Vitamin D, Neuromuscular Control and Falling Episodes in Australian Postmenopausal Women

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This degree is presented for the degree of Doctor of Philosophy

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2009

ACKNOWLEDGMENTS

I have always said that doing my PhD would be a part of my life and not my whole life. Therefore, I feel that I can look back and know that enjoying the journey was as important to me as the destination. Clichéd as it may sound it is true. I never set out to gain accolades or letters. This was my challenge, my struggle and my nemesis. If anything, this journey has taught me that I can do anything if I choose to. If I don't choose to or I change my mind, then the world won't fall apart. Life is too short and too precious to put on pause. To those I have frustrated along the way, I am sorry. However I am also truly thankful for your patience, persistence and understanding that it's just the way I am. I have been told several times that I am a 'jack of all trades but master of none'. I take this as a compliment. I hope that I am able to inspire others to try something because they want to, not because they have to. To keep searching until you find what you are looking for – for that year anyway.

To my soul mate Kris. You were here long before this struggle and I have no doubt you will be here for the next one. Your support and faith that I can do anything never falters and you are the one true person that has always demonstrated true belief in my ability. It's us against the dream takers sweet.

To our beautiful daughters Baylee and Taylor. Baylee, you were about to turn four years when I submitted this for the final time. Some may say you were the reason that I have taken so long to do this. To me, it's just a part of the story. I don't regret for a second taking you to the park when I could have been working on this. Thank you for being such a good little girl and letting mummy work on the computer when all you wanted were hugs. To our baby girl Taylor, I was eight months pregnant with you when I first submitted this. Now, as an eight month old you are a joy and make our

family complete. You were one of the driving forces of me finishing and I hope that I will inspire both of you girls to follow your dreams and always see the glass as half full.

To my principal supervisor, Associate Professor Richard Prince. I thank you for your persistence when most would have given up. Thank you for your understanding about some of the struggles I have had with my health and the challenges I have faced when Baylee has been sick. Thanks for the grumpy emails typed in capitals when I really did need a kick along. Thank you for the encouragement. I hope that you will always remember me and smile. I hope you get to have a rest.

Thanks you to the girls I worked with at the Bone and Calcium Research Group; Louise Richmond, who was instrumental in pushing recruitment along when things looked a little lost and kept everything organised and moving along, Christel Burgess who was all of our right hand man and helped with anything and everything, Carlie Dunford who struggled with me at the start to get recruitment going and helped throughout the entire course of the study, Jessica Lynch, Lee Hanlon-Morris, Simonne Heal, Georgina Wood and Bree Norton; you all chipped in and helped throughout the entire course of the study and without all of you I would never have got this data and the study would never have been run as well as it was. You were all fantastic to work with. I value all of your friendships and I would do everything again if it meant I got to work with all of you once more.

To Drs Amanda Devine and Ian Dick. Thank you for the chats and the extra assistance you gave along the way. You were both instrumental to this study and the department overall. I wish you both all the happiness in the future. Ian, I hope you have found your mountain to sit on.

To Dr Kathy Zhu. Thank you for all of your help at the end. Thank you for helping me manage a large and complicated dataset. Your approach is simple and methodical and thorough. All the best.

To Associate Professor Stephen Lord. Thank for the time you spent training me to use the Physiological Profile Assessment. Thank you for the helpful feedback and the friendship you have offered. I look forward to future conversations with you about work and life and to those dinners that turn into drinks that turn into late nights!

To Dr Peter Mills. For the development of the Digital Sway Program that was instrumental in achieving the sway paths for each patient at each visit. Without this program, it would have been near impossible to count every mm square manually. My eyes sincerely thank you.

To Dr David Lloyd. I wish I had more opportunity to have those long meaning of life conversations over coffee or a glass of wine with you. Unfortunately life didn't really turn out that way and I can say that I am truly sorry for how difficult the last few years have been for you. I hope you find the strength to find that smile and feel it from within. You are a truly intelligent, fun and interesting person and due to events outside our control, I feel that I missed an opportunity for a really good friendship with you. God Bless.

To myself, because I can and I have.

CONTENTS

ABSTRACT

Falls in the older population have devastating consequences on the psychological and physiological health of the individual. Due to the complexity of interacting factors associated with ageing, pathology and falling episodes, determination of a primary cause or set of causes has been difficult to establish. Deficits in components of neuromuscular control have been widely studied with the coordinated interaction of sensory and motor system components being presented as a fundamental factor in the reduction of falling episodes. A causal relationship between deficits in vitamin D status and falling episodes has also been suggested. Furthermore, a relationship between poor vitamin D status, falling episodes and poor neuromuscular performance has been reported.

The aims of the current study were designed to advance understanding in three aspects of the problem of falls prevention. Firstly an examination of the reliability of testing procedures commonly used in assessment of falls risk was undertaken. The Physiological Profile Assessment (PPA) testing procedure was selected as a commonly used tool and the reliability of its various components (sensory, motor and balance) was undertaken as an independent assessment of this approach to assessing falls propensity. Secondly, a case control study of fallers and non fallers was undertaken in which the neuromuscular tests evaluated in the reliability study were used to assess differences in neuromuscular control. The influence of vitamin D status on these measures was also considered. Thirdly, a 12-month randomised controlled trial of vitamin D/calcium supplementation or placebo/calcium was undertaken to identify the effect on falls outcome and individual measures of neuromuscular control.

The reliability study examined 27 women (regardless of fall status) over the age of 70 years who underwent repeat neuromuscular assessment one week apart. Intraclass

coefficient (ICC) was calculated using a two-way random model (3,1). Based on categories previously reported, components of the neuromuscular assessment that demonstrated excellent reliability were visual acuity, touch sensation, hand reaction time and muscle strength. Fair to good reliability was observed for contrast sensitivity, joint position sense and postural sway on the floor with eyes open and closed. Poor reliability was observed for postural sway on foam (eyes open). Overall, the current study reported a high proportion of agreement with the developers of the PPA as published in previous literature.

The case control study examined 100 non-fallers and 100 fallers over the age of 70 years who were selected irrespective of vitamin D status. This group underwent one assessment examining vitamin D status and neuromuscular control using the PPA, in addition to hip strength and Timed Up and Go (TUG) testing. Using either independent sample t-test or McNemar's test, results indicated fallers had significantly lower vitamin D status ($p=0.001$), were heavier ($p=0.04$), had poorer vision as assessed by contrast sensitivity ($p=0.02$) and visual acuity ($p=0.01$ (high acuity) and $p=0.001$ (low acuity), were weaker in their ankles, knees and hips ($p=0.01$ (ankle) $p=0.001$ (knee and hip)), had slower hand reaction time ($p=0.001$), poorer balance ($p=0.02$) and recorded slower times on the TUG ($p=0.001$). Using a Linear Regression model, determination of the effect of vitamin D on these measures following adjustment for falls status demonstrated significant partial correlations for hip flexor strength (partial $r = 0.16$, $p<0.05$), hip extensor strength (partial $r = 0.15$, $p<0.05$) and TUG (partial $r = 0.18$, $p<0.01$).

The randomised controlled study examined 302 women with a history of falls aged between 70 and 90 years of age. Participants were randomised to vitamin D/calcium or

placebo/calcium for 12 months. Results demonstrated a 19% reduction in the Relative Risk of falling in the treatment group. Secondly, this risk reduction was principally observed during the winter/spring months (OR 0.55 95%CI 0.32-0.96) and was only applicable to one-time fallers (OR 0.50 95% CI 0.28-0.88). Furthermore, supplementation proved effective in improving functionality (as assessed by TUG) and strength (Hip Adductor and Extensor) for those who were the slowest and weakest only ($p<0.05$). This effect on falling episodes was not observed until the 12-month assessment where 62.9% of the control group had reported a fall compared with 52.3% of the treatment group ($p<0.05$).

These results show that even in temperate zones, supplementation with vitamin D is required to effect a reduction in the risk of falling in community dwelling elderly women especially in the winter. However, there may be enough UVB at this latitude to sustain adequate levels of vitamin D in the summer to prevent falling. Secondly, the treatment effect on one-time fallers only indicate that while vitamin D may assist in improving vitamin D levels in multiple fallers, these individuals are more likely to require a wider intervention to address the complexity of factors to achieve any improvements in fall reduction.

In conclusion the current thesis reported reasonable levels of reliability for the Physiological Profile Assessment PPA which was able to distinguish between fallers and non-fallers. However the benefits of vitamin D supplementation on reducing falls propensity did not seem to be clearly reflected in the changes in the neuromuscular control following supplementation as tested in the PPA. The randomised controlled study highlighted that vitamin D deficiency is a major correctable cause of falling. Furthermore, there appears to be a ‘window of opportunity’ for neuromuscular deficits

to be corrected with supplementation. Specifically, this relates to improvements observed in those who were weakest in the study but in comparison to the greater population outside of the study, are least disabled.

These results support recommendations for future interventions and investigations of the role of vitamin D supplementation into falls risk reduction and neuromuscular measures. The current study indicates, that even in a sunny climate like Australia, vitamin D deficiency still exists. Identification of at risk groups in both a research and clinical setting, with appropriate interventions is critical to the continued investigation into what appears to be a related, yet still unclear area of vitamin D and falling episodes in older postmenopausal women.

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DEFINITIONS

Fall:	Defined as unintentionally coming to rest on the ground, floor, or other lower level.
Vitamin D status:	25 Hydroxyvitamin D unless otherwise stated.
PPA:	Physiological Profile Assessment

STRUCTURE OF THESIS

This thesis contains eight chapters plus references and appendices. Following the introductory chapter, a review of literature is presented in Chapter 2. This is split into the varying issues surrounding postural control in general, postural control and vitamin D status in fallers and considerations in concepts of balance and associated difficulties with the measurement of a complex set of body systems. This discussion leads to the current research question and the aims of the thesis, which is presented as a set of three separate studies namely a Reliability study, a Case-Control study and a Randomised Control study. Chapter 3 discusses the methodology used for each of the three studies and explains the differences in each study population. Explanations regarding anthropometric, biochemical, neuromuscular, falls and adverse events assessment; which is relatively consistent for all three studies is presented as a single section in this chapter. Chapter 4 discusses the statistical approach used for each of the three studies with a focus on challenges faced when assessing balance in this population and how this was dealt with. Chapter 5 presents the results and discussion for the reliability study, Chapter 6 the results and discussion for the case-control study and Chapter 7 the results and discussion for the randomised controlled study. Chapter 8 provides concluding comments by summarising the major findings and discussing the implications of these findings for both future research and for application in a clinical and rehabilitative setting.

1.0 INTRODUCTION

The need to examine factors associated with falling episodes is purported by the economic, social, health and personal costs connected to these events. As reported in Australia's Health 2006 [1], 13.1% of the Australian population as at 2005 were 65 years and over. Falls in the over 65-year age group were the single leading cause of injury related hospital care in Australia – accounting for over a third of hospital admissions. This statistic has stayed consistent from the Australia's Health 2002 report [2]. The rate of hospital admissions rises sharply with age and it is of concern to note that in those aged over 85 years of age, 9% were admitted to hospital. This high rate was almost entirely due to injuries sustained following a fall. These costs accounted for over $400 million in direct health care system costs nationally [2] and over $83 million in Western Australia [3].

These reported costs are financial in nature and do not account for the personal impact on the individual, their families and carers. Previous literature has identified consequences of falls to include fracture and fear of falling [4-6], increased hospital admissions and reduced quality of life [7], reduced functional status [8, 9], and increased risk of death and a range of nutritional deficiencies [10]. Falls are often considered a contributing reason for admission to a nursing home [11, 12]. Evidence has demonstrated that at two years following a fall requiring a geriatric consultation at an Emergency Department, 52% of patients (n=326) were in a long-term care facility and 34% were deceased [11]. Moreover, falls can also result in a "post fall syndrome" that includes dependence, loss of autonomy, confusion, immobilisation, depression, and restrictions in daily activities [8, 13].

2.0 REVIEW OF LITERATURE

2.1 The Balance Concept

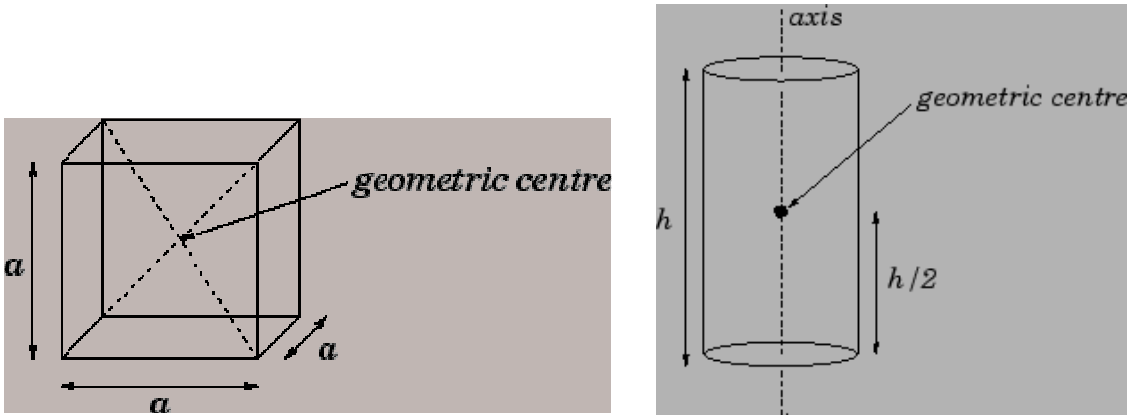
Balance is a generic term used to describe the dynamics of body posture to prevent falling. It is related to both the inertial forces acting on the body and the inertial characteristics of body segments [14]. Biological systems provide information as to where our bodies are situated in relation to the environment thus allowing an individual to maintain a desired position. The maintenance of normal and efficient balance is regulated by a complex interaction between the following parts of the nervous system:

a) The inner ears (also called the labyrinth): monitors the directions of motion, i.e. turning or forward-backward, side-to-side, and up-and-down.
b) The eyes observe where the body is in space (i.e. upside down, right side up, etc.) and also the directions of motion.
c) Skin pressure receptors such as those located in the feet sense what part of the body is down and touching the ground.
d) Muscle and joint sensory receptors report what parts of the body are moving.
e) The central nervous system (the brain and spinal cord) processes information from the four other systems to make coordinated sense of it all.

There is often a variety of terms used when explaining and reporting balance. These are often incorrect in nature and misleading to the reader. Terms often used interchangeably with balance include: centre of mass, centre of gravity, centre of pressure and limits of stability [14]. Therefore, it is important to identify and define these terms correctly.

Centre of mass (COM)

The COM is defined as the point representing the mean position of matter in the body. It is the point in or near an object at which the whole mass of the object may be considered to be concentrated. A symmetrical homogeneous object such as a cube or cylinder has its centre of mass at its geometrical centre (Figure 2.1a and 2.1b). Conversely, a hollow object (such as a cup) may have its centre of mass in space inside the hollow [15].



(a) **(b)**

Figure 2.1 Centre of Mass in a cube (a) or cylinder (b)

Centre of Gravity (COG)

The COG is the vertical projection of the COM onto the ground. This can be further explained in reference to Figure 2.2 [16]. In this figure, by attempting to balance the rectangle on a sharp edge - besides the force applied at the fulcrum the only other force applied is the weight of the object (Figure 2.2 (a)). Therefore the line of action passes to the right of the fulcrum. This is opposite with the fulcrum placed on the other side (Figure 2.2 (b)). If the position of the rectangle is maintained, the moment of the weight about the fulcrum is zero and therefore the line of action of the weight, or it's gravity line is established (Figure 2.2 (c)).

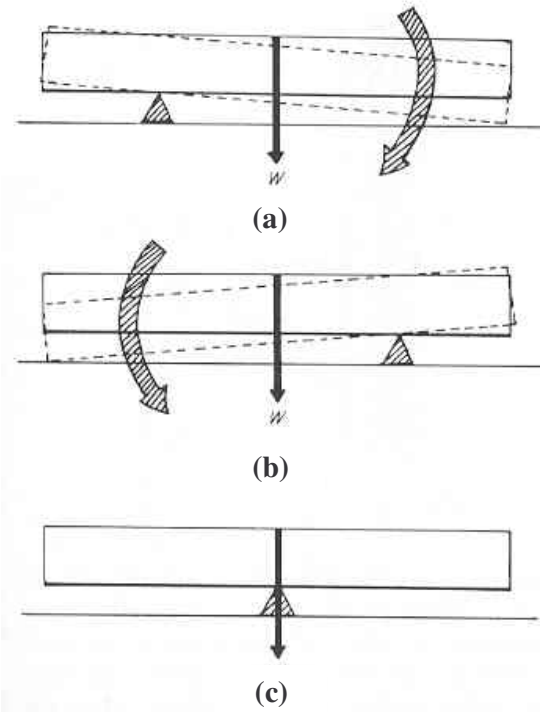


Figure 2.2 Moment of Weight of an object as a result of different placement of applied force (i.e.: fulcrum) - Horizontal plane

If this object is turned on it's side, two vertical planes are established (Figure 2.3 (a)) and it's line of gravity established as the line formed where the planes intersect (Figure 2.3 (b)). The COG is therefore the intersection of the horizontal and vertical line (Figure 2.3 (c)) [16].

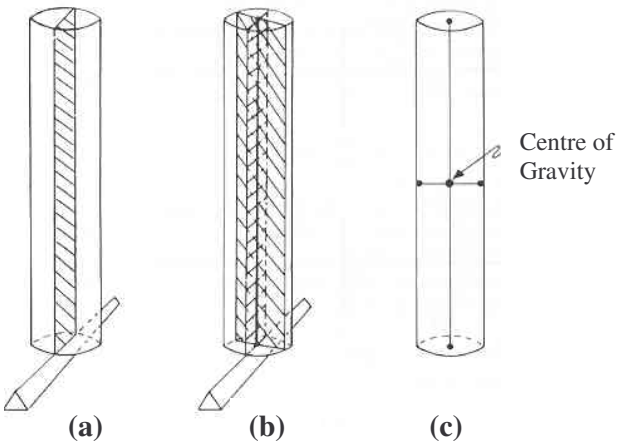


Figure 2.3 Moment of Weight of an object as a result of different placement of applied force (i.e.: fulcrum) - Vertical plane

Furthermore, the location of the COG can change as the position of the arms change. As represented in the case of a high jumper (Figure 2.4), the COG can lie within the substance of the body, move outside it as the angle between the arms is increased and return to lie within the body as the angle moves towards 180 degrees [16].

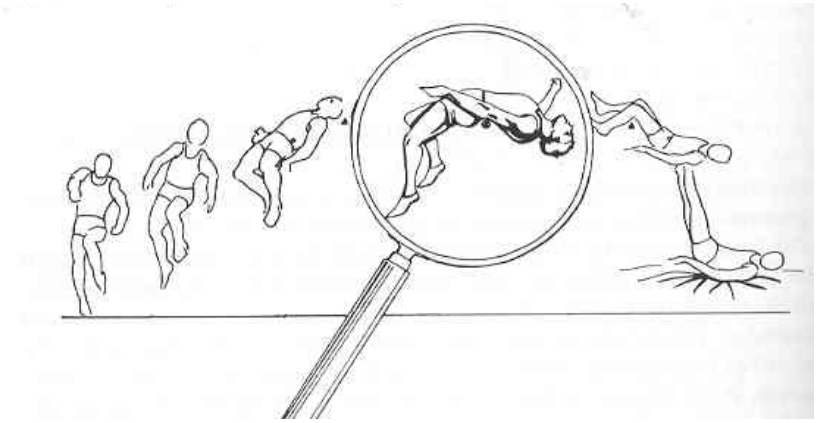


Figure 2.4 Movement of COG as a result of the position of the arms

Centre of Pressure (COP)

The COP is the location of the vertical ground reaction vector from a force platform. It is equal and opposite to a weighted average of the location of all downward (action) forces acting on the force plate. In the human, these action forces are under the motor control of the ankle muscles. Thus the COP is really the neuromuscular response to imbalances of the body's COG [14]. This is illustrated in Figure 2.5. In the situation of standing balance, the COPc is the control by ankle muscles and the COPv is the contribution due to the unloading and loading of the limb. When the feet are in tandem the COPv is the control by the hip adductors and adductors which control the Anterior-Posterior (AP) direction whilst the COPc is the control in the Medio-Lateral (ML) direction by the ankle invertors/evertors. Conversely, when the feet are side by side,

COPc is the synchronization of the ankles in the AP direction and COPv is the utlisation of the hip abductors and adductors in the ML direction.

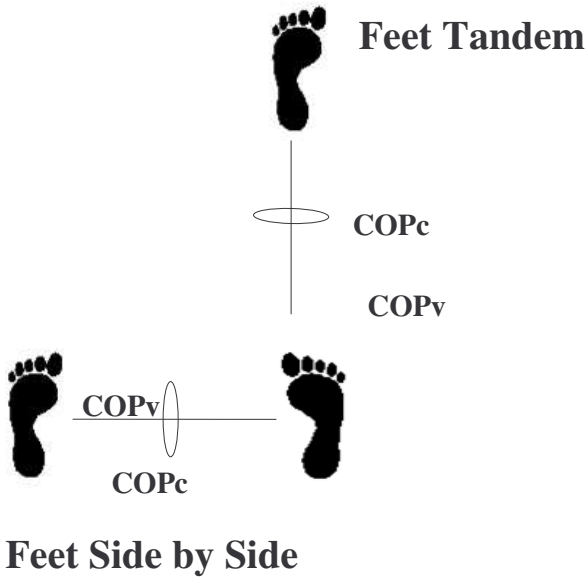


Figure 2.5 Control of COP with feet placement during standing
Adapted from [14]

Limits of stability (LOS)

The LOS are the area where COG can be altered without changing the base of support. They are determined by external and internal constraints. Specifically, external constraints limit LOS when the existing support surface does not offer sufficient resistance to apply forces against and the base of support are narrowed thus reducing the ability of the individual to lean in a narrowed direction. In Figure 2.6, it can be seen that with a wider base of support, the COG is lowered. Internally, the LOS is constrained where there are musculoskeletal (e.g. joint range of motion, flexibility, tone, strength, sensation, coordination, pain) and/or neuromuscular deficits. In the absence of any deficits, biomechanical limits are consistent with perceived limits, however certain

neurologic lesions can cause under or over perception of limits leading to abnormalities in balance stability [16].

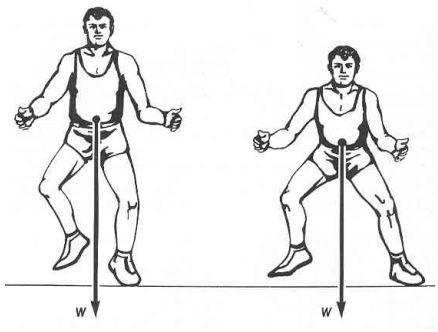


Figure 2.6 Alteration of the COG with a changing base of support

2.1.1 Influences on Balance: Age versus Pathology

The combination of age and pathological deterioration on balance is evident in the observed onset of falls and gait disorders seen in the older individual. Intrinsic factors include central processing (e.g. dementia), neuromotor (e.g. Parkinsons, stroke, peripheral, neuropathy), vision (e.g. cataracts, glaucoma, macular degeneration), vestibular (e.g. Meniere's disease), proprioception (e.g. peripheral neuropathy), musculoskeletal (e.g. arthritis, foot disorders) and systemic (e.g. postural hypotension, metabolic disease, cardio-pulmonary disease) [17]. Coupled with extrinsic factors such as environmental (e.g. a slippery/uneven surface, poor lighting), increased environmental demand (e.g. stairs, rising from a low chair and situational (e.g. changing of position, risk taking behaviour) [17] the risk of falls and subsequent injury is compounded.

2.1.2 Pathological influences on balance

Virtually all neuromuscular disorders result in some degeneration of the balance control system. Pathological changes impacting on balance include but are not limited to those

listed in Table 2.1 with specific neuropathological parameters related to some of these conditions presented in Table 2.2 [17].

Table 2.1 Pathological changes affecting balance

Hemorrhage	Infection	Stroke
Dementia	Hydrocephalus	Malignancy
Hydrocephalus	Brain tumors	Post traumatic lesions
CJD	Alzheimer's disease	Parkinson's disease
Huntingtons' disease	Pick's disease	

Table 2.2 Neuropathologic parameters related to pathological changes in balance

Distribution	**Severity Factors**	**Type**
Focal lesion	Location Size Depth	Hemorrhage, Tumour, Access, Trauma, Infarct
Multifocal lesion	Same as focal but severity can increase with number, progression and laterality	
Diffuse	Density Quantity Locations	Traumatic Hypoxic-ischaemic Inflammatory Degenerative Metabolic

The Central Nervous System can generally adapt to pathology until the individual is temporarily deprived of the compensating system. For example, a person with a vestibular deficit may rely heavily on vision, so when vision is taken away from them they can become unstable.

2.1.3 Age influences on balance

Declines in balance function as a result of age are thought to be due to changes in vision, kinesthetic and vestibular function and decreases in fast-twitch muscle fibres/loss of strength as a result of increased age [18]. Changes related to both neuroanatomic location and specific modality are demonstrated in Tables 2.3 and 2.4 [17].

Table 2.3 Age related changes and neuroanatomic location

Neuroanatomic location	Change
Anterior horn cells, sensory ganglion	25% decline
Brain weight	233g decline in weight from 3rd decade to 6th and 7th decade
Blood vessels and flow	Hyalinisation of small blood vessel wall Decline in cerebral flow Increase in cerebrovascular resistance
Neurotransmitters	Decline in acetylcholine, norepinephrine and dopamine concentrations
Muscles and peripheral nerves	Myelin changes & decrease in conduction velocity Skeletal muscle fibre loss Loss of sensory and motor axons

Adapted from [17]

Table 2.4 Age related changes and modality

Modality	Change
Auditory	Perceptive hearing loss for higher tones
Gait	Attitude of general flexion
	Decreased fluidity of movement
Motor	Diminished reaction time
	Impaired agility and coordination
	Reduced muscle bulk and power
Opthalamic	Decreased pupillary size
	Delayed pupillary reaction to light
	Diminished upward gaze
Olfactory	Diminished
Reflexes	Reduced or absent ankle reflex
Sensory	Impairment of vibratory sensation but preservation of proprioception

Adapted from [17]

Therefore to begin to understand where deficits may occur, the management of risk for the individual relates back to how they are able to effectively deal with balance challenges. Specifically, the current discussion examines intrinsic factors related to postural control and how these intrinsic factors adapt to extrinsic challenges.

2.2 Postural Control

Postural control is a complex motor skill that is derived from the interaction of various processes of the sensorimotor system [19]. The control of balance requires consideration of the task of the nervous system where balance is regulated by the co-ordination of sensory information an individual receives and the selection of an appropriate postural reaction in regards to standing, walking and interacting with the environment in a safe and effective way [19]. Specifically, sensory information is received via the visual, vestibular and somatosensory systems which gather information from the environment leading to a selection of co-ordinated postural reactions; including muscle strength and neuromuscular control, enabling the body to be kept aligned and able to perform motor activities. These postural reactions can also be explained in terms of postural control where the primary tasks of control are to maintain postural orientation (i.e. the alignment of body posture) and postural equilibrium (i.e. the position of the body's COM relative to the individual's base of support) [19, 20].

Postural control is critical in the assessment of risk factors for falling in the elderly [21]. Postural control and the coordinated interaction of components of the sensory and motor systems have been extensively reported in the role of reducing falls risk [21]. The understanding of the different contributions of the various physiological symptoms are fundamental in the application of a systematic approach to assess individual balance disorders [19].

2.2.1 The Sensory System and Postural Control

During Basic Stance

The ability to maintain postural control in varying environments is dependent on the sensory information received from the somatosensory, visual and vestibular systems. As an individual's external environment changes, so does the relative dependence on each of the senses for stability. For example, in a well-lit room with a firm base of support, the input from the somatosensory system is more dominant. However, if the surface became unstable the individual would have a greater reliance on the vestibular and visual systems to maintain postural control.

A greater risk of falls is common among people who have peripheral vestibular loss or somatosensory loss and CNS disorders, such as Alzheimer's disease, as they have a limited ability to adjust their sensory dependence from one sensory context to another [19].

During Locomotion

Vision influences postural stability as it provides information about the position and movement of body parts in relation to each other and to the external environment. The kinaesthetic system provides information related to a) the relative orientation of body parts, b) the movement of body parts, c) tension of the muscle and d) orientation of support surface and body with reference to the support surface. The vestibular system provides information regarding a) the angular acceleration and deceleration and velocity of the head, b) the linear acceleration and deceleration of the head and c) the orientation of the head with reference to gravity. The visual system allows for a) the orientation and movements of body parts and body referenced to the external environment and other body parts and b) the organisation and features (static and dynamic) of the external environment [20].

2.2.2 The Motor System and Postural Control

During Basic Stance

The utilisation of effective postural control and the role of the motor system is considerably different dependent on the situation. Three situations relevant to this discussion revolve around postural control adopted in a) standing, b) standing in response to balance disturbances and c) standing in response to movement.

Standing

Postural control during basic stance and its adaptation to the environment is based on background postural tone and postural reflexes originating from sensory system input. The primary constraint is the gravity vector thus requiring activation of extensor muscles to act against the gravity vector creating postural tone and stabilisation of the body's COG with respect to the ground [20].

The main force vector of the limbs, back and neck extensor muscles counteracts the effect of gravity. This is dependent on the integrity of myotatic reflex loop with higher levels of control required for normal subjects when experiencing threats to balance during quiet stance. Further, placing reactions also occur with cutaneous receptors in feet and visual and labyrinth placing reactions.

One of the most familiar reflexes is the stretch reflex, also known as the knee-jerk reflex and the myotatic reflex. In its simplest form it is a 2-neuron loop, one afferent neuron and one efferent neuron. The afferent neuron is connected to a muscle spindle, which detects stretch in the muscle. The efferent neuron is the motor neuron, which causes the muscle to twitch (Figure 2.7) [22].

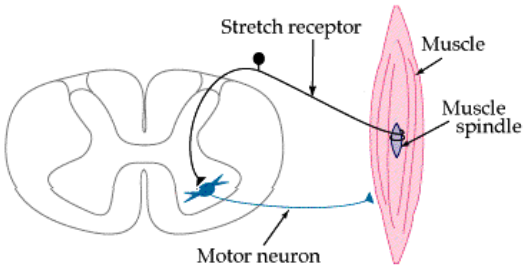


Figure 2.7 Myotactic reflex loop

In reality, there are several types of afferents reporting on the status of the muscle. On closer examination, the muscle spindle is a small group of muscle fibres separated from the rest of the muscle by a sheath of collagen. The sheath has a spindle or "fusiform" shape, called intrafusal fibres. This is in contrast to the extrafusal fibres, which are the power-generating muscle fibres. Two different types of nerve endings surround the intrafusal fibre monitoring the degree of stretch of the muscle and capsule. These two stretch receptors are classified according to diameter and conduction velocity. The largest and the fastest stretch receptor is the Ia fibre. When the muscle is stretching, the Ia fibre undergoes rapid firing and continual adapting as the muscle changes length. As soon as the muscle stops changing length and adopts a new position, the Ia adapts to the new length and stops firing. The second type of stretch receptor is the Ib fibre, which is slow adapting and is utilised when the muscle stands still. It also responds when the muscle is stretching, however maintains a firing rate after the muscle has stopped moving. The Ib fibres are embedded in the tendon, and monitor overall muscle tension (also called Golgi tendon organs) [22].

When the muscle gets shorter utilisation of the intrafusal fibre occurs. The intrafusal fibre contracts which results in the shortening of the entire spindle, which remains taut.

These small motor neurons causing the intrafusal muscle fibres to contract are g-motor neurons. The g-motor neurons are activated when the a-motor neuron is activated; therefore, as the muscle contracts so do the intrafusals [22].

When the stretch receptors fire, the a-motor neuron is excited, and the muscle contracts and when the Golgi tendon organ fires, the a-motor neuron is inhibited (via an inhibitory interneuron), and the muscle relaxes. The purpose here is that the stretch receptors tell the muscle when it needs a little more force - that despite intending to contract the muscle is lengthening thus allowing the maintenance of the correct muscle tone. The Golgi tendon organs begin to fire when the tension on the tendon is so great that there is risk of injury. They have a protective function, and therefore they signal the muscle to ease off before it tears [20].

Standing in response to balance disturbances

The aim of balance control is to respond to balance disturbances differing in direction, amplitude and velocity [20]. Research by Gurfinkel [23] demonstrated a reduced monosynaptic stretch reflex during disturbed stance compared to lying, sitting or standing. Discussions from this research suggest this allows postural control to be dominated by longer latency responses that may be spinally or supraspinally mediated. Therefore, they are more adaptable in a wide range of conditions.

This was further investigated by later research examining if there is a preprogrammed neural response or a simple mechanical coupling of ankle and hip motion [20]. Monitoring of the activity of muscles that contribute to the control of movement at ankle, knee and hip were examined when the subject was exposed to an unexpected movement (Figure 2.8) [24].

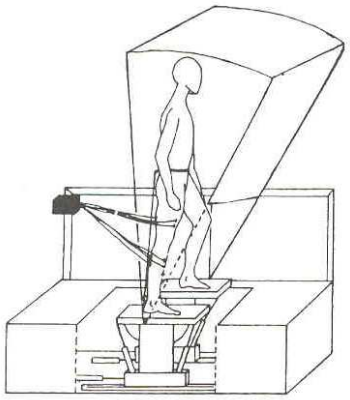


Figure 2.8 Postural control in relation to balance disturbances

Results indicated there is an adoption of different strategies depending on the type of unexpected movement. These results can be seen in Figure 2.9 [25].

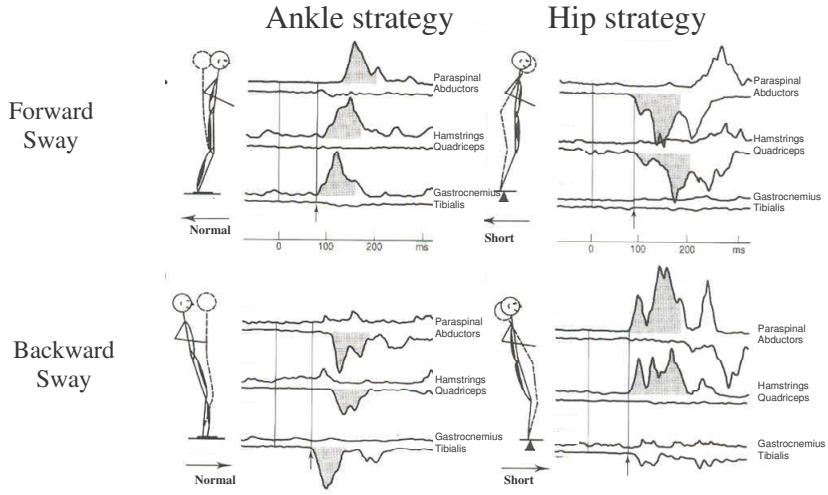


Figure 2.9 Strategies used in postural control in response to balance disturbances

Ankle Strategy

Ankle strategies are applied when there are forces applied to the ankles to develop rotations or torques that move the COG. The hip and knee joints stabilise and the order of the contraction response is: anterior tibialis, quadriceps then abdominal and hip

flexor muscles. This strategy is useful for small disruptions on a firm or wide support surface (Figure 2.10 (a)) [26].

Hip Strategy

Hip strategies are applied as the hip muscles generate flexion and extension. This occurs when the COG moves rapidly towards the LOS or is too close to LOS. The contraction response order is: paraspinals hamstrings and gastrocnemius muscles and is useful for compliant/narrow support surface when maintaining balance (Figure 2.10 (b)) [26].

Step Strategy

The step strategy is used as a final strategy to maintain balance. The aim of the step strategy is to widen the base of support by taking a step towards the direction of COG displacement. This occurs when COG is rapidly bought beyond the person's limit of stability and ankle or hip strategy is no longer effective (Figure 2.10 (c)) [26].

(a) Ankle Strategy **(b) Hip Strategy** **(c) Step Strategy**

Figure 2.10 Commonly used strategies for the correction sway

All of the above strategies require effective automatic postural responses. Normal latency and amplitude of muscle responses need to occur in a properly timed fashion after initial disruption. When there is a disruption to balance, the response of the motor system acts in a stereotyped, preprogrammed fashion as one of these three strategies. When there are lesions of the nervous system for example, an inappropriate or uncoordinated strategy may be adopted [17].

Standing in response to movement

In response to movement, organisation of posture occurs and is effected in the following ways: a) a *modular organisation* of the postural control system occurs, b) modular organisation is modified is *according to task* by changing joint stiffness of one or more joints in order to build up new modules, c) *regulation of posture* itself or d) an *egocentric reference frame* for the organisation of movement [20].

Anticipatory postural adjustments occur which act to compensate in advance for changes in posture and equilibrium caused by movement and are adaptable to task condition. The goals of these adjustments are to stabilise both the COG and the position or orientation of body segments [20].

In quiet stance, the goal of leg movements is to keep the COM safe within the base of support; this is achieved by ankle control in the AP plane and hip control in the ML plane. In unperturbed gait, the goal of gait initiation is to move the COM ahead of the base of support along medial border of foot. The goal of gait termination is to return the COM within its base of support and is achieved by the control of the head-arm-trunk segment in relation to the hips. When gait is disrupted, the postural response

organisation of the ankle muscles compensate for any disturbances [19]. This control of locomotion will be discussed in further detail in the following section.

During Locomotion

Neurobiomechanical basis for the control of locomotion.

The control of locomotion is complex in nature. To begin to understand this relationship, it is important to consider the overall design and functional specifications. This is represented in Figure 2.11.

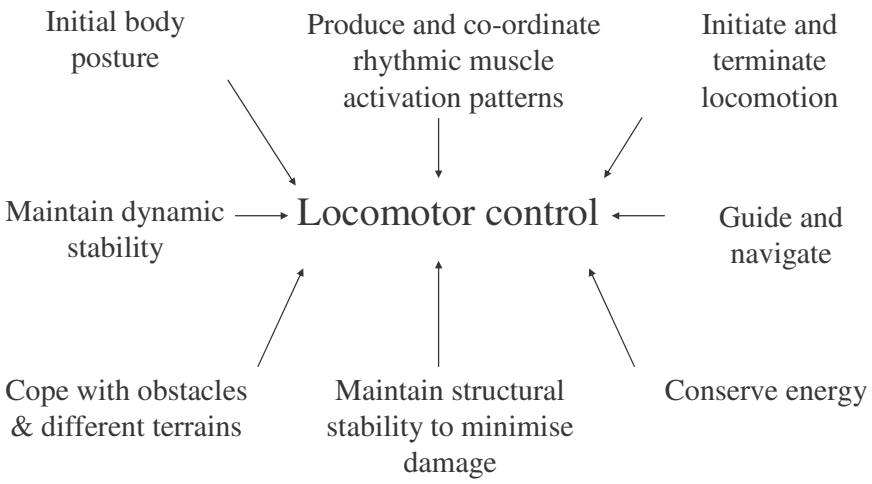


Figure 2.11 Design and functional specifications of locomotion

It is of interest to note certain evolutionary changes to muscle architecture and skeletal morphology to gain a better understanding of requirements and demand for efficient locomotion. Changes in muscle architecture over time has seen i) an increase in the size of gluteus maximus allowing for stabilisation of the torso in an upright position (AP plane) as opposed to a 'bent over stance', ii) reorientation of the anterior gluteals to prevent tipping of the trunk to the side during each step and iii) a change in the role of the hamstring from propulsion to controlling limb extension in swing phase. Further,

changes in the skeletal system has seen i) a shorter ilium allowing for a lowering of the COM, ii) the modification of the internal structure of the femoral neck and iii) the arching of the foot to act as a shock absorber [17]. This force output during locomotion is non-linear and interacts with each other. Force output of muscle is dependent on a) muscle activation, b) past history of activation, c) length of muscle and d) velocity of contraction.

2.3 Postural Control in Fallers

2.3.1 The Sensory System and Falls

Deficiencies in sensory system components have been associated with increases in body sway and increases in falling episodes. The relative contribution of these components vary however, with poor vision and peripheral sensation been reported as having a greater emphasis on sway and falls than vestibular sense. A 2006 review by Lord [27] on the existing body of research related to visual risk factors for falls in older people discusses the research that has examined both the role of vision in the maintenance of balance and the type of visual impairments predisposing the older person to falls. This review presents previous literature that shows that in the absence of vision, there is an increase in postural sway by 20-70% [28, 29]. Furthermore, misleading visual cues and poor performance in tests of distant contrast sensitivity [30] were independent predictors of increased sway in older people, a higher prevalence of poor contrast sensitivity has been identified in fallers than non-fallers and both poor contrast sensitivity and visual acuity has been associated with an increase in age and body sway in a reduced support setting, independent of disease [29].

Poor vision and falls research have produced inconsistent findings. In the recent review by Lord results citing visual acuity as a risk factor and having no significant association

have both been reported. Conversely, studies identifying contrast sensitivity to be strongly associated with falls have yielded more consistent results demonstrating that the inability to detect edges in a low contrast situation predisposes older people to falls [27].

Peripheral sensation such as touch sensitivity, joint position sense and vibration sense has a major role in the maintenance of neuromuscular control. An association between poor tactile sensitivity, joint position sense and vibration sense with increased body sway on a firm surface (eyes open/closed); poor joint position sense and vibration sense with increased body sway on a compliant surface (eyes open) and poor tactile sensitivity with increased body sway on a compliant surface (eyes closed) has been identified [21]. These results suggest that peripheral sensation in the lower limbs is more influential in the maintenance of balance under normal conditions (standing on a firm surface with eyes open or closed) with a diminished influence as the condition becomes unstable (standing on a foam surface with eyes closed).

There has been a lack of association between vestibular sense, body sway [21] and number of falls [31]. This is supported by suggestions that the role of the vestibular system on an unstable surface is to control the final position of the body and ensure the body is in equilibrium when controlling the body in the final moment of balance correction [32].

2.3.2 The Motor System and Falls

Deficiencies in muscle strength and joint mobility may prevent corrective postural movements being attained [26, 33]. Examination of 100 healthy volunteers aged 15 - 70 years of age have indicated a 6% decline per decade in maximum peak power, maximum average power and total cumulative work [34]. In older subjects in this

study, there were significantly longer muscle activation response latencies, a disrupted correlation between ankle muscle activity and ankle torque and increased neck muscle activation as demonstrated by studies of soleus, tibialis anterior and neck extensor muscles of the healthy elderly compared to young normal subjects [35]. These results indicate a reduced efficiency of muscle contraction with increased head movement in older individuals. This age associated decline is supported by recent studies [36] that compared neuromuscular capacity in subject groups above and below the age of 70. The results indicated that both losses of muscle mass and reduction in neural activation of the thigh muscles contribute to a decline in measures of maximal strength and force production with age.

Deficits in muscle strength and joint mobility can significantly influence falling episodes in elderly individuals. Poorer performance in measures of quadriceps and ankle dorsi-flexion strength and reaction time in multiple fallers compared to non-fallers and one-time fallers have been identified, with a significant difference also occurring between multiple fallers and one-time fallers [31].

These results have proved consistent with time. A 2006 synthesis of data demonstrated that muscle weakness and problems with gait and balance are the recurrent major risk factors for falls [37].

2.3.3 System Integration and Falls

The interactions of these systems have implications for postural stability in the older individual. It has been demonstrated by Lord and colleagues [21] that with eyes open on an unstable surface, body sway was greater in subjects with poor visual acuity, contrast sensitivity, quadriceps and ankle strength measures. Sway is also increased if the visual and peripheral environment is compromised. In addition, measures of

reduced static and dynamic balance were associated with increased reaction time measures, and poorer peripheral sensation and muscular strength measures.

This research examining postural control and falls demonstrates that reduced function of the visual and peripheral nervous system, muscle strength and reaction time have been associated with increases in age and falling episodes in an older population. What is not as well understood is the relative influence of these components and how they relate to falling episodes. Furthermore the integration of vitamin D physiology into the control of balance and prevention of falls is as yet in its infancy. This integration may provide us important information when applying preventative and rehabilitative techniques in the targeting of specific areas for improvement.

2.4 Vitamin D Physiology

The physiology of vitamin D metabolism is shown in table 2.12 [38]. This shows that Vitamin D is metabolised through a complex pathway. Ergocalciferol can be obtained directly from the diet. When the individual is exposed to sunlight, 7-dehydrocholesterol (7-DHC, provitamin D3), which is located in the epidermis, absorbs ultraviolet B

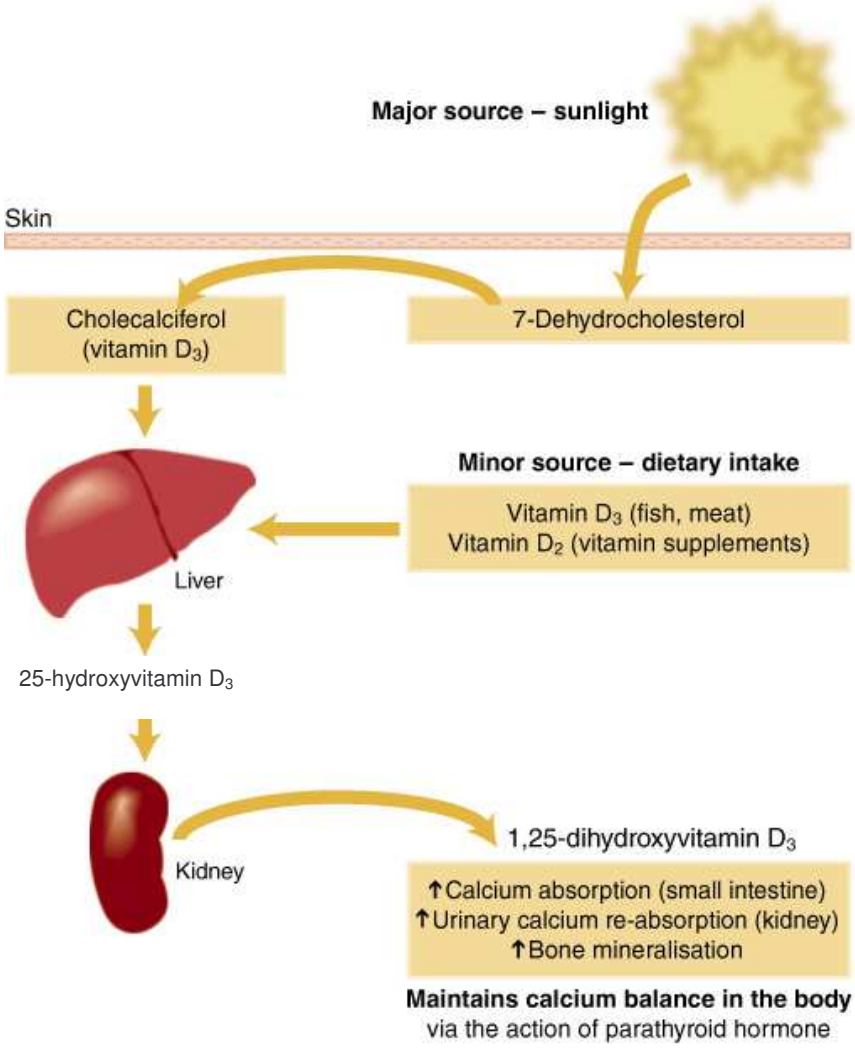


Figure 2.12: Vitamin D Metabolism [38]

(UVB) photons (290-315nm) and is converted to pre-vitamin D3 which, over several hours is transformed into cholecalciferol. This is transported from the skin into the circulation, binds to the vitamin D binding protein and is transported to the liver where

it undergoes hydroxylation to form 25 OHD [39]. Further metabolism to 1α, 25-dihydroxyvitamin D3 (1,25 OHD) occurs in the kidney and is the metabolite believed to be important for most biological actions associated with vitamin D [40]. Following metabolism, binding of 1,25 OHD to the vitamin D receptor (VDR) occurs. The VDR has 500-1000 times greater affinity for 1,25 OHD than 25 OHD produced in the liver, however serum concentrations of 25 OHD is represented 1000 times more than 1,25 OHD [41].

2.4.1 Sources of vitamin D

Vitamin D can be provided in two forms. Ergocalcifereol (vitamin D2) and Cholecalciferol (vitamin D3). Cholecalciferol is produced in the skin after exposure to the sun. This form is made commercially by the extraction of 7-dehydrocholesterol from wool fat, which then undergoes UVB irradiation and purification. Ergocalciferol is produced by the irradiation and purification of the ergosterol extracted from yeast. Both forms can be used in the fortification of foods and in multivitamins [42].

The primary source of vitamin D in humans is solar UVB (wavelengths of 290-315 nm) irradiation for the majority of the population [43, 44]. Casual sun exposure is the major source of vitamin D, with 90-95% of an individual's requirement for vitamin D coming from this exposure [44]. An example given by Holick [44], suggests that exposure to one minimal erythemal dose (MED) that can cause a slight pinkness in the skin, can raise the blood level of cholecalciferol equivalent to a person consuming 10 000 to 20 000 IU of vitamin D2.

Foods that naturally contain vitamin D include fish such as salmon, mackerel and sardines, some fish oils such as cod liver oil and egg yolks. Fortification of foods such as milk, orange juice, yoghurts, butter and cereals also provide vitamin D, however

fortification is not consistent in all countries. Finally, supplementation either through prescription or a multivitamin can also reduce the problem of vitamin D inadequacy.

2.4.2 Considerations in the definition of vitamin D deficiency

Estimates of the prevalence of 25 OHD deficiency or insufficiency are at the 1 billion people worldwide mark [43, 45]. According to the Australian and New Zealand position statement on vitamin D and bone health, severe vitamin D deficiency is generally defined as 25 OHD levels of less than 12.5 nmol/L and moderate vitamin D deficiency as between 12.5-25 nmol/L. Mild vitamin D deficiency (sometimes defined as insufficiency) is categorised as having levels between 25-50 nmol/L with levels above 50 nmol/L defined as normal [46].

2.4.3 Contributing factors to vitamin D deficiency

Certain populations are at increased risk of vitamin D inadequacy. As suggested by Holick [43], one of these groups is the elderly population where possible reduced sunlight exposure, less than optimum diet and/or failure to maintain a consistent regime of supplementation due to the already high requirement of other medicine intake exacerbates the risk of vitamin D deficiency. In addition certain populations are at increased risk of vitamin D deficiency. For example, despite the high UV environment in Saudi Arabian countries, a high prevalence of osteomalacia in Saudi Arabian women and rickets in Saudi Arabian children can be in part explained to the cultural practice of wearing clothing that covers their whole body and the avoidance of sunlight [43]. Other factors that may contribute to impaired vitamin D metabolism include skin pigmentation, medication use, body fat content and fat malabsorption [43].

Considering the inefficiencies in vitamin D metabolism reduced sunlight exposure can be a significant problem in the older adult. Previous research has shown that a 70 year

old person produces less than 30% of vitamin D compared to a young adult when exposed to the same amount of sunlight [47].

2.4.4 Considerations in the relationship of vitamin D deficiency to rickets and osteomalacia

Although 1,25OHD is the active form of vitamin D, it is the actual serum 25 OHD that is measured as it is the major circulating metabolite of vitamin D in the body and demonstrates inputs from both cutaneous synthesis and dietary intake.

Osteomalacia has been associated with generalised bone pain [48] and was first observed in the late 1600's. It wasn't until 1822 that it was suggested that this was due to lack of sunlight exposure and 1919 before it was reported that UV radiation resulted in radiological improvement in children with the disease [49].

Vitamin D deficiency is associated with increases in PTH resulting in phosphaturia and hypophosphataemia [45]. Low serum phosphate levels can compromise the calcium-phosphorous product resulting in a diminished mineralisation of collagen matrix and resultant condition of osteomalacia in adults or rickets in children.

2.4.5 Considerations in the relationship of Vitamin D deficiency to osteoporosis

Consideration of the consequences of vitamin D deficiency and bone health is an important factor when examining overall injury risk of the older person who is vitamin D deficient. A direct relationship between bone mineral density and serum levels of 25 OHD have been observed where the maximum density was achieved when 25 OHD levels reached 100 nmol/L or more. When levels were 75 nmol/L or less, a significant reduction of intestinal calcium absorption with an associated increase in PTH has been demonstrated [50]. These results show that there appears to be an inverse relationship

between 25 OHD levels and PTH levels. That is, there is a levelling off of PTH when 25 OHD levels reach 75-100 nmol/L [45]. This is of importance as PTH promotes tubular reabsorbtion of calcium and stimulation of the kidneys to produce 1,25 OHD. PTH also activates osteoblasts, which mobilises preosteoclasts into osteoclasts. This presence of osteoclasts results in dissolution of mineralised collagen matrix in bone. Examination of the effect on blood concentrations of PTH by increasing 25 OHD levels above 25 nmol/L with vitamin D therapy have been reported by Malabanan and colleagues [51] who examined a group of 35 patients with 25 OHD levels of 25-62.4 nmol/L who were prescribed 50 000 IU of oral vitamin D once a week for eight weeks and 1000-1500 mg of calcium daily. Overall, PTH decreased by 22% and 25 OHD levels rose 109%. Furthermore, when the subject group was stratified according to baseline 25 OHD levels observations included that for those with 25 OHD levels between 27.5-39.9 nmol/L had a resultant decrease in PTH levels of 35%, compared to those with levels between 40-49.9 nmol/L had decreases in PTH levels of 26%. For those who had 25 OHD levels between 50-60 nmol/L, PTH levels did not significantly decrease but 25 OHD levels increased by 66%.

2.4.6 Considerations in the relationship of vitamin D deficiency to muscle function

The purpose of assessing measures of postural control in a vitamin D deficient population lies in the fact that vitamin D deficiency can result in a loss of muscle tissue [41]. Inadequacies in vitamin D status have been associated with age related muscle weakness [52, 53]. A recent study by Bischoff-Ferrari [52] suggests there is an optimal level of 25 OHD concentrations for lower extremity function. Performance in functional assessments such as the 8-foot walk test and the sit to stand test was assessed. These tests, the authors argue, were selected to reflect the requirements of the lower extremities for functioning in everyday activities. It was observed that speed of

performance of these two tests improved as 25 OHD concentrations improved, with the greatest improvement reported at concentrations between 22.5 to 40 nmol/L and slightly less, yet significant improvements were still seen in the range of 40-94 nmol/L. This signifies that the lower the initial vitamin D status, the greater the improvement; up to 40 nmol/L. After 40 nmol/L steady improvements in lower extremity function can still be made up to 95 nmol/L.

Physiologically, it has been suggested that it is the active vitamin D metabolite (1,25 OHD) that binds to a specific vitamin D nuclear receptor (VDR) in the muscle tissue [54, 55]. This results in de novo protein synthesis, growth of the muscle cell and subsequent improvements in muscle function. Furthermore, research by Simpson and colleagues [54] demonstrated a direct action of 1,25 OHD on muscle. Specifically, they identified i) the presence of 1,25 OHD receptors in cultured myoblasts, myotubes and isolated rat muscle cells, ii) the ability of 1,25 OHD to inhibit myoblast cell proliferation and DNA synthesis, depending on dosing levels and iii) that 1,25 OHD receptors have their highest concentrations in cultures treated to increase myoblastic character.

There are currently three schools of thought as to the influence of vitamin D on muscle function summarised in Figure 2.13. A recent review characterises these as genomic and non-genomic influences [41]. Genomic influences result from i) mediation of gene transcription and ii) allelic variation of the VDR. Gene transcription mediation result following the binding of 1,25 OHD to the VDR. This is transported to the nucleus and undergoes various transcription processes determined by the gene transcription of mRNA. This pathway exerts its influences on muscle cell calcium uptake, phosphate transport across muscle cell membrane, phospholipid metabolism and cell proliferation and differentiation.

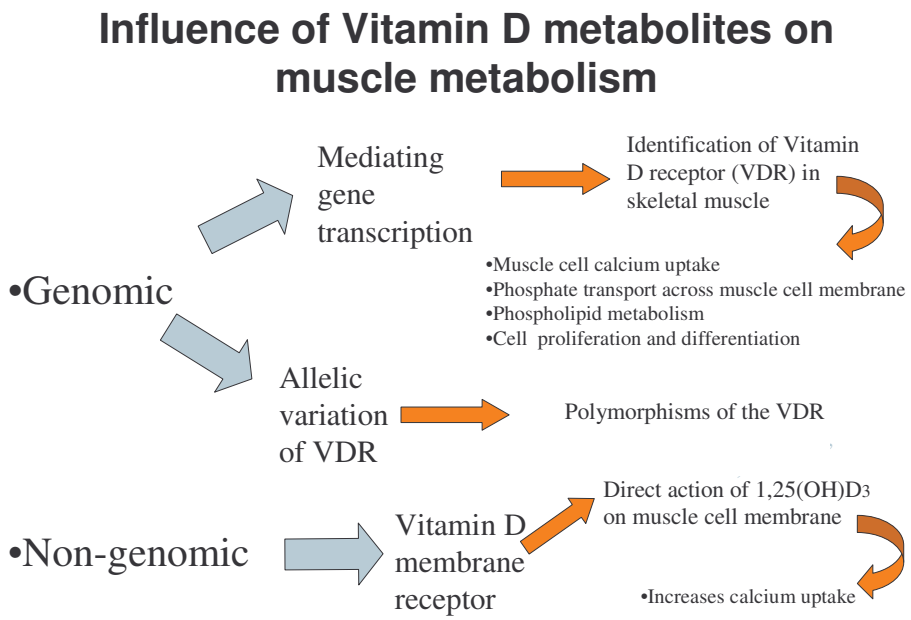


Figure 2.13 Influence of vitamin D metabolites on muscle metabolism

Evidence also suggests that allelic variation of the VDR can influence muscle metabolism. An earlier study by Geusens and colleagues [56] identified individuals with the presence of a homozygous recessive VDR genotype as having 23% greater quadriceps strength. This may indicate that the VDR has an active role in determining muscle strength, however the mechanisms of the influence of VDR polymorphisms are unknown.

Non-genomic effects have also been identified as having a direct influence on muscle metabolism by the vitamin D membrane receptor. Increased calcium uptake results from a direct action of 1,25 OHD on the muscle cell membrane, through voltage dependent calcium channels and calcium release-activated calcium channels. This explains rapid changes in the calcium metabolism of the muscle cell induced by vitamin D supplementation not explained by the previous slow genetic pathway. These effects have been well described but their functional significance remains unclear [41].

In consideration of the influence of vitamin D in muscle contraction, early animal studies have demonstrated a reduced ability of the sarcoplasmic reticulum (SR) for calcium uptake [57, 58] and a prolonged relaxation phase during muscle contraction [59] in vitamin D deficient rabbits and rats respectively. This is exemplified using the classical experiment of Huxley and Hanson in 1954 [60], which formed the cornerstone of the sliding filament mechanism of contraction. When the myofibrils are not constrained by the skeleton, they are able to contract irreversibly to about one tenth their starting length after irrigation with ATP and calcium ions. This defect in SR function exerts its influence through an increase in the intracellular content of calcium that results in actin and myosin becoming deprived of calcium binding proteins. This may have the effect of lowering the level of muscle activation, thereby increasing the relaxation phase of muscle contraction with subsequent loss of muscle tissue. This is supported in studies identifying Type II atrophy in osteomalacic patients [61]. When considering that Type II muscle fibres are recruited to avoid falling after sudden movements, it has been speculated that vitamin D deficient muscles are less likely to respond to quick disruptions, therefore making the elderly individual more prone to falling [62] although this has never been tested in vitamin D deficient people.

2.4.7 Considerations in the relationship of Vitamin D deficiency to postural control and falls in ageing

In addition to declines in functional ability, nutritional deficiencies in the elderly individual can occur [10]. Vitamin D deficiency can lead to declines in nutritional status and can be due to reductions in dietary intake and intestinal absorption of ergocalciferol, impaired skin formation of cholecalciferol and impaired hydroxylation of both precursors in the kidney [63].

Overall, poor nutritional status has been identified as being more likely to occur in individuals with a reduced ability for self-care [64, 65] and diminished cognitive status [64]. Furthermore, deterioration in measures of nutritional status has been reported in elderly subjects over four weeks of hospitalisation [66]. With this decline in function and nutritional status, it is evident that falling may result from a reduced level of functioning and increased nutritional risk, which may also lead to vitamin D deficiency. What is more difficult to ascertain is in relation of the cause effect relationship between falls, function and vitamin D status. Indeed there may be a cyclic effect of falling, reduced functioning and sunlight exposure resulting in vitamin D deficiency. Cross-sectional studies have identified low vitamin D levels as an independent risk factor for falling [67-69]. This is supported by literature demonstrating a significant association between low 25 OHD with reduced muscle strength [70, 71], increased body sway [69] and reduced physical function [72]. Moreover, prospective studies have identified a reduction in measures of sway [73], falling episodes [73, 74] and improvements in summed muscle strength [74] following vitamin D treatment.

A recent meta analysis [75] showed that a review of five randomised controlled trials (n=1237) demonstrated a 20% reduced risk of falling in older adults who have been treated with vitamin D. Sub group analysis shows that this is irrespective of type of vitamin D administered, duration of therapy and gender. There did appear to be a dosage threshold however in one study [76] administered 400 IU a day and did not observe any clinical efficacy in the prevention of falls in the elderly. Conversely, two trials administered 800 IU a day plus calcium showed a reduction in risk of falling [73, 74].

2.4.8 Considerations in the relationship of vitamin D deficiency to fracture risk

In a recent meta analysis of seven randomised clinical trials [50], examining fracture risk on older persons given 400 IU of vitamin D3 per day revealed little benefit to the risk of nonvertebral or hip fractures. When dosage was increased to 700-800 IU hip fracture risk was reduced by 26% and nonvertebral fracture was reduced by 23% when compared to calcium or placebo. Furthermore, the optimal prevention of nonvertebral and hip fracture occurred in those trials who allocated 700-800 IU of vitamin D3 a day was for those patients whose baseline 25 OHD levels were less than 42 nmol/L and whose average 25 OHD concentration rose to approximately 100 nmol/L. It is speculated that there is a level of 'antifracture efficacy' in that 25 OHD levels need to reach a certain level before reductions in fracture risk can be observed. This can be seen in an earlier study [77], which did not observe any reductions in fracture risk in patients receiving 800 IU of vitamin D3 a day however reported 25 OHD increases from 37.9 nmol/L to 61.9 nmol/L.

The complex relationship of falling has been discussed in that not one cause can be identified. The same argument can be said of fracture in that the pathogenesis of fracture can be attributed to any number of causes including falls and/or osteoporosis. Vitamin D plays a role in both, as does other factors such as seasonality and the attribution of any one cause to a fracture event is difficult to establish.

2.4.9 Considerations in the relationship of Vitamin D deficiency to other chronic diseases

Although not directly related to the current thesis, it is important to recognise that vitamin D deficiency is not isolated to the falling and bone health domain. In fact, deficiencies are associated with different facets of chronic diseases such as cancer, osteoarthritis, inflammatory diseases, diabetes, cardiovascular disease, schizophrenia,

depression, lung function and wheezing illnesses [43, 45]. These are important when considering the relative frailty of the older individual and supports the recommendations for adequate vitamin D intake and/or exposure. These other diseases and a brief explanation on how vitamin D deficiency exerts its influence is shown in Table 2.5.

Table 2.5 The effects of vitamin D deficiency on other diseases

Disease	Explanation	Source
Cancer	An increased risk of developing cancer as there is a greater cell differentiation and apoptosis of cancer cells.	[43]
Hodgkins Lymphoma	Cell growth is not regulated leading to cancer progression.	[43, 45]
Colon, Pancreatic, Ovarian	Higher mortality rate.	[43, 45]
Prostrate, Breast, Lung, Malignant Melanoma	Malignant cells more likely to survive as angiogenes is not prevented.	[43]
Cardiovascular Disease And Hypertension	Greater risk of CV Disease and Hypertension	[43, 45]
	Less control in the production of renin - the hormone which regulates blood pressure.	[45]
	Associated with congestive heart failure and blood levels of inflammatory factors.	[43]
Crohn's Disease	Increased risk of developing Crohn's Disease.	[43]
Diabetes Mellitus Type 1	Increased risk of developing Type 1 Diabetes for children who have low levels of Vitamin D during first year of life.	[43, 45]
	Decreased insulin production and increased insulin resistance.	[43]
	Associated with the metabolic syndrome.	[43]
	Inhibits an immune response to reduce the cytokine production and lymphocyte proliferation, which can destroy the insulin-secreting cells in the pancreas.	[45]
Inflammatory Bowel	Symptoms not prevented.	[45]
Lupis Erythematosus	Symptoms not alleviated.	[45]
Multiple Sclerosis	Increased risk of developing MS. Relapses more common.	[43, 45] [45]
Osteoarthritis	Progression of arthritis is greater.	[45]
Psoriasis	Greater risk of developing psoriasis and psoriatic lesions can be larger and more severe.	[45]
Rheumatoid Arthritis	Greater risk of developing and progression of the disease.	[43, 45]
Schizophrenia/ Depression	Increased incidence.	[43]
Tuberculosis	Monocyte/Macrophage prevented from initiating an immune response to destroy infectious agents. The disease is more aggressive.	[43]
Wheezing Illnesses	Increased risk of developing for children whose mothers where deficient in Vitamin D during pregnancy.	[43]

2.5 Considerations in Balance Assessment

Due to the multifactorial nature of falls assessment of falls risk is complex. The postural control mechanisms discussed previously include but are not limited to gait and balance disturbances, poor vision, neurological disease, low blood pressure, medication and a previous history of a fall [78].

The assessment of balance ability can be broadly classified into self-reported measurement, clinical/physical performance measurement and laboratory measurement [79]. Reproduction of results of a measurement instrument (even with adequate reliability) may be compromised due to changes in the environment, the task and/or the subject [80]. This needs to be considered in turn when assessing the most appropriate measure of balance to utilise.

2.5.1 Self reported tests of balance

Self reported tests of balance and associated function include self-reported abilities to perform a range of activities. For example, the individual 'rates' their ability to perform such items related to mobility such as walking indoors, outdoors (in varying weather conditions), transferring to and from bed/toilet/chair and ability to climb stairs. Other examples include basic activities of daily living where the individual is asked to rate their ability to go to the toilet on their own, dress themselves and manage their personal care or instrumental activities such as carrying out the shopping or catching public transport [81, 82]. Reported functional ability assessing mobility, basic and instrumental activities of daily living has been demonstrated to have similar associations with balance performance in a laboratory setting [81] with moderate to good reproducibility [82]. A key point presented by the latter study [82] is the reproducibility of self reported balance tests that can be compromised if the population is older or

cognitively impaired. This is supported by Lin and colleagues [79] who suggest that self-reports are more prone to memory errors as a result of aging.

2.5.2 Clinical tests of balance

Clinical tests of balance include tests administered in a clinical or rehabilitative setting. It is proposed by Lin and colleagues [79] that clinical measures are more likely to reduce the associated memory errors and reduce the impact of an individual incorrectly answering questions due to misunderstanding which is a criticism of the self-reported tests. Listed below are explanations of some frequently used clinical tests.

The *timed up and go test* (TUG) is a clinical test that is often used in practice and research settings. The TUG measures the time taken for a subject to stand from a standard chair with a height between 40cm and 50cm, walk 3metres at a normal pace, walk back to the chair and sit down. This test can sometimes be extended out to 10 metres. The time taken for the subject to complete this task is recorded in seconds.

The *one-leg stand* (OLS) requires the subject to stand barefoot on one leg and place their arms across their chest. Their hand is to touch their shoulders and their legs cannot touch each other. They are instructed to stand straight, look ahead with their eyes open and focus on an object about 3 feet in front of them. This can also be done with eyes closed. The test is timed and stopped when the raised leg touches the floor.

The *functional reach test* (FR) requires the subject to stand next to the wall with one arm raised 90 degrees with the fingers extended and a ruler mounted at shoulder height. The distance that the subject can lean forward without losing their balance without moving their feet is recorded.

The *Romberg test* is based on the ability to stand with the feet in a different position. The subject can be timed and graded according to the level that they reach. There are variations to this test such as the modified Romberg which includes standing on the right and left foot and the sharpened or tandem romberg where they are required to stand with feet directly in front of each other.

The *Tinetti balance scale* (TB) is a performance oriented assessment of mobility problems where a subject is graded according to their ability to achieve tasks such as standing, turning, bending down and sitting down.

Comparison data of several of the above clinical tests have been previously discussed [79]. Tests compared in this study were the TUG, TB, FR and OLS. The time to complete the tests; in order from longest to shortest were TB, TUG, FR and OLS. Refusal rates for TUG and TB were lower than for FR and OLS. The inability to perform the test for the OLS and FR were higher. All tests showed excellent discriminant ability for age, fall history, use of a walking aid and ADL disability. The TUG and TB were able to predict future falls and ADL decline whereas the OLS and FR were able to predict ADL decline only. These highlight the importance of careful instrument selection to allow for maximum performance, compliance and validity of test results.

There are still however, limitations that pertain to the use of clinical tests which has been discussed previously [83]. These include i) that use of clinical tests are restricted to physical limitations or sensory contributions ii) there is reliance on administrators subjective evaluation iii) they are not designed to detect change over time iv) they are

not designed to detect the extent or source of impairment and v) they are generally insufficient on their own as performance is often categorised into normal or abnormal.

2.5.3 Laboratory measures of balance

The aim of laboratory measures of balance is to objectively evaluate balance and postural stability under dynamic test conditions to reflect the challenges of daily life. Limitations presented previously include the fact that laboratory measures are time consuming, expensive, lack portability and require specially trained personnel [79]. Some examples of different laboratory measures include:

Capturing of kinetic data can be achieved by use of a *force plate* (Figure 2.14) [84] with kinetic calculations made by collecting ground reaction force data . This can be done by use of a tri-axial piezoelectric force transducers mounted within the corners of each plate to measure the three components (i.e. vertical, anterior-posterior, and medio-lateral) of the ground reaction force vector throughout the stance phase of gait. The force data are normalized to body weight. The initial slope of the vertical component of the ground reaction force vector is also calculated.

Figure 2.14 Kistler Forceplate

Alternatively, the aim of *dynamic posturography* is to objectively evaluate balance and postural stability under dynamic test conditions that reflect the challenges of daily life.

Dynamic posturography provides quantitative information about the ability to maintain balance (Figure 2.15) [85]. The patient, wearing a harness to prevent falls, stands on an enclosed platform surrounded by a visual field. By altering the angle of the platform or shifting the visual field, the test assesses movement coordination and the sensory organization of visual, somatosensory, and vestibular information relevant to postural control. Results of posturography have been used to determine what type of information (i.e., visual, vestibular, proprioceptive) can and cannot be used to maintain balance.

Figure 2.15 Dynamic posturography assessment

2.5.4 A compromise?

This research indicates that a compromise would potentially be beneficial. A combination of the quantitative measurement of the laboratory-based measures with the ease of assessment provided by the clinical measures could provide the greatest predictive value for falling.

Development of a sway meter has been utilised to assess postural sway (Figure 2.16) [86]. The sway meter was developed as part of a test battery and measures the displacement of the body at waist level. The device consists of a 40cm rod with a pen that extends from the lower back of the subject. The pen records the sway of the subject under different test conditions.

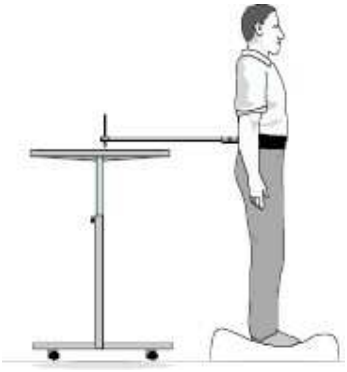


Figure 2.16 Postural sway meter for subject standing on foam surface

Sway performance using the sway meter has been assessed under different conditions in previous studies [21, 31]. An example of expected sway under different conditions is demonstrated in Figure 2.17. This ranges from a small amount of sway in Condition A where the individual stands on a hard floor with their eyes open to the greatest amount of sway in Condition D where an individual is standing on a thick piece of foam with their eyes closed. These tests are conducted for a 30 second period and are measured by either the medio-lateral and anterior-posterior distance of the sway paths and/or the distance of the sway path itself ie: the number of squares 1mm by 1mm traversed by the pen of the sway meter. This system was automated as part of the work undertaken for this research (see 3.4.4)

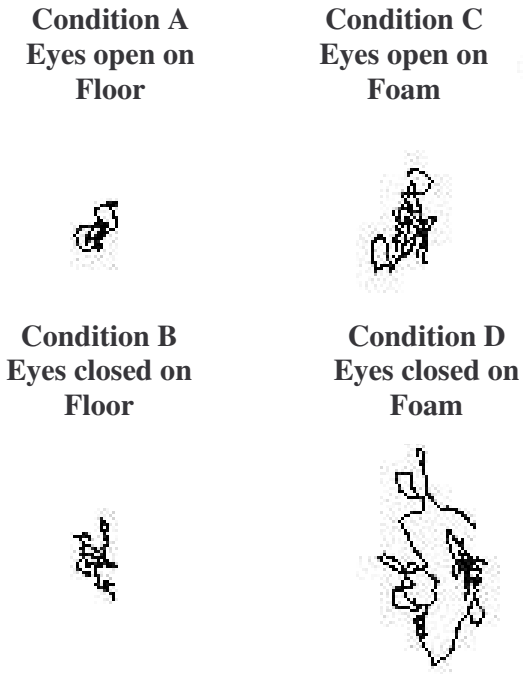


Figure 2.17 Expected sway under different conditions

2.6 The Physiological Profile Approach (PPA)

This sway meter is part of a larger assessment model developed by Lord and colleagues [86]. The FallScreen© was developed to act as a falls risk calculator and examines sensory, motor and the integrative functionality of these systems. There are two forms to this assessment: a short form and a long form. The short form is designed as a screening instrument suitable for General Practice surgeries, acute hospitals, and long-term care institutions. It takes only 15 minutes to administer and contains five items: a single assessment of vision, peripheral sensation, lower limb strength, reaction time and body sway. The long form is designed as a comprehensive instrument suitable for Rehabilitation and Physical Therapy and Occupational Therapy settings and for dedicated Falls Clinics. It takes 45 minutes to administer and contains 15 items: three

assessments of vision (high and low contrast visual acuity and edge contrast sensitivity), three assessments of peripheral sensation (tactile sensitivity, vibration sense and proprioception), assessments of three lower limb muscle groups (knee extensors, knee flexors and ankle dorsiflexors), assessments of both hand and foot reaction time and four assessments of body sway (sway on floor and foam with eyes open and closed).

2.6.1 Rationale for using PPA

The rationale for using components of this approach are summarised in Table 2.6. Physical assessment measures require stringent testing requirements due to the subjective nature of testing. Measurement error can arise from four main sources. These relate to i) the subject, ii) the testing, iii) the scoring and iv) the instrumentation [80]. Performance of the subject can be affected by their "mood, motivation, fatigue, health, fluctuations in memory (and performance), previous practice, specific knowledge and familiarity with test items" (Thomas & Nelson [80] p. 349). Testing errors can arise by the lack of quality instructions to enable the subject to carry out the task. Scoring errors can result if the tester is inexperienced or lacks competence with the way in which the scores are handled and instrumentation error can result if the equipment is not correctly calibrated or if the equipment is not able to effectively discriminate between groups.

Table 2.6 Rationale for use of individual tests in PPA

Criteria	Features
1. Simple to administer	Requires minimal training (one day on average)
2. Short administration time	Each test only takes a few minutes
3. Feasible for older people to undertake	Non invasive Excessive effort not required Does not cause any discomfort Tests remain challenging Acceptable to age group
4. Valid and reliable measures	High criterion validity i.e.: able to predict falling in older people.
5. Low technology and robust	Not intimidating Able to be used on large number of people
6. Portability	Lightweight and able to be moved around to various community and health care settings
7. Quantitative measurements	Provide continuously scored measurements to allow for analysis and to avoid floor and ceiling effects

Adapted from [86]

2.6.2 Data considerations in reporting performance

The reliability and validity of test measurements are instrumental to allow for effective analysis of continuous physical assessment data. The Intraclass Correlation Coefficient (ICC) has been suggested as the most suitable method [87]. This is based on the assumption that there is independence between measurement variability and the size of measurement [88]. To provide some context as to the interpretation of the ICC it has been suggested by that the categories are defined as excellent (ICC >0.75), fair to good (ICC 0.40-0.75) and poor (ICC <0.40) [87].

Lord and colleagues have reported on the reliability of the PPA in several publications [21, 86, 89]. Potentially the most comprehensive of these reports is the perspective article published in 2003 [86] which gives ICC estimates on all measures of the PPA with the exception of central stability. Based on ICC interpretations [87] discussed in the previous paragraph, vision (visual acuity, contrast sensitivity), lower limb strength (knee flexion and extension, ankle dorsiflextion), reaction time of the foot and balance with eyes closed (floor and foam) all demonstrated excellent reliability. Touch sensation, proprioception (joint position sense) and balance with eyes open (floor and foam) all showed fair to good reliability. The ICC with 95% CI is presented in Table 2.7 and exhibits results reported in the perspective article by Lord [86] in addition to several other papers by Lord reporting reliability for individual test items [21, 89] that were not reported in the prospective article.

Apart from the developers of the PPA, little has been published as to the reliability of these measures once administered outside the realms of literature published by Lord and colleagues. This is of relevance as this is commercially available to health care professionals [86] and it is the application of the PPA by external users that will be instrumental to the success of the PPA in identifying at risk individuals.

Table 2.7. Previously reported reliability of PPA test kit components

	ICC ((95% CI) [a]
Contrast sensitivity (db log contrast)	0.81 (0.70-0.88) [b]
High contrast visual acuity (log of MAR)	0.82 (0.66-0.91) [b]
Low contrast visual acuity (log of MAR)	0.81 (0.64-0.90) [b]
Touch Sensation (log^{10} 0.1mg pressure)	0.51 (0.19-0.74) [b]
Joint position sense (degrees)	0.50 (0.15-0.74) [b]
Hand reaction time (milliseconds)	0.69 (0.45-0.84) [b]
Foot reaction time (milliseconds)	0.78 (0.59-0.89) [b]
Ankle strength (kg)	0.88 (0.76-0.94) [b]
Knee flexor strength (kg)	0.88 (0.77-0.94) [b]
Knee extensor (kg)	0.97 (0.93-0.98) [b] 0.73 (0.47-0.88) [d (i)] 0.94 (0.87-0.98) [d (ii)]
Postural sway - Floor eyes open (mm)	0.68 (0.45-0.82) [c] 0.59 (0.29-0.79) [d]
Postural sway - Floor eyes closed (mm)	0.85 (0.72-0.92) [c]
Postural sway - Foam eyes open (mm)	0.57 (0.30-0.76) [c] 0.72 (0.46-0.86) [d]
Postural sway - Foam eyes closed (mm)	0.83 (0.69-0.91) [c]

[a] Intraclass Coefficient (ICC) CI = Confidence Interval
[b] Data obtained from 31 men and women aged between 76-87 years (Mean ± SD = 80.8 ± 3.1). ICC calculated using a two-way random model (2,1) [86].
[c] Data obtained from 34 men and women aged between 50-70 years (Mean ± SD = 62.4 ± 6.3). ICC calculated using a two-way random model (2,1) [86].
[d] Data obtained from 30 subjects who had suffered a hip fracture. This was comprised of 16 hospital inpatients 1-5 weeks post fracture (aged between 65-95 years) and 14 community dwellers 30-57 weeks post fracture (aged between 72-94 years). There were no systematic differences between ICC's for either group. Data obtained from ICC calculated using a two-way mixed model (3,1). [d(i)] Non affected leg [d(ii)] Affected leg

2.7 The Research Question

An association between reduced functioning and greater falls incidence in an elderly population with a low vitamin D status has been identified in the current literature review. Furthermore, with this decline in function and nutritional status, it is evident that falling can contribute to a reduced level of functioning and increased nutritional risk leading to vitamin D deficiency. This raises the question that, is it the presence of a reduction in function and vitamin D status that increases the risk of a falling episode or is it a result of reduced mobility and previous falling episodes? In addition, do these factors have some interaction with each other? That is, does a low vitamin D status contribute to poor function and subsequent falling episodes?

In order to gain further insight into the specific influences of vitamin D in relation to postural control measures, a complete assessment of sensory and motor measures and their interaction was considered necessary. In addition to the site of action of vitamin D the size of the treatment effect of vitamin D supplementation on the reduction of falls and measures of postural control remains uncertain.

Finally, The Physiological Profile Approach (PPA) has been identified as a reliable and valid compromise of balance performance. Apart from the developers of the PPA, little has been published as to the reliability of these measures once administered outside the realms of literature published by Lord and colleagues. This is of relevance as this is commercially available to health care professionals [86] and it is the application of the PPA by external users that will be instrumental to the success of the PPA in identifying at risk individuals.

To address these issues, the current thesis is structured as three separate studies. This will be a reliability study which will examine the performance of the PPA, a case control study which will begin to examine vitamin D status and neuromuscular control between fallers and non-fallers and a randomised controlled study which will examine the effect of vitamin D supplementation on neuromuscular performance and fall outcomes. The aims of each of these studies are set out in the following section.

2.8 Individual Study Aims

2.8.1 Reliability study

- Validate results from an existing independent research group using the same equipment for assessing neuromuscular control and falls risk. This was intended to contribute to the existing literature on the topic and identify issues that may arise once the PPA is placed in a health care setting allowing for further consideration with future use.

2.8.2 Case control study

- Categorise a population of elderly women according to vitamin D status.
- Determine measures of neuromuscular control that are associated with falling that discriminate between fallers and non-fallers.
- Examine overall differences in 25 OHD status between fallers and non-fallers.

2.8.3 Randomised control study

- Determine the effect on falls and neuromuscular measures following 12 months of treatment with calcium and vitamin D compared to calcium alone.
- Identify which components of the sensory, motor or postural sway measures that have the most significant improvement following vitamin D treatment.

Determine the size of the treatment effect to answer clinical questions as to the treatment and management of falls.

2.9 Hypotheses

- Fallers will have poorer postural control measures and lower vitamin D status than non-fallers.
- Poor postural control measures will be associated with low vitamin D status.
- Vitamin D treatment will have a higher correlation with reduced falls and improved measures of muscle strength and reaction time than placebo versus vitamin D in falling women.

2.10 Assumptions

1. It is assumed that the neuromuscular system will respond to the same vitamin D level as represented in serum vitamin D.
2. It is assumed that the subject's self-reporting of a fall will be accurate.

2.11 Delimitations

1. Intra-tester reliability testing will be performed prior to data collection.
2. The same instructions will be given to each subject for each measure.
3. Testing will be done in the same order for all subjects.

3.0 METHODS AND MATERIALS

3.1 Study Group patients

3.1.1 Reliability patients

Twenty seven women over the age of 70 who were living in Western Australia were randomly selected from a group of 1500 subjects who were currently participating in a 5-year study of the efficacy of calcium in the prevention of osteoporotic fracture. These women were selected from the electoral roll and had received a letter inviting them to join the study. Over 98% of women of this age are on the electoral roll.

Patients were excluded from the study if they were receiving bone active agents including calcium supplements or if they had significant current illness making it unlikely that they would survive the five years of the study. Although the patients entering the study were weighted in favour of those in higher socio-economic categories, disease burden and pharmaceutical consumption was similar to data obtained from whole populations of this age [90].

Participants were not selected based on a particular falls history.

3.1.2 Case control patients

Non fallers

One hundred women from the 5-year study discussed above were randomly selected to participate in the case control study. These women had not sustained a fall in the previous 12 months.

Fallers

The falls patients for the case control study were the first 100 consecutively recruited from the randomised controlled trial patients (details below) all of whom had fallen in the previous 12 months. All women were selected irrespective of vitamin D status.

3.1.3 Randomised control patients

Fallers

The subject group comprised of 302 women aged 70 to 90 years of age. The randomised controlled study was held in Perth Australia (latitude, 32° south) and subjects were recruited from April 2003 to October 2004. The recruitment process was by means of a letter sent to patients whose contact details were derived from three sources: patients attending the emergency departments of teaching hospitals, patients receiving local community home nursing services and the electoral roll (the latter providing details for more than 98% of women of this age range). The recruitment flow can be seen in Figure 3.1. The inclusion criteria were a history of falling in the past 12 months and a serum 25OHD concentration of less than 60 nm/L. The exclusion criteria included current vitamin D consumption; current consumption of bone or mineral active agents apart from calcium; a bone mineral density *z* score at the total hip site of less than −2.0; medical conditions or disorders that influence bone mineral metabolism, including laboratory evidence of renal insufficiency (a creatinine level more than 2-fold above the reference range); a fracture in the past 6 months; a Mini-Mental State Examination score of less than 24; or the presence of marked neurological conditions likely to substantially impair balance or physical activity, such as stroke and Parkinson disease.

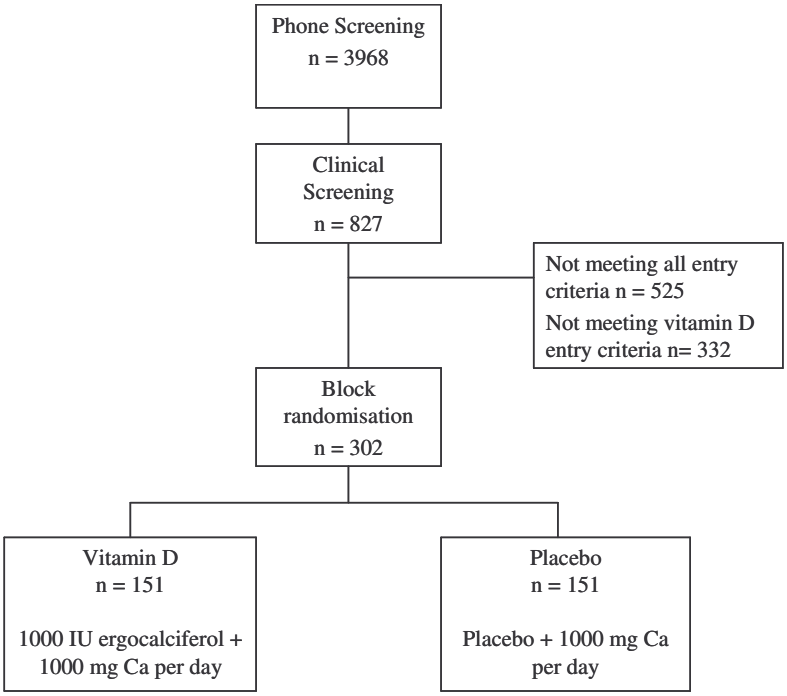


Figure 3.1: Recruitment flow chart

3.2 Ethics approval and consent process

3.2.1 Reliability and Case Control study (non-fallers)

Informed consent was obtained in writing from each participant after the study design and consent document had been approved by the Research Ethics Committee of the University of Western Australia.

3.2.2 Case Control and Randomised Control study (fallers)

The study was approved by the Human Research Ethics committee of the Sir Charles Gairdner Hospital, Nedlands Australia. Written informed consent was obtained from each participant.

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practices Guidelines and was registered with the Australian Clinical Trials Registry.

3.3 Study procedures

3.3.1 Reliability study

Subjects attended two clinic visits and underwent a neuromuscular testing specifically related to the Physiological Profile Assessment (PPA). The order of administrating these tests was: Contrast Sensitivity, Reaction Time, Tactile Sensitivity, Joint Position Sense, Lower Limb strength (ankle and knee), Postural Sway and Visual Acuity. These measures were repeated twice and performed on average seven days apart.

3.3.2 Case control study

Subjects attended one clinic visit and underwent anthropometry, neuromuscular and biochemistry testing. The order of administrating the neuromuscular assessments were:

Contrast Sensitivity, Reaction Time, Tactile Sensitivity, Vibration Sense, Joint Position Sense, Lower Limb Strength (ankle, knee and hip), Postural Sway, Visual Acuity and Timed Up and Go.

3.3.3 Randomised controlled study

All subjects attended four clinic visits (Screening, Baseline, 6 months and 12 months). At each visit, subjects underwent anthropometry, neuromuscular (Baseline, 6 and 12 months only) and biochemistry testing (all visits). The neuromuscular assessment was conducted in the following order: Contrast Sensitivity, Reaction Time, Tactile Sensitivity, Joint Position Sense, Lower Limb strength (ankle, knee and hip), Postural Sway, Visual Acuity and the Timed Up and Go Test. In addition phone calls to assess falls occurrence were conducted at 6 weeks, 3 months, 4 ½ months, 7 ½ months, 9 months and 10 ½ months (in addition to the three clinic visits) and adverse events were recorded at three monthly intervals. Administration of questionnaires and the neuromuscular test battery at the baseline, 6 and 12-month visit took approximately one hour per subject per visit.

Treatment

Participants received 1000 mg/d of calcium as calcium citrate (Citracal; Mission Pharmacal, Key Pharmaceutical Pty Ltd,Rhodes, Australia) for 12 months as two 250-mg calcium citrate tablets in the morning with breakfast and two 250-mg calcium citrate tablets with the evening meal. They were randomised to receive 1000 IU/d of ergocalciferol or identical placebo (Ostelin; Boots Healthcare, North Ryde, Australia) consumed with the evening meal for 12 months. The randomisation schedule to ergocalciferol or placebo was generated by an independent research scientist and was kept in the pharmacy department of the Sir Charles Gairdner Hospital, where the bottles were labeled and dispensed to the subjects. The randomisation procedure used a random number generator with a block size of 10 to assign participants to ergocalciferol or

placebo in a ratio of 1:1, thus ensuring equal recruitment to the two groups during the various seasons. The study subjects and the study staff remained blinded to the treatment code until all the data had been entered, evaluated for accuracy and the priori hypotheses reviewed. Adherence to the study medications was established by counting tablets returned at the clinic visits at 6 and 12 months.

3.4 Description of individual assessments

3.4.1 Anthropometry

Case control: measurements taken at only clinic visit

Randomised control study: measurements taken at baseline, 6 and 12-month clinic visits.

Height and weight were measured with the patients in light clothing and without shoes.

3.4.2 Biochemistry

Case control: sample collected at only clinic visit

Randomised control study: sample collected at screening, baseline, 6 and 12-month clinic visits.

A venous blood sample was collected from each participant. Participants had fasted overnight and serum 25OHD concentrations assessed by radioimmunoassay (DiaSorin, Stillwater, Minnesota). Serum calcium and phosphorus levels were assessed by routine laboratory methods.

3.4.3 Falls definition and recording

Case control: administered at only clinic visit

Randomised control study: administered at 6 weeks, 3 months, 4 ½ months, 7 ½ months, 9 months and 10 ½ months

A comprehensive falls questionnaire (Appendix One) was administered at baseline, 6 weeks, 3 months, 4½ months, 6 months, 7½ months, 9 months, 10½ months and 12 months. This was to effectively determine if the falling episode fitted into the definition required by the study. That is: "unintentionally coming to rest on the ground, floor, or other lower level". During the randomised control study, study staff interviewed subjects every 6 weeks via telephone or during clinic visits. The number of falls that had occurred in the previous 6 weeks and the associated features of the falls were recorded on a falls questionnaire.

3.4.4 Neuromuscular assessment

Reliability study: testing conducted twice, on average one week apart.

Case control study: testing conducted at only clinic visit

Randomised control study: testing conducted at baseline, 6 and 12-month clinic visits.

Sensory system measures

Contrast Sensitivity

Edge contrast sensitivity was assessed using the Melbourne Edge Test (MET) [91] (Figure 3.2). This test presents 20 circular patches containing edges with reducing contrast and assesses the minimum contrast level required to detect stimuli of varying frequencies. Correct identification of the orientation of the edges on the patches provides a measure of contrast sensitivity in decibel units, where dB = -10log10 contrast. Details of patient instructions are located in Appendix 2.

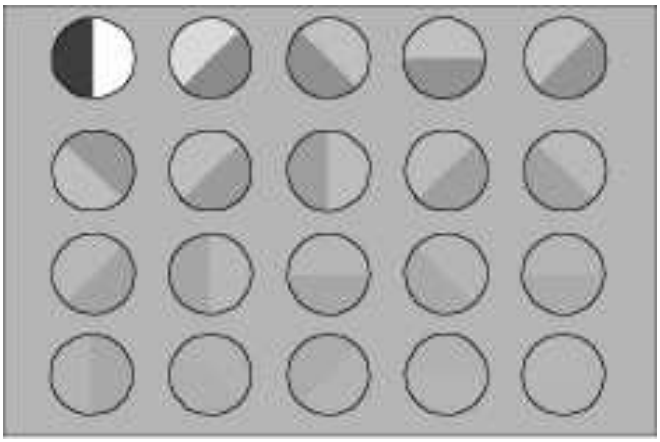


Figure 3.2 Melbourne Edge Test

Visual Acuity

Visual acuity was measured using a chart with high contrast visual acuity letters (similar to a Snellen scale) and low (10%) contrast letters, (where contrast = the difference between the maximum and minimum luminances divided by their sum). Acuity is assessed binocularly with subjects wearing their glasses (if needed) at a test distance of three metres and measured in terms of logarithim of the minimum angle resolvable (log of MAR) in minutes of arc (Figure 3.3) [91]. Details of patient instructions are located in Appendix 3 and 4.

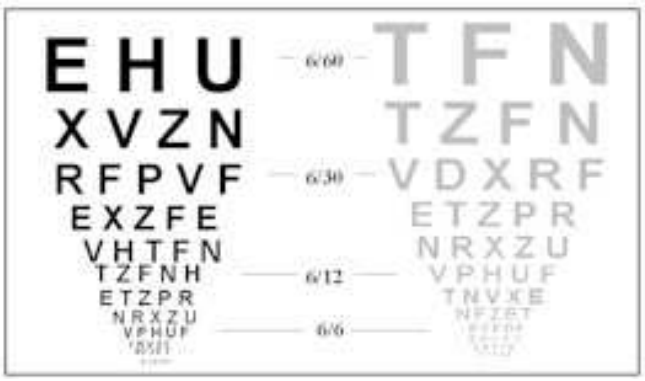


Figure 3.3 Visual Acuity Chart

Tactile Sensitivity

Tactile sensitivity was measured with a pressure aesthesiometer. This instrument contains eight nylon filaments of equal length, but varying in diameter. The filaments are applied to the centre of the lateral malleolus and measurements are expressed in logarithms of milligrams pressure (Figure 3.4) [91]. Details of patient instructions are located in Appendix 5.

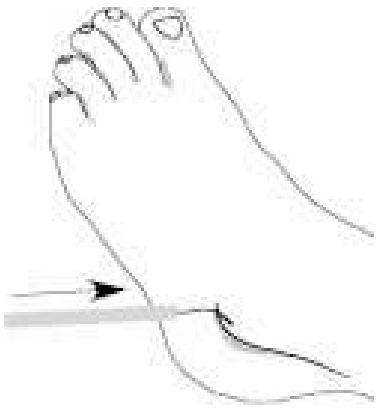


Figure 3.4 Tactile sensitivity test

Joint Position Sense

Joint position sense was assessed by asking seated subjects with eyes closed to align the lower limbs on either side of a 60cm by 60cm by 1cm thick clear acrylic sheet inscribed with a protractor. Any difference in matching the great toes was measured in degrees (Figure 3.5) [91]. Details of patient instructions are located in Appendix 6.

Figure 3.5 Joint position sense assessment

Motor measures

Reaction time

Reaction time was assessed using a light as the stimulus and depression of a switch (by the finger and foot) as the response. Reaction time was measured in milliseconds (Figure 3.7) [91]. Details of patient instructions are located in Appendix 7.

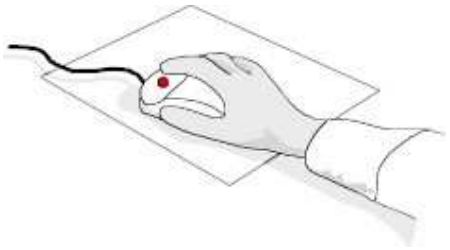


Figure 3.6 Reaction time (actual picture represents hand reaction time)

Lower Limb Strength

The strength of the muscle groups (hip flexors, extensors, abductors and adductors, knee flexors and extensors and ankle dorsiflexors) was measured while subjects were seated using a spring gauge. In each test, there were three trials and the greatest force recorded (kgs) (Figure 3.6) [91]. Details of patient instructions are located in Appendix 8.

Figure 3.7 Lower limb strength (actual picture represents knee extension)

Integration measures

Postural sway

Sway was measured using a sway-meter that measures displacements of the body at waist level. The device consists of a 40cm long rod with a vertically mounted pen at its end. The rod is attached to subjects by a firm belt and extends posteriorly. As subjects attempt to stand as still as possible, the pen records the sway of subjects on a sheet of millimetre graph paper fastened to the top of an adjustable height table (Figure 3.8) [91]. Testing is performed with the eyes open and closed on a firm surface and on a piece of medium density foam rubber (15cm) thick. Total sway (number of square millimetre squares traversed by the pen) in the 30-second period is recorded for the four tests. Details of patient instructions are located in Appendix 9 and an example of a participant results can be seen in Appendix 10.

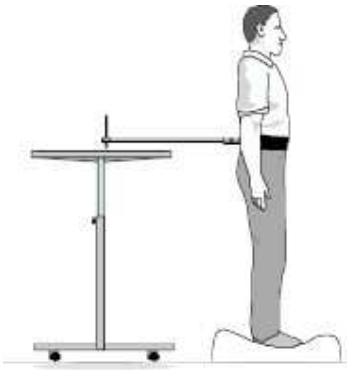


Figure 3.8 Sway meter

A digital sway program was developed to count the sway path. This program allowed for individual sway path analysis for each condition. This was done by digitally selecting the required region. Each region was calibrated spatially (1mm=~4.7 pixels) and an image of the sway path was superimposed onto the scanned document. This

allowed comparisons with the hard copy results and errors to be identified. Once the image was analysed the data was then exported to an excel spreadsheet. Results from 10 sway assessments were done to assess CV error for the computerised sway program. The CV calculation for each condition was as follows: floor, eyes open (5.79%), floor, eyes closed (4.87%) and foam, eyes open (12.81%). CV error for foam eyes closed was not done due to the majority of participants unable to complete the 30 seconds.

Timed Up and Go(TUG)

Subjects underwent the TUG. This measures the time it takes for a patient to stand from a seated position, walk 3 metres, turn around, walk back and sit down again (recorded in seconds).

3.4.5 Adverse event recording

Randomised control study: administered at 3 monthly intervals.

Using a previous validated method [92]; participants were asked to fill out an adverse event diary in which each contact with a health care provider was recorded. At three monthly intervals the diary was photocopied and returned to the patient. The event data were coded using the International Classification of Primary Care (ICPC2 Plus©) system database of disease coding (Family Medicine Research Unit, Department of General Practice, University of Sydney). Adverse events were grouped according to 17 categories identified by the ICPC2 Plus system.

4.0 STATISTICAL ANALYSIS

4.1 Reliability study

The distribution of data was assessed for skewness. Variables were assessed for skewness and those with either skewed paired variable was logged for normality. Intraclass Correlation Coefficient (ICC) was calculated to assess the reproducibility of the rank order of subjects for each test. The two-way mixed approach (3,1) with the consistency option was selected. The consistency option was chosen as it assumes that any shifts in the measured variable is not to be considered measurement error and any variability will be due to random variability in performance.

4.2 Case control study

Descriptive statistics were reported for the demographic and postural control measures for the 200 subjects according to falling status and significant differences between groups were calculated using independent sample t-test or McNemar's test. Linear Regression analysis was used to determine the effect of vitamin D on neuromuscular measures following adjustment for falls status. Specifically, each neuromuscular variable was entered individually as the dependent variable with vitamin D entered in at the first level in the model and falls status entered in at the second level in the model.

4.3 Randomised control study

The main intention-to-treat analysis included all 302 subjects enrolled. Logistic regression was used to evaluate the effects of ergocalciferol treatment on a person's risk of falling at least once during the one-year follow-up. The analytical approach was chosen because it enabled our results to be comparable with the outcome of a recently published meta-analysis [75]. In further analysis, multinomial logistic regression was used to model the effects on first falling in winter/spring vs summer/autumn. A similar

method was used to assess the treatment effect on 1 fall or more than 1 fall. In both multinominal logistic regression models, those who did not fall were used as the reference group, and no ordering was assumed. Summer/autumn was defined as the period from December to May and winter/spring as the period from June to November. The length of follow-up until the time of withdrawal for those who withdrew from the study or 1 year for those who completed the study was a covariate in all analyses. Odds ratios (ORs) obtained from the logistic regression models were transformed to relative risk (RR) by using the following formula: RR=OR/(1 − p0 _ p0_OR), where p0 is the probability of a fall in the control group. All tests were two-tailed, and the significance value was set at $P<0.05$.

4.4 Power calculations for randomised control study

Power calculations were performed prior to the commencement of the study. The falls rate in the control group was estimated to be at least 60% per annum. To detect a 37% reduction in the relative risk of falling, at an alpha of 0.05 and 90% power 113 subjects per group were needed (Fisher's exact test). Allowing for a 30% drop out rate, the number of subjects required per group was at least 147.

4.5 Considerations in measurement of sway

There were considerable difficulties in the assessment of sway performance. A substantial number of individuals were not able to complete the task in the reliability, case control and randomised control studies. An example of the proportions of fallers and non-fallers in the case control study and their relative completion rates can be seen in Figure 4.1. As shown, a greater proportion of fallers were unable to progress to the next sway test and a large proportion of both fallers and non-fallers were unable to complete the hardest stage of eyes closed on foam. Figure 4.1 shows that for both groups, there was a high level of agreement for task completion between fallers and non

fallers for the easiest sway test (sway on floor eyes open). As task difficulty increased (i.e.: eyes closed on floor to eyes open on foam), *floor effects* were observed where many individuals could not complete the entire 30 second testing period.

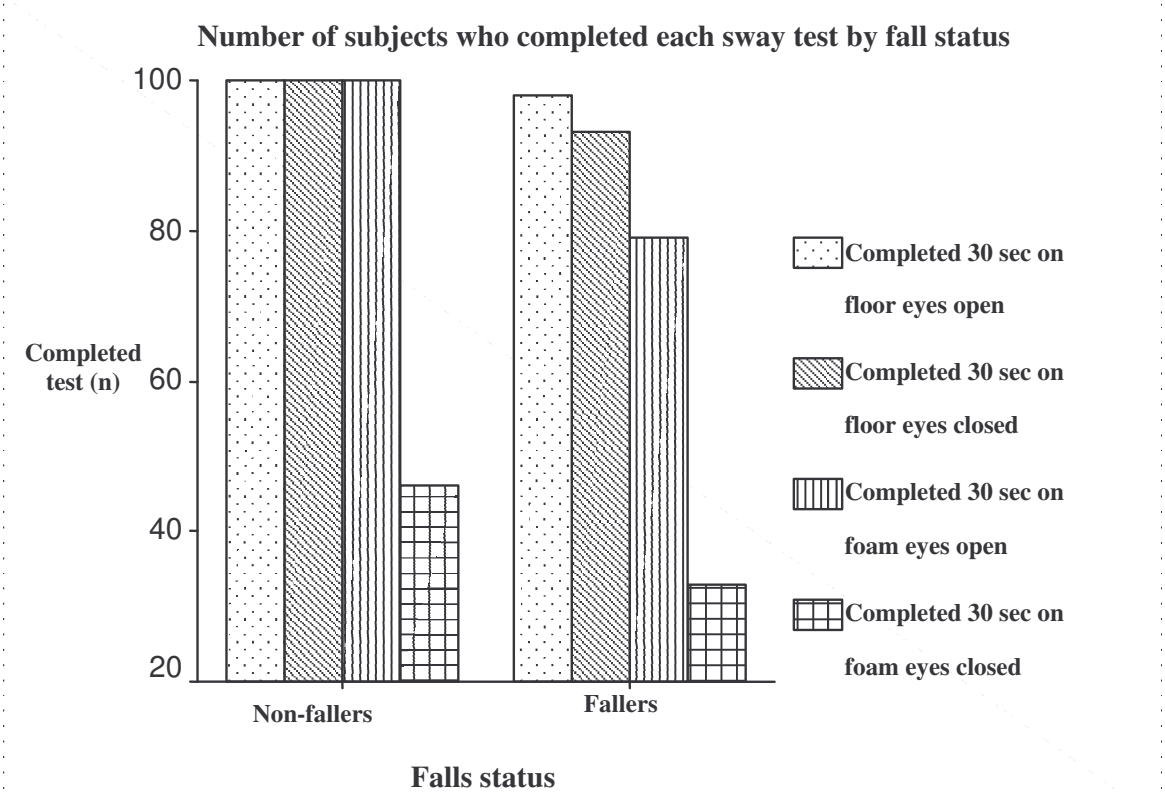


Figure 4.1 Proportion of subjects completing each sway test condition in the case control study

These floor effects compromised the assessment of sway path length as the output of the task required continuous recording for 30 seconds. It is due to this high non completion rate that the sway data for all three studies were reported and analysed using continuous data (i.e.: sway path length) as categorical reporting would have misrepresented the ability of the study population. Depending on the study the issue was dealt with in different ways as discussed in the sections on each study.

A second problem relates to the co correlations between the physiological tests irrespective of falls status. This is discussed in detail in Section 6.0 Case Control Study.

5.0 RELIABILITY STUDY

5.1 Overview

The reliability study examined 27 unselected community based women over the age of 70. Participants were selected irrespective of falls status. Neuromuscular testing was undertaken at two clinic visits (on average 7 days apart) using the Physiological Profile Assessment (PPA). This consisted of testing for sensory (vision, tactile, joint position sense), motor (muscle strength) and the interaction of sensory and motor systems (reaction time, sway and functionality). Statistical analysis comprised intra-class correlation coefficient (ICC) for each test using the two way mixed approach (3, 1). The detailed methodology for this study can be reviewed in Section 3.0 Methods and Methodology and statistical analysis explanation in Section 4.0 Statistical Analysis.

5.2 Results

With the exception of touch sensation, repeated measures t-test demonstrated no significant difference between the means of Trial 1 and 2 for any of the variables thereby indicating the absence of any order effects. Results for the ICC's are shown in Table 5.1.

Based on the categories defined by Fleiss [87], variables demonstrating excellent test retest reliability were visual acuity, touch sensation, hand reaction time and muscle strength Fair to good reliability was observed for contrast sensitivity, joint position sense and postural sway on the floor (eyes open/closed). Poor reliability was observed for postural sway on foam (eyes open). Reliability analysis was not done for postural sway on foam (eyes closed) as only five of the subjects were able to complete the test. For illustrative purposes the correlation between two measurements of vision (Figure 5.1a) and sway (Figure 5.1b) are shown.

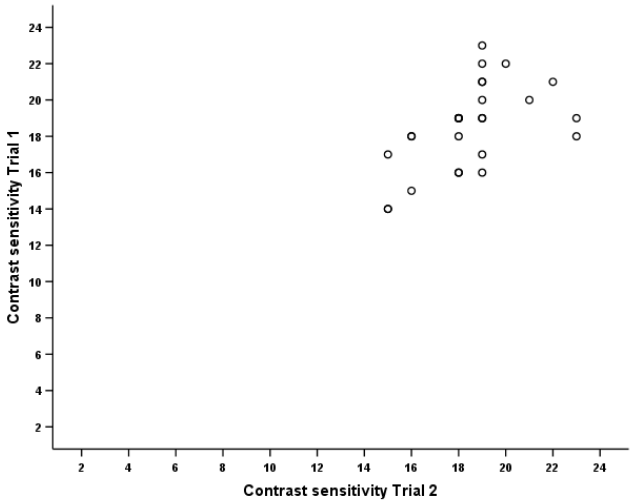
Table 5.1 Test-retest reliability data for postural control measures [a]

	ICC (95% CI) [b]
Contrast sensitivity (db log contrast)	0.55 (0.22-0.77)
High contrast visual acuity (log of MAR)	0.79 (0.58-0.90)
Low contrast visual acuity (log of MAR)	0.90 (0.80-0.95)
Touch Sensation ($\log^{10}$ 0.1mg pressure)	0.78 (0.57-0.89)
Joint position sense (degrees)	0.46 (0.10-0.71)
Hand reaction time (milliseconds)	0.87 (0.73-0.94)
Foot reaction time (milliseconds)	0.72 (0.48-0.86)
Ankle strength (kg)	0.88 (0.76-0.95)
Knee flexor strength (kg)	0.77 (0.55-0.89)
Knee extensor (kg)	0.88 (0.76-0.94)
Postural sway - Floor eyes open (mm) #	0.50 (0.12-0.75)
Postural sway - Floor eyes closed (mm) #	0.66 (0.35-0.84)
Postural sway - Foam eyes open (mm) #	0.25 (-0.17-0.61)

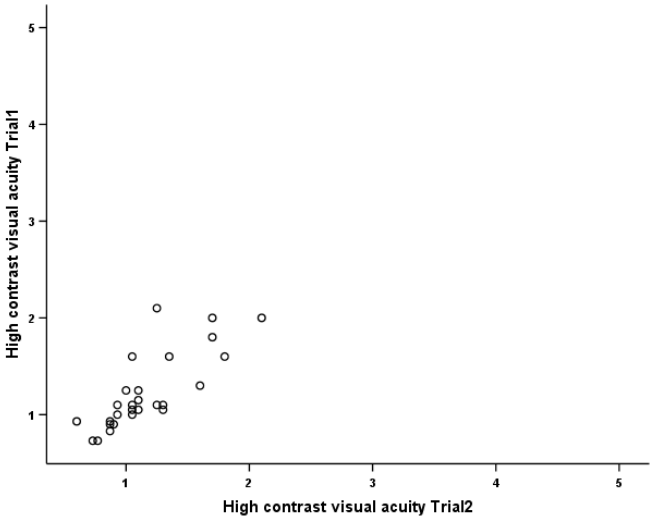
a Data from 27 women 70 years and over (Mean ± SD = 78.0 ± 4.34 years) tested on average 7 days apart.
b Intraclass coefficient (ICC) calculated using a two-way random model (3,1). CI = Confidence Interval; # Logged variables. Data for sway on foam with eyes closed not reported as only five subjects could complete the test.

Figure 5.1a Scatterplots showing comparison of the two tests of visual function

Vision:
Contrast Sensitivity
(db log contrast)



Vision:
High contrast visual acuity
(log of MAR)



Vision:
Low contrast visual acuity
(log of MAR)

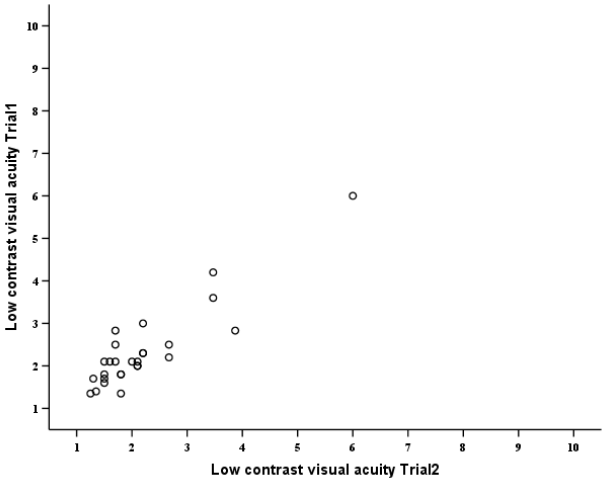
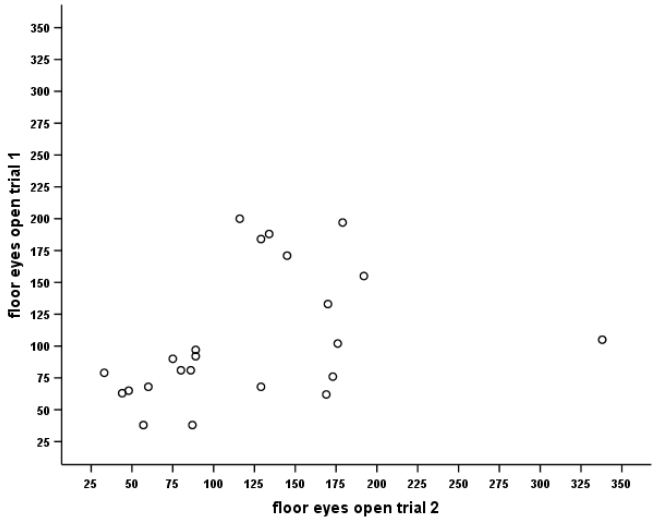
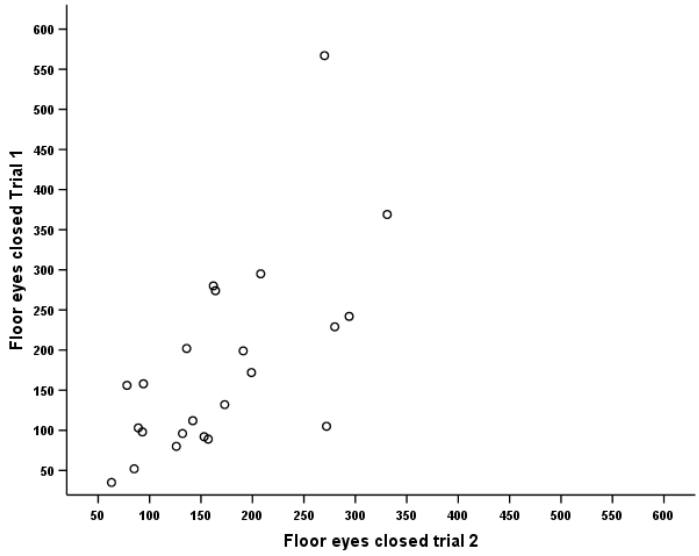


Figure 5.1b Scatterplots showing comparison of postural control measures

Postural sway path length floor eyes open (mm)



Postural sway path length floor eyes closed (mm)



Postural sway path length foam eyes open (mm)

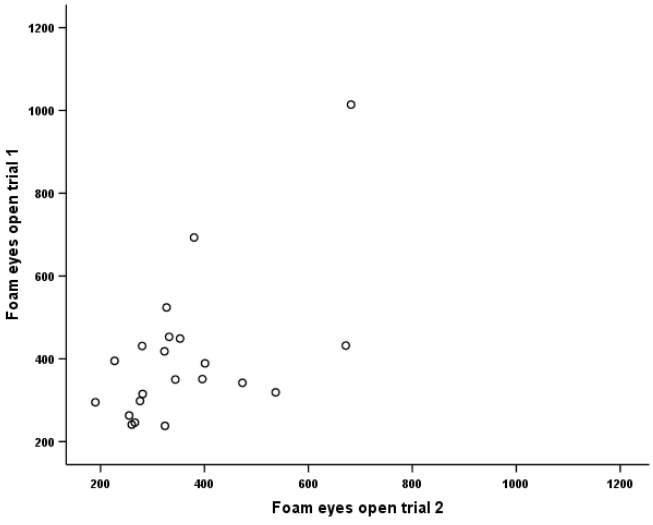


Table 5.2 demonstrates the level of agreement between our results previously reported by Lord and colleagues [86] based on ICC categories defined by Fleiss [87].

Table 5.2 Level of agreement between current reliability scores and those previously published by Lord and colleagues.

	Excellent (>0.75)	**Fair to good (0.40-0.75)**	**Poor (<0.40)**
Contrast sensitivity (db log contrast)	Lord	Us	
High contrast visual acuity (log of MAR)	Agreed		
Low contrast visual acuity (log of MAR)	Agreed		
Touch Sensation (log^{10} 0.1mg pressure)	Us	Lord	
Joint position sense (degrees)		Agreed	
Hand reaction time (milliseconds)	Lord	Us	
Foot reaction time (milliseconds)	Us	Lord	
Ankle strength (kg)	Agreed		
Knee flexor strength (kg)	Agreed		
Knee extensor (kg)	Agreed		
Postural sway - Floor eyes open (mm)		Agreed	
Postural sway - Floor eyes closed (mm)	Lord	Us	
Postural sway - Foam eyes open (mm)		Lord	Us
Postural sway - Foam eyes closed (mm)	Lord*		

* Data for sway on foam with eyes closed not reported as only five 5 subjects could complete the test.

Agreement was found on visual acuity, all strength measures, joint position sense and postural sway on floor (eyes open). There were differences in agreement by one category for contrast sensitivity, touch sensation, reaction time and postural sway on floor (eyes closed) and foam (eyes open).

5.3 Discussion

The present paper suggests that of the 14 test items used in the PPA, eight had excellent reliability, five had moderate reliability and one measure had poor reliability. In comparison to previous results by Lord [86], eight of the test items agreed with our results. Although the majority of Lords reliability measures were done using the ICC (2,1) method, we analysed our results using the ICC (3,1) method which has been more commonly reported. We also analysed our results using the ICC (2,1) method and did not observe any differences in results (data not reported).

Our results demonstrated excellent reliability for both measures of visual acuity, which was in agreement with Lord [86]. Our measure of contrast sensitivity demonstrated only fair to good reliability where Lord demonstrated excellent reliability. The explanation in regards to the variability within our sample could relate to the version used and the age group of our sample. Haymes & Chen [93] discussed the reduced test-retest reliability in a group of subjects with low vision (mean age 74years range 31-92years) in the Melbourne Edge Test (MET) 'original version' compared to the new 'light box' version. We used the original version which is a photographic card compared to the new 'light box' version which is laser beam that exposes test edges on lithographic film. This reduced test-retest reliability in those with low vision may be due to the scale of the dB. The version used in this paper has a scale between 1dB and 9dB that increases in 2dB steps and from 10 to 24dB, it increases in 1 dB steps. It has been discussed elsewhere [94] that if the number of steps is increased by a factor of n,

the reliability of the measurement will be improved by √n. This means that in those with low vision, reliability could be improved if the number of dB steps is increased at the lower end of the test. Vision pathology may have been more evident in our group compared to Lord's group, which could explain any differences between research groups. Furthermore, there could have been a difference in method of testing. The recommended testing difference is 40cm [93]. This is not stated in the test kit for Lord. Furthermore, the lighting may have been inadvertently different in the rooms where the tests were administered.

We reported excellent reliability for the touch sensation. There was however, a systematic shift in results from test to retest. This demonstrates a order/learning/habituation effect. It is thus appropriate to conclude that any variability between tests cannot be solely attributed to random variability in performance. Lord and colleagues reported a fair to good reliability. As with any psychophysical test, the magnitude for the threshold is affected by the psychological variability of the individual [95]. This includes factors such as motivation, stress (psychological and physiological), distraction, fatigue, noise and anxiety. Thus, this influences central processing factors resulting in a variation in the threshold.

There was a very close agreement in the ICC values for joint position sense reported in this paper and that of Lord (ICC = 0.46 95%CI 0.10-0.71 and ICC = 0.50 95%CI 0.15-0.75 respectively). This is deemed fair to good reliability as defined by Fleiss [87]. Previous reports on the reliability of active to active reproduction of the position of the ankle joint demonstrated excellent reliability using a more sophisticated potentiometer [96]. These authors state however, that little correlation has been observed between different measures of joint position sense. It has been discussed that this is because

different measures assess different aspects of proprioception and that different receptors are involved depending on the type of test used [96]. Therefore, it is difficult to speculate as to the effectiveness of measuring joint position sense when the method used varies.

Previous research have discussed mixed findings in regards to the reliability of the strength testing [97]. We demonstrated excellent reliability with all three strength measures for ankle dorsiflexion and knee flexion and extension. This is consistent with the reliability results reported by Lord for these muscle groups. Other reports of excellent ICC measures using a hand held testing device have been published on hip strength [97] and hip, knee and ankle strength [98].

Reliability in muscle strength testing is dependent on the population tested, the device used and the muscle group tested [97]. Furthermore, reliability and measurement error needs to be specifically reported for each population, muscle group tested and the measurement method [98]. This was the case in regards to our results and that of Lords. It can therefore be confidently said that the strength measures used as part of the PPA are reliable measures using the ICC method.

The variability in the sway measures could be attributed to the age difference between the two samples. While the age range for Lord's sample was 50-70, the range for our group was 70 years and above. This could explain the agreement between the two experimental situations for the easiest of the sway measures (i.e. eyes open on floor), the gradual decline in reliability and agreement with increased task difficulty (i.e. eyes closed on floor to eyes open on foam), to the observed floor effects observed in our sample in that sufficient numbers could not complete the test for the entire 30 seconds.

These age-related changes in balance are possibly due to changes in vision, kinesthetic and vestibular function and a reduction in fast-twitch muscle fibres with a subsequent loss of strength that occurs with increased age [18].

An alternative explanation relates to the issue of task difficulty. The sample reported by Lord for the most difficult sway test reported excellent reliability where we were unable to report any reliability for this measure as it was completed by five people. Helbostad [88] suggests that a U shaped relationship may exist when examining reliability of postural challenges. This is supported by previous literature that reports poor reliability for a quiet standing task in healthy young subjects [99]. That is, poor reliability is observed when the task is too easy or too difficult.

The research by Helbostad [88] is consistent with our theory that variability between measures increases with task difficulty. It conflicts however, with our theory that test-retest variability was due to age. Conversely, Helbostad found that test variability could not be accounted for age. It could however, be accounted for group based on clinical presentation. That is, Helbostad identified test-retest variability using triaxial piezoresistant accelorometer was more likely in stroke patients than in frail older adults due to behavioral characteristics associated with hemiparesis.

This raises the confounding issue of disease in relation to age. Virtually all neuromuscular disorders result in some degeneration of the balance control system. The CNS can generally adapt to pathology until the individual is temporarily deprived of the compensating system. For example, a person with a vestibular deficit may rely heavily on vision, so when vision is taken away from them they can become unstable. Pathologies with special balance challenges include chronic low back pain, scoliosis,

head injury, stroke, cerebellar disease, Parkinsons disease, vestibular deficits and peripheral neuropathies.

When examining the reliability of psychophysiological response profiles, the issue of temporal stability needs to be considered. The dependence of the stability addresses such issues as the type of task, the interval of time between tests and how the data is handled. While temporal stability coefficients describe the reproducibility between single physiological measures, they do not address the issue of whether complex response patterns are temporally stable. This is because the specificity of a response is dependent on the individual, the situation and the level of motivation. The systematic approach in addressing both the uniqueness of the individual in the response patterns and the trans-situational consequences of this uniqueness can be markedly varied [100].

The statistical process for determining reliability in the physical health domain has produced an interesting and prolonged debate. The use of a Pearson r correlation coefficient is bivariate statistics and not appropriate for repeated measures univariate statistics [101]. The use of ICC has come under criticism as it is influenced by the distribution of the data [102, 103]. Furthermore, Hopkins [104] states that the ICC is susceptible to the heterogeneity of the population. The population used in this study was of a heterogeneous nature. Furthermore, skewness of the data was checked and any skewed data logged, allowing the data to fall under a normal distribution. Thus, for this group, the use of ICC can be justified.

The decision to use the appropriate reliability measure needs to address both random and systematic error [101]. Random error relates to the variation observed within the subject and includes biological, psychological differences in the subject, variance with

the equipment and variance of the tester. Systematic error is non-random in its approach and is the difference between the means of scores across trials. Systematic error can be due to learning effects by the subject that are due to a lack of familiarisation of the test equipment by the subjects [101]. This is particularly relevant to older subjects who may have never been exposed to the type of equipment and their associated procedures. It has therefore been suggested that subjects are exposed to some familiarisation sessions with the aim of reducing systematic bias [101].

Based on our results and reports in the literature we have defined several limitations to the reliability study. Firstly, subjects were not excluded based on any obvious or subtle pathology that may have influenced their performance on any of the test items. Secondly, due to the age group of the sample, it may have been useful to conduct a familiarisation session to acquaint the participants with the test kit and remove any influences that may have affected random error.

This study allows for future recommendations to be made. Firstly, it is suggested that participants that are taking part in any reliability focused study, are shown the test items prior to data collection and given the opportunity to practice. This may reduce any learning effect that has been observed in some studies. Secondly, further reliability studies need to be done on sway. This is in relation to the instrument used (in this case the sway meter) and the population tested. It is suggested that there be a focus on an older population as this is the group at greatest risk of falling. Thirdly, to reduce external effects when assessing sway, it could be suggested that due to the potentially hazardous situation of testing sway in an older age group support bars, floor cushioning and two testers might allow for the limits of the subject to be tested while maintaining safety.

Finally, it has been stated previously that "reliability is fundamental to all aspects of clinical research, because without it we cannot have confidence in the data we collect, nor can we draw rational conclusions on those data" (Ottenbacher [97] p. 1425). This study has examined the reliability of the Physiological Profile Approach (PPA) used to identify individuals at risk of falling. This approach is currently being applied in health care settings and research institutions. Results have indicated reasonable reliability for measures of acuity, strength and central stability. This is in agreement with previous reliability studies done by the developers of the PPA. Fair to good reliability was observed for joint position sense and sway on floor with eyes open. It is postulated that a U shaped relationship exists when examining reliability of postural challenges. That is, poor reliability is observed when the task is too easy or too difficult. This highlights the importance that repeatability needs to be relevant to a target population and any comparisons made with caution. Consideration as to the complex issue of testing in the physical health domain and suitability of appropriate statistics needs to be applied.

6.0 CASE CONTROL STUDY

6.1 Overview

The case control study examined 100 non fallers recruited from population controls who had not sustained a fall in the previous 12 months and 100 fallers who had fallen at least once in the previous 12 months irrespective of vitamin D status.

Subjects attended one clinic visit and underwent anthropometry, biochemistry, neuromuscular testing and falls event recording. Neuromuscular testing was conducted using the Physiological Profile Assessment which examined sensory and motor function and the interaction of these systems. Additional tests implemented were hip strength and timed up and go. Descriptive statistics for demographic and postural control measures were reported according to falls status and significant differences assessment using independent sample t-test or McNemar's test. Linear Regression was used to determine the effect of vitamin D on neuromuscular measures following adjustment for falls status. The detailed methodology for this study can be reviewed in Section 3.0 Methods and Methodology and statistical analysis explanation in Section 4.0 Statistical Analysis.

6.2 Results

25OHD levels of fallers compared to non-fallers

Results for the case control study demonstrated that fallers had significantly lower 25 OHD levels compared to non-fallers (Mean ± SD; Fallers: 46.5 ±15.8 nmol/L, Non-fallers: 69.5 ± 20.0nmol/L) (Figure 6.1).

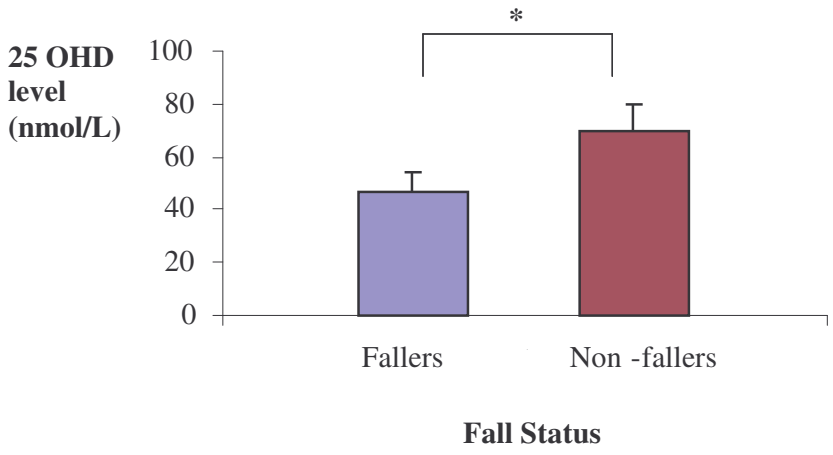


Figure 6.1 Mean 25 OHD levels of fallers and non-fallers* p<0.05

Neuromuscular performance of fallers compared to non-fallers

In relation to neuromuscular performance, fallers had poorer vision as assessed by contrast sensitivity (p=0.02) and visual acuity (p=0.01 (high acuity) and p=0.001 (low acuity), were weaker in their ankles, knees and hips (p=0.01 (ankle) p=0.001 (knee and hip), had slower hand reaction time (p=0.001), poorer sway balance (p=0.02) and recorded slower times on the Timed Up and Go Test (p=0.001) (Table 6.1).

Sway measures using foam and with eyes closed was not reported because of floor effects discussed in Section 4.0. Specifically, in the fallers group (n=100), only 33% of fallers could complete the eyes closed on foam task compared with 79% for eyes open on foam, 93% for eyes closed on floor and 98% for eyes open on floor.

Table 6.1 Demographic, biochemical and neuromuscular results

	Non-fallers (n=100)	Fallers (n=100)	p value[a]
Demographics and biochemistry			
Age (years)	78.5±2.5	77.6±5.6	NS
Weight (kg)	65.6 ±9.6	68.9±13.1	0.043
Height (cm)	157.9±6.0	157.9±6.3	NS
25OHD (nmol/L)	69.52±19.99	46.46±15.77	0.001
Sensory measures			
Contrast sensitivity (dB)	19.0 (18.0-20.0)	18 (16.0-19.0)	0.016
High contrast visual acuity (log of MAR)	1.1 (0.9-1.4)	1.3 (1.0-1.7)	0.011
Low contrast visual acuity (log of MAR)	2.0 (1.6-2.5)	2.3 (1.8-3.3)	0.001
Touch Sensation (log^{10} 0.1mg pressure)	3 (3.0-4.0)	3 (2.0-4.0)	NS
Joint position sense (difference in degrees)	1.4 (0.8-2.2)	1.8 (0.9-3.0)	NS
Motor measures (muscle strength (kg))			
Ankle plantar flexor	10.1±3.4	8.9±3.3	0.019
Knee flexor	12.4±3.1	10.8±3.3	0.001
Knee extensor	21.1±6.2	17.6±6.8	0.001
Hip flexor	17.6±5.3	13.9±5.2	0.001
Hip abductor	14.6±4.1	11.2±4.3	0.001
Hip extensor	18.0±5.5	14.0±5.2	0.001
Hip adductor	17.5±5.2	13.9±4.6	0.001
Integration of sensory and motor measures			
Hand reaction time (milliseconds)	239 (219 - 266)	260 (228 - 308)	0.001
Foot reaction time (milliseconds)	308 (272 - 360)	318 (276 - 379)	NS
Sway on Floor eyes open (mm)	90 (64 - 118)	102 (66 - 174)	0.023
Timed Up and Go (seconds)	9.0 (7.0-10.0)	12.0 (10.0-15.6)	0.001

a $p<0.05$
Results are mean ± SD or median and interquartile range or proportion.
NS not significant.
MAR Maximum Arc Resolvable.

Interrelations of the components of the Physiological Assessment Profile

Another aspect of the functional testing undertaken was the evidence that was found for co-correlation between the tests shown in Table 6.2. This shows that although weight was only correlated with Timed Up and Go, height was associated with some of sensory tests and with muscle strength. Interestingly sway was related to hip muscle strength tests and for reasons that are not obvious touch sensation. Visual function testing also showed a relationship to lower limb muscle strength perhaps related to the fact that reduced vision reduces physical activity and thereby muscle strength.

Table 6.2 Correlations between physiological balance measures in the case control study.

	Weight	Height	Contrast Sensitivity	Hand RT	Foot RT	Touch	Joint Position Sense	Ankle strength	Knee flexor strength	Knee extensor strength	Hip flexor strength	Hip abductor strength	Hip extensor strength	Hip adductor strength	High contrast visual acuity	Low contrast visual acuity	Floor Eyes Open converted to max
Height	**0.28 *****																
Contrast Sensitivity	ns	ns															
Hand RT	ns	ns	ns														
Foot RT	ns	ns	ns	**0.61 *****													
Touch Sensation	**0.14***	**0.16***	**0.21 *****	ns	ns												
Joint Position Sense	ns	**-0.19****	ns	ns	ns	ns											
Ankle strength	ns	**0.18***	ns	**-0.17***	**-0.28 *****	ns	**-0.25 *****										
Knee flexor strength	ns	**0.29 *****	**0.18 ****	**-0.26 *****	**-0.33 *****	ns	**-0.21 *****	**0.48 *****									
Knee extensor strength	ns	ns	**0.21 *****	**-0.29 *****	**-0.34 *****	**-0.22 *****	**-0.20 *****	**0.45 *****	**0.58 *****								
Hip flexor strength	ns	**0.20****	**0.15***	**-0.33 *****	**-0.29 *****	**-0.17***	**-0.19 ****	**0.44 *****	**0.58 *****	**0.61 *****							

Spearman Rank Correlation, *p<0.05, ** p<0.01, ***p<0.001

Table 6.2 (continued) Correlations between physiological balance measures in the case control study.

	Weight	Height	Contrast Sensitivity	Hand RT	Foot RT	Touch Sensation	Joint Position Sense	Ankle strength	Knee flexor strength	Knee extensor strength	Hip flexor strength	Hip abductor strength	Hip extensor strength	Hip adductor strength	High contrast visual acuity	Low contrast visual acuity	Floor Eyes Open converted to max
Hip abductor strength	ns	**0.15***	**0.21 *****	**-0.36 *****	**-0.35 *****	**-0.20 *****	**-0.21 *****	**0.43 *****	**0.59 *****	**0.62 *****	**0.78 *****						
Hip extensor strength	ns	ns	**0.22 *****	**-0.31 *****	**-0.32 *****	**-0.24 *****	**-0.22 *****	**0.45 *****	**0.58 *****	**0.67 *****	**0.80 *****	**0.73 *****					
Hip adductor strength	ns	**0.16***	**0.19****	**-0.34 *****	**-0.33 *****	**-0.21 *****	**-0.23 *****	**0.51 *****	**0.59 *****	**0.67 *****	**0.76 *****	**0.71 *****	**0.82 *****				
Log High visual acuity	ns	ns	**-0.39 *****	ns	ns	**0.21****	ns	ns	**-0.19****	**-0.23****	**-0.22****	**-0.26 *****	**-0.23****	**-0.22****			
Log Low visual acuity	ns	ns	**-0.47 *****	ns	ns	**0.15***	ns	ns	**-0.21****	**-0.20****	**-0.25 *****	**-0.26 *****	**-0.27 *****	**-0.24****	**0.82 *****		
Sway	ns	ns	ns	ns	ns	**0.16***	ns	ns	ns	**-0.21 *****	ns	**-0.17***	ns	**-0.18****	ns	ns	
Timed Up and Go	**0.23 *****	ns	**-0.20 *****	**0.39 *****	**0.38 *****	ns	ns	**-0.41 *****	**-0.48 *****	**-0.54 *****	**-0.49 *****	**-0.52 *****	**-0.55 *****	**-0.56 *****	**0.19****	**0.19****	**0.27 *****

Spearman Rank Correlation, *p<0.05, ** p<0.01, ***p<0.001

Effect of vitamin D on neuromuscular control measures

Following adjustment for falls status, linear regression analysis identified vitamin D to be correlated with neuromuscular measures, hip flexor strength (partial r = 0.16, $p<0.05$), hip extensor strength (partial r = 0.15, $p<0.05$) and Timed Up and Go Test (TUG) (partial r = 0.18, $p<0.01$) but not sensory or reaction time tasks (Table 6.3). When age was entered in as a covariate with falls status, the only variable that remained significantly correlated with 25 OHD was TUG (partial r = -0.15, $p<0.05$).

Table 6.3 Effect of vitamin D on neuromuscular control measures: with and without adjustment for falls status

	Partial Correlation 25 OHD	25 OHD Adjusted for falls status
Sensory measures		
Contrast sensitivity (dB)	0.15*	NS
High contrast visual acuity (log of MAR)	-0.16*	NS
Low contrast visual acuity (log of MAR)	NS	NS
Motor measures (muscle strength (kg))		
Ankle plantar flexor	0.14*	NS
Knee flexor	NS	NS
Knee extensor	0.16*	NS
Hip flexor	0.31**	0.16*
Hip abductor	0.31***	NS
Hip extensor	0.31***	0.14*
Hip adductor	0.25***	NS
Integration of sensory and motor measures		
Hand reaction time (milliseconds)	-0.14*	NS
Sway on Floor eyes open (mm)	NS	NS
Timed Up and Go (seconds)	-0.33***	-0.18**

Results are partial correlations with neuromuscular measure as dependent variable
MAR Maximum Arc Resolvable * p <0.05, ** p <0.01, ***p <0.001 NS not significant

6.3 Discussion

The current case control data demonstrates that fallers are significantly more likely to have a variety of deficits compared to non fallers.

Vision

Previous literature has yielded inconsistent reports in regards to the impact of impaired vision on falls. It has been suggested that contrast sensitivity, (i.e.: the ability to detect edges in a low contrast situation) may be a more accurate representation about an individual's ability to detect potential hazards at ground level [27]. Specifically, poor contrast sensitivity may increase the risk of the older person tripping on obstacles both inside (e.g.: mats, pets, coffee tables) and outside (e.g.: steps, kerbs, pavement cracks) the home. This is in contrast to visual acuity testing where the primary focus is in the measurement of fine detail.

The current study assessed both contrast sensitivity and visual acuity of participants and found both measures to be significantly associated with falling episodes. This is in contrast to other studies done by Lord and colleagues [29, 105, 106] who found contrast sensitivity rather than visual acuity to have stronger associations with fallers. The reasons for these differences may relate to sample size and patient selection differences.

Assessment of the clinical significance of the results observed in both contrast sensitivity and visual acuity requires reference to several papers which have discussed the reliability and validity of both the Melbourne Edge Test (MET) and Visual Acuity Chart [93] and normative data for contrast sensitivity values [107]. Haymes and Chen [93] report normal values for the MET based on literature published in 1986 by Verbaken and Johnston that normal values for the MET for those over 65 years of age with no ocular disease were 16 to 17 dB [108]. Our sample had higher scores for the

MET with non-fallers having a score of 19dB and fallers 18dB. Both the results of the current study and those by Verbaken and Johnston were based on the use of the 'original' MET which used a two-exposure photographic technique on semi-matte paper. More recently, establishment of normative values for use of the 'new' back-lit MET (discussed in Section 5.3 of the Reliability Study discussion) by Eperjesi and colleagues [107] demonstrated that in patients with normal vision, a reduction of 1.5 dB per decade after the age of 50 was observed. While this would yield a score of approximately 20 dB for a 70 year old, careful consideration needs to be made due to the previously reported reduced test-retest reliability of the 'new' MET version [93]. This is in part due to the fact that the 'new' version has increases in 2 dB steps up to 19 dB with 1 dB increases thereafter where the 'old' version has increases in 2 dB up to 9 dB with 1 dB thereafter. As has been discussed earlier in Section 5.3 of the Reliability Study discussion, use of finer (ie: 1 dB) steps at the more difficult end of the MET may improve the reliability for the 'new' back lit version [93, 94]. Further, results by Haymes reported an average of 1.7 dB higher score for the 'new' version compared to the 'low' version [93]. Therefore, our results are a significant contribution to existing normative data for contrast sensitivity in an older population. Specifically, it could be argued that our study utilised a more reliable method of assessing contrast sensitivity in an older female population over the age of 70 years.

Sensation

There were no differences reported between fallers and non-fallers for either touch sensation or joint position sense. According to the performance scoring of the touch thresholds proposed in the PPA falls assessment kit [91], a score of 3 indicates 'good sensation'. Therefore, the test may have not been sensitive enough to discriminate in this population. Likewise, there were minor differences in scores for joint position

sense with both groups scoring just out of the top 'good' category. Due to the nature of the groups, it is possible to speculate that the tests were not challenging enough to show any significance difference between groups.

Muscle strength

The significant differences observed in all measure of muscle strength is consistent with previous reports that identified poor measures of quadriceps and ankle dorsi-flexor strength and reaction time in multiple fallers compared to one time fallers compared to non fallers [31].

Reaction time

Our results demonstrated that hand reaction time but not foot reaction time was significantly different between fallers and non-fallers. This is consistent with results published by Lord [31] who identified reduced reaction time (hand reaction time only measured) between fallers and non-fallers. Lord argues that because simple reaction time requires an uncomplicated movement, it is focusing on the assessment of decision-time rather than movement-time thus suggesting an impairment in central nervous system processing speed in elderly fallers.

Sway

The only sway measure significantly associated with falling episodes was sway on the floor with eyes open. Comparisons for the other three measures of sway not possible using a continuous approach due to the numbers of participants unable to complete the test. This problem was discussed in both the Methodology section and the discussion for the Reliability study in that poor reliability was observed for these tests compared to the samples presented by Lord and colleagues [86]. Reasons for these differences could

be due to the differences in age between the participants presented by Lord compared to the current study. The Lord participants were aged between 50-70 years where the current study participants were all aged 70 years and over. Furthermore, the issue of task difficulty and associated floor effects have been discussed earlier as well as the potential for age related changes that may have an influence on balance.

The non completion of the most difficult sway task (ie: eyes closed on foam) was related to the increased age of the population observed and the interaction of the sensory and motor systems involved in the degree of sway an individual displays. For example, a reduction in fast-twitch muscle fibres that occur with age and the resultant loss of strength could explain the inability of the many individuals, irrespective of falls status, to complete the final sway task. Furthermore deficits in neuromuscular measures in the falls group can explain their added inability to complete the other measures of sway.

Timed Up and Go

There were significant associations between falling episodes and Timed Up and Go in that fallers were slower than non-fallers. Earlier research has reported that the Timed Up and Go was a sensitive (sensitivity=87%) and specific (specificity=87%) measure for identifying elderly individuals who are prone to falls [109]. The present results are in contrast to recent reports which state that the ability of the Timed Up and Go to classify fallers is poor, with limited clinical value [110].

Co-correlation of physical tests

The co-correlation of the physical tests highlights the inherent difficulties in assessing the complex and multifactorial domain of functional performance and falling episodes. This is further supported when examining the strength of the difference between fallers

and non-fallers in the Timed Up and Go test – an overall test of functionality, thus supporting the notion that overall deficits in neuromuscular control in fallers are evident and that it's components need to be carefully considered when determining a causal relationship with falls incidence.

Vitamin D status and components of the Physiological Profile Assessment

These results demonstrate that elderly female fallers had significantly lower 25OHD status than elderly female non-fallers supporting previous cross sectional literature that has identified low vitamin D levels as an associated risk factor for falling [67-69].

The study design problem of the co-correlation of vitamin D status with falls status was dealt with by adjusting for falls status in a univariate regression model. This showed that the only tests that were significantly different were those related to muscle function and Timed Up and Go (TUG). The effect of vitamin D on several of the hip strength measures and TUG, irrespective of falling status, strongly supports previous literature [70, 111] suggesting an influence of vitamin D on muscle function.

Some literature demonstrates a significant association between low 25-hydroxyvitamin D3 (25 OHD) and reduced muscle strength [70, 71], increased body sway [69]and reduced physical function [72]. As discussed earlier, insufficiency in vitamin D has been associated with age related muscle weakness [52, 53]. Specifically a study by Bischoff-Ferrari [52], demonstrated that adults aged 60 years and above with 25 OHD levels between 40-94 nmol/L had better lower extremity musculo-skeletal function than those with 25 OHD levels of less than 40 nmol/L. This is supported by other literature that identified a loss of muscle strength and mass (sarcopenia) with vitamin D inadequacy [112, 113].

The mechanisms behind the influence of reduced muscle strength and vitamin D deficiency is supported by earlier literature published by Simpson and colleagues in 1985 [54] which demonstrated both a direct action of 1,25 OHD on muscle and higher levels of VDR expression in young cultured skeletal myocytes compared to old myocytes. However it is uncertain as to whether reduced muscle strength is due to increases in age that result directly in a reduction in VDR expression or if it is the result of low serum vitamin D levels which result in a lowered stimulatory effect on the muscle VDR [114]. Investigations by Bischoff-Ferrari and colleagues demonstrated significant reductions in VDR expression in skeletal muscle with increases in age [114]. These authors suggest several underlying mechanisms behind this reduced expression. Firstly a reduction in VDR expression may directly reduce the functional ability of the muscle cells to respond to 1,25 OHD. Second, a reduction in levels of serum vitamin D or 1,25 OHD may result in reduction in down regulation of expression of VDR. These deficits may result in impaired protein synthesis of the muscle cells, reduced type II fibres and sarcopenia.

One of the major limitations of this study is that it was an epidemiological association study. Therefore a causal relationship between vitamin D status and postural control could not be confirmed conclusively. Previous longitudinal studies have identified a role for vitamin D in improvement in measures of neuromuscular control and falls [73, 74]. However, the study populations in these studies were not selected based on a prior history of falls. Furthermore, excessive fall rates were not accounted for in individual subjects as both studies reported declines observed in the mean number of falls per subject per treatment group and not number of fallers per treatment. Complete neuromuscular assessment was not carried out to determine the relative influence of the sensory and the motor system and improvements in muscle strength reported in one of

the studies [74] were not individual strength measures but a calculated summed muscle strength score. Furthermore, these studies were limited to an 8-week [73] and 12-week [74] study treatment phase and undertaken in the northern hemisphere.

Conclusions

Because of the problem of co-correlation it is difficult using case control studies to come to clear conclusions about the causation of the complex interactions resulting increased falls propensity. Based on the deficits in the existing knowledge outlined above, further investigation by means of a randomised controlled study was warranted and is presented in the following section. In particular it was decided to pursue the effect of vitamin D deficiency as one possible correctable cause of increased falls risk.

7.0 RANDOMISED CONTROL STUDY

7.1 Overview

The randomised controlled study comprised of 302 women aged 70 to 90 years of age. Primary inclusion criteria assessed at the screening visit were having sustained a fall in the past 12 months and a 25OHD serum concentration of less than 60nmol/L. Following screening, eligible participants were randomised to receive 1000mg/d of calcium citrate and 1000 IU/d of ergocalciferol (defined as vitamin D or ergocalciferol group) or 1000mg/d of calcium citrate and matched placebo for ergocalciferol (defined as placebo or control group). Participants attended three clinic visits (Baseline, 6 months and 12 months). At each visit participants underwent anthropometry, neuromuscular and biochemistry testing. Neuromuscular testing comprised of the Physiological Profile Assessment which assessed components of the sensory and motor system and the interaction of these systems. Further assessments were carried out examining hip strength and functionality (Timed Up and Go). Falls occurrence was reviewed every six weeks either at the visit or by telephone and adverse event recording was reviewed every three months. Logistic regression was used to evaluate the effects of ergocalciferol treatment on a person's risk of falling at least once during the 12 month study period. Multinomial logistic regression was used to model the effects of treatment on first falling according to season and the effect on 1 fall or more than 1 fall. The detailed methodology for this study can be reviewed in Section 3.0 Methods and Methodology and statistical analysis explanation in Section 4.0 Statistical Analysis.

7.2 Results

Participant flow

Participant flow through the study is shown in Figure 7.1. There were 827 subjects who attended the clinic screening visit. Of this group, 558 had serum 25OHD concentrations assessed with 215 (38%) being excluded due to concentrations above 60 nmol/L. Of the 302 participants enrolled into the study, 39 (12.9%) had 25OHD concentrations below 30 nmol/L.

Baseline characteristics of participants

Baseline characteristics according to treatment group of study participants are shown in Table 7.2. There were no differences between ergocalciferol and control groups with the exception that the women in the ergocalciferol group were significantly shorter ($p<0.05$). Following adjustment for baseline age and body weight, height was positively correlated with lower limb strength, showing significant association with ankle dorsiflexion, knee flexion and extension, and hip flexion, extension, abduction, and adduction strength. There was no difference in baseline co morbidity rates between the 2 groups.

Seasonal, discontinuation/lost to follow up and compliance comparisons

As a result of the block randomisation study design, there were no seasonal differences in the number of subjects enrolled in the two treatment groups, with 77.4% and 76.1% of subjects enrolled during winter/spring randomised to the ergocalciferol group and control group respectively. There was no difference between the ergocalciferol group and the control group in the number of subjects who discontinued medication or were lost to follow-up. Compliance was assessed from tablet counting with the rate of compliance with study medication in subjects who continued to receive the medication, was 86% in both groups.

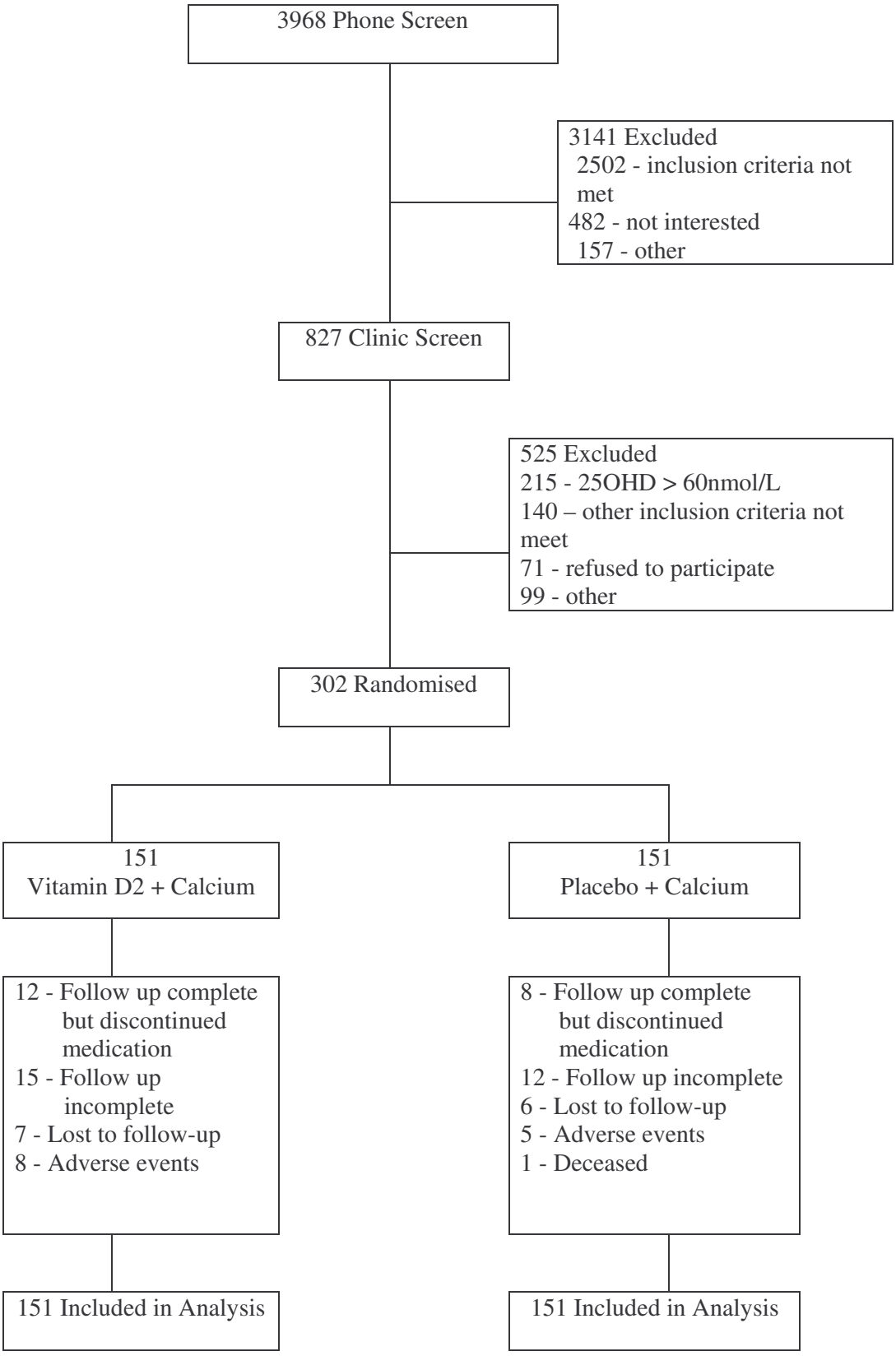


Figure 7.1 Participant flow for randomised control study

Table 7.1. Baseline characteristics of subjects

	Vitamin D + Ca (n = 151)	Placebo + Ca (n = 151)
Demography		
Age (years)	77.0 ± 4.2	77.4 ± 5.0
Mini mental state, units	28.5 ± 1.5	28.4 ± 1.6
Calcium intake, mg/day	1067 ± 484	1080 ± 426
Anthropometry		
Weight, kg	73.0 ± 13.9	71.5 ± 13.2
Height, cm	157.8 ± 6.3*	159.2 ± 6.1
Biochemistry		
25OHD, nmol/L	45.15 ± 12.59	44.28 ± 12.73
Serum calcium, mmol/l	2.43 ± 0.10	2.42 ± 0.09
Serum phosphate, mmol/l	1.18 ± 0.14	1.19 ± 0.13
Number of falls in the past 12 months, %		
1	59.6	57.6
2	27.2	26.5
3	9.9	13.2
>3	3.3	2.6
Physical activity and mobility		
Physical activity, kcal/day #	54.6 (2.9, 187.6)	52.0 (9.9, 130.0)
Timed Up and Go, seconds	11.3 ± 5.2	11.3 ± 5.3
Vision		
Edge contrast sensitivity, units	17.9 ± 2.2	18.1 ± 2.5
High visual acuity, units #	1.2 (1.0, 1.5)	1.3 (1.0, 1.6)
Low visual acuity, units #	2.2 (1.8, 3.2)	2.3 (1.7, 3.2)
Reaction time and peripheral sensation		
Hand reaction time, millisecond #	264.7 (233.2, 319.2)	264.0 (231.1, 323.4)
Foot reaction time, millisecond #	313.7 (274.3, 366.5)	323.0 (284.9, 392.7)
Tactile sensation, score	3.3 ± 1.2	3.1 ± 1.1
Proprioception, degrees	10.8 ± 8.3	10.5 ± 7.4
Lower limb muscle strength, kg		
Ankle dorsiflexion strength	11.4 ± 4.5	11.7 ± 4.3
Knee flexor strength	11.5 ± 3.7	11.7 ± 3.7
Knee extensor strength	17.7 ± 6.4	18.6 ± 7.2
Hip extensor strength	14.2 ± 5.8	14.3 ± 5.2
Hip abductor strength	11.8 ± 4.3	12.0 ± 4.8
Hip flexor strength	14.0 ± 5.0	14.4 ± 5.6
Hip adductor strength	14.0 ± 4.7	14.4 ± 5.0

Results are mean ± SD unless other wise stated, # median and interquartile range *Significantly lower than that of placebo, $p < 0.05$.

The effect of treatment on at least one fall over 12 months

Over the 12-month period, 53% (n=80) of subjects in the ergocalciferol group and 62.9% (n=95) of the control group sustained at least one fall (OR 0.66; 95%CI 0.41-1.06) (Figure 7.2). Due to the failure of the randomisation process to equalise the height of each group, the treatment group were significantly shorter (157.8±6.3cm) compared to the control group (159.2±6.1cm) (Table 7.1). Furthermore, height was a significant predictor of at least one fall (OR per cm increase in height, 0.94; 95% CI 0.91-0.98) (Figure 7.2). Further analysis demonstrated that when the effect of treatment on at least one fall was adjusted for baseline height, the ergocalciferol group had a reduced risk of falling in comparison to the control group (OR 0.61; 95% CI 0.37-0.99) (Figure 7.2). Calculation of a RR showed that the ergocalciferol group had a 19% RR reduction of falling.

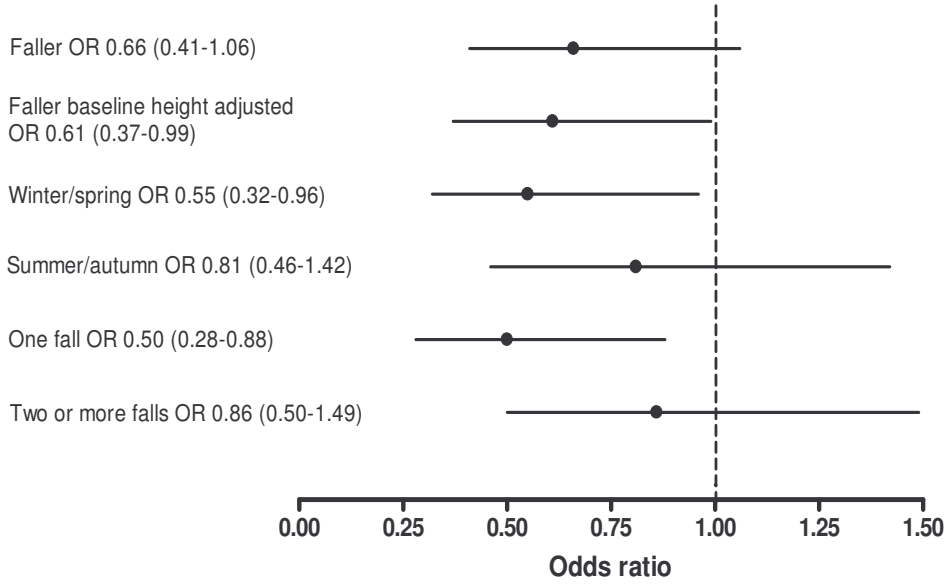


Figure 7.2 Treatment effect on falling status

The effect of treatment on falling status over 12 months

Over the 12-month study period approximately 40% of each of the treatment groups had reported a fall by 6 months (ergocalciferol 41.4%, control 40.4%). By 12 months, 62.9% of the control group had reported a fall compared with 52.3% of the ergocalciferol group (Figure 7.3).

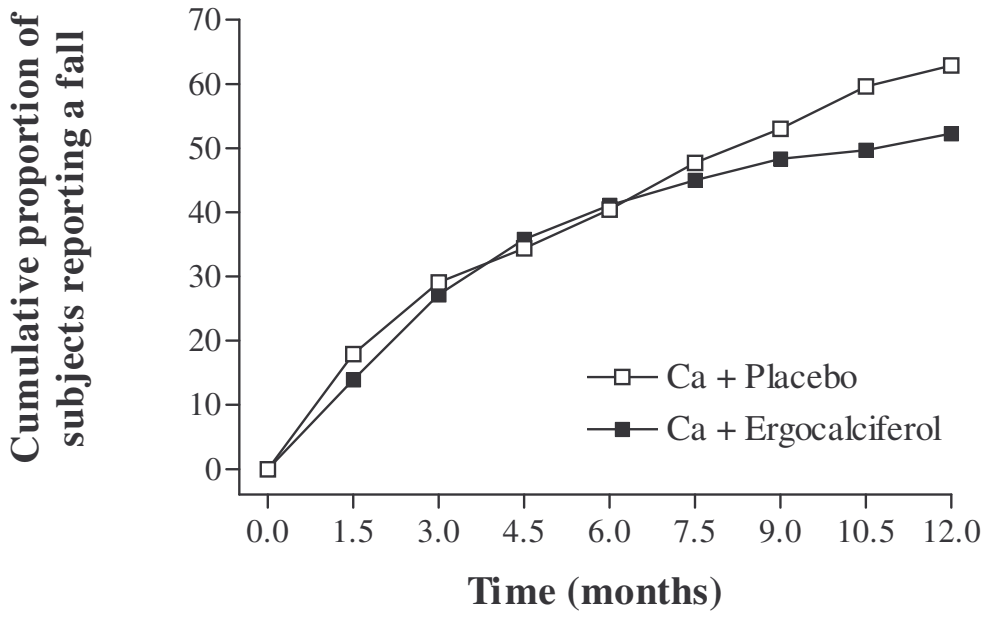


Figure 7.3 Proportion of subject reporting a fall by treatment groups

The effect of treatment on the number of falls over 12 months

The proportion of the entire group (n=302) reporting a single fall was 28% (n=83) with 31% (n=92) reporting two or more falls over 12 months. Of the entire falling population (n=175), the incidence of a single fall over 12 months was 47% (n=83) (ergocalciferol n=32 and control n=51) and 53% (n=92) for 2 or more falls (ergocalciferol n=48 and control n=44).

Multinomial logistic regression demonstrated that the ergocalciferol group were significantly less likely to sustain one fall compared to the control group (OR 0.50 95% CI 0.28-0.88). This result was not consistent for the occurrence of two or more falls where no differences were observed between the ergocalciferol and control group (OR 0.86 95%CI 0.50-1.49) (Figure 7.2).

Examination of the proportion of subjects who had fallen within each treatment code, demonstrated that 21.2% (n=32) and 31.8% (n=48) of the ergocalciferol group had sustained one fall or two or more falls respectively. In the control group, 33.2% (n=51) and 29.1% (n=44) reported one fall or two or more falls respectively (Figure 7.4). Chi square analysis demonstrated that the ergocalciferol group had a significant lower proportion of single falls, but not two or more falls, compared to the control group ($p<0.05$).

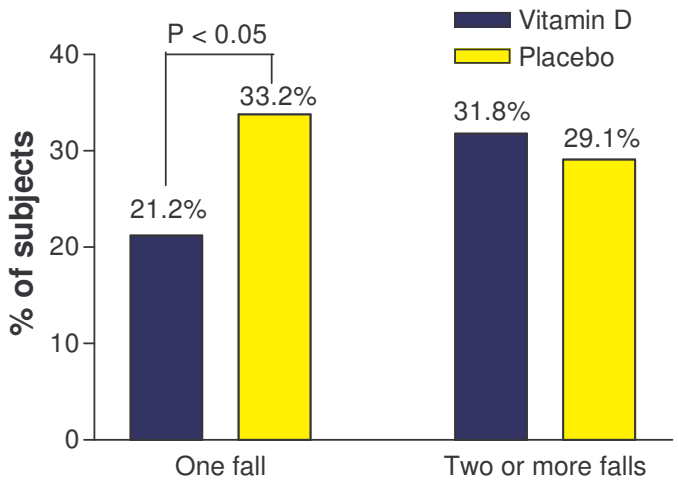


Figure 7.4 Fallers grouped by the number of falls

The effect of treatment on first fall according to season

The proportion of the entire group (n=302) reporting their first fall in winter/spring was 31% (n=92) with 28% (n=83) reporting their first fall in summer/autumn. Of the entire falling population (n=175), the incidence of the first fall in winter/spring was 53% (n=92) (ergocalciferol n=38 and control n=54) and 47% (n=83) for first fall in summer/autumn (ergocalciferol n=41 and control n=42).

Multinomial logistic regression demonstrated that the ergocalciferol group were significantly less likely to sustain the first fall in winter/spring compared to the control group (OR 0.55; 95% CI 0.32-0.96). This result was not consistent for the first fall in summer/autumn where no differences were observed between the ergocalciferol and control group (OR 0.81; 95%CI 0.46-1.42) (Figure 7.2).

Examination of the proportion of subjects who had at least one fall within each treatment code, demonstrated that 27.8% (n=42) and 25.2% (n=38) of the ergocalciferol group had their first fall in summer/autumn and winter/spring respectively. In the control group, 27.2% (n=41) and 35.8% (n=54) reported their first fall in summer/autumn and winter/spring respectively (Figure 7.5). Chi square analysis demonstrated that the ergocalciferol group had a significant lower proportion of a reported first fall in winter/spring, but not summer/autumn compared to the control group ($p<0.05$).

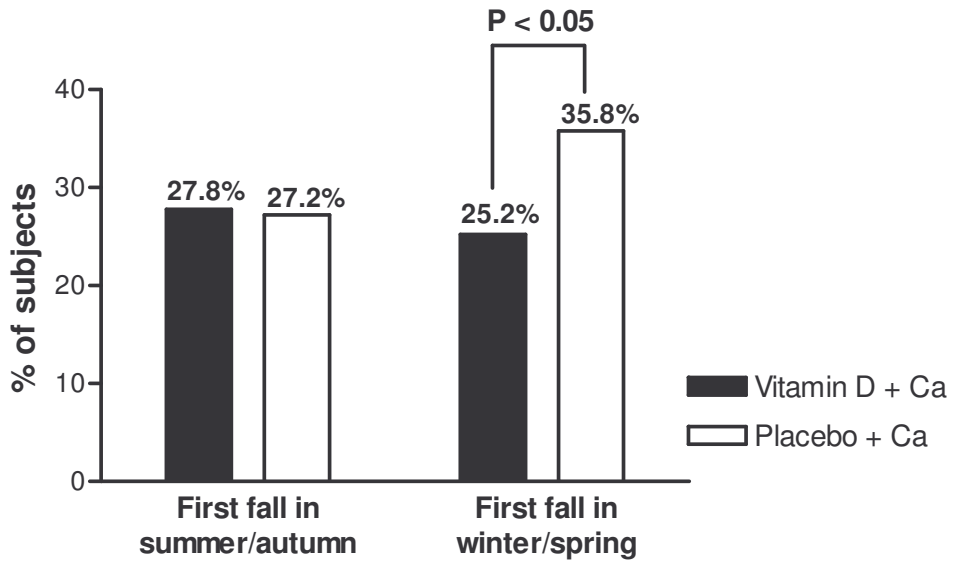


Figure 7.5 Proportion of subjects according to season of first fall

The effect of treatment on vitamin D status during the trial

Supplementation significantly improved 25 OHD status in summer/autumn and winter/spring whereas the status of the control group only improved in summer/autumn (Figure 7.6). Compared to the control group, mean circulating 25 OHD levels were 28.1% higher in the ergocalciferol group during winter/spring and 12.5% higher during summer/autumn.

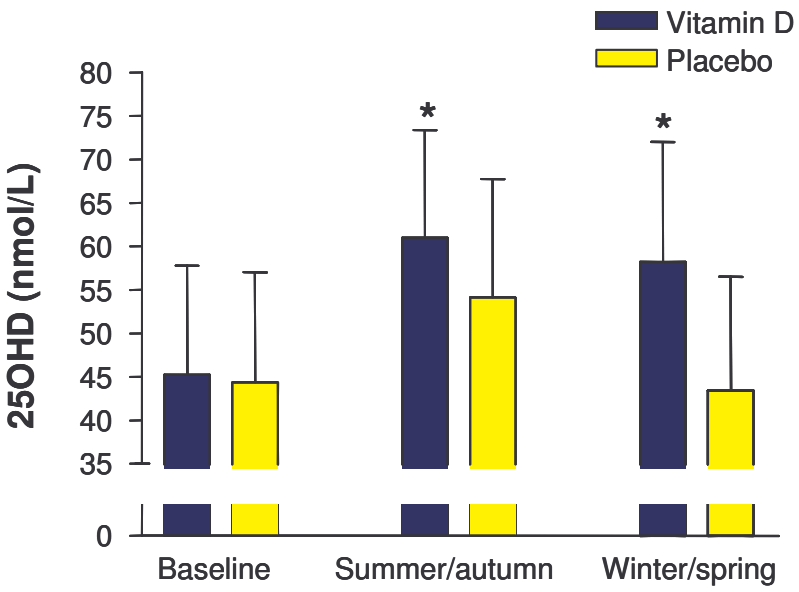


Figure 7.6 Vitamin D status during the trial *p<0.05

The effect of treatment on neuromuscular outcomes

In those in the lowest tertile for hip adductor and extensor strength and the slowest TUG tertile at baseline treatment with ergocalciferol improved outcomes compared to the control group (Figure 7.7).

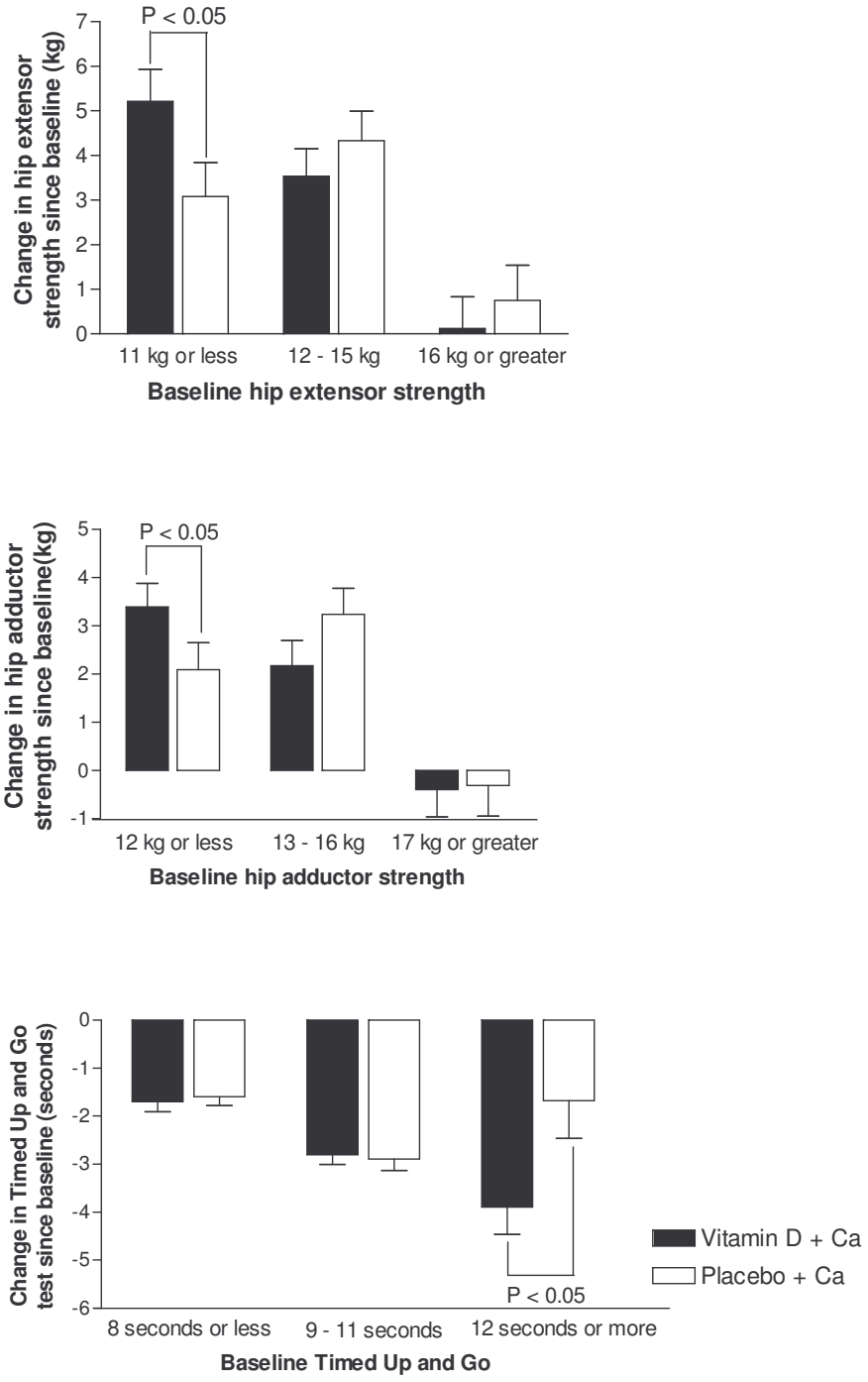


Figure 7.7 Treatment effects on muscle strength and mobility

Adverse events

There were no differences observed between the treatment groups, throughout the course of the study for the rate of incident cancer, ischemic heart disease, stroke, constipation or fracture (Figure 7.8). One participant in the ergocalciferol group had mild asymptomatic hypercalcemia on one occasion.

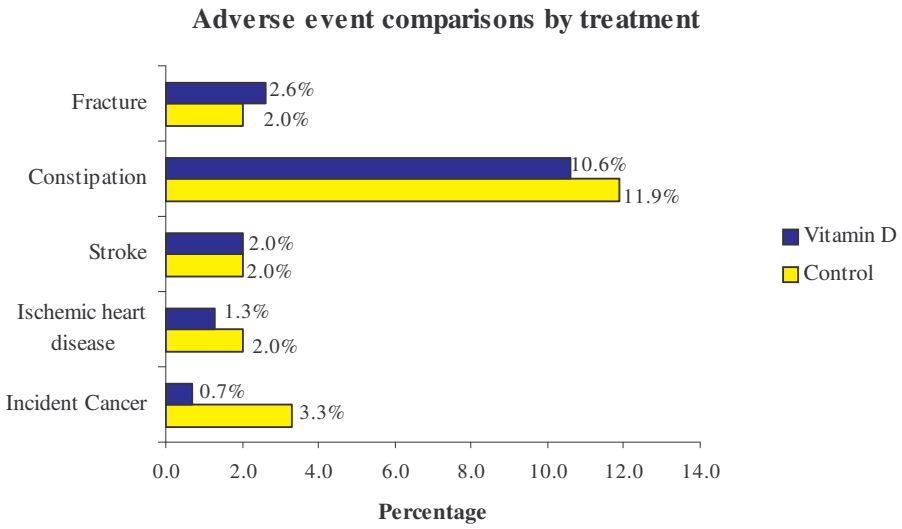


Figure 7.8 Comparisons of adverse events by treatment group

7.3 Discussion

The current study demonstrated a 19% reduction in the relative risk of community dwelling elderly females with vitamin D insufficiency and a history of falling following supplementation with ergocalciferol and calcium.

This is consistent with a recent meta analysis of randomised controlled trials [75] where a 20% reduced risk of falling in older adults who have been treated with vitamin D had been demonstrated. More specifically, this meta analysis showed that a review of 5

RCT's (n=1237) demonstrated a 20% reduced risk of falling in older adults who have been treated with Vitamin D. As reported earlier, sub group analysis shows that this is irrespective of type of vitamin D administered, duration of therapy and gender.

The current study also presented new findings in that the treatment group only experienced this significant reduction in falling episodes in the winter/spring season. This highlights the critical role that season plays in the variation of 25 OHD levels. The current study demonstrated that oral supplementation of ergocalciferol was only effective in reducing falls in the winter months when participants were unable to utilise the opportunity of increased exposure to UVB compared to the summer months. This supports suggestions in a previous study [115] that identified an increase in the risk of falling in winter. Specifically, this earlier research identified an increase in the rate of falls in winter. The population examined were 70 years and over. Interestingly, this effect was only observed in women, not men.

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This underlying theme of increased risk of falls and related injury is demonstrated in several studies conducted in Sydney [116] and New York [117] that reported a higher incidence of hip fracture in colder months. Lau and colleagues in Sydney [116] reported a consistent seasonal pattern for hip fracture incidence. This pattern demonstrated a peak during the winter months for hip fracture with mean daily minimum temperature being the single independent and consistent variable with monthly admission rates. This was in comparison to other weather variables such as, mean cloud cover, number of days with strong wind, number of days of fog, number of days of mist and number of days with 0.1 mm or more rainfall in a month. This is further supported by literature in the northern hemisphere that demonstrated an increased incidence of hip fracture in colder months [117] with supporting evidence that

it was ambient temperature that remained the primary associate of hip fractures as opposed to precipitation effects caused by rain or snow. Finally, in direct comparison to the climate in the present study, previous research in Perth demonstrated a relationship between 25OHD levels in hip fracture patients and ambient sunshine and exposure and ambient sunshine in the two months prior to the fracture incident [118].

The seasonal variation observed in the current study was potentially amplified due to the Mediterranean climate. In consideration of the latitude of Perth (32^{o}S) when comparing to the results of other studies presented in a recent meta analysis by Bischoff-Ferrari and colleagues [75], it is possible to speculate that the climate of Perth was enough to sustain those on placebo during the summer months. This supports recent suggestions by Holick [43] that at latitudes above 37^{o}N and below 37^{o}S, sunlight is insufficient in the winter season to mobilise the synthesis of vitamin D3.

The present study supports schools of thought that there appears to be an optimal level of 25OHD status where the individual is likely to enjoy the greatest benefits. As discussed earlier, performance in functional assessments that aim to reflect the requirement of the lower extremities for functioning in everyday activities (i.e. 8 foot walk test and the sit to stand test) was assessed [52]. Greatest improvement in the speed of performance was reported at concentrations between 22.5- 40 nmol/L and slightly less, yet still significant improvements seen in the range of 40-94 nmol/L. This signifies that the lower the initial vitamin D status, the greater the improvement; up to 40 nmol/L. After 40 nmol/L steady improvements in lower extremity function can still be made up to 95 nmol/L.

This supports findings of the present study that demonstrated improvements in several of the hip strength measures and the Timed Up and Go in those who were in the poorest performing tertile receiving vitamin D. This is supported by the Case Control Study performed discussed in the previous section which demonstrated an effect of vitamin D on muscle strength and functionality. Explanations for this effect on strength and function have been presented in the discussion section of the Case Control Study (Section 6.3). Specifically, this relates to the concepts of either a direct ageing effect with a subsequent reduction in VDR expression, the presence of low serum vitamin D levels resulting in lowered stimulatory influences on the muscle VDR or a combination of both. Further, a major association of an allelic variant of the vitamin D receptor genotype with muscle strength in elderly non obese women has been previously identified [56]. This suggests a genetic predisposition of strength decline may be linked to the vitamin D receptor. It has been suggested by Boland [53], that this effect might be mediated by de novo protein synthesis which affects muscle cell growth.

While the direct mechanism remains uncertain, what is clear is that there appears to be a common pathway that is shared by a variety of related components namely muscle strength, falls, fractures and vitamin D deficiency. This is more than a suggestion. Vitamin D deficiency appears to result in clinically significant muscle weakness. This is both at a cellular and clinical level. Specifically, Sorensen in 1979 demonstrated an increase in the cross sectional area and relative number of type II muscle fibres in 11 osteoporotic elderly women [111] following treatment with 1-α-hydroxyvitamin D. Clinically and more recently, improvements in sway [73] and muscle strength and reductions in falls risk [74] have resulted in suggestions pertaining to a stimulatory effect of the muscle VDR following vitamin D treatment [119].

Conversely, other studies have not shown any correction in muscle weakness following supplementation with 700 IU of vitamin D and 500mg of calcium for three years [120] and 400 IU units of vitamin D for two years [121]. These studies however, did not have falls outcome as a primary outcome, vitamin D doses were relatively low and participants were not selected due to a vitamin D deficient status.

The current study reported a treatment effect on those who had sustained a fall but not those who had multiple falls. This indicates that those who have a history of frequently falling are complex with a number of problems contributing to their frailty levels which may not be able to be treated with vitamin D alone. This example of supplementation of frail groups is supported by a recent study [122] that examined the role of vitamin D supplementation on falls prevention in older hospital inpatients following administration of 800 IU of vitamin D3 plus calcium to 216 patients aged 65 years and over in an acute geriatric unit in Scotland. Whilst falls were lower in the treatment group this was not statistically significant. Further, time to first fall was longer in treatment group but not statistically significant. Author suggestions for this non-significant result were due to the frailty and high levels of co morbidity and mortality.

The current study did not demonstrate a significant difference between treatment groups and proportion of participants who fell until the 12-month assessment. This is in contrast to other studies who have been able to identify falls reduction after a 8-week [73] and 12-week [74] study treatment phase. However, the limitations of these studies have been discussed earlier in that they report declines observed in the mean number of falls per subject per treatment group and not number of fallers per treatment thus making comparisons difficult.

There are several weaknesses to the current study. Firstly, differences in height between treatment groups were not accounted for in the randomisation process. In this study, height proved to be an important covariate as represented in other studies [123]. It is postulated that those who are shorter may have weaker leg muscle strength.

Secondly, whilst not necessarily a limitation, a stronger treatment effect may have been observed if cholecalciferol (vitamin D3) and not ergocalciferol (vitamin D2) had been used. This has been discussed in an earlier study by Armas and colleagues [124] who evaluated the relative potency of the vitamin D2 and vitamin D3 in 30 men aged between 20 and 61years over 30 days. Subjects were grouped as i) controls ii) one tablet of 50 000 IU vitamin D2 or iii) 10 tablets of 5000 IU vitamin D3. Results indicated that serum calciferol concentrations at day one and three were approximately equal, indicating that the absorption for either vitamin D2 or D3 was comparable. The mean change in total 25OHD (adjusted for mean seasonal change as demonstrated in control group), after day three demonstrated a fall for the vitamin D2 group back to baseline measures by day 14. Conversely, mean 25OHD for the vitamin D3 group continued to rise through day 14. By day 28 it had dropped slightly but was still higher than the highest mean 25 OHD change for the vitamin D2 group. It was suggested that the decline observed for the vitamin D2 group is a result of a substantially more rapid metabolism or clearance of the vitamin D2 metabolite. Further suggestions discuss the possibility that the vitamin D-binding protein (DBP) has a higher affinity for vitamin D3 resulting in a longer circulating half-life than vitamin D2 [124, 125].

Finally, the concept of ‘reliability of end points’ has previously been discussed in Section 5.3. It is a worthwhile discussion point that the end points of the current study

be considered differently in consideration of the degree of reproducibility of the measurements and the power of the randomised controlled study. The reliability study was able to identify which measures had poor reproducibility (e.g. sway) and is reflected in the non-reporting of this data for the randomised controlled study. It is likely that in consideration of the population and the difficulty of the tasks, the reproducibility of these measures would be improved by methodology related to improved familiarisation with equipment and the use of laboratory based equipment.

Conversely, the strengths of the current study were that it was a double-blind, randomised, placebo controlled study design. Furthermore, falls outcome was rigorously followed and reported on a 6 weekly basis.

The current study provides a solid background and contribution to existing literature on the issue of vitamin D, falls and in particular muscle strength. Associations between muscle strength, falls, fracture and vitamin D deficiency indicate a clinically important problem with strong recommendations as to further treatment and research into these areas. Ideally, a randomised controlled trial that examined falls and strength outcomes along with examination of VDR expression in muscle tissue would be an extremely useful and interesting contribution to this complex arena.

Furthermore, the current study emphasises the need for monitoring of vitamin D levels in additional to other fall related risk factors. Current recommendations vary, according to the relative age and deficiency of the individual. Previous suggestions have recommended an intake of 800-1000 IU per day in order to reduce the risk of fracture and 3000-5000 IU per day for at least a month to treat deficiencies [42]. In consideration of the definition of deficiency being levels of less than 50 nmol/L [45]

and the current group having mean baseline vitamin D levels of approximately 45 nmol/L, it is possible to speculate that community dwelling women over the age of 70 years of age with a history of falls require *at least* 1000IU per day to reduce the risk of future falls.

8.0 CONCLUDING COMMENTS AND FUTURE DIRECTIONS

Research into the relationship between neuromuscular control and it's relationship with vitamin D status is in its infancy. This is in consideration of the level of consistent and applicable knowledge available. The consequential nature and impact on function of low vitamin D status either directly or indirectly through falling episodes is complex and interesting.

The applicability of current knowledge is difficult due to differing populations, methodologies and interpretations. Furthermore, the complexity and multifactorial nature of factors associated with aging and falls in general have historically been a challenge to extrapolate cause and effect. However, the consistency in the core findings make it possible to identify key issues that allow focus on both future research directions and current application in a clinical and rehabilitative setting.

The aims of this thesis focused on methodology, associations and a causal relationship between neuromuscular control and vitamin D status. The difficulty highlighted with utilisation of a reliable, valid and accurate measure of balance, strength, reaction time, vision and peripheral sensation, which could still be used within a clinical and rehabilitative setting, was highlighted in the reliability study. Comparisons to another well-recognised research institution led by Stephen Lord in Sydney identified high levels of agreement with many assessments but lower levels of agreement on contrast sensitivity, touch sensation, reaction time and the majority of the sway measures. This may be attributed to the fact that the patients assessed in this thesis were older and frailer. This made scoring less reproducible and underlines the problem of developing reliable neuromuscular testing for varying patient categories

Examination of a group of fallers compared to non-fallers identified differences in weight, vitamin D status, vision, muscle strength, hand reaction time, sway and Timed Up and Go. This could not however, conclusively confirm a causal relationship between vitamin D and neuromuscular control in fallers because of the case control study design. These findings demonstrate a significant vitamin D effect on muscle strength and function, irrespective of falls status. Comparisons of the existing results with similar literature highlighted the difficulty in generalisations due to differing methodologies. Furthermore, research examining this demographic in an Australian setting was limited therefore warranting a randomised controlled trial.

The 12 month randomised controlled trial demonstrated several key issues. Firstly, a 19% reduction in the Relative Risk of community dwelling elderly females with vitamin D insufficiency and a history of falling following supplementation with ergocalciferol and calcium was demonstrated. Secondly, this risk reduction was only observed during the winter/spring months and was only applicable to one-time fallers. Furthermore, supplementation proved effective in improving functionality (as assessed by Timed Up and Go) and strength (Hip Adductor and Extensor) for those who were the slowest and weakest only. Finally, these effects were not observed until the 12-month assessment.

These results are of interest. Firstly, they suggest the climate of Perth and other similar temperate zones may be enough to sustain adequate levels of vitamin D in the summer thereby reducing falls. Secondly, the strength of the treatment can only be applied to those who have fallen once. That is, those with multiple falls are more complex in nature and while vitamin D may assist, a wider intervention is required to achieve any improvements in fall reduction. Finally, the length of time taken to see the effect could be due to the type of vitamin D used.

In conclusion, these results indicate that in temperate climates at latitude 32^{o}S, it is suggested that maintenance of 25OHD levels averaging 55 nmol/L for community dwelling vitamin D deficient women and 60nmol/L for those at risk of falling should be considered with dosage levels dependent on the relative deficiency of the patient.

In examination of the three studies overall, the current thesis reported similar levels of reliability for the Physiological Profile Assessment (PPA) as previously published. Furthermore, the PPA was able to distinguish between fallers and non-fallers in the case control study. The randomised controlled study highlighted that vitamin D deficiency is a major correctable cause of falling. Furthermore, there appears to be a 'window of opportunity' for neuromuscular deficits to be corrected with supplementation. Specifically, this relates to improvements observed in those who were weakest in the study but in comparison to the greater population outside of the study, are least disabled. Finally, changes in neuromuscular control following supplementation could not be identified through use of the PPA.

A multifactorial problem such as falling and a complex population of older individuals requires an individualised and multidisciplinary approach in the rehabilitation setting. Review of biochemical, physiological and psychological measures of each individual person is crucial in providing a tailored approach to prevention and treatment in order to minimise the devastating impact of falls on this population.

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10.0 APPENDIX ONE: FALLS QUESTIONNAIRE

The following questionnaire was administered at baseline, 6 weeks, 3 months, 4.5 months, 6 months, 7.5 months, 9 months, 10.5 months and 12 months.

1. No of falls in the last __ months

2. First Fall

First Fall Where

1. On the one level
2. In the shower/bath
3. Getting out of bed
4. Getting out of a chair
5. Walking up or down stairs
6. Whilst climbing on a chair/ladder
7. In the garden, street, shops etc

First Fall Activity

1. Exercising
2. Housework
3. Gardening
4. Shopping
5. Other

First Fall Movement

1. Standing still
2. Standing up (e.g. out of bed, chair or off toilet)
3. Getting out of bath/shower
4. Sitting down (e.g. onto chair or toilet)
5. Starting to walk
6. Stopping walking
7. Walking in a straight line
8. Walking but changing direction
9. Walking up stairs
10. Walking down stairs
11. Walking up ramp
12. Walking down ramp
13. Other

First Fall Direction

1. forwards
2. sideways
3. backwards
4. off bed/chair
5. other

First Fall Cause 1

1. A Trip *(defined as catching one's foot and losing balance)*
2. A Slippery Surface *(a slip is defined as sliding accidentally and losing balance)*
3. I Felt Faint
4. I Felt Dizzy/Giddy
5. I Lost My Balance
6. My Legs Gave Way
7. I Was Affected By Medications
8. I Was Affected By Alcohol
9. I'm Not Sure - I Was Suddenly on the Ground

First Fall Cause 2 }
First Fall Cause 3 } as per cause 1
First Fall Cause 4 }

First Fall Injury y/n? (Yes/No)

First Fall – injuries sustained1

1. Bruises
2. Cuts/Grazes
3. Broken Bone
4. Dislocations
5. Sprains
6. Back Pain
7. Other
8. None

First Fall – Fracture Site 1

1. Shoulder
2. Elbow
3. Wrist
4. Vertebrae
5. Hip
6. Knee
7. Ankle

First Fall – injuries sustained 2 }
First Fall – Fracture Site 2 }
First Fall – injuries sustained 3 } as per injuries and fracture site 1
First Fall – Fracture Site 3 }
First Fall – injuries sustained 4 }
First Fall – Fracture Site 4 }

Time spent on ground

1. No time spent
2. Between 0 and 5 minute
3. Between 5 and 15 minutes
4. Between 15 and 30 minutes
5. Between 30 minutes and 1 hour
6. More than 1 hour

Did you seek medical assistance? (Yes/No)

If you were 30 years younger and in the same circumstances, do you think you would have fallen?

(Yes/No)

As a result of the fall, have you lost confidence in walking?

(Yes/No)

Note: For multiple falls, this questionnaire was repeated for each fall episode.

11.0 APPENDIX TWO: INSTRUCTIONS - CONTRAST SENSITIVITY

"This test measures how well you can see an edge like a crack in the pavement of the edge of a gutter. As you can see there are 2 cards in this test. I want you to look at this (big) one but not touch it, as it is an unprotected photo. I want you to look at the circles one at a time (on the big chart) and tell me which way the line goes through the circle, that is, find the correct match for each one from the small card"

Source: [91]

12.0 APPENDIX THREE: INSTRUCTIONS - VISUAL ACUITY

“This test is a standard measure of vision. First of all I will get you to start with the high contrast chart – the ones with the darker letters. Read the letters out on the chart, moving down to the next line if you can.

[Record the lowest line that was correctly read and the number of letters correctly read on the line that at a distance of 3m. Repeat with the low contrast chart. If subject fails to read the top line, redo test at a distance of 1m. Score the test and convert the result using the visual acuity conversion chart (Appendix 4). Eg: If a person could only read 3 correct letters on line 9 then their score is 9-3].

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13.0 APPENDIX FOUR: VISUAL ACUITY CONVERSION CHART

VISUAL ACUITY CONVERSION CHART

Score	TEST DISTANCE 3M	1M
60-1	-	30.00
60-2	-	30.00
60-3	**10.00**	**30.00**
36-1	9.00	27.00
36-2	8.00	24.00
36-3	7.00	20.00
36-4	**6.00**	**18.00**
30-1	5.80	17.40
30-2	5.60	16.80
30-3	5.40	16.20
30-4	5.20	15.60
30-5	**5.00**	**15.00**
24-1	4.80	14.40
24-2	4.60	13.80
24-3	4.40	13.2
24-4	4.20	12.6
24-5	**4.00**	**12.00**
20-1	3.87	11.60
20-2	3.73	11.20
20-3	3.60	10.80
20-4	3.47	10.40
20-5	**3.33**	**10.00**
15-1	3.17	9.50
15-2	3.00	9.00
15-3	2.83	8.50
15-4	2.67	8.00
15-5	**2.50**	**7.50**
12-1	2.40	7.20
12-2	2.30	6.90
12-3	2.20	6.60
12-4	2.10	6.30
12-5	**2.00**	**6.00**
9-1	1.90	5.70
9-2	1.80	5.40
9-3	1.70	5.10
9-4	1.60	4.80
9-5	**1.50**	**4.50**
7.5-1	1.45	4.35
7.5-2	1.40	4.20
7.5-3	1.35	4.05
7.5-4	1.30	3.90
7.5-5	**1.25**	**3.75**
6-1	1.20	3.60
6-2	1.15	3.45
6-3	1.10	3.30
6-4	1.05	3.15
6-5	**1.00**	**3.00**

Score	TEST DISTANCE 3M	1M
5-1	0.97	2.90
5-2	0.93	2.80
5-3	0.90	2.70
5-4	0.87	2.60
5-5	**0.83**	**2.50**
4-1	0.80	2.40
4-2	0.77	2.30
4-3	0.73	2.20
4-4	0.70	2.10
4-5	**0.67**	**2.00**
3-1	0.63	1.90
3-2	0.60	1.80
3-3	0.57	1.70
3-4	0.53	1.60
3-5	**0.50**	**1.50**

If subject fails to see any letters at 1m
- give score of 30.00

17

Source: [91]

14.0 APPENDIX FIVE: INSTRUCTIONS - TOUCH THRESHOLDS

“This test measures sensation in the leg. As you can see there are eight rods, and attached to the end of each one is a plastic hair. The hairs on the end of the rods range from very thick (easy to feel) to very fine (hard to feel). I am going to find out the finest one of these hairs that you can detect on the tip of the ankle. I’ll demonstrate this first on the palm of your hand”.

[Place a thick rod on hand].
“This is a thick hair, so it is easy to feel”.

[Place a fine hair on hand].
“This is a fine hair so it is difficult to feel”

[Next follow with A-B test.]
“I’m now going to place a hair on your ankle once again. I’ll say ‘A’ then I’ll say ‘B’. I want you to tell me if the hair is placed on your ankle exactly when I say ‘A’ OR exactly when I say ‘B’.

[Record finest hair detected in the A-B test].

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15.0 APPENDIX SIX: INSTRUCTIONS - PROPRIOCEPTION

“This test measures what we call proprioception which is how well you can judge position and movement of your body segments. For this test I will place this sheet of Perspex between your legs. Now, raise both you legs together, (in a pigeon-toed action) and attempt to match the position of your big toes, so that if the plastic sheet were not there, you toes would be touching. OK, match them again a bit lower down. Now, a bit higher up. Now I want you to do the same thing again five times, but with your eyes closed. When you match them, keep them still so I can measure how accurate you are and don’t move them until I tell you.”

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16.0 APPENDIX SEVEN: INSTRUCTIONS - REACTION TIME

HAND

"This test is a test of your reaction time. A light will come on here and I want you to tap this button as fast as you can when the light comes on. So that you don't waste any time you can rest your finger on the surface of the button, provided it does not make a clicking noise. Is the switch box in a comfortable place?"

[Give 2 or 3 pre-practice trials to make sure they understand the procedure].

"OK, the emphasis is on speed so just concentrate on the light. We are going to this 20 times – the first 10 will be practice, then there will be 10 more after that"

[Reaction times that are notable slow, ie more than 150-200 msecs above "normal values' or notably fast (jumping the gun) ie less than 150 msecs.]

FOOT

"Now we are going to do another reaction time test, but this time I want to measure how quickly you can respond by moving your foot. The light will come on here and I want you to press your foot down on the pedal as fast as you can when the light comes on. So that you don't waste any time you can rest you foot on the pedal provided it does not make a clicking noise. Is the pedal in a comfortable place?"

[Give 2 or 3 pre-practice trials to make sure they understand the procedure]

"OK, the emphasis is on speed so just concentrate on the light. We are going to do this 20 times – the first 10 will be practice, then there will be 10 more after that."

[Reaction times that are notable slow, ie more than 150-200 msecs above "normal values' or notably fast (jumping the gun) ie less than 150 msecs.]

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17.0 APPENDIX EIGHT: INSTRUCTIONS - STRENGTH TESTS

Positioning of strap for each strength measure:

Ankle: Over foot at point which foot can exert greatest force.

Knee: Above ankle, just below end of calf muscle.

Hip: Above knee, just below end of quadriceps.

General instructions depending on site of measurement:

"This test measures the strength in the ankle/knee/hip muscles. I'm going to place a strap around your foot/back of shin/above knee."

[For ankle]

"Now, cross your arms, keep your heel on the footrest and forcefully raise the front of your foot – as strongly as you can. Rest, now again – as strongly as you can" etc,

[For knee]

"Hold on to the chair for support, now slowly and forcefully pull your leg back from the knee/push against the strap as strongly as you can. Rest, now again – as strongly as you can. See if you can do better" etc.

[For hip]

"Hold on to the chair for support, now slowly and forcefully pull your leg away from your midline as strongly as you can. Rest, now again – as strongly as you can. See if you can do better" etc. [Patient is in a standing position and moves clockwise so flexors/abductors/adductors/extensors are all assessed].

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18.0 APPENDIX NINE: INSTRUCTIONS - SWAY TEST

FLOOR

"This is a balance test. I'm going to put a strap around your waist. OK, now line up the insides of your feet on either side of this card. Now I want you to stand as still as you can for 30 seconds with your eyes open. Look slightly down and do not talk".

[Repeat with eyes closed]

FOAM

"Now I want you to very carefully step onto the middle of this piece of foam. Now line up the insides of your feet on either side of this card. Now stand as still as possible for 30 seconds. Again, look slightly down and do not talk. I am standing right here beside you and can support you if you lose balance"

[Repeat with eyes closed]

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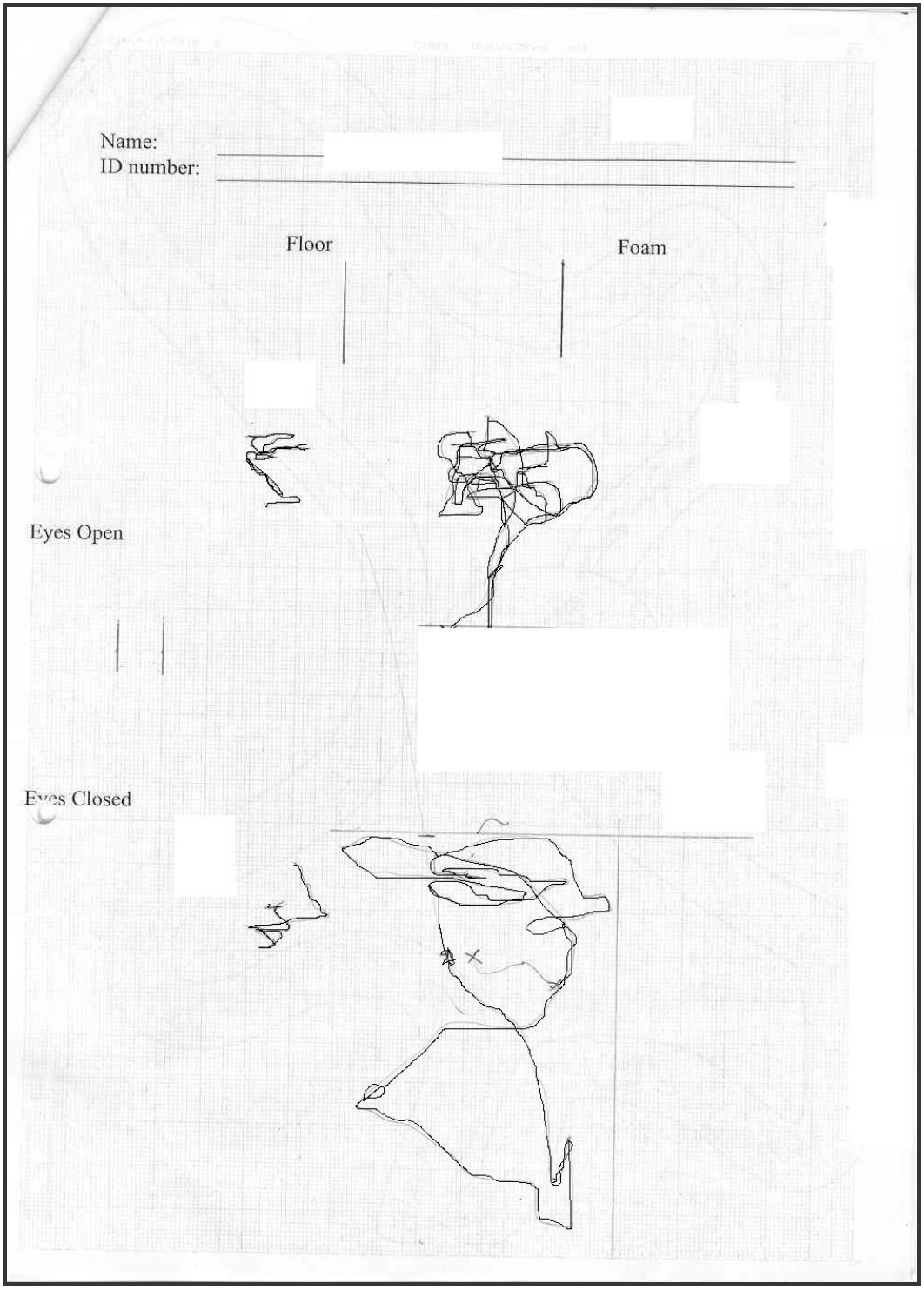
19.0 APPENDIX TEN: EXAMPLE OF SWAY TEST RESULTS



20.0 APPENDIX ELEVEN: PUBLICATIONS AND CONFERENCE PROCEEDINGS

Publications arising from this thesis

Prince, R.L., **Austin, N**. Devine, A. Dick, I. M. Bruce, D. Zhu, K.., *Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women.* Arch Intern Med, 2008. **168**(1): p. 103-8.

Other publications published during the thesis

Austin, N., Devine, A. Dick, I. Prince, R. Bruce, D., *Fear of falling in older women: a longitudinal study of incidence, persistence, and predictors.* J Am Geriatr Soc, 2007. **55**(10): p. 1598-603.

Zhu, K. **Austin, N.** Bruce, D. Devine, A. Ebeling, P. Prince R., *A randomised controlled trial of the effects of calcium with or without vitamin D on bone structure and bone related chemistry in elderly women with vitamin D insufficiency* JBMR **Accepted for publication**

Conference proceedings attended during the thesis

Quinn*, N., Bruce, D. Devine, A. Dhaliwal, S. Dick, I. and Prince ,R., *Determinants of Fear of Falling at 3 Years in Elderly Women:Effects of Incident Fracture.* Poster presentation for Australia and New Zealand Bone & Mineral Society, Annual Scientific Meeting 2002, Adelaide Australia

Quinn*, N., Devine, A. Dhaliwal, S. Dick, I. and Prince ,R., *Long term impact of perceived health on future falls and fracture in healthy elderly women. .* Poster presentation for Australia and New Zealand Bone & Mineral Society, Annual Scientific Meeting, 2003 Noosa, Australia.

Quinn*, N.,* Devine, A. Lloyd, D. Dhaliwal, S. Dick, I. and Prince ,R., *Reduced Hip Strength and Increased Weight are Associated with Falling in Healthy Elderly Women.* Oral presentation for International Society for Posture and Gait Research, 2003, Sydney Australia.

Austin, N., Devine, A. Dick, I. Zhu, K. and Prince R., *Vitamin D Status and Effects on Postural Control In Fallers and Non-Faller.* Poster presentation for Australia and New Zealand Bone & Mineral Society, Annual Scientific Meeting, 2007 New Zealand.

* Maiden name for Nicole Austin

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