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CARDIOVASCULAR DISEASE

Quantifying the dose-response of walking in reducing coronary heart disease risk: meta-analysis

Henry Zheng · Nicola Orsini · Janaki Amin · Alicja Wolk · Van Thi Thuy Nguyen · Fred Ehrlich

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Abstract The evidence for the efficacy of walking in reducing the risk of and preventing coronary heart disease (CHD) is not completely understood. This meta-analysis aimed to quantify the dose-response relationship between walking and CHD risk reduction for both men and women in the general population. Studies on walking and CHD primary prevention between 1954 and 2007 were identified through Medline, SportDiscus and the Cochrane Database of Systematic Reviews. Random-effect meta-regression models were used to pool the relative risks from individual studies. A total of 11 prospective cohort studies and one randomized control trial study met the inclusion criteria, with 295,177 participants free of CHD at baseline and 7,094 cases at follow-up. The meta-analysis indicated that an increment of approximately 30 min of normal walking a day for 5 days a week was associated with 19% CHD risk reduction (95% CI = 14–23%; *P-heterogeneity* = 0.56; I^2 = 0%). We found no evidence of heterogeneity between subgroups of studies defined by gender (P = 0.67); age of the study population (P = 0.52); or follow-up duration (P = 0.77). The meta-analysis showed that the risk for developing CHD decreases as walking dose increases. Walking should be prescribed as an evidence-based effective exercise modality for CHD prevention in the general population.

Keywords Coronary heart disease · Exercise · Meta-analysis · Physical activity · Walking

H. Zheng (✉) · V. T. T. Nguyen · F. Ehrlich
School of Public Health and Community Medicine, The University of New South Wales, Level 2, Samuels Building, Sydney, NSW, Australia
e-mail: henry.z@exercisemedicine.com.au

N. Orsini · A. Wolk
Division of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden

J. Amin
National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, Sydney, NSW, Australia

Introduction

Coronary heart disease (CHD) is the single most common cause of death, claiming more than 7.2 million lives worldwide each year, with disease burden predicted to reach 82 million disability-adjusted life years (DALYs) by 2020 [1]. Among its major risk factors is physical inactivity (2–5), accounting for 22% of CHD incidence [2]. There exists compelling evidence that physical activity is associated with CHD risk reduction [3–8].

Most studies, however, approach physical activity in composite terms without differentiating the types of physical activity involved. Little is known of the relative efficacy of different types of physical activity in reducing CHD risk. Physiological adaptations to exercise training are specific to the stimulus applied [9, 10]. The principle of specificity of exercise effect implies that different forms of exercise produce different results [11]. An effective intervention strategy for CHD prevention calls for identification and recommendation of best practices in physical activity.

Walking has been shown to be the most common and popular form of physical activity [12–14]. It is a sustained dynamic aerobic activity with comparatively minimal adverse effects [15]. Nevertheless, the specific role of walking in reducing the risk of cardiovascular disease has been addressed only minimally [16]. The evidence for the efficacy of walking in preventing CHD remains to be better

understood. A previous meta-analysis [17] focused on physical activity and cardiovascular disease reduction for women only. A more recent meta-analysis by Hamer and Chida [18] examined walking and primary prevention of cardiovascular disease (CVD) rather than CHD. Moreover, the meta-analysis only approached the dose-response relationship between walking and CVD by comparing the extremes of the distribution of walking rather than investigating the change of CHD risk (trend) according to different walking levels. The dose equals to the energy expended in physical activity and is one of the potential mediators of the health benefits of physical activity [19]. Derived from the product of frequency, duration and intensity, the dose measures the volume of exercise. To quantify the dose of physical activity needed to bring about a particular health benefit response is essential as far as physical activity intervention for health is concerned.

Promotion of exercise intervention against CHD requires a better understanding of the dose-response relationship. Given that walking is the main option for increasing physical activity in sedentary populations [15], we focused our meta-analysis on the relationship between dose of walking and response in reducing CHD risk for both men and women in the general population.

Methods

Search strategy

Medline, SportDiscus and the Cochrane Database of Systematic Reviews were searched to identify relevant studies using MeSH and combined terms "physical activity" or "exercise" or "walking" and "cardiovascular disease" or "coronary heart disease". Reference lists of retrieved articles were scanned for any other relevant studies. Previous systematic reviews [3, 4, 6–8, 15, 17, 20, 21] including the report of the surgeon general on physical activity and health [5] were also examined for studies eligible for inclusion. Conference proceedings were scanned for unpublished studies. Due to language resource constraints, the search was limited to English-language papers only. The search was restricted to 1954 to September 2007. The selection of studies and data extraction were conducted by two independent reviewers and discrepancies were resolved by consensus.

Outcome definition

In this meta-analysis, CHD referred to fatal and nonfatal myocardial infarction as defined by the studies included. Where angina pectoris (AP) was included in CHD as in two studies [22, 23], they were analyzed separately.

Inclusion and exclusion criteria

Studies were included for the meta-analysis only if they were primary prevention studies with walking assessed as an exposure and CHD as an outcome. Further, studies were only included if they reported estimates and standard errors or confidence intervals of relative risks (RRs) of the effect of walking on CHD, or provided sufficient data allowing for such statistics to be calculated. These estimates were only assessed if they, at a minimum, adjusted for age as a confounder. For papers based on the same study population, only the most recent publication was included.

In order to isolate and quantify the dose-response effect of walking in preventing CHD, studies were excluded if walking was combined with other types of physical activity. Studies were also excluded if the outcome was CVD rather than CHD.

Assessment of walking

A wide variety of physical activity assessment methods and measures were used to assess walking exposure including distance travelled [23–25], walking time [22, 26–28], energy expenditure [16, 29, 30], pace [22, 27, 29, 30] and frequency [31]. Where a study reported RRs of walking measured in both time and pace or MET-hours per week (one metabolic equivalent task or MET is the caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram per hour at rest) and pace, we pooled RRs of walking measured in pace for dose-response estimation as walking pace tends to be more validly reported [27, 32]. Where a study reported several RRs as a result of different levels of adjustment for confounders, only RRs with adjustment levels comparable to that of other studies were pooled [29]. In order to quantify walking dose on a comparable basis, we converted different walking measures to a uniform metric MET-hours/week for estimation. Where only walking time or pace was reported, normal walking for half an hour a day on average was assumed. Normal walking was commonly defined as walking at 2–2.9 miles/h [22, 27, 29]. In this meta-analysis, the pace of normal walking was assumed to be 2.5 miles/h on average on the firm surface with 3 METs assigned based on the updated compendium of physical activities [33].

Data extraction

Meta-analysis relies on an estimation of precision to pool effect sizes across studies. If a study did not report the standard errors or confidence intervals of RRs, then raw

data (CHD cases and sample size) were used to calculate the relative risk and confidence intervals. RRs were pooled with the lowest walking level as the reference. If a study used the highest walking level as the reference, the standard error of the log relative risk with the lowest walking level as the reference was estimated as [34],

$$\mathrm{SE}(\ln \mathrm{RR}) = \sqrt{(1-P)/(NP) + (1-P_i)/(N_i P_i)}$$

where P and N denote the event rate and sample size for the lowest walking level and P_i and N_i the event rate and sample size for ith walking level respectively.

Where relative risks and confidence intervals were only presented graphically [23] without numbers, we performed an image analysis with MATLAB (R2007b) to estimate the corresponding statistics.

Statistical analysis

The relationship between walking level and CHD risk was assessed using random-effect meta-regression models. Dose-response meta-analysis was carried out using the method proposed by Greenland and Orsini [35, 36] to compute study-specific slopes (linear trends) from the correlated natural log of the RRs across categories of walking. This method requires that the distribution of cases and non-cases or person-time and the RRs with its variance estimates for at least three quantitative exposure categories are known. For studies that did not provide the required data [26, 30, 31], we used the method proposed by Hamling et al. [37] to calculate cases and non-cases for each walking level. For each study, the median or mean level of walking for each category was assigned to each corresponding RR. When the median or mean walking level per category was not presented in the article, we assigned the midpoint of the upper and lower bounds in each category as the average walking level. If the upper bound was not provided, we assumed that it had the same amplitude as the preceding category. Statistical heterogeneity among studies was evaluated using both the Q statistic and the I^2 [38]. I^2 is the proportion of total variation contributed by between-study variation.

Due to lack of data reported it was not possible to perform a dose-response meta-analysis for the two studies with AP included in CHD [22, 23]. Therefore, we compared the risk of all non-referent walking levels versus the referent group using a random-effect model.

Sensitivity and subgroup analyses were also conducted to investigate potential sources of heterogeneity. We performed subgroup analyses by gender, mean age of the study population and follow-up duration. Publication bias was assessed using Egger's regression asymmetry test [39]. All statistical analyses were conducted using Stata (version 9.2; StataCorp, College Station, TX).

Results

Study characteristics

The search strategy yielded a total of 5,167 articles. After elimination of studies with irrelevant outcomes, secondary prevention studies, reviews, and other types of publications (editorial/comments/consensus statement/guidelines/letter/duplicate data, etc.), 503 papers containing primary data on physical activity and cardiovascular disease or associated risk factors were selected for further examination (see Fig. 1). A further 491 studies were excluded for either CHD not being an outcome or walking not being specifically assessed. A total of 11 prospective cohort studies and one

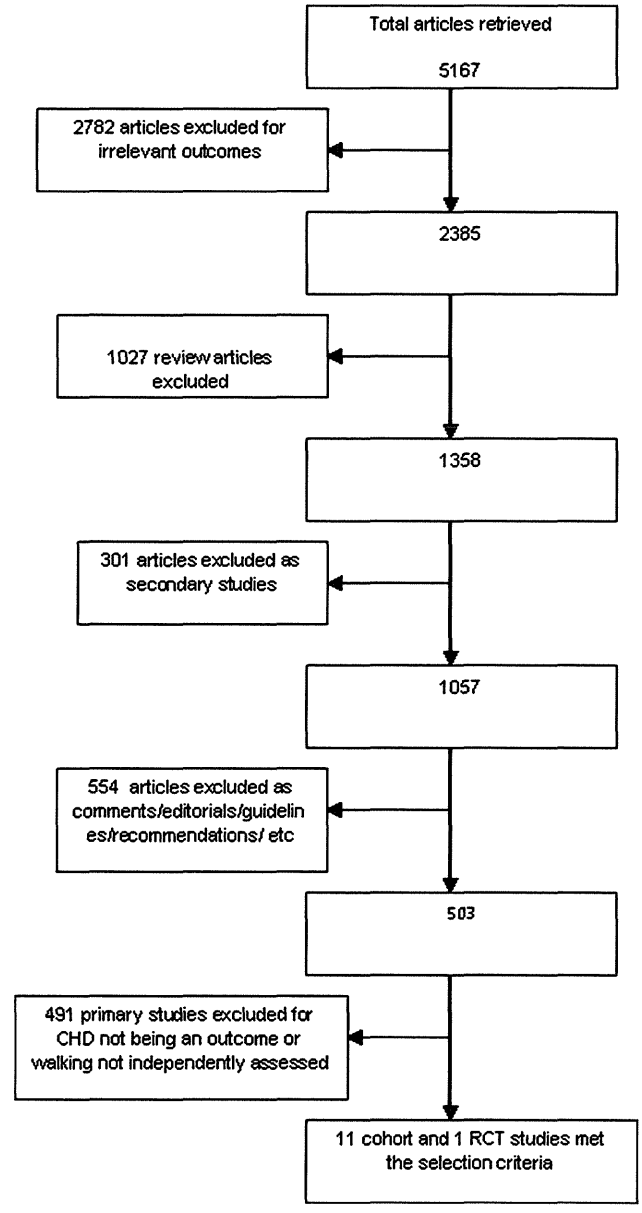

Fig. 1 Flow chart of search strategy

randomized control trial study met the inclusion criteria for the meta-analysis after. Of the 12 studies, 10 were conducted in the US (including 1 in Hawaii) and 2 in the UK, with study population sizes ranging from 196 to 73,745 and follow-up period ranging from 2 to 16 years. In total, the 12 studies involved 295,177 participants free of CHD at baseline and 7,094 cases at follow-up. The characteristics of the studies included in the meta-analysis are shown in Table 1.

Dose-response meta-analysis

Eight studies reporting RRs for walking exposure in at least three levels were included in our analysis of dose-response between walking and CHD risk reduction [16, 22, 24, 26–30]. Three studies (21, 23, 25) were excluded from this analysis because the walking variable was classified in only two levels (high vs. low). All the three excluded studies showed a decrease in CHD risk associated with high-level walking as compared to low-level walking.

The dose-response relationship between walking and CHD risk was analyzed according to the type of measure: MET-hours/week (Fig. 2), pace (Fig. 3), and time (Fig. 4). The CHD risk decreased by 11% (95% CI = 4–18%) for an increase of 8 MET-h/week with no evidence of heterogeneity across studies (*P-heterogeneity* = 0.21; I^2 = 37%). An increment of 8 MET-h/week is equivalent to an increment of approximately 30 min of normal walking a day for 5 days a week based on the conversion rate of walking at 2.5 miles/h = 3 METs according to the updated compendium of physical activities [33]. Regarding walking pace, an increment of 2 km/h was associated with 21% reduced risk of CHD (95% CI = 15–27%; Q = 1.79, *P-heterogeneity* = 0.62; I^2 = 0%). An increment of 3.5 h/week (30 min a day) of normal walking was inversely associated with CHD risk. As shown graphically in Fig. 4, an increment of 3.5 h/week of normal walking was significantly associated with 32% CHD risk reduction (95% CI = 11–48%) and no evidence of heterogeneity was found in the study-specific estimates (Q = 2.38, *P-heterogeneity* = 0.30; I^2 = 16%).

The dose-response relationship between walking and CHD risk in the eight studies [16, 22, 24, 26–30] where walking was based on a uniform measure of MET-hours/week was also investigated (Fig. 5). For studies reporting RRs for both pace and another type of walking measure (time or MET-hours/week), we only pooled RRs based on walking pace for the reason as stated in the method section [22, 27, 29, 30]. An increment of 8 MET-h/week was associated with 19% (95% CI = 14–23%) CHD risk reduction. There was no statistically significant heterogeneity across studies (Q = 5.81, *P-heterogeneity* = 0.56; I^2 = 0%). The linear trend estimates corresponding to an increment of 8 MET-h/week for each study are presented in Fig. 6. No publication bias was observed from the Egger's regression asymmetry test (P = 0.93). We also assessed non-linearity by estimating a quadratic meta-regression model and we found no evidence of better fit of the relative risk estimates as compared to the simpler linear model (P = 0.65).

To assess whether the three studies reporting only two walking levels comparing high versus low walking category could affect the dose-response meta-analysis we included them into the summary of the specific-study trend estimates [25, 31, 40]. The pooled trend estimate and 95% confidence interval did not change substantially; an increment of walking by 8 MET-h/week was associated with 19% lower (95% CI = 15–24%) CHD risk and no statistically significant heterogeneity across studies was detected (Q = 10.75, *P-heterogeneity* = 0.46; I^2 = 0%).

Sensitivity and subgroup analysis

The pooled estimate of two studies with CHD containing AP [22, 23] provided similar results to the eight studies whose endpoints did not contain AP. An increment of approximately 8 MET-h/week was associated with 18% (95% CI = 1–32%) lower risk for the outcome measure (Q = 1.62, *P-heterogeneity* = 0.20; I^2=0%).

In a sensitivity analysis iteratively removing each study from the overall analysis, the CHD risk reduction associated with an increment of 8 MET-h/week ranged from 20% (95% CI = 15–26%) when the study by Manson et al. [16] was excluded to 18% (95% CI = 13–22%) when the study by Lee et al. [27] was excluded. To evaluate whether the dose-response relationship varied across levels of study characteristics (Table 2), we conducted subgroup analyses by gender (male, female, mixed); mean age of the study population (>55 vs. ≤55 years); and follow-up duration (>6 vs. <6 years). We found no evidence of heterogeneity between subgroups of studies defined by gender (P = 0.67); age of the study population (P = 0.52); and follow-up duration (P = 0.77). By excluding from the dose-response meta-analysis the studies that adjusted only for age [16, 22], the pooled trend did not change substantially (RR = 0.81, 95% CI = 0.75–0.87). This is in agreement with the sensitivity analysis performed by removing one study at a time.

Discussion

Irrespective of walking measures in pace, time or energy expenditure, our meta-analysis results indicated that walking conferred protection against CHD in a dose-response manner. The sensitivity analysis suggested that the effect of walking in reducing CHD risk was consistent across study types and methods of analysis. An increment

Table 1 Characteristics of the studies included in the meta-analysis

Reference	Study design	Study size (cases)	Outcome	Age range	Gender	Follow-up (year)	Exposure category	Walking level	Relative risk with 95% CI[a]	Adjustment
Tanasescu et al. [29] US	Prospective cohort	44,452 (2,114)	CHD	40–75	Male	12	OW[b]	4-level in pace	4-level	Alcohol intake, smoking, parental history of myocardial infarction, nutrition intake, diabetes, cholesterol, hypertension
								<2 miles/h	1 (referent)	
								2–3 miles/h	0.74 (0.60–0.91)	
								3–4 miles/h	0.60 (0.45–0.79)	
								≥4 miles/h	0.50 (0.30–0.83)	
								5-level in MET	5-level	
								0–1.19 MET-h/week	1 (referent)	
								1.2–3.49	1 (0.83–1.21)	
								3.5–6.99	0.90 (0.74–1.10)	
								7–14.74	1.02 (0.84–1.23)	
								>14.75	0.82 (0.67–1.00)	
Manson et al. [16] US	Prospective cohort	73,743 (345)	CHD	50–79	Female	5.9	LW[c]	5-level in MET	5-level in MET-	Age
								None	h/week 1 (referent)	
								0.1–2.5 MET-h/week	0.71 (0.53–0.96)	
								2.6–5	0.60 (0.44–0.83)	
								5.1–10	0.54 (0.39–0.76)	
								>10	0.61 (0.44–0.84)	
Lee et al. [27] US	Prospective cohort	39,372 (320)	CHD	≥45	Female	4–7	LW	4-level in pace	4-level	Age, randomized treatment assignment; smoking, alcohol intake; saturated fat, fruits and vegetable; menopausal status, parental history of myocardial infarction, etc.
								Not walk regularly	1 (referent)	
								<3.2 km/h	0.56 (0.32–0.97)	
								3.2–4.7 miles/h	0.71 (0.47–1.05)	
								≥4.8 km/h	0.52 (0.30–0.90)	
								4-level in time	4-level	
								Not walk regularly	1 (referent)	
								1–59 min/week	0.86 (0.57–1.29)	
								1–1.5 h/week	0.49 (0.28–0.86)	
								≥2 h/week	0.48 (0.29–0.78)	
Sesso et al.[d] [23]	Prospective cohort	12,516 (2,135)	CHD + AP	39–88	Male	16	OW	4-level in distance	4-level	Age, body mass index, alcohol intake, hypertension, diabetes,etc.
								<5 km/week	1 (referent)	
								5–<10 km/week	0.88 (0.78–0.99)	
								10– <20 km/week	0.86 (0.75–0.96)	
								≥20 km/week	0.88 (0.78–0.99)	

Table 1 continued

Reference	Study design	Study size (cases)	Outcome	Age range	Gender	Follow-up (year)	Exposure category	Walking level	Relative risk with 95% CI[a]	Adjustment
Manson et al. [30] US	Prospective cohort	72,488 (377)	CHD	40–65	Female	8	OW	3-level in pace	3-level	Age, study period, smoking, body mass index, menopausal status, parental history of myocardial infarction, vitamin-supplement use, alcohol intake, history of hypertension, etc.
								<2 miles/h	1 (referent)	
								2–2.9 miles/h	0.75 (0.59–0.96)	
								≥3 miles/h	0.64 (0.47–0.88)	
								5-level in MET-h/week	5-level	
								≤0.5 MET	1 (referent)	
								0.6–2	0.78 (0.57–1.06)	
								2.1–3.8	0.88 (0.65–1.21)	
								3.9–9.9	0.70 (0.51–0.95)	
								≥10	0.65 (0.47–0.91)	
Hakim et al.[e] [24] US (Hawaii)	Prospective cohort	2,678 (109)	CHD	71–93	Male	2–4	LW	3-level in distance	3-level	Age, high-density lipoprotein cholesterol, hypertension, diabetes, alcohol intake, performed physical function score
								<0.25 mile/day	1 (referent)	
								0.25–1.5 miles/day	0.91 (0.61–1.37)	
								>1.5 miles/day	0.43 (0.25–0.73)	
Pereira et al. [40] US	Randomized trial	196 (13)	CHD	50–65	Female	10	OW	2-level	2-level	Nil
								3.8 miles/week	1 (referent)	
								8.75 miles/week	0.18 (0.04–0.80)	
Folsom et al. [31] US	Prospective cohort	14,040 (NA)	CHD	45–64	Female and male (separate)	4–7	LW	2-level in frequency	2-level (female)	Age, race, field centre
								Not often walk	1 (referent)	
								Very often walk	0.62 (0.35–1.09)	
								2-level in frequency	2-level (male)	
								Not often walk	1 (referent)	
								Very often walk	0.75 (0.53–1.06)	
LaCroix et al. [26] US	Prospective cohort	1,645 (NA)	CHD	≥65	Mixed gender	4–5	OW	3-level in time	3-level	Age, sex, functional status, smoking, body mass index, chronic disease score, self-rated health,alcohol intake
								<1 h/week	1 (referent)	
								1–4 h/week	0.93 (0.60–1.44)	
								>4 h/week	0.63 (0.38–1.03)	

Table 1 continued

Reference	Study design	Study size (cases)	Outcome	Age range	Gender	Follow-up (year)	Exposure category	Walking level	Relative risk with 95% CI[a]	Adjustment
Shaper et al. [28] UK	Prospective cohort	7,735 (245)	CHD	40–59	Male	8	RW[f]	5-level in time	5-level	Age, body mass index, social class and smoking
								None	1 (referent)	
								≤20 min/weekday	0.98 (0.66–1.47)	
								21–40	1.01 (0.70–1.46)	
								41–60	0.64 (0.39–1.06)	
								>60	1.13 (0.61–2.08)	
Morris et al. [22] UK	Case-cohort	9,376 (474)	CHD + AP[g]	45–64	Male	9.3	RW	4-level in time	4-level	Age
								None	1 (referent)	
								≤3.5 h/week	1.12 (0.83–1.51)	
								≤7 h/week	1.02 (0.72–1.44)	
								>7 h/week	1.20 (0.72–1.99)	
								4-level pace and time	4-level	
								Stroll	1 (referent)	
								Normal pace	0.71 (0.53–0.95)	
								Fairly brisk	0.78 (0.57–1.08)	
								Fast	0.21 (0.05–0.84)	
Paffenbarger et al. [25] US	Prospective cohort	16,936 (525)	HA[h]	35–74	Male	6–10	OW	2-level in distance	2-level	Age
								<5 city blocks/day	1 (referent)	
								5 city blocks	0.79 (0.65–0.96)	

[a] The RRs for walking were reported from the lowest to the highest with the lowest as the reference

[b] OW refers to overall walking

[c] LW leisure time walking

[d] The RRs were derived from the graphs published in the paper using image analysis with MATLAB software

[e] Relative risk was recalculated as the original study used the highest walking level as the reference

[f] RW refers to regular walking

[g] AP refers to angina pectoris

[h] HA refers to heart attack

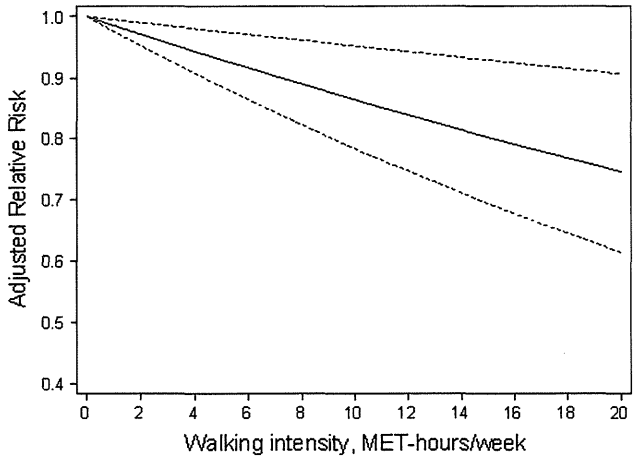

Fig. 2 Dose-response relationship between walking intensity (MET-hours/week) and risk of coronary heart disease. *Dotted lines* represent 95% confidence limits for the linear trend

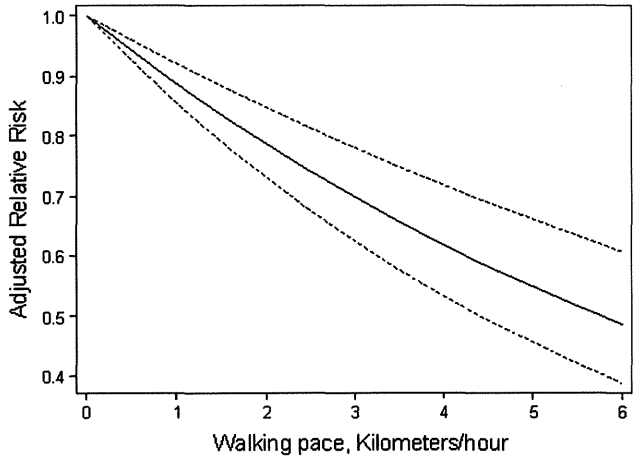

Fig. 3 Dose-response relationship between walking pace (km/h) and risk of coronary heart disease. *Dotted lines* represent 95% confidence limits for the linear trend

Fig. 4 Dose-response relationship between walking time (h/week) and risk of coronary heart disease. *Dotted lines* represent 95% confidence limits for the linear trend

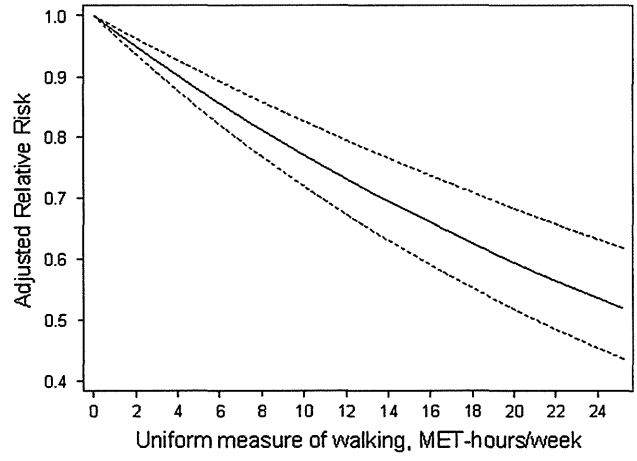

Fig. 5 Dose-response relationship between various measures of walking converted to a uniform measure (MET-hours/week) and risk of coronary heart disease. *Dotted lines* represent 95% confidence limits for the linear trend

of 8 MET-h/week or approximately 30 min of normal walking a day for 5 days a week was associated with a statistically significant 19% reduction in CHD risk.

As a dynamic aerobic physical activity, walking involves large skeletal muscle contraction of more than 50% of the body's total muscle mass for the average 75 kg man [15]. Walking at any pace for any duration expends energy, thus the potential to contribute to incremental favourable metabolic changes. This has important public health implications particularly for physically inactive or aging populations whose physiological response of any given absolute intensity of effort tends to be greater due to their low basal level of cardiorespiratory and muscular parameters [41, 42].

Our meta-analysis results revealed some variations of dose-response gradients. The variations of the gradients on a comparable basis may be partly attributable to the relative accuracy and validity of different walking measures. A study by Kriska [43] found that recall bias inherent with self-reported questionnaires gave rise to 50% or more of response variation even when one year activity patterns were reassessed after an interval of a few days, and the problem was particularly acute if intensities of effort were low. It has been reported that hard activity could be recalled more readily and more precisely than light or moderate effort [44, 45], and walking pace was suggested to be more validly reported than walking time or walking distance [27, 32]. One of the key findings from the meta-analysis by Berlin and Colditz [4] was that a larger health benefit of physical activity was associated with more valid study methods. As far as the study method is concerned, this may partly explain the greater magnitude of the dose-response gradient for walking measured in pace than in MET-hours/week or time in our results.

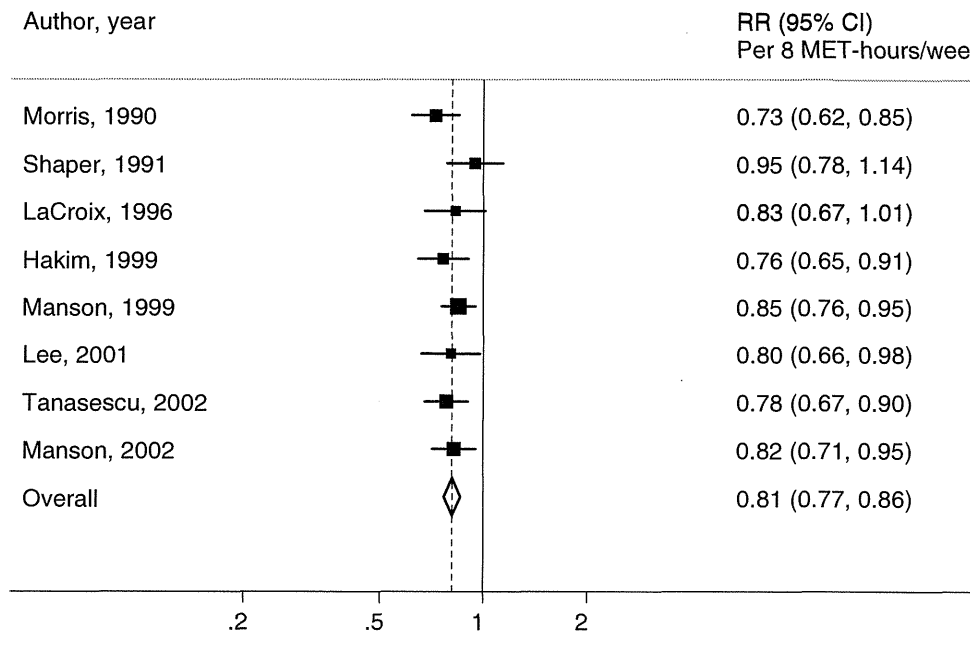

Fig. 6 Summary of study-specific trends (8 MET-h/week is equivalent to 30 min of normal walking a day for 5 days a week) examining the association between walking and risk of coronary heart disease. *Squares* indicate study-specific trend estimates (size of the squares reflects the inverse of the variance); *horizontal lines* indicate 95% confidence intervals; *diamond* indicates the summary relative risk estimate with 95% confidence interval. Test for heterogeneity: $Q = 5.81$, $P = 0.56$; $I^2 = 0\%$)

Table 2 Estimated pooled relative risks of coronary heart disease risk for an increase of 8 MET-h/week of walking levels according to different study characteristics

Characteristic of the study	No. studies	RR (95% CI)
Gender		
Male	4	0.79 (0.71–0.88)
Female	3	0.83 (0.77–0.90)
Mixed	1	0.83 (0.67–1.01)
Age (years)		
<55	4	0.82 (0.74–0.91)
>55	4	0.80 (0.73–0.86)
Follow-up duration (years)		
<6	4	0.80 (0.74–0.88)
>6	4	0.82 (0.74–0.90)

The results from the meta-analysis by Hamer and Chida [18] suggested that a dose-response effect was demonstrated at moderate pace walking (0.71, 0.62 to 0.81 $P < 0.001$) with health benefits achieved in the minimal walking category of approximately 3 h/week which equated to a casual or moderate walking pace of about 3 km/h. The variation in the pooled estimates between this meta-analysis and our meta-analysis reflected different exposure levels being compared. The meta-analysis by Hamer and Chida used the highest versus the lowest approach, comparing the point estimates of CHD risk based on the comparison of the extremes of the distribution of walking as mentioned earlier. The inherent limitation of such an approach lies in its inability to address the issue of referent and non-referent exposure-specific relative risks being likely correlated. By comparison, our meta-analysis used a dose-response gradient approach that takes into account such correlation [35, 36].

The physiological mechanisms underlying the dose-repose effect may be that energy expended during walking increases directly with walking pace [46] and an increase in cardiorespiratory fitness measured in maximum oxygen uptake (VO_{2max}) is proportional to the walking pace adopted [46, 47]. There is also evidence that the magnitude of the response to physical activity training is influenced most strongly by the intensity of training relative to the individual personal level of aerobic fitness [42]. Biologically, the dose-response effect may be mediated through a graded improvement in lipid profile [5, 48–51] and insulin sensitivity [52] with increasing exercise intensity or duration. A single bout of moderate-to-long duration aerobic exercise evoked a 4–6 mg/dl increase in the HDL-cholesterol levels of men and women [51]. The increase in serum HDL-cholesterol levels at 24 h after a bout of exercise performed at an oxygen uptake of 20% below the anaerobic threshold was greater when the exercise duration was 45 min as compared with 30 min [53]. Other pathways of the protective effect may include countering thrombosis by inhibiting clotting process and platelet aggregation [54, 55], deceasing systolic and diastolic pressure associated with favourable changes in plasma catecholamine levels [22, 56]. The marked vasodilatation in active skeletal muscle during walking can lead to sustained lowering of

peripheral resistance and blood pressure [15]. Treadmill walking improved flow-mediated dilation in the posterior tibial artery [57]. The repetitive increases in coronary and peripheral blood flow produced by exercise may facilitate coronary artery adaptation that enhances endothelial response to stress [58].

Our meta-analysis is limited due to the lack of complete data on walking intensity, duration and frequency, adherence to the basal walking levels and participation in other physical activity apart from walking, which makes it difficult to accurately quantify the walking dose. Misclassification of walking dose due to self-reported values was unavoidable. When walking doses were compared across studies, certain assumptions had to be made to convert different walking measures to a comparable uniform measure in MET-hours/week. We strongly suggest that future studies gather and report sufficient information on accurate quantification of walking dose and develop innovative golden standards for objective walking measurement using pedometers or accelerometers. Even though walking pace was suggested to be more validly reported than other measures, more research is needed to determine the relative accuracy and validity of different assessment methods and measures in order to identify the most reproducible, valid and accurate measures.

It is also worth noting that 10 of the 12 studies included in the meta-analysis were conducted in the US, which might involve country-related bias given that the level of sedentariness among populations may vary from country to country. For less sedentary populations, the effect of a 30-min normal walking a day for 5–7 days a week may not be as large as reported in the studies given the evidence that the physiological response of the physically inactive to any given absolute intensity of effort tended to be greater due to their low basal level of fitness as discussed above. Further research is needed on the effect of walking in reducing CHD risk among populations with different basal levels of physical activity and fitness.

Conclusion

Our meta-analysis suggested that walking confers a dose-response protection effect against CHD. The risk for developing CHD tends to decrease as walking dose increases. Given its low injury risk [59] and high sustainability [15], walking should be promoted as an ideal exercise intervention strategy for CHD prevention in the general population.

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III

１．18 歳以上における身体活動量の基準値策定に用いた文献

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A Prospective Study of Overweight, Physical Activity, and Depressive Symptoms in Young Women

Kylie Ball[1], Nicola W. Burton[2] and Wendy J. Brown[2]

This study examined the prospective associations of BMI, physical activity (PA), changes in BMI, and changes in PA, with depressive symptoms. Self-reported data on height, weight, PA, selected sociodemographic and health variables and depressive symptoms (CESD-10) were provided in 2000 and 2003 by 6,677 young adult women (22–27 years in 2000) participating in the Australian Longitudinal Study on Women's Health (ALSWH). Results of logistic regression analyses showed that the odds of developing depressive symptoms at follow-up (2003) were higher in women who were overweight or obese in 2000 than in healthy weight women, and lower in women who were active in 2000 than in sedentary women. Changes in BMI were significantly associated with increased odds of depressive symptoms at follow-up. Sedentary women who increased their activity had lower odds of depressive symptoms at follow-up than those who remained sedentary. Increases in activity among initially sedentary young women were protective against depressive symptoms even after adjusting for BMI changes. These findings indicate that overweight and obese young women are at risk of developing depressive symptoms. PA appears to be protective against the development of depressive symptoms, but does not attenuate the depressive symptoms associated with weight gain. However, among initially sedentary young women, even small increases in PA over time may reduce the odds of depressive symptoms, regardless of weight status.

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INTRODUCTION

Overweight/obesity and depression represent two of the most significant public health problems in developed countries (1,2). Cross-sectional evidence suggests that obese people are more likely to experience depression (3–6), but longitudinal cohort studies provide mixed evidence. Roberts and colleagues found a significant positive association between baseline BMI >85th percentile and self-reported depressive symptoms after 1 year (7), and a significant association between baseline BMI ≥30 kg/m^2 and *incident* but not *prevalent* symptoms after 5 years (8,9). Herva and colleagues found a positive prospective association between obesity at age 14 and depression at age 31, but not between overweight and depression (10). Women who gained weight from 14 to 31 years of age (to BMI >25 kg/m^2 at 31) were no more likely to report depressive symptoms than those who maintained healthy weight, but were twice as likely to report using antidepressants.

The relationship between obesity and depressive symptoms may be explained in part by physical inactivity (11). Individuals who are obese are more likely to be inactive than those of healthy weight (5,12–14), and some prospective studies have found an inverse relationship between physical activity (PA) and prevalent and incident depressive symptoms after 5 (refs. 15,16), 8 (refs. 17,18), 9 (ref. 19), and 20 years (20). Other studies however, have found no relationship after 5 (ref. 21), 15 years (22), and after excluding those depressed at baseline (23). Evidence from randomized controlled trials is limited but suggests that PA can ameliorate depressive symptoms (24,25). These studies have not reported on the concurrent weight and PA change among participants.

In light of the unclear relationships between overweight/obesity, PA and depression, the aims of this study were to examine, in a population-based sample of young women, the prospective associations over 3 years between (i) BMI and PA, and depressive symptoms; and (ii) *changes* in BMI and PA, and depressive symptoms. Young women were the focus of this study, because they comprise a group at high risk of weight gain (26), and of depression (27). It was hypothesized that (i) overweight and obesity would be positively associated, and PA would be negatively associated, with depressive symptoms at 3-year follow-up; (ii) the prospective association between overweight and obesity and depressive symptoms would be attenuated by PA;

[1]Centre for Physical Activity and Nutrition Research, Deakin University, Burwood, Victoria, Australia; [2]School of Human Movement Studies, The University of Queensland, Brisbane, Queensland, Australia. Correspondence: Kylie Ball (kylie.ball@deakin.edu.au)

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(iii) increased BMI would be associated with increased odds of depressive symptoms at 3-year follow-up; and (iv) sedentary women who increased their PA would demonstrate reduced odds of depressive symptoms, regardless of any change in BMI.

METHODS AND PROCEDURES

This study used data provided by participants in the Australian Longitudinal Study on Women's Health (ALSWH). Three age cohorts of women were selected randomly from the national Medicare health insurance database (which includes all citizens and permanent residents of Australia) (28). Further details of recruitment, response rates and surveys can be found at http://www.alswh.org.au. All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. Ethical clearance for the study was obtained from the University of Newcastle, Australia.

This paper focuses on the younger cohort (aged 18–23 years at baseline in 1996), and mail surveys conducted in 2000 and 2003 (since the outcome measure of depression was not included in earlier surveys). In total, 7,790 women responded to both surveys. Retention rates were 68% (2000) and 64% (2003), with attrition associated with lower education, being born outside Australia, and being a smoker. Further information on response rates, attrition and characteristics of nonrespondents is provided elsewhere (29). After exclusion of 927 pregnant women (and 186 who did not respond to the pregnancy question), data from 6,677 women were included in these analyses.

Measures

Surveys included the Center for Epidemiologic Studies Depression Scale (CESD-10) which has been well-validated and has good test-retest and predictive validity (30). CESD-10 scores of ≥10 were used to indicate depressive symptoms (30).

Participants were asked to report height and weight; BMI was calculated (BMI = weight kg/height m^2) and categorized as *underweight* (BMI < 18.5 kg/m^2), *healthy weight* (BMI 18.5–24.9 kg/m^2), *overweight* (BMI 25–29.9 kg/m^2) or *obese* (BMI ≥ 30 kg/m^2) (31). Women were categorized as *BMI maintainers* (2003 BMI within 5% of 2000 BMI), *BMI decreasers* (2003 BMI more than 5% lower than 2000 BMI) or *BMI increasers* (two categories: 2003 BMI more than 5% but less than or equal to 10% greater than 2000 BMI; or 2003 BMI more than 10% greater than 2000 BMI) (26).

PA items assessed the frequency and duration of walking (for recreation or transport), and of moderate- and vigorous-intensity activity in the last week. These questions have demonstrated reliability and validity (32,33). Total MET minutes/week were calculated as (walking minutes × 3.5) + (moderate minutes × 4) + (vigorous minutes × 7.5) (ref. 34), and PA was categorized as: *none* (0 to <40 MET minutes); *very low* (40 to <300); *low* (300 to <600); *moderate* (600 to <1,200); or *high* (≥1,200). The lower cut-point for the moderate category is equivalent to 150 min of moderate-intensity activity per week, as recommended in current Australian and US guidelines (e.g., ref. 35). PA change was categorized as: *remaining at none/very low level; increasing from none/very low to low, increasing from none/very low to moderate,* or *increasing from none/very low to high.*

The following covariates were assessed in 2003: highest educational qualification, marital status, occupation; smoking status, parity status (pregnant women were excluded), and existence of a serious health problem/disability (for details see Table 1).

Statistical analyses

All statistical analyses were performed using SPSS version 12 (SPSS for Windows, Release 11.0.0; SPSS, Chicago, IL). To maximize the number of women whose data could be included in these analyses, *missing* categories were created for PA, BMI and occupation. Analyses of variables associated with depressive symptoms (2003 CESD-10 ≥10) were conducted using χ^2-tests. Means and 95% confidence intervals (CIs) for depressive symptoms (continuous 2003 CESD-10 scores) were calculated for each 2000 BMI and 2000 PA category.

Table 1 Sociodemographic and health characteristics of women in the analysis sample, and proportions of women in each category with depressive symptoms (CESD ≥10) in 2003

	Analysis sample $n = 6,677$ (%)	CESD ≥10* $n = 1,691$ (26% of analytic sample) (%)
2003 Education		$P < 0.001$
No formal/year 10	9.2	34.9
Year 12	18.2	31.6
Trade/apprentice/certificate/ diploma	24.7	28.2
University degree/higher degree	47.9	20.3
2003 Marital status		$P < 0.001$
Never married	39.6	28.7
Married/de facto	57.1	22.3
Separated/divorced/widowed	3.3	53.3
2003 Occupation		$P < 0.001$
Manager/professional/associate professional	46.9	20.9
Trades/advanced clerical/service	15.4	25.3
Intermediate/elementary clerical/ sales/service/transport/laborer	20.6	29.1
No paid job	16.1	35.8
Missing	1.1	32.8
2003 Smoking status		$P < 0.001$
Never smoker	59.1	22.2
Ex-smoker	16.9	27.1
Current smoker	24.0	33.9
Parity status (women pregnant at either survey were excluded)		$P < 0.001$
Never had live birth	64.7	23.3
First birth between 2000 and 2003	8.5	21.0
First birth between 1996 and 2000	9.6	30.8
First birth before 1996	6.1	38.7
2003 Health problems		$P < 0.001$
Have health problem/disability	1.0	51.6
No health problem/disability	99.0	25.5
2000 BMI		$P < 0.001$
Healthy weight	57.8	23.0
Underweight	6.0	27.4
Overweight	18.1	28.2
Obese	9.1	35.1
2000 Physical activity		$P < 0.001$
None	8.7	35.6
Very low	17.4	28.6
Low	15.9	24.1
Moderate	23.6	24.8
High	32.1	23.1

*P values indicate significant association (assessed using χ^2-test) between predictor variable and depressive symptoms (CESD ≥10).

Since associations of PA and BMI category with 2003 CESD-10 scores were found to be nonlinear, 2003 CESD scores were dichotomized and analyzed using the logistic procedure. Crude and adjusted odds ratios (ORs) and 95% CIs were calculated for depressive symptoms (2003 CESD-10 ≥10). Two sets of models were used to investigate associations of 2000 BMI (Model 1) and 2000 PA (Model 2) with 2003 depressive symptoms. These models were: (i) unadjusted ORs (and 95% CI) for women in each 2000 BMI and each 2000 PA category; (ii) ORs (and 95% CI) adjusted for 2000 CESD-10 scores and for sociodemographic, behavioral and health covariates; (iii) ORs (and 95% CI) adjusted for the variables included in (ii), and for 2000 PA (Model 1) or 2000 BMI category (Model 2).

Similarly, the logistic procedure was used to calculate crude and adjusted ORs and 95% CI for depressive symptoms by change in BMI category (Model 1), or change in PA (Model 2). Model 2 included data from women in the none or very low PA categories in 2000. For Models 1 and 2, covariates were as described in (ii) and (iii) above. Model 2 was also examined after adjustment for change in BMI (hypothesis 4).

RESULTS

The sociodemographic and health characteristics of the 6,677 women in this analysis sample, and the proportions of women in each category with CESD-10 score ≥10 in 2003, are presented in Table 1. More than a quarter of the sample had CESD-10 scores >10, suggesting depressive symptoms in 2003, compared with 29% in 2000. Of those with depressive symptoms in 2000 (n = 1,861), 50% also had depressive symptoms in 2003; of those with no depressive symptoms in 2000, 16% (n = 705) had depressive symptoms in 2003.

Mean CESD-10 scores in 2003, by (2000) BMI and PA categories, are shown in Table 2. This table shows that, in general, mean CESD-10 scores in the healthy weight and overweight BMI categories decreased with increasing PA, with the largest difference observed between the none and very low PA categories. For the obese and underweight BMI categories, there was no consistent downward trend in CESD-10 scores with higher

Table 2 Mean CESD-10 scores in 2003 for women in each 2000 BMI and physical activity category

2000 BMI	2000 Physical activity	*n*	Mean CESD-10	95% CI	
Healthy weight	None	283	8.16	7.46	8.85
	Very low	659	7.05	6.65	7.47
	Low	585	6.35	5.95	6.74
	Moderate	898	6.32	5.99	6.66
	High	1,294	6.22	5.94	6.49
	Missing	87	5.49	4.61	6.36
Underweight	None	43	7.60	5.80	9.40
	Very low	69	6.68	5.58	7.78
	Low	66	6.55	5.43	7.66
	Moderate	90	7.08	5.92	8.24
	High	113	7.45	6.39	8.51
	Missing	10	6.50	1.43	11.57
Overweight	None	99	9.00	7.73	10.28
	Very low	201	7.35	6.60	8.08
	Low	185	7.16	6.42	7.90
	Moderate	299	6.99	6.43	7.55
	High	379	6.66	6.12	7.19
	Missing	21	8.60	5.91	11.29
Obese	None	76	8.58	7.23	9.94
	Very low	125	7.73	6.78	8.68
	Low	105	8.39	7.19	9.60
	Moderate	133	8.24	7.23	9.25
	High	146	7.76	6.87	8.66
	Missing	11	12.21	8.07	16.35

CI, confidence interval.

Table 3 Unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for 2003 CESD-10 scores ≥10 by 2000 BMI (Model 1) and 2000 physical activity (Model 2) categories

	N	Unadjusted OR	95% CI		OR adjusted for covariates[a]	95% CI		OR fully adjusted[b]	95% CI	
Model 1: 2000 BMI										
Healthy weight	3,858	1.00			1.00			1.00		
Underweight	401	1.26	0.99	1.60	1.09	0.84	1.43	1.09	0.83	1.42
Overweight	1,207	**1.32**	**1.14**	**1.53**	**1.21**	**1.02**	**1.43**	**1.21**	**1.03**	**1.43**
Obese	610	**1.81**	**1.50**	**2.18**	**1.34**	**1.09**	**1.67**	**1.33**	**1.08**	**1.65**
Missing	601	1.33	1.10	1.62	1.07	0.85	1.34	1.07	0.85	1.34
Model 2: 2000 physical activity										
None	583	1.00			1.00			1.00		
Very low	1,164	**0.72**	**0.58**	**0.90**	0.90	0.70	1.15	0.91	0.71	1.16
Low	1,061	**0.58**	**0.46**	**0.72**	**0.76**	**0.59**	**0.99**	**0.77**	**0.59**	**0.99**
Moderate	1,573	**0.60**	**0.49**	**0.74**	0.82	0.65	1.04	0.82	0.65	1.05
High	2,145	**0.54**	**0.45**	**0.66**	**0.78**	**0.62**	**0.98**	**0.79**	**0.63**	**1.00**
Missing	151	**0.61**	**0.41**	**0.93**	1.28	0.76	2.14	1.29	0.77	2.17

Significant associations shown in boldface.
[a]Covariates were 2003 highest educational qualification, 2003 marital status, 2003 occupation, 2003 smoking status, parity status across all surveys, 2003 health problem/disability and 2000 CESD-10 score. [b]Covariates were those above, as well as 2000 physical activity (Model 1) and 2000 BMI (Model 2).

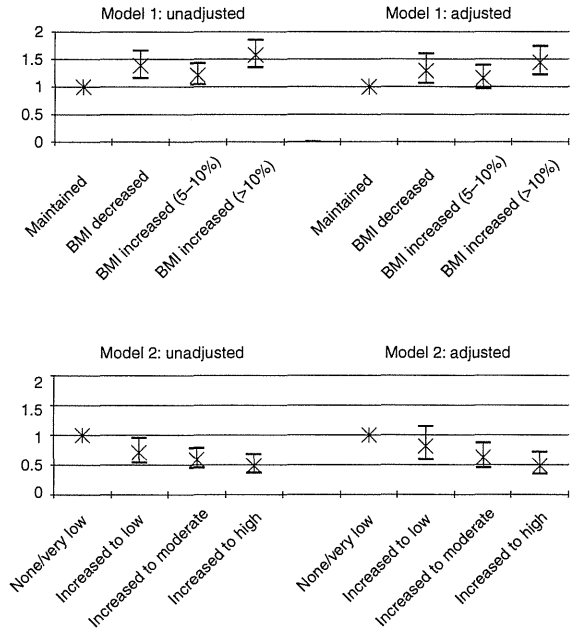

Figure 1 Unadjusted (left) and adjusted (right) odds ratios for 2003 CESD-10 ≥10 by changes in BMI and physical activity (PA). Model 1: changes in BMI from 2000 to 2003: referent category, maintained BMI within ±5% (N = 2,847); BMI decreased by >5% (N = 796); BMI increased by 5–10% (N = 1,132); BMI increased by >10% (N = 1,166). Model 2: includes only women who reported none/very low PA in 2000; increases in PA from 2000 to 2003: referent category, none/very low at both times (N = 749); none/very low to low (N = 315); none/very low to moderate (N = 353); none/very low to high (N = 301). Adjustment for 2003 highest educational qualification, 2003 marital status, 2003 occupation, 2003 smoking status, parity status across all surveys, 2003 health problem/disability and 2000 CESD-10 score. Additional covariates were 2000 PA (Model 1), and 2000 BMI (Model 2). Model 2 was also tested adjusting for change in BMI category rather than 2000 BMI (Model 2—data not shown).

levels of PA. Mean CESD-10 scores were generally higher for women in the obese BMI category than the healthy weight category, regardless of PA level.

The ORs (and 95% CIs) for depressive symptoms (CESD-10 ≥10) in 2003, by (2000) BMI and PA categories, are shown in Table 3. Compared with women in the healthy weight range, and after adjustment for all covariates, the odds of depressive symptoms in 2003 were higher among women who were overweight or obese in 2000 (Model 1, Table 3). Adjustment for PA level in 2000 had negligible impact on these ORs. In contrast, adjusted odds of depressive symptoms in 2003 were lower among women who reported any level of PA, compared with women who reported none (Model 2, Table 3). After adjustment for sociodemographic variables and BMI, ORs for depressive symptoms in 2003 became nonsignificant for the very low category, but remained significantly lower among women who reported low, moderate (borderline significant) or high levels of PA.

The associations between changes in BMI and changes in PA over 3 years and depressive symptoms (CESD-10 ≥10) in 2003 are shown in Figure 1. The upper panel shows that, compared with women who maintained their weight, women whose BMI changed had an increased risk of depressive symptoms in 2003. This was true for those whose BMI decreased, as well as for those whose BMI increased. However, after adjustment for the covariates, including PA in 2000, ORs were significant only for women whose BMI decreased (P = 0.014), or increased by >10% (P < 0.001).

Associations between changes in PA over 3 years and depressive symptoms in 2003 for women who reported none or very low PA in 2000 are shown in the second panel of Figure 1. Compared with women who maintained none or a very low level of PA, those who increased their PA level from none or very low to either a moderate or high level had significantly lower risk of depressive symptoms in 2003, which remained after adjustment for covariates and 2000 BMI, and also after adjustment for covariates and change in BMI (latter data not shown).

DISCUSSION

This cohort study of young women confirmed that both BMI and PA, and changes in these variables, are significantly associated with depressive symptoms over a 3-year period.

Our first hypothesis was confirmed with overweight and obesity positively associated, and PA negatively associated with depressive symptoms at 3-year follow-up. Compared with a referent category of healthy weight women, the odds of reporting depressive symptoms after 3 years were ~1.2 for overweight and 1.3 for obese women, even after adjustment for confounding variables. This finding is consistent with the 5-year study by Roberts *et al.* (8,9), but in contrast with the 17-year study findings of Herva *et al.* (10), who reported increased risk of depressive symptoms only among obese women. In addition, the present study showed that young women who reported even low levels of PA (equivalent to 75–150 min of moderate-intensity activity) had ~25% reduced odds of reporting depressive symptoms after 3 years. These results support a growing body of longitudinal research suggesting prospective associations of PA with depression (15–20).

Our second hypothesis was that the prospective association between overweight and obesity and depressive symptoms would be attenuated by PA. This was not supported by our results, which showed that the increased odds of depressive symptoms in overweight and obese women (compared with healthy weight women) at 3-year follow-up were not attenuated by adjustment for PA. Taken together, these results suggest that although PA was associated with a lower likelihood of depressive symptoms at follow-up, it did not ameliorate the odds of depressive symptoms at follow-up associated with overweight and obesity.

Our third hypothesis was that increased BMI at 3-year follow-up would be associated with increased odds of depressive symptoms at follow-up. This hypothesis was partly confirmed, in that large increases in BMI (>10%) were associated with depressive symptoms at follow-up after adjustment for covariates. This contrasts with the findings of Herva *et al.* (10), although women who gained weight in that study were more likely to report using antidepressants, which would suggest

some level of depressive symptoms. We also found an increase in the odds of depressive symptoms in women whose BMI *decreased* by >5% in this period, even after adjustment for ill health and other confounding factors. This may be attributable to factors that were not measured in this study, such as the occurrence of stressful life events, resulting in weight loss and depressive symptoms. Alternatively, women may have developed depressive symptoms if positive expectations associated with weight loss were not realized.

The final hypothesis was that sedentary women who increased their PA would demonstrate reduced odds of depressive symptoms at follow-up, irrespective of any BMI change. This was also supported, in that women who increased their PA (from the lowest level) had lower odds of depressive symptoms at follow-up than women who remained sedentary, and this association held after adjustment for relevant covariates and for change in BMI. This suggests, consistent with earlier research with mid-aged women from the ALSWH (16), that if sedentary young women could increase their PA, even by as little as 75 min per week, they would be at reduced risk of depressive symptoms.

The strengths of this study are the longitudinal cohort design, the large population-based sample, and the ability to control for multiple confounding variables. The major limitation is that data were collected by self-report, which is vulnerable to recall or social desirability bias. The survey items used, however, have acceptable reliability and validity. Due to the large number of categories, we assessed only a subset of all possible combinations of changes in PA levels. Despite the prospective design, and the fact that most of the relationships examined remained after adjustment for confounders that are known to impact on mental health, we are still unable to infer causality from these results.

In conclusion, increases in BMI and decreases in PA over time were significantly associated with depressive symptoms in these young women. The inter-relationships between BMI, PA and changes in these factors, and depressive symptoms are, however, complex. Notwithstanding, the results suggest that if young inactive women increase their PA, they will be less likely to develop depressive symptoms. Although some randomized controlled intervention trials have examined relationships between PA and depression (e.g., ref. 36), most of these have been conducted with clinical participants, and few have examined the independent and combined effects of *changes* in *both* BMI and PA. More randomized trials are required to confirm the results from this prospective study.

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DISCLOSURE

The authors declared no conflict of interest.

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