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Physical activity as a protective factor for dementia and Alzheimer's disease: systematic review, meta-analysis and quality assessment of cohort and case–control studies

Paula Iso-Markku ,[1,2] Urho M Kujala ,[3] Keegan Knittle ,[3] Juho Polet ,[3] Eero Vuoksimaa ,[1] Katja Waller [3]

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[1]Institute for Molecular Medicine Finland (FIMM), HiLIFE, University of Helsinki, Helsinki, Finland
[2]HUS Diagnostic Center, Clinical Physiology and Nuclear Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[3]Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

Correspondence to
Dr Paula Iso-Markku, Institute for Molecular Medicine Finland (FIMM), HiLIFE, University of Helsinki, Helsinki 00014, Finland;
paula.iso-markku@helsinki.fi

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ABSTRACT

Objective Physical activity (PA) is associated with a decreased incidence of dementia, but much of the evidence comes from short follow-ups prone to reverse causation. This meta-analysis investigates the effect of study length on the association.

Design A systematic review and meta-analysis. Pooled effect sizes, dose–response analysis and funnel plots were used to synthesise the results.

Data sources CINAHL (last search 19 October 2021), PsycInfo, Scopus, PubMed, Web of Science (21 October 2021) and SPORTDiscus (26 October 2021).

Eligibility criteria Studies of adults with a prospective follow-up of at least 1 year, a valid cognitive measure or cohort in mid-life at baseline and an estimate of the association between baseline PA and follow-up all-cause dementia, Alzheimer's disease or vascular dementia were included (n=58).

Results PA was associated with a decreased risk of all-cause dementia (pooled relative risk 0.80, 95% CI 0.77 to 0.84, n=257 983), Alzheimer's disease (0.86, 95% CI 0.80 to 0.93, n=128 261) and vascular dementia (0.79, 95% CI 0.66 to 0.95, n=33 870), even in longer follow-ups (≥20 years) for all-cause dementia and Alzheimer's disease. Neither baseline age, follow-up length nor study quality significantly moderated the associations. Dose–response meta-analyses revealed significant linear, spline and quadratic trends within estimates for all-cause dementia incidence, but only a significant spline trend for Alzheimer's disease. Funnel plots showed possible publication bias for all-cause dementia and Alzheimer's disease.

Conclusion PA was associated with lower incidence of all-cause dementia and Alzheimer's disease, even in longer follow-ups, supporting PA as a modifiable protective lifestyle factor, even after reducing the effects of reverse causation.

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INTRODUCTION

Worldwide, around 50 million people suffer from dementia. This number is projected to triple by 2050, with two-thirds of these people living in low-income and middle-income countries.[1] The economic burden of dementia is estimated to be as high as US$818 billion annually,[2] thus making dementia prevention a health priority in ageing societies. Physical inactivity is one of 12 potentially modifiable risk factors suggested to account for about 40% of old-age dementias.[3] Several pathways through which physical activity (PA) may prevent dementias have been proposed: decreased production of β-amyloid, increased removal of β-amyloid, improved brain vasculature and blood flow, and antioxidative and inflammatory processes in the brain,[4] as well as indirect pathways through improvements in sleep, mood and other cardiovascular risk factors.

Meta-analyses indicate an association between PA and decreased risk of all-cause dementia,[5–7] including in a dose–response manner.[8] However, many previous meta-analyses lack rigorous quality assessments,[7] and the association between PA and dementia appears absent when PA is measured before the age of 65[7 8] or in follow-ups longer than 10 years.[6 9] As the Alzheimer's disease process starts decades before diagnosis,[10] even studies with 10-year follow-ups are likely to include participants with preclinical Alzheimer's disease. Thus, studies assessing mid-life PA and old-age dementia diagnoses with a follow-up of at least 20 years are needed to confirm whether PA is a modifiable protective lifestyle factor of dementia.

This systematic review and meta-analysis examines if mid-life PA is a protective factor of all-cause dementia, Alzheimer's disease and vascular dementia. We examine separately studies with follow-ups longer than 20 years, high-quality studies and studies with younger cohorts to reduce the effect of reverse causality. Because the association of PA and dementia might potentially be modified by the apolipoprotein E (ApoE) genotype,[11–13] education,[14] PA type,[12 15] sample size[16] and funding source,[17] we additionally examine these factors as possible moderators of PA–dementia associations.

METHODS

This systematic review and meta-analysis is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[18] (see online supplemental material part 1) and was registered on PROSPERO (CRD42018083236). However, due to insufficient data, some registered analyses were not conducted and the original registered plan was adapted (online supplemental material part 1).

Eligibility criteria

Types of studies

We included prospective cohort studies and case–control studies with a baseline measure of PA and a follow-up measure of all-cause dementia, Alzheimer's disease or vascular dementia. Only studies with follow-ups longer than 1 year were included.

Types of participants

Participants were adults (≥20 years of age at baseline). We excluded studies where participants had some specific disease at baseline or where the cohort had established dementia or mild cognitive impairment at baseline. For populations that were older than mid-life (defined as mean or median age <55 years and maximum age <65 years or mean age plus 1 SD <60 years), a valid measure of baseline cognition was required to be reported. This was done to minimise the possibility of including cohorts with a prodromal state of dementia and to account for the long preclinical period of Alzheimer's disease[10] and the typical age of dementia onset.[19]

Types of exposure

We included studies assessing PA with objective measures or questionnaires. We excluded studies examining single bouts of PA, retrospectively reported PA, fitness levels or PA levels measured extending over the follow-up period.

Types of outcomes

Studies needed to report the association between PA and all-cause dementia, Alzheimer's disease or vascular dementia. We included studies that diagnosed dementia based on valid measures of cognition or register data, but excluded studies that based dementia diagnosis on cause of death data in more than 50% of the participants.

Types of reports

Full-text reports in English were included.

The decision rules that supplement these inclusion and exclusion criteria are described in online supplemental material part 1.

Search strategy

We conducted a systematic literature search in six electronic databases (PubMed, CINAHL, Scopus, PsycInfo, SPORTDiscus and Web of Science). Two reviewers conducted searches in all six databases, with the last search undertaken on 26 October 2021. The keywords of the original search included physical activity, physically active, sport, athletics, athlete, running, walking, physical training, dementia, Alzheimer's disease, Alzheimer's, cognition, cognitive, executive function, TELE (telephone assessment of dementia), TICS (Telephone Interview of Cognitive Status), MMSE (Mini-Mental State Examination), 3-MS (the Modified Mini-Mental State Examination), memory, processing speed, verbal fluency, semantic fluency, reasoning, delayed recall, prospective, longitudinal, follow-up, follow up, observational and cohort. In addition to the search results, individual studies known to the authors were added to the meta-analysis. Further details and example searches are described in the online supplemental material part 1.

Study selection

Inclusion was based on the assessments of two independent reviewers (PI-M+KW/JP/KK). Disagreements were discussed, and if consensus was not reached, a third independent researcher made the inclusion decision (UMK). Study screening was done in two phases: clearly irrelevant studies were excluded in the title and abstract phase, and thereafter, full-text manuscripts were reviewed. In cases where multiple studies reported similar outcome data from the same cohort, we only included the study with the best quality score, longest follow-up or largest sample size (in this order). Two studies that we excluded from the main meta-analyses (due to other reports from the same cohort being of a higher quality) were however included in the ApoE ε4 interaction analysis, as the studies included in the main meta-analyses from these same cohorts did not present any ApoE ε4 interaction analyses.[20 21]

Quality assessment

We developed a quality assessment tool specifically for this systematic review and meta-analysis to provide high transparency of the assessment and to account for the precise characteristics of the addressed study questions (see online supplemental material part 1). The new quality assessment tool assesses and scores the representativeness of the exposed cohort, PA assessment methods, demonstration that dementia was not present at start of study, methods used to control for confounders, outcome assessment methods, length of follow-up and loss to follow-up. We used three existing quality assessment tools to inform the development of our quality assessment tool: the Newcastle-Ottawa Quality Assessment Form for Cohort Studies,[22] the performance bias estimator by Shiri and Falah-Hassani[23] and the quality assessment tool for quantitative studies from the Effective Public Health Practice Project Quality Assessment.[24]

Two researchers reviewed the studies with the quality assessment tool independently (PI-M+KW/JP). Disagreements were resolved with discussion. If the study cited other papers, at maximum three papers were sought for the required information. We used a quality scoring system with three categories based on the assumption that studies of high quality have less possibility of reverse causation, the study cohort is not selected and the measurement of both dementia and PA is valid (good quality: ≥2.5+1+≥2.5 stars, moderate quality: ≥2+≥0.5+≥2 stars, poor quality: not reaching good or moderate quality).

Data extraction

The following outcomes and moderator data were extracted from the included studies: rates of all-cause dementia, Alzheimer's disease and vascular dementia incidence; PA levels; estimates of the associations between PA levels and all-cause dementia, Alzheimer's disease or vascular dementia; length of follow-up; sample age and gender make-up; sample size; country of origin; publication year; study design (including a twin study or not); work-related or leisure-time PA; confounders (age, cognition at baseline, chronic diseases, education, gender, vascular risk factors, ApoE ε4); follow-up and participation rate; gender interaction; stratification of results according to gender; ApoE ε4 interaction results; results stratified according to ApoE ε4 allele; number of adjusted confounders; study quality and funding (online supplemental material part 2). Two reviewers extracted the estimates of association (PI-M+KW/JP) and follow-up length (PI-M+KW). The likeness of the extractions was compared and disagreements were resolved by discussion. The estimates with the best quality assessment scores and the most extensive adjustments were included. For example, if baseline cognition was only measured and controlled for in one subgroup of the study sample, then data for that subgroup were extracted instead of the uncontrolled data from the full sample.

Studies using the WHO PA recommendation[25] as the category cut-off were also preferred if many estimates were presented. The data extraction of moderators other than follow-up length was done by one reviewer (PI-M).

Two researchers (PI-M and KW) independently assessed whether the PA categories and reference categories in each study met the WHO PA recommendation.[25] Disagreements were discussed until consensus was reached.

Patient involvement

This meta-analysis combines data from pre-existing data sets. No patients were involved in study design, planning the search strategies, planning the quality assessment or sensitivity analyses, implementation of the study, interpretation of the results or writing up the results.

Statistical analyses

Summary statistics were relative risks (RRs) with 95% CIs. For studies that did not report RR data, ORs or HRs were converted into RRs. OR data were converted to RRs using the formula RR=OR/(1−p0+p0*OR), when the outcome occurred in less than 10% of the sample, with p0=outcome incidence in the whole study population.[26] When the outcome was common (>10%), we used the square root transformation of OR as recommended by VanderWeele.[27] We transformed HRs into RRs using the following formula: RR = (1 − e^(HRxln(1 − r)))/r , where r is the incidence rate of dementia for the reference group.[28] A separate RR was calculated for each higher PA category reported in the included study by comparing each higher PA category to the lowest PA level in the study (eg, an inactive or reference category).

For the main meta-analyses, we pooled all estimates of the relationship between PA and all-cause dementia, Alzheimer's disease and vascular dementia, combining categorical and continuous measures of PA. We used a random-effects model with inverse-variance as the weighting method and estimated the statistical heterogeneity with DerSimonian-Laird method (indexed with the I^2 value). We conducted sensitivity analyses to examine the impacts of removing the study with largest sample size and highest weight on the overall result. An additional analysis examined this relationship within high-quality studies that had measured PA in mid-life and had a follow-up longer than 20 years.

Meta-regressions and comparative subgroup analyses examined the effects of baseline age, follow-up length and meeting the WHO PA recommendation on the association of PA and all-cause dementia, Alzheimer's disease and vascular dementia. Studies for which the reference category exceeded the WHO guidelines were excluded from the analysis of meeting the PA recommendations.

Next, we performed planned sensitivity analyses to examine the effects of sample size, PA type (leisure time or both leisure time and work related) and other covariates on the relationships of PA and all-cause dementia, Alzheimer's disease and vascular dementia. Additionally, we examined the effect of funding source (no commercial funding source vs at least one commercial funding source) on the associations. There were too few twin studies and studies addressing gender effects to conduct the prespecified sensitivity analyses of these issues. Finally, we examined only the highest PA level compared with the lowest PA level as has been done in earlier meta-analyses.[5 6 29]

Dose–response meta-analyses were performed to explore linear, quadratic and restricted cubic spline trends between PA levels and RRs of dementia onset. These were conducted in R with the 'dosresmeta' package.[30] A full description of the dose–response methods is available in online supplemental material part 3.

An additional preplanned sensitivity analysis was performed to examine if the presence of ApoE ε4 allele moderates the associations between PA and all-cause dementia, Alzheimer's disease and vascular dementia. Pooled estimates for the association of PA and all-cause dementia, Alzheimer's disease or vascular dementia were calculated separately for ApoE ε4 carriers and non-carriers, and a significance test compared the results across the two subgroups.[31]

Funnel plots were used to examine the potential publication bias. Primary analyses were conducted in Stata V.16.0 (StataCorp).

RESULTS

Database searches identified 16 324 articles, of which 15 658 were excluded based on title and abstract screening (figure 1). We assessed 666 full-text articles, 58 of which reported a study that fulfilled the inclusion criteria.[9 11 12 15 32–85] Overall, studies included 257 983 (range: 67–81 087), 128 261 (range: 300–71 157) and 33 870 (range: 638–20 639) participants for all-cause dementia, Alzheimer's disease and vascular dementia outcomes, respectively.

Methodological quality

Methodological quality is reported in online supplemental material part 2. The number of studies of high quality was very low (four all-cause dementia studies,[9 40 55 61] three Alzheimer's disease studies[9 12 40] and one vascular dementia study).[40] Selection, study length and follow-up rate were the most problematic domains of study quality, with 62%, 65% and 41% of studies receiving the lowest rating on these three quality domains, respectively.

PA and all-cause dementia

The mean incidence of all-cause dementia was 10.9% (total n in the analyses=257 983). When compared with the lowest PA category, the pooled RR in higher PA categories showed an association with a reduced risk of all-cause dementia (RR 0.80, 95% CI 0.77 to 0.84) (figure 2, table 1). Mean follow-up length was 12.9 years (SD 9.5), and mean baseline age was 67.0 (SD 12.9) years. There was substantial heterogeneity between the studies (I^2=68.7%), but neither baseline age, the length of follow-up nor study quality modified the association significantly (table 1). The result was similar within the 16 studies with at least 20 years of follow-up (RR 0.79, 95% CI 0.71 to 0.87, mean baseline age 50.5 (SD 7.8) years, mean follow-up 27.6 (SD 5.1) years and percentage of participants with dementia at follow-up 14.6%). In four high-quality studies, the pooled RR was 0.82 (95% CI 0.67 to 0.99), with a mean baseline age of 48.2 (SD 3.5) years and mean follow-up of 23.2 (SD 4.5) years and 7.6% of participants with dementia at follow-up. This was very similar to the pooled RR of 0.80 in all studies (table 1).

Only three studies were of high quality, had a young baseline age of 30–55 years and had a follow-up longer than 20 years. The pooled RR in these studies was also similar to the pooled RR in all studies, but not significant (pooled RR 0.79, 95% CI 0.62 to 1.01). Omitting the study with the largest sample size or the study with the largest weight did not significantly change the result (online supplemental table S1). Sample size, funding source, adjusting for ApoE ε4 status, baseline cognition or education did not significantly modify the association of PA

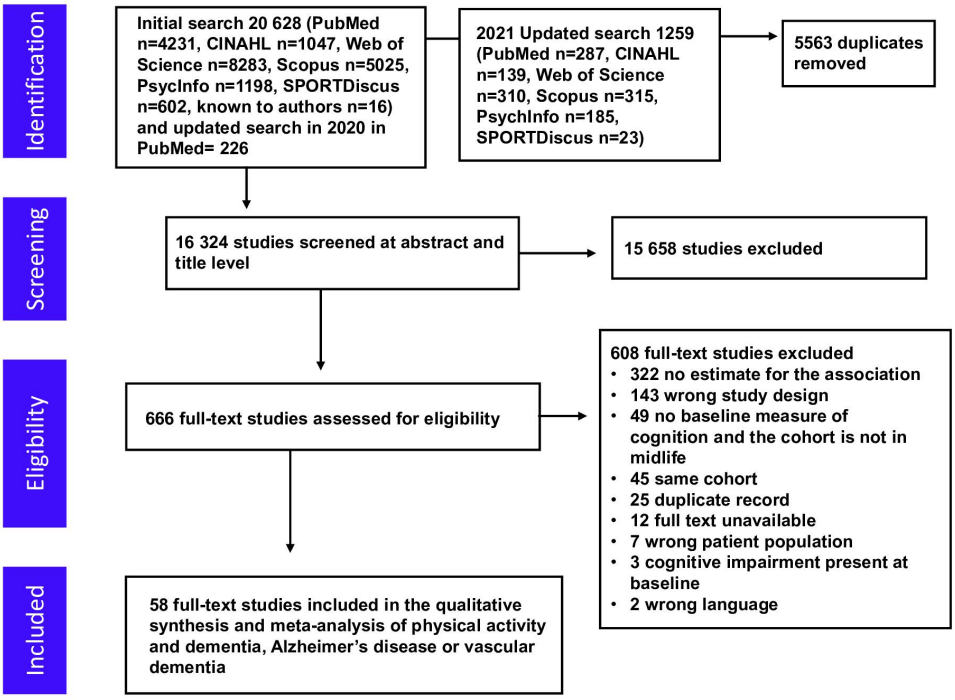

Figure 1 Flow diagram showing the screening process and the search results.

and all-cause dementia (online supplemental table S1). The risk of all-cause dementia did not significantly differ between PA levels meeting or not meeting the WHO recommendations of PA (table 1, test for heterogeneity between groups: p=0.202). The two studies examining the association of work-related PA and all-cause dementia showed an opposite trend than other PA (RR 1.25, 95% CI 0.98 to 1.59) (online supplemental table S1).

Significant linear, quadratic and cubic spline dose–response relationships were observed between increasing PA levels and lower all-cause dementia incidence (figure 3 and online supplemental material part 3). The funnel plot for studies of PA and all-cause dementia showed some asymmetry suggesting some publication bias (under-reporting of studies with no effect, figure 4).

PA and Alzheimer's disease

The mean incidence of Alzheimer's disease was 8.3% among 128 261 participants. Compared with the lowest PA category, the pooled RR in higher PA categories showed an association with lower incidence of Alzheimer's disease (RR 0.86, 95% CI 0.80 to 0.93; online supplemental figure S1 and table 2). The mean follow-up length was 11.5 (SD 8.8) years, and mean baseline age was 68.7 (SD 12.4) years. There was moderate heterogeneity between the studies (I^2=47.6%), and neither baseline age, the length of follow-up nor study quality modified the association significantly (table 2). This result was similar among the seven studies with at least 20 years of follow-up (RR 0.76, 95% CI 0.64 to 0.90, mean baseline age 52.8 (SD 8.9) years, mean follow-up 26.8 (SD 6.4) years and percentage of participants with Alzheimer's disease at follow-up 5.2%). Among the three high-quality studies, the pooled RR of 0.71 (95% CI 0.42 to 1.22) was non-significant (table 2). Neither sample size, adjustment for ApoE ε4, baseline cognition nor education significantly moderated the association between PA and Alzheimer's disease incidence (online supplemental table S2). The risk of all-cause dementia did not significantly differ between PA levels meeting or not meeting the WHO recommendations of PA (table 1, test for heterogeneity between groups: p=0.202).

Dose–response meta-analyses revealed a significant cubic spline trend between PA levels and Alzheimer's disease incidence, but linear and quadratic trends were non-significant (online supplemental material part 3). The funnel plot for studies of PA and Alzheimer's disease showed some asymmetry suggesting possibly small publication bias (under-reporting of results with no effect, online supplemental figure S2).

PA and vascular dementia

The mean incidence of vascular dementia was 3.8% among 33 870 participants. When compared with the lowest PA category, the pooled RR in higher PA categories showed an association with reduced incidence of vascular dementia (pooled RR 0.79, 95% CI 0.66 to 0.95) (online supplemental figure S3 and table S3). Mean follow-up length was 10.9 (SD 8.6) years, and mean baseline age was 67.0 (SD 8.5) years. Statistical heterogeneity between the studies was moderate (I^2=36.0%).

Neither baseline age, length of follow-up, meeting the WHO PA recommendation, adjusting for baseline cognition nor study quality significantly modified the association (online supplemental tables S3 and S4). There was only one high-quality study with follow-up longer than 20 years and baseline age between 30 and 55 years.[40] The association between PA and decreased incidence of vascular dementia was significant in this study.

Significant linear, quadratic and cubic spline dose–response relationships between PA and vascular dementia incidence were observed (online supplemental material part 3). The funnel plot for studies of PA and vascular dementia did not suggest publication bias (online supplemental figure S4).

ApoE ε4 interaction

Most studies that investigated ApoE ε4 interactions found no significant interactions (9 of 11 studies) (supplementary

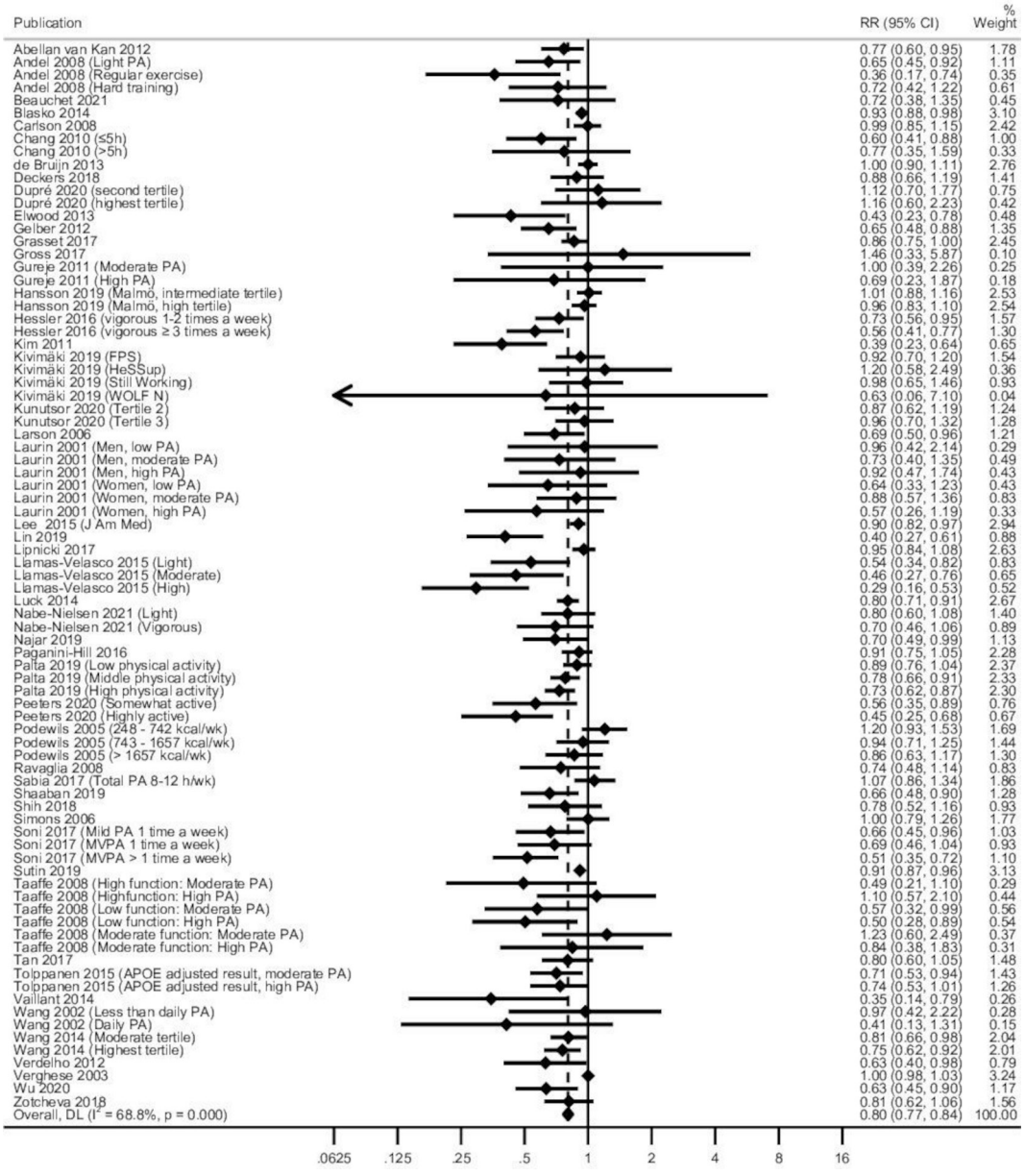

Figure 2 Longitudinal observational studies of physical activity (PA) and all-cause dementia: forest plot. APOE, apolipoprotein E; MVPA, moderate to vigorous physical activity; RR, relative risk.

sensitivity analyses for ApoE ε4 allele). In the studies that reported stratified results according to ApoE ε4 carrier status, the pooled RR between PA and all-cause dementia or Alzheimer's disease was similar for ApoE ε4 carriers (RR 0.81, 95% CI 0.67 to 0.98) and non-carriers (RR 0.72, 95% CI 0.56 to 0.92). Tests for heterogeneity between groups were invalid because of large heterogeneity between studies (online supplemental figures S5–S8).

DISCUSSION

This meta-analysis showed that higher PA levels were associated with lower incidence of all-cause dementia, Alzheimer's disease and vascular dementia. These associations were present for all-cause dementia and Alzheimer's disease in studies with long follow-ups (>20 years) and in cohorts with baseline age between 30 and 55 years. Neither baseline age nor follow-up length moderated the associations of PA with all-cause dementia or Alzheimer's disease. Data for vascular dementia were scarce, especially for long follow-ups, but the results supported an inverse association between PA and vascular dementia incidence.

Earlier meta-analyses investigating the associations between PA levels and dementia incidence have been based on short follow-ups,[5 29 86] and the results have only been significant in studies with short (<10 years) follow-ups[6 9] or elderly populations.[7 8] These factors can introduce the possibility of reverse causation, whereby PA levels are affected by dementia.[9] Participants' levels of PA may also change during long follow-ups.[87] In this study, we did not find evidence to suggest that reverse causation or regression dilution bias[88] affected the observed associations between PA and dementias. Our results therefore support the role of PA as a modifiable protective mid-life lifestyle factor of dementia. However, funnel plots for all-cause dementia and Alzheimer's disease suggested some publication bias.

In high-quality studies, a non-significant negative association was found between PA and Alzheimer's disease. However, with only three high-quality studies, the statistical power to show

Table 1 PA and all-cause dementia: main results, main sensitivity analyses with meta-regressions and subgroup analyses, and dose–response analysis

	Pooled RR	95% CI	I^2 (%)	Studies combined (n)	Beta estimate*	95% CI
All physical activity	0.80	0.77 to 0.84	68.7	49		
Baseline age (continuous)					1.00	0.98 to 1.02
Baseline age (categorical)						
Age group 30–55 years[9 33 35 36 39 40 42 55 61 62 66 73 77 80]	0.79	0.71 to 0.87	42.9	14		
Age group 55–69 years[44 45 57 58 81 83]	0.82	0.74 to 0.90	70.8	6		
Age group ≥70 years[11 32 34 37 38 41 43 46–54 56 59 60 63–65 72 74–76 79 82]	0.80	0.75 to 0.85	70.4	29		
Follow-up length (continuous)					1.00	0.97 to 1.03
Follow-up length (categorical)						
Follow-up length <5 years[38 43 46 51 52 54 63 75 78 79]	0.61	0.50 to 0.74	64.8	10		
Follow-up length 5–20 years[9 11 32 34 37 41 44 45 47–50 56–59 64 65 72 74 76 81–83]	0.86	0.82 to 0.90	64.2	24		
Follow-up length ≥20 years[9 33 35 36 39 40 42 53 55 60–62 66 73 77 80]	0.79	0.71 to 0.87	44.8	16		
Study quality (high vs moderate vs low)†					0.99	0.64 to 1.53
Low quality[9 11 32 34 35 38 41 43–47 49–51 56–58 60 62–66 72 74–76 78 79 81 83]	0.81	0.77 to 0.85	75.5	32		
Moderate quality[9 33 36 37 39 42 48 52–54 59 73 77 80 82]	0.79	0.72 to 0.86	28.4	15		
High quality[9 40 55 61]	0.82	0.67 to 0.99	58.9	4		
Meeting PA guidelines‡ [11 33 36 38 43 44 48 53–55 59–61 63 65 72 73 76 80 83]	0.82	0.76 to 0.87	22.0	20		
Not meeting PA guidelines‡ [9 11 32 33 36 38 44 45 47–49 51 57 58 61 62 65 66 72–75 77–79 83]	0.76	0.69 to 0.83	60.8	25		
Highest quality studies only: age group 30–55 years, follow-up length >20 years and high quality[40 55 61]	0.79	0.62 to 1.01	67.4	3		

*Beta estimate is the regression coefficient from the meta-regression examining the relationship of modifier or continuous PA on the log risk ratio of dementia.
†Study quality was assessed with a quality assessment tool we developed (see online supplemental material part 1 for details).
‡The test for heterogeneity between groups was non-significant (p=0.202).
.I^2, heterogeneity; PA, physical activity; RR, relative risk.

a significant association is low to moderate but the pooled RR estimate in high-quality studies (0.71) was similar to that obtained when including all studies (0.86). Additionally, the meta-regression estimate did not show significant moderation by study quality. Our inclusion criteria were also strict, as we excluded studies with baseline in old age and without a validated measure of cognition at baseline. This procedure reduces the risk of bias due to reverse causality, but led to fewer studies being included in the meta-analysis. The strict representativeness criterion may have unnecessarily limited the number of high-quality studies[88] and thereby increased the CIs of pooled risk estimates from high-quality studies.

Dose–response meta-analyses showed significant linear, quadratic and cubic inverse associations between PA levels and incidence of all-cause dementia and vascular dementia. The finding of a linear dose–response is in line with the results from Xu *et al*[8]; however, in our analysis, the effect of PA on all-cause dementia incidence was greatest when moving from extreme sedentariness to some PA. While a significant cubic spline relationship was observed between PA and Alzheimer's disease, the model only included two studies that examined the effects of PA levels greater than 1750 MET*min/week. More studies among more physically active cohorts are needed to conclusively determine whether more PAs offer greater protection at the higher end of the spectrum, or whether a moderate level of PA offers similar protective effects.

Our results contrast with those from Kivimäki *et al*[9] who examined individual participant data from many study cohorts worldwide (n=404 840). In that study, no associations were found between PA and all-cause dementia or Alzheimer's disease when follow-ups were longer than 10 years. Notably, the incidence of all-cause dementia in their meta-analysis was 0.5%. This is an exceptionally low all-cause dementia incidence rate, considering the global annual dementia incidence rate of 17.3% in adults over 60 years of age.[89] Two factors can explain this. First, the mean age at baseline was 45.5 years in Kivimäki *et al*.[9] As the mean follow-up length was 14.9 years, the mean age at the end of follow-up was approximately 60.4 years, but the mean age of all-cause dementia diagnosis in the study was 80.6 years. The result was similar in a subanalysis of persons aged 60 years or older.[9] The follow-up length of over 10 years may also contribute to reverse causation, considering the long preclinical period of Alzheimer's disease.[10] Therefore, these earlier results may be susceptible to bias from both early-onset dementias and reverse causation.

The very low all-cause dementia incidence rate in the Kivimäki *et al*'s[9] study may also be explained by the source of incidence rate data: the meta-analysis used register data (hospitalisations, medical reimbursements and death registers) and a few very large cohorts had only death register data. We excluded studies with dementia mortality as the outcome because the relatively low sensitivity of death registers to detect dementia cases may underestimate its association with risk or protective factors.[90] Further, dementia mortality in younger individuals is likely to reflect early-onset dementias. On the other hand, there may be a survival bias, whereby those with higher levels of PA live longer and are therefore at an increased risk of developing dementia.

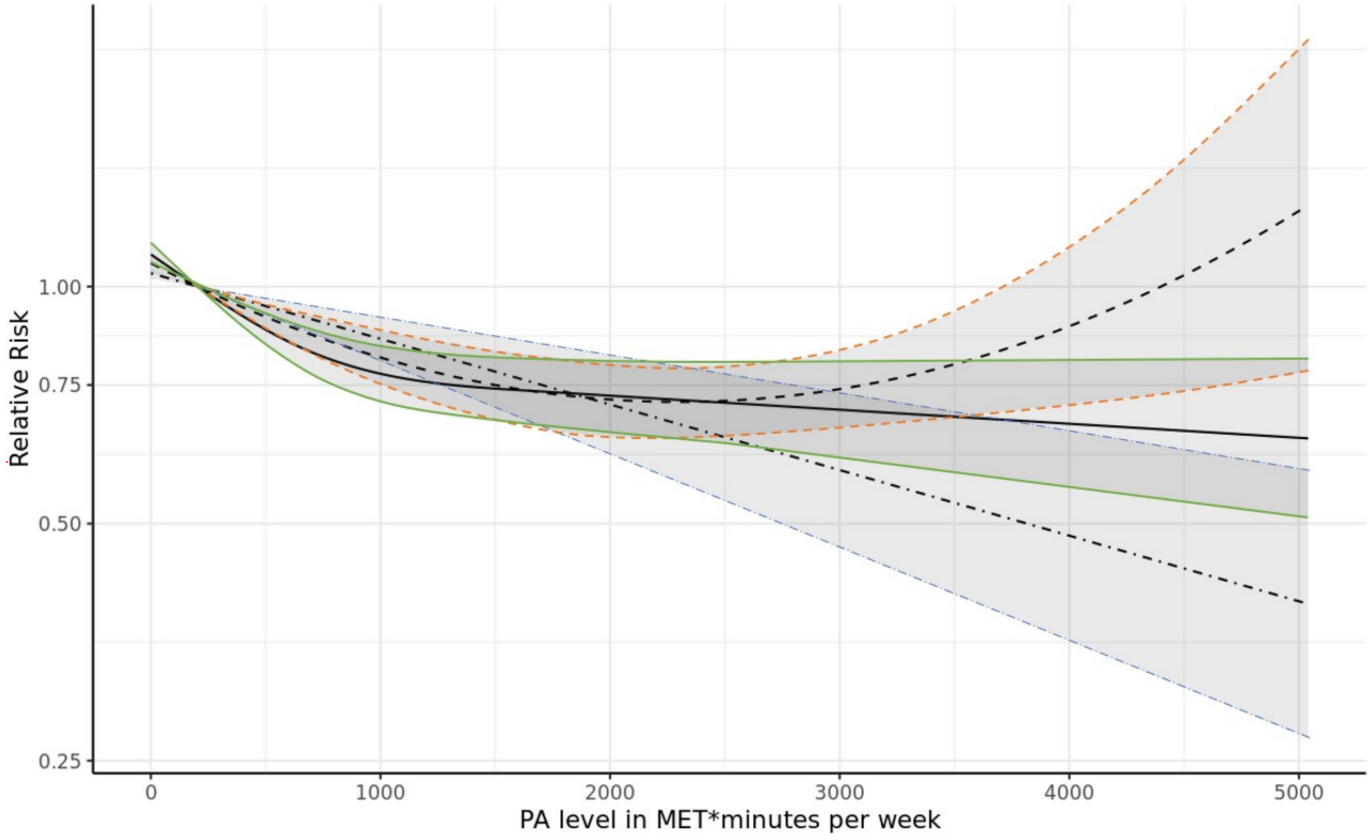

Figure 3 Dose–response analysis of physical activity (PA) levels and all-cause dementia incidence. Linear trend shown with dashed-dotted line and 95% CI in blue; quadratic trend shown with dashed line and 95% CI in orange; and cubic spline trend shown with solid line and 95% CI in green. MET, metabolic equivalent of energy expenditure.

The sensitivity analyses for all-cause dementia and Alzheimer's disease showed similar estimates among studies that controlled for baseline cognition. Studies have primarily assessed baseline cognition using short screening tests, which are known to result in ceiling effects, and most studies of younger cohorts did not assess cognitive ability at baseline. While many studies

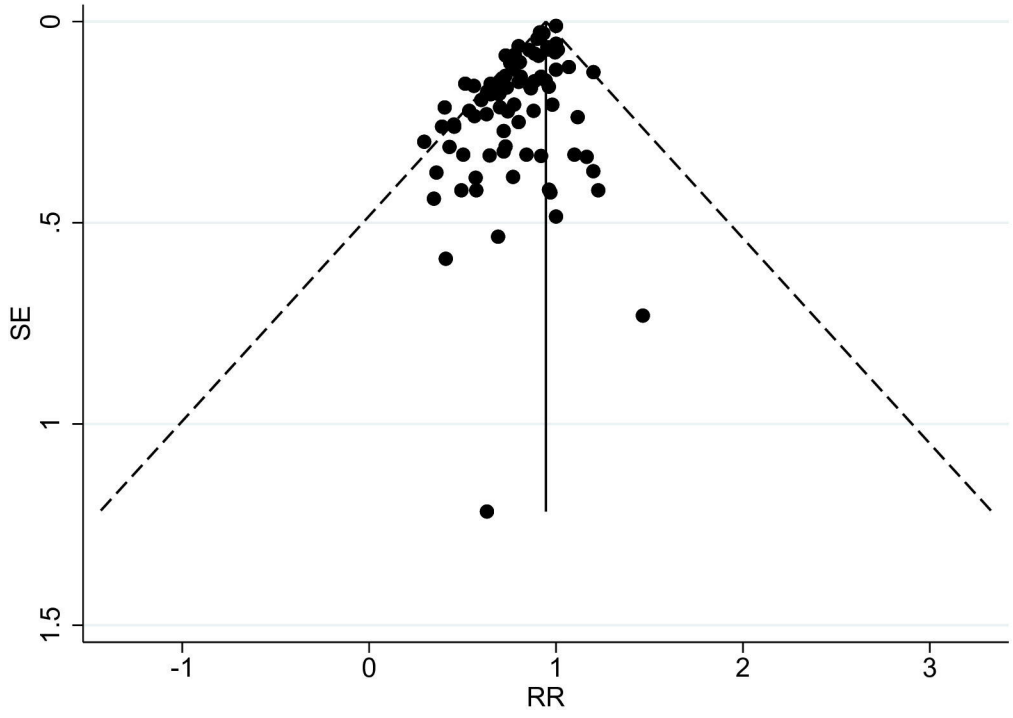

Figure 4 Funnel plot for the longitudinal observational studies on physical activity and all-cause dementia with pseudo-95% CIs. RR, relative risk.

Table 2 PA and Alzheimer's disease: main results, main sensitivity analyses with meta-regressions and subgroup analyses, and dose–response analysis

	Pooled RR	95% CI	I^2 (%)	Cohorts combined (n)	Beta estimate*	95% CI
All PA	0.86	0.80 to 0.93	47.6	24		
Baseline age (continuous)					1.00	0.97 to 1.03
Baseline age (categorical)						
Age group 30–55 years[9 12 33 40 77 80]	0.81	0.66 to 0.99	37.3	6		
Age group 55–69 years† [44]	1.09	0.96 to 1.24	0.0	1		
Age group ≥70 years[11 37 38 47 48 52 54 59 60 63 67–71 84 85]	0.84	0.77 to 0.93	48.5	17		
Follow-up length					1.00	0.96 to 1.04
Follow-up length <5 years[38 52 54 63 70 84]	0.93	0.79 to 1.08	48.4	6		
Follow-up length 5–20 years[9 11 37 44 47 48 59 67–69 71 85]	0.87	0.78 to 0.97	41.3	12		
Follow-up length ≥20 years[9 12 33 40 60 77 80]	0.76	0.64 to 0.90	16.9	7		
Study quality (low vs moderate vs high)‡					1.14	0.59 to 2.22
Low quality[9 11 44 47 60 63 67 68 70 71]	0.97	0.88 to 1.07	34.1	10		
Moderate quality[9 33 37 38 48 52 54 59 69 77 80 84 85]	0.81	0.74 to 0.90	24.0	13		
High quality [9 12 40]	0.71	0.42 to 1.22	71.8	3		
Meeting PA guidelines§ [11 12 33 38 44 47 48 54 59 60 63 68 69 71 80 84]	0.75	0.64 to 0.88	43.4	16		
Not meeting PA guidelines§ [9 11 33 38 44 48 67 69 77 80]	0.94	0.85 to 1.04	0.0	10		
Age group 30–55 years, high quality and follow-up length >20 years[12 40]	0.55	0.29 to 1.03	53.9	2		

*Beta estimate is the regression coefficient from the meta-regression examining the relationship of modifier or continuous PA on the log risk ratio of dementia.
†Only one study, not meta-analytical analysis.
‡Study quality was assessed with a quality assessment tool we developed (see online supplemental material part 1 for details).
§The test for heterogeneity between groups was non-significant (p=0.126).
I^2, heterogeneity; PA, physical activity; RR, relative risk.

collected information on baseline cognition, few adjusted for it in their analyses. Because baseline cognitive ability may be the most robust predictor of cognition later in life,[91] the absence of rigorous assessments of baseline cognition and failure to control for it in analyses should be seen as major limitations of the included studies and this meta-analysis. Physically active individuals may have higher cognitive reserve to start with,[92] so studies should examine whether early cognitive ability predicts PA later in life. In many studies investigating PA and other health outcomes, work-related PA shows an inverse association with leisure-time PA when adjusted for socioeconomic status or education.[93 94] This may also indicate that higher cognitive ability or other unmeasured confounding factors, and not leisure-time PA, may drive the association with a decreased incidence of dementia. Almost all studies in this field have adjusted their results for education level, a widely used proxy for higher cognitive reserve. Still, people with the same number of years of formal education may vary greatly in their cognitive abilities.[95] Many studies have suggested that ApoE ε4 carrier status modifies the relationship between PA and dementia.[11–13] Our ApoE ε4 interaction analyses suggest no such modification for all-cause dementia, Alzheimer's disease or vascular dementia.

Strengths

This meta-analysis includes extensive data and has examined the association of PA and dementia in longer follow-ups than earlier meta-analyses. Our quality assessment was specifically developed to account for the long preclinical period of dementia, and the quality assessment of PA has been developed in cooperation with sports and exercise medicine experts (KW and UMK). We also studied PA levels meeting a fixed threshold (WHO PA recommendation), and we addressed dose–response relationships between PA with all-cause dementia, Alzheimer's disease and vascular dementia incidence.

Limitations

Some limitations of this meta-analysis bear mentioning. Many studies used only rough PA measures (eg, a dichotomous yes or no question to describe exercise participation). These rough measures coupled with the midpoint or mean estimation of MET*min/week PA levels imply that the dose–response meta-analyses likely lack precision, especially when the PA levels within a group were wide. Future cohort studies should use objective or finer grain PA assessments and make individual participant data open whenever possible. Of the included studies, few were high quality, few reported on vascular dementia as an outcome and few had any robust measures of cognition at baseline. The stringent criterion of representativeness may have unnecessarily limited the number of high-quality studies. Additionally, some publication bias may have affected the results for all-cause dementia and Alzheimer's disease. We searched only studies published in English which is also a possible source of bias.[96] In addition, the impacts of PA modalities which are themselves associated with increased risk of dementia (eg, boxing)[97] are not accounted for in the results presented here.

CONCLUSIONS AND POLICY IMPLICATIONS

This meta-analysis found inverse associations between PA levels and incidence rates of all-cause dementia and Alzheimer's disease, even in studies with follow-ups longer than 20 years. This finding supports PA as a modifiable protective lifestyle factor of dementia. Policy makers should continue to promote PA in school and work-life reforms, city planning and health initiatives. However, these conclusions should be tempered slightly, as the meta-analysis was based on observational studies with known limitations compared with intervention studies, as high-quality studies were scarce and some publication bias was present. More research with long follow-ups, adjustment for baseline cognitive performance and valid measures of PA and dementia are

needed to confirm these findings. Finally, long-term randomised controlled trials of exercise interventions are needed to establish PA as a causative protective factor for dementia.

What is already known on this topic?

- Alzheimer's disease and related dementias are a major public health concern, and their prevalence is projected to multiply in the coming decades.
- There are no drugs to stop or reverse the dementia process, but lifestyle interventions in mid-life may help delay or prevent dementias.
- Physical inactivity is associated with an increased incidence of dementia, but whether this is due to reverse causation whereby lower physical activity results from the dementia process is under debate.

What this study adds

- In this meta-analysis of over 250 000 participants, physical activity was significantly associated with a decreased incidence of all-cause dementia and Alzheimer's disease, irrespective of follow-up length, baseline age and study quality.
- Physical activity was a protective factor for all-cause dementia and Alzheimer's disease, even in follow-ups longer than 20 years, suggesting that the association is not simply due to reverse causation.
- Policy makers should support intervention strategies targeting societal increases in physical activity in mid-life, as these may reduce dementia incidence.

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ORCID iDs
Paula Iso-Markku http://orcid.org/0000-0001-6683-919X
Urho M Kujala http://orcid.org/0000-0002-9262-1992
Keegan Knittle http://orcid.org/0000-0002-2108-7112
Juho Polet http://orcid.org/0000-0002-5305-127X
Eero Vuoksimaa http://orcid.org/0000-0002-6534-3667
Katja Waller http://orcid.org/0000-0002-0121-249X

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Supplementary material: Part 1

Methods

This meta-analysis examines the relationships between PA and the incidence of all-cause dementia, Alzheimer's disease, and vascular dementia. A separate meta-analysis will examine the also pre-registered relationship between PA and cognition outcomes. The study plan was submitted to PROSPERO 2.12.2017 (prior to the first search of the review 11.12.2017) but registration was accepted only after the study implementation (registration 8.1.2018).

The plan of the search has been described in PROSPERO (registration number CRD42018083236). The original searches were done in PsycInfo 11.12.2017, in PubMed 14.12.2017, in CINAHL 19.12.2017, in Web of Science 21.12.2017, in Scopus 21.12.2017, and in SPORTDiscus 15.1.2018 (for search terms, see the search strategy below).

The second search targeted only one database (PubMed) and articles published between 12.12.2017 to 10.12.2020 with reduced search terms ("physical activity", "exercise", "Alzheimer's disease", "cognition", "cognitive decline", "cognitive impairment", and "dementia") using the following filters: Humans, English, Adult 19+, Observational study. The second search was screened by one reviewer alone (PIM).

The third search was better targeted than the excessively wide original search and targeted only dementia. It was conducted in six databases with the search terms: physical activity, sport, walking, physical training, aerobic exercise, dementia, Alzheimer's disease, Alzheimer, prospective, longitudinal, follow-up, follow up, observational, cohort. The sensitivity of this search was tested first for two years from the original search (2015 and 2017) and was found to be good. This better targeted search found 3/3 of the physical activity and dementia articles from the original search from 2015 and 6/7 from the original search from year 2017 (the one study that this search did not find did not mention physical activity in the abstract or title). The searches were done to update the original search 19.10.2021 in CINAHL, 21.10.2021 in PubMed, Web of Science, PsycInfo and Scopus and 26.10.2021 in SPORTDiscus. Below are two search examples first from the original search and then two examples from the third search.

Most studies reported mean or median baseline age but for studies that did not, these were extrapolated. A few studies reported only that the association between physical activity and all-cause dementia, Alzheimer's disease, or vascular dementia was not significant. The authors of these studies were contacted via email to obtain effect size data of these associations, but no requests were fulfilled. Some studies reported the results for sensitivity analyses only partially and if the study quality was better in a partially reported sensitivity analysis, the authors were also contacted. Some of these requests were answered.

The search strategy

The search in CINAHL in 2017

1. physical activity
2. physically active
3. exercise*
4. sport*
5. athletics
6. athlete*
7. run*
8. walk*
9. physical training
10. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
11. dementia
12. Alzheimer*
13. Alzheimer's disease
14. cognition
15. cognitive decline
16. cognitive impairment
17. cognitive function
18. executive function
19. TELE
20. TICS
21. MMSE
22. 3-MS
23. memory
24. processing speed
25. verbal fluency
26. semantic fluency
27. reasoning
28. delayed recall
29. 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28
30. prospective
31. longitudinal
32. follow up
33. observational
34. cohort
35. 30 OR 31 OR 32 OR 33 OR 34
36. 10 AND 29 AND 35

Filters: English, Human, All adult

The search in Web of Science in 2017

1. physical activity
2. physically active
3. exercise*
4. sport*
5. athlet*
6. running
7. walking
8. physical training
9. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
10. dementia
11. Alzheimer*
12. cognition
13. cognitive
14. executive function
15. TELE
16. TICS
17. MMSE
18. 3-MS
19. memory
20. processing speed
21. verbal fluency
22. semantic fluency
23. reasoning
24. delayed recall
25. 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28
26. prospective
27. longitudinal
28. follow up
29. follow-up
30. observational
31. cohort*
32. 30 OR 31 OR 32 OR 33 OR 34
33. 10 AND 29 AND 35

LANGUAGES: (ENGLISH) AND **[excluding]: RESEARCH AREAS:** (GOVERNMENT LAW OR ASTRONOMY ASTROPHYSICS OR AUTOMATION CONTROL SYSTEMS OR TRANSPLANTATION OR ENERGY FUELS OR ORTHOPEDICS OR SUBSTANCE ABUSE OR NUTRITION DIETETICS OR METEOROLOGY ATMOSPHERIC SCIENCES OR ZOOLOGY OR ENGINEERING OR MATERIALS SCIENCE OR OPTICS OR SURGERY OR WATER RESOURCES OR MATHEMATICS OR COMPUTER SCIENCE OR ROBOTICS OR CRIMINOLOGY PENOLOGY OR CHEMISTRY OR AGRICULTURE OR PHARMACOLOGY PHARMACY OR GEOLOGY OR MARINE FRESHWATER BIOLOGY OR DENTISTRY ORAL SURGERY MEDICINE OR METALLURGY METALLURGICAL ENGINEERING OR VETERINARY SCIENCES OR LINGUISTICS OR THERMODYNAMICS OR BUSINESS ECONOMICS OR CONSTRUCTION BUILDING TECHNOLOGY)
AND **[excluding]: RESEARCH AREAS:** (PARASITOLOGY OR ARCHITECTURE OR PLANT SCIENCES OR MUSIC OR FISHERIES)

The search in CINAHL in 2021

1. physical activity
2. aerobic exercise
3. sport*
4. walking
5. physical training
6. 1 OR 2 OR 3 OR 4 OR 5
7. dementia
8. Alzheimer*
9. 7 OR 8
10. prospective study
11. longitudinal
12. follow-up
13. observational
14. cohort study
15. 10 OR 11 OR 12 OR 13 OR 14
16. 6 AND 9 AND 15

Filters: English, Human, All adult, 12/2017 – 10/2021, Research articles
Search field: Abstract

The search in Web of Science in 2021

1. ”physical activity”
2. ”aerobic exercise”
3. sport*
4. walking
5. ”physical training”
6. 1 OR 2 OR 3 OR 4 OR 5
7. dementia
8. Alzheimer*
9. 7 OR 8
10. prospective
11. longitudinal
12. follow-up
13. observational
14. cohort*
15. 10 OR 11 OR 12 OR 13 OR 14
16. 6 AND 9 AND 15

Articles (Document Types) and English (Languages) and 27TH ANNUAL MEETING OF THE SOCIETY FOR THE STUDY OF INGESTIVE BEHAVIOR SSIB or ALZHEIMER S ASSOCIATION INTERNATIONAL CONFERENCE (Exclude – Conference Titles) and Articles (Document Types) and Orthopedics or Surgery or Engineering or Medical Informatics or Obstetrics Gynecology or Urology Nephrology or Cell Biology or Dentistry Oral Surgery Medicine or Emergency Medicine or History or Mechanics or Oncology or Ophthalmology or Otorhinolaryngology or Respiratory System or Rheumatology or Social Work (Exclude – Research Areas)

Date range: 22.12.2017 – 21.10.2021

Field of search: Abstract

Specifications to the inclusion and exclusion criteria

Specifications to the inclusion and exclusion criteria at title and abstract screening phase in cases of disagreements:

The studies are included if

- The study is a longitudinal follow-up study addressing something else than physical activity as a dependent variable and dementia as an outcome but physical activity is mentioned as a covariate or it is unclear based on the abstract if physical activity is used as a covariate.
- The studies that have frailty as an independent variable with low physical activity is used as one of the criteria (or it is not clear what are the criteria according to the title and abstract) and dementia is the outcome variable.
- The studies that have healthy aging, survival or successful aging as an outcome measure with being undemented as one of the criteria or the criteria are not specified in the abstract and physical activity is one the dependent variables.

The studies are excluded if

- The study is a longitudinal follow-up study addressing something else than physical activity as a dependent variable and dementia as an outcome and covariates are listed in the abstract and physical activity is not one of them.
- Dementia mortality is the outcome variable.
- The study is considered to be cross-sectional because there is no indication in the title or the abstract that the study has a follow-up.
- The studies that are solely addressing the effects of scuba-diving or diving.
- The studies that are examining the effect of repetitive head trauma resulted from eg. boxing.
- The study addresses only a specific cohort of patients with a certain diagnosis or in for example “fallers”.
- Long-term physical activity during the follow-up is examined instead of baseline physical activity in only one time point.
- They study the effect of physical activity on structural brain changes and there is no indication in the title or abstract that dementia would also be measured.
- The study addresses the effect of sedentary hours in a day on cognition.
- The study addresses the effect of life-space mobility on dementia instead of the effect of physical activity.
- Baseline physical activity has not been measured or the estimate of physical activity is based on a single bout of physical activity.

Specifications to the precise inclusion and exclusion criteria at the full-text screening phase in cases of disagreements:

The study is included if

- Physical activity is only included as an independent variable that is a composite variable (eg. frailty) and the results for the components are mentioned separately, even if the actual numbers are not specified. If the results for the components are mentioned separately but no numbers are provided, the authors are contacted and asked for the numbers.
- There is a valid measure of baseline cognition or the population is in midlife. We define midlife as being 55 years old or younger and require that the cohort members are aged 55 years or less (mean age or median < 55 years and maximum age 65 years or +1 SD < 60 years).

The study is excluded if

- The study has used only orientation to date, day of week, month and year as a baseline measure of cognition.
- Studies in which dementia diagnosis was self-reported, based solely on disability scale or the main source (≥ 50%) of dementia diagnoses were death registers.

A quality assessment tool for the quality assessment of cohort studies addressing the association of physical activity and dementia or cognition

Note: A study can be given a maximum of one star for each numbered item within the Selection, Comparability and Outcome categories.

Selection

1) Representativeness of the exposed cohort

a) Truly representative (represents well the whole age group or the whole age group of any particular race and is not selected in regards to some disease, socio-economic status or for example only inhabitants of a nursing home, participation rate > 70% (of those alive) and sample size at least 1000 ***(one star)***

b) Truly or somewhat representative (participation rate 50-70%) and sample size > 1000 ***(half a star)***

c) Selected group in regards to some characteristic or participation rate < 50% or sample size < 1000

d) No description of the derivation of the cohort or participation rate lacks

2) Performance quality (adapted from (Br J Sports Med 2017;51:1410-18))

a) Good: PA assessed with a structured questionnaire of the duration, frequency and intensity of PA or the intensity of PA assessed with a structured question. Or PA assessed with an objective measure of PA (eg. accelerometer) **(one star)**

b) Moderate: Participation only in some types of sports assessed but other activities not considered or assessment of intensity lacks. Frequency or duration are assessed. **(half a star)**

c) Low: A “yes” or “no” question used. Frequency and duration not assessed. Or physical activity index on versatility of sports and somewhat physical household chores but not assessing intensity, frequency or duration. Or not described how exercise or physical activity was measured. (no star)

3) Demonstration that outcome of interest was not present at start of study

a) Yes. In a study population whose average age > 55 years, valid measure of cognition is used and demented individuals and individuals with mild cognitive impairment at baseline according to baseline cognition screening have been excluded or population is in midlife (mean age or median < 55 years and maximum age 65 years or +1 SD < 60 years) ***(one star)***

b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders

a) The study controls for the following four factors: age, sex (or all cohort members represent the same sex), some vascular risk factor† and education or a measure of general cognitive ability at baseline (education criterion is not needed if all cohort

members have the same education level). In addition, the results have been adjusted with baseline cognition in study population whose average age > 55 years **(one star)**

b) The study controls only for three of the factors presented above (age, sex, some vascular risk factor and education or a measure of general intelligence) or/and in study populations whose mean age > 55 years the results have not been adjusted with baseline cognition or the sociodemographic and health behaviors controlled for are not specified further **(half a star)**

c) Cohorts are not comparable on the basis of covariates controlled for (no star)

Outcome

1) Assessment of outcome

a) A validated measure of dementia ***(one star)***

b) Record linkage ***(half a star)***

c) Self report or other

d) No description

2) Was follow-up long enough for outcomes to occur

a) Yes (***one star)***

b) No

Indicate the median duration of follow-up and a brief rationale for the assessment above: 10 years in dementia studies.

3) Adequacy of follow-up of cohorts

a) Complete follow up- all subject accounted for ***(one star)***

b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20%* (when follow-up less than 10 years) or 30%* (when follow-up at least 10 years) of those alive or description of those lost suggested no different from those followed. ***(one star)***

c) Follow up rate less than 80%* (when follow-up less than 10 years) or less than 70%* (when follow-up longer than 10 years) and no description of those lost.

d) No statement

* Follow-up rates are calculated taking into account only the cohort members who have been alive at the time of the follow-up
† Vascular risk factor signifies a cardiovascular disease or information on smoking, body mass index, cholesterol levels, diet, blood pressure, diabetes or blood glucose.

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, moderate, and poor):
Good quality: Selection: 2,5 - 3 stars, Comparability: 1 star, Outcome: 2,5 - 3 stars
Moderate quality: Selection: 2-3 stars, Comparability: 0,5 -1 star, Outcome: 2-3 stars,
Poor quality: studies not reaching Moderate/Good quality

A quality assessment tool for the quality assessment of case-control studies addressing the association of physical activity and dementia or cognition

Note: A study can be given a maximum of one star for each numbered item within the Selection, Comparability and Outcome categories.

Baseline

1) Selection of controls:

a) Community controls **(half a star)**

b) Hospital controls

c) No description

2) Definition of controls:

a) No history of disease (endpoint) **(half a star)**

b) No description of source

3) Demonstration that outcome of interest was not present at start of study

a) Yes. In a study population whose average age > 55 years, valid measure of cognition is used and demented individuals and individuals with mild cognitive impairment at baseline according to baseline cognition screening have been excluded or population is in midlife (mean age or median < 55 years and maximum age 65 years or +1 SD < 60 years) **(one star)**

b) No

4) Performance quality (adapted from (Br J Sports Med 2017;51:1410-18))

a) Good: PA assessed with a structured questionnaire of the duration, frequency and intensity of PA or the intensity of PA assessed with a structured question. Or PA assessed with an objective measure of PA (eg. accelerometer). Additionally same method is used for cases and controls and non-response rate is the same for cases and controls. **(one star)**

b) Moderate: Participation only in some types of sports assessed but other activities not considered or assessment of intensity lacks. Frequency or duration are assessed. **(half a star)**

c) Low: A “yes” or “no” question used. Frequency and duration not assessed. Or physical activity index on versatility of sports and somewhat physical household chores but not assessing intensity, frequency or duration. (no star)

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders

a) The study controls for the following four factors: age, sex (or all cohort members represent same sex), some vascular risk factor† and education or a measure of general cognitive ability at baseline. In addition, the results have been adjusted with baseline cognition in study population whose average age > 55 years **(one star)**

b) The study controls only for three of the factors presented above (age, sex, some vascular risk factor and education or a measure of general intelligence) or in study populations whose mean age > 55 years the results have not been adjusted with baseline cognition **(half a star)**

c) Cohorts are not comparable on the basis of covariates controlled for (no star)

Outcome

1) Assessment of outcome

a) A validated measure of dementia (if many cognitive tests used, most validated) ***(one star)***

b) Record linkage ***(half a star)***

c) Self report or other

d) No description

2) Was follow-up long enough for outcomes to occur

a) Yes (***one star)***

b) No

Indicate the median duration of follow-up and a brief rationale for the assessment above: 10 years in dementia studies.

3) Is the case definition adequate?:

a) Yes, with a valid measure of dementia **(half a star)**

b) No, does not fulfil the criteria defined above

4) Representativeness of the cases:

a) Consecutive or obviously representative series of cases **(half a star)**

b) Potential for selection biases or not stated

† Vascular risk factor signifies a cardiovascular disease or information on smoking, body mass index, cholesterol levels, diet, blood pressure, diabetes or blood glucose.

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, moderate, and poor):

Good quality: Baseline: 2,5 - 3 stars, Comparability: 1 star, Outcome: 2,5 - 3 stars

Moderate quality: Baseline: 2-3 stars, Comparability: 0,5 -1 star, Outcome: 2-3 stars,

Poor quality: studies not reaching Moderate/Good quality

Deviations from the original study plan

1. We report the results in two parts
    - The numbers of subanalyses grew so large that we decided to split the systematic review and meta-analysis into two parts for clarity (one part for dementia and one part for cognition).
2. Our aim was to study what kind of physical activity is associated with decreased incidence of dementia
    - One aim was to compare the effect of the volume of physical activity and the intensity of physical activity but there weren't enough studies reporting a relation between the intensity of physical activity and dementia. Another aim was to examine the separately the effect of a rough measure of physical activity (yes or no question, number of different physical activities) or walking distance to more specific measures of physical activity (taking into account the volume, intensity and frequency of physical activity). During the examination of the physical activity measures of the included studies, we decided that it would be better and more clear way to categorize them by WHO physical activity recommendation threshold. This way, we can pinpoint a specific volume of physical activity and take into account whether the study actually is able to measure physical activity reliably enough to tell whether physical activity WHO recommendation is met. At this point, we also glanced the earlier meta-analyses more thoroughly and decided to do an analysis similar as in the most earlier meta-analyses (highest physical activity group vs lowest physical activity group) for better comparison with the earlier studies.
3. In addition to dementia and Alzheimer's disease, we collected the results separately for vascular dementia.
4. The method of measuring education was extracted with precision but was not examined with a separate sub-analysis because of vast heterogeneity in the classifications.
5. Data extraction of other modifiers than the length of the follow-up was done only by one researcher due to time and resource constraints.
6. The quality assessment tool was developed only after research plan was ready and adjusting for chronic diseases at baseline was not included because adjusting for education and some vascular risk factor was deemed more important.
7. We did not use Review Manager 5 but Covidence for handling data.
8. We conducted the prespecified moderator analyses but the classifications varied a little according to the data found (eg. follow-up length was grouped in a different way because we found many studies with follow-up length over 20 years).
    - Separate analyses were not done for according to the validity of physical activity measurement because we did a separate analysis according to meeting physical activity WHO recommendations as discussed earlier in point 2.
    - We did not perform separate analyses for different genders because there was not enough data: almost all studies presented results only for men and women jointly and very few studies reported the results for gender interaction test.
    - There was not enough data for a separate analysis for twin studies.
9. We aimed to include studies with "a valid physical activity questionnaire", but this criterion would have tremendously restricted the number of included studies, we ended up including also physical activity questionnaires that are not separately validated.

Supplementary analyses

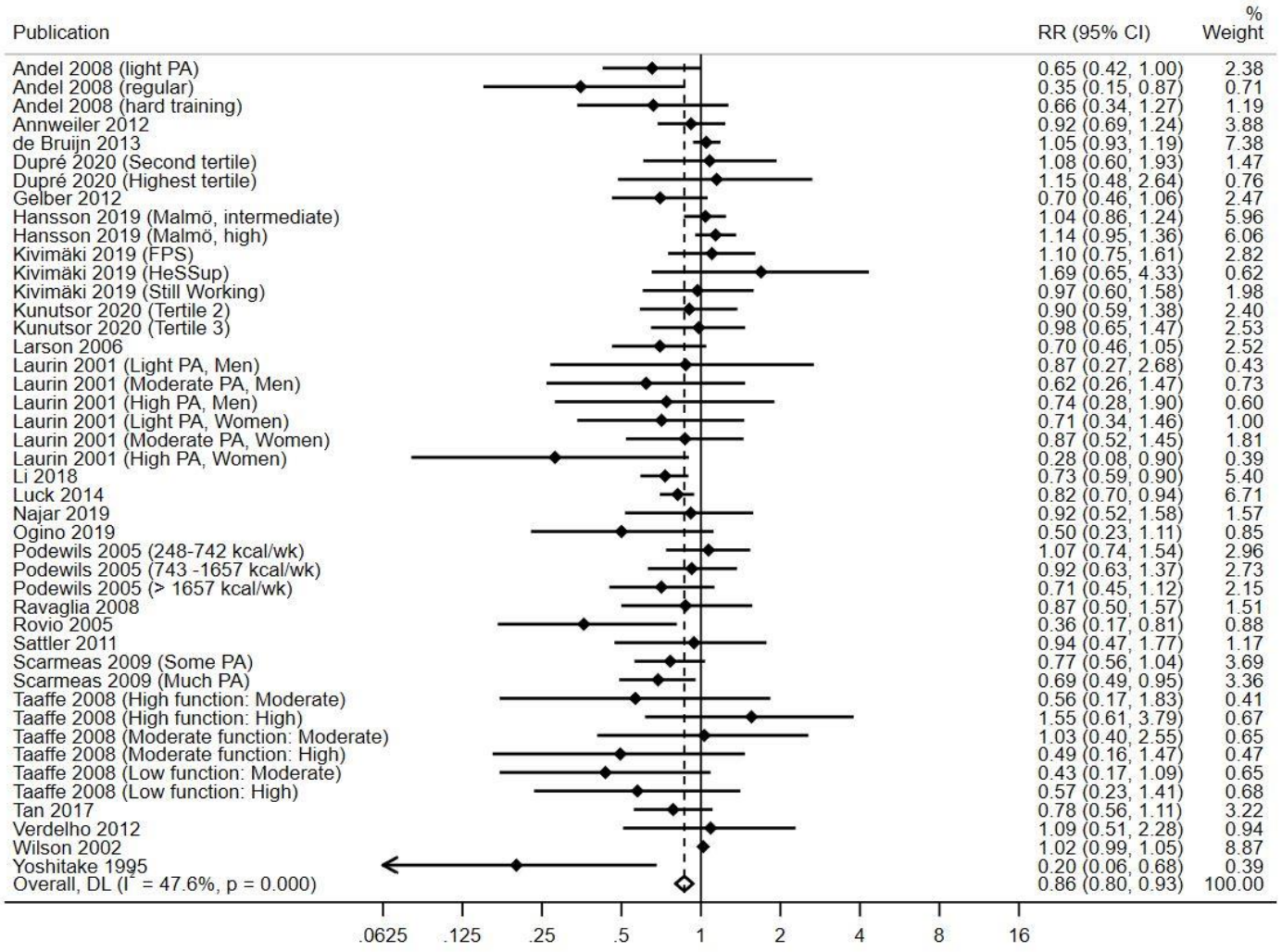
Supplementary Table S1. Physical activity and all-cause dementia, supplementary analyses

Subanalyses	Pooled RR	95% Confidence interval	I^2	Number of studies combined	b estimate†	95% Confidence intervals
Prospective cohort studies [8, 10, 26-30, 33, 36-39, 41-62, 68-79]	0.81	0.77, 0.85	68.4%	46		
Case-control studies [34, 35, 40]	0.70	0.52, 0.95	73.4%	3		
All physical activity without the study with the largest weight (Palta et al. 2019)	0.80	0.77, 0.84	68.0%	48		
All physical activity without the study with the largest sample size (Kivimäki et al. 2019)	0.80	0.76, 0.84	70.1%	48		
Work-related physical activity [13, 69]	1.25	0.98, 1.59	29.4%	2		
All PA						
Moderators						
Sample size					1.00	1.00, 1.00
Baseline cognition *, adjusted	0.79	0.72, 0.88	54.3%	12		
not adjusted	0.81	0.77, 0.85	70.1%	37		
Education *, adjusted	0.80	0.76, 0.85	69.0%	38		
not adjusted	0.78	0.69, 0.88	64.4%	11		
Chronic diseases *, adjusted	0.80	0.75, 0.85	71.0%	28		
not adjusted	0.81	0.76, 0.87	56.1%	21		
APOE ε4 status *, adjusted	0.82	0.76, 0.88	56.6%	15		
not adjusted	0.79	0.75, 0.84	69.5%	34		
Funding source *, only non-commercial	0.79	0.75, 0.84	72.2%	41		
also commercial or not told	0.83	0.78, 0.89	4.1%	9		
Number of confounders					1.01	0.95, 1.08

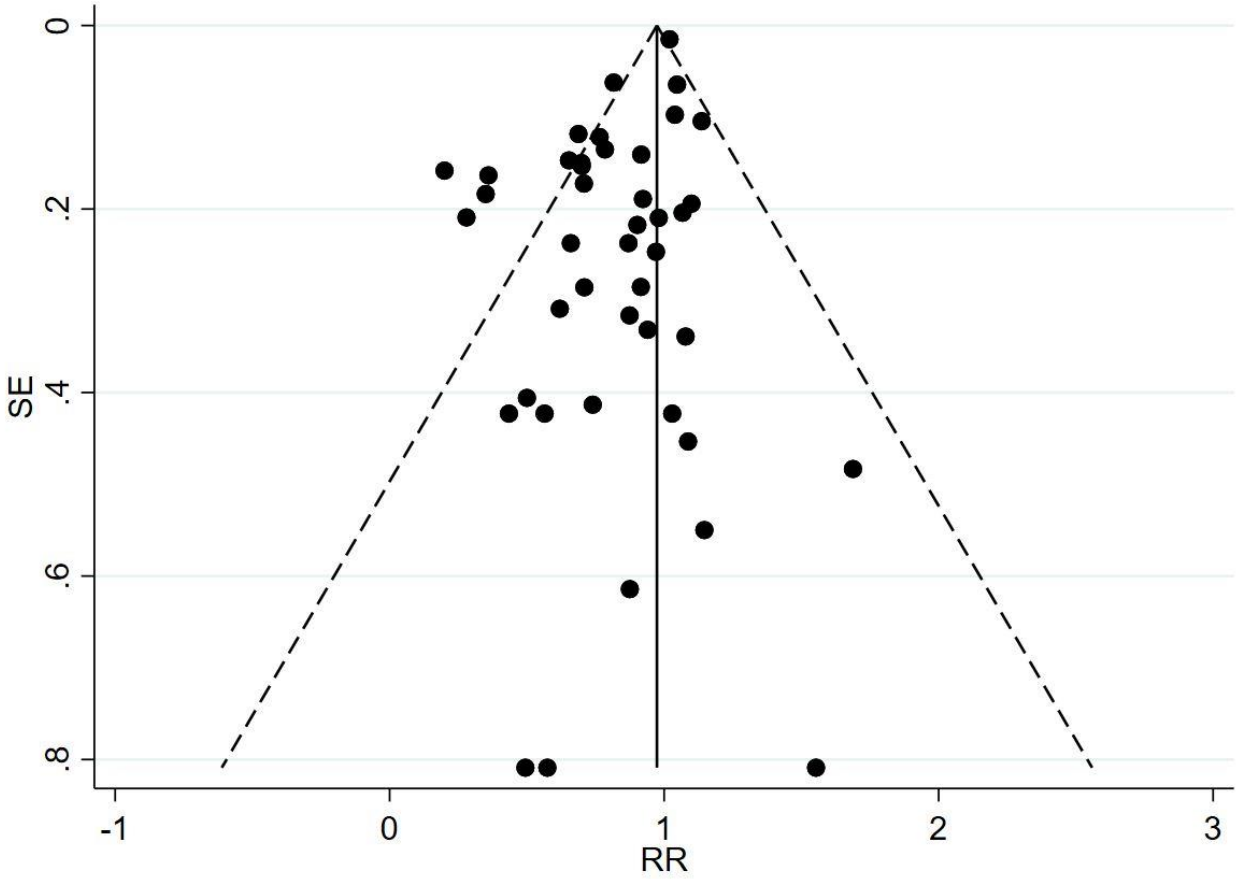
* Moderate heterogeneity observed (I^2 up to 70.1%) in one or more subgroups; tests for heterogeneity between subgroups are likely to be invalid

† Beta estimate is the regression coefficient from the meta-regression examining the relationship of modifier or continuous physical activity on the log risk ratio of dementia.

Supplementary Figure S1. Longitudinal observational studies of physical activity and Alzheimer's disease: forest plot



Supplementary Figure S2. Funnel plot for the longitudinal observational studies on physical activity and Alzheimer's disease with pseudo 95% confidence intervals.



Supplementary Table S2. Physical activity and Alzheimer's disease, supplementary analyses

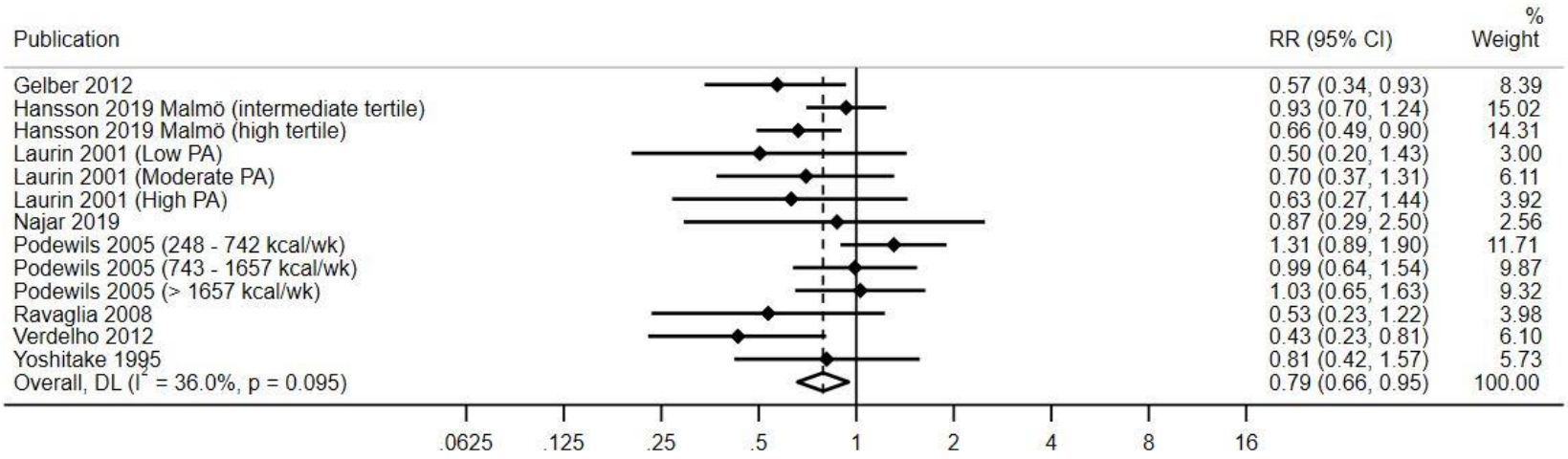
Subanalyses	Pooled RR	95% Confidence interval	I^2	Number of studies combined	b estimate†	95% Confidence intervals
Only leisure-time PA & quality moderate or high [11, 34, 77]	0.68	0.50, 0.92	45.2%	3		
Highest PA group vs lowest (1 highest vs 1 lowest)[8, 10, 11, 26, 29, 34, 37, 38, 40, 46, 47, 51, 56, 57, 60, 63, 65-68, 74, 77, 81, 82]	0.87	0.79, 0.95	55.7%	24		
Prospective cohort studies [8, 10, 11, 26, 29, 37, 38, 46, 47, 51, 56, 57, 60, 63, 65-68, 74, 77, 81, 82]	0.89	0.83, 0.96	43.3%	22		
Case-control studies [34, 40]	0.64	0.49, 0.83	0.0%	2		
All physical activity without the study with the largest weight (Hansson et al. 2019)	0.83	0.77, 0.91	48.5 %	23		
All physical activity without the study with the largest sample size (Kivimäki et al. 2019)	0.85	0.78, 0.92	50.4%	23		
All PA						
Moderators						
Sample size					1.00	1.00, 1.00
Baseline cognition †, adjusted	0.84	0.74, 0.95	41.6%	9		
not adjusted	0.88	0.80, 0.97	44.1%	15		
Education †, adjusted	0.85	0.78, 0.92	36.1%	20		
not adjusted	0.92	0.73, 1.16	45.9%	4		
Chronic diseases †, adjusted	0.82	0.74, 0.91	43.6%	17		
not adjusted	0.95	0.85, 1.06	26.7%	7		
APOE ε4 status ‡, adjusted	0.85	0.76, 0.94	53.5%	13		
not adjusted	0.88	0.77, 0.99	37.9%	11		
Funding source ‡, only non-commercial	0.86	0.79, 0.93	55.9%	22		
also commercial or not told	0.92	0.75, 1.12	0.0%	3		
Number of confounders					1.00	0.90, 1.12

* Beta estimate is the regression coefficient from the meta-regression examining the relationship of modifier or continuous physical activity on the log risk ratio of dementia

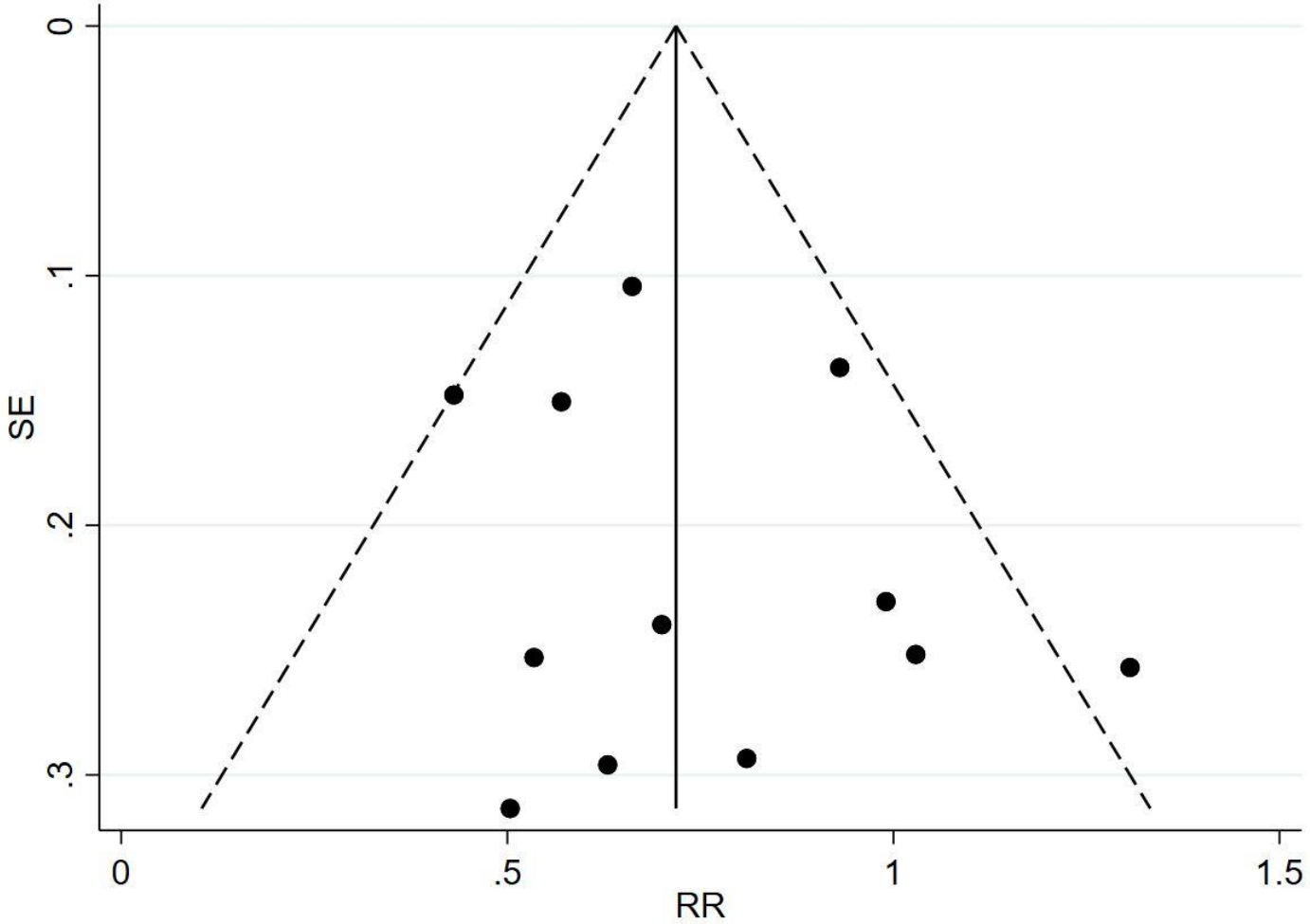
† Heterogeneity for between groups non-significant (P=.539 for baseline cognition, P=.489 for education, P=.059 for chronic diseases)

‡ Moderate heterogeneity observed (I^2 up to 70.1%) in one or more subgroups; tests for heterogeneity between subgroups are likely to be invalid

Supplementary Figure S3. Longitudinal observational studies of physical activity and vascular dementia: forest plot



Supplementary Figure S4. Funnel plot for the longitudinal observational studies on physical activity and vascular dementia with pseudo 95% confidence intervals.



Supplementary Table S3. PA and VaD: main results, main sensitivity analyses with meta-regressions and subgroup analyses, and dose-response analysis

	Pooled RR	95% Confidence interval	I^2	Number of cohorts combined	beta estimate ‡	95% Confidence interval
All PA	0.79	0.66, 0.95	36.0%	8		
Baseline age (continuous)					1.00	0.92, 1.10
Baseline age (categorical						
Age group 30-65 years [28, 42, 75]	0.75	0.59, 0.95	26.4%	3		
Age group 70-85 years [11, 49, 53, 62, 69]	0.81	0.62, 1.04	41.3%	5		
Follow-up length					1.00	0.89, 1.13
Follow-up length < 10 years [11, 49, 53, 62, 69]	0.81	0.62, 1.04	41.3%	5		
Follow-up length ≥10 years [28, 42, 75]	0.75	0.59, 0.95	26.4%	3		
Study quality (low vs moderate vs high)*					1.26	0.38, 4.13
Low quality [11, 28, 62, 69]	0.87	0.68, 1.10	55.3%	4		
Moderate quality [49, 53, 75]	0.64	0.44, 0.92	0.0%	3		
High quality † [42]	0.57	0.34, 0.94	0.0%	1		
Meeting PA guidelines [11, 28, 49, 53, 62, 69]	0.74	0.59, 0.93	22.7%	6		
Not meeting PA guidelines [11, 28, 49, 75]	0.95	0.73, 1.23	23.9%	4		
Age group 30-55 years, Quality high & Follow-up length > 20 years † [42]	0.57	0.34, 0.94	0.0%	1		

Abbreviations: RR= Relative risk, I^2=Heterogeneity, PA=Physical activity, VaD=Vascular dementia

* Study quality was assessed with a quality assessment tool we developed (See Supplementary Material Part 1 for details).

† Not a meta-analytical analysis, only one study

‡ Beta estimate is the regression coefficient from the meta-regression examining the relationship of modifier or continuous PA on the log risk ratio of dementia.

§ The test for heterogeneity between groups was non-significant (P=.159).

Supplementary Table S4. Physical activity and vascular dementia, supplementary analyses

Subanalyses	Pooled RR	95% Confidence interval	I^2	Number of studies combined	b estimate‡	95% Confidence intervals
Only leisure-time PA & quality moderate or high*	-	-	-	-		
Highest PA group vs lowest (1 highest vs 1 lowest) [10, 26, 40, 47, 51, 60, 67, 73]	0.68	0.56, 0.82	0.0%	8		
Prospective cohort studies [10, 26, 47, 51, 60, 67, 73]	0.81	0.68, 0.98	34.0%	7		
Case-control studies † [40]	0.57	0.34, 0.93	0.0%	1		
All physical activity without the study with the largest weight (Hansson et al. 2019)	0.78	0.62, 0.98	37.7%	7		
All physical activity without the study with the largest sample size (Hansson et al. 2019)	0.78	0.62, 0.98	37.7%	7		
All PA						
Moderators						
Sample size					1.00	1.00, 1.00
Baseline cognition §, adjusted	0.91	0.65, 1.27	55.9%	3		
not adjusted	0.73	0.62, 0.86	0.0%	5		
Education §, adjusted	0.78	0.64, 0.96	46.6%	6		
not adjusted	0.83	0.47, 1.45	0.0%	2		
Chronic diseases §, adjusted	0.73	0.62, 0.87	0.0%	6		
not adjusted	0.92	0.62, 1.37	65.7%	2		
APOE ε4 status §, adjusted	0.90	0.65, 1.24	54.0%	3		
not adjusted	0.74	0.62, 0.87	0.0%	5		
Funding source, only non-commercial	0.81	0.66, 1.00	47.5%	7		
also commercial or not told †	0.63	0.40, 0.99	0.0%	1		
Number of confounders					1.03	0.85, 1.26

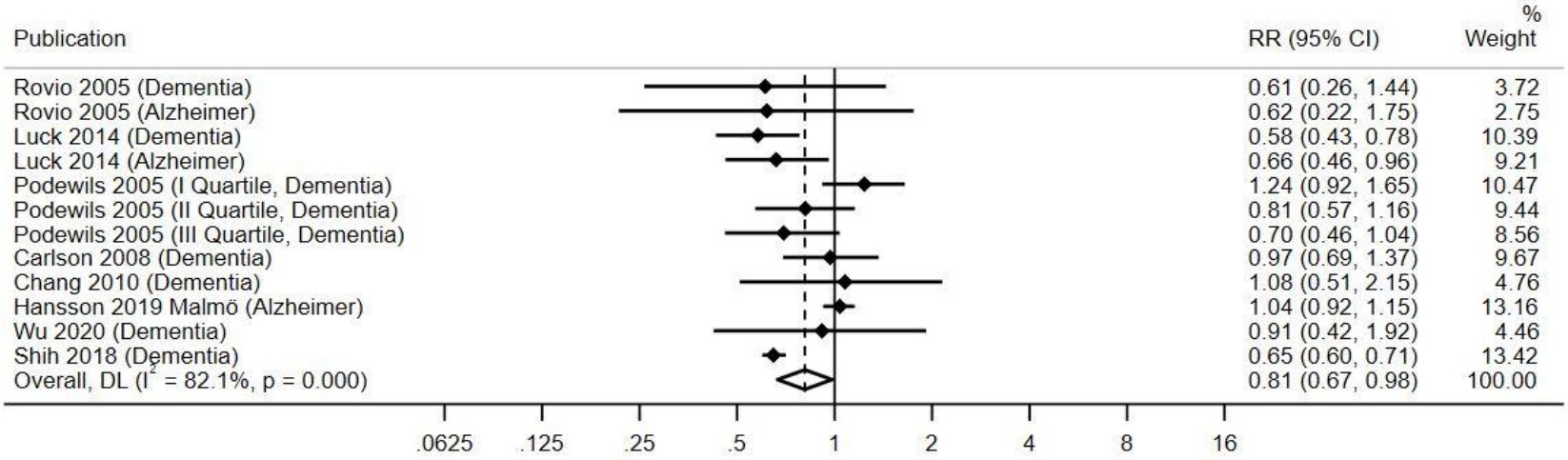
* No studies

† Not meta-analytical analysis, only one study

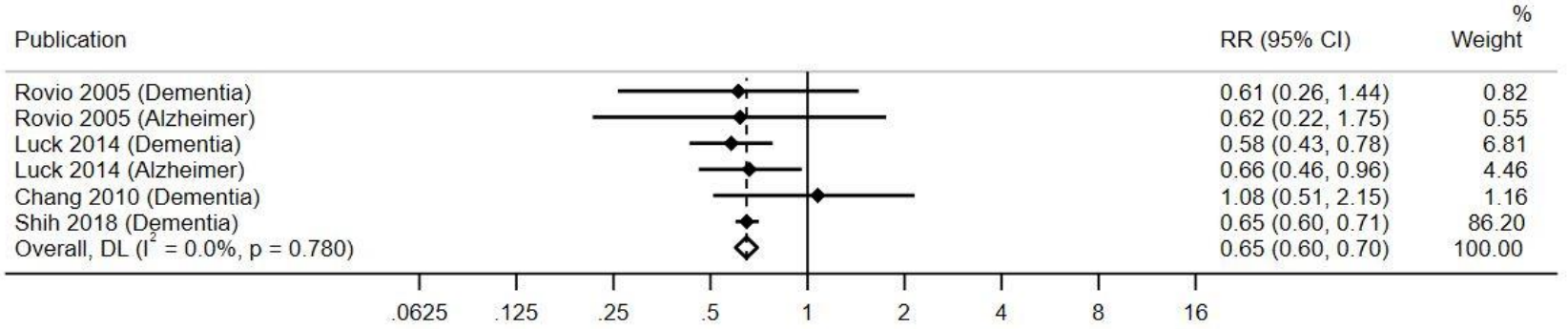
‡ Beta estimate is the regression coefficient from the metaregression examining the relationship of modifier or continuous physical activity on the log risk ratio of dementia.

§ The test for heterogeneity between groups was non-significant (P=.248 for baseline cognition, P=.846 for education, P=.305 for chronic diseases, P=.294 for apolipoprotein E ε4 allele).

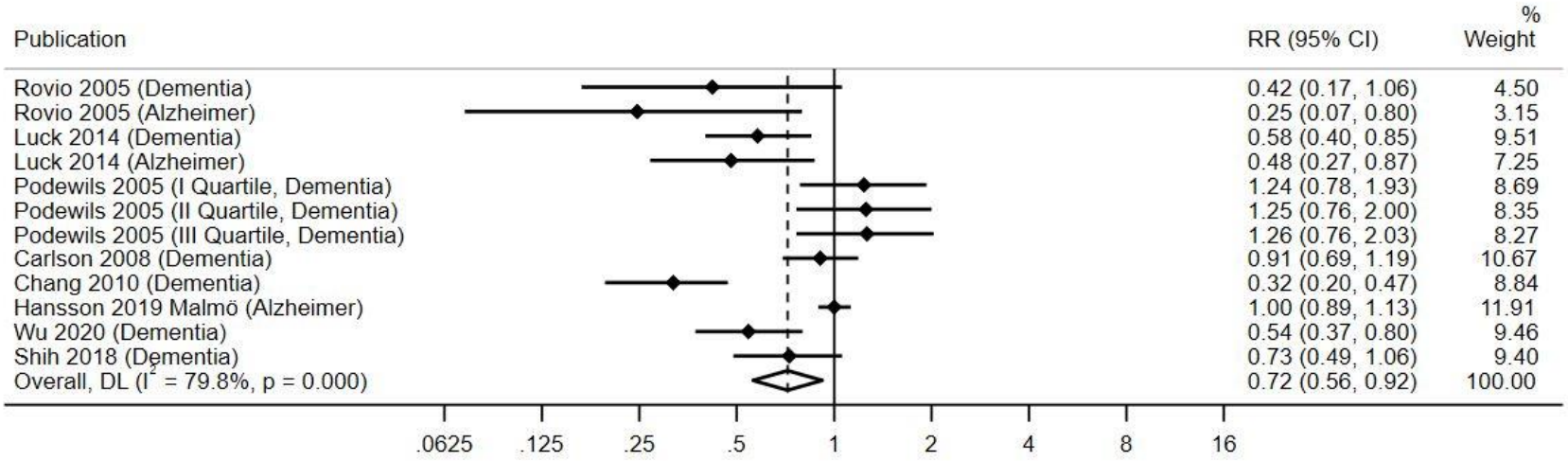
Supplementary Figure S5. Physical activity and all-cause dementia, Alzheimer's disease and vascular dementia in APOE ε4 carriers



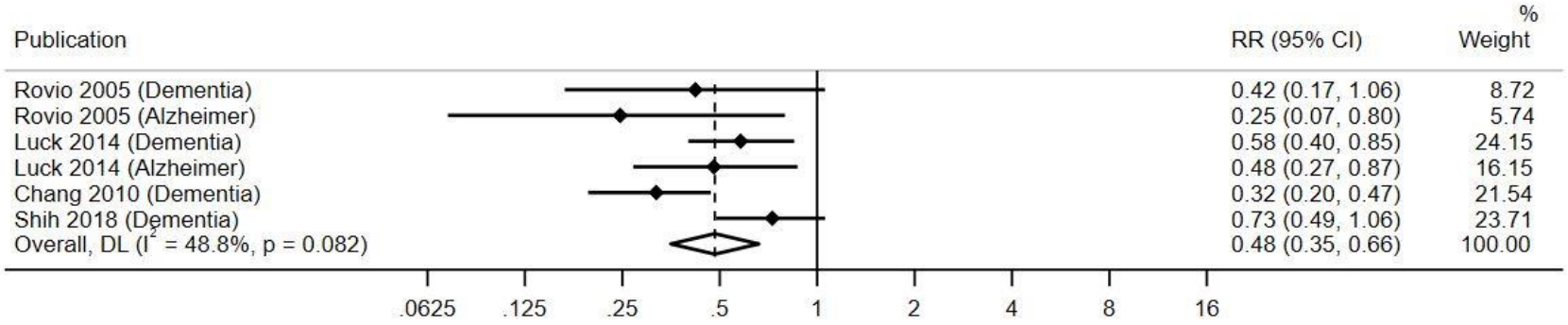
Supplementary Figure S6. Physical activity and all-cause dementia, Alzheimer's disease and vascular dementia in APOE ε4 carriers when study quality is good or moderate



Supplementary Figure S7. Physical activity and all-cause dementia, Alzheimer's disease and vascular dementia in APOE ε4 non-carriers



Supplementary Figure S8. Physical activity and all-cause dementia, Alzheimer's disease and vascular dementia in APOE ε4 non-carriers when study quality is good or moderate



Sensitivity analysis for APOE ε4 allele

To find out if APOE ε4 allele moderates the association between physical activity and dementia, we gathered information from the individual studies on APOE ε4 allele interaction analysis results and results reported separately for APOE ε4 carriers and noncarriers. 12 studies presented results from APOE ε4 interaction analyses (Hansson et al. 2019, Dupré et al. 2020, Tan et al. 2017, Taaffe et al. 2008, Podewils et al. 2005, Kim et al. 2011, Ravaglia et al. 2008, Lindsay et al. 2002, Paillard-Borg et al. 2009, Luck et al. 2014, Rovio et al. 2005, Shih et al. 2018). Most studies reported only results from interaction test not separating multiplicative and additive interaction, one study reported additive but not multiplicative interaction results and two studies reported both multiplicative and additive interaction results. The results were the following:

- 12 studies reported interaction analysis results
- 9 studies reported no interaction ((Hansson et al. 2019, Dupré et al. 2020, Tan et al. 2017, Taaffe et al. 2008, Rovio et al. 2005, Podewils et al. 2005, Luck et al. 2014, Kim et al. 2011, Ravaglia et al. 2008, Lindsay et al. 2002, Paillard-Borg et al. 2009)
- 2 studies reported no multiplicative interaction but significant or probable additive interaction (Luck et al. 2014, Rovio et al. 2005)
- 1 study reported no interaction on additive scale. The results were presented stratified according to APOE ε4 status but the result for multiplicative interaction was not given (Shih 2018).

Supplementary Material Part 3
Dose-response meta-analyses

Contents

Method description

Calculation of PA exposure levels

Following the procedure of Blond et al (1), we used the midpoint of the physical activity range (mean or median) from each group as the value for PA exposure. MET values for listed activities were taken from the included articles, or estimated using MET values of 3.5 for walking, 4.5 for moderate physical activity and 8.0 for sports participation or vigorous PA. For studies in which PA was assessed as bouts per week, one bout was estimated to be 30 minutes in duration unless otherwise specified in the included article. When physical activity levels were specified in calories per week, mean body weights reported in the articles were used for calculating MET-minutes using the formula

$$MET * minutes = \frac{60 * kcal}{kg}$$

Where mean body weight was not reported in an article, continental body weight averages were used in the calculation (2). In studies where it was not possible to directly calculate MET*minutes per week for each group, we imputed PA exposure values using the means from other similar studies. We used a cutoff of a maximum of 21 hours of moderate PA per week (3 hours X 7 days), and this corresponds to a maximum value of 5040 MET-minutes per week.

Dose-response meta-analyses

Dose-response meta-analyses were performed using the dosresmeta package (3) in R and visualizations were created using the shiny webapp based on this package (4). Two-stage random effects meta-analyses using the restricted maximum likelihood procedure were used to pool RRs. Among studies with at least 3 different PA exposure levels, dose–response meta-analyses explored linear, quadratic and restricted cubic spline trends within the data. Knots in the restricted cubic spline regression models were set at the 20th and 80th percentiles of the overall PA exposure distribution. As it was not possible to explore quadratic or spline trends among studies with only two different PA exposure levels, we only examined linear trends

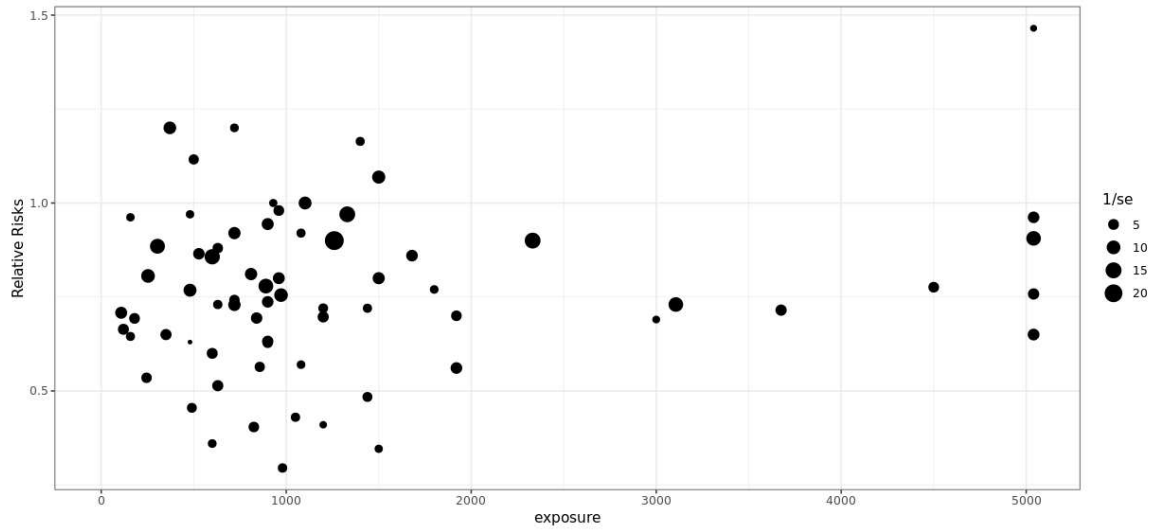
Iso-Markku P, *et al. Br J Sports Med* 2022;0:1–11. doi: 10.1136/bjsports-2021-104981

within this larger dataset that included all studies with at least two discrete PA exposure groups. We chose 200 MET min/week as the reference for the dose–response analyses as this was roughly equivalent to the mean MET*min per week value of reference groups in the included studies. Post-estimations based on the dose–response model were conducted to predict RRs and 95% CIs at specific MET*min per week values (approximately 200, 900, 2000, 3000, 4000, and 5000).

Results - All-cause dementia (A-CD)

Linear model including all studies (A-CD)

Scatter plot of RRs vs original exposure variable

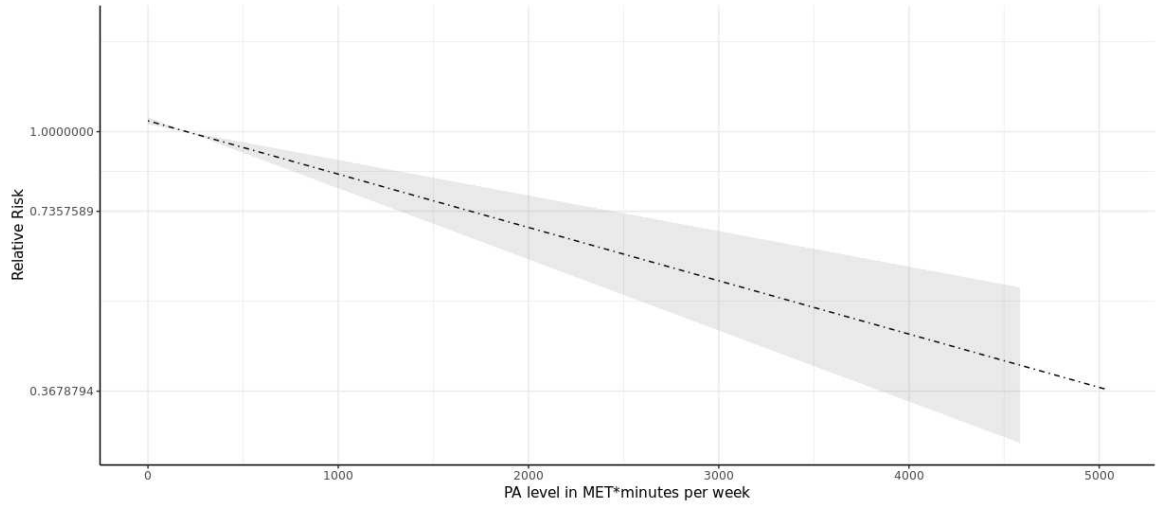


Linear Trend

```
Call:  dosresmeta(formula = logrr ~ exposure, id = id, type = type,
    cases = cases, n = n, data = dataset(), se = se, covariance = input$pscorr)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 34.6275 (df = 1), p-value = 0.0000

Fixed-effects coefficients
             Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
(Intercept)   -0.0002      0.0000  -5.8845    0.0000   -0.0003   -0.0001  ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Between-study random-effects (co)variance components
  Std. Dev
```

```
    0.0002

Univariate Cochran Q-test for residual heterogeneity:
Q = 123.3919 (df = 42), p-value = 0.0000
I-square statistic = 66.0%

43 studies, 43 values, 1 fixed and 1 random-effects parameters
   logLik        AIC        BIC
 276.7986  -549.5973  -546.1220
```

Graphical prediction

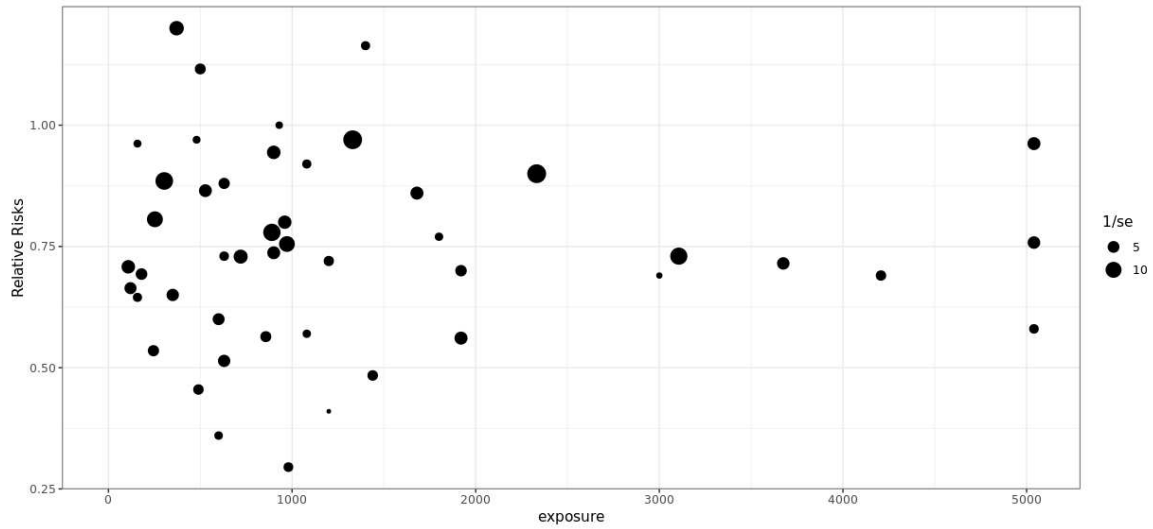


Analytical predictions

PA exposure	pred.lin	ci.lb.lin	ci.ub.lin
203.64	1.00	1.00	1.00
916.36	0.86	0.82	0.91
1934.55	0.70	0.62	0.79
2952.73	0.57	0.47	0.69
3970.91	0.46	0.36	0.60
4989.09	0.37	0.27	0.52

Models including studies with 3 or more PA exposure levels (A-CD)

Scatter plot of RRs vs original exposure variable



Linear Trend

```
Call:  dosresmeta(formula = logrr ~ exposure, id = id, type = type,
    cases = cases, n = n, data = dataset(), se = se, covariance = input$pscorr)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 21.4096 (df = 1), p-value = 0.0000

Fixed-effects coefficients
             Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
(Intercept)   -0.0002      0.0000  -4.6270    0.0000   -0.0003   -0.0001  ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Between-study random-effects (co)variance components
  Std. Dev
    0.0001

Univariate Cochran Q-test for residual heterogeneity:
Q = 57.7815 (df = 19), p-value = 0.0000
I-square statistic = 67.1%
```

```
20 studies, 20 values, 1 fixed and 1 random-effects parameters
   logLik        AIC        BIC
 128.2688  -252.5375  -250.6487
```

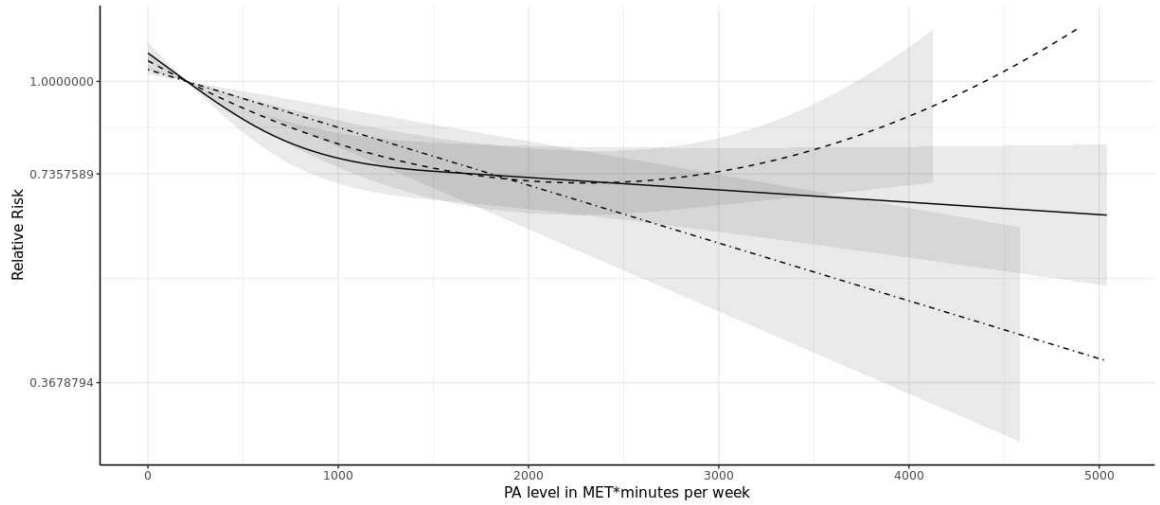
Spline model

```
Call:  dosresmeta(formula = logrr ~ rcs(exposure, knots), id = id, type = type,
    cases = cases, n = n, data = dataset(), se = se, covariance = input$pscorr)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 37.6403 (df = 2), p-value = 0.0000

Fixed-effects coefficients
                                          Estimate  Std. Error        z
rcs(exposure, knots)exposure.(Intercept)    -0.0005      0.0001  -5.5896
rcs(exposure, knots)exposure'.(Intercept)    0.0004      0.0001   4.5834
                                          Pr(>|z|)  95%ci.lb  95%ci.ub
rcs(exposure, knots)exposure.(Intercept)     0.0000   -0.0006   -0.0003  ***
rcs(exposure, knots)exposure'.(Intercept)    0.0000    0.0002    0.0006  ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Between-study random-effects (co)variance components
                              Std. Dev                          Corr
rcs(exposure, knots)exposure     0.0002  rcs(exposure, knots)exposure
rcs(exposure, knots)exposure'    0.0001                            -1

Univariate Cochran Q-test for residual heterogeneity:
Q = 58.7637 (df = 38), p-value = 0.0169
I-square statistic = 35.3%

20 studies, 40 values, 2 fixed and 3 random-effects parameters
   logLik        AIC        BIC
 222.9501  -435.9001  -427.7122
```

Quadratic trend

```
Call:  dosresmeta(formula = logrr ~ exposure + I(exposure^2), id = id,
    type = type, cases = cases, n = n, data = dataset(), se = se,
    covariance = input$pscorr)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 38.9658 (df = 2), p-value = 0.0000

Fixed-effects coefficients
                          Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb
exposure.(Intercept)       -0.0004      0.0001  -4.6303    0.0000   -0.0005
I(exposure^2).(Intercept)   0.0000      0.0000   3.3398    0.0008    0.0000
                          95%ci.ub
exposure.(Intercept)       -0.0002  ***
I(exposure^2).(Intercept)   0.0000  ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Between-study random-effects (co)variance components
               Std. Dev      Corr
exposure         0.0002  exposure
I(exposure^2)    0.0000        -1

Univariate Cochran Q-test for residual heterogeneity:
Q = 66.0653 (df = 38), p-value = 0.0032
I-square statistic = 42.5%

20 studies, 40 values, 2 fixed and 3 random-effects parameters
   logLik        AIC        BIC
 382.8104  -755.6209  -747.4329
```

Graphical prediction



Linear Trend (dot-dash); Spline Model with knots at 20 and 80% of distribution (solid); Quadratic Trend (dashed)

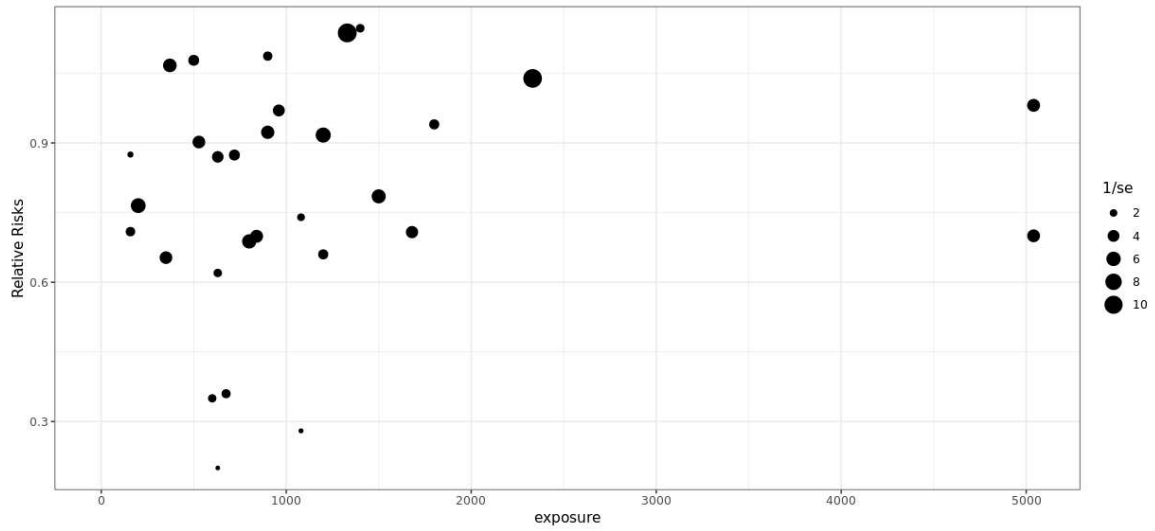
Analytical predictions

exposure	pred.lin	ci.lb.lin	ci.ub.lin	pred.spl	ci.lb.spl	ci.ub.spl	pred.quadr	ci.lb.quadr	ci.ub.quadr
203.64	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
916.36	0.87	0.82	0.92	0.79	0.73	0.85	0.83	0.77	0.89
1934.55	0.72	0.62	0.83	0.73	0.66	0.81	0.72	0.65	0.80
2952.73	0.59	0.47	0.74	0.70	0.61	0.80	0.74	0.66	0.82
3970.91	0.49	0.36	0.66	0.67	0.56	0.80	0.88	0.71	1.11
4989.09	0.40	0.27	0.59	0.64	0.51	0.81	1.24	0.78	1.99

Results - Alzheimer's disease (AD)

Linear model including all studies (AD)

Scatter plot of RRs vs original exposure variable

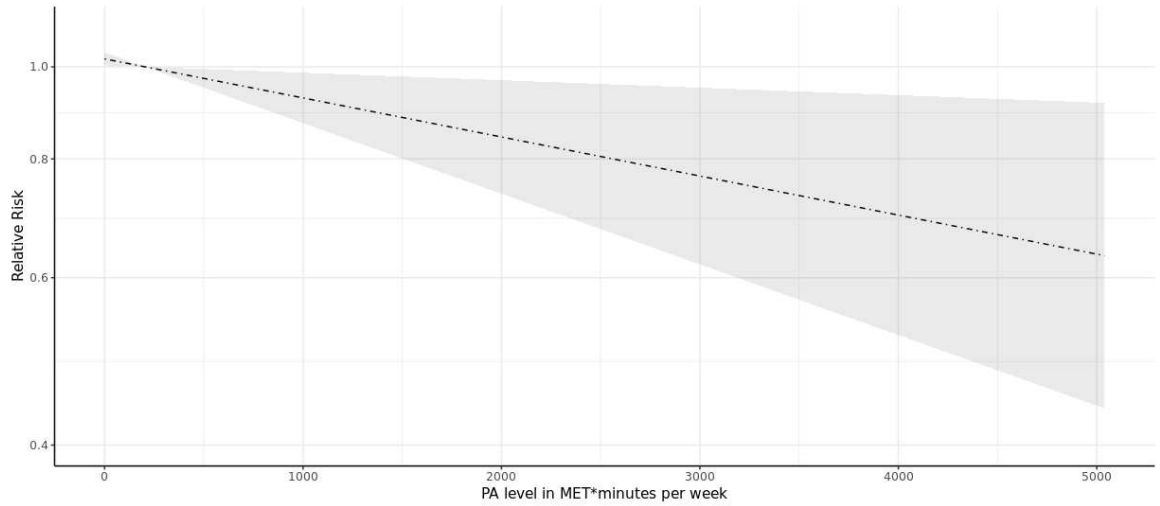


Linear Trend

```
Call:  dosresmeta(formula = logrr ~ exposure, id = id, type = type,
    cases = cases, n = n, data = dataset(), se = se, covariance = input$pscorr)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 5.8708 (df = 1), p-value = 0.0154

Fixed-effects coefficients
             Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
(Intercept)   -0.0001      0.0000  -2.4230    0.0154   -0.0002   -0.0000  *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Between-study random-effects (co)variance components
  Std. Dev
    0.0001

Univariate Cochran Q-test for residual heterogeneity:
Q = 28.3221 (df = 18), p-value = 0.0573
I-square statistic = 36.4%

19 studies, 19 values, 1 fixed and 1 random-effects parameters
   logLik        AIC        BIC
```

```
 118.7244  -233.4489  -231.6681
```

Graphical prediction

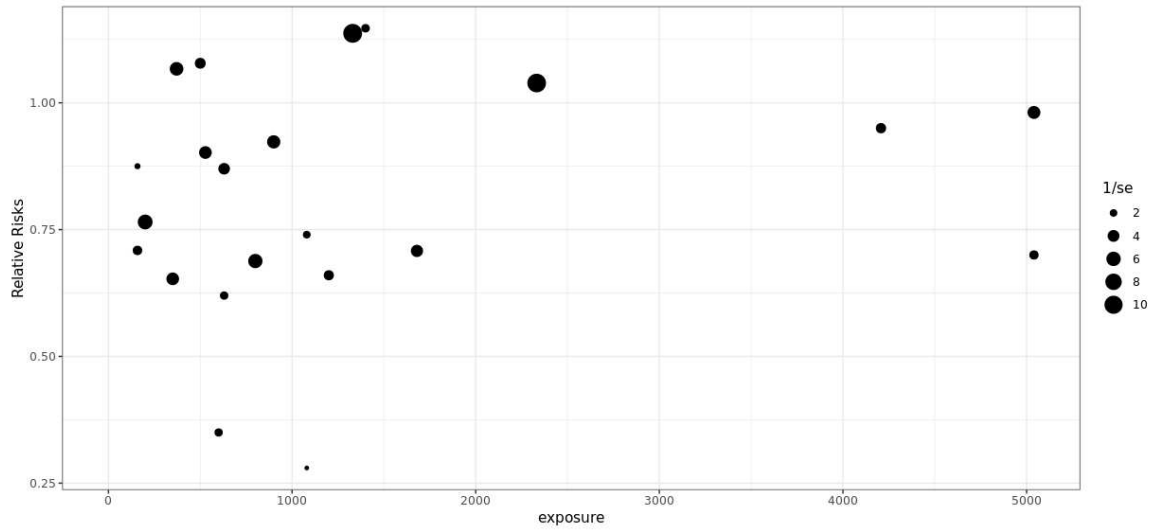


Analytical predictions

PA exposure	pred.lin	ci.lb.lin	ci.ub.lin
203.64	1.00	1.00	1.00
916.36	0.93	0.89	0.99
1934.55	0.85	0.74	0.97
2952.73	0.77	0.62	0.95
3970.91	0.70	0.52	0.93
4989.09	0.64	0.44	0.92

Models including studies with 3 or more PA exposure levels (AD)

Scatter plot of RRs vs original exposure variable



Linear Trend

```
Call:  dosresmeta(formula = logrr ~ exposure, id = id, type = type,
    cases = cases, n = n, data = dataset(), se = se, covariance = input$pscorr)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 2.1500 (df = 1), p-value = 0.1426

Fixed-effects coefficients
             Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
(Intercept)   -0.0001      0.0001  -1.4663    0.1426   -0.0002    0.0000
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Between-study random-effects (co)variance components
  Std. Dev
    0.0001

Univariate Cochran Q-test for residual heterogeneity:
Q = 10.8651 (df = 8), p-value = 0.2095
I-square statistic = 26.4%

9 studies, 9 values, 1 fixed and 1 random-effects parameters
   logLik        AIC        BIC
```

```
  55.4683  -106.9365  -106.7776
```

Spline model

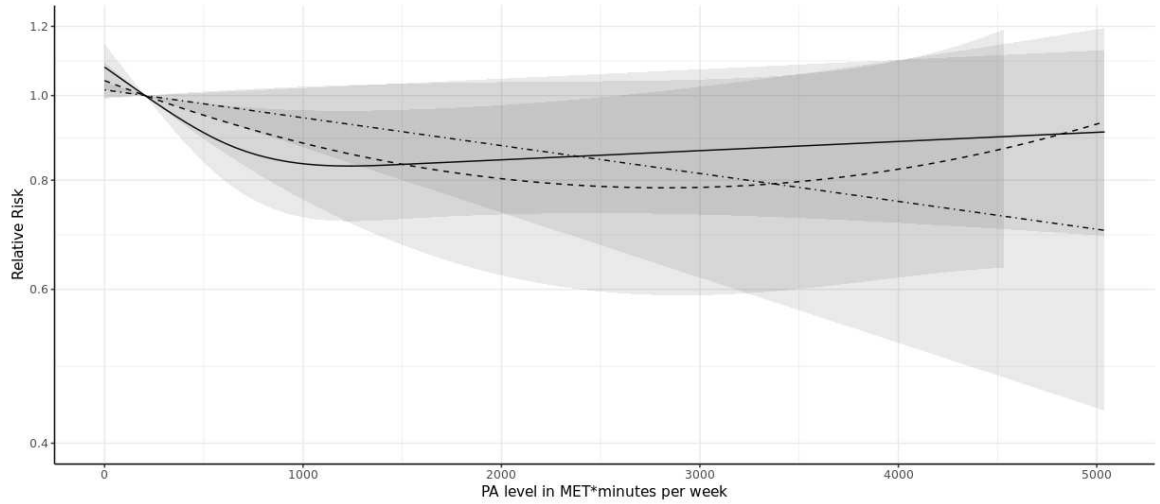
```
Call:  dosresmeta(formula = logrr ~ rcs(exposure, knots), id = id, type = type,
    cases = cases, n = n, data = dataset(), se = se, covariance = input$pscorr)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 6.2649 (df = 2), p-value = 0.0436

Fixed-effects coefficients
                                          Estimate  Std. Error        z
rcs(exposure, knots)exposure.(Intercept)   -0.0004      0.0001  -2.4593
rcs(exposure, knots)exposure'.(Intercept)   0.0003      0.0001   2.3245
                                          Pr(>|z|)  95%ci.lb  95%ci.ub
rcs(exposure, knots)exposure.(Intercept)     0.0139   -0.0007   -0.0001  *
rcs(exposure, knots)exposure'.(Intercept)    0.0201    0.0001    0.0006  *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Between-study random-effects (co)variance components
                              Std. Dev                          Corr
rcs(exposure, knots)exposure     0.0000  rcs(exposure, knots)exposure
rcs(exposure, knots)exposure'    0.0000                        0.9723

Univariate Cochran Q-test for residual heterogeneity:
Q = 16.9974 (df = 16), p-value = 0.3858
I-square statistic = 5.9%

9 studies, 18 values, 2 fixed and 3 random-effects parameters
   logLik        AIC        BIC
  85.2275  -160.4549  -156.5920
```

Quadratic trend

```
Call:  dosresmeta(formula = logrr ~ exposure + I(exposure^2), id = id,
    type = type, cases = cases, n = n, data = dataset(), se = se,
```

```
    covariance = input$pscorr)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 2.8700 (df = 2), p-value = 0.2381

Fixed-effects coefficients
                          Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb
exposure.(Intercept)       -0.0002      0.0001  -1.6085    0.1077   -0.0004
I(exposure^2).(Intercept)   0.0000      0.0000   1.3787    0.1680   -0.0000
                          95%ci.ub
exposure.(Intercept)         0.0000
I(exposure^2).(Intercept)    0.0000
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Between-study random-effects (co)variance components
               Std. Dev      Corr
exposure         0.0002  exposure
I(exposure^2)    0.0000        -1

Univariate Cochran Q-test for residual heterogeneity:
Q = 19.6762 (df = 16), p-value = 0.2352
I-square statistic = 18.7%

9 studies, 18 values, 2 fixed and 3 random-effects parameters
   logLik        AIC        BIC
 158.5896  -307.1793  -303.3163
```

Graphical prediction



Linear Trend (dot-dash); Spline Model with knots at 20 and 80% of distribution (solid); Quadratic Trend (dashed)

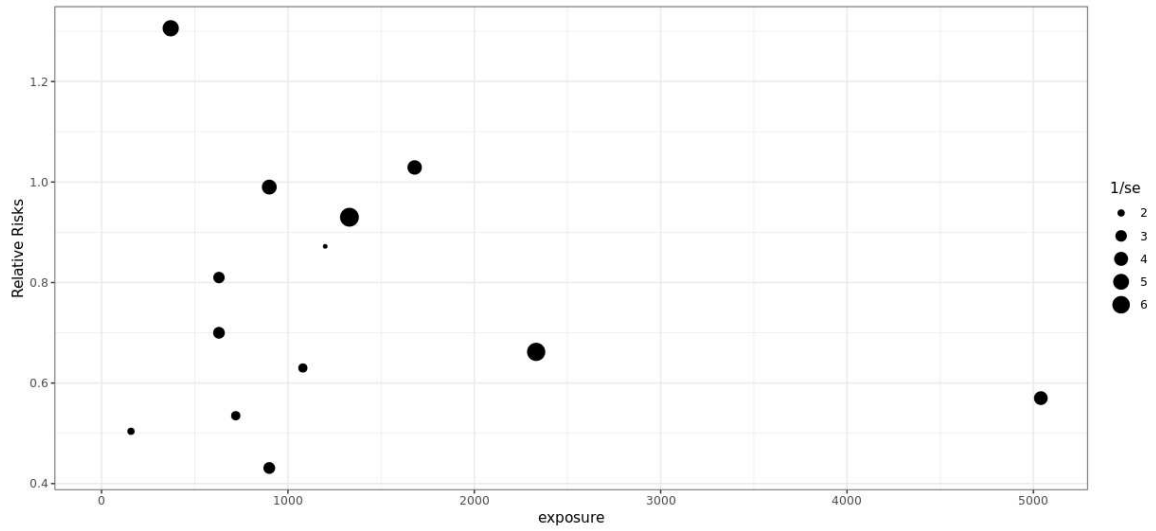
Analytical predictions

PA exposure	pred.lin	ci.lb.lin	ci.ub.lin	pred.spl	ci.lb.spl	ci.ub.spl	pred.quadr	ci.lb.quadr	ci.ub.quadr
203.64	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
916.36	0.95	0.88	1.02	0.84	0.73	0.96	0.89	0.78	1.02
1934.55	0.88	0.74	1.04	0.84	0.73	0.97	0.81	0.63	1.04
2952.73	0.82	0.62	1.07	0.86	0.73	1.02	0.78	0.59	1.04
3970.91	0.76	0.52	1.10	0.89	0.72	1.10	0.82	0.62	1.09
4989.09	0.70	0.44	1.13	0.91	0.69	1.19	0.93	0.64	1.34

Results - Vascular dementia (VD)

Linear model including all studies (VD)

Scatter plot of RRs vs original exposure variable

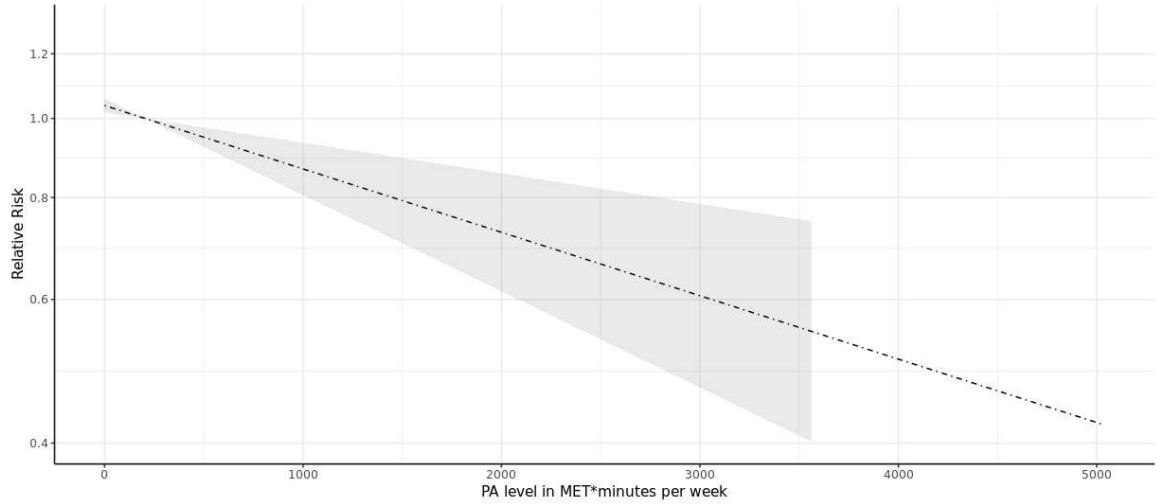


Linear Trend

```
Call:  dosresmeta(formula = logrr ~ exposure, id = id, type = type,
    cases = cases, n = n, data = dataset(), se = se, covariance = input$pscorr)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 14.3032 (df = 1), p-value = 0.0002

Fixed-effects coefficients
             Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
(Intercept)   -0.0002      0.0000  -3.7820    0.0002   -0.0003   -0.0001  ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Between-study random-effects (co)variance components
  Std. Dev
    0.0000

Univariate Cochran Q-test for residual heterogeneity:
Q = 8.2459 (df = 7), p-value = 0.3114
I-square statistic = 15.1%

8 studies, 8 values, 1 fixed and 1 random-effects parameters
  logLik       AIC       BIC
```

```
 45.5563  -87.1126  -87.2208
```

Graphical prediction

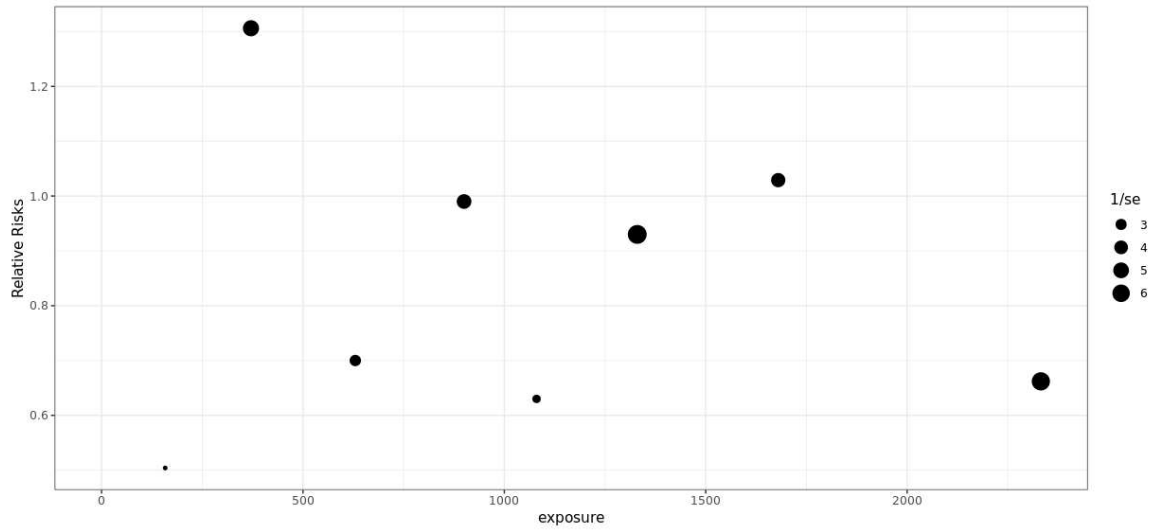


Analytical predictions

PA exposure	pred.lin	ci.lb.lin	ci.ub.lin
203.64	1.00	1.00	1.00
916.36	0.88	0.82	0.94
1934.55	0.73	0.62	0.86
2952.73	0.61	0.47	0.79
3970.91	0.51	0.36	0.72
4989.09	0.42	0.27	0.66

Models including studies with 3 or more PA exposure levels (VD)

Scatter plot of RRs vs original exposure variable



Linear Trend

```
Call:  dosresmeta(formula = logrr ~ exposure, id = id, type = type,
    cases = cases, n = n, data = dataset(), se = se, covariance = input$pscorr)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 7.8907 (df = 1), p-value = 0.0050

Fixed-effects coefficients
             Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
(Intercept)   -0.0002      0.0001  -2.8090    0.0050   -0.0004   -0.0001  **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Between-study random-effects (co)variance components
  Std. Dev
    0.0000

Univariate Cochran Q-test for residual heterogeneity:
Q = 1.1021 (df = 2), p-value = 0.5764
I-square statistic = 0.0%

3 studies, 3 values, 1 fixed and 1 random-effects parameters
  logLik       AIC       BIC
```

```
 14.2687  -24.5373  -27.1510
```

Spline model

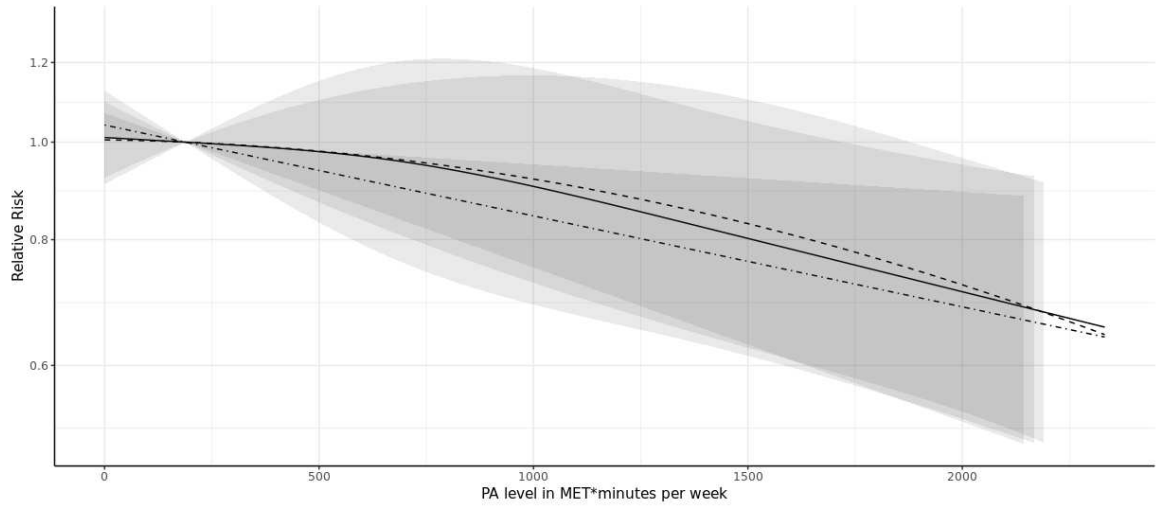
```
Call:  dosresmeta(formula = logrr ~ rcs(exposure, knots), id = id, type = type,
    cases = cases, n = n, data = dataset(), se = se, covariance = input$pscorr)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 8.1864 (df = 2), p-value = 0.0167

Fixed-effects coefficients
                                          Estimate  Std. Error        z
rcs(exposure, knots)exposure.(Intercept)    -0.0001      0.0003  -0.1959
rcs(exposure, knots)exposure'.(Intercept)   -0.0001      0.0003  -0.5438
                                          Pr(>|z|)  95%ci.lb  95%ci.ub
rcs(exposure, knots)exposure.(Intercept)     0.8447   -0.0006    0.0005
rcs(exposure, knots)exposure'.(Intercept)    0.5866   -0.0007    0.0004
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Between-study random-effects (co)variance components
                              Std. Dev                          Corr
rcs(exposure, knots)exposure     0.0000  rcs(exposure, knots)exposure
rcs(exposure, knots)exposure'    0.0000                       -0.9995

Univariate Cochran Q-test for residual heterogeneity:
Q = 1.5369 (df = 4), p-value = 0.8201
I-square statistic = 0.0%

3 studies, 6 values, 2 fixed and 3 random-effects parameters
  logLik       AIC       BIC
 24.6521  -39.3042  -42.3727
```

Quadratic trend

```
Call:  dosresmeta(formula = logrr ~ exposure + I(exposure^2), id = id,
    type = type, cases = cases, n = n, data = dataset(), se = se,
```

```
    covariance = input$pscorr)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 8.5347 (df = 2), p-value = 0.0140

Fixed-effects coefficients
                          Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb
exposure.(Intercept)       -0.0000      0.0003  -0.0541    0.9568   -0.0005
I(exposure^2).(Intercept)  -0.0000      0.0000  -0.8025    0.4223   -0.0000
                          95%ci.ub
exposure.(Intercept)         0.0005
I(exposure^2).(Intercept)    0.0000
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Between-study random-effects (co)variance components
               Std. Dev      Corr
exposure         0.0000  exposure
I(exposure^2)    0.0000    0.9446

Univariate Cochran Q-test for residual heterogeneity:
Q = 1.2812 (df = 4), p-value = 0.8646
I-square statistic = 0.0%

3 studies, 6 values, 2 fixed and 3 random-effects parameters
  logLik       AIC       BIC
 40.3790  -70.7581  -73.8266
```

Graphical prediction



Linear Trend (dot-dash); Spline Model with knots at 20 and 80% of distribution (solid); Quadratic Trend (dashed)

Analytical predictions

PA exposure	pred.lin	ci.lb.lin	ci.ub.lin	pred.spl	ci.lb.spl	ci.ub.spl	pred.quadr	ci.lb.quadr	ci.ub.quadr
188.48	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
424.00	0.95	0.92	0.99	0.98	0.87	1.12	0.99	0.90	1.08
895.11	0.86	0.78	0.96	0.92	0.71	1.20	0.93	0.75	1.16
1366.22	0.78	0.66	0.93	0.83	0.63	1.08	0.86	0.65	1.13
1837.33	0.71	0.56	0.90	0.74	0.56	0.98	0.76	0.57	1.01
2308.44	0.64	0.47	0.88	0.66	0.48	0.91	0.65	0.48	0.88

References

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3. Crippa A, Orsini N. Multivariate Dose-Response Meta-Analysis: The dosresmeta R Package. J Stat Softw. 2016 Aug 16;72:1–15.
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