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Submission Date: 2024-01-21
Accepted Date: 2024-04-16
Accepted Manuscript online: 2024-04-16

International Journal of Sports Medicine

Perimenopausal physical activity and dementia risk: A systematic review

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DOI: 10.1055/a-2307-8122

Please cite this article as: Simmons N, Rodriguez Ruiz M, Ronca F. Perimenopausal physical activity and dementia risk: A systematic review. International Journal of Sports Medicine 2024. doi: 10.1055/a-2307-8122

Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:
Mixed-gender studies predominate the current literature exploring the interaction between physical activity and dementia risk. Considering that menopause appears to contribute to females' increased risk of cognitive decline when compared to males, further clarity is required on the impact of physical activity in reducing late-life dementia risk specifically in perimenopausal females. A literature search of MEDLINE, EMBASE, Web of Science, SCOPUS and CINAHL databases yielded fourteen studies for review. A significant inverse relationship between perimenopausal leisure time physical activity, or physical fitness, and future all-cause dementia risk was found in most studies exploring this interaction. Higher levels of perimenopausal household physical activity and combined non-leisure time physical activity also displayed a favourable impact in lowering dementia risk. A dose-response effect was demonstrated, with approximately 10 MET-hour/week of leisure time physical activity required for significant dementia risk reduction. Three of four papers exploring causality provided analyses that are proposed to counter the 'reverse causation' argument, suggesting that physical activity may indeed have a protective role in reducing dementia risk post-menopause. The current systematic review provides promising results regarding the impact of pre- and perimenopausal physical activity on reducing late-life dementia risk, suggesting that promoting perimenopausal physical activity may serve as a crucial tool in mitigating the risk of post-menopausal cognitive decline.

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Thieme

Abstract

Mixed-gender studies predominate the current literature exploring the interaction between physical activity and dementia risk. Considering that menopause appears to contribute to females' increased risk of cognitive decline when compared to males, further clarity is required on the impact of physical activity in reducing late-life dementia risk specifically in perimenopausal females. A literature search of MEDLINE, EMBASE, Web of Science, SCOPUS and CINAHL databases yielded fourteen studies for review. A significant inverse relationship between perimenopausal leisure time physical activity, or physical fitness, and future all-cause dementia risk was found in most studies exploring this interaction. Higher levels of perimenopausal household physical activity and combined non-leisure time physical activity also displayed a favourable impact in lowering dementia risk. A dose-response effect was demonstrated, with approximately 10 MET-hour/week of leisure time physical activity required for significant dementia risk reduction. Three of four papers exploring causality provided analyses that are proposed to counter the 'reverse causation' argument, suggesting that physical activity may indeed have a protective role in reducing dementia risk post-menopause. The current systematic review provides promising results regarding the impact of pre- and perimenopausal physical activity on reducing late-life dementia risk, suggesting that promoting perimenopausal physical activity may serve as a crucial tool in mitigating the risk of post-menopausal cognitive decline.

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Introduction

Dementia covers a spectrum of neurodegenerative diseases resulting in cognitive decline. This can include the impairment of executive function, attention, memory and language leading to difficulties in performing activities of daily living. Already one of the most prevalent neurodegenerative diseases, global dementia incidence is increasing rapidly, and this trend is only expected to continue [1,2]. Dementia presents significant social and financial burdens, where the impacts of disease morbidity encompass all aspects of society, from the family unit to national health care systems [1]. Crucially, there is currently no cure for dementia, emphasising the paramount importance of disease prevention in this context.

Physical activity (PA) has been explored as a preventative tool against cognitive decline. Whilst there is a large degree in heterogeneity in the literature, the collective evidence seems reassuring. Several systematic reviews and meta-analyses have shown an inverse relationship between mid and late life PA and both dementia and cognitive decline [3,4,5,6]. Various mechanisms of action have been suggested including improved cardiovascular function, cerebral circulation, stimulation of neurotrophic factors and observed structural effects such as enhanced hippocampal volume and function [3, 4, 5]. Xu et al. also detailed a dose-response effect between leisure time physical activity (LTPA) and dementia incidence, finding an approximate 10% decrease in all-cause dementia for every 10 Metabolic equivalent of task (MET) hours per week [5].

So far, much of the literature focused on PA and dementia has considered both genders together. However, there are known gender differences in both physical activity levels and dementia incidence which warrant further investigation. Female sex is a known risk factor for dementia, not explained by greater longevity [7]. It has been hypothesised that this may be in part due to the neuroprotective effect of oestrogen, which is curtailed following reduced oestrogen levels through menopause [7]. In addition to the cardiovascular and neural effects of exercise, PA might offer further protective effects to perimenopausal women through its upregulation of estradiol (primary form of oestrogen) secretion in post-menopausal women [8].

Evidence from cohort studies with long follow up times also suggest that pre and perimenopausal fitness are inversely related to dementia risk [9]. Currently most literature details the impact of later-life PA and dementia incidence, resulting in a paucity of consensus on the interaction between pre and perimenopausal PA and late-life dementia incidence. This subsequently renders it difficult to investigate the possible preventative effects of lifelong PA specifically in women. To date there has not been a systematic review exploring the relationship between pre or perimenopausal PA and late-life dementia risk. Thus, given the availability of extant literature, the purpose of this review was to investigate whether perimenopausal physical activity is related to a reduction in dementia risk.

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Materials & Methods

Search strategy and study eligibility

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [10]. The literature search was conducted using MEDLINE, EMBASE, Web of Science, SCOPUS and CINAHL databases. The search terms used were 1. (“leisure time” or “recreational” or “free-time” or “spare time” or “lifetime” or “recreation” or “total” or “non-leisure time” or “occupational), 2. (“physical activity” or “exercise” or “physical exercise” or “training” or “fitness” or “sports” or “leisure activities” or “physical activity at midlife” or “pre-menopausal fitness OR activity” or “mid-to-late life physical fitness OR activity) and 3. (“dementia” or “Alzheimer’s disease” or “Parkinson’s disease” or “vascular dementia” or “mixed dementia” or “cognitive decline”). The bibliographies of relevant papers and systematic reviews were also screened manually.

Lifetime PA was included as a search term in attempt to address the general paucity of papers which explore PA at more than one time point. Inclusion of papers exploring PA levels at multiple timepoints provides the opportunity to examine dose-response relationships more accurately, whilst also providing more clarity on whether changes to PA are clinically relevant (for instance in reverse causation).

Articles had to meet the following eligibility criteria: 1) Mean participant age of ≤ 63; 2) explicit detailing of assessment of physical activity (including lifetime physical activity) and method for establishing dementia diagnosis; 3) population based cohort/ case-control studies; 4) Include specific sex-grouped data or access to such data in supplementary materials 5) papers were excluded if cognitive impairment was investigated without explicit all cause dementia data.

Two reviewers read the titles and abstracts procured from the literature search, screening them against the eligibility criteria. Any procedural disagreements were discussed and resolved by the two reviewers conducting the search.

Data extraction

Two reviewers extracted the required data. The basic information collected included descriptive information: author, year and date of study; the country and cohort of participants; number of participants at baseline testing and average years of follow up; cohort age; how physical activity and dementia status were assessed and any covariates examined in the study. The outcomes assessed were: total number of dementia cases included in the study; time to dementia from midlife examination; the mean age of dementia at onset and the hazard ratio, odds ratio or risk ratio between physical activity and dementia incidence.

Data quality and synthesis

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Two authors assessed study quality using the NIH quality assessment tool for cohort and case-control studies. Study results are presented using a narrative synthesis, with study data presented in table format [11].

Results

After the removal of duplications 3734 potentially relevant citations were identified. Following the screening of abstracts and titles 21 papers were selected for full paper review. 14 papers were selected for inclusion in the systematic review following screening against the eligibility criteria (Table 1,2,3). An overview of this process is provided in Figure 1.

Study Characteristics

Study characteristics are outlined in tables 1, and 3, which included a total of 1,304,231 female participants with a mean age of 53.6 years. Study sample size ranged from 191 to 1,136,846. 13 of the 14 studies included were longitudinal cohort studies [9, 12-23] with one additional case-control study [24]. Data from large-scale cohort studies were included, including the CADIE cohort study from Finland [17,20,21]; Swedish PPSW cohort study [9,13,18]; Swedish national march cohort study [22]; Danish national hospital register and Danish central population register [24]; Copenhagen city heart study and Copenhagen general population study [19]; the Million women Study [12]; UK Bio-bank [23]; Tromsø [15]; Japan Public health centre-based prospective disabling dementia study [14] and the Murakami cohort study [16].

Physical activity was predominantly assessed via the use of self-perceived questionnaires including the Saltin-Grimby physical activity level scale [9,15]; Japan public health centre-based prospect study-physical activity questionnaire [16]; international physical activity questionnaire [23] and Likert scale style questionnaires [12,14,17-22,24]. An objective assessment of physical fitness using a stepwise-increased maximal ergometer cycling test was utilised in one study [13].

Dementia diagnoses followed a relatively uniform assessment protocol, with mini-mental state examination and subsequent further cardiovascular and neuropsychiatric assessments for those scoring ≤24 on the MMSE predominantly used. Neuropsychiatric examinations were conducted by qualified healthcare professionals and consisted of psychiatric interviews, observations of mental symptoms, neuropsychiatric tests, and close informant interviews. Standardised criteria such as the Diagnostic and Statistical Manual of Mental Disorders, patient records systems and registry data were also used where applicable (Table 3).

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Covariate adjustments used in statistical analysis in the included studies are provided in table 3.

Quality of evidence

This study utilised the NIH risk of bias assessment tool for cohort and case-control studies. All studies were found to have minimum 10 of 14 and good quality evidence (Table 4,5).

Mid-life cardiovascular fitness

One study explored the impact of mid-life cardiovascular fitness and dementia risk [13]. Peak-workload, derived from cycle ergometry, was used to categorise participants into three groups. In their paper, Hörder et al. found that the high and low fitness groups had a lesser and greater risk of dementia respectively when using medium fitness as the comparator group (Table 3, [13]). The authors also reported that the mean time to dementia onset from midlife examination was five years longer when comparing the high (33 ± 2 years) and medium (28 ± 10 years) fitness groups [13]. Moreover, demonstrating that the mean age at dementia onset was 11 years later in the high fitness group (90 ± 3 years) when compared to the medium fitness group (79 ± 8 years) [13]. Ultimately, Hörder et al. present the evidence that perimenopausal cardiovascular fitness has a significant protective effect against post-menopausal dementia, both in terms of risk and in the age of onset.

Leisure time physical activity

All-cause dementia:

Kulmala et al. demonstrated that poor perceived physical fitness (using a likert-scale questionnaire) was associated with an increased odds ratio of all-cause dementia at first and second re-examination (Table 3, [17]). Similarly, Zhu et al. also found that moderate and high mid-life LTPA were protective against the development of dementia when compared to the low LTPA group (Table 3, [23]). A significant reduction in dementia risk was found by Ihara et al. when comparing the fourth and first quartiles for total daily physical activity (Table 3, [14]). Similar inverse associations were found for the domains of daily total moderate-to-vigorous physical activity (MVPA) and leisure time MVPA (Table 3, [14]). Kitamura et al. also found an inverse association between LTPA and dementia, with low, medium and high groups showing a reduced risk of dementia when compared to a reference group of zero metabolic equivalent hours (MET) per day (Table 3, [16]), and Floud et al. found a reduced risk of dementia when comparing active and inactive groups (Table 3, [12]).

In contrast, Mehlig et al. found no significant independent association between LTPA and dementia. However, when coupled with high BMI, low levels of LTPA resulted in a three-fold greater risk of dementia (Table 3, [18]). Najar et al. found no significant interaction between LTPA and all cause dementia (Table 3, [9]). Rovio et al. and

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Tolppanen et al. found no significant interaction between LTPA for all-cause dementia and Alzheimer's dementia and all cause-dementia respectively (Table 3, [20,21]).

In summary, five of the nine studies exploring the impact of LTPA on dementia risk found an inverse relationship between the two variables, and of the four studies that reported no relationship, one reported that the risk reduction became significant when pairing high BMI with low LTPA levels [18].

Non-Alzheimer's dementia

Rasmussen et al. reported that reduced LTPA was associated with an increased risk of non-Alzheimer's dementia when comparing low and high physical activity groups (Table 3, [19]). Najar et al. demonstrated that high mid-life LTPA was associated with reduced risk of mixed dementia and dementia with cerebrovascular disease (Table 3, [9]).

Shih et al. found that when comparing the zero hours and ≥ five LTPA hours a week groups, there was an inverse relationship between Parkinson's disease and LTPA (Table 3, [24]). Conversely Yang et al. found no association between general physical activity (LTPA, commuting and household activity) and Parkinson's disease, when comparing their low and high activity groups (Table 3, [22]).

Therefore, two studies demonstrated an inverse relationship between LTPA and the risk non-Alzheimer's dementia, mixed dementia and dementia with cerebrovascular disease, while two other studies provided conflicting results on the interaction between LTPA and Parkinson's disease risk.

Non-leisure-time physical activity

Four studies explored non-leisure time physical activity (NLTPA) via the modalities of commuting, occupational and household physical activity [16, 22-24]. Zhu et al. found an inverse relationship between household PA and dementia for the moderate and high activity groups when compared to those with lower activity (Table 3, [23]). Kitamura et al. support these findings, reporting a significant inverse relationship between NLTPA (commuting, occupational and housework activity) and dementia risk when comparing low and high activity groups (Table 3, [16]). When looking at occupational activity specifically, Zhu et al. found no association between low and high occupational related activity and dementia risk (Table 3, [23]).

Shih et al. found a trend towards an inverse association between Parkinson's disease and occupational PA when comparing low and high occupational activity (defined in MET-year) before the ages of 30 and 50 (Table 3, [24]), but these were not statistically significant. Yang et al. found no association between either household/commuting activity or occupational activity and Parkinson's disease risk (Table 3, [22]).

In summary two papers reported inverse relationships between NLTPA (household or combined household and other) and all-cause dementia risk, one paper reported no

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significant relationships specifically between occupational activity and dementia, and two other papers found no effect of NLTPA on Parkinson's disease.

Dose-response effect

A dose-response relationship between LTPA and mixed dementia was found by Najar et al., with incremental increases in risk reduction (stratified by both the time spent and intensity of physical activity) when comparing the third and second terciles to the first (Table 3, [9]). This relationship was also found between LTPA and dementia with cerebrovascular disease (Table 3, [9]). Similarly, a robust dose-dependent relationship was seen between LTPA and a reduction in dementia risk in Kitamura et al.'s study (Table 3, [16]). Both the third tercile (≥3 MET-hour/d) and second tercile (0.8 < x < 3 MET-hour/d) showed significant reductions in dementia risk in respect to the comparator group (Table 3, [16]), where the median dose of the second tercile (1.6 MET-hour/d) is roughly equivalent to the current WHO recommendation of 150 minutes/week of moderate intensity exercise [16]. In the same paper, Kitamura et al. also demonstrated a dose-dependent relationship between NLTPA and reduced risk of dementia, with the interaction only reaching significance when comparing the fourth (>36.7 MET-hour/d) and first quartiles (< 17.7 MET-hour/d) (Table 3, [16]).

Zhu et al. reported an interaction between exercise intensity and subsequent reduction in dementia risk. A significant inverse relationship was found between PA and dementia risk in participants undertaking 'vigorous and other exercise at leisure time' (Table 3, [23]). In participants who classified their main modality of PA as 'walking for pleasure', neither moderate (HR 1.04 [95% CI 0.93 – 1.17]) nor high activity (1.16 [95% CI 1.02-1.31]) were associated with a reduction in dementia risk [23]. Hence suggesting that LTPA must reach a certain intensity before a significant relationship can be found with dementia risk reduction. Johnsen et al. also displayed that high LTPA resulted in improved scoring in cognitive tests in both dementia-free participants and those who later developed dementia (Table 3[15]).

In summary, three studies provided evidence for a dose-response relationship between LTPA and dementia risk, where a higher exercise intensity, frequency, or both, related to a greater decrease in dementia risk. Additionally, one study found a similar dose-response relationship between NTLPA and dementia risk.

Exploring the Potential for Reverse Causation

Najar et al. assessed whether the associations between LTPA and dementia would maintain statistical significance following the removal of participants who developed dementia in the first 22 years of follow-up (Table 3, [9]). They found the preservation of the inverse relationships between LTPA and mixed dementia, and LTPA and dementia with CVD. This was alongside a strengthening of the inverse association between LTPA and all cause dementia, which reached significance following participant exclusion (Table 3, [9]). Floud et al. found a 60% higher dementia detection rate in inactive women compared to their active counterparts during the first five years of follow-up (Table 3, [12]). After 15 years of follow-up, however, the

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authors noted a weakening of the association although maintaining its statistical significance (Table 3, [12]). Kulmala et al. demonstrated that a decrease in LTPA levels between first and second re-examination were associated with an increased OR for dementia. A trend was found between reduced dementia risk and an increase in LTPA levels between follow-up periods, although the interaction did not reach statistical significance (Table 3, [17]).

In contrast, Ihara et al. found that the inverse relationship between total daily physical activity and dementia risk was no longer statistically significant following the exclusion of participants who developed dementia within nine years of study commencement (Table 3, [14]). This was the case for the associations between total MVPA and dementia and leisure time MVPA and dementia (Table 3, [14]).

In summary, three of four studies that explored causation in their data provided evidence that may counteract the reverse-causality argument, while one study did not.

Discussion

The objective of the current review was to investigate the relationship between perimenopausal physical activity and late-life dementia risk in women. The majority of studies included in the review identified a significant inverse relationship between the two variables. Ultimately suggesting that engaging in moderate intensity PA (between 0.8 and 3.8 MET-h/day, where 1.5 MET-h/day is equivalent to 30 minutes of brisk walking) at the onset of perimenopause could contribute to reducing the incidence of late-life dementia in women, with a potential for further reduction at higher doses [9,14,16,18, (Figure 2)]. While previous systematic reviews had thus far focused on mixed gender cohorts, and on the elderly [3-6,25,26], this is the first to explore the association between mid-life physical activity and late-life dementia risk specifically in women. The papers included here highlight the existence of a dose-response relationship between both LTPA and NLTPA and dementia risk in females, whilst providing evidence that these interactions could be independent of the ‘reverse causation effect’.

The menopausal transition period is associated with an increased risk of dementia, with the interaction between post-menopausal oestrogen loss and modifiable risk factors (including hypertension, diabetes, depression and physical activity) contributing to a greater dementia incidence in women compared to men [27,28]. Despite this, the majority of women do not meet the recommended levels of LTPA, and female engagement with PA has been shown to decline with age [27,28]. The present review provides evidence supporting the protective impact of LTPA against dementia risk via the modulation of cardiovascular risk factors. Mehlig et al. displayed that the relationship between LTPA and dementia only reached significance when pairing physical activity with BMI [18]. Additionally, Hörder et al. demonstrated the importance of cardiovascular fitness, finding a significant inverse relationship between peak workload and dementia incidence [13]. However, several studies found the maintenance of a significant inverse relationship between LTPA

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and dementia risk despite statistical adjustments for cardiovascular co-variables [9,13-16,19,23], hence suggesting that mid-life physical activity contributes independently, as a modifiable risk factor, to reducing dementia risk [5,20].

Indeed, it has been shown that the increased risk of dementia in females is not explained by risk-factor accumulation, nor by greater longevity [28,29]. The reduction in oestrogen secretion, which is associated with menopause, has been linked to an increased risk of Alzheimer's dementia, and a decrease in brain-derived neurotrophic factor (BDNF) which functions as a downstream modulator in the oestrogen signalling pathway in the brain [30,31,32]. Lower plasma levels of BDNF have been shown to correlate with reduced memory performance in post-menopausal women, with BDNF playing a key role in the promotion of neuronal growth, maturation and maintenance whilst enhancing synaptic plasticity and memory consolidation [31]. Importantly, exercise has been shown to increase circulating BDNF, which points to this as one possible mechanism through which physical activity counteracts the negative impacts of oestrogen reduction on brain health [31,33]. This pathway may help to provide a physiological explanation (alongside risk-factor modulation) of the findings of Kulmala et al., who demonstrated that while mid-life LTPA proved protective against later life dementia onset, a decline in mid to late life PA was associated with an increase in dementia risk [17]. However, it must also be noted that the 'reverse-causality principle' must be considered as an explanation for the aforementioned results [21].

Reverse causation suggests that the association between late-life physical activity and dementia risk could be secondary to a cognitive decline associated with dementia onset, which subsequently leads to decreased levels of physical activity [21,34,35]. Studies with short (<10 years) follow up times have been critiqued as being susceptible to bias due to reverse causation [25]. In this review, 11 of the 13 cohort studies included had a follow-up time of ≥ 10 years and a mean study age of 54 years, reducing the risk of reverse-causation confounding [35]. Najar et al. had a mean follow up time of 44 ± 10 years, and following the exclusion of participants who developed dementia within the first 22 years of follow up, they found a strengthening of the associations between LTPA and all cause, mixed dementia and dementia with CVD [9]. This is supported by a recent meta-analysis which analysed mixed-gender studies with follow up times >20 years and found no evidence of reverse causality [25]. However, while this suggests that mid-life LTPA in pre-menopausal women is a protective lifestyle factor, it must be noted that Floud et al. reported a weakened association after 15 years of follow up, whilst Ihara et al. found that significance in their data was removed after excluding participants who developed dementia within 9 years of the study [12,14]. Potential causes cited by the authors included: apathy due to pre-clinical disease, resulting in reduced caloric intake and PA levels, and the potential confounding impact of the association between low PA levels and co-morbidities which increase dementia risk [12,14]. Interestingly, Ihara et al. found that the significant negative association between LTPA and dementia remained in the male sample after excluding dementia diagnoses in the first 9 years of the study [14]. The authors hypothesised that LTPA in male cohorts promotes engagement in both cognitive and social activities, while this protective aspect of LTPA seems to be

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attenuated in female populations who typically engage in more stimulating day-to-day cognitive activities and have larger social groups than their male counterparts regardless of LTPA time [14]. In summary, while current research is still not conclusive, the majority of studies suggest that there is an inverse relationship between mid-life PA and dementia risk in females, which might indeed exhibit a causal link. Moreover, the continuation of these PA levels into late life appear to have a further protective effect.

Several papers outlined a dose-response relationship between LTPA and dementia risk reduction [9,13,16,23], with a greater risk reduction observed in the most active study terciles [9,16]. Kitamura et al. reported that LTPA of ≥ 21 MET hrs/week had the greatest reduction in dementia risk, which equates to at least five and a quarter hours a week of moderate intensity exercise [16]. This value is roughly double the recommendations provided by the WHO of completing 10 MET hrs/week or (4 MET x 150 minutes a week) of LTPA in mid-life [16,36].The WHO guidelines corresponded with the LTPA performed by the middle tercile of the same study, which was still associated with a 51% reduction in dementia risk [16,36]. Similar findings have been observed in a recent meta-analysis of mixed gender studies across an observed range of 0-45 MET-hour/week [5]. The results of this review support the current WHO guidelines of 10 MET hrs/week or 150 minutes/week of moderate intensity PA in order to significantly reduce dementia risk [16,36].

It has been reported that only 25.9% of middle-aged healthy women meet exercise guidelines if only assessed on LTPA alone, but that 73.4% appear to meet recommendations if NLTPA domains are included [37]. Therefore, NLTPA has been suggested as a possible route to increasing PA in women [37]. The interaction between NLTPA and dementia risk was explored in four studies [16, 22-24], where no associations were found with occupational activity [23], but a significant risk reduction effect was found when high occupational activity was combined with commuting and housework activity [16], and when high intensity household activity was compared to lower intensities [23]. One other study reported an association between NLTPA and Parkinson's, perhaps suggesting different mechanisms of action, or possibly a self-selection artefact in the occupational activities that can be undertaken by patients who are developing Parkinson's [24]. In sum, while there is little evidence surrounding NLTPA in women, these findings suggest that perhaps being active throughout the day, through multiple means, might be enough to offset sedentary leisure time in perimenopausal women. Additionally, whilst a specific association between occupational activity and dementia risk in women is not clear, it appears that unlike in male populations high levels of occupational PA in women are not linked to an increased risk of dementia [38,39,40]. Ultimately, however, the findings presented in this review suggest that household physical activity and combined NLTPA seem more likely to relate to a reduction in dementia risk in females than occupational physical activity.

The present study is not without its limitations. Primarily, there was a large heterogeneity in PA measurements adopted in these studies, and the subjective

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nature of the self-reported questionnaires implemented, constitute a known limitation in the field [21]. Only one study provided an objective assessment of physical fitness (cycle ergometry) [13]. The majority of studies utilised self- reported physical activity questionnaires, where a minority estimated METs (from self-reported questionnaires) or used multiple re-assessment periods of physical activity. Hence providing a source of measurement error in the current review. Furthermore, physical activity and physical fitness may have differential effects on reducing dementia risk and should be compared in order to start unpacking the mechanisms through which physical activity and exercise may help prevent, or delay, the onset of dementia. Additionally few studies included reported on the impact of PA on the incidence of dementia sub-types, limiting the ability to examine whether there is a variance in the impact of PA across these sub-types. Future work should take advantage of recent technological advances through objective measures of physical activity such as actigraphy, and objective fitness assessments, to address these questions.

In summary, the collective evidence on physical activity and dementia risk in perimenopausal women points towards an inverse association between LTPA and dementia risk, which is dose-dependent and might be independent of the ‘reverse causality’ principle. Future work should consider objective measures of physical activity or fitness to evaluate the effects of lifetime physical activity pre-menopause in reducing dementia risk later in life, and include follow up periods of greater than 20 years to further establish the interaction between physical fitness and dementia.

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Table 1. Baseline Characteristics of Included Studies

Authors	*Country*	*Cohort*	*Study Design*	*Sample Size (n)*	*Mean Age at baseline in years*
Floud et al. 2020	UK	The Million Women Study	Prospective Cohort	1,136,846	56 ± 5
Hörder et al. 2018	Sweden	PPSW*	Prospective Cohort	191	50.2 ± 7
Ihara et al. 2022	Japan	Japan Public Health Center-based Prospective Disabling Dementia Study	Prospective Cohort	23659	61.0 ± 7.5
Johnsen et al. 2022	Norway	Tromsø Study	Prospective Cohort	6332	62.7 ±7.7
Kitamura et al. 2022	Japan	Murakami Cohort Study	Prospective Cohort	7167	59.0 ± 9.3
Kulmala et al. 2014#	Finland	CAIDE*	Prospective Cohort	917	50.6 ± 6.0
Mehlig et al. 2014	Sweden	PPSW	Prospective Cohort	1448	47 ± 6.3
Najar et al. 2019	Sweden	PPSW	Prospective Cohort	800	47.2 ± 4.5
Rasmussen et al. 2022	Denmark	Copenhagen General Population Study/Copenhagen City Heart Study	Prospective Cohort	64513	57.7
Rovio et al. 2005 #	Finland	CAIDE	Prospective Cohort	549	50.6 ± 6.0
Shih et al. 2017	Denmark	Danish National Hospital Register/Danish Central Population Register	Case-control	3737 (Parkinson's Disease: 1828 Controls: 1909)	n/a
Tolpannen et al. 2015 #	Finland	CAIDE	Prospective Cohort	1653	50.6 ± 6.0
Yang et al. 2015 #	Sweden	Swedish National March Cohort	Prospective Cohort	27863	50.3 ± 17.1
Zhu et al. 2022	England, Scotland and Wales	UK Bio-bank	Prospective Cohort	27821	56.6#

*CAIDE = Cardiovascular risk actors, Aging and incidence of Dementia cohort study from Finland

*PPSW = Prospective Population Study of Women in Gothenburg, Sweden

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[#] Mean age and follow-up are pooled with male date

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Table 2. Mean follow-up period, Mean age at follow-up, Number of Dementia cases, Mean time to Dementia from Midlife Examination and Mean Age at Dementia Onset

Authors	*Mean Follow -up in years*	*Mean age at Follow-up in years*	*Number of Dementia Cases*	*Mean time to Dementia onset from Midlife Examination (years)*	*Mean Age at Dementia Onset (years)*
Floud et al. 2020	18 ± 3	74 ± 5	18,695	n/a	77 ± 4
Hörder et al. 2018	29	n/a	44 overall: Low Fitness Group (n=59) : 19 Medium Fitness Group (n=92) : 23 High Fitness Group (n=40): 2	29.0 overall: Low Fitness Group: 26 ± 10 Medium Fitness Group: 28 ± 10 High Fitness Group: 33 ± 2	80.5 overall: Low fitness group: 81 ± 7 Medium Fitness Group: 79 ± 8 High Fitness Group: 90 ± 3
Ihara et al. 2020	10	n/a	2321	9.5 ± 2.8	n/a
Johnsen et al. 2022	10.8 ±5.5	74.4 ± 9.2	651	n/a	81.6 (95% CI: 81.0-82.1)
Kitamura et al. 2022	8.3	n/a	150	n/a	n/a
Kulmala et al. 2014	18	1st re-examination: 71.3 ± 4.0 2nd re-examination: 78.6 ± 3.7	250*	n/a	n/a
Mehlig et al. 2014	34	n/a	165	29	n/a
Najar et al. 2019	44 ± 9.8	n/a	194	31.5 ± 7.7	79.8 ± 7.7
Rasmussen et al. 2022	43	n/a	1244 Non-Alzheimer's Dementia cases overall: Low Fitness Group	n/a	n/a

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			(n=28,136): 210 Medium Fitness Group (n=31,203): 698 High Fitness Group (n=5,174): 336		
Rovio et al. 2005	21 ± 4.9*	71.6 ± 4.1*	Dementia: 117 * Alzheimer's Disease: 76 *	n/a	n/a
Shih et al. 2017	n/a	n/a	n/a	n/a	60.8*
Tolpannen et al. 2015	28.3	1st re-examination: 71.3 ± 4.0 (900) 2nd re-examination 78.6 ± 3.7	148	n/a	n/a
Yang et al. 2015	12.6 ± 2.2	n/a	128	23.3	73.6 ± 8.7*
Zhu et al. 2022	10.66*	n/a	Dementia: 2,421 Vascular Dementia: 332 Alzheimer's Disease: 819 Other Dementia: 1216	n/a	n/a

*Pooled data for men and women

Standard Deviations and Confidence Intervals are included where available

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Table 3. Study Outcomes

Authors	*Method of Assessing PA/Cardiovascular Fitness*	*PA Measure*	*Parameter*	*Tool*	*Cognition*	*Adjustment*	*Effect Size (95% CI)*		*P values where available*
Floud et al. 2020	Questionnaire assessing frequency of *PA	PA as inactive vs active (Inactive: rarely/never or <1 time/week (Active: ≥ 1 time/week)	All-cause Dementia	Assessment of NHS Central Register and Information Services Division for ICD-10 Dementia diagnoses	Region of residence, educational qualifications, area deprivation, height, smoking, alcohol consumption, use of menopausal hormones, and BMI	RR = 1.59 (1.31-1.92) during <5 years FU RR = 1.18 (1.08-1.29) during 5-9.9 years FU RR = 1.09 (1.05-1.14) during 10-14.9 years FU RR= 1.05 (1.02-1.08) during >15 years FU		
	Questionnaire assessing frequency of PA	PA as inactive vs active (Inactive: rarely/never or <1 time/week (Active: ≥ 1 time/week)	Alzheimer's Disease	Assessment of NHS Central Register and Information Services Division for ICD-10 Dementia diagnoses	Region of residence, educational qualifications, area deprivation, height, smoking, alcohol consumption, use of menopausal hormones, and BMI	RR = 1.03 (0.97-1.09)		
	Questionnaire assessing frequency of PA	PA as inactive vs active (Inactive: rarely/never or <1 time/week (Active: ≥ 1 time/week)	Vascular Dementia	Assessment of NHS Central Register and Information Services Division for ICD-10 Dementia diagnoses	Region of residence, educational qualifications, area deprivation, height, smoking, alcohol consumption, use of menopausal hormones, and BMI	RR = 1.01 (0.94-1.09)		
	Questionnaire assessing frequency of PA	PA as inactive vs active (Inactive: rarely/never or <1 time/week (Active: ≥ 1 time/week)	Dementia, type unspecified	Assessment of NHS Central Register and Information Services Division for ICD-10 Dementia diagnoses	Region of residence, educational qualifications, area deprivation, height, smoking, alcohol consumption, use of menopausal hormones, and BMI	RR = 1.07 (1.02-1.12)		
Hörder et al. 2018	Step-wise increased ergometer cycling	Crude Peak Workload (W)	All-cause Dementia	Neuropsychiatric examinations	Age and body height	Low fitness	HR = 1.24 (0.67-2.32)	p > 0.05

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	test until exhaustion			performed by Geriatric Psychiatrists Medical Records for those lost to follow up (Swedish Hospital Discharge Registry)		Medium fitness HR = 1.0 High fitness HR = 0.12 (0.03-0.51)	p <0.05
	Step-wise increased ergometer cycling test until exhaustion	Crude Peak Workload (W)	All-cause Dementia	Neuropsychiatric examinations performed by Geriatric Psychiatrists Medical Records for those lost to follow up (Swedish Hospital Discharge Registry)	Age, body height, triglycerides, smoker, hypertension, wine consumption, physical inactivity, and income	Low fitness HR = 1.41 (0.72-2.79) Medium fitness HR = 1.0 High fitness HR = 0.12 (0.03-0.54)	p > 0.05 p <0.05
	Step-wise increased ergometer cycling test until exhaustion	Peak Workload/body Weight	All-cause Dementia	Neuropsychiatric examinations performed by Geriatric Psychiatrists Medical Records for those lost to follow up (Swedish Hospital Discharge Registry)	Age and body height	Low fitness HR = 1.43 (0.74-2.78) Medium fitness HR = 1.0 High fitness HR = 0.40 (0.16-0.99)	p > 0.05 p <0.05
	Step-wise increased ergometer cycling test until exhaustion	Peak Workload/body Weight	All-cause Dementia	Neuropsychiatric examinations performed by Geriatric Psychiatrists Medical Records for those lost to follow up (Swedish Hospital Discharge Registry)	Age, body height, triglycerides, smoker, hypertension, wine consumption, physical inactivity, income	Low fitness HR = 1.37 (0.62-3.02) Medium fitness HR = 1.0 High fitness HR = 0.35 (0.13-0.97)	p > 0.05 p <0.05
Ihara et al. 2022	Questionnaires assessing the metabolic equivalents of non-LTPA and LTPA	Daily Total Physical Activity (MET-h/d)	Dementia	Certification Records in the national LTCI system of Japan: Compulsory National Health Insurance System	Age and area	Q4 vs Q1, aHR = 0.72 (0.64-0.80)	p <0.001
	Questionnaires	Daily Total Physical	Dementia	Certification Records	Age, area, smoking	Q4 vs Q1, aHR = 0.75 (0.67-0.84)	p <0.001

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	assessing the metabolic equivalents of non-LTPA and LTPA	Activity (MET-h/d)		in the national LTCI system of Japan: Compulsory National Health Insurance System	status, alcohol intake status, BMI, past history of diabetes (yes or no), medication for hypertension (yes or no), and occupation	Excluding dementia in first 6 years: Q4 vs Q1, aHR = 0.84 (0.72-0.98) Excluding dementia in first 9 years: Q4 vs Q1, aHR = 0.93 (0.74-1.17)	p = 0.002 p = 0.51
	Questionnaires assessing the metabolic equivalents of non-LTPA and LTPA	Daily Total *MPVA	Dementia	Certification Records in the national LTCI system of Japan: Compulsory National Health Insurance System	Age, area	Q4 vs Q1, aHR = 0.71 (0.64-0.80)	p <0.001
	Questionnaires assessing the metabolic equivalents of non-LTPA and LTPA	Daily Total MPVA	Dementia	Certification Records in the national LTCI system of Japan: Compulsory National Health Insurance System	Age, area, smoking status, alcohol intake status, BMI, past history of diabetes (yes or no), medication for hypertension (yes or no), and occupation	Q4 vs Q1, aHR = 0.74 (0.66- 0.83) Excluding dementia in first 6 years: Q4 vs Q1, aHR = 0.81 (0.70-0.95) Excluding dementia in first 9 years: Q4 vs Q1, aHR = 0.87 (0.69-1.09)	p < 0.001 p = 0.001 p = 0.19
	Questionnaires assessing the metabolic equivalents of non-LTPA and LTPA	Leasure-time MVPA	Dementia	Certification Records in the national LTCI system of Japan: Compulsory National Health Insurance System	Age, area	Q4 vs Q1, aHR = 0.69 (0.62-0.76)	p <0.001
	Questionnaires assessing the metabolic equivalents of non-LTPA and LTPA	Leisure-time MVPA	Dementia	Certification Records in the national LTCI system of Japan: Compulsory National Health Insurance System	Age, area, smoking status, alcohol intake status, BMI, past history of diabetes (yes or no), medication for hypertension (yes or no), and occupation	Q4 vs Q1 aHR = 0.70 (0.63- 0.78) Q4 vs Q1 Excluding dementia in first 6 years: aHR = 0.78 (0.68-0.90) Excluding dementia in first 9 years: Q4 vs Q1 aHR = 0.91 (0.75-1.12)	p < 0.001 p <0.001 p = 0.59
Johnsen et al. 2022	Saltin-Grimby Physical Activity Level Scale	LTPA	Global Cognitive Function in cases who remained dementia-free	Global cognitive score determine as the individual mean score of *WT1, *WT2, *DCST, *FTT,	Model 1: Time and age	Dementia-free cases: Inactive Reference Active β = 0.15 (0.12- 0.18) Very Active β = 0.18 (0.13-0.22) Dementia cases:	 p < 0.001 p < 0.001

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			vs cases who developed dementia	*MMSE Dementia cases identified by end point register from local hospitals		Inactive Active Very Active	Reference β = 0.04 (-0.07-0.015) β = 0.26 (0.06-0.46)	 p > 0.05 p < 0.05
	Saltin-Grimby Physical Activity Level Scale	LTPA	Global Cognitive Function in cases who remained dementia-free vs cases who developed dementia	Dementia end point register from local hospitals	Model 2: Time, age and education	Dementia-free cases: Inactive Active Very Active Dementia cases: Inactive Active Very Active	 Reference β = 0.12 (0.08-0.15) β = 0.11 (0.07-0.16) Reference β = -0.01 (-0.12- 0.10) β = 0.17 (-0.33-0.37)	 p < 0.001 p < 0.001 p > 0.05 p > 0.05
	Saltin-Grimby Physical Activity Level Scale	LTPA	Global Cognitive Function in cases who remained dementia-free vs cases who developed dementia	Dementia end point register from local hospitals	Model 3: Time, age, education, comorbidity and lifestyle factors	Dementia-free cases: Inactive Active Very Active Dementia cases: Inactive Active Very Active	 Reference β = 0.09 (0.05-0.12) β = 0.08 (0.03- 0.13) Reference β = -0.05 (-0.17-0.06) β = 0.14 (-0.08-0.36)	 p < 0.001 p < 0.001 p > 0.05 p > 0.05
Kitamura et al. 2022	Japan Public Health Center-based prospective study-physical activity questionnaire (JPHC-PAQ)	Levels of LTPA (MET-h/d)	Dementia	Long term National Insurance Database	Age	0 Low Medium High	aHR = 1 (ref) aHR = 0.64 (0.40-1.01) aHR = 0.50 (0.32-0.78) aHR = 0.44 (0.29- 0.67)	p value for trend < 0.001
	Japan Public Health Center-based prospective study-physical activity questionnaire (JPHC-PAQ)	Levels of LTPA (MET-h/d)	Dementia	Long term National Insurance Database	Age, marital status, education, occupation, BMI, smoking habit, alcohol consumption, coffee consumption, non-leisure time PA, disease history	0 Low Medium High	aHR = 1 (ref) aHR = 0.59 (0.37-0.94) aHR = 0.49 (0.31-0.77) aHR = 0.44 (0.29-0.69)	p value for trend <0.001
	Japan Public Health Center-based prospective study-physical activity questionnaire (JPHC-	Quartiles of Non-Leisure-Time PA (Met-h/d)	Dementia	Long term National Insurance Database	Age	Q1 Q2 Q3 Q4	aHR = 1 (ref) aHR = 0.63 (0.41-0.97) aHR = 0.55 (0.36-0.86) aHR = 0.46 (0.29-0.72)	p value for trend <0.001

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	PAQ)							
	Japan Public Health Center-based prospective study-physical activity questionnaire (JPHC-PAQ)	Quartiles of Non-Leisure-Time PA (Met-h/d)	Dementia	Long term National Insurance Database	Age, marital status, education, occupation, BMI, smoking habit, alcohol consumption, coffee consumption, leisure-time PA, disease history	Q1 Q2 Q3 Q4	1 (ref) aHR = 0.67 (0.44-1.04) aHR = 0.65 (0.41-1.01) aHR = 0.54 (0.33-0.87)	p value for trend < 0.009
Kulmala et al. 2014	Likert-Scale questionnaire to assess perceived physical fitness	Levels of Perceived Physical Fitness at Midlife	Dementia	At re-examination MMSE scoring, Neurological, cardiovascular and neuropsychological examinations Diagnostic tests (MRI, CT, blood tests, CSF analysis, ECG) National Hospital Discharge Register	Gender, education	<u>Dementia until 1st re-examination (1998)</u> Good Satisfactory Poor <u>Dementia until 2nd re-examination (2005-2008)</u> Good Satisfactory Poor	 HR = 1 HR = 0.8 (0.5-1.43) HR = 2.0 (1.1-3.6) HR = 1 HR = 1.0 (0.8-1.3) HR = 1.5 (1.1-2.0)	 p ≥ 0.05 p ≤ 0.05 p ≥ 0.05 p ≤ 0.05
			Dementia	At re-examination MMSE scoring, Neurological, cardiovascular and neuropsychological examinations Diagnostic tests (MRI, CT, blood tests, CSF analysis, ECG) National Hospital Discharge Register	Gender, education, midlife cardio-/respiratory and musculoskeletal conditions, BMI and physical activity	<u>Dementia until 1st re-examination (1998)</u> Good Satisfactory Poor <u>Dementia until 2nd re-examination (2005-2008)</u> Good Satisfactory Poor	 HR = 1 HR = 0.8 (0.4-1.4) HR = 1.5 (0.8- 3.1) HR = 1 HR = 0.9 (0.7-1.2) HR = 1.2 (0.9-1.8)	 p ≥ 0.05 p ≥ 0.05 p ≥ 0.05 p ≥ 0.05
	Likert-Scale questionnaire to assess perceived physical fitness	Changes in perceived physical fitness from midlife to late life	Dementia	At re-examination MMSE scoring, Neurological, cardiovascular and neuropsychological examinations Diagnostic tests (MRI, CT, blood tests, CSF	Age, education, follow-up time, perceived physical fitness at midlife, history of cardio-cerebrovascular, respiratory, and musculoskeletal conditions, changes in	<u>Dementia until the 2nd re-examination (2005-2008)</u> Unchanged Declined Increased	 OR = 1 OR = 2.6 (1.2-5.8) OR = 1.7 (0.7-4.1)	 p ≤ 0.05 p ≥ 0.05

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				analysis, ECG) National Hospital Discharge Register	physical activity, BMI and APOEε4			
Mehlig et al. 2014	Likert-Scale Questionnaire to assess *LTPA	LTPA defined Active vs inactive combined with different levels of body habitus	Dementia	Psychiatric interview; observations of mental symptoms; neuropsychiatric tests; close informant interviews; DSM- III-R criteria and data from hospital discharge register	Age, education, smoking, consumption of alcohol, triglycerides, hypertension, and parenteral history of diabetes	Non-obese, active Non-obese, inactive Obese, active Obese, inactive **Obese x inactive**	HR = 1(ref) HR = 1.04(0.67-1.61) HR = 0.98 (0.51-1.90) HR = 3.31 (1.43-7.66) **HR = 3.26 (1.07-9.94)**	 p = 0.88 p = 0.95 p =0.005 P =0.04
Najar et al. 2019	Saltin-Grimby Physical Activity Level Scale	Physical activity as active vs inactive	Total Dementia	DSM-III-R criteria based on neuropsychiatric examinations and close informant reviews. Medical records obtained from the Swedish Hospital Discharge Registry for those lost to follow-up	Model 1: Age Model 2: Age and cognitive activity Model 3: Age, cognitive activity, smoking cigarettes, socioeconomic status		HR = 0.70 (0.49-1.02) HR = 0.70 (0.49-1.02) HR = 0.72 (0.50-1.04)	p > 0.05 p > 0.05 p > 0.05
	Saltin-Grimby Physical Activity Level Scale	Physical activity as active vs inactive	Alzheimer Disease	NINCDS-ADRDA* criteria based on neuropsychiatric examinations and close informant reviews. Medical records obtained from the Swedish Hospital	Model 1: Age Model 2: Age and cognitive activity Model 3: Age, cognitive activity, major depression, socioeconomic status		HR = 0.97 (0.55-1.70) HR = 0.97 (0.55-1.70) HR = 0.96 (0.54-1.69)	p > 0.05 p > 0.05 p > 0.05

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			Discharge Registry for those lost to follow-up			
Saltin-Grimby Physical Activity Level Scale	Physical activity as active vs inactive	Vascular Dementia	Similar criteria to NINDS-AIREN* criteria based on neuropsychiatric examinations and close informant reviews. Medical records obtained from the Swedish Hospital Discharge Registry for those lost to follow-up	Model 1: Age	HR = 0.65 (0.24-1.72)	p > 0.05
				Model 2: Age and cognitive activity	HR = 0.65 (0.24-1.72)	p > 0.05
				Model 3: Age, cognitive activity, socioeconomic status, hypertension	HR = 0.72 (0.27-1.93)	p > 0.05
Saltin-Grimby Physical Activity Level Scale	Physical activity as active vs inactive	Mixed Dementia	When both Alzheimer's disease and cerebrovascular disease were judged to contribute to dementia based on neuropsychiatric examinations and close informant reviews. Medical records obtained from the Swedish Hospital Discharge Registry for those lost to follow-up	Model 1: Age	HR = 0.42 (0.21-0.82)	p < 0.05
				Model 2: Age and cognitive activity	HR = 0.42 (0.21-0.82)	p < 0.05
				Model 3: Age, cognitive activity, education, smoking cigarettes, hypertension	HR = 0.43 (0.22-0.86)	p < 0.05
Saltin-Grimby Physical Activity Level Scale	Physical activity as active vs inactive	Dementia with Cerebrovascular Disease	As above. This group describes individuals with dementia and stroke without considering the temporal relationship between the occurrence of dementia and stroke.	Model 1: Age	HR = 0.45 (0.27-0.75)	p < 0.05
				Model 2: Age and cognitive activity	HR = 0.45 (0.27-0.74)	p < 0.05
				Model 3: Age, cognitive activity, education, socioeconomic status, smoking cigarettes,	HR = 0.43 (0.22-0.86)	p < 0.05

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				hypertension		
			Practically, this group includes vascular dementia, mixed dementia and Alzheimer's disease with cerebrovascular disease			
Saltin-Grimby Physical Activity Level Scale	Levels of Physical Activity	Mixed Dementia	When both Alzheimer's disease and cerebrovascular disease were judged to contribute to dementia based on neuropsychiatric examinations and close informant reviews. Medical records obtained from the Swedish Hospital Discharge Registry for those lost to follow-up	Education, smoking cigarettes, hypertension	<u>Hazard Ratios for dose-response relationship between physical activity and mixed dementia:</u> 2nd tertile vs 1st tertile: HR = 0.46 (0.23-0.92) 3RD tertile vs 1st tertile: HR = 0.27 (0.08-0.97)	 p < 0.05 p < 0.05
Saltin-Grimby Physical Activity Level Scale	Levels of Physical Activity	Dementia with Cerebrovascular Disease	As above. This group describes individuals with dementia and stroke without considering the temporal relationship between the occurrence of dementia and stroke. Practically, this group includes vascular dementia, mixed dementia and Alzheimer's disease with cerebrovascular disease	Education, socioeconomic status, smoking cigarettes, hypertension	<u>Hazard Ratios for dose-response relationship between physical activity and dementia with cerebrovascular disease</u> 2nd tertile vs 1st tertile: HR = 0.48 (0.28-0.80) 3rd tertile vs 1st tertile: HR = 0.42 (0.19-0.94)	 p < 0.05 p < 0.05
Saltin-Grimby Physical Activity	Physical activity as active vs inactive	Total Dementia	DSM-III-R criteria based on		<u>Excluding participants with dementia onset</u>	

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Level Scale			neuropsychiatric examinations and close informant reviews. Medical records obtained from the Swedish Hospital Discharge Registry for those lost to follow-up		<u>before 1990</u>	
				Model 1: Age	HR = 0.67 (0.45-0.99)	p < 0.05
				Model 2: Age and cognitive activity	HR = 0.70 (0.52-0.95)	p < 0.05
				Model 3: Age, cognitive activity, smoking cigarettes, socioeconomic status	HR = 0.67 (0.46-0.99)	p < 0.05
Saltin-Grimby Physical Activity Level Scale	Physical activity as active vs inactive	Alzheimer Disease	NINCDS-ADRDA* criteria based on neuropsychiatric examinations and close informant reviews. Medical records obtained from the Swedish Hospital Discharge Registry for those lost to follow-up		<u>Excluding participants with dementia onset before 1990</u>	
				Model 1: Age	HR = 0.93 (0.52-1.68)	p > 0.05
				Model 2: Age and cognitive activity	HR = 0.93 (0.52-1.68)	p > 0.05
				Model 3: Age, cognitive activity, major depression, socioeconomic status	HR = 0.91 (0.50-1.64)	p > 0.05
Saltin-Grimby Physical Activity Level Scale	Physical activity as active vs inactive	Vascular Dementia	Similar criteria to NINDS-AIREN* criteria based on neuropsychiatric examinations and close informant reviews. Medical records obtained from the Swedish Hospital Discharge Registry for those lost to follow-up		<u>Excluding participants with dementia onset before 1990</u>	
				Model 1: Age	HR = 0.73 (0.25-2.14)	p > 0.05
				Model 2: Age and cognitive activity	HR = 0.73 (0.25-2.13)	p > 0.05
				Model 3: Age, cognitive activity, socioeconomic status, hypertension	HR = 0.87 (0.29-2.56)	p > 0.05
Saltin-Grimby Physical Activity Level Scale	Physical activity as active vs inactive	Mixed Dementia	When both Alzheimer's disease and cerebrovascular		<u>Excluding participants with dementia onset before 1990</u>	

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				disease were judged to contribute to dementia based on neuropsychiatric examinations and close informant reviews. Medical records obtained from the Swedish Hospital Discharge Registry for those lost to follow-up	Model 1: Age		HR = 0.34 (0.17-0.71)	p < 0.05
					Model 2: Age and cognitive activity		HR = 0.34 (0.17-0.71)	p < 0.05
					Model 3: Age, cognitive activity, education, smoking cigarettes, hypertension		HR = 0.35 (0.17-0.73)	p < 0.05
	Saltin-Grimby Physical Activity Level Scale	Physical activity as active vs inactive	Dementia with Cerebrovascular Disease	As above. This group describes individuals with dementia and stroke without considering the temporal relationship between the occurrence of dementia and stroke. Practically, this group includes vascular dementia, mixed dementia and Alzheimer's disease	<u>Excluding participants with dementia onset before 1990</u>			
					Model 1: Age		HR = 0.42 (0.25-0.71)	p < 0.05
					Model 2: Age and cognitive activity		HR = 0.42 (0.25-0.71)	p < 0.05
					Model 3: Age, cognitive activity, education, socioeconomic status, smoking cigarettes, hypertension		HR = 0.44 (0.25-0.74)	p < 0.05
Rasmussen et al. 2022	Self-reported questionnaire assessing levels of LTPA and occupational physical activity	Levels of LTPA	Non-Alzheimer's dementia	National Danish Patient Registry and National Danish Causes of Death Registry	Multifactorially adjusted: Age, sex, BMI, diabetes mellitus, hypertension, education, smoking, alcohol intake, lipid-lowering therapy, postmenopausal hormonal replacement therapy, study population	High Moderate Low	HR = 1.00 (reference) HR = 1.02 (0.90 -1.17) HR = 1.33 (1.11-1.59)	p for trend = 0.007
	Self-reported questionnaire assessing levels of LTPA and	Levels of LTPA	Non-Alzheimer's dementia	National Danish Patient Registry and National Danish Causes of Death	Multifactorially adjusted as above plus **APOE genotype**	High Moderate	HR = 1.00 (reference) HR = 1.06 (0.90-1.24)	p for trend =

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	occupational physical activity			Registry		Low	HR = 1.52 (1.21-1.92)	0.003
	Self-reported questionnaire assessing levels of LTPA and occupational physical activity	Levels of LTPA	Non-Alzheimer's dementia	National Danish Patient Registry and National Danish Causes of Death Registry	Multifactorially adjusted as above plus **physical activity at work**	High Moderate Low	HR = 1.00 (reference) HR = 1.02 (0.89-1.17) HR = 1.32 (1.11-1.58)	p for trend = 0.008
Rovio et al. 2005	Likert-Scale Questionnaire to assess *PA	PA at midlife as active vs sedentary group (active = LTPA at least 2x/week Sedentary = LTPA less than 2x/week)	Dementia	MMSE for screening Neurological, cardiovascular and neuropsychological examinations Diagnoses of dementia made according to the Diagnostic and Statistical Manual of Mental Disorders Criteria and patient records	Age at re-examination, sex, education, follow-up time, and locomotor disorders, APOE ε4 genotype, midlife BMI, Systolic BP, cholesterol, history of myocardial infarction, stroke, diabetes mellitus, smoking status and alcohol drinking		OR= 0.44 (0.18-1.09)	p > 0.05
	Likert-Scale Questionnaire to assess *PA	PA as active vs sedentary group (active = LTPA at least 2x/week Sedentary = LTPA less than 2x/week)	Alzheimer's Disease	MMSE for screening Neurological, cardiovascular and neuropsychological examinations Diagnoses of dementia made according to the Diagnostic and Statistical Manual of Mental Disorders Criteria and patient records	Age at re-examination, sex, education, follow-up time, and locomotor disorders, APOE ε4 genotype, midlife BMI, Systolic BP, cholesterol, history of myocardial infarction, stroke, diabetes mellitus, smoking status and alcohol drinking		OR= 0.43 (0.14-1.28)	p > 0.05
Shih et al. 2017	Interview and Questionnaire assessing	Levels of Occupational Physical Activity	Parkinson's disease	Parkinson's Disease cases identified via the Danish National	Sex, education, smoking, coffee consumption, age,	**Entire work-life** < 70.0	OR = 1.00 (ref)	p for trend =

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occupational PA and LTPA	(MET-year)		Hospital Register using International Classification of Diseases codes	index age, and family history of Parkinson's disease	70.0-94.5 94.5 -125.8 ≥ 125. 8	OR = 1.00 (0,74-1.34) OR = 0.87 (0.63-1.18) OR = 0.89 (0.63-1.26)	0.39
					Prior to age 50 years		
					< 57.5 57.5-75.5 75.5-100.9 ≥ 100.9	OR = 1.00 (ref) OR = 0.95 (0.71-1.28) OR = 0.92 (0.68-1.23) OR = 0.75 (0.54-1.06)	p for trend = 0.12
					Prior to age 30 years		
					<21.3 21.3-33.5 33.5-45.5 ≥ 45.5	OR = 1.00 (ref) OR = 0.94 (0.71-1.24) OR = 0.77 (0.57-1.05) OR = 0.76 (0.54-1.08)	p for trend = 0.06
Interview and Questionnaire assessing occupational PA and LTPA	LTPA (hours/week)	Parkinson's Disease	Parkinson's Disease cases identified via the Danish National Hospital Register using International Classification of Diseases codes	Sex, education, smoking, coffee consumption, age, index age, and family history of Parkinson's disease	**Age (years) and Hours/week LTPA**		
					15-25: 0 1-4 ≥ 5	 OR = 1.00 (ref) OR = 1.11 (0.87- 1.41) OR = 1.03 (0.87-1.44)	 p for trend = 0.69
					25-50: 0 1-4 ≥ 5	 OR = 1.00 (ref) OR = 0.96 (0.87-1.21) OR = 0.86 (0.87-1.28)	 p for trend = 0.49
					≥ 50 : 0 1-4 ≥ 5	 OR = 1.00 (ref) OR = 0.75 (0.87-0.94) OR = 0.65 (0.87-0.99)	 p for trend = 0.01
Interview and Questionnaire assessing occupational PA and LTPA	Levels of Occupational PA (MET-year) and LTPA (hours/week)	Parkinson's Disease	Parkinson's Disease cases identified via the Danish National Hospital Register using International Classification of Diseases codes	Sex, education, smoking, coffee consumption, age, index age, and family history of Parkinson's disease	Multi-variable adjusted odds ratios of Parkinson's disease according to the combination of occupational and leisure-time PA prior to age 25 years:		
					Occupational PA	**LTPA**	**aOR**
					Low	0	1

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						Low	1-4 1.15
						Low	≥ 5 1.07
						High	0 0.87
						High	1-4 1.05
						High	≥ 5 0.87
Tolpanen et al. 2015	Life-time physical activity questionnaire	Levels of LTPA at midlife	Dementia	MMSE for screening Neurological, cardiovascular and neuropsychological examinations and patient records using International Classification of Diseases codes to identify dementia diagnoses	Model 1: Age, sex and education	High	OR = 1 (ref)
						Moderate	OR = 1.19 (0.81-1.75)
						Low	OR = 1.04 (0.70-1.55)
					Model 2: Age, sex, education, midlife BMI, marital status, occupational physical activity level, smoking, and cardiorespiratory and musculoskeletal conditions	High	OR = 1 (ref)
						Moderate	OR = 1.18 (0.80-1.74)
						Low	OR = 1.04 (0.70-1.55)
					Model 3: Model 2 + APOE genotype	High	OR = 1 (ref)
						Moderate	OR = 1.28 (0.85-1.92)
						Low	OR = 1.14 (0.75-1.74)
	Life-time physical activity questionnaire	Levels of LTPA at midlife	Alzheimer's Disease	MMSE for screening Neurological, cardiovascular and neuropsychological examinations and patient records using International Classification of Diseases codes to identify dementia diagnoses	Model 1: Age, sex and education	High	OR = 1 (ref)
						Moderate	OR = 1.05 (0.69-1.60)
						Low	OR = 0.97 (0.63-1.49)
					Model 2: Age, sex, education, midlife BMI, marital status, occupational physical activity level, smoking, and cardiorespiratory and musculoskeletal conditions	High	OR = 1 (ref)
						Moderate	OR = 1.03 (0.67-1.57)
						Low	OR = 0.96 (0.62-1.47)
					Model 3: Model 2 + APOE genotype	High	OR = 1 (ref)
						Moderate	OR = 1.09 (0.70-1.69)

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						Low	OR = 1.05 (0.67-1.65)	
Yang et al. 2015	Lifetime- Physical Activity Questionnaire	Household and Commuting activity (hours/week)	Parkinson's Disease	Parkinson's disease cases identified via first ever hospital admission or outpatient contact documented with diagnosis. These diagnoses were confirmed via the Swedish National Register	Sex, cigarette smoking, alcohol and coffee intake, BMI and educational level	< 2h/week 3-4 h/week 5-6 h/week > 6h/ week	HR = 1 (ref) HR = 0.68 (0.36-1.28) HR = 0.84 (0.46-1.56) HR = 0.67 (0.37-1.22)	p for trend = 0.39
	Lifetime- Physical Activity Questionnaire	Physically demanding level of occupational activity	Parkinson's Disease	Parkinson's disease cases identified via first ever hospital admission or outpatient contact documented with diagnosis. These diagnoses were confirmed via the Swedish National Register	Sex, cigarette smoking, alcohol and coffee intake, BMI and educational level	Mostly sedentary Moving a little Strenuous	HR = 1 (ref) HR = 0.90 (0.46-1.77) HR = 0.85 (0.40-1.83)	p for trend = 0.69
	Lifetime- Physical Activity Questionnaire	Total Level of Physical Activity (Energy Expenditure Questionnaire and MET-h/day)	Parkinson's Disease	Parkinson's disease cases identified via first ever hospital admission or outpatient contact documented with diagnosis. These diagnoses were confirmed via the Swedish National Register	Sex, cigarette smoking, alcohol and coffee intake, BMI and educational level	Low Medium High	HR = 1 (ref) HR = 1.16 (0.72-1.87) HR = 1.15 (0.71-1.85)	p for tend = 0.63
	Lifetime- Physical Activity Questionnaire	General Physical Activity (sum of household, commuting activity and leisure-time	Parkinson's Disease	Parkinson's disease cases identified via first ever hospital admission or outpatient contact documented with	Sex, cigarette smoking, alcohol and coffee intake, BMI and educational level	Low Medium High	HR = 1 (ref) HR = 0.81 (0.52-1.25) HR = 0.85 (0.54-1.34)	p for trend = 0.13

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		exercise: Energy Expenditure Questionnaire and MET-h/day)		diagnosis. These diagnoses were confirmed via the Swedish National Register				
	Lifetime- Physical Activity Questionnaire	Leisure-time exercise (Energy Expenditure Questionnaire and MET-h/day)	Parkinson's Disease	Parkinson's disease cases identified via first ever hospital admission or outpatient contact documented with diagnosis. These diagnoses were confirmed via the Swedish National Register	Sex, cigarette smoking, alcohol and coffee intake, BMI and educational level	Low Medium High	HR = 1 (ref) HR = 1.05 (0.69-1.60) HR = 1.06 (0.64-1.74)	p for trend = 0.83
Zhu et al. 2022	Self-Reported International Physical Activity Questionnaire	LTPA	Dementia	UK Bio-Bank Data (Inpatient data classified via the International Classification of Diseases)	Age, sex, ethnicity, Townsend deprivation index, education, income, BMI, smoking status, alcohol status, Charlson comorbidity index, history of hypertension, history of hyperlipidaemia, and family history of dementia	Low (<1st tertile) Moderate (1st-2nd tertile) High (> 2nd tertile)	HR = 1 (ref) HR = 0.72 (0.64-0.8) HR = 0.60 (0.51-0.70)	 p ≤ 0.05 p ≤ 0.05
	Self-Reported International Physical Activity Questionnaire	Housework-related physical activity	Dementia	UK Bio-Bank Data (Inpatient data classified via the International Classification of Diseases)	Age, sex, ethnicity, Townsend deprivation index, education, income, BMI, smoking status, alcohol status, Charlson comorbidity index, history of hypertension, history of hyperlipidaemia, and family history of dementia	Low (<1st tertile) Moderate (1st-2nd tertile) High (> 2nd tertile)	HR = 1 (ref) HR = 0.86 (0.77-0.97) HR = 0.75 (0.66-0.85)	 p ≤ 0.05 p ≤ 0.05
	Self-Reported International Physical Activity	Transport-related physical activity	Dementia	UK Bio-Bank Data (Inpatient data classified via the	Age, sex, ethnicity, Townsend deprivation index, education,	Low (<1st tertile) Moderate (1st-2nd tertile) High (> 2nd tertile)	HR = 1 (ref) HR = 1.08 (0.92-1.26) HR = 1.02 (0.88-1.19)	 p > 0.05 p > 0.05

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Questionnaire			International Classification of Diseases)	income, BMI, smoking status, alcohol status, Charlson comorbidity index, history of hypertension, history of hyperlipidaemia, and family history of dementia			
Self-Reported International Physical Activity Questionnaire	Occupational Physical Activity	Dementia	UK Bio-Bank Data (Inpatient data classified via the International Classification of Diseases)	Age, sex, ethnicity, Townsend deprivation index, education, income, BMI, smoking status, alcohol status, Charlson comorbidity index, history of hypertension, history of hyperlipidaemia, and family history of dementia	Low (<1st tertile) Moderate (1st-2nd tertile) High (> 2nd tertile)	HR = 1 (ref) HR = 1.05 (0.94-1.17) HR = 0.88 (0.77-1.02)	 p > 0.05 p > 0.05
Self-Reported International Physical Activity Questionnaire	Activity more related to "Walking for Pleasure"	Dementia	UK Bio-Bank Data (Inpatient data classified via the International Classification of Diseases)	Age, sex, ethnicity, Townsend deprivation index, education, income, BMI, smoking status, alcohol status, Charlson comorbidity index, history of hypertension, history of hyperlipidaemia, and family history of dementia	Low (<1st tertile) Moderate (1st-2nd tertile) High (> 2nd tertile)	HR = 1 (ref) HR = 1.04 (0.93-1.17) HR = 1.16 (1.02-1.31)	 p > 0.05 p ≤ 0.05

*PA = physical activity

*LTPA = Leisure-time physical activity

*MVPA = Moderate to vigorous physical activity

*MMSE= mini-mental state examination

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*WT1 = Word Test 1

*WT2 = Word Test 2

*DSCT = Digital Symbol Coding Test

*FTT= Finger Tapping Test

* NINCDS-ADRDA = National institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

* NINDS-AIREN = National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherce et l'Enseignement en Neurosciences

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Table 4. Risk of bias assessment- NIH cohort

	Rovio 2005	Kulmala 2014	Mehlig 2014	Tolpannen 2015	Yang 2015	Hörder 2018	Najar 2019	Floud 2020	Ihira 2022	Johnsen 2022	Kitamura 2022	Rasmussen 2022	Zhu 2022
Research objective stated?	+	+	+	+	+	+	+	+	+	+	+	+	+
Clearly defined study population?	+	+	+	+	+	+	+	+	+	+	+	+	+
Participation of at least 50%?	+	+	+	+	+	+	+	+	+	-	+	+	+
Subjects recruited from same/similar populations? Uniform inclusion and exclusion criteria?	+	+	+	+	+	+	+	+	+	+	+	+	+
Sample size or power description?	-	-	-	-	-	-	-	-	-	-	-	-	-
Exposure measured prior to outcomes?	+	+	-	+	+	+	+	+	+	+	+	+	+
Sufficient timeframe?	+	+	+	+	+	+	+	+	+	+	+	+	+
Categorisation of different levels of exposure?	+	+	+	+	+	+	+	+	+	+	+	+	+

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Clearly defined, valid, reliable independent variables?	+	+	+	+	+	+	+	+	+	+	+	+	+
Exposure assessed more than once over time?	+	+	+	+	+	-	-	+	+	+	-	-	-
Clearly defined, valid, reliable dependent variable?	+	+	+	+	+	+	+	+	+	+	+	+	+
Outcome assessors blinded to exposure status?	N/a	-	N/a	N/a	N/a	-	N/a	N/a	N/a	-	N/a	N/a	N/a
Loss to follow up less than 20% post baseline?	+	-	-	-	N/a	N/a	-	+	+	-	N/a	+	+
Confounding variables adjusted for statistically ?	+	+	+	+	+	+	+	+	+	+	+	+	+

Table 5. Risk of bias assessment -NIH case-control study

	Research objective state?	*Clearly defined study population?*	*Sample size justification?*	*Controls and cases recruited from similar populations?*	*Valid inclusion and exclusion criteria for participant selection?*	*Cases clearly differentiated from controls?*	*Random selection of cases/controls used in the study?*	*Use of concurrent controls?*	*Exposure occurring prior to development of condition?*	*Measures of exposure clearly defined?*	*Blinding of assessors?*	*Confounding variables adjusted for statistically ?*
Shih 2017	+	+	-	+	+	+	+	+	+	+	+	+

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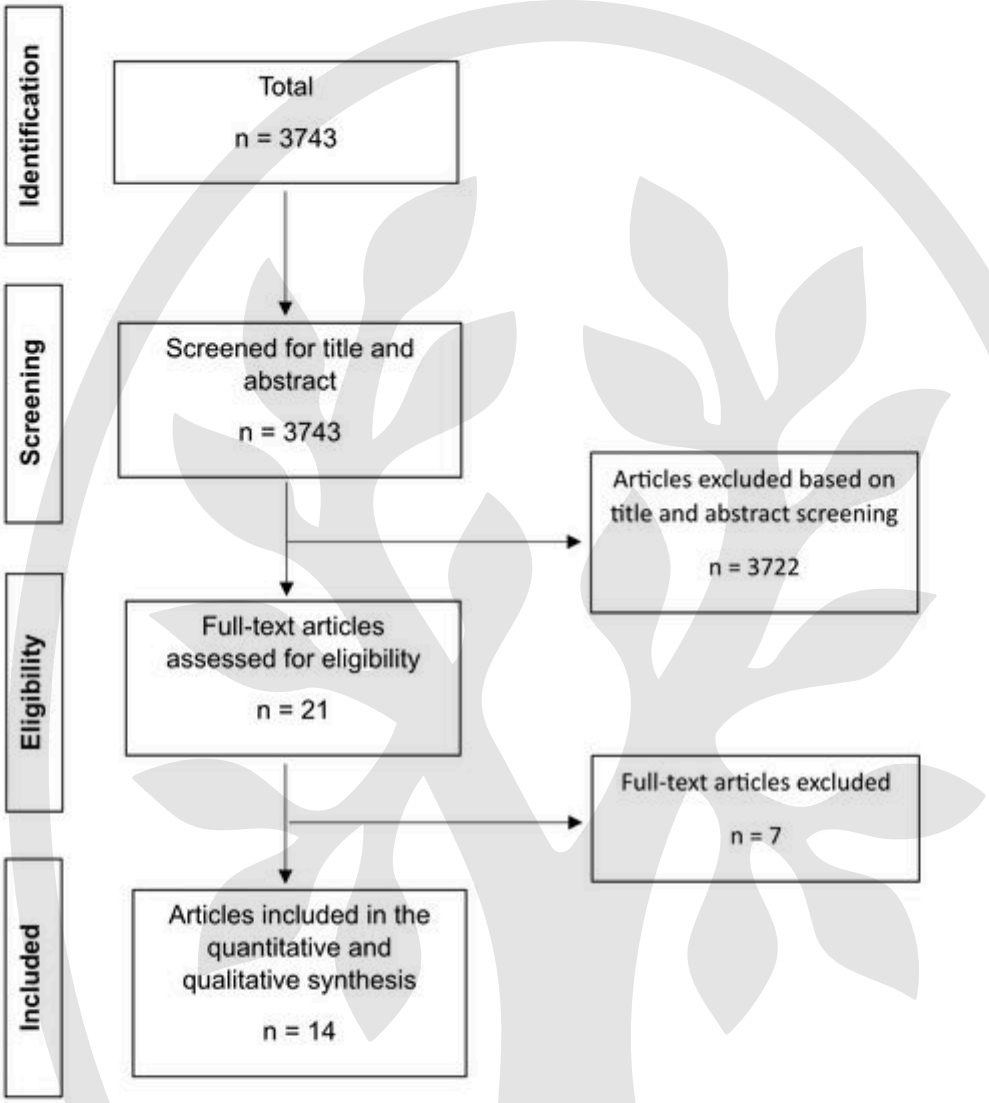
Figure 1. Flowchart of the selected articles



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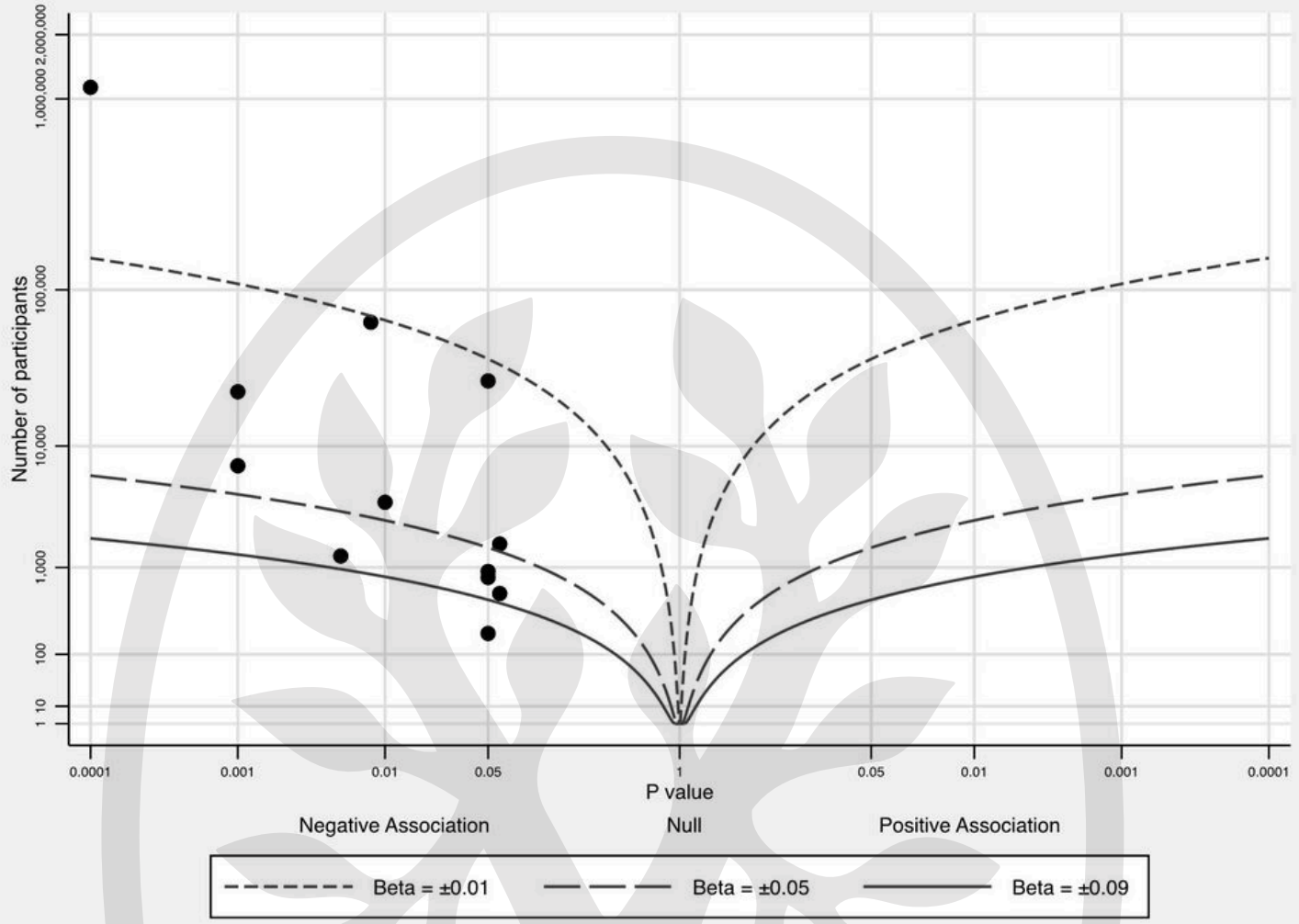

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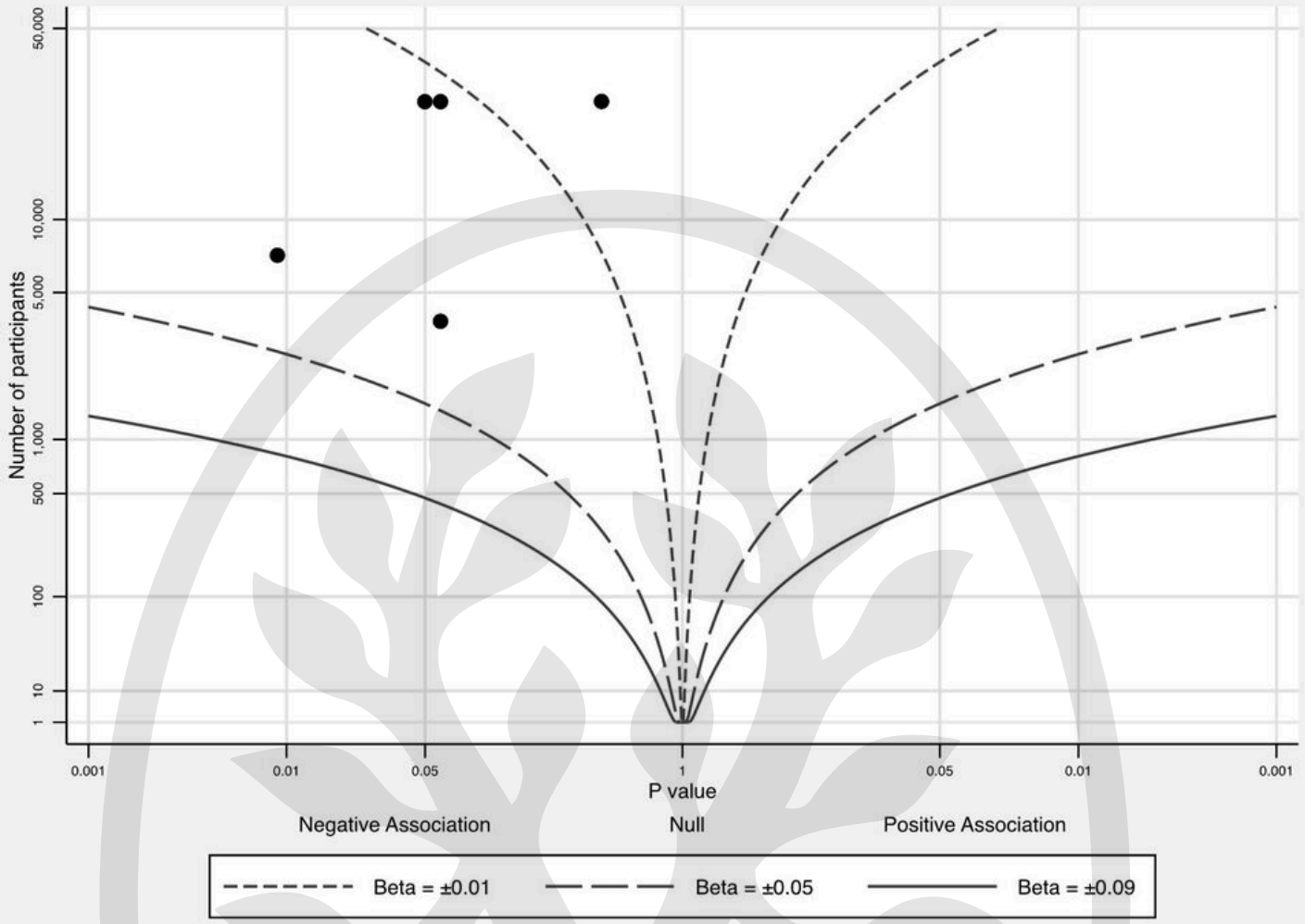

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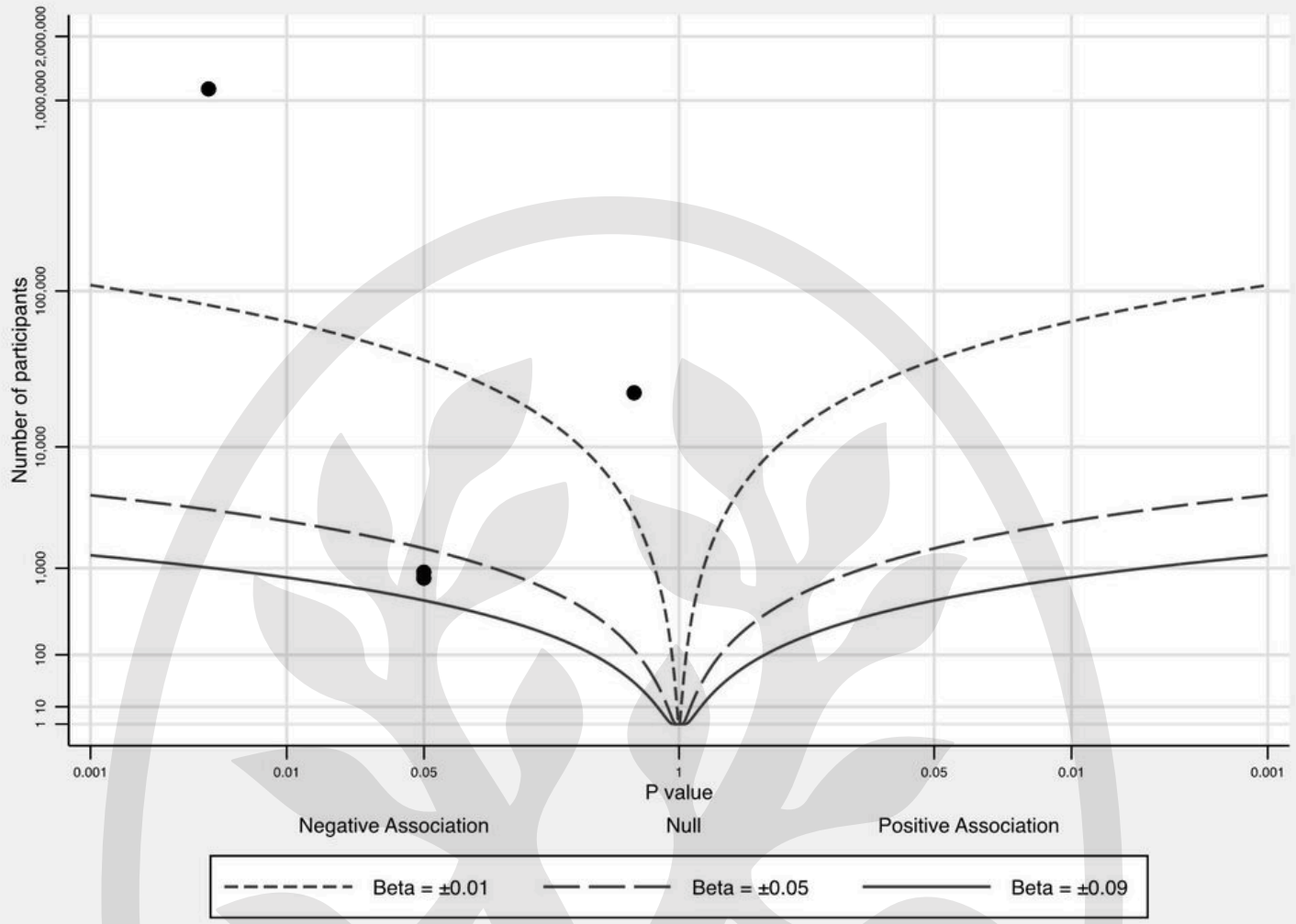

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