Leisure time physical activity and long-term cardiovascular and cancer outcomes: The Busselton Health Study.

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Abstract

The study aimed to investigate whether meeting leisure time physical activity recommendations was associated with reduced incident and fatal cancer or cardiovascular disease (CVD) in a community-based cohort of middle- to late-aged adults with long-term follow-up. At baseline, 2,320 individuals were assessed on a large number of lifestyle and clinical parameters including their level of physical activity per week, other risk factors (e.g. smoking and alcohol use) various anthropometric measures, blood tests and medical history. Individuals were linked to hospital and mortality registry data to identify future cancer and cardiovascular events (fatal and non-fatal) out to 15 years of follow-up. Cox regression analyses adjusted for relevant confounders identified *a priori* were used to estimate risk for all-cause, cancer-specific and CVD-specific mortality. In the full cohort an estimated 21% decreased risk for all-cause mortality (HR 0.79; 95% CI 0.66 - 0.96) and 22% decreased risk for fatal/non-fatal CVD events (HR 0.78; 95% CI 0.66 – 0.92) was associated with baseline self-reported physical activity levels of 150 minutes or more. After exclusion of those with chronic co-morbidities (CVD, cancer, diabetes, chronic obstructive pulmonary disease, hypertension treatment) at baseline, lower risk for fatal/non-fatal CVD events remained significantly associated with 150 minutes or more of physical activity (HR 0.77; 95% CI 0.62 – 0.96). Results from this well established prospective community-based cohort study support the role of leisure time physical activity in reducing all-cause mortality and CVD events (fatal/nonfatal) in the broader population studied. The data also suggest that physical activity associated reductions in risk for CVD events (fatal/nonfatal) were not overly impacted by prevalent key non-communicable diseases.

Background

Physical activity has gained increased notoriety for its role in prevention and improved prognosis of a number of non-communicable diseases, including cancer, cardiovascular disease, diabetes and chronic respiratory diseases [1]. It has been estimated [2, 3] that 150 minutes of moderate intensity physical activity per week may reduce risk for ischaemic heart disease (IHD) by approximately 30%, and breast and colon cancer by 21-25%. The national physical activity guidelines for Australians recommend 30 minutes of moderate intensity activity for adults on most days of the week or 150 minutes over 5 or more sessions [4]. Other countries have similar guidelines for adults, such as the 2008 physical activity guidelines for Americans [5] which recommends at least 150 minutes per week of moderate-intensity or 75 minutes vigorous-intensity activity per week.

Life expectancy is heavily influenced by physical activity, with physically active individuals reportedly able to achieve an estimated 30% risk reduction in all-cause death [6].

Improvements in CVD-specific survival have also been reported [6-8], in addition to improved cancer-specific survival for some cancer types [9-11].

Despite the mounting evidence estimating the degree of benefit gained from regular physical activity in terms of improving survival, differences in study follow-up periods, physical activity measurement, accuracy of outcome measurements, and availability of information on confounding factors lead to heterogeneity between studies. Information on co-morbid conditions, for example, has generally been self-reported and may be incomplete and/or may be prone to recall bias. Whilst the use of self-report is often the most efficient method for retrieving information on lifestyle factors, the use of medical records for identification of morbidities provides greater certainty regarding their accuracy.

The aim of this study was to investigate leisure time physical activity (LTPA) in relation to incident and fatal cancer and cardiovascular disease in a well characterised community-based cohort of middle-aged and older adults with long-term follow-up. Our study contained measurement of key confounding factors such as blood pressure, blood markers and anthropomorphic measurements, in addition to self-reported LTPA information. Furthermore,

linking the study's data with hospital admission and mortality allowed us to accurately obtain hospital related co-morbidities diagnosed by medical professionals.

Methods

Study design and participants

This is a prospective community-based cohort study. Invitations to participate were sent to adults listed on earlier Electoral Registers (registration to vote is compulsory in Australia) for the Busselton district and people were asked to complete a questionnaire and present at the survey centre in 1994/95 for a range of tests and blood collection. The Busselton community is almost entirely of white Caucasian background. A total of 4,843 adults participated in the survey (response rate 57%), after restricting to age 45-84 years this became 2,724 and, after excluding 372 who had missing data on key variables, this became 2,352. To avoid reverse causality (i.e. that participants stopped or reduced physical activity because they were very ill), we also omitted 32 participants who died within the first two years of follow-up thus leaving 2,320 for the main analyses. All participants gave informed consent and the 1994/95 survey was approved by the Human Research Ethics Committee of The University of Western Australia.

Baseline measurements and follow-up outcome events

The conduct and measurements of the 1994/95 Busselton health survey have been described previously [12]. Survey participants were asked to complete a comprehensive health and lifestyle questionnaire and to undergo various measurements and tests including anthropometry, spirometry, blood pressure and fasting blood samples were collected. Blood pressure (systolic and diastolic) was measured using a mercury sphygmomanometer after five minutes rest in a sitting position. Anthropometric measures were obtained by trained survey staff using standardised protocols. Smoking history, alcohol consumption, minutes of moderate- and vigorous-intensity leisure time physical activity per usual week, diabetes and medications were obtained by questionnaire. Alcohol consumption was labelled 'light' if consumption was ≤ 140 g/week and 'heavy' if > 140 g/week. Body mass index was defined as weight (kg) divided by height (m) squared. Blood measures available for this analysis include serum total and HDL cholesterol, plasma glucose and C-reactive protein (CRP).

The Human Research Ethics Committee of the Department of Health of Western Australia gave permission to access the hospital admission, cancer and death records from 1 January 1980 to 31 December 2010 using record linkage to the Western Australian Hospital Morbidity Data System, which records all hospital admissions to public and private hospitals in Western Australia, as well as cancer registrations and deaths [13]. International Classification of Diseases, 9th revision (ICD-9) codes were used for events up to 30 June 1999, and ICD-10 codes for subsequent events. History of cardiac and other conditions at baseline were defined as having any hospital admission for that condition during the 15 years before the survey (i.e. 1980 to 1994). The history variables based on hospital admissions were coronary heart disease (ICD9 410-414), atrial fibrillation (ICD9 427.3), heart failure (ICD9 428) and stroke (ICD9 430-437). A composite history of cardiovascular disease variable was based on coronary heart disease, atrial fibrillation, heart failure and stroke. History of cancer was based on non-skin cancer registrations (ICD10 C00-C42, C45-C97). Diabetes was based on self-reported doctor-diagnosed diabetes or on diabetes treatment (tablets/insulin) at the survey or a history of hospital admissions (ICD9 250). History of hypertension treatment was based on self-reported taking of anti-hypertensive medications at the survey or a history of hospital admissions for hypertension (ICD9 401-405). History of chronic obstructive pulmonary disease (COPD) was based on a history of hospital admissions (ICD9 490-496) or percent predicted FEV1 < 60% as measured at the survey.

Outcome events during the 15 year follow-up period from survey attendance to the end of 2010 were ascertained from hospital admission, cancer and death records. Five outcome events were analysed. Time to death from any cause, time to death from cardiovascular diseases (ICD9 390-459; ICD10 I00-99, G45), time to death from cancer (ICD9 140-200; ICD10 C00-C97), time to first fatal or non-fatal cardiovascular event defined as a hospital admission with a principal diagnosis of coronary heart disease (ICD9 410-414; ICD10 I20-25), stroke (ICD9 430-437; ICD10 I60-68, G45), congestive heart failure (ICD9 428; ICD10 I50), peripheral arterial disease (ICD9 440-448; ICD10 I70-79) or death from cardiovascular disease, and time to first fatal or non-fatal cancer event defined as a non-skin cancer registration (ICD10 C00-C42, C45-C97) or death from cancer.

Statistical analysis

Variables with skewed distributions were log transformed for use in regression models and descriptive results for these variables are presented in both untransformed and transformed scales. LTPA was calculated as (minutes/week of moderate intensity activities) + 2 × (minutes/week of vigorous intensity activity), as recommended by the Australian Institute of Health and Welfare [4]. Cox regression models for time from 1994/95 survey to first outcome event were used to obtain adjusted hazard ratios (and their 95% confidence intervals) for LTPA, considered both as a continuous variable (in minutes/week) and also as a dichotomous variable (0-149, 150+ minutes/week) where 150 minutes/week is the recommended level of physical activity sufficient for health benefits [4]. Results from Cox regression models are presented as estimated hazard ratios (with 95% confidence interval and p-value). Results are presented for the full cohort and also after excluding those with a chronic condition at baseline (cardiovascular disease, diabetes, cancer, COPD). The proportional hazards assumption was checked and found to apply for all outcomes.

Results

Table 1 shows the characteristics of the cohort overall and by LTPA <150 vs 150+ minutes/week. Overall, a total of 55% were female, mean age was 62 years, 9% were current smokers, 20% were moderate/heavy drinkers of alcohol, 6-10% of the cohort had each of the chronic conditions diabetes, cardiovascular disease, COPD and cancer and 24% had at least one of these chronic conditions, 29% had a history of treatment for hypertension, and the BMI, blood pressure, lipid and glucose profile is typical of middle aged and older community samples around that time. The overall mean LTPA was 221 minutes/week or 3.7 hours/week and 43% met the recommendation of at least 150 minutes/week.

The number of incident and fatal outcome events for the full cohort and after excluding those with a chronic condition at baseline is shown in Table 1. With 300 or more observed events there is over 85% power to detect a relative risk reduction of 30% (i.e. hazard ratio of 0.7) or greater when comparing the LTPA 150+ mins/week group to the <150 mins/week group. This cohort therefore has excellent power for deaths (all causes) and incident cancer and incident cardiovascular events.

Table 2 shows the adjusted hazard ratio estimates associated with an increase of 60 mins/week of LTPA (from the continuous LTPA model) and for the comparison of LTPA 150+ mins/week group to the <150 mins/week group. The models based on the full cohort have adjusted for relevant confounders and history of chronic conditions and the models based on the sub-cohort without chronic conditions have adjusted for relevant confounders. LTPA was a significant ($p<0.05$) independent risk factor for overall mortality (i.e. all cause death) in the full cohort but not in the sub-cohort without chronic conditions. LTPA as a continuous or dichotomous variable was not a significant independent risk factor for fatal and incident cancer in the full cohort and sub-cohort. However, LTPA was a significant independent risk factor for incident cardiovascular events in both the full cohort and sub-cohort. There was an estimated 22% relative risk reduction for 150+ versus < 150 mins/week ($p=0.003$) and 1.8% reduction for each additional 60 mins/week ($p=0.034$) in the full cohort and relative risk reductions of 23% ($p=0.019$) and 2.6% ($p=0.019$) respectively in the sub-cohort. The estimated relative risk reductions for fatal cardiovascular disease were similar to those for incident cardiovascular disease but these did not always reach statistical significance (due to lower statistical power). We also tested, via an interaction, whether the effect of LTPA on each outcome was significantly different for those aged < 65 years and 65+ years but none of these interaction tests reached statistical significance (ie all $p>0.05$).

Discussion

In this community-based cohort study, participants reporting leisure-time physical activity at recommended guidelines of 150 minutes or more had significantly and clinically relevant reduced risk (adjusted for confounding factors) out to 15 years for fatal or non-fatal CVD events. Risk for death from all causes was also reduced in those meeting physical activity guidelines; however there was no evidence of reduced risk for fatal or non-fatal cancer events in relation to increasing levels of physical activity. Generally, these associations (or lack thereof) appeared to be independent of participants' existing chronic comorbid conditions at baseline.

Physical activity has long been associated with healthy living and evidence exists for the benefits of physical activity in terms of reducing all-cause mortality risk [14-17], cardiovascular events and mortality, and cancer survival. Despite this, exercise as a treatment

option remains under-utilised by health professionals and, as a prevention measure, recommended physical activity levels are met only by approximately 40% of the adult community [18]. In part, a perceived lack of importance may be held by health professionals due to the relative lack of clinical trials in the area of exercise medicine [8], compared to pharmaceutical trials. The ease of medication use compared to the perceived time and effort taken to exercise is also likely to reduce its uptake by individuals. It is important therefore to conduct adequately powered clinical trials and longitudinal cohort studies in local populations to confirm and emphasise (both for medical professionals and at-risk individuals) the level of benefit potentially achievable for individuals.

Results from our longitudinal cohort study showed a 22% decreased risk of all-cause death during the study period was associated with performing 150 minutes or more leisure-time physical activity per week. The reduction in observed risk is in line with evidence from previous large cohort studies, however estimates do differ between studies [14, 19, 20]. In 2007, Leitzmann *et al.* reported 27-32% decreased risk of all-cause mortality, within their longitudinal cohort study of 252,925 individuals, in those performing recommended amounts of moderate- or vigorous-intensity leisure-time or recreational physical activity [20]. Their greater reduction in risk is likely attributable to the reference group containing only those considered inactive whereas our reference group contained those who did not achieve recommended levels. A recent longitudinal study on a US cohort by Behrens *et al.* [21] also found a significant, albeit lesser, 14% reduced risk for all-cause mortality over a similar follow-up to our study for those who met their recommended level of physical activity. The difference in magnitude of benefit could relate to a number of factors including differences in age restriction, race composition, and prevalence of other risk factors (smoking, diet, alcohol use, etc). Moreover, differences may be attributable to the use of 'leisure-time' physical activity in our study whereas Behren's study measured 'any' physical activity - including activity at work. Our use of leisure-time physical activity was based on the methodologies recommended by the Australian Institute of Health and Welfare [4] in order to allow comparison with other Australian studies in this area, who are likely also to follow this methodology.

Mechanisms and pathways through which physical activity may reduce all-cause mortality reduction are many-fold [22, 23]. One set of conditions for which physical activity seems to play a vital role in are cardiovascular conditions. Leisure-time physical activity has been implicated in lowering CVD occurrence [23, 24], hospitalisation [25] and survival [26, 27]. CVD is the leading underlying cause of death in Western Australia [28], Australia [29], and a majority of Western countries [30]. In our cohort, 150 mins or more of LTPA per week was associated with a 28% reduction in risk for death from CVD, and a 22% reduction in fatal + non-fatal CVD events. These risk estimates are similar to those from another observational study recently conducted within Western Australia, which found a 21% decreased risk for IHD-hospitalisations associated with performing 150 minutes or more of moderate/vigorous intensity LTPA per week [25]. The inverse relationship between moderate- and high-intensity LTPA and CVD risk has also been reported in a number of other international cohorts. A recent meta-analysis of 23 prospective epidemiological studies reported a 24% reduced risk for coronary heart disease (RR=0.76; 95% CI 0.71-0.81) in those with moderate levels of LTPA compared to those with low levels of LTPA [31]. Comparatively, those with high levels of LTPA were at approximately 34% reduced risk (RR=0.66; 95% CI 0.60-0.72) compared to those with low levels of LTPA [31].

It has been proposed that cancer incidence [32] and more so, survival following cancer [9, 33-36], may be associated with physical activity. In terms of physical activity's role in reducing cancer incidence, most evidence relates to colon, breast and endometrial cancers. Similarly, the positive association of physical activity on cancer survival has not been demonstrated for the majority of cancer types, with the exception of colon, breast and possibly prostate cancer [11]. The lack of association between LTPA and cancer-specific survival (or non-fatal + fatal cancer events) in our study may therefore relate to the aggregation of cancer types. Unfortunately we were unable to test this due to inadequate power for detecting associations with cancer type-specific outcomes – particularly cancer-mortality.

One of the major strengths of this study was the ability to retrieve all post-survey records related to hospital admissions, mortality and cancer diagnosis. This enabled long-term follow-up of key outcomes out to 15 years for the cohort, with sufficient incident events for

excellent power to detect significant differences in likelihood of the CVD-specific events (fatal + non-fatal), cancer-specific events (fatal + non-fatal), and all-cause mortality. Other strengths of this study include the generalisability of the study to the predominantly white Caucasian Busselton community which is likely to be representative of the broader Western Australian white Caucasian community. The corresponding limitation is that study results may not accurately reflect the relationship between physical activity and the various outcomes in non-Caucasian populations residing in Western Australia. A limitation of many observational studies is the inability to adequately control for confounding variables. In our study however, relevant anthropometric measures were obtained in addition to information on other chronic comorbid conditions and self-reported behavioural and lifestyle factors. This allowed for good control of confounding factors during analysis of the data.

In summary, results from this study suggest 150 minutes or more of moderate to vigorous intensity physical activity per week were associated with reduced future fatal/non-fatal cardiovascular events and all-cause mortality out to 15 years following baseline measurement of physical activity levels. We cannot definitively exclude the possibility that physical activity is acting as a surrogate marker for other risk factors (such as obesity). However our adjustment for key confounding factors, including BMI, suggests physical activity may act as an independent risk factor against cardiovascular events and all-cause mortality.

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Conflict of Interest: The authors declare no conflict of interest.

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Table 1: Characteristics of the study cohort (n=2,320) and number of outcome events. Table shows mean (SD) or percent unless otherwise indicated.

Characteristic	LTPA < 150 (n = 1,314)	LTPA ≥ 150 (n = 1,006)	All (n = 2,320)
LTPA (minutes/week)	15 (38)	491 (307)	221 (312)
LTPA 150+ minutes/week (%)			43.4
Gender			
Men (%)	45.7	44.5	45.2
Women (%)	54.3	55.5	54.8
Age (years)	62.8 (10.8)	60.6 (9.5)	61.9 (10.3)
Marital status			
Married or defacto (%)	79.1	82.6	80.6
Other (%)	20.9	17.4	19.4
Occupation			
Manager/Administrator	15.4	14.3	15.0
Professional/Para-professional	7.5	10.6	8.9
Tradesperson	5.1	3.8	4.5
Clerk/Sales person	6.2	8.9	7.4
Plant & machine operator/Labourer	20.2	17.6	19.1
Home duties	7.8	7.6	7.7
Independent means/Pensioner	32.8	33.2	33.0
Unknown	4.9	4.0	4.5
Smoking			
Never (%)	51.7	49.7	50.8
Ex (%)	38.2	41.8	39.8
Current (%)	10.1	8.4	9.4
Alcohol drinking			
Non (%)	10.0	6.7	8.6
Ex (%)	12.6	9.3	11.2
Light (%)	53.7	58.4	55.7
Moderate/Heavy (%)	18.9	22.5	20.5
Unknown (%)	4.7	3.1	4.0
Diabetes(%)	8.7	6.2	7.6
History of cardiovascular disease(%)	12.1	6.5	9.7
History of COPD(%)	7.4	4.9	6.3
History of cancer(%)	5.7	5.7	5.7
BMI (kg/m ²)	27.1 (4.3)	26.0 (3.8)	26.7 (4.1)
SBP (mmHg)	131 (18)	128 (18)	130 (18)
DBP (mmHg)	77 (10)	76 (10)	76 (10)
History of hypertension treatment(%)	33.5	22.6	28.8
Cholesterol (mmol/L)	5.95 (1.09)	5.88 (1.00)	5.92 (1.05)
HDL (mmol/L)	1.37 (0.41)	1.44 (0.41)	1.40 (0.41)
Glucose (mmol/L)*	4.90	4.90	4.90
	(4.60, 5.40)	(4.60, 5.20)	(4.60, 5.30)
log Glucose (mmol/L)	1.63 (0.20)	1.60 (0.16)	1.62 (0.18)
CRP*	2.10	1.50	1.80
	(1.00, 4.20)	(0.70, 3.30)	(0.80, 3.70)
log CRP	0.67 (1.19)	0.37 (1.18)	0.54 (1.19)

Number of outcome events
(full cohort n = 2,320)

Deaths (all causes)	384	185	569
Deaths (cardiovascular)	173	65	238
Deaths (cancer)	97	67	164
Fatal and non-fatal events (cardiovascular)	455	227	682
Fatal and non-fatal events (cancer)	314	214	528
Number of outcome events (excluding those with chronic conditions n = 1,764)			
Deaths (all causes)	197	121	318
Deaths (cardiovascular)	81	37	118
Deaths (cancer)	56	44	100
Fatal and non-fatal events (cardiovascular)	252	145	397
Fatal and non-fatal events (cancer)	218	158	376

*Median (inter-quartile range)

Table 2: Adjusted hazard ratios (95% confidence interval) for LTPA in relation to outcome events.

Full cohort	Death (all causes) ²	Death (cardiovascular) ³	Fatal or non-fatal event (cardiovascular) ³	Death (cancer) ⁴	Fatal or non-fatal event (cancer) ⁴
LTPA (minutes/week) ¹	0.980 (0.963 , 0.998)	0.977 (0.949 , 1.007)	0.984 (0.968, 1.000)	0.995 (0.967 , 1.025)	0.994 (0.978 , 1.011)
p-value	0.030	0.131	0.053	0.758	0.480
LTPA 150+ mins/week	0.794 (0.661 , 0.954)	0.735 (0.545 , 0.991)	0.791 (0.670 , 0.934)	0.989 (0.718 , 1.364)	0.899 (0.753 , 1.074)
p-value	0.014	0.044	0.005	0.948	0.242
Excluding those with chronic conditions	Death (all causes) ⁵	Death (cardiovascular) ⁵	Fatal or non-fatal event (cardiovascular) ⁵	Death (cancer) ⁶	Fatal or non-fatal event (cancer) ⁶
LTPA (minutes/week) ¹	0.979 (0.957 , 1.002)	0.974 (0.935 , 1.015)	0.977 (0.956 , 0.998)	0.986 (0.948 , 1.026)	0.985 (0.965 , 1.006)
p-value	0.076	0.207	0.032	0.499	0.150
LTPA 150+ mins/week	0.867 (0.683 , 1.101)	0.806 (0.530 , 1.226)	0.792 (0.640 , 0.980)	0.961 (0.640 , 1.442)	0.848 (0.688 , 1.045)
p-value	0.242	0.314	0.032	0.847	0.122

¹ Hazard ratio is for a change of 60 minutes/week in LTPA

² Adjusted for age, gender, marital status, smoking, alcohol, diabetes, history of cardiovascular disease, history of COPD, history of cancer, BMI, SBP, history of hypertension treatment, cholesterol, HDL, log glucose, log CRP

³ Adjusted for age, gender, marital status, smoking, alcohol, diabetes, history of cardiovascular disease, history of COPD, BMI, SBP, history of hypertension treatment, cholesterol, HDL, log glucose, log CRP

⁴ Adjusted for age, gender, marital status, smoking, alcohol, history of cancer, BMI, log CRP

⁵ Adjusted for age, gender, marital status, smoking, alcohol, BMI, SBP, history of hypertension treatment, cholesterol, HDL, log glucose, log CRP

⁶ Adjusted for age, gender, marital status, smoking, alcohol, BMI, log CRP