Leisure time physical activity and dementia risk: a dose-response meta-analysis of prospective studies

Wei Xu,1 Hui Fu Wang,2 Yu Wan,2 Chen-Chen Tan,2 Jin-Tai Yu,2 Lan Tan1,2

ABSTRACT

Background There is considerable evidence of the favourable role of more physical activity (PA) in fighting against dementia. However, the shape of the dose–response relationship is still unclear.

Objective To quantitatively investigate the relationship between dementia and PA.

Design PubMed, EMBASE, Ovid and the Cochrane Library were searched for prospective studies published from 1 January 1995 to 15 October 2016. Two types of meta-analyses were performed with a focus on the dose–response relationship using two stage generalised least squares regression.

Results The primary analysis exhibited a dose–response trend for all-cause dementia (ACD), Alzheimer’s disease (AD) but not for vascular dementia (VD). In the dose–response analysis, either ACD (p trend <0.005; p non-linearity=0.87) or AD (p trend <0.005; p non-linearity=0.10) exhibited a linear relationship with leisure time PA (LTPA) over the observed range (0–2000 kcal/week or 0–45 metabolic equivalent of task hours per week (MET-h/week)). Specifically, for every 500 kcal or 10 MET-h increase per week, there was, on average, 10% and 13% decrease in the risk of ACD and AD, respectively.

Conclusions We have reported, for the first time, the dose–response relationship between LTPA and dementia, further supporting the international PA guideline from the standpoint of dementia prevention.

INTRODUCTION

Dementia is a common neurodegenerative disease and its prevention has increasingly become the focus of the field, which to the best of our knowledge is attributed to three main reasons: (1) no cure or effective therapy is available for dementia; (2) the situation has been publicly highlighted, especially by the World Alzheimer Report 2015, reporting that over 46 million people live with dementia and the number is estimated to double every 20 years; (3) several lines of evidence showed that improved cognition and lowered dementia risk might be achievable via self-managing modifiable risk factors.1–3 This hypothesis has been encouragingly supported by epidemiological findings that the prevalence or incidence of dementia in Europe and the USA has stabilised or may even be declining.4–5

Physical activity (PA) is a common modifiable risk factor and it has been indicated that PA is negatively associated with the risk of dementia,6–13 although some reported no association,14 15 probably due to the heterogeneous methodologies and categorisation. Several international guidelines concerning PA have been developed based on pre-existing epidemiological evidences concerning chronic non-communicable diseases.16 17 Guidelines from the USA and the WHO recommend that adults do at least 150 min of moderate intensity aerobic PA or 75 min of vigorous intensity aerobic PA or an equivalent combination every week, and to double it for additional benefits.16 Recently, ‘Healthy Japan 21’ has proposed a project named ‘+10 min of PA per day’, calling on adults to perform 60 min of moderate to vigorous PA every day.17 Nonetheless, we know little about the dose–response relationship between dementia and PA, and to what extent the amount of PA in guidelines is effective in lowering the risk of dementia.

Thus we conducted a dose–response meta-analysis to quantify the association between dementia and PA, with a specific focus on leisure time PA (LTPA) (eg, sports,
exercises, recreational activities or activities excluding occupational and commuting activities).

**METHODS**

**Search strategy**

According to the recommendations of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group and the PRISMA 2009 guidelines (see the online supplementary file 1, table 1),18 19 we searched PubMed, EMBASE, Ovid and the Cochrane Library from 1 January 1995 to 15 October 2016. The 1995 cut-off was chosen to reflect possible changes in PA categorisation in analyses since publication of the 1995 US Centers for Disease Control and Prevention/American College of Sports Medicine guideline.20 We used the following key words, among others, for searching: physical activity, walking, exercise, exercise training, fitness, dementia, Alzheimer, prospective, cohort (see online supplementary file 1, table 2). No restrictions were imposed except that the language was limited to English. Bibliographies of eligible studies and relevant meta-analyses were hand-searched for potentially omitted studies (figure 1).

**SELECTION CRITERIA**

The inclusion criteria were as follows: (1) the study is a prospective cohort or prospective nested case-control study; (2) the study investigated the association between dementia (all-cause dementia (ACD), Alzheimer’s disease (AD) or vascular dementia (VD)) and PA; (3) PA is categorised into ≥3 layers, which can be reflective of the dose–response trend; (4) the study reported multi-adjusted level-specific relative ratio (RR), 95% confidence interval (CI) and, for the dose–response analysis, the level-specific case number and person-years or sufficient data for driving these numbers. Studies were excluded if they failed to meet any criteria detailed above. Additionally, if multiple articles were published based on the same cohort, we chose that with the longer follow-up or a larger sample size. Two investigators independently made the inclusion decisions and any controversies were resolved by discussion.

**Data extraction and quality evaluation**

Using a standardised sheet, two investigators independently extracted the data for each study, including the first author, publication year, cohort name, region (eg, Northern America, Europe, Africa), sample source (eg, community or database), gender (men, women or combined), age and health condition at baseline, follow-up, case number, sample size and person-years stratified by PA, diagnostic criteria, method of assessing PA, type of PA (eg, LTPA, occupational PA, walking or mixed PA), amount of PA, unit (eg, kcal/week, metabolic equivalent task-hours per week (MET-h/week)), duration (hours) of specific intensity of PA per week (h/week) and frequency (times/week), adjusted confounders and multi-adjusted RR and 95% CI (see online supplementary file 2). The study was evaluated using the Newcastle–Ottawa Quality Assessment Scale, which allowed a total score of up to 9 points and only studies with ≥7 points were further included.

**Statistical analysis**

Two types of meta-analyses were performed using the random effect model.21 First, summary RR and 95% CI for ‘highest versus lowest’ and ‘the second lowest versus lowest’ were calculated and compared to primarily evaluate whether a dose–response trend existed between dementia (ACD, AD and VD) and PA (irrespective of type). Next, a dose–response analysis was performed according to PA unit (eg, kcal/week, metabolic equivalent task-hours per week (MET-h/week)), duration (hours) of specific intensity of PA per week (h/week) and frequency (times/week), adjusted confounders and multi-adjusted RR and 95% CI (see online supplementary file 2). The study was evaluated using the Newcastle–Ottawa Quality Assessment Scale, which allowed a total score of up to 9 points and only studies with ≥7 points were further included.
The overall significance of the curve was examined by testing the joint effect of the spline transformations. A non-linear relationship was explored by testing the null hypothesis that the regression coefficients of the spline transformations were all equal to 0, as described in our previous study. However, we were only able to apply generalised least squares regression methods to assess LTPA as there were too few studies eligible for quantitative estimates of other types.

Data transformations were performed as the reference category is supposed to be the least exposure and the PA unit unified in the dose–response analysis. For studies where the reference group was not the lowest category, we regarded the lowest as the reference and recalculated the effect size (RR and 95% CI) using the method by Orsini et al. Further, ‘kcal/week’ and ‘MET-h/week’ were viewed as analytic units, both of which are comprehensive indexes as they incorporate intensity, duration and frequency. ‘MET’ is a physiological index describing the energy cost of PA and is defined as caloric expenditure per kilogram of body weight per hour of activity (see the formula below).

$$1 \text{ MET} = \frac{1}{1.25} \text{ kcal} \cdot \frac{1}{\text{kg} \cdot \text{h}}$$

To resolve the difference in PA units in different studies, we adopted the classification of Ainsworth et al. to categorise PA into low (1.6–2.9 METs), moderate (3–<6 METs) and vigorous (≥6 METs) intensity (we used here the mean value, eg 4.5 METs for moderate intensity), by which we converted the duration of specific intensity PA (h/week) to MET-h/week. On the other hand, 150min of moderate intensity PA is estimated by Sattelmair et al. to be roughly equivalent to 550 kcal for both genders combined. Accordingly, we conducted mutual transformation between kcal/week (Y) and MET-h/week (X).

$$\frac{4.5 \text{ [MET] } \cdot 2.5 \text{ [h]}}{550 \text{ [kcal]}} = \frac{X \text{ [MET-h]} }{Y \text{ [kcal]}}$$

In one study by Tolppanen et al., LTPA was assessed with the question: ‘How often do you participate in leisure time physical activity that lasts at least 20–30 min and causes breathlessness and sweating?’ It had been reported that ‘exercise vigorous enough to work up a sweat’ is equivalent to 30 min of moderate to vigorous intensity PA, for which we used 7 METs as a proxy according to Sattelmair et al. Otherwise, for those included in the dose–response analysis, the median or mean PA level for each category was assigned to each corresponding RR. When unavailable, we assigned the midpoint of the upper and lower boundary in each category as the mean PA level. For studies with an open ended upper boundary (eg, >8090 kcal/week or ≥3 times), we multiplied the given upper boundary by 1.25 and used this value (10113 kcal/week or 3.75 times in the example). For studies that reported PA by frequency (times/week), we converted the frequencies to hours per week by assigning a dose of 45 min per session, according to the estimated mean duration of activity per session from the HUNT study.

The heterogeneity among studies was assessed by Q test and I² statistic with a significance level of p<0.05. I² values with cut-offs of 30% and 50% are considered to indicate low (<30%), moderate (30–50%) and high (>50%) heterogeneity, respectively. Publication bias was evaluated using the Egger test, and where statistically significant bias was found, the trim and fill method was used to adjust it. In addition, we further conducted multiple subgroup analyses to explore the source of heterogeneity and to assess the potential interaction of study characteristics, including age, sex, geographic region, Newcastle–Ottawa Quality Assessment Scale scores, follow-up rate and duration, diagnosis criteria, sample size, PA unit, adjusted confounders (apolipoprotein E4 (APOE4), body mass index (BMI) and cardiovascular condition) and PA type (mixed PA, LTPA and walking). All statistical analyses were conducted using Stata V.12.0 (StataCorp, College Station, Texas, USA), with two tailed p<0.05 for statistical significance.

RESULTS

Figure 1 shows the procedure for literature searching. A total of 14 198 English papers were found after de-duplication; 13905 were excluded after reviewing the titles and abstracts, leaving 293 papers, among which 283 were full text available and the other 10 abstracts were reviewed and were not found to meet the inclusion criteria. Another seven potential papers were further identified from the references of relevant reviews. After a quick screening of the full text articles, 49 were considered potentially eligible and were included for detailed evaluation, after which 34 were finally excluded (see online supplementary file 1, table 3) and a total of 16 studies (15 for ACD, 8 for AD and 4 for VD) were included for the primary analysis and five studies for the dose–response analysis (4 for ACD and 4 for AD).

Description of studies included

Fifteen studies (10 in Europe, 4 in Northern America and 1 in Africa) with 37436 participants for ACD (table 1), 8 studies (4 in Europe and 4 in Northern America) with 25031 participants for AD (table 2) and 4 studies (2 in Europe and 2 in Northern America) with 16797 participants for VD were included in the primary analysis. During follow-up (3–31.6 years for ACD, 3.9–31.6 years for AD and 4–11.9 years for VD), at least 2665 (as case number was not given in two studies, 1337 and 343 participants who were not suffering from dementia at baseline were diagnosed with ACD, AD and VD, respectively. Four studies (2 in Europe and 2 in Northern America) with 9149 participants for ACD and 4 studies (1 in Europe and 3 in Northern America) with 9144 participants for AD were included in the dose–response analysis. During
### Table 1: Characteristics of studies included in the meta-analysis for all-cause dementia

<table>
<thead>
<tr>
<th>First author; year; country</th>
<th>Cohort and sample source</th>
<th>Sex; % women</th>
<th>Baseline age (years) (mean (SD) or range)</th>
<th>Follow-up (mean (SD) or range)</th>
<th>Dementia criteria</th>
<th>Sample size</th>
<th>Incident case</th>
<th>PA type</th>
<th>Amount of PA (unit)</th>
<th>Adjusted confounders</th>
<th>Multi-adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ravaglia 14 ; 2008; Italy</td>
<td>CHCS; community dwelling elders</td>
<td>C; 56.5%</td>
<td>73.1 (6.2)</td>
<td>31.4; 70%</td>
<td>DSM-IV criteria</td>
<td>100</td>
<td>NA</td>
<td>High (5) or (6)</td>
<td>Moderate (3) or (4)</td>
<td>Age, sex, education, BMI, smoking, alcohol consumption, hypertension, and Charlson index</td>
<td>0.70 (0.44 to 1.12)</td>
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<tr>
<td>Tolppanen 17 ; 2015; Finland</td>
<td>CHCS; community dwelling elders</td>
<td>C; 56.5%</td>
<td>73.1 (6.2)</td>
<td>31.4; 70%</td>
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</table>

**For qualitative and quantitative analysis:**

- **Only for qualitative meta-analysis:**
  - Age, sex, education, BMI, smoking, alcohol consumption, hypertension, and Charlson index (C: 0.43 (0.29 to 0.63) W: 0.69 (0.51 to 0.95) M: 0.61 (0.35 to 1.08))
  - Aging, education, and ADPOE genotype (C: 0.69 (0.55 to 0.88) W: 0.87 (0.70 to 1.08) M: 0.72 (0.55 to 0.94))
  - Aging, education, and ADPOE genotype (C: 0.63 (0.45 to 0.88) W: 0.83 (0.65 to 1.06) M: 0.59 (0.39 to 0.88))
  - Aging, education, and ADPOE genotype (C: 0.45 (0.30 to 0.69) W: 1.29 (0.95 to 1.75) M: 2.13 (1.47 to 3.07))
  - Aging, education, and ADPOE genotype (C: 0.39 (0.25 to 0.60) W: 1.14 (0.73 to 1.77) M: 2.24 (1.25 to 4.17))
  - Aging, education, and ADPOE genotype (C: 0.63 (0.43 to 0.91) W: 0.87 (0.70 to 1.08) M: 0.61 (0.35 to 1.08))
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**For quantitative and qualitative analysis:**

- Age, sex, education, and ADPOE genotype (C: 0.69 (0.55 to 0.88) W: 0.87 (0.70 to 1.08) M: 0.72 (0.55 to 0.94))
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<th>Baseline age (years) (mean (SD) or range)</th>
<th>Follow-up period (mean (SD) or range)</th>
<th>Disease criteria</th>
<th>Sample size</th>
<th>Incident cases</th>
<th>PT type</th>
<th>Amount of PA (unit)</th>
<th>Adjusted confounders</th>
<th>Multi-adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quevauviller et al. (2011, France)</td>
<td>Three-City study; population based study</td>
<td>C: 61%</td>
<td>73.9–79.9 (3.3)</td>
<td>4 (maximum); 52.3%</td>
<td>DMB-IV criteria</td>
<td>2091</td>
<td>147</td>
<td>Mixed-PA</td>
<td>Low</td>
<td>Age, education and the presence or absence of chronic medical illnesses, baseline score on the Blessed Information–Memory–Concentration test</td>
<td>1.00 (1.00 to 1.01)</td>
</tr>
<tr>
<td>Akbaraly et al. (2009, France)</td>
<td>Three-City study; population based study</td>
<td>C: 63%</td>
<td>73.9–78.3 (5.3)</td>
<td>4 (maximum); 92.3%</td>
<td>DSM-IV criteria</td>
<td>34</td>
<td>9</td>
<td>Mixed-PA</td>
<td>&lt; 5 points</td>
<td>Gender, educational level, occupational grade, study centre, mental status, hypoglycaemia, diabetes, vascular diseases history, hypertension, depression, symptoms, APOE genotype, lifestyle in daily life activity, and cognitive impairment assessed by MMSE</td>
<td>1.00 (1.00 to 1.01)</td>
</tr>
<tr>
<td>Verghese et al. (2009, USA)</td>
<td>Three-City study; population based study</td>
<td>C: 74%</td>
<td>78.9–79.6 (3.1)</td>
<td>5.1 (median); 96.1%</td>
<td>DSM-III-R criteria</td>
<td>36</td>
<td>124</td>
<td>Mixed-PA</td>
<td>≥ 10 points</td>
<td>Age, sex, educational level, and the presence or absence of chronic medical illnesses, baseline score on the Blessed Information–Memory–Concentration test</td>
<td>1.00 (1.00 to 1.01)</td>
</tr>
<tr>
<td>Wang et al. (2009, Sweden)</td>
<td>Three-City study; population based study</td>
<td>C: 100%</td>
<td>84 (75–98)</td>
<td>4.7; NA</td>
<td>Diagnostic and Statistical Manual of Mental Disorder-IV clinical criteria</td>
<td>35</td>
<td>114</td>
<td>Mixed-PA</td>
<td>No</td>
<td>Age, sex, education, baseline MMSE score, comorbidity, depressive symptoms and physical functioning</td>
<td>0.97 (0.91 to 1.04)</td>
</tr>
<tr>
<td>Abbott et al. (2009, USA)</td>
<td>Three-City study; population based study</td>
<td>M: 64%</td>
<td>75 (58–98)</td>
<td>3.95%</td>
<td>Leisure–walking</td>
<td>43</td>
<td>6</td>
<td>Mixed-PA</td>
<td>No</td>
<td>Age, sex, educational level, and the presence or absence of chronic medical illnesses, baseline score on the Blessed Information–Memory–Concentration test</td>
<td>0.95 (0.90 to 1.01)</td>
</tr>
</tbody>
</table>

Primary analysis and subgroup analysis

For ACD, there was heterogeneity between subgroups (figure 3). For AD, there was heterogeneity between subgroups (figure 4). For both ACD and AD, there was no heterogeneity between subgroups (figure 5). For both ACD and AD, there was no heterogeneity between subgroups (figure 6).

Only the primary analysis for ACD (n=15; see online supplementary file 1, table 4) was eligible for analysis for publication bias while the number of studies included in other analyses was small (n=10). No publication bias was revealed by funnel plot and statistical test (figure 1, table 5). The inverse association between subgroups was significant for both ACD and AD (figure 2). The inverse association between subgroups was significant for both ACD and AD (figure 2). The inverse association between subgroups was significant for both ACD and AD (figure 2). The inverse association between subgroups was significant for both ACD and AD (figure 2).
Table 2  Characteristics of studies included in the meta-analysis for Alzheimer’s disease

<table>
<thead>
<tr>
<th>First author; year and country</th>
<th>Cohort and sample source</th>
<th>Sex % women</th>
<th>Baseline age (mean (SD) or range)</th>
<th>Follow-up time (SD) and rate (%)</th>
<th>AD criteria</th>
<th>Sample size</th>
<th>Incident case</th>
<th>PA type</th>
<th>Amount of PA (unit)</th>
<th>Adjusted confounders</th>
<th>Multi-adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarmeas  ;2009; USA WHICAP; community dwelling elders</td>
<td>C; 69%</td>
<td>77.2 (6.4)</td>
<td>5.6 (3.3); 66%</td>
<td>NINCDS-ADRD A criteria</td>
<td>620</td>
<td>71</td>
<td>LTPA</td>
<td>Mixed PA</td>
<td>Median (hours/week)</td>
<td>Multifactorial</td>
<td>0.71 (0.51 to 0.98)</td>
</tr>
<tr>
<td>Ravaglia  ;2008; Italy CSBA; population based study</td>
<td>C; 53.5%</td>
<td>73.2 (6.3)</td>
<td>3.8 (0.7); 96%</td>
<td>NINCDS-ADRD A criteria</td>
<td>250</td>
<td>21</td>
<td>Mixed PA</td>
<td>Median (hours/week)</td>
<td>&gt;1774 kcal/week</td>
<td>Age, gender, education, and APOE genotype; cardiovascular disease; hypertension and hyperhomocysteinemia; basic activities of daily living (BADL) and instrumental activities of daily living (IADL)</td>
<td>0.80 (0.65 to 0.99)</td>
</tr>
<tr>
<td>Pedrali  ;2003, USA</td>
<td>QHC; community dwelling elders</td>
<td>C; 58.1%</td>
<td>74.8 (4.9)</td>
<td>5.2; 94%</td>
<td>NINCDS-ADRD A criteria</td>
<td>844</td>
<td>69</td>
<td>LTPA</td>
<td>Median (hours/week)</td>
<td>&gt;248 kcal/week</td>
<td>Age educational level, gender, ethnicity, APOE4; baseline MMSE scores; WHICAP white matter score; ADL, IADL, and social support score</td>
</tr>
<tr>
<td>Laurin  ;2001, Canada</td>
<td>CSHa; community dwelling elders</td>
<td>C; 60%</td>
<td>65 (6)</td>
<td>5.72%</td>
<td>NINCDS-ADRD A criteria</td>
<td>1165</td>
<td>61</td>
<td>LTPA</td>
<td>Regular</td>
<td>No regular PA; Age, sex and educational level</td>
<td>0.67 (0.46 to 0.98); 0.87 (0.51 to 1.48); 0.61 (0.25 to 1.50)</td>
</tr>
<tr>
<td>Neergaard  ;2013; Denmark</td>
<td>PRPP study RCT</td>
<td>W; 100%</td>
<td>70.1 (75.1)</td>
<td>17.9 (9.3); 94%</td>
<td>IQD10</td>
<td>1550</td>
<td>81</td>
<td>Mixed PA</td>
<td>None</td>
<td>Age, sex, education, BMI, smoking, vascular risk factors, and myocardial infarction</td>
<td>0.84 (0.59 to 1.21)</td>
</tr>
<tr>
<td>Arnl  ;2008; Sweden</td>
<td>STR; National Swedish Twin Registry</td>
<td>C; 61%</td>
<td>48.1 (5.3)</td>
<td>31.3; 70%</td>
<td>NINCDS-ADRD A criteria</td>
<td>397</td>
<td>31</td>
<td>LTPA</td>
<td>Leisure</td>
<td>Healthy lifestyle; Age, gender, education, BMI, smoking, alcohol consumption, and lifestyle factors</td>
<td>0.64 (0.41 to 1.00)</td>
</tr>
<tr>
<td>Alkema  ;2009; France</td>
<td>Three-City Study; population based study</td>
<td>C; 61%</td>
<td>73.6 (50.5–51)</td>
<td>51.5; 85%</td>
<td>NINCDS-ADRD A criteria</td>
<td>299</td>
<td>5</td>
<td>Leisure</td>
<td>Leisure time physical activity; Age, gender, education, BMI, smoking, alcohol consumption, and lifestyle factors</td>
<td>0.24 (0.14 to 0.88)</td>
<td></td>
</tr>
<tr>
<td>Aubert  ;2004, USA</td>
<td>HHS; population based study</td>
<td>M; 18%</td>
<td>64 (77–98)</td>
<td>4.3; NA</td>
<td>NINCDS-ADRD A criteria</td>
<td>600</td>
<td>30</td>
<td>Leisure</td>
<td>Leisure time walking</td>
<td>Age, APOE, baseline CASI score decline in Parkinson’s disease, physical performance score, education, BMI, childhood/sex sport engagement in Japan, status as a skilled professional, hypertension, diabetes, prevalent coronary heart disease, and total and HDL cholesterol</td>
<td>0.98 (0.90 to 1.05)</td>
</tr>
</tbody>
</table>

NINCDS-ADRD A, National Institute of Neurological Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association; 3MSE, Modified Mini-Mental State Examination; ADL, activities of daily living; APOE, apolipoprotein E; BMI, body mass index; C, control; CASI, Cognitive Abilities Screening Instrument; CDR, Clinical Dementia Rating; CHIC, Cardiovascular Health Care Project; CSBA, Control Study of Brain Aging; CSHA, Canadian Study of Health and Ageing; CSK, Canadian Study of Health and Ageing; HAAS, Honolulu-Area Aging Study; HKS, Helsingborg-Karlskrona; ICD, Instrumental activities of daily living; IQD10, International Quality of Dementia 10-item version; LTR, Lubben Social Network; LTPA, leisure time physical activity; MET, metabolic equivalent of task; MMSE, Mini-Mental State Examination; NA, not accessible; NINCDS-ADRD A, National Institute of Neurological Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association; O, original result; PA, physical activity; PRPP, Prospective Population Risk Project; RCT, randomised controlled trial; STR, Swedish Twin Registry; T, result after data transformation; WHICAP, Washington Heights-Inwood Columbia Aging Project.
Dose–response analysis

Five studies were included in the dose–response analysis, among which four reported mean LTPA level that varied from 0 to 2000 kcal/week or 45 MET-h/week. One study reported mixed PA (including LTPA and walking) with the upper limit surpassing 10000 kcal/week or 200 MET-h/week (see online supplementary file 2). Thus we first conducted the dose–response analysis of four studies to investigate the relationship of PA (irrespective of type) over a larger range (see online supplementary file 1, table 7). Next, we independently analysed the three studies that reported LTPA over a specific range of 0–2000 kcal/week or 0–45 MET-h/week.

By kcal/week, over 0–10000 kcal/week, a significant linear relationship between ACD and PA was established (p for heterogeneity=0.09; p for non-linearity=0.2), with a 4% decrease (95% CI 0.94 to 0.99) of ACD risk per 500 kcal/week increment (see online supplementary file 1, figure 2A). Nevertheless, the relationship for AD appeared to be non-linear (p for heterogeneity=0.19; p for non-linearity=0.03), with the slope flattening at 1000 kcal/week (see online supplementary file 1, figure 2B).

Figure 2  Primary analysis for Alzheimer’s disease (AD) and all-cause dementia (ACD). The summary result showed a more significant decrement in ACD or AD risk for high amounts of physical activity (PA) (RR 0.75, 95% CI 0.63 to 0.89 for ACD (A) and RR 0.72, 95% CI 0.58 to 0.90 for AD (C)) than low amounts of PA (RR 0.78, 95% CI 0.66 to 0.93 for ACD (B) and RR 0.80, 95% CI 0.67 to 0.95 for AD (D)).

Figure 3  Subgroup analysis for all-cause dementia (ACD) (A) and Alzheimer’s disease (AD) (B). The inverse association of ACD or AD with physical activity (PA) was highly statistically significant in most subgroups.
Figure 4  By kcal/week, over the observed range of 0–2000 kcal/week, either all-cause dementia (ACD) (p for heterogeneity=0.1; p for non-linearity=0.87) or Alzheimer’s disease (AD) (p for heterogeneity=0.14; p for non-linearity=0.1) showed a linear relationship with leisure time physical activity (LTPA). Per 500 kcal/week LTPA increase, the decrement in risk was 10% (95% CI 0.85 to 0.97) for ACD (A) and 13% (95% CI 0.79–0.96) for AD (C). By metabolic equivalent of task hours per week (MET-h), over the observed range of 0–45 MET-h/week of LTPA, a significant linear association for ACD (p for heterogeneity=0.11; p for non-linearity=0.86) or AD (p for heterogeneity=0.14; p for non-linearity=0.10) was identified, with the summary RR for each 10 MET-h/week increase of 0.91 (95% CI 0.85 to 0.97) (B) and 0.87 (95% CI 0.79 to 0.96) (D). Our findings are also supportive of the international physical activity (PA) guidelines (B,D). Filled circles are RRs corresponding to comparison categories in studies in Northern America; open circles are for studies in Europe. Size of circle is in proportion to sample size for each comparison group.

By MET-h, over 0–200 MET-h/week, it was indicated that a linear relationship existed between PA and ACD risk (p for heterogeneity=0.07; p for non-linearity=0.2) and a non-linear association between PA and AD risk (p for heterogeneity=0.19; p for non-linearity=0.03). The summary RR of ACD per 10 MET-h/week increase was 0.96 (95% CI 0.94 to 0.99) in the linearity analysis (see online supplementary file 1, figure 2C) while the curve of AD risk flattened at roughly 20 MET-h/week in the non-linearity analysis (see online supplementary file 1, figure 2D). On the other hand, over 0–45 MET-h/week of LTPA, a significant linear association for ACD (p for heterogeneity=0.11; p for non-linearity=0.86) or AD (p for heterogeneity=0.14; p for non-linearity=0.10) was identified, with the summary RR for each 10 MET-h/week increment of 0.91 (95% CI 0.85–0.97) (figure 4B) and 0.87 (95% CI 0.79–0.96) (figure 4D).

Further, we examined the influences of amount of PA recommended by some international institutions (USA, WHO and Japan), as described in the Introduction above. We found that individuals who met the minimum guideline recommended LTPA levels (so-called basic dose =11.25 MET-h/week) had a 10% lower risk of ACD (95% CI 0.83 to 0.96) (figure 4B) and a 14% lower risk of AD (95% CI 0.77 to 0.95) (figure 4D), and that those who met the advanced guideline (=22.5 MET-h/week) had a 20% lower risk of ACD (95% CI 0.69–0.93) (figure 4B) and a 27%
lower risk of AD (95% CI 0.59–0.91) (figure 4D) compared with those who had sedentary lifestyles.

**DISCUSSION**

PA is one of the most feasible interventions that people can take as a preventative practice against dementia. Our study identified that LTPA over a specific range (0–2000 kcal/week or 0–45 MET-h/week) was associated with a risk of dementia and AD in an inverse linear dose–response manner, such that an increase in LTPA by 10 MET-h/week or 500 kcal/week was associated with a ~13% and ~10% decrease in the risk for AD and dementia, respectively. In accordance with our results, a recent systematic review and meta-analysis of longitudinal studies also found that PA confers more protection against Alzheimer’s dementia than for other types, such as ACD and VD.38 Our findings are meaningful given that: (1) for the first time a linear relationship between LTPA and dementia has been reported, (2) the results are supportive of the international PA guidelines from the standpoint of dementia prevention and (3) the results will be greatly favourable to future work on dementia prevention, especially for formulating prevention guidelines as well as constructing predictive tools for assessing dementia risk in the twilight years.

At the Alzheimer’s International Conference 2016, it was highlighted that aerobic activity played a significant role in protecting our cognition. There are several potential mechanisms by which PA might act on dementia risk. First, as a hub factor, PA may act by influencing other risk factors for dementia, such as BMI, cardiovascular conditions (coronary heart disease, hypertension and stroke), cancer, diabetes mellitus type 2 and depression.29–41 Second, animal experiments have suggested that PA might contribute to increased neurogenesis, angiogenesis, synaptic plasticity, better cardiovascular conditions and lessened cerebral accumulation of Aβ.42 Third, human studies have indicated that adhering to aerobic activity for over 6 months can increase the hippocampal volume and improve memory function.43 Fourth, a gene–environmental interaction for PA has been revealed, such that the association between PA and dementia might be modified by genetic components, such as APOE444 and BDNF gene.45

There are several limitations. First, although the association between PA and AD became non-linear when the range in the amount of PA was extended, linearity stabilised for ACD. Also, due to the restriction of the observed amount of LTPA, further investigations warrant quantitative association between dementia and LTPA over an extended range. Second, we did not analyse other types of PA, such as housework, occupational PA, walking or commuting, due to data restrictions. Third, estimating PA level with subjective methods (such as self-reported answers to questionnaire) is a potential source of measurement error. In the present study, all studies included used a subjective approach to assessing PA level. Although objective recording methods, such as actigraphy, have been applied in research, no such longitudinal study has used this technology to date. Fourth, we did not conduct the dose–response analyses by gender, region or other study characteristics due to the constrained number of eligible articles in the literature. Fifth, studies with binary variables of PA (see online supplementary file 1, table 3) were excluded in both types of meta-analyses as we aimed to explore the dose–response trend. However, we have made comparison with the results of meta-analyses including those studies.

**CONCLUSIONS**

Either dementia or AD exhibited a linear relationship with LTPA over the observed range (0–2000 kcal/week or 0–45 MET-h/week). For every 500 kcal or 10 MET-h increase per week, there was an approximately 10% and 13% decrease in the risk of ACD and AD, respectively. Our findings are also supportive of some international PA guidelines.

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