



REVIEW

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A systematic review of the evidence for Canada's Physical Activity Guidelines for Adults

Darren ER Warburton^{1,2*}, Sarah Charlesworth^{1,2}, Adam Ivey^{1,2}, Lindsay Nettlefold^{1,2}, Shannon SD Bredin³

Abstract

This systematic review examines critically the scientific basis for *Canada's Physical Activity Guide for Healthy Active Living* for adults. Particular reference is given to the dose-response relationship between physical activity and premature all-cause mortality and seven chronic diseases (cardiovascular disease, stroke, hypertension, colon cancer, breast cancer, type 2 diabetes (diabetes mellitus) and osteoporosis). The strength of the relationship between physical activity and specific health outcomes is evaluated critically. Literature was obtained through searching electronic databases (e.g., MEDLINE, EMBASE), cross-referencing, and through the authors' knowledge of the area. For inclusion in our systematic review articles must have at least 3 levels of physical activity and the concomitant risk for each chronic disease. The quality of included studies was appraised using a modified Downs and Black tool. Through this search we identified a total of 254 articles that met the eligibility criteria related to premature all-cause mortality (N = 70), cardiovascular disease (N = 49), stroke (N = 25), hypertension (N = 12), colon cancer (N = 33), breast cancer (N = 43), type 2 diabetes (N = 20), and osteoporosis (N = 2). Overall, the current literature supports clearly the dose-response relationship between physical activity and the seven chronic conditions identified. Moreover, higher levels of physical activity reduce the risk for premature all-cause mortality. The current Canadian guidelines appear to be appropriate to reduce the risk for the seven chronic conditions identified above and all-cause mortality.

Introduction

There is considerable literature supporting the importance of habitual physical activity in the primary and secondary prevention of varied chronic conditions [1-16]. Routine physical activity is thought to be of benefit for over 25 chronic conditions [17]. Seven chronic diseases in particular have been associated with a physically inactive lifestyle including coronary artery disease, stroke, hypertension, colon cancer, breast cancer, type 2 diabetes (diabetes mellitus) and osteoporosis [18-20].

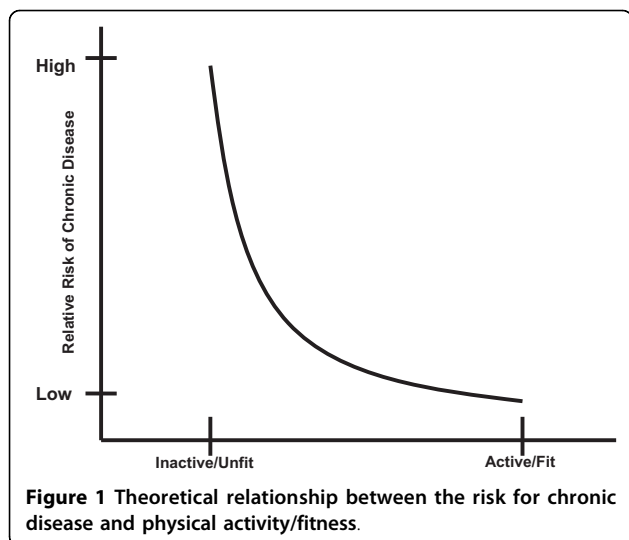
Canada has played a leading role in the development of physical activity guidelines for individuals across the lifespan. This includes the development (in 1998) of "Canada's Physical Activity Guide to Healthy Active Living" for adults between the ages of 20 and 55 yr [21], which was followed by "Canada's Physical Activity Guide to Healthy Active Living for Older Adults" [22], and "Canada's Physical Activity Guide to Healthy Active Living for Children and Youth" [23]. The adult

guidelines (which are now approximately 10 years old) state generally that 20-55 yr adults should accumulate 60 min of daily physical activity or 30 min of moderate to vigorous exercise on at least 4 days a week [18,19].

We reported recently that Canada's adult guidelines were consistent with other international guidelines and were supported by a compelling body of literature [18,19]. We revealed strong evidence that routine physical activity was effective in the primary prevention of cardiovascular disease, stroke, hypertension, breast cancer, colon cancer, type 2 diabetes and osteoporosis. Moreover, physical activity appears to play an important role in the prevention of obesity and obesity-related co-morbidities. However, implicit in the adult guidelines is the belief that there is a dose-response relationship between physical activity and the associated health benefits. Moreover, a central belief in these guidelines and most international physical activity guidelines is that the dose-response relationship is curvilinear with the greatest health benefits seen in physically inactive individuals who become "more physically active." In fact, a consistent pattern (shown in Figure 1) has been hypothesized, wherein

* Correspondence: darrenwb@interchange.ubc.ca

¹Cardiovascular Physiology and Rehabilitation Laboratory, University of British Columbia, Vancouver, Canada



there are marked changes in health status with relatively minor increments in physical activity/fitness in individuals that are the least active/fit. Generally, the health benefits have been thought to level off at the upper end of the physical activity/fitness continuum (Figure 1). However, recent work (such as that provided by Gledhill and Jamnik in the Canadian Physical Activity and Lifestyle Approach) has speculated that there are likely multiple dose-response curves for various endpoints [24].

The primary purpose of this systematic review was to examine critically the current literature to determine whether or not a dose-response relationship exists between habitual physical activity and chronic disease. In particular, we sought to determine whether the key messaging “Every little bit counts, but more is even better - everyone can do it!” of the adult physical activity guidelines is supported by a strong body of evidence.

Due to the breadth of literature, we have chosen to focus on the relationship between physical activity and all-cause mortality, and the seven chronic conditions that are thought to be reduced greatly with habitual physical activity (i.e., cardiovascular disease (excluding stroke), stroke, hypertension, colon cancer, breast cancer, type 2 diabetes and osteoporosis) (see Table 1). Owing to the nature of the physical activity guidelines, the emphasis of this paper was on primary prevention, despite the clear evidence that routine physical activity is also an effective secondary preventative strategy against many chronic conditions [16,18,19]. Accordingly, our primary objectives were to examine the evidence for a dose-response relationship between: 1) physical activity and all-cause mortality, and 2) physical activity and incidence of the following chronic conditions (cardiovascular disease (except stroke), stroke, hypertension, type 2 diabetes, colon cancer, breast cancer, and osteoporosis.

Table 1 Relative risks (RR) and population attributable risks (PAR%) for physical inactivity in Canada, Australia, and the USA.

Disease	Canada		Australia		USA	
	RR	PAR%	RR	PAR%	RR	PAR%
CHD	1.45	19.4	1.5	18	2.0	22
Stroke	1.60	24.3	2.0	16	na	Na
Hypertension	1.30	13.8	na	na	1.5	12
Colon Cancer	1.41	18.0	1.5	19	2.0	22
Breast Cancer	1.31	14.2	1.1	9	1.2	5
Type 2 Diabetes	1.50	21.1	1.3	13	1.5	12
Osteoporosis	1.59	24.0	1.4*	18*	2.0	18*

Source: Canadian Data [20]; Australian Data [161]; US Data: [162]. *Evaluated the incidence of falls/fractures.

Methods

Criteria for considering studies for this review

Our research team utilized a rigorous, systematic, and evidence-based approach to examine critically the levels of evidence on physical activity and the risk for premature mortality and chronic disease. Any studies that evaluated the relationship between at least **three** different levels of physical activity and mortality or incidence of chronic disease were eligible for inclusion. Therefore, excluded studies included those that examined only the most active versus least active populations (e.g., sedentary/inactive vs. physically active). Any form of physical activity/exercise measurement (e.g., self-report, pedometer, accelerometer, maximal aerobic power (VO₂ max)) was eligible for inclusion. The key outcomes were mortality and incidence of chronic disease. Only published, English language studies examining adults (e.g., 19-65 yr) were included. Participants must have previously been healthy (asymptomatic) adults without established chronic disease. There was no restriction according to study design.

To examine the relative risk reductions associated with physical activity, we calculated the mean and median risk reductions across studies focusing on the highest level versus the lowest level of physical activity/fitness. For each study we also determined whether or not a dose-response relationship was present (i.e., reflecting a progressive decrease in the risk with increasing physical activity/fitness levels).

Search strategy

Literature searches were conducted in the following electronic bibliographical databases:

- MEDLINE (1950-March 2008, OVID Interface);
- EMBASE (1980- March 2008, OVID Interface),
- CINAHL (1982- March 2008, OVID Interface);

- PsycINFO (1840- March 2008, Scholars Portal Interface);
- Cochrane Library (-March 2008),
- SPORTDiscus (-March 2008).

The Medical Subject Headings (MeSH) were kept broad. See tables 2, 3, 4, 5, 6, 7, 8 and 9 for the complete search strategy and keywords used. The electronic search strategies were created and carried out by researchers experienced with systematic reviews of the literature (DW and LN). The citations and applicable electronic versions of the article (where available) were downloaded to an online research management system (RefWorks, Bethesda, Maryland, USA).

Screening

Two reviewers (LN and SC) screened independently the title and abstract of the citations to identify potential

Table 2 Results of the MEDLINE literature search regarding all-cause mortality.

#	Searches (28 Feb 2008)	Results
1	exp Physical Fitness/	15236
2	Motor Activity/	49721
3	exp Physical Endurance/	15383
4	exp Exercise/	57742
5	exp Exertion/	88903
6	exp Sports/	71887
7	exp exercise therapy/	17231
8	exp exercise tolerance/	4192
9	exp health behaviour/	59409
10	leisure time physical activity.mp	996
11	occupational physical activity.mp	190
12	exp Pliability/	2279
13	exp Muscle Strength/	5717
14	musc\$ power.mp	965
15	exp Back/	12821
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	291635
17	dose-response.mp	321066
18	intensity.mp	142881
19	volume.mp	298471
20	exp Energy Metabolism/	206808
21	exp oxygen consumption/	83352
22	exp time factors/	763712
23	17 or 18 or 19 or 20 or 21 or 22	1651633
24	16 and 23	67698
25	exp Mortality/	190058
26	all cause mortality.mp	4618
27	25 or 26	192720
28	24 and 27	421
29	limit 28 to (english and humans and "all adult (19 plus years)")	279

Table 3 Results of the MEDLINE literature search regarding cardiovascular disease.

Search #	Searches (3 Mar 2008)	Results
1	exp Physical Fitness/	15244
2	Motor Activity/	49751
3	exp Physical Endurance/	15408
4	exp Exercise/	57806
5	exp Exertion/	88967
6	exp Sports/	71931
7	exp exercise therapy/	17243
8	exp exercise tolerance/	4205
9	exp health behaviour/	59467
10	leisure time physical activity.mp	998
11	occupational physical activity.mp	191
12	exp Pliability/	2289
13	exp Muscle Strength/	5731
14	musc\$ power.mp	965
15	exp Back/	12822
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	291817
17	dose-response.mp	321198
18	intensity.mp	142955
19	volume.mp	298620
20	exp Energy Metabolism/	206886
21	exp oxygen consumption/	83387
22	exp time factors/	764091
23	17 or 18 or 19 or 20 or 21 or 22	1652372
24	16 and 23	67760
25	exp Cardiovascular Diseases/	1411730
26	exp Heart diseases/	675083
27	exp Myocardial infarction/	116070
28	exp Death, Sudden Cardiac/	6772
29	exp Coronary Artery Disease/	18137
30	exp Coronary Disease/	144236
31	exp Vascular Diseases	1018275
32	25 or 26 or 27 or 28 or 29 or 30 or 31	1411730
33	24 and 32	9603
34	limit 33 to (english language and humans and "all adult (19 plus years)")	5544

articles for inclusion. Duplicate citations were removed. The reviewers were not blinded to the authors or journals. Biographies of key studies and reviews in the field were also cross-referenced for further articles. For those articles that appeared relevant, the full text was obtained and data was extracted using a common template. In cases of disagreement, discussion with a third reviewer (DW) was used to achieve consensus. Full (100%) consensus was achieved. All studies that were excluded during the citation and full-article screening processes were recorded along with the reasons for exclusion.

Table 4 Results of the MEDLINE literature search regarding stroke.

Search #	Searches (29 Feb 2008)	Results
1	exp Physical Fitness/	15241
2	Motor Activity/	49744
3	exp Physical Endurance/	15387
4	exp Exercise/	57764
5	exp Exertion/	88921
6	exp Sports/	71907
7	exp exercise therapy/	17237
8	exp exercise tolerance/	4196
9	exp health behaviour/	59430
10	leisure time physical activity.mp	996
11	occupational physical activity.mp	190
12	exp Pliability/	2288
13	exp Muscle Strength/	5720
14	musc\$ power.mp	965
15	exp Back/	12821
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	291718
17	dose-response.mp	321133
18	intensity.mp	142919
19	volume.mp	298526
20	exp Energy Metabolism/	206837
21	exp oxygen consumption/	83359
22	exp time factors/	763871
23	17 or 18 or 19 or 20 or 21 or 22	1651958
24	16 and 23	67720
25	exp Stroke/	45243
26	exp Cerebrovascular Disorders/	196243
27	exp Brain Ischemia/	58943
28	exp Brain Infarction/ or exp Cerebral Infarction	21357
29	exp Infarction, Middle Cerebral Artery/ or exp Intracranial Aneurysm/ or exp Subarachnoid	46725
30	Hemorrhage/ or exp Cerebral Hemorrhage/exp Ischemic Attack, Transient/	14753
31	25 or 26 or 27 or 28 or 29 or 30	196243
32	24 and 31	692
33	limit 32 to (english language and humans and "all adult (19 plus years)")	291

Data Extraction

Two reviewers (LN and SC) completed standardized data extraction forms, which were verified by two other reviewers (DW and SB). We extracted information regarding the study design, the country where the study was conducted, the participant characteristics, the sample size, the objectives of the study, the methodologies employed, the major outcomes (i.e., mortality, incidence of chronic disease, physical activity levels/classifications), and the comments and conclusions made based on the findings of the study. The reviewers were not blinded to the journal or the author names when extracting information from the articles.

Table 5 Results of the MEDLINE literature search regarding hypertension.

Search #	Searches (3 Mar 2008)	Results
1	exp Physical Fitness/	15244
2	Motor Activity/	49751
3	exp Physical Endurance/	15408
4	exp Exercise/	57806
5	exp Exertion/	88967
6	exp Sports/	71931
7	exp exercise therapy/	17243
8	exp exercise tolerance/	4205
9	exp health behaviour/	59467
10	leisure time physical activity.mp	998
11	occupational physical activity.mp	191
12	exp Pliability/	2289
13	exp Muscle Strength/	5731
14	musc\$ power.mp	965
15	exp Back/	12822
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	291817
17	dose-response.mp	3211987
18	intensity.mp	142955
19	volume.mp	298620
20	exp Energy Metabolism/	206886
21	exp oxygen consumption/	83387
22	exp time factors/	764091
23	17 or 18 or 19 or 20 or 21 or 22	1652372
24	exp Hypertension/	168466
25	exp Blood Pressure/	205571
26	exp Blood Pressure Determination/ or exp Blood Pressure Monitoring, Ambulatory/ or exp Blood Pressure Monitors/24 or 25 or 26	18244
27	16 and 23 and 27	336025
28	16 and 23 and 27	5647
29	limit 28 to (english language and humans and "all adult (19 plus years)")	3642

Level of Evidence

The approach used to establish the level and grade of evidence was consistent with that used during creation of the "Canadian clinical practice guidelines on the management and prevention of obesity in adults and children" [25]. The level of evidence provides information regarding the strength of the evidence in favour of physical activity/exercise in the primary prevention of premature mortality and the seven chronic diseases of primary interest. This evaluation process is based on a pre-defined and objective criteria (see Table 10).

The grade for each article provides information regarding whether physical activity is effective in the primary prevention of the varied conditions evaluated (Table 10). Where applicable this grade informs the reader about the potential risk of the physical activity. A study that receives the highest grading would indicate

Table 6 Results of the MEDLINE literature search regarding colon cancer.

Search #	Searches (3 Mar 2008)	Results
1	exp Physical Fitness/	15244
2	Motor Activity/	49751
3	exp Physical Endurance/	15408
4	exp Exercise/	57806
5	exp Exertion/	88967
6	exp Sports/	71931
7	exp exercise therapy/	17243
8	exp exercise tolerance/	4205
9	exp health behaviour/	59467
10	leisure time physical activity.mp	998
11	occupational physical activity.mp	191
12	exp Pliability/	2289
13	exp Muscle Strength/	5731
14	musc\$ power.mp	965
15	exp Back/	12822
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	291817
17	dose-response.mp	321198
18	intensity.mp	142955
19	volume.mp	298620
20	exp Energy Metabolism/	206886
21	exp oxygen consumption/	83387
22	exp time factors/	764091
23	17 or 18 or 19 or 20 or 21 or 22	1652372
24	exp Colonic Neoplasms/	51780
25	exp Rectal Neoplasms/	28011
26	exp Colorectal Neoplasms/	99982
27	exp Colorectal Neoplasms/, Hereditary Nonpolyposis/ or exp Intestinal Neoplasms.	117563
28	24 or 25 or 26 or 27	117563
29	16 and 23 and 28	108
30	limit 29 to (53nglish language and humans and "all adult (19 plus years)")	77

that the benefits clearly outweigh the risks and receive a strong recommendation.

Quality Assessment

The quality of each study was also established using the procedures of Gorber et al. [26]. Owing to the fact that only observational study designs were included in our systematic review, we used the Downs and Black [27] scale to assess the quality of non-randomized investigations. Similar to the work of Prince et al. [28] we chose to include the most relevant components of the scoring tool. Therefore, a modified version of the Downs and Black checklist was used with the final checklist consisting of 15 items with a maximum score of 15 points. Higher points reflected a superior quality of investigation.

Table 7 Results of the MEDLINE literature search regarding breast cancer.

Search #	Searches (28 Feb 2008)	Results
1	exp Physical Fitness/	15236
2	Motor Activity/	49721
3	exp Physical Endurance/	15383
4	exp Exercise/	57742
5	exp Exertion/	88903
6	exp Sports/	71887
7	exp exercise therapy/	17231
8	exp exercise tolerance/	4192
9	exp health behaviour/	59409
10	leisure time physical activity.mp	996
11	occupational physical activity.mp	190
12	exp Pliability/	2279
13	exp Muscle Strength/	5717
14	musc\$ power.mp	965
15	exp Back/	12821
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	291635
17	dose-response.mp	321066
18	intensity.mp	142881
19	volume.mp	298471
20	exp Energy Metabolism/	206808
21	exp oxygen consumption/	83352
22	exp time factors/	763712
23	17 or 18 or 19 or 20 or 21 or 22	1651633
24	exp Breast Neoplasms/	149817
25	16 and 23 and 24	296
26	limit 25 to (54 nglish language and humans and "all adult (19 plus years)")	216

Results

Physical Inactivity and All-Cause Mortality

A total of 2040 citations were identified during the electronic database search (Figure 2). Of these citations, 288 were identified in MEDLINE, 222 in EMBASE, 496 in Cochrane, and 1034 in the CINAHL/SportDiscus/PsychInfo search. A total of 167 duplicates were found, leaving a total of 1873 unique citations. A total of 1696 articles were excluded after scanning, leaving a total of 177 articles for full review. From these articles 130 were excluded after full review leaving 47 articles for inclusion in the systematic review. An additional 23 articles were added to the review based on the authors' knowledge of the area. The reasons for exclusion included review articles (n = 26), commentary (n = 10), did not report 3 levels of physical activity (n = 24), no objective measure of physical activity (n = 2), report (n = 15), not a formal study (n = 11), not related to all-cause mortality (n = 27), the participants were too young (n = 1), not able to retrieve articles (n = 7), and other (n = 7). Therefore, a total of 70 articles were included in the

Table 8 Results of the MEDLINE literature search regarding type 2 diabetes.

Search #	Searches (29 Feb 2008)	Results
1	exp Physical Fitness/	15241
2	Motor Activity/	49744
3	exp Physical Endurance/	15387
4	exp Exercise/	57764
5	exp Exertion/	88921
6	exp Sports/	71907
7	exp exercise therapy/	17237
8	exp exercise tolerance/	4196
9	exp health behaviour/	59430
10	leisure time physical activity.mp	996
11	occupational physical activity.mp	190
12	exp Pliability/	2288
13	exp Muscle Strength/	5720
14	musc\$ power.mp	965
15	exp Back/	12821
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	291718
17	dose-response.mp	321133
18	intensity.mp	142919
19	volume.mp	298526
20	exp Energy Metabolism/	206837
21	exp oxygen consumption/	83359
22	exp time factors/	763871
23	17 or 18 or 19 or 20 or 21 or 22	1651958
24	16 and 23	67720
25	exp Blood Glucose/or exp Diabetes Mellitus, Type 2/	132583
26	exp Hyperglycemia/	16214
27	exp Glucose Intolerance/ or exp Glucose Tolerance Test/	24986
28	exp Hyperinsulinism/	30490
29	25 or 26 or 27 or 28	165157
30	29 and 24	3006
31	Limit 30 to (english language and humans and "all adult (19 plus years)")	1985

Table 9 Results of the MEDLINE literature search regarding osteoporosis.

Search #	Searches (29 feb 2008)	Results
1	exp Physical Fitness/	15241
2	Motor Activity/	49744
3	exp Physical Endurance/	15387
4	exp Exercise/	57764
5	exp Exertion/	88921
6	exp Sports/	71907
7	exp exercise therapy/	17237
8	exp exercise tolerance/	4196
9	exp health behaviour/	59430
10	leisure time physical activity.mp	996
11	occupational physical activity.mp	190
12	exp Pliability/	2288
13	exp Muscle Strength/	5720
14	musc\$ power.mp	965
15	exp Back/	12821
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	291718
17	dose-response.mp	321133
18	intensity.mp	142919
19	volume.mp	298526
20	exp Energy Metabolism/	206837
21	exp oxygen consumption/	83359
22	exp time factors/	763871
23	17 or 18 or 19 or 20 or 21 or 22	1651958
24	exp Osteoporosis, Postmenopausal/ or exp Osteoporosis/	31532
25	exp Fractures, Bone/ or exp Bone Density/	125269
26	exp Bone Diseases/ or exp Bone Diseases, Metabolic/	308084
27	exp "Bone and bones"/	369634
28	exp Tensile Strength/	12050
29	exp Compressive Strength	2838
30	24 or 25 or 26 or 27 or 28 or 29	642158
31	16 and 23 and 30	2138
32	limit 31 to (english language and humans and "all adult (19 plus years)")	1193

systematic review of the literature regarding the relationship between physical activity and premature mortality.

The majority of the studies included in our systematic review were prospective cohort investigations (Table 11). These studies involved a total of 1,525,377 participants; averaging 21,791 participants per study (range 302-252,925). There were a total of 111,125 reported cases of premature all-cause mortality (ranging per study from 43-10,952). The total length of study follow-up for the prospective cohort studies averaged 11.1 yr (ranging from 0.5-28 yr). The articles were published over a 22 yr period ranging from 1985 to 2007. These studies involved large samples of men and women from regions throughout the world.

We observed a mean 31% lower risk for all-cause mortality in the most active individuals. The median risk reduction was 32%. It is important to highlight that many of these studies included women, with sub-analyses that revealed similar risk reductions between sexes. Our findings are consistent with previous reports [15,16,29-31]. The majority (90%) of the studies supported the health benefits of physical activity demonstrating a significant risk reduction in physically active individuals. *The level of evidence would be considered to be a Level 2A based on the presence of overwhelming evidence from observational trials.* The studies examined were generally of a good quality with a mean (and median) score of 12 out of 15 (range 10-14).

Table 10 The levels and grade of evidence scaling criteria applied to the articles.

Level of Evidence	Criteria
Level 1	Randomized control trials without important limitations
Level 2	<ul style="list-style-type: none"> • Randomized control trials with important limitations • Observational studies (non-randomized clinical trials or cohort studies) with overwhelming evidence
Level 3	Other observational studies (prospective cohort studies, case-control studies, case series)
Level 4	Inadequate or no data in population of interest Anecdotal evidence or clinical experience

Grade of Evidence	Criteria
Grade A	Strong recommendation (action can apply to most individuals in most circumstances) <ul style="list-style-type: none"> • Benefits clearly outweigh risks (or vice-versa) • Evidence is at Level 1, 2, or 3
Grade B	Weak recommendation (action may differ depending on individual's characteristics or other circumstances) <ul style="list-style-type: none"> • Unclear if benefits outweigh risks • Evidence is at Level 1, 2, or 3
Grade C	Consensus recommendation (alternative actions may be equally reasonable) <ul style="list-style-type: none"> • Unclear if benefits outweigh risks • Evidence is at Level 3 or 4

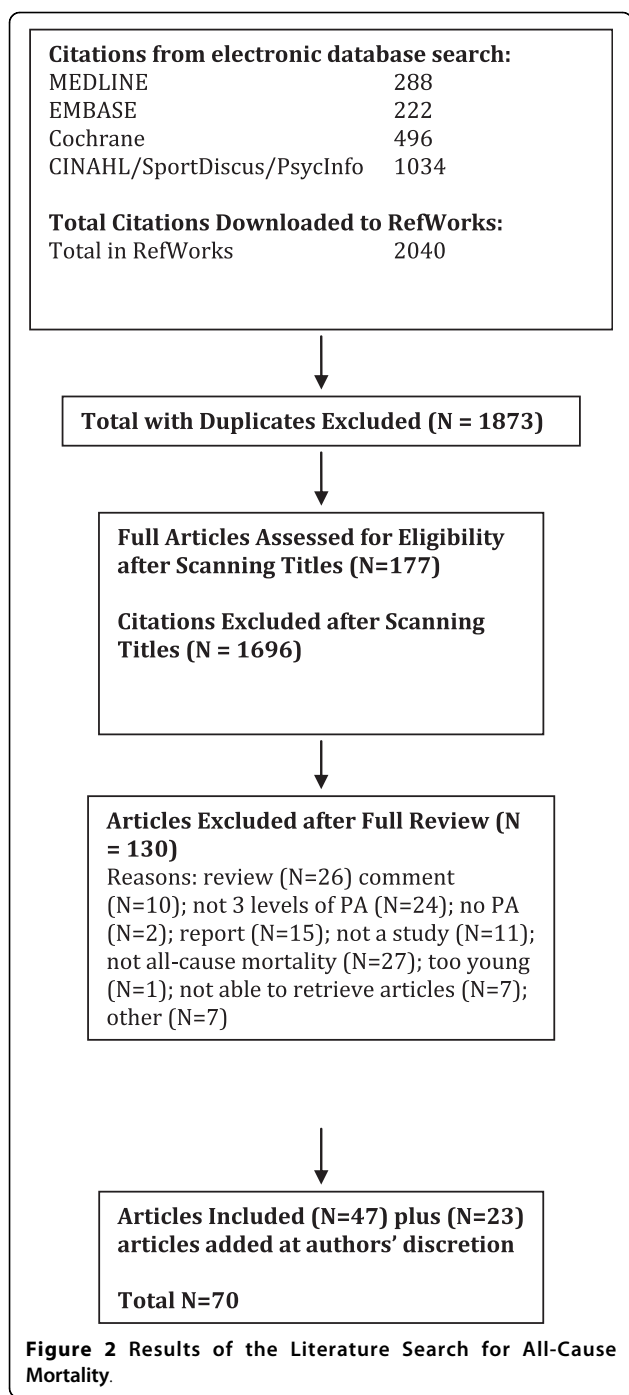
A clear dose-response relationship was also observed with marked reductions in the risk for all-cause mortality occurring with relatively small increments in physical activity (Figure 3). To examine more closely the temporal relationship between physical activity and all-cause mortality we calculated the (unadjusted) relative risks associated with incremental levels of physical activity/fitness using the reported cases of all-cause mortality and the number of participants (per group) in each investigation. In some instances, we were required to calculate the number of participants based on the reported incidence rates and person years, or based on data obtained directly from the authors (2 investigations). We were not able to obtain this information in 18 investigations, and as such this analysis was restricted to the remaining 52 investigations. There was considerable variability in the methods of classifying the physical activity/fitness levels of the participants. Accordingly, Figure 3 illustrates the mean relative risk reduction according to three separate study types including those that subdivided participants into tertiles, quartiles and quintiles, respectively. This figure demonstrates clearly the dose-response relationship between physical activity and all-cause mortality. Collectively, the literature is consistent indicating that the current Canadian guidelines (approximately 4.2 MJ/wk, 1000 kcal/wk) are associated with a 20-30% lower risk for premature all-cause mortality, with greater health benefits with high volumes and/or intensities of activity. In our analyses it was apparent that the greatest differences in risk occurred between the lowest adjacent activity/fitness categories, suggesting that sedentary individuals can markedly

reduce their risk for all-cause mortality with relatively minor increments in physical activity. This is consistent with the current messaging of Canada's physical activity guidelines.

The strength of the relationship between physical fitness and premature mortality has been well-established [6,32,33]. In our analyses there were greater risk reductions in studies that took objective measures of physical fitness. We observed an average risk reduction of approximately 45%, which was consistent between men and women. A risk reduction of greater than 50% was not uncommon in these studies. For instance, Myers et al. (2004) reported that being fit or physically active was associated with greater than 50% lower mortality risk in men. They also noted that a 4.2 MJ/wk (1000 kcal/wk) increase in physical activity, or a 1 metabolic equivalent (MET) higher physical fitness level was associated with a mortality benefit of around 20%. It is also important to highlight that longitudinal studies evaluating changes in physical activity or fitness have revealed a lower premature mortality risk [16,34-41]. As we previously reported, routine physical activity or elevated physical fitness also appears to reduce the risk for premature mortality in individuals with risk factors for chronic disease [42,43].

Implications

Since the seminal work of Morris and colleagues (in the 1950s [44,45]) and the early work of Paffenbarger (in the 1970s [46,47]) there has been considerable research (especially epidemiological evidence) documenting the health benefits of engaging in routine physical activity and/or being physically fit [17,48]. Both physical activity



(a behaviour) and physical fitness (an attained state) appear to be related to health status in a dose-dependent fashion, with physical fitness demonstrating the strongest relationship [18,19]. Numerous reports indicate that physical inactivity and/or low physical fitness are associated with an increased risk for chronic disease and premature all-cause and disease-specific mortality [2,43,49-51]. Some of the most compelling research includes the relationship between physical activity/

fitness and all-cause mortality. As demonstrated below and in Table 11 and Figure 1, this literature is extensive.

The assessment of the relationship between all-cause mortality is complicated by the inclusion of deaths related to suicides, homicide, and accidents [18,19,52]. Nonetheless, the available evidence is incontrovertible; individuals who are habitually physically active and/or physically fit are at a markedly reduced risk for premature all-cause mortality [15,16,18,19]. In Canada, physical inactivity is a major cause of premature mortality from diseases of the cardiovascular system (33.3%), cancers (29.1%), and type 2 diabetes (3.5%) [53]. Globally, physical inactivity has been linked with 2 million premature deaths per year, including 22% of cases of coronary heart disease, and 10-16% of cases of breast cancer, colon cancer, rectal cancer and type 2 diabetes [54]. As such, the promotion of the health benefits of physical activity is of paramount importance for the effective prevention of chronic disease and premature mortality on a national and international scale.

In summary, there is a clear dose-response relationship between physical activity and premature all-cause mortality. Physically active individuals have an approximate risk reduction of 31% in comparison to physically inactive individuals. When objective measures of aerobic fitness are taken the risk reductions are even greater approximating 45%.

Recommendation #1

For a reduced risk for premature mortality, it is recommended that individuals should participate in 30 min or more of moderate to vigorous exercise on most days of the week. Greater health benefits appear to occur with higher volumes and/or intensities of activity. [Level 2, Grade A]

Primary Prevention of Cardiovascular Disease

In our systematic search of the literature, a total of 9408 citations were identified during the electronic database search (Figure 4). Of these citations, 5973 were identified in MEDLINE, 2561 in EMBASE, 193 in Cochrane, and 681 in the CINAHL/SportDiscus/PsychInfo search. A total of 923 duplicates were found, leaving a total of 8485 unique citations. A total of 8138 articles were excluded after scanning, leaving a total of 347 articles for full review. An additional 20 articles were added through cross-referencing. From these articles 319 were excluded after full review leaving 33 articles for inclusion in the systematic review. The reasons for exclusion included non-experimental studies (n = 45), only effect on cardiovascular disease risk factors (n = 115), did not report 3 levels of physical activity (n = 12), subjects less than 18 yr of age (n = 4), reviews, summaries, dissertations, thesis, and abstracts (n = 30), clinical population (n = 14), not on cardiovascular disease or did not fit

Table 11 Studies examining the relationship between physical activity and all-cause mortality.

Publication Country Study Design Quality Score	Objective	Population	Methods	Outcome	Comments and Conclusions
Blair et al 1989 [7]	To study physical fitness (PF) and risk of all-cause mortality in men and women.	<ul style="list-style-type: none"> n = 13,344 (10,224 men; 3,120 women) Sex: Men and women Age: 20->60 years (yr) Characteristics: Participants were given a preventative Medicine examination including maximal treadmill exercise test 	Baseline and 8 year follow-up	<ul style="list-style-type: none"> 283 deaths 	Low levels of PF increase the risk for premature mortality.
USA			PF assessment: Maximal treadmill exercise test.	Adjusted risk ratio (RR), 95% confidence interval (CI)	
Prospective cohort			Fitness categorized into quintiles: Men		
D & B score = 12			<ul style="list-style-type: none"> Q1 = least fit Q2 Q3 Q4 Q5 = most fit 	<ul style="list-style-type: none"> Q1 = 3.44 (2.05-5.77) Q2 = 1.37 (0.76-2.50) Q3 = 1.46 (0.81-2.63) Q4 = 1.17 (0.63-2.17) Q5 = 1.00 (referent) 	
				Women	
				<ul style="list-style-type: none"> Q1 = 4.65 (2.22-9.75) Q2 = 2.42 (1.09-5.37) Q3 = 1.43 (0.60-3.44) Q4 = 0.76 (0.27-2.11) Q5 = 1.00 (referent) 	
Myers et al 2004 [32]	To determine the effects of PF and physical activity (PA) on all-cause mortality.	<ul style="list-style-type: none"> n = 6,213 Sex: Men Age: Mean 59.0 ± 11.2 yr Characteristics: Men referred for exercise testing 	Baseline and mean 5.5 ± 2.0 year follow-Up	<ul style="list-style-type: none"> 1,256 deaths 	Being fit or active is associated with >50% reductions in mortality risk.
USA				PF Level hazard ratio (HR) (95% CI)	
Prospective cohort			PF assessment: Treadmill test to measure VO ₂ peak	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.59 (0.52-0.68) G3 = 0.46 (0.39-0.55) G4 = 0.28 (0.23-0.34) 	PF predicted mortality more strongly than PA.
D & B score = 12			PA assessment: Self reported PA divided into 4 groups	<ul style="list-style-type: none"> PA Level HR (95% CI) G1 = 1.00 (referent) 	Increasing PA (by 1000 kcal/wk or 1 MET) confers a mortality benefit of 20%.

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Blair et al 1995 [36]	To evaluate the relationship between changes in PF and risk of mortality in men.	<ul style="list-style-type: none"> • n = 9,777 • Sex: Men • Age: 20-82 yr • Characteristics: Participants were given a preventative medicine examination including maximal treadmill exercise test 	<ul style="list-style-type: none"> • G2 = 0.63 (0.36-1.10) • G3 = 0.42 (0.23-0.78) • G4 = 0.38 (0.19-0.73) • 223 deaths 	Men who maintained or increased adequate PF had a reduced risk for all-cause mortality than individuals who were consistently unfit.
USA	Prospective cohort	<ul style="list-style-type: none"> • Sex: Men • Age: 20-82 yr • Characteristics: Participants were given a preventative medicine examination including maximal treadmill exercise test 	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • RR (95% CI) • G2 = 0.56 (0.41-0.75) • G3 = 0.52 (0.38-0.70) • G4 = 0.33 (0.23-0.47) 	Men who maintained or increased adequate PF had a reduced risk for all-cause mortality than individuals who were consistently unfit.
D & B score = 13	Prospective cohort	<ul style="list-style-type: none"> • Sex: Men • Age: 20-82 yr • Characteristics: Participants were given a preventative medicine examination including maximal treadmill exercise test 	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • RR (95% CI) • G2 = 0.56 (0.41-0.75) • G3 = 0.52 (0.38-0.70) • G4 = 0.33 (0.23-0.47) 	Men who maintained or increased adequate PF had a reduced risk for all-cause mortality than individuals who were consistently unfit.
Bijnen et al 1999 [37]	To examine the association of PA at baseline and 5 years	<ul style="list-style-type: none"> • n = 472 • Sex: Men • Age: >65 yr • Characteristics: Mostly independently living elders (~95%) • Zutphen Elderly Study 	<ul style="list-style-type: none"> • 118 deaths 	Recent levels of PA were more important for mortality risk than PA 5 years previously.
Netherlands	Retrospective cohort	<ul style="list-style-type: none"> • Sex: Men • Age: >65 yr • Characteristics: Mostly independently living elders (~95%) • Zutphen Elderly Study 	<ul style="list-style-type: none"> • Multivariate adjusted RR (95% CI) • PA in 1985: Lowest tertile = 1.00 (referent) Middle tertile = 1.25 (0.79- 1.99) • Walking = 0.97 (0.60-1.57) • Bike = 0.97 (0.59-1.57) • Gardening = 0.66 (0.39-1.10) • Other = 1.08 (0.66-1.78) • Heavy activity = 0.73 (0.45-1.17) • Non heavy activity = 0.89 (0.57-1.40) 	Recent levels of PA were more important for mortality risk than PA 5 years previously.
D & B score = 12	Retrospective cohort	<ul style="list-style-type: none"> • Sex: Men • Age: >65 yr • Characteristics: Mostly independently living elders (~95%) • Zutphen Elderly Study 	<ul style="list-style-type: none"> • Multivariate adjusted RR (95% CI) • PA in 1985: Lowest tertile = 1.00 (referent) Middle tertile = 1.25 (0.79- 1.99) • Walking = 0.97 (0.60-1.57) • Bike = 0.97 (0.59-1.57) • Gardening = 0.66 (0.39-1.10) • Other = 1.08 (0.66-1.78) • Heavy activity = 0.73 (0.45-1.17) • Non heavy activity = 0.89 (0.57-1.40) 	Recent levels of PA were more important for mortality risk than PA 5 years previously.

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Highest tertile
• Total activity = 1.25 (0.73-2.12)
• Walking = 0.94 (0.58-1.55)
• Bike = 1.07 (0.61-1.88)
• Gardening = 0.77 (0.42-1.39)
• Other = 1.24 (0.74-2.07)
• Heavy activity = 0.76 (0.44-1.32)
• Non heavy activity = 0.94 (0.58-1.53)
PA in 1990:
Lowest tertile = 1.00 (referent)
Middle tertile
• Total activity = 0.56 (0.35-0.89)
• Walking = 0.82 (0.51-1.32)
• Bike = 0.49 (0.29-0.82)
• Gardening = 1.67 (1.00-2.79)
• Other = 0.93 (0.53-1.65)
• Heavy activity = 1.19 (0.73-1.92)
• Non heavy activity = 0.61 (0.38-0.99)
Highest tertile
• Total activity = 0.44 (0.25-0.80)
• Walking = 1.17 (0.70-1.96)
• Bike = 0.43 (0.23-0.80)
• Gardening = 1.03 (0.55-1.94)
• Other = 0.74 (0.44-1.23)
• Heavy activity = 0.72 (0.40-1.31)
• Non heavy activity = 0.65 (0.40-1.05)

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Gregg et al 2003 [39]	To examine the relationship of changes in PA and mortality among older women.	<ul style="list-style-type: none"> • n = 9,518 	Baseline (1986-1988) and median 10.6 year follow-up (1992-1994)	<ul style="list-style-type: none"> • 2,218 deaths 	Increasing and maintaining PA levels could lengthen life for older women but appears to provide less benefit for women aged at least 75 years and those with poor health status.
USA	<ul style="list-style-type: none"> • Sex: Women • Age: ≥ 65 yr • Characteristics: White community dwelling participants from 4 US research centres 	PA Assessment: Questionnaire, divided into quintiles of PA (kcal/wk)	PA	Multivariate adjusted HRR (95% CI): Quintiles of total	
Prospective cohort		Q1= <163 Q2 = 163-503 Q3 = 504-1045 Q4 = 1046-1906 Q5 = ≥ 1907	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.73 (0.64-0.82) • Q3 = 0.77 (0.68-0.87) • Q4 = 0.62 (0.54-0.71) • Q5 = 0.68 (0.59-0.78) 	Walking HRR (95% CI)	
D & B score = 13		Quintiles of walking(kcal/wk) Q1 = <70 Q2 = 70-186 Q3 = 187-419 Q4 = 420-897 Q5 = 898	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.91 (0.81-1.02) • Q3 = 0.78 (0.68-0.88) • Q4 = 0.71 (0.63-0.82) • Q5 = 0.71 (0.62-0.82) 	Multivariate adjusted HRR (95% CI)	
Wannamethee et al 1998 [40]	To study the relationship between heart rate, PA and all-cause mortality.	<ul style="list-style-type: none"> • n = 5,934 	Baseline (1978-1980) and 12-14 year follow-up	<ul style="list-style-type: none"> • 219 deaths 	Maintaining or taking up light or moderate PA reduces mortality in older men.

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

			Multivariate adjusted RR (95% CI), PA
UK	<ul style="list-style-type: none"> • Sex: Men • Age: Mean 63 yr • Characteristics: Healthy, sedentary (4,311 were considered "healthy" in 1992) • The British Regional Heart Study 	PA assessment: Questionnaire, split into groups PA score G1 = Inactive/occasional G2 = Light G3 = Moderate G4 = Moderately vigorous/Vigorous Regular walking (min/d) G1 = 0 G2 = <20 G3 = 21-40 G4 = 41-60 G5 = ≥ 60 Recreational activity, 4 groups G1 = Inactive/fairly Inactive G2 = Average 4 hr/weekend G3 = Fairly active >4 h/weekend G4 = Very active Sporting activity, 3 Groups G1 = None G2 = Occasional G3 = >1 time/month	• G1 = 1.00 (referent) • G2 = 0.61 (0.43-0.86) • G3 = 0.50 (0.31-0.79) • G4 = 0.65 (0.45-0.94) Regular walking • G1 = 1.00 (referent) • G2 = 1.15 (0.73-1.79) • G3 = 1.06 (0.75-1.50) • G4 = 0.97 (0.65-1.46) • G5 = 0.62 (0.37-1.05) Recreational activity • G1 = 1.00 (referent) • G2 = 0.95 (0.43-1.07) • G3 = 0.68 (0.43-1.07) • G4 = 0.34 (0.35-1.00) Sporting activity • G1 = 1.00 (referent) • G2 = 0.50 (0.25-1.03) • G3 = 0.88 (0.64-1.23)
Paffenbarger et al 1986 [63]	<ul style="list-style-type: none"> • n = 16,936 To examine the PA and life-style characteristics of Harvard alumni for the relationship with all-cause mortality. 	12-16 year follow-up (1962 to 1978) Records of freshman year physical examinations and records of intercollegiate sport	• 1,413 deaths The findings suggest a protective effect of exercise against all-cause mortality.
USA	<ul style="list-style-type: none"> • Sex: Men • Age: 35-74 • Characteristics: Harvard alumni 	Those who walked	Age adjusted RR (95% CI): • G1 = 1.00 (referent)
Prospective cohort			

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

D & B score = 14	<ul style="list-style-type: none"> • G2 = 0.85 • G3 = 0.79 	Trend $p = 0.0009$
PA assessment: Mailed questionnaires surveying post college	Physical Activity Index (95% CI):	
PA	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.78 • G3 = 0.73 • G4 = 0.63 • G5 = 0.62 	
Exercise reported: Walking (miles/wk) 3 groups	<ul style="list-style-type: none"> • G6 = 0.52 • G7 = 0.46 • G8 = 0.62 	Trend $p = <0.0001$
PA index (kcal/wk) 3 groups:	<ul style="list-style-type: none"> G1 = <500 G2 = 500-999 G3 = 1000-1499 G4 = 1500-1999 G5 = 2000-2499 G6 = 2500-2999 G7 = 3000-3499 G8 = >3500 	
Schnohr et al 2007 [64]	To determine the impact of walking duration and intensity on all-cause mortality.	Denmark
Denmark	<ul style="list-style-type: none"> • n = 7,308 (3,204 male; 4,104 female) • Sex: Male and female • Age: 20-93 yr • Characteristics: Participants with no history of CHD, stroke or cancer and who had no difficulty in walking • The Copenhagen City Heart Study 	<ul style="list-style-type: none"> • 1,391 deaths
Prospective cohort	PA assessment: Questionnaire, 4 durations and 3 intensities	Multivariate adjusted HR (95% CI):
D & B score = 12	Men	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.38 (0.25-0.58)
		The findings indicate that the relative intensity and not duration of walking is the most important in relation to all-cause mortality.

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

			<ul style="list-style-type: none"> • G3 = 0.38 (0.18-0.79) • G4 = 0.69 (0.44-1.07) • G5 = 0.37 (0.26-0.54) • G6 = 0.33 (0.18-0.61) • G7 = 0.78 (0.50-1.23) • G8 = 0.41 (0.29-0.59) • G9 = 0.33 (0.20-0.54) • G10 = 0.43 (0.22-0.82) • G11 = 0.42 (0.29-0.60) • G12 = 0.28 (0.16-0.48)
	Duration (hours/day)		
	1 = <0.5		
	2 = 0.5-1		
	3 = 1-2		
	4 = >2		
	Intensity		
	Slow intensity (SI)		
	Average intensity (AI)		
	Fast intensity (FI)		
	12 groups		Women
	G1 = 1 and SI		• G1 = 1.00 (referent)
	G2 = 1 and AI		• G2 = 0.82 (0.52-1.29)
	G3 = 1 and FI		• G3 = 0.78 (0.27-2.21)
	G4 = 2 and SI		• G4 = 1.22 (0.82-1.81)
	G5 = 2 and AI		• G5 = 0.74 (0.52-1.05)
	G6 = 2 and FI		• G6 = 0.56 (0.33-0.96)
	G7 = 3 and SI		• G7 = 0.94 (0.60-1.47)
	G8 = 3 and AI		• G8 = 0.87 (0.61-1.23)
	G9 = 3 and FI		• G9 = 0.48 (0.28-0.83)
	G10 = 4 and SI		• G10 = 0.88 (0.40-1.88)
	G11 = 4 and AI		• G11 = 0.64 (0.44-0.95)
	G12 = 4 and FI		• G12 = 0.38 (0.21-0.69)
Kushi et al 1997 [65]	To evaluate the association between PA and all-cause mortality in postmenopausal women.	<ul style="list-style-type: none"> • n = 40417 • Sex: Women • Age: 55-69 yr • Characteristics: Postmenopausal Iowa women 	<ul style="list-style-type: none"> • 2,260 deaths
USA			The results demonstrate a graded inverse association between PA and all-cause mortality in postmenopausal women.
Prospective cohort			
		PA assessment: Questionnaire for frequency of moderate and vigorous LTPA	Multivariate adjusted Frequency of moderate PA per week RR (95% CI):
			<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.71 (0.63-0.79) • G3 = 0.63 (0.56-0.71) • G4 = 0.59 (0.51-0.67)
	D & B score = 13	Divided by frequency/week	

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

<p>G1 = Rarely/never G2 = 1 time/week to a few times/month G3 = 2-4 times/week G4 = >4 times/week</p> <p>Activity index G1 = Low G2 = Medium G3 = High</p> <p>Frequency of vigorous PA per week</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.83 (0.69-0.99) • G3 = 0.74 (0.59-0.93) • G4 = 0.62 (0.42-0.90) <p>Trend p = 0.009</p>	<p>Trend p = <0.001</p>
<p>Baseline (1977) and 8 year follow-up (1985)</p> <p>• n = 10,269</p> <p>• Sex: Men</p> <p>• Age: 45-84 yr (in 1977)</p> <p>• Characteristics: Participants with no reported life-threatening disease</p> <p>PA Assessment: Questionnaire – blocks walked daily, stairs climbed daily and type, frequency and duration of weekly sports and recreational activities</p> <p>Physical activity index (kcal/wk) Sports and recreational activities Light <4.5 METs Moderate >4.5 METs Weekly lists of deaths were obtained from the Harvard college alumni office</p>	<p>• 476 deaths</p> <p>Beginning moderately vigorous sports activity was associated with lower rates of death from all causes among middle aged and older men.</p> <p>Beginning moderate sports activity was associated with 23% lower risk of death (95% CI 4%-42%, p = 0.015) than those not taking up moderate activity</p>
<p>Paffenbarger et al 1993 [67]</p> <p>To analyze changes in the lifestyles of Harvard College alumni, and the association of these changes with mortality.</p>	<p>USA</p> <p>Prospective cohort D & B score = 13</p>

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

	Proportional hazard models with Poisson regression methods			
Katzmarzyk and Craig 2002 [154]	To quantify the relationship between musculoskeletal fitness and all-cause mortality.	• n = 8,116 (3,933 male; 4,183 female)	Baseline (1981) and 13 year follow-up	• 238 deaths RR (95% CI) adjusted for age, smoking status, body mass and VO_{2max}
Canada		• Sex: Men and women	Musculoskeletal fitness (sit ups, push ups, grip strength, sit and reach) measures divided into quartiles	Some components of musculoskeletal fitness are predictive of mortality.
Prospective cohort		• Age: 20-69 yr • Characteristics: Participants who had musculoskeletal fitness measurements taken	Q1 = lowest Q2 Q3 Q4 = highest	Sit ups Men • Q1 = 2.72 (1.56-4.64) • Q2 = 1.32 (0.73-2.41) • Q3 = 1.61 (0.90-2.87) • Q4 = 1.00 (referent)
D & B score = 11		• Canadian Fitness Survey	Cox proportional hazard ratio model	Women • Q1 = 2.26 (1.15-4.43) • Q2 = 2.24 (1.07-4.67) • Q3 = 1.27 (0.59-2.72) • Q4 = 1.00 (referent) Push-ups Men • Q1 = 1.25 (0.77-2.05) • Q2 = 1.17 (0.71-1.90) • Q3 = 0.94 (0.55-1.62) • Q4 = 1.00 (referent) Women • Q1 = 0.61 (0.32-1.17) • Q2 = 0.81 (0.45-1.47) • Q3 = 0.87 (0.48-1.58) • Q4 = 1.00 (referent) Grip strength (kg) Men • Q1 = 1.49 (0.86-2.59)

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

<p>Andersen et al 2000 [163]</p> <p>To evaluate the relationship between levels of OPA, LTPA, cycling to work and sports participation and all-cause mortality.</p>	<p>• n = 30,640 (17,265 men; 13,375 women)</p> <p>14.5 year follow-up</p>	<p>• Q2 = 1.42 (0.82-2.45) • Q3 = 1.59 (0.95-2.68) • Q4 = 1.00 (referent)</p> <p>Women</p> <p>• Q1 = 1.08 (0.58-1.99) • Q2 = 0.62 (0.44-1.56) • Q3 = 1.25 (0.70-2.23) • Q4 = 1.00 (referent)</p> <p>Sit and reach (cm)</p> <p>Men</p> <p>• Q1 = 1.06 (0.64-1.74) • Q2 = 1.01 (0.61-1.66) • Q3 = 1.20 (0.74-1.95) • Q4 = 1.00 (referent)</p> <p>Women</p> <p>• Q1 = 1.18 (0.66-2.10) • Q2 = 1.07 (0.60-1.91) • Q3 = 0.77 (0.44-1.46) • Q4 = 1.00 (referent)</p>
<p>Denmark</p> <p>Prospective cohort</p>	<p>PA assessment: Questionnaire for LTPA, divided into:</p> <p>• Sex: Men and women • Age: 20-93 years (yr)</p> <p>G1 = Low G2 = Moderate G3 = High</p>	<p>Incidence of all-cause mortality and PA</p> <p>Multivariate adjusted RR (95% CI)</p> <p>Age 20-44 yr</p> <p>Men</p> <p>• G1 = 1.00 (referent) • G2 = 0.73 (0.56-0.96) • G3 = 0.74 (0.55-1.01)</p> <p>Women</p> <p>• G1 = 1.00 (referent)</p>
<p>D & B score = 13</p>	<p>LTPA was inversely associated with all-cause mortality in both men and women in all age groups.</p>	

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

<p>Barengo et al 2004 [164]</p>	<p>To investigate whether moderate or high LTPA are associated with reduced CVD and all-cause mortality, independent of CVD risk factors and other forms of PA in men and women.</p>	<p>n = 31,677 (15,853 men; 16,824 women)</p> <p>Sex: Men and women</p> <p>Age: 30-59 yr</p> <p>Characteristics: Participants from eastern and south-western Finland</p>	<p>20 year follow-up</p> <p>PA assessment: Questionnaire self administered to measure OPA, LTPA and commuting activity</p>	<p>HRR (95% CI)</p> <p>Men</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.75 (0.54-1.04) • G3 = 0.66 (0.42-1.05) <p>Women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.73 (0.65-0.83) • G3 = 0.66 (0.56-0.77) <p>Age >65 yr</p> <p>Men</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.62 (0.53-0.73) • G3 = 0.60 (0.50-0.72) <p>Women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.52 (0.45-0.61) • G3 = 0.49 (0.39-0.61) <p>All age groups</p> <p>Men</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.72 (0.66-0.78) • G3 = 0.71 (0.65-0.78) <p>Women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.65 (0.60-0.71) • G3 = 0.59 (0.52-0.67) 	<p>Moderate and high levels of LTPA and OPA are associated with reduced premature all-cause mortality.</p>
<p>Finland</p>				<p>LTPA</p> <ul style="list-style-type: none"> • 1.00 (referent) = low • 0.91 (0.84-0.98) = mod, Men 	

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Prospective cohort			
D & B score = 14		<ul style="list-style-type: none"> • 0.79 (0.70-0.90) = high, Men • 0.89 (0.81-0.98) = mod, women • 0.98 (0.83-1.16) = high, women 	
	OPA		
		<ul style="list-style-type: none"> • 1.00 (referent) = low • 0.75 (0.68-0.83) = mod, men • 0.77 (0.71-0.84) = active, men • 0.79 (0.70-0.89) = mod, women • 0.78 (0.70-0.87) = active, women 	
Bath 2003 [165]	To examine differences between older men and women on the self-rated health mortality relationship.	<ul style="list-style-type: none"> • n = 1,042 (406 men; 636 women at baseline) • Sex: Men and women • Age: >65 yr • Characteristics: Community-dwelling Elderly 	The self-rated health-mortality relationship can be explained by health and related factors among older men and women.
UK			
Prospective cohort		<ul style="list-style-type: none"> • The Nottingham Longitudinal Study of Activity and Ageing 	
D & B score = 11		Baseline, 4 and 12 years post	Number of deaths: At 4 years 242 (106 men; 136 women)
		General physical health 14-item health index (Ebrahim et al 1987) scoring from 0-14 (no health problems – multiple health problems)	At 12 years 665 (287 men; 378 women)
		PA assessment: Self-rated health surveys, divided into 3 levels of PA: High Medium Low	Multivariate adjusted HR (95% CI)
		Men after 4 years	Men after 4 years
		<ul style="list-style-type: none"> • High = 1.00 (referent) • Med = 1.19 (0.61-2.33) • Low = 1.51 (0.75-3.03) 	<ul style="list-style-type: none"> • High = 1.00 (referent) • Med = 1.19 (0.61-2.33) • Low = 1.51 (0.75-3.03)
		Women after 4 years	Women after 4 years
		<ul style="list-style-type: none"> • High = 1.00 (referent) • Med = 1.03 (0.58-1.82) • Low = 1.51 (0.86-2.67) 	<ul style="list-style-type: none"> • High = 1.00 (referent) • Med = 1.03 (0.58-1.82) • Low = 1.51 (0.86-2.67)
		Men after 12 years	Men after 12 years

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

		Cox proportional hazards regression Models	
		<ul style="list-style-type: none"> • High = 1.00 (referent) • Med = 1.28 (0.94-1.74) • Low = 1.13 (0.82-1.55) Women after 12 years	
		<ul style="list-style-type: none"> • High = 1.00 (referent) • Med = 1.20 (0.90-1.61) • Low = 1.23 (0.93-1.62) 	PA may protect against all-cause mortality in elderly men
Bijnen et al 1998 [166]	To describe the association between PA and mortality (CVD, stroke, all-cause) in elderly men.	<ul style="list-style-type: none"> • n = 802 • Sex: Men • Age: 64-84 yr • Characteristics: Retired Dutch men 	10 year follow-up PA assessment: Questionnaire, divided into groups; Multivariate adjusted RR (95% CI) <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.80 (0.63-1.02) • G3 = 0.77 (0.59-1.00) p = 0.04
Netherlands			
Prospective cohort			
D & B score = 12			
Blair et al 1993 [167]	To evaluate the relationship of sedentary living habits to all-cause mortality in women.	<ul style="list-style-type: none"> • n = 3,120 • Sex: Women • Age: Not available • Characteristics: Participants were given a preventative medicine examination 	Baseline and 8 year follow-up Age adjusted death rates (per 10,000 person years) by fitness <ul style="list-style-type: none"> • Low Fitness = 40 • Mod Fitness = 16 • High Fitness = 7 There is a graded inverse relationship between PF and all-cause mortality in women.
USA			
Prospective			
D & B score = 14		PA assessment: Questionnaire	The lack of relationship between PA and death rate was believed to be due to an inadequate assessment of PA.
		No difference between levels of PA	

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Blair et al 1996 [168]	To review the association of PF to all-cause and CVD mortality.	<ul style="list-style-type: none"> n = 32,421 (25,341 men; 7,080 women) 	Baseline and average 8 year follow-up (range 0.1-19.1 years)	<ul style="list-style-type: none"> 601 deaths in men <p>The study observed a steep inverse gradient of death rates across low, moderate and high PF levels. The association was strong and remained after adjustment for potential confounding factors.</p>
USA		<ul style="list-style-type: none"> Sex: Men and women Age: 20-80 yr (mean 43 yr) 	PF assessment: Treadmill test; duration was used to assign participants to sex specific groups:	<ul style="list-style-type: none"> 89 deaths in women <p>RR (95% CI) in low PF vs. high PF</p>
Prospective cohort		<ul style="list-style-type: none"> Characteristics: Participants were excluded if they did not reach 85% of their age predicted maximal heart rate on the maximal exercise treadmill test 	<ul style="list-style-type: none"> Men <p>Men</p>	<ul style="list-style-type: none"> 1.52 (1.28-1.82) Women 2.10 (1.36-3.26) Adjusted deaths per 10,000 person years according to PF
D & B score = 14		<ul style="list-style-type: none"> Aerobics Center Longitudinal Study 	<ul style="list-style-type: none"> Low (least fit 20%) Moderate (next 40%) High (most fit 40%) Proportional hazard modeling 	<ul style="list-style-type: none"> Men Low = 49 Med = 27 High = 23 Women Low = 29 Med = 13 High = 14
Boyle et al 2007 [169]	To examine the association between PA and the risk of incident disability, including impairment in activities of daily living and instrumental activities of daily living in community based older persons free from dementia.	<ul style="list-style-type: none"> n = 1,020 Sex: Men and women Age: 54-100 yr 	2.6 year follow-up	<ul style="list-style-type: none"> 156 deaths <p>The risk of death decreased 11% with each hour of PA/wk.</p>
			PA assessment: Questionnaire, hr/wk of PA	HR for all-cause mortality
			Incidence of all-cause mortality	

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

USA	<ul style="list-style-type: none"> • Characteristics: Participants from 40 retirement communities across Chicago • Rush Memory and Aging Project • n = 7,187 (3,742 men; 3,445 women) • Sex: Men and women • Age: 30-69 yr • Characteristics: Participants were healthy and physically active during leisure time 	<p>The risk of death was 11% lower for each hr/wk of PA</p> <p>Participants who achieved recommended amounts of MPA or VPA were at a significantly lower risk of death than their sedentary counterparts.</p> <p>RR (95% CI) for achieving recommended PA vs. not achieving recommendation</p> <p>Women</p> <ul style="list-style-type: none"> • MPA = 0.65 (0.51-0.82) • VPA = 0.78 (0.57-1.08) • MPA or VPA = 0.60 (0.47-0.75) <p>Men</p> <ul style="list-style-type: none"> • MPA = 0.90 (0.77-1.01) • VPA = 0.74 (0.61-0.90) • MPA or VPA = 0.80 (0.68-0.94)
Prospective cohort D & B score = 13		
Bucksch et al 2005 [170]	<p>To examine the effect of moderately intense PA on all-cause mortality.</p> <p>PA assessment: Questionnaire (Minnesota Leisure Time Physical Activity questionnaire) divided into groups based on: Achieving recommended amount of MPA (30 min, 5 d/wk (≥ 2.5 h/wk))</p>	<p>Baseline (1984-1986) and 12-14 yr follow-up (1998)</p> <p>943 deaths</p> <p>RR (95% CI) for volume of lifestyle activities (kcal/kg/wk) Women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.79 (0.57-1.08) • G3 = 0.68 (0.50-0.94) • G4 = 0.57 (0.41-0.79) <p>p < 0.001</p> <p>Men</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent)
Germany		
Prospective cohort D & B score = 13		
	<p>Achieving recommended amount of VPA (20 min, 3 d/wk (≥ 1 h/wk))</p> <p>Volume of lifestyle activities (kcal/kg/wk)</p> <p>G1 = 0 G2 = <14 G3 = 14-33.5 G4 = ≥ 33.5</p>	

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Bucksch and Helmert 2004 [171]	To examine LTPA and premature death in the general population of former West Germany.	<ul style="list-style-type: none"> n = 7,187 (3,742 men; 3,445 women) Sex: Men and women Age: 30-69 yr Characteristics: Participants were selected on the basis of the German Cardiovascular Prevention Study 	Baseline (1984-1986) and 12-14 year follow-up (1998)	<ul style="list-style-type: none"> G2 = 0.98 (0.76-1.17) G3 = 0.80 (0.63-1.00) G4 = 0.91 (0.74-1.13) <p>p = 0.20</p> <p>Adjusted for age, other recommendation, social class, smoking, BMI, cardio risk factor index, alcohol intake, chronic disease index and dietary factors</p>	<p>943 deaths</p> <p>RR (95% CI)</p> <p>Men, LTPA</p> <ul style="list-style-type: none"> G1 = 1.00 (referent) 	LTPA is inversely associated with all-cause mortality in men and women.
Germany					<ul style="list-style-type: none"> G2 = 0.85 (0.78-0.93) G3 = 0.64 (0.50-0.82) G4 = 0.70 (0.54-0.91) <p>p < 0.001</p> <p>Men, LTPA index</p>	
Prospective cohort						
D & B score = 14		<ul style="list-style-type: none"> The National Health Survey of the German Federal Institute of Population Research (1984-1998) 			<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.92 (0.70-1.23) G3 = 0.89 (0.69-1.17) G4 = 0.61 (0.44-0.84) <p>p < 0.001</p>	
			The LTSA-index (kcal/kg/wk)		<p>Women, LTPA</p> <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.93 (0.82-1.04) G3 = 0.69 (0.48-0.98) G4 = 0.57 (0.35-0.94) <p>p < 0.01</p>	
						Mortality – Records from the mandatory population registries
						<p>Women, LTPA index</p> <ul style="list-style-type: none"> G1 = 1.00 (referent)

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

	<p>Cox proportional hazard regression model</p> <ul style="list-style-type: none"> • G2 = 0.68 (0.45-1.01) • G3 = 0.79 (0.51-1.21) • G4 = 0.46 (0.25-0.85) p < 0.01 <p>Adjusted for age, social class, smoking, BMI, cardio risk factor index, alcohol intake, chronic disease index and dietary factors</p>		
<p>Carlsson et al 2006 [172]</p>	<p>To investigate the association between PA and mortality in post-menopausal women.</p>	<ul style="list-style-type: none"> • n = 2,7734 • Sex: Women • Age: 51-83 yr • Characteristics: Women who participated in a population based Screening programme in 1987 	<p>Baseline (1997) and 2-7 year follow-up (1999-2004)</p> <p>1,232 deaths</p> <p>The study indicates that even fairly small amounts of activity will reduce mortality in older women.</p>
<p>Sweden</p>		<p>PA assessment: Questionnaires for: METs/day, different PA (walking/biking), LTPA, OPA, household PA, TV watching and reading</p>	<p>RR (95% CI) adjusted for lifestyle and medical problems</p>
<p>Prospective cohort</p>		<ul style="list-style-type: none"> • The Swedish Mammography Cohort 	<p>PA (METs/day)</p> <ul style="list-style-type: none"> • >50 = 1.00 (referent) • 45-50 = 1.05 (0.77-1.42) • 40-45 = 1.09 (0.81-1.46)
<p>D & B score = 12</p>			<ul style="list-style-type: none"> • 45-40 = 1.26 (0.94-1.70) • <35 = 2.56 (1.85-3.53)
		<p>Mortality – Records from the National Population Register</p>	<p>Different PA</p> <p>Walking/biking (min/d)</p> <ul style="list-style-type: none"> • > 90 = 1.00 (referent) • 60-90 = 1.01 (0.76-1.34) • 40-60 = 0.92 (0.70-1.20) • 20-40 = 0.96 (0.75-1.23) • <20 = 1.16 (0.90-1.50) • Almost never = 1.94 (1.51-2.50)

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

<p>LTPA (hr/wk)</p> <ul style="list-style-type: none"> • >5 = 1.00 (referent) • 4-5 = 0.95 (0.74-1.22) • 2-3 = 1.02 (0.83-1.26) • 1 = 1.09 (0.88-1.36) • <1 = 1.91 (1.56-2.35) <p>OPA</p> <ul style="list-style-type: none"> • Heavy manual labour = 1.00 (referent) • Walking/lifting/ a lot carrying = 0.96 (0.55-1.70) • Walking/lifting/ not a lot carrying = 1.00 (0.60-1.68) • Mostly standing = 0.91 (0.52-1.61) • Seated 50% of time = 0.97 (0.58-1.62) • Mostly sedentary = 1.93 (1.15-3.25) <p>Household work (hr/d)</p> <ul style="list-style-type: none"> • >8 h/d = 1.00 (referent) • 7-8 = 0.68 (0.49-0.93) • 5-6 = 0.66 (0.51-0.87) • 3-4 = 0.83 (0.64-1.06) • 1-2 = 0.89 (0.69-1.15) • <1 = 1.73 (1.30-2.32) <p>Adjusted for age</p>	<p>OPA</p> <ul style="list-style-type: none"> • Heavy manual labour = 1.00 (referent) • Walking/lifting/ a lot carrying = 0.96 (0.55-1.70) • Walking/lifting/ not a lot carrying = 1.00 (0.60-1.68) • Mostly standing = 0.91 (0.52-1.61) • Seated 50% of time = 0.97 (0.58-1.62) • Mostly sedentary = 1.93 (1.15-3.25) <p>Household work (hr/d)</p> <ul style="list-style-type: none"> • >8 h/d = 1.00 (referent) • 7-8 = 0.68 (0.49-0.93) • 5-6 = 0.66 (0.51-0.87) • 3-4 = 0.83 (0.64-1.06) • 1-2 = 0.89 (0.69-1.15) • <1 = 1.73 (1.30-2.32) <p>Adjusted for age</p>	<p>Some PA is better than none in protecting against all-cause mortality. The benefits are independent of body weight.</p>
<p>Crespo et al 2002 [173]</p> <p>Puerto Rico</p>	<p>To study the relationship between PA and obesity with all-cause mortality in Puerto Rican men.</p> <p>• n = 9,136 (1962-1965)</p> <p>• Sex: Men</p>	<p>Baseline and 12 year follow-up</p> <p>1,445 deaths</p>
<p>Prospective cohort</p> <p>D & B score = 12</p>	<p>PA assessment: Questionnaire, divided into 4 groups based on METs</p> <p>G1 = low</p> <p>G2</p> <p>G3</p> <p>G4 = high</p> <p>• Age: 35-79 yr</p> <p>• Characteristics: Participants with no known coronary heart disease</p>	<p>Multivariate OR (95% CI) adjusted for age</p> <p>• C1 = 1.00 (referent)</p> <p>• C2 = 0.67 (0.57-0.78)</p>

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

	<ul style="list-style-type: none"> • The Puerto Rico Heart Health Program 	
	<ul style="list-style-type: none"> • C3 = 0.63 (0.54-0.74) • C4 = 0.54 (0.46-0.64) 	
	<ul style="list-style-type: none"> • $p < 0.0001$ 	
	<ul style="list-style-type: none"> • Multivariate adjusted OR (95% CI) 	
	<ul style="list-style-type: none"> • C1 = 1.00 (referent) • C2 = 0.68 (0.58-0.79) • C3 = 0.63 (0.54-0.75) • C4 = 0.55 (0.46-0.65) 	
	<ul style="list-style-type: none"> • $p < 0.0001$ 	
	<ul style="list-style-type: none"> • 926 deaths 	In the study, an inverse association of both LTPA and walking pace with mortality from all-causes was seen.
Davey Smith et al 2000 [174]	To examine the relationship of PA and various causes of death.	Baseline (1969-1970) and 25 year follow-up
UK	<ul style="list-style-type: none"> • Sex: Men 	PA assessment: Questionnaire with 3 groups for walking pace (Slower, same, faster) and 3 groups for LTPA (inactive, moderately active, active)
Prospective cohort D & B score = 13	<ul style="list-style-type: none"> • Age: 40-64 yr • Characteristics: Participants from rural northern Japan • Whitehall study 	Age adjusted RR (95% CI) for walking pace
		<ul style="list-style-type: none"> • Slower = 2.47 (2.2-2.8) • Same = 1.35 (1.2-1.5)
		<ul style="list-style-type: none"> • Faster = 1.00 (referent) • $p < 0.001$
		Fully adjusted RR (95% CI) for walking pace
		<ul style="list-style-type: none"> • Slower = 1.87 (1.6-2.1) • Same = 1.21 (1.1-1.3) • Faster = 1.00 (referent) • $p < 0.001$
		Age adjusted RR (95% CI) for LTPA
		<ul style="list-style-type: none"> • Inactive = 1.44 (1.3-1.6) • Mod = 1.13 (1.0-1.2) • Active = 1.00 (referent) • $p < 0.001$
		Fully adjusted RR (95% CI) for LTPA
		<ul style="list-style-type: none"> • Inactive = 1.20 (1.1-1.3) • Mod = 1.07 (1.0-1.2) • Active = 1.00 (referent) • $p < 0.001$

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Eaton et al 1995 [175]	To determine whether self-reported PA predicts a decreased rate of CHD and all-cause mortality in middle aged men.	• n = 8,463	21 year follow-up	• 2,593 deaths	Baseline levels of self-reported LTPA predicted a decreased rate of CHD and all-cause mortality.
Europe, Israel, mid eastern Asia, Northern Africa		• Sex: Men	PA assessment: Questionnaire for LTPA	Age adjusted RR (95% CI) LTPA	
Prospective cohort		• Age: ≥40 yr	G1 = Sedentary	• G1 = 1.00 (referent)	
D & B score = 12		• Characteristics: Government employees without known CVD	G2 = Light	• G2 = 0.84 (0.74-0.94)	
			G3 = Light daily	• G3 = 0.81 (0.73-0.90)	
			G4 = Heavy	• G4 = 0.84 (0.72-0.98)	
			OPA		
			Questionnaire for OPA	• G1 = 1.00 (referent)	
			G1 = Sitting	• G2 = 0.99 (0.88-1.12)	
			G2 = Standing	• G3 = 1.09 (0.99-1.20)	
			G3 = Walking	• G4 = 1.16 (1.03-1.30)	
			G4 = Physical labour		
Fang et al 2005 [176]	To assess the association of exercise and CVD outcome among persons with different blood pressure status.	• n = 9,791 (3,819 men; 5,972 women)	17 year follow-up	Incidence of all-cause mortality and PA	A significant effect of exercise on mortality in normotensive subjects was not found.
USA		• Sex: Men and women	PA assessment: Questionnaire with 3 groups	Multivariate adjusted HR (95% CI)	
Prospective cohort		• Age: 25-74 yr	G1 = Least exercise	• G1 = 1.00 (referent)	
D & B score = 12		• Characteristics: Non-institutionalized participants	G2 = Moderate exercise	• G2 = 0.75 (0.53-1.05)	
			G3 = Most exercise	• G3 = 0.71 (0.45-1.12)	
Fried et al 1998 [177]	To determine the disease, functional and personal characteristics that jointly predict mortality.	• n = 5,886	5 year follow-up	• 646 deaths	PA was a predictor of 5-year mortality.
USA		• Sex: Men and women	PA assessment: Self reported exercise (5 groups)	Incidence of all-cause mortality and PA	
Prospective cohort		• Age: ≥65 yr	MPA or VPA (kJ/wk)	Multivariate adjusted RR (95% CI)	
D & B score = 11		• Characteristics: Community dwelling elders	G1 = ≤282	• G1 = 1.00 (referent)	
			G2 = 283-1789	• G2 = 0.78 (0.60-1.00)	
			G3 = 1790-4100	• G3 = 0.81 (0.63-1.05)	
			G4 = 4101-7908	• G4 = 0.72 (0.55-0.93)	
			G5 = >7908	• G5 = 0.56 (0.43-0.74)	
				p < 0.005	

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Fujita et al 2004 [178]	To examine the relationship between walking duration and all-cause mortality in a Japanese cohort.	• n = 41,163 (20,004 men; 21,159 women)	Baseline (1990) and 11 year follow-up (2001)	• 1,879 deaths	Time spent walking was associated with a reduced risk for all-cause mortality.
Japan	• Sex: Men and women	PA assessment: Questionnaire Walking, 3 levels: G1 = ≤30 min G2 = 30 min to 1 hr G3 = ≥1 hr	Age and sex adjusted RR (95% CI) for time spent walking (hr/d)		
Prospective cohort	• Age: 40-64 yr	Cox proportional hazard model	Whole group		
D & B score = 13	• Characteristics: Healthy, sedentary		• G1 = 1.22 (1.09-1.35) • G2 = 1.09 (0.95-1.22) • G3 = 1.00 (referent) p < 0.001		
	Men only		• G1 = 1.14 (1.00-1.30) • G2 = 1.03 (0.90-1.19) • G3 = 1.00 (referent) p = 0.061		
	Women only		• G1 = 1.40 (1.16-1.68) • G2 = 1.23 (1.01-1.49) • G3 = 1.00 (referent) p < 0.001		
		RR (95% CI) for time spent walking (hr/d) (adjusted for age, education, marital status, past history of diseases, smoking, drinking, BMI and dietary variables)	Whole group		
			• G1 = 1.17 (1.04-1.31) • G2 = 1.06 (0.93-1.20) • G3 = 1.00 (referent) p = 0.011		
	Men		• G1 = 1.08 (0.94-1.25) • G2 = 0.98 (0.84-1.14) • G3 = 1.00 (referent) p = 0.318		
	Women		• G1 = 1.38 (1.12-1.70)		

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Glass et al 1999 [179]	To examine any association between social activity, productive activity and PA and mortality in older people.	• n = 2,761 (1,169 men; 1,143 women)	13 year follow-up	Incidence of all-cause mortality by fitness activity quartile	More active elderly people were less likely to die than those who were less active.
USA	• Sex: Men and women		PA assessment: Interview, Amount of activity	13 yr mortality by amount of activity	
Prospective cohort D & B score = 12	• Age: ≥ 65 yr • Characteristics: Healthy elders		G1 = Low G2 = Low-medium G3 = Medium-high G4 = High	• G1 = 74.0 • G2 = 69.8 • G3 = 62.4 • G4 = 55.2	
Gulati et al 2003 [180]	To determine whether exercise capacity is a predictor for all-cause mortality in asymptomatic women.	• n = 5,721	Baseline (1992) and 8 year follow-up (2000)	• 180 deaths	This study confirmed that exercise capacity is an independent predictor of death in asymptomatic women, greater than what has been previously established among men.
USA	• Sex: Women		PF Assessment: Treadmill stress test Exercise capacity (METs) G1 = <5 G2 = 5-8 G3 = >8	For every 1 MET increase there was a reduced death risk of 17% ($p < 0.001$)	
Prospective cohort D & B score = 11	• Age: Mean 52 ± 11 yr • Characteristics: Asymptomatic women • St. James Women Take Heart Project			Age-adjusted RR • G1 = 2.0 (1.3-3.2) • G2 = 1.6 (1.1-2.4) • G3 = 1.00 (referent)	
Haapanen et al 1996 [181]	To examine the association between LTPA and all-cause mortality.	• n = 1,072	Baseline and a 10 yr 10 month follow-up	Adjusted for Framingham Risk Score • G1 = 3.1 (2.1-4.8) • G2 = 1.9 (1.3-2.9) • G3 = 1.00 (referent)	Low PA is a risk factor for all-cause mortality.
Finland	• Sex: Men	PA assessment: Self-reported LTPA, divided into 4 groups by EE (kJ/wk) G1 = 0-3349 G2 = 3350-6279 G3 = 6280-8791 G4 = >8791		RR (95% CI) according to EE group	

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Prospective cohort D & B score = 14	<ul style="list-style-type: none"> • Age: 35-63 yr • Mortality-National Death Index search • Characteristics: Healthy, sedentary • Cox proportional HR 	<ul style="list-style-type: none"> • G1 = 2.74 (1.46-5.14) • G2 = 1.10 (0.55-2.21) • G3 = 1.74 (0.87-3.50) • G4 = 1.00 (referent) 	<ul style="list-style-type: none"> • 208 deaths 	<p>The findings in older physically capable men indicate that regular walking is associated with a lower overall mortality rate.</p>
Hakim et al 1998 [182] USA Prospective cohort D & B score = 12	<ul style="list-style-type: none"> • To examine the association between walking and mortality in retired men. • n = 707 • Sex: Men • Age: 61-81 yr • Characteristics: Retired non-smoking men who were physically capable of participating in low intensity activities on a daily basis • Honolulu Heart Program 	<ul style="list-style-type: none"> • Baseline and 12 yr follow-up • PA assessment: Questionnaire • Distance walked (miles/day) • G1 = 0.0-0.9 • G2 = 1.0-2.0 • G3 = 2.1-8.0 	<ul style="list-style-type: none"> • RR (95% CI) according to distance walked • Adjusted for age • G1 vs. G3 = 1.9 (1.3-2.9) • G1 vs. G3 = 1.6 (1.2-2.2) • G2 vs. G3 = 1.2 (0.8-1.7) • Trend $p = 0.002$ • Adjusted for risk factors • G1 vs. G3 = 1.8 (1.2-2.7) • G1 vs. G2 = 1.5 (1.1-2.1) • G2 vs. G3 = 1.1 (0.8-1.7) • Trend $p = 0.01$ 	<p>Questionnaire respondents who reported engaging in VPA less than twice a week experienced a 37% reduced risk of all-cause mortality compared with respondents who reported a lower frequency of VPA.</p>
Hillsdon et al 2004 [183] UK Prospective Cohort D & B score = 11	<ul style="list-style-type: none"> • To examine whether VPA is associated with all-cause mortality. • n = 10522 (4929 men; 5593 women) • Sex: Men and women • Age: 35-64 yr • Characteristics: Healthy, sedentary • OXCHECK study 	<ul style="list-style-type: none"> • >10 year follow-up • PA assessment: Questionnaire for frequency of VPA • G1 = Never, <1 time/month • G2 = <2 times/wk • G3 = >2 times/wk • Mortality - Recorded from the Office of National Statistics 	<ul style="list-style-type: none"> • 825 deaths • Age and sex adjusted RR (95% CI) • G1 = 1.00 (referent) • G2 = 0.57 (0.42-0.79) • G3 = 0.72 (0.54-0.95) • Fully adjusted RR (95% CI) • G1 = 1.00 (referent) • G2 = 0.63 (0.45-0.89) • G3 = 0.81 (0.60-1.09) 	<p>Questionnaire respondents who reported engaging in VPA less than twice a week experienced a 37% reduced risk of all-cause mortality compared with respondents who reported a lower frequency of VPA.</p>

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Hu et al 2005 [184]	To examine the association of PA and BMI and their combined effect with the risk of total, CVD and cancer mortality.	<ul style="list-style-type: none"> n = 47,212 (22,528 men; 24,684 women) Sex: Men and women Age: 25-64 yr Characteristics: Participants from eastern Finland 	Cox proportional HR 17.7 year follow-up	• 7,394 deaths Regular PA is an important indicator for decreased risk of all-cause mortality. PA has a strong independent effect on mortality.
Finland				
Prospective cohort				
D & B score = 12				
Hu et al 2004 [185]	To examine the association of BMI and PA with death.	<ul style="list-style-type: none"> n = 116,564 Sex: Women Age: 30-55 yr Characteristics: Females free of known CVD and cancer 	Baseline (1976) and 24 year follow-up	• 10,282 deaths Reduced PA is a strong and independent predictor of death.
USA				
Prospective cohort				
D & B score = 11				
Kampert et al 1996 [186]	To examine PF and PA in relation to all-cause and cancer mortality.	<ul style="list-style-type: none"> n = 32,421 (25,341 men; 7,080 women) 	Cox proportional HR Baseline (1970) and ~8 year follow-up (1989)	• 690 deaths The data support the hypothesis that an active and fit way of life delays death.

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Study	Population	Design	Exposure	Outcome	Results
USA	Prospective cohort		<ul style="list-style-type: none"> Sex: Men and women Age: 20-88 yr (mean ~43) Characteristics: Predominantly white and from the middle and upper socioeconomic strata 	<ul style="list-style-type: none"> PA assessment: Questionnaire, divided into quintiles of activity (min/wk) Male activity categories Sedentary = 855 C1-2 = 1,072 C3 = 1,292 C4 = 1,453 C5 = 1,601 Females activity categories Sedentary = 605 C1-2 = 792 C3 = 979 C4-5 = 1,158 Cox proportional HR 	<ul style="list-style-type: none"> Adjusted RR (95% CI) by quintiles of activity Men Sedentary = 1.00 (referent) C1-2 = 0.71 (0.58-0.97) C3 = 0.83 (0.59-1.16) C4 = 0.57 (0.30-1.08) C5 = 0.92 (0.29-2.88) Trend $p = 0.011$ Women Sedentary = 1.00 (referent) C1-2 = 0.68 (0.39-1.17) C3 = 0.39 (0.09-1.65) C4-5 = 1.14 (0.27-4.80) Trend $p = 0.217$
D & B score = 13					
Kaplan et al [187]	USA	Prospective cohort	<ul style="list-style-type: none"> n = 6,131 (3298 men; 2833 women) Sex: Men and women Age: 16-94 yr Characteristics: Northern Californian adults 	<ul style="list-style-type: none"> To assess LTPA and its association with all cause mortality. 28 year follow-up PA assessment: Three questions about PA, with scores 0 (never), 2 (sometimes) or 4 (often). Tertiles of PA score T1 = 0-2 T2 = 4-6 T3 = 8-12 	<ul style="list-style-type: none"> 1,226 deaths Incidence of all-cause mortality and PA Death rates/1000 person years Men T1 = 24.68 T2 = 11.37 T3 = 7.59 Women T1 = 18.03
D & B score = 13					<p>The data provide further support for the importance of PA and indicate that the protective effect of PA is a robust one.</p>

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Khaw et al 2006 [188]	To examine the relationship between PA patterns over 1 year and total mortality.	<ul style="list-style-type: none"> n = 22,191 (9,984 men; 12,207 women) Sex: Men and women Age: 45-79 yr Characteristics: Community living participants 	8 year follow-up	<ul style="list-style-type: none"> 1,553 deaths 	Even very moderate levels of usual PA are associated with reductions in mortality.
UK			PA assessment: Questionnaire, divided into 4 groups of PA	Incidence of all-cause mortality and PA Adjusted RR (95% CI)	
Prospective cohort			G1 = Inactive G2 = Moderately inactive G3 = Moderately active G4 = Active	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.83 (0.73-0.95) G3 = 0.68 (0.58-0.80) G4 = 0.68 (0.57-0.81) Age <65 <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 1.01 (0.78-1.31) G3 = 0.81 (0.62-1.07) G4 = 0.82 (0.62-1.09) Age >65 <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.77 (0.66-0.91) G3 = 0.65 (0.53-0.79) G4 = 0.64 (0.50-0.80) 	
D & B score = 13					
Kohl et al 1996 [189]	To determine the association of maximal exercise hemodynamic responses with risk of all-cause mortality.	<ul style="list-style-type: none"> n = 26,621 (20,387 men; 6,234 women) 	Average 8.1 year follow-up	<ul style="list-style-type: none"> 348 deaths in men and 66 in women 	The results suggest an exaggerated SBP or an attenuated heart rate response to maximal exercise may indicate an elevated risk for mortality.
USA		<ul style="list-style-type: none"> Sex: Men and women Age: Male mean 42.2 yr; female mean 41.9 Yr 		Adjusted RH (95% CI) by maximal exercise test HR	
Prospective cohort		<ul style="list-style-type: none"> Characteristics: Apparently healthy patients of a preventive medicine centre 	PF assessment: Maximal exercise test HR (bpm), divided into 4 Groups: G1 = <171 G2 = 171-178 G3 = 179-188 G4 = >188	<ul style="list-style-type: none"> Q1 = 1.00 (referent) Q2 = 0.61 (0.44-0.85) Q3 = 0.69 (0.51-0.93) Q4 = 0.60 (0.41-0.87) Trend $p < 0.05$	
D & B score = 12					

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

<p>Women</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.23 (0.65-2.32) • Q3 = 0.69 (0.30-1.63) • Q4 = 0.71 (0.22-2.24) <p>Trend $p > 0.05$</p>							<p>LTPA is associated with reduced mortality, even after genetic and other familial factors are taken into account.</p>
<p>Kujala et al 1998 [190]</p>	<p>To investigate LTPA and mortality in a cohort of twins.</p>	<p>Baseline 1975 and death outcome from 1977-1994</p>	<p>n = 15,902 (7,925 men; 7,977 women)</p>	<p>Sex: Men and women Age: 25-64 yr Characteristics: Healthy, Finnish same sex twins</p>	<p>PA assessment: Questionnaire, quintiles of fitness in MET hours/day</p>	<p>Adjusted for age and sex</p>	<p>HR (95% CI)</p> <ul style="list-style-type: none"> • Sedentary = 1.00 (referent) • OE = 0.71 (0.62-0.81) • CE = 0.57 (0.45-0.74) <p>Trend $p = 0.001$</p>
<p>Finland</p>							
<p>Prospective cohort</p>			<p>The Finnish Twin Cohort</p>				
<p>D & B score = 13</p>				<p>Q1 = <58 Q2 = 59-1.29 Q3 = 1.30-2.49 Q4 = 2.50-4.49 Q5 = >4.50</p>	<p>Categorized into: -Sedentary -Occasional exerciser (OE) -Conditioning exerciser (CE)</p>	<p>Adjusted for age, sex, smoking</p>	<p>Adjusted for age, sex, smoking, occupational group, alcohol</p> <ul style="list-style-type: none"> • Sedentary = 1.00 (referent) • OE = 0.76 (0.67-0.87) • CE = 0.68 (0.53-0.88) <p>Trend $p = 0.001$</p>
							<p>HR (95% CI) among 434 same sex twin pairs compared with sedentary category in 1975</p> <ul style="list-style-type: none"> • Sedentary = 1.00 (referent) • OE = 0.66 (0.46-0.94)

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

	<ul style="list-style-type: none"> • CE = 0.44 (0.23-0.83) 	<p>Trend $p = 0.005$</p> <p>Adjusted for smoking</p> <ul style="list-style-type: none"> • Sedentary = 1.00 (referent) • OE = 0.70 (0.48-1.01) • CE = 0.56 (0.29-1.09) <p>Trend $p = 0.04$</p> <p>Adjusted for smoking, occupational group, alcohol</p> <ul style="list-style-type: none"> • Sedentary = 1.00 (referent) • OE = 0.73 (0.50-1.07) • CE = 0.56 (0.29-1.11) <p>Trend $p = 0.06$</p> <p>OR (95% CI) in quintiles among 434 same sex twin pairs compared with sedentary category in 1975</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.85 • Q3 = 0.72 • Q4 = 0.68 • Q5 = 0.60 	
LaCroix et al [191]	<p>1996</p> <p>To determine whether walking is associated with a reduced risk of CVD hospitalization and death in older adults.</p>	<p>4.2 year follow-up</p> <ul style="list-style-type: none"> • n = 1,645 (615 men; 1030 women) • Sex: Men and women • Age: ≥ 65 yr <p>Characteristics: Participants from a group health co-operative</p>	<p>RR (95% CI) by category of walking</p> <p>Walking more than 4 hr/wk was associated with a reduced risk of mortality from all-causes.</p>
USA	<p>PA assessment: Questionnaire for walking h/wk, divided into 3 groups</p> <p>G1 = <1 hr/week G2 = 1-4 hr/week G3 = >4 hr/week</p>	<p>Men</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.78 (0.43-1.45) • G3 = 0.89 (0.49-1.62) <p>Women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.50 (0.28-0.90) • G3 = 0.48 (0.25-0.83) <p>Age 65-74 yr</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.81 (0.40-1.61) 	
Prospective cohort			
D & B score = 12			

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Lam et al 2004 [192]	To investigate the relationship LTPA and mortality in Hong Kong.	<ul style="list-style-type: none"> n = 24,079 cases (13,778 men; 10,301 women); 	10 years prior	<ul style="list-style-type: none"> G3 = 1.13 (0.60-2.15) 	The data confirm and extend previous findings in Caucasian populations on the association between LTPA and longevity.
Hong Kong		<ul style="list-style-type: none"> n = 13,054 controls (3,918 men; 9,136 women) 	PA assessment: Questionnaire for LTPA, divided into 3 groups	<ul style="list-style-type: none"> Age ≥75 yr G1 = 1.00 (referent) G2 = 0.63 (0.37-1.08) G3 = 0.46 (0.25-0.84) 	
Case-Control		<ul style="list-style-type: none"> Sex: Men and women 	G1 = <1 times per month	High functioning	
D & B score = 12		<ul style="list-style-type: none"> Age: ≥35 yr Characteristics: All ethnic Chinese 	G2 = 1-3 times per month	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.73 (0.38-1.41) G3 = 0.89 (0.48-1.65) 	
Lan et al 2006 [193]	To investigate the relationship between exercise and all-cause mortality.	<ul style="list-style-type: none"> n = 2,113 (1,081 men; 1,032 women) 	Baseline and 2 year follow-up	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.60 (0.54-0.67) G3 = 0.66 (0.60-0.73) 	
Taiwan		<ul style="list-style-type: none"> Sex: Men and women 	G3 = ≥4 times per month	Women	
Prospective cohort		<ul style="list-style-type: none"> Age: ≥65 yr Characteristics: Non-institutionalized elders 	PA assessment: Questionnaire for LTPA (frequency/wk)	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.81 (0.74-0.88) G3 = 0.71 (0.66-.077) 	Older persons are recommended to expend at least 1000 kcal/wk through regular exercise for mortality reduction.
D & B score = 13		<ul style="list-style-type: none"> Taiwan National Health Interview Survey 	G1 = Sedentary G2 = 1 time/wk G3 = ≥2 times/wk	HR (95% CI) by LTPA frequency	Protection of exercise against death also increases with the number of activities.

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

<p>Laukkanen et al 2001 [194]</p>	<p>To examine the relationship between maximal oxygen uptake and overall mortality.</p>	<p>n = 1,294</p> <p>Sex: Men</p> <p>Age: 42.0-61.3 yr (mean 52.1)</p> <p>Characteristics: Men free from CVD, COPD, and cancer at baseline</p>	<p>Baseline and 10.7 year follow-up</p> <p>124 deaths</p>
<p>Finland</p>	<p>Prospective cohort</p>	<p>PF assessment: Exercise tolerance test, 4 groups by maximal oxygen uptake (ml/kg/min)</p> <p>Maximal oxygen uptake</p> <p>G1 = 1.00 (referent)</p> <p>G2 = 1.47 (0.71-3.01)</p> <p>G3 = 2.79 (1.44-5.39)</p> <p>G4 = 3.85 (2.02-7.32)</p> <p>Linear trend $p = <0.001$</p>	<p>Adjusted RR (95% CI) by quartile</p>
<p>D & B score = 14</p>	<p></p>	<p></p>	<p>PF has a strong, graded, inverse association with overall mortality.</p>

Trend $p = <0.001$
 Multivariate adjusted

Questionnaire for EE (kcal/wk), divided into 5 groups:

G1 = Sedentary
 G2 = <500
 G3 = 500-999
 G4 = 1000-1999
 G5 = ≥ 2000

G1 = 1.00 (referent)
 G2 = 0.70 (0.50-0.98)
 G3 = 0.35 (0.15-0.82)
 Trend $p = 0.014$

HR (95% CI) by EE

Adjusted for age and sex

G1 = 1.00 (referent)
 G2 = 0.64 (0.41-1.01)
 G3 = 0.55 (0.35-0.85)
 G4 = 0.30 (0.17-0.53)
 G5 = 0.24 (0.12-0.48)
 Trend $p <0.001$

Multivariate adjusted

G1 = 1.00 (referent)
 G2 = 0.80 (0.49-1.30)
 G3 = 0.74 (0.46-1.17)
 G4 = 0.50 (0.27-0.90)
 G5 = 0.43 (0.21-0.87)
 Trend $p = 0.043$

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

			<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 2.22 (1.08-4.55) • G3 = 2.23 (1.11-4.49) • G4 = 3.94 (2.01-7.74) Linear trend $p < 0.001$	Test duration <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 2.22 (1.08-4.55) • G3 = 2.23 (1.11-4.49) • G4 = 3.94 (2.01-7.74)
			G4 = <27.6 Test duration (min) G1 = >11.2 G2 = 9.6-11.2 G3 = 8.2-9.5 G4 = <8.2	
Lee and Paffenbarger 2000 [195]	To compare various levels of PA with mortality.	<ul style="list-style-type: none"> • n = 13,485 	Baseline and 15 year follow-up • 2,539 deaths	The study provides some support for recommendations that emphasize MPA. A benefit of VPA is also evident.
		<ul style="list-style-type: none"> • Sex: Men • Age: Mean 57.5 yr • Characteristics: Men who matriculated as undergraduates in 1916-1950 	PA assessment: Questionnaires for LTPA index (including walking, stair climbing, sports and recreational activity),	RR (95% CI) <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.80 (0.72-0.88) • G3 = 0.74 (0.65-0.83) • G4 = 0.80 (0.69-0.93) • G5 = 0.73 (0.64-0.84)
USA				
Prospective cohort		<ul style="list-style-type: none"> • The Harvard Alumni Health Study 		
D & B score = 12			5 groups (kJ/wk) G1 = <4200 G2 = 4200-8399 G3 = 8400-12599 G4 = 12600-16799 G5 = ≥ 16800	Trend $p = < 0.001$
Lee et al 1995 [196]	To examine the independent association of vigorous and non-vigorous PA with longevity.	<ul style="list-style-type: none"> • n = 17,321 	Follow-up 22-26 years • 3,728 deaths	There is a graded inverse relationship between PA and mortality. Vigorous, but not non-vigorous activities are associated with longevity.
		<ul style="list-style-type: none"> • Sex: Men • Age: Mean 46 yr 	PA assessment: Questionnaires for EE (kJ/wk), quintiles	

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

USA	Q1= 1.00 (referent)			
Prospective cohort	<ul style="list-style-type: none"> • Q2 = 0.94 (0.86-1.04) • Q3 = 0.95 (0.86-1.05) • Q4 = 0.91 (0.83 - 1.01) • Q5 = 0.91 (0.82-1.00) 	<ul style="list-style-type: none"> • Characteristics: Harvard University alumni, without self-reported physician diagnosed cardiovascular disease, cancer or chronic obstructive pulmonary disease 	<ul style="list-style-type: none"> • Q1 = ≤ 630 • Q2 = 630-1680 • Q3 = 1680-3150 • Q4 = 3150-6300 • Q5 = >6300 	<ul style="list-style-type: none"> • RR (95% CI) by EE (Vigorous activity, kJ/wk) <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.88 (0.82-0.96) • Q3 = 0.92 (0.82-1.02) • Q4 = 0.87 (0.77-0.99) • Q5 = 0.87 (0.78-0.97)
D & B score = 12		<ul style="list-style-type: none"> • The Harvard Alumni Health Study 		
USA	<ul style="list-style-type: none"> • n = 8,421 	<ul style="list-style-type: none"> • Baseline 1988 and follow-up 1993 	<ul style="list-style-type: none"> • 1,234 deaths 	<ul style="list-style-type: none"> • The results suggest that regular PA generating 1000 kcal/wk or more should be recommended for lowering mortality rates. Among those with no major risk factors, even 1-2 episodes per week generating 1000 kcal or more can postpone mortality.
Prospective cohort	<ul style="list-style-type: none"> • Sex: Men • Age: Mean 66 yr 	<ul style="list-style-type: none"> • Characteristics: Participants free of major chronic disease 	<ul style="list-style-type: none"> • PA assessment: Questionnaire for PA (kcal/wk), 4 groups 	<ul style="list-style-type: none"> • Age adjusted RR (95% CI) by PA pattern <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.75 (0.63-0.90) • G3 = 0.82 (0.63-1.07) • G4 = 0.61 (0.53-0.69)
D & B score = 11		<ul style="list-style-type: none"> • The Harvard Alumni Health Study 	<ul style="list-style-type: none"> • G1 = <500 (Sedentary) • G2 = 500-999 (Insufficiently active) • G3 = ≥ 1000 (Weekend warrior) • G4 = Regularly active 	<ul style="list-style-type: none"> • Multivariate adjusted <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.75 (0.62-0.91) • G3 = 0.85 (0.65-1.11)

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Leitzmann et al 2007 [198]	To examine PA guidelines in relation to mortality.	• n = 252,925 (142,828 male; 110,097 women)	Baseline and 6 month follow-up	• G4 = 0.64 (0.55-0.73) • 7,900 deaths	Following PA guidelines is associated with lower risk of death. Mortality benefit may also be achieved by engaging in less than recommended activity levels.
USA		• Sex: Men and women	PA assessment: Questionnaire for MPA and VPA, 5 groups each MPA (h/wk)	Multivariate adjusted RR (95% CI) according to activity	
Prospective cohort		• Age: 50-71 yr • Characteristics: Participants free of CVD, cancer or emphysema • The National Institute of Health-American Association of Retired Persons		MPA • G1 = 1.00 (referent) • G2 = 0.85 (0.79-0.93) • G3 = 0.79 (0.74-0.85) • G4 = 0.76 (0.71-0.82) • G5 = 0.68 (0.63-0.74) Trend $p = <0.001$ VPA • G1 = 1.00 (referent) • G2 = 0.77(0.71-0.83) • G3 = 0.77 (0.72-0.82) • G4 = 0.68 (0.63-0.73) • G5 = 0.71 (0.66-0.77) Trend $p = <0.001$	
D & B score = 13		G1 = sedentary G2 = <1 G3 = 1-3 G4 = 4-7 G5 = >7 VPA (frequency/wk) G1 = inactive G2 = <1 G3 = 1-2 G4 = 3-4 G5 = ≥ 5 Cox proportional HR			
Leon et al 1997 [199]	To examine the long-term association of LTPA and risk of death from coronary heart disease and all-causes.	• n = 12,138	16 year follow-up	• 1,904 deaths	The data suggest that a relatively small amount of daily moderate intensity LTPA can reduce premature mortality in middle-aged and older men at high risk for CHD.
		• Sex: Men • Age: 35-57 yr	PA assessment: Minnesota LTPA questionnaire, categorized by frequency/month and average duration, deciles (min/d)	Multivariate adjusted RR (95% CI) by deciles of LTPA	

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

USA	<ul style="list-style-type: none"> • Characteristics: Men who at entry to the study were free of clinical evidence of CHD or other serious medical problems but were at the upper 10%-15% of a CHD probability score distribution derived from the FHS data 	<ul style="list-style-type: none"> • D1 = 1.00 (referent) • D2-4 = 0.85 (0.73-0.99) • D5-7 = 0.87 (0.75-1.02) • D8-10 = 0.83 (0.71-0.97) 	
Prospective cohort			
D & B score = 12			
	<ul style="list-style-type: none"> • Multiple Risk Factor Intervention Trial 	<ul style="list-style-type: none"> • D1 = 4.9 • D2-4 = 22.7 • D5-7 = 53.9 • D8-10 = 140.4 	
		Cox proportional HR	
Lissner et al 1996 [200]	<ul style="list-style-type: none"> • To examine the relationship of OPA and LTPA on all-cause mortality in women. 	<ul style="list-style-type: none"> • n = 1,405 • Sex: Women • Age: 38-60 yr • Characteristics: Free from major disease at baseline 	<ul style="list-style-type: none"> • 277 deaths
Sweden		<ul style="list-style-type: none"> • PA assessment: Questionnaire for OPA and LTPA, 3 groups 	<ul style="list-style-type: none"> • RR (95% CI) by LTPA
Prospective cohort			<ul style="list-style-type: none"> • 20 year follow-up • LTPA during age 20-38 years • Low = 1.00 (referent) • Med = 0.66 (0.34-1.26) • High = 0.46 (0.21-1.01)
D & B score = 10		<ul style="list-style-type: none"> • The Gothenburg Prospective Study of Women 	<ul style="list-style-type: none"> • LTPA during age 39-60 years • Low = 1.00 (referent) • Med = 0.56 (0.35-0.90) • High = 0.44 (0.22-0.91)
		<ul style="list-style-type: none"> • Proportional hazard regression 	<ul style="list-style-type: none"> • LTPA during the past 12 months • Low = 1.00 (referent) • Med = 0.56 (0.39-0.82) • High = 0.45 (0.24-0.86)
			<ul style="list-style-type: none"> • 20 year follow-up • OPA during age 20-38 years
			<ul style="list-style-type: none"> • Decreases in PA as well as low initial levels are strong risk factors for mortality.

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Manini et al 2006 [201]	To determine whether energy expenditure is associated with all-cause mortality in older adults.	<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)
USA		<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)
Prospective cohort		<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)
D & B score = 13		<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)
	Mean follow-up of 6.15 years	<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)
	PA assessment: Questionnaire, divided into tertiles of PA EE (kcal/d)	<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)
	T1 = <521 T2 = 521-770 T3 = >770	<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)
	Adjusted for age, sex, race and study site	<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)
	Trend <i>p</i> = 0.009	<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)
	Adjusted for age, sex, race, study site, weight, height, percent body fat and sleep duration	<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)
	T1 = 1.00 (referent) T2 = 0.63 (0.29-1.18) T3 = 0.37 (0.15-0.76)	<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)
	Trend <i>p</i> = 0.004	<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)
	Adjusted for age, sex, race, study site, self rated health, education, smoking, CVD, lung disease, diabetes, hip or knee osteoarthritis, osteoporosis, cancer and depression	<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)
	T1 = 1.00 (referent) T2 = 0.57 (0.30-1.09) T3 = 0.31 (0.14-0.69)	<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)
	Trend <i>p</i> = 0.004	<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)
	Free-living activity EE was strongly associated with lower risk of mortality.	<ul style="list-style-type: none"> • n = 302 (150 men; 152 women) • Sex: Men and women 	<ul style="list-style-type: none"> • Low = 1.00 (referent) • Med = 0.59 (0.18-1.87) • High = 0.50 (0.16-1.58)

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Matthews et al 2007 [202]	To determine the effects of exercise and non-exercise PA on mortality.	<ul style="list-style-type: none"> n = 67,143 Sex: Women Age: 40-70 yr Characteristics: Women without heart disease, stroke or cancer 	<ul style="list-style-type: none"> Baseline and an average of 5.7 year follow-up 	<ul style="list-style-type: none"> T3 = 0.33 (0.15-0.74) Trend $p = 0.007$ 1,091 deaths 	Overall PA levels are an important determinant of longevity.
China			PA assessment: Interview to report (MET hr/d), 4 groups Overall activity	RR (95% CI)	
Prospective cohort		<ul style="list-style-type: none"> The Shanghai Women's Health Study 		Multivariate adjustment	
D & B score = 12			<ul style="list-style-type: none"> G1 = ≤ 9.9 G2 = 10.0-13.6 G3 = 13.7-18.0 G4 = ≥ 18.1 	Overall activity (MET hr/d) <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.81 (0.69-0.96) G3 = 0.67 (0.57-0.80) G4 = 0.61 (0.51-0.73) Trend $p = 0.000$	
			Adult exercise	Adult exercise (MET hr/d) <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.84 (0.74-0.96) G3 = 0.77 (0.59-0.99) G4 = 0.64 (0.36-1.14) Trend $p = 0.008$	
Menotti and Seccareccia 1985 [203]	To investigate the relationship between OPA and all-cause mortality.	<ul style="list-style-type: none"> n = 99,029 Sex: Men Age: 40-59 yr Characteristics: Men employed on the Italian railway system 	<ul style="list-style-type: none"> Baseline and 5 year follow-up 	<ul style="list-style-type: none"> 2,661 deaths 	The results suggest that PA may play a role in the prediction of fatal events.
Italy			PA assessment: Questionnaire Men at risk classified by 3 levels of PA and 3 levels of job responsibility, combined to create 8 groups of PA-job responsibility	Age adjusted death rates per 1000 over 5 years classified by PA only <ul style="list-style-type: none"> Sedentary = 26.20 Moderate = 27.05 Heavy = 27.35 	
Prospective cohort			Cox proportional hazard models		

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

D & B score = 12				Age adjusted death rates per 1,000 over 5 years classified by PA and job responsibility	
			<ul style="list-style-type: none"> • G1 = sedentary – low • G2 = sedentary – med • G3 = sedentary – high • G4 = moderate – low • G5 = moderate – med • G6 = moderate – high • G7 = heavy – low • G8 = heavy – med 	<ul style="list-style-type: none"> • G1 = 30.00 • G2 = 25.20 • G3 = 25.80 • G4 = 26.30 • G5 = 28.50 • G6 = 25.80 • G7 = 26.90 • G8 = 30.80 	
Mensink et al 1996 [204]	Germany	To compare various indices for PA and their association with cardiovascular risk factors as well as total and CVD mortality.	<ul style="list-style-type: none"> • n = 15,436 (7,689 men; 7,797 women) • Sex: Men and women • Age: 25-69 yr • Characteristics: Participants from communities in Western Germany 	5-8 year follow-up	Incidence of all-cause mortality and PA
Prospective cohort	Germany		<ul style="list-style-type: none"> • PA assessment: Questionnaire • Total activity, 3 groups 	Adjusted RR (95% CI)	An inverse relation of PA and total mortality.
D & B score = 12			<ul style="list-style-type: none"> • G1 = Low • G2 = Moderate • G3 = High 	Total activity, men	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.56 (0.30-1.04) • G3 = 0.78 (0.42-1.44)
			<ul style="list-style-type: none"> • LTPA, 3 groups • G1 = Low • G2 = Moderate • G3 = High 	Total activity, women	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.24 (0.60-2.58) • G3 = 1.29 (0.58-2.85)
			<ul style="list-style-type: none"> • Conditioning activity, 3 groups • G1 = No activity • G2 = Moderate • G3 = High 	LTPA, men	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.61 (0.35-1.05) • G3 = 0.79 (0.48-1.31)
			<ul style="list-style-type: none"> • Sports activity, 4 groups • G1 = no sports • G2 = <1 hour • G3 = 1-2 hours • G4 = >2 hours 	LTPA, women	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.94 (0.51-1.75) • G3 = 0.81 (0.44-1.49)
				Conditioning activity, men	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.76 (0.44-1.34) • G3 = 0.67 (0.36-1.25)

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

	Conditioning activity, women	
• G1 = 1.00 (referent)		
• G2 = 0.38 (0.13-1.06)		
• G3 = 0.80 (0.42-1.54)		
Sports Activity, men		
• G1 = 1.00 (referent)		
• G2 = 0.49 (0.26-0.95)		
• G3 = 0.57 (0.30-1.09)		
• G4 = 0.36 (0.16-0.79)		
Sports activity, women		
• G1 = 1.00 (referent)		
• G2 = 0.38 (0.12-1.23)		
• G3 = 0.52 (0.23-1.17)		
• G4 = 0.28 (0.07-1.17)		
Incidence of all-cause mortality and PA		A wide range of customary or habitual PA, can provide indices showing both cross sectional and predictive validity for 10 year mortality.
Morgan and Clarke 1997 [205]	10 year follow-up	
To assess the value of broadly based customary PA scores in predicting 10-year mortality in elderly people.	• n = 1,042 (407 men; 635 women)	
UK	• Sex: Men and women	PA assessment: Questionnaire for PA, 3 groups
Prospective cohort	• Age: ≥65 yr	HR (95% CI)
	• Characteristics: British elders	Men
	• Nottingham Longitudinal Study of Activity and Aging	• G1 = 1.59 (1.12-2.25)
		• G2 = 1.35 (0.96-1.89)
		• G3 = 1.00 (referent)
D & B score = 12	G1 = Low G2 = Intermediate G3 = High	Women
		• G1 = 2.07 (1.53-2.79)
		• G2 = 1.53 (1.12-2.09)
		• G3 = 1.00 (referent)
Myers et al 2002 [206]	Baseline and mean 6.2 ± 3.7 year follow-up	Exercise capacity is a more powerful predictor of mortality among men than other established risk factors for CVD.
To compare PF and PA levels with all-cause mortality.	• n = 6,213	• 1,256 deaths
UK	• Sex: Men	
	• Age: Mean 59 ± 11 yr	Age adjusted RR (95% CI) by quintile

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

USA	<p>• Characteristics: Participants with a normal exercise test result (n = 2,534) and participants with an abnormal exercise test or CVD or both (n = 3,679)</p> <p>PF assessment: Treadmill test for VO₂ peak, divided into quintiles (METs)</p> <ul style="list-style-type: none"> • Q1 = 4.5 (3.0-6.8) • Q2 = 2.4 (1.5-3.8) • Q3 = 1.7 (1.1-2.8) • Q4 = 1.3 (0.7-2.2) • Q5 = 1.00 (referent) <p>Q1 = Lowest level 1.0-5.9 Q2 Q3 Q4 Q5 = Highest level ≥13.0</p>		
Prospective cohort			
D & B score = 12			
Ostbye et al 2002 [207]	<p>To analyze the effect of smoking and other modifiable risk factors on ill health, defined in a multidimensional fashion.</p> <p>• n = 12,956</p> <p>• Sex: Men and women</p> <p>• Age: 50-60 yr</p>	<p>6 year follow-up</p> <p>• 782 deaths</p>	<p>Quitting smoking and increasing exercise levels are the lifestyle interventions most likely to improve overall health.</p>
USA	<p>• Characteristics: Participants from the Health and Retirement Study (HRS) only</p>	<p>PA assessment: Questionnaire for PA, 4 groups</p> <p>G1 = Sedentary G2 = Light G3 = Moderate G4 = Heavy</p>	<p>Incidence of all-cause mortality and PA</p> <p>Death rates (95% CI) per 1000 population/yr</p> <ul style="list-style-type: none"> • G1 = 20.6 (17.8-24.0) • G2 = 9.1 (8.1-9.5) • G3 = 8.3 (7.5-9.2) • G4 = 4.4 (3.5-5.6)
Prospective cohort			
D & B score = 13			
Paffenbarger et al 1994 [208]	<p>To study the adoption or maintenance of PA and other optional lifestyle patterns for their influence on mortality rates of Harvard College alumni.</p> <p>• n = 14,786</p> <p>• Sex: Men</p> <p>• Age: 45-84 yr (in 1977)</p>	<p>Follow-up between 1977 and 1988</p>	<p>Adopting a physically active lifestyle delays mortality and extends longevity.</p> <p>RR (95% CI) of mortality according to PA</p>

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Rockhill et al 2001 [210]	To determine the association between recreational PA and mortality in women.	<ul style="list-style-type: none"> Health and Retirement Study n = 80,348 	Baseline (1980) and follow-up between 1982-1996	<ul style="list-style-type: none"> 4,871 deaths 	People who are more physically active are at reduced mortality risk relative to those who are less active.
USA		<ul style="list-style-type: none"> Sex: Women Age: 30-55 yr Characteristics: Free from CVD or cancer at baseline Nurses Health Study 		Multivariate adjusted RR (95% CI) by (hr/wk)	
Prospective cohort			PA assessment: Questionnaire in 1980 and up-dated every 2-4 years, 5 groups of PA (hr/wk)	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.82 (0.76-0.89) G3 = 0.75 (0.69-0.81) G4 = 0.74 (0.68-0.81) G5 = 0.71 (0.61-0.82) 	
D & B score = 11			G1 = <1 G2 = 1-1.9 G3 = 2-3.9 G4 = 4-6.9 G5 = ≥7	p<0.001	
Rosengren and Wilhelmsen 1997 [211]	To investigate the effect of OPA and LTPA on risk of death.	<ul style="list-style-type: none"> n = 7,142 	Baseline (1970-1973) and 20 year follow-up	<ul style="list-style-type: none"> 2,182 deaths 	The study demonstrates the protective effect of LTPA on mortality.
Sweden		<ul style="list-style-type: none"> Sex: Men Age: 47-55 yr Characteristics: Without symptomatic CHD 	PA assessment: Postal questionnaires, 3 groups:	Unadjusted RR (95% CI)	
Prospective cohort			G1 = Sedentary G2 = Moderately active G3 = Regular exercise	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.74 (0.68-0.82) G3 = 0.73 (0.68-0.79) 	
D & B score = 13				Multivariate adjustment	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.84 (0.77-0.93) G3 = 0.83 (0.77-0.90)

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Schnohr et al 2003 [212]	To assess the associations of regular LTPA and changes in LTPA with risk of death.	• n = 7,023 (4,471 men; 5,676 women)	18 year follow-up	• 2,725 deaths	Maintaining or adopting a moderate or high degree of PA was associated with lower risk of death.
Denmark	• Sex: Men and women	• Age: 20-79 yr	PA assessment: Questionnaire, 9 groups	Incidence of all-cause mortality and PA and changes in PA	
Prospective cohort	• Characteristics: Participants from the Copenhagen City Heart Registered Population	G1 = Low-low G2 = Low-moderate G3 = Low-high G4 = Moderate-low G5 = Moderate-Moderate G6 = Moderate-high G7 = High-low G8 = High-moderate G9 = High-high	Adjusted RR (95% CI)	Men • G1 = 1.00 (referent) • G2 = 0.64 (0.49-0.83) • G3 = 0.64 (0.47-0.87) • G4 = 0.73 (0.56-0.96) • G5 = 0.71 (0.57-0.88) • G6 = 0.64 (0.51-0.81) • G7 = 1.11 (0.76-1.62) • G8 = 0.66 (0.51-0.85) • G9 = 0.61 (0.48-0.76)	Women • G1 = 1.00 (referent) • G2 = 0.75 (0.57-0.97) • G3 = 0.72 (0.50-1.05) • G4 = 0.70 (0.54-0.91) • G5 = 0.64 (0.52-0.79) • G6 = 0.58 (0.45-0.73) • G7 = 0.72 (0.48-1.07) • G8 = 0.61 (0.47-0.80) • G9 = 0.66 (0.51-0.85)
D & B score = 12					
Schnohr et al 2004 [213]	To examine whether the relationship between established risk factors and mortality differs with socioeconomic status as measured by level of education.	• n = 30,635 (16,236 men; 14,399 women)	16 year follow-up	• 10,952 deaths	The study shows the strong predictive effect of PA on mortality is independent of education level.

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

	Socioeconomic status assessment: level of education	Incidence of all-cause mortality and PA stratified by years of education
Denmark	<ul style="list-style-type: none"> • Sex: Men and women • Age: 20-93 yr • Characteristics: Participants from the Copenhagen City Heart Registered Population 	
Prospective cohort D & B score = 12	PA assessment: Questionnaire 4 groups of PA G1 = none or very little G2 = 2-4 h/wk of LPA G3 = >4 h/wk of LPA or 2-4 h/wk of high level activity G4 = Competition level or >4 h/wk of hard level activity	Deaths <8 years of education Men G1 = 916 G2 = 1693 G3 = 1012 G4 = 67 Women • G1 = 872 • G2 = 1298 • G3 = 346 • G4 = 10 8-11 years of education Men • G1 = 432 • G2 = 1040 • G3 = 616 • G4 = 33 Women • G1 = 363 • G2 = 852 • G3 = 268 • G4 = 10 >11 years of education Men • G1 = 104 • G2 = 302 • G3 = 182 • G4 = 11 Women

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Schnohr et al [214]	To investigate the association between LTPA and mortality.	<ul style="list-style-type: none"> n = 4,894 (2,136 men; 2,758 women) Sex: Men and women Age: 20-79 yr Characteristics: Healthy males and women 	Baseline (1976) and start of follow-up in 1981-1983 (to 2000)	<ul style="list-style-type: none"> G1 = 48 G2 = 129 G3 = 61 G4 = 3 1,787 deaths 	Long-term moderate or high PA was associated with significantly lower mortality in men and women.
Denmark				RR (95% CI)	
Prospective cohort			PA assessment: Survey for LTPA, 3 groups:	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.64 (0.56-0.73) G3 = 0.56 (0.48-0.65) 	
D & B score = 13		The Copenhagen City Heart Study	<ul style="list-style-type: none"> G1 = Low G2 = Mod G3 = High 	<ul style="list-style-type: none"> Trend $p < 0.001$ Multivariate adjustment G1 = 1.00 (referent) G2 = 0.78 (0.68-0.89) G3 = 0.75 (0.64-0.87) Trend $p = 0.001$ 	
Schooling et al 2006 [215]	To examine how a comprehensive assessment of baseline health status affects the relationship between obesity or PA and mortality.	<ul style="list-style-type: none"> n = 54,088 (17,849 men; 36,239 women) Sex: Men and women Age: ≥ 65 yr Characteristics: Chinese elders 	4.1 year follow-up	<ul style="list-style-type: none"> 3,819 deaths 	PA, which normally has a negative relationship with adiposity, had the largest impact on survival for the health states, with the strongest inverse relationship between BMI and mortality.
Hong Kong			PA assessment: Interview for PA min/d, 3 groups	Incidence of all-cause mortality and PA	
Prospective cohort			<ul style="list-style-type: none"> G1 = None G2 = ≤ 30 min/d G3 = ≥ 30 min/d 	Adjusted HR (95% CI)	
D & B score = 13				<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.83 (0.76-0.91) G3 = 0.73 (0.67-0.80) Trend $p < 0.001$ 	

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Sundquist et al 2004 [216]	To study the association between varying levels of PA and all-cause mortality in the elderly.	<ul style="list-style-type: none"> n = 3,206 (1,414 men; 1,792 women) Sex: Men and women Age: ≥65 yr Characteristics: Non-institutionalized elders 	Baseline (1988-1989) and follow-up in 2000 PA assessment: Questionnaire for PA, 5 groups	<ul style="list-style-type: none"> 1,806 deaths 	Even occasional PA decreases the risk of mortality among elderly people.
Sweden					
Prospective cohort					
D & B score = 12					
Talbot et al 2007 [217]	To investigate how changes in LTPA affect all-cause mortality.	<ul style="list-style-type: none"> n = 2,092 (1,316 men; 776 women) Sex: Men and women Age: 19-90 yr 	Baseline in 1958 for males and in 1978 for females and an average follow-up of 21.2 ± 9.4 years for men and 10.2 ± 5.6 years for women	<ul style="list-style-type: none"> 628 deaths (538 male; 90 female) 	Greater declines in total and high-intensity LTPA are independent predictors of all-cause mortality.
USA					

RR (95% CI) for standard deviation of rate of change in LTPA

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Prospective cohort	<ul style="list-style-type: none"> • Characteristics: Community residents; generally with above average income, high education and with good or excellent self related health 	<p>(If RR is <1 then a SD increase is associated with decrease mortality. If RR is >1, then a SD increase is associated with increase in mortality)</p>
D & B score = 13	<p>PA assessment: Questionnaire for LTPA (METs min/24 h), 3 groups</p> <p>G1 = low</p> <p>G2 = medium</p> <p>G3 = high</p> <p>Rate of change (ROC)</p>	<p>Multivariate adjustment</p> <p>Men <70 years</p> <ul style="list-style-type: none"> • G1 = 0.96 (0.84-1.08) • G2 = 0.91 (0.79-1.04) • G3 = 0.42 (0.33-0.53) • ROC low = 0.90 (0.80-1.01) • ROC med = 1.01 (0.90-1.14) • ROC high = 0.78 (0.65-0.94) <p>Men >70 years</p> <ul style="list-style-type: none"> • G1 = 0.95 (0.82-1.10) • G2 = 0.89 (0.76-1.05) • G3 = 0.78 (0.62-0.97) • ROC low = 1.07 (0.93-1.24) • ROC med = 1.13 (1.00-1.27) • ROC high = 0.91 (0.75-1.12) <p>Women <70 years</p> <ul style="list-style-type: none"> • G1 = 0.75 (0.53-1.07) • G2 = 0.61 (0.36-1.03) • G3 = 0.80 (0.50-1.30) • ROC low = 1.02 (0.74-1.40) • ROC med = 1.38 (0.86-2.28) • ROC high = 0.90 (0.63-1.27) <p>Women >70 years</p> <ul style="list-style-type: none"> • G1 = 0.85 (0.63-1.15) • G2 = 0.78 (0.39-1.59) • G3 = 0.62 (0.32-1.22) • ROC low = 1.10 (0.85-1.42) • ROC med = 0.96 (0.46-2.03) • ROC high = 0.70 (0.40-1.22)

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Trolle-Lagerros et al 2005 [218]	To quantify the effect of PA on overall mortality in younger women and to assess the effect of past versus current activity.	<ul style="list-style-type: none"> n = 99,099 11.4 year follow-up 1,313 deaths 	Current: PA substantially reduces mortality among women. The association is observed even with low levels of PA and is accentuated with increased PA.
Sweden and Norway	<ul style="list-style-type: none"> Sex: Women Age: 30-49 yr 	PA assessment: Questionnaire using a 5 point scale, 5 groups	Incidence of all-cause mortality and PA past and current
Retrospective cohort	<ul style="list-style-type: none"> Characteristics: Participants from Norway and one region of Sweden 	G1 = Sedentary	Adjusted HR (95% CI)
D & B score = 13	<ul style="list-style-type: none"> G2 = Low G3 = Moderate G4 = High G5 = Vigorous 	PA at enrolment	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.78 (0.61-1.00) G3 = 0.62 (0.49-0.78) G4 = 0.58 (0.44-0.75) G5 = 0.46 (0.33-0.65)
		Trend $p < 0.0001$	Trend $p < 0.0001$
		PA at age 30 yr	PA at age 30 yr
		<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.79 (0.55-1.15) G3 = 0.90 (0.64-1.28) G4 = 0.98 (0.68-1.42) G5 = 0.96 (0.65-1.44) 	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.79 (0.55-1.15) G3 = 0.90 (0.64-1.28) G4 = 0.98 (0.68-1.42) G5 = 0.96 (0.65-1.44)
		Trend $p = 0.22$	Trend $p = 0.22$
		PA at age 14 yr	PA at age 14 yr
		<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.95 (0.66-1.38) G3 = 0.96 (0.69-1.34) G4 = 0.88 (0.62-1.25) G5 = 1.06 (0.75-1.51) 	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.95 (0.66-1.38) G3 = 0.96 (0.69-1.34) G4 = 0.88 (0.62-1.25) G5 = 1.06 (0.75-1.51)
		Trend $p = 0.62$	Trend $p = 0.62$
Villeneuve et al 1998 [219]	To examine the relationship between PF, PA and all-cause mortality.	Baseline (1981) and 7 year follow-up	There was a reduction in mortality risk associated with even modest participation in activities of low intensity.
Canada	<ul style="list-style-type: none"> Sex: Men and women Age: 20-69 yr 	PA assessment: Questionnaire for EE (kcal/kg/day), 5 groups	LTPA, men

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

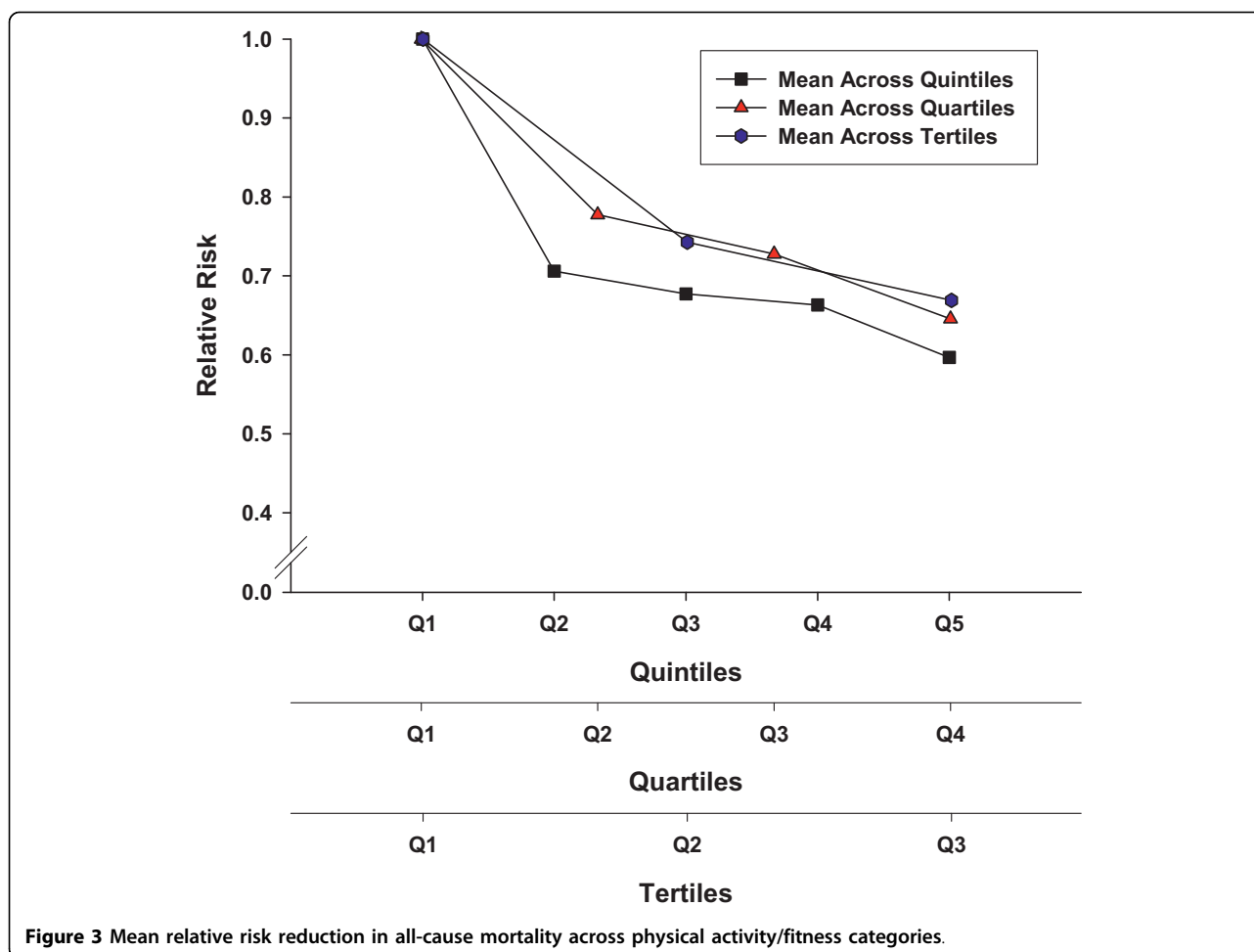
Prospective cohort	<ul style="list-style-type: none"> • Characteristics: Asymptomatic for CVD 	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.81 (0.59-1.11) • G3 = 0.79 (0.54-1.13) • G4 = 0.86 (0.61-1.22) • G5 = 0.82 (0.65-1.04)*
D & B score = 11	<p>Canadian Fitness Survey</p> <p>G1 = 0-<0.5 G2 = 0.5-<1.5 G3 = 1.5-<3.0 G4 = ≥ 3.0 G5 = ≥ 0.5</p> <p>PF levels: Recommended Minimum</p> <p>Undesirable Refusal</p>	<p>Non vigorous LTPA, men</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.81 (0.56-1.17) • G3 = 0.70 (0.44-1.13) • G4 = 0.82 (0.53-1.27) • G5 = 0.78 (0.59-1.04)* <p>LTPA, women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.94 (0.69-1.30) • G3 = 0.92 (0.64-1.34) • G4 = 0.71 (0.45-1.11) • G5 = 0.88 (0.68-1.04)* <p>Non vigorous LTPA, women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.97 (0.69-1.36) • G3 = 0.87 (0.57-1.33) • G4 = 0.72 (0.43-1.21) • G5 = 0.89 (0.67-1.17)* <p>RR (95% CI) by fitness levels, adjusted for age, sex and smoking Recommended = 1.00 (referent)</p> <ul style="list-style-type: none"> • Minimum = 1.02 (0.69-1.51) • Undesirable = 1.52 (0.72-3.18) • Refusal = 1.04 (0.45-2.39)
Weller and Corey 1998 [220]	<p>To study the relationship between PA and mortality in women.</p> <ul style="list-style-type: none"> • n = 6620 • Sex: Women • Age: ≥;30 yr 	<p>Baseline and 7 year follow-up</p> <ul style="list-style-type: none"> • 449 deaths <p>OR (95% CI)</p>

PA is inversely associated with risk of death in women.

Table 11: Studies examining the relationship between physical activity and all-cause mortality. (Continued)

Canada	<ul style="list-style-type: none"> • Characteristics: Without known heart disease • Canadian Fitness Survey 	PA assessment: Questionnaires for: EE (kcal/kg/d), quartiles	EE (kcal/kg/d) <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.91 (0.66-1.25) • Q3 = 0.94 (0.72-1.23) • Q4 = 0.89 (0.67-1.17)
Prospective cohort		Q1 = lowest Q2 = Q3 = Q4 = highest LTPA, 3 groups G1 = Sedentary G2 = Mod G3 = High	LTPA levels <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.63 (0.46-0.86) • G3 = 0.76 (0.59-0.98)
D & B score = 11		Walking, 3 groups G1 = < half the time G2 = half the time G3 = > half the time	Walking <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.64 (0.49-0.82) • G3 = 0.64 (0.47-0.86)
Yu et al 2003 [221]	To examine the relationship between LTPA and all-cause mortality.	Baseline and 10 year follow-up	• 252 deaths
UK	<ul style="list-style-type: none"> • n = 1,975 • Sex: Men • Age: 49-64 yr • Characteristics: Without a history of CHD at baseline 	PA assessment: Questionnaire (Minnesota LTPA index, kcal/d), 3 group	Age adjusted HR (95% CI) <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.73 (0.54-0.99) • G3 = 0.74 (0.55-1.04) Trend $p = 0.046$
Prospective cohort		G1 = Light to no activity G2 = Moderate activity G3 = Heavy activity	Multivariate adjusted <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.79 (0.58-1.08) • G3 = 0.76 (0.56-1.04) Trend $p = 0.083$
D & B score = 11			The study found a strong inverse association between heavy LTPA and all-cause mortality.

D & B score, Downs and Black quality score; PF, physical fitness; YR, years; RR, risk ratio; 95% CI, 95% confidence interval; PA, physical activity; VO2 peak, peak oxygen consumption; HR, hazard ratio; min/d, minutes per day; kcal/wk, kilocalories per week; LTPA, leisure-time physical activity; MET, metabolic equivalent; VO2 max, maximal oxygen consumption; OPA, occupational physical activity; CVD, cardiovascular disease; hr/wk, hours per week; MPA, moderate physical activity; kcal/kg/wk, kilocalories per kilogram per week; KJ/wk, kilojoules per week; EE, energy expenditure; G, groups; EE, energy expenditure; BMI, body mass index; C, class; kg/m², kilogram by meters squared; HR, heart rate; BPM, beats per minute; MVPA, moderate to vigorous physical activity; OR, odds ratio; Q, quartile or quintile; RCT, randomized clinical trial; T, tertiles; TPA, total physical activity; VPA, vigorous physical activity; mL/kg/min, milliliters per kilogram per minute.

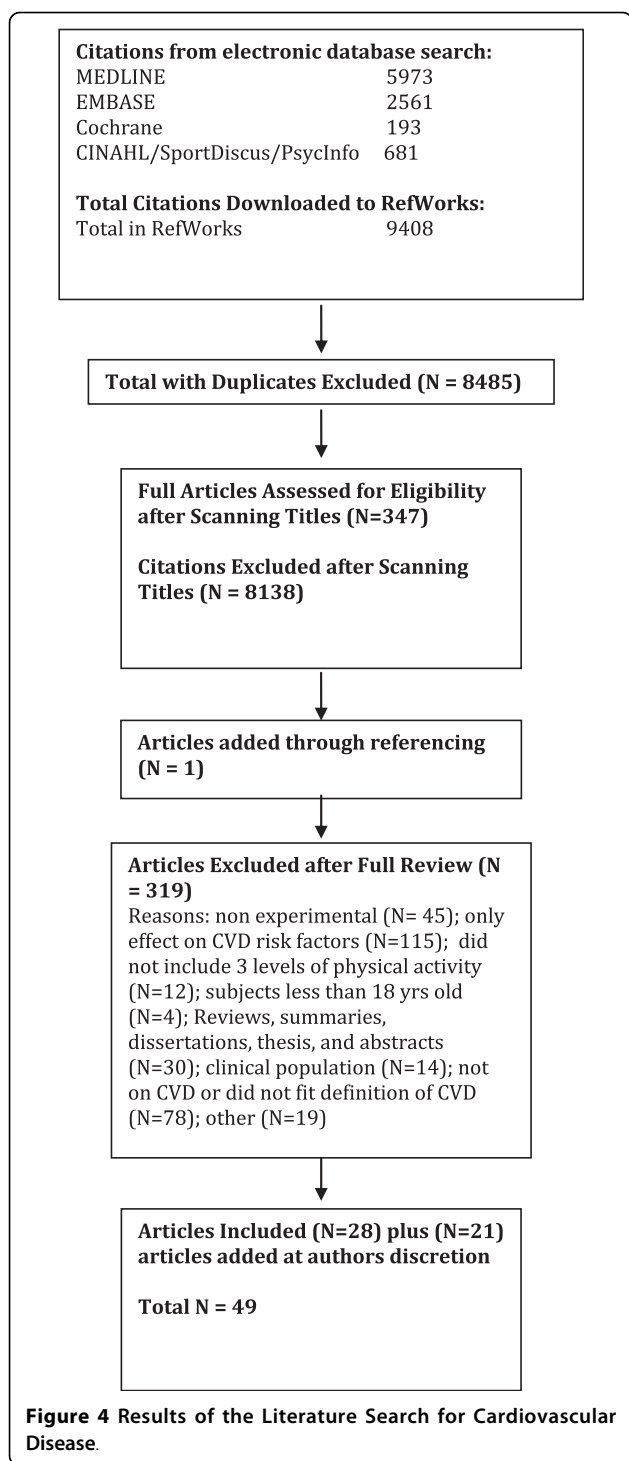


definition of cardiovascular disease ($n = 78$), and other ($n = 19$). Therefore, a total of 49 articles were included in the systematic review of the literature regarding the relationship between physical activity and the incidence of cardiovascular disease.

The majority of the studies included in our systematic review were prospective cohort investigations (Table 12). These studies involved a total of 726,474 participants; averaging 12,313 participants per study (range 680-88,393). There were a total of 34,815 reported cases of cardiovascular disease (ranging per study from 42-2,596). The total length of study follow-up for the prospective cohort studies averaged 14.1 yr (ranging from 2-29 yr). The articles were published over a 32 yr period ranging from 1975 to 2007. These studies involved large samples of men and women from regions throughout the world.

Similar to the all-cause mortality data, the risk for cardiovascular disease demonstrates a graded inverse dose-response relationship to physical activity and fitness. The relative reduction in the incidence of cardiovascular disease averages 33% (median risk reduction of 36%),

with greater risk reductions in studies that employed objective measures of aerobic fitness. It is not uncommon for studies to demonstrate a 50% or higher risk reduction when an objective measure of physical fitness was taken (Table 12). The importance of physical activity may actually be underestimated owing to multivariate control for many confounding factors (as discussed previously) and the fact that effects of within-person variation in physical activity are often not considered [55]. The relative risk reduction appears to be similar for men and women, and also appear to extend to non-Caucasian populations [56]. Some evidence also exists indicating that small amounts of physical activity are associated with lower cardiovascular-disease related mortality [57,58]. Similar to all-cause mortality, physical activity confers health benefits independent of other known risk factors [42,59]. *Collectively, the level of evidence would be considered to be Level 2A based on the presence of overwhelming evidence from observational trials.* The quality of the investigations was generally high with a mean (and median) Downs and Black score of 12 (range 9-14).



Implications

Research in the field began with the landmark work of Morris and colleagues, which demonstrated that men in physically demanding occupations (bus conductors and postmen) had a significantly lower risk of heart disease than individuals who worked in less demanding jobs (bus drivers and office workers) [45]. Since then

considerable research has examined the relationship between physical activity and the risk for cardiovascular disease. In fact, several systematic reviews of the literature have been developed regarding the role of habitual physical activity in the primary and secondary prevention of cardiovascular disease [33,60-62]. The research to date has been consistent and compelling, habitual physical activity reduces markedly the risk for cardiovascular disease.

Based on the available literature, there is compelling evidence that the recommendation of 30 min of moderate intensity exercise on most days of the week (equivalent to 4.2 MJ/wk or 1000 kcal/wk) reaches a threshold associated with significant reductions in cardiovascular-related mortality [32,63]. Brisk walking has also been shown to be preferable to a slower pace [64]. However, weekly exercise volumes of less than 4.2 MJ (1000 kcal) may be cardio-protective [14,59,65-67]. For instance, Lee et al. (2001) found that as little as 1 hr/wk of walking was associated with a 50% lower cardiovascular disease mortality in one sample of women. Wisloff et al. [58] reported that a single weekly bout of self-reported high intensity exercise was associated with a lower risk of cardiovascular death relative to those reporting no activity in both men (RR = 0.61, 95% CI = 0.49-0.75), and women (RR = 0.49, 95% CI = 0.27-0.89). Moreover, no additional benefit was seen with higher durations or frequency of exercise sessions [58]. The authors stated that this evidence challenges "current recommendations that require at least 1000 kcal of caloric expenditure per week to achieve exercise-induced protection against premature cardiovascular death." However, this research is in fact supportive of the Canadian guidelines which recognize the potential health benefits of low volumes of physical activity as reflected by the statement "Every little bit counts, but more is even better - everyone can do it!" It however should be noted that the statement "more is even better" is supported by a strong evidence base.

Recommendation #2

For a reduced risk for cardiovascular disease-related events and mortality, it is recommended that individuals participate in 30 min or more of moderate to vigorous exercise on most days of the week. Greater health benefits appear to occur with high volume and/or intensities of activity. Health benefits may also occur with as little as one hr of brisk walking per week. [Level 2, Grade A]

The Primary Prevention of Stroke

Stroke affects a significant proportion of Canadian society with approximately 50,000 new cases each year [68]. The relationship between physical activity and the risk for stroke is compelling, supporting at least a 25-

Table 12 Studies examining the relationship between physical activity and cardiovascular disease.

Publication Country Study Design Quality Score	Objective	Population	Methods	Outcome	Comments and Conclusions
Paffenbarger and Hale 1975 [47] USA	To evaluate the role of PA in reducing coronary mortality among longshoremen	<ul style="list-style-type: none"> n = 6,351 Sex: Men Age: 35-74 yr Characteristics: Longshoreman 	22 years of follow up, or until reached the age of 75 yr PA assessment: Energy and oxygen cost requirements of longshoring jobs	RR (95% CI) Sudden death <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 3.5 G3 = 2.8 Delayed death <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 1.4 G3 = 1.5 Unspecified death <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 1.1 G3 = 1.6 	VPA is associated with reduced risk of coronary mortality, particularly sudden cardiac death.
Prospective cohort D & B score = 12			Activity level G1 = Heavy (5.2-7.5 kcal/min) G2 = Moderate (2.4-5.0 kcal/min) G3 = Light (1.5-2.0 kcal/min)		
Manson et al 2002 [56] USA	To compare the roles of walking and vigorous exercise in the prevention of CV events in a large, ethnically diverse cohort of postmenopausal women.	<ul style="list-style-type: none"> n = 73,743 Sex: Women Age: 50-79 yr Characteristics: Healthy, Post Menopausal 	Enrolment from 1994-98 Clinic visit for baseline screening, PA assessment: Questionnaire for: Total exercise (MET- hr/wk) G1 = 0-2.4 G2 = 2.5-7.2	<ul style="list-style-type: none"> Number of New Cases: 345 Total Number of CVD events: 1551 Age adjusted RR (95% CI) Total exercise (MET-hr/wk) G1 = 1.00 (referent) G2 = 0.73 (0.53-0.99) 	Both walking and VPA are associated with substantial reductions in the incidence of CHD events.
Prospective cohort		<ul style="list-style-type: none"> Women's Health Initiative Observational Study 			

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

D & B score = 12	G3 = 7.3-13.4 G4 = 13.5-23.3 G5 = ≥ 23.4	• G3 = 0.69 (0.51-0.95) • G4 = 0.68 (0.50-0.93) • G5 = 0.47 (0.33-0.67) <i>p</i> = <0.001	Walking (MET-hr/wk)	• G1 = 1.00 (referent) • G2 = 0.71 (0.53-0.96) • G3 = 0.60 (0.44-0.83) • G4 = 0.54 (0.39-0.76) • G5 = 0.61 (0.44-0.84) <i>p</i> = 0.004	Walking (MET-hr/wk)	• G1 = 1.00 (referent) • G2 = 0.71 (0.53-0.96) • G3 = 0.60 (0.44-0.83) • G4 = 0.54 (0.39-0.76) • G5 = 0.61 (0.44-0.84) <i>p</i> = 0.004
	Time for VPA (min)	Vigorous exercise	• G1 = 1.00 (referent) • G2 = 1.12 (0.79-1.60) • G3 = 0.56 (0.32-0.98) • G4 = 0.73 (0.43-1.25) • G5 = 0.58 (0.34-0.99) <i>p</i> = 0.008	• G1 = 1.00 (referent) • G2 = 1.12 (0.79-1.60) • G3 = 0.56 (0.32-0.98) • G4 = 101-150 • G5 = > 150		
	Outcome Measure: Incidence of CVD and CHD	<i>p</i> = 0.008				
Wisloff et al 2006 [58]	To study the association between the amount and intensity of exercise and CVD mortality.	• n = 56,072 (27,143 men; 28,929 women)	Length of follow-up: 16 ± 4 yr	• Number of Cases: 1,603 male, 993 female	Men and women who exercise to a moderate degree and spend less than the recommended energy (< 1000 kcal/wk) are at lower risk of dying from heart disease than those who never exercise.	
Norway	• Sex: Men and women	Multivariate RR (95% CI)	PA assessment: Questionnaire for LTPA, 4 groups	Men		
Prospective cohort	• Age: ≥ 20 yr		Men	Men		
	• Characteristics: Free form CVD		Q1 = None	• Q1 = 1.00 (referent)		
	• HUNT study		Q2 = 1/wk >30 min high	• Q2 = 0.66 (0.50-0.87)		
D & B score = 12			Q3 = 2-3/wk > 30 min high	• Q3 = 0.83 (0.65-1.06)		
			Q4 = ≥ 4/wk > 30 min high	• Q4 = 0.77 (0.59-1.01)		
			Women	• Q1 = 1.00 (referent)		

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Women	<ul style="list-style-type: none"> • Q2 = 0.63 (0.31-1.29) • Q3 = 0.66 (0.32-1.34) • Q4 = 0.86 (0.45-1.62) 	
Q1 = None	Q2 = 1/wk ≤ 30 min low	
Q2 = 1/wk ≤ 30 min low	Q3 = 1/wk ≤ 30 min high	
Q3 = 1/wk ≤ 30 min high	Q4 = 2-3/wk ≤ 30 min low	
Q4 = 2-3/wk ≤ 30 min low	Outcome Measure: Ischaemic heart disease mortality	
Outcome Measure: Ischaemic heart disease mortality	Cox proportional HR	
Cox proportional HR	Recruitment of Participants: Sept 1992-May 1995	<ul style="list-style-type: none"> • Number of Cases: 244
Lee et al 2001 [59]	<ul style="list-style-type: none"> • n = 39,372 	Even light to moderate activity is associated with lower CHD rates in women.
USA and Puerto Rico	<ul style="list-style-type: none"> • Sex: Women • Age: ≥ 45 yr • Characteristics: Healthy • Women's Health Study 	
Prospective cohort	<ul style="list-style-type: none"> • PA assessment: Questionnaires Divided into 4 or 5 groups: 	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.86 (0.57-1.29) • G3 = 0.49 (0.28-0.86) • G4 = 0.48 (0.29-0.78)
D & B score = 12	Time spent walking	<ul style="list-style-type: none"> • p = <0.001
	<ul style="list-style-type: none"> • G1 = No regular walking • G2 = 1-59 min/wk • G3 = 1.0-1.5 h/wk • G4 = ≥ 2.0 h/wk 	Walking pace
	Walking pace (km/h)	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.56 (0.32-0.97) • G3 = 0.71 (0.47-1.05) • G4 = 0.52 (0.30-0.90)
	<ul style="list-style-type: none"> • G1 = No regular walking • G2 = 3.2 • G3 = 3.2-4.7 • G4 = ≥ 4.8 	<ul style="list-style-type: none"> • p = 0.02
	EE (kcal/wk)	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.79 (0.56-1.12) • Q3 = 0.55 (0.37-0.82) • Q4 = 0.75 (0.50-1.12)
	G1 = 200	
	G2 = 200-599	

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

	G3 = 600-1499 and G4 = 1500 or more		$p = 0.03$		
	Energy expenditure for VPA (kcal/wk)		Energy expended VPA (kcal/wk)		
	G1 = No vigorous, <200 kcal/wk		• G1 = 1.00 (referent)		
	G2 = No vigorous, ≥ 200 kcal/wk		• G2 = 0.65 (0.46-0.91)		
			• G3 = 1.18 (0.79-1.78)		
			• G4 = 0.96 (0.60-1.55)		
			• G5 = 0.63 (0.38-1.04)		
	G3 = Vigorous, 1-199 kcal/ wk				
	G4 = Vigorous, 200-499 kcal/wk				
	G5 = Vigorous, ≥ 500 kcal/wk				
Paffenbarger et al 1993 [67]	To analyze changes in the lifestyle of Harvard Alumni and the associations of these changes to mortality.	• n = 10,269	Alumni who increased their PA index to 2000 kcal or more per week had a 17% lower risk of death from CHD than those who were sedentary ($p = 0.507$)	Moderately vigorous sports activity was associated with lower rates of death from CHD among middle aged and older men	
USA		• Sex: Men • Age: 45-84 yr • Characteristics: Health, Harvard College Alumni			
Prospective cohort			PA assessment: Mailed questionnaires included questions on type, duration, intensity, frequency of PA.	Men who took up moderate took up moderately vigorous activity had a 41% lower risk than those who continued not to engage in such activity ($p =$ 0.044)	
D & B score = 13			Outcome Measure: CHD deaths between 1977 and 1985		
			Cox proportional hazards model		
			Poisson regression methods		
			The Mantel extension of the Mantel-Haenszel test		
Haapanen et al 1997 [77]	To examine the association between duration and intensity of LTPA and the risk of CHD.	• n = 2,840 (1,500 men; 1,340 women)	Length of Follow-up: 10 yrs	• Incident Rates (per 1000 person-years) for CHD = 108 for men and 75 for women.	Total EE had an inverse and independent association with risk of CHD in middle aged Finnish men but not among women.

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Study	Study Design	Population	PA assessment: Questionnaire for LTPA EE (kcal/wk)	Outcome Measure: CHD mortality	Multivariate RR (95% CI) LTPA and CHD mortality
Finland	Prospective cohort	<ul style="list-style-type: none"> Sex: Men and women Age: 35-63 yr Characteristics: Healthy 	<ul style="list-style-type: none"> Men G1 = 0-1100 G2 = 1101-1900 G3 = >1900 	<ul style="list-style-type: none"> Men G1 = 1.98 G2 = 1.33 G3 = 1.00 (referent) 	
D & B	score = 13		<ul style="list-style-type: none"> Women G1 = 0-900 G2 = 901-1500 G3 = >1500 	<ul style="list-style-type: none"> Women G1 = 1.25 G2 = 0.73 G3 = 1.00 (referent) 	
Barengo et al 2004 [164]	Prospective cohort	<ul style="list-style-type: none"> To investigate whether moderate or high LTPA are associated with a reduced CVD and all-cause mortality, independent of CVD risk factors and other forms of PA in men and women. n = 31,677 (15,853 men; 16,824 women) Sex: Men and women Age: 30-59 Characteristics: Participant from eastern and south-western Finland 	<ul style="list-style-type: none"> 20 year follow-up PA assessment: Questionnaire for LTPA and OPA, 3 groups G1 = Low activity G2 = Moderate activity G3 = High activity 	<ul style="list-style-type: none"> Number of Cases (Men): 1,661 Number of Cases (Women): 778 HR (95% CI) LTPA, men G1 = 1.00 (referent) G2 = 0.91 (0.82-1.00) G3 = 0.83 (0.69-0.99) LTPA, women (referent) G1 = 1.00 G2 = 0.83 (0.71-0.96) G3 = 0.89 (0.68-1.18) OPA, men G1 = 1.00 (referent) G2 = 0.75 (0.64-0.87) G3 = 0.77 (0.69-0.87) OPA, women 	<ul style="list-style-type: none"> Moderate and high levels of LTPA and OPA are associated with reduced CVD mortality.
Finland	Prospective cohort				
D & B	score = 14				

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Bijnen et al 1998 [166]	To describe the association between the PA pattern of elderly men and CHD mortality.	<ul style="list-style-type: none"> n = 802 Sex: Men Age: 64-84 yr 	Length of Follow-up: 10	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.73 (0.60-0.88) G3 = 0.77 (0.65-0.91) 	PA did not show a protective effect on death from CHD.
Netherlands	Characteristics: Free from Serious illness		PA assessment: Questionnaire, divided into 3 groups	RR (95% CI)	
Prospective cohort			G1 = Lowest	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.63 (0.38-1.05) G3 = 0.85 (0.51-1.44) 	
D & B score = 13	Ethnicity: Dutch Zutphen Elderly Study		Outcome Measure: CHD Mortality		
Davey-Smith et al 2000 [174]	To examine the association between two measures of physical activity (LTPA and usual walking pace) with cause specific mortality (CHD).	<ul style="list-style-type: none"> n = 6,702 Sex: Men Age: 40-64 yr Whitehall Study 	Cox Proportional HR Length of Follow-up: 25 yrs	<ul style="list-style-type: none"> Number of Cases: 955 	Inverse associations of both LTPA and walking pace with mortality from CHD were seen.
England			PA assessment: Questionnaire during examination for walking pace and LTPA	RR (95% CI) by walking pace	
Prospective cohort			Walking pace	<ul style="list-style-type: none"> G1 = 1.45 (0.9-2.2) G2 = 1.30 (1.1-1.6) G3 = 1.00 (referent) 	
D & B score = 11			G1 = Slower G2 = Same G3 = Faster		
			LTPA	<ul style="list-style-type: none"> p < 0.01 Multivariate RR (95% CI) by LTPA level G1 = 1.24 (1.0-1.5) G2 = 0.94 (0.8-1.2) G3 = 1.00 p < 0.05 	
			G1 = Inactive		

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

		G2 = Moderate G3 = Active			
Eaton et al 1995 [175]	To determine whether self reported PA predicts a decreased risk of CHD.	Moderate Active	Outcome Measure: CHD Mortality	Cox Proportional HR	Baseline levels of self reported LTPA predicted a decreased rate of CHD.
USA					
Prospective cohort					
D & B score = 11					
Hillsdon et al 2004 [183]	To examine whether a short, easily administered measure of PA is associated with the risk of death from all causes and specific causes.				
UK					
Prospective cohort					
D & B score = 11					

G2 = Moderate

G3 = Active

Outcome Measure: CHD Mortality

Cox Proportional HR

Length of Follow-up: 21 yrs

Number of Cases: 709

Age adjusted RR (95% CI) by LTPA level

- G1 = 1.00 (referent)
- G2 = 0.79 (0.63-0.99)
- G3 = 0.73 (0.59-0.89)

PA assessment: Interview

LTPA

Characteristics: Healthy, free of CHD

Sex: Men

Age: 40 yr

Ethnicity: Israeli

G1 = Sedentary

G2 = Light

G3 = Light Daily

G4 = Heavy

OPA

G1 = Sitting

G3 = Walking

G4 = Physical Labour

Outcome Measure: CHD Death

Cox Proportional HR

Length of Follow-up: > 10 yrs

Number of Cases: 155

Age adjusted RR (95% CI) by OPA level

- G1 = 1.00 (referent)
- G2 = 0.99 (0.75-1.18)
- G3 = 0.94 (0.78-1.12)
- G4 = 0.87 (0.67-1.10)

PA assessment: Questionnaire, 3 groups:

G1 = Never / <1 time/month

G2 = <2 times/wk

G3 = ≥ 2 times/wk

Characteristics: no history of chest pain

Sex: Men and women

Age: 35-64 yr

Ethnicity: no history of chest pain

Characteristics: no history of chest pain

Sex: Men and women

Age: 35-64 yr

Characteristics: no history of chest pain

Characteristics: no history of chest pain

Self reported VPA is associated with the risk of future mortality.

Multivariate RR (95% CI) by PA level

- G1 = 1.00 (referent)
- G2 = 0.46 (0.19-1.12)
- G3 = 0.96 (0.53-1.75)

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

	Outcome Measure: IHD mortality	Cox proportional HR	Age Adjusted RR (95% CI)	A relatively small amount (10-36 min/d) of daily moderate intensity LTPA can significantly reduce premature mortality from CHD in middle aged men at high risk for CHD.
Leon et al 1997 [199]	To study the relationship of PA to CHD in a well defined population at above average risk for CHD over a 16 yr observation period.	<ul style="list-style-type: none"> n = 12,138 	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.71 (0.56-0.91) 	
USA		<ul style="list-style-type: none"> Sex: Men Age: 35-57 yr 	<ul style="list-style-type: none"> G3 = 0.75 (0.59-0.96) 	
Prospective cohort		<ul style="list-style-type: none"> PA assessment: Questionnaire at baseline (Minnesota LTPA questionnaire), divided/grouped into deciles of LTPA (min/d) 	<ul style="list-style-type: none"> G4 = 0.69 (0.54-0.96) 	
D & B score = 11		<ul style="list-style-type: none"> Characteristics: Free of CHD but in the upper 10-15% of a CHD probability risk score 	<ul style="list-style-type: none"> Multivariate adjusted RR (95% CI) G1 = 1.00 (referent) G2 = 0.75 (0.54-0.96) G3 = 0.81 (0.64-1.04) G4 = 0.75 (0.59-0.96) 	
		<ul style="list-style-type: none"> Multiple risk factor intervention trial 		
		<ul style="list-style-type: none"> Length of Follow-up: 20 yrs 	<ul style="list-style-type: none"> Number of Cases: 684 	There appears to be a protective effect of LTPA on CHD-related death.
Rosengren et al 1997 [211]	To examine the long term effect of OPA and LTPA on the risk of death from CHD.	<ul style="list-style-type: none"> n = 7,142 Sex: Men Age: 47-55 yr 	<ul style="list-style-type: none"> Multivariate RR (95% CI) for LTPA G1 = 1.00 (referent) G2 = 0.84 (0.71-1.00) G3 = 0.84 (0.73-0.96) 	
Sweden		<ul style="list-style-type: none"> Characteristics: Swedish men 		
Prospective cohort		<ul style="list-style-type: none"> PA assessment: Questionnaire for LTPA, 3 groups G1 = Sedentary G2 = Moderately active 		

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

D & B score = 13	G3 = Regular exercise	Outcome Measure: CHD death	Proportional HR	Number of Cases: 292	There was an inverse and significant dose-response association between LTPA and CHD-related mortality.
Schnohr et al 2006 [214]	<ul style="list-style-type: none"> n = 4,894 (2,136 men; 2,758 women) 	Participants included in the study were only those whose PA levels did not change over 5 years	Adjusted RR (95% CI) Whole group	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.71 (0.51-0.99) G3 = 0.56 (0.38-0.82) 	
Denmark	<ul style="list-style-type: none"> Sex: Men and women 	PA assessment:	Men	<ul style="list-style-type: none"> G1 = referent G2 = survived 4.9 yrs longer G3 = survived 6.8 yrs longer 	
Prospective cohort	<ul style="list-style-type: none"> Age: 20-79 yr 	Questionnaire LTPA	Men		
D & B score = 12	<ul style="list-style-type: none"> Characteristics: Healthy Copenhagen City Heart Study 	Cox proportional HR	Men		
Weller et al 1998 [220]	<ul style="list-style-type: none"> n = 6,620 Sex: Women Age: ≥ 30 yr Characteristics: Canadian Women 	Length of Follow-up: 7 yrs	Women	<ul style="list-style-type: none"> G1 = referent G2 = survived 5.5 yrs longer G3 = survived 6.4 yrs longer 	LTPA is inversely associated with risk of fatal MI.
Canada	<ul style="list-style-type: none"> Sex: Women Age: ≥ 30 yr Characteristics: Canadian Women 	PA assessment: Questionnaire, 4 groups for LTPA (kcal/kg/day) and non-LTPA (kcal/kg/day)	OR (95% CI) by LTPA	<ul style="list-style-type: none"> Q1 = 1.00 (referent) Q2 = 0.61 (0.07-1.19) Q3 = 0.84 (0.52-1.37) Q4 = 0.63 (0.36-1.09) 	
Prospective cohort	<ul style="list-style-type: none"> Age: ≥ 30 yr Characteristics: Canadian Women 	LTPA (kcal/kg/day)	OR (95% CI) by non-LTPA		
D & B score = 9					

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

			<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.71 (0.44-1.16) • Q3 = 0.57 (0.33-0.97) • Q4 = 0.49 (0.26-0.92)
			Non-LTPA (kcal/kg/day) Q1 = ≥ 0 Q2 = ≥ 2.8 Q3 = ≥ 5.9 Q4 = ≥ 9.9 Outcome Measure: Fatal MI Logistic regression analysis
Yu et al 2003 [221]	To examine the optimal intensity of LTPA to decrease the risk of CHD mortality in middle aged British men.	<ul style="list-style-type: none"> • n = 1,975 • Sex: Men • Age: 49-64 yr • Characteristics: Healthy, no previous history of CHD 	<ul style="list-style-type: none"> • Number of Cases: 82
UK			PA assessment: Questionnaire (Minnesota LTPA questionnaire), 3 groups Multivariate adjusted HR (95% CI) <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.74 (0.44-1.25) • G3 = 0.55 (0.31-0.98) p = 0.039
Prospective cohort			Relationship was not significant for low- moderate intensity LTPA and OPA.
D & B score = 11			
Altieri et al 2004 [222]	To assess the possible protective role of PA on CHD.	<ul style="list-style-type: none"> • n = 985 (507 men, 478 women) • Sex: Men and women • Age: < 79 yr 	Number of Cases: 507 OR (95% CI) for CHD and OPA <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.63 (0.39-1.03) • Q3 = 0.56 (0.35-0.90)
Italy			
Case Control			LTPA from 15-19 yrs as well as OPA from 30 - 39 yrs both have a significant inverse relationship with risk of non fatal acute MI.

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

D & B score = 11	<ul style="list-style-type: none"> • Characteristics: Case: Patients admitted to Hospital with non-fatal Acute MI. Controls: Patients admitted to hospital for acute condition unrelated to known or potential risk factors for acute MI 	Q4 = highest • Q4 = 0.57 (0.34-0.95)	p = 0.045	Outcome Measure: Non Fatal acute MI Unconditional logistic regression	Length of Follow-up: 25 yr • Number of Cases: 837	A suggestion that the symptomatic nature of ischemia appeared to modify the affects of
UK	To examine the relationship between physical activity and three mortality endpoints in healthy persons.	<ul style="list-style-type: none"> • n = 6,474 • Sex: Men • Age: 40-64 yr 	• Number of Dropouts: 158	PA assessment: Questionnaire for LTPA, divided into 3 groups:	HR (95% CI) for CHD and LTPA	PA on total and CHD mortality.
Prospective cohort		<ul style="list-style-type: none"> • Characteristics: British civil servants who underwent a resting ECG 	<ul style="list-style-type: none"> • G1 = 1.14 (0.9-1.4) • G2 = 0.94 (0.8-1.1) • G3 = 1.00 (referent) 	G1 = Inactive G2 = Moderate G3 = Active		
D & B score = 13				Outcome Measure: CHD mortality Cox Proportional HR		
Chen and Millar [224]	To examine the potential protective effect of LTPA on the incidence of heart disease and depression.	<ul style="list-style-type: none"> • n = 15,670 • Sex: Men and women • Age: ≥ 20 yr 	• 100 cases	PA assessment: EE from self administered questionnaire, 4 groups (kcal/kg/day)	Adjusted OR (95% CI)	Regular and at least MPA can be beneficial to heart health.
Canada		<ul style="list-style-type: none"> • Characteristics: Healthy and free from heart disease 	<ul style="list-style-type: none"> • G1 = 5.0 (1.84-13.59) • G2 = 3.7 (1.26-10.67) • G3 = 1.00 (referent) 			
Prospective cohort						

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

D & B score = 11	National Population Health Survey	<ul style="list-style-type: none"> G1 = Sedentary G2 = Light (<1.5) G3 = Moderate (1.5-2.9) G4 = Active (≥ 3) Outcome Measure: CHD incidence Multiple logistic regression	<ul style="list-style-type: none"> • G4 = 1.3 (0.41-3.89) 	PA during middle age predicts lower risk of CHD	
Conroy et al 2005 [225]	To examine the relationship between 1) PA during young adulthood and middle age, and 2) PA during each time period and CHD during middle age and older women.	<ul style="list-style-type: none"> • n = 37,169 • Sex: Women • Age: ≥ 45 yr 	Length of Follow-up: 9 yrs	Number of Cases: 477	PA during middle age predicts lower risk of CHD
US	<ul style="list-style-type: none"> • Characteristics: Healthy women health professionals • Women's Health Study 	PA assessment: Questionnaire for EE (kcal/wk) and months/yr	Multivariate RR (95% CI) Baseline PA and incidence of CHD	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.62 (0.48-0.80) • G3 = 0.61 (0.48-0.79) • G4 = 0.61 (0.46-0.81) 	
Cohort study D & B score = 11		Baseline PA (kcal/wk)	<ul style="list-style-type: none"> G1 = <200 G2 = 200-599 G3 = 600-1499 G4 = ≥ 1500 	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.76 (0.57-1.02) • G3 = 0.95 (0.72-1.24) • G4 = 1.04 (0.78-1.39) • G5 = 0.81 (0.58-1.14) 	Past PA and incidence of CHD Past PA and incidence of CHD
		Past PA			
		Months per year			
		G1 = 0			
		G2 = 1-3			
		G3 = 4-6			
		G4 = 7-9			
		G5 = 10-12			
		Outcome Measure: Incidence of CHD			
		Cox proportional hazard regression			

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Dorn et al 1999 [226]	To examine the long-term relationships between total PA and mortality from all causes and CHD in the general population.	• n = 1,461 (698 men; 763 women)	Length of Follow-up: 29 years	• Number of Cases: 109 men, 81 women	PA favorably influences mortality risks in non- obese men and younger women.
USA	• Sex: Men and women	PA assessment: Questionnaire	Multivariate RR (95% CI) for PAI in non- obese men	• 0.40 (0.19-0.88) for 1 kcal/kg/h	
Prospective cohort	• Age: 15-96 yr	Outcome Measure: CHD	Multivariate RR (95% CI) for PAI in obese men	• 1.86 (0.86-4.03) for 1 kcal/kg/h	
D & B score = 11	• Characteristics: Healthy, free from CHD, diabetes, and Stroke.	Mortality			
	• Ethnicity: White.	Cox Proportional Hazard Ratio	Multivariate RR (95% CI) for PAI in women < 60 yrs	• 0.42 (0.11-1.52) for 1 kcal/kg/h	
			Multivariate RR (95% CI) for PAI in women > 60 yrs	• 1.78 (0.77-4.09) for 1 kcal/kg/h	
Folsom et al 1997 [227]	To examine the association of PA at baseline with CHD incidence.	• n = 13,999 (6,166 men; 7833 women)	Length of Follow-up: 4-7 yrs	• Number of Cases: 223 men, 97 women, Multivariate RR (95% CI) LTPA, men	No significant relationships.
USA	• Sex: Men and women	PA assessment: Questionnaire during home interview, divided into quartiles of LTPA and sports activity			
Prospective cohort	• Age: 45-64 yr	Q1 = Low		• Q1 = 1.00 (referent) • Q2 = 1.08 (0.75-1.55)	
	• Characteristics: no CHD at baseline	Q2		• Q3 = 0.83 (0.51-1.36)	
		Q3		• Q4 = 0.89 (0.59-1.35)	
D & B score = 9	• Ethnicity: Black and non Black	Q4 = High	LTPA, women		
	• Atherosclerosis Risk in Communities Study		• Q1 = 1.00 (referent) • Q2 = 0.74 (0.42-1.31)		
			• Q3 = 1.07 (0.55-2.09)		

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

<p>Fransson et al 2004 [228]</p>	<p>To estimate the influence of LTPA and OPA on acute MI.</p>	<p>• n = 4069 (2,742 men; 1,327 women)</p>	<p>Exercise seems to reduce the risk of MI.</p>
<p>Sweden</p>	<p>• Sex: Men and Women</p>	<p>PA assessment: Questionnaire for LTPA, 5 groups</p>	<p>• Number of Cases: 1,204 men, 550 women</p>
<p>Case Control</p>	<p>• Age: 45-70 yr</p> <p>• Characteristics: Cases: Diagnosed with acute MI</p>	<p>G1 = Seldom G2 = Sometimes G3 = 1x/wk G4 = 2-3x/wk G5 = >3x/wk</p>	<p>OR (95% CI) LTPA, men • G1 = 1.00 (referent) • G2 = 0.76 (0.61-0.95) • G3 = 0.67 (0.51-0.88) • G4 = 0.63 (0.49-0.83) • G5 = 0.53 (0.38-0.73)</p>
<p>D & B score = 12</p>	<p>• Stockholm Heart: Epidemiology</p>	<p>Questionnaire for total physical activity, 3 groups</p> <p>G1 = Passive G2 = Somewhat active G3 = Active</p> <p>Questionnaire for sitting at work, 3 groups</p> <p>G1 = Less than half the time G2 = About half the time G3 = More than half the time</p>	<p>LTPA, women • G1 = 1.00 (referent) • G2 = 0.69 (0.49-0.98) • G3 = 0.38 (0.25-0.58) • G4 = 0.62 (0.38-1.01) • G5 = 0.31 (0.15-0.66)</p> <p>Total physical activity, men • G1 = 1.00 (referent) • G2 = 0.66 (0.47-0.94)</p>
<p>Outcome Measure: CHD incidence Poisson Regression</p>			
<p>• Q4 = 0.64 (0.34-1.24)</p>			
<p>Multivariate RR (95% CI) Sports, men</p>			
<p>• Q1 = 1.00 (referent)</p>			
<p>• Q2 = 1.15 (0.79-1.68)</p>			
<p>• Q3 = 1.03 (0.68-1.54)</p>			
<p>• Q4 = 0.83 (0.56-1.23)</p>			
<p>Sports, women</p>			
<p>• Q1 = 1.00 (referent)</p>			
<p>• Q2 = 0.99 (0.58-1.67)</p>			
<p>• Q3 = 0.64 (0.32-1.27)</p>			
<p>• Q4 = 0.72 (0.37-1.38)</p>			

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

<p>Fransson et al 2006 [229]</p>	<p>To evaluate whether LTPA compensates for the increased risk of acute MI associated with overweight and obesity.</p>	<p>n = 4069 (2,742 men; 1,327 women)</p>	<p>PA Assessment: Questionnaire for LTPA, 3 groups</p>	<p>Number of Cases: 1204 men, 550 women</p>	<p>Regular LTPA seems to provide protection against MI and non-fatal MI.</p>
<p>Sweden</p>	<p>• Sex: Men and women</p>	<p>• G1 = Very little /occasional walks</p>	<p>Multivariate OR (95% CI) for acute MI</p>	<p>LTPA, men</p>	<p>• G1 = 1.00 (referent)</p>
<p>Case Control</p>	<p>• Age: 45-70 yr</p>	<p>G2 = Occasional / once per week</p>	<p>• G1 = 1.00 (referent)</p>	<p>• G2 = 0.70 (0.58-0.84)</p>	<p>• G2 = 0.70 (0.58-0.84)</p>
<p>D & B score = 12</p>	<p>• Characteristics: Cases: had acute MI</p>	<p>G3 = Twice per week or more</p>	<p>• G3 = 0.57 (0.46-0.71)</p>	<p>LTPA, women</p>	<p>• G3 = 0.57 (0.46-0.71)</p>
<p>Outcome Measure: Acute MI</p>	<p>• G3 = 0.46 (0.31-0.69)</p>	<p>Outcome measure: Acute MI</p>	<p>• G1 = 1.00 (referent)</p>	<p>• G2 = 0.52 (0.40-0.68)</p>	<p>• G2 = 0.52 (0.40-0.68)</p>
<p>Conditional and unconditional logistics regression</p>	<p>Total physical activity, women</p>	<p>• G3 = 0.44 (0.30-0.65)</p>	<p>Multivariate OR (95% CI) for non-fatal MI</p>	<p>LTPA, men</p>	<p>• G3 = 0.44 (0.30-0.65)</p>
<p>Conditional and unconditional logistics regression</p>	<p>Sitting at work, men</p>	<p>• G1 = 1.00 (referent)</p>	<p>• G1 = 1.00 (referent)</p>	<p>• G2 = 0.91 (0.73-1.15)</p>	<p>• G2 = 0.91 (0.73-1.15)</p>
<p>Conditional and unconditional logistics regression</p>	<p>Sitting at work, women</p>	<p>• G1 = 1.00 (referent)</p>	<p>• G1 = 1.00 (referent)</p>	<p>• G2 = 0.77 (0.51-1.17)</p>	<p>• G2 = 0.77 (0.51-1.17)</p>
<p>Conditional and unconditional logistics regression</p>	<p>Sitting at work, men</p>	<p>• G3 = 0.47 (0.31-0.69)</p>	<p>• G3 = 0.47 (0.31-0.69)</p>	<p>• G3 = 0.47 (0.31-0.69)</p>	<p>• G3 = 0.47 (0.31-0.69)</p>

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Haapanen-Niemi 2000 [230]	To investigate the independent associations and the possible interaction of BMI, LTPA and perceived physical performance and functional capacity with the risk of mortality.	• n = 2,212 (1,090 men; 1,122 women)	Length of Follow-up: 16 yrs	LTPA, women	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.64 (0.48-0.86) • G3 = 0.58 (0.39-0.87) • Number of Cases: 208 all cause deaths, 54% of those CVD, 73% of CVD deaths due to CHD 	Increase perceived PF is associated with a reduced risk of CHD mortality in men.
Finland	• Sex: Men and women	PA assessment: Postal Survey				
Prospective cohort	• Age: 35-63 yr	Total LTPA energy expenditure (kcal/wk)			Multivariate RR (95% CI) Total LTPA EE index and CHD mortality, men	
D & B score = 13	• Characteristics: Healthy	G1 = High			• G1 = 1.00 (referent)	
	• Ethnicity: Finnish	G2 = Moderate			• G2 = 0.88 (0.44-1.76)	
		G3 = Low			• G3 = 1.70 (0.90-3.21)	
		Perceived physical fitness compared to age-mates			p = 0.056	
		G1 = Better			Multivariate RR (95% CI)	
		G2 = Similar			Perceived physical fitness, men	
		G3 = Worse			• G1 = 1.00 (referent)	
		Outcome Measure: CHD mortality			• G2 = 2.82 (1.06-7.46)	
					• G3 = 4.64 (1.56-13.84)	
					p = 0.011	
					Total LTPA EE index and CHD mortality, women	
					Cox proportional HR	
					• G1 = 1.00 (referent)	
					• G2 = 0.43 (0.16-1.16)	
					• G3 = 1.17 (0.51-2.68)	
					p = 0.046	
					Multivariate RR (95% CI)	
					Perceived physical fitness, women	
					• G1 = 1.00 (referent)	
					• G2 = 0.82 (0.32-2.16)	
					• G3 = 1.89 (0.57-6.27)	
					p = 0.154	

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Kannel et al 1986 [231]	To examine the role of low levels of OPA and LTPA in the development of CV morbidity and mortality over the short and long term.	Length of Follow-up: 24 yrs	• Number of Cases: 220 mortality, 371 morbidity	Rate of CHD Mortality and Morbidity decreases with increased level of PA but no association was found with physical demand of work
USA	<ul style="list-style-type: none"> • n = 1,166 • Sex: Men • Age: 45-65 yr • Characteristics: 	PA assessment: Questionnaire during examination	Cumulative 24 year age adjusted rate per 1000 people	
Prospective cohort		PA index: G1 = <29	24 hr PA index for LTPA CHD mortality • G1 = 255 • G2 = 184	
D & B score = 11		G2 = 30-34 G3 = >34	• G3 = 152 p < 0.01	
		Physical demand of work	24 hr PA index for LTPA CHD incidence • G1 = 414 • G2 = 353 • G3 = 311	
		G1 = Sedentary G2 = Light G3 = Medium G4 = Heavy		
		Outcome Measure: CHD mortality and Morbidity	Physical demand of work and CHD mortality • G1 = 216 • G2 = 209 • G3 = 169 • G4 = 170	
		Cox proportional HR		
			Physical demand of work and CHD incidence: • G1 = 355 • G2 = 405 • G3 = 307 • G4 = 325	
Kaprio et al 2000 [232]	To examine the contribution of genetic and other familial factors to the relationship between LTPA and CHD.	Length of Follow-up: 18 yrs	• Number of Cases: 723	LTPA compared to being sedentary helps prevent CHD in men.
Finland	<ul style="list-style-type: none"> • n = 8,205 • Sex: Men • Age: 25-69 yr • Characteristics: Same sex twin pairs, free of CVD 	PA assessment: Questionnaire for LTPA, 3 groups:	Multivariate RR (95% CI) • G1 = 1.00 (referent)	

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Prospective cohort				<ul style="list-style-type: none"> • G2 = 0.84 (0.70-1.01) • G3 = 0.68 (0.50-0.92) 	
D & B score = 12				<ul style="list-style-type: none"> • G1 = Sedentary • G2 = Occasional Exercisers • G3 = Conditioning Exercisers 	<ul style="list-style-type: none"> • p = 0.010
				Outcome Measure: Hospitalization or death from CHD	
				Poisson regression	
Lakka et al 1994 [233]	To investigate the independent associations of LTPA and maximal oxygen uptake with the risk of acute MI.	<ul style="list-style-type: none"> • n = 1,166 	Baseline examination: 1984-1989		Conditioning LTPA and VO ₂ max had an inverse, graded and independent association with the risk
Finland		<ul style="list-style-type: none"> • Sex: Men • Age: 42-61 yr 		Adjusted RH (95% CI) by conditioning PA level	
		<ul style="list-style-type: none"> • Characteristics: Healthy with normal ECG 	PA assessment: Questionnaire for conditioning PA (h/wk), 3 groups (h/wk)		
Prospective cohort			<ul style="list-style-type: none"> • G1 = <0.7 • G2 = 0.7 	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.11 (0.58-2.12) 	
		<ul style="list-style-type: none"> • Kuopio Ischaemic Heart Disease Risk Factor Study 	<ul style="list-style-type: none"> • G3 = >2.2 	<ul style="list-style-type: none"> • G3 = 0.31 (0.12-0.85) 	
D & B score = 13				Adjusted RG (95% CI) by VO ₂ max	
				<ul style="list-style-type: none"> • G1 = 1.00 • G2 = 0.76 (0.38-1.50) • G3 = 0.26 (0.10-0.68) 	
				PF assessment: VO ₂ max (ml/kg/min)	
			<ul style="list-style-type: none"> • G1 = <28.0 • G2 = 28.0-33.6 • G3 = >33.6 		
			Outcome event: acute MI		
			Cox proportional HR		

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

<p>Laukkanen et al 2004 [234]</p>	<p>To determine whether VO_{2peak} predicts CVD morbidity and mortality in a sample of men as related to conventional risk factors, medications or underlying chronic disease.</p>	<p>• 1,294 healthy; 1,057 unhealthy</p>	<p>PF Assessment: VO_2 peak (ml/kg/min) measured by exercise test with an electrically braked cycle ergometer, divided into quartiles</p>	<p>• Number of Cases: 204 CV deaths; 323 non-fatal coronary events</p>	<p>Dose-response relationship between directly measured PF and CVD death among healthy men at baseline.</p>
<p>Finland</p>	<p>• Sex: Men</p>	<p>• Age: 42-60 yr</p>	<p>• Characteristics: Healthy and not healthy participants</p>	<p>Healthy men with low VO_2 peak (lowest quartile) had an increased risk</p>	
<p>Prospective cohort</p>			<p>Q1 = <27.6</p>	<p>Adjusted RR (95% CI) by PF quartile Fatal MI</p>	
<p>D & B score = 11</p>	<p>• Kuopio Ischaemic Heart Disease Risk Factor Study</p>		<p>Q2 = 27.6-32.2</p>	<p>• 3.29 (0.86-12.90)</p>	<p>Unfit men with unfavorable risk profiles are the risk group that would benefit the most from preventative measures.</p>
			<p>Q3 = 32.3-37.1</p>		
			<p>Q4 = >37.2</p>	<p>Non-Fatal MI</p>	
			<p>Outcome Measure: Incidence of fatal and non fatal CVD during 13 year follow-up</p>	<p>• 2.16 (1.12-4.18)</p>	
			<p>Cox proportional HR</p>		
<p>Lee et al 2000 [235]</p>	<p>To investigate whether different durations of exercise episode are associated with different risk of CHD.</p>	<p>• n = 7,307</p>	<p>Baseline survey in 1988</p>	<p>• Number of Cases: 482</p>	<p>Longer durations of PA bouts are not associated with decreased CHD risk compared with shorter bouts, once total EE is taken into account.</p>
<p>USA</p>	<p>• Sex: Men</p>	<p>• Age: Mean 66.1 ± 7.5</p>	<p>PA assessment: Survey for EE (kJ/wk), divided into 5 groups and episodes of PA (min), divided into 6 groups</p>	<p>Multivariate adjusted RR (95% CI) by EE</p>	
<p>Prospective cohort</p>	<p>• Characteristics: Healthy</p>	<p>• Harvard Alumni Study</p>		<p>• G1 = 1.00 (referent)</p>	
				<p>• G2 = 0.80 (0.57-1.12)</p>	
				<p>• G3 = 0.80 (0.55-1.16)</p>	
				<p>• G4 = 0.74 (0.47-1.17)</p>	
				<p>• G5 = 0.62 (0.41-0.94)</p>	

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

D & B score = 12	<p>Energy expenditure (kJ/wk)</p> <p>G1 = <4,200</p> <p>G2 = 4,200-8,399</p> <p>G3 = 8,400-12,599</p> <p>G4 = 12,600-16,799</p> <p>G5 = ≥ 16,800</p> <p>Duration of PA episode (min)</p> <p>G1 = None</p> <p>G2 = 1-15</p> <p>G3 = 16-30</p> <p>G4 = 31-45</p> <p>G5 = 46-60</p> <p>G6 = >60</p> <p>Outcome Measure: Fatal and Non Fatal CHD</p> <p>Proportional hazards regression</p>	<p>As long as the total EE is similar, more frequent shorter bouts or longer less frequent bouts have an equivalent reduction in CHD risk.</p> <p>Multivariate adjusted RR (95% CI) by duration of PA episode</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.15 (0.70-1.87) • G3 = 1.01 (0.68-1.51) • G4 = 1.11 (0.67-1.84) • G5 = 1.18 (0.77-1.80) • G6 = 1.25 (0.83-1.87)
Lee et al 2003 [236]	<p>USA</p> <p>n = 7,337</p> <p>Sex: Male</p> <p>Age: Mean 66.1 yr</p> <p>Characteristics: Healthy</p> <p>Harvard Alumni Study</p>	<p>PA assessment: Survey rating usual level of exertion when exercising, divided into tertiles</p> <p>Number of Cases: 551</p> <p>Multivariate adjustment RR (95% CI)</p> <ul style="list-style-type: none"> • T1 = 1.00 (referent) • T2 = 0.87 (0.70-1.09) • T3 = 0.92 (0.75-1.14)
Prospective cohort	<p>Energy expenditure (kcal/wk)</p> <p>T1 = <1000</p> <p>T2 = 1000-2499</p> <p>T3 = ≥ 2500</p> <p>Cox proportional HR</p>	<p>Inverse association between relative intensity of PA and the risk of CHD.</p>
D & B score = 13		

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Lemaitre et al 1999 [237]	To investigate whether regular participation in moderate intensity activity confers overall protection from sudden primary cardiac arrest.	<ul style="list-style-type: none"> • n = 355 cases, 503 controls • Sex: Men and women • Age: 25-74 yr • Characteristics: Previously healthy prior to primary cardiac arrest. Control Subjects: Individually matched to case patients on age (within 7 years) and sex at a ratio of about 2:1 were randomly selected from community by random-digit dialing 	PA assessment: Interview (with spouses) for LTPA, 7 groups	<ul style="list-style-type: none"> • 355 cases 	Participation in moderate intensity LTPA was associated with a decreased risk of primary cardiac arrest.
USA			G1 = No activity G2 = Gardening only ≤ 60 min/wk G3 = Gardening only > 60 min/wk	RR (95% CI) • G1 = 1.00 (referent) • G2 = 0.52 (0.21-1.28) • G3 = 0.34 (0.13-0.89)	
Case control			G4 = Walking ≤ 60 min/wk G5 = Walking > 60 min/wk G6 = Moderate intensity LTPA (not walking or gardening) G7 = High intensity LTPA	<ul style="list-style-type: none"> • G4 = 0.45 (0.17-1.19) • G5 = 0.27 (0.11-0.67) • G6 = 0.31 (0.13-0.74) • G7 = 0.34 (0.16-0.75) 	
D & B score = 11			Logistic regression analysis		
Lemaitre et al 1995 [238]	To examine whether LTPA decreases the risk of MI in postmenopausal women.	<ul style="list-style-type: none"> • n = 1,193 • Sex: Women • Age: Mean 67 yr • Characteristics: Postmenopausal Cases: Diagnosed with non-fatal MI Controls: free from MI 	PA assessment: Phone interview for LTPA, divided into quartiles of EE (mean kcal/wk)	<ul style="list-style-type: none"> • Number of Cases: 268 	Risk of MI among postmenopausal women is decreased by 50% with modest LT energy expenditures, equivalent to 30-45 min of walking for exercise three times per week
USA			Q1 = 71 Q2 = 472 Q3 = 1183 Q4 = 3576	Multivariate RR (95% CI) • Q1 = 1.00 (referent) • Q2 = 0.52 (0.34-0.80) • Q3 = 0.40 (0.26-0.63) • Q4 = 0.40 (0.25-0.63) p = <0.001	
Case control			Outcome Measure: Diagnosed with non-fatal MI	Logistic regression analysis	
D & B score = 11					

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Li et al 2006 [239]	To examine independent and joint associations of PA and adiposity with CHD incidence.	<ul style="list-style-type: none"> n = 88,393 Sex: Women 	Length of Follow-up: 20 yrs	<ul style="list-style-type: none"> Number of Cases: 2,358 Number of Dropouts: <2% lost to follow-up contributes to the development of CHD in women. 	Physical inactivity independently contributes to the development of CHD in women.
USA		<ul style="list-style-type: none"> Age: 34-59 yr Characteristics: Nurses 	PA assessment: Questionnaire for LTPA (hr/wk), 3 groups	up	
Prospective cohort		<ul style="list-style-type: none"> Nurses' Health Study 		Multivariate HR (95% CI)	
D & B score = 12			G1 = ≥3.5 G2 = 1-3.49 G3 = <1	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 1.34 (1.18-1.51) G3 = 1.43 (1.26-1.63) 	
			Outcome Measure: CHD incidence		
			Cox proportional HR		
Lemaitre et al 1995 [240]	To evaluate the effect of PA on MI occurrence.	<ul style="list-style-type: none"> n = 1,107 (726 controls, 381 cases) 	PA assessment: Questionnaire, 3-5 groups depending on variable	OR (95% CI),	PA level was inversely associated with occurrence of MI in both sexes, although the association presented a significant linear trend only for women; in men it suggested a u-shaped relation.
Portugal		<ul style="list-style-type: none"> Sex: Men and women 	Total PA (MET hr/day), men	Total PA, men	
Case control		<ul style="list-style-type: none"> Age: ≥ 40 yr Characteristics: Case: Admitted to Hospital and diagnosed with first episode of MI. Control: Healthy, no history of CHD 	G1 = 28.3-32.1	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.54 (0.33-0.88) G3 = 0.34 (0.20-0.59) G4 = 0.59 (0.36-0.98) 	
D & B score = 12			G2 = 32.2-33.3	<ul style="list-style-type: none"> G5 = 0.90 (0.56-1.45) 	
			G3 = 33.4-36.5 G4 = 36.6-40.3 G5 = 40.4-83.1	Trend <i>p</i> = 0.827 Total PA, women	
			Total PA (MET hr/day), women	<ul style="list-style-type: none"> Q1 = 1.00 (referent) Q2 = 0.39 (0.21-0.73) 	

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Lovasi et al 2007 [241]	To investigate the shape of the relationship between LTPA and MI risk.	n = 4,094	Q1 = 28.9-32.7 Q2 = 32.8-34.1 Q3 = 34.2-37.8 Q4 = 37.8-70.6	• Q3 = 0.33 (0.17-0.64) • Q4 = 0.22 (0.11-0.47) p = <0.001	Sport participation, men • G1 = 1.00 (referent)	PA assessment: Telephone interview (Minnesota LTPA Questionnaire)	Number of Cases: 697	Time engaged in LTPA, even non strenuous LTPA was associated with a lower risk of MI, and the shape of this relationship was non-linear
USA	• Sex: Men and women • Age: 64 ± 9 yr • Characteristics: Group Health Cooperative Members	Sport participation (MET hr/day), men G1 = 0.0 G2 = 0.1-1.0 G3 = 1.1-2.0 G4 = 2.1-3.6 G5 = 3.7-15.4	• G2 = 0.36 (0.19-0.69), • G3 = 0.72 (0.41-1.26), • G4 = 0.42 (0.23-0.76), • G5 = 0.31 (0.16-0.62) p = <0.001	Adjusted OR (95% CI) LTPA and non fatal CHD • G1 = 1.00 (referent)	Strenuous LTPA G1 = None G2 = non strenuous LTPA G3 = Any Strenuous LTPA	• G2 = 0.88 (0.66-1.17) • G3 = 0.62 (0.46-0.83) • G4 = 0.61 (0.45-0.82) • G5 = 0.59 (0.44-0.80)	Adjusted RR (95% CI) Strenuous LTPA and non Fatal CHD • G1 = 1.00 (referent) • G2 = 0.76 (0.59-0.99) • G3 = 0.53 (0.40-0.70)	
D & B score = 11	Outcome measure: non fatal CHD Logistic regression							

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Manson et al 1999 [242]	To assess the comparative roles of walking and vigorous exercise in the prevention of coronary events in women.	• n = 72,488	PA assessment:	• Number of Cases: 645 coronary events	Both walking and VPA are associated with a substantial reductions in incidence of CHD. Risk reductions for each were similar hen total PAy was similar. Walking 3 or more hours per week could reduce the risk of CHD by 30-40%.
USA	• Sex: Women		Questionnaire with detailed information on PA.		
	• Age: 40-65 yr			Multivariate RR (95% CI) by total PA score	
	• Characteristics: Healthy, no Previous history of CHD			• G1 = 1.00 (referent)	
Prospective cohort			Total PA score	• G2 = 0.88 (0.71-1.10)	
			G1 = 1-2.0	• G3 = 0.81 (0.64-1.02)	
			G2 = 2.1-4.6	• G4 = 0.74 (0.58-0.95)	
			G3 = 4.7-10.4	• G5 = 0.66 (0.51-0.86)	
D & B score = 12			G4 = 10.5-21.7	p = 0.002	
			G5 = >21.7		
			Walking, in those who did not participate in VPA: (MET hr/wk)	Multivariate RR (95% CI) by walking activity	
			G1 = 0.5	• G1 = 1.00 (referent)	
			G2 = 0.6-2.0	• G2 = 0.78 (0.57-1.06)	
			G3 = 2.1-3.8	• G3 = 0.88 (0.65-1.21)	
			G4 = 3.9-9.9	• G4 = 0.70 (0.51-0.95)	
			G5 = ≥ 10	• G5 = 0.65 (0.47-0.91)	
				p = 0.02	
			Walking pace (mph)	Multivariate RR (95% CI) by walking pace	
			G1 = <2.0	• 1.00 (referent)	
			G2 = 2.0-2.9	• 0.75 (0.59-0.96)	
			G3 = ≥ 3.0	• 0.64 (0.47-0.88)	

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Mora et al 2007 [243]	To investigate whether differences in several CV risk factors mediate the effect of PA on reduced risk of CVD.	<ul style="list-style-type: none"> n = 27,055 10.9 ± 1.6 yr of follow up Number of Cases: 640 	<ul style="list-style-type: none"> Sex: Women Age: ≥ 45 yr Characteristics: Healthy Women's health study 	<ul style="list-style-type: none"> PA assessment: Questionnaires at study entry for categories of EE from PA (kcal/wk), 4 groups HR (95% CI), basic model <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.84 (0.67-1.06) G3 = 0.76 (0.61-0.96) G4 = 0.62 (0.48-0.82) G1 = <200 G2 = 200-599 	<ul style="list-style-type: none"> While all sets of risk factors should some mediation on the effect of PA on CHD none made the relationship insignificant 	<ul style="list-style-type: none"> There remained a borderline significant inverse association between PA and risk of CHD after adjustment for all sets of risk factors.
D & B score = 13						
O'Connor et al 1995 [244]	To examine the association between intensity of exercise and CHD risk	<ul style="list-style-type: none"> n = 680 (532 men and 148 women) 	<ul style="list-style-type: none"> Sex: Men and women Age: < 76 yr Characteristics: Cases: Diagnosed MI (non-fatal), no previous history of CHD. Controls: no history of CHD. 	<ul style="list-style-type: none"> PA assessment: Home interview for PA, divided into quartiles Q1 = Lowest Q2 Q3 Q4 = Highest Cox proportional HR Adjusted OR (95% CI) by PA level, men <ul style="list-style-type: none"> Q1 = 1.00 (referent) Q2 = 0.60 (0.32-1.13) Q3 = 0.41 (0.21-0.78) Q4 = 0.41 (0.22-0.77) Adjusted OR (95% CI) by PA level, women <ul style="list-style-type: none"> Q1 = 1.00 (referent) 	<ul style="list-style-type: none"> Significant inverse association between PA level and the risk of non fatal MI in men, which persisted after adjustment for other risk factors. 	
USA						
Case control						
D & B score = 12						

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

	Moderate- vigorous sports men Cut-points kcal/wk	<ul style="list-style-type: none"> • Q2 = 1.07 (0.27-4.17)
	Q1 = Lowest	<ul style="list-style-type: none"> • Q3 = 2.02 (0.56-7.38)
	Q2	<ul style="list-style-type: none"> • Q4 = 1.29 (0.31-5.35)
	Q3	<ul style="list-style-type: none"> • $p = 0.51$
	Q4 = Highest	<ul style="list-style-type: none"> Adjusted OR (95% CI) by moderate-vigorous sports, men
	Moderate- vigorous sports Women	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.12 (0.60-2.10)
	Cut-points kcal/wk	<ul style="list-style-type: none"> • Q3 = 0.61 (0.30-1.24) • Q4 = 0.43 (0.20-0.92)
	Q1 = Lowest	<ul style="list-style-type: none"> • $p = 0.02$
	Q2	
	Q3	
	Q4 = Highest	<ul style="list-style-type: none"> Adjusted OR (95% CI) by moderate-vigorous sports, women
	Logistic regression analysis	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.31 (0.37-4.66) • Q3 = 1.90 (0.44-8.28) • Q4 = 0.35 (0.07-1.84)
		<ul style="list-style-type: none"> • $p = 0.62$
Rastogi et al 2004 [245]	To examine the relation between PA and CHD risk in India.	<ul style="list-style-type: none"> • n = 1,050
USA	PA assessment: Questionnaire	Number of Cases: 350
D & B	• Sex: Men and women	Observed a strong and dose dependent inverse association between LTPA and non fatal CHD.
score = 12	• Age: 21-74 yr	Multivariate OR (95% CI) by LTPA
	• Characteristics: Cases: Diagnosed with MI (non fatal) Controls: non- cardiac patients	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.96 (0.59-1.55)
	G2 = 0-145	<ul style="list-style-type: none"> • G3 = 0.44 (0.27-0.71)
	G3 = ≥145	<ul style="list-style-type: none"> • $p = 0.001$
	Sedentary time (min/d)	Multivariate OR (95% CI) by sedentary time
	G1 = <70	<ul style="list-style-type: none"> • G1 = 1.00 (referent)
	G2 = 70-130	<ul style="list-style-type: none"> • G2 = 1.15 (0.68-1.95)
	G3 = 130-215	<ul style="list-style-type: none"> • G3 = 1.04 (0.61-1.76)
	G4 = ≥215	<ul style="list-style-type: none"> • G4 = 1.88 (1.09-3.21)

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

		Outcome Measure: Non-fatal MI	Conditional logistic regression	23 year follow-up	Number of Cases: 789	PA was associated with a significant reduction in the risk of CHD morbidity and mortality.
Rodriguez et al 1994 [246]	To examine the relationship between PA and 23 yr incidence of CHD morbidity and mortality.	• n = 7,074	• Sex: Men	• Age: 45-64 yr	• T1 = 1.00 (referent)	
USA	Characteristics: Japanese-American living in Oahu, Hawaii in 1965, < 65 years to reduce effect of retirement on PA levels	PA assessment: Questionnaire for PA index, divided into tertiles			Age adjusted RR (95% CI), CHD incidence	
Prospective cohort		T1 = Low			• T2 = 1.01 (0.86-1.19)	These data support the hypothesis that PA is associated with a favorable profile of CVD risk factors.
D & B score = 11		T2 = Moderate			• T3 = 0.83 (0.86-1.19)	
		T3 = High			Multivariate adjusted RR (95% CI), CHD incidence	
		Cox proportional regression model			• T1 = 1.00 (referent)	
					• T2 = 1.07 (0.90-1.26)	This study did not show a dose-response relationship since the medium tertile of PA showed increased rates of CHD compared to the inactive group.
					• T3 = 0.95 (0.80-1.14)	
					Age adjusted RR (95% CI), CHD mortality	
					• T1 = 1.00 (referent)	
					• T2 = 1.12 (0.88-1.44)	
					• T3 = 0.74 (0.56-0.97)	
					Multivariate adjusted RR (95% CI)	
					• T1 = 1.00 (referent)	
					• T2 = 1.19 (0.93-1.53)	
					• T3 = 0.85 (0.65-1.13)	

p = 0.02

• The Honolulu Heart Program

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Author(s)	Objective	n	Study Design	PA assessment	Number of Cases	Outcome
Rothenbacher et al 2003 [247]	To estimate the risk for CHD associated with LTPA.	n = 791 (312 cases; 479 controls)	Case-control	Interview	312	LTPA showed a clear inverse association with risk of CHD.
Germany				LTPA (h/wk) G1 = 0 G2 = <1 G3 = 1-2 G4 = >2	Multivariate OR (95% CI), LTPA Winter • G1 = 1.00 (referent) • G2 = 0.48 (0.27-0.84) • G3 = 0.54 (0.369-0.82) • G4 = 0.27 (0.19-0.47)	
Case control	Age: 40-68 yr Characteristics: Cases: stable CHD diagnosed within 2 years, no recent MI, Controls: no history of CHD.					
D & B score = 12						
Seccarecchia and Menotti 1992 [248]	To examine the relationship between OPA and the risk of CHD death.	n = 1,621	Prospective cohort	25 year of follow-up	189 cases	Increase in OPA is inversely related to risk of CHD death.
Italy				Workday activity by bike/foot, (min/workday) G1 = <15 G2 = 15-30 G3 = 30-60 G4 = >60	Summer • G1 = 1.00 (referent) • G2 = 0.85 (0.47-1.53) • G3 = 0.60 (0.38-0.95) • G4 = 0.39 (0.26-0.59)	
Prospective cohort				Outcome Measure: non fatal CHD Unconditional logistic regression, linear regression model	Multivariate OR (95% CI), workday activity by bike/foot • G1 = 1.00 (referent) • G2 = 0.53 (0.30-0.93) • G3 = 0.36 (0.21-0.62) • G4 = 0.58 (0.36-0.94)	
D & B score = 11				PA assessment: Questionnaire for OPA (kcal/d), 3 groups G1 = Sedentary, < 2400 G2 = Moderate, 2400-3199 G3 = Heavy ≥ 3200	Age Standardized CHD and deaths rates: • G1 = 18.9 ± 3.1 • G2 = 13.1 ± 1.7 • G3 = 11.0 ± 0.9	

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

	Indicators of PF including HR, vital capacity, FEV in 3/4 of sec, and corrected arm circumference (minus contribution of fat). End Point: Fatal CHD			
Sesso et al 2000 [249]	To examine the association of the quantity and intensity of PA with CHD risk and the impact of other coronary risk factors.	• n = 12,516 • Sex: Men • Age: 39-88 yr • Characteristics: Healthy • Harvard Alumni	PA assessment: Questionnaire	Number of Cases: 2,135 L-Shaped association between PA and the risk of CHD, with a reduction in CHD risk of approximately 20% for total PA levels >4200 kJ/wk
USA			PA Index (kJ/wk) G1 = <2100 G2 = 2100-4199 G3 = 4200-8399 G4 = 8400-12599 G5 = >12600	Multivariate HR (95% CI) • G1 = 1.00 (referent) • G2 = 0.90 (0.79-1.03) • G3 = 0.81 (0.71-0.92) • G4 = 0.80 (0.69-0.93) • G5 = 0.81 (0.71-0.94) p = 0.003
Prospective cohort		Study		
D & B score = 12				Suggests that vigorous activities are associated with a reduced risk of CHD, whereas moderate or light PA has no clear association with risk of CHD.
Sundquist et al 2005 [250]	To examine the long term effect of LTPA on incident cases of CHD.	• n = 5,196 (2,645 men, 2,551 women)	PA assessment: Questionnaire Levels of PA	Positive long term effect of LTPA on CHD risk among men and women.
Sweden		• Sex: Men and women	Q1 = None Q2 = Occasionally Q3 = 1-2 times per week Q4 = Vigorous ≥2 times per week	Age and sex adjusted RR (95% CI) • Q1 = 1.00 (referent) • Q2 = 0.72 (0.51-1.00) • Q3 = 0.64 (0.46-0.89) • Q4 = 0.46 (0.29-0.74)
Prospective cohort		Age: 35-74 yr • Characteristics: Those not hospitalized for CHD in the last 2 years and those who rate their general health as poor were excluded		Multivariate adjusted RR (95% CI)
D & B score = 11			Outcome Measure: Fatal or non fatal CHD	• Q1 = 1.00 (referent) • Q2 = 0.76 (0.55-1.07) • Q3 = 0.74 (0.53-1.04) • Q4 = 0.59 (0.37-0.95)
			Cox regression model	

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Talbot et al 2002 [251]	To examine the contributions of LTPA and aerobic fitness to the risk of coronary events in healthy younger and older adults.	<ul style="list-style-type: none"> • n = 689 • Sex: Men • Age: 51.6 ± 16.8 yr • Characteristics: Community dwelling 	Surveys began in 1960 and were completed on every visit	<ul style="list-style-type: none"> • Number of Cases: 63 	In younger men PF predicts a reduced risk of CHD but not LTPA.
USA				<ul style="list-style-type: none"> • After adjusting for coronary risk factors there was: 	
Prospective cohort			PA assessment: Survey for LTPA (97 activities) at every visit.	RR: 0.53 (p < 0.001) and	In older men, high intensity LTPA and PF appear to be of similar importance in reducing CHD risk.
D & B score = 12		<ul style="list-style-type: none"> • Baltimore Longitudinal Study of Aging 	PF assessment: Treadmill VO ₂ max test on alternate visits	RR: 0.61 (p = 0.024) in older men.	
			Unpaired t-tests and chi square tests. Cox Proportional hazards Analysis	Total LTPA was unrelated to coronary risk in either age group. With 3 levels of LTPA intensity substituted for total LTPA: RR = 0.39 for tertile 3 vs. tertile 1	
Tanasescu et al 2002 [252]	To assess the amount, type and intensity of PA in relation to risk of CHD in men.	<ul style="list-style-type: none"> • n = 44,452 • Sex: Men • Age: 40-75 yr • Characteristics: Health professionals, no history of CHD and in good health 	PA assessment: Questionnaire	<ul style="list-style-type: none"> • Number of Cases: 1,700 	Total PA, running, weight training, and walking were associated with a reduced risk for CVD.
USA			Total PA (MET hr/wk)	<ul style="list-style-type: none"> • Age adjusted HR (95% CI) by total PA 	
Prospective cohort			Q1 = 0-6.32	• Q1 = 1.00 (referent)	
			Q2 = 6.33-14.49	• Q2 = 0.85 (0.74-0.98)	
			Q3 = 14.50-25.08	• Q3 = 0.78 (0.67-0.92)	
			Q4 = 25.09-41.98	• Q4 = 0.72 (0.62-0.83)	The average exercise intensity was associated with a reduced risk (independent of total PA).
D & B score = 11		<ul style="list-style-type: none"> • Health Professionals follow-up study 	Q5 = > 41.99	• Q5 = 0.58 (0.49-0.68)	
			Exercise intensity (METs)	p = .001	
			G1 = Low-1-4	Age adjusted HR (95% CI) by exercise intensity	
				• G1 = .00 (referent)	

Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Vatten et al 2006 [253]	<p>G2 = Mod.-4-6 G3 = High 6-12 Walking pace independent of total volume of PA (mph)</p> <p>Q1 = <2 Q2 = 2-3 Q3 = 3-4 Q4 = > 4</p> <p>Outcome Measure: Nonfatal MI or Fatal CHD occurring during follow-up</p> <p>Cox proportional HR</p>	<p>• G2 = 0.94 (0.83-1.04) • G3 = 0.83 (0.72-0.97)</p> <p>$p = 0.02$ Age adjusted HR (95% CI) by walking pace • Q1 = 1.00 (referent) • Q2 = 0.72 (0.54-0.94) • Q3 = 0.61 (0.45-0.81) • Q4 = 0.51 (0.31-0.84)</p> <p>$p < 0.001$</p>
Norway	<p>• n = 54,284 (27,769 men, 26,515 women)</p> <p>• Sex: Men and women</p> <p>Age: ≥ 20 yr</p> <p>• Characteristics: Free from CVD at baseline</p> <p>• HUNT study</p>	<p>• Number of Cases: 2,462</p> <p>Increased PA reduces the risk of death in women, but not in men.</p>
Prospective cohort	<p>PA assessment: Questionnaire Divided into 4 groups</p> <p>Q1 = High Q2 = Medium Q3 = Low Q4 = Never</p> <p>Outcome Measure: Ischemic heart disease mortality</p> <p>Cox proportional HR</p>	<p>Multivariate HR (95% CI), men • Q1 = 1.00 (referent) • Q2 = 1.01 (0.89-1.16) • Q3 = 0.98 (0.84-1.14) • Q4 = 1.18 (1.00-1.38)</p> <p>$p = 0.11$</p> <p>Multivariate HR (95% CI), women • Q1 = 1.00 (referent) • Q2 = 1.23 (1.01-1.51) • Q3 = 1.54 (1.24-1.91) • Q4 = 1.52 (1.23-1.88)</p> <p>$p < 0.001$</p>
D & B score = 12		

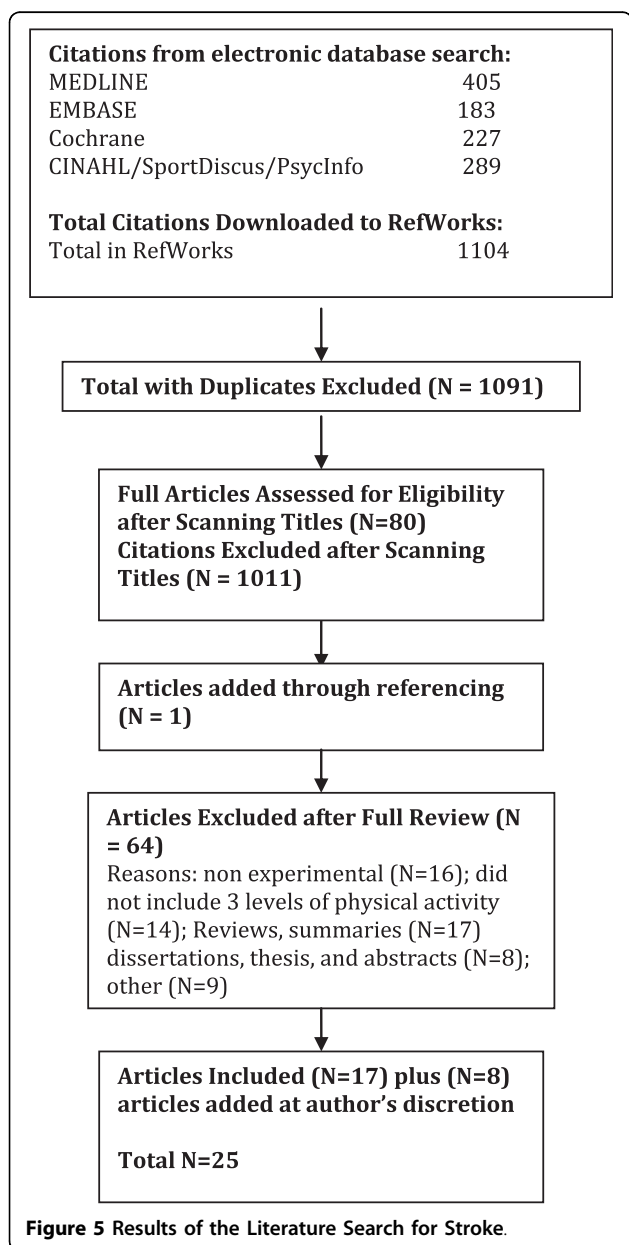
Table 12: Studies examining the relationship between physical activity and cardiovascular disease. (Continued)

Wagner et al 2002 [254]	To investigate if the association between PA patterns and incidence of coronary events could explain the gradient in CHD observed between 2 countries.	• n = 9,758	Length of Follow-up: 5 yrs	Number of Cases: 167 hard CHD, 154 angina events	Beneficial effect of LTPA EE on hard CHD incidence in middle aged men.
Ireland/France	• Sex: Men and women	• Age: 50-59 yr	PA assessment: Questionnaire for LTPA, 3 groups:	Number of Dropouts: < 2%	
Prospective cohort	• Characteristics: Healthy at Baseline		G1 = Lowest	HR (95% CI), hard events	
			G2 = Middle	• G1 = 1.00 (referent)	
			G3 = Highest	• G2 = 0.73 (0.51-1.05)	
D & B score = 12			Outcome Measure: CHD hard events and Angina	• G3 = 0.66 (0.46-0.96)	
			Cox proportional HR	p = 0.04	
				HR (95% CI), angina	
				• G1 = 1.00 (referent)	
				• G2 = 0.83 (0.55-1.25)	
				• G3 = 1.28 (0.88-1.86)	
				p = 0.10	

D & B score, Downs and Black quality score; YR, years; G, groups; CHD, coronary heart disease; RR, risk ratio; 95% CI, 95% confidence interval; PA, physical activity; VPA, vigorous physical activity; CV, cardio vascular; MET, metabolic equivalent; kcal/wk, kilocalories per week; Q, quartile or quintile; km/h, kilometers per hour; LTPA, leisure-time physical activity; HR, hazard ratio; OPA, occupational physical activity; kcal/kg/day kilocalories per kilogram per day; MI, myocardial infarction; ECG, electrocardiogram; kcal/kg/h kilocalories per kilogram per hour; mph, miles per hour; CVD, cardiovascular disease.

30% risk reduction in the most active individuals [31]. In fact, in a review of the literature Katzmarzyk and Janssen [20] reported that lack of physical activity carried a relative risk of 1.60 (95% CI = 1.42-1.80) for stroke, similar to or higher than that for coronary heart disease (1.45), hypertension (1.30), colon cancer (1.41), breast cancer (1.31), type 2 diabetes (1.50), and osteoporosis (1.59).

In our systematic review of the literature, a total of 1104 citations were identified during the electronic database search (Figure 5). Of these citations, 405 were identified in MEDLINE, 183 in EMBASE, 227 in Cochrane, and 289 in the CINAHL/SportDiscus/PsycInfo search.



A total of 13 duplicates were found, leaving a total of 1091 unique citations. A total of 1011 articles were excluded after scanning, leaving a total of 80 articles for full review. An additional 9 articles were retrieved through cross-referencing and the authors' knowledge of the field. From these articles 64 were excluded after full review leaving 25 articles for inclusion in the systematic review. The reasons for exclusion included non-experimental/weak design (poor execution introducing bias) (n = 16), did not contain three levels of physical activity or not possible to determine dose-response relationship (n = 14), reviews, summaries, meta-analyses (n = 17), dissertations, thesis, abstracts (n = 8), and other (n = 9). Therefore, a total of 25 articles were included in the systematic review of the literature regarding the relationship between physical activity and the primary prevention of stroke (Table 13).

The data providing dose-response information is all observational in nature, involving both case control and cohort investigations. These studies (predominantly prospective cohort designs) included a total of 479,336 participants; averaging 17,753 subjects per study (range 428-73,265). There were a total of 12,361 reported cases of stroke (ranging per study from 32-2,863). The total length of study follow-up for the prospective cohort studies averaged 13.2 yr (ranging from 6-26 yr). The articles were published over a 14 yr period ranging from 1993 to 2007. These studies involved large samples of men and women from regions throughout the world including studies from the USA (11), UK (2), Iceland (1), Denmark (2), Norway (4), Netherlands (1), Finland (2), Japan (1), Australia (1) and Greece (1). Very few studies [69,70] examined non-Caucasian participants.

We found strong evidence that physical activity was associated with a reduced risk for stroke. The level of evidence was consistent with a Level 3A classification. We observed an average risk reduction of 31% across all studies (median = 29%). In comparison to cardiovascular disease, there was more variability in the risk reductions in stroke in the highest activity/fitness group. The quality of the investigations was also generally quite good with a mean (and median) Downs and Black score of 13 (range 11-15).

The risk reductions appear to be even greater in studies that assessed physical fitness directly. For instance, in data from the Aerobics Center Longitudinal Study [71] the high fitness group (estimated peak METs = 13.1) and the moderate fitness group (estimated peak METs 10.5) had significantly lower risks of stroke mortality (68 and 63%, respectively) than the least fit men (estimated peak METs 8.5).

A dose-response relationship did emerge when examining the literature. However, as illustrated by others this was extremely variable amongst studies and varied

Table 13 Studies examining the relationship between physical activity and stroke.

Publication Country Quality Score	Objective	Population	Methods	Outcome	Comments and Conclusions
Wisloff et al 2006 [58]	To assess exercise amount and intensity in relation to subsequent CVD mortality (including stroke).	<ul style="list-style-type: none"> n = 27,143 men, 28,929 women Sex: Men and women Age: ≥ 20 yr Characteristics: free from CVD HUNT Study 	16 year follow up	Multivariate adjusted RR (95% CI) Men	Both high and low-intensity exercise may be associated with a reduced risk of stroke in both men and women.
Norway			PA Assessment: Questionnaire	G1 = 1.00 (referent) G2 = 0.90 (0.70-1.17) G3a = 0.90 (0.64-1.26) G3b = 0.59 (0.27-1.27) G3c = 0.62 (0.40-0.95) G3d = 0.51 (0.31-0.86) G4a = 0.72 (0.49-1.05) G4b = 0.63 (0.31-1.30) G4c = 1.02 (0.72-1.44) G4d = 0.59 (0.37-0.92) G5a = 0.97 (0.70-1.36) G5b = 0.68 (0.27-1.66) G5c = 0.81 (0.65-1.20) G5d = 0.67 (0.49-1.11)	
Prospective cohort			G1 = None G2 = <1/wk G3a = 1/wk ≤ 30 min low G3b = 1/wk ≤ 30 min high G3c = 1/wk > 30 min low G3d = 1/wk > 30 min high G4a = 2-3/wk ≤ 30 min low G4b = 2-3/wk ≤ 30 min high G4c = 2-3/wk > 30 min low G4d = 2-3/wk > 30 min high G5a = ≥ 4/wk ≤ 30 min low G5b = ≥ 4/wk ≤ 30 min high G5c = ≥ 4/wk > 30 min low G5d = ≥ 4/wk > 30 min high	RR (95% CI) Women G1 = 1.00 (referent) G2 = 1.01 (0.81-1.25) G3a = 0.88 (0.68-1.15) G3b = 0.98 (0.46-2.10) G3c = 0.63 (0.42-0.94) G3d = 1.00 (0.50-1.98) G4a = 0.91 (0.70-1.17) G4b = 1.44 (0.78-2.65) G4c = 0.62 (0.44-0.88) G4d = 0.77 (0.36-1.66) G5a = 0.74 (0.56-0.99) G5b = 0.40 (0.10-1.62) G5c = 0.63 (0.45-0.89) G5d = 0.51 (0.21-1.26)	
D & B score = 12			Outcome Measure: IHD mortality Cox proportional HR		

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

	Abbott et al 2003 [69]	Prospective cohort	D & B score = 14	Gillium et al 1996 [70]	Prospective cohort	D & B score = 12
USA	To examine the way in which risk factor effects on the incidence of thromboembolic and hemorrhagic stroke can change over a broad range of ages.	<ul style="list-style-type: none"> • n = 7,589 • Sex: Men • Age: 45-93 yr 	<ul style="list-style-type: none"> • Characteristics: Free from CHD and stroke at enrollment; Japanese ancestry living on the island of Oahu, Hawaii. • Honolulu Heart Program 	<ul style="list-style-type: none"> • n = 2,368 men, 2,713 women • Sex: Men and women • Age: 45-74 yr • Ethnicity: Black and white • NHANES I 	<ul style="list-style-type: none"> • Sex: Men and women • Age: 45-74 yr • Ethnicity: Black and white • NHANES I 	<ul style="list-style-type: none"> • Sex: Men and women • Age: 45-74 yr • Ethnicity: Black and white • NHANES I
	6, 15 and 26 year follow up	PA assessment: Using PA index over a 24 hour period PA information collected at study enrollment 1965-1968 and updated at physical examinations that occurred at 6, 15 and 26 years into follow-up.	Grouped into 4 age groups, yr: G1 = 45-54 G2 = 55-64 G3 = 65-74 G4 = 75-93	11.6 year follow up Cox proportional HR	PA assessment: Questionnaire divided into tertiles: T1 = Low T2 = Medium T3 = High Outcome Measure: Total Stroke Cox proportional HR	PA assessment: Questionnaire divided into tertiles: T1 = Low T2 = Medium T3 = High Outcome Measure: Total Stroke Cox proportional HR
	Incidence rates per 1000 of stroke:					
		<ul style="list-style-type: none"> • G1 = 9.0 (49) • G2 = 17.8 (124) • G3 = 33.4 (112) • G4 = 48.1 (111) 				
	The protective effect of PA on reducing risk of stroke increased with age.		Incidence of stroke event increased with advancing age p <0.001 There appeared to be a small protective effect within each age group. Inverse relations increased with age (p = 0.046). The protective effect of PA became significant in men >77 years (p = 0.032)	Outcome Measure: diagnosis of fatal and non fatal stroke during 26 years of follow-up		
				Number of Cases: 249 white women, 270 white men, 104 black		
				RR (95% CI) Black men and women Recreational PA • T1 = 1.33 (0.67-2.63) • T2 = 1.33 (0.63-2.79) • T3 = 1.00 (referent)		
				Non-recreational PA • T1 = 1.40 (0.90-2.16)		
				Sedentary behaviour was found to be associated with increased risk of stroke.		

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

	<ul style="list-style-type: none"> • T2 = 1.41 (0.74-2.70) • T3 = 1.00 (referent)
RR (95% CI) White men age 45-64	
Recreational PA	<ul style="list-style-type: none"> • T1 = 1.24 (0.63-2.41) • T2 = 1.17 (0.61-2.27) • T3 = 1.00 (referent)
Non-recreational PA	<ul style="list-style-type: none"> • T1 = 1.07 (0.40-2.86) • T2 = 1.75 (1.04-2.96) • T3 = 1.00 (referent)
RR (95% CI) White women age 45-64	
Recreational PA	<ul style="list-style-type: none"> • T1 = 3.13 (0.95-10.32) • T2 = 1.80 (0.52-6.22) • T3 = 1.00 (referent)
Non-recreational PA	<ul style="list-style-type: none"> • T1 = 3.51 (1.66-7.46) • T2 = 1.07 (0.57-1.99) • T3 = 1.00 (referent)
RR (95% CI) White men age 65-74	
Recreational PA	<ul style="list-style-type: none"> • T1 = 1.29 (0.58-1.88) • T2 = 0.86 (0.58-1.28) • T3 = 1.00 (referent)
Non-recreational	<ul style="list-style-type: none"> • T1 = 1.82 (1.15-2.88) • T2 = 1.20 (0.88-1.64) • T3 = 1.00 (referent)
RR (95% CI) White women age 65-75	
Recreational PA	<ul style="list-style-type: none"> • T1 = 1.55 (0.95-2.53) • T2 = 1.27 (0.76-2.12) • T3 = 1.00 (referent)
Non-recreational PA	<ul style="list-style-type: none"> • T1 = 1.82 (1.10-3.02) • T2 = 1.42 (1.01-2.00) • T3 = 1.00 (referent)

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

<p>Lee and Blair 2002 [71]</p>	<p>To examine the association between PF and stroke mortality in men.</p>	<p>n = 16,878</p> <ul style="list-style-type: none"> • Sex: Men • Age: 40-87 yrs • Aerobics Center Longitudinal Study 	<p>Baseline medical evaluation between 1971 and 1994 with average follow up period of 10 years</p>	<p>Average estimated maximal METs</p> <ul style="list-style-type: none"> • T1 = 8.5 MET • T2 = 10.5 MET • T3 = 13.1 MET 	<p>Moderate and high levels of PF were associated with lower risk of stroke mortality in men.</p>
<p>USA</p>	<p>Prospective cohort</p>	<p>PF assessment: Maximal exercise tolerance test, divided into tertiles</p>	<p>RR (95% CI) adjusted for age and exam year</p> <ul style="list-style-type: none"> • T1 = 1.00 (referent) • T2 = 0.35 (0.16-0.77) • T3 = 0.28 (0.11-0.71) <p>Trend p = 0.005</p>	<p></p>	<p></p>
<p>D & B score = 13</p>	<p></p>	<p>T1 = Low T2 = Moderate T3 = High</p> <p>Cox proportional HR</p>	<p>Baseline measurement in 1986 with follow-up questionnaire in 1988 and 1992</p>	<p>407 cases of stroke (258 ischemic strokes, 67 subarachnoid hemorrhages, 42 intracerebral hemorrhages, and 40 strokes of unknown type)</p>	<p>PA, including moderate-intensity exercise such as walking, is associated with a substantial reduction in risk of total and ischemic stroke in a dose- response manner.</p>
<p>Hu et al 2000 [72]</p>	<p>To examine the association between PA and risk of total stroke and stroke sub- types in women.</p>	<p>n = 72,488</p> <ul style="list-style-type: none"> • Sex: Women • Age: 40-65 yr • Characteristics: Nurses • Nurses' Health Study 	<p>PA assessment: Questionnaire for total PA (MET h/wk), divided into quintiles, walking activity (MET h/wk) divided into quintiles and walking pace</p>	<p>Multivariate RR (95% CI) for total stroke by total PA level</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.98 • Q3 = 0.82 • Q4 = 0.74 • Q5 = 0.66 <p>p = 0.005</p>	<p></p>
<p>USA</p>	<p>Prospective cohort</p>	<p>Total PA (MET h/wk)</p> <p>Q1 = 0 - 2.0 Q2 = 2.1 - 4.6 Q3 = 4.7 - 10.4 Q4 = 10.5-21.7</p>	<p></p>	<p>Multivariate RR (95% CI) for ischemic Stroke by total PA level</p>	<p></p>
<p>D & B score = 13</p>	<p></p>	<p></p>	<p></p>	<p></p>	<p></p>

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.87 • Q3 = 0.83 • Q4 = 0.76 • Q5 = 0.52 <p>p = 0.003</p>
Q5 = > 21.7	
Walking activity (MET h/wk)	
Q1 = 0.5	
Q2 = 0.6 - 2.0	
Q3 = 2.1 - 3.8	
Q4 = 3.9 - 10	
Q5 = 10	
Multivariate RR (95% CI) for total stroke by walking activity	
Walking pace (mph)	
G1 < 2.0	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.76 • Q3 = 0.78 • Q4 = 0.70 • Q5 = 0.66
G2 = 2-2.9	
G3 3.0	
Outcome measure: Stroke incidence	p = 0.01
	Multivariate RR (95% CI) for ischemic stroke by walking activity
Pooled logistic regression	
Cox proportional HR	
	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.77 • Q3 = 0.75 • Q4 = 0.69 • Q5 = 0.60
	p = 0.02
	Multivariate RR (95% CI) for total stroke by usual Walking Pace
	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.81 • G3 = 0.49
	p < 0.001
	Multivariate RR (95% CI) for ischemic stroke by usual walking pace
	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.71 • G3 = 0.47
	p < 0.001

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

Lee et al 1999 [74]	To examine the association between exercise and stroke risk	• n = 21,823	11.1 year follow up	Number of Cases: 533	VPA is associated with a decreased risk of stroke in men.
USA		• Sex: Men • Age: 40-84 yr	PA assessment: Questionnaire for frequency of VPA, divided into 4 groups	Multivariate RR1 (95% CI) for total stroke by VPA	
Prospective cohort			G1 < 1 time/week G2 = 1 time/week G3 = 2-4 times/week G4 ≥ 5 times/week	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.79 (0.61-1.03) • G3 = 0.80 (0.65-0.99) • G4 = 0.79 (0.61-1.03) 	Inverse association with PA seemed to be mediated through beneficial effects on body weight, BP, cholesterol and glucose tolerance.
D & B score = 13			RR1 = adjusted for smoking, alcohol consumption, history of angina and parental history of MI at <60 years	<p>p = 0.04</p> <p>RR2 (95% CI) for total stroke by VPA</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.81 (0.61-1.07) • G3 = 0.88 (0.70-1.10) • G4 = 0.86 (0.65-1.13) 	
			RR2 = adjusted for all of the above plus, BMI, history of, hypertension, high cholesterol and diabetes	<p>p = 0.25</p> <p>RR2 (95% CI) for ischemic stroke by VPA</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.90 (0.66-1.22) • G3 = 0.95 (0.74-1.22) • G4 = 0.97 (0.71-1.32) 	
			Outcome Measure: Total Stroke (Ischemic and Hemorrhagic)	<p>p = 0.81</p> <p>RR2 (95% CI) for hemorrhagic stroke by VPA</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.54 (0.25-1.13) • G3 = 0.71 (0.41-1.23) • G4 = 0.54 (0.26-1.15) 	
			Cox proportional HR	<p>p = 0.10</p>	

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

	10 year follow up	Number of Cases: 47	No significant finding
Bijmen et al 1998 [166]	To describe the association between the PA patterns of elderly men and stroke mortality.	• n = 802	
Denmark	PA assessment: Questionnaire for LTPA, divided into tertiles	Multivariate adjusted RR (95% CI) • T1 = 1.00 (referent) • T2 = 0.65 (0.33-1.25) • T3 = 0.55 (0.24-1.26)	
Prospective cohort	T1 = Lowest T2 T3 = Highest	p = 0.12	
D & B score = 15	Outcome Measure: Stroke Mortality Cox proportional HR		
Schnohr et al 2006 [214]	To describe the association between different levels of LTPA and subsequent causes of death (stroke).	• n = 2136 men, 2,758 women	Although RR for of death from stroke was below 1 for both moderate and high compared with low PA, this association did not reach the level of statistical significance.
Copenhagen	PA assessment: Questionnaire for LTPA, divided into 3 groups	• G1 = 1.00 (referent) • G2 = 0.64 (0.39-1.05) • G3 = 0.70 (0.41-1.21) Trend p = 0.4	
Prospective cohort	G1 = Low PA (<4 METS) G2 = Moderate PA (4-6 METS) G3 = High PA (>6 METS)	RR (95% CI), multivariate: • G1 = 1.00 (referent) • G2 = 0.67 (0.40-1.12) • G3 = 0.76 (0.43-1.34)	
D & B score = 13	Multivariate Analysis Kaplan-Meier Plots Linear, Logistical and Cox Regression.	Trend p = 0.6	
Vatten et al 2006 [253]	To investigate whether obesity-related CV mortality could be modified by PA.	• n = 26,515 men, 27,769 women	Lower levels of TPA are associated with an increased risk of stroke.

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

Norway	<ul style="list-style-type: none"> • Sex: Men and women • Age: 20 yr • Characteristics: Free from CVD at baseline 	PA assessment: Questionnaire for total amount of PA, divided into 4 groups	Multivariate HR (95% CI), men <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.05 (0.85-1.30) • Q3 = 1.21 (0.95-1.54) • Q4 = 1.35 (1.05-1.74) <p>p = 0.009</p>
Prospective cohort	<ul style="list-style-type: none"> • HUNT study 	G1 = High G2 = medium G3 = low G4 = never	Multivariate HR (95% CI), women <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.16 (0.93-1.45) • Q3 = 1.45 (1.14-1.86) • Q4 = 1.45 (1.14-1.83) <p>p < 0.001</p>
D & B score = 14		Outcome Measure: Stroke mortality Cox proportional HR	
Agnarsson et al 1999 [255]	<ul style="list-style-type: none"> • n = 4,484 • Sex: Men • Age: 45-80 	Length of Follow-up: 10.6 ± 3.6 years	Number of Cases: 249 Apparent protective effect of regular continued LTPA in middle age men on the risk of ischemic stroke.
Iceland	<ul style="list-style-type: none"> • Characteristics: no history of Stroke 	PA assessment: Questionnaire for LTPA (h/wk) and type of activity (intensity), each divided into 3 groups	Adjusted for age and smoking RR (95% CI) for total stroke by LTPA level <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.84 (0.63-1.13) • G3 = 0.73 (0.40-1.35)
Prospective cohort	<ul style="list-style-type: none"> • Reykjavik Study 	LTPA summer/winter G1 = none G2 = ≤ 5 h/wk G3 = ≥ 6 h/wk	Adjusted for age and smoking RR (95% CI) for ischemic stroke by LTPA level <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.72 (0.51-1.01)
D & B score = 13		Type of Activity	

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

<p>G1 = none G2 = low intensity G3 = high intensity</p>	<p>• G3 = 0.78 (0.41-1.48)</p>
<p>Outcome Measure: Total and ischemic Stroke</p>	<p>RR (95% CI) for total stroke by type of activity • G1 = 1.00 (referent) • G2 = 0.75 (0.53-1.08) • G3 = 1.10 (0.78-1.57)</p>
<p>Cox proportional HR</p>	<p>RR (95% CI) for ischemic stroke by type of activity • G1 = 1.00 (referent) • G2 = 0.72 (0.44-1.07) • G3 = 0.96 (0.64-1.44)</p>
<p>Ellekjaer et al 2000 [256]</p>	<p>Number of cases: 457 This study demonstrates a consistent, negative association between PA and stroke mortality in women.</p>
<p>Norway</p>	<p>Baseline 1984-1986: 2 self administered questionnaires and clinical measurements included in the screening program.</p>
<p>Prospective cohort</p>	<p>• n = 14,101 • Sex: Women • Age: 50 yr • Characteristics: free from stroke at baseline</p>
<p>D & B score = 14</p>	<p>Multivariate RR (95% CI), all age groups • G1 = 1.00 (referent) • G2 = 0.77 • G3 = 0.52</p>
<p>PA assessment: Questionnaire for LTPA, divided into 3 groups</p>	<p>Multivariate RR (95% CI), age 50-69 years • G1 = 1.00 (referent) • G2 = 0.57 • G3 = 0.42</p>
<p>Outcome Measure: Death from stroke</p>	<p>p = 0.0021 Multivariate RR (95% CI), age 70-79 years</p>
<p>G1 = low G2 = medium G3 = high</p>	<p>The most active women had approx. 50% lower risk of death from stroke compare to inactive women.</p>

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

		Cox proportional HR	
Evenson et al 1999 [257]	To examine the relationship between PA and ischemic stroke risk.	<ul style="list-style-type: none"> n = 14,575 Sex: Men and women Age: 45-64 yr Atherosclerosis Risk in Communities Study 	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.79 G3 = 0.56 p = 0.0093 Multivariate RR (95% CI), age 80-101 years G1 = 1.00 (referent) G2 = 0.91 G3 = 0.57 p = 0.1089
USA Prospective cohort	7.2 year follow up	PA assessment: Questionnaire (Baecke questionnaire)	PA was weakly associated with a reduced risk of ischemic stroke among middle aged adults.
D & B score = 14	Outcome Measure: Ischemic Stroke	Multivariate adjusted RR (95% CI) by sport	Number of Dropouts: 0%
	Multivariate Poisson and Cox proportional HR	Multivariate adjusted RR (95% CI) by LTPA	Sport: Incidence of Ischemic Stroke
		<ul style="list-style-type: none"> Q1 = 1.00 (referent) Q3 = 0.83 (0.52-1.32) 	
		Multivariate adjusted RR (95% CI) by OPA	
		<ul style="list-style-type: none"> Q1 = 1.00 (referent) Q2 = Q3 = 0.89 (0.57-1.37) 	
Haheim et al 1993 [258]	To determine the risk factors of stroke incidence and mortality.	<ul style="list-style-type: none"> n = 14,403 Sex: Men Age: 40-49 yr 	<ul style="list-style-type: none"> Q1 = 1.00 (referent) Q2 = Q3 = 0.69 (0.47-1.00)
	Baseline Screening from May 1972-December 1973.	HR (95% CI) for stroke incidence	Increased LTPA is associated with a reduced risk of stroke incidence but not mortality.
		<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.64 (0.38-1.08) 	

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

Norway				PA assessment: Questionnaire for LTPA, divided into groups	• G3 = 0.36 (0.15-0.80)	
Prospective cohort					HR (95% CI) for stroke mortality	
D & B score = 14				G1 = Sedentary G2 = Moderate G3 = Intermediate or Great Outcome Measure: Incidence of stroke morbidity and mortality until study end date, December 31, 1984. Cox proportional HR	• G1 = 1.00, (referent) • G2 = 0.82 (0.33-2.35) • G3 = 0.29 (0.03-1.51)	
Hu et al 2005 [259]	To assess the relationship of different types of PA with total and type-specific stroke risk.	• n = 47,721		PA assessment: Mailed questionnaire for LTPA, OPA and commuting PA, divided into groups as follows:	RR (95% CI) by LTPA, men	A high level of LTPA reduces the risk of all subtypes of stroke. Daily active commuting also reduces the risk of ischemic stroke.
Finland		• Sex: Men and women • Age: 25-64 • Characteristics: Healthy at baseline			• G1 = 1.00 (referent) • G2 = 0.83 • G3 = 0.72 p < 0.001	
Prospective cohort				LTPA levels: G1 = Low G2 = Moderate G3 = High OPA: G1 = Light G2 = Moderate G3 = Hard	RR (95% CI) by LTPA, women • G1 = 1.00 (referent) • G2 = 0.86 • G3 = 0.75 p = 0.007	
D & B score = 13				Commuting PA: G1 = Motorized or no work, G2 = walking or cycling 1-29 min G3 = walking or cycling ≥ 30 min.	RR (95% CI) by LTPA, men and women • G1 = 1.00 (referent) • G2 = 0.85 • G3 = 0.73 p < 0.001	
					RR (95% CI) by OPA, men	• Not significant

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

Kiely et al 1994 [260]	To examine the influence of increased PA on stroke risk in members of the Framingham study cohort.	n = 1,897 men and women	Outcome Measure: Incidence of fatal or non-fatal stroke occurring during follow-up until end of 2003. Mean follow-up of 19 years.	RR (95% CI) by OPA, women • Not significant RR (95% CI) by OPA, men and women • G1 = 1.00 (referent) • G2 = 0.90 • G3 = 0.87 p = 0.007
USA	Sex: Men and women		Cox proportional hazard	RR (95% CI) by commuting PA, men • G1 = 1.00 (referent) • G2 = 0.91 • G3 = 0.85 p = 0.047
Prospective cohort	Age: 28-62 yr Characteristics: Free from stroke	PA assessment: Questionnaire for metabolic work done during a typical 24 hr period, divided into 3 groups	Baseline measurement in 1954-1955 and follow up in either 1968-1969 or 1971- 1972	RR (95% CI) by commuting PA, men and women • G1 = 1.00 (referent) • G2 = 0.86 • G3 = 0.85 p = 0.018
			Multivariate adjusted RR (95% CI) at first examination, men (mean age 50 years)	p = 0.002 Medium and high levels of PA among men are protective against stroke relative to low levels. • G1 = 1.00 (referent) • G2 = 0.90 (0.62-1.31) p = 0.59 • G3 = 0.84 (0.59-1.18) p = 0.31

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

D & B score = 12			Protective effect of PA was slightly less for high levels of PA compared to medium levels for older men.
Multivariate adjusted RR (95% CI) at first examination, women (mean age 50 years)	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.21 (0.89-1.63) $p = 0.23$ • G3 = 0.89 (0.60-1.31) $p = 0.54$ 	<p>G1 = Low G2 = Medium G3 = High</p> <p>Outcome Measure: Incidence of stroke, as defined by the first occurrence of atherothrombotic brain infarctions, cerebral embolism or other type of stroke, during 32 years of follow-up.</p>	Multivariate adjusted RR (95% CI) at second examination, men (mean age 63 years)
	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.41 (0.24-0.89) $p = 0.0007$ • G3 = 0.53 (0.34-0.84) $p = 0.0007$ 	Multivariate adjusted RR (95% CI) at second examination, women (mean age 64 years)	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.97 (0.64-1.47) $p = 0.67$ • G3 = 1.21 (0.75-1.96) $p = 0.43$
Cox proportional HR		PA assessment:	Stroke patients are less physically active in the week preceding an ischemic stroke when compared to age and sex-matched controls. Increasing PASE score was inversely, log-linearly and significantly associated with OR for ischemic stroke.
Krøger et al 2007 [261]	To compare the reported level of PA performed during the week preceding an ischemic stroke with that of community controls.	<ul style="list-style-type: none"> • n = 127 cases • n = 301 controls 	Univariate OR (95% CI)
Denmark	<ul style="list-style-type: none"> • Sex: Men and women • Age: ≥ 40 yr 	Questionnaire about PA 1 week prior to stroke (cases) and 1 week prior to questionnaire (controls), divided into PASE scores and quartiles	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.51 (0.28-0.95) • Q3 = 0.27 (0.14-0.54)

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

Case control	<ul style="list-style-type: none"> • Characteristics: Case: Stroke Patients (20% had history of Stroke), Controls: 4% had history of stroke 	<ul style="list-style-type: none"> • Q4 = 0.08 (0.03-0.20) 	
D & B score = 14	<p>Q1 = 0-49 Q2 = 50-99 Q3 = 100-149 Q4 = 150+</p> <p>Outcome measure: Ischemic stroke</p> <p>Chi squared Kruskal-Wallis Statistics Multivariate conditional logistic regression</p>	<p>Multivariate OR (95% CI) PASE Score</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.53 (0.26-1.08) • Q3 = 0.27 (0.12-0.59) • Q4 = 0.09 (0.03-0.25) 	
Kurl et al 2003 [262]	<p>To examine the relationship of PF with subsequent incidence of stroke. Also to compare PF with conventional risk factors as a predictor for future stroke.</p> <ul style="list-style-type: none"> • n = 2,011 	<p>Multivariate HR (95% CI), any stroke</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.39 (0.70-2.77) • Q3 = 1.32 (0.66-2.65) • Q4 = 2.30 (1.18-4.06) 	<p>Low PF was associated with an increased risk of any stroke and ischemic stroke.</p>
Finland	<ul style="list-style-type: none"> • Sex: Men • Age: 42, 48, 54 or 60 yrs 		
Prospective cohort	<ul style="list-style-type: none"> • Characteristics: Free from stroke or pulmonary disease • Kuopio Ischaemic Heart Disease Risk Factor Study 	<p>Trend $p = 0.01$</p>	
D & B score = 14	<p>PF assessment: Maximal exercise test on cycle ergometer. VO_2 max (ml/kg/min) divided into quartiles</p> <p>Q1 = >35.3 Q2 = 30.3-35.3 Q3 = 25.2-30.2</p>	<p>Multivariate HR (95% CI), ischemic stroke</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.28 (0.56-2.94) • Q3 = 1.64 (0.74-3.65) • Q4 = 2.40 (1.09-5.25) <p>Trend $p = 0.01$</p>	

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

	Q4 = <25.2	Outcome Measure: Stroke incidence Cox proportional HR	Higher levels of PA assessed using a single simple pragmatic tool based on both OPA and LTPA is associated with reduced stroke risk
Myint et al 2006 [263]	To examine the association between a combination of OPA and LTPA with risk of subsequent stroke.	n = 22,602	Model A: Used all 4 categories of PA
UK	Sex: Men Age: 40-79 yr Characteristics: Healthy at baseline	1993-1997	HR (95% CI), men and women • G1 = 1.00 (referent) • G2 = 0.78 (0.61-1.00)
Prospective cohort	European Prospective Investigation in Cancer-Norfolk	PA assessment: Questionnaire for PA (includes LTPA and OPA) divided into 4 groups	• G3 = 0.66 (0.49-0.91) • G4 = 0.70 (0.49-0.99)
D & B score = 11		G1 = Inactive G2 = moderately inactive G3 = moderately active G4 = active	p = 0.024 HR (95% CI), men • G1 = 1.00 (referent) • G2 = 0.75 (0.52-1.09) • G3 = 0.55 (0.35-0.86) • G4 = 0.67 (0.43-1.05)
		Outcome Measure: Incidence of fatal and non fatal stroke.	p = 0.41 Women not significant p = 0.50
		Cox proportional HR	Model B: Used 3 categories of PA (G3 and G4 combined) HR (95% CI), men and women • G1 = 1.00 (referent) • G2 = 0.78 (0.61-1.00) • G3 = 0.68 (0.52-0.88) p = 0.009 HR (95% CI), men • G1 = 1.00 (referent) • G2 = 0.75 (0.52-1.09), • G3 = 0.61 (0.43-0.86) p = 0.019

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

Noda et al 2005 [264]	To examine the impact of exercise on CVD (stroke) mortality in Asian populations.	• n = 31,023 men, 42,242 women	9.7 year follow up	Number of Cases: 186 men, 141 women	PA through walking and sports participation may reduce the risk of mortality from ischemic stroke
Japan	• Sex: Men and women	• Age: 40 -79 yr	PA assessment: Questionnaire for PA (walking and sports participation (h/day), divided into quartiles:	Number of Dropouts: 3.4%	Multivariate adjusted HR (95% CI) by duration of walking PA, men
Prospective cohort	• Ethnicity: Asian	Q1 = <0.5 Q2 = 0.5 Q3 = 0.6-0.9 Q4 = >1.0	• Q1 = 1.03 (0.63-1.69) • Q2 = 1.00 (referent) • Q3 = 0.56 (0.35-0.91) • Q4 = 0.71 (0.49-1.02)	Multivariate adjusted HR (95% CI) by duration of walking PA, women	• Q1 = 1.38 (0.82-2.33) • Q2 = 1.00 (referent) • Q3 = 0.56 (0.32-0.97) • Q4 = 0.73 (0.48-1.13)
D & B score = 13	Outcome Measure: Death from ischemic stroke	Cox proportional HR	Multivariate adjusted HR (95% CI) by sport PA, men	Multivariate adjusted HR (95% CI) by sport PA, women	• Q1 = 1.34 (0.86-2.08) • Q2 = 1.00 (referent) • Q3 = 1.22 (0.66-2.25) • Q4 = 0.84 (0.45-1.57) • Q1 = 1.07 (0.64-1.77) • Q2 = 1.00 (referent) • Q3 = 0.62 (0.25-1.58) • Q4 = 0.73 (0.31-1.70)

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

Paganini-Hill and Barreto 2001 [265]	To identify risk factors and preventative measures for stroke in elderly men and women.	• n = 4,722 men, 8,532 women • Sex: Men and women Age: 44-101 yr • Characteristics: no previous history of stroke. Residence of a retirement community in Southern California	Baseline survey in 1981- 1982.	Multivariate adjusted RR (95% CI) for total hemorrhagic occlusion by exercise, men • Q1 = 1.00 (referent) • Q2 = 0.88 Q3 = 0.83	Emphasized role of lifestyle modification in the primary prevention of stroke.
USA					
Prospective cohort					
D & B score = 13					
Pitsavos et al 2004 [266]	To investigate the interaction between PA in men with LVH on stroke mortality.	• n = 489 • Sex: Men • Age: 40-59 yr • Characteristics: Those without LVH • Corfu Cohort (Greece) from Seven Countries Study	Poisson Regression 40 year follow up	Multivariate adjusted RR (95% CI) for total hemorrhagic occlusion by exercise, women • Q1 = 1.00 (referent) • Q2 = 0.91 • Q3 = 0.85	PA reduced the risk of stroke in men without LVH.
USA					
Prospective cohort					
D & B score = 12					

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

Sacco et al 1998 [267]	To investigate the association between LTPA and ischemic stroke.	<ul style="list-style-type: none"> n = 369 case, 678 control 	Case Subjects were recruited during hospitalization, self referral or from monitoring non hospitalized stroke. Controls were eligible if they had never been diagnosed with stroke and were >39 years.	LTPA was related to a decreased occurrence of ischemic stroke in elderly, multiethnic, urban subjects.
USA		<ul style="list-style-type: none"> Sex: Men and women 		O R (95% CI) for duration of LTPA and stroke
Case control		<ul style="list-style-type: none"> Age: > 39 yr Characteristics: Case Subjects: Diagnosed with first cerebral infarction after July 1, 1993. Control Subjects: Never diagnosed with stroke 		<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.42
D & B score = 14		<ul style="list-style-type: none"> Northern Manhattan Stroke Study 	PA assessment: Questionnaire Divided into duration of LTPA (h/wk) G1 = 0 G2 = <2 G3 = 2-<5 G4 = ≥ 5 Multivariate conditional logistic regression Baseline data collection from 1982-1983 in East Boston (MA), New Haven (CT) and Iowa and Washington counties (IA).	<ul style="list-style-type: none"> G3 = 0.35 G4 = 0.31
Simonsick et al 1993 [268]	To examine the association between recreational PA among physically capable older adults and incidence of selected chronic diseases and mortality over 3 and 6 years.	<ul style="list-style-type: none"> n = 1,815 Sex: Men and women Age: ≥ 65 yrs 		No consistent relationship between PA and stroke was found after 3 or 6 years across all 3 population cohorts.
			After 3 years Iowa	OR (95% CI) Stroke and activity level

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

USA	<ul style="list-style-type: none"> • Characteristics: Physically capable to do heavy work around the house, walk up and down a flight of stairs and walk a half mile without help. 	<ul style="list-style-type: none"> • T1 = 0.22 (0.08-0.61)
Prospective cohort		<ul style="list-style-type: none"> • T2 = 1.05 (0.60-1.84) • T3 = 1.00 (Referent)
D & B score = 12		
	PA assessment: Questionnaire	
	T1 = High	New Haven
	T2 = Moderate and	OR (95% CI) Stroke and activity level
	T3 = Inactive	<ul style="list-style-type: none"> • T1 = 1.06 (0.38-2.95) • T2 = 1.26 (0.54-2.92) • T3 = 1.00 (Referent)
	<ul style="list-style-type: none"> • Established Populations for Epidemiologic Studies of the Elderly 	
	Outcome Measure: Stroke incidence during 3 and 6 year follow-ups.	East Boston
		OR (95% CI) Stroke and activity level
		<ul style="list-style-type: none"> • T1 = 0.59 (0.17-1.95) • T2 = 1.08 (0.52-2.27) • T3 = 1.00 (Referent)
	Logistic Regression	After 6 years
		Iowa
		OR (95% CI) Stroke and activity level
		<ul style="list-style-type: none"> • T1 = 0.56 (0.31-1.00) • T2 = 0.97 (0.64-1.48) • T3 = 1.00 (Referent)
		New Haven
		OR (95% CI) Stroke and activity level
		<ul style="list-style-type: none"> • T1 = 1.05 (0.52-2.12) • T2 = 1.29 (0.72-2.32) • T3 = 1.00 (Referent)
		East Boston
		OR (95% CI) Stroke and activity level
		<ul style="list-style-type: none"> • T1 = 1.21 (0.56-2.61)

Table 13: Studies examining the relationship between physical activity and stroke. (Continued)

Thrift et al 2002 [269]	To examine whether intracerebral hemorrhage is associated with dynamic or static exercise.	<ul style="list-style-type: none"> n = 662 Sex: Men and women Age: 18-80 yr Characteristics: Cases: first episode of intracerebral hemorrhage Controls: Neighbours of cases 	PA assessment: Interview, divided into 3 groups: frequency of vigorous activity	<ul style="list-style-type: none"> T2 = 1.73 (0.98-3.06) T3 = 1.00 (Referent) 	Number of Cases: 331	Findings not significant after multivariate analysis.
Australia					Multivariate OR (95% CI) by frequency of VPA	
Case control					<ul style="list-style-type: none"> G1 = Never G2 = Rarely G3 = Once or more per month 	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.68 (0.36-1.27) G3 = 0.66 (0.39-1.11)
D & B score = 14					<ul style="list-style-type: none"> p = 0.094 OPA level Multivariate OR (95% CI) by OPA level G1 = Sedentary G2 = Light to moderate G3 = Heavy 	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.94 (0.59-1.48), p = 0.773 G3 = 1.18 (0.57-2.46), p = 0.650
			Outcome Measure: Intracerebral hemorrhage			
			Multiple logistic regression			

D & B score, Downs and Black quality score; YR, years; wk, week; CVD, cardiovascular disease; G, groups; PA, physical activity; CHD, coronary heart disease; RR, risk ratio; 95% CI, 95% confidence interval; T, tertile; PF, physical fitness; MET, metabolic equivalent; Q, quartile or quintile; OPA, occupational physical activity; LTPA, leisure-time physical activity; HR, hazard ratio; VPA, vigorous physical activity; LVH, left ventricular hypertrophy.

according to the type of stroke (ischemic or haemorrhagic) [52]. For instance, 12 studies (46%) revealed a dose-response relationship in one or more measures of occupational and/or leisure-time physical activity and the risk for stroke. It is difficult to determine the minimal and optimal physical activity dosage for the prevention of stroke. Brisk walking has been associated with a lower risk of total and ischemic stroke [72]. In the Harvard Alumni study, the risk of stroke was lower at a weekly energy expenditure of 4.2-8.4 MJ/wk (1000-1999 kcal/wk) (RR = 0.76 (95% CI, 0.59 to 0.98)). With expenditures of 8.4-12.6 MJ/wk (2000-2999 kcal/wk) the RR dropped to 0.54 (0.38 to 0.76) [73]. Thus, the recommended daily expenditure of Canada's physical activity guidelines is sufficient to reduce the risk for stroke. Further research is required to clearly determine the risk reductions at exercise volumes less than 4.2 MJ/wk (1000 kcal/wk).

In summary, the results of these studies (taken as a whole) indicate that occupation- and leisure time-related physical activity are inversely related to the risk for stroke. Both physically active men and women have a lower risk of stroke, and it appears that this benefit may be present for both ischemic and haemorrhagic stroke [74]. The relationship between physical activity and stroke appears to be consistent between men and women. Unfortunately, relatively limited data exists in non-Caucasian populations.

Recommendation #3

For a reduced risk of stroke, it is recommended that individuals should participate in 30 min or more of moderate to vigorous exercise on most days of the week. Brisk walking appears to be protective against the development of stroke. It remains to be determined whether lower volumes of physical activity lead to a reduced risk for stroke. [Level 3, Grade A]

Primary Prevention of Hypertension

A total of 6287 citations were identified during the electronic database search (Figure 6). Of these citations, 4054 were identified in MEDLINE, 1360 in EMBASE, 253 in Cochrane, and 620 in the CINAHL/SportDiscus/PsychInfo search. A total of 40 duplicates were found, leaving a total of 6247 unique citations. A total of 6167 articles were excluded after scanning, leaving a total of 80 articles for full review. An additional five articles were found through cross-referencing and the reviewers' personal files. From these articles 72 were excluded after full review for the following reasons: weak design (n = 4), did not contain three levels of physical activity or not possible to determine dose-response relationship (n = 19), reviews, summaries, meta-analyses (n = 8), not dealing with hypertension (n = 2), only reported on changes in blood pressure (n = 27), clinical population

(n = 7), and other (n = 6). Therefore, a total of 12 articles were included in the systematic review of the literature regarding the relationship between physical activity and the primary prevention of hypertension. The majority of the literature examining the dose-response (for at least three levels of physical activity/fitness) involved prospective cohort analyses (83%).

As shown in Table 14, 12 investigations examined the dose-response (i.e., three or more levels) relationship between physical activity and the incidence of hypertension. This involved a total of 112,636 participants, averaging 10,240 subjects per study (range 1,243-41,837).

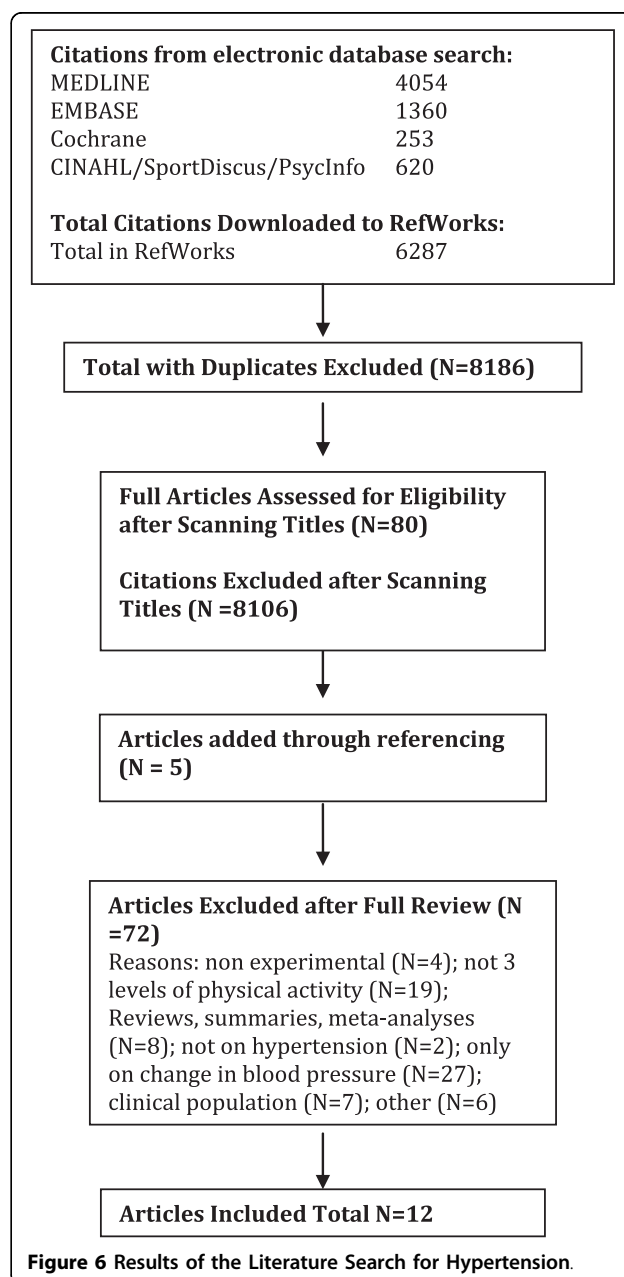


Figure 6 Results of the Literature Search for Hypertension.

Table 14 Studies examining the relationship between physical activity and hypertension.

Publication Country Study Design Quality Score	Objective	Population	Methods	Outcome	Comments and Conclusions
Rankinen et al 2007 [75]	To investigate the contributions of DNA sequence variation in candidate genes, PF and BMI, as well as their interactions to the incidence of hypertension.	<ul style="list-style-type: none"> n = 629 cases; 605 controls 	10 year follow up	PF showed the strongest association with HTN risk among all subjects as well as sex-specific models. Each 1-MET increment in PF was associated with 19% (12- 14%), 16% (9-22%), 32% (17- 45%) risk reduction in all subjects, men and women respectively.	PF is a significant predictor of the risk of hypertension.
USA		<ul style="list-style-type: none"> Sex: Men and women 	All subjects required to have 2 clinic visits at least 2 years apart.		
Case control		<ul style="list-style-type: none"> Age: Case: 43.3 (9.2) yr Control: 42.7 (8.9) yr 	PF assessment: treadmill test (Blake protocol)		
D & B score = 13		<ul style="list-style-type: none"> Characteristics: Healthy with BP 134/86 mmHg or less at their first clinic visit. Cases: those who developed hypertension during the follow-up period. Controls were those who did not develop hypertension 	<p>Outcome measure: Incidence of hypertension during follow-up. Incident cases of hypertension were defined as physician diagnosed hypertension with medication or SBP \geq 140 mmHg and/of DBP \geq 90 mmHg t-tests and chi-square tests</p> <p>Logistic regression modelling</p>	When divided into quartiles on the basis of sex specific MET cut-offs, the third and fourth quartiles had a 58% (41-71%) and 63% (47-75%) lower risk of hypertension compared to the 1 st quartile.	
Pereira et al 1999 [76]	To examine PA and incident hypertension in men and women.	<ul style="list-style-type: none"> n = 7,459 	PA Assessment: Questionnaire for leisure, sport and work index, divided into quartiles	White Men	There is an inverse association between PA and incident hypertension in White middle aged men. White men in the highest quartiles of sport and leisure activity had statistically significant reductions in the odds of developing hypertension of 23 and 34% respectively, compared to men in the lower quartiles.
USA		<ul style="list-style-type: none"> Sex: Men and women Age: 45-65 yr 	Q1 = Lowest Q2	Leisure Index Model 1	
Prospective cohort		<ul style="list-style-type: none"> Characteristics: No history of angina, MI, evidence of MI, angioplasty or other CV surgery or hypertension 	Q3	<ul style="list-style-type: none"> Q1 = 1.00 (referent) Q2 = 0.95 (0.70-1.28) 	
D & B score = 12		<ul style="list-style-type: none"> Atherosclerosis Risk in Communities Study 	Q4 = Highest	<ul style="list-style-type: none"> Q3 = 0.83 (0.63-1.09) Q4 = 0.64 (0.46-0.89) 	
		Model 1 adjusted for: Age, education, baseline BP and study centre			

Table 14: Studies examining the relationship between physical activity and hypertension. (Continued)

Haapanen et al 1997 [77]	To assess the association between PA and hypertension.	• n = 732 men; 796 women	10 year follow up (1980 baseline)	<p>Model 2 adjusted for: Covariates in model 1 and smoking, alcohol consumption, parental history of hypertension, energy, sodium, potassium and caffeine intake, BMI, waist to hip ratio, menopausal status and hormone use</p> <p>Outcome Measure: Incidence of hypertension as defined as a SBP 140 mmHg and/or a DBP 90 mmHg or use of antihypertensive medications.</p> <p>Unconditional logistic regression Orthogonal polynomial coefficients</p> <p>Leisure Index Model 2</p> <p>• Q1 = 1.00 (referent) • Q2 = 0.99 (0.72-1.35) • Q3 = 0.86 (0.65-1.13) • Q4 = 0.66 (0.47-0.94) Trend $p = 0.01$</p> <p>Women</p> <p>Sport Index Model 1</p> <p>• Q1 = 1.00 (referent) • Q2 = 1.26 (0.78-2.05) • Q3 = 1.06 (0.61-1.84) • Q4 = 1.92 (1.12-3.29) Trend $p = 0.04$</p> <p>Men</p> <p>Sport Index Model 1</p> <p>• Q1 = 1.00 (referent) • Q2 = 1.23 (0.91-1.66) • Q3 = 0.92 (0.70-1.22) • Q4 = 0.74 (0.54-1.02) Trend $p = 0.02$</p> <p>Sport Index Model 2</p> <p>• Q1 = 1.00 (referent) • Q2 = 1.26 (0.93-1.71) • Q3 = 0.95 (0.71-1.26) • Q4 = 0.77 (0.55-1.08) Trend $p = 0.05$</p>
				<p>Increased EE during LTPA and increased intensity of these activities were associated with reduced risk for incident hypertension (age adjusted) in men but not women.</p>

Table 14: Studies examining the relationship between physical activity and hypertension. (Continued)

Finland Prospective cohort D & B score = 11	<ul style="list-style-type: none"> • Sex: Men and women • Age: 35-65 years • Characteristics: Free of hypertension at baseline. Excluded those unable to participate in regular PA due to poor health 	<p>PA assessment: Questionnaire for EE (kcal/wk), divided into tertiles</p> <p>Male</p> <p>T1 = Low = 0-1100</p> <p>T2 = Medium = 1101-1900</p> <p>T3 = High >1900</p> <p>Female</p> <p>T1 = Low = 0-900</p> <p>T2 = Medium = 901-1500</p> <p>T3 = High = > 1500</p> <p>Outcome measure: Incidence of hypertension through self reported diagnosis and death certificates</p> <p>Cox proportional HR</p>	<p>Male:</p> <ul style="list-style-type: none"> • T1 = 1.00 (referent) • T2 = 1.66 • T3 = 1.73 <p>Trend $p = 0.021$</p> <p>Female:</p> <ul style="list-style-type: none"> • T1 = 1.00 (referent) • T2 = 0.94 • T3 = 1.16 <p>Trend $p = 0.648$</p>	
Paffenbarger et al 1983 [78] USA Prospective cohort D & B score = 12	<ul style="list-style-type: none"> • n = 14,998 • Sex: Men • Age: 35-74 yr • Characteristics: free of hypertension Harvard Alumni Study 	<p>To examine the relationship of student and alumnus PA patterns and other characteristics with incident hypertension.</p> <p>PA Assessment: Questionnaire for PA based on number of stairs ascended, blocks walked and hours per week of light and vigorous sports play, yard work etc.</p> <p>Outcome measure: Diagnosis of hypertension by physicians using criteria of SBP > 160 mmHg and/or DBP > 95 mmHg</p> <p>Multivariate estimates</p>	<p>There was no significantly reduced risk for hypertension in men who climbed 50 plus stairs per day (compared to < 50 stairs); who walked 5 plus blocks per day (compared to < 5 blocks); or who played light sports (compared to those who did not).</p> <p>The 59% of men who did engage in vigorous sports were at 35% greater risk of hypertension than the 41% who did not.</p> <p>RR = 1.35</p> <p>Trend $p = <0.001$</p> <p>Alumni on the low side of the physical activity index (< 2000 kcal/wk) had a 30% increased risk of hypertension then those \geq 2000 kcal/wk.</p> <p>RR = 1.30</p> <p>Trend $p = 0.004$</p>	<p>Contemporary vigorous exercise was inversely related to hypertension risk.</p>

Table 14: Studies examining the relationship between physical activity and hypertension. (Continued)

			PA Assessment: Questionnaire for weekly sports play, divided into tertiles	RR (95% CI)	Lack of vigorous sports play independently increased the risk of developing hypertension.
Paffenbarger et al 1997 [79]	To investigate the quantity and intensity of energy expenditure required to delay hypertension and prevent premature death.	• n = 6,390			
USA					
Prospective cohort		• Sex: Men	T1 = None	• T1 = 1.00 (referent)	
D & B score = 12		• Age: 45-84 yr	T2 = Light Only (< 4.5 METs)	• T2 = 1.04 (0.77-1.40)	
		• Characteristics: Free of hypertension, CHD, diabetes, COPD and potentially malignant cancer in 1977	T3 = Moderately vigorous (≥ 4.5 METs)	• T3 = 0.77 (0.62-0.96)	
		• Harvard Alumni Study	Outcome measure: Incident hypertension	Trend <i>p</i> = 0.004	
Hu et al 2004 [81]	To discover whether regular PA can reduce the risk of hypertension in normal weight and overweight men and women.	• n = 8,302 men; 9,139 women	11 year follow up	Multivariate adjusted HR (95% CI), men	Regular PA can reduce the risk of hypertension. The protective effect of PA was observed in both sexes regardless of level of obesity.
Finland		• Sex: Men and women	PA assessment: Questionnaire for OPA, LTPA and commuting PA, divided into tertiles	• T1 = 1.00 (referent)	
Prospective cohort		Age: 25-64 yr	T1 = Low	• T2 = 0.63	
D & B score = 13		Characteristics: Healthy and free of hypertension at baseline	T2 = Medium	• T3 = 0.59	
			T3 = High	Trend <i>p</i> = < 0.001	
			Outcome Measure: Incidence of drug treated hypertension	Multivariate adjusted HR (95% CI), women	
			Cox proportional HR	• T1 = 1.00	
				• T2 = 0.82	
				• T3 = 0.71	
				Trend <i>p</i> = 0.005	
Gu et al 2007 [82]	To determine the 8-year incidence of HTN and its risk factors among Chinese adults.	• n = 10,525	Baseline Examination in 1991 with 8 year follow up	RR (95% CI), men	Increasing PA has the potential to reduce incidence of hypertension.
China		• Sex: Men and women	PA assessment: Questionnaire administered by trained staff, divided into groups	• G1 = 1.00 (referent)	
Prospective cohort		Age: ≥ 40 yr	G1 = Low	• G2 = 1.12 (0.86-1.46)	
D & B score = 13		Characteristics: Healthy and free from hypertension at baseline.	G2 = Medium	• G3 = 1.27 (1.10-1.47)	
			G3 = High	RR (95% CI), women	

Table 14: Studies examining the relationship between physical activity and hypertension. (Continued)

	<p>Outcome measure: HTN as defined at SBP \geq 140 mmHg and/or DBP \geq 90 mmHg or current use of antihypertensive medication</p> <p>t-tests, chi squared tests, Cochran-Armitage modeling, Modified Poisson approach</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.14 (0.98-1.34) • G3 = 1.22 (1.02-1.45) 			
<p>Hayashi et al 1999 [83]</p> <p>Japan</p> <p>Prospective cohort</p> <p>D & B score = 12</p>	<p>To investigate the association of the duration of the walk to work and LTPA with the risk for hypertension.</p> <p>• n = 6,017</p> <p>• Sex: Men</p> <p>• Age: 35-60 yr</p> <p>• Characteristics: Free from HTN at baseline. All employees at gas company in Osaka Japan. All had sedentary jobs.</p>	<p>PA assessment: Questionnaire on health related behaviours and exercise Walk time to work</p> <p>T1 = 0-10 min</p> <p>T2 = 11-20 min</p> <p>T3 = \geq 21 min</p> <p>Outcome measure: Diagnosed with hypertension (as defined by a SBP \geq 160 mmHg, a DBP \geq 95 mmHg, or use of antihypertensive medication)</p> <p>Cox proportional HR</p> <p>Trend $p = < 0.001$</p>	<p>RR (95% CI) Frequency walk time to work (minutes)</p> <ul style="list-style-type: none"> • T1 = 1.00 (referent) • T2 = 0.65 (0.47-0.90) • T3 = 0.72 (0.59-0.88) 	<p>The duration of walk to work was associated with a decreased risk of hypertension even after adjustment.</p> <p>Regular PA (at least once weekly) was inversely related to the risk of incident hypertension</p>
<p>Nakanishi et al 2005 [84]</p> <p>Japan</p> <p>Prospective cohort</p>	<p>To examine the relationship of overall PA to the risk of developing hypertension in normotensive Japanese male office workers over a 7 year observation period.</p> <p>• n = 2,548</p> <p>• Sex: Men</p> <p>• Age: 35-59 yr</p>	<p>7 year follow up</p> <p>Multivariate adjusted RR (95% CI) by PA level only</p> <p>Q1 = 1.00 (referent)</p> <p>Q2 = 0.84 (0.72-0.98)</p>	<p>The rate of rise in both SBP and DBP in each follow-up year decreased with higher EE and that the risk of developing hypertension decreased in a dose dependent manner with higher daily life activity level.</p> <p>Analysis stratified by the presence of or absence of a risk factor showed the negative association of daily life activity with the risk of developing hypertension for men at both low and high risk. This tendency was also observed among men in all 3 categories of normotension.</p>	<p>PA assessment: 1-day activity record and reported the type and frequency on a weekly basis of LTPA, divided into quartiles (kcal/kg/d)</p>

Table 14: Studies examining the relationship between physical activity and hypertension. (Continued)

D & B score = 12	<ul style="list-style-type: none"> • Characteristics: Healthy at baseline; No hypertension or CHD; All office workers for a Japanese company 	<ul style="list-style-type: none"> • Q1 = <33.3 • Q2 = 33.3-36.9 • Q3 = 37.0-40.3 • Q4 = 40.4 	<ul style="list-style-type: none"> • Q3 = 0.75 (0.63-0.88) • Q4 = 0.54 (0.45-0.64) 	
	<p>3 categories of normotensive BP Low Normal: SBP < 120, DBP < 80 Normal: SBP 120-130, DBP 80- 85 High Normal: SBP 130-139 DBP 85-89</p>		<p>Trend $p = < 0.001$ Multivariate adjusted RR (95% CI) by PA level, low normal BP</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) 	
	<p>3 categories of normotensive BP Low Normal: SBP < 120, DBP < 80 Normal: SBP 120-130, DBP 80- 85 High Normal: SBP 130-139 DBP 85-89</p>		<ul style="list-style-type: none"> • Q2 = 0.70 (0.47-1.05) 	
	Cox proportional hazard model		<ul style="list-style-type: none"> • Q3 = 0.55 (0.37-0.83) • Q4 = 0.43 (0.28-0.65) 	
			<p>Trend $p = < 0.001$ Multivariate adjusted RR (95% CI) by PA level, normal BP</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.89 (0.68-1.16) • Q3 = 0.69 (0.52-0.91) • Q4 = 0.50 (0.37-0.68) 	
			<p>Trend $p = < 0.001$ Multivariate adjusted RR (95% CI) by PA level, high normal BP</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.86 (0.69-1.07) • Q3 = 0.88 (0.69-1.11) • Q4 = 0.60 (0.46-0.78) 	
Foy et al 2006 [85]	<p>To examine whether insulin resistance is associated with the effect of vigorous or moderate PA on baseline BP.</p> <ul style="list-style-type: none"> • n = 1,599 	Baseline examination in 1992-1993	<p>Unadjusted OR (95% CI)</p>	<p>Participants who meet or exceed current caloric expenditure recommendations for VPA demonstrate significantly less hypertension than do sedentary or underactive individuals.</p>

Table 14: Studies examining the relationship between physical activity and hypertension. (Continued)

USA	<ul style="list-style-type: none"> • Sex: Men and women 	PA assessment: VPA over the past year was determined via a 1-year recall of physical activity (kcal/d), divided into 3 groups	<ul style="list-style-type: none"> • T1 = 1.00 (referent)
Cross sectional	<ul style="list-style-type: none"> • Age: 40-69 yr 	<ul style="list-style-type: none"> • T1 = O 	<ul style="list-style-type: none"> • T2 = 0.69 (0.53-0.88)
D & B score = 12	<ul style="list-style-type: none"> • Characteristics: Community dwelling adults • Insulin Resistance Atherosclerosis Study 	<ul style="list-style-type: none"> • T2 = 1-149 kcal/day • T3 = > 150 kcal/day 	<ul style="list-style-type: none"> • T3 = 0.57 (0.45-0.74) • Trend $p = < 0.001$
			Adjusted OR (95% CI)
			<ul style="list-style-type: none"> • T1 = 1.00 (referent) • T2 = 0.82 (0.62-1.09) • T3 = 0.73 (0.55-0.98)
			Trend $p = 0.004$
Folsom et al 1990 [270]	<ul style="list-style-type: none"> • n = 41,837 	Baseline mailed survey in 1986: Pa assessment: Questionnaire for LTPA	<ul style="list-style-type: none"> • 978 cases
USA	<ul style="list-style-type: none"> • Sex: Women 	T1 = Low T2 = Medium T3 = High	Age Adjusted RR (95% CI)
Prospective cohort	<ul style="list-style-type: none"> • Age: 55-69 years (yr) 		<ul style="list-style-type: none"> • T1 = 1.00 (referent)
D & B score = 12	<ul style="list-style-type: none"> • Characteristics: All free of HTN at baseline 	Mantel-Haenszel method Multiple logistic regression	<ul style="list-style-type: none"> • T2 = 0.9 (0.7-1.1) • T3 = 0.7 (0.6-0.9)
Levenstein et al 2001 [271]	<ul style="list-style-type: none"> • n = 1,031 men, 1,326 women 	Questionnaires in 1965 and 1974, cohort followed until 1994	LTPA predictor of hypertension OR (95% CI)
USA	<ul style="list-style-type: none"> • Sex: Men and women 	PA assessment: LTPA rated on a scale of 0-16 points and analysed as a continuous variable	<ul style="list-style-type: none"> • All Subjects: 0.94 (0.91-0.97)
Prospective cohort	<ul style="list-style-type: none"> • Characteristics: Free of hypertension at baseline 	Outcome measure: Incidence of hypertension (defined as those who are taking antihypertensive medications)	<ul style="list-style-type: none"> • Women: 0.90 (0.87-0.94)
D & B score = 13	<ul style="list-style-type: none"> • Alameda cohort study 	Logistic regression analysis	<ul style="list-style-type: none"> • Men: 0.98 (0.94-1.02)

D & B score, Downs and Black quality score; Yr, years; PF, physical fitness; BMI, body mass index; MET, metabolic equivalent; PA, physical activity; MI, myocardial infarction; G, groups; Q, quartile or quintile; 95% CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; EE, energy expenditure; kcal/wk, kilocalories per week; T, tertile; RR, risk ratio; HR, hazard ratio; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; OPA, occupational physical activity; LTPA, leisure-time physical activity; BP, blood pressure; kcal/day, kilocalories per day.

High PA reduced the risk of hypertension only before adjusting for other factors.

Risk of HTN was reduced with increases in LTPA in women.

There were a total of 11,441 reported cases of hypertension (ranging per study from 118-2,936). The total length of study follow-up averaged 8.6 yr (ranging from 0-16 yr). The articles were published over a 24 yr period ranging from 1983 to 2007.

All studies reviewed demonstrated positive effects of physical activity on the risk for hypertension. Of these studies all (7; 58%) revealed an inverse and graded relationship between hypertension and at least one measure of physical activity or fitness. Across all studies, when comparing the most active/fit group versus the least active/fit group we found an average RR of 0.68 (median = 0.70, range 0.37 to 0.90). Therefore, we observed that physical activity/fitness was associated with an average risk reduction of 32% for hypertension. It should be noted that the study [75] demonstrating the largest risk reduction (63%) evaluated cardiorespiratory fitness directly during a maximal treadmill test. This supports research (as discussed previously) which indicates that physical fitness is a better predictor of chronic disease than physical activity [6,18,19,32,33]. *Taken as a whole, the level of evidence can be classified as Level 3A.* The quality of studies was generally good with a mean Downs and Black score of 11 (median = 11, range = 10-12).

Five studies showed variable results (i.e., no clearly defined dose-response) while generally supporting the inverse relationship between physical activity/fitness and hypertension [76-80]. The variability in the response appears to be the result of different activity/fitness classifications and/or differing subject populations. For instance, some studies revealed that the dose-response relationships differed between genders and/or ethnicities [76,77]. Pereira et al. [76] revealed a 30% reduction in the risk for hypertension in the most active white men. There were graded dose-response relationships between indices of both leisure and sport activities in the white men.

However, there was a lack of association between physical activity and hypertension in white women and African American men and women. Similarly, Haapenen et al. [77] revealed a stronger association in men than in women. However, it should be noted clearly that other studies included in this systematic review evaluated women demonstrating a graded response [81]. Moreover, several studies were conducted with non-Caucasian populations and demonstrated a dose-dependent benefit [82-85]. In fact, data was obtained from varied regions of the world including USA (7), Japan (2), China (1), and Finland (1). Therefore, there is evidence to suggest that the protective effects of physical activity with respect to hypertension are transferable to women and non-Caucasian populations. However, further research is clearly warranted that examines the relationship between physical activity and hypertension in persons of

different ethnicities. Moreover, further research is needed to determine the effects of impact of socio-economic status on the observed relationships.

Some studies have indicated that vigorous activity is required to reduce the risk for hypertension. For instance, Paffenbarger [78] revealed that Harvard Alumni who did not engage in vigorous sports play were at a 35% higher risk for developing hypertension. However, there was no difference in the risk for hypertension in men who climbed >50 stairs per day, walked more than 5 city blocks daily, or engaged in light sports only. Similarly, the Paffenbarger and Lee [79] study revealed that moderately vigorous sports play was associated with a lower risk for hypertension, but physical activity (kcal/wk), walking distance (km/wk) and the amount of stairs climbed (floors/wk) were not significant predictors of the risk for hypertension. Collectively, this research group concluded that these findings highlighted the importance of the intensity of effort.

However, it should be noted that many of the studies in our systematic review observed the protective effect with moderate intensity physical activities. Findings from randomized controlled trials have also provided strong evidence that moderate intensity aerobic exercise is sufficient to reduce blood pressure and the risk for hypertension, particularly in at risk individuals [86,87]. The American College of Sports Medicine [88] recently advocated that to prevent hypertension, individuals should exercise on most, and preferably all, days of the week at a moderate intensity, for 30 min or more per day (continuous or accumulated). They also recommended supplementing endurance type activities with resistance exercise. This is supported by research indicating that moderate intensity resistance training can reduce blood pressure [89]. Collectively, this research and our current summary of the dose-response literature indicates that physical activity levels that are of a moderate to vigorous intensity are sufficient to lead to marked reductions in the risk for hypertension.

Implications

The impact of hypertension on North American society is enormous. In the US, 31% of non-institutionalized adults over the ages of 20 are currently thought to have hypertension [90]. In Canada, approximately 20% of adults report a diagnosis of hypertension including over 4 million Canadians [91-93]. It has been estimated that a 55 yr old Canadian with normal blood pressure has a greater than 90% chance of developing hypertension before the age of 80 yr [92]. The primary prevention of hypertension is of paramount importance to the attenuation of the risks and costs associated with hypertension and related comorbidities.

There is clear evidence that routine physical activity and/or increased physical fitness reduce greatly the risk

for hypertension in both normotensive and hypertensive individuals [18,19]. Extensive research has been conducted in the area including numerous prospective trials and various randomized controlled trials. Numerous reviews of the literature (of epidemiological and randomized controlled trials) have supported an inverse relationship between physical activity/fitness and in the incidence of hypertension [20,87,89,94-102]. In a recent systematic review of the prospective literature, Katzmarzyk and Janssen (2004) calculated that physically inactive individuals were at a 30% higher risk for hypertension (RR = 1.30 (95% CI = 1.16-1.46)) with a population attributable risk of 13.8% in Canada [20]. Acute bouts of exercise have also been shown to lead to transient changes in blood pressure that are potentially of health benefit [98]. For instance, blood pressure is often reduced after a single exercise session for 12-22 hr [88,103].

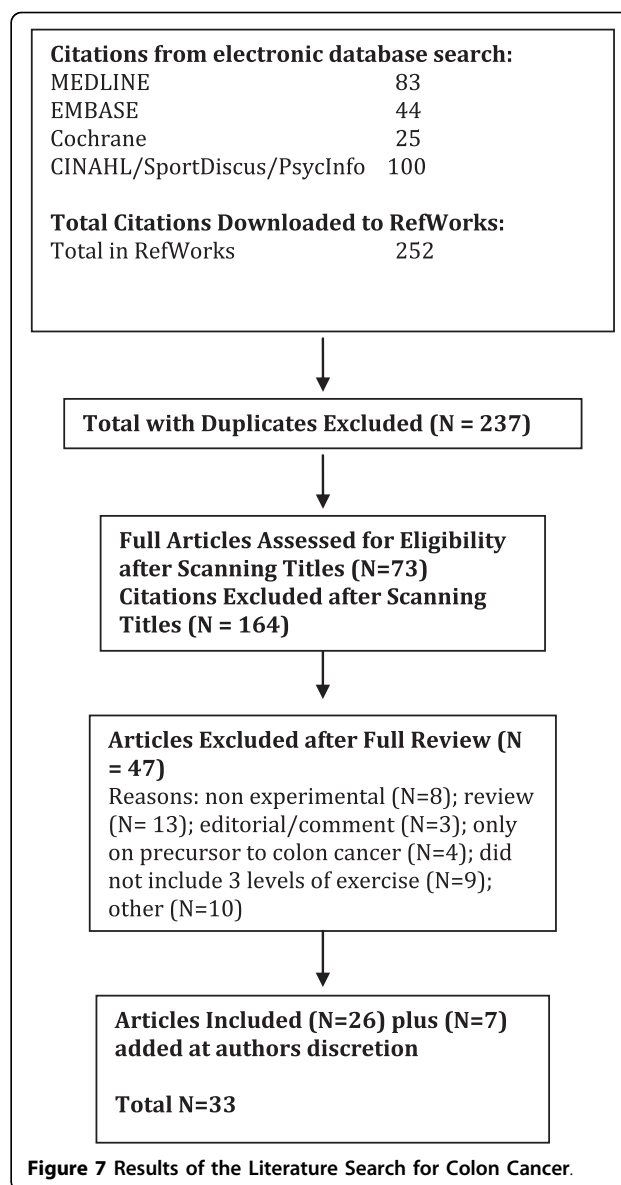
It is clear that routine physical activity is effective in both the primary and secondary prevention of hypertension. However, the optimal dosage of physical activity/exercise remains somewhat unclear. Our review of the literature examined critically the relationship between multiple levels of physical activity/fitness and the incidence of hypertension (in individuals without diagnosed hypertension). As identified above this evidence was compelling supporting the protective effects of habitual physical activity in the primary prevention of hypertension.

Recommendation #4

For a reduced risk for hypertension, it is recommended that individuals should participate in 30 min or more of moderate to vigorous exercise on most days of the week. [Level 3, Grade A]

**Primary Prevention of Colon and Breast Cancer
 Colon Cancer**

In our systematic search of the colon cancer literature, a total of 252 citations were identified during the electronic database search (Figure 7). Of these citations, 83 were identified in MEDLINE, 44 in EMBASE, 25 in Cochrane, and 100 in the CINAHL/SportDiscus/PsychInfo search. A total of 15 duplicates were found, leaving a total of 237 unique citations. A total of 164 articles were excluded after screening, leaving a total of 73 articles for full review. From these articles 47 were excluded after full-text review leaving 26 articles for inclusion, and an additional 7 articles were added from the authors' personal files. The reasons for exclusion included non-experimental/weak design (n = 8), reviews, summaries, meta-analyses (n = 13), editorial/comment (n = 3), not dealing specifically with colon cancer (n = 4), did not contain three levels of physical activity or not possible to determine dose-response relationship



(n = 9), and other (n = 10). Therefore, a total of 33 articles were included in the systematic review of the literature regarding the relationship between physical activity and the primary prevention of colon cancer.

These studies involved a total of 1,433,103 participants; averaging 43,427 participants per study (range 142-413,044). There were a total of 17,959 reported cases of colon cancer (ranging per study from 93-1,993). The total length of study follow-up for the prospective cohort studies averaged 10.7 yr (ranging from 4-26 yr). The articles were published over a 23 yr period ranging from 1985 to 2008. These studies involved large samples of men and women from regions throughout the world.

A dose-dependency of this relationship was present in the majority of the studies. When comparing the most

active/fit group versus the least active/fit group we found a mean risk reduction of 30% (median = 32%) across all studies. The most compelling literature was that which evaluated the relationship between moderate-to-vigorous leisure time physical activity. Based on the literature reviewed and the volume of activity assessed it would appear that Canada's guidelines for physical activity are sufficient to lower the risk for the development of colon cancer in asymptomatic adults. *The level of evidence would be considered to be Level 2A.* The studies were generally of a higher quality with a mean Downs and Black score of 13 (median = 14, range = 11-15).

It should be noted that there was considerable variability in the findings and conclusions of the studies (Table 15). As discussed later, the literature was further confounded by the fact that the relative risks associated with physical activity were often controlled (through multivariate analyses) for various potential confounding factors, which may actually inappropriately decrease the level of risk reduction associated with physical activity [31]. Moreover, similar to other chronic conditions this literature was limited greatly by the lack of consistent physical activity assessment and description. In many instances, it was difficult to determine the actual absolute volume and/or intensity of activity for each category of comparison. However, despite these limitations the results of these studies (taken as a whole) indicate that both occupation- and leisure time-related physical activity are inversely related to the risk of colon cancer.

Breast Cancer

As reviewed eloquently by others, the epidemiological evidence relating physical activity to a decreased incidence of breast cancer is persuasive. A recent systematic review of the literature found that more than 60 observational trials have examined the relationship between physical activity and breast cancer [31]. Previous reviews of the literature have revealed compelling and consistent findings indicating that habitual physical activity is associated with a reduced risk for breast cancer ranging from 20-80% [31,104].

Various investigations have attempted to evaluate the dose-response relationship between physical activity and the incidence of breast cancer (Table 16). Despite the volume of evidence available questions still remain regarding the minimal and optimal volume of exercise required to reduce the risk for breast cancer. As discussed by others [31,104] the findings are as varied as the investigations.

In our systematic search of the literature, a total of 571 citations were identified during the electronic database search (Figure 8). Of these citations, 228 were identified in MEDLINE, 89 in EMBASE, 56 in Cochrane, and 198 in the CINAHL/SportDiscus/PsychInfo search.

A total of 46 duplicates were found, leaving a total of 571 unique citations. A total of 411 articles were excluded after scanning, leaving a total of 114 articles for full review. From these articles 77 were excluded after full review leaving 37 articles for inclusion in the systematic review. An additional 6 articles were found through the reviewers' personal files. The reasons for exclusion included not containing three levels of physical activity or not possible to determine dose-response relationship (n = 1), reviews, summaries, meta-analyses (n = 20), report (n = 5), editorial/comment (n = 21), not a research article (N = 11), not dealing specifically with breast cancer (n = 4), not relevant (n = 5), not primary prevention (n = 3), and other (n = 10). Therefore, a total of 43 articles were included in the systematic review of the literature regarding the relationship between physical activity and the primary prevention of breast cancer.

The data providing dose-response information is all observational in nature, involving both case control and cohort investigations. These studies involved a total of 1,861,707 participants averaging 44,326 subjects per study (range 526-680,000). There were a total of 80,247 reported cases of breast cancer (ranging per study from 109-17,986). The total length of study follow-up for the prospective cohort studies averaged 10.5 yr (ranging from 4-31 yr). The articles were published over a 14 yr period ranging from 1993-2007. These studies involved large samples of men and women from regions throughout the world.

The literature with respect to the primary prevention of breast cancer is as compelling as that found with respect to colon cancer. There is strong evidence that routine physical activity is associated with a reduced risk for the development of breast cancer. However, this literature is also confounded by many shortcomings (similar to other cancer literature) including considerable variability in the statistical analyses employed, the physical activity measurement tools used, and the experimental designs.

The overall risk reduction for breast cancer for individuals that are habitually physically active (at or above Canada's guidelines for physical activity) is thought to approximate 20-40% [31,105]. In our analyses, we found very similar findings. When comparing the most active group versus the least active group we found a mean (and median) risk reduction of 20% across all studies. *The level of evidence would be considered to be Level 2A.* Generally, the articles were of high quality with a mean Downs and Black score of 13 (median = 13, range = 9-14).

A dose-dependency of this relationship is also generally present in the majority of the studies. For instance, greater than 50% studies revealed a dose-response

Table 15 Studies examining the relationship between physical activity and colon cancer.

Publication Country Study Design Quality Score	Objective	Population	Methods	Outcome	Comments and Conclusions
Hou et al 2004 [272]	To examine the effect of various forms of PA on colon cancer risk, with particular attention to commuting PA.	<ul style="list-style-type: none"> n = 931 case, 1,552 control Sex: Men and women Age: 30-74 yr Characteristics: Case: diagnosed with CC. controls: selected randomly from residents of urban Shanghai. 	PA assessment: Interview for the following variables	<ul style="list-style-type: none"> Number of cases: 931 	Regular frequent PA over a long period of time reduces risk of CC.
China				Multivariate OR (95% CI) by OPA, men <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 1.23 (0.93-1.64) G3 = 0.81 (0.59-1.19) 	
Case control D & B score = 14			OPA (kJ/min) G1 = <8 G2 = 8-12 G3 = >12 Commuting PA (MET hr/wk) G1 = <48.3 G2 = 48.3-94.3 G3 = >94.3	Multivariate OR (95% CI) by OPA, women <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.96 (0.69-1.16) G3 = 0.64 (0.39-1.02) p = 0.10	
			LTPA (MET hr/wk) G1 = < 9.2 G2 = 9.2-13.6 G3 = >13.6	Multivariate OR (95% CI) Commuting PA, men <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 1.11 (0.31-1.23) G3 = 0.52 (0.27-0.87) p < 0.009	
			Outcome Measure: incident CC	p < 0.001	
			Multiple logistic regression	Multivariate OR (95% CI) Commuting PA, women <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.87 (0.42-1.52) G3 = 0.56 (0.21-0.91) p = 0.007	
				Multivariate OR (95% CI) LTPA, men <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 1.17 (0.13-1.95) G3 = 0.72 (0.41-1.07) p = 0.06	

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

<p>Boutron-Ruault et al 2001 [273]</p> <p>France</p> <p>Case control</p> <p>D & B score = 13</p>	<p>To determine which step of the adenoma-carcinoma pathway was influenced by OPA and recreational PA.</p> <p>• n = 480</p> <p>• Sex: Men and women</p> <p>• Age: 30-79 years</p> <p>• Characteristics: Cases had 1st diagnosis of colorectal adenoma, controls were polyp free.</p>	<p>PA assessment: Questionnaire and classified into 3 groups</p> <p>G1 = Low</p> <p>G2 = Medium</p> <p>G3 = High</p>	<p>Number of cases: 171</p> <p>Age and gender adjusted OR (95% CI), OPA</p> <p>• G1 = 1.00 (referent)</p> <p>• G2 = 1.3 (0.8-2.0)</p> <p>• G3 = 0.5 (0.3-0.9)</p> <p>p = 0.005</p>	<p>Multivariate OR (95% CI) LTPA, women</p> <p>• G1 = 1.00 (referent)</p> <p>• G2 = 1.03 (0.41-1.59)</p> <p>• G3 = 0.84 (0.13-2.25)</p> <p>p = 0.15</p> <p>A sedentary lifestyle was associated with a high risk of CC.</p>
<p>Brownson et al 1991 [274]</p> <p>USA</p> <p>Case control</p>	<p>To investigate the risks of 16 cancer types in relation to OPA.</p> <p>• n = 17,147</p> <p>• Sex: Men</p> <p>• Age: ≥ 20 yr</p> <p>• Characteristics: White, working</p>	<p>PA assessment: Medical records and classified into 3 groups:</p> <p>OPA</p> <p>G1 = Low - Activity required <20% of time</p> <p>G2 = Moderate - Activity required 20-80% of time</p>	<p>Number of cases: 1,838</p> <p>Age and gender adjusted OR (95% CI), Global PA</p> <p>• G1 = 1.00 (referent)</p> <p>• G2 = 0.8 (0.5-1.2)</p> <p>• G3 = 0.3 (0.2-0.6)</p> <p>p = 0.0003</p>	<p>OPA is inversely related to risk of CC.</p> <p>Multivariate OR (95% CI)</p> <p>G1 = 1.00 (referent)</p> <p>G2 = 1.2 (1.0-1.5)</p> <p>G3 = 1.1 (1.0-1.3)</p>

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

D & B score = 15	G3 = High - Activity required >80% of time	Outcome Measure: CC	Maximum likelihood estimates	11 year follow up	Number of cases: 243	p = 0.05
Calton et al 2006 [275]	To examine the relationship between PA and colon cancer risk in women.			• n = 31,783		Results do not support the hypothesis that PA is related to a lower incidence of CC in women.
USA		PA Assessment: Questionnaire / Phone interviews for the following variables, divided into 4 or 5 groups		• Sex: Women	Multivariate RR (95% CI), TPA	
Prospective cohort				• Age: 61.1 yr	• G1 = 1.00 (referent)	
D & B score = 12				• Characteristics: Free from cancer at baseline	• G2 = 1.45 (0.98-2.15)	
					• G3 = 1.16 (0.77-1.75)	
					• G4 = 1.27 (0.84-1.91)	
					• G5 = 1.15 (0.76-1.75)	p = 0.77
					Multivariate RR (95% CI), MPA	
					• G1 = 1.00 (referent)	
					• G2 = 1.23 (0.82-1.83)	
					• G3 = 1.47 (0.99-2.21)	
					• G4 = 0.94 (0.61-1.46)	
					• G5 = 1.07 (0.70-1.62)	p = 0.80
					Multivariate RR (95% CI), VPA	
					• Q1 = 1.00 (referent)	
					• Q2 = 1.19 (0.85-1.66)	
					• Q3 = 0.87 (0.59-1.29)	
					• Q4 = 1.10 (0.78-1.55)	p = 0.80
					Q1 = 0	
					Q2 = 0.1-1.0	

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

	Q3 = 1.1-2.0 Q4 = 2.1-14.0	Outcome Measure: Incidence of CC Cox proportional HR	7 year follow up	Number of cases: 940	Increased amounts of time spent in recreational PA is associated with substantially lower risk of CC.
Chao et al 2004 [276]	To examine how the characteristics of recreational PA affect its association with colon cancer incidence among older.	<ul style="list-style-type: none"> • n = 151,174 (70,403 men; 80,771 women) • Sex: Men and women • Age: mean 63 yr • Cancer prevention study II Nutrition Cohort 			
USA	PA assessment: Questionnaire for the following variables			Multivariate RR (95% CI) by recreational PA, men	
Prospective cohort	Recreational PA (h/wk)			<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.91 (0.69-1.19) • G3 = 0.72 (0.52-1.01) • G4 = 0.86 (0.64-1.15) • G5 = 0.77 (0.54-1.08) • G6 = 0.58 (0.39- 0.87) 	
D & B score = 12	G1 = None G2 = <2 G3 = 2-3 G4 = 4-6 G5 = 7 G6 = ≥ 8			p = 0.007	
	Recreational (MET h/wk)			Multivariate RR (95% CI) by recreational PA, women	
	G1 = None G2 = <7, 7-13 G3 = 14-23 G4 = 24-29 G5 = ≥ 30			<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.01 (0.70-1.44) • G3 = 1.01 (0.68-1.49) • G4 = 0.97 (0.66-1.43) • G5 = 1.03 (0.65-1.65) • G6 = 0.65 (0.39-1.11) 	
	Walking (h/wk)			p = 0.14	
	Q1 = None Q2 = <4 Q3 = 4-6 Q4 = ≥ 7			Multivariate RR (95% CI) by recreational PA, men and women	
	Walking plus other			<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.94 (0.75-1.16) • G3 = 0.83 (0.65-1.07) • G4 = 0.89 (0.71-1.12) 	

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

activities (h/wk)	• G5 = 0.85 (0.64-1.12)
Q1 = None	• G6 = 0.60 (0.44-0.83)
Q2 = <4	<i>p</i> = 0.002
Q3 = 4-6	Multivariate RR (95% CI) by MET h/ wk men
Q4 = ≥ 7	• G1 = 1.00 (referent)
Outcome Measure: Incidence of CC	• G2 = 0.90 (0.68-1.18)
Cox proportional HR	• G3 = 0.83 (0.59-1.16)
	• G4 = 0.75 (0.55-1.01)
	• G5 = 0.86 (0.63-1.19)
	• G6 = 0.60 (0.41-0.87)
	<i>p</i> = 0.005
	Multivariate RR (95% CI) by MET h/ wk women
	• G1 = 1.00 (referent)
	• G2 = 1.02 (0.71-1.46)
	• G3 = 0.98 (0.65-1.47)
	• G4 = 1.0 (0.68-1.47)
	• G5 = 0.94 (0.60-1.48)
	• G6 = 0.77 (0.48-1.24)
	<i>p</i> = 0.15
	Multivariate RR (95% CI) by MET h/ wk men and women
	• G1 = 1.00 (referent)
	• G2 = 0.93 (0.75-1.16)
	• G3 = 0.88 (0.68-1.13)
	• G4 = 0.84 (0.66-1.06)
	• G5 = 0.89 (0.68-1.15)
	• G6 = 0.65 (0.49-0.87)
	<i>p</i> = 0.002
	Multivariate RR (95% CI) by walking, Men
	• Q1 = 1.00 (referent)
	• Q2 = 0.87 (0.66-1.15)
	• Q3 = 0.83 (0.60-1.16)
	• Q4 = 0.88 (0.61-1.25)
	<i>p</i> = 0.34

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

	<p>Multivariate RR (95% CI) by walking, women</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.00 (0.70-1.44) • Q3 = 1.08 (0.71-1.63) • Q4 = 1.18 (0.71-1.95) <p>$p = 0.41$</p> <p>Multivariate RR (95% CI) by walking plus other activities, men</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.73 (0.53-1.02) • Q3 = 0.85 (0.58-1.24) • Q4 = 0.53 (0.36-0.78) <p>$p = 0.02$</p> <p>Multivariate RR (95% CI) by walking plus other activities, women</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.99 (0.67-1.47) • Q3 = 0.72 (0.43-1.19) • Q4 = 0.59 (0.36-0.98) <p>$p = 0.07$</p>	
<p>Colbert et al 2001 [277]</p> <p>USA Prospective cohort</p> <p>D & B score = 13</p>	<p>To examine the association between OPA and LTPA and colon cancer in male smokers.</p> <ul style="list-style-type: none"> • n = 29,133 • Sex: Men • Age: 50-69 yr • Characteristics: Smokers • Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study <p>PA assessment: Interview for OPA and LTPA</p> <p>OPA</p> <p>G1 = Non-worker G2 = Sedentary G3 = Light G4 = Moderate</p> <p>LTPA</p> <p>G1 = Sedentary G2 = Active</p>	<p>Number of cases: 152</p> <p>Multivariate RR (95% CI) by OPA</p> <ul style="list-style-type: none"> • G1 = 0.61 (0.39-0.98) • G2 = 1.00 (referent) • G3 = 0.60 (0.34-1.04) • G4 = 0.45 (0.26-0.78) <p>$p = 0.003$</p> <p>Multivariate RR (95% CI), by LTPA</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.82 (0.59-1.13) <p>OPA is protective against CC in a dose-response manner.</p>

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

			Outcome Measure: Incident CC	Cox proportional HR		Occupational EE is inversely related to risk of CC.
Dosemeci et al 1993 [278]	To examine associations between PA and cancer sites among workers in Turkey.	<ul style="list-style-type: none"> n = 6,236 (3,486 cases in men and 379 cases in women; 2,127 control men and 244 control women) 	PA assessment: Stanford Occupational Classification code system.	Number of cases: 93		
Turkey	<ul style="list-style-type: none"> 93 cases for CC 			Multivariate OR (95% CI) by total occupational EE		
Case control	<ul style="list-style-type: none"> Sex: Men and women Age: not indicated 			<ul style="list-style-type: none"> G1 = 1.6 (0.9-2.8) G2 = 1.1 (0.6-2.0) 		
D & B score = 13	<ul style="list-style-type: none"> Characteristics: All hospitalized Cases; Diagnosed with CC. Controls: included subjects diagnosed as non-cancers and cancers which there is no suggestion of an association with PA. 		Total Occupational EE (kj/min)	<ul style="list-style-type: none"> G3 = 1.0 (referent) 		
			G1 = <8			
			G2 = 8-12	p = 0.04		
			G3 = >12	When adjusted for socioeconomic status p = 0.03		
			Sitting time at work (h/d) Levels:	Multivariate OR (95% CI) by sitting time at work		
			G1 = <2	<ul style="list-style-type: none"> G1 = 1.00 (referent) 		
			G2 = 2-6	<ul style="list-style-type: none"> G2 = 1.5 (0.9-2.5) 		
			G3 = >6	<ul style="list-style-type: none"> G3 = 1.5 (0.8-3.0) 		
			Outcome Measure: Incident CC	When adjusted for socioeconomic status p = 0.03		
			Maximum likelihood estimates			
Friedenreich et al 2006 [279]	To investigate the role of PA in the development of colon cancer.	<ul style="list-style-type: none"> n = 413,044 	4 year follow-up	Multivariate RR (95% CI), TPA		Inverse association between PA and risk of CC, particularly for right sided tumours.
UK	<ul style="list-style-type: none"> Sex: Men and women Age: 35-70 yr Characteristics: Free of cancer at baseline European Prospective Investigation into Nutrition and Cancer. (EPIC) 		PA assessment: modified Baecke Questionnaire	<ul style="list-style-type: none"> Q1 = 1.00 (referent) Q2 = 0.92 (0.76-1.12) Q3 = 0.86 (0.70-1.04) Q4 = 0.78 (0.59-1.03) 		
Prospective cohort			TPA			
			Q1 = Inactive	p = 0.04		

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

D & B score = 14	Q2 = Moderately inactive Q3 = Moderately active Q4 = Active Household PA (MET-h/wk) Q1 = <19.5 Q2 = 19.5-39.6 Q3 = 39.6-73.9 Q4 = ≥ 73.9	Multivariate RR (95% CI), TPA and right sided CC • Q1 = 1.00 (referent) • Q2 = 1.79 (0.59-1.06) • Q3 = 0.64 (0.47-0.86) • Q4 = 0.65 (0.43-1.00) p = 0.004	
Giovannucci et al 1995 [280]	To examine the association between PA and colon cancer.	Multivariate RR (95% CI), TPA and right sided CC • Q1 = 1.00 (referent) • Q2 = 0.97 (0.75-1.27) • Q3 = 0.84 (0.64-1.12) • Q4 = 0.74 (0.54-1.02) p = 0.05	A moderate level of PA was related to a substantially lower risk of CC in this cohort of middle age to elderly men.
USA	Sex: Men Age: 40-75 yr Characteristics: Health professionals	Cox proportional HR 6 year follow-up Multivariate RR (95% CI) • G1 = 1.00 (referent) • G2 = 0.73 (0.48-1.10) • G3 = 0.94 (0.63-1.39) • G4 = 0.78 (0.51-1.20) • G5 = 0.53 (0.32-0.88) p = 0.03	
Prospective cohort	Health Professionals Follow-up Study	Outcome Measure: Incidence of colon cancer	
D & B score = 12	Mantel-Haenszel estimator and logistic regression		
Isumura et al 2006 [281]	To examine the relationship of OPA, LTPA, commuting, housework and shopping with colorectal cancer risk	PA assessment: Questionnaire and interview for the following variables Number of cases: 778	Adds to the evidence that PA confers decreased risk of CC, especially of distal CC in both men and women.
Japan	Sex: Men and women	Multivariate OR (95% CI) for all CC by OPA, men • G1 = 1.00 (referent) • G2 = 0.9 (0.6-1.4)	
Case control	Age: 20-74 yr	OPA, men	

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

D & B score = 12	
<ul style="list-style-type: none"> • Characteristics: Free from cancer at baseline 	<ul style="list-style-type: none"> • G3 = 0.7 (0.4-1.0)
<ul style="list-style-type: none"> • Fukuoka colorectal cancer study 	<ul style="list-style-type: none"> G1 = Sedentary G2 = Moderate G3 = Hard <p>$p = 0.06$</p>
<ul style="list-style-type: none"> OPA, women G1 = Sedentary G2 = Active 	<ul style="list-style-type: none"> Multivariate OR (95% CI) for proximal CC by OPA, men • G1 = 1.00 (referent) • G2 = 1.2 (0.6-2.2) • G3 = 0.7 (0.4-1.4)
<ul style="list-style-type: none"> Total non-OPA, men (MET-h/wk) G1 = 0.0 G2 = 0.1-15.9 G3 = 16.0 	<ul style="list-style-type: none"> Multivariate OR (95% CI) for distal CC by OPA, men • G1 = 1.00 (referent) • G2 = 0.8 (0.4-1.4) • G3 = 0.6 (0.4-1.0) <p>$p = 0.047$</p>
<ul style="list-style-type: none"> Total non-OPA women (MET hr/wk) G1 = 0.0 G2 = 0.1-15.9 G3 = 16.0 	<ul style="list-style-type: none"> Multivariate OR (95% CI) for all CC by non-OPA, men • G1 = 1.00 (referent) • G2 = 0.9 (0.6-1.4) • G3 = 0.8 (0.5-1.2) <p>$p = 0.22$</p>
<ul style="list-style-type: none"> Moderate or hard non-OPA, men (MET hr/wk) G1 = 0.0 G2 = 0.1-14.9 G3 = ≥ 15.0 	<ul style="list-style-type: none"> Multivariate OR (95% CI) for proximal CC by non-OPA, men • G1 = 1.00 (referent) • G2 = 1.2 (0.6-2.1) • G3 = 0.9 (0.5-1.7) <p>$p = 0.69$</p>
<ul style="list-style-type: none"> Moderate or hard non-OPA, women (MET hr/wk) G1 = 0.0 G2 = 0.1-14.9 G3 = 15.0 	<ul style="list-style-type: none"> Multivariate OR (95% CI) for distal CC by non-OPA, men • G1 = 1.00 (referent) • G2 = 0.8 (0.5-1.3)
<ul style="list-style-type: none"> Outcome Measure: Incident CC 	<ul style="list-style-type: none"> Multiple logistic regression analysis

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

<ul style="list-style-type: none">• G3 = 0.7 (0.4-1.1)
<i>p</i> = 0.19
Multivariate OR (95% CI) for all CC by non-OPA, women
<ul style="list-style-type: none">• G1 = 1.00 (referent)• G2 = 0.9 (0.5-1.5)• G3 = 0.8 (0.5-1.4)
<i>p</i> = 0.45
Multivariate OR (95% CI) for proximal CC by non-OPA, women
<ul style="list-style-type: none">• G1 = 1.00 (referent)• G2 = 1.5 (0.7-3.3)• G3 = 1.6 (0.7-3.6)
<i>p</i> = 0.41
Multivariate OR (95% CI) for distal CC by non-OPA, women
<ul style="list-style-type: none">• G1 = 1.00 (referent)• G2 = 0.7 (0.4-1.3)• G3 = 0.6 (0.3-1.1)
<i>p</i> = 0.12
Multivariate OR (95% CI) for all CC by moderate or hard non-OPA, men
<ul style="list-style-type: none">• G1 = 1.00 (referent)• G2 = 0.8 (0.6-1.2)• G3 = 0.8 (0.5-1.1)
<i>p</i> = 0.24
Multivariate OR (95% CI) for proximal CC by moderate or hard non-OPA, men
<ul style="list-style-type: none">• G1 = 1.00 (referent)• G2 = 1.1 (0.6-2.1)• G3 = 1.0 (0.6-1.8)
<i>p</i> = 0.99
Multivariate OR (95% CI) for distal CC by moderate or hard non-OPA, men
<ul style="list-style-type: none">• G1 = 1.00 (referent)• G2 = 0.7 (0.4-1.1)• G3 = 0.7 (0.4-1.0)
<i>p</i> = 0.12

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

				<p>Multivariate OR (95% CI) for all CC by moderate or hard non-OPA, women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.0 (0.6-1.6), • G3 = 0.8 (0.5-1.4) <p>p = 0.35</p> <p>Multivariate OR (95% CI) for proximal CC by moderate or hard non-OPA, women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.3 (0.6-2.5) • G3 = 1.3 (0.6-2.7) <p>p = 0.59</p> <p>Multivariate OR (95% CI) for distal CC by moderate or hard non-OPA, women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.8 (0.5-1.5) • G3 = 0.5 (0.3-1.1) <p>p = 0.41</p>
Johnsen et al 2006 [282]	To investigate the effects of OPA on colon cancer incidence.	n = 54,478 (28,356 men, 26,122 women)	7.6 year follow-up	<p>Number of cases: 140 women, 157 men</p> <p>Number of dropouts: <0.8%</p>
Denmark Prospective cohort		<p>Sex: Men and women</p> <p>Age: 50-64 yr</p> <p>Characteristics: Free of Cancer at baseline</p> <p>Diet, Cancer and Health Study</p>	<p>PA assessment: Questionnaire for OPA by MET score, 4 groups</p> <p>Q1 = Sitting</p> <p>Q2 = Standing</p> <p>Q3 = Manual</p> <p>Q4 = Not working</p>	<p>Multivariate RR (95% CI), men</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.11 (0.69-1.77) • Q3 = 1.17 (0.77-1.79) • Q4 = 0.95 (0.58-1.55)
D & B score = 13			Outcome Measure: Incidence of colon cancer	<p>Multivariate RR (95% CI), women</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.15 (0.68-1.93) • Q3 = 1.34 (0.83-2.16) • Q4 = 0.96 (0.60-1.53)
			Cox proportional HR	

No support for the hypothesis that OPA measured by MET-score may be associated with a lower risk of CC.

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

Larsen et al 2006 [283]	To examine the relationship between PA and colorectal cancer.	<ul style="list-style-type: none"> n = 6,961 	PA assessment: Questionnaire (scored from 2-12), divided into quartiles:	Number of cases: 108	Inactivity was not a significant risk factor for advanced colonic neoplasia.
Norway		<ul style="list-style-type: none"> Sex: Men and women Age: 50-64 Characteristics: No history of colorectal surgery, radiotherapy, cardiopulmonary disease, anticoagulant therapy, coronary episode. 	Q1 = 2-4 Q2 = 5 Q3 = 6 Q4 = 7-12 Outcome Measure: Positive test for colonic neoplasia	RR (95% CI) • Q1 = 1.00 (referent) • Q2 = 0.61 (0.32-1.16) • Q3 = 0.75 (0.45-1.26) • Q4 = 0.56 (0.34-0.92) p = 0.04 Multivariate RR (95% CI) • Q1 = 1.00 (referent) • Q2 = 0.64 (0.33-1.25) • Q3 = 0.82 (0.47-1.43) • Q4 = 0.67 (0.39-1.16) p = 0.23	
Cross-sectional evaluation within a randomized controlled trial					
D & B score = 13					
Larsson et al 2006 [284]	To investigate the association between PA and colorectal cancer.	<ul style="list-style-type: none"> n = 45,906 Sex: Men Age: 45-79 yr 	7.1 year follow-up	Number of cases: 309 (133 proximal, 138 distal)	Results support a role of PA in reducing the risk of CC.
Sweden		<ul style="list-style-type: none"> Characteristics: Free of cancer at baseline 	PA assessment: Questionnaire for the following variables LTPA (min/day) Q1 = <10 Q2 = 10-29 Q3 = 30-59	Multivariate HR (95% CI) by LTPA • Q1 = 1.00 (referent) • Q2 = 0.66 (0.43-1.02) • Q3 = 0.68 (0.46-1.01) • Q4 = 0.56 (0.37-0.83) p = 0.01	
Prospective cohort					
D & B score = 14					

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

<p>Q4 = ≥ 60 Home/housework PA (h/day)</p> <p>Q1 = none Q2 = <1 Q3 = 1-2 Q4 = ≥ 3</p> <p>Incidence of Proximal CC(h/day)</p> <p>G1 = <1 G2 = 1-2 G3 = ≥ 3</p> <p>Outcome Measure: Incident CC</p> <p>Cox proportional HR</p>	<p>Q4 = ≥ 60</p> <p>Home/housework PA (h/day)</p> <p>Q1 = none Q2 = <1 Q3 = 1-2 Q4 = ≥ 3</p> <p>Incidence of Proximal CC(h/day)</p> <p>G1 = <1 G2 = 1-2 G3 = ≥ 3</p> <p>Outcome Measure: Incident CC</p> <p>Cox proportional HR</p>	<p>Multivariate HR (95% CI) by home/ housework PA</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.75 (0.58-0.97) • Q3 = 0.75 (0.58-0.97) • Q4 = 0.68 (0.48-0.96) <p>p = 0.01</p> <p>Multivariate HR (95% CI) for distal CC by LTPA</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.51 (0.28-0.93) • Q3 = 0.50 (0.29-0.87) • Q4 = 0.40 (0.22-0.70) <p>p = 0.01</p> <p>Multivariate HR (95% CI) for proximal CC by home/housework PA</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.78 (0.53-1.14) • G3 = 0.50 (0.29-0.89) <p>p = 0.02</p>
<p>Lee and Paffenbarger [285]</p> <p>USA</p> <p>Prospective cohort</p> <p>D & B score = 13</p>	<p>To predict cancer risk using prospective assessments of PA.</p> <ul style="list-style-type: none"> • n = 17,607 • Sex: Men • Age: 30-79 yr • Characteristics: Healthy at baseline • Harvard College Alumni <p>26 year follow-up</p> <p>PA assessment: Questionnaire for PA level (kcal/wk)</p> <p>Number of dropouts: 14%</p> <p>Multivariate RR (95% CI), Model A: PA in 1962/1966 and updated in 1977</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.07 (0.81-1.42) • G3 = 1.08 (0.81-1.46) <p>p = 0.58</p>	<p>Number of cases: 280</p> <p>Found a trend, of borderline statistical significance toward decreasing CC risk with increasing PA.</p>

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

<p>Lee et al 1997 [286]</p>	<p>To investigate whether PA alters the risk of developing CC in men.</p>	<p>• n = 20,614</p>	<p>10.9 year follow-up</p>	<p>Number of cases: 217</p>	<p>Data does not support the hypothesis that PA is related inversely to risk of developing CC.</p>
<p>USA</p>	<p>Sex: Men Age: 40-84 yrs</p>	<p>Characteristics: Physicians, free of cancer at baseline</p>	<p>PA assessment: Questionnaire for the following variables</p>	<p>Multivariate RR (95% CI), frequency of PA at baseline</p>	<p>Multivariate RR (95% CI), Model B: PA in both 1962/1966 and 1977</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.75 (0.42-1.35) • G3 = 0.94 (0.54-1.64) <p>p = 0.76</p>
<p>Prospective cohort</p>	<p>Physicians Health Study</p>	<p>Frequency of PA at baseline (times/week)</p>	<p>G1 = <1 G2 = 1 G3 = 2-4 G4 = 5+</p>	<p>RR (95% CI), frequency of PA at baseline and 36 months</p>	<p>RR (95% CI), frequency of PA at baseline and 36 months</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.1 (0.7-1.7) • G3 = 1.2 (0.8-1.6) • G4 = 1.1 (0.7-1.6) <p>p = 0.6</p>
<p>D & B score = 15</p>	<p>Outcome Measure: Incidence of fatal and non-fatal CC</p>	<p>Outcome Measure: Incidence of fatal and non-fatal CC</p>	<p>Cox proportional HR</p>	<p>Cox proportional HR</p>	<p>Cox proportional HR</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.2 (0.5-2.7) • G3 = 1.4 (0.9-2.3) • G4 = 1.3 (0.9-2.0)

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

Study	Objectives	Study Design	Population	Exposure	Outcome	Results
Lee et al 2007 [287]	To examine the association between PA and the risk of developing CRC in Japanese men and women.	Prospective cohort	Japan	6 year follow-up	Number of cases: 154 proximal CC, 166 distal CC	PA may prevent CC among Japanese men.
			<ul style="list-style-type: none"> • n = 65,022 • Sex: Men and women • Age: 40-69 yr • Characteristics • Ethnicity: Japanese 	<p>PA assessment: Questionnaire for PA level (median MET hr/d)</p> <p>Q1 = 28.25 Q2 = 33.25 Q3 = 35.25 Q4 = 43.75</p> <p>Outcome Measure: Incidence of CC</p> <p>Cox proportional HR</p>	<p>Multivariate RR (95% CI) for CC men</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.87 (0.61-1.26) • Q3 = 0.62 (0.41-0.95) • Q4 = 0.58 (0.39-0.87) <p>p = 0.006</p> <p>Multivariate RR (95% CI) for proximal CC men</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.89 (0.52-1.51) • Q3 = 0.44 (0.22-0.86) • Q4 = 0.29 (0.14-0.60) <p>p < 0.001</p> <p>Multivariate RR (95% CI) for distal CC Men</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.92 (0.54-1.54) • Q3 = 0.75 (0.42-1.33) • Q4 = 0.89 (0.53-1.51) <p>p = 0.685</p> <p>PA level and incidence of CC women</p> <p>Total CC</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.03 (0.65-1.64) • Q3 = 0.91 (0.57-1.47) • Q4 = 0.89 (0.54-1.49) <p>p = 0.610</p> <p>Proximal CC women</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.14 (0.61-2.12) • Q3 = 1.01 (0.53-1.89) 	
						D & B score = 13

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

<p>Longnecker et al 1995 [288]</p>	<p>To examine the relationship between OPA and vigorous LTPA and the risk of cancer of the right colon and rectum.</p>	<p>• n = 242 rectal cancer and 703 controls</p>	<p>PA assessment: Interview for vigorous LTPA and OPA (coded and self-reported), divided into groups:</p>	<p>Number of cases: 163</p>	<p>The amount of time spent at vigorous LTPA was associated with a decreased risk of cancer of the right colon.</p>
<p>USA</p>	<p>• Sex: Men • Age: ≥ 31 yr • Characteristics: Case: Diagnosed with adenocarcinoma of the right colon or rectum. Controls: Both community and hospital. No history of large bowel cancer.</p>	<p>RR (95% CI) by vigorous LTPA</p>	<p>• G1 = 1.00 (referent) • G2 = 0.73 (0.23-2.29)</p>	<p>• Q4 = 0.55 (0.24-1.26) p = 0.151 Distal CC women • Q1 = 1.00 (referent) • Q2 = 1.09 (0.52-2.29) • Q3 = 0.77 (0.34-1.74) • Q4 = 1.37 (0.66-2.85) p = 0.401</p>	
<p>Case control</p>	<p>Vigorous LTPA (h/wk)</p>	<p>• G3 = 0.47 (0.16-1.36) • G4 = 0.60 (0.35-1.00)</p>	<p>p = 0.03</p>		
<p>D & B score = 14</p>	<p>Coded lifetime OPA</p>	<p>Multivariate OR (95% CI) by vigorous LTPA</p>	<p>• G1 = 1.00 (referent) • G2 = 0.81 (0.26-2.54) • G3 = 0.36 (0.11-1.14) • G4 = 0.57 (0.33-0.97)</p>	<p>p = 0.06</p>	
	<p>Self reported lifetime OPA</p>	<p>Multivariate OR (95% CI) by coded lifetime OPA</p>	<p>• G1 = 1.00 (referent) • G2 = 0.79 (0.39-1.61) • G3 = 0.79 (0.36-1.74) • G4 = 0.99 (0.30-3.22)</p>		

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

<p>Mai et al 2007 [289]</p>	<p>To examine in detail the relationship between recreational PA and invasive CC among women.</p>	<p>n = 120,147</p> <ul style="list-style-type: none"> • Sex: Women • Age: 22-84 yr • Characteristics: no prior history of CC 	<p>7 year follow-up</p>	<p>Number of cases: 395</p>	<p>Modest inverse association between recreational PA and CC.</p>
<p>USA</p>					
<p>Prospective cohort</p>					
<p>D & B score = 15</p>					
			<p>PA assessment: Questionnaire</p>	<p>RR (95% CI) by MPA over past 3 years</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.95 (0.72-1.24) • G3 = 0.78 (0.62-0.97) 	
			<p>MPA over past 3 yrs (h/wk/yr)</p>	<p>p = 0.02</p>	
			<p>G1 = 0-0.50 G2 = 0.51-1.99 G3 = ≥ 2.00</p>	<p>RR (95% CI) by strenuous + moderate (lifetime) PA:</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.79 (0.56-1.11) • G3 = 0.64 (0.44-0.93) 	
			<p>Strenuous + Moderate (lifetime) PA (h/wk/yr)</p>	<p>p = 0.04</p>	
			<p>G1 = 0.0-0.50 G2 = 0.51-3.99 G3 = ≥ 4.00</p>		
			<p>Outcome Measure: Incidence of invasive adenocarcinoma of the colon</p>		
			<p>Cox proportional HR</p>		
<p>Martinez et al 1997 [290]</p>	<p>To examine whether LTPA could significantly influence the risk of CC in women.</p>	<p>n = 89,448</p> <ul style="list-style-type: none"> • Sex: Women 	<p>6 year follow-up</p>	<p>Number of cases: 212</p>	<p>Significant inverse association between LTPA and incidence of CC in women.</p>

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

USA	<ul style="list-style-type: none"> Age: 30-55 yr Characteristics: Nurses, free from cancer at baseline 	PA assessment: Questionnaire for LTPA	Multivariate RR (95% CI) for all CC <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.71 (0.44-1.15) G3 = 0.78 (0.50-1.20) G4 = 0.67 (0.42-1.07) G5 = 0.54 (0.33-0.90) p = 0.03 Multivariate RR (95% CI) for distal CC <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.92 (0.48-1.79) G3 = 0.81 (0.43-1.55) Mantel-Haenszel Estimator and logistic regression models <ul style="list-style-type: none"> G4 = 0.71 (0.36-1.41) G5 = 0.31 (0.12-0.77) p = 0.01 Multivariate RR (95% CI) for proximal CC <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.54 (0.23-1.22) G3 = 0.79 (0.40-1.56) G4 = 0.62 (0.30-1.32) G5 = 0.77 (0.38-1.58) p = 0.67
Prospective cohort			
D & B score = 14			
Nilsen et al 2008 [291]	To study the separate associations of recreational PA with the incidence of, and mortality from cancer in the ascending, transverse, descending and sigmoid segments of the colon.	17 year follow-up	Number of cases: 736 Strong inverse associations between recreational PA and risk of cancer morbidity and mortality of the transverse and sigmoid colon but no association for cancer in the ascending and descending colon.
Norway	<ul style="list-style-type: none"> Sex: Men and women Age: not indicated Characteristics: Free from cancer at baseline 	PA assessment: Questionnaire for frequency and duration of recreational PA	HR (95% CI) by frequency of recreational PA, men <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.84 (0.60-1.19)
Prospective cohort			

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

• Nord-Trøndelag Health Study

D & B score = 14

Frequency of Recreational PA (times per week)	<ul style="list-style-type: none"> • G3 = 0.82 (0.58-1.17) • G4 = 0.81 (0.57-1.15) • G5 = 0.77 (0.54-1.09)
G1 = none	$p = 0.18$
G2 = <1	HR (95% CI) by frequency of recreational PA, women
G3 = 1	• G1 = 1.00 (referent)
G4 = 2-3	• G2 = 0.91 (0.66-1.25)
G5 = ≥ 4	• G3 = 0.79 (0.57-1.09)
Duration of recreational PA (min per exercise)	• G4 = 0.66 (0.47-0.92)
G1 = none	• G5 = 0.99 (0.72-1.36)
G2 = <15	$p = 0.35$
G3 = 15-30	HR (95% CI) by duration of recreational PA, men
G4 = 31-60	• G1 = 1.00 (referent)
G5 = >60	• G2 = 1.07 (0.71-1.60)
Intensity of recreational PA	• G3 = 0.80 (0.57-1.12)
G1 = none	• G4 = 0.68 (0.48-0.97)
G2 = Low	• G5 = 0.74 (0.50-1.08)
G3 = Moderate/High	$p = 0.02$
Summary score for recreational PA	HR (95% CI) by duration of recreational PA, women
G1 = None	• G1 = 1.00 (referent)
G2 = Low	• G2 = 0.85 (0.59-1.23)
G3 = High	• G3 = 0.81 (0.60-1.09)
By subsite-specific (transverse colon, descending colon, sigmoid colon) CC	• G4 = 0.73 (0.53-1.01)
	• G5 = 0.84 (0.53-1.34)
Levels of REC PA:	$p = 0.10$
	HR (95% CI) by intensity of recreational PA, men

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

G1 = None	• G1 = 1.00 (referent)
G2 = < 1 x/wk	• G2 = 0.83 (0.62-1.12)
G3 = low score	• G3 = 0.74 (0.52-1.06)
G4 = high score	<i>p</i> = 0.11
Outcome Measure: Incidence of fatal and non fatal CC	HR (95% CI) by intensity of recreational PA, women
Cox proportional HR	• G1 = 1.00 (referent) • G2 = 0.77 (0.59-1.01) • G3 = 0.89 (0.60-1.32) <i>p</i> = 0.33
	HR (95% CI) by summary score for recreational PA, men
	• G1 = 1.00 (referent) • G2 = 0.85 (0.62-1.16) • G3 = 0.69 (0.48-0.98) <i>p</i> = 0.06
	HR (95% CI) by summary score for recreational PA, women
	• G1 = 1.00 (referent) • G2 = 0.86 (0.64-1.01) • G3 = 0.72 (0.53-0.98) <i>p</i> = 0.03
	HR (95% CI) by total CC and recreational PA, incidence
	• G1 = 1.00 (referent) • G2 = 0.88 (0.70-1.12) • G3 = 0.87 (0.70-1.08) • G4 = 0.73 (0.58-0.92) <i>p</i> = 0.009
	HR (95% CI) by subsite specific CC and recreational PA, death
	• G1 = 1.00 (referent) • G2 = 0.87 (0.64-1.18) • G3 = 0.79 (0.59-1.04) • G4 = 0.56 (0.41-0.78) <i>p</i> < 0.001
	HR (95% CI) for transverse CC incidence and recreational PA
	• G1 = 1.00 (referent)

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

					<ul style="list-style-type: none"> • G2 = 0.75 (0.44-1.28) • G3 = 0.66 (0.41-1.08) • G4 = 0.44 (0.25-0.78) <p>$p = 0.004$</p> <p>HR (95% CI) for transverse CC death and recreational PA</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.73 (0.36-1.49) • G3 = 0.40 (0.19-0.82) • G4 = 0.33 (0.14-0.76) <p>$p = 0.002$</p> <p>HR (95% CI) for sigmoid CC incidence and recreational PA</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.88 (0.59-1.32) • G3 = 0.68 (0.46-1.01) • G4 = 0.48 (0.31-0.75) <p>$p < 0.001$</p> <p>HR (95% CI) for sigmoid CC death and recreational PA</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.78 (0.45-1.35) • G3 = 0.51 (0.30-0.87) • G4 = 0.29 (0.15-0.56) <p>$p < 0.001$</p>
Schnohr et al 2005 [292]	To assess the association between LTPA and incidence of cancer in the general population.	n = 28,259 (15,043 men, 13,216 women)	14 year follow-up	<ul style="list-style-type: none"> • Number of cases: 215 men, 108 women <p>For the most active men, VPA was associated with a non-significant lower risk of CC.</p>	
Denmark			PA assessment: Questionnaire for LTPA	Multivariate RR (95% CI), men	
Prospective cohort		• Sex: Men and women	G1 = Low G2 = Moderate	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.08 (0.74-1.57) 	
D & B score = 13		• Age: 20-93 yr • Characteristics: Free from cancer at baseline • Copenhagen Heart Study, The Copenhagen County Centre of Preventive Medicine and the Copenhagen Male Study	G3 = Vigorous Outcome Measure: Incidence of CC	<ul style="list-style-type: none"> • G3 = 0.72 (0.47-1.11) <p>$p = 0.06$</p> <p>Multivariate RR (95% CI), women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) 	

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

	Cox proportional HR			
Slattery et al 1988 [293]	<ul style="list-style-type: none"> • G2 = 1.02 (0.70-1.50) • G3 = 0.90 (0.56-1.46) 	<ul style="list-style-type: none"> • n = 229 cases, 384 controls 	<ul style="list-style-type: none"> • To assess the relationship of PA and diet with the development of CC in Utah. 	<ul style="list-style-type: none"> • PA shows an inverse relationship with incidence of CC.
USA	<ul style="list-style-type: none"> • p = 0.68 	<ul style="list-style-type: none"> • Sex: Men and women 	<ul style="list-style-type: none"> • PA assessment: Interview for the following variables 	<ul style="list-style-type: none"> • Number of cases: 229
Case control	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.19 (0.67-2.13) 	<ul style="list-style-type: none"> • Age: 40-79 yr • Characteristics: Case: Diagnosed with CC Controls: no history of cancer 	<ul style="list-style-type: none"> • TPA 	<ul style="list-style-type: none"> • Multivariate OR (95% CI) by TPA, men
D & B score = 13	<ul style="list-style-type: none"> • Q3 = 0.88 (0.48-1.69) • Q4 = .70 (0.38-1.29) 		<ul style="list-style-type: none"> • Q1 = Low • Q2 • Q3 • Q4 = high 	<ul style="list-style-type: none"> • Multivariate OR (95% CI) by TPA, women
	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.97 (0.56-1.69) • Q3 = 0.91 (0.52-1.60) • Q4 = 0.48 (0.27-0.87) 		<ul style="list-style-type: none"> • Intense PA • G1 = none • G2 = low • G3 = high • Non-intense PA 	<ul style="list-style-type: none"> • Multivariate OR (95% CI) by intense PA, men
	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.83 (0.40-1.75) • G3 = 0.27 (0.11-0.65) 		<ul style="list-style-type: none"> • Q1 = Low • Q2 • Q3 • Q4 = high 	<ul style="list-style-type: none"> • Multivariate OR (95% CI) by intense PA, women
	<ul style="list-style-type: none"> • G2 = 0.55 (0.23-1.34) 		<ul style="list-style-type: none"> • Outcome Measure: Diagnosed with CC • Multiple logistic regression analysis 	<ul style="list-style-type: none"> • Multivariate OR (95% CI) by non-intense PA, men
	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.40 (0.76-2.57) • Q3 = 0.93 (0.51-1.72) • Q4 = 1.25 (0.68-2.29) 			<ul style="list-style-type: none"> • Multivariate OR (95% CI) by non-intense PA, women
	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.09 (0.62-1.90) 			<ul style="list-style-type: none"> • Multivariate OR (95% CI) by non-intense PA, women

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

Slattery et al 1997 [294]	To examine the relationship between weekly PA patterns (source, duration and frequency) and CC.	<ul style="list-style-type: none"> n = 1,993 cases, 2,410 controls 	PA Assessment: Interview, adapted CARDIA PA history	<ul style="list-style-type: none"> Number of cases: 1,993 	High level of leisure time VPA during the past 20 yrs was associated with a reduced risk of CC in both men and women. The same associations were not observed with leisure time MPA.
USA	<ul style="list-style-type: none"> Sex: Men and women 			<ul style="list-style-type: none"> • Q3 = 0.94 (0.53-1.66) • Q4 = 0.53 (0.29-0.95) 	
Case control	<ul style="list-style-type: none"> Age: 30-79 yr Characteristics: Cases: diagnosed with first primary CC. Controls: no history of CC 		Recent leisure time VPA	<ul style="list-style-type: none"> Multivariate OR (95% CI) by recent leisure time VPA, men • Q1 = 1.00 (referent) • Q2 = 0.80 (0.64-1.01) 	
D & B score = 14			Q1 = None Q2 Q3 Q4 = High	<ul style="list-style-type: none"> • Q3 = 0.84 (0.66-1.05) • Q4 = 0.69 (0.55-0.87) 	
	The Three Centered Diet, Activity and Lifestyle Colon Cancer Study		Leisure time VPA	<ul style="list-style-type: none"> Multivariate OR (95% CI) by recent leisure time VPA, women • Q1 = 1.00 (referent) 	The greatest inverse association was observed when activities were performed for longer periods of time per session.
			Q1 = Low Q2 Q3 Q4 = High	<ul style="list-style-type: none"> • Q2 = 0.79 (0.61-1.02) • Q3 = 0.83 (0.64-1.07) • Q4 = 0.86 (0.67-1.10) 	
			Current PA (min)	<ul style="list-style-type: none"> Multivariate OR (95% CI) by leisure time VPA, men 	
			G1 = <30 G2 = 30-60 G3 = ≥ 60	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.97 (0.76-1.25) • Q3 = 0.86 (0.67-1.09) • Q4 = 0.61 (0.47-0.79) 	
			LTPA (ranked by time per session)	<ul style="list-style-type: none"> Multivariate OR (95% CI) by leisure time VPA, women 	
			Q1 = None Q2 = Low - <30 min Q3 = moderate - 30-60 min Q4 = high ->60 min	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.75 (0.59-0.95) • Q3 = 0.68 (0.53-0.87) • Q4 = 0.63 (0.48-0.83) 	
			Number of activity session per week		

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

G1 = None	Multivariate OR (95% CI) by current MPA time per week
G2 = 1	
G3 = 2-4	• Q1 = 1.00 (referent)
G4 = 5-7	• Q2 = 1.00 (0.83-1.21)
G5 = >7	• Q3 = 0.90 (0.76-1.07)
	• Q4 = 0.92 (0.77-1.10)
Outcome Measure: Diagnosed with CC	Multivariate OR (95% CI) by current VPA time per week
Unconditional regression models	• Q1 = 1.00 (referent)
	• Q2 = 0.90 (0.73-1.12)
	• Q3 = 0.89 (0.71-1.10)
	• Q4 = 0.83 (0.69-0.98)
	Multivariate OR (95% CI) by leisure time MPA time per session
	• Q1 = 1.00 (referent)
	• Q2 = 1.20 (0.91-1.59)
	• Q3 = 1.09 (0.83-1.42)
	• Q4 = 1.08 (0.82-1.42)
	Multivariate OR (95% CI) by leisure time VPA time per session
	• Q1 = 1.00 (referent)
	• Q2 = 0.86 (0.74-0.99)
	• Q3 = 0.76 (0.64-0.90)
	• Q4 = 0.68 (0.52-0.87)
	Multivariate OR (95% CI) by number of MPA sessions/wk
	• G1 = 1.00 (referent)
	• G2 = 1.02 (0.79-1.30)
	• G3 = 0.86 (0.72-1.02)
	• G4 = 0.91 (0.81-1.14)
	• G5 = 1.02 (0.82-1.27)
	Multivariate OR (95% CI) by number of VPA sessions/wk
	• G1 = 1.00 (referent)
	• G2 = 0.72 (0.56-0.92)
	• G3 = 0.87 (0.73-1.03)
	• G4 = 1.00 (0.81-1.25)
	• G5 = 0.84 (0.61-1.15)

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

Slattery et al 1997 [295]	To determine how physical inactivity interacts with other components of energy balance in determining risk of CC.	<ul style="list-style-type: none"> n = 1,993 cases, 2,410 controls Sex: Men and women Age: 30-79 yr Characteristics: Cases: diagnosed with first primary CC. Controls: no history of CC The Three Centered Diet, Activity and Lifestyle Colon Cancer Study 	PA Assessment: Interview for lifetime VPA (PA index) Q1 = 10-12 Q2 = 7-9 Q3 = 4-6 Q4 = <4	Number of cases: 1,993 Multivariate OR (95% CI), men <ul style="list-style-type: none"> Q1 = 1.00 (referent) Q2 = 1.60 (1.11-1.75) Q3 = 1.59 (1.26-2.01) Q4 = 1.63 (1.26-2.12) Multivariate OR (95% CI), women <ul style="list-style-type: none"> Q1 = 1.00 Q2 = 1.14 (0.86-1.52) Q3 = 1.13 (0.85-1.49) Q4 = 1.59 (1.21-2.10) 	These results support previous findings that physical inactivity is associated with an increased risk of developing CC.
USA					
Case control			Outcome Measure: Diagnosed with CC		
D & B score = 14			Unconditional regression models		
Takahashi et al 2007 [296]	To investigate the association between time spent walking each day and the risk of CRC.	<ul style="list-style-type: none"> n = 20,519 men, 21,469 women Sex: Men and women Age: 40-64 yr Characteristics: Free from cancer at baseline 	7 year follow-up	Number of cases: 101 Number of dropouts: 3.5%	Time spent walking per day was associated with a lower risk of colon cancer in men but not in women.
Japan			PA assessment: Questionnaire for time spent walking (h/day)		
Prospective cohort			G1 = <0.5 G2 = 0.5-1 G3 = >1	Multivariate RR (95% CI), men <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.72 (0.43-1.21) G3 = 0.38 (0.22-0.64) p < 0.001	
D & B score = 12			Outcome Measure: Incidence of CC	Time spent walking and incidence of CC Multivariate RR (95% CI), women <ul style="list-style-type: none"> G1 = 1.00 G2 = 2.68 (0.94-7.68) G3 = 1.79 (0.64-4.96) p = 0.42	
			Cox proportional HR		

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

Tang et al 1999 [297]	To investigate the association between PA, water intake and risk of CRC in a hospital based case controlled study.	<ul style="list-style-type: none"> n = 163 cases, 163 controls Sex: Men and women Age: 33-80 yr Characteristics: Cases: Hospital patients diagnosed with colorectal cancer Controls: Hospital patients in hospital for other reasons, free of CRC. 	PA assessment: Interview LTPA METs G1 = Sedentary G2 = Moderate (< 20 MET) G3 = Active (≥ 20 MET)	<ul style="list-style-type: none"> Number of cases: 163 Multivariate RR (95% CI), men <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 2.22 (0.68-7.21) G3 = 0.19 (0.05-0.77) <p>$p = 0.03$</p> Multivariate RR (95% CI), women <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.52 (0.13-2.03) G3 = 0.63 (0.18-2.18) 	Found a negative association between LTPA and the risk of CC among men.
Taiwan					
Case control					
D & B score = 14					
Tavani et al 1999 [298]	To investigate the relationship between PA and risk of CC in both sexes at different ages.	<ul style="list-style-type: none"> n = 5,379 (1,225 cases and 4,154 controls) Sex: Men and women Age: 19-74 yr 	PA assessment: Questionnaire on activity at work and during leisure time G1 = Highest G2 G3 G4 G5 = Lowest OPA at 30-39 yrs old Q1 = Highest Q2 Q3 Q4 = Lowest Outcome Measure: Diagnosis of CC	<ul style="list-style-type: none"> Number of cases: 537 women, 688 men Multivariate OR (95% CI) for CC by OPA at age 15-19 yr, men <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.89 (0.64-1.23) G3 = 0.72 (0.54-0.97) G4 = 0.54 (0.40-0.74) G5 = 0.47 (0.31-0.71) <p>$p < 0.01$</p> Multivariate OR (95% CI) for CC by OPA at age 15-19 yr, women <ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.73 (0.55-0.96) G3 = 0.91 (0.69-1.21) G4 = 0.62 (0.44-0.89) 	The study confirms that OPA is protective against CC.
Italy					
Case control					
D & B score = 13					

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

Unconditional multiple Logistic Regression	$p < 0.05$
Multivariate OR (95% CI) for CC by OPA at age 30-39 yr, men	
• G1 = 1.00 (referent)	
• G2 = 1.01 (0.75-1.37)	
• G3 = 0.79 (0.59-1.06)	
• G4 = 0.71 (0.52-0.97)	
• G5 = 0.64 (0.44-0.93)	
$p < 0.01$	
Multivariate OR (95% CI) for CC by OPA at age 30-39 yr, women	
• G1 = 1.00 (referent)	
• G2 = 0.65 (0.46-0.93)	
• G3 = 0.57 (0.41-0.79)	
• G4 = 0.49 (0.33-0.72)	
$p < 0.01$	
Multivariate OR (95% CI) for CC by OPA at age 50-59 yr, men	
• G1 = 1.00 (referent)	
• G2 = 1.06 (0.78-1.43)	
• G3 = 0.85 (0.63-1.14)	
• G4 = 0.68 (0.49-0.95)	
• G5 = 0.69 (0.45-1.05)	
$p < 0.01$	
Multivariate OR (95% CI) for CC by OPA at age 50-59 yr, women	
• G1 = 1.00 (referent)	
• G2 = 0.69 (0.47-1.00)	
• G3 = 0.68 (0.46-1.00)	
• G4 = 0.75 (0.47-1.20)	
$p = > 0.05$	
Multivariate OR (95% CI) for ascending CC by OPA at age 30-39 yr	No significant associations for men or women
Multivariate OR (95% CI) for transverse and descending CC by OPA at age 30-39 yr, men	
• Q1 = 1.00 (referent)	
• Q2 = 0.92 (0.51-1.67)	

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

				<ul style="list-style-type: none"> • Q3 = 0.76 (0.43-1.37) • Q4 = 0.46 (0.24-0.87) <p>$p < 0.05$</p> <p>Multivariate OR (95% CI) for transverse and descending CC by OPA at age 30-39 yr, women</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.51 (0.23-1.10) • Q3 = 0.39 (0.19-0.80) • Q4 = 0.29 (0.12-0.71) <p>$p < 0.01$</p> <p>Multivariate OR (95% CI) for sigmoid CC by OPA at age 30-39 yr, men</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 1.02 (0.65-1.57) • Q3 = 0.78 (0.51-1.20) • Q4 = 0.54 (0.34-0.85) <p>$p < 0.01$</p> <p>Multivariate OR (95% CI) for sigmoid CC by OPA at age 30-39 yr, women</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.62 (0.36-1.05) • Q3 = 0.71 (0.44-1.15) • Q4 = 0.58 (0.32-1.03) <p>$p > 0.05$</p>
Thune et al 1996 [299]	To examine the association between self-Reported OPA and LTPA and the subsequent risk of CC.	n = 81,516 (53,242 men, 28,274 women)	16.3 year follow up	<p>Number of cases: 236 men, 99 women</p> <p>An inverse dose-response relationship between TPA and risk of CC was observed in women. In men this inverse dose-response was found only for those 45 yrs or older at study entry.</p>
Norway Prospective cohort		<ul style="list-style-type: none"> • Sex: Men and women • Age: 20-49 yr • Characteristics: Free from cancer at baseline 	<p>PA assessment: Questionnaire for TPA (OPA plus recreational PA (combined))</p> <p>G1 = Sedentary G2 = Moderate G3 = Active</p>	<p>Multivariate RR (95% CI) for total CC, men</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.18 (0.76-1.82) • G3 = 0.97 (0.63-1.50) <p>$p = 0.49$</p>
D & B score = 14				

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

	Multivariate RR (95% CI) for total CC, women
	• G1 = 1.00 (referent)
	• G2 = 0.97 (0.33-2.77)
	• G3 = 0.63 (0.39-1.04)
	<i>p</i> = 0.04
	Multivariate RR (95% CI) for proximal CC, men
	• G1 = 1.00 (referent)
	• G2 = 1.16 (0.57-2.34)
	• G3 = 0.96 (0.47-1.93)
	<i>p</i> = 0.64
	Multivariate RR (95% CI) for proximal CC, women
	• G1 = 1.00 (referent)
	• G2 = 1.22 (0.51-2.94)
	• G3 = 0.62 (0.30-1.28)
	<i>p</i> = 0.10
	Multivariate RR (95% CI) for distal CC, men
	• G1 = 1.00 (referent)
	• G2 = 1.29 (0.72-2.33)
	• G3 = 0.99 (0.55-1.80)
	<i>p</i> = 0.53
	Multivariate RR (95% CI) for distal CC, women
	• G1 = 1.00 (referent)
	• G2 = 0.84 (0.32-2.17)
	• G3 = 0.61 (0.30-1.23)
	<i>p</i> = 0.15
	Multivariate RR (95% CI) for total CC, men < 45 yrs at entry
	• G1 = 1.00 (referent)
	• G2 = 2.02 (0.78-5.21)
	• G3 = 2.23 (0.88-5.66)
	<i>p</i> = 0.13
	Multivariate RR (95% CI) for total CC, women < 45 yrs at entry
	• G1 = 1.00 (referent)
	• G2 = 0.96 (0.39-2.40)

Outcome Measure:
 Incidence of CC
 Cox proportional HR

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

	<ul style="list-style-type: none"> • G3 = 0.62 (0.31-1.23) 	
	<p>$p = 0.13$</p>	
	<p>Multivariate RR (95% CI) for total CC, men ≥ 45 yrs at entry</p>	
	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.96 (0.59-1.58) • G3 = 0.66 (0.40-1.10) 	
	<p>$p = 0.04$</p>	
	<p>Multivariate RR (95% CI) for total CC, women ≥ 45 yrs at entry</p>	
	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.99 (0.41-2.39) • G3 = 0.66 (0.33-1.33) 	
	<p>$p = 0.19$</p>	
<p>Vena et al 1985 [300]</p>	<p>To assess the relationship between lifetime OPA and the risk of CC.</p>	<p>• n = 1,641 (210 cases, 1,431 control)</p> <p>PA assessment: Questionnaire</p> <p>Number of work years in jobs with sedentary or light work (yr)</p> <p>G1 = None G2 = 1-20 G3 = >20</p> <p>OR (95% CI) by number of work years in jobs with sedentary or light work</p> <p>• G1 = 1.00 (referent) • G2 = 1.49 • G3 = 1.97</p> <p>OR (95% CI) by proportion of years in jobs with sedentary or light work</p> <p>• G1 = 1.00 (referent)</p> <p>• G2 = 1.53 • G3 = 1.58 • G4 = 2.10</p> <p>OR (95% CI) by proportion of life in jobs with sedentary or light work</p> <p>G1 = None G2 = 0.01-0.50 G3 = 0.41-0.99 G4 = 1.00 (referent)</p>
<p>USA</p>	<p>• Sex: Men</p>	<p>CC risk increased with increasing amount and proportion of time in jobs involving only sedentary or light work.</p>
<p>Case control</p>	<p>• Age: 30-79 yr</p> <p>• Characteristics: Cases: admitted to hospital. Diagnosis of CC Controls: Admitted to hospital. Diagnosed with non-neoplastic non-digestive diseases</p>	
<p>D & B score = 15</p>		

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.66 • G3 = 1.83 		
<p>Proportion of life in jobs with sedentary or light work</p>			
<p>G1 = None</p>			
<p>G2 = 0.01-0.40</p>			
<p>G3 = 0.41-1.00</p>			
<p>Outcome Measure: diagnosed with CC</p>			
<p>Multiple logistic regression</p>			
<p>PA assessment: Questionnaire Job title and industry names</p>	<p>Number of cases: 87 men, 13 women</p>	<p>To investigate the influence of OPA on the risk of CC in a developing country.</p>	<p>This study presents a weak inverse association between CC and PA.</p>
<p>USA</p>	<p>OR (95% CI) Sitting time and CC</p>	<p>• n = 87 men cases, 13 women cases, 371 controls</p> <p>• Sex: Men and women</p>	<p>Only 2 of the 4 measures of activity showed evidence of an increased CC risk for sedentary jobs (time spent sitting and occupational EE) though neither was statistically significant.</p>
<p>Case control</p>	<p>Levels (Sitting time, energy expenditure)</p>	<p>• Age: 14-97 yr</p>	<p>• G1 = 1.00 (referent)</p>
<p>D & B score = 11</p>	<p>G1 = High</p>	<p>• Characteristics: Cases: Diagnosed with CC Controls: cancer cases other than colon, rectum and lung cancer.</p>	<p>• G2 = 1.0 (0.5-2.0)</p>
	<p>G2 = Moderate</p>		<p>• G3 = 1.5 (0.7-2.9)</p>
	<p>G3 = Sedentary</p>		<p>p = 0.145</p>
	<p>Outcome Measure: Diagnosed with CC</p>		<p>OR (95% CI) Energy Expenditure and CC</p>
			<p>• G1 = 1.00 (referent)</p>
			<p>• G2 = 1.5 (0.7-3.3)</p>
			<p>• G3 = 1.6 (0.8-3.6)</p>
			<p>p = 0.143</p>
<p>White et al 1996 [302]</p>	<p>PA assessment: Phone interview</p>	<p>• n = 871 (251 men, 193 women cases, 233 men & 194 women controls)</p>	<p>• Number of cases: 251 men & 193 women</p>
<p>USA</p>	<p>Total PA (episodes/wk)</p>		<p>RR (95% CI) by total PA, men</p>
<p>Case control</p>	<p>G1 = 0</p>	<p>• Sex: Men and women</p>	<p>• G1 = 1.00 (referent)</p>
<p>D & B score = 14</p>	<p>G2 = <1</p>		<p>• G2 = 0.81 (0.45-1.44)</p>
	<p>G3 = 1-<2</p>		<p>• G3 = 0.53 (0.30-0.94)</p>
	<p>G4 = 2-<4</p>	<p>• Age: 30-62 yr</p>	<p>• G4 = 0.57 (0.33-1.00)</p>
			<p>The results of this study show modest support that recreational PA is associated with a reduced risk of CC.</p>

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

<ul style="list-style-type: none"> • Characteristics: Cases: Diagnosed with CC, no previous history or CC or inflammatory bowel 	G5 = ≥ 4	<ul style="list-style-type: none"> • G5 = 0.57 (0.40-1.11)
	Moderate-high intensity PA (episodes/wk)	<i>p</i> = 0.03
	RR (95% CI) by total PA, women	
	G1 = 0	• G1 = 1.00 (referent)
	G2 = <1	• G2 = 1.17 (0.57-2.40)
	G3 = 1-<2	• G3 = 1.27 (0.65-2.45)
	G4 = ≥ 2	• G4 = 0.59 (0.34-1.04)
		• G5 = 1.09 (0.61-1.97)
	High intensity PA (episodes/wk)	<i>p</i> = 0.52
	RR (95% CI) by total PA, men and women	
	G1 = 0	• G1 = 1.00 (referent)
	G2 = <1	• G2 = 0.94 (0.60-1.47)
	G3 = ≥ 1	• G3 = 0.77 (0.50-1.19)
	METS/wk	• G4 = 0.57 (0.39-0.85)
	Q1 = 0	
	Q2 = <7.30	• G5 = 0.83 (0.57-1.22)
	Q3 = 7.30-17.88	<i>p</i> = 0.04
	Q4 = ≥ 17.88	
	Outcome Measure: Diagnosed with CC	RR (95% CI) by moderate-high intensity PA, men
	Unconditional logistic regression	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.84 (0.49-1.43) • Q3 = 0.75 (0.42-1.36) • Q4 = 0.66 (0.41-1.05)
		<i>p</i> = 0.07
		RR (95% CI) by moderate-high intensity PA, women
		<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.07 (0.58-1.97) • G3 = 1.00 (0.51-1.98) • G4 = 0.74 (0.42-1.29)
		<i>p</i> = 0.37
		RR (95% CI) by moderate-high intensity PA, men and women

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

• Q1 = 1.00 (referent)
• Q2 = 0.93 (0.62-1.39)
• Q3 = 0.86 (0.55-1.34)
• Q4 = 0.70 (0.49-1.00)
<i>p</i> = 0.05
RR (95% CI) by high intensity PA, men
• G1 = 1.00 (referent)
• G2 = 0.85 (0.48-1.52)
• G3 = 0.57 (0.35-0.92)
<i>p</i> = 0.02
RR (95% CI) by high intensity PA, Women
• G1 = 1.00 (referent)
• G2 = 1.02 (0.51-2.04)
• G3 = 0.74 (0.43-1.28)
<i>p</i> = 0.31
RR (95% CI) by high intensity PA, men and women
• G1 = 1.00 (referent)
• G2 = 0.93 (0.59-1.44)
• G3 = 0.64 (0.45-0.92)
<i>p</i> = 0.02
RR (95% CI) by METs/wk, men
• Q1 = 1.00 (referent)
• Q2 = 0.64 (0.38-1.07)
• Q3 = 0.59 (0.37-0.96)
• Q4 = 0.69 (0.42-1.13)
<i>p</i> = 0.05
RR (95% CI) by METs/wk, women
• Q1 = 1.00 (referent)
• Q2 = 0.87 (0.51-1.49)
• Q3 = 1.20 (0.69-2.08)
• Q4 = 0.74 (0.41-1.34)
<i>p</i> = 0.62
RR (95% CI) by METs/wk, women
• Q1 = 1.00 (referent)
• Q2 = 0.73 (0.50-1.06)
• Q3 = 0.80 (0.56-1.16)
• Q4 = 0.73 (0.50-1.06)
<i>p</i> = 0.08

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

Wolin et al 2007 [303]	To assess the relationship between PA and risk of CC in women.	n = 79,295	16 year follow-up	Number of cases: 547 (245 distal, 302 proximal) Number of dropouts: 10%	A significant inverse association exists between PA, including moderate intensity, such as walking, and risk of CC in women that is more pronounced for distal tumours.
USA	<ul style="list-style-type: none"> Sex: Women Age: 40-65 yr Characteristics: Nurses, no history of CC, ulcerative colitis and Crohn's disease 	PA assessment: Questionnaire			
Prospective cohort			Level of PA	Multivariate RR (95% CI) for distal CC by level of PA	
			G1 = <2	• G1 = 1.00 (referent)	
			G2 = 2.1-4.5	• G2 = 0.93 (0.64-1.36)	
			G3 = 4.6-10.3	• G3 = 0.99 (0.68-1.44)	
			G4 = 10.4 - 21.4	• G4 = 0.87 (0.59-1.29)	
			G5 = ≥ 21.5	• G5 = 0.54 (0.34-0.84)	
D & B score = 14	Nurses' Health Study		MPA or VPA (hr/wk)	p = 0.004	
			G1 = 0	Multivariate RR (95% CI) for proximal CC by level of PA not significant p = 0.77	
			G2 = <1		
			G3 = 1-1.9		
			G4 = 2-3.9		
			G5 = ≥ 4	Multivariate RR (95% CI) for all CC by MPA or VPA	
			Outcome Measure: Fatal and non fatal CC	• G1 = 1.00 (referent)	
			Cox proportional HR	• G2 = 0.85, (0.64-1.14)	
				• G3 = 0.74 (0.53-1.04)	
				• G4 = 0.56 (0.33-0.94)	
				p = 0.01	
				Multivariate RR (95% CI) for distal CC by MPA or VPA	
				• G1 = 1.00 (referent)	
				• G2 = 1.10 (0.73-1.66)	
				• G3 = 0.63 (0.36-1.10)	
				• G4 = 0.51 (0.22-1.17)	
				p = 0.04	
				Multivariate RR (95% CI) for proximal CC by MPA or VPA not significant p = 0.12	

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

Zhang et al 2006 [304]	To examine the relationship between LTPA and OPA and the risk of CC by anatomic site and to evaluate their joint effect on the risk of CC.	n = 585 cases 2,172 controls	PA assessment: Questionnaire for the following variables	Number of cases: 585	Found a significant inverse association between reported LTPA and risk of CC with a slightly stronger association for the right colon than the left in both men and women.
USA	Sex: Men and women	Moderate-Strenuous LTPA	Multivariate OR (95% CI) by moderate-strenuous LTPA, men and women	G1 = 1.00 (referent)	
Case control	Age: 40-85 yr	G1 = <1 month	G2 = 0.7 (0.5-1.1)		
D & B score = 15	Characteristics: Case: diagnosed with CC Control: no history of CC.	G2 = 1-4 months G3 = ≥ 2 weeks	G3 = 0.6 (0.4-0.8) p = 0.003	Multivariate OR (95% CI) by moderate-strenuous LTPA, men	The joint effect of OPA and LTPA suggested that the risk was lowest for those with high OPA and non-OPA.
	Outcome Measure: CC		G1 = 1.00 (referent) G2 = 0.9 (0.5-1.7) G3 = 0.5 (0.3-0.9) p = 0.02		
	Unconditional logistic regression models			Multivariate OR (95% CI) by moderate-strenuous LTPA, women	
			G1 = 1.00 (referent) G3 = 0.5 (0.3-1.0) G3 = 0.6 (0.4-0.9) p = 0.02	Multivariate OR (95% CI) by moderate-strenuous LTPA, men and women	
			G1 = 1.00 (referent) G2 = 0.7 (0.5-1.1) G3 = 0.8 (0.6-1.1) p = 0.53	Multivariate OR (95% CI) by moderate-strenuous LTPA, men	
			G1 = 1.00 (referent) G2 = 0.9 (0.5-1.5)		

Table 15: Studies examining the relationship between physical activity and colon cancer. (Continued)

	<ul style="list-style-type: none"> • G3 = 0.8 (0.6-1.2)
$p = 0.55$	
Multivariate OR (95% CI) by moderate-strenuous LTPA, women	
	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.6 (0.3-1.1) • G3 = 0.8 (0.5-1.2)
$p = 0.62$	
Multivariate OR (95% CI) by moderate-strenuous LTPA and OPA, OPA-Low	
	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.5 (0.3-0.9) • G3 = 0.8 (0.5-1.2)
$p = 0.41$	
Multivariate OR (95% CI) by moderate-strenuous LTPA and OPA, OPA-Medium	
	<ul style="list-style-type: none"> • G1 = 0.7 (0.5-1.1) • G2 = 0.7 (0.4-1.3) • G3 = 0.5 (0.3-0.8)
$p = 0.04$	
Multivariate OR (95% CI) by moderate-strenuous LTPA and OPA, OPA-High	
	<ul style="list-style-type: none"> • G1 = 0.9 (0.5-1.6) • G2 = 0.6 (0.3-1.3) • G3 = 0.5 (0.3-0.8)

D & B score, Downs and Black quality score; YR, years; PA, physical activity; OPA, occupational physical activity; kJ/min, kilojoules per minute; G, groups; MET, metabolic equivalent; HR, hazard ratio; RR, risk ratio; OR, odds ratio; 95% CI, confidence interval; LTPA, leisure-time physical activity; CC, colon cancer; TPA, total physical activity; MDA, moderate physical activity, h/d, hours per day; VPA, vigorous physical activity; h/wk, hours per week.

Table 16 Studies examining the relationship between physical activity and breast cancer.

Publication Country Study Design Quality Score	Objective	Population	Methods	Outcome	Comments and Conclusions
Rockhill et al 1999 [106]	To examine the effect of PA on the risk for BC.	<ul style="list-style-type: none"> n = 121,701 	PA assessment: Self-reported LTPA, grouped into hr/wk	3,137 cases of BC	Women who engaged in 7 or more hours per week of MVPA had a 20% lower risk of BC. An inverse dose-response relationship existed between PA and BC incidence.
USA		<ul style="list-style-type: none"> Sex: Women Age: 30-55 yr 16-yr follow-up Characteristics: Free of BC 		RR (95% CI) for BC and LTPA	
Prospective cohort				<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.88 (0.79-0.98) G3 = 0.89 (0.81-0.99) G4 = 0.85 (0.77-0.94) G5 = 0.82 (0.70-0.97) 	
D & B score = 13		<ul style="list-style-type: none"> The nurses Health Study 	<ul style="list-style-type: none"> G4 = 4.0-6.9 G5 = ≥7 Multivariate pooled logistic regression 		
				Trend $p = 0.004$	
Sesso et al 1998 [107]	To examine the association between PA and BC among postmenopausal women.	<ul style="list-style-type: none"> n = 1,566 	31-yr follow-up	109 cases of BC	There is an inverse relationship between PA and BC in post-menopausal women.
USA		<ul style="list-style-type: none"> Sex: Women Age: 45.5 	PA assessment: Questionnaire at baseline, divided into tertiles (kcal/wk)	RR (95% CI) for BC and PA	
Prospective cohort		<ul style="list-style-type: none"> Characteristics: Free of BC 		<ul style="list-style-type: none"> T1 = 1.00 (referent) T2 = 0.92 (0.58-1.45) T3 = 0.73 (0.46-1.14) 	
D & B score = 14			<ul style="list-style-type: none"> T1 = <500 T2 = 500-999 T3 = ≥ 1,000 	RR (95% CI), post-menopausal women only	
				<ul style="list-style-type: none"> T1 = 1.00 (referent) T2 = 0.95 (0.58-1.57) T3 = 0.49 (0.28-0.86) 	
Dosemeci et al 1993 [278]	To conduct a multiple-site case-control study of 15 cancers to examine associations between PA, SES, and these cancer sites among workers.	<ul style="list-style-type: none"> n = 2,643 control group 	Cases: obtained from an oncological treatment center from 1979-1984	31 men had BC and 241 women had BC	This study shows the sitting-time index showed an elevated risk of female BC for sedentary jobs without SES adjustment.

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

Turkey	<ul style="list-style-type: none"> • n = 2,127 men and n = 244 women) • Sex: Men and women • Characteristics: Cases - diagnosed with one of the 15 cancers being examined. Control Group - subjects diagnosed with non-cancers, cancers of the buccal cavity, esophagus, liver, bone, soft tissue, brain, lymphoma and other cancer sites for which there is no suggestion on an association with PA 	Adjusted SES OR (95%CI), men	The slightly elevated risk of male BC was based on a small number and disappeared when the risk was adjusted for SES.
Case control	Controls: pulled from the same hospital as the cases	<ul style="list-style-type: none"> • G1 = 1.40 (0.60-3.90) • G2 = 1.10 (0.40-3.10) • G3 = 1.00 (referent) 	The slightly elevated risk of male BC was based on a small number and disappeared when the risk was adjusted for SES.
D & B score = 12	PA assessment: OPA (k/min) G1 = <8 G2 = 8-12 G3 = >12	Trend $p = 0.34$	Trend $p = 0.34$
Bernstein et al 1994 [305]	To determine whether young women who regularly participate in PA during their reproductive years had a reduced risk of BC.	Adjusted SES OR (95%CI), women	PA may substantially reduce a women's lifetime risk of BC.
USA	<ul style="list-style-type: none"> • n = 1,090 (545 cases; 545 controls) • Sex: Women • Age: ≤ 40 yr • Characteristics: White women matched for age and parity 	<ul style="list-style-type: none"> • G1 = 1.10 (0.60-2.10) • G2 = 0.90 (0.50-1.80) • G3 = 1.00 (referent) 	Trend $p = 0.23$
Case control	PA assessment: Questionnaire for overall participation in PA after menarche (h/wk), PA within 10 years after menarche (h/wk), each divided into 5 groups:	Adjusted OR (95% CI) by PA after menarche	PA may substantially reduce a women's lifetime risk of BC.
D & B score = 15	G1 = none G2 = 0.1-0.7 G3 = 0.8-1.6	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.95 (0.64-1.41) • G3 = 0.65 (0.45-0.96) • G4 = 0.80 (0.54-1.17) • G5 = 0.42 (0.27-0.64) 	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.95 (0.64-1.41) • G3 = 0.65 (0.45-0.96) • G4 = 0.80 (0.54-1.17) • G5 = 0.42 (0.27-0.64)

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

Bernstein et al 2005 [306]	To examine the relationship between BC risk and lifetime and time- or age-specific measures of LTPA among white and black women.	<ul style="list-style-type: none"> • n = 9,187 (4,538 cases; 4,649 control) • Sex: Women • Age: 35-64 • Ethnicity: White (including Hispanics) or Black 	<ul style="list-style-type: none"> • G4 = 1.7-3.7 • G5 = ≥ 3.8 Logistic regression	Trend $p = 0.0001$ Adjusted OR (95% CI) by PA within 10 years after menarche <ul style="list-style-type: none"> • None = 1.00 (referent) • 0.1-1.2 = 0.93 (0.63-1.38) • 1.3-2.9 = 0.78 (0.52-1.19) • 3.0-5.5 = 0.69 (0.45-1.05) • ≥5.6 = 0.70 (0.47-1.06) Trend $p = 0.027$ Adjusted OR (95% CI) by PA after menarche, nulliparous women <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.81 (0.42-1.57) • G3 = 0.65 (0.35-1.21) • G4 = 0.94 (0.53-1.67) • G5 = 0.73 (0.38-1.41) Trend $p = 0.43$ Adjusted OR (95% CI) by PA after menarche, parous women <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.06 (0.65-1.74) • G3 = 0.65 (0.40-1.06) • G4 = 0.70 (0.42-1.18) • G5 = 0.38 (0.16-0.50) Trend $p < 0.0001$	This study supports an inverse association between PA and BC among black women and among white women.
USA			Multivariate adjusted OR (95%CI) annual MET h/wk, White participants	Controls: random-digit dialing methods	

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

Case control	<ul style="list-style-type: none"> • Characteristics: Case Group: histologically confirmed cases of invasive BC • Control Group: healthy 	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.84 (0.71-0.99) • G3 = 0.89 (0.75-1.04) • G4 = 0.82 (0.69-0.97) • G5 = 0.81 (0.69-0.96) <p>Trend $p = 0.09$</p>	<p>PA assessment: Questionnaire for lifetime PA (MET h/wk), divided into 5 groups G1 = Inactive</p> <p>G2 = ≤ 2.2 G3 = 2.3-6.6 G4 = 6.7-15.1 G5 = ≥ 15.2</p> <p>Unconditional logistic regression modeling</p> <p>Multivariate adjusted OR (95%CI) annual MET h/wk, Black participants</p>	<p>The relationship appears to be similar between black and white women.</p>	
D & B score = 13					
Carpenter et al. 1999 [307]	<ul style="list-style-type: none"> • n = 2,027 (1,123 case; 904 control) • Sex: Women • Age: 55-64 yr • Ethnicity: White (including Hispanic) • Characteristics: post-menopausal, English-speaking, born in USA, Canada or Western Europe 	<ul style="list-style-type: none"> • n = 2,027 (1,123 case; 904 control) • Sex: Women • Age: 55-64 yr • Ethnicity: White (including Hispanic) • Characteristics: post-menopausal, English-speaking, born in USA, Canada or Western Europe 	<p>Cases: diagnosed with primary invasive or in situ BC</p> <p>Controls: individually matched to each case patient based on birth date and race</p> <p>PA assessment: Questionnaire for lifetime PA (MET hr/wk), divided into 3 groups G1 = no activity G2 = 0.1-17.59</p>	<p>1,123 cases of BC</p> <p>Multivariate adjusted OR (95%CI)</p> <p>Trend $p = 0.003$</p>	<p>Strenuous exercise appears to reduce BC risk among post-menopausal women who do not gain sizable amounts of weight during adulthood.</p>
USA					
Case control					
D & B score = 15					

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

		G3 = ≥17.6	
		Conditional logistic regression	
Carpenter et al 2003 [308]	To examine the effects of obesity and lifetime exercise patterns on post-menopausal BC risk according to family history.	<ul style="list-style-type: none"> n = 3,511 (cases n = 1,883, controls) n = 1,628 Sex: Women Age: 55-72 Characteristics: Postmenopausal Women 	1,883 cases of BC Adjusted OR (95% CI) by lifetime exercise between menarche and reference date (MET hr/wk)
USA			Exercise independent of body size seemed to exert a protective effect primarily among women with a negative family history.
Case control D & B score = 15		Lifetime exercise between menarche and reference date (MET hr/wk)	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.85 (0.71-1.03) G3 = 0.87 (0.69-1.10) G4 = 1.02 (0.79-1.30)
		Average exercise activity in 10 years prior to reference date (MET hr/wk)	<ul style="list-style-type: none"> G5 = 0.66 (0.48-0.90) Trend $p = 0.07$
		G1 = 0 G2 = 0.1-6.9 G3 = 7.0-13.9 G4 = 14.0-24.4 G5 = ≥24.5	Adjusted OR (95% CI) by average exercise activity in 10 years prior to reference date (MET hr/wk)
			<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.93 (0.71-1.22) G3 = 0.92 (0.70-1.19) G4 = 0.86 (0.65-1.11) G5 = 0.75 (0.55-1.02) Trend $p = 0.05$
Chang et al 2006 [309]	To address the independent and combined effects of energy intake, BMI, and PA on BC incidence in women.	<ul style="list-style-type: none"> n = 27,541 	764 women developed BC The study suggests that energy intake, BMI and physical inactivity are each independently and positively associated with BC risk.

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

USA	<ul style="list-style-type: none"> Sex: Women Age: 55-74 	<ul style="list-style-type: none"> Characteristics: no history of any cancer (nonmelanoma skin cancer patients were included in the trial) Prostate, Lung, colorectal, and Ovarian Cancer Screening Trial 	<p>PA assessment: Questionnaire for vigorous PA (h/wk), divided into 6 groups</p> <p>G1 = 0</p> <p>G2 = <1</p> <p>G3 = 1</p> <p>G4 = 2</p> <p>G5 = 3</p> <p>G6 = ≥4</p>	<p>Multivariate adjusted RR (95% CI)</p>	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 0.89 (0.69-1.15) G3 = 0.96 (0.73-1.26) G4 = 0.90 (0.70-1.16) G5 = 1.02 (0.79-1.30) G6 = 0.78 (0.61-0.99) <p>Trend $p = 0.153$</p>	<p>Cox proportional HR</p>	<p>Total cases diagnosed n = 849</p>	<p>These data among pre-menopausal women suggest that there is no overall association between PA and risk of BC. The findings also suggest that the effect of PA could be substantially modified by the underlying degree of adiposity.</p>
USA	<ul style="list-style-type: none"> Sex: Women Age: 25-42 	<ul style="list-style-type: none"> Characteristics: pre-menopausal, no history of cancer other than nonmelanoma skin cancer 	<p>To evaluate the relationship between PA and risk of pre-menopausal BC by type of activity and within subgroups of adiposity and oral contraceptive use.</p> <p>PA assessment: Self report on 8 activities (walking or hiking, jogging (>10 min mile), running, Biking, racquet sports, lap swimming, calisthenics/aerobics other aerobic activities) to calculate MET scores (MET hr/wk), divided into 5 groups:</p> <p>G1 = <3</p> <p>G2 = 3-8.9</p> <p>G3 = 9-17.9</p> <p>G4 = 18-26.9</p> <p>G5 = ≥27</p>	<p>Multivariate adjusted RR (95% CI)</p>	<ul style="list-style-type: none"> G1 = 1.00 (referent) G2 = 1.05 (0.82-1.34) G3 = 0.96 (0.75-1.23) G4 = 1.05 (0.80-1.37) G5 = 1.07 (0.84-1.36) <p>Trend $p = 0.69$</p>	<p>Cox proportional HR</p>	<p>4,863 cases of BC</p>	<p>There was evidence of a graded inverse relationship between the intensity of work related activity and the incidence of BC.</p>
USA	<ul style="list-style-type: none"> Sex: Women 	<ul style="list-style-type: none"> n = 11,646 (4,863 cases and 6,783 controls). 	<p>To evaluate the effect of OPA on BC risk.</p> <p>PA assessment: Telephone interview to estimate OPA, divided into tertiles:</p> <p>T1 = Sedentary</p>	<p>OR (95% CI)</p>	<ul style="list-style-type: none"> T1 = 1.00 (referent) 	<p>T1 = Sedentary</p>	<p>4,863 cases of BC</p>	<p>There was evidence of a graded inverse relationship between the intensity of work related activity and the incidence of BC.</p>

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

Case control	<ul style="list-style-type: none"> • Age: <74 yr 	<ul style="list-style-type: none"> • T2 = Medium activity jobs • T3 = Heavy jobs 	<ul style="list-style-type: none"> • T2 = 0.86 (0.77-0.97) • T3 = 0.82 (0.63-1.08) 	
D & B score = 14	Logistic regression models			
Coogan and Aschengrau 1999 [312]	To evaluate the effect of OPA on BC risk.	<ul style="list-style-type: none"> • n = 903 (233 case; 670 control) 	233 cases of BC	There was no evidence that holding a job of medium/heavy activity reduced BC.
USA	<ul style="list-style-type: none"> • Sex: Women • Age: <50 - 80+ • Ethnicity: White, Black or Other • Characteristics: must have worked outside the home. Cases: All incident cases of BC reported to the Massachusetts Cancer Registry from 1983 to 1986 were eligible 	<ul style="list-style-type: none"> T1 = Exclusively sedentary T2 = Exclusively light T3 = Exclusively medium or heavy 	OR (95%CI) <ul style="list-style-type: none"> • T1 = 1.00 (referent) • T2 = 1.20 (0.70-1.90) • T3 = 0.90 (0.40-1.90) 	The study was limited by OPA misclassification and by the lack of information on LTPA.
Case control	Miettinen's test-based method and Fisher's exact method			
D & B score = 14	Trend $p = 0.63$			
Dallal et al 2007 [313]	To examine the relationship between LTPA and invasive and in situ BC among women.	<ul style="list-style-type: none"> • n = 110,599 	2,649 cases of invasive BC	The results support a protective role of strenuous long-term exercise activity against invasive and in situ BC and suggest differing effects by hormone receptor status.
USA	<ul style="list-style-type: none"> • Sex: Women • Age: 20-79 	<ul style="list-style-type: none"> • Ethnicity: White, Black, Hispanic, Asian, American Indian or other • Characteristics: California resident at baseline and no history of BC • California Teachers Study cohort 	593 cases of in situ BC	
Prospective cohort	PA assessment: Self-reported participation in moderate and strenuous activities to estimate annual strenuous physical activity (hr/wk), divided into quintiles			
D & B score = 12	Multivariate adjusted RR (95% CI) for invasive BC			
	<ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.93 (0.85-1.02) • Q3 = 0.88 (0.78-0.99) • Q4 = 1.02 (0.88-1.18) • Q5 = 0.80 (0.69-0.94) 			

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

		Cox proportional HR	
			Trend $p = 0.02$ Multivariate adjusted RR (95% CI) for in situ BC <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.96 (0.79-1.17) • Q3 = 0.86 (0.67-1.11) • Q4 = 0.95 (0.70-1.30) • Q5 = 0.69 (0.48-0.98) Trend $p = 0.40$
Dirx et al 2001 [314]	To evaluate the relationship between PA and BC risk with specific emphasis on interaction with other aspects of energy balance.	<ul style="list-style-type: none"> • n = 62,537 	7.3 yr follow-up 1,208 cases of incident BC The current study supports the hypotheses that PA is related inversely to BC risk in postmenopausal women.
Netherlands		<ul style="list-style-type: none"> • Sex: Women • Age: 55-69 	
Case study		<ul style="list-style-type: none"> • Characteristics: healthy, postmenopausal 	
D & B score = 11			PA assessment: Questionnaire for total recreational PA (min/day), divided into quartiles Multivariate adjusted RR (95% CI) <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.84 (0.67-1.07) • Q3 = 0.78 (0.60-1.00) • Q4 = 0.76 (0.58-0.99)
			Q1 = <30 Q2 = 30-60 Q3 = 61-90 Q4 = >90 Exponentially distributed failure time regression models Trend $p = 0.003$
Dorn et al 2003 [315]	To examine the associations between LTPA and OPA across the lifespan and pre- and post-menopausal BC.	<ul style="list-style-type: none"> • n = 1,550 (740 case; 810 control) 	740 cases of BC The study supports the hypothesis that strenuous LTPA is associated with a reduced risk of BC risk in both pre- and post menopausal women
USA		<ul style="list-style-type: none"> • Sex: Women • Age: 40-85 • Characteristics: Case Group – histologically confirmed incidence of BC. Control Group – healthy 	
Case control		<ul style="list-style-type: none"> • Controls: randomly selected and frequency matched on age and county with the cases. 	Multivariate adjusted OR (95%CI), pre- menopausal <ul style="list-style-type: none"> • G1 = 1.00 (referent)

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

D & B score = 13	<p>PA assessment: Questionnaire for lifetime strenuous PA (hr/yr)</p> <p>G1 = 0 G2 = 1-273 G3 = 274-545 G4 = >546</p> <p>Logistic regression</p> <p>Multivariate adjusted OR (95%CI), post-menopausal</p> <ul style="list-style-type: none"> • G2 = 0.94 (0.64-1.38) • G3 = 0.73 (0.44-1.22) • G4 = 1.07 (0.57-2.02) <p>Trend $p = 0.82$</p>	
Drake 2001 [316]	<p>To evaluate PA as a predictor of BC and describe BC risk factors in this sample.</p> <p>n = 4,520</p> <p>Sex: Women Age: 21-86</p> <p>Characteristics: no diagnosis of BC at entry</p> <p>Aerobic Center Longitudinal Study</p>	<p>Increased frequency of a specific PA (jogging) was found to have an important protective role in BC incidence.</p> <p>150 incident cases of breast cancer</p> <p>OR (95% CI) for BC and PA</p> <p>Activity type</p> <ul style="list-style-type: none"> • G1 = 1.32 • G2 = 1.08 • G3 = 1.35 <p>Trend $p = 0.05$</p> <p>G1 = Aerobic (job, bike, aerobic dance) G2 = Moderate (golf, walk) G3 = Weight training</p> <p>Chi-square</p>

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

Friedenreich et al 2001 [317]	To examine the type and dose of PA and the time periods in life when PA may be specifically associated with BC risk.	• n = 2,470 (1,233 case; 1,237 control)	Cases: in situ and invasive cases of BC from 1995-1997	1,233 cases of BC	This study provides evidence that lifetime PA reduces risk of post-menopausal BC.
Canada	• Sex: Women	• Age: ≤ 80	Controls: matched to cases on age and place of residence	OR (95%CI), pre-menopausal	• Q1 = 1.00 (referent)
Case Control	• Characteristics: Case Group - Alberta residents, English speaking, capable of completing an in-person interview. Control Group - no history of cancer diagnoses excluding nonmelanoma skin cancer			• Q2 = 1.15 (0.78- 1.70)	
D & B score = 13			PA assessment: Questionnaire for lifetime PA (MET hr/wk/yr), divided into quartiles by menopausal status	• Q3 = 1.15 (0.78- 1.69)	
			Pre-menopausal	• Q4 = 1.07 (0.72- 1.61)	
			Q1 = <86.6	Trend <i>p</i> = 0.50	
			Q2 = 86.6-108.3	OR (95%CI), post-menopausal	
			Q3 = 108.3-134.9	• Q1 = 1.00 (referent)	
			Q4 = ≥ 134.9	• Q2 = 0.73 (0.55- 0.98)	
			Post-menopausal	• Q3 = 0.75 (0.56- 1.00)	
			Q1 = <104.8	• Q4 = 0.70 (0.52- 0.94)	
			Q2 = 104.8-128.1	Trend <i>p</i> = 0.003	
			Q3 = 128.1-160.9		
			Q4 = ≥ 160.9		
			Logistic regression		
Friedenreich et al 2001 [318]	To examine the influence of frequency, duration, and intensity of PA on risk of BC and to compare BC risks associated with self-reported versus assigned intensity of PA.	• n = 2,470 (1,233 case; 1,237 control)	Cases: in situ and invasive cases of BC	1,233 cases of BC	This study found that moderate-intensity activities were the major contributors to the decrease in BC risk found in this study.
Canada	• Sex: Women	• Age: ≤ 80	Controls: matched to cases on age and place of residence	Multivariate adjusted OR (95% CI), pre- menopausal	• Q1 = 1.00 (referent)
Case control					

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

D & B score = 13	<ul style="list-style-type: none"> Characteristics: Case Group – resident of Alberta, English speaking and able to complete an in-person interview. Control Group – free of any cancer diagnosis excluding nonmelanoma skin cancer 	<ul style="list-style-type: none"> PA assessment: Questionnaire for lifetime PA questionnaire (MET hr/wk/yr), divided into quartiles 	<ul style="list-style-type: none"> Q2 = 1.19 (0.80- 1.76)
	<ul style="list-style-type: none"> Q1 = <288 Q2 = 28.8-35.4 Q3 = 35.4-42.7 Q4 = ≥ 42.7 	<ul style="list-style-type: none"> Q3 = 1.33 (0.90- 1.96) Q4 = 1.07 (0.71- 1.62) 	
	<ul style="list-style-type: none"> Logistic regression 	<ul style="list-style-type: none"> Trend $p = 0.52$ Multivariate adjusted OR (95% CI), post- Menopausal 	
		<ul style="list-style-type: none"> Q1 = 1.00 (referent) Q2 = 0.85 (0.64- 1.14) Q3 = 0.83 (0.62- 1.10) Q4 = 0.69 (0.51- 0.93) 	
		<ul style="list-style-type: none"> Trend $p = 0.006$ 	
Friedenreich and Rohan 1995 [319]	<ul style="list-style-type: none"> To describe the association between LTPA and BC. 	<ul style="list-style-type: none"> Cases: first diagnosis of BC in 1982 and 1984 	<ul style="list-style-type: none"> Adjusted OR (95%CI), pre-menopausal
Australia Case control	<ul style="list-style-type: none"> n = 902 (451 case; 451 control) 		<ul style="list-style-type: none"> This study found some evidence (of borderline statistical significance) that recreational PA is associated with decreased risk of BC.
	<ul style="list-style-type: none"> Sex: Women Age: 20-74 yr 		
	<ul style="list-style-type: none"> Characteristics: Australian women 	<ul style="list-style-type: none"> Controls: Randomly selected from the electoral roll, matched on date of birth to each case PA assessment: Self reported PA (kcal/wk), divided into quartiles 	
D & B score = 13		<ul style="list-style-type: none"> Q1 = 0 Q2 = 1-2,000 Q3 = 2000-4000 Q4 = >4000 	<ul style="list-style-type: none"> Q1 = 1.00 (referent) Q2 = 0.77 (0.36- 1.65) Q3 = 0.48 (0.22- 1.03) Q4 = 0.60 (0.30- 1.17)
	<ul style="list-style-type: none"> Logistic regression models 	<ul style="list-style-type: none"> Trend $p = 0.09$ Adjusted OR (95%CI), post-menopausal 	
		<ul style="list-style-type: none"> Q1 = 1.00 (referent) Q2 = 0.74 (0.46- 1.18) Q3 = 0.88 (0.53- 1.48) Q4 = 0.73 (0.44- 1.20) 	
		<ul style="list-style-type: none"> Trend $p = 0.32$ 	

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

<p>Gammon et al 1998 [320]</p>	<p>To examine the association between LTPA and BC among young women.</p>	<p>• n = 3,173 (1,668 case; 1,505 control)</p>	<p>Cases: women diagnosed with BC between 1990-1992</p>	<p>1,668 cases of BC</p>	<p>The study's data does not support the hypothesis of a reduced risk of BC among young women with increased recreational PA in adolescence, young adulthood or during the year prior to the interview, or with the average PA over the three time periods</p>
<p>USA</p>	<p>• Sex: Women</p>	<p>• Age: <45</p>	<p>Controls: were matched to cases by age group and geographic center</p>	<p>Multivariate adjusted OR (95%CI)</p>	<p>• Q1 = 1.00 (referent)</p>
<p>Case control</p>	<p>• Characteristics: Case Group – diagnosed with invasive or in situ BC. Control Group - healthy</p>	<p>PA assessment: Questionnaire for recreational PA, for ages 12- 13 yr, age 20 yr and 1 year prior to the interview. Divided into quartiles MET score</p>	<p>Q1 = 1.62-18.07 Q2 = 18.08-30.00 Q3 = 30.01-42.95 Q4 = 42.96-98.00</p>	<p>• Q2 = 0.79 (0.63- 0.98)</p>	<p>Trend $p = 0.42$</p>
<p>D & B score = 13</p>	<p>Logistic regression</p>	<p>Cases: diagnosed with BC between 1992-1994</p>	<p>712 cases of BC</p>	<p>Hispanic and non- Hispanic women with high PA during non- OPA were at substantially reduced risk of BC.</p>	
<p>Gilliland et al 2001 [321]</p>	<p>To investigate the relationship of PA with BC risk in Hispanic and non- Hispanic White women</p>	<p>• n = 1,556 (712 case; 844 control)</p>	<p>Cases: diagnosed with BC between 1992-1994</p>	<p>712 cases of BC</p>	
<p>USA</p>	<p>• Sex: Women</p>	<p>• Age: between 35-74 at diagnosis</p>	<p>Controls: matched on ethnicity, age and seven health planning districts</p>	<p>Adjusted OR (95%CI), pre-menopausal Hispanic</p>	
<p>Case control</p>	<p>• Ethnicity: Hispanic and non-Hispanic White</p>	<p>PA assessment: Self-reported non-OPA (MET hr/wk score)</p>	<p>G1 = <25</p>	<p>• G1 = 1.00 (referent)</p>	<p>• G2 = 1.17 (0.53- 2.55)</p>
<p>D & B score = 13</p>	<p>• Characteristics: Case Group – diagnosed with in situ or invasive BC and residents of New Mexico at time of diagnosis. Control Group – healthy</p>	<p>G2 = 25-50 G3 = 50-80 G4 = ≥ 80</p>	<p>Logistic regression</p>	<p>Trend $p < 0.001$</p>	<p>Adjusted OR (95%CI), pre-menopausal non- Hispanic</p>
				<p>• G1 = 1.00 (referent)</p>	<p>• G2 = 1.35 (0.64- 2.85)</p>

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

<p>Hsing et al 1998 [322]</p>	<p>To evaluate the role of selected demographic, lifestyle, and anthropometric factors in the risk for male BC.</p>	<p>n = 690 (178 case; 512 control)</p>	<p>Cases: selected from 18,733 decedents included in the 1986 NMFS conducted by the US</p>	<p>178 cases of BC</p>	<p>This study suggests that obesity increases the risk of male BC, possibly through hormonal mechanisms, while dietary factors, PA and SES indicators also deserve further investigation.</p>
<p>USA</p>	<p>Sex: Men</p>	<p>Age: 25-74</p>	<p>National Center for Health Statistics (NCHS)</p>	<p>Adjusted OR (95%CI)</p>	
<p>Case control</p>	<p>Ethnicity: Black and White</p>	<p>Characteristics: Case Group – deceased. Control Group – dying (or deceased) of causes other than BC</p>	<p>Controls: selected from male decedents dying of causes other than BC</p>	<p>G1 = 1.00 (referent) G2 = 0.60 (0.30- 1.10) G3 = 1.30 (0.80- 2.00)</p>	
<p>D & B score = 12</p>	<p>PA assessment: Questionnaire (frequency and intensity), divided into groups</p>	<p>G1 = Regular G2 = Irregular G3 = Hardly any</p>	<p>Logistic regression analysis</p>	<p>Trend <i>p</i> = 0.019</p>	
<p>Hu et al 1997 [323]</p>	<p>To study breast cancer focusing on breast-feeding, body weight, and PA as well as reproductive histories on pre- and post-menopausal Japanese women.</p>	<p>n = 526 (157 case; 369 control)</p>	<p>Cases: Histologically confirmed cases of BC from 1989-1993.</p>	<p>157 cases of BC</p>	<p>Reduced risk of pre- menopausal BC was associated with high EE in PA during teenage years, although the trend was not statistically significant.</p>

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

					Unadjusted RR (95%CI), pre-menopausal
Japan					
Case control					
D & B score = 13	<ul style="list-style-type: none"> • Sex: Women • Age: 26-75 • Characteristics: Case Group – histologically confirmed cases of BC and resident of Gifu prefecture at time of diagnosis. Control Group – no breast disease or hormone-related (ovarian, endometrial and thyroid) cancers 	<ul style="list-style-type: none"> • Controls: individuals who had the screening test for BC during the same period 	<p>PA assessment: Questionnaire for TPA (kcal/wk), divided into groups</p> <p>G1 = 0 G2 = 1-649 G3 = ≥ 650</p>	<ul style="list-style-type: none"> • G3 = 1.01 (0.54- 1.87) <p>Trend $p = 0.876$</p>	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.74 (0.38- 1.44)
John et al 2003 [324]	To examine BC risk in relation to lifetime histories of MPA and VPA including LTPA, transportation household and outdoor chores, and OPA in a multiethnic population.	<ul style="list-style-type: none"> • n = 2,870 (1,277 case; 1,593 control) 	<p>Cases: diagnosed between 1995-1998</p>	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.53 (0.69- 3.54) • G3 = 1.39 (0.61- 3.13) 	<p>This study supports previous reports of a reduced risk of BC in physically active women.</p>
USA					
Case control					
D & B score = 12	<ul style="list-style-type: none"> • Sex: Women • Age: 35-79 • Ethnicity: Latina, African-American and White 	<ul style="list-style-type: none"> • Controls: randomly selected according race/ethnicity and age distribution of cases <p>PA assessment: In-person interview for lifetime PA (hr/wk), divided into groups</p> <p>Pre-menopausal</p> <p>G1 = <9.1 G2 = 9.1-20.7 G3 = ≥ 20.7</p> <p>Post-menopausal</p> <p>G1 = <96 G2 = 96-21.6 G3 = ≥ 21.7</p>	<p>Logistic regression models</p>	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.84 (0.49- 1.45) • G3 = 0.73 (0.42- 1.28) 	<p>Multivariate adjusted OR (95%CI), pre- menopausal Latinas</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.84 (0.49- 1.45) • G3 = 0.73 (0.42- 1.28) <p>Multivariate adjusted OR (95%CI), pre- menopausal African Americans</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.00 (0.55- 1.84) • G3 = 0.68 (0.35- 1.34)

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

	Logistic regression modeling			
	Multivariate adjusted OR (95%CI), pre- menopausal Whites			
	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.82 (0.42- 1.58) • G3 = 0.76 (0.36- 1.61) 			
	Multivariate adjusted OR (95%CI), post- menopausal Latinas			
	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.82 (0.55- 1.24) • G3 = 0.81 (0.54- 1.22) 			
	Multivariate adjusted OR (95%CI), post- menopausal African Americans			
	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.78 (0.52- 1.17) • G3 = 0.71 (0.47- 1.07) 			
	Multivariate adjusted OR (95%CI), post- menopausal Whites			
	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.94 (0.64- 1.37) • G3 = 0.91 (0.60- 1.41) 			
Kruk 2007 [325]	To examine the association between all types of PA and BC risk among Polish women.	n = 590 (268 case; 322 control)	PA assessment: Questionnaire for lifetime PA (MET hr/wk/yr), divided into groups	The results of this study provide evidence of an inverse association between PA and the risk of BC.
Poland		Sex: Women	G1 = <110	
Case control		Age: 35-75 yr	G2 = 110-150	
D & B score = 13		Characteristics: Polish women. Cases: Identified from the Szczecin Regional Cancer Registry. Controls: matched on age and place of residence	G3 = > 150	
			Multivariate adjusted OR (95%CI), pre- menopausal	
			<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.45 (0.14- 1.44) 	
			Multivariate adjusted OR (95%CI), post- menopausal	
			<ul style="list-style-type: none"> • G3 = 0.44 (0.14- 1.37) 	
			Trend $p = 0.42$	
			Multivariate adjusted OR (95%CI), post- menopausal	
			<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.60 (0.33- 1.09) • G3 = 0.31 (0.21- 0.70) 	
			Trend $p = 0.002$	

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

	To examine the relationship between LTPA and BC risk.	n = 822 (cases n = 257, control n = 565)	PA assessment: Questionnaire for LTPA (METs), divided into groups	Adjusted OR (95% CI)	The findings provide further support to the hypothesis that increased LTPA throughout life is associated with a decreased risk of BC.
Poland Case control D & B score = 13	• Sex: Women • Age: 35-93 yr		G1 = Low G2 = Medium G3 = High	• G1 = 1.00 (referent) • G2 = 0.57 (0.36- 0.89) • G3 = 0.22 (0.14- 0.35) Trend $p < 0.0001$	
Lahmann et al 2007 [327]	To examine the association of PA with pre- and post-menopausal BC risk.	• n = 218,169	Baseline and 6.4 year follow-up	3,423 cases of BC	Increasing PA reduces BC risk.
Europe (9 countries)	• Sex: Women			Multivariate adjusted HR (95% CI) by TPA, pre-menopausal	
Prospective cohort	• Age: 20-80			• Q1 = 1.00 (referent)	
D & B score = 12	• The European Prospective Investigation into Cancer and nutrition study		PA assessment: Interviews and questionnaire for TPA and recreational PA, each divided into quartiles	• Q2 = 1.02 (0.84- 1.24)	
			TPA Index	• Q3 = 0.84 (0.68- 1.04)	
			Q1 = Inactive	• Q4 = 1.02 (0.77- 1.36)	
			Q2 = Moderately inactive	Trend $p = 0.267$	
			Q3 = Moderately active	Multivariate adjusted HR (95% CI) by TPA, Post-menopausal	
			Q4 = Active	• Q1 = 1.00 (referent)	
			Recreational PA (MET hr/wk)	• Q2 = 0.89 (0.79- 1.00)	
			Q1 = <14	• Q3 = 0.84 (0.74- 0.96)	
			Q2 = 14-24	• Q4 = 0.92 (0.76- 1.12)	
			Q3 = 25-42	Trend $p = 0.06$	
			Q4 = >42	Multivariate adjusted HR (95% CI) by recreational PA, pre-menopausal	
			Cox proportional index	• Q1 = 1.00 (referent)	
				• Q2 = 0.91 (0.75- 1.10)	
				• Q3 = 0.95 (0.78- 1.14)	
				• Q4 = 0.94 (0.76- 1.15)	
				Trend $p = 0.580$	
				Multivariate adjusted HR (95% CI) by recreational PA, post-menopausal	

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

<p>Lee et al 2001 [328]</p>	<p>To examine the association between PA and BC risk.</p>	<p>• n = 39,322</p>	<p>Baseline and 4 year follow-up</p>	<p>411 cases of BC</p>	<p>The data suggest that PA during middle age and older is not uniformly associated with decreased BC risk. Among post-menopausal women only, higher levels of PA may decrease the risk of BC.</p>
<p>USA</p>	<p>• Sex: Women • Age: ≥ 45 yr</p>	<p>• Characteristics: Healthy women</p>	<p>PA assessment: Questionnaire</p>	<p>Multivariate adjusted RR (95% CI) by PA, all women</p>	<p>• Q1 = 1.00 (referent) • Q2 = 1.05 (0.94- 1.17) • Q3 = 0.92 (0.83- 1.03) • Q4 = 0.96 (0.85- 1.08) Trend $p = 0.176$</p>
<p>Prospective cohort</p>	<p>Women's Health Study</p>	<p>PA (kJ/wk), divided into quartiles</p>	<p>Q1 = <840 Q2 = 840-2519 Q3 = 2520-6299 Q4 = ≥ 6300</p>	<p>Multivariate adjusted RR (95% CI) by PA, post-menopausal only</p>	<p>• Q1 = 1.00 (referent) • Q2 = 1.04 (0.77- 1.40) • Q3 = 0.86 (0.64- 1.17) • Q4 = 0.80 (0.58- 1.12) Trend $p = 0.11$</p>
<p>D & B score = 12</p>	<p>VPA (kJ/wk), divided into quintiles</p>	<p>Q1 = none Q2 = 1-839 Q3 = 840-2099 Q4 = 2100-4199 Q5 = ≥ 4200</p>	<p>Proportional hazard regression</p>	<p>Multivariate adjusted RR (95% CI) by VPA, all women</p>	<p>• Q1 = 1.00 (referent) • Q2 = 0.97 (0.68- 1.39) • Q3 = 0.78 (0.54- 1.12) • Q4 = 0.67 (0.44- 1.02) Trend $p = 0.03$</p>
				<p>Multivariate adjusted RR (95% CI) by VPA, post-menopausal only</p>	<p>• Q1 = 1.00 (referent) • Q2 = 1.02 (0.70- 1.48) • Q3 = 1.11 (0.78- 1.58) • Q4 = 0.97 (0.66- 1.44) • Q5 = 0.98 (0.69- 1.40) Trend $p = 0.98$</p>
				<p>Multivariate adjusted RR (95% CI) by VPA, post-menopausal only</p>	<p>• Q1 = 1.00 (referent) • Q2 = 0.93 (0.57- 1.50)</p>

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

Magnusson et al 2005 [329]	To report the relationship between pre-menopausal BC, body fatness at age 10 years and in adulthood, and sports participation during puberty, late adolescence and early adulthood from three related case-control studies.	• n = 3,108 (1,560 cases; 1,548 controls)	PA assessment: Interview for sports participation (h/wk in the following age categories (12-14 yr, 16-18 yr, 20-30 yr, 12-30 yr, around age of diagnosis)	<ul style="list-style-type: none"> • Q3 = 0.91 (0.57- 1.47) • Q4 = 0.93 (0.57- 1.50) • Q5 = 0.76 (0.47- 1.24) 	An inverse association between body fatness but not PA at a young age and the risk of BC in pre-menopausal women.
UK	• Sex: Women	• Age: Study 1 = 36 yr, study 2 = 36-45 yr, study 3 = 46-54 yr	Sports participation (h/wk)	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.04 (0.93- 1.17) • G3 = 1.03 (0.93- 1.14) 	
Case control	• Characteristics: White women with no previous malignancy, mental handicap or illness		G1 = 0-1 G2 = 2-3 G3 = ≥ 4	<p>Trend $p = 0.95$</p> <p>Adjusted RR (95% CI), 16-18 yr</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.95 (0.83- 1.09) • G3 = 0.89 (0.79- 1.02) <p>Trend $p = 0.20$</p> <p>Adjusted RR (95% CI), 20-30 yr</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.90 (0.76- 1.08) • G3 = 1.01 (0.81- 1.26) <p>Trend $p = 0.73$</p> <p>Adjusted RR (95% CI), 12-30 yr</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.99 (0.89- 1.11) • G3 = 1.01 (0.88- 1.16) <p>Trend $p = 0.94$</p> <p>Adjusted RR (95% CI), around age of diagnosis</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.84 (0.71- 1.00) • G3 = 1.06 (0.86- 1.32) <p>Trend $p = 0.82$</p>	

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

Malin et al 2005 [330]	To evaluate a pattern of behavioral exposures indicating positive energy balance would be associated with increased BC risk.	• n = 3,015 (1,459 cases; 1,556 control) • Sex: Women • Age: Mean ~47 yr • Characteristics: Residents of urban Shanghai	PA assessment: Questionnaire for PA (MET hr/d/yr), divided into groups G1 = 0 G2 = 0.1-2.92 G3 = >2.92	OR (95% CI) • G1 = 1.86 (1.44- 2.41) • G2 = 1.33 (0.96- 1.83) • G3 = 1.00 (referent)	The study suggests that promotion of behavioral patterns that optimize energy balance maybe a viable option for BC prevention.
China Case control D & B score = 12		Shanghai Breast Cancer Study			
Margolis et al 2005 [331]	To study the association between PA and incident invasive BC.	• n = 99,504 • Sex: Women • Age: 30-49 (mean 41 yr)	Baseline and 9.1 year follow-up	1,166 cases of BC	No evidence of a protective effect of PA on BC risk was found.
Norway/Sweden Prospective cohort D & B score = 13		• The Norwegian- Swedish Women's Lifestyle and Health Study	PA assessment: Questionnaire for PA using a 5 point scale and for competitive PA (years of participation), each divided into groups PA level (5 point scale) G1 = None G2 = Low G3 = Moderate G4 = High G5 = Vigorous Competitive PA (years) G1 = None G2 = 1-4 G3 ≥ 5	Multivariate adjusted RR (95% CI) by PA level, at enrollment • G1 = 1.00 (referent) • G2 = 1.35 (0.96- 1.90) • G3 = 1.26 (0.91- 1.74) • G4 = 1.19 (0.85- 1.67) • G5 = 1.24 (0.85- 1.82) Trend $p = 0.85$ Multivariate adjusted RR (95% CI) by PA level, at age 30 • G1 = 1.00 (referent) • G2 = 1.03 (0.64- 1.66) • G3 = 1.16 (0.74- 1.81) • G4 = 1.06 (0.67- 1.68) • G5 = 1.20 (0.77- 1.95) Trend $p = 0.60$ Multivariate adjusted RR (95% CI) by PA level, at age 14 • G1 = 1.00 (referent) • G2 = 0.93 (0.62- 1.39) • G3 = 0.94 (0.65- 1.35) • G4 = 1.07 (0.73- 1.55) • G5 = 1.05 (0.72- 1.54) Trend $p = 0.14$	

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

<p>McTiernan et al 1996 [332]</p> <p>USA</p> <p>Case control</p> <p>D & B score = 13</p>	<p>To investigate the relationship between LTPA and BC.</p> <p>n = 1,029 (cases n = 537, controls n = 492)</p> <p>Sex: Women</p> <p>Age: 50-64</p>	<p>PA assessment: Questionnaire (Minnesota LTPA Questionnaire) for LTPA (hr/wk), divided into groups</p> <p>G1 = None</p> <p>G2 = 0.1-1.5</p> <p>G3 = 1.6-2.5</p> <p>G4 = 2.6-3.5</p> <p>G5 = 3.6-5.0</p> <p>G6 = >5</p> <p>Calculated categories of EE (total time x intensity code)</p> <p>G1 = Lowest</p> <p>G6 = Highest</p>	<p>Multivariate adjusted RR (95% CI) by years of competitive PA</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.21 (0.95- 1.54) • G3 = 0.95 (0.75- 1.19) <p>Trend $p = 0.96$</p> <p>Adjusted OR (95% CI) by LTPA during adulthood, all ages and menopausal status</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.1 (0.7-1.6) • G3 = 0.7 (0.4-1.1) • G4 = 0.7 (0.4-1.1) • G5 = 0.6 (0.4-0.9) • G6 = 1.1 (0.7-1.6) <p>Trend $p = 0.29$</p> <p>Adjusted OR (95% CI) by LTPA during adulthood, aged ≥ 55 yr, post-menopausal only</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.8 (0.5-1.3) • G3 = 0.5 (0.3-0.9) • G4 = 0.6 (0.4-1.1) • G5 = 0.4 (0.2-0.8) • G6 = 0.8 (0.5-1.3) <p>Trend $p = 0.03$</p> <p>Adjusted OR (95% CI) by category of total EE in adulthood, all ages and menopausal status</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.2 (0.8-2.0) • G3 = 0.9 (0.6-1.3) • G4 = 0.6 (0.4-0.9) • G5 = 0.9 (0.6-1.5) • G6 = 0.9 (0.6-1.4) <p>Trend $p = 0.25$</p>	<p>The results indicate a weak negative association between PA and risk of BC in middle-aged women.</p>
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Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

McTiernan et al 2003 [333]	To examine the association between current and past LTPA and incidence of BC in post-menopausal women.	• n = 74,171	Baseline and mean follow-up of 4.7 years	Adjusted OR (95% CI) by category of total EE in adulthood, aged ≥ 55 yr, post-menopausal only • G1 = 1.00 (referent) • G2 = 0.8 (0.4-1.4) • G3 = 0.7 (0.4-1.2) • G4 = 0.5 (0.3-0.8) • G5 = 0.8 (0.5-1.3) • G6 = 0.6 (0.4-1.0) Trend <i>p</i> = 0.009	Increased PA is associated with reduced risk for BC in post-menopausal women.
USA	• Sex: Women	• Age: 50-79	PA assessment: Questionnaire for TPA (MET hr/wk), moderate or strenuous PA (hr/wk) and strenuous PA (hr/wk), each divided into groups	Adjusted RR (95% CI) by TPA • G1 = 1.00 (referent) • G2 = 0.90 (0.77-1.07) • G3 = 0.82 (0.68-0.97) • G4 = 0.89 (0.76-1.00) • G5 = 0.83 (0.70-0.98) • G6 = 0.78 (0.62-1.00) Trend <i>p</i> = 0.03	Longer duration provides the most benefit however need not be strenuous.
Prospective cohort	• Characteristics: Women from the Women's Health Initiative Observational Study	• G1 = none • G2 = 0-5.0 • G3 = 5.1-10.0 • G4 = 10.1-20.0 • G5 = 20.1-40 • G6 = ≥ 40.0	Moderate or strenuous PA (hr/wk) G1 = none G2 = ≤ 1 G3 = 1.1-2.0 G4 = 2.1-3.0 G5 = 3.1-4.0 G6 = 4.1-7.0 G7 = >7.0	Adjusted RR (95% CI) by TPA, BMI ≤ 24.13 • G1 = 1.00 (referent) • G2 = 0.78 (0.57-1.10) • G3 = 0.70 (0.51-0.97) • G4 = 0.80 (0.60-1.10) • G5 = 0.68 (0.51-0.92) • G6 = 0.63 (0.43-0.93) Trend <i>p</i> = 0.03	
D & B score = 13		Strenuous PA (hr/wk) G1 = none G2 = ≤ 1.0		Adjusted RR (95% CI) by TPA, BMI 24.14-28.44 • G1 = referent	

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

<p>G3 = 1.1-2.0 G4 = 2.1-4.0 G5 = >4.0 Cox proportional hazard ratio</p>	<ul style="list-style-type: none"> • G2 = 0.72 (0.53-0.98) • G3 = 0.78 (0.57-1.10) • G4 = 0.77 (0.58-1.00) • G5 = 0.85 (0.64-1.10) • G6 = 0.78 (0.52-1.20) <p>Trend $p = 0.74$ Adjusted RR (95% CI) by TPA, BMI >28.44</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.10 (0.88-1.50) • G3 = 0.90 (0.67-1.20) • G4 = 1.00 (0.79-1.30) • G5 = 0.89 (0.65-1.20) • G6 = 0.94 (0.57-1.60) <p>Trend $p = 0.30$ Adjusted RR (95% CI) by current moderate or strenuous PA</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.92 (0.78-1.10) • G3 = 0.91 (0.79-1.10) • G4 = 0.94 (0.81-1.10) • G5 = 0.99 (0.83-1.20) • G6 = 0.91 (0.78-1.10) • G7 = 0.79 (0.63-0.99) <p>Trend $p = 0.12$ Adjusted RR (95% CI) by current strenuous PA</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.94 (0.80-1.10) • G3 = 0.95 (0.80-1.10) • G4 = 0.93 (0.78-1.10) • G5 = 0.91 (0.67-1.20) <p>Trend $p = 0.25$</p>	<p>1,673 cases of BC from the 40,318 included in the analysis (2,545 cases from total prior to exclusion) Adjusted HR (95% CI) by VPA</p>	<p>The results of the study suggest that BC risk may vary according to various combinations of the components of energy balance.</p>
<p>Navarro Silvera et al 2006 [334] Canada</p>	<p>To study the independent and combined associations of VPA, energy consumption and BMI with risk of subsequent BC.</p>	<p>Baseline and 164 year follow-up n = 40,318 in analysis (49613 prior to exclusion) Sex: Women</p>	<p>PA assessment: Questionnaire for VPA (min/d), divided into groups</p>

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

Prospective cohort D & B score = 13	<ul style="list-style-type: none"> • Age: 40-59 • Characteristics: Canadian women with no history of BC • National Breast Screening Study (NBSS) 	<p>G1 = none G2 = Any G3 = 0-30 G4 = 30-60 G5 > 60</p> <p>Cox proportional hazard ratio</p>	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.98 (0.85-1.13) • G3 = 1.06 (0.88-1.27) • G4 = 0.98 (0.83-1.16) • G5 = 0.93 (0.78-1.10) <p>Trend $p = 0.38$</p> <p>Adjusted HR (95% CI) by VPA, pre-menopausal</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.91 (0.75-1.10) • G3 = 1.02 (0.80-1.31) • G4 = 0.88 (0.70-1.11) • G5 = 0.87 (0.68-1.09) <p>Trend $p = 0.23$</p> <p>Adjusted HR (95% CI) by VPA, post-menopausal</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.06 (0.87-1.30) • G3 = 1.08 (0.81-1.42) • G4 = 1.11 (0.87-1.41) • G5 = 1.00 (0.78-1.29) <p>Trend $p = 0.96$</p>
Patel et al 2003 [335] USA Prospective cohort D & B score = 14	<ul style="list-style-type: none"> • n = 72,608 • Sex: Women • Age: 50-74 • Characteristics: Postmenopausal women • The American Cancer Society Cancer Prevention Study II (CPS-II) Nutritional Cohort 	<p>Baseline and 5 year follow-up</p> <p>PA assessment: Questionnaire for LTPA (METs hr/wk) at various times during life, divided into groups</p> <p>G1 = none G2 = 0.1-6.9 G3 = 7.0-17.5 G4 = 17.6-31.5 G5 = 31.6-42.0 G6 = >42.0</p>	<p>Adjusted RR (95% CI), LTPA at study entry</p> <ul style="list-style-type: none"> • G1 = 0.86 (0.70- 1.04) • G2 = 1.00 (referent) • G3 = 0.92 (0.81- 1.04) • G4 = 0.94 (0.81- 1.09) • G5 = 0.77 (0.56- 1.06) • G6 = 0.71 (0.49- 1.02) <p>The study shows a lower risk of post-menopausal BC is associated with regular PA.</p>

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

	LTPA at 10 years prior to study, calculated MET score and categorized into groups:	Trend $p = 0.08$ (among active women $p = 0.03$)
None		Adjusted RR (95% CI), LTPA at age 40 yr
Slight		• G1 = 1.03 (0.88- 1.21)
Moderate		• G2 = 1.00 (referent)
Heavy		• G3 = 1.05 (0.92- 1.20)
Cox proportional hazard ratio		• G4 = 1.01 (0.87-1.18)
		• G5 = 1.16 (0.92- 1.46)
		• G6 = 0.79 (0.61- 1.03)
		Trend $p = 0.31$ (among active women $p = 0.36$)
		Adjusted RR (95% CI), LTPA at 10 years prior to study entry
		• None = 0.80 (0.51- 1.25)
		• Slight = 1.00 (referent)
		• Moderate = 0.93 (0.83- 1.04)
		• Heavy = 0.87 (0.68- 1.13)
		Trend $p = 0.32$ (among active women, trend $p = 0.16$)
Patel et al 2003 [336]	To evaluate the association between lifetime LTPA and BC risk. $n = 1,183$ (cases $n = 616$) $n = 567$, controls $n = 616$)	Adjusted OR (95% CI)
USA		The findings suggest that PA may modify the risk of in situ BC particularly in women without a family history of BC.
Case control	PA assessment: Calendar reporting for lifetime exercise activity (MET h/wk), divided into groups	
D & B score = 14	G1 = None G2 = 0.0-3.0 G3 = 3.0-8.0 G4 = 8.0-16.0 G5 = 16.0-32.0 G6 = >32.0	• G1 = 1.00 (referent) • G2 = 0.70 (0.48- 1.03) • G3 = 0.65 (0.44- 0.96)
	Sex: Women Age: 35-64 Characteristics: White and Black women	• G4 = 0.61 (0.41- 0.92) • G5 = 0.63 (0.40- 0.98) • G6 = 0.65 (0.39- 1.08)
	Unconditional logistical regression	Trend $p = 0.27$ (among exercisers only $p = 0.81$)
Rintala et al 2002 [337]	To obtain an estimate of BC incidence in association with self-rated OPA. $n = 680,000$	17,986 cases of BC
	in 5 classes (1=low, 5=high)	The results support the hypothesis that OPA, if high enough, markedly reduced BC risk.

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

Finland Prospective cohort D & B score = 11	<ul style="list-style-type: none"> • Sex: Women • Age: Women born in 1930-1969 • Characteristics: Finish women 	Class 1 = Jobs sitting and light hand tasks Class 2 = Handling of heavier items (conveyor belt) Class 3 = Jobs involving body motion Class 4 = Jobs involving walking up stairs or long distances, bending and carrying Class 5 = Same as class 4 except heavy tasks were performed for most of the day Poisson regression models	Adjusted RR (95% CI), age 25-39 years <ul style="list-style-type: none"> • C1+2 = 1.00 (referent) • C3 = 0.99 (0.85- 1.17) • C4 = 0.90 (0.76- 1.07) • C5 = 0.68 (0.51- 1.93)
Rockhill et al 1998 [338] USA Prospective cohort D & B score = 12	<ul style="list-style-type: none"> • n = 372 • Sex: Women • Age: 25-42 • Characteristics: Nurses • The Nurses Health Study 	Baseline and 6 year follow-up PA assessment: Questionnaire for MVPA (h/wk) G1 = <1 G2 = 1.0-1.9 G3 = 2.0-3.9 G4 = 4.0-6.9 G5 = ≥ 7 Logistic regression	Trend Adjusted RR (95% CI), age ≥ 55 years <ul style="list-style-type: none"> • C1+2 = 1.00 (referent) • C3 = 1.02 (0.94- 1.11) • C4 = 0.99 (0.91- 1.09) • C5 = 0.84 (0.70- 1.00) Trend Adjusted RR (95% CI), age 40-54 years <ul style="list-style-type: none"> • C1+2 = 1.00 (referent) • C3 = 1.01 (0.96- 1.07) • C4 = 1.04 (0.98- 1.11) • C5 = 0.82 (0.71- 0.94)

The findings do not support a link between PA in late adolescence or in the recent past and BC risk among young adult women.

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

Slattery <i>et al</i> 2007 [339]	To evaluate the BC risk associated with TPA and VPA at ages 15, 30 and 50 years and the referent year prior to diagnosis/selection.	<ul style="list-style-type: none"> • n = 4,850 Non-Hispanic white; n = 3,128 (Cases n = 1,527 controls n = 1601); Hispanic American Indian: n = 1,722 (cases n = 798, controls n = 924) • Sex: Women • Age: <50 yr • Characteristics: Non- Hispanic white and Hispanic American Indian 	PA assessment: Questionnaire for TPA (activity score) and lifetime VPA (hr/wk)	1527 cases of BC (non-Hispanic white; 798 cases of BC (Hispanic American Indian)	The data suggest that PA is important in reducing risk of BC in non-Hispanic white and Hispanic American Indian women.
USA			TPA score	OR (95% CI) by TPA score, non-Hispanic white	
Case control			G1 = 0-3		
D & B score = 12			G2 = 4-6		
			G3 = 7-9	• G1 = 1.00 (referent)	
			G4 = 10-12	• G2 = 0.78 (0.52- 1.17)	
			Lifetime VPA	• G3 = 0.84 (0.57- 1.22)	
			G1 = None	• G4 = 0.70 (0.44- 1.12)	
			G2 = <1.0	Trend <i>p</i> = 0.26	
			G3 = 1.0-2.9	OR (95% CI) by TPA score, Hispanic American Indian	
			G4 = ≥ 3.0	• G1 = 1.00 (referent)	
			Multivariable logistic regression	• G2 = 1.49 (0.98- 2.26)	
				• G3 = 1.21 (0.80- 1.84)	
				• G4 = 0.97 (0.53- 1.76)	
				Trend <i>p</i> = 0.90	
				OR (95% CI) by lifetime VPA, non-Hispanic white	
				• G1 = 1.00 (referent)	
				• G2 = 0.66 (0.36- 1.23)	
				• G3 = 0.73 (0.40- 1.34)	
				• G4 = 0.69 (0.37- 1.27)	
				Trend <i>p</i> = 0.68	
				OR (95% CI) by lifetime VPA, Hispanic American Indian	
				• G1 = 1.00 (referent)	
				• G2 = 1.15 (0.67- 1.96)	
				• G3 = 1.19 (0.70- 2.03)	
				• G4 = 1.09 (0.62- 1.90)	
				Trend <i>p</i> = 0.84	
Sprague <i>et al</i> 2007 [340]	To investigate the relationship between L.TPA and strenuous OPA and BC risk.	<ul style="list-style-type: none"> • n = 15,710 (1,689 cases in situ; 6,391 invasive and 7,630 controls) • Sex: Women • Age: 20-69 	PA assessment: Questionnaire for lifetime TPA (hr/wk and MET hr/wk), divided into groups	Adjusted OR (95% CI) for in situ BC by lifetime TPA (hr/wk)	The results provide further evidence that for most women, PA may reduce the risk of invasive BC.
USA			Lifetime total PA (hr/wk)	• G1 = 1.00 (referent)	
Case control			G1 = 0	• G2 = 0.92 (0.72-1.19)	

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

D & B score = 13	The Collaborative Breast Cancer Study	G2 = 0.1-15.0	G3 = 0.83 (0.62-1.13)
		G3 = 15.1-30.0	G4 = 0.86 (0.59- 1.24)
		G4 = > 300	Trend $p = 0.22$
		MET hr/wk	Adjusted OR (95% CI) for in situ BC by lifetime TPA (MET hr/wk)
		G1 = 0.0	• G1 = 1.00 (referent)
		G2 = 0.1-62.5	• G2 = 0.93 (0.72- 1.20)
		G3 = 62.6-125.0	• G3 = 0.82 (0.61- 1.10)
		G4 = > 125.0	• G4 = 0.82 (0.57- 1.17)
			Trend $p = 0.10$
			Adjusted OR (95% CI) for invasive BC by lifetime TPA (hr/wk)
			• G1 = 1.00 (referent)
			• G2 = 0.88 (0.76- 1.03)
			• G3 = 0.87 (0.73- 1.05)
			• G4 = 0.85 (0.67- 1.07)
			Trend $p = 0.22$
			Adjusted OR (95% CI) for invasive BC by lifetime TPA (MET hr/wk)
			• G1 = 1.00 (referent)
			• G2 = 0.89 (0.76- 1.04)
			• G3 = 0.82 (0.68- 0.99)
			• G4 = 0.88 (0.71- 1.09)
			Trend $p = 0.12$
Steindorf et al 2003 [34]	To clarify the relationship between PA and BC risk.	n = 1,246 (360 cases; 886 controls)	360 cases of BC
Germany	Sex: Women	PA assessment: Computer assisted telephone interview for TPA (MET hr/wk) at various ages	The data do not suggest an inverse association between PA and BC risk in pre-menopausal women.
Case control	Age: Mean. cases 41.9 yr; controls 42.5 yr	TPA at age 12-19 yr	Multivariate adjusted OR (95% CI) by TPA at age 12-19 yr
D & B score = 13		G1 = 13.0-55.7	• G1 = 1.00 (referent)
		G2 = 55.8-88.7	• G2 = 1.07 (0.75- 1.52)
		G3 = 88.8-134.0	• G3 = 1.00 (0.70- 1.42)
		G4 = 134.1-695.9	• G4 = 0.73 (0.50- 1.07)
		TPA at age 20-30 yr	Trend $p = 0.44$

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

Tehard et al 2006 [342]	To investigate the type, duration, frequency and intensity of PA required to reduce the risk of BC.	France
G1 = 6.4-69.0	n = 90,509	Multivariate adjusted OR (95% CI) by TPA at age 20-30 yr
G2 = 69.1-109.0	Sex: Women	• G1 = 1.00 (referent)
G3 = 109.1-160.4	Age: 40-65	• G2 = 0.95 (0.67- 1.37)
G4 = 160.5-728.8	Characteristics: French women insured with Mutuelle Generale de l'Education Nationale	• G3 = 0.85 (0.59- 1.23)
TPA at age 12-30 yr (both)	E3N Cohort Study	• G4 = 0.96 (0.67- 1.39)
G1 = 17.2-70.4	Total recreational PA (MET hr/wk)	Trend $p = 0.32$
G2 = 70.5-104.0	G1 = Inactive	Multivariate adjusted OR (95% CI) by TPA at age 12-30 yr
G3 = 104.1-145.5	G2 = <16.0	• G1 = 1.00 (referent)
G4 = 145.6-564.4	G3 = 16.0-22.3	• G2 = 0.97 (0.68- 1.38)
Logistic regression	G4 = 22.3-33.8	• G3 = 0.68 (0.46- 0.99)
G4 = 0.94 (0.65- 1.35)	G5 = ≥33.8 = 0.81	G4 = 0.94 (0.65- 1.35)
Trend $p = 0.29$	Walking (min/d)	Trend $p = 0.29$
3,424 cases of BC	G1 = <500	BC risk was reduced, especially with VPA.
Multivariate adjusted RR (95% CI) by TPA	G2 = 500-2000	Multivariate adjusted RR (95% CI) by walking duration
• G1 = 1.00 (referent)	G1 = 1.00 (referent)	• G1 = 1.00 (referent)
• G2 = 1.05 (0.93- 1.17)	G2 = 0.82 (0.71- 0.93)	• G2 = 0.82 (0.71- 0.93)
• G3 = 0.94 (0.83- 1.05)	G3 = 0.94 (0.84- 1.06)	• G3 = 0.94 (0.84- 1.06)
• G4 = 0.90 (0.80- 1.02)	G4 = 0.88 (0.79- 0.98)	• G4 = 0.88 (0.79- 0.98)
Trend $p < 0.05$	G5 = 0.81 (0.72- 0.92)	• G5 = 0.81 (0.72- 0.92)
Multivariate adjusted RR (95% CI) by total recreational PA	Trend $p < 0.01$	Trend $p < 0.01$
• G1 = 1.00 (referent)	Multivariate adjusted RR (95% CI) by walking duration	Multivariate adjusted RR (95% CI) by walking duration
• G2 = 0.82 (0.71- 0.93)	• G1 = 1.00 (referent)	• G1 = 1.00 (referent)
• G3 = 0.94 (0.84- 1.06)	• G2 = 1.03 (0.95- 1.11)	• G2 = 1.03 (0.95- 1.11)
• G4 = 0.88 (0.79- 0.98)		
• G5 = 0.81 (0.72- 0.92)		

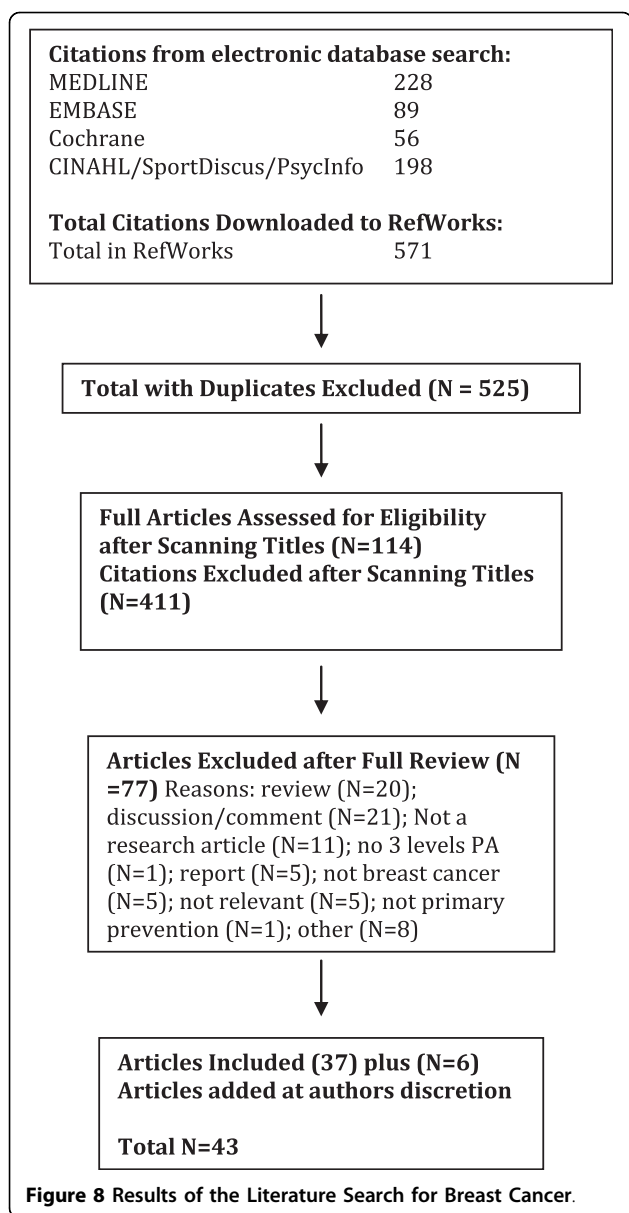
Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

<p>G3 = >2000 MPA (hr/wk) G1 = Inactive G2 = 0 G3 = 1-4 G4 = 5-13 G5 = 14 VPA (hr/wk) G1 = Inactive G2 = 0 G3 = 1-2 G4 = 3-4 G5 = 5 Cox proportional hazard ratio</p>	<p>G3 = 0.91 (0.81- 1.02) Trend $p = 0.45$ Multivariate adjusted RR (95% CI) by MPA • G1 = 1.00 (referent) • G2 = 0.80 (0.60- 1.05) • G3 = 0.87 (0.79- 0.94) • G4 = 0.86 (0.74- 0.99) • G5 = 0.89 (0.65- 1.24) Trend $p < 0.01$ Multivariate adjusted RR (95% CI) by VPA • G1 = 1.00 (referent) • G2 = 0.90 (0.81- 0.99) • G3 = 0.88 (0.79- 0.97) • G4 = 0.82 (0.71- 0.95) • G5 = 0.62 (0.49- 0.78) Trend $p < 0.0001$</p>	<p>• G3 = 0.91 (0.81- 1.02) Trend $p = 0.45$ Multivariate adjusted RR (95% CI) by MPA • G1 = 1.00 (referent) • G2 = 0.80 (0.60- 1.05) • G3 = 0.87 (0.79- 0.94) • G4 = 0.86 (0.74- 0.99) • G5 = 0.89 (0.65- 1.24) Trend $p < 0.01$ Multivariate adjusted RR (95% CI) by VPA • G1 = 1.00 (referent) • G2 = 0.90 (0.81- 0.99) • G3 = 0.88 (0.79- 0.97) • G4 = 0.82 (0.71- 0.95) • G5 = 0.62 (0.49- 0.78) Trend $p < 0.0001$</p>
<p>Thune et al 1997 [343] Norway Prospective cohort D & B score = 14</p>	<p>To investigate whether everyday exercise is related to the risk of BC. • n = 25,624 • Sex: Women • Age: 20-54</p>	<p>Baseline and mean follow-up of 14 years PA assessment: Self-reported LTPA and OPA, divided into groups LTPA G1 = Sedentary G2 = Moderate G3 = Regular exercise OPA G1 = Sedentary G2 = Walking G3 = Lifting G4 = Heavy manual labor During work Pre-menopausal G1 = Sedentary G2 = Walking G3 = Lifting or heavy manual labor</p>
<p>LTPA and OPA are associated with a reduced risk of BC.</p>	<p>Adjusted RR (95% CI) by LTPA • G1 = 1.00 (referent) • G2 = 0.93 (0.71- 1.22) Trend $p = 0.04$ Adjusted RR (95% CI) by LTPA, pre- menopausal • G1 = 1.00 (referent) • G2 = 0.77 (0.46- 1.27) • G3 = 0.53 (0.25- 1.14) Trend $p = 0.10$ Adjusted RR (95% CI) by LTPA, post- menopausal • G1 = 1.00 (referent) • G2 = 1.00 (0.72- 1.39) • G3 = 0.67 (0.41- 1.10) Trend $p = 0.15$ Adjusted RR (95% CI) by OPA</p>	<p>LTPA and OPA are associated with a reduced risk of BC. Adjusted RR (95% CI) by LTPA • G1 = 1.00 (referent) • G2 = 0.93 (0.71- 1.22) Trend $p = 0.04$ Adjusted RR (95% CI) by LTPA, pre- menopausal • G1 = 1.00 (referent) • G2 = 0.77 (0.46- 1.27) • G3 = 0.53 (0.25- 1.14) Trend $p = 0.10$ Adjusted RR (95% CI) by LTPA, post- menopausal • G1 = 1.00 (referent) • G2 = 1.00 (0.72- 1.39) • G3 = 0.67 (0.41- 1.10) Trend $p = 0.15$ Adjusted RR (95% CI) by OPA</p>

Table 16: Studies examining the relationship between physical activity and breast cancer. (Continued)

<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.84 (0.63- 1.12) • G3 = 0.74 (0.52- 1.06) • G4 = 0.48 (0.25- 0.92) <p>Trend $p = 0.02$</p> <p>Adjusted RR (95% CI) by OPA, pre- menopausal</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.82 (0.50- 1.34) • G3 = 0.48 (0.24- 0.95) <p>Trend $p = 0.03$</p> <p>Adjusted RR (95% CI) by OPA, post- menopausal</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.87 (0.61- 1.24) • G3 = 0.78 (0.52- 1.18) <p>Trend $p = 0.24$</p>				
<p>Women with low OPA had an increased risk of BC; the incidence of BC was reduced in women with high-activity jobs.</p>				
<p>Standardized incidence ratios</p> <ul style="list-style-type: none"> • G1= 131 • G2 = 95 • G3 = 79 				
<p>PA assessment: Interview for OPA, divided into groups</p> <p>G1 = Low G2 = Moderate G3 = High</p>				
<p>Women with low OPA had an increased risk of BC; the incidence of BC was reduced in women with high-activity jobs.</p>				
<p>Standardized incidence ratios</p> <ul style="list-style-type: none"> • G1= 131 • G2 = 95 • G3 = 79 				

D & B score, Downs and Black quality score; YR, years; PA, physical activity; BC, breast cancer; LTPA, leisure-time physical activity; g, group; HR, hazard ratio; RR, risk ratio; OR, odds ratio; 95% CI, confidence interval; T, tertile; MET, metabolic equivalent; MET/wk, metabolic equivalent per week; OPA, occupational physical activity; MET h/wk/yr, metabolic equivalent per hour per week per year; kcal/wk, kilocalories per week; TPA, total physical activity; VPA, vigorous physical activity.



relationship in one or more measures of occupational and/or leisure-time physical activity and the risk for breast cancer. Moreover, the majority of studies demonstrated the greatest risk reduction at the highest activity level. With respect to the minimal and optimal volume of exercise required, Lee [105] stated that 30-60 min/day of moderate-to-vigorous physical activity is required to decrease the risk for breast cancer. This belief is strongly supported by the literature. However, others have shown significant risk reductions at lower exercise volumes. For instance, Rockhill et al. [106] showed significant reductions (12% or greater) in the risk for breast cancer in women who accumulated at least 1 hr of moderate or vigorous physical activity per week.

Similarly, Sesso et al. (1998) revealed that there was an 8% reduction in the risk for breast cancer with a relatively small energy expenditure of 500-999 kcal/wk. Further risk reductions were observed with higher energy expenditures (= 1000 kcal/wk = 51% reduction in the risk). As discussed above, Monninkhof et al. revealed a 6% decrease in breast cancer risk for each additional hour of physical activity per week [104]. Taken as a whole, it would therefore appear that Canada's guidelines for physical activity are more than appropriate for reducing the risk for breast cancer. Further research however is required to determine the minimal volume of exercise that is effective in the primary prevention of breast cancer.

Implications

There is a preponderance of data linking physical inactivity to site-specific cancers, particularly of the breast and colon [31,104-109]. The protective effects of physical activity also appear with other forms of cancer (such as endometrial cancer) [110]. In an important review of the literature Lee revealed that physically active women have a 20-30% lower risk of breast cancer, and physically active men and women have a 30-40% lower risk of colon cancer [105]. A more recent systematic review of the literature revealed a 20-80% lower risk of breast cancer in post-menopausal women [104], with a weaker association in pre-menopausal women. Considering data from both pre- and post-menopausal women the authors demonstrated that physically active individuals had a 15-20% lower risk of breast cancer. Monninkhof et al. also reported a 6% lower risk of breast cancer for each additional hour of physical activity per week [104]. This level of risk reduction was also supported by the U.S. Department of Health and Human Services during its recent evaluation of the literature [31].

Our current reviews of the literature support previous work in the field including the finding of a dose-response relationship between physical activity and cancers of the breast and colon [104,105,109]. It would appear that 30-60 min/day of moderate-to-vigorous physical activity is associated with a lower risk of breast and colon cancer.

Recommendation #5

For a reduced risk for site specific cancers (such as colon cancer and breast cancer), it is recommended that individuals should participate in 30 min or more of moderate to vigorous exercise on most days of the week. [Level 2, Grade A]

Primary Prevention of Type 2 Diabetes

In comparison to other chronic conditions, there is relatively limited literature examining the relationship between multiple levels of physical activity/fitness and the incidence of type 2 diabetes. All of the literature

examining the dose-response (for at least three levels of physical activity/fitness) involved prospective cohort analyses. A total of 3655 citations were identified during the electronic database search (Figure 9). Of these citations, 2038 were identified in MEDLINE, 1116 in EMBASE, 118 in Cochrane, and 372 in the CINAHL/SportDiscus/PsychInfo search. A total of 614 duplicates were found, leaving a total of 3041 unique citations. A total of 2865 articles were excluded after scanning, leaving a total of 176 articles for full review. From these articles 156 were excluded after full review leaving 20

articles for inclusion in the systematic review of the literature regarding the relationship between physical activity and type 2 diabetes. The reasons for exclusion included non-experimental/weak design (N = 18), three levels of physical activity not reported (N = 16), reviews, summaries, or meta-analyses (N = 41), not related to type 2 diabetes (N = 71), and other (N = 10).

As shown in Table 17, 20 investigations examined the dose-response (i.e., three or more levels) relationship between physical activity and the incidence of type 2 diabetes. This involved a total of 624,952 subjects, averaging 32,892 subjects per study (range 1,543-87,907). There were a total of 19,325 cases of type 2 diabetes (ranging per study from 78-4,030). The total length of follow-up averaged 9.3 yr (ranging from 3 -16.8 yr). The articles were published over a 16 yr period ranging from 1991 to 2007.

Of these studies 100% revealed an inverse relationship between type 2 diabetes and levels of physical activity or fitness. When comparing the most active/fit group versus the least active/fit group we found an average risk reduction of 42% (median = 44%). Therefore in our analyses the most physically active/fit had a 42% lower risk of developing type 2 diabetes. The majority (84%) of these studies revealed incremental reductions in the risk for type 2 diabetes with increasing activity/fitness levels. Therefore, the health benefits with respect to type 2 diabetes prevention appear to continue across the physical activity/fitness continuum. Similar to other clinical conditions, the dose-response relationship is such that small changes in activity levels yield marked reductions in the risk for type 2 diabetes. The health benefits of exercise appear to be particularly prevalent in individuals at high risk for developing type 2 diabetes (e.g., those with a high body mass index, the metabolic syndrome, a history of hypertension and/or a family history of type 2 diabetes). *The level of evidence relating physical activity to the primary prevention of type 2 diabetes would be considered to be Level 2A.* The quality of the investigations was generally high with a mean (and median) Downs and Black score of 13 (range 11-14).

As with other conditions it is difficult to separate the effects of volume and intensity of exercise. However, small changes in activity levels clearly can have a large effect on the risk for and incidence of type 2 diabetes. For instance, Hu and coworkers [111] revealed that nurses (n = 68,497) who engaged in 1 hr/day of brisk walking had 24% less obesity and 34% less type 2 diabetes (over a 6-year follow-up). These authors estimated that approximately 30% of new cases of obesity and 43% of new cases of type 2 diabetes could be prevented by adopting an active lifestyle including less than 10 hr/wk of television watching and ≥ 30 min/d of brisk walking. Similarly, over a 5-year period, male physicians who

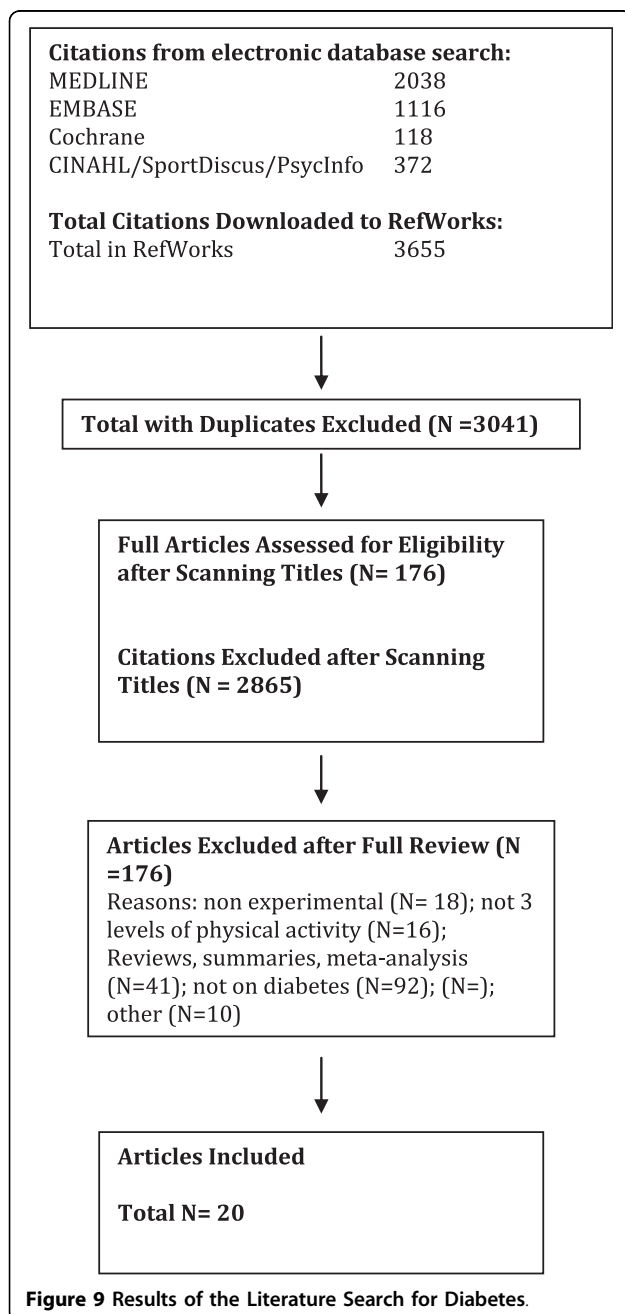


Table 17 The relationship between physical activity and the development of type 2 diabetes.

Publication Country Study Design Quality Score	Objective	Population	Methods	Outcome	Comments and Conclusions
Haapanen et al 1997 [77]	To examine the association of PA and the risk of CHD, hypertension and T2D.	<ul style="list-style-type: none"> n = 1,340 men, 1,500 women Age: 35-63 yr 	10 yr follow-up	Number of cases: 118	LTPA has a preventative effect on T2D.
Finland			PA assessment: Self-reported LTPA (kcal/wk), divided into groups	Age-adjusted RR (95% CI), men <ul style="list-style-type: none"> G1 = 1.54 (0.83-2.84) G2 = 1.21 (0.63-2.31) G3 = 1.00 (referent) 	
Prospective cohort				$p = 0.374$	
D & B score = 14			Men G1 = 0-1100 G2 = 1101-1900 G3 = >1900 Women (kcal/wk) G1 = 0-900 G2 = 901-1500 G3 = >1500 Cox proportional HR	Age-adjusted RR (95% CI), women <ul style="list-style-type: none"> G1 = 2.64 (1.28-5.44) G2 = 1.17 (0.50-2.70) G3 = 1.00 (referent) $p < 0.006$	
Hu et al 2003 [111]	To examine the relationship between sedentary behaviours (particularly prolonged television watching) and risk of obesity and T2D in women.	<ul style="list-style-type: none"> n = 68,497 (diabetes specific analyses) 	6 yr follow-up	Number of cases: 1515	Sedentary behaviours (especially television watching) are associated with an increased risk for obesity and T2D.
USA			PA assessment: Self-reported PA and sedentary behaviour	Each 2-h/d increment in TV watching was associated with a 23% (95% CI, 17%-30%) increase in obesity and a 14% (95% CI, 5%- 23%) increase in risk of T2D	
Prospective cohort			Outcome measure: onset of obesity and T2D	Each 2-h/d increment in sitting at work was associated with a 5% (95% CI, 0%-10%) increase in obesity and a 7% (95% CI, 0%- 16%) increase in T2D	Light to moderate PA was associated with a significantly lower risk for obesity and T2D.
D & B score = 13			Multivariate analyses adjusting for age, smoking, dietary factors, and other covariates	Standing or walking around at home (2 h/d) was associated with a 9% (95% CI, 6%-12%) reduction in obesity and a 12% (95% CI, 7%- 16%) reduction in T2D	

Table 17: The relationship between physical activity and the development of type 2 diabetes. (Continued)

<p>• Characteristics:</p> <p>Free of T2D, CVD, or cancer at baseline</p> <p>• Nurses' Health Study</p>	<p>Each 1 hour per day of brisk walking was associated with a 24% (95% CI, 19%-29%) reduction in obesity and a 34% (95% CI, 27%- 41%) reduction in T2D</p>	
<p>Manson et al 1992 [112]</p> <p>To examine the association between regular exercise and the subsequent development of T2D.</p> <p>• n = 21,271</p> <p>• Sex: Men</p> <p>• Age: 40-84 yr</p> <p>• Characteristics:</p> <p>Free of diagnosed diabetes, CVD and cancer at baseline</p>	<p>5 yr follow-up</p> <p>PA assessment: Questionnaire Fpr VPA (enough to develop sweat)</p> <p>The age-adjusted incidence of T2D:</p> <ul style="list-style-type: none"> • 369 cases per 100,000 person- years in men who engaged in VPA less than once weekly • 214 cases per 100,000 person- years in those exercising at least five times per week (p trend < 0.001) 	<p>Number of cases: 285</p> <p>Exercise appears to reduce the development of T2D even after adjusting for BMI.</p>
<p>USA</p> <p>Prospective cohort</p> <p>D & B score = 14</p>	<p>Exercise frequency (times/wk)</p> <p>G1 = < Weekly</p> <p>G2 = At least weekly</p> <p>Times per week</p> <p>G1 = 0</p> <p>G2 = 1</p> <p>G3 = 2-4</p> <p>G4 = >5</p> <p>Outcome measure: Incidence T2D</p>	<p>Age-adjusted RR (95% CI) by exercise frequency</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.64 (0.51- 0.82) <p>Age-adjusted RR (95% CI) by exercise frequency</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.77 (0.55-1.07) • G3 = 0.62 (0.46-0.82) • G4 = 0.58 (0.40-0.84) <p>Age- and BMI-adjusted RR (95% CI) by exercise frequency</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent)

Table 17: The relationship between physical activity and the development of type 2 diabetes. (Continued)

<p>Hu et al. 2001 [114]</p> <p>USA</p> <p>Retrospective cohort</p> <p>D & B score = 13</p>	<p>To examine the relationship between dietary and lifestyle factors in relation to the risk for T2D.</p> <p>• n = 84,941</p> <p>• Sex: Women</p> <p>• Age: 40-75 yr</p> <p>• Characteristics: participants had no history of diabetes, CVD, or cancer.</p>	<p>16 yr follow-up</p> <p>PA assessment: Questionnaire For PA (h/wk), divided into groups</p> <p>Q1 = <0.5 Q2 = 0.5-1.9 Q3 = 2.0-3.9 Q4 = 4.0-6.9 Q5 = ≥7.0</p> <p>Outcome measure: Incidence of T2D Cox regression</p>	<p>Number of cases: 3300</p> <p>Multivariate-adjusted RR (95%)</p> <p>• Q1 = 1.00 (referent)</p> <p>• Q2 = 0.89 (0.77-1.02)</p> <p>• Q3 = 0.87 (0.75-1.00)</p> <p>• Q4 = 0.83 (0.71-0.96)</p> <p>• Q5 = 0.71 (0.56-0.90)</p>	<p>The majority of T2D could be prevented through healthy living.</p>
<p>Sato et al 2007 [116]</p> <p>Japan</p> <p>Prospective cohort</p>	<p>To examine the relationship between walking to work and the development of T2D.</p> <p>• n = 8,576</p> <p>• Sex: Men</p> <p>• Age: 40-55 yr</p> <p>• Kansai Healthcare Study</p>	<p>4 yr follow-up</p> <p>PA assessment: For time spent walking to work, divided into tertiles</p> <p>T1 = 0-10 min T2 = 11-20 min T3 = ≥20 min</p>	<p>Number of cases: 878</p> <p>OR (95% CI)</p> <p>• T1 = 1.00 (referent)</p> <p>• T2 = 0.86 (0.70-1.06)</p> <p>• T3 = 0.73 (0.58-0.92)</p> <p>Significant difference was seen between ≤ 10 min and ≤ 20 min only (p = 0.0007)</p>	<p>The duration of a walk to work is an independent predictor of the risk for T2D.</p>

• G2 = 0.71 (0.56- 0.91)
 Age- and BMI-adjusted RR (95% CI) by exercise frequency
 • G1 = 1.00 (referent)
 • G2 = 0.78 (0.56-1.09)
 • G3 = 0.68 (0.51-0.90)
 • G4 = 0.71 (0.49-1.03)

Table 17: The relationship between physical activity and the development of type 2 diabetes. (Continued)

D & B score = 14	
	Outcome measure: Incidence of T2D
Hu G et al 2003 [117]	<p>PA assessment: Questionnaire For OPA, LTPA and commuting PA</p> <p>Multivariate adjusted HR (95% CI) for OPA, men</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.67 (0.44-1.01) • G3 = 0.73 (0.52-1.02) <p>Moderate and high OPA, commuting PA or LTPA significantly reduces risk of T2D in middle aged adults.</p>
Finland	<p>PA assessment: Questionnaire For OPA, LTPA and commuting PA</p> <p>Multivariate adjusted HR (95% CI) for OPA, women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.72 (0.46-1.12) • G3 = 0.78 (0.52-1.18) <p>Multivariate adjusted HR (95% CI) for OPA, women</p>
Prospective cohort	<p>PA assessment: Questionnaire For OPA, LTPA and commuting PA</p> <p>Multivariate adjusted HR (95% CI) for OPA, men and women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.70 (0.52-0.96) • G3 = 0.74 (0.57-0.95) <p>Multivariate adjusted HR (95% CI) for commuting PA, men</p>
D & B score = 12	<p>PA assessment: Questionnaire For OPA, LTPA and commuting PA</p> <p>Multivariate adjusted HR (95% CI) for commuting PA, women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 1.00 (0.71-1.42) • G3 = 0.75 (0.46-1.23) <p>Multivariate adjusted HR (95% CI) for commuting PA, women</p>

Table 17: The relationship between physical activity and the development of type 2 diabetes. (Continued)

	<ul style="list-style-type: none"> • G3 = 0.57 (0.34-0.96) <p>Multivariate adjusted HR (95% CI) for commuting PA, men and women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.96 (0.74-1.25) • G3 = 0.64 (0.45-0.92) <p>Multivariate adjusted HR (95% CI) for LTPA, men</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.78 (0.57-1.06) • G3 = 0.84 (0.52-1.37) <p>Multivariate adjusted HR (95% CI) for LTPA, women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.81 (0.58-1.15) • G3 = 0.85 (0.43 -1.66) <p>Multivariate adjusted HR (95% CI) for LTPA, men and women</p> <ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.81 (0.64-1.20) • G3 = 0.84 (0.57-1.25) 	
<p>Hsia et al 2005 [118] USA</p>	<p>To evaluate the relationship between PA and the incidence of T2D in a large, diverse group of older women.</p> <p>• n = 87,907</p> <p>PA assessment: Questionnaire for frequency and duration of 4 walking speeds and 3 other activities classified by intensity (light, moderate, strenuous)</p> <p>• Sex: Women</p> <ul style="list-style-type: none"> • Age: White 63.8 ± 7.3, African American 61.9 ± 7.3, Hispanic 60.5 ± 7.1, Asian/Pacific Islander 63.7 ± 7.6, American Indian 61.5 ± 8.0 	<p>Number of cases: 2,271</p> <p>There is a strong inverse relationship between PA and T2D. There is a stronger relationship between PA and T2D in Caucasian women than in minority women. This may be explained by less precise risk estimates in minority women.</p>
<p>Prospective cohort</p>	<p>Multivariate adjusted HR (95% CI) by walking, Caucasian</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.85 (0.74-0.87) • Q3 = 0.87 (0.75-1.01) • Q4 = 0.75 (0.64-0.89) • Q5 = 0.74, (0.62-0.89) <p>Trend $p < 0.001$</p> <p>Q1 = Low Q2 = Q3 =</p>	
<p>D & B score = 11</p>		

Table 17: The relationship between physical activity and the development of type 2 diabetes. (Continued)

	Q4 =	Multivariate adjusted HR (95% CI) by TPA, Caucasian
	Q5 = High	• Q1 = 1.00 (referent)
	<ul style="list-style-type: none"> • Ethnicity: White n = 74,240; African American n = 6,465; Hispanic n = 3,231; Asian/Pacific Islander 2,445; American Indian n = 327 	<ul style="list-style-type: none"> • Q2 = 0.88 (0.76- 1.01) • Q3 = 0.74 (0.64- 0.87) • Q4 = 0.80 (0.68- 0.94) • Q5 = 0.67 (0.56- 0.81) Trend $p = 0.002$
	Cox proportional HR	
	<ul style="list-style-type: none"> • Characteristics: participants had no history of diabetes, were not on any antidiabetic medications • Women's Health Initiative 	
Wannamethee et al 2000 [120]	To examine the role of components of the insulin resistance syndrome in the relationship between PA and the incidence of T2D and CHD.	Number of cases: 196
England, Wales and Scotland	<ul style="list-style-type: none"> • Sex: Men • Age: 40-59 yr • Characteristics: No history of heart disease, diabetes or stroke 	Multivariate adjusted RR (95% CI) Q1 = 1.00 (referent) Q2 = 0.66 (0.42-1.02) Q3 = 0.65 (0.41-1.03) Q4 = 0.48 (0.28-0.83) Q5 = 0.46 (0.27-0.79) $p < 0.005$
Prospective cohort	PA assessment: Questionnaire for TPA Physical activity groups were identified and scored: Q1 = None Q2 = Occasional Q3 = Light Q4 = Moderate	
D & B score = 14		The relationship between PA and T2D appears to be mediated by serum insulin and components of the insulin resistance syndrome. However, these factors do not appear to explain the inverse relationship between PA and T2D.

Table 17: The relationship between physical activity and the development of type 2 diabetes. (Continued)

	<p>Q5 = Moderately vigorous/vigorous</p> <p>The men were classified according to current smoking status, alcohol consumption, and social class</p> <p>Cox proportional HR</p>	<p>MPA (sporting activity once a week or frequent lighter- intensity activities such as walking, gardening, do-it yourself projects) are sufficient to produce a significant reduction in risk of both CHD and T2D.</p>
<p>Manson et al 1991 [121]</p> <p>USA</p> <p>Prospective cohort</p> <p>D & B score = 13</p>	<p>To examine the association between regular VPA and the incidence of T2D.</p> <ul style="list-style-type: none"> • n = 87,253 • Sex: Women • Age: 34-59 yr • Characteristics: Free of diagnosed diabetes, cardiovascular disease and cancer <p>PA assessment: Questionnaire</p> <p>Frequency of weekly exercise (0-++4)</p> <p>8 yr follow-up</p>	<p>Number of cases: 1303 Women who engage in VPA at least once per week had reduced adjusted RR of T2D RR = 0.66 (0.6- 0.75)</p> <p>PA is promising in the primary prevention of T2D.</p> <p>The reduction in risk remained significant after adjustment for BMI RR = 0.84 (0.75-0.95)</p> <p>When analysis was restricted to the first 2 years after ascertainment of PA level and to symptomatic disease as the outcome, the age- adjusted RR of those who exercised was 0.50, and age and body-mass index adjusted RR was 0.69 (0.48-1.0)</p> <p>Analysis also restricted to the first 2 yr after the assessment of PA level and to symptomatic diabetes</p> <p>Multivariate adjustments for age, body-mass index, family history of diabetes, and other variables did not alter the reduced risk found with exercise</p> <p>Multivariate analysis</p> <p>Family history of diabetes did not modify the effect of exercise, and risk reduction with exercise was evident among both obese and non-obese women</p>

Table 17: The relationship between physical activity and the development of type 2 diabetes. (Continued)

Helmrich et al 1994 [122]	To examine the relationship between PA and the development of T2D.	n = 5,990	98,524 man-years of follow-up (1962-1976)	Number of cases: 202	Increased PA is effective in preventing T2D.
USA	Sex: Men Age: 39-68 yr Characteristics: healthy, asymptomatic	PA assessment: Questionnaire for LTPA (walking, stair climbing, sports etc; kcal/wk) Blocks walked/day	RR (95% CI) by blocks walked per day	• T1 = 1.00 (referent) • T2 = 1.30	The protective benefit is especially pronounced in those individuals who have the highest risk of disease.
Further review of the data reported by Helmich et al. 1991	University of Pennsylvania Alumni Health Study	LTPA (kcal/wk) kcal were assigned to each activity and added together	p = 0.80 LTPA was inversely related to development of T2D	• T3 = 0.92	
Prospective cohort		Lowest < 500 Highest ≥ 3500 Blocks walked/day T1 = <5 T2 = 5-14 T3 = ≥ 15 Cox proportional HR	Same findings to that reported in 1991		
D & B score = 14					
Helmrich et al 1991 [123]	To examine the Relationship between PA and the Subsequent development of T2D.	n = 5,990	98,524 man-years of follow-up (1962-1976)	Number of cases: 202	Increased PA is effective in preventing T2D.
USA	Sex: Men Age: 39-68 yr Characteristics: healthy, asymptomatic	PA assessment: Questionnaire for LTPA kcal/wk: stairs climbed/day and blocks walked/day, divided into groups	LTPA was inversely related to the development of type 2 diabetes		The protective benefit is especially pronounced in those individuals who have the highest risk of disease.

Table 17: The relationship between physical activity and the development of type 2 diabetes. (Continued)

Prospective cohort		RR (95% CI) by sports played
University of Pennsylvania Alumni Health Study D & B score = 13	All activities LTPA	• G1 = 1.00 (referent) • G2 = 0.90 • G3 = 0.69 • G4 = 0.65 Trend $p = 0.02$
	Q1 = <500	
	Q2 = 500-999	
	Q3 = 1000-1499	
	Q4 = 1500-1999	RR (95% CI) by Flights of stairs climbed/day • T1 = <5 = 1.00 (referent) • T2 = 0.78 • T3 = 0.75 Trend $p = 0.07$
	Q5 = 2000-2499	
	Q6 = 2500-2999	
	Q7 = 3000-3499	
	Q8 = ≥ 3500	RR (95% CI) by Blocks walked/day • T1 = 1.00 (referent) • T2 = 1.31 • T3 = 0.93 Trend $p = 0.80$
	Sports played	
	G1 = None	
	G2 = Moderate	
	G3 = Vigorous	Age adjusted RR (95% CI) by all activities • Q1 = 1.00 (referent) • Q2 = 0.94 • Q3 = 0.79 • Q4 = 0.78 • Q5 = 0.68 • Q6 = 0.90
	G4 = Moderate and Vigorous	
Stairs climbed per day	• Q1 = 1.00 (referent) • Q2 = 0.94 • Q3 = 0.79 • Q4 = 0.78 • Q5 = 0.68 • Q6 = 0.90	
T1 = <5		
T2 = 5-14		
T3 = ≥ 15	Blocks walked per day T1 = <5	
Blocks walked per day		

Table 17: The relationship between physical activity and the development of type 2 diabetes. (Continued)

D & B score = 12	<p>T3 = High Outcome measure: Incidence of impaired fasting glucose and T2D</p> <ul style="list-style-type: none"> • T3 = 1.00 (referent) OR (95% CI) for developing T2D • T1 = 3.7 (2.4 –5.8) • T2 = 1.7 (1.1–2.7) • T3 = 1.00 (referent) 	
Katzmarzyk et al 2007 [126]	<p>To examine the relationships among adiposity, PA, PF and the development of T2D in a diverse sample of Canadians.</p>	<p>Number of cases: 78 (37 in men, 41 in women)</p>
Canada	<ul style="list-style-type: none"> • n = 1,543 (709 men and 834 women) • Sex: Men and women 	<p>Adiposity and PF are important predictors of the development of T2D.</p>
Prospective cohort	<p>PF assessment: Questionnaire</p>	<p>PA was associated with 23% lower odds of developing diabetes and maximal METs was also associated with significantly lower odds of developing diabetes (OR = 0.28)</p>
D & B score = 13	<p>PA assessment: LTPA Questionnaire</p>	
Burchfiel et al 1995 [345]	<p>To examine the relationship between PA and T2D.</p>	<p>Number of cases: 391</p>
USA	<ul style="list-style-type: none"> • n = 6,815 • Sex: Men (Japanese-American) • Age: 45-68 yr • Characteristics: Free of diabetes at baseline • Canadian Physical Activity Longitudinal Study 	<p>PA is associated inversely and independently with incident T2D.</p>
Prospective cohort	<p>PA assessment: Questionnaire PA index (based on intensity and duration of activity)</p>	<p>The age-adjusted 6-year cumulative incidence of diabetes decreased progressively with increasing quintile of physical activity from 73.8 to 34.3 per 1,000 (p < 0.0001, trend)</p>
D & B score = 13	<p>Levels of activity: Q1 = Basal - Sleeping reclining Q2 = Sedentary Q3 = Slight - Casual walking Q4 = Moderate - Gardening Q5 = Heavy - Lifting, shoveling</p> <p>Outcome measure: Self-reported T2D (clinically recognized)</p>	

Statistics: GLM

Table 17: The relationship between physical activity and the development of type 2 diabetes. (Continued)

Dziura et al 2004 [346]	To determine the prospective relation between reports of habitual PA, 3-year change in body weight, and the subsequent risk of T2D in an older cohort.	<ul style="list-style-type: none"> • n = 2,135 • Sex: Men and women • Age: ≥ 65 yr • Ethnicity: 83% White, 15% African American, 2% Non-white 	PA assessment: Questionnaire for 4 types of activities (walking, gardening/housework, physical exercises, active sports or swimming) and frequency of participation measured with a PA score:	118 cases of T2D	Observation of an inverse relationship between reported PA and rate of T2DM.
USA				Incident density of T2D = 6.6/1000 person years	
Prospective cohort				Diabetes (n = 118) PA score: 2.17 ± 1.7 'Some' PA: 78%	Subjects reporting some PA at baseline experienced a rate of T2D over 50% lower relative to those reporting no PA.
D & B score = 12		<ul style="list-style-type: none"> • Characteristics: Healthy asymptomatic 	Never (score 0) Sometimes (score 1) Often (score 2) Pearson product moment correlation coefficient and Cox proportional HR	Non-Diabetes (n = 2017) PA score: 2.34 ± 1.7 'Some' PA: 84%	
Hu et al. 1999 [347]	To quantify the dose-response relationship between total PA and incidence of T2D in women.	<ul style="list-style-type: none"> • n = 70,102 	8 yr of follow-up	Number of cases: 1419	Increased PA is associated with substantial reduction in risk of T2D including PA of moderate intensity and duration.
USA		<ul style="list-style-type: none"> • Sex: Women • Age: 40-65 yr • Characteristics: participants had no history of diabetes, CVD, or cancer 	PA assessment: Questionnaire for TPA (MET hr/wk) and VPA (6 METs)	Multivariate-adjusted RR (95% CI) of by TPA	
Prospective cohort	To examine the health benefits of walking in comparison to more vigorous activity.		TPA (MET hr/wk)	<ul style="list-style-type: none"> • Q1 = 1.0 (referent) • Q2 = 0.77 (0.66-0.90) 	
D & B score = 12			<ul style="list-style-type: none"> Q1 = 0-2.0 Q2 = 2.1-4.6 Q3 = 4.7-10.4 Q4 = 10.5-21.7 • Q5 = ≥ 21.8 	<ul style="list-style-type: none"> • Q3 = 0.75 (0.65-0.88) • Q4 = 0.62 (0.52-0.73) • Q5 = 0.54 (0.45-0.64) 	
		Nurses' Health Study	MET score	Trend $p < 0.001$	
			Q1 = ≤ 0.5	Multivariate-adjusted RR (95% CI) among women who did not perform vigorous exercise (MET's):	
			Q2 = 0.6-2.0	<ul style="list-style-type: none"> • Q1 = 1.0 (referent) • Q2 = 0.91 (0.75-1.09) • Q3 = 0.73 (0.59-0.90) • Q4 = 0.69 (0.56-0.86) • Q5 = 0.58 (0.46-0.73) 	
			Q3 = 2.1-3.8		
			Q4 = 3.9-9.9		
			Q5 = ≥ 10.0		

Table 17: The relationship between physical activity and the development of type 2 diabetes. (Continued)

		Outcome measures: Incidence of T2D		Trend p < 0.001	
Hu et al 2001 [348]	To examine the role of prolonged television watching on the risk for T2D.	• n = 37,918	10 year follow-up	Number of cases: 1058	Increasing PA is associated with a significant reduction in risk for T2D, whereas a sedentary lifestyle indicated by prolonged TV watching is related directly to increased risk.
USA		• Sex: Men • Age: 40-75 yr	PA assessment: Questionnaire for PA (MET hr/wk) and TV watching (h/wk), each divided into quintiles	Multivariate-adjusted RR (95% CI) by PA	
Prospective cohort		• Characteristics: participants had no history of diabetes, CVD, or cancer • Health Professionals' Follow-up Study	Q1 = 0-5.9	• Q1 = 1.00 (referent)	
D & B score = 11			Q2 = 6.0-13.7	• Q2 = 0.78 (0.66 - 0.93)	
			Q3 = 13.8-24.2	• Q3 = 0.65 (0.54 - 0.78)	
			Q4 = 24.3-40.8	• Q4 = 0.58 (0.48 - 0.70)	
			Q5 = ≥ 40.9	• Q5 = 0.51 (0.41 - 0.63)	
			Time spent watching television per week (h/wk)	Trend p < 0.001	
			Q1 = 0-1	• Q1 = 1.00 (referent)	
			Q2 = 2-10	• Q2 = 1.66 (1.15 - 2.39)	
			Q3 = 11-20	• Q3 = 1.64 (1.12 - 2.41)	
			Q4 = 21-40	• Q4 = 2.16 (1.45 - 3.22)	
			Q5 = >40	• Q5 = 2.87 (1.46 - 5.65)	
			16 yr follow-up	Trend p < 0.001	
Rana et al 2007 [349]	To examine the individual and combined association of obesity and physical inactivity with the incidence of T2D.	• n = 68,907		Number of cases: 4,030	This study found that obesity and physical inactivity independently contributed to the development of T2D.
USA		• Sex: Women	PA assessment: Questionnaire for average amount of time/week MET hours per week spent in MVPA (≥ 3 METs), divided into quintiles	Multivariate-adjusted RR (95% CI) by MVPA:	The benefits of PA were not limited to lean women; among those who were overweight and obese, physically active women tended to be at lower risk for T2D than sedentary women.
Prospective cohort		• Age: 30-55 years age range in 1976 (note: 1986 was the baseline year for the study)			

Table 17: The relationship between physical activity and the development of type 2 diabetes. (Continued)

<p>D & B score = 12</p>	<p>• Characteristics: No history of diabetes, CVD or cancer • Nurses' Health Study</p> <p>Q1 = <2.1 Q2 = 2.1-4.6 Q3 = 4.7-10.4 Q4 = 10.5-21.7 Q5 = ≥ 21.8</p> <p>Cox proportional HR</p>	<p>• Q1 = 2.37 (2.15-2.16) • Q2 = 1.92 (1.73-2.13) • Q3 = 1.48 (1.34-1.64) • Q4 = 1.40 (1.26-1.55) • Q5 = 1.00 (referent) Trend $p < 0.001$</p>	
<p>Sawada et al 2003 [350]</p>	<p>To examine the association between PF and the incidence of T2D.</p> <p>Japan</p> <p>• n = 4,747 • Sex: Men • Age: 20-40 yr</p> <p>PF assessment: Maximal aerobic power estimate ml/kg/min using a submaximal cycle ergometer test, divided into quartiles</p> <p>Q1 = 32.4 ± 3.1</p>	<p>Number of cases: 280</p> <p>Age-adjusted RR (95% CI)</p> <p>• Q1 = 1.00 (referent) • Q2 = 0.56 (0.42-0.75) • Q3 = 0.35 (0.25-0.50) • Q4 = 0.25 (0.17-0.37) Trend $p < 0.001$</p>	<p>Low PF is associated with a higher risk for the development of T2D.</p>
<p>Prospective cohort</p>	<p>• Characteristics: Free of diabetes, CVD, hypertension, tuberculosis, and gastrointestinal disease at baseline</p> <p>Q2 = 38.0 ± 2.5 Q3 = 42.4 ± 3.0 Q4 = 51.1 ± 6.2</p> <p>Outcome measure: Incidence of T2D</p>	<p>Multivariate adjusted RR (95% CI)</p> <p>• Q1 = 1.00 (referent) • Q2 = 0.78 (0.58-1.05) • Q3 = 0.63 (0.45-0.89) • Q4 = 0.56 (0.37-0.84) Trend $p = 0.001$</p>	
<p>D & B score = 13</p>	<p>To examine the relative contributions and joint association of PA and BMI with T2D.</p> <p>Weinstein et al 2004 [351]</p> <p>• n = 37,878</p> <p>6.9 year follow up</p> <p>Cox proportional HR</p>	<p>Number of cases: 1,361</p>	<p>Although BMI and physical inactivity are independent predictors of incident diabetes, the magnitude of the association with BMI was greater than with PA in combined analyses. These findings underscore the critical importance of adiposity as a determinant of T2D.</p>

Table 17: The relationship between physical activity and the development of type 2 diabetes. (Continued)

USA	PA assessment: Questionnaire for walking per week (h/wk) and TPA (kcal/wk), divided into groups and quartiles respectively	Multivariate-adjusted HR (95% CI) by time spent walking
Prospective cohort	<ul style="list-style-type: none"> • Sex: Women • Age: 45+ years • Health care professionals • Characteristics: No history of CVD, cancer or diabetes 	<ul style="list-style-type: none"> • G1 = 1.00 (referent) • G2 = 0.95 (0.82-1.10) • G3 = 0.87 (0.73 -1.02)
D & B score = 12	<p>Walking per week (h/wk)</p> <p>G1 = no walking</p> <p>G2 = <1</p> <p>G3 = 1-1.5</p> <p>G4 = 2-3</p> <p>G5 = ≥ 4</p> <p>TPA (kcal/wk)</p> <p>Q1 < 200</p> <p>Q2 = 200-599</p> <p>Q3 = 600-1,499</p> <p>Q4 ≥ 1500</p> <p>Cox proportional HR</p>	<ul style="list-style-type: none"> • G4 = 0.66 (0.54-0.81) • G5 = 0.89 (0.73-1.09) <p>Trend $p = 0.004$</p> <p>Multivariate-adjusted HR (95% CI) by TPA</p> <ul style="list-style-type: none"> • Q1 = 1.00 (referent) • Q2 = 0.91 (0.79-1.06) • Q3 = 0.86 (0.74-1.01) • Q4 = 0.82 (0.70-0.97) <p>Trend $p = 0.01$</p>

D & B score, Downs and Black quality score; YR, years; PA, physical activity; CHD, coronary heart disease; T2D, type 2 diabetes; LTPA, leisure-time physical activity; g, group; kcal/wk, kilocalories per week; HR, hazard ratio; RR, risk ratio; OR, odds ratio; 95% CI, confidence interval; CVD, cardiovascular disease; OPA, occupational physical activity; PF, physical fitness; MET, metabolic equivalent; MET/wk, metabolic equivalent per week.

exercised vigorously at least once weekly had a 29% lower incidence of type 2 diabetes than individuals who did not exercise regularly [112]. These authors also revealed that physical activity that was sufficient to cause sweating was associated with a lower incidence of type 2 diabetes. Other research has also demonstrated that moderate-to-vigorous physical activity (≥ 5.5 METs for at least 40 min per week) and/or aerobic fitness levels above $31 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ are associated with a lower risk of type 2 diabetes in middle-aged men [113] with the effect being the greatest in high-risk individuals. Therefore, it would appear that Canada's recommendations for physical activity are sufficient to reduce the risk for type 2 diabetes.

In 2001, Hu et al. [114] reported very interesting and compelling research regarding the role of lifestyle factors in the development of type 2 diabetes. Using data from the Nurses' Health Study, they defined a low-risk group according to five lifestyle factors including BMI, a healthy diet, the participation in moderate-to-vigorous physical activity for at least 30 min per day, no current smoking, and the consumption of an average of at least one-half serving of an alcoholic beverage per day. They revealed that the women in the low risk group had a RR for type 2 diabetes of only 0.09 (CI 0.05-0.17) in comparison to the rest of the cohort. They also found that 91% of the cases of type 2 diabetes in this cohort (CI 83-95%) could be attributed to the five lifestyle factors. This research provided compelling evidence that the majority of type 2 diabetes could be prevented through healthy living [115].

As reviewed in Table 17 there is evidence that leisure-time, occupational and commuting-related leisure time activities significantly reduce the risk for the development of type 2 diabetes. For instance, a recent study by Sato and colleagues [116] revealed that the walking distance to work was directly related to the incidence of type 2 diabetes in 8,576 Japanese men followed for 4 years. The risk reduction was approximately 27% in the participants who walked to work for ≥ 21 min compared to those who did so for ≥ 10 min. These findings are similar to that found by Hu et al. who reported that moderate occupational, commuting and leisure-time physical activities all had a significant inverse relationship to risk in middle-aged men and women [117].

Although ethnicity is often not reported in the current research, the studies examined in our systematic review came from a variety of countries and regions. Data was obtained from studies from the USA, Canada, UK, Japan, and Finland. For instance, Hsia et al. (2005) conducted a prospective 5-year study of 87,907 post-menopausal women, finding a strong graded inverse relationship between physical activity and type 2 diabetes. The relationship was stronger in "Caucasian" than

in minority (African-American, Hispanic or Asian) women. The authors postulated this finding might reflect less precise risk assessments in minority women [118]. As we have outlined previously, further research is clearly warranted that examines the relationship between physical activity and type 2 diabetes in persons of different ethnicities. Moreover, further research is needed to determine the effects of socio-economic status on the observed relationships. Nonetheless, the research is compelling, habitual physical activity appears to be highly effective in the primary prevention of type 2 diabetes.

Implications

In 1992, the consensus panel from the International Conference on Physical Activity, Fitness and Health (held in Toronto, Canada) [17] indicated that physical activity can effectively reduce the risk for, and incidence of, type 2 diabetes. Over 15 years later, the research is compelling; habitual physical activity is an effective primary preventative strategy against the development of type 2 diabetes [111-113,118-123]. As shown in our analyses, numerous observational studies have revealed that regular physical activity is associated with a lower risk of developing type 2 diabetes [111-113,118-123]. Moreover, increased aerobic fitness is inversely associated with the risk of type 2 diabetes [113,124]. It is also apparent that both aerobic and resistance type activities reduce the risk for type 2 diabetes [125,126].

Although it is difficult to determine the dose-response between physical activity and type 2 diabetes in the majority of the current randomized controlled trials, these trials have revealed important findings. Influential exercise and/or lifestyle intervention trials have demonstrated clearly the health benefits of physical activity/exercise in the prevention of type 2 diabetes. For instance, in the Diabetes Prevention Program (US), 3,234 high-risk participants were randomly assigned to one of three groups: a) a placebo control, b) metformin drug therapy (850 mg twice daily), and c) a lifestyle intervention. The authors revealed that the lifestyle intervention (including physical activity for at least 150 minutes per week) was more effective than metformin (alone) (respective reductions in incidence 58% and 31%) [127]. Similarly, Tuomilehto et al. (2001) conducted a randomized controlled trial with middle-aged, overweight subjects with impaired glucose tolerance (172 males and 350 females). The authors reported a significant reduction in the incidence of type 2 diabetes in the intervention group (which received advice regarding moderate intensity exercise (30 min/day) and dietary control). The lifestyle intervention reduced the risk of type 2 diabetes by approximately 54% in women and 63% in men [128]. In a review of the literature, Williamson et al. revealed modest weight loss via diet and

physical activity reduced the incidence of type 2 diabetes in high risk individuals by 40-60% over a 3-4 year period [129]. Collectively, the epidemiological and randomized controlled trials provide compelling evidence supporting the role of habitual physical activity in the primary prevention of type 2 diabetes.

Recommendation #6

For a reduced risk for type 2 diabetes, it is recommended that individuals should participate in 30 min or more of moderate to vigorous exercise on most days of the week. [Level 2, Grade A]

Primary Prevention of Osteoporosis

The protective effects of physical activity and exercise training on bone health are well documented. In fact, the relationship between indicators of bone health (such as bone mineral density or bone mineral content) and physical activity have been evaluated extensively (see Table 18). Numerous exercise intervention trials have revealed that aerobic and resistance activities have a beneficial effect on bone mineral density across the lifespan [16]. In fact, several systematic reviews of the literature [130-135] and major consensus statements [136] have shown clearly the potential benefits of both aerobic and resistance training on bone health (particularly in post-menopausal women). It has been estimated that exercise interventions prevent or reverse at least 1% of bone loss per year in the lumbar spine and the femoral neck of pre- and post-menopausal women [130,137].

Exercise has also been shown to significantly reduce the risk and/or number of falls in comparison to inactive controls [138-142]. Moreover, fracture risk and/or incidence has been shown to be reduced in active individuals [143-145]. Case-control studies of older persons who suffered a hip fracture have revealed that these individuals had significantly lower physical activity levels throughout adulthood [136,146]. Observational studies have also revealed an inverse relationship between the incidence of fractures and physical activity [147-149]. For instance, Joakimsen et al. revealed lower fracture rates in individuals who performed more weight-bearing activities [148]. Similarly, Kujala et al. [147] in a 21-year prospective study revealed that intense activity was associated with a lower incidence of hip fracture (Hazard Ratio = 0.38, 95% CI = 0.16-0.91). Feskanich et al. (2002) also revealed that moderate physical activity was inversely related to the risk of hip fracture in postmenopausal women [149]. In a review of observational trials, Katzmarzyk and Janssen [20] revealed that the fracture risk was markedly higher in habitually inactive individuals (RR = 1.59 (95% CI = 1.40-1.80)) with a population attributable risk of 24% in Canada.

There is clear evidence that exercise training is of benefit for bone health and accordingly reduces the risk for

osteoporosis. However, remarkably limited research has actually examined the relationship between routine physical activity and the prevalence and/or incidence of osteoporosis (Figure 10). In our systematic search of the osteoporosis literature, a total of 3655 citations were identified during the electronic database search (Figure 7). Of these citations, 1888 were identified in MEDLINE, 236 in EMBASE, 82 in Cochrane, and 481 in the CINAHL/SportDiscus/PsychInfo search. A total of 276 duplicates were found, leaving a total of 2411 unique citations. A total of 2059 articles were excluded after screening, leaving a total of 352 articles for full review. From these articles all 352 were excluded after full-text review. The reasons for exclusion included non-experimental/weak design (n = 87), did not contain three levels of physical activity or not possible to determine dose-response relationship (n = 38), reviews, summaries, meta-analyses (n = 39), not dealing specifically with osteoporosis (n = 21), only on change in bone mineral density (N = 123), clinical population (N = 10), bone metabolism (N = 13), fractures (N = 3), population < 18 yrs (N = 11), and other (N = 7). An additional 2 articles were found through the authors' knowledge of the field.

As identified in our systematic search, the majority of the literature has dealt with the relationship between physical activity and indicators of bone health and/or the incidence of fractures. However, a recent observational trial [150] has provided evidence supporting the ability of physical activity to reduce the incidence of osteoporosis. For instance, Robitaille et al. revealed a dose-response relationship between physical activity level and the prevalence of reported osteoporosis in 8073 women aged ≥ 20 yr in the National Health and Nutrition Examination Survey, 1999-2004 [150]. Those performing no physical activity were at a higher risk than those who engaged in moderate (<30 MET hr/wk) and high (>30 MET hr/wk) levels of physical activity. There was a dose-response relationship with the highest physical activity group having the lowest prevalence of osteoporosis. Similarly, Keramat et al. [151] in a case-control investigation revealed that physical activity was protective against the development of osteoporosis.

At this time it is difficult to define clearly the actual dose-response required to cause a reduction in the incidence of osteoporosis. It is clear that bone adaptations to exercise are load dependent and site specific [9,10,16,152]. As such, physical activities that involve significantly loading/impact are often advocated for the prevention of osteoporosis. It has been shown that running 15-20 miles per week is associated with bone mineral accrual or maintenance. Longer distances however may be associated with reduced bone mineral density [136].

Feskanich et al. reported that the risk of hip fracture was lowered by 6% for each increase of 3 MET-hours

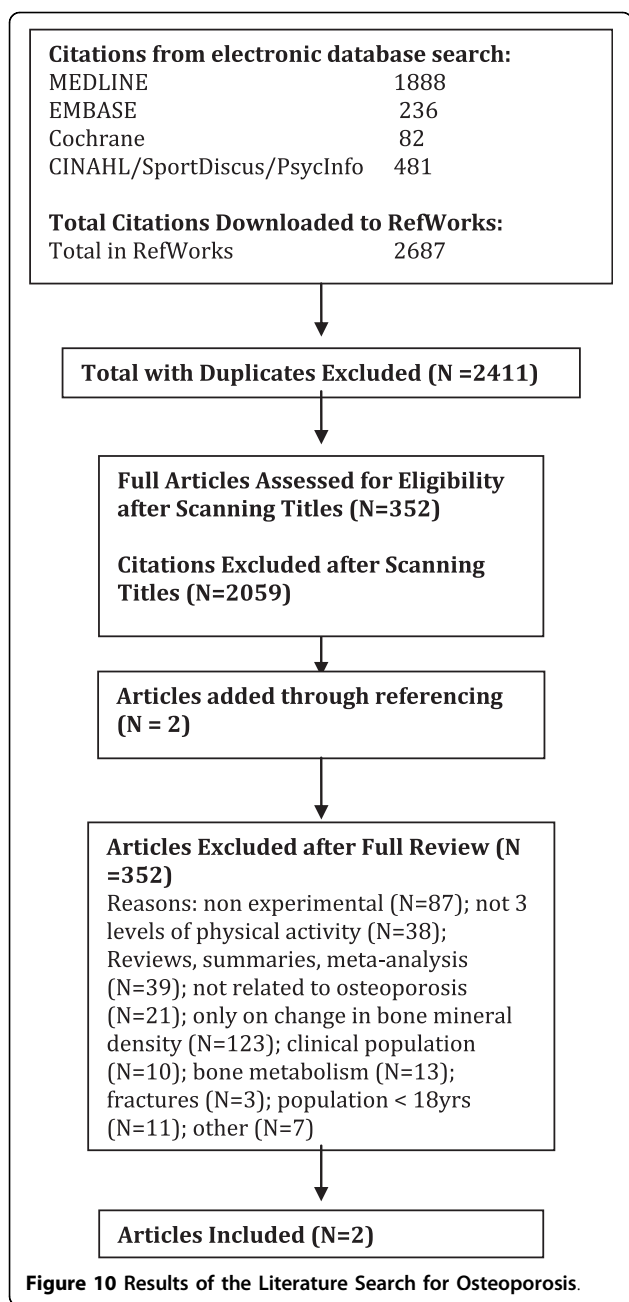
Table 18 Studies examining the relationship between physical activity and osteoporosis.

Publication Country Study Design Quality Score	Objective	Population	Methods	Outcome	Comments and Conclusions
Robitaille et al 2008 [150]	To assess the relationship between the physician- diagnosed osteoporosis and family history and examine whether osteoporosis risk factors account for this relationship.	<ul style="list-style-type: none"> n = 8,073 Sex: Women Age: ≥ 20 yrs Characteristics: American women Study: NHANES (1999-2004) 	PA assessment: Questionnaire. Level of PA was expressed in MET (hr/wk)	Prevalence of reported osteoporosis in US women by PA level	Prevalence of osteoporosis declines with increasing PA in a dose-response manner.
USA			G1 = 0 G2 = <30 G3 = ≥ 30	PA level (% prevalence) <ul style="list-style-type: none"> G1 = 11.0 (9.8-12.4) G2 = 7.1 (6.0-8.4) G3 = 3.9 (2.8-5.4) 	
Cross-sectional			Muscle strengthening activities were expressed in frequency/wk Times/week	p < 0.001	
D & B score = 10				PA level (age adjusted) <ul style="list-style-type: none"> G1 = 8.9 (7.7-10.1) G2 = 8.4 (7.3-9.7) G3 = 6.2 (4.4-8.5) 	
			G1 = 0 G2 = <2 G3 = ≥ 2	p < 0.01	
			Criteria for diagnosis of osteoporosis: Self-reported physician diagnosed	Muscle strengthening (% prevalence)	
			Chi-square	<ul style="list-style-type: none"> G1 = 8.1 (7.2-9.1) G2 = 3.1 (1.7-5.5) G3 = 7.4 (5.8-9.4) 	
				p < 0.001	
				Muscle strengthening (age adjusted) <ul style="list-style-type: none"> G1 = 7.8 (6.9-8.7) G2 = 6.7 (3.8-11.8) G3 = 9.5 (7.6-11.9) 	
				p < 0.05	
Keramat et al 2008 [151]	To assess risk factors for osteoporosis in postmenopausal women from selected BMD centers in Iran and India.	<ul style="list-style-type: none"> Iran n = 363; 178 case, 185 control 	Study period 2002 – 2005	OR (95% CI) of osteoporosis in exercisers vs. non-exercisers. Iran (age adjusted)	Exercise was shown as protective factor in both countries and it remained significant after adjustment for age weight and height in Iran.

Table 18: Studies examining the relationship between physical activity and osteoporosis. (Continued)

Iran and India	<ul style="list-style-type: none"> India n = 354; 203 case, 151 control 	PA assessment: Questionnaire. PA was categorized as exercises, other exercises (eg, swimming, aerobics, weight training) and walking	
Case control	<ul style="list-style-type: none"> Sex: Women Age: Iran Case = 58.2 (7.1) yr; Iran Control = 55.7 (6.0) yr; India Case = 58.9 (8.1) yr; India Control = 56.4 (7.5) yr Characteristics: Cases had BMD > 2.5 SD below average of young normal bone density in L1-L4 spine region and/or total femoral region. Controls had BMD < 1 SD below normal 	<p>BMD assessment: DEXA</p> <p>Multinomial logistic regression</p>	<ul style="list-style-type: none"> Exercises = 0.4 (0.2-0.7) Other exercises = 0.4 (0.2-0.6) Regular Walking = 0.5 (0.3- 0.8)
D & B score = 11			Walking and other exercises were shown as protective factors in Iranian subjects.
			Iran (age, weight, height adjusted)
			<ul style="list-style-type: none"> Exercises = 0.4 (0.2-0.7) Other exercises = 0.3 (0.2-0.6) Regular Walking = 0.4 (0.2- 0.8)
			India (age adjusted)
			<ul style="list-style-type: none"> Exercises = 0.4 (0.3-0.9) Other exercises = NS Regular Walking = NS
			India (age, weight, height adjusted)
			<ul style="list-style-type: none"> Exercises = NS Other exercises = NS Regular Walking = 0.4 (0.2- 0.8)
			Ethnicity: Indian and Iranian

D & B score, Downs and Black quality score; YR, years; MET/wk, metabolic equivalent per week; G, groups; PA, physical activity; BMD, bone mineral density; SD, standard deviation; DEXA, dual energy x-ray absorptiometry; NS, not significant.



per week of activity (or 1 hr/wk of walking at an average pace) [149]. There was a linear reduction with increasing physical activity level. Walking for at least 4 hr/wk was also associated with a 41% lower risk of hip fracture compared to less than 1 hr/wk [149]. The work of Robitaille et al. also indicated that moderate levels of physical activity are sufficient to reduce the prevalence of osteoporosis [150].

In summary, there is preliminary evidence to indicate that the current Canadian physical activity guidelines are sufficient to maintain and/improve bone health. However,

further research is clearly required, in particular research that examines the relationship between physical activity and the incidence of osteoporosis in both men and women from varied ethnic backgrounds. Currently, the level of evidence would be considered to be at a Level 3A. The quality of the investigations was generally low with a mean (and median) Downs and Black score of 11.

Recommendation #7

For a reduced risk for osteoporosis, it is recommended that individuals should participate in load bearing activities for 30 min or more on most days of the week. [Level 3, Grade A]

Other Considerations

Musculoskeletal Fitness and Health

In the present analyses, all indices of physical activity/fitness were incorporated into our systematic reviews. Although the majority of the data is related to aerobic activities, it should be noted that many of these activities also had a significant musculoskeletal component. Moreover, direct measurements of musculoskeletal fitness were included in various studies included in our review. Although there is limited information available (in comparison to aerobic activities) there is compelling evidence that musculoskeletal fitness is also positively associated with health status [9,10,16].

Warburton and colleagues [9,10] in two reviews of the literature reported that enhanced musculoskeletal fitness is associated positively with glucose homeostasis, bone health, functional independence, mobility, psychological well-being, and overall quality of life and negatively associated with fall risk, morbidity and premature mortality. They also reported that interventions that increase musculoskeletal fitness also have a significant positive effect on the health status of the individuals with a low musculoskeletal reserve (e.g., the frail elderly).

In an evaluation of the current literature some key findings emerge. Grip strength has particularly been shown to be inversely related to premature mortality and/or morbidity (e.g., functional limitations) [153-156]. Rantanen et al. (1998) reported that those individuals with the lowest grip strength had a higher rate of mortality at a younger age (over a 27- year period) than their counterparts with higher muscular strength. Furthermore, they revealed that those with a faster rate of decline in muscular strength (>1.5% per year) or a very low grip strength (<21 kg) had a greater incidence of chronic diseases, such as type 2 diabetes, stroke, arthritis, coronary heart disease, and pulmonary disorders. It was shown that those in the lowest grip strength tertile had an 8-fold increased risk for disability. Individuals with high muscular strength have also been shown to develop less functional limitations in comparison to their counterparts with lower strength over a 5-year period [157].

Katzmarzyk and colleagues [126,154,158] in Canada have also demonstrated a positive relationship between musculoskeletal fitness and health status. For instance, Katzmarzyk and Craig (2002) revealed that there was a significantly higher risk of premature mortality in the lower quartile of sit-ups in both men (RR = 2.72) and women (RR = 2.26). Grip strength was also predictive of mortality in men (RR = 1.49), but not women. In a recent study, Mason et al. revealed that musculoskeletal fitness was a significant predictor of weight gain over a 20-year period [158]. Importantly, they also reported that individuals with low musculoskeletal fitness had 78% greater odds of significant weight gain (≥ 10 kg) compared to those with high musculoskeletal fitness. These studies provide direct support for the inclusion of resistance and flexibility training in Canada's physical activity guidelines for adults [3,159].

Recommendation #8

For improved health status and reduced risk for chronic disease and disability, it is recommended that individuals should include daily activities that tax the musculoskeletal system [Level 2, Grade A]

Limitations

It is important to note that for each chronic condition, the methods used to determine the relationship between physical activity and the specific clinical outcome were often quite varied. For instance, early work in the field generally controlled for few confounding variables (such as age). In comparison, current literature often controls for a myriad of potential confounding variables. These discrepancies make the comparison of the relative risk reductions between studies and across clinical conditions more difficult. Moreover, the multivariate analyses (controlling for various potential confounding factors) may inappropriately decrease the level of risk reduction associated with physical activity and the clinical endpoint [31]. This is owing to the fact that some of the health benefits associated with physical activity may be mediated through these variables [31].

There was often considerable variability in the findings and major conclusions of the studies examined. Often the available literature was limited by the lack of a clear standard for assessing physical activity. In many instances, it was extremely difficult to determine the actual dosage of physical activity used to group the participants. This lack of clarity makes it very difficult to clearly define the dose-response relationship between physical activity and various chronic conditions.

Conclusions

There is incontrovertible evidence that regular exercise is an effective preventative strategy against premature mortality, cardiovascular disease, stroke, hypertension,

colon cancer, breast cancer, and type 2 diabetes. There is also compelling indirect evidence to support the protective effects of physical activity with respect to osteoporosis. In many instances the dose-response relationship is linear with further health benefits with increasing levels of activity. The current Canadian physical activity guidelines for adults are sufficient to reduce the risk for multiple chronic diseases simultaneously. The acknowledgement that every bit of exercise counts towards health benefits (with greater benefits at higher energy expenditures) is consistent with the literature and a reasonable message to promote to the general population. However, further investigation is likely required to evaluate the relationship between physical activity and health status in non-Caucasian populations.

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Author details

¹Cardiovascular Physiology and Rehabilitation Laboratory, University of British Columbia, Vancouver, Canada. ²Experimental Medicine Program, Faculty of Medicine, University of British Columbia, Vancouver, Canada. ³Cognitive and Functional Learning Laboratory, University of British Columbia, Vancouver, Canada.

Authors' contributions

DW was responsible for the conceptualization and design of the systematic review, the generation of the systematic review terms, oversaw the data collection, evaluated each article included in the review, and was responsible for creating and revising the manuscript. SC was involved in the data collection, the critical review of the articles, the creation of the tables contained in the article and the revision of the manuscript. AI assisted with the data collection, the critical review of the articles, and the creation and the revision of tables in the manuscript. LN assisted with the generation of the systematic review terms, the retrieval of articles, and the generation and revision of the tables. SB was involved in the conceptualization and design of the systematic review, the generation of the systematic review terms, oversaw the data collection, the review of the articles, and was responsible for creating and revising the manuscript. All authors have read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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