</td>
</tr>
<tr>
<td>VAT</td>
<td>Visual Association Test</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>95% CI</td>
<td>95% confidence interval</td>
</tr>
</tbody>
</table>
To the best of my knowledge, this thesis contains no material published by any other person, except for the contributions of my co-authors, as clearly acknowledged in the text of this thesis. Several collaborators have helped to bring this series of related publications to fruition. Collaborators assisted with study design, analysis or interpretation of the following chapters and related publications as follows:


For this Chapter, data from the QoLCog baseline study were used. I designed the study, acted as Chief Investigator, and carried out subject recruitment and collection of data, analyzed the data and wrote the manuscript. Joanna Pop assisted recruitment and data collection at the Royal Perth Hospital site under my supervision. Osvaldo Almeida assisted in study design, data analyses, data interpretation and manuscript revision. Helman Alfonso assisted in data management and data analyses.


For this Chapter, data from the QoLCog baseline and follow-up study were used. I designed the study, acted as Chief Investigator, and carried out subject recruitment and collection of data, analyzed the data and wrote the manuscript. Osvaldo Almeida assisted in study design, data analyses, data interpretation and manuscript revision. Helman Alfonso assisted in data management and data analyses.

**Chapter 5:** Bosboom, P.R., Almeida, O.P. (2014). Cognitive domains and Health

For this Chapter, data from the QoLCog baseline and follow-up study were used. I designed the study, acted as Chief Investigator, and carried out subject recruitment and collection of data, analyzed the data and wrote the manuscript. Joanna Pop assisted recruitment and data collection at the Royal Perth Hospital site under my supervision. Osvaldo Almeida assisted in study design, data analyses, data interpretation and manuscript revision. Helman Alfonso assisted in data management and data analyses.


For this Chapter, data from the QoLCog baseline and follow-up study were used. I designed the study, acted as Chief Investigator, and carried out subject recruitment and collection of data, analyzed the data and wrote the manuscript. Joanna Pop assisted recruitment and data collection at the Royal Perth Hospital site under my supervision. Osvaldo Almeida assisted in study design, data analyses, data interpretation and manuscript revision.


For this Chapter, initially the manuscript for this paper included data of the QolCog study, of which I designed the study, acted as Chief Investigator, and carried out subject recruitment and collection of data, but due to low prevalence of PHM in this cohort, we decided to withdraw the data of the QolCog study from this manuscript (see note at end of this Chapter). We included this chapter as post-hoc analyses and further relied on the Dementia In Residential Care Trial (DIRECT) study (see study protocol in Appendix C), which was led by Christopher Etherton-Beer. I analyzed and interpreted the data and
wrote the manuscript. I took the leadership in the design of the quality of life aspects of the study. Osvaldo Almeida and Christopher Etherton-Beer assisted in study design, data analyses, data interpretation and manuscript revision. Helman Alfonso assisted in data management and data analyses.

I have obtained permission from my co-authors to include co-authored work in this thesis. No part of this thesis has been used to obtain any other degree.

Ms Pascalle Bosboom (Candidate)

I confirm that the candidate has obtained permission from co-authors to include co-authored work in this thesis.

Winthrop Professor Osvaldo Almeida (Supervisor)
PEER REVIEWED INTERNATIONAL JOURNAL PUBLICATIONS


PUBLISHED ABSTRACTS


OTHER RESEARCH OUTPUT FROM THIS THESIS

POSTERS

CONFERENCE ABSTRACTS
4. Beer and Bosboom (2010). Perspectives of quality of life among people with dementia living in the community and care facilities. Data from the ‘DIRECT’ (Dementia in Residential Care: Education Intervention Trial) and QOLCog Studies (Quality of Life and cognition in Alzheimer’s disease), Dementia Networking Seminar Series, Dementia Training Study Centre, Curtin University of Technology, 19-10-2010.
5. **Bosboom P.R.** (June 2013). The role of cognition in change of health related quality of life in Alzheimer's disease. Clinic Forum by the Aged & Community Services Western Australia.

**PRESENTATIONS AT SCIENTIFIC MEETINGS**


2. **Bosboom P.R.** (2007). Quality of Life in Dementia – Agree or not agree, that’s the question. 1st Internal WACHA Symposium. 31/08/2007.


6. Beer and **Bosboom** (2010). Perspectives of quality of life among people with dementia living in the community and care facilities. Data from the ‘DIRECT’ (Dementia in Residential Care: Education Intervention Trial) and QoLCog Studies (Quality of Life and cognition in Alzheimer’s disease), Dementia Networking Seminar Series, Dementia Training Study Centre, Curtin University of Technology, 19-10-2010.


INTRODUCTION TO THESIS BY PUBLICATION

The candidate’s work is submitted as a thesis by publications (that is, a series of published papers, and one accepted manuscript). The work conducted for this thesis followed the prospectively approved thesis program (i.e. the QoLCog study) with no major changes. In addition to the approved program, selected data from the DIRECT study (protocol added as appendix) were included for broadening the analyses in order to examine the thesis matter and achieve broader understanding and relevance of the findings.

The background literature relevant to the entire thesis, the key issues and research questions identified at the start of this thesis research are presented in an introductory chapter (Chapter 1). The primary objective, aims of the interrelated studies, hypotheses and overall methodology of the thesis are described in Chapter 2. To unify the thesis, an overview of the studies conducted for the thesis is presented in the fore matter. The majority of the remainder of the thesis is presented as a series of papers describing the studies undertaken (Chapters 3-7). In order for each publication to be interesting in its own right, and stand alone as a separate manuscript, the chapters include relevant background, methods and discussion. The summary of the findings and conclusions are presented and discussed in Chapter 8.

The references for the entire thesis are collected at the end of the thesis in Bibliography. Copies of the peer reviewed publications related to this thesis, documents related to recruitment and assessments for this research and other related documents are collected in the Appendices (respectively A, B and C).

OVERVIEW OF CHAPTERS, STUDIES AND PUBLICATIONS

The primary focus of this thesis is to examine the relationship between cognitive decline and the change over time of Health Related Quality of Life (HRQoL) ratings by people diagnosed with mild to moderate Alzheimer’s disease (AD) and HRQoL ratings by their primary informal carer. The thesis utilized different data sources to examine aspects of the study objectives. This section will present an overview to clarify how chapters, studies and publications are related.
OVERVIEW OF CHAPTER 3: DIFFERENT FACTORS ASSOCIATED WITH COMPLEMENTARY HRQoL RATINGS BY PEOPLE WITH AD AND FAMILY CARERS

Reference

Research question
We designed this study to determine: (1) the agreement in QoL ratings between community-dwelling patients with mild to moderate dementia and family carers; and (2) the factors associated with self-reported and two types of carer-reported QoL ratings: carer–carer perspective and carer–patient perspective.

Study design
A cross-sectional study was carried out of 80 community-dwelling patients with the diagnosis of probable Alzheimer’s disease (AD) of mild or moderate severity according to NINCDS-ADRD criteria, and their 80 family carers (i.e. QoLCog study I).

Interpretation
This paper established that mild to moderate community-dwelling AD patients and their carers (with different perspectives) agree within an acceptable range in QoL ratings, but the ratings are driven by different factors, and consequently are not interchangeable but complementary. The findings suggest that both ratings provide valuable information when used separately, not in a composite score as originally indicated.

OVERVIEW OF CHAPTER 4: PREDICTORS OF CHANGE IN HRQoL SELF-RATINGS AND CARER-RATINGS FOR COMMUNITY-DWELLING PEOPLE WITH ALZHEIMER’S DISEASE

Reference
Bosboom, P.R.; Alfonso, H.; Almeida, O.P. (2013). Determining the predictors of change in Quality of Life self-ratings and carer-ratings for community-dwelling
Research question
To determine the factors that mediate changes in Health Related Quality of Life (HRQoL) ratings by community-dwelling people with Alzheimer's disease (AD) and their informal carers over a period of 18 months.

Study design
An 18-month longitudinal study of 80 community-dwelling older adults diagnosed with probable AD of mild or moderate severity (NINCDS-ADRD criteria) and their family carers (i.e. QoLCog study I and II).

Interpretation
This paper established that HRQoL self- and carer-ratings of community-dwelling people with AD do not decline at same rate over 18 months and changes are associated with different factors. The findings suggest that interventions designed to optimise quality of life of people with AD should consider carefully whose HRQoL ratings they wish to change.

Overview of Chapter 5: Stability of the association between cognitive domains and HRQoL ratings in Alzheimer’s disease.

Reference:

Research question
To determine if the association between cognitive domains in AD and HRQoL remains the same in 18 months.

Study design
An 18-month longitudinal study of 80 community-dwelling older adults diagnosed...
with probable AD of mild to moderate severity and family carers, and 61 healthy elderly controls (i.e. QoLCog study I and II). As primary outcome of interest we used the QoL-AD (separate scores for self and carer). Specific cognitive functions were assessed with a broad range of neuropsychological measures, which were later grouped into cognitive domains following factor analyses at the baseline and 18-months assessments. Other explanatory variables included demographics, psychopathology, burden-of-care, and medication use. Separate EFA’s were conducted for each group: 1) all participants with AD at baseline (N=80), 2) selection of participants with AD at baseline who did not complete follow-up assessment (N=33), 3) selection of participants with AD at baseline who also completed follow-up (N=47), 4) these same participants at 18-month follow-up (N=47), 5) controls at baseline (N=61) and 6) controls at follow-up (N=61).

Interpretation
This paper established that HRQoL ratings are not consistently associated with specific cognitive domains in AD and that cognitive enhancing focused (pharmacological) therapies may fail to enhance the HRQoL of people with AD.

**OVERVIEW OF CHAPTER 6: DO CHANGES IN COGNITIVE FUNCTIONS PREDICT CHANGES IN HRQOL IN PEOPLE WITH AD LIVING IN THE COMMUNITY?**

Reference

Research question
To determine if decline of specific cognitive functions commonly associated with AD predict which patients maintain or experience a deterioration of their HRQoL over 18 months.

Study design
We completed an 18-month longitudinal study of 47 community-dwelling older adults diagnosed with probable AD of mild or moderate severity and their family carers (i.e.
QoLCog study I and II). The primary outcomes of interest were 18-month change in self-reported and carer-reported ratings on the QoL-AD. The main explanatory variables were 18-month change in specific cognitive functions using a broad range of established tests.

**Interpretation**
This paper established that changes in specific cognitive functions are not associated with changes in HRQoL ratings in AD, suggesting that interventions that limit their focus to improving specific cognitive functions as expressed by cognitive scores of people with mild to moderate AD living in the community might fail to enhance participants’ HRQoL.

**Overview of Chapter 7: HRQoL and the use of potentially harmful medications among people with dementia living in residential aged care facilities**

**Reference**

**Research question**
We designed this study to determine the association of exposure to PHM, operationalized by three different measures, with self-reported HRQoL among people with dementia residing in RACFs.

**Study design**
Cross-sectional DIRECT study of 351 people aged ≥65 years diagnosed with dementia residing in RACFs and with MMSE ≤24. For complete DIRECT study protocol, see attached as appendix. Using regression analyses, we calculated crude and adjusted mean differences between groups exposed and not exposed to PHM according to potentially inappropriate medications (PIMs; identified by Modified Beers criteria), Drug Burden Index (DBI) and polypharmacy (i.e. ≥5 medications).
**Interpretation**

This chapter was added as post-hoc analyses aimed to clarify the prevalence of PHM and whether the exposure to PHM could have confounded other findings. This paper established that the prevalence of exposure to PHM is high in RCFs but very low in the community. Exposure to PHM, as identified by DBI >0 and by polypharmacy (i.e. ≥5 medications), but not by PIMs (Modified Beers criteria), is inversely associated with self-reported HRQoL for people with dementia living in RACFs. With regards to clinical tools, our data suggest that DBI and polypharmacy may be better predictors of HRQoL than PIMs by Modified Beers criteria. This study supports the recommendation that, with the overall aim of improving QoL as outcome of care for PWD in RACFs, efforts should be made to avoid the use of PHM through quality use of medicine initiatives.

**ADDITIONAL PUBLICATION, REFERENCED IN CHAPTER 8 GENERAL DISCUSSION:**

**Reference**


**Research question**

As a component of the establishment of a large randomized controlled trial of educational interventions (i.e. the DIRECT study) to improve the health related quality of life of people with dementia living in residential care facilities, we aimed to determine the feasibility and inter-rater reliability of assessment of quality of life, using the self-rated QOL-AD administered by two interviewers.

**Study design**

Inter-rater reliability study. For complete DIRECT study protocol: see appendix.

**Interpretation**

This paper confirmed that the QOL-AD can be implemented in routine research settings with good overall inter-rater reliability after relatively little training of research staff, although agreement of individual items was at best moderate, indicating
the importance of objective assessment of inter-rater reliability, or the inherent instability of self-rated quality of life in RACFs.

**ADDITIONAL PUBLICATION, REFERENCED IN CHAPTER 8 GENERAL DISCUSSION:**

*Reference*


*Research question*

We aimed to determine the influence of resident and informant perspective and place of residence on rating of QoL of PWD.

*Study design*

Two cross-sectional studies, i.e. cross-sectional QoLCog study I, and cross-sectional DIRECT study. For complete DIRECT study protocol: see attached as appendix. Sixty-five healthy older controls, 50 PWD living in the community, 50 PWD living in RACFs, and their informal carers (informants) participated.

*Interpretation*

This chapter was added as post-hoc analyses aimed to clarify whether place of residence may influence HRQoL ratings. This paper established that the perspective of informants and the place of residence of PWD may influence informant ratings of participants’ HRQoL. There is substantial variation in HRQoL rating for PWD residing in RACFs. The findings indicate that researchers and service agencies may need to gather HRQoL ratings from multiple sources, and consider the perspective of informants. Differences between places of residence are briefly discussed.
CHAPTER 1.

HEALTH RELATED QUALITY OF LIFE
IN ALZHEIMER’S DISEASE -
LITERATURE REVIEW
1.1. INTRODUCTION
The primary aim of this thesis is to determine the relative contribution of cognitive decline to changes in Health Related Quality of Life (HRQoL) in people diagnosed with probable mild to moderate Alzheimer’s disease (AD). This introductory chapter reviews the literature on the research topic to identify the key issues that need to be addressed and to establish the relevance of this research. The introduction will first address facts on the worldwide ageing population with individuals over the age of 65 years representing the fastest growing segment of the general population, accompanied by a dementia epidemic. This will be followed by an introduction to the concept and relevance of HRQoL as primary outcome measure in dementia. An overview will be provided about the clinical characteristics of AD, accounting for the highest percentage of all dementias and the type of dementia which will be the focus of this thesis research. In the absence of a cure the emphasis at present in research and clinical practice rests primarily on interventions to optimize HRQoL, which forms the base to discuss the main challenges of the assessment and interpretation of HRQoL ratings in AD. This is followed by a critical review of the incomplete and sometimes conflicting research findings about factors that are associated with HRQoL ratings and the limited research on factors that predict changes in HRQoL during the progression of the disease. The emphasis will be on what is known about the role of cognitive decline, the clinical hallmark of typical AD, as predictor of change in HRQoL ratings. At the end of this introductory chapter the key issues, which will be used as arguments for the thesis hypotheses, will be summarized.

1.2. THE AGEING POPULATION

1.2.1. DEMOGRAPHICS: THE CHANGING AGE PROFILE
Ageing of the population is a worldwide phenomenon (UN, Population Division, World Population Ageing 1950-2050, Report 2001). The ageing population is a shift in the distribution of the population towards older age, which is reflected in a large decline in overall fertility and increase in number of people reaching older ages, causing a rise of the proportion of the population that is elderly. While the world has never seen an aged population as currently exists, it is projected that in the coming decades even more people will reach older ages, that is, under current mortality conditions, almost 3 of every 4 newborns in the world will survive to age 60, and about 1 of every 3 to age 80
years. For the period 2045-2050, approximately 7 of every 8 newborns will survive to age 60, and more than half to age 80 (UN, Population Division, World Population Ageing 1950-2050, Report 2001). Of the 150,000 people who die each day across the globe, about two-thirds die of age-related causes; in developed countries the proportion is even higher, reaching 90%.

The potential support ratio is an alternative way of expressing the numerical relationship between those more likely to be economically productive and those more likely to be dependants. It is the inverse of the old-age dependency ratio, that is, the number of people in the working ages of 15-64 for every person 65 or older. The number of working-age people per older person is expected to drop globally by more than 50 per cent over the next 50 years (see Figure 1.1). In 2000, there were fewer than 5 persons in the working ages for every person 65 or older in Europe; by 2050, there will be fewer than 2 (UN, 2008). An increase in the old-age dependency ratio indicates a situation in which an increasing number of potential beneficiaries of health funds (mainly those aged 65 and over) are supported by a relatively smaller number of potential contributors (those in the economically active ages of 15-64). This trend tends to impose heavier demands on the working-age population in order to maintain a stable flow of benefits to the older groups.

![Figure 1.1. The percentage of the world's population that will be over 65 between 1950-2050 (adapted from the UN World Population Prospect, 2008).](image)

Also, the continuing increase of the parent support ratio (i.e. a measure that has been commonly used to assess the demands on families to provide support for their oldest-old members) indicates that more and more frequently the young-old will find themselves responsible for the care of one or more oldest-old family members. The
increasing number of people in their fifties and sixties are likely to have surviving parents or other very old relatives. Because people are living longer and thus are more likely to experience multiple chronic diseases, more and more adults are expected to face the need to care for very old and sometimes frail relatives. In 2050, the parent support ratio in the more developed regions is projected to reach 28, up from 9 in the year 2000. By 2050, Japan is projected to have by far the world’s highest ratio, of 56. In that same year, the number of people aged 85 or over for every hundred people aged 50-64 is expected to surpass 30 in another 15 countries or areas, mostly in Europe.

This thesis focuses on the Australian older age population. In 2004, the Australian Government’s Intergenerational Report (IGR) projected that over the next 40 years, the proportion of the population aged over 65 years will almost double to around 25 per cent. At the same time, growth in the population of traditional workforce age – 15 to 64 – is expected to slow to almost zero. The number of Australians aged 65 and over is expected to increase rapidly, from around 2.5 million in 2002 to 6.2 million in 2042 (Australian Government, The Treasury, Report Australia’s Demographic Challenges, 2004). That is, from around 13 per cent of the population to around 25 per cent. For Australians aged 85 and over, the growth will be even more rapid, from around 300,000 in 2002 to 1.1 million in 2042 (see Figure 1.2). In 2002, there were more than five people of working age to support every person aged over 65. By 2042, there will only be 2.5 people of working age supporting each person aged over 65 years.

![Figure 1.2. Australian Population Growth Indices by age group (adapted from: Australian Government, The Treasury, Report Australia’s Demographic Challenges, 2004).](image-url)
1.2.2. AGE-RELATED CHRONIC DISEASES

The demographic ageing has resulted in the increased prevalence of age-related chronic diseases. Chronic disease has been defined as illness (or: abnormal condition) that is prolonged in duration, does not often resolve spontaneously, and is rarely cured completely (Australian Institute of Health and Welfare, 2012). Chronic diseases are complex and varied in terms of their nature, how they are caused and the extent of their community impact. While some chronic diseases make large contributions to premature death, others contribute more markedly to disability (i.e. an umbrella term for impairments, activity limitations and participation restrictions, referring to the negative aspects of the interaction between an individual with a health condition and that individual’s contextual environmental and personal factors (Leonardi et al., 2006).

The World Health Organization (WHO) reported that, globally, of the 58 million deaths in 2005 approximately 35 million were caused by chronic diseases. They were reported to be the major cause of death among adults in almost all countries and the toll is projected to increase by a further 17% in the next 10 years (WHO, 2005).

In Australia the ageing of the population has also played a key role in the rise in prevalence of chronic disease. In the 2007-08 National Health Survey nearly all people aged 65 years and over reported having at least one long-term condition (with more than 80 per cent of people in this age group having three or more long-term conditions) compared with only 27% of children (Australian Institute of Health and Welfare, 2010, page 298). Chronic diseases are leading causes of death and disability in Australia and are associated with high use of health care services, contributing to major funding pressures in Australian health care that are expected to rise over coming decades as prevalence increases. The results of the 2007-08 National Health Survey show a high prevalence of chronic diseases among Australians, including long-term mental or behavioural conditions (Australian Bureau of Statistics, 2010). Given the increasing prevalence of chronic diseases and the enormous associated personal, social and economic cost to the community, and in order to strengthen national investment and infrastructure in preventive health, the Australian Government established the Australian National Preventive Health Agency in 2011. Key functions of the Agency included the provision of evidence-based advice on national preventive health issues and promotion of behavioural change in the community through education and awareness programs. Dementia, considered by the Australian Government as a separate health issue, is one of the nine National Health Priority Areas. The epidemiology of dementia will be discussed in the following section.
1.2.3. **THE EPIDEMIOLOGY OF DEMENTIA**

The ageing of the population has resulted in an increase in the number of people living with dementia. Dementia is not a single specific disease: it is a broad term describing a syndrome associated with more than 100 different diseases that are characterized by the impairment of brain functions, causing impairment in cognitive abilities like memory. Although the type and severity of symptoms and their pattern of development varies with the type of dementia, the condition is usually chronic, progressive and irreversible (DSM-IV).

Prevalence estimates vary, but dementia is thought to affect about 2.5 per cent of all people over 65 years, and prevalence doubles every 5 years with increasing age, so that about 10 per cent of all people over 75, and 40% of all people over 85, are affected (Turner, 2003). In 2000 approximately 25 million people lived with dementia; with another increase of 38 million expected for the following 30 years (Wimo et al., 2003). A systematic review (Prince et al., 2013) of the global literature on the prevalence of dementia (1980-2009) showed that in 2010 35.6 million people lived with dementia worldwide, with numbers expected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050. Taken together, dementia presents an enormous health, social, economic and personal challenge given the large and growing number of older people affected by dementia worldwide (Prince et al., 2013).

Because of the alarming global figures, in 2012 the WHO published a report to raise awareness of dementia as a public health priority, to articulate a public health approach and to advocate for action (WHO, 2012). The WHO recognized the lack of awareness and understanding of dementia in most countries, resulting in stigmatization, barriers to diagnosis and care, and the impact on caregivers, families and societies physically, psychologically and economically. The report was expected to enable governments, policy-makers, and other stakeholders to address the impact of dementia as an increasing threat to global health, and to promote dementia as a public health and social care priority worldwide.

In Australia, dementia was the third leading cause of recorded death in 2010 (Australian Bureau of Statistics, 2012). For people aged 65 years and older, dementia was the second leading cause of burden of disease and the leading cause of disability burden. According to the Australian Institute of Health and Welfare there were over 321,600 Australians living with dementia in 2012. This number was expected to increase by one third to 400,000 in the next decennia. The projections for 2050 are that, without a medical breakthrough, the number of people living with dementia in Australia will be
close to 900,000 by 2050 (Access Economics, 2009). An estimated 1.2 million Australians are caring for someone with dementia (Alzheimer’s Australia, 2011). The current cost of dementia to the health and aged care sectors is estimated to be at least $4.9 billion per annum (Australian Institute of Health and Welfare, 2012); by 2060 spending on dementia is set to outstrip that of any other health condition (Access Economics, 2009).

Given the alarming global figures of the aging population and dementia being recognized as a public health priority, the interest in and relevance of measuring the outcome of interventions for people with dementia has increased. A key consideration is whether interventions generalize to improve someone’s perception of his or her quality of life. As being the focus of this thesis, the concepts quality of life (QoL) and health related quality of life (HRQoL) will be introduced in the following section.

1.3. HRQOL AS OUTCOME MEASURE IN DEMENTIA

In order to understand the concept QoL, a brief historical overview will be given on the conceptual approaches to QoL, the difference and overlap of the concepts QoL and HRQoL, QoL in old age, a model for HRQoL in dementia, and its relevance in dementia as outcome measure.

1.3.1. THE CONCEPTS QoL AND HRQoL

The concept QoL was introduced at the end of the 1950s when investigators perceived that social improvement not only included material prosperity, but also a general feeling of wellness (see review by Zautra & Goodhart, 1979). The various ways QoL has been defined and assessed since its introduction, depended on the field of study (i.e. Economics, Social Sciences or Medicine), the context in which it has been used (e.g. clinical issues, research trial), and the conceptual orientation of the investigator (with emphasis on social, health related and/or psychological indicators).

QoL is a widely used concept, although there is limited agreement on its definition or how it should be measured. The most widely used definition is the one proposed by the World Health Organization (WHO) in 1997: “Individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to
salient features of their environment.” This definition refers to a subjective balance between expectations versus experiences in real life, a balance that can change over time, depending on a broad range of factors, including health. The Constitution of the WHO defines health as "A state of complete physical, mental, and social well-being, not merely the absence of disease". It follows that the measurement of health and the effects of health care must include an estimation of life quality and this can be assessed by measuring the improvement in the QoL related to health care.

Although the terms QoL and HRQoL overlap in meaning and are used interchangeably in literature, each concept has its own meaning. That is, QoL is a broader concept that covers all aspects of life, as defined by the WHO, while HRQoL has a focus on the effects of health (or a specific disease) and the impact of health (or disease) related factors on someone’s experienced quality of life. The evaluation of one’s QoL includes evaluation of all features of a person’s life, whereas the evaluation of HRQoL is connected to an individual’s health or specific diagnosis-related factors.

With regard to using QoL or HRQoL as outcome measure, HRQoL measures are considered to be more sensitive at detecting disease-related changes, while generic QoL measures facilitate comparisons across different populations, with or without specific diseases, as is often required in policy decision making. Approaches to measuring QoL and HRQoL vary in breath (Brod et al., 1999; Jonker et al., 2004; Lawton 1994; Rabins et al., 1999; Volicer & Bloom, 1999).

Some authors have argued that the QoL definition by the WHO can be considered ‘health-related’ QoL (i.e. HRQoL), as it focuses on aspects that are affected by health or disease and thus mostly addresses limitations and handicaps (Jonker et al., 2004). In this thesis, we will use the term QoL as described by the WHO definition (1997), which includes a broad ranging concept affected in a complex way. Were possible we will distinguish between QoL and HRQoL, but when citing other studies I will refrain from changing the terminology as used in that particular study.

1.3.2. THE RELEVANCE OF HRQoL AS OUTCOME MEASURE
The interest in QoL as a relevant outcome measure in clinical trials increased in epidemiological (i.e. describing the subjectively perceived health and social status of given populations) and health studies (i.e. assessing benefits of treatments in terms of QoL) (Power et al., 1999). Exponential growth in reports relating to development and evaluation of QoL measures was noted in 2002 (Garrat et al.) for a number of chronic conditions (e.g. asthma, epilepsy, HIV, schizophrenia). QoL has become well
established as a multi-dimensional and integrative concept with important links to economics and ethics (Mack & Whitehouse, 2001), and has become an increasingly important outcome measure in both research and clinical practice (Ready & Ott, 2003).

With regard to dementia, there is growing consensus that HRQoL can capture elements of experienced outcomes not detected by standard symptom measures (Banerjee et al., 2009; Mack & Whitehouse, 2001). Dementia is recognized as one of the principal causes of disability and decreased QoL among older adults (Scholzel-Dorenbos et al., 2007). Growing expectations for positive aging amongst older adults and policy concern about the rising costs of age-related health care and institutionalization underlie the sharp rise in (HR)QoL research in this filed (Brown et al., 2004; St John & Montgomery, 2010). In fact, low HRQoL is a strong predictor of adverse health outcomes such as nursing home placement and death (Billotta et al., 2011). Consequently, HRQoL outcomes are now recommended as essential in dementia prevention research (Halvorsrud & Kalfoss, 2007), and as key-outcomes for assessing the efficacy of pharmacological and therapeutic interventions in dementia care (Katona et al., 2007).

1.3.3. FACTORS ASSOCIATED WITH QoL AT OLDER AGE

The growth of interest in QoL for the older population can be illustrated by the growth in number of publications on ‘quality of life’ in PubMed, as presented in Figure 1.3. We did separate searches for ‘Quality of life middle age and older’, ‘quality of life Alzheimer’s disease’, and ‘quality of life dementia’.

Figure 1.3. Number of publications on ‘quality of life’ in PubMed (as per 22-06-2014). Green bars represent all publications on ‘quality of life’; red bars the number of publications on ‘quality of life in Alzheimer’s disease’; blue bars the number of publications on ‘quality of life in dementia’.
Chapter 1

Recommending a selection of reviews is challenging, given that over the last 5 years approximately 350 reviews related to QoL in later life have been published. In short, meta-analytic and longitudinal studies reveal a considerable degree of stability in measures of QoL, life satisfaction, self-esteem, and depression during middle and older age (e.g., Bengtson, Reedy, & Gordon, 1985; Blazer, 1993; Diener & Suh, 1997; Stock, Okun, Haring, & Witter, 1983). While chronic illnesses often drive the QoL of older people (Levasseur et al., 2009), chronic diseases and disabilities are associated with poorer QoL (e.g. Asakawa et al., 2000), behavioural, psychological, social, environmental and economic resources can also influence scores. For example, health promoting behaviours assist with the management of chronic illnesses (Browning et al., 2012), and personal control over one’s life activities and environment can influence perceptions of QoL in the face of illness (Mollenkopf & Walker, 2007). Social resources, including social activities and social support, are key influences on QoL particularly in impoverished environments such as low SES neighbourhoods (Bowling et al., 2013; Mollenkopf & Walker, 2007). Also, positive self-perceptions of ageing are important influences on QoL (Levasseur et al., 2009; Levy, Slade, & Kasl, 2002). A recent study by Trigg et al. (2012) showed that negative attitudes to aging had a direct impact on the self-reported QoL ratings of people with dementia: the view of aging as a time of psychosocial loss was most significant for people with dementia and suggests that negative stereotypes of dementia need to be challenged. There are indications that subjective memory concern is directly linked to QoL (Gates et al., 2014; Montejo et al., 2011), although conflicting results have been noted (Berwig et al., 2009; Mol et al., 2007).

An important report by Levasseur et al. (2009) explored the perceptions and lived experience of community-dwelling older adults about their QoL in regards to personal factors, social participation and environment. A qualitative design was used to extend existing work on QoL focusing on functioning components and advanced QoL conceptualization. Based on a semi-structured interview guide, two individual in-depth interviews were conducted with 18 participants (aged 63–92; 12 women) with various levels of ability and QoL. Personal factors, such as health, inner life and behavioral abilities, were found to be essential for QoL. Being occupied and doing activities associated with good health habits were also important. Accomplishment of social roles was, for the majority of participants, more significant than daily activities. The physical and social environment must be adapted to the person’s needs and preferences. Participants’ perceptions differed only slightly according to their ability and QoL levels.
Findings show the critical role of adaptation to disabilities and aging for better QoL. A sense of control over one’s own life also has beneficial effects. These results highlight the importance of considering perceptions about personal factors, social participation and environmental factors in older adults’ QoL (Levasseur et al., 2009).

A challenging but important issue is the comparability of measures of QoL in specific groups, such as normal ageing, mild cognitive impairment, or specific neurodegenerative diseases, creating the possibility to conduct longitudinal studies among a heterogeneous group of middle and older aged adults, is highly desirable, but the impact of cognitive deficits and impaired insight on applicability and validity of generic instruments is sparsely studied (Geschke et al., 2013).

Regarding dementia, it was Lawton (1983; 1991; 1994, 1997) who most extensively explored the concept of QoL. He adapted his original framework for ‘the good life’ to ‘frail elderly’, and later to older people with dementia. He defined QoL as ‘the multidimensional evaluation, by both intra-personal and social normative criteria, of the person environment system of an individual in time past, current, and anticipated” (1991, p. 6). On theoretical grounds, Lawton (1994) distinguished four ‘sectors’ of QoL: 1) Behavioural competence; 2) Objective environment; 3) Domain-specific perceived QoL; and 4) Psychological well-being. Several other investigators have elaborated on Lawton’s framework to study QoL of at older age and QoL of people with dementia or developed distinctive approaches, based on different theoretical assumptions or on focus groups, consisting of professional caregivers, informal caregivers and patients (Brod et al., 1999; Logsdon et al., 1999; Rabins et al., 1999). The most recent and frequently cited model of QoL in dementia is that proposed by Jonker et al. in 2004.

1.3.4. A MODEL FOR HRQoL OF LIFE IN DEMENTIA

Jonker et al. (2004) reviewed the conceptual developments in QoL research concerning dementia, and noted that up till that point in time only a few researchers had presented a conceptual framework for a disease-specific QoL in dementia (Brod et al., 1999; Rabins et al., 1997; Volicer et al, 1999; Gurland & Katz, 1997), often with their concepts based on the work by Lawton (1994). They analysed and compared the four models and found that none of the existing models had conceptualized the relationships between traditional clinical variables in dementia and health status measures. They proposed that QoL in dementia consists of multiple dimensions (so called sectors by Lawton, 1994) that may consist of multiple domains, and that a model for QoL in dementia should address all aspects of the life of a person with dementia, including those aspects not
affected by dementia, (e.g. religion). They acknowledged that when developing an adequate QoL model for dementia, the selection of the domains is the most crucial, but also a highly controversial step.

With this in mind, Jonker and colleagues (2004) proposed a hierarchical model for QoL in dementia (see Figure 1.4, an extended version of their illustration) that includes the interrelation between dimensions. It addresses all aspects of life of a person with dementia, including those not directly affected by dementia. Thus, this approach is disease-specific, but not limited to dimensions or domains of the model that are driven by the disease. As it is disease-specific, this model could arguably be considered a HRQoL model. They based their dimensions and domains on the review of existing research (including the focus groups in the studies of Brod et al., 1999, and Rabins et al., 1999). They suggested that the model could be used to support the formulation of strategies to improve QoL of people with dementia and to guide the choice of instruments for specific research and interventions goals.

![Figure 1.4. Hierarchic relationships between QoL dimensions in dementia (modified from Jonker et al., 2004). The examples are added to their original illustration.](image)

Recently, Gates and colleagues (2014) applied Jonker et al.’s model in a framework for Mild Cognitive Impairment (MCI), which was empirically tested in order to inform interventions. Their study provided empirical support for a hierarchical model in MCI that explained 61% of the variance (Gates et al., 2014). The clinical aspects (as in Jonker et al.’s model at level 1) of MCI, depression and social support, were interrelated, and subsequently influenced secondary evaluations of QoL (at level 2). Also, memory concern in the form of complaints and self-rated memory function was significantly associated with cognitive and daily function, independently of
negative affect. Memory concern was also linked to low satisfaction with social support and depressive symptoms. With the exception of cognitive and daily functions, which were not associated, all other level 1 factors were statistically associated with QoL scores. The results identified several clinical targets and entry points for intervention. These included the importance of reducing memory concern and addressing low mood. Their findings, and findings from other studies (Lee et al., 2013), support the applicability of Jonker et al.’s model of QoL in dementia (2004) for identification of intervention goals (with dementia related and non-related factors at level 1) in order to increase QoL of people with dementia.

Taken together, while the concept of HRQoL in dementia still lacks a universally accepted definition, new efforts to improve the conceptualisation of HRQoL in dementia have emerged, including the persuasive model proposed by Jonker and colleagues (2004).

There are several possible causes of dementia, but the most frequent cause is AD, accounting for approximately 50-70 per cent of all dementia diagnoses (Ballard et al., 2011). As this type of dementia will be the focus of this thesis, the following section will summarize the clinical characteristics of AD with emphasis on cognitive decline and interventions.

1.4. DEMENTIA OF THE ALZHEIMER’S DISEASE (AD) TYPE

In this section the diagnosis, neuropathology, prevalence and risk factors of AD will be briefly discussed. Subsequently, the clinical characteristics, particularly cognitive decline, will be presented in greater detail to provide an understanding of why these clinical features can all be considered as possible factors that mediate QoL. This will be followed by a summary of available interventions and the relevance of optimal QoL.

1.4.1. DIAGNOSIS OF AD

In 1906 the German psychiatrist and neuropathologist Aloysius “Alois” Alzheimer reported “a peculiar disease”, a case of a woman aged 51 years, Auguste D, with severe amnesia, aphasia, unfounded suspicion about her family (hallucinations) and other psychological changes. At post-mortem, while performing a brain autopsy, he noted severe atrophy, dense deposits surrounding the nerve cells (neuritic plaques), and inside the nerve cells he observed twisted bands of fibers (neurofibrillary tangles). It was in 1910 that Emil Kraepelin, a German psychiatrist, first named “Alzheimer’s disease” in
the eight edition of his book *Psychiatry*. This degenerative brain disorder still bears his name, and when found during an autopsy, these plaques and tangles are used to confirm the diagnosis of AD. Alois Alzheimer is now recognized not only for his ground-breaking observations of a major disease, but also for using new scientific tools to determine how clinical symptoms related to specific brain pathology. In 1976, neurologist Robert Katzman identified AD as the most common cause of dementia and a major public health challenge (Katzman, 1976).

In 1984, representatives from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) developed a uniform set of criteria to enable clinicians and researchers to maintain consistency in the diagnosis. They included aspects of medical history, clinical examination, neuropsychological testing, and laboratory assessments (McKhann et al. 1984). The criteria were developed with the intent of accurately associating the clinical symptoms with the neuropathological manifestations after death. Levels of certainty were established that were labelled as *definite* for autopsy-confirmed disease, *probable* for the typical clinical syndrome without intervening issues, and *possible* for diagnoses complicated by disorders that might contribute to the dementia. The criteria facilitated estimates of the prevalence and incidence rates of clinically diagnosed probable and possible AD.

With advances in neuropsychological assessment, brain imaging, and neuropathological, biochemical and genetic understanding of this disease, the NINCDS-ADRDA criteria were reviewed in 2011 (McKhann et al., 2011). The criteria for dementia are presented in Table 1.1; the updated criteria for probable AD are presented in Table 1.2.

In comparison, the new criteria define not only the dementia of AD, but also incorporate a fuller spectrum of cognitive ageing, and imply the existence of an intermediate stage of mild cognitive impairment (MCI) that precedes the dementia (Albert et al., 2011). A third, even earlier, stage of “preclinical AD” has also been suggested. This prodromal period is characterized by the presence of biomarkers, such as brain amyloid deposition and cerebrospinal fluid tau and amyloid, that can be detected in vivo in asymptomatic individuals years before the onset of cognitive decline (Perrin et al., 2009; Sperling et al., 2009; 2011; Jack et al., 2010). At present, the recommended use of biomarkers to detect AD applies only to research. Neuropsychological assessment continues to provide reliable symptom markers of AD that are critical for early diagnosis (Weintraub et al., 2012).
Table 1.1 Criteria for All-Cause Dementia (McKhann et al., 2011)

- Cognitive or behavioural symptoms that
  - Interfere with the ability to function at work or at usual activities
  - Represent a decline from previous levels of functioning and performing
  - Are not explained by delirium or major psychiatric disorder

- Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a bedside mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.

- The cognitive or behavioural impairment involves a minimum of 2 of the following domains:
  - Impaired ability to acquire and remember new information. Symptoms include repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, and getting lost on a familiar route
  - Impaired reasoning and handling of complex tasks, poor judgment. Symptoms include poor understanding of safety risks, inability to manage finances, poor decision-making ability, and inability to plan complex or sequential activities
  - Impaired visuospatial abilities. Symptoms include inability to recognize faces or common objects or to find objects in direct view despite good acuity and inability to operate simple implements or orient clothing to the body
  - Impaired language functions (speaking, reading, writing). Symptoms include difficulty thinking of common words while speaking, hesitations, and speech, spelling, writing errors
  - Changes in personality, behaviour, or comportment. Symptoms include uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviours, and socially unacceptable behaviours.

The criteria for probable AD retained the framework of the 1984 NINCDS-ADRDA criteria, but expand its breadth by including biomarker enhancements to the diagnosis of AD dementia (Jack et al., 2010). Also, the set of newly proposed criteria include the recognition of both amnestic and non-amnestic symptom onset and alterations in numerous other cognitive domains. Further, cerebrovascular disease is now recognized as a contributor to dementia, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment, the presence of multiple or extensive infarcts, or severe burden of hyperintense white matter lesions by MRI. Accordingly, the presence of substantial cerebrovascular pathology reduces the certainty of a clinical diagnosis of AD to ‘possible’.
Table 1.2 Criteria for Probable Alzheimer’s disease (McKhann et al., 2011)

Meets criteria for dementia, and in addition, has the following characteristics:

- Insidious onset; symptoms have a gradual onset over months to years, not sudden over hours or days.
- Clear-cut history of worsening of cognition by report or observation.
- The initial and most prominent cognitive deficits are evident on history and examination in 1 of the following categories:
  - Amnestic presentation: it is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least 1 other cognitive domain.
  - Nonamnestic presentations:
    - Language presentation: the most prominent deficits are in word finding, but deficits in other cognitive domains should be present.
    - Visuospatial presentation: the most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
    - Executive dysfunction: the most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

As summarized by Ballard et al. (2011), an accurate diagnosis of dementia enables the detection of potentially treatable disorders that contribute to cognitive impairment, such as depression, vitamin deficiencies and hypothyroidism, and allows patients and families to plan their future lives and finances, including advance directives and optimum treatment and care. With the prospect of development of AD modifying drugs, early and accurate diagnosis and the ability to provide a prognosis is essential.

1.4.2. NEUROPATHOLOGY

The pathological hallmarks of AD include amyloid plaques and neurofibrillary tangles, cerebral amyloid angiopathy, glial responses, neuronal and synaptic loss (Serrano-Pozo et al., 2011). The staging of pathological changes proposed by Braak & Braak (1991) has formed the basis of our current understanding of the progression of the cognitive deficits in AD (Nelson et al., 2012). Nelson et al. (2012) provided a clear review of the literature on correlation of AD neuropathologic changes with cognitive status, on the background of the many challenges related to the study of the clinicopathologic correlates of cognitive impairment in the elderly. For example, most persons in advanced old age have significant non-AD brain lesions that may alter cognition independently of
AD. Moreover, many people with AD also have vascular changes and white matter lesions, and it is increasingly acknowledged that AD and vascular dementia often co-exist, a situation referred to as mixed dementia (Morris et al., 2003). Nelson et al. (2012) concluded that the evidence from many independent research centres strongly supports the existence of a specific disease, as defined by the presence of Aβ plaques and neurofibrillary tangles. Although Aβ plaques may play a key role in AD pathogenesis, the severity of cognitive impairment correlates best with the burden of neocortical neurofibrillary tangles (Nelson et al., 2012).

Serrano-Pozo et al. (2011) stated that classical neuropathological lesions including senile amyloid plaques and neurofibrillary tangles, define AD, but they suggested that these represent the “tip of the iceberg” of the pathological alterations that cause the cognitive decline associated with AD. Indeed, the development of new biomarkers and imaging tools has made evident that these neuropathological stigmata of AD starts accumulating a decade or more before the clinical diagnosis of dementia. Synaptic loss, plasticity changes, neuronal loss, and the presence of soluble microscopic oligomeric forms of Aβ and of tau, likely contribute to the progressive neural system failure that occurs over decades. An understanding of this natural history of the disease is critical to design primary or secondary prevention strategies to halt the disease progression before the damage to the neural system becomes irreversible (Serrano-Pozo et al., 2011).

Importantly, the pathophysiological process of AD is thought to begin many years before the diagnosis of AD dementia (Morris et al., 2005). This long “preclinical” phase of AD would provide a critical opportunity for therapeutic intervention; however, the link between the pathological cascade of AD and the emergence of clinical symptoms needs to be further elucidated. Therefore, in 2011 the National Institute on Aging and the Alzheimer’s Association convened an international workgroup to review the biomarker, epidemiological and neuropsychological evidence, and to develop recommendations to determine the factors which best predict the risk of progression from “normal” cognition to mild cognitive impairment and AD dementia (Sperling et al., 2011). They proposed a conceptual framework and operational research criteria, based on the prevailing scientific evidence to date, to test and refine these models with longitudinal clinical research studies. Their model of the clinical trajectory of AD is presented in Figure 1.5.
The use of the strict research criteria, like the NINCDS-ADRDA (1984), is associated with diagnostic accuracy of at least 80% (Beach et al., 2012; Blacker et al., 1994). As changes at the neurobiological level have a direct impact on cognitive functioning (Morris, 2005) and there is a complex but predictable correlation between AD pathologic hallmarks and cognitive impairment (Nelson et al., 2012), the role of cognitive or neuropsychological assessment is central to the diagnostic assessment of AD. Despite the clear potential of biomarkers for detecting evidence of the AD pathophysiological process, it is important not to lose sight of the potential that behavioural markers hold for early identification (Sperling et al., 2011). In persons who meet the core criteria of probable AD the biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process. However, the National Institute of Aging & Alzheimer’s Association Workgroups do not advocate the use of biomarkers for routine diagnostic purposes at current time.

1.4.3. Prevalence

In 2005 Alzheimer Disease International commissioned an international group of experts to reach an evidence-based Delphi consensus on dementia prevalence and estimated incidence in 14 World Health Organization regions, based on epidemiological data acquired over recent years. The results suggested that 24.2 million people lived with dementia in 2001, the majority of whom are thought to have AD, with 4.6 million new cases arising every year, with 42.3 million cases expected by 2020 and 81.1 million by 2040 (Ferri et al. 2005). Figure 1.6 shows studies that have estimated the age-specific incidence of AD by sex and by ethnic group (Mayeux & Stern, 2012). These studies illustrate the consistent increase in incidence with age, from approximately 0.5% per
year among individuals aged 65–70 to approximately 6–8% for individuals over age 85. The rapid rise in the incidence of AD with advancing age, combined with the relatively long duration of the illness, accounts in large part for the high prevalence of the disease worldwide. Taken together, the prevalence figures demonstrate the global epidemic of AD represents a major public health concern and has been identified as a research priority (Ballard et al., 2011).

Figure 1.6. The annual incidence rate (per 100 person-years) for Alzheimer disease. This graph is an estimate of data collected in 24 published studies (modified from Mayeux & Stern, 2012).

1.4.4. Associated Factors

Increasing age is the best established risk factor for dementia. Studies of prevalence and incidence of dementia and AD have consistently shown an almost exponential increase with advancing age, with both the prevalence and incidence doubling every five years (Fratiglioni et al., 2000; Miech et al., 2002). Among the list of risk factors for AD, vascular factors are among the most consistently reported (Launer, 2002). Diabetes, hypertension, smoking, obesity, and dyslipidaemia have all been found to increase the risk of AD (Anstey et al., 2008; 2011; Lu et al., 2009; Petersen et al., 2008; Sharp et al., 2011). Interestingly cerebrovascular disease, including large cortical infarcts, single strategically placed infarcts, multiple small infarcts, cerebral haemorrhage, cortical changes owing to hypoperfusion, white matter changes and vasculopathies, are all antecedents to dementia (Mayeux & Stern, 2012). Other risk factors for AD include genetic factors, although only a small proportion of all individuals with dementia suffer from familial forms of dementia caused by autosomal dominant mutations (Lander, 1996).

Ballard et al. (2011) summarized the evidence regarding modifiable risk factors for AD. They concluded that, at present, reduction of the risk of developing AD depends mostly upon lifestyle changes and improved treatment or prevention of medical
conditions that confer additional risk (Ballard et al., 2011). In addition, meta-analyses and systematic reviews provide robust evidence that cognitive reserve - a concept combining the benefits of education, occupation, and mental activities (Valenzuela & Sachdev, 2006) - physical activity and exercise (Hamer & Chida, 2009), midlife obesity (Beydoun et al., 2008), alcohol intake (Anstey et al., 2009), and smoking (Lee et al., 2010) are the most important modifiable risk factors for AD. Taken together, there is now strong evidence of potential risk and protective factors for AD, dementia, and cognitive decline, but further work is needed to understand these better and to establish whether interventions can substantially lower these risks (Ballard et al., 2011).

1.4.5. COGNITIVE DECLINE

1.4.5.1. NEUROPSYCHOLOGICAL PROFILE OF AD

Neuropsychological assessment has featured prominently over the past 30 years in the characterization of dementia associated with AD. Clinical neuropsychological methods have identified the earliest, most definitive cognitive and behavioural symptoms of illness, contributing to the identification, staging, and tracking of the disease (Weintraub et al., 2012).

Diagnostic assessment of dementia and related disorders requires a comprehensive multidisciplinary evaluation (Clare, 2008). Next to a medical evaluation and neuroimaging, which may provide crucial evidence of brain changes typical or atypical for underlying causes of cognitive impairment, assessment of dementia also requires a detailed neuropsychological examination to identify cognitive impairment, the cardinal clinical feature of dementia (Albert et al., 2011; American Psychiatric Association, 2013; Beck et al., 2014; Clare, 2008; Dubois et al., 2007; Knopman et al., 2001; McKhann et al., 2011). A comprehensive neuropsychological examination encompassing several cognitive domains can provide a pattern of altered and preserved functions, which is valuable to early detection, differential diagnosis and even prognosis of progression in predementia stages (Peña-Casanova et al., 2012). The use of adapted and standardized instruments is necessary to properly estimate cognitive and functional performance in AD. Thus, current practice guidelines, including the new Diagnostic and Statistical Manual of Mental Disorders (5th edition; DSM-V; American Psychiatric Association, 2013), recommend neuropsychological assessment in the care of older adults to identify and differentiate types of dementia (Blacker et al., 1994; Cox, 2011; Knopman et al., 2001; McKhann et al., 2011).

Partial similarities in presentation of AD and other medical and psychiatric
conditions presenting with cognitive impairment (i.e. Mild Cognitive Impairment, Vascular Dementia, Frontotemporal Dementia, vitamin B deficiency states, and Major Depressive Disorder) pose diagnostic challenges. But in the last decennia numerous studies identified specific neuropsychological patterns among a wide range of cognitive domains for AD and other conditions (e.g. Beck et al., 2014; Braaten et al., 2006; Hodges, 2007; Lezak, 2004). This requires a thorough neuropsychological assessment for the identification of specific cognitive comparative profiles, as it will assist in 1) clarifying the absence or presence of, extent, and nature of cognitive impairment, 2) supporting the differential diagnosis of medical and psychiatric disorders, whether dementia is present and what sub-type, 3) identifying treatment needs, 4) individualizing intervention programs and 5) evaluating intervention efficacy. The use of single metacognitive summary scores (such as Mini Mental State Examination, MMSE, Folstein et al., 2001; Alzheimer's Disease Assessment Scale-cognitive subscale, ADAS-Cog, Rosen et al., 1984; and the Cambridge Cognitive Examination-revised, CAMCOG-R, Roth et al., 1999) dilutes potentially important differential contributions from different neuropsychological domains or specific cognitive functions (Kessels et al., 2009) and may overlook treatment responses on specific cognitive functions (Beck et al., 2014). Of course, an understanding of the person’s current circumstances and past experiences, education and occupation, allows findings to be viewed and interpreted in an appropriate context and any changes in behavioural, emotional and functional abilities should also be considered.

The following section will review the neuropsychological features of AD and how these differ from age-related cognitive decline. As AD causes progressive deterioration of cognitive functioning, the stages of decline will also be discussed.

1.4.5.2. Stages of Progressive Deterioration

AD, at least in the early stages, is typically characterized by impairments in episodic memory; however, for a diagnosis of AD other deficits should also be apparent (DSM-V, American Psychiatric Association, 2013; McKhann et al., 2011). As the clinical features change during the progression of the disease, the profile of typical cognitive impairment is often described by dividing the progressive nature of AD in stages (i.e. mild, moderate and severe). To quantify the severity of symptoms of dementia, scales like the Clinical Dementia Rating (CDR, Morris et al., 1993) are commonly used. The CDR has demonstrated high validity and reliability for this purpose, but it requires a considerable amount of data to be collected both from the patient and from an informant.
Therefore, Perneczky et al. (2006) mapped MMSE scores onto CDR categories to determine how well the MMSE performs as a surrogate of the CDR as a timesaving method of staging dementia. The MMSE discriminated well between CDR stages 0.5, 1, 2, and 3, but performed poorly in the separation between CDR stages zero and 0.5. The MMSE ranges were 30 for no, 26-29 for questionable, 21-25 for mild, 11-20 for moderate, and 0-10 for severe dementia. This has become a commonly used method of staging dementia.

As Weintraub et al. (2012) reviewed, over the past 30 years, neuropsychological assessment has featured centrally in characterizing the dementia associated with AD, identifying the most salient and earliest cognitive and behavioural symptoms and contributing to the staging and tracking of the disease (Albert, 1996; Flicker et al., 1984; Locascio et al., 1995; Morris et al., 1989; Salmon and Bondi, 2009; Storandt and Hill, 1989; Storandt, 1991; Storandt et al., 1998; Welsh et al., 1991, 1992). As research has increasingly focused on earlier stages of the illness, it has become clear that biological markers of AD can precede cognitive and behavioural symptoms by years. It has also become clear that the early symptoms of AD represent the selective targeting by disease of specific, “large-scale” neuroanatomical networks, with clinical deficits consistent with the anatomical locus of impact (Price et al., 1993; Seeley et al., 2009; Weintraub and Mesulam, 2009; Weintraub et al., 1996). In the usual case, AD pathology is initially selective for limbic regions that subserve episodic memory, which leads to a circumscribed memory deficit in the early stages of the disease (Braak and Braak, 1991; Jack et al., 1997; de Toledo-Morrell et al., 2000). It is only as pathology progresses to other neocortical regions over time that additional cognitive symptoms emerge and the full dementia syndrome becomes apparent (Braak and Braak, 1996a, 1996b; Braak et al., 1999; Jack et al., 2000).

As dementia progresses from early to late stages, symptom domain boundaries become blurred and inconsistent cognitive profiles may evolve. Thus, neuropsychological profiles are most informative at the early stages. The development of fluid and neuroimaging biomarkers could improve diagnosis and eventually be used to measure treatment effects. However, neuropsychological characterization remains essential to understanding the individual patient’s deficits so that (pharmacological and non-pharmacologic) interventions can be appropriately selected and applied (Weintraub et al., 2005). The most prominent and typical neuropsychological features of AD will be described in the following paragraphs, largely based on the recent review by Weintraub et al. (2012) and there will be references to other reviews on specific cognitive areas.
1.4.5.3. **Episodic Memory**

The most prominent clinical feature of AD is a slowly progressive decline of memory with an insidious onset (Albert & Blacker, 2006; Forstl & Kurz, 1999; Grossman et al., 2006; Petersen et al., 2001; Weintraub et al., 2012). As the earliest neurofibrillary changes that are part of the pathology of AD usually affect medial temporal lobe structures (e.g., hippocampus, entorhinal cortex; see Braak and Braak, 1991), interrupting the neural network critical for episodic memory function, it is not surprising that a deficit in the ability to learn and remember new information (i.e., anterograde amnesia) is the clinical hallmark of AD pathology (Weintraub et al., 2012). However, the amyloid pathology that likely occurs years prior to the onset of symptoms (Morris et al., 1996; Reiman et al., 1996; Moonis et al., 2005; Mintun et al., 2006; Becker et al., 2010; De Meyer et al., 2010) is not particularly abundant in the medial temporal lobe, but instead in the regions comprising the “default mode network” (Buckner et al., 2005; Sperling et al., 2009). These changes in the default mode network, comprised of a set of functionally interconnected cortical areas (posterior cingulate, inferior parietal lobule, lateral temporal neocortex, ventromedial and dorsomedial prefrontal cortex) that project heavily to medial temporal lobe structures (Buckner et al., 2008), presage cell death in the hippocampus by years (Weintraub et al., 2012).

Various studies have shown that patients with AD are impaired on episodic memory tests that use a variety of cognitive procedures (e.g., free recall, recognition, paired-associate learning) across virtually all modalities (e.g., auditory, visual, olfaction) (for review, see Salmon, 2000). As reviewed by Weintraub et al. (2012), evidence suggests that the episodic memory deficit of AD patients is due in large part to ineffective consolidation or storage of new information. Early studies that characterized the episodic memory deficit in AD used word list learning tasks such as the California Verbal Learning Test (CVLT, Delis et al., 1991). These studies consistently showed that AD patients rapidly forget information over time and are equally impaired (relative to age-matched controls) on recognition and free recall components of the tasks. This pattern of performance is consistent with impaired consolidation rather than ineffective retrieval of new information (Delis et al., 1991). Indices of rapid forgetting have important clinical utility for the early detection and differential diagnosis of AD. Many studies have shown that measures of rapid forgetting can differentiate mildly demented AD patients from healthy elderly controls with 85% to 90% accuracy (Flicker et al., 1984; Butters et al., 1987; Knopman and Ryberg, 1989; Morris et al., 1991; Welsh et al., 1991; Tröster et al., 1993). Additional mechanisms contributing to episodic memory
impairment in AD include deficits in executive functioning (see next section), including increased sensitivity to interference due to decreased inhibitory processes leading to the production of intrusion errors (Fuld et al., 1982; Jacobs et al., 1990; Delis et al., 1991) and defective use of semantic information to support encoding (see Martin et al., 1985; Dalla Barba and Wong, 1995; Dalla Barba and Goldblum, 1996).

1.4.5.4. EXECUTIVE FUNCTIONING, WORKING MEMORY & ATTENTION

One area of cognitive functioning that is commonly affected in AD is executive functioning (EF) (Allain et al., 2013; Reed et al., 2007; Schroeter et al., 2012). EF is an umbrella term for various and complex high level cognitive functions that manage (regulate, control) the co-ordination of several subprocesses to achieve a particular goal in a flexible manner (Elliot, 2003). Most attempts to define EF resort to a list of cognitive (sub)functions such as task-switching, inhibition, planning, working memory, problem solving, which reflects the fact that EF is by no means a unitary concept (Royall et al., 2002; Elliot, 2003). As described by Elliot (2003), unlike other cognitive domains (such as memory), there is no intuitive lay concept that incorporates the essence of EF. In an attempt to define EF, Elliot proposed that EF are those involved in complex cognitions, such as solving novel problems, modifying behaviour in the light of new information, generating strategies or sequencing complex actions; the flexible co-ordination of sub-processes to achieve a specific goal is the responsibility of executive control systems; when these systems break down, behaviour becomes poorly controlled, disjointed and disinhibited (Elliot, 2003). Also, it is important to recognize both the unity and diversity of EF and that subdividing EFs is a useful approach to studying the organization and roles of EFs (Miyake et al., 2000).

Deficits in EFs negatively affect everyday activities and hamper the ability to cope with other cognitive and behavioural demands. There is a large and growing body of research indicating that EF deficits are present in the earliest stages of AD (Collette et al., 1999; Jefferson et al., 2006; Perry & Hodges, 1999). Longitudinal studies investigating pre-diagnostic symptomatology and staging of AD reported that EF impairment is present before clinical diagnosis, with declining EF occurring between 2 to 3 years before diagnosis (Albert, 1996; Amieva et al., 2005; Grober et al., 2008). More specifically, EF deficits, in addition to difficulties with delayed recall, predict subsequent progression from MCI to AD (Albert et al., 1996). Reduced ability to mentally manipulate information may be a particularly early feature based on a well-controlled study showing that very mild AD patients were significantly impaired relative
to cognitively normal controls on tests that required set shifting, self-monitoring or sequencing, but not on tests that required cue-directed attention or verbal problem solving (Lefleche and Albert, 1995). A number of other studies have shown that AD patients are impaired on difficult problem-solving tests that require mental manipulation such as the Tower of London puzzle (Lange et al., 1995), the modified Wisconsin Card Sorting Task (Bondi et al., 1993), tests of relational integration (Waltz et al., 2004), and other tests of executive functions such as the Porteus Maze Task, Part B of the Trail-Making Test, and the Raven Progressive Matrices (Grady et al., 1988). These deficits in EF have been hypothesized to reflect AD pathology, especially neurofibrillary tangle burden, in prefrontal cortex. This regional prefrontal cortex pathology is particularly pronounced in a subset of AD patients who present early on with predominant executive dysfunction (Johnson et al., 1999; Waltz et al., 2004). This again highlights the impact of anatomical specificity of pathology on the disruption of distinct neocortical networks.

EF, working memory and attention have been conceptualized as separate and as related constructs (see e.g. Baddeley 2012; Finke et al., 2013; McCabe et al., 2010). Tests of working memory (like Digit Span backward) and EF share common underlying attention components (McCabe et al., 2010). As reviewed by Weintraub et al. (2012), the deficit in mental manipulation exhibited by patients with AD may also be expressed on tests of working memory. Working memory refers to a processing system whereby information that is the immediate focus of attention is temporarily held in a limited-capacity, language- or visually-based, immediate memory buffer while being manipulated by a “central executive” (Baddeley, 2003). Studies indicate that the working memory deficit of patients with AD is initially mild and primarily involves disruption of the central executive with relative sparing of immediate memory (Baddeley et al., 1991; Collette et al., 1999). It is not until later stages of AD that all aspects of the working memory system become compromised (Baddeley et al., 1991; Collette et al., 1999). Consistent with this model, mildly affected AD patients are often impaired on complex attention tasks that are dependent upon the effective allocation of attentional resources (e.g., dual-processing tasks) or that require efficient disengagement and shifting of attention (for reviews, see Parasuraman and Haxby, 1993; Perry and Hodges, 1999). In contrast, the ability to focus and sustain attention is usually only affected in later stages of the disease. This is apparent in the essentially normal performance of mildly demented AD patients on tests of immediate attention span compared with supraspan tests (Cherry et al., 2002).
There is extensive literature of theoretical models and growing number of publications related to the role these cognitive functions have or might have in preclinical and clinical AD, including areas of focus of future interventions (Gibbons et al., 2012; Martyr & Clare, 2012; Zartman et al., 2013). The findings of a recent meta-analysis support the growing evidence for a link between ADL and EF in early AD (Martyr & Clare, 2012). It has been recommended that clinicians should consider rehabilitation techniques designed to improve EF, as this may contribute to maintain functional ability, which in turn supports independence and contributes to an increased QoL (Martyr & Clare, 2012).

1.4.5.5. Visuospatial Abilities

Patients with AD often exhibit deficits in visuospatial abilities at some point in the course of the disease (Cronin-Golomb and Amick, 2001; Hodges, 2007; Weintraub et al., 2012). It has been suggested that visuospatial deficits may occur early, even during preclinical stages (Johnson et al., 2009). Changes in visuospatial function are apparent on visuoconstructional tasks and on tasks that require visuoperceptual abilities and visual orientation. The visuoperceptual deficit exhibited by patients with AD may arise, in part, from the loss of effective interaction between distinct and relatively intact cortical information processing systems (Morrison et al., 1991).

Deficits in visual information processing and in selective attention and divided attention are observed in the course of normal ageing but are exacerbated in individuals with AD (Greenwood et al., 1997; Parasuraman and Greenwood, 1998; Parasuraman et al., 1995, 2000). In addition, visual motion detection has been shown to decline in some individuals with MCI, and more so in those with a diagnosis of AD dementia, suggesting that this symptom may constitute an independent marker of those likely to have AD pathology (Mapstone, 2003). The narrowing of the window of visuospatial attention has been demonstrated with the Useful Field of View (UFOV) paradigm in which reaction time to peripheral visual targets is measured in the presence of various levels of distracting visual stimuli (Ball et al., 1988). Older individuals react more slowly to peripheral stimuli compared to younger controls, and patients with AD show an even greater impairment. These deficits may account for the increased incidence of car crashes in patients with AD (Ball & Owsley, 2003; Rizzo et al., 1997).
1.4.5.6. **Language & Semantic Knowledge**

Older adults with mild AD are often impaired on tests of object naming (Bayles and Tomoeda, 1983; Martin and Fedio, 1983; Bowles et al., 1987; Hodges et al., 1991), verbal fluency (Martin and Fedio, 1983; Butters et al., 1987; Monsch et al., 1992), and semantic categorization (Aronoff et al., 2006). The underlying nature of these deficits has been debated (see Nebes, 1989), but there is evidence that they reflect deterioration in the structure and content of semantic memory (i.e., general knowledge of facts, concepts, and meanings of words) that supports language. Knowledge for particular items or concepts and the associations between them may be disrupted as the neuropathology of AD encroaches upon the temporal, frontal and parietal association cortices in which they are thought to be diffusely stored (Hodges and Patterson, 1995; Hodges, 2007).

As summarised by Weintraub et al. (2012), evidence for a deterioration of semantic memory in AD comes from several studies that probed for knowledge of particular concepts across different modes of access and output (e.g., fluency, confrontation naming, sorting, word-to-picture matching and definition generation). These studies assume that loss of knowledge, as opposed to impaired retrieval of intact knowledge, would lead to consistency of performance across items (Chertkow and Bub, 1990; Hodges et al., 1992). Loss of knowledge of the attributes and associations that define a particular semantic category is also thought to reduce the ability of patients with AD to efficiently generate words from a small and highly related set of exemplars during tests of verbal fluency. Thus, patients with AD are more impaired on category fluency (e.g., generating lists of animals) than letter fluency (e.g., generating words beginning with a specific letter) (Butters et al., 1987; Monsch et al., 1992; Henry et al., 2004, 2005). The fact that patients with AD are more impaired on fluency tasks that place greater demands on the integrity of semantic memory is consistent with the notion that they have a deterioration in the structure and organization of semantic memory rather than a general inability to retrieve or access semantic knowledge (Rohrer et al., 1995, 1999).

1.4.6. **Other Clinical Characteristics**

1.4.6.1. **Dependency in Activities of Daily Living**

A diagnosis of AD also requires indication of impairment in the ability to perform activities of daily living (ADL) in addition to loss of cognitive function and behavioural changes (see tables 1.1 and 1.2). ADL vary in complexity and difficulty (Spector et al.,
Basic ADL (bADL; Katz et al., 1963) include self-care functions (eating, bathing, dressing, toileting), while Instrumental ADL (iADL; Lawton and Brody, 1969) involve more complex tasks required for independent living (using transport, shopping, preparing meals, laundry).

Conventionally, progression of ADL inabilities are viewed as proportional to the severity of the disease. That is, while bADLs tend to be preserved in early stage AD, iADLs are vulnerable to the effects of AD, with evidence of a direct link with cognitive status (Njegovan et al., 2001; Vitaliano et al., 1984). Some argue that the progressive inability to perform ADL is the most visible manifestation of dementia and the subsequent loss of independence (Potkin, 2002). Progressive deterioration in ADL eventually brings patients to the later stages of dependency and, in most cases, to institutionalization, which is linked to an increased need in caregiver assistance (Bullock & Hammond, 2003). A patient's level of dependency is often used as a global (proxy) measurement reflecting a certain level of severity, resource consumption and QoL (Kurz et al., 2003).

Recently, Marshall et al. (2013) reviewed the evidence of ADL impairment across the AD spectrum and concluded that bADL impairment is detected in the transition from mild to moderate dementia and beyond, while iADL impairment is detected at the transition from MCI to dementia, even at earlier stages of MCI. Since ADLs are intrinsically linked to cognition and behaviour, it is likely that changes in ADL will track closely with changes in cognition and behaviour (Marshall et al., 2013). Based on the proposed dynamic model of Jack et al. (2010), Marshall et al., (2013) presented a hypothetical model of timing of the development of ADL impairment along the AD spectrum compared with cognitive impairment and pathologic changes. In line with research focus on developing more sensitive cognitive measures to try to capture the at-risk group of preclinical AD, based on this model they suggested that a sensitive measure of complex ADL that can capture the earliest functional impairment will allow the detection of earliest alterations in ADL in minimally symptomatic individuals at the stage of preclinical AD and at the transition to MCI.

The measurement of ADL, which also enables monitoring of the effectiveness of therapeutic interventions, can be performed using a number of ADL scales. Marshall et al. (2013) provide a brief overview of commonly used subjective and performance-based ADL scales. Most available scales of ADL are subjective and informant-based. Currently, there are reliable, subjective and performance-based scales for iADL at the stage of MCI and AD dementia that have been linked to AD biomarkers, but there are
very few scales that have the potential to detect the earliest functional deficits in preclinical AD and its transition to MCI. Therefore, developing more sensitive, ecologically valid scales for ‘complex ADL’ – term introduced by Marshall et al. (2013) - is vital to the goal of improving the detection of preclinical AD and the prediction of progression to MCI and AD dementia.

1.4.6.2. Behavioural and Psychological Symptoms of Dementia

Behavioural and psychological symptoms of dementia (BPSD), also known as neuropsychiatric symptoms, represent a heterogeneous group of non-cognitive symptoms and behaviours (Finkel et al., 1996). BPSD are a common manifestation of dementia irrespective of its subtype. It is estimated that BPSD affect up to 90% of all dementia patients over the course of their illness (Cerejeira et al., 2012).

As recently reviewed by Cerejeira et al. (2012), BPSD are heterogeneous and largely unpredictable, affecting the emotional experience, thought content, perception and motor function. BPSD include agitation, aberrant motor behaviour, anxiety, elation, irritability, depression, apathy, disinhibition, delusions, hallucinations and sleep or appetite changes. Although these symptoms can be present individually, it is more common that various psychopathological features co-occur simultaneously in the same patient. Distinguishing accurately between BPSD symptoms can be challenging considering the overlap between symptoms, for example, depression and apathy.

The pathogenesis of BPSD has not been clearly delineated but it is probably the result of a complex interplay of psychological, social, and biological factors (Cerejeira et al., 2012). Recent studies have emphasized the role of neurochemical, neuropathological and genetic factors underlying the clinical manifestations of BPSD. Growing evidence suggests that the neurobiological basis of BPSD in AD and related dementias is a loss of cholinergic neurons and a resultant decline in acetylcholine (ACh) in brain regions which regulate behavioural and emotional responses, such as the limbic system (Robert, 2002).

There is an overall agreement that BPSD are very common regardless of the type of dementia and are present in virtually all patients during the course of their disease. Even in the early stages of cognitive impairment, neuropsychiatric symptoms are frequent (Monastero et al., 2009). In community-dwelling subjects with dementia, neuropsychiatric symptoms are generally less frequent (56–98%) and severe than in patients recruited in hospital or long-term care facilities (91–96%). When looking at individual symptoms in dementia patients, the most prevalent BPSD are apathy,
depression, irritability, agitation and anxiety, while the rarest are euphoria, hallucinations, and disinhibition. The most clinically significant symptoms are depression, apathy, and anxiety. Importantly, 50% of patients have at least four neuropsychiatric symptoms simultaneously (Frisoni et al., 1999).

BPSD are among the most distressing manifestations of AD. They strongly correlate with the degree of functional and cognitive impairment, are independently associated with high levels of distress among patients and caregivers, long-term hospitalization, misuse of medication, increased use of health care resources and increased health care costs (Cerejeira et al., 2012; Grossberg, 2002). Thus, in addition to cognitive deterioration, BPSD are a relevant and meaningful clinical target for intervention (Katona et al., 2007; Fernandez et al., 2010).

The assessment of neuropsychiatric symptoms requires a thorough examination to collect specific and detailed information about the clinical history, patient’s subjective experiences, and objective behaviour. Information from a reliable family member or caregiver is essential to obtain adequate characterization of neuropsychiatric disturbances from the patient’s own ecological context as many abnormal symptoms cannot be elicited during the clinical interview (Cerejeira et al., 2012). Several validated instruments have been developed to quantify BPSD based on data collected from clinical assessment of dementia patients and caregivers’ interviews with some scales assessing a wide range of neuropsychiatric symptoms and others focusing on specific symptoms (e.g., aggression and agitation).

Currently, one of the most extensively used instruments to assess BPSD is the Neuropsychiatric Inventory (NPI) whose validity and reliability has been well established in several languages (Cummings, 1997). It consists of a semi-structured interview retrospectively assessing 12 symptoms based on the caregiver information: delusions, hallucinations, agitation, depression, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, night time behaviour disturbances, and eating behaviour abnormalities.

1.4.6.3. Loss of Awareness

Although unawareness of cognitive deficits has often been reported in patients with probable AD and has attracted considerable interest among researchers, there are as yet very few clear findings to support understanding or guide practice. This is probably partly due to differing perspectives of the concept and the difficulty how to measure it. In 1995, Vasterling et al. reported that unawareness (i.e. measured as patient minus care
giver disagreement) was most prominent in ratings of memory and self care, less prominent in ratings of anxiety and irritability, and absent in ratings of depression and health status. Following this, Starkstein et al. (1996) examined the possibility that anosognosia (i.e. lack of awareness) in AD for cognitive deficits and anosognosia for behavioural problems have different neuropsychological and psychiatric correlates. They used the anosognosia questionnaire-dementia (AQ-D, Migliorelli et al., 1995), a quantified scale with established reliability and validity in AD, and identified two domains of anosognosia in AD: unawareness of cognitive deficits and unawareness of behavioural problems, and demonstrated different cognitive and psychiatric correlates for these disorders. This questionnaire has been used frequently since, but other methods have been proposed (e.g. clinician’s ratings of a person’s level of awareness, Verhey et al., 1993).

More recently Clare (2004) underlined that the complexity of the awareness concept is reflected in the range of terminology adopted to describe states of awareness, including ‘insight’, ‘anosognosia’, and ‘denial’, and that there is no single clear definition of awareness used by researchers in the field of dementia. Often these terms are used inconsistently, with the result that researchers intending to explore ‘awareness’ study different phenomena. In addition, the terms are frequently used interchangeably despite different conceptual backgrounds and underlying assumptions. A central issue relates to whether awareness is viewed as determined solely by neurological factors, or as a product of interaction between neurological and psychosocial factors, and the socio-environmental context (Clare, 2008; for a thorough review, see Clare, 2004a; 2004b). Ownsworth et al. (2006) suggested that neuropsychological models might constitute a complete explanation in some cases where very specific disturbances of awareness follow from focal neurological injuries, but that would be unlikely for broader awareness deficits typically seen in progressive neurological disorders of gradual onset, such as dementia. Clare argues that if we consider that awareness has a biological foundation, it is still important to acknowledge that its behavioural expression and the interpretation of that expression by others, will be influenced by social and psychological factors and psychosocial processes (Clare et al., 2008). They actually showed that the level of awareness that individuals have of the changes they are undergoing is variable, and is likely to be determined by an interaction between neuropsychological impairments and psychological reaction (Clare, 2008). Her work and the work of Prigatano (1999) have been influential in our understanding of the role and treatment of psychological factors in coping styles and awareness.
A prominent model (Stuss et al., 1991; 2001) which might be particularly useful in our way of thinking about disturbances of awareness in AD offers four different levels of awareness: 1) being able to take in something of what is going on around us (i.e. basic level of awareness); 2) ability to register changes in aspects of functioning (which can be domain specific, such as memory); 3) the way we monitor our actions and use what we know about our current level of functioning to make decisions about how we behave in particular situations (if impaired, behaviour may seem disinhibited, risky or inappropriate to others); and 4) the way in which awareness at all levels relates to the experience of self-awareness or sense of identity. One might argue that in AD the ability to register aspect of memory (level 2 in Stuss’ model) is hampered, and typical impairment in executive function will likely interfere with the way we monitor our action (level 3). However, one might expect that for people with AD the basic level of awareness (level 1) might retain unaffected until the very last severe stages of the disease and contribute to the experience of self-awareness or sense of identity and QoL (level 4).

Clare (2008) argued that a better understanding of a person’s level of awareness provides a rationale for offering tailored interventions in our aim to increase the person’s and their carer’s QoL. It appears that people with dementia who have higher level of awareness may also experience more depression and emotional distress (Clare et al., 2004), drawing out possible implications for interventions.

The association between awareness and HRQoL may be salient, but very few studies had considered the possible implications of the level of awareness on experienced HRQoL in AD.

1.4.7. INTERVENTIONS

Since its discovery more than 100 years ago, there have been many scientific breakthroughs in AD research (Ballard et al., 2011; Hampel et al., 2014). Over the last decade, scientists have substantially progressed in understanding potential environmental, genetic and other risk factors for AD, the neurobiological processes leading to formation of plaques and tangles in the brain, and the brain regions that are affected. However, at present, there is no cure for AD. Without a cure for the disease, the term ‘treatment’ of AD, although often used, can be misleading. Therefore the term ‘interventions’, also regularly used, might be more applicable, which is also reflected in most recent reviews on this matter.
1.4.7.1. Pharmacological interventions

With regards to pharmaceutical interventions at the start of this research, symptomatic treatments of AD have been widely available since the mid-1990s (see review Ballard et al., 2011). Cholinesterase inhibitors were thought to improve cognition and indirectly help function and behaviour in patients with AD. Evidence from clinical trials and clinical practice is that the effect of cholinesterase inhibitors (i.e. donepezil, rivastigmine and galantamine, licensed for mild-to-moderate AD) on cognition is modest (1.5–2 points on the mini mental state examination over 6–12 months), with additional short-term (3–6 months) improvement in cognition and global outcome and some stabilization of function over this period (Birks et al., 2006; 2009; Hansen et al., 2008; Loy & Schneider, 2006). Memantine (i.e. licensed for moderate-to-severe AD) improves cognitive performance and function over a 6-month period compared with placebo (Gauthier et al., 2008; McShane et al., 2006) and preliminary evidence suggests that memantine might also be beneficial in the prevention and management of agitation and aggression (Lopez et al., 2009).

Next to AD symptomatic drugs, antipsychotic agents are commonly used to treat agitation, aggression, and psychosis in patients with dementia, but benefits are moderate, and serious adverse events include sedation, parkinsonism, chest infections, and an increased risk of stroke and death (Ballard & Howard, 2006; Ballard et al., 2009). It should also be noted that use of medication in older age is complicated by several factors, including changes in pharmacokinetics and the presence of multiple comorbidities (Basger et al, 2008; Elmstahl et al., 1998; Gallagher et al., 2008). Concomitant medical conditions and polypharmacy can exacerbate cognitive decline and increase the risk of cerebrovascular disease and therefore should be used to best practice standards. Guidelines advise that the potential benefits and risks should be carefully balanced, other non-pharmacological approaches used when possible, and long-term prescription avoided (Ballard et al., 2011). Unfortunately, the use of potentially harmful medications (PHMs) is common in later life and is associated with an increased risk of unfavourable health outcomes, including adverse drug events, morbidity, mortality and increased healthcare use (Beer et al., 2011; Franic & Jiang, 2006; Gurwitz et al., 2000; Klarin et al., 2005; Lau et al., 2005; Lindley et al., 1992). Consequently, use of PHM is a source of concern that is likely to become more prevalent as the population ages (Hamilton et al., 2009; Spinewine et al., 2007), and may further compromise the quality of life of older people with dementia.
1.4.7.2. FROM MEDICAL MODEL TO BIOPSYPHOSOCIAL FRAMEWORK

In recent years, the way in which we view and understand dementia has undergone considerable changes which is reflected in intervention approaches. Developments have made a powerful case for moving beyond a standard disease model to consider dementia within a biopsychosocial framework and place the person with dementia in context (e.g. Clare, 2008). Presenting an alternative paradigm to the medical model, Kitwood (1997) proposed a dialectical model, which suggests that the manifestation and progression of AD in any one individual are influenced by the interplay of neurological impairment, physical health and sensory acuity, personality, biographical experience and social psychology, in terms of environment, communication and interaction. Acknowledging that AD involves changes and needs at biological, psychological and social levels, and is experienced in context of beliefs and practices indicates that a comprehensive explanatory framework can be encompassed within a biopsychosocial approach (Clare, 2008). Clare (2008) considered using such a biopsychosocial approach to expand our conceptualization of dementia and to provide pointers for interventions. Since interventions at different levels may have an interactive effect, the benefits derived from one single intervention may be evident across several areas. Table 1.3 presents an overview of the range of issues and interventions that can be considered.

In a detailed discussion on possible interventions at particularly the psychological and social levels through a neuropsychological rehabilitation approach within a therapeutic framework supporting the experience of an optimum QoL, with a scholarly overview with convincing arguments (i.e. Neuropsychological rehabilitation and people with dementia, 2008), Clare suggests that rehabilitation interventions that aim to impact on the disability and handicap resulting from the underlying neurological impairments, and in particular to reduce excess disability, have the potential to benefit the experienced QoL people with AD and their families.

In 2010, Gauthier et al. concluded, also in line with a biopsychosocial approach, in their review on management of behavioural problems in AD, that the evidence from clinical trials of both non-pharmacological and pharmacological treatments, and from neurobiological studies, provided a range of management options that can be tailored to individual needs. They suggested that non-pharmacological interventions (including psychosocial/ psychological counseling, interpersonal management and environmental management) should be attempted first, followed by the least harmful medication for the shortest time possible (Gauthier et al., 2010).
<table>
<thead>
<tr>
<th>Level</th>
<th>Areas to assess</th>
<th>Possible interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biological level</strong></td>
<td>Genetic vulnerability</td>
<td>None available</td>
</tr>
<tr>
<td></td>
<td>Brain changes; neurological changes</td>
<td>Medication aimed at slowing progression</td>
</tr>
<tr>
<td></td>
<td>Physical health issues; mobility and sensory impairments</td>
<td>Treatment for physical health issues, chronic pain; promote mobility</td>
</tr>
<tr>
<td></td>
<td>Medication side-effects, interactions</td>
<td>Management, reduction medication</td>
</tr>
<tr>
<td><strong>Psychological level</strong></td>
<td>Neuropsychological issues, i.e. cognitive decline, cognitive specific deficits, impact daily functioning</td>
<td>Comprehensive neuropsychological assessment to identify cognitive strengths and weaknesses; interventions to assist with effects of cognitive impairments, e.g. strategies management memory and executive functioning problems; interventions to develop adaptive behaviours</td>
</tr>
<tr>
<td></td>
<td>Individual psychological needs (incl. life history, personality, culture, coping and defensive mechanisms)</td>
<td>Support groups, psychotherapy/counselling (variety of techniques like CBT); life review, identity maintenance, coping strategies</td>
</tr>
<tr>
<td></td>
<td>Neuropsychiatric symptoms (e.g., depression, anxiety)</td>
<td>Non-pharmacological and pharmacological interventions</td>
</tr>
<tr>
<td></td>
<td>Richness of environment and level of stimulation</td>
<td>Environmental adaptation and enrichment</td>
</tr>
<tr>
<td><strong>Social level</strong></td>
<td>Social networks, social interactions and communication skills</td>
<td>Enhance social networks; carer(s) training/psychoeducation positive interactions and communication skills</td>
</tr>
<tr>
<td></td>
<td>Needs of primary carer(s); dyadic communication</td>
<td>Interventions for carer(s), e.g. psychoeducation, support groups, individual therapy or counselling; couple of family therapy or counselling</td>
</tr>
<tr>
<td></td>
<td>Needs of other family members</td>
<td>Support, psychoeducation, support groups, individual therapy or counselling; couple of family therapy or counselling</td>
</tr>
<tr>
<td></td>
<td>Care practices, interactions and attitudes in formal settings</td>
<td>Staff training and environmental enrichment</td>
</tr>
<tr>
<td></td>
<td>Experience of societal discrimination and stigma</td>
<td>Approaches to counter negative attitudes</td>
</tr>
<tr>
<td></td>
<td>Social and financial situations; access to services and resources</td>
<td>Equitable access to services, assistance with benefit claims</td>
</tr>
</tbody>
</table>
1.4.7.3. **Views on Future Directions of Interventions for AD**

Since the introductions of the updated diagnostic criteria for AD in 2011, numerous reviews appeared with new future directions of finding effective interventions for AD. In their review, Hampel et al (2014) noted that recent advances in understanding the molecular mechanisms underlying various paths toward the pathogenesis of AD has begun to provide new insight for interventions to modify disease progression. The evolving knowledge gained from multidisciplinary basic research has begun to identify new concepts for treatments and distinct classes of therapeutic targets; as well as putative disease-modifying compounds that are now being tested in clinical trials. There is a mounting consensus that such disease modifying compounds and/or interventions are more likely to be effectively administered as early as possible in the cascade of pathogenic processes preceding and underlying the clinical expression of AD. Their review summarizes not only present knowledge regarding biological markers but also unresolved questions on the status of surrogate indicators for detection of the disease in asymptomatic people and diagnosis of AD (Hampel et al., 2014).

Mangialasche et al. (2012) reviewed the evidence supporting dementia/AD prevention and discussed key aspects that need to be considered when planning preventive strategies. They concluded that epidemiological findings strongly suggest that the life-course approach model and the multifactorial nature of dementia and AD should be considered when planning any preventive strategy. Epidemiological research provides a substantial amount of evidence of modifiable risk factors (e.g. lifestyle) and protective factors – as discussed in previous section - that can be addressed to prevent or delay onset of AD and dementia. More recently, Imtiaz et al. (2014) reviewed the literature and noted that research on AD has recently undergone a paradigm shift from identification of potential risk factors to using this information for developing interventions to prevent or delay the onset of dementia as well as identifying special high-risk populations who could benefit from different interventions.

Recently published guidelines and reviews mentioned above suggest that the most opportune time to treat individuals with AD is during the preclinical phase of the disease. This is a phase when individuals are defined as clinically normal but exhibit evidence of amyloidosis, neurodegeneration and subtle cognitive/behavioural decline. It has recently been argued that while standard cognitive tests are useful for detecting cognitive decline at the stage of mild cognitive impairment, they were not designed for detecting the subtle cognitive variations associated with this biomarker stage of preclinical AD (Rentz et al., 2013). However, neuropsychologists are attempting to
meet this challenge by designing newer cognitive measures and questionnaires derived from translational efforts in neuroimaging, cognitive neuroscience and clinical/experimental neuropsychology. The review by Rentz et al. (2013) is a selective summary of several novel, potentially promising, approaches that are being explored for detecting early cognitive evidence of preclinical AD in presymptomatic individuals.

Recent systematic reviews specifically on non-pharmacological approaches (e.g., Cooper et al., 2012; McLaren et al., 2013; Olazaran et al., 2010) concluded that the current literature provides clinical trial evidence that non-pharmacologic interventions can delay progression of functional impairment or disability among community-dwelling dementia patients, but the clinical significance of this early evidence is uncertain (McLaren et al., 2013). Cooper argued that preliminary evidence indicated that coping strategy-based family carer therapy with or without a patient activity intervention improved QoL of people with dementia living at home. GCST was the only effective intervention in a higher quality trial for those in care homes, but we did not find such evidence in the community. Olazaran et al. (2010) conducted a systematic review and meta-analysis of the efficacy of non-pharmacological therapies in AD. They concluded that they emerge as a useful, versatile and potentially cost-effective approach to improve outcomes and QoL in AD and related disorders for both the people with dementia and caregiver. Recently Herholz et al. (2013) provided an overview of recent studies involving cognitive training and reminiscence, stimulating and challenging experiences such as visual art and music, physical activities, and electromagnetic stimulation; findings on neuroplasticity in the ageing brain and their relevance for cognitive improvement in patients with neurodegenerative diseases; cognitive reserve and possible mechanisms that drive neuroplasticity and new learning. They identified promising avenues for future intervention strategies and research, such as combinations of cognitive and pharmaceutical interventions, and individual strategies adapted to the disease stage and tailored to the needs, predispositions and preferences of patients (Herholz et al., 2013).

Taken together, due to limitations associated with current pharmacological approaches, non-pharmacological approaches for people with dementia are receiving renewed attention, although inclusion of psychosocial interventions in dementia guidelines is yet to gain widespread acceptance (Vasse et al., 2012).

The sheer number of people affected by dementia, and the great impact that the disorder has on patients and their families, is such that in our ageing society HRQoL in AD has become a major health-related concern (Mack & Whitehouse, 2001). Moreover,
AD is a complex disorder, often requiring interventions from a range of disciplines and services (Mack & Whitehouse, 2001). While alternatives for the prevention and treatment of AD may emerge in the future, the emphasis of present research and clinical practice rests primarily on interventions that optimize HRQoL (Banerjee et al., 2009). There is now a growing consensus that HRQoL, which can capture elements of health not detected by standard symptom measures, should be included as an outcome in AD clinical trials (Mack & Whitehouse, 2001; Banerjee et al., 2009). The key issue now is to identify the clinical modifiable factors that do drive changes in HRQoL in AD in order to develop effective interventions.

1.5. CHALLENGES IN ASSESSMENT & INTERPRETATION OF HRQOL RATINGS IN AD

Over the last two decades HRQoL as outcome measure in AD has gained recognition. To illustrate this, Figure 1.7 shows the increase in the number of publications related to QoL in dementia, and the relative increase of publications related to QoL in AD in particular.

![Figure 1.7](image_url)

Figure 1.7. Number of publications on ‘quality of life in dementia’ and ‘quality of life in Alzheimer’s disease’ in PubMed (as per 22-06-2014). Blue bars represent the number of publications on ‘quality of life in dementia; green bars the number of publications on ‘quality of life in Alzheimer’s disease’. 
Although HRQoL is now recognized as one of the most important and relevant clinical outcomes in AD research and clinical care (Jonker et al., 2004; Rabins, 2000; Mack & Whitehouse, 2001; Walker et al., 1998; Whitehouse et al., 2003; Winblad et al., 1997), the association between HRQoL and easily measurable clinical variables is not as simple or straightforward as in other diseases (Banerjee et al., 2009). HRQoL assessment is unique, because the concept itself includes a subjective component that is fundamental to its measurement. It could be argued that for people diagnosed with AD, measuring HRQoL is just as important as measuring disease severity, disease progression, cognitive decline, BPSD symptoms, awareness and independence in activities of daily living. The subjective nature of HRQoL provides healthcare professionals with the opportunity of incorporating the subjective experiences of people with AD, their value systems as well as their carers into their assessments, and consequently into their interventions. However, there are important challenges in assessing and interpreting HRQoL ratings in AD.

1.5.1. **Assessing HRQoL in People with Cognitive Impairment, the Cardinal Feature of AD**

One of the first recognized challenges in assessing HRQoL in AD are the cognitive deficits associated with the disease. At the same time, it is important to understand the impact of cognitive decline on the experienced HRQoL, an area that is yet to be explored in detail.

In 1995, the WHO defined QoL as “The individual’s perceptions of their position in life in the context of the culture and value system in which they live, and in relationship to their goals, expectations, and standards”. This definition requires that individuals have the cognitive capacity to make complex subjective judgments. Older people with cognitive impairment may face particular challenges in evaluating and expressing their QoL in accordance with this definition. Hence, many questions have been raised about the ability of older adults diagnosed with AD to make such judgments because of the cognitive impairments associated with their disease. It might be expected that the typical cognitive deficits of AD could influence the person’s ability to comprehend HRQoL questions or communicate their subjective state. So for long it was generally assumed that patients with AD would not be able to rate their own QoL and proxies were asked to do so on their behalf: dementia may interfere with understanding, ability to remember relevant events, making comparisons across complex domains and communicating (Rabins, 2000).
The question of whether the rating of one’s QoL relies on specific cognitive functions is not straightforward, and there are limited empirical data in this area. Varying deficits in memory, attention, and language influence the ability to comprehend questions or communicate one’s own subjective states, which are arguably required to complete a QoL rating scale.

To accommodate this population, if self-reports are to be useful, it is necessary to design measures that facilitate rating despite cognitive impairment. Comprehension of questions and selection of appropriate responses can be facilitated by the use of explicit instructions, face-to-face administration by a trained interviewer, and use of visual cues to remind the respondent of the response options. In addition, a trained interviewer can assess the respondent’s comprehension by asking follow-up questions when the response is unclear or inconsistent. Such a measurement was not available until the late 1990s (Brod et al., 1999; Logsdon et al., 1999).

Change in assumption that patients with AD would not be able to rate their own QoL was significantly influenced by two papers: 1) ‘Not knowing where I am doesn’t mean I don’t know what I like – cognitive impairment and QoL responses in elderly people’, by Mozley et al. (1999); and 2) ‘Assessing quality of life in older adults with cognitive impairment’, the pioneering investigation of Logsdon’s et al. (2002). Both their findings indicated that this assumption is not well founded and that individuals with AD can rate their own QoL well into the later stages of progression of the disease.

Firstly, the observational study by Mozley et al. (1999) showed that of 213 elderly residents who scored 10 or higher on the MMSE only respondents who were not able to respond to the questions assessing orientation to place (2 out of 5), language (3 out of 8) and attention (2 out of 5) could not rate their QoL. They concluded that a high proportion of elderly people can answer questions about their QoL, even in the presence of significant cognitive deficits.

Secondly, Logsdon et al. presented a psychometric analysis of a new measure, the Quality of Life – Alzheimer’s disease (QoL-AD) Scale (Logsdon et al., 1999; 2002) that seemed to fulfil the general requirements mentioned above. With a large sample of AD patients (N=177) and caregivers they examined the impact of cognitive impairment on the reliability and validity of the measure. Their study evaluated the ability of individuals with progressive cognitive impairment to provide a rating of their own QoL and clarified the point at which they can they no longer reliably do so.

The QoL-AD is a 13-item questionnaire designed to provide both a patient report and a caregiver report of the patient’s QoL. To facilitate its use with cognitively
impaired individuals, the QoL-AD uses simple and straightforward language, responses are structured in a four-choice format that is consistent across all questions, and all items are rated according to the patient’s current QoL. Specific items for the QoL-AD were selected to reflect Lawton’s four domains of QoL in older adults. To ensure content validity the items were reviewed by AD patients and caregivers, and, to maximize construct validity, by experts in the field of geriatrics and gerontology. A prior study of AD patients and caregivers (Logsdon et al., 1999) found that the measure had good internal reliability (α = 0.89) and test-retest reliability over a 1-week interval (0.76 and 0.92 for patient and caregiver, respectively). Subjects were 177 AD patients who met criteria for “probable” or “possible” AD (McKhann et al., 1984) and their carers. They were community-dwelling, and the caregiver lived or spent every day with them. Patients’ mean age was 77.2 years (SD = 7.0), education of 13.4 years (SD = 3.3), and mean MMSE score 16.4 (SD = 7.3). The primary differences between patients who could complete the QoL-AD and those who could not were associated with cognitive and functional status. Age, education, and duration of dementia were not significantly different between the two groups. Mean MMSE score for patients who were unable to complete the measure was 4.1 (SD = 3.2, range 0–10), compared with 18.1 (SD = 5.9, range 4–29) for those who could complete the measure (F (1,175) = 120.2, p < .001). MMSE scores were not significantly correlated with either patient- or caregiver-reported QoL-AD scores (r = 0.12 and 0.02, respectively).

Taken together, Logsdon et al.’s study demonstrated that it is possible for individuals with dementia to reliably and validly rate their own QoL. All but 22/177 subjects completed the QoL-AD. Of those who completed the interview, MMSE scores ranged from 4 to 29, and no subject who scored 11 or higher on the MMSE failed or refused to complete the QoL-AD.

Other studies have since confirmed that measuring QoL in older people with cognitive impairment is reliable (for example, Abrahamson, Clark, Perkins, & Arling, 2012; Ready et al., 2006; Woods et al., 2014).

In answer to the question of this section, the evaluation of QoL for people with mild to moderate dementia has been transformed in recent years since the introduction of tailored self-reported HRQoL measures in the late 90s. Where previously cognitive impairments were considered obstacles for the self-reporting of QoL, a number of measures have since been developed that enable people with dementia to complete ratings reliably. The current consensus is that self-reported HRQoL ratings by AD patients represent a unique and valid perspective of QoL and that self-reported should be
given precedence over care-reported QoL (Banerjee et al., 2009; Brod et al., 1999; Logsdon et al., 2002; Sands et al., 2004; Scholzel-Dorenbos et al., 2007; Trigg et al., 2012).

1.5.2. AVAILABLE INSTRUMENTS TO ASSESS HRQoL IN DEMENTIA

The detailed review by Ready & Ott in 2003 presented, compared, and critiqued the existing HRQoL measures specifically designed for dementia populations developed over the preceding 10 years. Nine measures were reviewed with a focus on conceptualizations of HRQoL, psychometric data, targeted patient population, and administration and scoring procedures. They highlighted differences in definitions of HRQoL, assessment procedures, and methods that were used to establish the validity of these instruments. The characteristics of those nine HRQoL dementia scales are presented in Table 1.4.

One of the most noticeable similarities among the instruments was that their development was strongly influenced by Lawton's model of QoL (section 1.5.5). The differences appeared to stem from variances in how this model was implemented. As Ready & Ott (2003) emphasized, without a gold standard against which to compare HRQoL assessments, establishing the validity of HRQoL measures is perhaps the most challenging aspect of scale development. The review showed that investigators approached the issue in different ways, revealing their conceptualizations of HRQoL in dementia. For example, some scales were developed based on the concept that high QoL is indicated by the presence of specific clinical characteristics (such as presence of positive affect and the relative absence of negative affect (Albert et al., 1996; Ready et al., 2002). Also, dementia HRQoL instruments varied in whether or not patients participate in the assessment, which Ready & Ott (2003) considered a critical factor because of the highly subjective nature of HRQoL assessments. The QoL-AD (Logsdon et al., 2002) was the single measure that included both patient and proxy report for patients diagnosed with dementia at all stages of the disease. Ready & Ott (2003) concluded that several instruments with promising preliminary psychometric data were available. They recommended that future research should seek to 1) establish the responsiveness of HRQoL scales for dementia to change over time, 2) identify factors that affect reports of HRQoL, 3) determine how perceived HRQoL affects decisions regarding the care of dementia patients, and 4) evaluate interventions to increase patient’s HRQoL. Since then, the field has developed rapidly and there has been progressive improvement in methodology and measurement (Perales et al., 2013).
Table 1.4. Characteristics of dementia HRQoL scales (modified version from Ready & Ott, 2003)

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Patient-report</th>
<th>Proxy-report</th>
<th>Psychometric data(^a)</th>
<th>Patient population(^b)</th>
<th>Subscales</th>
<th>Response scale</th>
<th>Time frame</th>
<th>No of items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity and Affect Ratings (Albert et al., 1996; 1999)</td>
<td>No</td>
<td>Yes</td>
<td>Yes (N = 130)</td>
<td>Mild-severe dementia, Institutional- and home-care settings</td>
<td>Positive affect Negative affect Activity</td>
<td>Affect: 5-point scale (never - greater than or equal to 3 times/day) Activity: frequency</td>
<td>Affect: previous 2-weeks Activity: previous week</td>
<td>21</td>
</tr>
<tr>
<td>Alzheimer Disease Related Quality of Life (ADRQL, Rabins et al., 1999)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>All stages</td>
<td>Social interaction Awareness of self Feelings &amp; mood Enjoyment of activities Response to surroundings</td>
<td>Dichotomous (agree/ disagree)</td>
<td>Previous 2 weeks</td>
<td>48</td>
</tr>
<tr>
<td>Cornell Brown Scale for Quality of Life (CBS, Ready et al., 2002)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (N = 50)</td>
<td>Mild-moderate dementia, Home-care setting</td>
<td>None</td>
<td>5 point (negative end – positive end)</td>
<td>Previous week</td>
<td>19</td>
</tr>
<tr>
<td>Dementia Care Mapping (DCM, Beavis et al., 2002; Brooker et al., 1998, Fossey et al., 2002)</td>
<td>No</td>
<td>Yes (obs.)</td>
<td>Yes (N = 19-177)</td>
<td>Moderate-severe dementia, Institutional-care setting</td>
<td>Well-being Social withdrawal Activity</td>
<td>Well-being: 6 point (extreme ill-being–extreme well-being)</td>
<td>Every 5 minutes for 6 hours</td>
<td>26</td>
</tr>
<tr>
<td>Dementia Quality of Life (DQoL, Brod et al., 1999)</td>
<td>Yes</td>
<td>No</td>
<td>Yes (N = 99)</td>
<td>Mild-moderate dementia, Home-care setting</td>
<td>Self-esteem Positive affect Negative affect Aesthetics Feelings of belonging</td>
<td>5 point (never –very often) and (not at all – very)</td>
<td>Recently</td>
<td>30</td>
</tr>
<tr>
<td>Psychological Well-being in Cognitively Impaired Persons (PWB-CIP, Burgener and Twigg, 2002)</td>
<td>No</td>
<td>Yes</td>
<td>Yes (N = 96)</td>
<td>Mild-moderate dementia, Home-care setting</td>
<td>Positive interaction Frustrated/ agitated Discontent</td>
<td>4 point (never – frequently)</td>
<td>Previous 24 hours</td>
<td>11</td>
</tr>
<tr>
<td>Quality of Life in Late-Stage Dementia (QUALID, Weiner et al., 2000)</td>
<td>No</td>
<td>Yes</td>
<td>Yes (N = 42)</td>
<td>Severe dementia, Institutional setting</td>
<td>None</td>
<td>5 point (different options of frequency)</td>
<td>Previous week</td>
<td>11</td>
</tr>
<tr>
<td>Quality of Life –Alzheimer’s Disease (QoL-AD), Logsdon et al., 1999, 2002</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (N = 177)</td>
<td>Mild-severe dementia, Home-care setting</td>
<td>None</td>
<td>4 point (poor –excellent)</td>
<td>Present</td>
<td>13</td>
</tr>
<tr>
<td>Quality of Life Assessment Schedule (QOLAS, Selai et al., 2001)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (N = 22)</td>
<td>Mild-moderate dementia, Home-care setting</td>
<td>Physical Psychological Social/family Usual activities Cognitive</td>
<td>6 point (no problem – it could not be worse)</td>
<td>Present</td>
<td>10</td>
</tr>
</tbody>
</table>

\(^a\) Psychometric data regarding the reliability and/or validity of the instrument have been published or presented. Sample sizes for psychometric studies are indicated.

\(^b\) Patient population for which the instrument was developed and/or from which psychometric data were collected.
Recent studies indicate that meaningful data on HRQoL can be obtained using both subjective and proxy measures of disease-specific HRQoL in dementia (Banerjee et al., 2009; Ready & Ott, 2003, Scholzel-Dorenbos et al., 2007).

Moniz-Cook et al. (2008) challenged the lack of consensus about which outcome measures to use to evaluate the effectiveness of psychosocial interventions in dementia care and the ability to compare different studies. They used an interactive collaborative, evidence-based approach to identify the best of currently available outcome measures for European psychosocial intervention research. Their review suggested that the QoL-AD was the measure of choice in the evaluation of HRQoL in psychosocial interventions (Moniz-Cook et al., 2008).

Most recently, Perales et al. (2013) argued that there has been much development on the measurement of dementia-specific HRQoL over the last two decades. This is a reflection of the importance of assessing HRQoL in this group of people (Karlawish et al., 2000; Whitehouse, 2000; Moniz-Cook et al., 2008). Perales et
al. (2013) identified 15 dementia-specific HRQoL instruments with variations depending on their country of development and validation, dementia severity, data collection method, operationalization of HRQoL in dementia, psychometric properties, and administration and scoring methods.

The QoL-AD was the only measure included in all reviews listed (Table 1.5). In dementia research, and in AD in particular, the QoL-AD has become the most used HRQoL scale.

1.5.3. Difference between self and carer-reported HRQoL ratings

In accordance with the WHO definition of QoL, the primacy of self-report to measure HRQoL should be emphasised (Banerjee et al., 2009). Self-report directly involves the individual in the assessment, taking into account his or her subjective experiences, and places value on the perspective of the person. This reflects respect for the autonomy of the individual which is important from a clinical and ethical standpoint.

Informants other than the person with dementia (whether staff or family carers) may have a different appraisal of the person’s HRQoL. Several studies have reported differences in HRQoL ratings between patients with dementia and their caregivers (paid or unpaid), with patients’ ratings commonly yielding higher scores than carers’ (Thorgrimsen et al., 2003; Sands et al., 2004; Hoe et al., 2007; Conde-Sala et al., 2009). These differences between self and carer-reported HRQoL ratings have been interpreted as indicative of low level of agreement (e.g. Conde-Sala et al., 2009), disagreement (e.g. Vogel et al., 2006), moderately low correlation (Smith et al., 2005b), and even high correlation (e.g. Hoe et al., 2007). It is unclear whether raters simply disagree, or agree but are subject to systematic rater bias, with carers’ ratings shifted downwards.

As reviewed by Banerjee et al. (2009), in a head-to-head comparison, Sloane et al. (2005) showed that proxy-rated measures (QoL-D, QoL-AD and ADRQL) were consistently associated, though modestly, with cognitive impairment, activity limitation, depression and agitation. Patient-rated measures (QoL-D, QoL-AD, DQoL) showed no such associations. Proxy characteristics, such as carer burden and carer depression, as well as education and support for staff, appear to influence ratings, and proxy ratings are generally lower than those of people with dementia (Vogel et al., 2006). While often held as a function of a lack of insight on the part of people with dementia, or an over-critical attitude being taken by carers, it may also be that within dementia there is a process of adaptation to disability and gradual adjustment of expectation taking place (which will be further discussed in section 1.5.3). Equally, it is useful to note that this
discrepancy is not just seen in dementia, so to ascribe it immediately to subject error on the basis of cognitive impairment or lack of insight is an unsatisfactory response (Banerjee et al., 2009). One way of minimizing these proxy effects appears to be the requirement for proxies to rate by substituted judgment ‘as if’ they were the person with dementia rather than proxies giving their own direct opinion of the person with dementia’s QoL (Karlawish et al., 2001). Banerjee et al. (2009) suggested comparing both approaches using the same scale. Given the progressive nature of the disorders and the impairments that are a real part of the dementias, there would appear to be true value in having measurement approaches of HRQoL that enable both self-report and proxy-report data to be generated and for these to be deployed and understood together. At the very least they would provide complementary views of the same construct.

1.5.4. THE DISABILITY PARADOX AND THE RESPONSE SHIFT THEORY: HIGH QUALITY OF LIFE AGAINST ALL ODDS?

The reported differences between patient and carer HRQoL ratings, as discussed in previous paragraphs, are also found in other chronic diseases and have been considered in the context of the so called “disability paradox” – a tendency for caregivers to report lower HRQoL than the patients (Albrecht and DeVlieger, 1999; Ready and Ott, 2003; Vogel et al., 2006). This phenomenon illustrates the possibility of adaptation and resilience despite adversity (Livingston et al., 2008), which can be counterintuitive to external observers, such as carers (paid or unpaid). As patients can adapt to disease, their health and HRQoL expectations may change which is referred to as a response shift effect. In this section these two related phenomena will be explored followed by noteworthy models and considerations on how they might contribute to our understanding of the experienced HRQoL of people with AD over time.

The seemingly surprising result that persons with severe impairments tend to report higher QoL, including perceived health, regardless of their condition, is the so-called "disability paradox", firstly described by Albrecht and DeVlieger (1999). They explored the question “Why do many people with serious and persistent disabilities report that they experience a good or excellent QoL when to most external observers these individuals seem to live an undesirable daily existence?” They used a qualitative approach to develop an explanation of this paradox using semi-structured interviews with 153 persons with disabilities. They found that 54.3% of the respondents with moderate to serious disabilities reported having an excellent or good QoL. Analysis of the interviews revealed that for both those who report that they have a good and those
who say they have a poor QoL, QoL is dependent upon finding a balance between body, mind and spirit in the self and on establishing and maintaining an harmonious set of relationships within the person's social context and external environment.

More recently, Fellinghauer et al. (2012) examined the role of contextual factors (i.e. the personal and environmental situation) in light of the disability paradox in a large study (N=18,760). They concluded that the disability paradox seems to dissolve when contextual factors are taken into account. Contextual factors may be responsible for some persons with impairments engaging in activities. In turn, persons with impairments may only then perceive lower QoL when they experience activities and participation limitation. This suggests that interventions at the level of the environment may reduce the number of persons who perceive lower QoL (Fellinghauer et al. 2012). Thus, against the odds, impairments do not necessarily lead to decreased perceived QoL if the translation of impairments into activities and participation limitations can be avoided. Similarly, impairments do not necessarily lead to activities and participation limitations.

Modifiable environmental factors, such as social supports, moderate or mediate the relationship between body and activity and participation. Therefore, the number of persons with impairments who feel healthy and show high levels of performance in activity and participation may be increased with appropriate contextual interventions.

As patients adapt to disease, their HRQoL expectations can change over time, which is referred to as a response shift (RS) effect. Sprangers & Schwartz (1999) suggested that patients confronted with a life-threatening or chronic disease are faced with the necessity to accommodate their illnesses. An important mediator of this adaptation process is 'response shift' which involves changing internal standards, values and the conceptualization of QoL. Their response shift model (presented in figure 1.8.) suggests that a change in health state (the catalyst) leads to an interactive and dynamic response shift process.

Stable personality characteristics (i.e., antecedents) interact with mechanisms (i.e., cognitive, affective, or behavioural processes that individuals use to deal with life changes) to promote response shifts. In turn, these shifts result in a level of perceived QoL that may be higher or lower than expected based on objective criteria. The response shift process is hypothesized to be iterative, happening continuously or repeatedly over time as part of a positive or negative adaptation process.

The proposed model of Sprangers and Schwartz (1999) provides a framework for thinking about the meaning of response shift in clinical research. Presumably, integrating response shift into QoL research would allow a better understanding of how
QoL is affected by changes in health status and would direct the development of reliable and valid measures for assessing changes in QoL.

In an effort to clarify how important response shift effects are in interpreting QoL outcomes, Schwartz et al. (2006) conducted a meta-analysis of extant response shift studies. Extensive literature searches and multiple contacts with researchers circa 2005 resulted in the collection of 494 articles united by a shared keyword of “response shift.” Only 28 published longitudinal studies that measured response shift were retained. One of their important observations was that response shift effects differ according to disease trajectory. For example, in populations in which total cure is likely, response shift is much less prevalent than in populations where residual disability (see Finkelstein et al., 2009) or disease progression (Schwartz et al., 2004; Visser et al., 2000) is expected. The meta-analysis, in its documentation of the small effect size and variability of results, served to pave the way for more sophisticated and interpretable response shift approaches (Schwartz, 2010).

Importantly, focus on response shift in HRQoL in dementia during the progression of the disease, including the preclinical and MCI stage, has so far been limited, given the small number of longitudinal studies (reviewed in section 1.7). However, significant contributions to this field of research include the extensive work by Linda Clare’s group (Clare, 2002, and onwards). In 2002 Clare described that the onset of dementia places major demands on coping resources, and that the development of adaptive coping strategies is crucial in optimizing well-being and minimizing excess
disability. Understanding how people with early-stage dementia naturally attempt to adjust and cope is an important starting point in developing interventions that can enhance self-efficacy and adaptive coping (Clare 2002).

Clare suggested that the process of making sense of the experience and adapting to changes constitutes an ongoing reiterative cycle (Clare, 2003). The model she proposed includes 5 interrelated processes in response to the changes that are occurring: registering, reacting, explaining, experiencing and adjusting. As people engage in each of these processes, their responses fall somewhere along a continuum between self-maintaining and self-adjusting stances (Clare et al., 2005). She found that coping methods typically include practical strategies for managing the impact of memory and other cognitive difficulties in an attempt to maintain functioning and independence and compensate for changes. As the condition progresses, the process of coming to terms with dementia and moving towards acceptance of one's condition is likely to be an ongoing process of negotiation aimed at reaching a balance between hope and despair. This model and subsequent research formed the basis for further development of interventions in the early stages of dementia (Clare, 2008). Although the subjective experience of moderate to severe dementia is less well delineated, Clare’s model introduced a neuropsychological rehabilitation approach within a holistic, psychotherapeutic framework of care and support for people with dementia, helping them to manage, bypass or overcome cognitive problems.

Another model worth mentioning is the model of HRQoL in dementia proposed by Byrne-Davis et al. (2006) based on theories of coping and response shift. Twenty-five participants took part in one of nine focus groups. The groups included participants with mild to severe dementia with ages ranging from 49 to 93 years. Results indicated that most of the participants were willing and able to talk about their HRQoL. However, few people with dementia talked about disease-orientated issues (or: clinical features), such as activities of daily living, cognitive difficulties and other disease orientated issues. One of the hypothesized explanations was that cognitive difficulties might not have been mentioned a lot in their groups because the individuals with dementia lacked insight into the fact that they had a dementing illness. Equally, they might not have mentioned their cognitive problems because there is currently no curative treatment for AD and they had, therefore, accepted their disease and were focusing on other important and potentially changeable issues. The latter would be more in line with the phenomena described in this section. Moreover, Byrne-Davis et al. (2006) concluded that change in HRQoL could be the result of a change in internal processes and adaptation alone in the
absence of any external changes. In this way, response shift is the essence of HRQoL, rather than a measurement anomaly. Positive or negative change in health status, therefore, may not lead to positive or negative change in HRQoL, as HRQoL is also affected by internal processes. They proposed that HRQoL will be responsive to a combination of the external inputs and the internal processing of the individual, and therefore change in HRQoL brought about through change in health status may be transient or may not occur at all (Byrne-Davis et al., 2006).

The theoretical considerations and research findings described in this section challenge the choice of factors that intuitively are expected to be included in driving factors of HRQoL in AD, and that a substantial volume of research has focused on (in particular episodic memory impairment). A related question is whether mediating factors are actually stable or change during the progression of the disease for patients with AD as well as for their carers has hardly been challenged.

1.5.5. A CONCEPTUAL FRAMEWORK FOR MULTIPLE PROXY PERSPECTIVES

The subjective nature of HRQoL assessment would dictate that the person with dementia should be the primary informant in the assessment. However, as self-assessment of HRQoL can be challenging or impossible for some people (Guyatt et al., 1993; Sneeuw et al., 1997; Teunissen et al., 1998), a proxy such as a health care professional or family caregiver may be asked to assess the patient’s HRQoL (Scholzel-Dorenbos et al., 2007). Also, some instruments rely on composite scores.

As clearly described by Pickard & Knight (2005), proxy assessments address some troublesome issues about internal validity (i.e., ability to detect HRQoL differences) and external validity (i.e., generalizability) in outcomes research. Proxy assessment commonly replaces patient self-assessment in clinical trials that include HRQoL outcomes to avoid excluding patients who cannot respond for themselves. This may compromise the validity of the ratings (Pickard et al., 2004). In addition to substitution for patient assessment, proxy assessments can inform clinical decisions about patient care by reinforcing information provided by self-assessment or by providing additional, complementary information about the patient. Thus, proxy assessments may substitute for patient self-assessment of HRQoL, or complement/reinforce self-assessment by eliciting the proxy’s view of patient HRQoL.

Pickard & Knight (2005) delineate between proxy perspectives as follows: a proxy may assess a patient as the proxy thinks the patient would rate his or herself [proxy-patient], or the proxy may assess the patient from the proxy’s perspective
[proxy-proxy] (e.g., daughter reported HRQoL of a mother with AD). The proxy-patient viewpoint is intended to elicit substituted judgment, where the proxy projects themselves into the body and mind of the patient for the purpose of responding to the HRQoL assessment. In contrast, the proxy-proxy perspective purposefully elicits an assessment of HRQoL that may diverge from the patient’s own perceptions without compromising the validity of either construct. Each proxy perspective has the potential to provide valuable information that may converge or diverge to varying degrees with patient self-assessment of HRQoL (Pickard & Knight, 2005).

Pickard & Knight presented a conceptual framework followed from: (1) the need to recognize that different proxy perspectives can be elicited; (2) the need to develop a basis for selecting and understanding the potential information imparted from a proxy assessor according to the perspective elicited. Figure 1.9 (next page) represents their proposed framework for understanding how potential differences may arise in HRQoL assessment depending on the proxy perspective. Three perspectives of HRQoL assessment are shown: patient self-assessment (i.e., patient-patient perspective), proxy assessment from the patient’s view (i.e., proxy-patient perspective), and proxy assessment from the proxy’s view (i.e., proxy-proxy perspective). The first part of the term (i.e., patient, proxy) refers to the source of the assessment, and the second part of the term (i.e., patient, proxy) refers to the perspective of the assessment.

As shown in Figure 1.9, aspects of the HRQoL assessment are common to both proxy perspectives. However, HRQoL assessment from the proxy-proxy perspective can impart unique information, represented by region “b” of Figure 1.9, defined as the intra-proxy gap. The intra-proxy gap represents the extent to which HRQoL assessments from the proxy-patient and proxy-proxy perspective are different. The proxy-proxy perspective can potentially provide an assessment of the patient that expands upon and/or clarifies the patient’s view of their HRQoL, and may be desirable in addition to assessment from the patient perspective. The extent to which the proxy-proxy perspective is informative will depend upon the proxy’s ability to provide reinforcing or complementary information on the HRQoL of the patient. This may be particularly relevant in situations where the proxy can knowledgeably expand upon the health state of the patient, such as when the patient is cognitively impaired.

Importantly, through this framework, Pickard & Knight (2005) have sought to call attention to the need for proxy versions of HRQoL measures to be standardized according to proxy perspective, clearly stating the specific perspective to be taken by proxy raters in the instructions and item wording.
If a specific proxy viewpoint is not clearly expressed in the instructions and not carefully incorporated into wording of the items, the perspective elicited in a study may be inadvertently placed at the proxy’s discretion, creating unintended error variance in the proxy assessments. The viewpoint of the proxy should be disclosed in every study employing proxy assessments, in order to provide greater insight into the comparability of patient-proxy dyadic agreement across studies. They suggested that research agendas that investigate the hypothesized intra-proxy gap will help elucidate the extent and nature of the difference in different contexts, and factors that may explain systematic differences that contribute to the gap (Pickard & Knight, 2005). Such investigations may serve to support the validity of each perspective, to evaluate the contribution of proxy perspectives in different settings, to guide the selection of proxy perspective for a given application, to inform the design of studies that may require proxy raters, and to understand how proxy assessments can better inform medical decision making at the bedside and at the policy level.

Given these important considerations, and knowing that 1) HRQoL proxy ratings are frequently used in dementia research, and 2) proxy perspectives are not always explicitly described in instruction of HRQoL measures, there is a clear need to delineate the patient and proxy perspectives in research designed to identify factors that drive HRQoL ratings in dementia.
1.5.6. **HRQoL in AD at Different Stages**

Little is known about the natural history of HRQoL in AD over time (Banerjee et al. (2009). It has been argued that one of the reasons that the conceptualizations of HRQoL in dementia vary is that particular instruments were developed for patients at different stages of dementia, and that the relevant life domains for HRQoL might vary with the progression of the disease (Ettema et al., 2005). For example, it has been reported that in the early stages of dementia enjoyment of discretionary activities is relevant (Brod et al., 1999a), while this is no longer important in severe dementia (Hurley et al., 1992).

As a consequence, some instruments are unsuitable for assessing HRQoL in the whole range of mild to severe dementia. This presents a problem for the daily care for people with dementia and for the evaluation of interventions aimed at improving HRQoL, as changes in HRQoL with the progression of the disease are difficult to detect and assess with existing instruments. This certainly has become more topical since the interest is now certainly more focused not only on the trajectory of AD from early stages onwards, but also on the preclinical stage.

In 2005 Ettema et al. argued that adaptation over time is a major outcome in studies investigating interventions aimed at improving HRQoL in chronic conditions, but until then, it has not been used in the definition of HRQoL in dementia. They offered the following conceptual definition: dementia-specific HRQoL is the multidimensional evaluation of the person-environment system of the individual, in terms of adaptation to the perceived consequences of the dementia (Ettema et al., 2005). Based on the reports by Droes et al. (1991; 1996; 1998; 2000) - suggesting that adaptation as a major indication of HRQoL is as useful in dementia as in other chronic diseases - they took the position that an adaptation process is always found, and should be incorporated in the definition. After reviewing the literature up to 2007, the same group (Schölzel-Dorenbos, Ettema, et al., 2007) concluded that severity of dementia, care type, setting, and the specific QoL domains an intervention focuses on, determine which QoL instrument will be most appropriate in a specific situation. They advised that one should not assume that any instrument for QoL is automatically suitable to evaluate the effect of every intervention in all care-settings and stages of dementia. If the main focus in daily practice is on aspects that are not measured with the applied instrument, the effectiveness of the intervention cannot be assessed adequately.

The issue of the applicability of a generic, health related, or any combination or parallel use of a QoL measure on the background of the longer trajectory of AD ranging from preclinical to severe dementia stages has not been addressed in literature so far.
1.5.7. IS THERE EVIDENCE FOR EFFECTIVENESS OF PHARMACOLOGICAL AND NON-PHARMACOLOGICAL INTERVENTIONS TO IMPROVE HRQoL IN AD?

As the available pharmacological treatments for AD do not seem to affect disease progression (Ito et al., 2010), it is important that we develop interventions that improve the HRQoL of patients with AD. The cholinesterase inhibitors donepezil, galantamine and rivastigmine improve the cognitive scores of patients with AD compared with placebo (Birks, 2006). Most relevant to the current thesis is that treatments with cholinesterase inhibitors do not improve HRQoL scores (Cooper et al., 2013). A recent systematic review of over 1000 papers published until early 2011 found that only 15 randomized clinical trials (RCTs) and one Cochrane review measuring (HR)QoL as (secondary) outcome, of which 11 showed that treatment with cholinesterase inhibitors improved cognitive scores, but not (HR)QoL in people with dementia (Cooper et al., 2013). The authors warned that none of the studies that reported improvement in cognition provided treatment beyond 24 weeks, so it may be that this time frame was too short for improvements in HRQoL to become apparent. It, therefore, remains unclear whether treatments that improve cognition improve HRQoL in the long term.

Also, it seems that the general assumption is that improved episodic memory, the most prominent initial clinical feature in most cases of AD, should lead to a concurrent improvement in HRQoL (McKhann et al., 2011; Mol et al., 2007; Pena-Casanova et al., 2012; Reed et al., 2007; Takeda et al., 2006). In available RCTs, the most frequently used outcome measure has been cognitive function as measured by the Alzheimer’s Disease Assessment Scale – Cognitive section (ADAS-Cog, Rosen et al., 1984), with changes in scores being largely driven by changes in episodic memory (Hansen et al., 2008). Regulatory authorities recognize a four-point change on the ADAS-Cog at 6 months as indicating a clinically important difference, although the clinical relevance of this 4-point change has been questioned (Rockwood et al., 2007). It has also been shown that improvements on cognitive screening tools, like the MMSE or the ADAS-Cog, should be viewed with caution as repeated administration of these assessments can lead to practice effects, and only changes of the magnitude of at least 4 points should be regarded as significant (e.g. Clarke et al., 1999). As pointed at by Ballard et al. (2011), such outcome measures used in RCTs for the purpose of regulatory approval do not translate well into day-to-day practice (Ballard et al., 2011). Consequently, all dementia RCTs should include HRQoL as an outcome measure, as it cannot be presumed from improvements in cognition or other symptomatic outcomes (Cooper et al., 2012).
Available evidence is also limited about the effect of non-pharmacological interventions on the HRQoL of people with AD (Cooper et al., 2012). In a systematic review to evaluate the effectiveness and impact of cognitive stimulation interventions aimed at improving cognition for people with dementia, fifteen RCTs were included (Woods et al., 2012). In secondary analyses with smaller total sample sizes, benefits were noted on self-reported QoL (standardized mean difference: 0.38 [95% CI: 0.11, 0.65]). They concluded there was consistent evidence from multiple trials that cognitive stimulation programs benefit cognition in people with mild to moderate dementia over and above medication effects. However, the trials were of variable quality with small sample sizes and only limited details of the randomization method were available for a number of trials. They recommended that other outcomes need more exploration, but that improvements in self-reported QoL were promising. However, they conducted a meta-analysis with only 3 of the 15 RCTs (i.e. Buschert et al., 2011, Coen et al., 2011, and Spector et al., 2003) that used a HRQoL measure, (i.e. in all three studies the QoL-AD, Logsdon et al., 1999). What was not acknowledged was that 1) the study of Buschert et al. (2011) only showed a benefit for the participants with MCI, not for the participants with AD; 2) the study of Coen et al. (2011) was not traceable in any database index (only a link to a power point presentation with same authors and title, which stated that they aimed to replicate Spector et al.’s (2003) findings, but the association between CS and QoL-AD in their study did not reach significance); 3) the study of Spector et al. (2003) did indeed find a significant association between cognitive stimulation therapy and QoL-AD, but they did not state whether the original composite rating (from informant rating and patient rating) was used, or only the self-reported version of the QoL-AD, which can have implications for further interpretation. In other words, the analyses and interpretations appear to be based on untraceable or non-published data, incorrectly cited data and HRQoL data of unclear rater.

Cooper et al. (2012) also conducted a systematic review of the effectiveness of non-pharmacological interventions to improve HRQoL of people with AD. Pooled analyses from 20 RCTs found that family carer coping strategy-based interventions might improve HRQoL. In one high-quality study (Vickrey et al., 2006), a care management system improved HRQoL of community-dwelling people with dementia. Cooper et al. (2012) concluded that preliminary evidence indicated that coping strategy-based family carer therapy with or without a patient activity intervention improved HRQoL of people with dementia living at home.
Taken together, further research is needed, to develop interventions aimed to increase HRQoL among people with dementia and to test the effectiveness.

1.5.8. **SUMMARY OF THE CHALLENGES**

In summary, this section (1.5) critically evaluated the challenges in assessing and interpreting HRQoL ratings in AD in our aim to identify factors that drive HRQoL in AD. *Firstly*, assessing HRQoL in AD is possible. Where previously cognitive impairments were considered as obstacles for self-reported QoL in AD, a number of measures have now been developed that people with dementia are able to complete reliably, enabling the perspective of the person with dementia to be taken into account. There has been much development on the measurement of dementia-specific HRQoL over the last two decades; in dementia research, and in AD in particular, the QoL-AD has become the most used HRQoL scale in the field. *Secondly*, although other informants are sometimes used when assessing HRQoL, informants other than the person with dementia (whether staff or family carers) may have a different appraisal of the person’s HRQoL; it is unclear whether raters simply disagree, or agree but are subject to systematic rater bias, with carers’ ratings shifted downwards. There would appear to be true value in having measurement approaches to HRQoL that enable both self-report and proxy-report data to be generated and for these to be deployed and understood together. *Thirdly*, proxy assessments raise some troublesome issues about internal and external validity in outcome research. One way of minimizing the proxy effects might be for proxy versions of HRQoL measures to be standardized according to proxy perspective, clearly stating the specific perspective to be taken by proxy raters in the instructions and item wording. *Fourthly*, little is known about the natural history of HRQoL in AD over time there is the possibility of adaptation and resilience despite adversity, which can be counterintuitive to external observers, such as carers (paid or unpaid); as patients can adapt to disease, their health and HRQoL expectations may change (i.e. a response shift effect) over time. The question whether mediating factors are stable or change during the progression of the disease for patients with AD as well as for their carers has hardly been challenged. *Fifthly*, there is no consistent evidence that any drug improves HRQoL in AD. Recommendations are that all dementia trials should include HRQoL as an outcome, as this is important to patients, and cannot be presumed from improvements in cognition or other symptomatic outcomes, especially if the latter are small. Theoretical considerations and research findings challenge the choice of factors that intuitively are expected to be included in driving factors of
HRQoL in AD, and that a substantial volume of research has focused on (in particular episodic memory impairment). Further research is needed to develop interventions aimed at increasing HRQoL among people with dementia. To do so, we have to enhance our understanding of the factors that drive HRQoL during disease progression, in order to focus our interventions on the right target(s) for this growing population.

1.6. WHAT DRIVES HRQOL IN AD?

The question that had certainly not been convincingly addressed at the start of this research, relates to the clinically modifiable factors that influence the experienced HRQoL by people with AD. Numerous potential explanatory variables have been suggested (Banerjee et al., 2009; Conde-Sala et al., 2009; Garre-Olmo et al., 2002; Hoe et al., 2006; 2007; Hurt et al., 2010; Karlawish et al., 2001; Logsdon et al., 2002; Sands et al., 2004; Schiffczyk et al., 2010; Selwood et al., 2005; Snow et al., 2005; Thorgrimsen et al., 2003; Vogel et al., 2006), including the type of relationship between the person with AD and the carer, functional autonomy, cognitive and neuropsychiatric symptoms of the patient, caregiver burden, caregiver depression, patients’ anosognosia, and gradual adjustment to their goals and expectations. However, available studies about factors that are associated with HRQoL ratings and factors that predict changes in HRQoL during the progression of the disease show incomplete and sometimes conflicting findings. These findings will be critically reviewed in this section.

1.6.1. AVAILABLE CROSS-SECTIONAL STUDIES

At the start of this thesis, I completed a literature review to generate data regarding (HR)QoL and associated factors in people with dementia. PubMed was searched for publications from any date up to January 2006, using multiple formulations of keywords (including Alzheimer’s disease, dementia, ‘quality of life’, ‘health related quality of life’ and the names of - at that stage known - HRQoL instruments (as listed in Table 1.4, e.g. DQoL, Brod et al., 1999; QoL-AD, Logsdon et al., 1999). This was supplemented by detailed inspection of the reference lists for papers identified. Excluded were publications that: 1) only used indicators of (HR)QoL, such as ADL or IADL (e.g. Albert et al., 2001; Kurz et al., 2003); 2) only used a single item QoL survey (James et al., 2005); 3) only reported psychometric data as part of validation studies of new instruments or translated instruments (e.g. Thorgrimsen et al., 2003; Smith et al., 2005); 4) Opinions without new data (e.g. Merchant & Hope, 2004; Selai, 2001); or 5)
conference abstracts (e.g. Karlawish et al., 2004). Included were publications reporting on new instruments that reported on the instrument’s association(s) with clinical variables, such as measures of depression and cognition (e.g. Logsdon et al., 2002). All findings refer to the patient’s (HR)QoL, not the carer’s QoL. Table 1.6 provides an overview of all selected cross-sectional studies and summarizes their key findings. Table 1.7 provides an overview of follow-up studies and their findings. Cross-sectional and longitudinal studies will be reviewed separately.

The overview of the identified cross-sectional studies up till January 2006 (Table 1.6) shows that 6 out of the 10 studies (60%) used the QoL-AD as outcome measure; 6 out 10 studies (60%) included people with dementia living in the community; the majority (9 out of 10) of the studies were conducted in the USA (90%); half the selected studies were published in 2005. Regarding the study population, half of the studies included a heterogeneous group of people with dementia (e.g. Gonzalez-Salvador et al., 2000; Sloan et al., 2005), or dementia clinic outpatients with a range of cognitive impairment (Ready et al., 2002). The studies also differed with regard to the living arrangements, varying from patients with dementia living in residential care facilities (Edelman et al., 2004; Gonzalez-Salvador et al., 2000; Sloane et al., 2005; Winzelberg et al., 2005), outpatients from memory clinics (Ready et al., 2002), people with dementia receiving services from diverse facilities that specialize in dementia care (Harvey et al., 2005), to AD patients living in the community (Hoe et al., 2005; Logsdon et al., 2002; Ready et al., 2004; Shin et al., 2005). Most studies focused on a limited number of potential explanatory factors (or: predictors), or an isolated clinical feature (e.g. Shin et al., 2005), while there has been concern that by focusing on one particular area (e.g. global cognitive function, as measured with the MMSE, or neuropsychiatric features, measured with the NPI) other equally important factors associated with HRQoL in AD might be neglected (Banerjee et al., 2006; 2009). The varying study characteristics make the comparability of the findings problematic.
Table 1.6. Overview characteristics cross-sectional studies related to or focused on factors associated with QoL or HRQoL ratings in dementia or Alzheimer's disease (before January 2006)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>QoL measure</th>
<th>Participants</th>
<th>N</th>
<th>Setting/population</th>
<th>Other variables included</th>
<th>Type of carers</th>
<th>Type of study</th>
<th>Factors associated with QoL</th>
<th>Other results</th>
<th>Conclusion by authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvey et al.</td>
<td>2005</td>
<td>USA</td>
<td>QoL-AD</td>
<td>Caregiver/patient (dementia); 93% patients probable AD</td>
<td>183</td>
<td>12 geographically divers sites that specialize in dementia care</td>
<td>MMSE</td>
<td>Family carers</td>
<td>Validation study. Cross-sectional study.</td>
<td>There were no significant correlations with the patient QOL-AD scores and DSS scores.</td>
<td>DSS (caregiver reported) subscales were moderately-to-highly correlated with the QoL-AD, NPI, MMSE, and PDS</td>
<td>Dementia Severity Scale excellent psychometric properties and appears to be useful both in clinical practice and research endeavors</td>
</tr>
<tr>
<td>Hoe et al.</td>
<td>2005</td>
<td>UK</td>
<td>QoL-AD HSQ (derived from the SF-36)</td>
<td>People with Alzheimer's disease, severe stage (MMSE &lt;12)</td>
<td>79</td>
<td>Community dwelling</td>
<td>MMSE Cornell Scale for Depression in Dementia NPI ADCS-ADL HADS</td>
<td>Family carers</td>
<td>Validation study. Cross-sectional study.</td>
<td>QoL does not decrease as cognition worsens.</td>
<td>The QoL-AD showed internal consistency and construct validity as it correlated with ability to look after self, fewer limitations due to physical health, positive mood status and low levels of apathy.</td>
<td>This throws into question most people's assumption that decreasing cognition worsens QoL. We consider that it may be important to inform the public of this, as living wills are used increasingly in our culture.</td>
</tr>
<tr>
<td>Shin et al.</td>
<td>2005</td>
<td>USA</td>
<td>QoL-AD</td>
<td>Patients with probable or possible AD and their caregivers</td>
<td>62</td>
<td>Community dwelling</td>
<td>NPI</td>
<td>Family caregivers</td>
<td>Cross-sectional study</td>
<td>Caregiver QoL-AD was negatively correlated with agitation/aggression, anxiety, disinhibition, irritability/lability, and total NPI score. Patient QoL on both patient and caregiver ratings was negatively correlated with depression. Caregiver QoL was negatively correlated with distress related to agitation/aggression, disinhibition, irritability/lability, and total NPI distress.</td>
<td>Patient-reported QoL-AD ratings at different levels of cognitive functioning were not correlated with caregiver-reported ratings. The lack of relationship between patient and caregiver assessments of patient QoL was evident in both mildly and moderately affected patients.</td>
<td>Neuropsychiatric symptoms of AD patients adversely affect both patient and caregiver QoL. These results suggest that identifying and treating neuropsychiatric symptoms in AD may improve both patient and caregiver QoL.</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Country</td>
<td>QoL measure</td>
<td>Participants</td>
<td>N</td>
<td>Setting/ population</td>
<td>Other variables included</td>
<td>Type of carers</td>
<td>Type of study</td>
<td>Factors associated with QoL</td>
<td>Other results</td>
<td>Conclusion by authors</td>
</tr>
<tr>
<td>------------------</td>
<td>------</td>
<td>---------</td>
<td>------------------------------</td>
<td>--------------------</td>
<td>-------</td>
<td>---------------------</td>
<td>--------------------------</td>
<td>----------------</td>
<td>--------------</td>
<td>-----------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Sloane et al.</td>
<td>2005</td>
<td>USA</td>
<td>QoL-AD QoL-D ADRQL DQoL DCM RSoC-QoL PGC-ARS</td>
<td>People with dementia residents in 45 facilities for long-term care</td>
<td>421</td>
<td></td>
<td>MMSE MDS-COGS MDS-ADL CSD CMAI PGC-PIS care provider</td>
<td>Cross-sectional study</td>
<td></td>
<td>Resident cognition and activities of daily living (ADLs) function were associated with most quality-of-life measures but predicted no more than a quarter of the observed variance in any measure.</td>
<td>Most instruments had good to excellent dispersion and interrater reliability, and most scales had good to excellent internal consistency. Proxy measures tended to correlate best with each other, less well with observational measures, and least well with resident measures.</td>
<td>Various measures and sources of data provide different perspectives on quality of life. No “gold standard” exists; so a combination of methods and sources is likely to provide the most complete picture of quality of life.</td>
</tr>
<tr>
<td>Winzelberg et al.</td>
<td>2005</td>
<td>USA</td>
<td>QoL-AD</td>
<td>143 nursing assistants providing care to 335 residents</td>
<td>N/a</td>
<td>(no pts with dementia)</td>
<td>35 residential care/assisted living (RC/AL) facilities and 10 nursing homes in four states</td>
<td>Nursing assistants</td>
<td>A cross-sectional survey.</td>
<td>QoL scores were most strongly associated with resident clinical conditions, including severity of cognitive and functional impairments, depression, and behavioral symptoms of dementia. There was an independent positive association between nursing assistants' ratings of resident QoL and their own attitudes regarding dementia-person-centered care as well as training.</td>
<td>n/a</td>
<td>Quality-of-life ratings by nursing assistants may be influenced by their attitudes about dementia and their confidence in addressing residents' fundamental care needs.</td>
</tr>
<tr>
<td>Edelman et al.</td>
<td>2004</td>
<td>USA</td>
<td>Dementia Care Mapping (DCM)</td>
<td>People with dementia</td>
<td>166</td>
<td></td>
<td>ADL Cornell Depression Scale for Dementia (CDSD) MMSE Cumulative Illness Ratings Scale – Geriatrics Professional carers/ nurses</td>
<td>Cross-sectional study</td>
<td></td>
<td>Both cognitive status and functional status were found to be associated with DCM scores. Moreover, DCM was sensitive in differentiating among persons with four levels of cognitive impairment.</td>
<td>n/a</td>
<td>Implications for practice are discussed.</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Country</td>
<td>QoL measure</td>
<td>Participants</td>
<td>N</td>
<td>Setting/population</td>
<td>Other variables included</td>
<td>Type of carers</td>
<td>Type of study</td>
<td>Factors associated with QoL</td>
<td>Other results</td>
<td>Conclusion by authors</td>
</tr>
<tr>
<td>-------------------</td>
<td>------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------------------------------------------</td>
<td>-----</td>
<td>--------------------</td>
<td>------------------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>---------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ready et al.</td>
<td>2004</td>
<td>USA</td>
<td>DQoL</td>
<td>Patients with mild AD (n = 26), Mild Cognitive Impairment (MCI, n = 30), and older adults controls (n = 23).</td>
<td></td>
<td>Community dwelling?</td>
<td>MMSE, NPI, IADL, Carer’s depression (GDS)</td>
<td>Family caregivers</td>
<td>Cross sectional</td>
<td>Regression analyses indicated that neuropsychiatric symptoms were the most consistent predictors of QoL.</td>
<td>Patient-informant agreement for MCI (M=0.24), AD (M=0.48), and controls (M=0.49) did not differ significantly. Self-reported QoL did not differ significantly across the 3 groups. For caregiver-reports, QoL in MCI did not differ from controls but was significantly greater than QoL in AD for 2 of 6 scales, and QoL in controls was greater than AD for 4/6 scales.</td>
<td>Results suggest that future investigators should carefully consider gathering QoL information from both informants and patients because they provide unique information regarding patient QoL and, to date, neither source of information has been established to be superior.</td>
</tr>
<tr>
<td>Logsdon et al.</td>
<td>2002</td>
<td>USA</td>
<td>QoL-AD</td>
<td>Patients with “probable” or “possible” AD; mean MMSE score 16.6 (SD = 7.3)</td>
<td>177</td>
<td>Community dwelling</td>
<td>MMSE, Physical and Instrumental Self-Maintenance Scale, Revised Memory and Behavior Problem Checklist, GDS, Pleasant Events Schedule—AD—Short Form, MOS, Screen for Caregiver Burden, Center for Epidemiologic Studies Depr Scale</td>
<td>Actively involved caregiver who lived with them or spent every day with them</td>
<td>Cross sectional</td>
<td>Correlation between caregiver and patient reports was greatest for subjects in the middle tertile of cognitive function, but cognitive ability did not seem to be the most salient explanatory factor because the correlations of both the lowest and highest cognitive groups were similar. Higher QoL related to less impairment in behavioral competence, better psychological status, less impaired physical function, and a better interpersonal environment.</td>
<td>Completers scored between 4 and 29 on the MMSE, whereas non-completers all scored 10 or lower. The level of agreement between patient and caregiver ratings of QoL was modest.</td>
<td>The QoL-AD seems to be reliable and valid for individuals with MMSE scores greater than 10. Further research is needed to clarify the relationship between patient and caregiver reports of patient QoL and to identify factors that influence QoL throughout the progression of dementia.</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Country</td>
<td>QoL measure</td>
<td>Participants</td>
<td>N</td>
<td>Setting/population</td>
<td>Other variables included</td>
<td>Type of carers</td>
<td>Type of study</td>
<td>Factors associated with QoL</td>
<td>Other results</td>
<td>Conclusion by authors</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------</td>
<td>---------</td>
<td>--------------------------------------</td>
<td>--------------</td>
<td>------</td>
<td>--------------------</td>
<td>--------------------------</td>
<td>-----------------</td>
<td>---------------</td>
<td>-----------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ready et al.</td>
<td>2002</td>
<td>USA</td>
<td>Cornell-Brown Scale for QoL</td>
<td>Dementia clinic outpatients with a range of cognitive impairment</td>
<td>50</td>
<td></td>
<td>CDR, MMSE, VASD</td>
<td>Family caregivers</td>
<td>Evaluation study</td>
<td>Positive correlation between QoL scores and visual analogue positive mood ratings (Spearman rho = 0.63) and a negative correlation between QoL and dementia severity as measured by CDR (Spearman rho = -0.35).</td>
<td>Psychometric properties of a new scale, the Cornell-Brown Scale for QoL, were examined.</td>
<td>Reliability and validity were not adversely affected by patient cognitive impairment.</td>
</tr>
<tr>
<td>Gonzalez-Salvador et al.</td>
<td>2000</td>
<td>USA</td>
<td>ADRQL</td>
<td>People with dementia</td>
<td>120</td>
<td>Residing in long-term care facility</td>
<td>MMSE, SIRS, PGDRS, CSDD</td>
<td>Facility staff members</td>
<td>Cross-sectional, case-control design</td>
<td>In univariate analyses, worse orientation, greater physical dependency, depression, and treatment with anxiolytics were associated with lower ADRQL scores. In multivariate analyses, lower scores were associated with worse orientation, greater physical dependency, depression, and anxiolytic treatment.</td>
<td>Residents exhibited better QoL than expected.</td>
<td>Future longitudinal studies should address if reorientation, activity therapy, treatment of depression, and avoidance of benzodiazepines might improve QoL in this population. Interventions that might improve orientation and physical abilities should also be studied in future research on QoL.</td>
</tr>
</tbody>
</table>
On the background of the challenges of assessing and interpreting HRQoL ratings as discussed earlier, it is of concern that 1) different HRQoL measures used in selected studies require different raters who may have a different appraisal of the person’s HRQoL, maybe driven by other factors; 2) in some studies weighing methods are applied for a HRQoL composite score, giving supremacy to one of the rates (i.e. patient or carer); 3) several studies did not provide details on how an informant was asked to rate the person’s HRQoL question(s) (e.g. to rate by substituted judgment ‘as if’ they were the person with dementia, or, to give their own direct opinion of the person with dementia’s HRQoL); and 4) carer-ratings can include family carers, professional carers or both, which has not always been specified.

This situation creates methodological issues, and makes it almost impossible to compare findings and clarify the factors that are associated with self or carer-ratings. This is clearly emphasized by the head-to-head comparison of several (HR)QoL measures in one study by Sloane et al. (2005). They administered the QoL-AD, DQoL, ADRQL, QoL-D, DCM, as well as the Resident and Staff Observation Checklist — QOL (RSOC-QoL) and the Philadelphia Geriatric Center Affect Rating Scale (PGC-ARS) with a large group of people with dementia residing in 45 facilities for long-term care (N=421). They found that various measures and sources of data provided different perspectives on quality of life that were associated with disparate clinical factors (Sloane et al., 2005). Yet, in the following paragraphs an attempt is made to summarize existing knowledge. Please note that new studies that have been published since January 2006, and are listed and discussed in the overall discussion section of this thesis (see Chapter 8).

### 1.6.1.1. FACTORS ASSOCIATED WITH SELF-REPORTED HRQoL RATINGS

The selected studies as listed in Table 1.6 included 8 out of 10 studies with self-reported HRQoL ratings: that is, 6 studies measured self-rated HRQoL with the QoL-AD (i.e. Edelman et al., 2004; Harvey et al., 2005; Hoe et al., 2005; Logsdon et al., 2002; Shin et al., 2005; Sloane et al., 2005), 2 studies with the DQoL (Ready et al., 2004; Sloan et al., 2005), and one study with the Cornell-Brown Scale for QoL (Ready et al., 2002). The study by Sloan et al. (2005) included two measures with self-reported HRQoL ratings (i.e. QoL-AD, DQoL).

The selected publications presented limited data based on studies with a well-defined AD population that included a wide range of candidate associated factors for self-reported HRQoL ratings in AD, including demographic, living arrangements,
medical background, use of medications, BPSD, awareness, ADL, IADL and burden of care (except the study by Logsdon et al. (2002), which included AD patients with a broad range of severity as measure by the MMSE).

Logsdon et al. (2002) examined the reliability and validity of patient and caregiver reports of patient’s HRQoL with the QoL-AD (Logsdon et al., 1999) (177 AD patient-caregiver pairs). AD patients fulfilled criteria for “probable” or “possible” AD based on a comprehensive diagnostic evaluation, and were required to be community dwelling, ambulatory, and to have an actively involved caregiver who lived with them or spent every day with them. Mean MMSE score for patients who were unable to complete the measure was 4.1 (SD = 3.2, range 0–10), compared with 18.1 (SD = 5.9, range 4–29) for those who could complete the measure ($F (1,175) = 120.2, p < .001$). Self-reported QOL-AD scores were not significantly associated with the MMSE ($r = 0.12$), but significantly associated with ADL ($r = -0.31$), GDS scores ($r = -0.51$), RMBPC depression subscale ($r = -0.22$), higher frequency of pleasant events ($r = 0.30$), caregiver burden ($r = -0.21$), and MOS physical function ($r = 0.22$). Interestingly, when they divided the subjects into tertiles by cognitive level, psychological status, as measured by the GDS, remained prominent in its relationship to patient-reported HRQoL at all levels of cognitive functioning. Thus, it seems that, regardless of cognitive status, depression has a strong impact on QoL-AD self-ratings. In other domains, considerable variability was found in correlations between QOL-AD scores and related measures: differences in frequency distributions of the measures across cognitive levels are a possible explanation for these findings. However, there was no evidence of “floor” or “ceiling” effects, and the variance of each measure was relatively similar across groups. They concluded that with larger samples, more significant correlations could be identified.

The study by Hoe et al. (2005) focused on people with severe dementia and included 79 people diagnosed with severe AD and their caregivers. Of their 79 patients, 41 (52%) were able to complete the QOL-AD, providing evidence for the validity and reliability of the QOL-AD in people with MMSE scores of 3–11. Unfortunately this study did not provide or analysed carer-reported HRQoL ratings separately. That is, Hoe et al. (2005), a well-cited study, used a composite QoL-AD score (i.e. self-reported ratings were given twice the weight of the carer’s and a weighted mean score was calculated and used for further analyses). Therefore their findings are uninformative regarding associations with specific raters.

Other studies that used the QoL-AD also found that self-reported ratings were
associated with mood (Shin et al., 2005). Studies that used the DQoL found correlations between the self-reported DQoL ratings and NPI and ADL scores (Ready et al., 2004). The study by Ready et al. (2002) used the Cornell-Brown Scale for QoL – which showed a positive correlation with the visual analogue positive mood ratings and a negative correlation with the CRD – but as this scale can not be separated in self- and carer-reported ratings we are not able to differentiate the correlation they of factors associated with self-rated HRQoL (Ready et al., 2002).

Taken together, these findings show some evidence that mood and functional status, or ADL, are associated with lower perceived self-reported HRQoL, while other factors included in some studies, like cognition as assessed by the MMSE, were not.

1.6.1.2. Factors associated with carer-reported HRQoL ratings

The studies listed in Table 1.6 included 8 of 10 studies with carer-reported HRQoL ratings: that is, 6 studies measured patients’ HRQoL with the QoL-AD (i.e. Edelman et al., 2004; Harvey et al., 2005; Hoe et al., 2005; Logsdon et al., 2002; Shin et al., 2005; Sloane et al., 2005), one study with the ADRQL (Gonzalez-Salvador et al., 2000), and another with the Cornell-Brown Scale for QoL (Ready et al., 2002). The study by Sloan et al. (2005) included several measures of carer-reported HRQoL ratings (i.e. QoL-AD, DCM, ADRQL). Unfortunately some of these studies did not provide or analysed carer-reported HRQoL ratings separately. Hoe et al. (2005), a well-cited study, used a composite QoL-AD score (i.e. self-reported ratings were given twice the weight of the carer’s and a weighted mean score was calculated and used for further analyses). Winzelberg et al. (2005) used nursing assistants’ QoL-AD ratings.

The selected publications reported limited data based on studies with a well-defined AD population that included a wide range of measurable candidate associated factors for carer-reported HRQoL ratings in AD, including demographic, living arrangements, medical background, use of medications, BPSD, awareness, ADL, IADL and burden of care, apart from the study by Logsdon et al. (2002) who included AD patients with a broad range of severity as measure by the MMSE. In Logsdon et al.’s (2002) study, carer-reported QQL-AD scores were not significantly associated with MMSE scores ($r = 0.02$), but significantly associated with ADL ($r = -0.37$), IADL ($r = -0.26$), RBMPC memory ($r = -0.27$), RMBPS disruptive ($r = -0.42$), GDS scores ($r = -0.52$), RMBPC depression subscale ($r = -0.23$), higher frequency of pleasant events ($r = 0.44$), caregiver burden ($r = -0.52$), MOS limitations-physical ($r = 0.20$), and MOS physical function ($r = 0.43$). Other studies that used the QoL-AD also found that carer-
reported ratings were associated with NPI depression, but also with distress related to agitation/aggression, disinhibition, irritability/lability and total score on the NPI (Shin et al., 2005). Winzelberg et al. (2005) also used nursing assistant rated QoL-AD and found that their ratings were most strongly associated with the patients’ clinical conditions, including severity of cognitive and functional impairment, depression, and behavioural symptoms of dementia. Their study found an independent positive association between the informant’s rating on the QoL-AD and their attitudes regarding dementia-person-centered care (i.e. a positive correlation between the Person-Centered subscale and QOL-AD scores; p=.006), as well as being well-training (Winzelberg et al., 2005).

Sloan et al. (2005), who administered and evaluated a broad range of (HR)QoL measures (see Table 1.6), found that patients’ cognition and ADL were associated with most (HR)QoL measures, although these predicted no more than 25% of the observed variance in any measure (Sloan et al., 2005).

Edelman et al. (2004) administered the DCM, which is only informant-rated, with 166 people with dementia, together with a variety of other measures tapping on dementia associated clinical factors. Both cognitive status (as measured with the MMSE) and functional status were found to be associated with DCM scores (Edelman et al., 2004). The study by Gonzalez-Salvador et al. (2000) with people with dementia living in long-term care facilities (N=120) used the ADRQL as HRQoL measure. Their results showed that lower ADRQL scores were associated with worse orientation, greater physical independency, depression, and treatment with anxiolytics. The study by Ready et al. (2002) used the Cornell-Brown Scale for QoL – which showed a positive correlation with the visual analogue positive mood ratings and a negative correlation with the CRD – but, as mentioned before, this scale does not separate self- and carer-reported ratings (Ready et al., 2002).

Overall, findings show several clinical factors associated with carer-reported HRQoL, with strongest correlations found between carer-rated HRQoL measures and neuropsychiatric symptomatology (including depression and other symptoms as rated on the NPI), caregiver burden, cognitive function of the patient, physical independency of the patient, and frequency of pleasant events.

1.6.2. Predictors of change in HRQoL in AD

One major objective of measuring HRQoL over time is determining the extent to which treatments, interventions or disease progression can affect patients’ HRQoL at different stages of a progressive disease like AD. To do so, we first need to enhance our
understanding about the typical natural history of HRQoL in dementia and the variables that mediate HRQoL change over time. The observed lack of knowledge on these critical matters was noted by Banerjee et al. in 2009, a few years after the start of this research, who stated that at that time we knew almost nothing about the natural history of HRQoL in AD, or what attributes or interventions promote or inhibit HRQoL for people with dementia. Based on a systematic review of papers published by October 2007 they concluded that there is a pressing need for studies of HRQoL in representative samples of people with dementia that gather both cross-sectional and longitudinal data. Also, a failure to include broad outcome measures such as HRQoL, and the reliance on measures of discrete functions such as cognition, could lead to the potential beneficial effects of interventions being overlooked or undervalued, or the potential adverse effects of intervention being missed (Banerjee, 2007). Banerjee et al (2009) advised that signs are clear from those that assess the quality of evidence available on new technologies and who decide whether interventions should be applied, that data demonstrating improvement in HRQoL would be of value in making the case for intervention in dementia. Existing longitudinal data will be critically reviewed in the following section.

1.6.2.1. AVAILABLE LONGITUDINAL STUDIES

The number of longitudinal observational studies that explored the change of HRQoL ratings in dementia over time is small, and their findings are hard to compare, because of the diversity in study characteristics, including measures, settings, living arrangements, and in- and exclusion criteria.

I completed a literature review to generate longitudinal data regarding (HR)QoL and clinical predictors in people with dementia. PubMed was searched for publications from any date up to January 2007, using multiple formulations of keywords (including Alzheimer’s disease, dementia, ‘quality of life’, ‘health related quality of life’ and the names of - at that stage known - HRQoL instruments (as listed in Table 1.4, e.g. DQoL, Brod et al., 1999; QoL-AD, Logsdon et al., 1999). This was supplemented by detailed inspection of the reference lists for papers identified. All findings refer to the patient’s (HR)QoL, not the carer’s QoL. Table 1.7 provides an overview of all selected longitudinal studies and summarizes the key findings.

Only four longitudinal observational studies that focused on the change of HRQoL ratings in dementia were identified (Lyketsos et al., 2003; Martin-Cook et al., 2005; Selwood et al., 2005; Wlodarczyk et al., 2004). New longitudinal studies that
have been published since are further considered in the overall discussion at the end of this thesis (see Chapter 8).

As summarized in Table 1.7, 3 of the studies identified provided longitudinal data on heterogeneous groups of people with dementia, except for the study by Wlodarczyk et al. (2004) that included patients with AD of mild to moderate severity (N=100, MMSE 10-25). Their study presented a data subset of a global donepezil trial involving over 1100 patients in 18 countries. However, the AQoL they administered as a measure of QoL is associated with methodological and conceptual issues, in the sense that it is a utility score derived from scores on four dimensions, all presented on scales from 1.00 (best possible HRQoL state measured by the dimension) to 0.00 (worst possible HRQoL state measured by the dimension). Dimension scores are weighted and combined, using a multiplicative model, onto a life–death scale. All AQoL weights were obtained using time trade-off from a weighted random sample of the Victorian population, designed to ensure representativeness of the Australian population. The utility index represents a life–death scale, where the scale range is from 1.00 (HRQoL states equivalent to full health), 0.00 (death equivalent HRQoL states) and −0.04 (worse than death equivalent HRQoL states). The worse than death HRQoL equivalent states are necessary to allow for people who commit suicide or euthanasia. As such, the AQoL is suitable for the computation of quality-adjusted life years (QALYs). Utility scores are valuable for economic decision makers, as they facilitate the calculation of quality-adjusted life years for use in cost–utility analysis. Utility measures allow a comparison, not only between AD patients undergoing different interventions, but also between AD and other disease states. However, this is a fundamentally different approach. A health utility measure assess the value or desirability of a state of health against an external metric, while a health status measures describe a person’s functioning in 1 or more domains (e.g., physical functioning or mental status) without an external metric. Therefore, the values of the findings of this study are basically outside the purpose of this thesis topic.

The study by Lyketsos et al. (2003) of people with dementia (N=120) living in long-term care facilities, administered the ADRQL, which provided longitudinal data of carer-rated HRQoL over a period of 2 years. Only a small mean decline of 5% was found between baseline and follow-up at 2 years, while almost half of the patient’s HRQoL as rated by their professional carers stayed the same or improved. Of the baseline variables assessed, only a lower baseline ADRQL score was associated with greater decline in ADRQL score at follow-up. There was no association between
sociodemographic variables, baseline ratings of dementia severity (MMSE), ADL impairment, behavioral impairment, and depression, or MMSE change during follow-up and ADRQL decline. One limitation of the study was the high dropout rate of 61%. The authors advised that the predictors of QoL change are complex and require further investigation.

The study by Martin-Cook et al. (2005) also provided carer-rated HRQoL longitudinal data as measured by the QUALID. They reported on the responsiveness of the QUALID as an outcome measure in a clinical trial of two psychotropic medications. A significant positive relationship was found between QUALID scores and improvement in behavioural symptoms, as measured by the NPI, and a negative association was found with adverse medication effects (Martin-Cook et al., 2005). Limitations of this study include the absence of a control group and non-blinded raters.

Selwood and colleagues (2005) conducted a one-year follow-up study. Their sample was selected from inpatient, day hospital, nursing home and residential home settings within a London Mental Health Trust. The self-reported QoL-AD, DQoL and EQ-5D were assessed at baseline and repeated one-year later. Fifty-eight people were traced and of these 40 (69%) were alive at follow up. There was no mean change in HRQoL over the one-year period, however around half of the people had increases or decreases in their HRQoL. The only significant predictor of the DQoL as well as the QoL-AD at follow-up was initial HRQoL score on those measures. HRQoL, measured with the QoL-AD as well as the DQoL, at follow-up correlated significantly with depression and anxiety, but not with cognition. They concluded that future research should investigate how HRQoL changes over longer time periods with larger samples and in relation to specific interventions (Selwood et al., 2005).
Table 1.7. Overview characteristics of longitudinal observational studies in predictors of change of HRQoL ratings in dementia (until January 2007)

| Authors               | Year | Country | QoL instr/s as primary outcome | Study design | N at BL | N at FU | % Dropout | Setting/population | Other variables included | Change in self-rated HRQoL | Change in carer-rated HRQoL | Type of carers | Predictors self-ratings | Predictors carer-ratings |
|-----------------------|------|---------|-------------------------------|--------------|---------|---------|-----------|-------------------|---------------------------|---------------------------|----------------|------------------------|------------------------|
| Lyketsos et al.       | 2003 | USA     | ADRQL                         | BL and FU at 2 yrs | 120     | 47      | 61%       | Long-term care facilities | Demographics MMSE CSDD PGDRS | N/A                      | Small mean decline of 5% (but nearly 50% stayed the same or improved) | Professional       | N/A                    | BL QoL rating            |
| Wlodarczyk et al.     | 2004 | Australia | Assessment of QoL (AQoL) scale | Data presented are a subset of a global donepezil trial involving over 1100 pts in 18 countries. FU for 24 weeks. Assx at baseline, 12 and 24 weeks. | 100     | 100     | n/a       | 20 elderly day care centers | MMSE IADL | Patient-rated AQoL utility scores were related to patient MMSE and IADL scores. | Caregiver-rated AQoL correlated with MMSE and IADL scores. | Family caregivers | Patient and caregiver-rated AQoL scores correlated (r=0.37, P=0.0038) for all levels of disease severity. Within AQoL domains, the correlation between patient and caregiver ratings is lowest for physical senses and psychological well-being, and highest for independent living and social relationships |
(Continued)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>QoL instr/s as primary outcome</th>
<th>Study design</th>
<th>Incl. PWD</th>
<th>N at BL</th>
<th>N at FU</th>
<th>% Dropout</th>
<th>Setting/ population</th>
<th>Other variables included</th>
<th>Change in self-rated QoL</th>
<th>Change in carer-rated QoL</th>
<th>Type of carers</th>
<th>Predictors self-ratings</th>
<th>Predictors carer-ratings</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Martin-Cook et al.</td>
<td>2005</td>
<td>USA</td>
<td>QUALID</td>
<td>Secondary analyses comparing outcome measures used in a double-blind randomized double-blind 2 week trial of two antipsychotics (olanzapine and risperidone) for treatment of BPSD</td>
<td>PWD 'with measurable behavioural disturbances'</td>
<td>31</td>
<td>31</td>
<td>n/a</td>
<td>Extended care facilities</td>
<td>NPI MMSE Withdrawn Behavior subscale of the Multidimensional Observation Scale for Elderly Subjects (MOSES) Clinical Global Impression (CGI)</td>
<td>N/A</td>
<td>N/A</td>
<td>Nurse or nurse aid</td>
<td>N/A</td>
<td>Behavioural symptoms, adverse medication effects</td>
</tr>
<tr>
<td>4 Selwood et al.</td>
<td>2005</td>
<td>UK</td>
<td>QoL-AD DQoL EQ-5D</td>
<td>BL and FU at 1 yr PWD aged 65+ (MMSE mean 16.1, SD 6.5 at BL)</td>
<td>60</td>
<td>29</td>
<td>52%</td>
<td>Various living arrangements</td>
<td>Demographics MMSE CSDD RAID</td>
<td>No mean change</td>
<td>N/A</td>
<td>BL QoL rating</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.6.2.2. Impact of Changes in Cognitive Functioning on HRQoL over Time

It is often assumed that the essence of HRQoL, when considered as a personal evaluation by the individual of his or her own life, cannot be (completely) unrelated to one of the central characteristics of AD: deterioration of cognitive functioning. It seems intuitive that awareness of cognitive dysfunction (like disabling forgetfulness) should have an impact on the level of experienced HRQoL from the very early stages of AD. However, the relationship between cognitive impairment and HRQoL in AD remains unclear.

As reviewed in previous two sections, some studies showed no association between HRQoL and cognition, while others found mild to moderate correlations, basically depending on the rater. That is, some studies found that in dementia HRQoL does not decrease as cognition deteriorates over time (e.g. Logsdon et al., 2002; Selwood et al., 2005), which contradicts the general assumption that declining cognition is associated with declining HRQoL. In addition, there was no evidence of the potential impact of cognitive decline over time on HRQoL ratings, or the impact of specific cognitive domains and functions, although the need to focus research on this unresolved issue was clearly recognized (e.g. Logsdon et al., 2002; Selwood et al., 2005).

Findings of the few studies that had included investigation of the long-term association between overall cognition and HRQoL in dementia relied on brief cognitive screening tests, such as the MMSE and the Cambridge Cognitive Examination of the Elderly revised version (CAMCOG-R), which have limited sensitivity to measure specific cognitive functions, such as executive function (Kessels et al., 2009; Martyr and Clare, 2012).

This data paucity is in contrast with research in other chronic conditions, which has shown strong evidence for a relationship between cognitive decline and HRQoL. For example, Tozzi et al. (2003) showed that for people with HIV, cognitive impairment is significantly associated with poor HRQoL. Specifically, poor performance on the Digit Symbol Coding Test (WAIS) was the strongest predictor of poor HRQoL. Another example: in a large multicentre study, Perrine et al. (1995) examined the relationship between objectively assessed cognitive functioning and self-reported HRQoL in 275 patients with epilepsy. Mood, psychomotor speed, verbal memory, and language correlated significantly with selected scales of the HRQoL in Epilepsy-89 inventory (P < .0001) and were predictive of overall HRQoL (P < .002 to P < .0001). The mood factor showed the highest correlations (r = -.20 to r = -.73).

However, in dementia research, findings published until the time this thesis
started suggested that a global cognition measure (as measured with e.g. MMSE or the ADAS-Cog) does not appear to be an important independent predictor of self-reported HRQoL. If the focus of AD clinical trials is to improve or preserve the HRQoL of persons with AD, maybe the importance of global cognitive measures should not be overemphasized, primary outcomes of studies should include HRQoL measures and other measures (such as depression) that have the greatest impact on patient’s experienced HRQoL. A key issue is that no study to date has focused on the question of whether specific cognitive domains or functions (e.g., executive functions) are associated with HRQoL in AD, on the background of a wide range of other possible confounding factors like BPSD and awareness. To be clearer, we were not aware of a study in this field that had included a wide range of specific cognitive functions as candidate associated factors for self-reported or carer-reported HRQoL ratings in AD at the time the work for this thesis started.

With regards to specific cognitive deficits, the impact that the typical decline in specific cognitive functions in AD have on the HRQoL has not been investigated systematically, although evidence from other chronic disorders suggests that deficits in specific cognitive domains affect HRQoL ratings in different ways (Barker-Collo, 2006; Hermann, 1993; Klonoff et al., 1986; Newman et al., 2001; Perrine et al., 1995; Tolman and Kurtz, 2012). Even though it seems that the general assumption that improved episodic memory, the most prominent initial clinical feature in most cases of AD, should lead to a concurrent improvement in HRQoL (McKhann et al., 2011; Mol et al., 2007; Pena-Casanova et al., 2012; Reed et al., 2007; Takeda et al., 2006) surprisingly few studies have investigated the long-term association between HRQoL ratings and loss of specific cognitive capacities, and most have limited their analyses to global cognitive measures (Lyketsos et al., 2003; Missotten et al., 2007; Selwood et al., 2005; Tatsumi et al., 2009). Therefore, it is unclear whether specific cognitive functions, such as episodic memory or executive functioning, have a more prominent role in driving changes in HRQoL over time in this population.

A limited body of research using carer-reports to measure the HRQoL in AD provided data suggesting that the greater the cognitive impairment of the older person with AD the lower the carer-reported HRQoL ratings (Edelman et al., 2005; Hoe et al., 2006; Wlodarczyk et al., 2004). The latter seems consistent with evidence of a relationship between cognitive impairment in dementia and negative carer outcomes (Savundranayagam et al., 2005; Donaldson et al., 1997), as cognitive decline appears to
increase burden of care (Schultz et al., 2003). In addition, more recent data suggest that the association between cognitive functioning and the HRQoL in AD as rated by the carer may not progress in a linear manner (Missotten et al., 2007).

A related area in need of further investigation is the relationship between HRQoL and awareness or insight. At the start of this thesis relatively little was known about this potentially crucial factor in our understanding of experienced HRQoL in AD. It seems intuitive that being aware of cognitive decline might adversely impact on HRQoL. However, it remains unclear what (if any) the effect of a person with dementia’s insight into their condition has on their HRQoL. Investigations into the relationship between patient insight and HRQoL have produced inconclusive results (Ready et al., 2004; Vogel et al., 2006), albeit with relatively small samples. It was Hurt et al. in 2009 that investigate the relationship between insight and HRQoL in a sample (N=174) of patients with AD and their carers. Insight was found to be differentially related to patient perceptions of HRQoL in mild and moderate dementia. Within moderate dementia, impaired insight was associated with better perceived HRQoL. Conversely, cognition, but not insight, was associated with impaired HRQoL in mild dementia. Insight was not found to be associated with carer perceptions of patient HRQoL. The findings suggest that insight plays a complex role in evaluations of HRQoL in dementia. People with moderately severe dementia and impaired insight into their condition showed a tendency to perceive their QoL as better. For those with mild dementia, and therefore potentially higher levels of insight, this protective effect was not observed. This has implications for interventions that focus on increasing patient awareness and orientation, as impairment of insight appears to have a positive impact upon HRQL and needed further research. Since then a growing number of studies have significantly contributed to our knowledge of the role of awareness of cognitive decline on QoL in dementia (for example, Clare et al., 2012; Schoo et al., 2013; Sousa et al., 2013).

Another related matter is the evidence that the underlying cognitive structure may not be stable during the course of AD (Chapman et al., 2010; Hayden et al., 2011; Johnson et al., 2009; Kanne et al., 1998; Siedlecki et al., 2008). That is, data from a recent study (Hayden et al., 2011) indicated that across levels of cognition (i.e. normal, mild cognitive impairment, dementia), the factor structure of cognitive functions varied. Another study (Siedlecki et al., 2008) reporting results from explorative and confirmatory factor analyses suggested that the memory construct represents something
different in healthy older adults, questionable dementia and AD, consistent with the underlying neuropathology. This may have implications for the association between specific cognitive deficits and HRQoL at different points in time. Once again, although specific cognitive deficits associated with AD, such as episodic memory, are expected to undermine HRQoL, we are not aware of any studies that have investigated the stability of the underlying cognitive structure and how such a structure might be associated with HRQoL ratings at different stages of the illness compared with healthy older adults. If the factor structures of cognition in AD at different points in time are comparable, and if the factors express meaningful identifiable cognitive functions, then results would be consistent with a stable relationship between cognitive functions and HRQoL over time (e.g., episodic memory could be a stable domain driving HRQoL in people with AD throughout the course of their illness). Conversely, if the underlying cognitive structure is not stable over time, then different cognitive domains might influence HRQoL as the disease progresses.

1.7. **KEY ISSUES – THE RATIONALE FOR THIS THESIS**

Given the growing number of people with AD and the pressures of healthcare costs, there is a need for high quality effective interventions and evaluation of the health care services for the older adults diagnosed with AD in Australia. It is imperative that we enable health planners to measure the effects of interventions, thereby reducing health care costs and improving HRQoL for this growing group of people in our society. We considered that this research could extend our knowledge of factors that influence the HRQoL of people with AD, and thus our interpretation of this increasingly used outcome measure. If we are able to identify the mediating factors, this would enable us to design strategies to improve the QoL of the ever increasing number of people with AD in our society.

Hence, the key issues that this thesis aimed to address were:

Key issue 1: There is an urgent need for the identification of the factors that drive changes HRQoL in AD.

Key issue 2: There is an urgent need to identify the clinically modifiable factors that do drive changes in HRQoL in AD in order to develop effective interventions.

Key issue 3: Although there are indications that improvement of episodic memory, the most prominent feature in most cases of early AD, should lead to a
concurrent improvement of HRQoL in AD, proof that this is the case is lacking. In fact, the impact of cognitive decline on the experienced HRQoL is arguably one of the least explored crucial questions in this field of research. There is a need to clarify whether and how cognitive decline is a significant mediating factor in HRQoL throughout the progression of AD.

Key issue 4: There are no longitudinal studies with emphasis on the relation between global cognitive decline or increase in specific cognitive deficits and change in HRQoL in AD over time.

Key issue 5: The question of whether an association between cognitive domains (such as memory and executive functions) and other mediating factors (such as BPSD) are actually stable or change during the progression of the disease has not been established.

Key issue 6: Previous studies on HRQoL in AD only used global cognitive screening tools (e.g. MMSE) to assess cognitive impairment, while studies that focused on HRQoL in relation to cognition in other chronic diseases showed a significant correlation with specific cognitive domains and/or specific functions (including verbal episodic memory, psychomotor speed, language) measured on a broader range of specific neuropsychological tests.

Key issue 7: Little is known about the impact of awareness on experienced HRQoL in AD.

Key issue 8: Pickard & Knight’s (2005) consideration of the importance of delineating between proxy perspectives in this field has not been explored in regard to the effect this might have on assessment and interpretation of HRQoL ratings in AD.

Key issue 9: Longitudinal data to determine the factors that drive HRQoL ratings at different stages of AD are required on a well-defined and homogeneous study population living in a well-defined setting, based on a validated HRQoL measure with established sensitivity to detect change over time.

Taken together, the relationship between cognitive decline and HRQoL in AD was a minimally explored area, although it is of great clinical and research significance. We believed that the research would offer significant contribution to our understanding
of the relative contribution of cognitive decline to changes in HRQoL in people with dementia of the AD type, and to the assessment and interpretation of HRQoL ratings in AD. This in turn would lay the groundwork for the applicability of HRQoL in AD as outcome measure in future studies designed to develop treatments and interventions for AD, as well as for clinical practice.

These key issues let to the aims of the study, which are presented in the next section of this thesis.
CHAPTER 2.

AIMS, HYPOTHESES AND GENERAL METHODOLOGY
2.1 INTRODUCTION
This chapter describes the overall aims of the study, hypotheses and methodology, including study design, recruitment of participants, process for collection of data, strategies used to measure HRQoL, details of the neuropsychological test, details of the additional questionnaires, and procedures associated with each clinical assessment. This chapter also provides a broad overview of the statistical methods used and ethical approval.

2.2. AIMS OF THESIS
We designed five inter-related observational studies to examine the relative contribution of cognitive decline to changes in HRQoL in older adults diagnosed with mild to moderate AD.

These five studies were designed to determine:

• Study 1: (1) the agreement between community-dwelling people with mild to moderate AD and their family carers HRQoL ratings; (2) whether the perspective of family carer-rated HRQoL (i.e. carer–carer perspective and carer–patient perspective) changes HRQoL outcomes; (3) the factors that independently contribute to self-reported and carer-reported HRQoL ratings (i.e. carer–carer perspective and carer–patient perspective);

• Study 2: (4) whether self-reported and carer-reported HRQoL change over a period of 18 months; (5) the factors that mediate changes in HRQoL ratings in people with AD over a period of 18 months; (6) the factors that mediate changes in HRQoL ratings by family carers over a period of 18 months;

• Study 3: (7) whether the underlying cognitive domains of people with AD remain stable over 18 months compared with controls free of dementia; (8) whether the associations between cognitive domains and carer and self-reported HRQoL ratings remain stable over 18 months;

• Study 4: 9) whether the deterioration of specific cognitive functions commonly associated with AD predict which patients maintain or experience a deterioration of their HRQoL ratings over a period of 18 months;

• Study 5: 10) the prevalence and association of exposure to potentially harmful medication with HRQoL.
The secondary aims were:

(1) To confirm the feasibility and inter-rater reliability of assessment of HRQoL, using the self-rated QoL-AD administered by two interviewers.

(2) To determine the influence of the place of residence on agreement between self-reported and informant ratings.

For the secondary aims we partially relied on the Dementia In Residential Care Trial (DIRECT) study (see study protocol in Appendix C2).

2.3. HYPOTHESES

Given the findings and assumptions reflected in literature as described in the Introduction (Chapter 1) of this thesis, for our sample of people diagnosed with AD at mild to moderate stage living in the community, it was hypothesized that:

Study 1:

(1) Patients and carers do not agree in their ratings of HRQoL, regardless of the perspective adopted by the carer (i.e. rating as the carer sees it or how the carer believes the patient sees it).

(2) The instructed perspective of informant has significant influence on carer-rated HRQoL as outcome measure (i.e. carer–carer perspective and carer–patient perspective).

(3) HRQoL ratings by carers, but not patients, would be directly correlated with the global cognitive function of patients.

Study 2:

(4) Self-reported and carer-reported HRQoL ratings as measured with the QoL-AD do change over a period of 18 months time.

(5) Changes in HRQoL ratings by people with AD are directly associated with changes in BPSD, but not with global cognitive decline.

(6) Changes in HRQoL ratings by carers are directly associated with changes in global cognitive functioning and instrumental activities of daily living and inversely associated with changes in BPSD and carer’s burden-of-care.
Study 3:

(7) The underlying cognitive domains structure in a sample of older adults with mild to moderate AD living in the community is not stable over 18 months compared with controls free of dementia.

(8) Changes in specific cognitive domains, i.e. episodic memory and executive functions as measured with specific neuropsychological tests, are directly associated with changes in the QoL-AD self-ratings and carer-ratings.

Study 4:

(9) Specific cognitive functions, i.e. episodic memory and executive functions, are directly correlated with HRQoL self-ratings and carer-ratings, as measured by the QoL-AD total score.

Study 5:

(10) Exposure to potentially harmful medication (PHM) is inversely associated with self-reported HRQoL ratings.

With regards to the hypotheses of secondary aims:

(11) The feasibility and inter-rater reliability of assessment of HRQoL, using the self-rated QoL-AD administered, is good.

(12) The place of residence has influence on agreement between self-reported and informant HRQoL ratings.

2.4. CREATIVE COMPONENT

At the time of proposal the strength of the thesis research included its innovation in addressing the following:

• To the best of our knowledge, this was the first longitudinal study with emphasis on the relation between cognitive decline and change of HRQoL in AD over time, by conducting a cross-sectional study and an 18-month follow-up study of people with mild to moderate AD and healthy older adults as controls.

• Previous studies on HRQoL in dementia only used global cognitive measures (e.g. MMSE) to assess cognitive impairment. However, a large proportion of studies that focused on HRQoL in relation to cognition in other chronic diseases showed a
significant correlation with specific cognitive domains and/or specific functions. In these studies a more extensive and not just a global cognitive assessment was used. Therefore, we included multiple cognitive domains and specific cognitive functions by using an extensive neuropsychological test battery in addition to global cognitive measures. The selection of specific cognitive domains and functions to be included relied on a thorough literature review regarding the evidence of cognitive deficits associated with (pre-) clinical AD compared with normal aging (e.g. Albert et al., 2001). In order to get an extensive, detailed, and well-validated cognitive assessment, the selection of the neuropsychological tests and questionnaires for this study was based on their psychometric properties, clinical utility, and findings from previous studies that focused on the relation between cognition and QoL in other chronic diseases.

- At the time this research effort started, this was the first study that included insight and awareness as a possible mediating factor of HRQoL in dementia.
- Based on Pickard & Knight’s (2005) consideration of the importance of delineating between proxy perspectives in this field, in our study the next-of-kin were asked to give a proxy-patient perspective (i.e. asking a proxy to assess as they think the patient would respond), as well as a proxy-proxy perspective (i.e. to provide their own perspective on the patients HRQoL).

It was anticipated that this thesis would significantly contribute to the understanding of the association between cognitive decline and HRQoL ratings in older adults with dementia of the AD type, and to lay the groundwork for future studies designed to optimize the HRQoL of people with dementia of the AD type.

2.5. SIGNIFICANCE
The national and state and territory data, commissioned from Access Economics by Alzheimer’s Australia, indicate that in 2005, the total number of Australians with dementia passed the 200,000 mark (1% of the population). By 2050 the total number of people with dementia in Australia will exceed 730,000 (2.8%) of the projected population. Given the growing number of people with dementia and the pressures of healthcare costs, there is a need for high quality evaluation of the health care services for older adults in Australia. It is imperative that we enable health planners to measure the effects of interventions for reducing health care costs and improving QoL for this
growing group. We believe this research extends our knowledge of factors that influence the HRQoL of people with dementia, and thus our interpretation of this widely used outcome measure. If we can identify the mediating factors, it can help us to look at ways of improving the delivery of health services for older adults with and without dementia in our aging society. This can have a large return for the society as a whole.

2.6. RESEARCH DESIGN

The research was designed as five inter-related studies. The data for the Quality of Life and Cognition (QoLCog) study 1, 2, 3, and 4 were obtained from an 18-month longitudinal observational study of 80 subjects with diagnosis probable AD (NINCDS-ADR criteria) with MMSE $\geq 10$, and 75 healthy older adults as controls.

The data for the post-hoc analyses, study 5, were obtained from the Dementia In Residential Care Trial (DIRECT) conducted at the Western Australia Centre for Health and Ageing. The DIRECT study is a prospective randomized controlled trial of educational interventions aiming to improve QoL of PWD living in RACFs, conducted in the metropolitan area of Perth, Western Australia. The protocol of the DIRECT trial has been published (Beer et al., 2010), and appears on the Appendix (C2) of this thesis. This study, of which I led the component related to HRQoL, will be described in chapter 7.

2.7. PARTICIPANTS

2.7.1. RECRUITMENT

AD patients were primarily recruited from the Memory Clinic of Royal Perth Hospital and various geriatric and mental health services in Perth metropolitan area. The supervisor (OA) is a consultant at the Inner City Memory Clinic, which had approximately 500 potentially eligible patients on its books. Outpatients who fulfilled the in- and exclusion criteria were invited to participate in this research with a recruitment letter (N=196), signed by the clinician involved. A flowchart of participants from invitation to inclusion of Study I is included in the Appendices of this thesis and in Chapter 5; the flow of participants during the 18 months of follow-up is also included in the Appendices of this thesis and in Chapter 7.
Participants for the control group, healthy people aged 65+ and their next-of-kin (NoK), were recruited by invitation letter from studies that were already running at the School of Psychiatry and Clinical Neurosciences. In addition, we advertised to add to the procedure of further recruitment of control, via paper adds, radio interview, and brochures.

2.7.2. INCLUSION CRITERIA

Patients: People diagnosed with probable Alzheimer’s disease, with mild (MMSE score 21-25) or moderate severity of dementia (MMSE score 11-20; ranges based on Perneczky, et al., 2006), who were living in the community. A primary carer as next-of-kin had to be able to participate as informant for this research. For the clinical diagnosis at the time of recruitment the NINCDS-ADRDA criteria for probable Alzheimer’s disease (McKhann et al., 1984) were applied.

Controls: Cognitively intact control subjects had to be free of cognitive complaints and not meet criteria for Alzheimer’s disease or Minimal Cognitive Impairment (MCI). New potential control subjects were tested with the Telephone Interview for Cognitive Screening (TICS, Brandt et al., 1988; see form in Appendices).

2.7.3. EXCLUSION CRITERIA

We excluded people with a positive history of alcohol or substance abuse, and those with a medically unstable illness that could compromise survival (such as metastatic cancer). Participants with AD could be consuming cholinesterase inhibitors or memantine, but could not be participating concurrently in an experimental study of medications for AD. All participants were competent in written and spoken English.

2.8. MEASURES

2.8.1. HEALTH RELATED QUALITY OF LIFE (HRQoL)

The primary outcome of interest were the HRQoL ratings as measured with the Quality of Life-AD (QoL-AD, Logsdon et al., 1999; 2002). The QoL-AD is a brief and widely used HRQoL scale for the assessment of people with dementia, which has well-established psychometric properties (Logsdon et al., 2002; Thorgrimsen et al., 2003) and is considered the measure of choice to assess the impact of interventions in dementia care (Moniz-Cook et al., 2008). In the longitudinal study by Logsdon et al. (2002), 155 of the 177 patients interviewed were able to complete the QOL-AD. Mean MMSE for
non-completers was 4.1 compared to 18.1 for completers (range 4–29). The scale is composed of 13 items that measure different domains of functioning, selected to reflect relevant areas of the HRQoL of older adults with AD. Each item offers four possible answers that range from 1 (‘poor’) to 4 (‘excellent’), producing a total score that can range from 13 to 52 – higher scores indicate better HRQoL. Patient and carer versions are available. Self-ratings and carer-ratings were treated as separate outcome measures and not as a composite score. The manual and original forms are included in the Appendices (section B).

2.8.2. COGNITIVE EXPLANATORY MEASURES

2.8.2.1. GLOBAL COGNITIVE MEASURE

The Cambridge Cognitive Examination of the Elderly, revised version (CAMCOG-R, Rother et al., 1998). The CAMCOG-R is a widely used global cognitive measure that assesses various aspects of orientation, memory, language, praxis, attention and executive function. The CAMCOG-R can be divided into 10 different subscores, each covering a specific cognitive domain: orientation, language (comprehension and expression), memory (recent, remote, and new learning), attention/calculation, praxis, abstract thinking, and perception. Total scores on the CAMCOG-R range between 0 (severe cognitive impairment) and 105 (no cognitive impairment). To enhance the assessment of executive function, two additional items measuring mental flexibility were added. Based on combined scores of the verbal item ‘ideational fluency’, the non-verbal item ‘visual reasoning’, and two items from the original CAMCOG, the verbal fluency item (naming animals) and the ‘abstract reasoning’ item, a separate executive function score was derived. Performance on these two new items did not, however, contribute to the total CAMCOG-R score. The form is included in the Appendices (section B).

2.8.2.2. SPECIFIC NEUROPSYCHOLOGICAL MEASURES

We used a battery of established neuropsychological tests to assess specific cognitive functions commonly affected by AD: episodic memory, naming, language comprehension, word fluency, psychomotor speed, inhibition, cognitive switching, working memory, visuospatial organisation and constructional abilities (Reed et al., 2007; Schmand et al., 2011). All forms are included in the Appendices (section B).
• The **Boston Naming Test** short 30-item version (**BNT30**) (Graves et al., 2004). The total score (maximum 30) was calculated by adding the number of correct items without the correct responses following semantic or phonetic cues.

• The short form of the **California Verbal Learning Test** (**CVLT-II**) (Woods et al., 2006). The following scores were included: total recall on Trial 1 to 4 (maximum 36), short delay free recall, short delay cued recall, long delay free recall, long delay cued recall, and yes/no recognition hits (all maximum 9).

• The **Delis-Kaplan Executive Function System** (**D-KEFS**) (Delis et al., 2001) subtest Word Fluency (i.e. the total score for **Letter Fluency**, **FAS**, and the total score for **Category Fluency**, **Animals and Boys names**); and subtest **Trail Making Test** (i.e. the minutes to complete the five conditions: 1) Visual scanning, 2) Number sequencing, 3) Letter sequencing, 4) Number-Letter switching, and 5) Motor speed).

• **Digit Span Subtest of the Wechsler Adult Intelligence Scale III** (**WAIS-III**) (Wechsler, 1997): total score on Digit Span Forward (maximum 16), Digit Span Backward (maximum 14), the length of the correctly replied longest Digit Span Forward (maximum 9) and the length of the correctly replied longest Digit Span Backward (maximum 8).

• **Digit Symbol Coding** subtest of the **WAIS-III** (Wechsler, 1997; Joy et al., 2004). The contribution of speed to Digit Symbol Coding has been operationalized as the **Digit Symbol Copy** test (Wechsler, 1997): the number of correct responses produced over 2 minutes.

• The **Neuropsychological Assessment Battery** (**NAB**) **Screening Module Language** subtest for auditory comprehension (Stern and White, 2003): the total score (maximum 56).

• **Rey Complex Figure Test** (**RCFT**) RCFT copy by drawing and recall by drawing (Meyers and Meyers, 1995): the total scores for copy and for recall (both to a maximum 36).

• The **Visual Association Test** (**VAT**), a brief paired-associate learning test, based on imagery mnemonics (Lindeboom et al., 2002): maximum score is 6.

## 2.8.3. Other Study Measures

We collected demographic, lifestyle and medical background information at the baseline and the 18-month assessments. This included information on gender, country of birth,
education, marital status, and number of children born alive. At the baseline and the 18-month assessment we asked participants about their lifestyle and clinical information, including living arrangements (alone, living with others than the carer, living with the carer), religion practice, practising hobbies, involvement in community activities, use of medication, medical conditions, alcohol use and smoking, falls during the preceding 6 months, visit(s) to (General Practitioner (GP) or hospital, admission to hospital over the past 6 months, and sensory impairment (hearing and vision). Participants with AD and their carers compiled a list of all prescription and non-prescription medications used by the person with AD during the past month. Medications were coded according to the World Health Organization Anatomical, Therapeutic, and Chemical (ATC) Classification System. The Participant and Informant General Questionnaire as developed for this research is included in the Appendices (section B) of this thesis.

The following measures (listed in alphabetical order) were selected to collect information about behavioural and psychological symptoms of dementia, awareness, and independence in activities of daily life from different perspectives (e.g. AQ consists of self-reported and carer-reported versions of patient’s performance in basic and instrumental activities of daily living). All forms are included in the Appendices (section B).

- **Anosognosia Questionnaire** (AQ, Migliorelli et al., 1995; Starkstein et al., 2006). This is a 30-item questionnaire divided into two sections. The first assesses performance in basic activities of daily living (bADL) and instrumental activities of daily living (iADL). The second examines changes in mood and behaviour. Two forms of the AQ are used: form A is independently answered by the patient and form B by the carer only. The final score is obtained by subtracting the scores on form B from A. Thus, positive scores indicate that the caregiver rated the patient as more impaired than the patient himself/herself.

- **Guidelines for the Rating of Awareness Deficits** (GRAD, Verhey et al., 1983; Zanetti et al., 1999). The GRAD is a scale designed to measure awareness of memory and other cognitive deficits. Through a four-question structured interview and open conversation, the clinician rates insight in a score range from 1 to 4, lower scores implying lower insight. The scale has good psychometric properties (Verhey et al., 1993).
• **Hospital Anxiety and Depression Scale** (HADS, Zigmond et al., 1983). The HADS has robust psychometric properties for the assessment of symptoms of depression (HADS-D) and anxiety (HADS-A) in people of all ages, including those with medical comorbidity (Flynt & Rifat, 2002; Mykletun et al., 2010). Reliability has been shown in a range of settings, and there is evidence that it is a suitable measure of anxiety and depression in populations of older adults with or without cognitive impairment or dementia (Clare et al., 2002; Richmond et al., 2011; Wands et al., 1990).

• **Informant Questionnaire on Cognitive Decline in the Elderly** (IQCODE, Jorm, 1994, Knafelc et al., 2003). The IQCODE was designed to measure the severity of cognitive and functional decline of participants with AD according to the subjective view of the informant. The IQCODE has good internal consistency, reliability and face-validity (Jorm, 1989; 1994).

• **Katz’ Activities of Daily Living scale** (ADL, Katz et al., 1963; 1983). This is a widely used scale that measures basic activities of daily living (including personal care, clothing, moving, going to the toilet, eating) as reported by a carer. Each scale item is rated as ‘independent’, ‘needs assistance’ and ‘dependent’, with higher scores indicating greater dependence.

• **Lawton and Brody’s instrumental activities of daily living (IADL) assessment scale** (Lawton & Brody et al., 1969). This was used to assess abilities in IADL, such as ability to complete phone calls, shopping, driving and using money according to an informant. This measure has good validity (Vittengl et al., 2006). Again, each scale item is rated as ‘independent’, ‘needs assistance’ and ‘dependent’, with higher scores indicating greater dependence.

• **Neuropsychiatric Inventory** (NPI, Cummings et al., 1994; 1997). The NPI is a widely used interviewer-rated scale for rating Behavioral and Psychological Symptoms of Dementia (BPSD). The NPI consists of 12 subscales that assess the frequency and severity of delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, irritability, disinhibition, aberrant motor activity, nighttime behavior disorder, and appetite or eating change. The score of each subscale is calculated by multiplying the frequency (range 1–4) by the severity (range 1–3), and the sum yields an overall NPI score (range: 0–144). The NPI carer distress subscale (NPI-D) scale provides a quantitative measure of the distress experienced by carers (ranging from 0 ‘not at all’, to 5 ‘very severely or extremely’) in each domain
assessed (Kaufer et al., 1998). The NPI has good psychometric properties (Cummings et al., 1997).

2.9. DATA COLLECTION
We posted the study questionnaire, as well as the AQ, HADS, IQCODE, Katz’ ADL and Lawton & Brody’s IADL scales to participants for completion prior to a face-to-face assessment. During the face-to-face assessment, responses to each of the study questionnaires were checked for completeness, and factual information regarding demographic facts and clinical characteristics were checked for accuracy with the carer. All assessments were completed by a senior clinical neuropsychologist (PB). The QoL-AD was administered with the participant with AD and their carer separately. The same procedures were used at the 18-month assessment.

2.10. STATISTICAL ANALYSES
The data were managed with Microsoft Excel and analyzed with STATA (i.e. latest versions available at the time of the research stage; StataCorp, College Station, Texas). Continuous variables were summarized by their mean and standard deviation (SD), and categorical variables by their count and proportions. We calculated the 18-month change of scores as the score at 18 months minus the score at baseline and subsequently standardized (z-scores) these differences to create a uniform scale for all tests.). All statistical tests reported are two-tailed. For detailed description of the statistical analyses, I refer to the specific section of each of the studies reported in chapters 3 to 9.

2.11. SAMPLE SIZE AND POWER CONSIDERATIONS
Previous studies in the field of QoL in dementia (with different QoL measures and only global cognitive measures) showed inconsistency regarding whether there is a significant correlation (and in what direction) between cognitive impairment and QoL in dementia, ranging from is from r= 0 to .497. As such, we did not expect to find a correlation exceeding .5. However, because we would use a much wider range of more specific and well-validated instruments, assessing a wider range of cognitive functions, this would at least improve studies done so far. Nevertheless, because this is a difficult field in terms
of methodology, $r = .4$ was used to calculate power. Because we expected a moderate effect (correlation coefficient under the null hypothesis of .4) in the cross-sectional data, at a significance level of .05 and desired power of .80, we needed $N = 78.982$ to test our hypotheses. However, because we were aware that the longitudinal study might have higher requirements and taking into account loss at the 18-month follow-up and death (20%), we aimed to recruit 100 patients so that even with a 20% dropout for the follow-up study, we would have the power to detect longitudinal effect. We expected that $N=80$ of controls would be sufficient. As indication, with a 20% dropout, the follow-up study would be completed by 60 participants and would have enough power (>80%) to be able to declare a correlation of $r = .4$ as significant at the level of 5%. We acknowledged that in other similar studies in the field, as reviewed in chapter 1 (table 1.7), the dropout percentages were high (i.e. 52-61%). In anticipation, we calculated that if the percentage of dropout at follow-up in this study were 54% or higher (with only less than 37 participants left at follow-up), the study would no longer have 80% power to declare a correlation of .4 between HRQoL and cognitive scores as significant.

2.12. ETHICAL APPROVAL
The four Ethics Committees of the University of Western Australia, Royal Perth Hospital, Mercy Hospital, and Western Australian Department of Health - NMAHS Mental Health approved the study protocol. All participants and their carers provided written informed consent, and the project was conducted in accordance with the Helsinki Declaration of Human Rights. Copies of written consent forms as developed and used for this study are included in the Appendices (section B).
CHAPTER 3.

DIFFERENT FACTORS ASSOCIATED
WITH COMPLEMENTARY HRQOL RATINGS
BY PEOPLE WITH AD AND FAMILY CARERS

3.1. ABSTRACT

**Background:** Quality of life (QoL) in dementia is a complex construct and factors that predict QoL ratings are unclear. We designed this study to determine: (1) the agreement in QoL ratings between community-dwelling patients with mild to moderate dementia and family carers; and (2) the factors associated with self-reported and two types of carer-reported QoL ratings: carer–carer perspective and carer–patient perspective.

**Methods:** A cross-sectional study was carried out of 80 community-dwelling patients with the diagnosis of probable Alzheimer’s disease (AD) of mild or moderate severity according to NINCDS-ADRDA criteria, and their 80 family carers. The QoL-AD was the primary outcome measure. We collected patients’ self-reported QoL ratings and two types of carer-reported QoL ratings: carer–patient and carer–carer perspectives. Explanatory variables included demographics, lifestyle, and clinical information from patients and carers, along with cognition, awareness, psychopathology, burden-of-care, and functionality in daily life. Bland-Altman plots guided the interpretation of agreement by visualizing the distribution of all the ratings. Univariate and multivariate regression analyses were conducted to examine the contribution of candidate explanatory factors.

**Results:** Patients and their carers showed good agreement in their QoL ratings, although the total scores of carers (regardless of perspective) were lower than the scores of patients. Depression, insight and use of anti-dementia agents were associated with QoL self-ratings, whereas cognitive function was directly associated and depression inversely associated with carers’ QoL ratings.

**Conclusion:** Mild to moderate community-dwelling AD patients and their carers (with different perspectives) agree within an acceptable range in QoL ratings but the ratings are driven by different factors, and consequently are not interchangeable but complementary. They provide valuable information when used separately, not in a composite score.

3.2. INTRODUCTION

Quality of life (QoL) is a complex construct that encompasses information about various relevant aspects of a person’s life. For this reason, interventions designed to treat people with dementia are expected to improve not only one specific aspect like memory, but their QoL (Banerjee et al., 2009).

Although increasing emphasis has been placed on the QoL of patients with dementia over the past two decades (Mack and Whitehouse, 2001), its evaluation is not
simple or straightforward. For example, several assessment tools have been introduced to research and clinical practices (e.g. Logsdon et al., 1999; Ready and Ott, 2003; Smith et al., 2005a; 2005b) since the subjective nature of the concept of QoL has been highlighted, but still there is no agreement on how best to define QoL in dementia, nor an agreed procedure to assess it (Banerjee et al., 2006; 2009; Rabins and Black, 2007). It is unclear who should provide the information about the various components commonly used to assess QoL: i.e. the patient, the carer (paid or unpaid), or both (e.g. Karlawish et al., 2001; Fossey et al., 2002; Logsdon et al., 1999; 2002; Smith et al., 2005a; Vogel et al., 2006). There is also uncertainty about whether the patient’s sum of item ratings should have precedence over the carer’s ratings in a composite score (Logsdon et al., 1999), as it has been argued that the perception of QoL of the patient should not be dismissed (Conde-Sala et al., 2009). Finally, if carers are asked to rate the QoL of people with dementia, should they be asked to rate it as they (as carer) perceive it or according to what they believe would be the perception of the patient (Logsdon et al., 1999; Pickard and Knight, 2005; Smith et al., 2005b)? Would these different perspectives yield different QoL ratings?

Several studies have reported differences in QoL ratings between patients with dementia and their caregivers (paid or unpaid), with patients’ ratings commonly yielding higher scores than carers’ (Thorgrimsen et al., 2003; Sands et al., 2004; Hoe et al., 2007; Conde-Sala et al., 2009). These differences between patient and proxy ratings are also found in other chronic diseases and have been discussed in the context of the so called “disability paradox” – a tendency for caregivers to report lower levels of QoL than the patients (Albrecht and Devlieger, 1999; Ready and Ott, 2003; Vogel et al., 2006). This phenomenon illustrates the possibility of adaptation and resilience despite adversity (Livingston et al., 2008), which can be counterintuitive to external observers, such as carers (paid or unpaid). For example, older adults with Alzheimer’s disease (AD) tend to rate their QoL as highly as people of the same age without dementia (Ready et al., 2004; James et al., 2005). These differences between self-reported and carer-reported QoL ratings have been interpreted as indicative of low level of agreement (e.g. Conde-Sala et al., 2009), disagreement (e.g. Vogel et al., 2006), moderately low correlation (Smith et al., 2005b), and even high correlation (e.g. Hoe et al., 2007). In other words, it is unclear if the differences between QoL ratings simply disagree or agree but are subject to systematic rater bias, with carers’ ratings shifted downwards.

Another question that has not been conclusively addressed relates to the factors
that influence the perception of QoL in patients and other informants. So far, a number of potential explanatory factors have been suggested (Karlawish et al., 2001; Garre-Olmo et al., 2002; Logsdon et al., 2002; Thorgrimsen et al., 2003; Sands et al., 2004; Selwood et al., 2005; Snow et al., 2005; Hoe et al., 2006; 2007; Schiffczyk et al., 2010; Vogel et al., 2006; Banerjee et al., 2009; Conde-Sala et al., 2009; Hurt et al., 2010), including the type of relationship between patient and carer, functional autonomy, cognitive and neuropsychiatric symptoms of the patient, caregiver burden, caregiver depression, patients’ anosognosia, and gradual adjustment to their goals and expectations. However, most studies examining factors associated with QoL in dementia have focused on a limited number of predictors, an isolated feature, or specific population groups, such as patients with dementia living in residential care facilities. In addition, there is some concern that by focusing on one particular area (e.g. cognitive function) other equally important factors associated with QoL in dementia might be neglected (Banerjee et al., 2006; 2009). If we aim to develop more efficacious and targeted interventions to improve the QoL of people with dementia, we will need to enhance our understanding of the factors associated with QoL in this population.

We designed the present study to determine: (1) the agreement in QoL ratings between community-dwelling patients with mild to moderate dementia and family carers; and (2) the factors associated with self-reported and two types of carer-reported QoL ratings: carer–carer perspective and carer–patient perspective. Based on the findings of the studies described above, we hypothesized that patients and carers do not agree in their ratings of QoL, regard- less of the perspective adopted by the carer (i.e. rating as the carer sees it or how the carer believes the patient sees it). We also predicted that QoL ratings by carers, but not patients, would be directly correlated with the cognitive function of patients.

3.3. METHODS

3.3.1. STUDY DESIGN

This study was designed as a cross-sectional study. It was also a stand-alone study, i.e. not part of a larger study designed for another purpose.

3.3.2. PARTICIPANTS AND SETTING

This project reports data on 80 patients with AD and their carers. We recruited 80
community-dwelling patients with the diagnosis of probable AD of mild/moderate severity (Perneczky et al., 2006) to NINCDS-ADR D criteria (McKhann et al., 1984). All participants had a total score of 10 or more on the Mini-Mental State Examination (MMSE; Folstein et al., 1975) at the time of recruitment. The carer had to have regular contact with the patient with AD (i.e. at least three times per week over the preceding year). Recruitment was conducted from various sources, such as memory clinics in the Perth metropolitan area and advertisements in the local media.

We excluded from participation people with a positive history of alcohol or substance abuse (APA, 1994), and those with a medically unstable illness that could compromise survival (such as metastatic cancer). Participants with AD could be taking cholinesterase inhibitors or memantine, but could not be participating concurrently in an experimental study of medications for AD. All participants were competent in written and spoken English.

The Ethics Committees of the University of Western Australia, Royal Perth Hospital, Mercy Hospital, and Western Australian Department of Health–NMAHS Mental Health approved the study protocol. All participants and their carers provided written informed consent, and the project was conducted in accordance with the Helsinki Declaration of Human Rights.

3.3.3. OUTCOME MEASURE

The QoL-AD was the primary outcome measure of this study (Logsdon et al., 1999; 2002). The QoL-AD is a short, easy to administer, widely used Health Related Quality of Life (HR-QoL) instrument for the assessment of people with dementia that has well-established psychometric properties (Logsdon et al., 2002; Thorgrimsen et al., 2003; Whitehouse et al., 2003). The scale is composed of 13 items that measure different domains of functioning, selected to reflect relevant domains of the QoL of older adults. Each item offers four possible answers that range from scores of 1 (“poor”) to 4 (“excellent”), producing a total score ranging from 13 to 52, where higher scores indicate better QoL. Patient and carer versions are available. Item 7 “Marriage” of the QoL-AD did not apply in this sample, because 36% of the participants were widowed. For that reason, this item was not included in the total score in this study.

In order to delineate between different carer perspectives (Pickard and Knight, 2005), we asked every carer to complete the QoL-AD carer version in two different ways: carer–patient perspective and carer–carer perspective. The instructions of the
original carer form of the QoL-AD (Logsdon et al., 1999) are not explicit regarding which perspective the carer should use to ascribe his/her rating. That is, the instructions are as follows: “Please think about each item, and rate your relative’s current quality of life in each area.” Therefore we used two carer forms for each carer: one for the carer–patient perspective (the carer rating the scale as he/she believes the patient would rate it) and one for the carer–carer perspective (the carer rating the scale as they see it).

To avoid a priming effect, the two forms were both handed out simultaneously (or put on the desk in front of the carer), and instructions (also printed on top of each form) were read aloud as follows: “The following questions are about your relative’s quality of life. When thinking about your relative’s quality of life, there are different aspects you can think of, some of which are listed below, like his/her physical health (point to item 1). Please think about each item. We would like you to rate these items in two different ways: one, how you think your relative would rate his/her current quality of life, and two, how you rate your relative’s quality of life, so your opinion about his/her quality of life. There are no right or wrong answers; the answers on one form might be different from the other, the answers might be the same.” In addition, the patient and their carer were assessed separately.

3.3.4. EXPLANATORY VARIABLES

We collected demographic, lifestyle, and clinical information from participants and their carers, including age, gender, country of birth, education, marital status, number of children born alive, living arrangements (alone, living with others than the carer, living with the carer), religious practice, hobbies, involvement in community activities, use of medication, medical conditions, alcohol use and smoking, falls in the last six months, visit(s) to general practitioner (GP) or hospital, admission to hospital in the last six months, and sensory impairment (hearing and vision).

In addition, we assessed participants with the following instruments:

- Cambridge Cognitive Examination of the Elderly (CAMCOG-R; Roth et al., 1998): the CAMCOG-R is a widely used neuropsychological test that assesses various aspects of orientation, memory, language, praxis, attention, and executive function. Possible scores range from 0 to 105, with higher scores indicating better cognitive function.
- Hospital Anxiety and Depression Scale (HADS, Zigmond and Snaith, 1983): the
HADS has robust psychometric properties for the assessment of symptoms of depression (HADS-D) and anxiety (HADS-A) in people of all ages (e.g. Mykletun et al., 2001), including those with medical comorbidity (Flint and Rifat, 2002). Reliability has been shown in a range of settings, and there is evidence that it is a suitable measure of anxiety and depression in populations of older adults with or without cognitive impairment or dementia (Clare et al., 2002; Richmond et al., 2011).

- Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE, Jorm, 1994; Knafelc et al., 2003): the IQCODE was designed to measure the severity of cognitive and functional decline of the patient according to the subjective view of an informant. The IQCODE has good internal consistency, reliability, and face validity (Jorm and Jacomb, 1989; Jorm, 1994).

- Guidelines for the Rating of Awareness Deficits (GRAD, Verhey et al., 1993; Zanetti et al., 1999): the GRAD is a scale designed to measure awareness of memory and other cognitive deficits. Through a four-question structured interview and open conversation, the physician rates insights from 1 to 4, with lower scores implying lower insight. The scale has good psychometric properties (Verhey et al., 1993).

- Anosognosia Questionnaire (AQ, Migliorelli et al., 1995; Starkstein et al., 2006): this is a 30-item questionnaire divided into two sections. The first assesses performance in basic activities of daily living (BADL) and instrumental activities of daily living (IADL). The second examines changes in mood and behavior. Two forms of the AQ are used: Form A is independently answered by the patient, Form B by the carer. The final score is obtained by subtracting the scores on Form B from Form A. Thus, positive scores indicate that the caregiver rated the patient as more impaired than the patient himself/herself.

- Katz’s Activities of Daily Living scale (ADL; Katz et al., 1963; Katz, 1983): this is a widely used scale to measure basic activities (including personal care, clothing, moving, going to the toilet, eating) as reported by the carer. Each scale item is rated as “independent,” “needs assistance,” and “dependent,” with higher scores indicating greater dependence.

- Lawton and Brody’s (1969) IADL assessment scale: this was used to assess abilities in instrumental activities of daily living (IADL), such as making phone calls, shopping, driving, and using money, according to an informant. This measure has good validity (e.g. Vittengl et al., 2006). Again, each scale item is rated as “independent,” “needs assistance,” and “dependent,” with higher scores indicating greater dependence.
• Neuropsychiatric Inventory (NPI; Cummings et al., 1994; Cummings, 1997): the NPI is a widely used interviewer-rated scale for rating behavioral and psychological symptoms of dementia (BPSD). The NPI consists of 12 subscales that assess the frequency and severity of delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, irritability, disinhibition, aberrant motor activity, night-time behavior disorder, and appetite or eating change. The score of each subscale is calculated by multiplying the frequency (range 1–4) by the severity (range 1–3), and the sum yields an overall NPI score (range: 0–144). The NPI carer distress subscale (NPI-D) provides a quantitative measure of the distress experienced by carers (ranging from 0 “not at all,” to 5 “very severely or extremely”) in each domain assessed (Kaufer et al., 1998). The NPI has good psychometric properties (Cummings, 1997).

3.3.5. Procedures
We posted the study questionnaire, as well as the HADS, IQCODE, AQ, ADL, and IADL scales to participants for completion prior to a face-to-face assessment, which took place at the hospital or the home of participants (whichever was the most convenient for participants). During the face-to-face assessment, responses to each of the posted questionnaires were checked for completeness and the QoL-AD, GRAD, NPI, and CAMCOG-R were administered. The QoL-AD was administered with the patient and the carer separately to avoid awareness of each other’s answers.

3.3.6. Statistical methods
This project was originally designed as a hypothesis generating study. The aim was to identify potentially modifiable factors associated with QoL in AD that could be targeted by interventions. We provisionally estimated, based on the findings of previous studies (Logsdon et al., 2002; Edelman et al., 2005; Vogel et al., 2006; Hoe et al., 2007), that the association between cognitive function and QoL scores would be moderate to poor for the patient ($r = 0.15$) and moderate ($r = 0.45$) for the carer. With $\alpha$ of 5% (two-tailed) and power of 80%, we calculated that we would need a sample size of 74 participants. We recruited 80 people with AD.

Continuous variables were described by their mean and standard deviations, and categorical variables by their count and proportions. We logged or squared continuous variables whenever appropriate. For further analyses, the following variables were square transformed: HADS Anxiety, HADS Depression, NPI total score, and NPI burden-of-
care subscore. The IQCODE was log transformed. Variables at baseline were compared using Student’s t-tests or Pearson’s $\chi^2$ statistics. Pearson’s correlations were computed to assess the association between self- and carer-ratings of the QOL-AD total score, demographic variables, and other exposure measures. The guidelines of the original QoL-AD scale (Logsdon et al., 1999) recommend that the total score should be the sum of patients’ ratings multiplied by two and carers’ ratings multiplied by one. However, in order to compare the three different perspectives in our study, all ratings were kept separate.

Bland-Altman plots were generated to guide the interpretation of agreement (defined as within the range of 1.96 SD) between self-reported and carer-reported ratings of QoL, by visualizing the distribution of all the ratings. A series of stepwise backwards regression analyses were performed, with a 0.05 level of significance as level of removal from the model. Case complete analysis was conducted, as the small number of missing values did not warrant imputation methods.

Data were analyzed using the SPSS software statistical package (version 11.0, SPSS Inc, USA) and STATA (version 10.1, StataCorp, 2009).

3.4. RESULTS
The mean age of our 80 patients with AD was 78.3 years (SD 7.9; range 56–92), 67.5% were women, and 75% lived with their carer. The mean age of the carers was 66.6 years (SD 14.5) and 57.5% were women. The demographic and clinical characteristics of participants are summarized in Table 3.1.

3.4.1. AGREEMENT ON HRQoL RATINGS
The mean total QoL-AD score by self-rating (mean ± standard deviation; 34.7 ± 5.3) was higher than the carer–carer rating (29.5 ± 5.4; t-paired = 7.04, $p < 0.001$). The mean total QoL-AD score by self-rating was also higher than the carer–patient rating (32.1 ± 6.1; t-paired = 3.91, $p < 0.001$). Carer–carer ratings were lower than carer–patient ratings (t-paired = 4.60, $p < 0.001$).
Table 3.1. Characteristics of the AD patients and their carers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient</th>
<th>Carer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: mean (SD)</td>
<td>78.3 (7.9)</td>
<td>66.6 (14.5)</td>
</tr>
<tr>
<td>Sex: female (%)</td>
<td>67.5%</td>
<td>57.5%</td>
</tr>
<tr>
<td>Born overseas: n (%) yes</td>
<td>37 (46.2%)</td>
<td>61.4%</td>
</tr>
<tr>
<td>Education in years: mean (SD)</td>
<td>10.2 (2.2)</td>
<td>11.1 (12.6)</td>
</tr>
<tr>
<td>Education, 10 years completed: (%) yes</td>
<td>56.3%</td>
<td>5.0 (3.8)</td>
</tr>
<tr>
<td>Marital status: married; widowed; divorced: (%)</td>
<td>63.8%; 30%; 5%</td>
<td>5.7 (3.5)</td>
</tr>
<tr>
<td>Number of children: mean (SD)</td>
<td>3.3 (1.8)</td>
<td>4.7 (3.3)</td>
</tr>
<tr>
<td>Hearing, using hearing aids: n (%) yes</td>
<td>26 (32.5%)</td>
<td>0.7 (1.4)</td>
</tr>
<tr>
<td>Vision, using glasses: n (%) yes</td>
<td>79 (98.7%)</td>
<td>7.5 (3.5)</td>
</tr>
<tr>
<td>Driving car: n (%) yes</td>
<td>25 (31.3%)</td>
<td></td>
</tr>
<tr>
<td>Practicing religion: n (%) yes</td>
<td>37 (46.3%)</td>
<td></td>
</tr>
<tr>
<td>Practicing hobbies: n (%) yes</td>
<td>43 (53.8%)</td>
<td></td>
</tr>
<tr>
<td>Involvement in community activities: n (%) yes</td>
<td>32 (40%)</td>
<td></td>
</tr>
<tr>
<td>Current smoking: n (%) yes</td>
<td>3 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Current use of alcohol: n (%) yes</td>
<td>59 (73.7%)</td>
<td></td>
</tr>
<tr>
<td>Falls last 6 months: n (%)</td>
<td>14 (17.5%)</td>
<td></td>
</tr>
<tr>
<td>Visit to GP last 6 months: (0; 1–3; 4–6; 7+ %)</td>
<td>3.8; 43.8; 37.5; 15%</td>
<td></td>
</tr>
<tr>
<td>Visit or admission to hospital last 6 months: n (%)</td>
<td>26 (32.5%)</td>
<td></td>
</tr>
<tr>
<td>Number of medications: mean (SD)</td>
<td>5.6 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Number of medications: (0; 1–2; 3–4; 5+ %)</td>
<td>2.5; 13.8; 30; 53.8%</td>
<td></td>
</tr>
<tr>
<td>Use of anti-AD medication: % yes</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Use of psychotropic drugs (excluding anti-AD): % yes</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>CAMCOG-R: mean (SD)</td>
<td>63.5 (14.9)</td>
<td></td>
</tr>
<tr>
<td>IQCODE: mean (SD)</td>
<td>4.2 (0.6)</td>
<td></td>
</tr>
<tr>
<td>GRAD: mean (SD)</td>
<td>3.1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Anosognosia questionnaire by patient</td>
<td>48.8 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Anosognosia questionnaire by carer</td>
<td>61.4 (14.2)</td>
<td></td>
</tr>
<tr>
<td>NPI</td>
<td>11.1 (12.6)</td>
<td></td>
</tr>
<tr>
<td>HADS anxiety: mean (SD)</td>
<td>5.0 (3.8)</td>
<td></td>
</tr>
<tr>
<td>HADS depression: mean (SD)</td>
<td>4.7 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Katz’ ADL: mean (SD)</td>
<td>0.7 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Lawton’s IADL: mean (SD)</td>
<td>7.5 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Carer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: mean (SD)</td>
<td>66.6 (14.5)</td>
<td></td>
</tr>
<tr>
<td>Sex: female (%)</td>
<td>57.5%</td>
<td></td>
</tr>
<tr>
<td>Carer type, spouse; other family; friend: (%)</td>
<td>61.4%; 38.6%; 0%</td>
<td></td>
</tr>
<tr>
<td>Living together: (%) yes</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>NPI burden-of-care subscore: mean (SD)</td>
<td>6.7 (7.1)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AD = Alzheimer’s disease; GP = general practitioner; CAMCOG-R = Cambridge Cognitive Examination of the Elderly Revised; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; GRAD = Guidelines for the Rating of Awareness Deficits; NPI = Neuropsychiatric Inventory; HADS = Hospital Anxiety and Depression Scale; Katz ADL = Katz’ Activities of Daily Living scale; IADL = Lawton and Brody’s Instrumental Activities of Daily Life assessment scale.

Figures 3.1a and 3.1b show the agreement between patients and their carers in the rating of the QoL-AD using Bland-Altman plots. The results demonstrate that there was acceptable agreement in the rating of the QoL-AD between patients and their carers (i.e.
within the ±1.96 SD range). Only 2/79 self-ratings (i.e. 2.5%) did not agree with the carer–carer ratings (i.e. fell outside the ±1.96 SD range, see Figure 3.1a), and 4/80 (5%) self-ratings did not agree with the carer–patient ratings (Figure 3.1b). However, there was a systematic difference in the rating of the QoL-AD, with patients rating their own QoL more highly than their carers (or, vice-versa, carers rating the QoL of patients systematically lower than the patients themselves).

Figure 3.1a. Bland-Altman plot for agreement on the QoL-AD total score between AD patients and carer with carer–carer perspective.

Figure 3.1b. Bland-Altman plot for agreement on the QoL-AD total score between AD patients and carer with carer–patient perspective.

A difference of 0 would indicate perfect agreement, as indicated by the red line. The average difference between patient and carer is indicated with a blue line. The ±1.96 SD and –1.96 SD area are indicated with green lines. Item 7 (QoL in relation to “Marriage”) was not included in the total score of the QoL-AD score, because “Marriage” (or other form of relationship) was not applicable to 36% of the participants with AD. Abbreviations: Pt = patient with Alzheimer’s disease; PrPr = carer with carer–carer perspective; PrPt = carer with carer–patient perspective; QoL-AD ts = QoL-AD assessment scale total score.
3.4.2. **Factors associated with HRQoL ratings**

### 3.4.2.1. *Univariate analyses*

The independent associations between QoL ratings and exposure factors are summarized in Table 3.2. Apart from “living together” for the carer–carer ratings, demographic factors were not associated with QoL. Cognitive function, as measured by the CAMCOG-R, was not associated with self-ratings of QoL, but showed a significant positive correlation with both carer ratings. We also found that self-reported QoL ratings were inversely associated with anxiety, depression, NPI, and GRAD scores. For the carer–carer ratings of QoL, we found an inverse association with the IQCODE, HADS depression, and Katz ADL scores. The carer–patient QoL ratings were inversely associated with HADS depression, NPI, ADL, and IADL scores, as well as with the number of medications. The carer–patient QoL ratings showed a direct association with the cognitive scores of patients.

### 3.4.2.2. *Multivariate analyses*

We used backwards linear regression to examine the association between measured exposures and QoL ratings (Table 3.3). The final model of the predictors of QoL self-ratings explained 48.3% of the variance ($p < 0.001$). The individual explanatory variables that retained significance in the multivariate model were insight and depression scores (inverse association), and use of anti-dementia drugs (direct association).

The parsimonious model investigating the factors associated with QoL carer–carer ratings explained 44.6% of the variance of the data ($p < 0.001$). QoL ratings showed a direct association with the CAMCOG-R and HADS anxiety scores, and an inverse association with the total number of medications that patients consumed, HADS depression, NPI ratings, and not cohabiting with the patient.

For the carer–patient QoL ratings, the final parsimonious model explained 37.5% of variance of the data ($p < 0.001$). QoL ratings showed a direct association with the CAMCOG-R and NPI burden-of-care, and inverse association with the age of the carer, HADS depression, and NPI scores.

We completed a backwards stepwise regression to determine the variables that were significantly associated with the difference in QoL ratings of patients and carer (carer–carer view). These results are summarized in Table 3.4. CAMCOG-R, NPI, and HADS anxiety scores explained about 31% of the variance of these data.
Table 3.2. Univariate analyses of independent associations between QoL ratings and exposure factors

<table>
<thead>
<tr>
<th>Demographics</th>
<th>By Pt</th>
<th>Carer-Carer perspective</th>
<th>Carer-Patient perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patient in years</td>
<td>-0.01 (-0.15, 0.14)</td>
<td>0.943 (0.02, -0.14)</td>
<td>0.822 (-0.06, -0.23)</td>
</tr>
<tr>
<td>Female patient</td>
<td>1.95 (-0.53, 4.43)</td>
<td>0.122 (0.68, -1.91)</td>
<td>0.602 (0.53, -2.38)</td>
</tr>
<tr>
<td>Years of school education</td>
<td>0.27 (-0.27, 0.82)</td>
<td>0.320 (0.26, -0.29)</td>
<td>0.357 (0.23, -0.41)</td>
</tr>
<tr>
<td>Marital status married</td>
<td>-0.35 (-2.79, 2.11)</td>
<td>0.780 (-1.89, -4.36)</td>
<td>0.132 (1.06, -1.77)</td>
</tr>
<tr>
<td>Female carer</td>
<td>0.92 (-1.46, 3.29)</td>
<td>0.445 (0.82, -1.62)</td>
<td>0.507 (0.39, -3.15)</td>
</tr>
<tr>
<td>Age of carer in years</td>
<td>0.05 (-0.03, 0.13)</td>
<td>0.246 (0.08, -0.01)</td>
<td>0.071 (0.07, -0.16)</td>
</tr>
<tr>
<td>Living together</td>
<td>-0.65 (-3.37, 2.07)</td>
<td>0.636 (-3.36, -6.03)</td>
<td>0.015 (0.47, -2.68)</td>
</tr>
<tr>
<td>Cognitive scores</td>
<td>-0.03 (-0.11, 0.04)</td>
<td>0.400 (0.14, 0.06)</td>
<td>0.000 (0.12, 0.03)</td>
</tr>
<tr>
<td>CAMCOG-R</td>
<td>5.00 (-3.03, 13.04)</td>
<td>0.219 (-11.76, -19.45)</td>
<td>0.003 (2.46, -11.97)</td>
</tr>
<tr>
<td>IQ-CODE (log transformed)</td>
<td>-3.48 (-5.90, -1.06)</td>
<td>0.005 (0.11, -2.48)</td>
<td>0.931 (-0.89, -3.83)</td>
</tr>
<tr>
<td>Awareness</td>
<td>-0.03 (-0.03, 0.14)</td>
<td>0.222 (-0.13, -0.22)</td>
<td>0.002 (0.06, -0.16)</td>
</tr>
<tr>
<td>HADS anxiety (squared)</td>
<td>-2.39 (-3.44, -1.36)</td>
<td>0.000 (-0.41, -1.65)</td>
<td>0.506 (1.14, -2.54)</td>
</tr>
<tr>
<td>HADS depression (squared)</td>
<td>-3.78 (-4.98, -2.58)</td>
<td>0.000 (-2.44, -3.92)</td>
<td>0.002 (3.58, -5.14)</td>
</tr>
<tr>
<td>NPI score (squared)</td>
<td>-0.67 (-1.28, -0.05)</td>
<td>0.035 (-1.11, -1.70)</td>
<td>0.000 (-0.93, -1.63)</td>
</tr>
<tr>
<td>NPI burden-of-care (squared)</td>
<td>-0.73 (-1.56, 0.09)</td>
<td>0.082 (-1.01, -1.83)</td>
<td>0.016 (-0.73, -1.69)</td>
</tr>
<tr>
<td>Functionality</td>
<td>-3.48 (-5.90, -1.06)</td>
<td>0.005 (0.11, -2.48)</td>
<td>0.931 (-0.89, -3.83)</td>
</tr>
<tr>
<td>Katz’ ADL</td>
<td>0.51 (-2.82, 3.84)</td>
<td>0.761 (-4.04, -7.25)</td>
<td>0.014 (-5.14, -8.79)</td>
</tr>
<tr>
<td>Lawton and Brody’s IADL</td>
<td>0.07 (-0.28, 0.41)</td>
<td>0.701 (-0.64, -0.96)</td>
<td>0.000 (-0.57, -0.96)</td>
</tr>
<tr>
<td>Medication</td>
<td>-0.73 (-3.44, -1.36)</td>
<td>0.000 (-2.44, -3.92)</td>
<td>0.002 (3.58, -5.14)</td>
</tr>
<tr>
<td>Number of medications</td>
<td>2.34 (-0.07, 4.76)</td>
<td>0.057 (1.89, -0.62)</td>
<td>0.138 (1.95, -8.88)</td>
</tr>
<tr>
<td>Use of anti-dementia drugs</td>
<td>-1.49 (-3.84, 0.86)</td>
<td>0.209 (-1.17, -3.59)</td>
<td>0.341 (-2.26, -4.95)</td>
</tr>
</tbody>
</table>

Abbreviations: CAMCOG-R = Cambridge Cognitive Examination of the Elderly Revised; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; GRAD = Guidelines for the Rating of Awareness Deficits; AQ = Anosognosia Questionnaire; HADS = Hospital Anxiety and Depression Scale; NPI = Neuropsychiatric Inventory; Katz ADL = Katz’ Activities of Daily Living scale; IADL = Lawton and Brody’s Instrumental Activities of Daily Life assessment scale; CI = confidence interval.
Table 3.3. Final predictive models of three different views on QoL ratings based on stepwise backwards regression analyses

<table>
<thead>
<tr>
<th>Predictor</th>
<th>β Coefficient</th>
<th>R²</th>
<th>Adj. R²</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-ratings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-dementia drugs</td>
<td>2.10</td>
<td>0.458</td>
<td>0.435</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GRAD</td>
<td>-2.94</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS depression(^{1})</td>
<td>-3.43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>49.23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Carer–carer ratings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of medication</td>
<td>-0.32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAMCOG-R</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS anxiety(^{1})</td>
<td>1.49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS depression(^{1})</td>
<td>-1.73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI total score(^{1})</td>
<td>-1.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living together</td>
<td>-3.43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>28.53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Carer–patient ratings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAMCOG-R</td>
<td>0.13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carer age</td>
<td>-0.08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS depression(^{1})</td>
<td>-2.77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI total score(^{1})</td>
<td>-1.97</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI burden-of-care(^{1})</td>
<td>2.28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>35.38</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CAMCOG-R = Cambridge Cognitive Examination of the Elderly Revised; GRAD = Guidelines for the Rating of Awareness Deficits; HADS = Hospital Anxiety and Depression Scale; NPI = Neuropsychiatric Inventory. \(^{1}\) Squared.
Table 3.4. Post-hoc model of difference between self-reported and carer-carer reported QoL ratings based on stepwise backwards regression analyses (parsimonious model)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>β Coefficient</th>
<th>R²</th>
<th>Adj. R²</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td></td>
<td>0.309</td>
<td>0.279</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAMCOG-R</td>
<td>–0.17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t = –3.77, p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS Anxiety (squared)</td>
<td>–2.51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t = –3.73, p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI total score (squared)</td>
<td>0.85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t = 2.28, p = 0.026</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>18.73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t = 5.63, p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CAMCOG-R = Cambridge Cognitive Examination of the Elderly Revised; HADS = Hospital Anxiety and Depression Scale; NPI = Neuropsychiatric Inventory.

Finally, as the QoL-AD includes an item that assesses mood (depression), it is possible that the association between QoL ratings and the HADS-D could have been driven by this overlap. Post-hoc analyses were performed, where we excluded the item “mood” from the QoL-AD total score and reran all predictive models. The associations remained unchanged (data not shown).

We also performed post-hoc analyses to examine the associations of the original QoL-AD composite score with the measured explanatory variables in our dataset. We did this separately for the carer–carer and the carer–patient QoL-ratings. The only significant associations remaining were the HADS depression for both viewpoints and the age of the carer for the carer–carer viewpoint.

3.5. DISCUSSION
The results of the present study led us to reject our first hypothesis that QoL ratings by patients with mild to moderate AD and QoL ratings by their carers show an acceptable level of agreement, although carers systematically underrate QoL compared with patients. We also found that the factors that drive QoL ratings in people with mild to moderate dementia vary according to the rater and his/her perspective: cognitive function is directly correlated with QoL ratings of carers, but not with patients’ QoL ratings, whereas depressive symptoms are inversely associated with QoL ratings of both
patients and carers. In addition, QoL ratings according to the carer–carer perspective are inversely associated with the number of medications consumed by the patient, symptoms of anxiety, and living together, while the carer–patient perspective is inversely associated with the carers’ age and burden of care. The differences between patients’ and carers’ QoL ratings were associated with cognitive scores and neuropsychiatric symptoms.

The findings are limited by some characteristics of the study. First, regarding internal validity, this is an observational cross-sectional study that shows associations rather than causality. Consequently, we cannot dismiss the possibility of reverse causality entirely (e.g., poor QoL causing patients to become depressed). Longitudinal data would be valuable in this regard, as the temporal sequence between exposure and outcome can be observed in a more reliable manner. Secondly, this study had a reasonable sample size (N = 80 AD patients and their carers), but multiple testing may have contributed to produce some chance associations. We would argue, however, that the consistency of our observations with those of other studies suggests this would be an unlikely explanation for our findings (Garre-Olmo et al., 2002; Thorgrimsen et al., 2003; Sands et al., 2004; Snow et al., 2005; Hoe et al., 2006; 2007; Conde-Sala et al., 2009; Schiffczyk et al., 2010). Thirdly, we considered the main effect of variables, but refrained from examining the possible interactions between risk factors because of relatively small numbers.

Regarding the generalizability of our findings, the participants of this study were not randomly selected, i.e., only patients diagnosed with AD with a cognitive severity of mild to moderate (MMSE ≥ 10) were selected, and most were known to the specialized services we approached for recruitment. At this point it is unclear if these results would be equally applicable to people with severe AD living in the community or to those living in residential care facilities.

This study has the merit of having used, for the first time, an approach to analyze the distribution of all QoL ratings of older adults with AD and their carer that goes beyond the absolute concordance of scores. Our finding of a discrepancy in QoL ratings is in line with the findings of other studies (Thorgrimsen et al., 2003; Sands et al., 2004; Ready et al., 2006; Hoe et al., 2007; Conde-Sala et al., 2009). However, the way the ratings behave has not been described with the use of Bland-Altman plots as a visual guide in the interpretation of this discrepancy. With this approach, we were able to demonstrate that carers and patients show acceptable agreement in their ratings (i.e., within ±2 SD), although carers systematically underestimate QoL ratings compared
with the patients. This finding is in line with the suggested disability paradox that we have previously described.

In addition, our results suggest that agreement between raters occurs across the range of mild to moderate dementia. One might therefore expect that changes of scores over time according to patients would be rated in the same direction by carers (i.e. if QoL scores decline according to the patient, they will also decline according to the carer, and vice-versa). Longitudinal studies will be required to confirm such a prediction.

We also used a novel approach to ascertain QoL that allowed carers to rate the perceived QoL of patients using two different perspectives: carer–carer and carer–patient perspectives (Pickard and Knight, 2005). Our results show that the scores yielded by such an approach are not interchangeable, although both agree with the ratings of patients according to Bland-Altman plots. In fact, the demographic and clinical variables associated with these ratings overlap but are not the same. This highlights the need for consistency in the use of raters and of perspectives to ascribe QoL scores to older people with mild to moderate AD.

Our findings suggest that the double weighting of the patient ratings according to the original instructions of the QoL-AD privileges the ratings of the patient as opposed to the carer and might be less informative than using separate ratings. Information about clinical factors that are associated with disparate views of patients and carers is lost in the original administration. It may be more informative, for clinicians and researchers, to use the ratings of patient and carer as complementary and not as a composite score, and to be more explicit about which viewpoint of the carer was used. For example, falling QoL ratings according to the patient might suggest the presence of depressive symptoms, while falling QoL ratings according to the carer might indicate cognitive decline.

The predictive models revealed that self-reported QoL (as measured with the QoL-AD) are inversely associated with depression and insight, and directly associated with the use of anti-dementia drugs. The observed association between QoL and depression is in line with previous studies (Sands et al., 2004; Selwood et al., 2005; Snow et al., 2005; Hoe et al., 2006; 2007; Vogel et al., 2006; Conde-Sala et al., 2009), as is the association with anti-dementia agents (Birks, 2006; Hoe et al., 2007). As previously described by Hoe et al. (2007), the link between self-reported QoL and the use of cholinesterase inhibitors may have been due to reverse causality, and this is an issue that requires further investigation.
Carers’ perspectives of the patients’ QoL was inversely associated with the severity of depressive symptoms (as one of the main predictors) and directly associated with cognitive scores. As already noted by Conde-Sala et al. (2009), previously reported associations with lower QoL ratings – namely apathy, autonomy of ADL, and caregiver burden – could be considered to be related to depression, i.e. depressive symptoms increase functional disability (ADL), increase presence of non-cognitive symptoms, and increase caregiver burden (Garre-Olmo et al., 2002). In many ways, it is not surprising that QoL-AD scores were associated with depression, particularly because one of the 13 items of the QoL-AD measures the perception of QoL in relation to the patient’s mood. Post-hoc analyses were performed in which we excluded the item “mood” from the QoL-AD total score and reran the predictive models. This revealed that the associations remained unchanged, and therefore we can be confident that depression has a significant impact on non-specific aspects of QoL.

With regards to the inverse association of self-reported QoL and insight (or awareness), this finding is in line with the study of Hurt et al. (2010), who showed that insight was related to patient’s perception of QoL. That is, they found that impairment in insight is associated with better self-reported QoL in moderate dementia, but insight was not associated with carer perception of the patient’s QoL. Our data suggest that carers do not seem to consider the degree of awareness as a predictor of patients’ experience of QoL.

Both carer perspectives showed a moderate inverse association between QoL and cognitive scores, in contrast to patients’ self-report. It is possible that patients with AD adapt their expectations as time goes by, and that the link between cognitive function and QoL is not linear or is subject to a threshold effect. The disability paradox (Albrecht and Devlieger, 1999) and the response shift theory (Schwartz et al., 2007) may explain these associations, at least in part. Longitudinal data would be required to determine how changes in cognitive function and insight modulate QoL in people with AD.

We are not aware of a study in this field that included a similar wide range of measurable patient and carer candidate predictors of QoL in mild to moderate AD (i.e. demographic, lifestyle, medical background, cognitive, psychobehavioral, depression, anxiety, insight, (I)ADL factors and burden-of-care). Hoe et al. (2007) also concluded that QoL ratings by patients with AD and carers are different regarding the predictors of reduced QoL, but they restricted their analyses of possible predictors to demographics, ADL, and neuropsychiatric symptoms of AD. Our study included a broader range of
risk factors. Other important differences between the study of Hoe et al. (2007) and our own are: (1) they included AD patients living at home and in 24-hour residential care settings (36.6%) whereas we restricted our participants to community-dwelling people with AD patients; (2) Hoe et al. included AD patients with MMSE scores ranging from 0–29 (mean 14.7, SD 8.3) whereas our participants with AD had MMSE scores of 10 or more (mild to moderate dementia); and (3) we included two different carers’ viewpoints, a strategy that has not been explored in any particular setting. This enabled us to model the contribution of clinically modifiable variables to QoL in mild to moderate dementia from different views.

To conclude, these findings show that mild to moderate community-dwelling AD patients and their carers (regardless of the carer’s perspective used) agree within an acceptable range in their QoL ratings, but with a systematic tendency of higher ratings by patients. Notwithstanding this agreement, the ratings of QoL provided by patients and carers with different perspectives are driven by different factors and, consequently, are not interchangeable. This has implications for research and clinical practice. When conducting research investigating the predictors and effectiveness of clinically targeted interventions on HR-QoL in dementia, it may be necessary to consider the choice of rater and the rater’s perspective. Also, if improved QoL is “the ultimate goal” of our clinical interventions, then the use of different raters may be more informative than a unified composite score.
CHAPTER 4.

DETERMINING THE PREDICTORS OF CHANGE IN HRQOL SELF-RATINGS AND CARER-RATINGS FOR COMMUNITY-DWELLING PEOPLE WITH ALZHEIMER’S DISEASE

4.1. **Abstract**

**Background:** Little is known about how people with dementia perceive their Health Related Quality of Life (HRQoL) as the disease progresses and the factors that drive self- and carer-ratings over time. The aim of this study was to determine the factors that mediate changes in HRQoL ratings by community-dwelling people with Alzheimer's disease (AD) and carers over a period of 18 months.

**Methods:** We completed an 18-month longitudinal study of 80 community-dwelling older adults diagnosed with probable AD of mild or moderate severity (NINCDS-ADRD criteria) and their family carers. The primary outcome of interest was the 18-month change in HRQoL ratings as measured with the Quality of Life-AD (QoL-AD, separately by carer and by self). Explanatory variables included demographics, lifestyle, cognition, awareness, psychopathology, burden-of-care, use of medication and functionality in daily life.

**Results:** We found a significant decline (8.7%, $p = 0.003$) in QoL-AD carer-ratings, but not in self-ratings. The final parsimonious model of predictors of changes in QoL-AD self-ratings explained 22.6% of the variance; only changes on HADS Anxiety retained significance. The final model of predictors of changes in carer-ratings explained 55.0% of the variance: i.e. changes on IQCODE, changes on HADS Depression, practicing hobbies at 18 months, and number of visit(s) or admission(s) to hospital.

**Conclusion:** HRQoL self- and carer-ratings of community-dwelling people with AD do not decline at the same rate over 18 months and changes are associated with different factors. Interventions designed to optimise quality of life of people with AD should consider carefully whose HRQoL ratings they wish to change.

4.2. **Introduction**

As the proportion of cases of dementia in the community increases, it is important to improve our understanding of outcomes that are of clinical relevance to people with dementia and their carers. Quality of life (QoL) is one such an outcome (Banerjee et al., 2009). It is well established that dementia, of which Alzheimer’s disease (AD) is the most frequent cause, affects cognitive functioning, capacity for independent living, mood, behavior control and awareness of developing difficulties and changes. However little is known about how people with dementia perceive their Health Related Quality of Life (HRQoL) as the disease progresses and the factors that drive this subjective
experience over time. Cross-sectional studies have shown that behavioural and psychological symptoms of dementia (BPSD) (Banerjee et al., 2006; Bosboom et al., 2012; Conde-Sala et al., 2009; Hurt et al., 2008; Karttunen et al., 2011; Logsdon et al., 2002; Ready et al., 2004; Selwood et al., 2005; Shin et al., 2005; Tatsumi et al., 2009; Wetzels et al., 2010), exposure to psychotropic drugs (Balard et al., 2001; Wetzels et al., 2010), reduced functional autonomy (Ballard et al., 2001; Conde-Sala et al., 2009), higher burden-of-care (Conde-Sala et al., 2009; Sands et al., 2004), and some demographic characteristics - e.g. younger age of patient (Banerjee et al., 2006); female gender (Conde-Sala et al., 2009) - adversely affect HRQoL in dementia.

Some findings have been inconsistent, which is partly due to the use of different definitions of HRQoL or disparate measures to assess explanatory variables, such as awareness. For example, one study (Vogel et al., 2006) found that in early stages of AD decreased awareness of deficits (as rated by clinician on a categorical three-point scale) was not associated with QoL, while another study (Hurt et al., 2010) showed that insight (as rated by clinician with a dichotomous rating of the question “Do you have problems with memory or thinking?”) was associated with HRQoL self-ratings, but not HRQoL carer-ratings, and the latter only for people with moderate dementia.

There are also inconsistent findings regarding the relationship between HRQoL in dementia and cognition. Some studies (Hurt et al., 2010; Wetzels et al., 2010; Wlodarczyk et al., 2004) have reported a significant direct association between HRQoL and cognitive function (i.e., better cognitive function is associated with better HRQoL and vice-versa), but others have failed to replicate these findings (Banerjee et al., 2006; Selwood et al., 2005; Vogel et al., 2006). For example, Vogel et al. (2006) observed that their 48 participants with early Alzheimer’s disease (MMSE ≥ 20) showed no evidence of association between MMSE scores and HRQoL self-ratings. These conflicting results might have been due to the application of limited measures of cognitive function (e.g. the Mini-Mental State Examination), inclusion in some studies of heterogeneous populations of ‘dementia’ known to have distinctive cognitive profiles (e.g. MCI, frontotemporal dementia, and alcohol-induced amnestic disorder), and inclusion in some studies of people with AD at different stages of dementia. The results of randomized placebo-controlled trials of cholinesterase inhibitors suggest that active treatment improves HRQoL ratings. However, according to a systematic review (Takeda et al., 2006), data on self-rated HRQoL were reported by only three donepezil trials, and none of them used a validated scale for the assessment of quality of life.
We also know very little about the natural history of HRQoL in dementia and the variables that mediate HRQoL change over time (Heggie et al., 2011; Lyketsos et al., 2003; Missotten et al., 2007; Selwood et al., 2005; Tasumi et al., 2009). Interestingly, currently available longitudinal data with different instruments indicate that people with dementia experience no or only a small change in HRQoL ratings over time (Heggie et al., 2011; Lyketsos et al., 2003; Selwood et al., 2005; Tasumi et al., 2009), and that changes in HRQoL in dementia do not evolve in a strictly linear manner (Missotten et al., 2007). However, the number of longitudinal studies that explored the change of HRQoL ratings in dementia is small, and their findings are hard to compare, because of the diversity QoL instruments and cognitive measures (Heggie et al., 2011; Tasumi et al., 2009), settings (e.g. long-term care facilities (Lyketsos et al., 2003); various living arrangements (Selwood et al., 2005); non-institutionalized patients in rural and remote areas (Heggie et al., 2011)), and variability in inclusion criteria (e.g. a heterogeneous group of older adults with some form of cognitive deterioration including Mild Cognitive Impairment, Frontotemporal Dementia and Normal Pressure Hydrocephalus (Heggie et al., 2011)). Therefore, we require longitudinal data on a well-defined and homogeneous study population living in a similar setting (e.g. community), that is based on a validated HRQoL measure with established sensitivity to detect change over time.

The question regarding the rater of HRQoL is also relevant. Several studies have reported differences in HRQoL ratings between patients with dementia and their caregivers, with patients’ ratings commonly yielding higher scores than carers’ (Conde-Sala et al., 2009; Sands et al., 2004; Thorgrimsen et al., 2003). However, a recent study showed that people with Alzheimer’s disease and their carers show acceptable agreement in their HRQoL-ratings (i.e. difference between the ratings of AD patients and their carers fall within 1.96 SD of the mean difference of scores), even though their scores are comparatively higher and associated with factors when compared with the ratings of carers (Bosboom et al., 2012). We concluded that self- and carer-ratings are not interchangeable but complementary and should be treated separately.

This longitudinal study was designed to determine the factors that mediate changes in HRQoL ratings by community-dwelling people with AD and carers over a period of 18 months. Based on existing data (Bosboom et al., 2012), we hypothesized that changes in HRQoL scores of people with AD and their carers are associated with different mediating factors. We predicted that (1) changes in HRQoL ratings by carers
would be directly associated with changes in cognitive functioning and instrumental activities of daily living and inversely associated with changes in BPSD and carer’s burden-of-care and; (2) that changes in HRQoL ratings by people with AD would be directly associated with changes in BPSD but not with cognitive decline.

4.3. METHODS

4.3.1. STUDY DESIGN

Eighteen-month longitudinal study of the QoL of older adults with Alzheimer’s disease.

4.3.2. PARTICIPANTS AND SETTING

We recruited 80 community-dwelling volunteers with the diagnosis of probable AD according to NINCDS-ADRDA criteria (McKhann et al., 1984). All participants had a total score of 10 or more on the Mini-Mental State Examination (MMSE, Folstein et al., 1975) at the time of enrolment. Family carers had face-to-face contact with their person with AD at least 3 times per week over the preceding year. Participants were recruited from various mental health and aged care services in the Perth metropolitan area.

We excluded people with a positive history of alcohol or substance abuse, and those with a medically unstable illness that could compromise survival (such as metastatic cancer). Participants with AD could be consuming cholinesterase inhibitors or memantine, but could not be participating concurrently in an experimental study of medications for AD. All participants were competent in written and spoken English.

Assessments were conducted between November 2006 and January 2010. The Ethics Committees of the University of Western Australia, Royal Perth Hospital, Mercy Hospital, and Western Australian Department of Health - NMAHS Mental Health approved the study protocol. All participants and their carers provided written informed consent, and the project was conducted in accordance with the Helsinki Declaration of Human Rights.

4.3.3. OUTCOME MEASURE

The primary outcome of interest was the 18-month change in HRQoL ratings as measured with the Quality of Life-AD (QoL-AD. Logsdon et al., 1999; 2002). The QoL-AD is a brief and widely used HRQoL scale for the assessment of people with dementia, which has well-established psychometric properties (Logsdon et al., 2002; Thorgrimsen et al., 2003) and is considered the measure of choice to assess the impact
of interventions in dementia care (Moniz-Cook et al., 2008). In the longitudinal study by Logsdon et al. (2002), 155 of the 177 patients interviewed were able to complete the QOL-AD. Mean MMSE for non-completers was 4.1 compared to 18.1 for completers (range 4 – 29). The scale is composed of 13 items that measure different domains of functioning, selected to reflect relevant domains of the HRQoL of older adults. Each item offers 4 possible answers that range from 1 (‘poor’) to 4 (‘excellent’), producing a total score that can range from 13 to 52 – higher scores indicate better HRQoL. Patient and carer versions are available. For the carer-ratings the carers were asked to rate the HRQoL scale as they see it, according to their opinion. We have previously shown that QoL-AD ratings of people with AD and carers provide valuable information when used separately, not as a composite score (Bosboom et al., 2012). Therefore the self-ratings and carer-ratings were treated as separate outcome measures and not as a composite score. Item 7, “Marriage”, of the QoL-AD was not used in this study because 36% of the participants were widowed or not in a relationship. We calculated the percentage of the maximum QoL-AD score (%MaxSe) by dividing the total raw score by the maximum scale score and multiplying this figure by 100.

4.3.4. EXPLANATORY VARIABLES
We collected information on gender, country of birth, education, marital status, and number of children born alive. At the baseline and the 18-month assessment we asked participants about their lifestyle and clinical information, including living arrangements (alone, living with others than the carer, living with the carer), religion practice, hobbies, involvement in community activities, use of medication, medical conditions, alcohol use and smoking, falls during the preceding 6 months, visit(s) to (General Practitioner (GP) or hospital, admission to hospital over the past 6 months, and sensory impairment (hearing and vision). Participants with AD and their carers compiled a list of all prescription and non-prescription medications used by the person with AD during the past month. Medications were coded according to the World Health Organization Anatomical, Therapeutic, and Chemical (ATC) Classification System. We considered that participants with AD were subject to polypharmacy if they consumed more than 5 medications per day on a regular basis (Gnjidic et al., 2012). Psychotropic drugs were categorised as follows: any psychotropic (ATC-codes N05 and N06), antipsychotics (N05A), anxiolytics (N05B), hypnotics (N05C), and antidepressants (N06A).
Other study measures completed at the baseline and the 18-month assessments included:

- The Cambridge Cognitive Examination of the Elderly, revised version (CAMCOG-R, Rother et al., 1998). The CAMCOG-R is a widely used neuropsychological test that assesses various aspects of orientation, memory, language, praxis, attention and executive function. The CAMCOG-R can be divided into 10 different subscores, each covering a specific cognitive domain: orientation, language (comprehension and expression), memory (recent, remote, and new learning), attention/calculation, praxis, abstract thinking, and perception. Total scores on the CAMCOG-R range between 0 (severe cognitive impairment) and 105 (no cognitive impairment). To enhance the assessment of executive function, two additional items measuring mental flexibility were added. Based on combined scores of the verbal item ‘ideational fluency’, the non-verbal item ‘visual reasoning’, and two items from the original CAMCOG, the verbal fluency item (naming animals) and the ‘abstract reasoning’ item, a separate executive function score was derived. Performance on these two new items did not, however, contribute to the total CAMCOG-R score.

- Hospital Anxiety and Depression Scale (HADS, Zigmond et al., 1983). The HADS has robust psychometric properties for the assessment of symptoms of depression (HADS-D) and anxiety (HADS-A) in people of all ages, including those with medical comorbidity (Flynt & Rifat, 2002; Mykletun et al., 2010). Reliability has been shown in a range of settings, and there is evidence that it is a suitable measure of anxiety and depression in populations of older adults with or without cognitive impairment or dementia (Clare et al., 2002; Richmond et al., 2011; Wands et al., 1990).

- Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE, Jorm, 1994, Knafelc et al., 2003). The IQCODE was designed to measure the severity of cognitive and functional decline of participants with AD according to the subjective view of the informant. The IQCODE has good internal consistency, reliability and face-validity (Jorm, 1989; 1994).

- Two measures of awareness were employed. Firstly, the Guidelines for the Rating of Awareness Deficits (GRAD, Verhey et al., 1983; Zanetti et al., 1999) was administered. The GRAD is a scale designed to measure awareness of memory and other cognitive deficits. Through a four-question structured interview and open conversation, the clinician rates insight in a score range from 1 to 4, lower scores
implying lower insight. The scale has good psychometric properties (Verhey et al., 1993). The second measure of awareness administered was the Anosognosia Questionnaire (AQ, Migliorelli et al., 1995; Starkstein et al., 2006). This is a 30-item questionnaire divided into two sections. The first assesses performance in basic activities of daily living (bADL) and instrumental activities of daily living (iADL). The second examines changes in mood and behaviour. Two forms of the AQ are used: form A is independently answered by the patient and form B by the carer only. The final score is obtained by subtracting the scores on form B from A. Thus, positive scores indicate that the caregiver rated the patient as more impaired than the patient himself/herself.

- **Katz’ Activities of Daily Living scale (ADL, Katz et al., 1963; 1983).** This is a widely used scale that measures basic activities of daily living (including personal care, clothing, moving, going to the toilet, eating) as reported by a carer. Each scale item is rated as ‘independent’, ‘needs assistance’ and ‘dependent’, with higher scores indicating greater dependence.

- **Lawton and Brody’s instrumental activities of daily living (IADL) assessment scale (Lawton & Brody et al., 1969).** This was used to assess abilities in IADL, such as ability to complete phone calls, shopping, driving and using money according to an informant. This measure has good validity (Vittengl et al., 2006). Again, each scale item is rated as ‘independent’, ‘needs assistance’ and ‘dependent’, with higher scores indicating greater dependence.

- **Neuropsychiatric Inventory (NPI, Cummings et al., 1994; 1997).** The NPI is a widely used interviewer-rated scale for rating Behavioral and Psychological Symptoms of Dementia (BPSD). The NPI consists of 12 subscales that assess the frequency and severity of delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, irritability, disinhibition, aberrant motor activity, nighttime behavior disorder, and appetite or eating change. The score of each subscale is calculated by multiplying the frequency (range 1–4) by the severity (range 1–3), and the sum yields an overall NPI score (range: 0–144). The NPI carer distress subscale (NPI-D) scale provides a quantitative measure of the distress experienced by carers (ranging from 0 ‘not at all’, to 5 ‘very severely or extremely’) in each domain assessed (Kaufer et al., 1998). The NPI has good psychometric properties (Cummings et al., 1997).
4.3.5. PROCEDURES
We posted the study questionnaire, as well as the HADS, IQCODE, AQ, ADL and IADL scales to participants for completion prior to a face-to-face assessment. During the face-to-face assessment, responses to each of the study questionnaires were checked for completeness and the QoL-AD, GRAD, NPI, and CAMCOG-R were administered. The QoL-AD was administered with the participant with AD and the carer separately. The same procedures were used for the 18-month assessment. The rationale for the choice of an 18 months interval was that a more common interval of 6 months might be too short for an observational study without an intervention, and because of the evidence that cognitive function in this population declines significantly during this period of time (Roth et al., 1998).

4.3.6. STATISTICAL ANALYSES
Continuous variables were described by their mean and standard deviations, and categorical variables by their count and proportions. We transformed continuous variables, whenever necessary, to complete parametric analyses. Unpaired data were compared using Student’s t-tests for continuous variables, or Pearson’s chi-square ($\chi^2$) for categorical variables. Fisher’s Exact Test was applied to 2X2 tables when the number in one or more of the cells was < 5. Intra-individual differences over time were investigated with paired t-tests and McNemar chi-square tests. We performed a series of regression analyses to investigate the change in exposures associated with 18-month changes in QoL ratings (using p>0.05 for removal of variables from the model). Stepwise backward linear regression was performed to examine the association between the measured exposures and the changes in QoL ratings for all explanatory variables identified with a p-value of < 0.05 in the univariate analyses. This approach enabled us to model the independent contribution of measured factors on change of HRQoL ratings according to both the patient and his/her carer. Alpha was set at 5% and all statistical tests reported are two-tailed. The data were managed and analyzed with STATA version 12.1 (StataCorp, College Station, TX).

4.4. RESULTS
4.4.1. PARTICIPANTS WITH AD AND CARERS AT BASELINE
The mean age of the 80 participants with AD was 78.3 years (± Standard Deviation 7.9; range 56-92), 67.5% were women, and 75% lived with their carer. The mean age of the
family carers was 66.6 years (± 14.5), 61.4% of them were spouses, and 57.5% were women. The mean number of years in education of people with AD was 10.2 (± 2.2) and 56.3% had completed a minimum of 10 years of education. The flow of participants during the 18 months of follow-up is presented in Figure 4.1.

**Figure 4.1.** Flow of participants during the 18 months of follow-up of the older adults diagnosed with Alzheimer’s disease. Assessments took place at baseline and after 18 months.
4.4.2. CLINICAL CHARACTERISTICS AT BASELINE AND 18-MONTH FOLLOW UP

The demographic and clinical characteristics of participants with AD who completed both the baseline and follow-up assessments (n = 47) are summarized in Table 4.1. By 18 months, 6 participants with AD (11.5%) had relocated to a residential aged care facility.

Table 4.1. Comparison of the clinical characteristics of participants with AD at baseline and 18-month follow up assessments (n = 47)

<table>
<thead>
<tr>
<th>n</th>
<th>Baseline assessment</th>
<th>18-month assessment</th>
<th>p&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject related – lifestyle and medical background</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Practicing hobbies, n (%)</td>
<td>3</td>
<td>25 (56.8%)</td>
<td>22 (50%)</td>
</tr>
<tr>
<td>Involvement community activities, n (%)</td>
<td>3</td>
<td>19 (43.2%)</td>
<td>10 (22.7%)</td>
</tr>
<tr>
<td>Driving car, n (%)</td>
<td>3</td>
<td>15 (34.1%)</td>
<td>4 (9.1%)</td>
</tr>
<tr>
<td>Hearing, i.e. using hearing aids, n (%)</td>
<td>4</td>
<td>3 (6.9%)</td>
<td>2 (4.7%)</td>
</tr>
<tr>
<td>Vision, i.e. using glasses, n (%)</td>
<td>3</td>
<td>44 (100%)</td>
<td>44 (100%)</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>4</td>
<td>1 (2.3%)</td>
<td>3 (6.9%)</td>
</tr>
<tr>
<td>Current use of alcohol, n (%)</td>
<td>6</td>
<td>29 (70.7%)</td>
<td>29 (70.7%)</td>
</tr>
<tr>
<td>Falls last 6 months, n (%)</td>
<td>4</td>
<td>9 (20.9%)</td>
<td>14 (31.8%)</td>
</tr>
<tr>
<td>Visit to GP last 6 months, i.e. &gt;4 visits, n (%)</td>
<td>3</td>
<td>23 (52.3%)</td>
<td>38 (86.4%)</td>
</tr>
<tr>
<td>Visit(s) or admission(s) hospital last 6 m, n (%)</td>
<td>3</td>
<td>15 (34.1%)</td>
<td>15 (34.1%)</td>
</tr>
<tr>
<td>Number of medications, mean (SD)</td>
<td>2</td>
<td>5.9 (3.5)</td>
<td>6.0 (3.3)</td>
</tr>
<tr>
<td>Polypharmacy, i.e. ≥5 meds, n (%)</td>
<td>2</td>
<td>27 (61.4%)</td>
<td>29 (65.9%)</td>
</tr>
<tr>
<td>Use of anti-Alzheimer medication&lt;sup&gt;b&lt;/sup&gt;, n (%)</td>
<td>2</td>
<td>30 (66.7%)</td>
<td>29 (64.4%)</td>
</tr>
<tr>
<td>Use of psychotropic drugs (excl. anti-AD), n (%)</td>
<td>2</td>
<td>23 (51.1%)</td>
<td>22 (48.9%)</td>
</tr>
<tr>
<td>Subject related – cognition, awareness, BPSD, functional independence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAMCOG-R, mean (SD)</td>
<td>1</td>
<td>63.2 (12.1)</td>
<td>48.9 (19.8)</td>
</tr>
<tr>
<td>IQCODE, mean t (SD)</td>
<td>6</td>
<td>68.9 (8.2)</td>
<td>71.9 (8.5)</td>
</tr>
<tr>
<td>GRAD, mean (SD)</td>
<td>0</td>
<td>3.2 (0.5)</td>
<td>2.6 (0.5)</td>
</tr>
<tr>
<td>AQ self ratings, mean (SD)</td>
<td>10</td>
<td>47.9 (9.3)</td>
<td>49.5 (15.4)</td>
</tr>
<tr>
<td>AQ carer ratings, mean (SD)</td>
<td>4</td>
<td>60.8 (11.4)</td>
<td>70.3 (13.9)</td>
</tr>
<tr>
<td>NPI, mean (SD)</td>
<td>1</td>
<td>9.3 (11.8)</td>
<td>13.1 (16.3)</td>
</tr>
<tr>
<td>HADS Anxiety, mean (SD)</td>
<td>3</td>
<td>5.2 (3.9)</td>
<td>5.3 (3.3)</td>
</tr>
<tr>
<td>HADS Depression, mean (SD)</td>
<td>3</td>
<td>4.6 (3.3)</td>
<td>5.3 (3.5)</td>
</tr>
<tr>
<td>Katz’ ADL, mean (SD)</td>
<td>1</td>
<td>0.4 (0.9)</td>
<td>1.7 (1.9)</td>
</tr>
<tr>
<td>Lawton’s IADL, mean (SD)</td>
<td>4</td>
<td>6.6 (3.2)</td>
<td>10.2 (3.4)</td>
</tr>
<tr>
<td>Carer related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI burden of-care subscore mean (SD)</td>
<td>2</td>
<td>5.3 (5.7)</td>
<td>7.8 (8.1)</td>
</tr>
</tbody>
</table>

Abbreviations: AQ, Anosognosia Questionnaire; BPSD, Behavioural and Psychological Symptoms of Dementia; CAMCOG-R, Cambridge Cognitive Examination of the Elderly Revised; GRAD, Guidelines for the Rating of Awareness Deficits; HADS, Hospital Anxiety and Depression Scale; IADL, Lawton and Brody’s Instrumental Activities of Daily Life assessment scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; Katz’ ADL, Katz’ Activities of Daily Living scale; NPI, Neuropsychiatric Inventory.<sup>a</sup>

<sup>a</sup>Nominal variables, McNemar’s test (paired proportions, 2-tailed); for continuous variables, non-parametric or paired t test (2-tailed).

<sup>b</sup>I.e. donepezil hydrochloride (Aricept), rivastigmine (Exelon), and galantamine hydrobromide (Reminyl). Both at baseline and follow-up none of the participants were taking tactrine (Cognex) or memantine (Ebixa); none of the participants was taking rivastigmine (Exelon) at follow-up.

<sup>c</sup>At 18m FU not all of the AD participants were able to complete all self-rated questionnaires, i.e. the AQ by pt n=37; and HADS n=38, which explains the relative high percentage of missing n for the AQ and HADS.
At the end of the follow up period cognitive function, as measured by the CAMCOG-R, had deteriorated \( (p < 0.001) \), as had ADL and IADL \( (p < 0.001) \), and awareness \( (p < 0.001) \). As the CAMCOG-R encompasses all the MMSE items, we calculated the MMSE total scores, which indicated a decline to moderate stage at 18-month follow-up assessment (mean average at baseline for the completers 19.3; ±4.4; at follow-up 15.1; ±5.6; \( p < 0.001 \)). At follow-up there were 9 participants with a MMSE ts <10.

The proportion of participants with AD who were involved in community activities and participants who were driving declined over 18 months time \( (p = 0.007 \) and \( p < 0.001 \) respectively), whereas the number of visits to GPs during the preceding 6 months increased \( (p < 0.001) \). At the 18-month assessment the NPI burden-of-care ratings were higher compared with baseline \( (p = 0.029) \).

**Figure 4.2.** This box plot shows the change of QoL-AD according to the ratings of participants with AD and their carers, i.e. at baseline and at 18 months assessments. Paired t-tests comparing QoL-AD (i.e. percentage of maximum score) by self-rating at baseline and 18 months showed no significant change \( (-1.2 \pm 10.2, 95\%CI -1.8, 4.2; p = 0.427) \), but comparing QoL-AD by carer-ratings showed a significant decline \( (-5.4 \pm 11.4 95\%CI 1.9, 8.8; p = 0.003) \).
4.4.3 QoL-AD RATINGS

Data for participants with AD who completed both the baseline and follow-up assessments (n = 47) showed a significant decline (8.7%, p = 0.003) in carer-reported QoL-AD ratings (%Max Score) (mean baseline 62.2 ± 10.5; mean 18-months 56.8 ± 11.5; t-paired = 3.124, p = 0.003), but not according to self-reported QoL-AD ratings (mean baseline 71.9 ± 11.5; mean 18-months 70.7 ± 10.5; t-paired = 0.802, p = 0.427). The difference between the self-reported and the carer-rated QoL at 18-months was significant (p = 0.001) (Figure 4.2).

4.4.4. FACTORS ASSOCIATED WITH CHANGES IN HRQoL-RATINGS

4.4.4.1. UNIVARIATE ANALYSES

The independent associations between the change in HRQoL ratings and the change in the continuous variables are summarized in Table 4.2. For the variation of changes in self-reported HRQoL ratings, we found an inverse association with change in anxiety (i.e. HADS Anxiety), and with change in depression (i.e. HADS Depression).

<table>
<thead>
<tr>
<th></th>
<th>Change in self-ratings QoL-AD (FU minus BL)</th>
<th>Change in carer-ratings QoL-AD (FU minus BL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95%CI</td>
</tr>
<tr>
<td>Cognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAMCOG-R</td>
<td>0.21</td>
<td>(-0.01, 0.42)</td>
</tr>
<tr>
<td>IQ-CODE</td>
<td>-0.15</td>
<td>(-0.63, 0.34)</td>
</tr>
<tr>
<td>Awareness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRAD clinician’s rating</td>
<td>-0.61</td>
<td>(-5.61, 4.39)</td>
</tr>
<tr>
<td>AQ self ratings</td>
<td>0.17</td>
<td>(-0.09, 0.43)</td>
</tr>
<tr>
<td>AQ carer ratings</td>
<td>-0.22</td>
<td>(-0.49, 0.05)</td>
</tr>
<tr>
<td>BPSD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI*</td>
<td>-0.62</td>
<td>(-2.10, 0.86)</td>
</tr>
<tr>
<td>HADS anxiety*</td>
<td>-6.09</td>
<td>(-9.89, -2.82)</td>
</tr>
<tr>
<td>HADS depression*</td>
<td>-4.27</td>
<td>(-8.16, -0.39)</td>
</tr>
<tr>
<td>Functional independence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Katz’ ADL</td>
<td>0.09</td>
<td>(-1.54, 1.73)</td>
</tr>
<tr>
<td>Lawton’s IADL</td>
<td>0.02</td>
<td>(-0.98, 1.03)</td>
</tr>
<tr>
<td>Burden-of-care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI burden-of-care*</td>
<td>-0.57</td>
<td>(-2.49, 1.36)</td>
</tr>
<tr>
<td>Medication exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of medications</td>
<td>-0.05</td>
<td>(-1.28, 1.18)</td>
</tr>
</tbody>
</table>

Abbreviations: FU, follow up assessment; BL, baseline assessment; AQ, Anosognosia Questionnaire; BPSD, Behavioural Psychological Symptoms of Dementia; CAMCOG-R, Cambridge Cognitive Examination of the Elderly Revised; GRAD, Guidelines for the Rating of Awareness Deficits; HADS, Hospital Anxiety and Depression Scale; HRQOL, health related quality of life; IADL, Lawton and Brody’s Instrumental Activities of Daily Life assessment scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; Katz’ ADL, Katz’ Activities of Daily Living scale; NPI, Neuropsychiatric Inventory; QoL, Quality of life; QoL-AD, Quality of life in Alzheimer’s disease; 95% CI, 95% confidence interval.

*Scores were square-root transformed.
For changes in the carer-ratings, we found a direct association with changes on the CAMCOG-R, and inverse associations with changes on the AQ (as reported by carer), the NPI, the HADS Depression, and the NPI Burden-of-care scores.

Further analyses of the associations between HRQoL ratings and the dichotomous variables at baseline and at 18-months assessments, showed no significant association for the self-reported HRQoL ratings. For the carer-reported HRQoL ratings at baseline we found an inverse association with the use of alcohol by the participant with AD ($p = 0.006$), and an inverse association with the number of visits or admission(s) to hospital in the last six months ($p < 0.001$). For the carer-reported HRQoL at 18-months we found a direct association with practicing hobbies by the participant with AD ($p = 0.049$).

### 4.4.4.2. Multivariate analyses

We used stepwise backward linear regression to examine the association between the measured exposures and the changes in HRQoL ratings for all explanatory variables identified with a $p$-value of $< 0.05$ in the univariate analyses. We did this separately for the changes in self-ratings and carer-ratings on the QoL-AD (Table 4.3).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Predictors</th>
<th>$\beta$ Coefficient</th>
<th>$R^2$</th>
<th>Adjusted $R^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in QoL-AD self-ratings</td>
<td>Increase HADS Anxiety</td>
<td>$-6.09$</td>
<td>$0.2262$</td>
<td>$0.2047$</td>
<td>$0.0025$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$t = -3.24$, $p = 0.003$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in QoL-AD carer-ratings</td>
<td>Increase IQCODE</td>
<td>$-0.41$</td>
<td>$0.5504$</td>
<td>$0.4838$</td>
<td>$0.0002$</td>
</tr>
<tr>
<td></td>
<td>$t = -2.16$, $p = 0.039$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increase HADS Depression</td>
<td>$-4.76$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$t = -3.00$, $p = 0.006$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Practicing hobbies at 18 months</td>
<td>$6.87$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$t = 2.48$, $p = 0.020$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of visit(s) or admission(s) to hospital last 6 months at baseline</td>
<td>$-8.82$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$t = -3.12$, $p = 0.004$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4.3. Final predictive models of change over time in QoL-AD self-ratings and carer-ratings based on stepwise backwards regression analyses**

*Abbreviations: HADS, Hospital Anxiety and Depression Scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; QoL-AD, Quality of life in Alzheimer’s disease.

*Change between baseline and 18-months assessments.*
The final parsimonious model of the predictors of changes in the QoL-AD self-ratings explained 22.6% of the variance (p < 0.003). The only individual explanatory variable that retained significance was changes on HADS Anxiety scores (-6.09, 95%CI -9.89, -2.28, p = 0.003). The final parsimonious model of the predictors of changes in the QoL-AD carer-ratings explained 55.0% of the variance (p = 0.002). The individual explanatory variables that retained significance in the multivariate model were changes on the IQCODE (-0.41, 95%CI -0.79, -0.02, p = 0.039), changes on the HADS Depression (-4.76, 95%CI -8.01, -1.50, p = 0.006), practicing hobbies at 18 months (6.87, 95%CI 1.19, 12.55, p = 0.020), and the number of visit(s) or admission(s) to hospital over the last 6 months at baseline (-8.82 95%CI -14.63, -3.01, p = 0.004).

4.4.5. POST-HOC ANALYSES

Firstly, we performed post-hoc analyses to determine explanatory associations in the subgroup of the participants with AD whose HRQoL-ratings declined compared with those that remained the same or improved. We found that the participants with AD whose self-ratings on the QoL-AD declined during follow up (i.e. 44.7%) showed a significant decline on the AQ by carer-rating (p = 0.042), and a significant increase on NPI scores (p = 0.030) compared with those whose self-rating scores remained the same or improved. No other significant differences were found between these subgroups for the self-ratings.

For the changes in carer-ratings on the QoL-AD, we found that the subgroup of carers whose ratings pointed to a decline in the HRQoL of the participant with AD (i.e. 57.5%) showed evidence of greater decline on the CAMCOG-R (mean change -18.2 ± 13.1; t = -2.35, p = 0.023) compared to the subgroup of carer-ratings that remained the same or improved (-9.1 ± 12.9); less decrease in awareness (GRAD, p=0.048); more cognitive decline as perceived by the carer (AQ by carer, p = 0.009); increase in HADS Depression (p = 0.018); increase on the NPI (p = 0.011); and, a higher burden-of-care (NPI Burden-of-care, p = 0.015). No other significant differences were found between these subgroups for the carer-ratings.

We also performed post-hoc analyses to determine specific characteristics of the participants who did not complete the follow-up assessment and with that the generalizability of our findings by comparing the characteristics at baseline of participants. People with AD who dropped out used more hearing aids (2.7%; p = 0.013) and had higher average IADL ratings (p = 0.019). We also compared the HRQoL
scores of the dropouts versus the completers at baseline, but found no significant differences (p > 0.05; data not shown).

4.5. DISCUSSION

4.5.1. MAIN FINDINGS
The results of this study show that HRQoL scores of people with AD do not change significantly over 18 months according to self-rating, but decline according to the ratings of carers. Changes in HRQoL self- and carer-ratings are associated with different factors. Carers ascribe significant associations between HRQoL and cognitive and functional/physical decline, but for people with AD the subjective experience of anxiety is the most relevant association with declining HRQoL. Consequently, interventions designed to maintain or improve quality of life in AD should take these findings into account, as changes in self- and carer-ratings are not associated with the same factors.

4.5.2. LIMITATIONS
The study has weaknesses and strengths that merit comment. Firstly, there was a relatively high number of participants lost to follow up (35%, including deaths). Although we did not find significant differences in HRQoL ratings between the completers and dropouts at baseline, loss of power due to healthy participant bias could potentially explain our findings. It is of note that the few available longitudinal studies focusing on changes in HRQoL self-ratings of people with dementia showed similar or higher attrition: 73% of their sample over one year (Heggie et al., 2011); 52% over one year (Selwood et al., 2005); and one study could not collect HRQoL data from 31% of their sample after 2 years (Tatsumi et al., 2009). Given the nature and impact of AD, such a loss to follow up might be difficult to overcome.

Secondly, missing data for self-reported AQ and HADS at 18 months was high (20%) because participants were unable to complete these two questionnaires due to cognitive impairment, even though they were able to complete the less cognitive demanding QoL-AD. To check for the possibility of a bias towards the null hypothesis (type II error), we performed post-hoc analyses and found no significant difference between the mean change overtime of the QoL-AD self-ratings of participants who were or not able to complete the AQ and HADS at 18-months (t = -0.30, p = 0.765).
Thirdly, we considered the main effects of variables, but refrained from examining the possible interactions between explanatory factors because of small numbers could have contributed to introduce type II error. Fourthly, we collected no more than two points of assessment with an 18 months time interval; this design limits us in further interpretations regarding the linear or non-linear development of QoL ratings over time. Fifthly, we acknowledge that three participants in our study were aged <65 at baseline (i.e. 56, 61 and 62), and one of these three participants completed the follow-up assessment at 18-months (i.e. who was 62 at baseline). Detailed analysis did not identify the few younger participants as outliers at baseline or at follow-up. Therefore, we felt there was no compelling reason to exclude this participant from further analyses in this study.

Regarding the generalizability of our findings, the participants of this study were not randomly selected (i.e. only adults diagnosed with probable AD of mild-moderate severity at baseline with a MMSE score of ≥10), and were known to the specialized services we approached for recruitment (Bosboom et al., 2012). It is unclear if these results would be equally applicable to people with AD living in residential care facilities.

Although it would have been of interest to explore differences and changes in HRQoL self-ratings in patients with mild, moderate and severe stages of dementia, the small sample size of our study prevented us from doing this.

HRQoL in dementia is a complex construct and its assessment is neither simple nor straightforward. Although there is emerging evidence on the predictive and explanatory value of disease specific measures of HRQoL in people with dementia (Banerjee et al., 2009), quality of life encompasses aspects of a person’s life that go beyond the constraints imposed by the disease. The instrument used in this study, the QoL-AD, is a specific measure of HRQoL, so we are unable to comment on other relevant aspects of the quality of life of participants.

4.5.3. INTERPRETATION OF THE FINDINGS
HRQoL does not change substantially over 18 months according to the view of patients. These results are in line with some of the few previous studies (Heggie et al., 2011; Selwood et al., 2005; Tatsumi et al., 2009), although time frames (ranging from 1 year to 2 years), inclusion criteria (PWD aged 65+ (Selwood et al., 2005); people with AD (Tatsumi et al., 2009); heterogeneous group of older adults with some form of cognitive
deterioration including mild cognitive impairment, AD, frontotemporal dementia and normal pressure hydrocephalus, (Heggie et al., 2011)), and the average mean on the MMSE at baseline (i.e. 16.1 +6.5, Selwood et al., 2005; 21.7 +2.7, Tatsumi et al., 2009; no data provided, Heggie et al., 2011) varied across the studies. The other two longitudinal studies in this field (Lyketsos et al., 2003; Missotten et al., 2007) used the Alzheimer Disease Related Quality of Life (ADRQL), which only takes into account the views of the carer. Such an approach may be problematic, as self- and carer-ratings are not interchangeable (Bosboom et al., 2012). In contrast, we found a significant decline in the HRQoL carer-ratings over this same time-period, which is consistent with the results reported by others (Tatsumi et al., 2009), although such a decline does not seem to occur in a linear fashion (Missotten et al., 2007).

When we compared HRQoL self- and carer-ratings at baseline, we found an acceptable level of agreement (i.e. rating differences within ±1.96 SD range), although patients overestimated their HRQoL compared with carers (Bosboom et al., 2012). The longitudinal data show that self- and carer HRQoL ratings diverge over 18 months, and such a change is associated with different factors. We found that 22.6% of the changes in HRQoL self-ratings were associated with changes in symptoms of anxiety. The finding that changes in the use of medications are not associated with changes in QoL self- or carer-ratings are consistent with the results of two recent systematic reviews (Cooper et al., 2012a; 2012b), who found no evidence that medications affect HRQoL in people with dementia. Anxiety is among the most frequently reported neuropsychiatric symptoms in people with AD (e.g. 40% of neuropathologically confirmed AD cases, Echavarri et al., 2012), and our results indicate that it plays a more prominent role in determining HRQoL changes than cognitive function. Hence, a shift of focus to interventions to manage anxiety symptoms might be required if we wish to choose interventions that improve the quality of life of people with AD living in the community. Current guidelines recommend non-pharmacological interventions (including psychological counseling, interpersonal management and environmental management) as first-line treatment for neuropsychiatric symptoms (Gauthier et al., 2010). However, at present there is no consistent evidence about specific behavioural strategies for clinical management of anxiety in dementia (Carejeira et al., 2012), and trial data on people with AD remain scant (Blay et al., 2012; Wolitky-Taylor et al., 2010). This situation must change.
Changes in HRQoL carer-ratings were associated with changes in cognition and depression scores of the person with AD, burden of care due to visits to hospital, and engagement of the person with AD in hobbies. These factors predicted 55% of the change in carer-ratings in our final model. It seems that the inevitable cognitive deterioration associated with AD affects the views of people with AD and their carers differently. It has been suggested that the attitude to ageing and dementia and suggested that negative stereotypes of dementia should be challenged (Trigg et al., 2011). One recent study found a weak association between HRQoL self- and carer-ratings in a cross-sectional study and observed that awareness of memory function was the strongest association with self-ratings, whereas activities in daily living function and enjoyment of activities were significantly associated with carer-ratings (Trigg et al., 2011).

4.5.4. CONCLUSION
Our results indicate that HRQoL self- and carer-ratings of people with Alzheimer’s disease living in the community do not decline at the same rate over 18 months. In addition, we found that anxiety is associated with changes in self-rated HRQoL, whereas cognitive scores, retention of hobbies and interests, and burden of care are associated with changes in carer-rated HRQoL. Consequently, interventions designed to optimise the quality of life of people with AD should consider carefully whose HRQoL ratings they wish to change.
CHAPTER 5.

STABILITY OF THE ASSOCIATION BETWEEN COGNITIVE DOMAINS AND HEALTH-RELATED QUALITY OF LIFE IN ALZHEIMER’S DISEASE

5.1 ABSTRACT

Background: The nature of the association between the cognitive decline and quality of life during the course of Alzheimer’s disease (AD) has not been studied in detail. We designed this study to determine if the association between cognitive domains in AD and Health Related Quality of Life (HRQoL) changed over 18 months.

Methods: We recruited 80 community-dwelling older adults with mild to moderate AD and 61 healthy elderly controls as well as their next-of-kin. The primary outcome measure was the Quality of Life-AD (QoL-AD). Specific cognitive functions were assessed with a broad range of neuropsychological measures, which were later grouped into cognitive domains following factor analyses at the baseline and 18-month assessments. Other explanatory variables included demographics, psychopathology, burden-of-care, and use of medication.

Results: Self-reported QoL-AD scores were not associated with any of the identified cognitive domains at either assessment. The cognitive domains of people with AD changed between baseline and the 18-month assessment, as did the association of these factors with carer-rated HRQoL. The HRQoL scores assigned by the next-of-kin declined alongside a general measure of cognitive function.

Conclusion: These results indicate that HRQoL is not consistently associated with specific cognitive domains in AD and that cognitive enhancing focused therapies may fail to affect the HRQoL of people with AD.

5.2 INTRODUCTION

Cognitive impairment is a core feature of Alzheimer’s disease (AD) (McKhann et al., 2011) that is expected to undermine the Health Related Quality of Life (HRQoL) of those affected (Banerjee et al., 2009; Droes et al., 2006; Jonker et al., 2004; Kaplan et
al., 2010; Miche et al., 2012; Rabins, 2000). Specific cognitive deficits have been associated with diminished HRQoL in other chronic diseases, such as epilepsy, schizophrenia, Parkinson's disease, traumatic brain injury and multiple sclerosis (Anderson et al., 2011; Barker-Collo, 2006; Hermann, 1993; Leroi et al., 2012; Perrine et al., 1995; Tolman and Kurtz, 2012) but, surprisingly, the relationship between the inevitable cognitive decline of AD and HRQoL during the course of the illness has not been studied in detail (Hoe et al., 2006; Logsdon et al., 2002; Novelli and Caramelli, 2010; Vogel et al., 2006). Few studies have investigated the long-term association between overall cognition and HRQoL in dementia (Bosboom et al., 2013; Heggie et al., 2012; Lyketsos et al., 2003; Missotten et al., 2007; Selwood et al., 2005; Tatsumi et al., 2009; Vogel et al., 2012). However, their findings have relied on brief cognitive screening tests, such as the Mini-Mental State Examination (MMSE) and the Cambridge Cognitive Examination of the Elderly revised version (CAMCOG-R), which have limited sensitivity to measure specific cognitive functions, such as executive function (Kessels et al., 2009; Martyr and Clare, 2012).

A limited body of research using carer-reports to measure the HRQoL of the AD patient they cared for has provided data suggesting that the greater the cognitive impairment of the older person with AD the lower the carer-reported HRQoL ratings (Banerjee et al., 2009; Edelman et al., 2005; Hoe et al., 2006; Wlodarczyk et al., 2004). The latter seems consistent with evidence of a relationship between cognitive impairment in dementia and negative carer outcomes (Savundranayagam et al., 2005; Donaldson et al., 1997), as cognitive decline appears to increase burden of care (Schultz et al., 2003). In addition, some data suggest that such association between cognitive functioning and the HRQoL of people with AD as rated by the carer may not progress in a linear manner (Missotten et al., 2007). Thus, declining cognition may compromise the stability of the association between HRQoL and cognition in AD, which adds to the
complexity of determining the factors that drive HRQoL in AD as the disease progresses.

There is also evidence that the underlying cognitive structure may not be stable during the course of AD (Chapman et al., 2010; Hayden et al., 2011; Johnson et al., 2009; Kanne et al., 1998; Siedlecki et al., 2008). For example, data from one study (Hayden et al., 2011) indicated that across levels of cognition (i.e. normal, mild cognitive impairment, dementia), the factor structure of cognitive functions varied. Another study (Siedlecki et al., 2008) reporting results from explorative and confirmatory factor analyses suggested that the memory construct represents something different in healthy older adults, questionable dementia and AD, consistent with the underlying neuropathology. This may have implications for the association between specific cognitive deficits and HRQoL at different points in time.

Although specific cognitive deficits associated with AD, like episodic memory, are expected to undermine HRQoL, we are not aware of any studies that have investigated the stability of the underlying cognitive structure and how such a structure might be associated with HRQoL ratings at different stages – with regards to severity of functional impairment - of the illness compared with healthy older adults. If the factor structures of cognition in AD at different points in time are comparable, and if the factors express meaningful identifiable cognitive functions, then results would be consistent with a stable relationship between cognitive functions and HRQoL over time (e.g., episodic memory could be a stable domain driving HRQoL in people with AD throughout the course of their illness). Conversely, if the underlying cognitive structure is not stable over time, then different cognitive domains might influence HRQoL as the disease progresses.
This study aimed to determine whether: (1) the underlying cognitive structure in a sample of older adults with mild to moderate AD living in the community is stable over 18 months compared with controls free of dementia, and (2) the associations between cognitive structure and carer and self-reported HRQoL ratings remain stable over 18 months.

5.3 METHODS

5.3.1 STUDY DESIGN

Eighteen-month longitudinal observational study of the HRQoL of older adults with Alzheimer’s disease and healthy older adults.

5.3.2 PARTICIPANTS AND SETTING

We recruited 80 community-dwelling volunteers with the diagnosis of probable AD according to NINCDS-ADRDA criteria (McKhan, 1984). All participants had a total score of 10 or more on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) at the time of enrolment. Carers had face-to-face contact with the person with AD at least three times per week over the preceding year. Participants were recruited from various mental health and aged care services in the Perth metropolitan area.

Participants for the control group were aged 65 years or over and were recruited together with their next of kin from other studies running at the School of Psychiatry and Clinical Neurosciences. We only included cognitively intact control subjects, i.e. volunteers who did not have cognitive complaints, with an MMSE of $\geq 26$, and also did not meet criteria for Alzheimer’s disease or Mild Cognitive Impairment (MCI). We included 65 control pairs in this study.

We excluded people with a positive history of alcohol or substance abuse, and those with a medically unstable illness that could compromise survival (such as
metastatic cancer). Participants with AD could be taking cholinesterase inhibitors or memantine, but could not be participating concurrently in an experimental study of medications for AD. All participants were competent in written and spoken English.

Assessments were conducted between November 2006 and January 2010. The Ethics Committees of the University of Western Australia, Royal Perth Hospital, Mercy Hospital, and Western Australian Department of Health - NMAHS Mental Health approved the study protocol. All participants and their carers provided written informed consent, and the project was conducted in accordance with the Helsinki Declaration of Human Rights.

### 5.3.3 Outcome Measure

The primary outcome of interest was HRQoL ratings at baseline and 18 months as measured with the HRQoL measure, specifically developed for people with AD, the Quality of Life-AD (QoL-AD, Logsdon et al. (1999)). The QoL-AD is a brief and widely used disease-specific HRQoL scale for the assessment of people with dementia, that has well-established psychometric properties (Logsdon et al., 2002; Thorgrimsen et al., 2003) and is considered the measure of choice to assess the impact of interventions in dementia care (Moniz-Cook et al., 2008). The scale is composed of 13 items that measure different domains of functioning, selected to reflect relevant domains of the HRQoL of older adults. Each item offers 4 possible answers that range from 1 (‘poor’) to 4 (‘excellent’), producing a total score that can range from 13 to 52 – higher scores indicate better HRQoL.

Patient and carer versions are available. For the carer-ratings, carers were asked to rate the QoL-AD scale as they see it, according to their opinion. We have previously shown that ratings on the QoL-AD of people with AD and carers provide valuable information when used separately, not as a composite score (Bosboom et al., 2012).
Item 7, “Marriage”, of the QoL-AD was not used in this study because 36% of the participants were widowed or not in a relationship. Therefore, to overcome possible misinterpretation of the total scores of our observations, we calculated the percentage of the maximum QoL-AD score (%MaxSc) by dividing the total raw score by the maximum scale score and multiplying this figure by 100.

5.3.4 EXPOSURES: COGNITIVE FUNCTIONS

(A) SPECIFIC COGNITIVE FUNCTIONS

We used a battery of established neuropsychological tests to assess specific cognitive functions commonly affected by AD: episodic memory, naming, language comprehension, word fluency, psychomotor speed, inhibition, cognitive switching, working memory, visuospatial organisation and constructional abilities (Reed et al., 2007; Schmand et al., 2011).

- The Boston Naming Test short 30-item version (BNT30) (Graves et al., 2004). The total score (maximum 30) was calculated by adding the number of correct items without the correct responses following semantic or phonetic cues.

- The short version of the California Verbal Learning Test (CVLT-II) (Woods et al., 2006). The following scores were included: total recall on Trial 1 to 4 (maximum 36), short delay free recall, short delay cued recall, long delay free recall, long delay cued recall, and yes/no recognition hits (all maximum 9).

- The Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001) subtest Word Fluency (i.e. the total score for Letter Fluency, FAS, and the total score for Category Fluency, Animals and Boys names); and subtest Trail Making Test (i.e. the minutes to complete the five conditions: 1) Visual
scanning, 2) Number sequencing, 3) Letter sequencing, 4) Number-Letter switching, and 5) Motor speed).

- **Digit Span Subtest of the Wechsler Adult Intelligence Scale III (WAIS-III)** (Wechsler, 1997): total score on Digit Span Forward (maximum 16), Digit Span Backward (maximum 14), the length of the correctly replied longest Digit Span Forward (maximum 9) and the length of the correctly replied longest Digit Span Backward (maximum 8).

- **Digit Symbol Coding** subtest of the WAIS-III (Wechsler, 1997; Joy et al., 2004). The contribution of speed to Digit Symbol Coding has been operationalized as the **Digit Symbol Copy** test (Wechsler, 1997): the number of correct responses produced over 2 minutes.

- The **Neuropsychological Assessment Battery (NAB) Screening Module Language** subtest for auditory comprehension (Stern and White, 2003): the total score (maximum 56).

- **Rey Complex Figure Test (RCFT)** RCFT copy by drawing and recall by drawing (Meyers and Meyers, 1995). : the total scores for copy and for recall (both to a maximum 36).

- The **Visual Association Test (VAT)**, a brief paired-associate learning test, based on imagery mnemonics (Lindeboom et al., 2002): maximum score is 6.

**Global Cognitive Functioning**

The **Cambridge Cognitive Examination of the Elderly**, revised version (CAMCOG-R) is a widely used cognitive measure that provides a general measure of cognitive function, and has shown sensitivity over time (Roth et al., 1998). The total score on the CAMCOG-R ranges between 0 (severe cognitive impairment) and 105 (no cognitive impairment).
5.3.5 OTHER STUDY MEASURES

We collected demographic, lifestyle and medical background information at the baseline and the 18-month assessments. Other study measures administered included: Anosognosia Questionnaire (AQ, Starkstein et al., 2006), Guidelines for the Rating of Awareness Deficits (GRAD, Verhey et al., 1993), Hospital Anxiety and Depression Scale (HADS, Zigmond and Snaith (1983)), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE, Jorm and Jacomb (1989)), Katz’ Activities of Daily Living scale (Katz, 1983), Lawton and Brody’s Instrumental Activities of Daily Living scale (Lawton & Brody’s IADL, Lawton and Brody (1969)), and Neuropsychiatric Inventory (NPI, Cummings (1997)). These measures were selected to collect information about behavioural and psychological symptoms of dementia, awareness, and independence in activities of daily life from different perspectives (e.g. AQ consists of self-reported and carer-reported versions of patient’s performance in basic and instrumental activities of daily living).

5.3.6 PROCEDURES

We posted the study questionnaire, as well as the AQ, HADS, IQCODE, Katz’ ADL and Lawton & Brody’s IADL scales to participants for completion prior to a face-to-face assessment. During the face-to-face assessment, responses to each of the study questionnaires were checked for completeness, and factual information regarding demographic facts and clinical characteristics were checked for accuracy with the carer. All assessments were completed by a senior clinical neuropsychologist (PB). The QoL-AD was administered with the participant with AD and their carer separately. The same procedures were used at the 18-month assessment.
5.3.7 **Statistical analyses**

Continuous variables were described by their mean and standard deviations (±SD). We log-transformed continuous variables when necessary, to complete parametric analyses. Unpaired data were compared using Student’s t-tests for continuous variables. Wilcoxon signed-rank test was used as a non-parametric test when numerical data were not normally distributed.

We performed Exploratory Factor Analyses (EFA) with the cognitive variables of interest separately at baseline and at follow-up in order to evaluate the similarity of underlying latent components of cognitive structure in AD at two different time points. We applied factor analyses as multivariate technique to identify underlying factors that are relatively independent from one another. EFA differentiates between common and unique variance, so that the factors represent commonality between variables. Commonality of a measured variable is the amount of variance accounted for by the factor. Inclusion of variables with low commonality in the analysis may create distortion in the factor solution, and inclusion of variables with low commonality may reduce the probability of replicating the factor pattern. Therefore, cognitive variables identified with low commonality in the factor analyses were excluded.

Prior to the factor analyses, we performed the Bartlett's test for sphericity and the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy. Bartlett's test determines if our samples originated from populations with equal variances, or total ranges of values and can be used to detect if a tested population has a non-normal distribution. It calculates the determinant of the matrix of the sums of products and cross-products (S) from which the intercorrelations matrix is derived. The determinant of the matrix S is converted to a chi-square statistic and tested for significance. The null hypothesis is that the intercorrelations matrix comes from a population in which the
variables are non-collinear (i.e. an identity matrix) and that the non-zero correlations in the sample matrix are due to sampling error. KMO is an index for comparing the magnitudes of the observed correlation coefficients to the magnitudes of the partial correlation coefficients. Large values for the KMO measure indicate that a factor analysis of the variables is suitable: 0.90 or above is considered excellent; 0.80 or above, meritorious; 0.70 or above, middling; 0.60 or above, mediocre; 0.50 or above, miserable; and below 0.50, unacceptable. According to the Kaiser criteria, factors were retained when eigenvalues were equal or higher than 1. We also inspected the scree plot. Once the factors were extracted we applied orthogonal varimax rotation to foster interpretability by maximizing factor loadings close to 1.0 and minimizing factor loadings close to 0.

Linear multiple regression analyses (crude and adjusted) were performed of the self-reported and carer-reported QoL-AD %MaxSc with 1) global cognition (as measured with the CAMCOG-R) and 2) the identified cognitive factors (with the EFA as described above). We adjusted for univariate associations that were identified in separate studies (these included HADS Anxiety, HADS Depression, NPI total score, NPI Burden of care, number of patient’s medications, use of alcohol by the patient, number of visits or admission(s) to hospital in the last six months; for further details please see Bosboom et al., 2012; 2013a). This was performed for the different groups at the two points in time separately. Due to the multiple comparisons and the explorative nature of these analyses, alpha was set at 1%.

All statistical tests reported are two-tailed. The data were managed and analyzed with STATA version 12.1 (StataCorp, College Station, TX).
5.4 RESULTS

5.4.1 CHARACTERISTIC OF PARTICIPANTS AT BASELINE AND 18-MONTH FOLLOW-UP

The mean age of the 80 participants with AD was 78.3 years (± 7.9; range 56-92), 68.8% were women, and 75% lived with their carer. The mean age of the carers was 66.6 years (± 14.5), 61.4% of them were spouses, and 57.5% were women. The mean number of years in education of people with AD was 10.2 (± 2.2) and 56.3% had completed a minimum of 10 years of education.

The flow of participants with AD during the 18 months of follow-up and their demographic and clinical characteristics have been reported elsewhere (Bosboom et al., 2013). Briefly, 88 older adults with AD and their carer agreed to participate; an appointment for assessment was scheduled and all information and questionnaires were sent to their home. 8 discontinued due to various reasons, including move to residential care. At the end of the follow up period, cognitive function, as measured by the CAMCOG-R, had deteriorated (i.e. completers (N=47) mean baseline 63.2 ± 12.1; mean 18-months 48.9 ± 19.8, p < 0.001), as had ADL, IADL, and awareness (all p < 0.001). The proportion of participants who were involved in community activities and participants who were driving after 18 months declined (p = 0.007 and p < 0.001 respectively), whereas the number of visits to GPs during the preceding 6 months increased (p < 0.001). At the 18-month assessment, the NPI burden-of-care was higher than at baseline (p = 0.029).

Participants with AD who were not available for follow up used more hearing aids at baseline (2.7%; p= 0.013) and had higher (i.e. better) average IADL ratings (p = 0.019) compared with participants who completed the follow-up assessment (n = 47). Further demographic and clinical characteristics (including anosognosia) have been reported elsewhere (Bosboom et al., 2012, 2013a).

The mean age of the 65 healthy older adults at baseline was 75.7 years (± 6.3;
range 66 - 92), 51.7% woman, and 60% lived in the same household with the informant. The mean age of informants in the control group was 64.8 years (± 14.1), 58.7% of them were spouses, and 18.46% were women. The mean number of years in education of the controls was 12.4 years (± 2.7 and 83.3% had completed a minimum of 10 years of education. There were no significant differences in clinical features between baseline and follow-up assessment.

5.4.2 COMPARISON RAW SCORES ON COGNITIVE AND HRQoL MEASURES

The calculated percentage of the maximum QoL-AD scores (%MaxSc) by all participants and subgroups at the two different points in time, and the raw scores on global and specific cognitive tests by all participants (i.e. AD and controls) at the two different points in time assessments are presented in a separate supplemental file. Participants with AD experienced significant decline across most cognitive measures, apart from letter fluency, and TMT 1, possible due to floor effect. A comparison of specific cognitive scores at baseline between participants with AD who completed and did not complete the follow-up assessment revealed significantly lower scores for the dropouts on digit span backwards, digit span longest span backwards, NAB language comprehension, and RCFT copy. A comparison of global and specific cognitive scores of controls between baseline and follow-up assessments revealed only Digit Symbol Copy was higher (better) and TMT 4 performance was significantly lower at follow-up (see separate supplemental file).

5.4.3 EXPLORATIVE FACTOR ANALYSES (STUDY AIM 1)

Separate EFA’s were conducted for each group, i.e. (1) all participants with AD at baseline (N = 80), (2) selection of participants with AD at baseline who did not completed the follow-up assessment (‘dropouts’, N = 33), (3) selection of participants
with AD at baseline who also completed the follow-up assessment (‘completers’, N = 47), (4) these same AD participants at 18-month follow-up (N = 47), (5) controls at baseline, and (6) controls at follow-up. The results of the six obtained models are presented in Table 5.1. Only variables with factor loadings > 0.5 were included in the table.

5.4.3.1. **MODEL 1: AD TOTAL GROUP AT BASELINE (N=80)**

At baseline, the eigenvalue >1 rule suggested three factors. Inspection of the three-factor model (explaining 82.7% of the total variance), showed that three factors yielded a solution with one mixed factor (i.e. Factor 1, variables tapping into varied cognitive functions that explained 34.7% of the variance), and two additional distinct factors (i.e. Factor 2, attention & working memory, explaining 28.4% of the variance; and Factor 3, episodic memory, explaining 19.7% of the variance). The NAB language comprehension test, included in Factor 2 of this model, requires understanding of the prompt that can hold several units of information (e.g. “Point to the 3-sided shape that is the color of the sky”, or “Point to the number that shows how many hours there are in a day”), which can arguably be compromised by deficits in attention & working memory.

5.4.3.2. **MODEL 2: AD DROPOUTS AT BASELINE (N=33)**

In the group of dropouts at baseline, the eigenvalue >1 rule yielded four factors (82.5%), but the scree plot suggested a three-factor model. When we subsequently explored a four-model and a three-factor model for this group, a better interpretable solution was identified with a three-factor model with 76.8% total variance explained. This three-factor model identified two factors comprising variables tapping on mixed cognitive functions, i.e. Factor 1 explaining 31.9% of the variance, and Factor 2 explaining 26.3% of the total variance.
Table 5.1. Results of Explorative Factor Analyses of neuropsychological variables from participants at baseline and at 18-month follow-up

<table>
<thead>
<tr>
<th>All at BL (N=80)</th>
<th>Dropouts at BL (N=33)</th>
<th>Completers at BL (N=47)</th>
<th>Completers at FU (N=47)</th>
<th>Controls at baseline</th>
<th>Controls at FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartlett test: Chi² = 1509.07, p = &lt;0.001; KMO = 0.838; Variance 3 factor model = 82.7%</td>
<td>Bartlett test: Chi² = 780.73, p = &lt;0.001; KMO = 0.668; Variance 3 factor model = 76.8%</td>
<td>Bartlett test: Chi² = 799.92, p = &lt;0.001; KMO = 0.755; Variance 3 factor model = 75.2%</td>
<td>Bartlett test: Chi² = 645.52, p = &lt;0.001; KMO = 0.710; Variance 3 factor model = 85.0%</td>
<td>Bartlett test: Chi² = 626.90, p = &lt;0.001; KMO = 0.749; Variance 3 factor model = 83.7%</td>
<td></td>
</tr>
<tr>
<td><strong>Factor 1 Mixed</strong> (Eigenvalue = 5.82; 34.7%)</td>
<td><strong>Factor 1 Mixed</strong> (Eigenvalue = 6.66; 31.9%)</td>
<td><strong>Factor 1 Mixed</strong> (Eigenvalue = 6.33; 34.7%)</td>
<td><strong>Factor 1 Mixed</strong> (Eigenvalue = 6.64; 47.5%)</td>
<td><strong>Factor 1 Mixed</strong> (Eigenvalue = 4.65; 39.6%)</td>
<td></td>
</tr>
<tr>
<td>TMT 1</td>
<td>-0.70</td>
<td>TMT 1</td>
<td>-0.66</td>
<td>TMT 1</td>
<td>-0.75</td>
</tr>
<tr>
<td>Digit Symbol Coding</td>
<td>0.77</td>
<td>Digit Symbol Coding</td>
<td>0.76</td>
<td>Digit Symbol Coding</td>
<td>0.80</td>
</tr>
<tr>
<td>Digit Symbol Copy</td>
<td>0.73</td>
<td>Digit Span left fwd</td>
<td>0.88</td>
<td>Digit Symbol Copy</td>
<td>0.81</td>
</tr>
<tr>
<td>Digit Span forward</td>
<td>-0.73</td>
<td>Digit Span forward</td>
<td>0.88</td>
<td>Digit Span forward</td>
<td>0.80</td>
</tr>
<tr>
<td>Digit Span backward</td>
<td>0.77</td>
<td>Digit Span backward</td>
<td>0.76</td>
<td>Digit Span backward</td>
<td>0.76</td>
</tr>
<tr>
<td>Digit Span left fwd</td>
<td>0.85</td>
<td>Digit Span left bwd</td>
<td>0.85</td>
<td>Digit Span left bwd</td>
<td>0.80</td>
</tr>
<tr>
<td>NAB Comprehension</td>
<td>0.63</td>
<td>NAB Comprehension</td>
<td>0.76</td>
<td>NAB Comprehension</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Factor 2 Attention &amp; WM</strong> (Eigenvalue = 1.57; 28.4%)</td>
<td><strong>Factor 2 Attention &amp; WM</strong> (Eigenvalue = 0.51; 21.5%)</td>
<td><strong>Factor 2 Attention &amp; WM</strong> (Eigenvalue = 0.79; 23.8%)</td>
<td><strong>Factor 2 Attention &amp; WM</strong> (Eigenvalue = 2.17; 21.1%)</td>
<td><strong>Factor 2 Attention &amp; WM</strong> (Eigenvalue = 2.74; 23.9%)</td>
<td></td>
</tr>
<tr>
<td>Digit Span forward</td>
<td>0.93</td>
<td>TMT 2</td>
<td>-0.89</td>
<td>Digit Span forward</td>
<td>0.90</td>
</tr>
<tr>
<td>Digit Span backward</td>
<td>0.77</td>
<td>TMT 3</td>
<td>-0.89</td>
<td>Digit Span backward</td>
<td>0.78</td>
</tr>
<tr>
<td>Digit Span left fwd</td>
<td>0.85</td>
<td>TMT 5</td>
<td>-0.57</td>
<td>Digit Span left bwd</td>
<td>0.85</td>
</tr>
<tr>
<td>NAB Comprehension</td>
<td>0.63</td>
<td>NAB Comprehension</td>
<td>0.76</td>
<td>NAB Comprehension</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Factor 3 Episodic Memory</strong> (Eigenvalue = 3.30; 19.2%)</td>
<td><strong>Factor 3 Episodic Memory</strong> (Eigenvalue = 3.36; 19.0%)</td>
<td><strong>Factor 3 Episodic Memory</strong> (Eigenvalue = 2.67; 14.9%)</td>
<td><strong>Factor 3 Episodic Memory</strong> (Eigenvalue = 1.69; 16.5%)</td>
<td><strong>Factor 3 Episodic Memory</strong> (Eigenvalue = 2.32; 20.2%)</td>
<td></td>
</tr>
<tr>
<td>CVLT-II sdrf</td>
<td>0.71</td>
<td>CVLT-II sdrf</td>
<td>0.63</td>
<td>CVLT-II sdrf</td>
<td>0.74</td>
</tr>
<tr>
<td>CVLT-II ldrf</td>
<td>0.79</td>
<td>CVLT-II ldrf</td>
<td>0.89</td>
<td>CVLT-II ldrf</td>
<td>0.73</td>
</tr>
<tr>
<td>CVLT-II ldr</td>
<td>0.81</td>
<td>CVLT-II ldr</td>
<td>0.87</td>
<td>CVLT-II ldr</td>
<td>0.80</td>
</tr>
<tr>
<td>RCFT recall</td>
<td>0.55</td>
<td>RCFT recall</td>
<td>0.65</td>
<td>RCFT recall</td>
<td>0.58</td>
</tr>
<tr>
<td>VAI</td>
<td>0.56</td>
<td>VAI</td>
<td>0.77</td>
<td>VAI</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Abbreviations: BL, baseline; BNT30, Boston Naming Test, 30-item version; bwd, backward; Completers, participants who completed baseline and follow-up assessment; CVLT-II, CVLT-II, California Verbal learning Test, 2nd edition; Dropouts, participants who completed baseline assessment; EF, Executive Functioning; FU, follow-up; fwd, forward; KMO, Kaiser-Meyer-Olkin measure of sampling adequacy; lgst bwd, longest backward; lgst ffd, longest forward; NAB Comprehension, Neuropsychological Assessment Battery - Screening Module Language, Auditory Comprehension; RCFT, Rey Complex Figure Test; SD, Standard Deviation; TMT, Trail Making Test; VAT, Visual Association Test; WM, Working Memory. 1) Factor loadings after orthogonal varimax rotation. Only variables with factor loadings of >0.5 are included in this table.
Factor 3 appeared as a factor containing variables representing tests tapping on episodic memory, explaining 18.5% of the variance.

5.4.3.3. **Model 3: AD completers at baseline (N = 47)**

In the group of completers at baseline, the eigenvalue >1 rule suggested four factors. However, inspection of this four-factor model, showed that they yielded a solution that was difficult to interpret and that had tests contributing to more than one factor. When we subsequently explored a three-factor model for this group, a better interpretable solution was identified with 75.2% total variance explained. This three-factor model identified the first factor comprising mixed variables tapping on several cognitive functions (i.e. Factor 1 explaining 34.7% of the variance) and two distinct factors (i.e. Factor 2, Attention & Working Memory, explaining 21.5% of the variance; and Factor 3, Episodic Memory, explaining 19.0% of the variance).

Comparing the models for the total baseline group (N = 80) with the completers at baseline (N = 47), there were no substantial differences between the three cognitive factors identified in both models. It was noted that the RCFT copy was eliminated from Factor 1 and the NAB Language comprehension test was eliminated from Factor 2. For the completers the CVLT-II recognition was added to Factor 3.

5.4.3.4. **Model 4: AD completers at follow-up (N = 47)**

In the same group of completers at 18-month follow-up, the eigenvalue >1 rule suggested a four-factor model (explained variance of 80.7%). However, further inspection showed that this four-factor model yielded a difficult to interpret solution. Subsequently, when we explored a three-factor model for this group, the total variance explained was slightly lower (75.2%), but this three-factor model identified a better solution with two mixed factor (i.e. Factor 1 explaining 38.1% of the variance of the
model; Factor 2 explaining 23.8% of the total variance), and one more distinct factor (i.e. Factor 3, episodic memory, explaining 14.9% of the variance).

Comparing the two identified models for the completers group at baseline and at 18-months follow-up, it was noted that Factors 1 and 2 showed differences between the two assessments in time. At both times, the factors that explained the largest percentage of variance of the models included tests tapping on several cognitive functions. Taken together, Factors 1 and 2 in both models did not seem to be stable over time.

Also, a qualitative comparison of the two identified models for the dropouts at baseline and the completers at follow-up showed that these models were largely similar, which might be indicative of worse cognitive functioning of the dropout group at baseline compared to the completers.

Comparing the four identified EFAs models, the factor with more distinct tests tapping specifically on episodic memory seemed stable over time.

5.4.3.5. MODELS 5 & 6: CONTROLS AT BASELINE AND AT FOLLOW-UP (N=61)

Separate EFA’s were conducted for the controls as baseline and at 18-month follow-up (N = 61). Comparing the two identified three-factor models for the controls at baseline and at follow-up it was noted that factors identified contained tests scores tapping on similar cognitive functions, indicating stability between the two points in time assessments.

5.4.4. ASSOCIATIONS BETWEEN IDENTIFIED COGNITIVE FACTORS AND HRQoL ACROSS GROUPS AND TWO POINTS IN TIME (STUDY AIM 2)

The results of the crude and adjusted univariate regression analyses for identified cognitive factors and overall cognitive functioning as measured with the CAMCOG-R are presented in Table 5.2. The associations between QoL-AD ratings and overall
cognitive functioning as measured with the CAMCOG-R for the participants with AD have been reported elsewhere (Bosboom et al., 2013a). In summery, for changes in the QoL-AD carer-ratings we found a direct association with changes on the CAMCOG-R total score, but no significant association for the changes in the QoL-AD self-ratings. For comparison, we have included those figures in Table 5.2.

With the level of significance set at 1% (due to the multiple comparisons in this table), the only associations that reached significance were for the carer-reported QoL-AD, but not for self-reported QoL-AD. That is, in the Alzheimer dropouts subgroup at baseline we found a direct association between the identified cognitive factor 2 (which included TMT 2, TMT 3, TMT 4, TMT 5, Digit Symbol Coding, Digit Symbol Copy, Letter fluency and RCFT Copy, see Table 5.1) and the QoL-AD as reported by the carer (p < 0.001). This association was no longer statistically significant after adjustment for anxiety (HADS Anxiety), depression (HADS Depression), NPI, NPI Burden of care and number of medications (p =0.062). This association was not significant at baseline for the AD completers (p = 0.071), but was statistically significant at follow-up for the AD completers (p = 0.005), although significance was lost after adjustment (p = 0.112).

For the Alzheimer patients total group at baseline we found a direct association between global cognitive functioning (i.e. the CAMCOG-R total score) and the QoL-AD as reported by the carer (p < 0.001). This association remained significant after adjustment for anxiety (HADS Anxiety), depression (HADS Depression), NPI, NPI Burden of care and number of medications (p < 0.001). Further examination of data at baseline showed a direct association for AD dropouts (p = 0.005), but not for completers (p = 0.068). In addition, this association between global cognition and carer-reported QoL-AD did not reach significance at the follow-up assessment.
Table 5.2. Regression analyses (crude and adjusted) of the QoL-AD with global cognition and identified cognitive factors

<table>
<thead>
<tr>
<th>Group &amp; time</th>
<th>Cognition</th>
<th>Crude</th>
<th>Adjusted&lt;sup&gt;1)&lt;/sup&gt;</th>
<th>Carer-reported QoL-AD</th>
<th>Adjusted&lt;sup&gt;1)&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(\beta)</td>
<td>99%CI</td>
<td>(p)</td>
<td>(\beta)</td>
</tr>
<tr>
<td>Controls</td>
<td>CAMCOG-R</td>
<td>0.45</td>
<td>(-0.40, 1.31)</td>
<td>0.281</td>
<td>-0.05</td>
</tr>
<tr>
<td>at BL</td>
<td>Factor 1. Episodic memory</td>
<td>2.57</td>
<td>(-0.51, 5.65)</td>
<td>0.088</td>
<td>2.12</td>
</tr>
<tr>
<td></td>
<td>Factor 2. Attention &amp; WM</td>
<td>1.35</td>
<td>(-1.75, 4.45)</td>
<td>0.366</td>
<td>1.39</td>
</tr>
<tr>
<td></td>
<td>Factor 3. EF</td>
<td>-1.66</td>
<td>(-5.00, 1.68)</td>
<td>0.305</td>
<td>0.84</td>
</tr>
<tr>
<td>Controls</td>
<td>CAMCOG-R</td>
<td>0.32</td>
<td>(-0.17, 0.81)</td>
<td>0.178</td>
<td>0.17</td>
</tr>
<tr>
<td>at FU</td>
<td>Factor 1. Epis. mem. &amp; speed</td>
<td>2.72</td>
<td>(-0.11, 5.55)</td>
<td>0.030</td>
<td>4.46</td>
</tr>
<tr>
<td></td>
<td>Factor 2. Attention &amp; WM</td>
<td>0.11</td>
<td>(-2.54, 2.76)</td>
<td>0.929</td>
<td>3.24</td>
</tr>
<tr>
<td></td>
<td>Factor 3. EF</td>
<td>2.09</td>
<td>(-0.60, 4.78)</td>
<td>0.109</td>
<td>0.85</td>
</tr>
<tr>
<td>AD total group (N=80)</td>
<td>CAMCOG-R</td>
<td>-0.07</td>
<td>(-0.25, 0.11)</td>
<td>0.442</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>Factor 1. Mixed</td>
<td>2.08</td>
<td>(-0.56, 4.72)</td>
<td>0.106</td>
<td>2.07</td>
</tr>
<tr>
<td>at BL</td>
<td>Factor 2. Attention &amp; WM</td>
<td>-1.13</td>
<td>(-3.58, 1.32)</td>
<td>0.371</td>
<td>3.00</td>
</tr>
<tr>
<td></td>
<td>Factor 3. Episodic memory</td>
<td>-2.49</td>
<td>(-2.54, -2.44)</td>
<td>0.058</td>
<td>-2.36</td>
</tr>
<tr>
<td>AD completers (N=47)</td>
<td>CAMCOG-R</td>
<td>-0.09</td>
<td>(-0.39, 0.21)</td>
<td>0.530</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>Factor 1. Mixed</td>
<td>1.22</td>
<td>(-2.42, 4.86)</td>
<td>0.485</td>
<td>1.27</td>
</tr>
<tr>
<td>at BL</td>
<td>Factor 2. Attention &amp; WM</td>
<td>-0.13</td>
<td>(-3.74, 3.48)</td>
<td>0.942</td>
<td>-0.47</td>
</tr>
<tr>
<td></td>
<td>Factor 3. Episodic memory</td>
<td>-4.02</td>
<td>(-7.55, -0.49)</td>
<td>0.021</td>
<td>-2.08</td>
</tr>
<tr>
<td>AD completers (N=47)</td>
<td>CAMCOG-R</td>
<td>0.08</td>
<td>(-0.47, 0.63)</td>
<td>0.292</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Factor 1. Mixed</td>
<td>0.50</td>
<td>(-3.14, 4.14)</td>
<td>0.772</td>
<td>1.39</td>
</tr>
<tr>
<td>at FU</td>
<td>Factor 2. Mixed</td>
<td>1.83</td>
<td>(-1.82, 5.48)</td>
<td>0.296</td>
<td>5.24</td>
</tr>
<tr>
<td></td>
<td>Factor 3. Episodic memory</td>
<td>-3.75</td>
<td>(-7.29, -0.21)</td>
<td>0.031</td>
<td>3.89</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; BL, baseline; CAMCOG-R, Cambridge Cognitive Examination of the Elderly Revised; Completers, participants who completed baseline and follow-up assessment; Dropouts, participants who completed baseline assessment; EF, Executive Functioning; FU, follow-up; HADS, Hospital Anxiety and Depression Scale; HRQoL, Health Related Quality of life; IADL, Lawton and Brody’s Instrumental Activities of Daily Life assessment scale; Katz’ ADL, Katz’ Activities of Daily Living scale; NPI, Neuropsychiatric Inventory; QoL-AD, Quality of life in Alzheimer’s disease; WM, working memory. 1) Adjusted for identified univariate associations exclusive cognition related variables, including HADS Anxiety, HADS Depression, NPI total score, and number of medications. Note: due to the multiple comparisons in this table the level of significance was set at 1% (see *).
For the AD participants who completed follow-up, the carer-rated QoL-AD was directly associated with factor 2 (which included TMT 2, TMT 3, TMT 4, TMT 5, Digit Symbol Coding, Digit Symbol Copy, Letter fluency and RCFT Copy, see Table 5.2) ($\beta = 5.24$, $p = 0.005$). It was noted that the tests included in Factor 2 were all the same for the dropouts at baseline as for the completers at follow-up.

For the AD dropouts at baseline, the carer-rated QoL-AD was directly associated with factor 3 (episodic memory) ($\beta = 6.49$, $p = 0.002$).

5.5. DISCUSSION

The results of this study confirmed that (1) the underlying cognitive structure of AD is not stable over 18 months compared with controls free of cognitive impairment, and showed that (2) the relationship between cognitive domains and HRQoL is different for self- and carer-reported ratings. Self-reported HRQoL ratings were not associated with any of the identified cognitive domains at any time, whereas carer-reported HRQoL ratings were directly associated with varying cognitive domains over time. These findings indicate that carers’ perception of the meaning of ‘overall cognitive impairment’ and of particular cognitive factors on HRQoL of the person with AD changes during the course of the disease (for example, it is conceivable that carers view the ability to organize a meal or to communicate with ease his/her experiences and desires to others as more important to the QoL of the person with AD than memory lapses, but this view might change over time). In contrast to the AD group, we found a stable underlying cognitive structure and no associations of any of the identified factors with the HRQoL-ratings in healthy older adults.

Our study design has limitations that we wish to acknowledge. Firstly, a relatively large number of participants were lost to follow up (35%, including deaths).
Although we did not find significant differences in HRQoL ratings between completers and dropouts at baseline, loss of power and bias due to the selection of healthier participants might have affected the results and the generalizability of the findings. For example, the findings suggest that executive functions and speed of information processing are associated with the carer-reported QoL-AD ratings at baseline but not at follow-up, but this is not supported by the restriction of the sample to AD completers at baseline. This lack of association for the AD completers could be due to loss of power or a healthier participant bias (i.e., people with these types of cognitive impairment are more likely to drop out). Secondly, we only collected data at two time-points separated by an 18-month interval. Consequently, we are unable to make inferences about changes over shorter or longer periods of time. Thirdly, three participants in our study were younger than 65 years at baseline (i.e. 56, 61 and 62) and could, potentially, have a cognitive profile that is different from that of people with late-onset Alzheimer’s disease. However, only one of them completed the follow-up assessment (i.e., age 62 years at baseline) and detailed analysis did not identify these three participants as outliers. Fourth, our subjects were volunteers with mild to moderate dementia living in the community and recruited from various sources. We cannot be certain that they represent well the population of people with AD. Fifth, although it would have been of interest to explore differences and changes in HRQoL self-ratings in patients with mild, moderate and severe stages of dementia, our modest sample size precluded any attempt to complete such analyses. Sixth, the widely used QoL-AD is a specific measure of HRQoL, so we are unable to comment on other relevant aspects of the quality of life of participants that are not assessed by this instrument.

This study has the merit of having investigated both patients and carers’ HRQoL ratings, which provides valuable information about these separate views and their association with cognitive domains. A previous study (Bosboom et al., 2012) showed
differences between self- and carer-ratings for predictors of HRQoL as measured with the QoL-AD, suggesting that information about clinical factors is lost when a composite measure is used in the analysis. Another strength of this study is the use of a broad spectrum of well-established neuropsychological tests assessing specific cognitive abilities in multiple cognitive domains considered to be relevant in this population. This allowed us to investigate associations between specific cognitive domains and HRQoL that might have been missed by previous studies that limited their assessments of cognition to the MMSE or similar general measures of cognitive function. We acknowledge that the number of (sub)test taps on specific cognitive domains were limited and restricted further differentiation within cognitive domains, in particular executive functioning.

We are not aware of any previous study that analyzed the stability of the underlying cognitive structure in AD and how this relates to HRQoL self and carer-ratings at different stages – with regards to severity of functional impairment - of AD compared with healthy older adults. These novel findings contribute to improve our understanding of the impact specific cognitive deficits might have on perceived HRQoL at different stages of the disease. As we found that carer-reported HRQoL ratings were directly associated with executive functioning and speed of information processing at baseline but not at follow-up, it seems that these specific cognitive functions, not episodic memory, have a direct influence on how the carer perceives the HRQoL of the person with AD early in the course of the illness.

We know little about which interventions may promote or hinder HRQoL in AD (Banerjee et al., 2009; Cooper et al., 2012). Recently Cooper et al. (2012) reviewed 20 randomized controlled trials (RCTs) reporting the effectiveness of non-pharmacological interventions in improving HRQoL in dementia, and found only one reporting preliminary evidence that coping strategy-based family carer therapy improves the
HRQoL of people with dementia living at home. Our study indicates that further research into how coping with consequences of deficits in executive functioning and speed of information processing might also improve the carer-reported HRQoL.

The observation of the similarity in the cognitive factor structure for dropouts at baseline and for completers at follow-up, and the notion that the dropouts were on average slightly more impaired than completers at baseline, might raise questions about the relationship between severity of AD and HRQoL ratings. However, separate analyses examining associations in the subgroups of participants with AD who had mild (i.e. MMSE of 20 or higher) or moderate dementia (i.e. MMSE 10-19) at the time of enrolment, showed no significant differences in self-reported or carer-reported HRQoL between these dementia subgroups (Bosboom et al., 2013b). We also performed analyses to determine specific characteristics of the participants who did not complete the follow-up assessment by comparing the characteristics at baseline of participants. People with AD who dropped out used more hearing aids (2.7%; p = 0.013) and had higher (i.e. better) average IADL ratings (p = 0.019). Our data do not support the idea of a consistent linear relationship between severity of cognitive decline in AD and HRQoL.

A recent systematic review of pharmacological interventions for people with AD found only 15 RCTs measuring QoL, indicating that most RCTs in dementia to date have not included, or did not report, a QoL outcome (Cooper et al., 2013). There was no compelling evidence that pharmacological treatment improves HRQoL in people with dementia (Cooper et al., 2013). Our finding that cognition is not associated with self-rated HRQoL is consistent with these results and suggests that treatments that focus solely on cognition (like episodic memory) are unlikely to measurably affect the quality of life of patients with AD. Future studies should seek to confirm these results and determine more effective strategies to enhance the quality of life of people with AD.
This study demonstrates for the first time that the cognitive structure in people with AD changes with time and that those changes have no bearing of how patients perceive their HRQoL. These results highlight the need for the development of interventions that are more relevant to the HRQoL of older adults with AD.

In conclusion, the findings of this study indicate instability of the underlying cognitive structure in AD and its association with HRQoL ratings over a period of 18 months. These findings, if confirmed by other studies, suggest that attempts to improve certain cognitive domains, such as episodic memory, might not necessarily improve the quality of life of patients with AD. Whether educating carers about the implications of executive dysfunction and decreased information processing speed on the daily function of people with AD will have a measurable impact on their perception of the patient’s quality of life remains to be determined.
CHAPTER 6.

DO CHANGES IN SPECIFIC COGNITIVE FUNCTIONS PREDICT CHANGES IN HRQOL IN PEOPLE WITH ALZHEIMER’S DISEASE?

6.1. ABSTRACT

**Background:** Currently available pharmacological treatments in Alzheimer’s disease (AD) have been associated with modest benefits to cognition, but the impact on health related quality of life (HRQoL) is less well established. Our aim was to determine if decline of specific cognitive functions commonly associated with AD predict which patients maintain or experience a deterioration of their HRQoL over 18 months.

**Methods:** We completed an 18-month longitudinal study of 47 community-dwelling older adults diagnosed with probable AD of mild or moderate severity (NINCDS-ADRD criteria) and their family carers. The primary outcomes of interest were 18-month change in self-reported and carer-reported ratings on the Quality-of-Life-AD (QoL-AD). The main explanatory variables were 18-month change in specific cognitive functions using a broad range of established tests. Because of multiple comparisons, alpha was set at 1%.

**Results:** 26/47 and 20/47 participants with AD showed evidence of stable or increased QoL-AD over 18 months according to self-report and carer-report. Logistic regression analyses showed that for every increase in one standardized score of CVLT-II short delay free recall the odds of stable/increased self-rated QoL-AD over 18 months were 0.27 (95%CI: 0.11, 0.67; p = 0.005). After adjustment for anxiety and depression, this inverse association no longer met study criteria for statistical significance (adjusted OR: 0.31, 95%CI: 0.11, 0.86; p = 0.025). None of the other standardised changes of cognitive scores were associated with self-rated or carer-rated QoL-AD grouping.

**Conclusion:** Changes in specific cognitive functions are not associated with changes in HRQoL ratings in AD. Findings suggest that interventions that limit their focus to improving cognitive functions of people with mild to moderate AD living in the community might fail to have an impact on participants’ HRQoL.

6.2. INTRODUCTION

Maintaining health related quality of life (HRQoL) is a key aim of interventions designed to treat people diagnosed with Alzheimer’s disease (AD). Currently available pharmacological treatments (i.e., cholinesterase inhibitors donepezil, galantamine and rivastigmine, and memantine) have been associated with modest but statistically significant benefits to cognitive function (Hansen et al., 2008), but the impact of their use on HRQoL is less well established. A recent systematic review of over 1000 papers
published until early 2011 found that only 15 trials and one Cochrane review reported quality of life outcomes, of which 11 showed that treatment with cholinesterase inhibitors improved cognitive scores but not quality of life (Cooper et al., 2013).

It seems that the general assumption is that improved episodic memory, the most prominent initial clinical feature in most cases of AD, should lead to a concurrent improvement in HRQoL (McKhann et al., 2011; Mol et al., 2007; Pena-Casanova et al., 2012; Reed et al., 2007; Takeda et al., 2006). In clinical trials, the most frequently used measure of cognitive function is the Alzheimer’s Disease Assessment Scale – Cognitive section (Rosen et al., 1984), with changes in scores being largely driven by changes in episodic memory (Hansen et al., 2008). Regulatory authorities recognize a four-point change on the ADAS-Cog at 6 months as indicating a clinically important difference, although the clinical relevance of this 4-point change has been questioned (Rockwood et al., 2007).

The impact that the decline in specific cognitive functions has on the HRQoL of people with AD has not been investigated systematically (Banerjee et al., 2009; Mol et al., 2007), although evidence from other chronic disorders suggests that specific cognitive deficits affect HRQoL ratings in different way (Barker-Collo, 2006; Hermann, 1993; Klonoff et al., 1986; Newman et al., 2001; Perrine et al., 1995; Tolman and Kurtz, 2012). Even though cognitive decline is a key feature of AD (McKhan et al., 2011; Pena-Casanova et al., 2012), surprisingly few studies have investigated the long-term association between HRQoL ratings and loss of cognitive capacities, and most have limited their analyses to global cognitive measures (Bosboom et al., 2012; Bosboom et al.; Lyketsos et al., 2003; Missotten et al., 2007; Selwood et al., 2005; Tatsumi et al., 2009). Therefore, it is unclear whether specific cognitive functions, such as episodic memory, language or executive functioning, have a more prominent role in driving changes in HRQoL over time in this population.

We designed the present study to determine whether the deterioration of specific cognitive functions commonly associated with AD predict which patients maintain or experience a deterioration of their HRQoL ratings over a period of 18 months.

6.3. METHODS
6.3.1 STUDY DESIGN
18-month longitudinal observational study of older adults with probable AD.
6.3.2. PARTICIPANTS AND SETTING
We recruited 80 community-dwelling volunteers with the diagnosis of probable AD according to NINCDS-ADRDA criteria (McKhann et al., 1984). All participants had a total score of 10 or more on the Mini-Mental State Examination (MMSE) at the time of enrolment (Folstein et al., 1975). Carers had face-to-face contact with the person with AD at least three times per week over the preceding year. Participants were recruited from various mental health and aged care services in the Perth metropolitan area.

We excluded people with a positive history of alcohol or substance abuse, and those with a medically unstable illness that could compromise survival (such as metastatic cancer). Participants with AD could be consuming cholinesterase inhibitors or memantine, but could not be participating concurrently in an experimental study of medications for AD. All participants were competent in written and spoken English. Assessments were conducted between November 2006 and January 2010.

The Ethics Committees of the University of Western Australia, Royal Perth Hospital, Mercy Hospital, and Western Australian Department of Health - NMAHS Mental Health approved the study protocol. All participants and their carers provided written informed consent, and the project was conducted in accordance with the Helsinki Declaration of Human Rights.

For the purposes of this study, we limited our analysis to 47 participants with AD and their carers who provided information for the baseline and 18-month follow up assessments. Details about the baseline characteristics of participants have been reported elsewhere (Bosboom et al., 2012).

6.3.3. PRIMARY OUTCOME – CHANGE IN HRQoL
The primary outcome measure of the study was the Quality of Life-AD scale (QoL-AD). The QoL-AD is a brief and widely used HRQoL tool developed to assess quality of life in people with dementia. The scale has well-established psychometric properties and is considered the most appropriate way of measuring the impact of interventions for dementia (Logsdon et al., 2002; Thorgrimsen et al., 2003). Its 13 items assess different domains of functioning, which were selected to reflect critical domains of the HRQoL of people with AD. Each item offers 4 possible answers that range from 1 (‘poor’) to 4 (‘excellent’), producing a total rating that can range from 13 to 52 – higher ratings indicate better HRQoL. Patient and carer versions are available.

Bosboom and colleagues have shown that the instructions offered to carers on
how to rate the scale can affect the ratings (Bosboom et al., 2012). Hence, in the present study, carers were specifically instructed to rate the quality of life of the person with AD they cared for according to their own perception. Also, QoL-AD ratings of people with AD and carers provide valuable information when used separately, not as a QoL-AD composite ratings (Bosboom et al., 2012). For this reason, we treated the self and carer ratings as separate outcome measures. Item 7, “Marriage”, of the QoL-AD was excluded because 36% of participants were widowed or not in a relationship. We calculated the percentage of the maximum QoL-AD score (%MaxSc) by dividing the total raw score by the maximum scale score and multiplying this figure by 100. The primary outcome measure was the %MaxSc at 18-month minus the %MaxSc at baseline.

6.3.4. **EXPOSURES: CHANGE IN COGNITIVE FUNCTIONING**

**(a) SPECIFIC COGNITIVE FUNCTIONS**

We used a broad battery of established neuropsychological tests to assess specific cognitive functions commonly affected by AD: episodic memory, naming, language comprehension, word fluency, psychomotor speed, inhibition, cognitive switching, working memory, visuospatial organisation and constructional abilities (Reed et al., 2007; Schmand et al., 2011).

- The Boston Naming Test short 30-item version (BNT30) is a visual naming test of object ink drawings ranging in familiarity from common to less common objects (Graves et al., 2004). The test is commonly used to assess expressive language (i.e. naming impairment). The total score (maximum 30) was calculated by adding the number of correct items without the correct responses following semantic or phonetic cues.

- The California Verbal Learning Test (CVLT-II) is a robust measure of episodic verbal learning that allows for the use of a semantic association strategy, with good psychometric properties, including test-retest reliability and usefulness in longitudinal evaluations (Woods et al., 2006). We selected the Short Form that features a list of nine words in three categories. The following scores were included: total recall on Trial 1 to 4 (maximum 36), short delay free recall, short delay cued recall, long delay free recall, long delay cued recall, and yes/no recognition hits (all maximum 9).
The Delis-Kaplan Executive Function System (D-KEFS) represents a set of tests designed to assess various aspects of executive functioning (Delis et al., 2001). The subtests can be administered as stand-alone tests. We selected the subtest Word Fluency and calculated the total score for Letter Fluency (FAS) and the total score for Category Fluency (Animals and Boys names). We also used the subtest Trail Making Test and calculated the total scores on the five conditions, that is 1) Visual scanning, 2) Number sequencing, 3) Letter sequencing, 4) Number-Letter switching, and 5) Motor speed.

Digit Span Subtest of the Wechsler Adult Intelligence Scale III (WAIS-III) was used to assess attention and working memory (Wechsler, 1997). Digit Span Forward is considered a measure of efficiency of attention (i.e. freedom of distractibility). Digit Span Backward requires the examinee to repeat digits in the reverse order of presentation, and is thought to require storage plus the concurrent processing requirement to mentally reorder the information. We calculated the total score on Digit Span Forward (maximum 16), and on Digit Span Backward (maximum 14). We also calculated the length of the correctly replied longest Digit Span Forward (maximum 9) and Digit Span Backward (maximum 8).

Digit Symbol Coding subtest of the WAIS-III (Wechsler, 1997) was selected as psychomotor speed measure, although motor persistence, sustained attention and visuomotor coordination may also contribute to performance (Wechsler, 1997; Schear and Sato, 1989). Research suggests that speed is the prime determinant of Digit Symbol Coding performance, with memory playing a subsidiary role (Joy et al., 2004). The contribution of speed to Digit Symbol Coding has been operationalized as the Digit Symbol Copy test (Wechsler, 1997). Digit Symbol Copy is essentially Digit Symbol stripped of the coding element. Symbols are printed in the upper half of each box; examinees are instructed to copy each symbol into the lower half. We calculated the number of correct responses produced over 2 minutes.

The Neuropsychological Assessment Battery (NAB) is a comprehensive modular battery of tests developed to assess various cognitive skills in adults aged 18-97 years (Stern and White, 2003). We used the NAB Screening Module Language subtest for auditory comprehension (including colours, shapes and numbers) and calculated the total score (maximum 56).
Rey Complex Figure Test (RCFT) assesses visuospatial organisation and construction abilities (RCFT copy by drawing), as well as visual memory (RCFT recall by drawing) (Meyers and Meyers, 1995). The participants were requested to copy the complex figure and, without pre-notice, reproduce it after a 3-minute delay. We calculated the total scores for copy and for recall (both to a maximum 36).

The Visual Association Test (VAT) is a brief paired-associate learning test, based on imagery mnemonics in which participants have to remember visually presented line drawing of unusual pairs of interacting objects or animals, for example an ape holding an umbrella (Lindeboom et al., 2002). At the assessment, participants are presented one element of the pair as prompt (e.g., monkey—?). Initially, participants are asked to name each object presented and, immediately afterwards, the person is presented with one object from the pair and asked to name the other. Responses may be oral, written, drawn, or mimed. One point is awarded if the response is sufficiently clear to distinguish the target object from the other objects used in the test. The maximum score is 6 points.

(B) GLOBAL COGNITIVE FUNCTIONING

The Cambridge Cognitive Examination of the Elderly, revised version (CAMCOG-R) is a widely used cognitive measure that provides a general measure of cognitive function, and has shown sensitivity over time (Roth et al., 1998). The total score on the CAMCOG-R ranges between 0 (severe cognitive impairment) and 105 (no cognitive impairment).

6.3.5. OTHER STUDY MEASURES

We collected demographic, lifestyle and medical background information at the baseline and the 18-month assessments. Other study measures administered included: Anosognosia Questionnaire (AQ), Hospital Anxiety and Depression Scale (HADS), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Katz’ Activities of Daily Living scale, Lawton and Brody’s Instrumental Activities of Daily Living scale (Lawton & Brody’s IADL), and Neuropsychiatric Inventory (NPI) (Bosboom et al., 2012). These measures were selected to collect information about behavioural and psychological symptoms of dementia, awareness, and independence in activities of daily life from different perspectives (e.g. AQ consists of self-reported and
carer-reported versions of patient’s performance in basic and instrumental activities of daily living).

6.3.6. PROCEDURES

We posted the study questionnaire, as well as the AQ, HADS, IQCODE, Katz’ ADL and Lawton & Brody’s IADL scales to participants for completion prior to a face-to-face assessment. During the face-to-face assessment, responses to each of the study questionnaires were checked for completeness, and factual information regarding demographic facts and clinical characteristics were checked for accuracy with the carer. All assessments were completed by a senior clinical neuropsychologist (PB). The QoL-AD was administered with the participant with AD and their carer separately. The same procedures were used for the 18-month assessment.

6.3.7. STATISTICAL ANALYSES

The data were managed and analyzed with STATA version 12.1 (StataCorp, College Station, Texas). Continuous variables were summarized by their mean and standard deviation (SD), and categorical variables by their count and proportions. Pearson correlations were performed to identify bivariate associations. We used the change in QoL-AD ratings to group participants into two groups: stable or improved versus declining QoL-AD ratings over 18 months. We then compared the baseline and 18-month scores on the cognitive tests of these subgroups using non-parametric Wilcoxon signed-rank tests (the distribution of scores was skewed and did not improve sufficiently after logarithmic transformation).

We calculated the 18-month change of scores as the score at 18 months minus the score at baseline, and subsequently standardized (z-scores) these differences to create a uniform scale for all tests. Logistic regression analyses were used to calculate the crude odds ratio (OR) and respective 95% confidence interval (95%CI) of stable/improved QoL ratings by standardized changes of specific cognitive domains. Variables that showed a lack of sensitivity to change on visual inspection of histograms were excluded from the analyses. Finally, we adjusted the logistic regression models for sociodemographic, lifestyle and clinical variables that were associated with changes in quality of life and with cognitive function (Bosboom et al., 2013). Given the number of comparisons that we planned to make, alpha was set at 1%. All statistical tests reported are two-tailed.
6.4. RESULTS

6.4.1. PARTICIPANTS

The mean age (± SD) of the 47 participants with AD was 78.7 ± 8.2, years (range 62-92) at the time of entry into the study. 72.3% were women and the mean number of years of education was 10.2 ± 2.1 years (range 8-16). After 18 months, measures of ADL, IADL and awareness had deteriorated. The proportion of participants who were involved in community activities and participants who were driving had decreased, while the number of visits to GPs during the preceding 6 months increased, as did the burden-of-care at follow-up. Further details regarding the demographic and clinical characteristics of participants have been reported elsewhere (Bosboom et al., 2013).

6.4.2. CHANGES IN HRQoL OVER 18 MONTHS

There was a significant decline (8.7%, p = 0.003) in carer-reported QoL-AD ratings (+%MaxSc) over 18 months (mean baseline 62.2 ± 10.5; mean 18-months 56.8 ± 11.5; t-paired = 3.124, p = 0.003), but not in self-reported QoL-AD (mean baseline 71.9 ± 11.5; mean 18-months 70.7 ± 10.5; t-paired = 0.802; p = 0.427). Of the carer-reported QoL-AD ratings, 20 (42.6%) remained stable or increased over 18 months, while for self-reported QoL-AD ratings 26 (55.3%) remained stable or increased over 18 months.

6.4.3. CHANGES IN COGNITION OVER 18 MONTHS

The cognitive scores at baseline and after 18 months of participants with stable/improved and worse QoL-AD are presented in Table 6.1. For the subgroup of stable/increased as well as the subgroup of decreased self-reported QoL-AD ratings we found a significant decline on the scores of the CAMCOG-R (z = 4.02, p < 0.001; z = 3.74, p < 0.001), Digit Symbol copy (z = 3.27, p = 0.001; z = 3.08, p = 0.002), and NAB Language comprehension (z = 3.49, p < 0.001; z = 3.09, p = 0.002). In addition, for the subgroup of participants with AD who had stable/increased self-reported QoL-AD ratings, we found a significant decline on the CVLT-II trial 1-4 (z = 3.31, p < 0.001), CVLT-II short delay free recall (z = 3.63, p < 0.001), CVLT-II long delay free recall (z = 2.63, p = 0.009), CVLT-II long delay cued recall (z = 2.56, p = 0.010), and Digit Span forward (z = 2.63, p = 0.009). For participants with AD and decreased self-reported QoL-AD ratings, we observed a significant decline on the Digit Span backward scores (z = 2.72, p = 0.007).
For the subgroup with stable/increased as well as the subgroup with decreased carer-reported QoL-AD ratings, we observed a significant decline on the CAMCOG-R (z = 3.01, p = 0.003; z = 4.41, p < 0.001), Digit Symbol copy (z = 2.89, p = 0.004; z = 3.54, p < 0.001), and NAB Language comprehension (z = 2.74, p = 0.006; z = 3.81, p < 0.001). In addition, for the subgroup of participants with AD with stable/increased carer-reported QoL-AD ratings, we found significant decline on the CVLT-II long delay free recall (z = 2.62, p = 0.009),; for the subgroup of AD participants with decreased carer-reported QoL-AD ratings, we found significant decline on the CVLT-II 1-4 (z = 3.39, p =<0.001), Digit Span backward (z = 2.80, p = 0.005), Digit Span longest backward (z = 2.69, p = 0.007), Digit Symbol Coding (z = 3.13, p = 0.002), RCFT recall (z = 2.63, p = 0.008), TMT 3 (z = -2.66, p = 0.008), and TMT 5 (z = -2.88, p = 0.004).

6.4.4. COGNITIVE MEASURES AND ASSOCIATION WITH HRQoL AFTER 18 MONTHS
Logistic regression analyses (Table 6.2) showed that for every increase in one standardized (z) score on the ‘CVLT-II short delay free recall’ the odds of stable/increased self-rated QoL-AD over 18 months were 0.27 (95%CI: 0.11, 0.67; p = 0.005). After adjustment for differences on the HADS Anxiety and Depression scores, this inverse association no longer met the study criteria for statistical significance (adjusted OR: 0.31, 95%CI: 0.11, 0.86; p = 0.025). None of the other standardised changes of cognitive scores were associated with self-rated QoL-AD grouping.

For the carer-reported QoL-AD ratings, we found that an increase of one standardized (z) score on the CAMCOG-R increased the odds of stable/increased carer-ratings on the QoL-AD over 18 months by 2.3 times, but not at a statistically significant level (95%CI: 1.06, 5.15; p = 0.036). In addition, we found that an increase on category fluency (crude OR: 2.29, 95%CI: 1.06, 4.98, p = 0.035; adjusted OR: 5.52, 95%CI: 1.06, 28.80, p = 0.043), and Digit Symbol Coding (crude OR: 2.25, 95%CI: 1.04, 4.85, p = 0.039; adjusted OR: 1.85, 95%CI: 0.71, 4.85, p = 0.210) increased the odds of stable/increased carer-ratings, but failed to reach threshold for statistical significance. Change in standardized time to complete the TMT 5 was associated with an OR of 0.16, (95%CI: 0.03, 0.86, p = 0.032).
Table 6.1. Comparison of raw scores on cognitive tests by participants with Alzheimer’s disease at baseline and 18-months follow-up, separately for subgroups of self-reported or carer-reported stable/increased or declined QoL-AD ratings.

<table>
<thead>
<tr>
<th>Tests</th>
<th>QoL-AD stable/increased</th>
<th>Self-reported</th>
<th>QoL-AD declined</th>
<th>Carer-reported</th>
<th>QoL-AD stable/increased</th>
<th>Self-reported</th>
<th>QoL-AD declined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=26</td>
<td>n=21</td>
<td>n=20</td>
<td>n=27</td>
<td>n=26</td>
<td>n=21</td>
<td>n=27</td>
</tr>
<tr>
<td>CAMCOG-R</td>
<td>64.5 (12.7)</td>
<td>61.4 (11.2)</td>
<td>64.1 (13.7)</td>
<td>62.5 (10.9)</td>
<td>52.0 (18.9)</td>
<td>45.0 (20.7)</td>
<td>55.0 (20.1)</td>
</tr>
<tr>
<td>BNT30 correct</td>
<td>13.4 (8.5)</td>
<td>12.6 (10.3)</td>
<td>14.4 (8.7)</td>
<td>12.0 (9.7)</td>
<td>10.9 (8.3)</td>
<td>10.9 (10.1)</td>
<td>14.1 (8.7)</td>
</tr>
<tr>
<td>Category fluency</td>
<td>19.2 (7.3)</td>
<td>18.2 (9.1)</td>
<td>19.1 (7.0)</td>
<td>18.5 (8.9)</td>
<td>17.2 (8.9)</td>
<td>14.1 (11.8)</td>
<td>19.6 (7.6)</td>
</tr>
<tr>
<td>CVLT-II trial 1-4</td>
<td>16.1 (4.9)</td>
<td>11.6 (8.7)</td>
<td>15.6 (4.6)</td>
<td>12.8 (8.5)</td>
<td>11.7 (6.5)</td>
<td>9.8 (8.7)</td>
<td>14.3 (5.6)</td>
</tr>
<tr>
<td>CVLT-II sdfr</td>
<td>2.5 (1.7)</td>
<td>1.1 (1.8)</td>
<td>2.0 (1.9)</td>
<td>1.7 (1.9)</td>
<td>0.7 (0.9)</td>
<td>0.9 (1.4)</td>
<td>1.1 (1.2)</td>
</tr>
<tr>
<td>CVLT-II ldfr</td>
<td>0.9 (1.6)</td>
<td>0.5 (1.1)</td>
<td>1.0 (1.4)</td>
<td>0.5 (1.4)</td>
<td>0.1 (0.3)</td>
<td>0.2 (0.7)</td>
<td>0.3 (0.8)</td>
</tr>
<tr>
<td>CVLT-II hits</td>
<td>1.0 (1.1)</td>
<td>1.1 (1.8)</td>
<td>1.4 (1.7)</td>
<td>0.8 (1.2)</td>
<td>0.4 (0.6)</td>
<td>0.9 (1.4)</td>
<td>0.8 (1.3)</td>
</tr>
<tr>
<td>CVLT-II VAT</td>
<td>5.5 (3.3)</td>
<td>3.9 (4.1)</td>
<td>5.4 (3.1)</td>
<td>4.3 (4.1)</td>
<td>4.5 (3.3)</td>
<td>3.7 (3.9)</td>
<td>5.9 (2.9)</td>
</tr>
<tr>
<td>Digit Span forward</td>
<td>8.1 (1.9)</td>
<td>7.7 (2.5)</td>
<td>7.8 (1.5)</td>
<td>7.9 (2.6)</td>
<td>6.8 (2.8)</td>
<td>5.7 (3.5)</td>
<td>7.3 (1.2)</td>
</tr>
<tr>
<td>Digit Span backward</td>
<td>5.0 (2.0)</td>
<td>4.6 (1.8)</td>
<td>4.9 (1.8)</td>
<td>4.8 (2.0)</td>
<td>4.2 (2.4)</td>
<td>2.8 (2.2)</td>
<td>4.1 (1.6)</td>
</tr>
<tr>
<td>Digit Span lgst fwd</td>
<td>5.4 (1.1)</td>
<td>5.2 (1.6)</td>
<td>5.4 (0.9)</td>
<td>5.3 (1.5)</td>
<td>4.5 (2.0)</td>
<td>3.9 (2.4)</td>
<td>5.1 (0.7)</td>
</tr>
<tr>
<td>Digit Span lgst bwd</td>
<td>3.9 (1.1)</td>
<td>3.6 (1.1)</td>
<td>3.8 (0.9)</td>
<td>3.8 (1.2)</td>
<td>3.3 (1.8)</td>
<td>2.6 (1.9)</td>
<td>3.6 (1.3)</td>
</tr>
<tr>
<td>Digit Symbol coding</td>
<td>26.2 (13.8)</td>
<td>19.2 (16.8)</td>
<td>29.9 (16.6)</td>
<td>18.1 (12.9)</td>
<td>22.5 (19.0)</td>
<td>12.7 (14.6)</td>
<td>29.9 (16.9)</td>
</tr>
<tr>
<td>Digit Symbol copy</td>
<td>59.8 (29.9)</td>
<td>48.7 (35.3)</td>
<td>70.3 (27.5)</td>
<td>44.2 (32.2)</td>
<td>35.4 (29.7)</td>
<td>25.7 (29.4)</td>
<td>51.4 (25.2)</td>
</tr>
<tr>
<td>Letter fluency</td>
<td>22.2 (13.5)</td>
<td>14.4 (14.6)</td>
<td>22.8 (12.9)</td>
<td>15.5 (14.9)</td>
<td>21.0 (14.1)</td>
<td>13.4 (13.4)</td>
<td>23.1 (13.1)</td>
</tr>
<tr>
<td>NAB comprehension</td>
<td>53.6 (5.1)</td>
<td>52.8 (3.8)</td>
<td>53.3 (5.5)</td>
<td>53.2 (3.9)</td>
<td>47.5 (14.1)</td>
<td>42.4 (19.4)</td>
<td>49.5 (10.8)</td>
</tr>
<tr>
<td>RCFT copy</td>
<td>20.5 (8.7)</td>
<td>19.6 (9.5)</td>
<td>21.3 (9.8)</td>
<td>19.1 (8.2)</td>
<td>18.5 (12.6)</td>
<td>13.4 (13.0)</td>
<td>19.9 (11.9)</td>
</tr>
<tr>
<td>RCFT recall</td>
<td>2.4 (2.9)</td>
<td>1.4 (2.3)</td>
<td>2.7 (2.7)</td>
<td>1.4 (2.5)</td>
<td>1.8 (3.5)</td>
<td>0.7 (1.8)</td>
<td>2.3 (3.7)</td>
</tr>
<tr>
<td>TMT 1 (sec.)</td>
<td>46.5 (34.3)</td>
<td>65.4 (45.9)</td>
<td>42.6 (28.1)</td>
<td>64.5 (46.3)</td>
<td>50.1 (33.7)</td>
<td>76.3 (54.0)</td>
<td>43.3 (28.3)</td>
</tr>
<tr>
<td>TMT 2</td>
<td>93.9 (34.0)</td>
<td>106.9 (44.9)</td>
<td>83.7 (34.8)</td>
<td>64.5 (46.3)</td>
<td>112.0 (41.1)</td>
<td>124.6 (33.1)</td>
<td>104.1 (41.9)</td>
</tr>
<tr>
<td>TMT 3</td>
<td>109.1 (34.5)</td>
<td>119.1 (38.0)</td>
<td>107.4 (37.3)</td>
<td>118.3 (35.4)</td>
<td>124.3 (42.9)</td>
<td>132.8 (33.9)</td>
<td>115.1 (47.4)</td>
</tr>
<tr>
<td>TMT 4</td>
<td>216.2 (43.3)</td>
<td>236.6 (14.4)</td>
<td>224.8 (37.9)</td>
<td>226.7 (31.9)</td>
<td>233.7 (20.3)</td>
<td>237.1 (13.3)</td>
<td>231.9 (22.8)</td>
</tr>
<tr>
<td>TMT 5</td>
<td>61.3 (34.9)</td>
<td>75.6 (45.6)</td>
<td>59.4 (33.7)</td>
<td>74.2 (44.2)</td>
<td>85.2 (51.1)</td>
<td>93.9 (51.7)</td>
<td>58.7 (31.7)</td>
</tr>
<tr>
<td>VAT</td>
<td>1.9 (8.8)</td>
<td>1.2 (1.5)</td>
<td>1.9 (1.7)</td>
<td>1.3 (1.7)</td>
<td>1.0 (1.6)</td>
<td>0.9 (1.4)</td>
<td>1.5 (1.6)</td>
</tr>
</tbody>
</table>

Abbreviations: BL, baseline assessment; BNT30, Boston Naming Test 30 items version; bwd, backward; CAMCOG-R, Cambridge Cognitive Examination of the Elderly Revised; CVLT-II, California Verbal Learning Test version II; fwd, forward; FU, follow up assessment; ldfr, long delay cued recall; ldfr, long delay free recall; Igst, longest; NAB, Neuropsychological Assessment Battery Language Comprehension; RCFT, Rey Complex Figure Test; sdfr, short delay free recall; TMT, Trail Making Test (D-KEFS); QoL, Quality of life; QoL-AD, Quality of life in Alzheimer’s disease; VAT, Visual Association Test; 95% CI, 95% confidence interval.

* Non-parametric Wilcoxon signed-rank test.
Table 6.2. Odds ratio (95\% CI) of stable or higher QoL-AD ratings (i.e. %MaxSc) per standardized change in cognitive scores over 18-months.

<table>
<thead>
<tr>
<th>Changes on (sub)tests:</th>
<th>Self-reported QoL-AD</th>
<th>Carer-reported QoL-AD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI p</td>
<td>OR 95% CI p</td>
</tr>
<tr>
<td>CAMCOG-R</td>
<td>1.34 (0.73, 2.44) 0.334</td>
<td>2.33 (1.06, 5.15) 0.036(^2)</td>
</tr>
<tr>
<td>BNT30 correct</td>
<td>0.91 (0.49, 1.68) 0.755</td>
<td>1.45 (0.75, 2.80) 0.266</td>
</tr>
<tr>
<td>Category fluency</td>
<td>1.29 (0.69, 2.38) 0.419</td>
<td>2.29 (1.06, 4.98) 0.035(^3)</td>
</tr>
<tr>
<td>CVLT-II trial 1-4</td>
<td>0.62 (0.31, 1.25) 0.178</td>
<td>1.78 (0.84, 3.77) 0.129</td>
</tr>
<tr>
<td>CVLT-II sdrv</td>
<td>0.27 (0.11, 0.67) 0.005(^1)</td>
<td>1.09 (0.58, 2.03) 0.795</td>
</tr>
<tr>
<td>CVLT-II ldcr</td>
<td>0.68 (0.35, 1.33) 0.259</td>
<td>0.68 (0.35, 1.31) 0.249</td>
</tr>
<tr>
<td>CVLT-II hits</td>
<td>0.84 (0.45, 1.56) 0.573</td>
<td>1.48 (0.76, 2.87) 0.249</td>
</tr>
<tr>
<td>Digit Span forward</td>
<td>1.21 (0.65, 2.27) 0.534</td>
<td>1.85 (0.87, 3.94) 0.110</td>
</tr>
<tr>
<td>Digit Span backward</td>
<td>1.54 (0.80, 2.94) 0.195</td>
<td>1.52 (0.79, 2.91) 0.208</td>
</tr>
<tr>
<td>Digit Span lr gfd</td>
<td>1.17 (0.63, 2.16) 0.626</td>
<td>1.89 (0.90, 3.98) 0.091</td>
</tr>
<tr>
<td>Digit Span lr gbd</td>
<td>1.26 (0.68, 2.36) 0.463</td>
<td>1.98 (0.96, 4.09) 0.065</td>
</tr>
<tr>
<td>Digit Symbol coding</td>
<td>1.27 (0.68, 2.37) 0.460</td>
<td>2.25 (1.04, 4.85) 0.039(^4)</td>
</tr>
<tr>
<td>Digit Symbol copy</td>
<td>0.94 (0.51, 1.75) 0.853</td>
<td>1.41 (0.73, 2.73) 0.311</td>
</tr>
<tr>
<td>Letter fluency</td>
<td>0.99 (0.54, 1.79) 0.972</td>
<td>1.21 (0.66, 2.23) 0.536</td>
</tr>
<tr>
<td>NAB comprehension</td>
<td>1.36 (0.72, 2.56) 0.339</td>
<td>2.04 (0.78, 5.31) 0.146</td>
</tr>
<tr>
<td>RCFT copy</td>
<td>1.59 (0.84, 3.01) 0.158</td>
<td>1.66 (0.85, 3.24) 0.137</td>
</tr>
<tr>
<td>RCFT recall</td>
<td>1.03 (0.56, 1.88) 0.934</td>
<td>1.22 (0.66, 2.27) 0.528</td>
</tr>
<tr>
<td>TMT 1 (sec.)</td>
<td>0.81 (0.43, 1.50) 0.501</td>
<td>0.71 (0.35, 1.43) 0.338</td>
</tr>
<tr>
<td>TMT 2</td>
<td>1.01 (0.56, 1.84) 0.968</td>
<td>1.12 (0.61, 2.06) 0.716</td>
</tr>
<tr>
<td>TMT 3</td>
<td>1.04 (0.57, 1.89) 0.894</td>
<td>0.73 (0.39, 1.38) 0.330</td>
</tr>
<tr>
<td>TMT 5</td>
<td>1.15 (0.63, 2.11) 0.652</td>
<td>0.16 (0.03, 0.86) 0.032(^5)</td>
</tr>
<tr>
<td>VAT</td>
<td>0.68 (0.35, 1.32) 0.253</td>
<td>1.21 (0.64, 2.31) 0.554</td>
</tr>
</tbody>
</table>

Abbreviations: BL, baseline assessment; BNT30, Boston Naming Test 30 items version; blwd, backward; CAMCOG-R, Cambridge Cognitive Examination of the Elderly Revised; CVLT-II, California Verbal Learning Test version II; fwd, forward; FU, follow up assessment; ldcr, long delay cued recall; ldfr, long delay free recall; lgst, longest; NAB, Neuropsychological Assessment Battery Language Comprehension; RCFT, Rey Complex Figure Test; sdrv, short delay free recall; TMT, Trail Making Test (D-KEFS); QoL, Quality of life; QoL-AD, Quality of life in Alzheimer’s disease; VAT, Visual Association Test; 95% CI, 95% confidence interval.

Note. Significant p-values were adjusted for identified univariate associations (i.e. p < 0.05) for difference between bl and fu in self- and carer-rated QoL-AD, exclusive cognition related variables (Bosboom et al., 2013):

1 After adjustment for differences on the HADS Anxiety and HADS Depression: adjusted OR 0.31 (95% CI 0.11, 0.86), p = 0.025.
2 After adjustment for differences on the HADS Depression, NPI, NPI Burden-of-care: adjusted OR 4.99 (95% CI 1.21, 20.64), p = 0.026.
3 After adjustment for differences on the HADS Depression, NPI, NPI Burden-of-care: adjusted OR 5.52 (95% CI 1.06, 28.80), p = 0.043.
4 After adjustment for differences on the HADS Depression, NPI, NPI Burden-of-care: adjusted OR 1.85 (95% CI 0.71, 4.85), p = 0.210.
5 After adjustment for differences on the HADS Depression, NPI, NPI Burden-of-care: adjusted OR 0.14 (95% CI 0.02, 1.10), p = 0.062.
6.4.5. POST-HOC ANALYSES

One of the items of the QoL-AD specifically requires participants to indicate how one’s memory functioning is related to one’s quality of life (i.e. item 5 ‘Memory’ of the QoL-AD questionnaire). The change over 18 months of self-ratings and carer-ratings were not statistically significant (data not shown). To determine the association between the self-reported QoL-AD item ‘Memory’ and scores on specific memory tests, we performed pairwise correlation analyses. Self-reported ‘Memory’ was directly associated with the QoL-AD rating at baseline as well as at follow-up (resp. $r = 0.48, p < 0.001; r = 0.43, p < 0.003$).

At the baseline and 18-month assessments, the carer-reported QoL-AD item ‘Memory’ was directly associated with the QoL-AD total score (resp. $r = 0.52, p =< 0.001; r = 0.36, p = 0.017$). The difference over 18 months of the carer-reported item ‘Memory’ was directly associated with the difference on the QoL-AD total score ($r = 0.51, p <0.001$).

Finally, we performed exploratory analyses to examine associations in the subgroups of participants with AD who had mild (total score on the MMSE of 20 or higher) or moderate dementia (MMSE 10-19) at the time of enrolment. We found no significant differences between these subgroups on changes in the self-reported HRQoL or the carer-reported HRQoL (data not shown).

6.5. DISCUSSION

6.5.1 MAIN FINDINGS
The results of this study show that a decline of episodic memory over 18 months is associated with stable or improved self-reported HRQoL in people with AD. We found no evidence of association between changes of specific cognitive functions and changes in carer-reported HRQoL. These findings are not consistent with the hypothesis that changes in episodic memory are directly associated with changes in HRQoL ratings, and are at odds with the expectation that interventions that improve episodic memory in AD should also improve the quality of life of participants.

6.5.2. LIMITATIONS
We acknowledge that our study limited the collection of data to two time-points. Consequently, we are unable to comment whether the observed changes are linear or
not, or if changes over shorter or longer periods of time would show a different pattern of association with HRQoL. Secondly, one of our participants had early-onset AD (age 62 years) and could, conceivably, have a different cognitive profile compared with the remainder of the sample, although detailed analysis did not suggest that this participant was an outlier. Thirdly, our participants were volunteers with mild to moderate dementia living in the community. We cannot be certain that they represent well the population of people with AD, in particular those with more severe illness living in residential care facilities. Fourthly, the QoL-AD is a measure of HRQoL, so we are unable to comment on other relevant aspects of the quality of life of participants that were not assessed by the QoL-AD. Fifthly, due to the multiple comparisons and the risk of chance associations, we elected to apply a stringent criterion of statistical significance (i.e. alpha of 1%). It is unclear whether this would have increased the risk of type II error, although the strength of the associations that we observed were small and, even if statistically significant, would most likely have been of limited clinical relevance. We also acknowledge that a relatively high number of participants was lost to follow up (35%, including 7 deaths). Although we did not find significant differences in HRQoL ratings between completers and dropouts at baseline, loss of power and bias due to the selection of healthier participants could conceivably have affected the results and compromised the generalizability of the findings.

This study has the merit of applying the previously recommended separate use of the patient’ and carer (as proxy) rated QoL-AD total rather than composite scores (Bosboom et al., 2012). Also, by applying a broad spectrum of well-established neuropsychological tests assessing cognitive abilities commonly associated with AD, we were able to investigate associations between specific cognitive functions and HRQoL that could have been missed by previous studies that had limited their assessments to global cognitive measures like the MMSE, ADAS-Cog or CAMCOG-R. This study contributes to the recognized lack of knowledge about the course of HRQoL in dementia (Banerjee et al., 2009).

6.5.3. INTERPRETATION OF THE FINDINGS

To our knowledge, this is the first study that investigated the association between specific cognitive functions and HRQoL of people with AD, as reported by the patients and their carers. We found that for every increase in one standardized score on the ‘CVLT-II short delay free recall’ the odds of stable/increased self-rated QoL-AD over
18 months decreased 73%. After adjustment for differences on the HADS Anxiety and HADS Depression scores, this inverse association lost significance with alpha set at 1%. These results raise questions regarding the assumption that improved memory scores associated with interventions will lead to improved HRQoL ratings. They may also suggest that as the disease progresses the increasing severity of cognitive deficits are offset by decreasing awareness of impairment, and that this may override the impact of cognitive changes on the HRQoL scores of people with AD.

HRQoL ratings have been associated with information processing speed in multiple sclerosis (Barker-Collo, 2006); memory and constructional abilities in closed-head injury (Klonoff et al., 1986); psychomotor speed, verbal memory and language in epilepsy (Perrine et al., 1995); executive functioning, processing speed, concentration, working memory and verbal memory in schizophrenia (Tolman and Kurtz, 2012); various specific cognitive deficits, including visual perception, in stroke (Nys et al., 2006). In AD, our findings indicate that interventions that aim to optimize self-reported HRQoL may benefit from focusing on areas other than primarily cognitive function, such as, symptoms of anxiety and depression (Bosboom et al., 2012; Cooper et al., 2013; Tatsumi et al., 2009; Bosboom et al., 2013). A large proportion of people with AD are affected by behavioural and psychological symptoms of dementia (BPSD) at some point during the course of their illness, and evidence from clinical trials of both non-pharmacological and pharmacological treatments provides a range of multidisciplinary management options that can be tailored to individual needs (Gauthier et al., 2010; Wolfs et al., 2008). Current findings support the recommendation that improving our management of BPSD might favorably affect the HRQoL of people with mild to moderate AD and, possibly, contribute to delay the transition from home to residential care (Wolfs et al., 2008).

6.5.4. CONCLUSION

Our results indicate that changes in specific cognitive functions are not associated with changes in the HRQoL ratings of people with AD. These findings, if confirmed by other studies, would suggest that interventions that focus solely on improving the cognitive function of people with AD might fail to improve their quality of life. If improving the quality of life of people with AD is the ultimate aim of our interventions, then factors other than performance on cognitive tests should gain greater prominence in our treatment plans.
CHAPTER 7.

USE OF POTENTIALLY HARMFUL MEDICATIONS AND HEALTH-RELATED QUALITY OF LIFE AMONG PEOPLE WITH DEMENTIA LIVING IN RESIDENTIAL AGED CARE FACILITIES

7.1. ABSTRACT

**Background:** Use of potentially harmful medications (PHMs) is common in people with dementia living in Residential Aged Care Facilities (RACFs) and increases the risk of adverse health outcomes. Debate persists as to how PHM use and its association with quality of life should be measured. We designed this study to determine the association of exposure to PHM, operationalized by three different measures, with self-reported Health-Related Quality of Life (HRQoL) among people with dementia in RACFs.

**Methods:** Cross-sectional study of 351 people aged >65 years diagnosed with dementia residing in RACFs and with MMSE <24. The primary outcome measure was the self-rated Quality of Life – Alzheimer’s disease questionnaire (QoL-AD). We collected data on patients’ medications, age, gender, MMSE total score, Neuropsychiatric Inventory total score, and comorbidities. Using regression analyses, we calculated crude and adjusted mean differences between groups exposed and not exposed to PHM according to potentially inappropriate medications (PIMs; identified by Modified Beers criteria), Drug Burden Index (DBI) >0 and polypharmacy (i.e. >5 medications).

**Results:** Of 226 participants able to rate their QoL-AD, 56.41% were exposed to at least one PIM, 82.05% to medication contributing to DBI 1 0, and 91.74% to polypharmacy. Exposure to PIMs was not associated with self-reported QoL-AD ratings, while exposure to DBI >0 and polypharmacy were (also after adjustment); exposure to DBI >0 tripled the odds of lower QoL-AD ratings.

**Conclusion:** Exposure to PHM, as identified by DBI >0 and by polypharmacy (i.e. >5 medications), but not by PIMs (Modified Beers criteria), is inversely associated with self-reported HRQoL for people with dementia living in RACFs.

7.2. INTRODUCTION

The use of potentially harmful medications (PHMs) is common in later life and is associated with an increased risk of unfavourable health outcomes, including adverse drug events, morbidity, mortality and increased healthcare use (Beer et al., 2011; Franic & Jiang, 2006; Gurwitz et al., 2000; Klarin et al., 2005; Lau et al., 2005; Lindley et al., 1992). Use of medication in older age is complicated by several factors, including changes in pharmacokinetics and the presence of multiple comorbidities (Basger et al, 2008; Elmstahl et al., 1998; Gallagher et al., 2008). Consequently, use of PHM is a source of concern that is likely to become more prevalent in the future as the world’s
population ages (Hamilton et al., 2009; Spinewine et al., 2007).

Observational studies have found use of PHM among Australians, with a worryingly high prevalence of the use of antipsychotics, antidepressants, and sedative-hypnotic drugs (Hollingworth et al., 2001). In a recent study we also found evidence that people with dementia (PWD) living in Residential Aged Care Facilities (RACFs) in Western Australia continue to be frequently exposed to polypharmacy, prescription of contraindicated medications, antipsychotics, medications with high anticholinergic burden, and combinations of potentially inappropriate medications (PIMs) (Somers et al., 2010). These patterns of prescribing are not always in agreement with existing evidence-based guidelines (Hamilton et al., 2009; Ballard & Howard, 2006; Burke & Tariot, 2009). Thus, there is a pressing need to know more about the epidemiology and sociology of medication use by older adults in Australia that in many cases may be unnecessary, costly and potentially harmful.

Despite its importance, there is still debate as how to identify the use of PHM and several methods or clinical tools have been proposed. A common approach is the use of the Beers criteria (Fick et al., 2003). The Beers criteria comprise a list of PIMs that should be avoided altogether, as well as doses, frequencies and duration of other medications that should be avoided in older adults. Use of PIMs has been associated with higher medical costs, increased rates of adverse drug events and poorer health outcomes (Fick et al., 2003; Roughead et al., 2007). A more recently developed tool is the Drug Burden Index (DBI), a measure of total exposure to anticholinergic and sedative medications that incorporates the principle of dose-response and maximal effect (Hilmer et al., 2007). DBI has been independently associated with poorer performances in physical and cognitive function in a population of well-functioning community-dwelling older people in the USA (Hilmer et al., 2009). Similar associations have been reported by Cao and colleagues (2008). Recently, Gnjidic et al. (2012) compared the DBI with the Beers criteria in older adults in low-level residential aged care. They found that the Beers criteria did not predict functional outcome, but the DBI did. Another measure to identify the use of PHM, which could assist healthcare practitioners, is polypharmacy (e.g. quantified as ≥5 medications at one time). Polypharmacy per se also appears to be a risk factor for PIM use and adverse outcomes (Frazier, 2005; LeCouteur et al., 2004). However, this apparent relationship may be confounded by the burden of multiple chronic diseases in the older population (Lawlor et al., 2003). Consequently, it is still unclear which of the proposed measures to identify
use of PHM best predicts health outcomes of older people.

The use of PHM has been associated with lower quality of life (Olsson et al., 2001), but this area has been thus far neglected. Health-related quality of life (HRQoL) measures have been identified as important multidimensional outcome measures for the treatment of chronic conditions and are increasingly valued to assess the effect of any intervention on recipients’ interpretation of outcomes (Banerjee et al., 2009; Baumeister et al., 2005; Norris et al., 2008). Surprisingly, the potential association of the use of PHM – by different measures – with HRQoL in older adults has only been studied to a limited extent (Franic & Jiang, 2006; Henderson et al. 2006). Franic and Jiang (2006) found that PIM use was not a significant predictor of HRQoL in a cohort of community-dwelling older adults, while polypharmacy was a significant predictor of HRQoL. The latter association was also reported by Henderson et al. (2006). The identification of robust PHM indicators may be useful for clinicians in their decisions on choosing interventions supporting the improvement of HRQoL of PWD living in RACFs.

This study aimed to determine the association between self-reported HRQoL ratings (as measured with a widely used HRQoL measure, the Quality of Life – Alzheimer’s disease questionnaire, QoL-AD) of PWD living in RACFs and use of PHM, as identified by three different measures, i.e. the PIMs by Modified Beers criteria, DBI and polypharmacy. We hypothesized that self-reported HRQoL ratings would be inversely associated with the PIMs by Beers criteria, the presence of a DBI (i.e. >0) and polypharmacy (i.e. number of medications ≥5).

7.3. METHODS
7.3.1. STUDY DESIGN AND SETTING
The observational data for this cross-sectional study were obtained from the Dementia in residential care: education intervention trial (DIRECT) conducted by the Western Australia Centre for Health and Ageing. The DIRECT study is a prospective randomized controlled trial of educational interventions aiming to improve QoL of PWD living in RACFs, conducted in the metropolitan area of Perth, Western Australia. All RACFs in the Perth Metropolitan area were sent information (n = 184) regarding the DIRECT study and of those, 36 RACFs agreed to participate. Participating RACFs compiled a list of residents to be screened for study participation. General practitioners (GPs) working at the facility and residents meeting the inclusion criteria were invited to
take part. The protocol of this trial has been described in detail elsewhere (Beer et al., 2010).

7.3.2. PARTICIPANTS
All participants of the DIRECT study (n = 351) were permanent residents of a low-level or high-level RACF, aged ≥65 years, with a clinical diagnosis of dementia and a Mini Mental State Examination (MMSE) total score of ≤24. The exclusion criteria included: (1) subject is identified by facility as medically unstable or as suffering from delirium, or in the terminal stages of a comorbid illness; and (2) subject is unable to participate in assessment instruments in English (Beer et al., 2010).

The Human Research Ethics Committee at the University of Western Australia approved this study (RA 4/1/1685). All GPs and RACFs provided written agreement to participate. Research staff applied structured written and verbal consent procedures when the residents of the RACFs with cognitive impairment were approached. The assent of the ‘next of kin’ was required for participation of people with cognitive impairment deemed unable to provide informed consent. This trial was registered (ACTRN12607000417482) on 17/08/2007.

7.3.3. OUTCOME OF INTEREST
The QoL-AD was the primary outcome measure of this study (Logsdon et al., 1999; 2002). The QoL-AD is a short, easy to administer, widely used HRQoL instrument that was designed specifically to assess PWD, with well-established psychometric properties (Logsdon et al., 2002; Thorgrimsen et al., 2003). The scale is composed of 13 items that measure different areas of functioning, selected to reflect relevant areas of the QoL of older adults. Each item offers 4 possible answers that range from 1 (‘poor’) to 4 (‘excellent’), producing a total score where higher scores indicate better QoL. Patient and carer versions are available. The QoL-AD has been modified to produce a 15-item scale (maximum score 60) to assess the QoL of PWD living in RACFs according to a standard set of instructions (Edelman et al., 2005; Sloane et al., 2005).

We have previously shown that QoL-AD ratings of patients and carers are driven by different factors (Bosboom et al., 2012), and provide valuable information when used separately, not as a composite score. For this reason we used only the ratings provided by patients in this study (n = 226). Similarly to the study of Bosboom et al. (2012), item 7 (‘marriage’) of the QoL-AD did not apply to this population. For that
reason this item was not included in the total score. For further comparison possibilities, we calculated the percentage of the maximum QoL-AD score (%MaxSc) by dividing the total raw score by the number of items and multiplying this figure by 100.

### 7.3.4. Exposure Variables

Research staff audited participants’ clinical records to compile a list of all medicines the participants were prescribed at the time of data collection, either as a regular or pro re nata (PRN or ‘as required’) medication. Data on all medications was collected, including conventional medications as well as herbal medications, vitamins and minerals. The drug database was cleaned by removing duplicate drugs, correcting spelling errors, and by converting all drugs to generic names. Medications (including all ‘as required’ medications) were coded according to the World Health Organization Anatomical, Therapeutic, and Chemical Classification System.

To identify the use of PHM, the following measures were used:

- Firstly, we identified PIMs by the Modified Beers criteria (Fick et al., 2003). These definitions and the corresponding data sources have been described elsewhere (Beer et al., 2011). Participants taking at least one PIM were classified as exposed to PIM according to the Modified Beers criteria.
- Secondly, we calculated the DBI. The DBI is an evidence-based tool that utilizes pharmacologic principles to calculate an individual’s total exposure to anticholinergic and sedative medications (Hilmer et al., 2007). The DBI for each participant was calculated as the sum of exposure to each anticholinergic or sedative drug using the equation described by Hilmer et al. (2007) and applied by Gnjidic et al. (2009; 2010). Participants taking at least one anticholinergic or one sedative medication were classified as exposed to DBI.
- Thirdly, we counted the number of medicines for every participant to determine the number of medicines and subsequently the prevalence of participants exposed to polypharmacy, i.e. defined as $\geq$5 medicines (Gnjidic et al., 2012).

### 7.3.5. Other Study Measures

We collected demographic and clinical information from participants, including age (in years), gender and prevalent comorbidities. Comorbidity was classified according to the following groups: cardiovascular diseases (including angina, history of heart attack,
hypertension), cerebrovascular diseases (including history of stroke), respiratory
diseases (including asthma, chronic bronchitis, lung emphysema), heart failure, arthritis
or osteoarthritis, other musculoskeletal disorders (including osteoporosis),
malignancies, mental health disorders other than dementia (including depression,
anxiety), metabolic disorders (including diabetes I or II, thyroid disorders), neurological
disorders (including epilepsy) and others (including allergies).

In addition, we assessed participants’ cognitive abilities with the MMSE
(Folstein et al., 1975) and behavioural and psychological symptoms associated with
dementia using the Neuropsychiatric Inventory (NPI, Cummings, 1997), which was
rated by staff informants. The NPI total score was calculated by the sum of the
frequency rating times the severity rating for all items. Staff informants were required to
have known the resident for at least 2 weeks, and to have observed that resident at least
10 times, for a minimum of one hour in total during the previous two weeks.

7.3.6. **Procedures**
Research assistants were trained in the standard administration of the assessment tools
(including the QoL-AD, MMSE and NPI) and adequate inter-rater reliability was
established (Beer et al., 2009). In face-to-face interviews, participants (PWD) were
handed their own copy of the questionnaire that they could follow, if able to.
Participants were able to indicate responses verbally or by circling the response. If a
participant was unable to offer responses to more than two items, they were considered
unable to complete the measure and their results were excluded from the analyses.

7.3.7. **Statistical Methods**
This project was originally designed as a hypothesis-driven study. We hypothesized that
HRQoL ratings would be inversely associated with the Beers criteria for PIMs, the
presence of a DBI (i.e. >0) and polypharmacy (i.e. ≥5 medications). Continuous
variables were described by their mean and standard deviations, and categorical
variables by their count and proportions.

Initially, we treated the primary outcome (QoL-AD %MaxSc) as a continuous
variable and, using linear regression modelling, we calculated the crude mean
differences between the groups that were exposed to PHM according to the different
definitions (i.e. Modified Beers criteria, DBI and polypharmacy). We calculated the
adjusted mean differences, firstly adjusted for age, gender, MMSE total score and NPI
total score, and later added the number of prevalent morbidities. Trying to identify nonlinear relationships, we subsequently treated the outcome (QoL-AD %MaxSc) as a categorical variable by dividing it in tertiles to investigate possible threshold effects, and performed logistic regression to investigate the association between the outcome and the Modified Beers criteria, DBI and polypharmacy. Two models were used: the first contained no adjustments (crude model), the second model was adjusted for age, gender, MMSE total score, NPI total score and number of comorbidities. Results are presented with their associated 95% confidence intervals. We declared as significant alpha values <0.05 and all statistical tests were two-tailed. Data were managed and analysed using the statistical package STATA (version 10, StataCorp, 2009).

7.4. RESULTS

7.4.1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Table 7.1 summarizes the demographic and clinical characteristics of the 226 participants that were included in this study. The mean age of the selected participants was 85.9 ± 7.7 years (range 58–100), 74.8% were women, and the mean MMSE total score was 15.9 ± 5.9 (interquartile range, IQR, 21–12). The mean NPI total score was 19.8 ± 23.7 and the mean burden-of-care subscore of the NPI was 6.9 ± 9.3. The average number of comorbidities was 3.2 ± 1.6 (range 0–8).

7.4.2. PREVALENCE OF PHM USE

The prevalence of PHM according to the Modified Beers criteria, DBI, and polypharmacy is also presented in table 7.1.

One hundred and twenty-four participants were exposed to at least one PIM (56.9%); 76 of those 124 used only 1 PIM (61.3%), 41 used 2 PIMs (33.1%) and 7 used 3 PIMs (5.6%). The most common PIMs by Modified Beers criteria in this sample were temazepam (n = 46, 37.1% of the 124 participants exposed to PIM), bisacodyl (n = 12, 9.7%), oxazepam (n = 12, 9.7%), digoxin (n = 11, 8.9%), diazepam (n = 6, 4.8%), dipyridamole (n = 5, 4.0%), and amitriptyline (n = 4, 3.2%).

A total of 178 (78.8%) participants were exposed to medications leading to a DBI of >0: 82 participants (46.1%) were taking an anticholinergic medication and 96 (53.9%) were taking sedative medications.

All participants were using at least one medication. A total of 18 of the
participants (7.9%) were exposed to 1 to 4 medications at the time of the study; 208 (92.0%) of the participants were identified with polypharmacy (i.e. using \( \geq 5 \) medications at one point in time). The mean number of medications was 10.2 \( \pm \) 4.04 (median 10, range 1–21).

### Table 7.1. Demographic and clinical characteristics of the participants (PWD living in RACFs) and the prevalence of use of PHM.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PWD in RACFs (n = 226)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>85.9 ( \pm ) 7.7</td>
</tr>
<tr>
<td>Female sex</td>
<td>169 (74.8)</td>
</tr>
<tr>
<td>MMSE</td>
<td>15.9 ( \pm ) 5.9</td>
</tr>
<tr>
<td>NPI</td>
<td>19.8 ( \pm ) 23.7</td>
</tr>
<tr>
<td>NPI burden-of-care subscore</td>
<td>6.9 ( \pm ) 9.3</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9 (3.9)</td>
</tr>
<tr>
<td>1–2</td>
<td>65 (28.8)</td>
</tr>
<tr>
<td>3–4</td>
<td>106 (46.9)</td>
</tr>
<tr>
<td>5–6</td>
<td>44 (19.5)</td>
</tr>
<tr>
<td>7–8</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>PIM(s) by Modified Beers criteria</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>102 (45.1)</td>
</tr>
<tr>
<td>( \geq 1 )</td>
<td>124 (54.9)</td>
</tr>
<tr>
<td>DBI</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>48 (21.2)</td>
</tr>
<tr>
<td>Anticholinergic medication(s)</td>
<td>82 (36.3)</td>
</tr>
<tr>
<td>Sedative medication(s)</td>
<td>96 (42.5)</td>
</tr>
<tr>
<td>( \geq 0 )</td>
<td>178 (78.8)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1–2</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>3–4</td>
<td>12 (5.3)</td>
</tr>
<tr>
<td>5–6</td>
<td>20 (8.9)</td>
</tr>
<tr>
<td>7–8</td>
<td>37 (16.4)</td>
</tr>
<tr>
<td>9–10</td>
<td>59 (26.1)</td>
</tr>
<tr>
<td>11–12</td>
<td>32 (14.2)</td>
</tr>
<tr>
<td>13–14</td>
<td>26 (11.5)</td>
</tr>
<tr>
<td>15–16</td>
<td>17 (7.5)</td>
</tr>
<tr>
<td>17–18</td>
<td>9 (3.9)</td>
</tr>
<tr>
<td>19–20</td>
<td>5 (2.2)</td>
</tr>
<tr>
<td>21</td>
<td>3 (1.3)</td>
</tr>
</tbody>
</table>

**Abbreviations:** DBI = drug burden index; MMSE = mini mental state examination; NPI = Neuropsychiatric Inventory; PHM = potentially harmful medication; PIM = potentially inappropriate medication; PWD = people with dementia. The values are the means \( \pm \) SD, or numbers with percentages in parentheses.
Table 7.2. Differences in self-reported QoL-AD ratings (i.e. %MaxSc on the QoL-AD) according to exposure to PHM

<table>
<thead>
<tr>
<th>Measure</th>
<th>No exposure</th>
<th>Exposure</th>
<th>Crude</th>
<th>Adjusted&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Adjusted&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>mean ± SD</td>
<td>mean difference (95% CI)</td>
<td>mean difference (95% CI)</td>
</tr>
<tr>
<td>IM(s) by Beers criteria</td>
<td>102</td>
<td>124</td>
<td>70.21±10.32</td>
<td>−1.79 (−4.40 to 0.81)</td>
<td>−1.68 (−4.04 to 0.68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.157</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−1.49 (−3.86 to 0.88)</td>
</tr>
<tr>
<td>DBI &gt;0</td>
<td>48</td>
<td>178</td>
<td>73.02±10.77</td>
<td>−4.82 (−7.94 to −1.70)</td>
<td>−4.38 (−7.51 to −1.24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−4.07 (−7.25 to −0.89)</td>
</tr>
<tr>
<td>Polypharmacy (≥5)</td>
<td>18</td>
<td>208</td>
<td>74.17±10.71</td>
<td>−5.37 (−10.12 to 0.61)</td>
<td>−5.54 (−10.26 to −0.82)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−4.96 (−9.79 to −0.12)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Adjusted for age, gender, MMSE total score and NPI total score using linear regression modeling.

<sup>2</sup> Adjusted for age, gender, MMSE total score, NPI total score and number of comorbidities using linear regression modeling.

<sup>3</sup> Number of medications consumed per day ≥5.

Table 7.3. Odds ratios (95% CI) of self-reported QoL-AD ratings (i.e. %MaxSc on the QoL-AD) according to exposure to PHM

<table>
<thead>
<tr>
<th>Measure</th>
<th>Tertile QoL-AD %MaxSc&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Exposed</th>
<th>Crude</th>
<th>Adjusted&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (n = 226)</td>
<td>n (%)</td>
<td>OR</td>
<td>95% CI P</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIM(s) by Beers criteria</td>
<td>Highest tertile</td>
<td>71</td>
<td>35 (49.3)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Middle tertile</td>
<td>81</td>
<td>46 (56.8)</td>
<td>1.35 (0.71–2.56) 0.356</td>
</tr>
<tr>
<td></td>
<td>Lowest tertile</td>
<td>74</td>
<td>43 (58.1)</td>
<td>1.43 (0.74–2.75) 0.288</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.35 (0.70–2.58) 0.370</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.28 (0.65–2.53) 0.475</td>
</tr>
<tr>
<td>DBI &gt;0</td>
<td>Highest tertile</td>
<td>71</td>
<td>46 (64.8)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Middle tertile</td>
<td>81</td>
<td>69 (85.2)</td>
<td>3.13 (1.43–6.84) 0.004</td>
</tr>
<tr>
<td></td>
<td>Lowest tertile</td>
<td>74</td>
<td>63 (85.1)</td>
<td>3.11 (1.39–6.96) 0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.47 (1.54–7.83) 0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.75 (1.18–6.42) 0.019</td>
</tr>
<tr>
<td>Polypharmacy (≥5)</td>
<td>Highest tertile</td>
<td>71</td>
<td>62 (87.3)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Middle tertile</td>
<td>81</td>
<td>76 (93.8)</td>
<td>2.21 (0.70–6.92) 0.175</td>
</tr>
<tr>
<td></td>
<td>Lowest tertile</td>
<td>74</td>
<td>70 (94.6)</td>
<td>2.54 (0.75–8.66) 0.136</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.43 (0.73–8.10) 0.150</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.64 (0.71–9.83) 0.148</td>
</tr>
</tbody>
</table>

<sup>1</sup> Tertiles QoL-AD %MaxSc as follows: highest tertile 73.34–96.67; middle tertile 66.517–73.33; lowest tertile 43.33–66.516.

<sup>2</sup> Adjusted for age, gender, MMSE total score, NPI total score and number of comorbidities.
7.4.3. ASSOCIATION OF PHM WITH HRQoL

The mean QoL-AD total score by self-rating was 41.5 ± 5.9 (range 26–58), corresponding to a mean QoL-AD %MaxSc of 69.2 ± 9.9 (range 43.3–96.7). Table 7.2 shows the differences in self-reported QoL-AD ratings according to the use of PHM. The use of ≥1 PIM(s) was not associated with the self-reported QoL-AD in this group of PWD living in RACFs, but both DBI >0 and polypharmacy were, including after adjustments were made for other measured factors. Similarly, a logistic regression analysis using QoL-AD %MaxSc tertiles showed that DBI >0 tripled the odds of participants being in the middle or lowest tertile of QoL ratings (Table 7.3).

7.5 DISCUSSION

Our study indicates that the relevance of PHM in modulating QoL for PWD living in RACFs depends on how this concept is defined. We found that more than half of the PWD living in RACFs were exposed to at least one PIM (by Modified Beers criteria), over 80% were using medications that contributed to a DBI >0, and over 90% were exposed to polypharmacy (i.e. using ≥5 medications). Our data show that QoL ratings were lower in PWD living in RACFs exposed to DBI >0 or polypharmacy.

Interpretation of the results should be considered in light of design of the study. Its cross-sectional nature does not allow us to infer that the use of PHM causes a decline in the QoL of patients, and the possibility of reverse causality (low QoL leading to an increase in the prescription of medications) cannot be ruled out. Secondly, this study only included PWD living in Western Australian RACFs who were aged 65 years or older. Therefore, the findings may not be generalizable to the wider population of older PWD living in the community or in other settings. Thirdly, we did not include data regarding characteristics of the RACFs from where participants were recruited. In addition, the sample of participating RACFs is likely to be subject to volunteer bias, which might have reduced the power of the study to detect relevant associations (type II error). Also, data on depression was partly retrieved from the NPI, but information on insight was not available, and this might have limited our ability to adjust the analyses for these known confounders associated with self-reported QoL (Bosboom et al., 2012). Finally, we did not validate the quality of care provided, which may be an important consideration given that factors such as use of restraints and the incidence of falls may be influenced by facility and staff-related factors (Beer et al., 2010).
We also acknowledge that we might have introduced a bias by only including PWD living in RACFs who were able to self-rate QoL-AD. Although we have previously shown (Beer et al., 2010) that the majority of PWD living in RACFs can rate their own QoL (64% in the DIRECT study sample), it needs to be noted that PWD able to self-rate the QoL-AD have higher MMSE (median 17; IQR 12–21) compared with less able people (median 5; IQR 0–11). Therefore, the interpretations of our findings are restricted to PWD with moderate or mild dementia living in RACFs.

Another issue to bear in mind involves the exposure to ‘potentially’, not ‘definitely’, harmful medications. Although the risks associated with polypharmacy have been widely reported (Frazier, 2005), so are the potential benefits of therapies that lead to cure (e.g. antibiotics) or mitigate distressing symptoms (e.g. pain relief). The development of sound evidence-based strategies that lead to the appropriate use of multiple medications and, at the same time, avoid the undesirable consequences of polypharmacy are urgently needed.

Our study has the merit of having used three different operationalisations to identify the use of PHM in PWD living in RACFs in a moderately large sample (n = 226), which as far as we are aware, has not been done before. Despite its importance, there is still debate as to how to identify the use of PHM and while several methods and clinical tools have been proposed, we are not aware of another study that included simultaneously PIM, DBI and polypharmacy as exposures of interest. In this regard, our study is of clinical relevance and the findings suggest that DBI and polypharmacy can assist healthcare practitioners identify PHM that may compromise the QoL of PWD living in RACFs.

Importantly, the differences that we found were subtle and their clinical relevance uncertain. That is, being exposed to polypharmacy or to drugs contributing to a DBI >0 is associated with 5% lower self-ratings on a widely used HRQoL questionnaire (also after adjustment for possible confounding variables including the number of comorbidities and neuropsychiatric symptoms). At this point, we are unable to state whether such a difference is of immediate or future clinical relevance, but these results suggest a possible intervention opportunity for healthcare practitioners through quality use of medicines.

The prevalence of PIM in our group of participants was high, i.e. more than half of the participants were exposed to ≥1 PIM(s). It was unexpected that use of PIM (by Modified Beers criteria) would not be associated with the self-reported QoL-AD in this group of PWD living in RACFs given that the use of PIMs has been associated with
increased rate of adverse drug events and poorer health outcomes (Fick et al., 2003; Roughead et al., 2007). However, our results are consistent with the finding of Franic and Jiang (2006), who reported that PIM use was not a significant predictor of HRQoL in a cohort of community-dwelling older adults. Our finding that the use of PIM (by Modified Beers criteria) was not associated with HRQoL while the DBI and polypharmacy were, suggests an advantage of the DBI and polypharmacy over PIMs by Modified Beers criteria as predictors of self-reported HRQoL for this population. Furthermore, the lack of reliable information regarding the dosage of certain medications used by our participants (such as hypnotic benzodiazepines) may have led to some misclassification and dilution of the association between PIM and QoL ratings.

The mechanisms that explain the observed association of DBI and polypharmacy with self-rated QoL in this population are uncertain and might be confounded by factors we did not include in our study. It is well known that polypharmacy is a risk factor for adverse health outcomes (Frazier, 2005). But this apparent relationship may be confounded by the burden of multiple chronic diseases (Lawlor et al., 2003). In our study the number of multiple comorbidities did not affect the association between BDI or polypharmacy with HRQoL. A similar comparison could be made for the possible influence of neuropsychiatric symptoms, which one might expect to increase the risk of exposure to medications, but adjustment for this (with the NPI) had no obvious effect on the association between HRQoL and DBI or polypharmacy. The longitudinal implications of our findings should be explored by future studies.

In conclusion, use of PHM is common and is inversely associated with the self-reported HRQoL in PWD living in RACFs. With regards to clinical tools, our data suggest that DBI and polypharmacy may be better predictors of HRQoL than PIMs by Modified Beers criteria. This study supports the recommendation that, with the overall aim of improving QoL as outcome of care for PWD in RACFs, efforts should be made to avoid the use of PHM through quality use of medicine initiatives.

Note. In addition to the data analyzed and presented above, we also looked at our community sample regarding the prevalence of PHM. Due to the very low prevalence of PHM in the community sample further investigation would not reach enough power to make reasonable conclusions. Therefore these data were not further investigated.
CHAPTER 8.

GENERAL DISCUSSION
8.1. INTRODUCTION

The impact of cognitive decline on the experienced HRQoL of older adults diagnosed with AD is critical but poorly explored question in dementia research. Given that there is no cure for AD, effective strategies to optimize the HRQoL for older adults diagnosed with AD in Australia are essential. It is imperative that we are able to target the accurate – and modifiable - factors that drive HRQoL and measure the effects of interventions, thereby limiting or even reducing health care costs associated with the rising number of people diagnosed with AD.

The research work of this thesis consisted of five inter-related studies designed to address the following aims:

- Study 1: to determine (1) the agreement between community-dwelling people with mild to moderate AD and their family carers HRQoL ratings; (2) whether the instructed perspective of family carer-rated HRQoL (i.e. carer–carer perspective and carer–patient perspective) changes HRQoL outcomes; (3) the factors that independently contribute to self-reported and carer-reported HRQoL ratings (i.e. carer–carer perspective and carer–patient perspective);
- Study 2: to determine (4) whether self-reported and carer-reported HRQoL change over a period of 18 months; (5) the factors that mediate changes in HRQoL ratings by community-dwelling people with AD over a period of 18 months; (6) the factors that mediate changes in HRQoL ratings by family carers over a period of 18 months;
- Study 3: to determine (7) whether the underlying cognitive domains of people with AD remain stable over 18 months compared with controls free of dementia; (8) whether the associations between cognitive domains and carer and self-reported HRQoL ratings remain stable over 18 months;
- Study 4: to determine 9) whether the deterioration of specific cognitive functions commonly associated with AD predict which patients maintain or experience a deterioration of their HRQoL ratings over a period of 18 months.
- Study 5: as post-hoc analyses, to determine 10) the prevalence and association of exposure to potentially harmful medication with HRQoL.

8.2. SUMMARY OF FINDINGS

This research has generated the following findings:

• Based on the baseline data, study 1 (chapter 3) showed acceptable agreement in
HRQoL ratings between community-dwelling people with AD at mild to moderate stage and their carers (requested to provide two differently instructed perspectives, i.e. carer-carer and carer-patient). Only 2/79 self-ratings (i.e. 2.5%) showed poor agreement with the carer–carer ratings (i.e. fell outside the ±1.96 SD range), and 4/80 (5%) self-ratings with the carer–patient ratings. However, there was a systematic shift in the rating of the QoL-AD, with patients rating their own HRQoL more highly than carers (or, vice-versa, carers rating the HRQoL of patients systematically lower than the patients themselves). The self-ratings, carer-carer ratings and carer-patient ratings on the QoL-AD were associated with different factors. The self-reported HRQoL ratings were inversely associated with insight and depression (as rated by the GRAD), depression (as rated by the HADS) and directly associated with the use of antidementia medications (cholinesterase inhibitors). HRQoL ratings by carer–carer perspective were inversely associated with the number of medications consumed by the patient (i.e., polypharmacy associated with worse HRQoL), symptoms of anxiety, and living together; while carer–patient perspective was inversely associated with the carers’ age and burden-of-care.

• Analyses of the longitudinal data in study 2 (chapter 4) revealed that carer-rated QoL-AD (carer-carer perspective) declined 8.7% over 18-months, but self-rated QoL-AD remained stable. The difference between the self-reported and the carer-reported HRQoL at 18-month follow-up was significant ($p = 0.001$). The final parsimonious model of predictors of changes in QoL-AD self-ratings explained 22.6% of the variance; only changes in the Hospital Anxiety and Depression Scale Anxiety retained significance. The final model of predictors of changes in carer-ratings explained 55.0% of the variance: that is, changes on Informant Questionnaire on Cognitive Decline in the Elderly, changes in the Hospital Anxiety and Depression Scale Depression, practicing hobbies at 18 months, and number of visit(s) or admission(s) to hospital.

• With analyses of the longitudinal data obtained with a broad range of well-established neuropsychological measures, study 3 (chapter 5) demonstrated that self-reported QoL-AD scores were not associated with any of the identified cognitive domains at baseline or after 18 months. The structure of the cognitive domains of people with AD changed between baseline and follow-up, as did the association of these domains with carer-rated HRQoL. Executive functioning impairment and decrease in speed of information processing seemed to have a negative impact at
earlier stage of AD, but not at follow-up on patient’s HRQoL as viewed by the carer, although this impact was overshadowed by behavioural and psychosocial symptoms. The HRQoL scores assigned by the next-of-kin declined alongside a general measure of cognitive function.

- Study 4 (chapter 6) established that changes in specific cognitive functions were not associated with changes in self-rated or carer-rated HRQoL in AD. Although logistic regression showed that for every increase in one standardized score of California Verbal Learning Test-II short delay free recall the odds of stable/increased self-rated QoL-AD over 18 months were 0.27 (95%CI: 0.11, 0.67; \( p = 0.005 \)). This association was no longer statistically significant after the analyses were adjusted for symptoms of depression and anxiety (adjusted OR: 0.31, 95%CI: 0.11, 0.86; \( p = 0.025 \); alpha set at 1% because of multiple comparisons). None of the other standardized changes of cognitive scores were associated with self-rated or carer-rated QoL-AD grouping.

- The results of study 5 (chapter 7) showed that exposure to potentially harmful medications (PHM) was inversely associated with self-reported HRQoL in people with AD. However, the prevalence of exposure to PHM in our community sample was very low.

- Post-hoc analyses - with data from a large randomized controlled trial of educational interventions to improve HRQoL of PWD living in RACFs (i.e. the DIRECT study) - confirmed that the QoL-AD can be implemented in routine research settings with relatively little training of research staff, with a good overall reliability being indicated by the intra-class correlation coefficient to the total QoL-AD scores (Beer, Bosboom, Almeida, Flicker, 2009).

### 8.3. CONCLUSIONS REGARDING ORIGINAL STUDY HYPOTHESES

With regards to the hypotheses the findings of study 1 (chapter 3):

1. Partly support the hypothesis that patients and carers do not agree in their ratings of HRQoL, regardless of the perspective adopted by the carer (i.e. rating as the carer sees it or how the carer believes the patient sees it). That is, the raters agreed within an acceptable range in HRQoL ratings, given that only 2.5% of self-ratings did not agree with the carer–carer ratings (i.e. fell outside the \( \pm 1.96 \) SD range), and only 5% self-ratings did not agree with the carer–patient ratings. However, the findings revealed a systematic difference in the rating of the QoL-AD, with patients systematically rating their own
HRQoL more highly than their carers (or, vice-versa, carers rating the HRQoL of patients systematically lower than the patients themselves).

(2) Support the hypothesis that the instructed perspective of the informant (i.e. carer–carer perspective or carer–patient perspective) influences on carer-rated HRQoL as outcome measure, given the finding that the carer-carer QoL-AD ratings were lower than the carer-patient ratings (t-paired = 4.60, \( p < 0.001 \)).

(3) Support the hypothesis that HRQoL ratings by carers, but not patients, are directly correlated with patients’ global cognitive function, as measured with patients’ total score on the CAMCOG-R.

The findings of study 2 (chapter 4):

(4) Partly support the hypothesis that carer-reported HRQoL ratings, as measured with the QoL-AD, do change over a period of 18 months, but rejected the hypothesis that self-reported HRQoL ratings remained stable over time: the carer-rated QoL-AD (carer-carer perspective) declined 8.7% (\( p = 0.003 \)) over 18-months, but self-rated QoL-AD remained stable.

(5) Partly support the hypothesis that changes in HRQoL ratings by people with AD are inversely associated with changes in symptoms of anxiety (not with other symptoms of BPSD), and, as expected, not with global cognitive decline.

(6) Partly support the hypothesis that changes in HRQoL ratings by carers are directly associated with changes in global cognitive functioning and changes in carer’s burden-of-care, but, not as anticipated, inversely associated with changes in BPSD or instrumental activities of daily living.

The findings of study 3 (chapter 5):

(7) Confirmed the hypothesis that the underlying cognitive domains structure in a sample of older adults with mild to moderate AD living in the community is not stable over 18 months compared with controls free of dementia.

(8) Rejected the hypothesis that changes in specific cognitive domains, i.e. episodic memory and executive functions as measured with specific neuropsychological tests, would be associated with changes in the QoL-AD self-ratings and carer-ratings. The findings actually showed that 1) self-reported HRQoL was not associated with any of the identified cognitive domains at either assessment, and that 2) carer-reported HRQoL ratings were
directly associated with executive functioning and speed of information processing at baseline, but not at follow-up. It seems that these two cognitive domains, not episodic memory, may have greater influence on how the carer perceives the HRQoL of the person with AD early in the course of the illness.

The findings of study 4 (chapter 6):

(9) Rejected the hypothesis that specific cognitive functions, i.e. episodic memory and executive functions, would be directly correlated with HRQoL self and carer-reported HRQoL ratings. In fact, changes in specific cognitive functions were not associated with changes in HRQoL ratings in AD.

The findings of study 5 (chapter 7):

(10) Confirmed the hypothesis that exposure to potentially harmful medications (PHM) is inversely associated with self-reported HRQoL ratings. That is, the findings showed that exposure to PHM, as identified by DBI 1 0 and by polypharmacy (i.e. ≥5 medications), but not by PIMs (Modified Beers criteria), is inversely associated with self-reported HRQoL for people with dementia living in RACFs.

With regards to the hypotheses of the secondary research aims (Beer, Bosboom, Almeida, Flicker, 2009; Bosboom et al., 2010):

(11) Confirmed the hypothesis that the feasibility and inter-rater reliability of assessment of HRQoL, using the self-rated QoL-AD administered, is good.

(12) Confirmed the hypothesis that the place of residence (i.e. community-dwelling or residing in a RACF) influences the degree of agreement between self-reported and informant HRQoL ratings, given the substantial variation in HRQoL ratings for PWD residing in RACFs.

8.4. LIMITATIONS & STRENGTHS

This study has limitations that should be acknowledged. Firstly, this study had a reasonable sample size at baseline (N=80 AD patients and their carers), but type I error cannot be entirely dismissed for some of the associations observed. We would argue,
however, that the consistency of our cross-sectional observations with those of other studies suggests this would be an unlikely explanation for our findings (Conde-Sala et al., 2009; Garre-Olmo et al., 2002; Hoe et al., 2006; 2007; Sands et al., 2004; Schiffczyk et al., 2010; Snow et al., 2005; Thorgrimsen et al., 2003).

Secondly, we considered the main effects of variables, but refrained from examining the possible interactions between explanatory factors to decrease multiple comparisons and, when this occurred, we adjusted our analysis accordingly.

Thirdly, a relatively high number of participants were lost to follow-up (35%, including deaths). Although we did not find significant differences in HRQoL ratings between the completers and dropouts at baseline, loss of power because of healthy participant bias could potentially explain our findings. It is of note that the few available longitudinal studies focusing on changes in HRQoL self-ratings of PWD showed similar or higher attrition: 73% of their sample over 1 year (Heggie et al., 2012); 52% over 1 year (Selwood et al., 2005); and 1 study (Tatsumi et al., 2009) could not collect HRQoL data from 31% of their sample after 2 years. Given the nature and impact of AD to patients and carers, such a loss to follow-up might be difficult to overcome. Also, as discussed in the Method section (chapter 2), the dropout percentage did not reach the threshold (i.e. with only less than 37 participants left at follow-up) at which the study would no longer have sufficient statistical power.

Fourthly, missing data for self-reported AQ and HADS at 18 months (study 2) was high (20%), because participants were unable to complete these questionnaires reliably, even though they were able to complete the less demanding QoL-AD. To check for the possibility of a bias towards the null hypothesis, we performed post-hoc analyses (study 2) and found no significant difference between the mean change overtime of the QoL-AD self-ratings of participants who were or were not able to complete the AQ and HADS at 18 months ($t = -0.30, p = 0.765$).

Fifthly, we collected data on two time-points only (baseline and 18-months), which limited interpretation regarding the shape of changes of HRQoL ratings over time (i.e., linear or non-linear).

Sixthly, three participants in the study were aged less than 65 years at baseline (i.e., 56, 61, and 62), and one of them completed the follow-up assessment at 18 months (62 years-old at baseline). These early-onset cases could, conceivably, have a different cognitive profile compared with the remainder of the sample. However, detailed test analysis did not identify these participants as outliers at baseline or at follow-up. Therefore, there was no compelling reason to exclude these participants from the
analyses.

Also, because of multiple comparisons, in particular in study 4, and the risk of chance associations, we elected to apply a stringent criterion of statistical significance for study 4 (i.e., alpha of 1%). It is unclear whether this would have increased the risk of type II error, although the strength of the associations that we observed were small and, even if statistically significant, would most likely have been of limited clinical relevance.

Regarding the generalizability of our findings, the participants of this study were not randomly selected from a community representative sample of people living with AD. Hence, there is a degree of uncertainty regarding the generalizability of the findings. In addition, the results may not be applicable to people with severe AD (i.e., MMSE<10) or to those living in residential care facilities.

Although it would have been of interest to explore differences and changes in HRQoL self-ratings in patients with mild, moderate, and severe stages of dementia, our sample size prevented us from doing this.

HRQoL in dementia is a complex construct and its assessment is neither simple nor straightforward. Although there is emerging evidence on the predictive and explanatory value of disease-specific measures of HRQoL in PWD, QoL encompasses aspects of a person’s life that go beyond the constraints imposed by the disease. The instrument used in this study, the QoL-AD, is a specific measure of HRQoL, so we are unable to comment on other relevant aspects of the QoL of participants.

To our knowledge this is the first study that examined the relative contribution of global cognitive decline and specific cognitive deficits to changes in HRQoL in older adults diagnosed with mild to moderate AD with a broad range of well-established neuropsychological tests. Also, this body of work has the merit of having used, for the first time, an approach to analyze the distribution of all HRQoL ratings of older adults with AD and their carer that goes beyond the absolute concordance of scores. Our finding of discrepant HRQoL ratings is in line with the findings of other studies (Conde-Sala et al., 2009; Hoe et al., 2007; Ready et al., 2006; Sands et al., 2004; Thorgrimsen et al., 2003). However, the way the ratings behave had not been described before using Bland-Altman plots as a visual guide in the interpretation of this discrepancy. With this approach, we were able to demonstrate that carers and patients show acceptable agreement in their ratings (that is, within ±2SD), but carers systematically underestimate HRQoL ratings compared with patients (or vice-versa). This finding is in line with the suggested disability paradox reviewed in chapter 1.
Another strength of this study is the use of a novel approach that allowed carers to rate the perceived HRQoL of patients using two different perspectives: carer–carer and carer–patient perspectives, based on the theoretical considerations by Pickard and Knight (2005) as discussed in the literature review (chapter 1). The findings highlight the need for clarity and consistency in the use of informant perspectives to ascribe HRQoL scores to older people with mild to moderate AD. Also, this research was the first to apply a broad spectrum of well-established neuropsychological tests assessing cognitive abilities commonly associated with AD, next to a measure of global cognition (i.e. the CAMCOG-R). With that, we were able to investigate associations between specific cognitive functions and HRQoL that could have been missed by previous studies that had limited their cognitive assessments to global cognitive measures like the MMSE or ADAS-Cog.

8.5. IMPLICATIONS OF THE FINDINGS

8.5.1. WHAT ARE THE IMPLICATIONS OF THE FINDINGS FOR ASSESSING AND INTERPRETING HRQoL IN PEOPLE WITH AD?

Firstly, the findings emphasize the value of having complementary approaches to the assessment of HRQoL in AD that enable both self- and proxy-reported data to be considered. Carers’ ratings are not the same as patients’ HRQoL ratings, and these ratings are associated with different factors, indicating that interventions to change HRQoL ratings require different targets. A key finding from this research is that the inevitable cognitive deterioration associated with the progression of AD affects the views about the HRQoL of people with AD and their carers differently over time. Practically, this provides a strong case for the solely separate and complementary use of self-reported and informant-reported HRQoL ratings, not as a composite score. Patients systematically rate their own HRQoL more highly than their carers (or, vice-versa, carers rate the HRQoL of patients systematically lower than the patients themselves). In addition, HRQoL ratings by carers decline over time alongside cognitive deterioration, while the natural progression over time of HRQoL ratings by patients with mild to moderate AD does not show marked changes in association with cognitive decline.
Hence, the rating of the QoL-AD as a composite score, and analyses based on a composite score, might need to be reconsidered.

This research demonstrated that a carer-carer perspective of the HRQoL of patients with AD is not the same as a carer-patient perspective. The perspective of the carer as informant (i.e. carer–carer perspective or carer–patient perspective) influences the ascribed scores. Therefore, it is necessary that the explicit viewpoint of the carer be used both in research and clinical practice.

Our findings also highlight the fact that the variables associated with changes in self-reported HRQoL ratings are different from those expected in a condition marked by progressive cognitive decline, such as AD. That is, HRQoL ratings by carers, but not patients, are influenced by patients’ global cognitive function; changes in HRQoL ratings by people with AD are not correlated with specific cognitive impairment, including the ability to learn new information (i.e. episodic memory), while a substantial volume of research has focused on this as a driving factor of, or even substitute for, HRQoL in AD. Carers ascribe significant associations between patients’ HRQoL and cognition and functional/physical decline, but for people with AD disturbances of mood and anxiety symptoms are the most relevant association with declining HRQoL. These results are consistent with the response shift theory, which suggests that the subjective experienced HRQoL in AD is no longer influenced by one’s ability to form new memories. The point of change is unclear, as this research only captures longitudinal observations at two points in time after the clinical diagnosis of AD has been established which makes considerations that include perceptions of HRQoL at previous pre-clinical stages uncertain. Moreover, carers’ perception of the meaning of “overall cognitive impairment” and of the impact of limitations in specific cognitive domains on HRQoL of the person with AD changes during the course of the disease. These novel findings enhance our understanding of the impact cognitive decline might have on perceived HRQoL at different stages of the disease from the perspective of patients and carers.

Additional analyses based on data obtained from the DIRECT study (Beer, Bosboom, Almeida, Flicker, 2009; included in Appendix) showed that the QOL-AD can be implemented in routine research settings with good overall inter-rater reliability after minimal training of staff, although agreement of individual items was moderate, indicating the importance of objective assessment of inter-rater reliability, or the inherent instability of self-rated HRQoL in RACFs (Bosboom et al., 2010, included in Appendix).
8.5.2. What are the implications of the findings for interventions to enhance HRQoL in AD?

This research demonstrates for the first time that the specific or domain related cognitive changes have limited influence on how patients diagnosed with mild to moderate AD perceive their HRQoL over time. Moreover, this body of research does not support the idea of a consistent linear relationship between severity of cognitive decline in AD and HRQoL. This highlights the need for the development of interventions that are more relevant to the HRQoL of older adults with AD, as interventions that limit their focus to improving cognitive functions of people with mild to moderate AD living in the community might fail to enhance participants’ HRQoL. Also, when developing interventions designed to optimise HRQoL of people with AD one should consider carefully whose ratings of the patient’s HRQoL they wish to change. Interventions to change self-reported or carer-reported ratings of patient’s HRQoL may require different targets.

The findings indicate that anxiety plays a more prominent role in determining HRQoL changes than cognitive function. Hence, a shift of focus to interventions that successfully manage anxiety and mood symptoms might be required if we wish to improve the HRQoL of people with AD living in the community. In contrast, educating carers about how to manage the progressive decline of specific cognitive deficits in executive functioning and speed of information processing may improve their perspective of patients’ HRQoL.

Our results also support the recommendation that efforts should be made to avoid the use of PHM through quality use of medicine initiatives, as exposure to PHM is inversely associated with self-reported HRQoL for people with dementia living in RACFs.

8.5.3. What are the implications to Jonker et al.’s model?

The model for HRQoL in dementia proposed by Jonker and colleagues (2004) is supported by the findings of this research. The finding that HRQoL in AD is not solely associated with dementia-related factors, such as cognitive decline, fits with their approach of including aspects of life of a person with dementia that are not necessarily affected by the illness. Therefore, the implementation of these findings could be further guided by this model, like other studies have recently done (Gates et al., 2014), to support the formulation of strategies that guide interventions to optimize HRQoL of people living with AD.
8.6. THESIS RESULTS IN CONTEXT OF ADVANCEMENT IN THE FIELD AND FUTURE DIRECTIONS

One of the key issues identified at the start of this research was the lack of longitudinal studies with emphasis on the relationship between HRQoL in AD and cognitive deficits. The impact of cognitive decline on the experienced HRQoL was arguably one of the least explored questions in this field of research, while the need to clarify whether and how cognitive decline is a significant mediating factor in HRQoL throughout the progression of AD was acknowledged. Indeed, as far as we are aware, this research was the first to report longitudinal data on factors associated with HRQoL ratings on a well-defined and homogeneous study population living in a well-defined setting, based on a validated HRQoL measure with established sensitivity to detect change over time, a broad range of well-established neuropsychological tests, and a wide range of other explanatory variables.

Longitudinal observational studies that aimed to determine the predictors of change of HRQoL ratings in dementia are listed in Table 8.1. Five longitudinal studies were published since the start of this thesis (Conde-Sala et al., 2014; Heggie et al., 2012; Missotten et al., 2007; Tatsumi et al., 2009; Vogel et al., 2012). Apart from the study conducted by Missotten et al. (2007), all these studies obtained longitudinal HRQoL data by using the QoL-AD as HRQoL measure. Consistent with one of the key findings of our research, all new studies that collected self-reported QoL-AD ratings found no changes over periods of time varying from 1 year (Heggie et al., 2012) to 3 years (Conde-Sala et al., 2014). These studies reported high drop-out rates, varying from 31% (Tatsumi et al., 2009) to 73%, though the latter included a very heterogeneous group of study participants (Heggie et al., 2012). Conde-Sala et al (2014) also found patient’s self-ratings of QoL-AD remain generally stable over time, whereas those of caregivers show a decline, with significant discrepancies in relation to specific patient and caregiver factors.

The results of study 2 (Bosboom et al., 2013) demonstrated that HRQoL does not change substantially over 18 months according to the view of patients. These results are in line with some of these new studies (Conde-Sala et al., 2014; Heggie et al., 2012; Selwood et al., 2005; Tatsumi et al., 2009), although timeframes (ranging from 1 to 2 years), inclusion criteria (PWD aged 65+9; people with AD; heterogeneous group of older adults with some form of cognitive deterioration including MCI, AD, FTD, and Normal Pressure Hydrocephalus, Heggie et al., 2012), and the average mean on the MMSE at baseline (i.e., 16.1+6.59; 21.7+2.7, Tatsumi et al., 2009; no data provided,
Heggie et al., 2012) varied across these surveys. The two oldest longitudinal studies in this field (Lyketsos et al., 2003; Missotten et al., 2007) used the Alzheimer Disease Related Quality of Life, which only takes into account the views of the carer. Such an approach may be problematic, as self-ratings and carer-ratings are not interchangeable (Bosboom et al., 2012). In contrast, we found a significant decline in the HRQoL carer-ratings over this same time period, which is consistent with the results reported by others (Tatsumi et al., 2009), although such a decline may not occur in a linear manner (Missotten et al., 2007).

Our longitudinal data showed that HRQoL self-ratings and carer-ratings diverge over 18 months, and such a change is associated with different factors. The results are consistent with those reported by Conde-Sala et al. (2014), in which the participants were followed up at 12, 24, and 36 months after baseline. In that study, patients’ QoL-AD ratings did not differ significantly across the four time-points. By contrast, caregiver ratings showed a significant decline trend over time. The overall discrepancy between patient and caregiver ratings increased over the 36 months of follow-up, and especially after 12 months, coinciding with more severe dementia.

Our finding that changes in the use of medications are not associated with changes in QoL self-ratings or carer-ratings are consistent with the results of 2 recent systematic reviews (Cooper et al., 2012; 2013), which found no evidence that the use of cholinesterase inhibitors affect HRQoL in PWD. Anxiety is among the most frequently reported neuropsychiatric symptoms in people with AD (e.g., 40% of neuropathologically confirmed AD cases, Echavarri et al., 2013), and our results indicate that it plays a more prominent role in determining HRQoL changes than cognitive function. Hence, a shift of focus to interventions that successfully manage anxiety symptoms may be required if we wish to improve the HRQoL of people with AD living in the community. Current guidelines recommend non-pharmacological interventions (including psychological counseling, interpersonal management, and environmental management) as first-line treatment for neuropsychiatric symptoms (Gauthier et al., 2010). However, at present there is no consistent evidence about specific behavioral strategies for clinical management of anxiety in dementia, and trial data on people with AD remain scant (Blay and Marinho, 2012; Wolitzky-Taylor et al., 2010). Research in this area is urgently needed.

Also, this thesis showed that changes in HRQoL carer-ratings are associated with changes in cognition and depression scores of the person with AD, burden-of-care due to visits to hospital, and engagement of the person with AD in hobbies. These
factors predicted 55% of the change in carer-ratings in our final model. It seems that the inevitable cognitive deterioration associated with AD affects the views of people with AD and their carers differently. This suggests that negative stereotypes of dementia may need to be addressed (Trigg et al., 2012). In addition, the study by Conde-Sala et al. (2014) found that the most notable discrepancies between patient and caregiver ratings were observed in the presence of anosognosia, which was associated with higher QoL-AD scores in the patient; agitation, apathy, and functional deficits were associated with lower ratings among caregivers. Greater burden-of-care and poorer carer’s mental health were significantly related to lower carer-rated patient’s HRQoL.

The results of study 3 (Bosboom et al., 2014b) confirmed that (a) the underlying cognitive structure of AD is not stable over 18 months compared with controls free of cognitive impairment and showed that (b) the relationship between cognitive domains and HRQoL is different for self- and carer-reported ratings. We are not aware of any previous study that analyzed the stability of the underlying cognitive structure in AD and how this relates to HRQoL self and carer-ratings at different stages—with regard to severity of functional impairment—of AD compared with healthy older adults. These novel findings contribute to improve our understanding of the impact specific cognitive deficits might have on perceived HRQoL at different stages of the disease. As we found that carer-reported HRQoL ratings were directly associated with executive functioning and speed of information processing at baseline but not at follow up, it seems that these specific cognitive domains, not episodic memory, have greater influence on how the carer perceives the HRQoL of the person with AD early in the course of the illness.

We know little about which interventions may promote or hinder HRQoL in AD (Banerjee et al., 2009; Burgener et al., 2013; Cooper et al., 2012; Hoe et al., 2013). Recently, Cooper and colleagues (2012) reviewed 20 randomized controlled trials (RCTs) reporting the effectiveness of non-pharmacological interventions in improving HRQoL in dementia and found only one reporting preliminary evidence that coping strategy-based family carer therapy improves the HRQoL of people with dementia living at home. Our study indicates that further research into how coping with consequences of deficits in executive functioning and speed of information processing might also improve the carer-reported HRQoL.

A recent systematic review of pharmacological interventions for people with AD found 15 RCTs measuring QoL as an outcome, indicating that most RCTs in dementia to date have not included, or did not report, QoL (Cooper et al., 2013). There was no compelling evidence that pharmacological treatment improves HRQoL in people with
dementia (Cooper et al., 2013). Our finding that cognition is not associated with self-rated HRQoL is consistent with these results and suggests that treatments that focus solely on cognition are unlikely to measurably affect the QoL of patients with AD. Future studies should seek to confirm these results and determine more effective strategies to enhance the QoL of people with AD.

The results of study 4 (Bosboom et al., 2014a) revealed novel findings that for every increase in one standardized score on the “CVLT-II short delay free recall,” the odds of stable/increased self-rated QoL-AD over 18 months decreased 73%. After adjustment for differences on the HADS Anxiety and HADS Depression scores, this inverse association lost significance with alpha set at 1%. These results raise questions regarding the assumption that improved memory scores associated with interventions will lead to improved HRQoL ratings. They may also suggest that as the disease progresses, the increasing severity of cognitive deficits are offset by decreasing awareness of impairment, and that this may override the impact of cognitive changes on the HRQoL scores of people with AD. This suggestion is consistent with the finding that greater anosognosia is associated with higher self-reported HRQoL, especially in advanced stages of AD (Conde-Sala et al., 2013).

HRQoL ratings have been associated with information processing speed in multiple sclerosis (Barker-Collo, 2006); memory and constructional abilities in closed-head injury (Klonoff et al., 1986); psychomotor speed, verbal memory, and language in epilepsy (Perrine et al., 1995); executive functioning, processing speed, concentration, working memory, and verbal memory in schizophrenia (Tolman and Kurtz, 2012); and various specific cognitive deficits, including visual perception, in stroke (Nys et al., 2006). In AD, our findings indicate that interventions that aim to optimize self-reported HRQoL may benefit from focusing in areas other than cognitive function, such as symptoms of anxiety and depression (Bosboom et al., 2012; Bosboom et al., 2013; Burgener et al., 2013; Cooper et al., 2013; Tatsumi et al., 2009). This research found no evidence that the progressive decline of specific cognitive functions commonly associated with AD predicts change in HRQoL carer-ratings. It should be emphasized that this is based on objective measures, not on how the consequences of cognitive decline are experienced by the carer in daily life. A large proportion of people with AD are affected by BPSD at some point during the course of their illness, and evidence from clinical trials of both non-pharmacological and pharmacological treatments provides a range of multidisciplinary management options that can be tailored to individual needs (Wolfs et al., 2008; Gauthier et al., 2010). Current findings support the
recommendation that improving our management of BPSD might favorably affect the HRQoL of people with mild to moderate AD and, possibly, contribute to delay the transition from home to residential care (Wolfs et al., 2008).

Since publication, the studies included in this research have been cited 36 times in other peer-reviewed publications. That is study 1 (Bosboom et al., 2012a) has been cited 19 times; study 2 (Bosboom et al., 2013) has been cited 5 times; study 3 (Bosboom et al., 2014b) has not been cited (yet); study 4 (Bosboom et al., 2014a) has been cited twice; study 5 (Bosboom et al., 2012b) has been cited 4 times. The additional publication with post-hoc analyses for this research has been cited 6 times (Beer et al., 2009).

Finally, our results require replication from other longitudinal studies, preferably with a more prolonged follow up time-frame and including a cohort of participants with pre-clinical AD (e.g., mild cognitive impairment). In addition, whether the presently identified mediating and clinically modifiable factors when implemented as interventions targets will have a measurable impact on self-reported and carer-reported HRQoL ratings of community dwelling patients with AD remains to be determined.
**Table 8.1. Overview characteristics of longitudinal observational studies in predictors of change of HRQoL ratings in dementia (until July 2014)**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>QoL instr/s as primary outcome</th>
<th>Study design</th>
<th>Incl. PWD</th>
<th>N at BL</th>
<th>N at FU</th>
<th>% Dropout</th>
<th>Setting/ population</th>
<th>Other variables included</th>
<th>Change in self-rated HRQoL</th>
<th>Change in carer-rated HRQoL</th>
<th>Type of carers</th>
<th>Predictors self-ratings</th>
<th>Predictors carer-ratings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyketsos et al.</td>
<td>2003</td>
<td>USA</td>
<td>ADRQL</td>
<td>BL and FU at 2 yrs</td>
<td>PWD, i.e. AD, vascular dementia or other form (mean age 80.4, SD 7.3; MMSE mean 8.4, SD 7.2)</td>
<td>120</td>
<td>47</td>
<td>61%</td>
<td>Long-term care facilities</td>
<td>Demographics MMSE CSDD PGDRS</td>
<td>N/A</td>
<td>Small mean decline of 5% (but nearly 50% stayed the same or improved)</td>
<td>Professional</td>
<td>N/A</td>
<td>BL QoL rating</td>
</tr>
<tr>
<td>Wlodarczyk et al.</td>
<td>2004</td>
<td>Australia</td>
<td>Assessment of QoL (AQoL) scale</td>
<td>Data presented are a subset of a global donepezil trial involving over 1100 pts in 18 countries. FU for 24 weeks. Assx at baseline, 12 and 24 weeks.</td>
<td>AD patients, mild-moderate severity (MMSE 10-25)</td>
<td>100</td>
<td>100</td>
<td>n/a</td>
<td>20 elderly day care centers</td>
<td>MMSE IADL</td>
<td>Patient-rated AQoL utility scores were related to patient MMSE and IADL scores.</td>
<td>Caregiver-rated AQoL correlated with MMSE and IADL scores.</td>
<td>Family caregivers</td>
<td>The result indicate that a decline in AD patient cognition results in a decline in patient HRQoL, and the more the patients are able to do for themselves, the better their HRQoL.</td>
<td>Patient and caregiver-rated AQoL scores correlated (r=0.37, P=0.0038) for all levels of disease severity. Within AQoL domains, the correlation between patient and caregiver ratings is lowest for physical senses and psychologic al well-being, and highest for independent living and social relationships</td>
</tr>
</tbody>
</table>

(Continued on next page)
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>QoL instr/s as primary outcome</th>
<th>Study design</th>
<th>Incl. PWD</th>
<th>N at BL</th>
<th>N at FU</th>
<th>% Dropout</th>
<th>Setting/ population</th>
<th>Other variables included</th>
<th>Change in self-rated QoL</th>
<th>Change in carer-rated QoL</th>
<th>Type of carers</th>
<th>Predictors self-ratings</th>
<th>Predictors carer-ratings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin-Cook et al.</td>
<td>2005</td>
<td>USA</td>
<td>QUALID</td>
<td>Secondary analyses comparing outcome measures used in a double-blind randomized double-blind 2 week trial of two antipsychotics for treatment of BPSD</td>
<td>PWD ‘with measurable behavioural disturbances’</td>
<td>31</td>
<td>31</td>
<td>n/a</td>
<td>Extended care facilities</td>
<td>NPI, MMSE, Withdrawn Behavior subscale of the Multidimensional Observation Scale for Elderly Subjects (MOSES), Clinical Global Impression (CGI)</td>
<td>N/A</td>
<td>Improveme nt in the QUALID was significantly related to improvement in scores for the NPI total (p = 0.02) and inversely related to the number of reported adverse events (p = 0.03).</td>
<td>Nurse or nurse aid</td>
<td>N/A</td>
<td>Behavioural symptoms, adverse medication effects</td>
</tr>
<tr>
<td>Selwood et al.</td>
<td>2005</td>
<td>UK</td>
<td>QoL-AD DQoL, EQ-5D</td>
<td>BL and FU at 1 yr</td>
<td>PWD aged 65+ (MMSE mean 16.1, SD 6.5 at BL)</td>
<td>60</td>
<td>29</td>
<td>52%</td>
<td>Various living arrangements</td>
<td>Demographics, MMSE, CSDD, RAID</td>
<td>No mean change</td>
<td>N/A</td>
<td>N/A</td>
<td>BL QoL rating</td>
<td>N/A</td>
</tr>
<tr>
<td>Missotten et al.</td>
<td>2007</td>
<td>Belgium</td>
<td>ADRQL</td>
<td>BL and FU1 at 1yr and FU2 at 2 yrs</td>
<td>PWD aged 65+ (mean age 82.4, SD 7.0; MMSE mean 10.2, SD 6.8 at BL)</td>
<td>356</td>
<td>127</td>
<td>64%</td>
<td>Living at home or in RACF (25 different institutions)</td>
<td>Demographics, MMSE, CAMCOG (i)ADL, CDR-M, CERAD/BRSD</td>
<td>N/A</td>
<td>Did not develop in strictly linear manner following decline of clinical state; improved at FU1, declined at FU2</td>
<td>Professional &amp; Family</td>
<td>N/A</td>
<td>MMSE &amp; CDR explained 40% of variance</td>
</tr>
</tbody>
</table>

(Continued on next page)
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>QoL instr/s as primary outcome</th>
<th>Study design</th>
<th>Incl. PWD</th>
<th>N at BL</th>
<th>N at FU</th>
<th>% Dropout</th>
<th>Setting/ population</th>
<th>Other variables included</th>
<th>Change in self-rated QoL</th>
<th>Change in carer-rated QoL</th>
<th>Type of carers</th>
<th>Predictors self-ratings</th>
<th>Predictors carer-ratings</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Tatsumi et al.</td>
<td>2009</td>
<td>Japan</td>
<td>QoL-AD</td>
<td>BL and FU at 2 yrs</td>
<td>AD (mean age 71.8, SD 8.0; MMSE 21.7, SD 2.7 at BL)</td>
<td>140</td>
<td>96</td>
<td>31%</td>
<td>Community-dwelling</td>
<td>Demographics MMSE NPI ADL</td>
<td>No mean change</td>
<td>Declined</td>
<td>Family</td>
<td>-</td>
<td>ADL and NPI</td>
</tr>
<tr>
<td>7 Heggie et al.</td>
<td>2012</td>
<td>Canada</td>
<td>QoL-AD</td>
<td>BL and FU at 1 yr</td>
<td>Heterogeneous incl. AD, MCI, FTD, LBD, NPH, other mixed etiologies (mean age 71.5, SD 9.3)</td>
<td>119</td>
<td>32</td>
<td>73%</td>
<td>Non-institutionalized pts in rural and remote areas</td>
<td>Demographics MODIFIED MMSE NPI CES-D (I)ADL ZB BSI FAQ</td>
<td>No mean change</td>
<td>No mean change</td>
<td>Family</td>
<td>Depression and (I)ADL</td>
<td>Caregiver-burden (I)ADL and symptom severity</td>
</tr>
<tr>
<td>8 Vogel et al.</td>
<td>2012</td>
<td>Denmark</td>
<td>QoL-AD, EQ-VAS</td>
<td>BL, FU at 12 and FU 36 months</td>
<td>AD, mild</td>
<td>N=102</td>
<td>N=102</td>
<td>selectio n</td>
<td>Community-dwelling</td>
<td>Cornell Scale for Depression in Dementia (CSDD), ADL Inventory (ADCS-ADL), MMSE and NPI-Q</td>
<td>Not rated</td>
<td>Declined</td>
<td>Family</td>
<td>Not rated</td>
<td>At 12 months associations with mood, MSE, and ADL; at 36 months only with ADL</td>
</tr>
<tr>
<td>9 Bosboom et al.</td>
<td>2013</td>
<td>Australia</td>
<td>QoL-AD</td>
<td>BL and 18 months FU</td>
<td>AD, mild to moderate severity</td>
<td>N=80</td>
<td>N=47</td>
<td>41%</td>
<td>Community-dwelling</td>
<td>Broad selection of BPSD questionnaires, demographic factors, and neuropsychological tests</td>
<td>No mean change</td>
<td>Declined</td>
<td>Family</td>
<td>HRQoL self-ratings and carer-ratings of community-dwelling people with AD do not decline at same rate over 18 months and changes are associated with different factors for different raters.</td>
<td></td>
</tr>
<tr>
<td>10 Bosboom et al.</td>
<td>2014</td>
<td>Australia</td>
<td>QoL-AD</td>
<td>BL and 18 months FU</td>
<td>AD, mild to moderate severity</td>
<td>N=80</td>
<td>N=47</td>
<td>41%</td>
<td>Community-dwelling</td>
<td>Broad selection of BPSD questionnaires, demographic factors, and neuropsychological tests</td>
<td>No mean change</td>
<td>Declined</td>
<td>Family</td>
<td>Changes in specific cognitive functions are not associated with changes in HRQoL ratings in AD.</td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Country</td>
<td>QoL instr/s as primary outcome</td>
<td>Study design</td>
<td>Incl. PWD</td>
<td>N at BL</td>
<td>N at FU</td>
<td>% Drop-out</td>
<td>Setting/ population</td>
<td>Other variables included</td>
<td>Change in self-rated QoL</td>
<td>Change in carer-rated QoL</td>
<td>Type of caregivers</td>
<td>Predictors self-ratings</td>
<td>Predictors carer-ratings</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>-------------</td>
<td>--------------------------------</td>
<td>--------------</td>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
<td>------------</td>
<td>---------------------</td>
<td>------------------------------------------------------------------------------------------</td>
<td>--------------------------</td>
<td>----------------------------</td>
<td>----------------------</td>
<td>--------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Bosboom et al.</td>
<td>2014</td>
<td>Australia</td>
<td>QoL-AD</td>
<td>BL and 18 months FU</td>
<td>AD, mild to moderate severity</td>
<td>N=80</td>
<td>N=47</td>
<td>41%</td>
<td>Community-dwelling</td>
<td>Broad selection of BPSD questionnaires, demographic factors, and neuropsychological tests</td>
<td>No mean change</td>
<td>Declined</td>
<td>Family</td>
<td>HRQoL is not consistently associated with specific cognitive domains in AD. HRQoL declined alongside a general measure of cognition.</td>
<td></td>
</tr>
<tr>
<td>Conde-Sala et al.</td>
<td>2014</td>
<td>Spain</td>
<td>QoL-AD</td>
<td>AD</td>
<td>N=337</td>
<td>N=119</td>
<td>65%</td>
<td>Non-institutionalized patients (n=119)</td>
<td>GDS AQ-D</td>
<td>No mean change</td>
<td>Declined</td>
<td>Family</td>
<td>Significant discrepancies in relation to specific patient and caregiver factors. The factors associated with greater discrepancies between patient and caregiver ratings of patient’s QoL were severity of dementia, anosognosia, depression and cognitive status in patients, and female gender in caregivers.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BIBLIOGRAPHY


Australian Institute of Health and Welfare 2012, *Australia's health 2012*, AIHW,


psychotropic drugs', *Int Psychogeriatr*, vol. 13, no. 1, pp. 93-106.


Beavis, D, Simpson, S & Graham, I 2002, 'A literature review of dementia care
mapping: methodological considerations and efficacy', *J Psychiatr Ment Health Nurs*, vol. 9, no. 6, pp. 725-36.


Beydoun, MA & Beason-Held, LL 2008, 'Does hypertension interact with body weight to impact cognitive function in the elderly?: Emerging evidence', *Am J*


Browning, C, Heine, C & Thomas, S 2012, 'Promoting ageing well: Psychological contributions', in *Applied topics in health psychology*, eds L Ricciardelli & M
Caltabiano, Wiley-Blackwell.


Cox, D 2011, 'The role of neuropsychological testing in the care of older adults.', *BCMJ*, vol. 53, no. 8, pp. 416-420.


Dalla Barba, G & Goldblum, MC 1996, 'The influence of semantic encoding on


Droes, RM 2007, 'Insight in coping with dementia: listening to the voice of those who suffer from it', *Aging Ment Health*, vol. 11, no. 2, pp. 115-8.


Foldi, NS, Lobosco, JJ & Schaefer, LA 2002, 'The effect of attentional dysfunction in


Franic, DM & Jiang, JZ 2006, 'Potentially inappropriate drug use and health-related quality of life in the elderly', *Pharmacotherapy*, vol. 26, no. 6, pp. 768-78.


Frazier, SC 2005, 'Health outcomes and polypharmacy in elderly individuals: an integrated literature review', *J Gerontol Nurs*, vol. 31, no. 9, pp. 4-11.


Garre-Olmo, J, Lopez-Pousa, S, Vilalta-Franch, J, Turon-Estrada, A, Hernandez-


Hamilton, HJ, Gallagher, PF & O'Mahony, D 2009, 'Inappropriate prescribing and adverse drug events in older people', *BMC Geriatr*, vol. 9, p. 5.


Hayden, KM, Jones, RN, Zimmer, C, Plassman, BL, Browndyke, JN, Pieper, C, Warren, LH & Welsh-Bohmer, KA 2011, 'Factor structure of the National Alzheimer's Coordinating Centers uniform dataset neuropsychological battery: an evaluation of invariance between and within groups over time', *Alzheimer Dis*
Assoc Disord, vol. 25, no. 2, pp. 128-37.


Henderson, JA, Buchwald, D & Manson, SM 2006, 'Relationship of Medication Use to Health-Related Quality of Life Among a Group of Older American Indians', Journal of Applied Gerontology, vol. 25, no. 1 suppl, pp. 89S-104S.


mild cognitive impairment and normal controls', *Arch Clin Neuropsychol*, vol. 21, no. 5, pp. 405-12.


Kim, YS, Nibbelink, DW & Overall, JE 1994, 'Factor structure and reliability of the...
Alzheimer's Disease Assessment Scale in a multicenter trial with linopirdine', *J Geriatr Psychiatry Neurol*, vol. 7, no. 2, pp. 74-83.


Landis, JR & Koch, GG 1977, 'The measurement of observer agreement for categorical data', *Biometrics*, vol. 33, no. 1, pp. 159-74.


Lau, DT, Kasper, JD, Potter, DE, Lyles, A & Bennett, RG 2005, 'Hospitalization and death associated with potentially inappropriate medication prescriptions among
elderly nursing home residents', *Arch Intern Med*, vol. 165, no. 1, pp. 68-74.


Lindley, CM, Tully, MP, Paramsothy, V & Tallis, RC 1992, 'Inappropriate medication is a major cause of adverse drug reactions in elderly patients', Age Ageing, vol. 21, no. 4, pp. 294-300.


Logsdon, RG, McCurry, SM & Teri, L 2007, 'Evidence-Based Interventions to Improve Quality of Life for Individuals with Dementia', Alzheimers care today, vol. 8, no. 4, pp. 309-318.


Lucas Carrasco, R 2007, '[Quality of life and dementia]', *Med Clin (Barc)*, vol. 128, no. 2, pp. 70-5.


Nadkarni, NK & Black, SE 2006, 'Cognitive outcomes.', in *Trial designs and outcomes in dementia therapeutic research.*, eds R Rockwood & S Gauthier, Taylor & Francis, Boca Raton, FL.


Olsson, IN, Runnamo, R & Engfeldt, P 2001, 'Medication quality and quality of life in the elderly, a cohort study.', Health Qual Life Outcomes, vol. 9, p. 95.


Perales, J, Cosco, TD, Stephan, BC, Haro, JM & Brayne, C 2013, 'Health-related

Pereira, FS, Yassuda, MS, Oliveira, AM & Forlenza, OV 2008, 'Executive dysfunction correlates with impaired functional status in older adults with varying degrees of cognitive impairment', *Int Psychogeriatr*, vol. 20, no. 6, pp. 1104-15.


Prigatano, GP & Morrone-Strupinsky, J 2010, 'Advancing the profession of clinical neuropsychology with appropriate outcome studies and demonstrated clinical skills', *Clin Neuropsychol*, vol. 24, no. 3, pp. 468-80.


Ready, RE & Ott, BR 2003, 'Quality of Life measures for dementia', *Health Qual Life Outcomes*, vol. 1, p. 11.


Schroeder, K, Huber, CG, Jelinek, L & Moritz, S 2013, 'Subjective well-being, but not subjective mental functioning shows positive associations with neuropsychological performance in schizophrenia-spectrum disorders', Compr Psychiatry.


Serrano-Pozo, A, Frosch, MP, Masliah, E & Hyman, BT 2011, 'Neuropathological alterations in Alzheimer disease', *Cold Spring Harb Perspect Med*, vol. 1, no. 1, p. a006189.


Siedlecki, KL, Honig, LS & Stern, Y 2008, 'Exploring the structure of a
neuropsychological battery across healthy elders and those with questionable dementia and Alzheimer's disease', *Neuropsychology*, vol. 22, no. 3, pp. 400-11.


Sprangers, MA & Aaronson, NK 1992, 'The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: a review', *J Clin Epidemiol*, vol. 45, no. 7, pp. 743-60.


Stock, WA, Okun, MA, Haring, MJ & Witter, RA 1983, 'Age and subjective well-


Vitaliano, PP, Breen, AR, Albert, MS, Russo, J & Prinz, PN 1984, 'Memory, attention,


Weintraub, D & Katz, IR 2005, 'Pharmacologic interventions for psychosis and agitation in neurodegenerative diseases: evidence about efficacy and safety',

Weintraub, S & Mesulam, M 2009, 'With or without FUS, it is the anatomy that dictates the dementia phenotype', *Brain*, vol. 132, no. Pt 11, pp. 2906-8.


World Health Organisation 2012, The Anatomical Therapeutic Chemical Classification
System with Defined Daily Doses (ATC/DDD).


NOTE: Appendices A and D removed due to copyright restrictions.
DOUMENTS RELATED TO RECRUITMENT

1. Example Recruitment Letter ............................................................
2. Information Sheet QoLCog Study ......................................................
3. Media Statement New Study .............................................................
4. Brochure QoLCog Study .................................................................
5. Phone Screening Manual ...................................................................
6. Recruitment Checklists ........................................................................
7. Telephone Interview for Cognitive Screening .....................................
8. Example Confirmation Letters to Participant and Informant .......
9. Flowchart Participants Study I from Recruitment Sources ......
10. Flowchart Participants Study I and II ...............................................
Dear ***,

I am writing to advise you of an important study that we are currently running at the University of Western Australia (please see attached Information Sheet). I would be most grateful if you would take a moment to familiarise yourself with the study and consider if you would agree to participate.

Mrs Pascalle Bosboom will be contacting you within the next couple of weeks to clarify any questions that you may have.

Thank you for your time and for considering your participation with this study.

Yours sincerely,

Prof Osvaldo Almeida,
Geriatric Psychiatrist

Enclosed: Information Sheet
Quality of Life and Cognition STUDY (QoLCog)  
- Patient Information Sheet -  

Investigator: Pascale Bosboom  
WA Centre for Health and Aging (WACHA) of  
the University of Western Australia and the Royal Perth Hospital

Introduction
Most people agree that the term “Quality of Life” (QoL) includes the concept of whether one’s life meets expectations. It has become a widely used term in both research and clinical practice. As for other age groups, many doctors, nurses, psychologists and other health care workers are becoming more interested in finding ways to increase the QoL of older people. Yet, we do not have much knowledge about some factors that might play a major role in the QoL for healthy older people, or for people with dementia. For example, what exactly is the impact of forgetfulness, which is common in the elderly and those with Alzheimer’s disease, on one’s QoL?

We are conducting this study to develop a better understanding about the impact of so-called ‘cognitive’ problems (like forgetfulness, word finding difficulty, and disorientation) on the QoL of older people with Alzheimer’s disease. With this in mind, we are recruiting two groups of older adults: people with Alzheimer’s disease and people with no obvious memory problems (controls).

What are you expected to do?

☐ If you agree to help us with this research and signed the Consent Form, we will ask you to complete some questionnaires (about your QoL, your living situation, your general health) at home. We will also ask your next-of-kin to complete some questionnaires (with similar questions, about your QoL) at home. These questionnaires will take approximately 20 minutes of your time.

☐ In addition, we will ask you and your next-of-kin to visit Royal Perth Hospital, where we will ask you to complete some paper-and-pencil tests, to assess your memory, language, and other skills. For a few of the tests your answers (for example reading a word list) will be audio-taped, so we will be able to score your answers correctly after the testing is completed. An experienced Clinical Neuropsychologist will perform these tests. Your next-of-kin will also be asked to complete some questionnaires. This visit will take 2 to 3 hours.

☐ After 18 months you and your next-of-kin will be invited to repeat all questionnaires and paper-and-pencil tests in the same way.
☐ There are no risks or side effects that can be expected; none of the procedures of this study are harmful. You might find some of the paper-and-pencil tests tiring, so please let us know if you would like a break.

☐ You don’t have to enter this study if you do not want to — whatever you decide to do, your future treatment will not be affected by your decision.

☐ Participation in this study will be at no financial cost to you.

Who might benefit from it?

☐ Clinical relevant information might arise as part of the assessment. If that is the case, we will, with your and your next-of-kin’s permission, inform your general practitioner.

☐ Your contribution to this research can help us to improve the way health services for older people with and without Alzheimer’s disease in our aging society are delivered.

How we will handle your personal information
All information obtained will be handled in strict confidence and in compliance with all privacy laws (in Australia, Privacy Act 1988). Your name will not appear on trial documents or publications. Only duly authorized persons will have access to your data.

Do you have any questions?
There are several sources for further information:

1. Ask your doctor any questions you like to be answered about this study.

2. If you have any questions during the study, please contact the chief investigator of this study:
   Pascalle Bosboom by phone (92243417) during normal business hours on Monday or Tuesday; or you can leave a message with our secretary (ph. 92242855).

This research project has been approved by the Ethics Committee at Royal Perth Hospital. Further information may be obtained from the Chief Investigator or from Clin Prof J A Millar, Chairman of the Ethics Committee, telephone (08) 9224 2244.
August 9, 2007

Media Statement

NEW STUDY ASSESSES ALZHEIMER'S QUALITY OF LIFE ISSUES

A new project by West Australian researchers is seeking to understand how some key factors in dementia, such as forgetfulness, might impact the quality of life of people diagnosed with Alzheimer's disease.

The project is being run by the WA Centre for Health and Ageing (WACHA), based at the Western Australian Institute for Medical Research (WAIMR).

It is being undertaken by clinical neuropsychologist and University of Western Australia PhD student Pascalle Bosboom and WACHA research director Professor Osvaldo Almeida.

By 2050, the number of Western Australians with dementia is projected to increase to over 79,000.

"Alzheimer's disease accounts for up to 70 per cent of all cases of dementia and, with our ageing population, the prevalence of it is on the rise, so research looking at how to manage the impact of the disease on patients' quality of life is very important," said Mrs Bosboom.

"This study will probe, for example, what the impact is of forgetfulness or word finding difficulty – common problems linked to Alzheimer's disease – on a person's quality of life.

"The hope is that, by enhancing our understanding of the factors that influence quality of life, we may be able to improve the long-term health outcomes of people with dementia."

Professor Almeida said, "Over the past few years, we have studied in detail the molecular mechanisms that contribute to the development of Alzheimer's disease, but have neglected to investigate the various factors that contribute to determine the quality of life of patients and their carers. This project aims to move this aspect of our current knowledge forwards."

People diagnosed with Alzheimer's disease aged over 65 who are living in the community and healthy volunteers aged over 65 with no obvious signs of memory problems are needed to assist with the study.

Volunteers will be asked to complete a few short questionnaires, as well as undergo some paper and pencil tests to assess their cognitive functions (like memory).

Those interested in taking part in the study should phone Pascalle Bosboom on 9224 3417 or Cheryl Ackoy on 9224 2855 for further information.

WACHA's research aims to improve the health of older people by investigating common conditions of later life including dementia, falls, depression, immobility and residential care.

-ENDS-

MEDIA CONTACT:
Natalie Papadopoulos, WAIMR Media Consultant, m 0407 984 435, o 9388 9280
For further information, please contact us:

Ms Pascalle Bosboom
Clinical Neuropsychologist
Research Coordinator
QoLCog study
Phone: (08) 9224 3417

Ms Cheryl Ackoy
Research Coordinator
WACHA
Phone: (08) 9224 2855

The project is being run by the WA Centre for Health and Ageing (WACHA), based at Ainslie House, Royal Perth Hospital.

Please visit our website: www.wacha.org.au

Interested in the Quality of Life of people diagnosed with Alzheimer’s disease and their carers?

The QoLCog study is looking for volunteers!
• Have you been diagnosed with Alzheimer’s disease?
• Are you caring for a person with Alzheimer’s disease?
• Are you both living in the community?

The QoLCog study aims to develop a better understanding of the impact of cognitive problems - like forgetfulness and disorientation - on the quality of life of people with Alzheimer’s disease and their carers. By increasing our understanding of factors that influence the quality of life of people with, dementia we may be able to improve their long-term health outcomes.

Participants and Next-of-Kin will be sent questionnaires about their general health and quality of life to complete. The researcher will arrange a convenient time to conduct a further assessment on memory, concentration and other cognitive tests.

After 18 months you will be asked to repeat the questionnaires and the cognitive assessment.

The QoLCog study is being undertaken by Clinical Neuropsychologist Ms Pascalle Bosboom, and WACHA Research Director, Professor Osvaldo Almeida.
QoLDEMCOG study
Phone screening MANUAL

- Recruitment of patients & informants for study I -

Introduction:
"My name is Pascalle Bosboom from Royal Perth Hospital. I am following up a letter that was recently sent to you by ***. The letter informed you of an important study that we are currently running at RPH. In the letter, Prof. **** asked you to consider participating in our study. Did you receive the letter? Do you have a few minutes to talk about this now?

[As a reminder:] “Just to remind you, ...”

It is a study to see what causes changes in the quality of life for people who have problems with their memory.

The study involves some memory tests and health questionnaires and will take place at Royal Perth Hospital. We will repeat this assessment after 18 months.

→ See text on Information Sheet

"Would you be interested in this study?"

"May I ask you some more questions to see if it would be appropriate for you to participate?"

General screening questions:

1. Forgetfulness/assessed/diagnosis
   □ Do you have any difficulty with your memory?
   □ Has this been assessed by a doctor?
   □ What was the outcome of this assessment?

2. Current severe medical illness/hospitalisation
   □ Do you suffer from any severe medical illness?
   □ Is this likely to lead to a hospital admission in the next 6 months?
     (If necessary give example such as severe heart disease, cancer, planned large operation, etc).
   (Explain that the study requires people to return for assessments over a period of 18 months, so it is probably better for them, if they do not enroll in the current study. However, if appropriate, ask if we can keep their details for our register in case other studies come up in the future for which they may be eligible.)

3. Vascular issues
   □ Have you ever been told by a doctor that you have had a stroke or heart attack, or any other serious heart problem?
   □ If so, when?
     (If had clinically relevant stroke – exclude)
4. Sight/hearing
   □ Are you able to see OK?
   (Corrected to normal vision with glasses is ok)
   □ Is your hearing adequate?
   (Use of hearing aid is ok, if they can hear someone speak in a quiet room).

5. Visit RPH
   □ Are you able to visit RPH during weekdays to attend the assessments?
   (i.e. not working F/T, or too far away to travel).

6. Participant in other study
   □ Are you in any other trials/studies at the moment?
   (If so, exclude until finished).

7. Fluent English
   □ Is English your mother tongue, or are you a fluent English speaker?
   (If not, exclude from study)

Conclusion:

➔ If medical problem or other unfulfilled requirement:
   “Because of your ***, this study will probably not be suitable for you. Thanks for your time today.”
   (Take name, tick box if ok to contact for other studies)

➔ If unclear regarding somatic illnesses:
   “Because of your ***, it might be a good idea to find out if your General Practitioner/referring specialist (OA, NL, or LF) would be happy for you to participate in this study. I can send you the information anyway, and if you are visiting a doctor soon, you could discuss this with them. I can ring you again in a few weeks time to see what they say.”

➔ If OK on general screening questions:
   “Do you have a relative or spouse I can talk to as well, about your participation for this study?”
   (if NO, explain that it is necessary for participation in this study; if YES, ask NOK following questions)

Next-of-Kin general questions:
   “My name is Pascalle Bosboom from Royal Perth Hospital. With this call I am following up a letter that was recently sent to your *** (partner/wife/husband/mother/father/relative/friend) by ***. The letter informed of an important study that we are currently running at RPH. In the letter, Prof. *** asked your *** (relative/friend) to consider participating in our study. Did you read the letter? Do you have a few minutes to talk about this now?

[As a reminder:] “Just to remind you, ...”
It is a study to see what causes changes in the quality of life for people who have problems with their memory.

The study involves some memory tests and health questionnaires and will take place at Royal Perth Hospital. We will repeat this assessment after 18 months.

"Would you be interested in this study?"

"May I ask you some more questions to see if it would be appropriate for you and your *** (relative/friend) to participate?"

→ Repeat all general screening Qs again (as above).

→ Give conclusion (as above).

1. If eligible, also ask NOK if he/she wants to participate as informant.
2. If ok, advice that Information sheet and consent forms will be sent out in the mail, along with some questionnaires for the patient and informant (NOK) to fill out.
3. Explain about the questionnaires that need to be completed at home. These can be brought in when they come in for their first assessment.
4. Advise on details of first visit (i.e. will take 2 hours, at Ainslie House, involves memory and questionnaires).
5. Make the booking for the first RPH assessment.
6. Advice what they will need to bring (e.g. glasses, hearing aid, medication list, completed questionnaires).
7. Ask if they have suitable means to get to RPH.
8. Repeat that a letter will be sent out which will explain everything that we have talked about, and will have all booking details on it.

Name Patient: ___________________________ Age: ___ DOB: _______

Address: _______________________________________________________

Contact Numbers: _______________________________________________

Name Next-of-Kin: ___________________________

Address: _______________________________________________________

Contact Numbers: _______________________________________________

Special needs (e.g. transport): ___________________________

Date of assessment: ______________ Place: _________________________

Contact later if not suitable now? YES NO

NOTES:
Name of Patient: Mr/Mrs/Ms/Dr ___________________________  DOB:__/__/____

Address: ____________________________________________  Age: _______ (must be 65+)

Telephone:  
Home ___________________________
Work ___________________________
Mobile ___________________________

Date called:__/__/____ (time: ____ hrs)  → result:  
Date called:__/__/____ (time: ____ hrs)  → result:  
Date called:__/__/____ (time: ____ hrs)  → result:  

General screening Qs:

<table>
<thead>
<tr>
<th>Q.</th>
<th>Patient:</th>
<th>NOK:</th>
<th>OK</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. forgetfulness/diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- memory problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- assessed by doctor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. current severe medical issue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- no severe medical issue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- no hospital admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. vascular issues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- no stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- no heart attack</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- no high blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. sight/hearing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- normal vision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- normal hearing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. visit RPH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- able to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. participant other study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. fluent in English</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- yes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*NOTES regarding conclusion

Conclusion:

A. Does not fulfil criteria (i.e. ____________)  → excluded
B. Unclear at this point in time (i.e. ____________)  → to be discussed *
C. Ok on general screening questions

QoLDemCog
Name of CONTROL: Mr/Mrs/Ms/Dr
DOB: __/__/____
Address: __________________________________________ Age: _____ (must be 65+)

Telephone: Home ___________________________ NOK/INFORMANT: ___________________________
Work _______________________________________
Mobile _______________________________________

Date called: __/__/____ (time: ____ hrs) → result: ___________________________________________
Date called: __/__/____ (time: ____ hrs) → result: ___________________________________________
Date called: __/__/____ (time: ____ hrs) → result: ___________________________________________

Contact later if not suitable now? __________________________________________________________

What are the best week days and times to contact you?

<table>
<thead>
<tr>
<th>CONTACT</th>
<th>yes/no</th>
<th>Best times</th>
<th>Worst times</th>
<th>notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuesday</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wednesday</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thursday</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friday</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

General screening Qs:

1. MEMORY
   □ Do you have any difficulty with your memory?
   □ Do you forget where you have left things more than you used to?
   □ Do you forget names of close friends or relatives?
   □ Have you ever been in your own neighbourhood and forgotten your way?

   If no difficulty with memory, skip following Qs
   □ When did this difficulty begin?
   □ Did it come on suddenly?
   □ Has it become better or worse since it started?
   □ Has your memory been assessed by a doctor? When/where?
   □ What was the outcome of this assessment?

<p>| Answered by | Answered by |
| CONTROL:    | NOK/INFORMANT: |
| Yes | No | ? | Yes | No | ? |
| Duration in months:..... | Duration in months:..... |
| sudden | gradual | ? | sudden | gradual | ? |
| □ Worse | □ Remained same | □ Better | □ Worse | □ Remained same | □ Better |
| yes | no | | yes | no | |
| □ SMC | □ MCI | □ Dementia | □ SMC | □ MCI | □ Dementia |</p>
<table>
<thead>
<tr>
<th>2. General health</th>
<th>Answered by</th>
<th>OK</th>
<th>Answered by</th>
<th>OK</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Do you have any difficulties with your physical health? (check vascular issues)</td>
<td>Yes</td>
<td>No</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>□ Do you suffer from any severe medical illness?</td>
<td>Yes</td>
<td>No</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>□ Is this likely to lead to a hospital admission in the next 6 months?</td>
<td>Yes</td>
<td>No</td>
<td>?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Sight/hearing</th>
<th>Answered by</th>
<th>OK</th>
<th>Answered by</th>
<th>OK</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ difficulties with vision</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>□ difficulties with hearing</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Visit RPH</th>
<th>Answered by</th>
<th>OK</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ able to</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Participant other study</th>
<th>Answered by</th>
<th>OK</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ no</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. Fluent in English</th>
<th>Answered by</th>
<th>OK</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*NOTES regarding general screening Qs:

→ Do the COGNITIVE SCREENING (see separate form)

Conclusion: 

Conclusion:

□ Does not fulfil following criteria: ___________________________ → to be excluded
□ Unclear at this point in time, i.e. ___________________________ → to be discussed
□ Ok on general screening questions, but not on cognitive screening → to be excluded
□ Eligible for QoLDemCog study as CONTROL

Date of 1st assessment: ____/____/____ Time: ____ hrs

Place of 1st assessment: ______________________________________

Special Needs: _____________________________________________
PART D: Cognitive Screen - TICS-M

Now I would like to ask you a few questions to check your concentration and your memory.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Please tell me your full name</td>
</tr>
<tr>
<td>2.</td>
<td>What is your age?</td>
</tr>
<tr>
<td>3.</td>
<td>What is today’s date? (w/o looking @ calendar) Need date, month and year for 3 pts</td>
</tr>
<tr>
<td>4.</td>
<td>Day of week?</td>
</tr>
<tr>
<td>5.</td>
<td>Season?</td>
</tr>
<tr>
<td>6.</td>
<td>Phone number? (same as note)</td>
</tr>
<tr>
<td>7.</td>
<td>Count backwards from 20 (Correct = 2, 1 error : 1, more : 0)</td>
</tr>
<tr>
<td>8.</td>
<td>I will read a list of 10 words, when I finish I want you to tell me as many as you remember. Please don’t write them down. (Read 1 word per 2 seconds).</td>
</tr>
</tbody>
</table>

Cabin, Pipe, Elephant, Chest, Silk, Theatre, Watch, Whip, Pillow, Giant

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>9.</td>
<td>Subtract 7 from 100 then keep subtracting 7 from that number 93, 86, 79, 72, 65</td>
</tr>
<tr>
<td>10.</td>
<td>What do people usually use to cut paper? (scissors or shears)</td>
</tr>
<tr>
<td>11.</td>
<td>How many things are in 1 dozen? (12)</td>
</tr>
<tr>
<td>12.</td>
<td>What do you call a kind of prickly plant that lives in the desert? (cactus/prickly pear)</td>
</tr>
<tr>
<td>13.</td>
<td>What animal does wool come from? (lamb/sheep)</td>
</tr>
<tr>
<td>14.</td>
<td>Please say this exactly: “No ifs, ands or buts”</td>
</tr>
<tr>
<td>15.</td>
<td>“Methodist Episcopal”</td>
</tr>
<tr>
<td>16.</td>
<td>What is the name of the monarch (of the commonwealth)? (fully correct = 2, partially = 1)</td>
</tr>
<tr>
<td>17.</td>
<td>What is the full name of the current Prime minister? (full name = 2, one name = 1)</td>
</tr>
<tr>
<td>18.</td>
<td>With finger, please tap phone 5 times. (Correct = 2, different tap = 1)</td>
</tr>
<tr>
<td>19.</td>
<td>What is opposite of East? (WEST)</td>
</tr>
<tr>
<td>20.</td>
<td>What is opposite of Generous?</td>
</tr>
<tr>
<td>21.</td>
<td>Remember word list that you repeated before? Now tell me as many words as you remember. (circle recalled words)</td>
</tr>
</tbody>
</table>

Cabin, Pipe, Elephant, Chest, Silk, Theatre, Watch, Whip, Pillow, Giant

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>

TICS TOTAL /50

If TICS below 19: will need to speak to relative or ask them to see a doctor about memory difficulty before attending the screening visit.
If TICS above 38: let them know that they have done quite well on the memory task, and that we will not book them for a baseline visit right away but may do so in the future if we are still looking for participants.

Thank you for taking the time to answer these questions.
ADDRESS (to Participant)

DATE

Dear ***,

I would like to thank you for your participation in this study. Your valuable time and effort are very much appreciated.

With this letter, I would like to confirm the details of your appointment, as we recently discussed on the phone:

Date: __________________________________________
Time: __________________________________________
Place: _________________________________________
Name of accompanying next-of-kin: ________________________

Please make sure that you read all the information. We expect you to come together with your next-of-kin to this appointment. Please remember to bring the following:

☐ Signed Consent Forms
☐ Completed questionnaires
☐ Any reading glasses or hearing aids that would normally use
☐ A list of your current medications/supplements
On your first visit
Your visit will involve an assessment of general health. You will be asked a number of questions about your health (past and present). We will also ask you to complete some paper and pencil activities which are designed to measure different aspects of memory, concentration and other thought processes. You will also be asked to fill out a few short, simple questionnaires relating to these aspects and your quality of life. This first visit is expected to last approximately 2 hours.

Contact address
If you have any problems or questions prior to your visit, or in case you need to cancel or reschedule the appointment, please contact me by phone (92243417) during normal business hours, or you can leave a message with our secretary on 9224 2855.

Thank you again for you assistance with this study. Your valuable time and effort will help to make this study possible. I look forward to meeting you soon.

Yours sincerely,

Pascalle Bosboom
QolDemCog Study co-ordinator
ADDRESS (to Informant)

DATE

Dear ***,

I would like to thank you for your participation in this study. Your valuable time and effort are very much appreciated.

With this letter, I would like to confirm the details of your appointment, as we recently discussed on the phone:

Date: ____________________________
Time: ____________________________
Place: ____________________________
You are next-of-kin of: ____________________________

Please make sure that you read all the information. We expect you to come together with *** to this appointment. Please remember to bring the following:

☐ Signed Consent Forms
☐ Completed questionnaires
☐ Any reading glasses or hearing aids that would normally use
☐ A list of his/her current medications/supplements
On the first visit
***’s visit will involve an assessment of general health and mental state. He/she will be asked a number of questions about his/her mental and physical health (past and present). We will also ask him/her to complete some paper and pencil activities which are designed to measure different aspects of memory, concentration and other thought processes. He/she will also be asked to fill out a few short, simple questionnaires relating to these aspects and his/her quality of life.

As next-of-kin you will be asked to complete some questionnaires regarding his/her cognitive functioning and general wellbeing. This first visit is expected to last approximately 2 hours.

Contact address
If you have any problems or questions prior to your visit, or in case you need to cancel or reschedule the appointment, please contact me by phone (92243417) during normal business hours, or you can leave a message with our secretary on 9224 2855.

Thank you again for you assistance with this study. Your valuable time and effort will help to make this study possible. I look forward to meeting you soon.

Yours sincerely,

Pascallo Bosboom
QoDemCog Study co-ordinator
Figure a. Flowchart participants. The diagram shows the flow of participants from the time of invitation to inclusion in the study.
**Figure 1.** Flow of participants during the 18 months of follow-up of the older adults diagnosed with Alzheimer’s disease. Assessments took place at baseline and after 18 months.
**Alzheimer’s group**

Eligible Pts and carer approached with recruitment letter (N=196)

108 Excluded

- n = 87 Refused, change of circumstances (e.g. admitted to Nursing Home, medical comorbidity) or no carer as informant available.
- n = 21 Not traceable, no reply to letters or...

Pts and carer eligible and agreed to participate (N=88)

8 Discontinued

- Cancelled appointment; change of circumstances.

Pts and Informant completed baseline study (N=80)

16 Discontinued (20%)

- Declined or cancelled appointment (by Pt or carer) due to change of circumstances (i.e. severe comorbidity, hospitalization, 1 carer deceased, 1 carer dementia)
- 7 Deceased (8.8%)
- 5 Untraceable (6.3%)
  - No response, no registration of death or hospitalization

Pts and Informant completed follow-up study (N=52)

**Control group**

Eligible healthy older adult and informant approached with recruitment letter (N=79)

5 Excluded

- Change of circumstances (e.g. medical comorbidity) or no carer as informant available.

Healthy older adult and informant eligible and agreed to participate (N=74)

0 Discontinued

Healthy older adult and informant completed baseline study (N=74)

3 Discontinued (4.1%)

- Declined or cancelled appointment due to change of circumstances.
- 0 Deceased
- 0 Untraceable

Healthy older adult and informant completed follow-up study (N=71)

**Figure b.** Flow of participants during the 18 months of follow-up of the older adults diagnosed with Alzheimer’s disease and the healthy older adults as Controls. Assessment took place at baseline and after 18 months.
APPENDICES C

DOCUMENTS RELATED TO ASSESSMENT

1. CHECKLIST AND ORDER OF ASSESSMENT ............................................
2. MANUAL ASSESSMENT INSTRUCTIONS ...................................................
3. CONSENT FORMS ...................................................................................
4. QUESTIONNAIRES ............................................................................... 
5. QoL-AD - PATIENT & TWO CARER VERSIONS .....................................
6. NEUROPSYCHOLOGICAL TESTS PROTOCOLS ....................................
Checklist Preparation for Baseline Assessment

**Standard:**
- Stopwatch
- Watch
- 2 Pencils
- 2 Pen
- Tape recorder
- Blanc tape
- Blanc pieces of paper
- Instructions protocol booklet

**Test material:**
- Self Rating Perf. Visual Scale
- D-KEFS – stimulus booklet
- CAMCOG-r – stimulus booklet
- VAT – stimulus booklet
- NAB Lang. – stimulus booklet
- BNT - stimulus booklet
- D-KEFS - stimulus booklet
- WAIS-III - instruction booklet
- WTAR – reading card

**Extra copies of ‘sent home’ Qs:**
- Consent forms
- Patient General Q
- HADS – participant
- Anosognosia Q – participant
- Anosognosia Q – informant
- KATZ - informant
- IADL - informant
- IQ-CODE – informant

**Set Qs for participant:**
- GRAD
- QoL-AD – participant
- Abbrev SEQOL - participant
- Self Rating Perf. – prospective
- CAMCOG-r - scoring form
- CVLT-II - scoring form
- VAT - scoring form
- NAB Language - scoring form
- BNT - scoring form
- D-KEFS Verbal Fluency - scoring form
- D-KEFS TMT - scoring form
- WAIS-III Digit Span - scoring form
- WAIS-III Digit Symbol - scoring form
- WTAR - scoring form
- Self Rating Perf. – retrospective

**Set Qs for informant:**
- QoL-AD – I perspective 1
- QoL-AD – I perspective 2
- Abbrev SEQOL - Informant
- NPI
## Checklist & order of Baseline Assessment

<table>
<thead>
<tr>
<th>Instrument/item/check</th>
<th>Y/N</th>
<th>Comment / time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheque name, place, and time of appointment</td>
<td>□</td>
<td>→ see Correspondence File</td>
</tr>
<tr>
<td>Welcome participant &amp; informant</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>Write down time started</td>
<td>□</td>
<td>Start: . . . .</td>
</tr>
<tr>
<td>Read general instructions</td>
<td>□</td>
<td>→ See Instruction Booklet</td>
</tr>
<tr>
<td>Cheque signed Informed Consent Forms</td>
<td>□</td>
<td>→ Hand over copies!</td>
</tr>
<tr>
<td>Cheque completed Qs by participant</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>Cheque completed Qs by informant</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>Ask participant to sign Tape Recording Consent Form</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>Ask informant to complete set of forms separately</td>
<td>□</td>
<td>→ Explain different versions!</td>
</tr>
<tr>
<td>Assessment with Participant in following order:</td>
<td>□</td>
<td>Start: . . . .</td>
</tr>
<tr>
<td>□ GRAD</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ Abbr. SEQOL</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ QoL-AD</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ Self Rating Performance - prospective</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ CAMCOG-r</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ Rey Copy</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ NAB screening Language</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ Rey Recall (3')</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ CVLT-II encoding &amp; recall short delay</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ D-KEFS TMT</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ CVLT-II recall long delay (10')</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ WAIS-III Digit Symbol</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ VAT</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ WAIS-III Digit Span</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ D-KEFS Verbal Fluency</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ BNT</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ WTAR</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>□ Self Rating Performance - retrospective</td>
<td>□</td>
<td>. . . . . . . .</td>
</tr>
<tr>
<td>Cheque completed set of forms by informant</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>Debriefing</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>Cheque details (address of participant and informant)</td>
<td>□</td>
<td></td>
</tr>
</tbody>
</table>

Finished: . . .
## INTRODUCTION MANUAL

> **Introduction**  
After welcoming the participant and his/her informant (i.e. caregiver/next-of-kin), introduce yourself and give an explanation of what the aim of the study is.

<table>
<thead>
<tr>
<th>Say:</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Thank you very much for seeing me. My name is **<em>, and I am a clinical neuropsychologist. We are doing research about how elderly rate their QoL. I would like to explain what the study is about and how you can be of great help to us. Did you read the Information Sheet?</em></td>
</tr>
<tr>
<td>Show the Information Sheet.</td>
</tr>
</tbody>
</table>

> **Assessment today**  
Check whether the participant is aware of the aims of the assessment today. Give an explanation of the aim of today (this morning/afternoon).

<table>
<thead>
<tr>
<th>Say:</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>I will be asking you about how you are feeling, what you think about your memory, and how you think you are functioning in your daily life. Some of the questions may not seem relevant to you, but it would be helpful if you would answer them all. I would also like to do some paper and pencil tests to look at all kinds of skills, like your memory, language and concentration. Like other people, you will find some tests more easy, and others more difficult. Please give your best effort on all questions.</em></td>
</tr>
</tbody>
</table>

> **Confidentiality**  
Explain the confidentiality and what will happen with the information obtained.

<table>
<thead>
<tr>
<th>Say:</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Everything you tell me is highly confidential and will only be discussed with my supervisor and those people involved directly in this research and in your care. I want to assure you that whatever you decide will in no way affect any treatment you might need.</em></td>
</tr>
</tbody>
</table>
➢ Consent form
For research purposes it is necessary to obtain informed consent from the subject. The statement that we read out to the participant and informant is as follows:

Say:
I would also like to ask the person who knows you well, that is [name of caregiver/informant], some questions. Before we start, I must make sure that you and your next-of-kin have signed the consent form to show that you agree to take part in this study.
Did you already read and sign it (at home)?
If they have not signed the consent form yet, please ask them to read it carefully and sign it.

Say:
Could you please read and sign this consent form? If you have any questions about anything on the consent form, please ask me and we will go through it.

➢ Tape recording consent form
In order to assess language skills as accurately as possible, it is necessary to obtain tape recording informed consent from the subject as well. The statement that we read out to the participant and informant is as follows:

Say:
I would also like to ask you, whether you agree that I will make tape recordings at some times during the testing. The reason for this is, that I want to make sure to rate your answers correctly. So it can be very helpful if I can listen to the recording of your answers after our meeting. No names will be used on the tapes. Could you please read and sign this tape recording consent form? If you have any questions about anything on the consent form, please ask me and we will go through it.
Collecting ‘take-home’ questionnaires
Collect the questionnaires that were handed by the physician. Ask participant and informant.

Say:
Did you manage to complete the questionnaires that were sent to your home address [or: handed to you by your doctor]?

If not, they have to be completed today. Make sure to complete the General Pt Questionnaire with both participant and informant (considering the importance of demographic data etc.)

Say:
Can we have a look at them? I would like to suggest that we complete these questionnaires before we continue.

If yes, check if they are all completed and if the informant gave any help with the General Pt Questionnaire (which would be favourable considering the importance of demographic data etc.)

Say:
Can we have a look at them?
Did you have help from your spouse/friend/carer? 

Further procedure today
Describe the procedure of today’s assessment.

Say:
Now I just like to go over what we’ll be doing today very briefly. Like I said, I am going to do some paper and pencil activities with you. This assessment does not involve a medical check-up. These include concentration, memory and language activities. Some include answering questions, or remembering some information, or writing things down. We will do this testing together, while your spouse/friend/carer [name] is waiting for you outside this room. Most people find the assessment interesting and worthwhile; some find it a bit tiring. If you need a short rest break and were possible, you can have a short break. I expect to be finished within 1.5 hours.
➢ Participant & Informant separate

Show participant the QoL-AD; see separate instruction on the form.

Say:
I would like you (participant) to have a look at this questionnaire [QoL-AD]. In the mean time, I will show your spouse/friend/caregiver were he/she can wait for us. I’ll be right back and we will go through it together.

Show informant were he/she could wait during the testing with the participant. Make sure that she will stay within reach if necessary. Complete the NPI together with the informant. Ask her/him to complete the QoL-AD 1, QoL-AD 2 questionnaires.

Say:
➔ See instruction NPI and QoL-AD.
At the end of the assessment:

☐ Thank for participation

☐ Debriefing
  ➔ Explain what will happen with the data
  ➔ Explain they will be contacted in about 18 months
  ➔ Ask if there are any questions
  ➔ Ask if there are any things they like to discuss

☐ Check all details for correspondence
  ➔ Address participant
  ➔ Address informant

☐ Plans for moving, travel or anything alike
TEST SESSION WITH PARTICIPANT ONLY

➢ General test instructions to participant

Explain to the participant that you will be reading verbatim the instructions of the tasks and questionnaires, and that you will not be able to give the correct answers.

Say:
We are going to do this as quickly as possible. There are some things that you should know to help me doing this.
First, I may not be able to tell you whether you’ve got the right answer or not, because that could harm the results of the study.
Also, I’ll be reading instructions to you from these pages in front of me. Please bear with me as I have to give these instructions to everyone the same way – so even though you may know how to do a task, I still have to read through all the instructions.
Last but not least, I would appreciate it very much if you could give the best effort you can.

Do you have any questions?

See further instruction per instrument on the following pages
Patient

I, .................................................. (NAME OF PARTICIPANT) agree to participate in the above study. I have read and understood the attached Information Sheet and I have retained a copy of the signed document. I have been given the opportunity to ask questions about the study by the investigator. I understand that I may withdraw from the study at any time without affecting any future medical treatment.

Signed........................................ Date..............................

Next-of-kin

I, .................................................. (NAME OF NEXT-OF-KIN) agree for .................................................. (NAME OF PARTICIPANT) to participate in the above named study. I have read and understood the attached Information Sheet and I have retained a copy of the signed document. I have been given the opportunity to ask questions about the study by the investigator. I understand that we may withdraw from the study at any time without affecting any future medical treatment.

Signed........................................ Date..............................

This research project has been approved by the Ethics Committee at Royal Perth Hospital. Further information may be obtained from the Chief Investigator or from Clin Prof J A Millar, Chairman of the Ethics Committee, telephone (08) 9224 2244.
I, .................................................. (NAME OF PARTICIPANT) agree to participate in the above study. I have read and understood the attached Information Sheet and I have retained a copy of the signed document. I have been given the opportunity to ask questions about the study by the investigator. I understand that I may withdraw from the study at any time without affecting any future medical treatment.

Signed..........................................  Date..........................

This research project has been approved by the Ethics Committee at Royal Perth Hospital. Further information may be obtained from the Chief Investigator or from Clin Prof J A Millar, Chairman of the Ethics Committee, telephone (08) 9224 2244.
Quality of Life and Cognition STUDY (QoLCog)
- Informant Consent Form -

Investigator: Pascale Bosboom
WA Centre for Health and Aging (WACHA) of
the University of Western Australia and the Royal Perth Hospital

I, ........................................ (NAME OF INFORMANT)
agree to participate in the above study as the informant for
........................................ (NAME OF CONTROL).
I have read and understood the attached Information Sheet and I have
retained a copy of the signed document. I have been given the opportunity
to ask questions about the study by the investigator. I understand that I
may withdraw from the study at any time without affecting any future
medical treatment.

Signed........................................ Date............................

This research project has been approved by the Ethics Committee at Royal Perth Hospital.
Further information may be obtained from the Chief Investigator or from Clin Prof J A Millar,
Chairman of the Ethics Committee, telephone (08) 9224 2244.
Tape Recording Consent Form

1. At times sessions are taped for the purpose of supervising or research protocol.

2. Only the researcher, peer or supervisor of this study will hear the recordings.

3. All information on the tape will remain strictly confidential. Tapes will be kept in a locked cabinet.

4. You have the right to request the taping be turned off at any point during the assessment.

I, ____________________________ (Participant’s name) have read and understood the above information. I hereby consent to have a tape made on the above conditions.

Participant’s signature: ____________________________

Researcher’s signature: ____________________________

Date:   /   /
GENERAL QUESTIONNAIRE

Instructions:
Please fill in this questionnaire and bring it with you to your next appointment. Most of the questions simply require that you place a tick next to your answer; for some questions you will need to write your answer on the line provided. Please ask someone who is close to you to help you answer some of the questions that you are not sure about. Thank you.

1) Today’s date: □□/□□/□□ (day/month/year)

2) Date of birth: □□/□□/□□ (day/month/year)

3) Age: □□ years

4) Sex: □ Male □ Female

5) Handedness: □ Right □ Left □ Mixed/uncertain

6) Country of birth:
□ Australia
□ Other country (Please specify): __________________________

If you ticked ‘Other’, how long have you been living in Australia?
□□ years

7) Language spoken at home:
□ English
□ Other language (Please specify): __________________________

If you ticked ‘Other’, how would you rate your English?
□ Fluent
□ Average
□ Poor
8) Marital Status:

- [ ] Single/Never married
- [ ] Separated
- [ ] Living with partner
- [ ] Divorced
- [ ] Married
- [ ] Widowed

9) Number of children: [ ] children

10) Highest year of primary or secondary school completed:

- [ ] Year 8 or lower
- [ ] Year 9
- [ ] Year 10
- [ ] Year 11
- [ ] Year 12 or equivalent

11) Highest qualification completed after leaving School:

*(Please specify the name of the qualification)*

- [ ] Trade certificate: __________________________
- [ ] Diploma: __________________________
- [ ] Bachelor degree: __________________________
- [ ] Master degree: __________________________
- [ ] PhD degree: __________________________
- [ ] Other *(Please specify)*: __________________________

12) Employment status:

- [ ] Working full time, paid
- [ ] Working part time, paid
- [ ] Working full time, volunteer work
- [ ] Working part time, volunteer work
- [ ] Retired/On pension since [ ] (Please specify the year)
- [ ] Other *(Please specify)*: __________________________
13) **Current living arrangement:**

- [ ] Own home, with spouse and child(ren) living at home
- [ ] Own home, with spouse
- [ ] Own home, with child(ren) living at home
- [ ] Own home, alone
- [ ] Independent unit in residential care facility
- [ ] Home of relative
- [ ] Hostel
- [ ] Nursing Home
- [ ] Other (*Please specify*): ______________________

14) **Who is the person who most frequently supports you in your daily needs?**

- [ ] Husband or wife/spouse/partner
- [ ] Daughter or son
- [ ] Other family member (*Please specify*): ________________
- [ ] Friend
- [ ] Neighbour
- [ ] Professional caregiver/nurse
- [ ] Other person (*Please specify*): ______________________

15) **How many times a week do you see that person [see question 14]?**

- [ ] Daily or at least 5 days a week
- [ ] At least 4 days a week
- [ ] At least 3 days a week
- [ ] At least 2 days a week
- [ ] At least 1 day a week

16) **Do you drive a car?**

- [ ] No, never had my driver’s licence
- [ ] Yes
- [ ] No, not any more
17) **What is your religion?**

☐ Catholic  ☐ Hindu

☐ Anglican  ☐ Buddhist

☐ Protestant  ☐ No religion

☐ Jewish  ☐ Other (Please specify):

☐ Muslim

*If NO, go to question 20*

18) **Do you practise your religion?**

☐ No

☐ Yes

19) **Do you go to a particular place of worship (e.g. church), or are you part of a congregation?**

☐ No

☐ Yes, ________________ (Please specify)

20) **Do you have hobbies you practise?**

☐ No

☐ Yes, ________________ (Please specify)

21) **Are you involved in (other) community activities (e.g. sport club, book club) where others are involved?**

☐ No

☐ Yes

22) **Are you using glasses?**

☐ Never

☐ Only for reading, driving etc.

☐ Always

23) **Are you using hearing aids?**

☐ No, my hearing is normal

☐ No, but my hearing is not so good

☐ Yes, for one ear

☐ Yes, for both ears
24) **Have you ever smoked?**

- No (If NO, go to question 25)
- Yes

  a) **Do you still smoke now?**

    - Every day
    - Not every day
    - Not at all

  b) **If you no longer smoke, how long ago did you give up smoking?** □□ years ago

25) **Did you ever drink alcohol?**

- No (If NO, go to question 26)
- Yes

  a) **During the last 12 months, how often have you had a drink with alcohol?**

    - Not at all (go to question 26)
    - Less than once a month
    - Less than once a week
    - Weekly
    - Daily or almost daily

  b) **How many alcoholic drinks do you consume on a typical occasion when you are drinking?**

    - 1 or 2
    - 3 or 4
    - 5 or 6
    - More

26) **Do you have a close relative (a parent, brother or sister) who has, or has had, dementia or Alzheimer’s disease?**

- Yes, dementia caused by Alzheimer’s disease
- Yes, dementia, but not sure if it was Alzheimer’s disease
☐ No/don’t know

27) **Have you ever been told by a doctor (or: nurse, psychologist) that you have, or have had, any of the following conditions?**
*(Please tick the box if the answer is Yes)*

☐ Arthritis

☐ Diabetes (high blood sugar)

☐ Angina (pain from the heart)

☐ Hypertension

☐ Stroke

☐ Heart attack

☐ Heart failure

☐ Asthma

☐ Chronic bronchitis

☐ Emphysema

☐ Osteoporosis

☐ Head Injury

☐ Epilepsy

☐ Cancer (not skin cancer)

☐ Thyroid disorder(s)

☐ Dependence on drugs or alcohol

☐ Allergy

☐ Depression

☐ Anxiety disorder

☐ Learning difficulties

☐ Other condition: _______

28) **Please list all the tablets, inhalers, and other medicines you have taken during the past two weeks, including those you don’t take regularly. Be sure to include prescriptions and any non-prescriptions (such as obtained from the chemist or supermarket, vitamin or mineral supplements, or herbal or natural medicines):**

<table>
<thead>
<tr>
<th>Name of medication</th>
<th>Dose (e.g., 50 mg)</th>
<th>Frequency (e.g., 1/day)</th>
<th>Reason/indication</th>
<th>How long have you been taking this?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
29) **How many times have you seen your General Practitioner (GP) during the last 6 months?**
   - □ 0
   - □ 1-3 times
   - □ 4-6 times
   - □ 7 times or more

30) **Have you been to a Hospital during the last 6 months? (More than one answers is possible)**
   - □ No
   - □ Yes, to the Emergency Department, because *(Please specify)* 
   - □ Yes, I had an appointment with a Medical Specialist *(Please specify)* 
   - □ Yes, I had an appointment with another Medical Specialist *(Please specify)* 
   - □ Yes, I was admitted to Hospital for □ □ days, because *(Please specify)* 

31) **Did you have a fall to the ground during the last 6 months?**
   - □ No  *(If NO, go to question 32)*
   - □ Yes
   
   a) **How many times did you fall?**
       - □ 1  □ 2  □ 3  □ 4+
   
   b) **Did you have to seek medical attention (e.g. Doctor, Hospital) because you injured as a result of any these falls?**
       - □ No
32) In relation to your health, how do you feel now?

**My physical health:**
- [ ] Excellent
- [ ] Very good
- [ ] Good
- [ ] Fair
- [ ] Poor

**My mental health:**
- [ ] Excellent
- [ ] Very good
- [ ] Good
- [ ] Fair
- [ ] Poor

33) How would you rate the quality of your life now? (Please base your answer on what you believe quality of life to be)

- [ ] Very high
- [ ] High
- [ ] Neither high nor low
- [ ] Low
- [ ] Very low

34) How easy did you find it to fill out this questionnaire?

- [ ] Very easy
- [ ] Easy
- [ ] Neither easy nor difficult
- [ ] Difficult
- [ ] Very difficult

Any comments:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE!
ANOSOGNOSIA QUESTIONNAIRE – PARTICIPANT VERSION

Instructions:
Please fill in this questionnaire and bring it with you to your next appointment. The questions simply require that you circle one of the four given options (Never, Sometimes, Often or Always) that best fits your answer. Thank you.

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Do you have problems remembering the date?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Do you have problems orienting yourself to new places?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Do you have problems remembering telephone calls?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Do you have problems understanding conversations?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Do you have problems signing your name?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Do you have problems understanding what you read in the newspaper?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Do you have problems keeping your personal belongings in order?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Do you forget where you leave things in the house?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Do you have problems writing notes or letters?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Do you have problems handling money?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Do you have problems orienting yourself to your neighbourhood?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Do you have problems remembering appointments?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Do you have problems doing your favourite hobbies?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Do you have problems communicating with people?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Do you have problems doing mental calculations?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Question</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------------------------------------------------------------------</td>
<td>-------</td>
<td>-----------</td>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>16</td>
<td>Do you have problems remembering things you have to buy?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>17</td>
<td>Do you have problems with loss of bowel/bladder control?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>18</td>
<td>Do you have problems understanding the plot in a movie?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>19</td>
<td>Do you have problems orienting yourself in your house?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>20</td>
<td>Do you have problems doing home activities (cooking/cleaning/fixing things)?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>21</td>
<td>Do you have problems feeding yourself?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>22</td>
<td>Do you have problems keeping your cheque-book/account/payments in order?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>23</td>
<td>Are you more rigid in your decisions, with less capacity to cope with situations?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>24</td>
<td>Are you more self-centered, paying less attention to other people’s needs?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>25</td>
<td>Are you more irritated? Do you easily lose temper?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>26</td>
<td>Do you have crying episodes?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>27</td>
<td>Do you laugh in inappropriate situations?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>28</td>
<td>Are you more interested in sexual themes, talking or reading about sex?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>29</td>
<td>Have you lost interest in hobbies or activities you used to like?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>30</td>
<td>Do you feel depressed?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
</tbody>
</table>

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE.
The Hospital Anxiety and Depression Scale (HADS) – by PARTICIPANT

Instructions:
Please fill in this questionnaire and bring it with you to your next appointment. Please read each question and put a tick next to one statement, which comes closest to how you have been feeling in the past week. Don’t think too long over making your choice, because your immediate reaction will probably be more accurate than a long thought out response.

1. I feel tense or ‘wound up’:
   □ Most of the time  
   □ A lot of the time  
   □ From time to time, occasionally  
   □ Not at all

2. I still enjoy the things I used to enjoy:
   □ Definitely as much  
   □ Not quite so much  
   □ Only a little  
   □ Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen:
   □ Very definitely and quite badly  
   □ Yes, but not too badly  
   □ A little, but it doesn’t worry me  
   □ Not at all

4. I can laugh and see the funny side of things:
   □ As much as I always could  
   □ Not quite so much now  
   □ Definitely not so much now  
   □ Not at all

5. Worrying thoughts go through my mind:
   □ A great deal of the time  
   □ A lot of the time  
   □ From time to time, but not too often  
   □ Only occasionally

6. I feel cheerful:
   □ Not at all  
   □ Not often  
   □ Sometimes  
   □ Most of the time
<table>
<thead>
<tr>
<th>ID</th>
<th>I can sit at ease and feel relaxed:</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>□ Definitely</td>
</tr>
<tr>
<td></td>
<td>□ Usually</td>
</tr>
<tr>
<td></td>
<td>□ Not often</td>
</tr>
<tr>
<td></td>
<td>□ Not at all</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>I feel as if I am slowed down:</td>
</tr>
<tr>
<td></td>
<td>□ Nearly all the time</td>
</tr>
<tr>
<td></td>
<td>□ Very often</td>
</tr>
<tr>
<td></td>
<td>□ Sometimes</td>
</tr>
<tr>
<td></td>
<td>□ Not at all</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>I get a sort of frightened feeling like ‘butterflies’ in the stomach:</td>
</tr>
<tr>
<td></td>
<td>□ Not at all</td>
</tr>
<tr>
<td></td>
<td>□ Occasionally</td>
</tr>
<tr>
<td></td>
<td>□ Quite often</td>
</tr>
<tr>
<td></td>
<td>□ Very often</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>I have lost interest in my appearance:</td>
</tr>
<tr>
<td></td>
<td>□ Definitely</td>
</tr>
<tr>
<td></td>
<td>□ I don’t take as much care as I should</td>
</tr>
<tr>
<td></td>
<td>□ I may not take quite as much care</td>
</tr>
<tr>
<td></td>
<td>□ I take just as much care as ever</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>I feel restless as if I have to be on the move:</td>
</tr>
<tr>
<td></td>
<td>□ Very much indeed</td>
</tr>
<tr>
<td></td>
<td>□ Quite a lot</td>
</tr>
<tr>
<td></td>
<td>□ Not very much</td>
</tr>
<tr>
<td></td>
<td>□ Not at all</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>I look forward with enjoyment to things:</td>
</tr>
<tr>
<td></td>
<td>□ As much as I ever did</td>
</tr>
<tr>
<td></td>
<td>□ Rather less than I used to</td>
</tr>
<tr>
<td></td>
<td>□ Definitely less than I used to</td>
</tr>
<tr>
<td></td>
<td>□ Hardly at all</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>I get sudden feelings of panic:</td>
</tr>
<tr>
<td></td>
<td>□ Very often indeed</td>
</tr>
<tr>
<td></td>
<td>□ Quite often</td>
</tr>
<tr>
<td></td>
<td>□ Not very often</td>
</tr>
<tr>
<td></td>
<td>□ Not at all</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>14</td>
<td>I can enjoy a good book or radio or TV program:</td>
</tr>
<tr>
<td></td>
<td>□ Often</td>
</tr>
<tr>
<td></td>
<td>□ Sometimes</td>
</tr>
<tr>
<td></td>
<td>□ Not often</td>
</tr>
<tr>
<td></td>
<td>□ Very seldom</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>
**ANOSOGNOSIA QUESTIONNAIRE – INFORMANT VERSION**

**Instructions:**
*Please fill in this questionnaire and bring it with you to your next appointment. The questions simply require that you circle one of the four given options (Never, Sometimes, Often or Always) that best fits your answer. Thank you.*

<table>
<thead>
<tr>
<th></th>
<th>Does s/he have problems remembering the date?</th>
<th>Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Does s/he have problems orienting yourself to new places?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>2</td>
<td>Does s/he have problems remembering telephone calls?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>3</td>
<td>Does s/he have problems understanding conversations?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>4</td>
<td>Does s/he have problems signing her/his name?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>5</td>
<td>Does s/he have problems understanding what s/he reads in the newspaper?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>6</td>
<td>Does s/he have problems keeping her/his personal belongings in order?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>7</td>
<td>Does s/he forget where s/he leaves things in the house?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>8</td>
<td>Does s/he have problems writing notes or letters?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>9</td>
<td>Does s/he have problems handling money?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>10</td>
<td>Does s/he have problems orienting her/himself to her/his neighbourhood?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>11</td>
<td>Does s/he have problems remembering appointments?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>12</td>
<td>Does s/he have problems doing her/his favourite hobbies?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>13</td>
<td>Does s/he have problems communicating with people?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>14</td>
<td>Does s/he have problems doing mental calculations?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Does s/he have problems remembering things s/he has to buy?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>17</td>
<td>Does s/he have problems with loss of bowel/bladder control?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>18</td>
<td>Does s/he have problems understanding the plot in a movie?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>19</td>
<td>Does s/he have problems orienting her/himself in her/his house?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>20</td>
<td>Does s/he have problems doing home activities (cooking/cleaning/fixing things)?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>21</td>
<td>Does s/he have problems feeding her/himself?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>22</td>
<td>Does s/he have problems keeping her/his cheque-book/ accounts/payments in order?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>23</td>
<td>Is s/he more rigid in her/his decisions, with less capacity to cope with situations?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>24</td>
<td>Is s/he more self-centered, paying less attention to other people’s needs?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>25</td>
<td>Is s/he more irritated? Does s/he easily lose temper?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>26</td>
<td>Does s/he have crying episodes?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>27</td>
<td>Does s/he laugh in inappropriate situations?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>28</td>
<td>Is s/he more interested in sexual themes, talking or reading about sex?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>29</td>
<td>Has s/he lost interest in hobbies or activities s/he used to like?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>30</td>
<td>Does s/he feel depressed?</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
</tbody>
</table>

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE.
Instrumental Activities of Daily Living (Lawton & Brody’s IADL) – BY INFORMANT

Instructions:
Please fill in this questionnaire and bring it with you to your next appointment. The following questions assess the functional ability of older people in relation to activities in daily living. Please tick one of the statements that comes closest to your answer. Thank you.

A  ABILITY TO USE TELEPHONE

☐ Operates telephone on own initiative, looks up and dials numbers.  I
☐ Dials a few well-known numbers.  A
☐ Answers telephone but does not dial.  A
☐ Does not use telephone at all.  D

B  SHOPPING

☐ Takes care of all shopping needs independently.  I
☐ Shops independently for small purchases.  A
☐ Needs to be accompanied on any shopping trip.  A
☐ Completely unable to shop.  D

C  FOOD PREPERATION

☐ Plans, prepares and serves adequate meals independently.  I
☐ Prepares adequate meals if supplied with ingredients.  A
☐ Heats serves and prepares meals, or prepares meals but does not maintain adequate diet.  A
☐ Needs to have meals prepared and served.  D

D  HOUSEKEEPING

☐ Maintains house alone or with occasional assistance (e.g. “heavy work domestic help”)  I
☐ Performs light daily tasks such as dishwashing, bedmaking.  A
☐ Performs light daily tasks, but cannot maintain acceptable level of cleanliness.  A
☐ Needs help with all home maintenance tasks.  A
☐ Does not participate in any housekeeping tasks.  D
E  LAUNDRY
  □ Does personal laundry completely.  
  □ Launders small items, rinses stockings, etc.   
  □ All laundry must be done by others.  

F  MODE OF TRANSPORT
  □ Travels independently on public transportation or drives own car.  
  □ Arranges own travel via taxi, but does not otherwise use public transportation.  
  □ Travels on public transportation when accompanied by another.  
  □ Travels limited to taxi or automobile with assistance of another.  
  □ Does not travel at all.  

G  RESPONSIBILITY FOR OWN MEDICATIONS
  □ Is responsible for taking medication in correct dosages at correct time.  
  □ Takes responsibility if medication is prepared in advance in separate dosage.  
  □ Is not capable of dispensing own medication.  

H  ABILITY TO HANDLE FINANCES
  □ Manages financial matters independently (budgets, writes cheques, pays rent, bills, goes to bank), collects and keeps track of income.  
  □ Manages day-to-day purchases, but needs help with banking, major purchases etc.  
  □ Incapable of handling money.  

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE.
**Instructions:**
*Please fill in this questionnaire and bring it with you to your next appointment.*
The following questions assess the functional ability of older people in relation to basic activities in daily living. Please tick one of the statements which comes closest to your answer. Thank you.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>
| 1 | **BATHING**
|   | □ Receives no assistance, bathes self completely
|   | □ Receives assistance in bathing, only one part of the body (such as the back)
|   | □ Receives assistance in bathing, more than one part of the body (or requires total bathing)
|   |   |
| 2 | **DRESSING**
|   | □ Gets clothes and gets completely dressed without assistance
|   | □ Gets clothes and gets completely dressed without assistance, but needs help tying shoes
|   | □ Receives assistance in getting clothes or in getting dressed or stays partly or completely undressed
|   |   |
| 3 | **TOILETING**
|   | □ Goes to the toilet room, cleans self, and arranges without assistance (may use one object of support, such as cane or night bedpan)
|   | □ Receives assistance in going to toilet room, or cleansing self, or in arranging clothes, or in use of night bedpan
|   | □ Receives complete assistance, or doesn’t use toilet room
|   |   |
| 4 | **TRANSFER**
|   | □ Moves in and out of bed/chair without assistance (may use object for support such as cane or walker)
|   | □ Moves in and out of bed/chair with assistance
|   | □ Does not get out of bed
|   |   |
| 5 | **CONTINENCE**
|   | □ Controls urination and bowel movement completely by self
|   | □ Has occasional accidents
|   | □ Supervision helps keep urine or bowel control, catheter is used, or is incontinent
|   |   |
| 6 | **FEEDING**
|   | □ Feeds self without assistant
|   | □ Feeds self but needs assistance in cutting meat or buttering bread
|   | □ Receives assistance in feeding or is fed partly or completely by using tubes or intravenous fluids
**Short IQCODE – BY INFORMANT**

**Instructions:**
Please fill in this questionnaire and bring it with you to your next appointment.

Now we want you to remember what your friend or relative was like 10 years ago and to compare it with what he/she is like now. 10 years ago was in 19___. Below are situations where this person has to use his/her memory or intelligence and we want you to indicate whether this has improved, stayed the same or got worse in that situation over the past 10 years. Note the importance of comparing his/her present performance with 10 years ago. So if 10 years ago this person always forgot where he/she had left things, and he/she still does, then this would be considered "Hasn't changed much". Please indicate the changes you have observed by circling the appropriate answer.

Compared with 10 years ago how is this person at:

<table>
<thead>
<tr>
<th></th>
<th>Remembering things about family and friends e.g. addresses, occupations, birthdays</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Remembering things that have happened recently</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>3</td>
<td>Recalling conversations a few days later</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>4</td>
<td>Remembering his/her address and telephone number</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>5</td>
<td>Remembering what day and month it is</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>6</td>
<td>Remembering where things are usually kept</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>7</td>
<td>Remembering where to find things which have been put in a different place from usual</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>ID</td>
<td>DATE</td>
<td>QoLCog</td>
<td>BL</td>
<td>FU</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>----</td>
<td>------</td>
<td>--------</td>
<td>----</td>
<td>----</td>
<td>---------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Knowing how to work</td>
<td>familiar machines around</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>the house</td>
<td>the house</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Learning to use a new</td>
<td>gadget or machine around</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>the house</td>
<td>the house</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Learning new things in</td>
<td>general</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>general</td>
<td>general</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Following a story in a</td>
<td>book or on TV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>book or on TV</td>
<td>book or on TV</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Making decisions on</td>
<td>everyday matters</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>everyday matters</td>
<td>everyday matters</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Handling money for</td>
<td>shopping</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>shopping</td>
<td>shopping</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Handling financial matters</td>
<td>e.g. the pension, dealing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>e.g. the pension, dealing</td>
<td>with the bank</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Handling other everyday</td>
<td>arithmetic problems e.g.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>arithmetic problems e.g.</td>
<td>knowing how much food to</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>knowing how much food</td>
<td>buy, knowing how long</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>between visits from</td>
<td>between visits from</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>family or friends</td>
<td>family or friends</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Using his/her intelligence</td>
<td>to understand what's going</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>to understand what's going</td>
<td>on and to reason things</td>
</tr>
</tbody>
</table>

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE.
**Neuro Psychiatric Inventory (NPI) – BY INFORMANT**

**Instructions:**
See ‘Instructions for administration of the NPI’ in original manual.

<table>
<thead>
<tr>
<th>Item</th>
<th>N/A</th>
<th>Absent</th>
<th>Frequency</th>
<th>Severity</th>
<th>F x S =</th>
<th>Distress carer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropsychiatric features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Delusions</td>
<td>X</td>
<td>O</td>
<td>1 2 3 4</td>
<td>1 2 3</td>
<td>=</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>B. Hallucinations</td>
<td>X</td>
<td>O</td>
<td>1 2 3 4</td>
<td>1 2 3</td>
<td>=</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>C. Agitation</td>
<td>X</td>
<td>O</td>
<td>1 2 3 4</td>
<td>1 2 3</td>
<td>=</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>D. Depression</td>
<td>X</td>
<td>O</td>
<td>1 2 3 4</td>
<td>1 2 3</td>
<td>=</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>E. Anxiety</td>
<td>X</td>
<td>O</td>
<td>1 2 3 4</td>
<td>1 2 3</td>
<td>=</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>F. Euphoria</td>
<td>X</td>
<td>O</td>
<td>1 2 3 4</td>
<td>1 2 3</td>
<td>=</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>G. Apathy</td>
<td>X</td>
<td>O</td>
<td>1 2 3 4</td>
<td>1 2 3</td>
<td>=</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>H. Disinhibition</td>
<td>X</td>
<td>O</td>
<td>1 2 3 4</td>
<td>1 2 3</td>
<td>=</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>I. Irritability</td>
<td>X</td>
<td>O</td>
<td>1 2 3 4</td>
<td>1 2 3</td>
<td>=</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>J. Aberrant motor behaviour</td>
<td>X</td>
<td>O</td>
<td>1 2 3 4</td>
<td>1 2 3</td>
<td>=</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td><strong>Neurovegetative Changes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K. Night-time behaviour</td>
<td>X</td>
<td>O</td>
<td>1 2 3 4</td>
<td>1 2 3</td>
<td>=</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>L. Appetite/eating changes</td>
<td>X</td>
<td>O</td>
<td>1 2 3 4</td>
<td>1 2 3</td>
<td>=</td>
<td>1 2 3 4 5</td>
</tr>
</tbody>
</table>

**NPI Total Score**

= 1 2 3 4 5
GRAD (rating awareness) – by clinician

**Instructions:**
The GRAD is composed of 4 questions. After these questions, the clinician aims to get an impression of the degree and the nature of cognitive symptoms (i.e. by cognitive testing). Scoring is made directly after the assessment.

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please tell me about the reason why you are here for?</td>
<td></td>
</tr>
<tr>
<td>Do you have any complaints or problems?</td>
<td></td>
</tr>
<tr>
<td>How is your memory functioning? Do you think you have memory problems?</td>
<td></td>
</tr>
<tr>
<td>So, there are no memory problems at all? Is everything all right with you?</td>
<td></td>
</tr>
</tbody>
</table>

**Scoring:**
- Intact awareness = 4
- Mildly impaired = 3
- Severely impaired = 2
- Absent = 1

(Detailed instructions that will be used: Verhey et al., 1993; Zanetti et al., 1999)
Quality of Life in AD (QoL-AD) – participant version

Instructions for interviewer:
Administer according to standard instructions (see Instructions for the Interviewer)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Physical health</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Energy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Mood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Living situation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Family</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Marriage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Friends</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Self as a whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Ability to do chores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Ability to do things for fun</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Money</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Life as a whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments:

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE.
Quality of Life in AD (QoL-AD) – informant version B

Instructions:
The following questions are about your relative’s quality of life. When you think about your relative’s life, there are different aspects, some of which are listed below. Please think about each item, and rate how you think your relative would rate his/her current quality of life in each area using one of four words: poor, fair, good, or excellent. Please rate his/her opinion on these items based on his/her life at the present time (that is, within the past few weeks). If you have questions about any item, please ask the person who gave you this form for assistance.

Please, circle your response:

<table>
<thead>
<tr>
<th></th>
<th>Physical health</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Energy</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>3</td>
<td>Mood</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>4</td>
<td>Living situation</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>5</td>
<td>Memory</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>6</td>
<td>Family</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>7</td>
<td>Marriage</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>8</td>
<td>Friends</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>9</td>
<td>Self as a whole</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>10</td>
<td>Ability to do chores</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>11</td>
<td>Ability to do things for fun</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>12</td>
<td>Money</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>13</td>
<td>Life as a whole</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

Any comments?

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE.
Instructions:
The following questions are about your relative’s quality of life. When you think about your relative’s life, there are different aspects, some of which are listed below. Please think about each item, and rate your opinion about your relative’s current quality of life in each area using one of four words: poor, fair, good, or excellent. Please rate these items based on your relative’s life at the present time (that is, within the past few weeks). If you have questions about any item, please ask the person who gave you this form for assistance.

Please, circle your response:

<table>
<thead>
<tr>
<th></th>
<th>Physical health</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Energy</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>3</td>
<td>Mood</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>4</td>
<td>Living situation</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>5</td>
<td>Memory</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>6</td>
<td>Family</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>7</td>
<td>Marriage</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>8</td>
<td>Friends</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>9</td>
<td>Self as a whole</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>10</td>
<td>Ability to do chores</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>11</td>
<td>Ability to do things for fun</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>12</td>
<td>Money</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>13</td>
<td>Life as a whole</td>
<td>Poor</td>
<td>Fair</td>
<td>Good</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

Comments:

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE.
Quality of Life-AD
Instructions for Interviewers

The QOL-AD is administered in interview format to individuals with dementia, following the instructions below. Hand the form to the participant, so that he or she may look at it as you give the following instructions (instructions should closely follow the wording given in bold type):

I want to ask you some questions about your quality of life and have you rate different aspects of your life using one of four words: poor, fair, good, or excellent.

Point to each word (poor, fair, good, and excellent) on the form as you say it.

When you think about your life, there are different aspects, like your physical health, energy, family, money, and others. I’m going to ask you to rate each of these areas. We want to find out how you feel about your current situation in each area.

If you’re not sure about what a question means, you can ask me about it. If you have difficulty rating any item, just give it your best guess.

It is usually apparent whether an individual understands the questions, and most individuals who are able to communicate and respond to simple questions can understand the measure. If the participant answers all questions the same, or says something that indicates a lack of understanding, the interviewer is encouraged to clarify the question. However, under no circumstances should the interviewer suggest a specific response. Each of the four possible responses should be presented, and the participant should pick one of the four.

If a participant is unable to choose a response to a particular item or items, this should be noted in the comments. If the participant is unable to comprehend and/or respond to two or more items, the testing may be discontinued, and this should be noted in the comments.

As you read the items listed below, ask the participant to circle her/his response. If the participant has difficulty circling the word, you may ask her/him to point to the word or say the word, and you may circle it for him or her. You should let the participant hold his or her own copy of the measure, and follow along as you read each item.

1. First of all, how do you feel about your physical health? Would you say it’s poor, fair, good, or excellent? Circle whichever word you think best describes your physical health right now.

2. How do you feel about your energy level? Do you think it is poor, fair, good, or excellent? If the participant says that some days are better than others, ask him or her to rate how she/he has been feeling most of the time lately.

3. How has your mood been lately? Have your spirits been good, or have you been feeling down? Would you rate your mood as poor, fair, good, or excellent?

4. How about your living situation? How do you feel about the place you live now? Would you say it’s poor, fair, good, or excellent?

5. How about your memory? Would you say it is poor, fair, good, or excellent?

6. How about your family and your relationship with family members? Would you describe it as poor, fair, good, or excellent? If the respondent says they have no family, ask about brothers, sisters, children, nieces, nephews.

© 1996, Rebecca Logsdon, PhD; University of Washington
7. How do you feel about your marriage? How is your relationship with (spouse's name). Do you feel it's poor, fair, good, or excellent? Some participants will be single, widowed, or divorced. When this is the case, ask how they feel about the person with whom they have the closest relationship, whether it's a family member or friend. If there is a family caregiver, ask about their relationship with this person. If there is no one appropriate, or the participant is unsure, score the item as missing. If the participant's rating is of their relationship with someone other than their spouse, note this and record the relationship in the comments section.

8. How would you describe your current relationship with your friends? Would you say it's poor, fair, good, or excellent? If the respondent answers that they have no friends, or all their friends have died, probe further. Do you have anyone you enjoy being with besides your family? Would you call that person a friend? If the respondent still says they have no friends, ask how do you feel about having no friends—poor, fair, good, or excellent?

9. How do you feel about yourself—when you think of your whole self, and all the different things about you, would you say it's poor, fair, good, or excellent?

10. How do you feel about your ability to do things like chores around the house or other things you need to do? Would you say it's poor, fair, good, or excellent?

11. How about your ability to do things for fun, that you enjoy? Would you say it's poor, fair, good, or excellent?

12. How do you feel about your current situation with money, your financial situation? Do you feel it's poor, fair, good, or excellent? If the respondent hesitates, explain that you don't want to know what their situation is (as in amount of money), just how they feel about it.

13. How would you describe your life as a whole. When you think about your life as a whole, everything together, how do you feel about your life? Would you say it's poor, fair, good, or excellent?

**SCORING INSTRUCTIONS FOR THE QOL:**
Points are assigned to each item as follows: poor=1, fair=2, good=3, excellent=4.
The total score is the sum of all 13 items.
NEUROPSYCHOLOGICAL TESTS
INSTRUCTIONS AS PER ORIGINAL MANUAL AND FORMS

CAMCOG-r
REY COMPLEX FIGURE TEST
NAB LANGUAGE SCREENING MODULE
CVLT-II SHORT FORM
D-KEFS SUBTEST TMT
WAIS-III SUBTEST DIGIT SYMBOL
VISUAL ASSOCIATION TEST
WAIS-III SUBTEST DIGIT SPAN
D-KEFS SUBTEST VERBAL FLUENCY
BNT-30
WTAR

FURTHER DETAILS AND REFERENCES DESCRIBED IN THESIS
### Section C Interviewer observations

To be recorded at the end of the interview.  
*Code 'yes' only if the characteristic is markedly present.*

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>207. Self-neglect</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>208. Uncooperative behaviour.</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>209. Suspiciousness.</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>210. Hostile or irritable: e.g. angry response.</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>211. Silly, incongruent or bizarre behaviour.</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>212. Slow and underactive: e.g. sits abnormally still, delay in response to questions.</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>213. Restless: e.g. fidgeting, pacing, unnecessary movements.</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>214. Anxiety and fear: appears frightened, worried or somatically tense out of proportion to the situation.</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>215. Depressed mood: looks sad, mournful, tearful, voice low or gloomy.</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>216. Lability of mood: rapidly changes from sad to happy, friendly to irritable. Code 2 if extreme</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>217. Flat affect: lack of spontaneous emotion or emotional response to interviewer; monotonous voice and lack of gestures.</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>218. Hallucinating: behaves as though hears voices or sees visions, or admits to doing so.</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>219. Speech very rapid and difficult to follow.</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>220. Speech very slow with pauses between the words.</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>221. Speech restricted in quantity; e.g. answers questions but no spontaneous expressions.</td>
<td>No 0</td>
<td>Yes 1</td>
</tr>
<tr>
<td>222. Speech rambling or incoherent, irrelevant answers to questions.</td>
<td>No 0</td>
<td>Yes 1</td>
</tr>
<tr>
<td>223. Speech slurred.</td>
<td>No 0</td>
<td>Yes 1</td>
</tr>
<tr>
<td>224. Perseveration.</td>
<td>No 0</td>
<td>Yes 1</td>
</tr>
<tr>
<td>225. Lack of insight into present disability.</td>
<td>No 0</td>
<td>Yes 1</td>
</tr>
<tr>
<td>226. Clouding of consciousness.</td>
<td>No 0</td>
<td>Yes 1</td>
</tr>
<tr>
<td>227. Peculiar use of terms, e.g. neologisms.</td>
<td>No 0</td>
<td>Yes 1</td>
</tr>
<tr>
<td>228. Speaks to self.</td>
<td>No 0</td>
<td>Yes 1</td>
</tr>
<tr>
<td>229. Impaired ability to focus, sustain or shift attention.</td>
<td>No 0</td>
<td>Yes 1</td>
</tr>
<tr>
<td>230. Impaired judgment of situations and/or persons.</td>
<td>No 0</td>
<td>Yes 1</td>
</tr>
<tr>
<td>231. Hypochondriacal preoccupations with somatic discomfort.</td>
<td>No 0</td>
<td>Yes 1</td>
</tr>
</tbody>
</table>