Midlife physical activity, psychological distress, and dementia risk: The HUNT Study

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Abstract

Background: Physical activity (PA) is associated with a decreased dementia risk, whereas psychological distress (distress) is linked to an increased dementia risk.

Objective: We investigated independent and joint associations of midlife moderate-to-vigorous PA (MVPA) and distress with incident dementia.

Methods: Our study comprised 28,916 participants aged 30-60 years from the Nord-Trøndelag Health Study (HUNT1, 1984-1986). Data on MVPA and distress from HUNT1 was linked to the Health and Memory Study in Nord-Trøndelag for dementia case identification. Participants were followed from 1995 until 2011. We used adjusted Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI).

Results: In fully adjusted analyses, MVPA was associated with a reduced dementia risk (HR 0.81, 95% CI 0.62-1.06), compared to no MVPA. Distress was associated with an increased dementia risk (HR 1.30, 95% CI 0.99-1.70). Compared to distressed participants not taking part in MVPA, non-distressed no-MVPA participants had a reduced dementia risk (HR 0.72, 95% CI 0.54-0.96). The same applied to distressed MVPA participants (HR 0.50, 95% CI 0.22-1.14), and non-distressed MVPA participants (HR 0.63, 95% CI 0.44-0.90). Our results indicated an additive interaction between MVPA and distress on dementia risk.

Conclusion: Our results suggest that midlife MVPA reduces risk of incident dementia among both distressed and non-distressed individuals.

Keywords: dementia; exercise; stress, psychological; depression; anxiety; cognition

INTRODUCTION

As populations across the globe age, the prevalence of dementia is predicted to increase substantially. Worldwide, roughly 46.8 million individuals were living with dementia in 2015, and this number is predicted to rise to 131.5 million by 2050 [1]. Dementia is among the top ten most burdensome conditions among older adults, and has a significant impact on economy and healthcare resources, as well as on the patient, the patients' family, and caregivers [1]. Thus, efforts to find effective preventive and treatment strategies for dementia and cognitive decline have intensified [2].

Physical activity (PA) is considered an important lifestyle factor for promoting healthy aging [3]. A large body of research suggests that PA may reduce the risk of cognitive decline and dementia [4, 5], and a recent meta-analysis demonstrated a dose-response relationship with a 10% reduction in risk of all-cause dementia per each 10 additional metabolic equivalent task-hours per week [6]. Results from observational studies suggest that the intensity of PA may be an important factor in the prevention of cognitive decline [7], dementia [8], and dementia-related mortality [9]. The World Health Organization recommends moderate-to-vigorous PA (MVPA) in order to improve cardiorespiratory and muscular fitness, bone health, and reduce the risk of non-communicable diseases [10]. Hence, considering the intensity of PA when studying its association with dementia is of interest.

Higher levels of psychological distress, characterized by general symptoms of depression and anxiety and hereinafter referred to as distress, have been associated with an increased risk of cognitive decline [11], dementia [12, 13], and dementia-related mortality [14]. The Lancet Commission on dementia prevention, intervention, and care recently listed depression as one of the main lifestyle-related risk factors for dementia, alongside physical inactivity [2]. However,

PA and exercise have been found to reduce symptoms of depression and anxiety in both clinical [15, 16] and non-clinical populations [17]. Studies suggest a link between PA, cognitive function, and depressive symptoms [18, 19], indicating that PA may improve cognitive function among individuals suffering from depression [18] or with high levels of depressive symptoms [19]. A large prospective study found that both low and high intensity leisure-time PA reduces the risk of dementia-related mortality among individuals with and without distress [20]. However, the latter study was limited by using dementia-related mortality as endpoint. Dementia-related deaths are often misclassified [21] and underreported [22], and using dementia-related mortality as endpoint does not take individuals living with dementia into account. This warrants further investigation of the association of PA and risk of incident dementia, rather than dementia-related mortality, among individuals with distress.

In this study, we linked data from a large population-based health study with data on incident dementia obtained from hospitals and nursing homes. The aim of our study was to investigate the independent and joint associations of MVPA and distress during midlife with dementia risk up to 27 years later.

METHODS

Study population

Data was collected from the first wave of the Nord-Trøndelag Health Study (HUNT1), a large population-based health study carried out in 1984-1986. All inhabitants of the Nord-Trøndelag County in Norway aged ≥20 years were invited, and 77,212 people (89.4%) participated [23]. Details on the HUNT1 study are described elsewhere [23]. To investigate the associations of

MVPA and distress with dementia risk, the current study linked data from HUNT1 to information on dementia status from the Health and Memory Study in Nord-Trøndelag (HMS) [24].

Dementia status – The Health and Memory Study in Nord-Trøndelag

The HMS was set up to identify individuals with dementia within the Nord-Trøndelag County in Norway, so that data from the HUNT studies could be used to prospectively investigate risk and protective factors for dementia in this population [24]. In the present study, data from the HMS were linked to data from HUNT1 through Norwegian personal identification numbers.

The HMS consists of two dementia panels, the hospital and the nursing home panel. The hospital panel comprises 920 dementia patients who were diagnosed at the two hospitals in the county during 1995-2010. Four specialists in geriatrics and old-age psychiatry were responsible for the diagnostic workup. Of the 920 dementia cases in the hospital panel of the HMS, 44.6% were classified as Alzheimer's disease (AD), 17.7% as vascular dementia (VaD), 12.6% as mixed AD/VaD, 2.5% as frontotemporal dementia (FTD), 4.5% as dementia with Lewy's bodies (DLB), and 18.1% had other or unspecified dementia. The nursing home panel comprises 620 patients with dementia examined by specially trained nurses in nursing homes in the county during 2010-2011. Two medical specialists independently set a dementia diagnosis, according to the tenth revision of the International Classification of Diseases 10 (ICD-10) criteria, using all available information. Of the 620 dementia cases in the nursing home panel of the HMS, 60.5% were classified as AD, 14.7% as VaD, 6.0% as mixed AD/VaD, 13.7% as FTD, 3.9% as DLB, and 1.3% as other or unspecified dementia. Details on dementia ascertainment, measurements, and findings in the two panels have been described previously [24]. As 106 participants were assessed both at a hospital and at a nursing home, the total sample of the HMS comprised 1,434

participants diagnosed with dementia. Exact date of diagnosis was available only for the hospital panel. Date of diagnosis for the nursing home panel was estimated based on next-of-kin's retrospective report of the first symptoms of dementia.

Weekly moderate-to-vigorous physical activity

In HUNT1, participants were asked about the intensity and frequency of their PA during a typical week. PA was defined as going on a walk, skiing, swimming, exercising, or participating in organized sports. The participants were provided with five options regarding the frequency of their weekly PA, ranging from 1) never, to 5) nearly every day. They were further provided with three options regarding the intensity of their weekly PA, given that they participated in PA at least once a week: 1) I take it easy, I don't get out of breath or break into a sweat, 2) I push myself until I'm out of breath and break into a sweat, and 3) I practically exhaust myself. The PA questionnaire in HUNT1 has been validated against objective measures of PA and the International Physical Activity Questionnaire [25].

In our study, PA as strenuous as "I push myself until I'm out of breath and break into a sweat" or "I practically exhaust myself" was considered an indication of MVPA. Participants who reported taking part in MVPA at least once a week were regarded as MVPA participants, whereas participants who reported not taking part in PA, or who reported taking part in light PA, were regarded as no MVPA participants.

Psychological distress

Distress was assessed in HUNT1 with the Anxiety and Depression Index (ADI-4), consisting of four items addressing issues of nervousness, calmness, mood, and vitality. The nervousness and

calmness items had four response alternatives, ranging from 1) almost all the time, to 4) never. The mood and vitality questions had seven response alternatives; mood, ranging from 1) very downhearted, to 7) very cheerful, and vitality, ranging from 1) very strong and fit, to 7) very tired and worn out. Scores on the "nervousness" and "mood" items were reversed before all four items were z-scored. The standardized scores were summed and categorized into a dichotomous variable (no distress/distress) using a cut-off at the 88th percentile. The ADI-4 has been validated against the Norwegian version of the Hospital Anxiety and Depression Scale (HADS), and a cut-off at the 88th percentile on the ADI-4 has shown to be a reasonable indicator of caseness of distress when evaluated against the HADS total cut-off (sensitivity = 0.51; specificity = 0.93; Cohen's $\kappa = 0.55$) [26]. The HADS is a self-assessment scale [27], and has shown to be a reliable instrument for detecting and assessing symptom severity of anxiety and depression in somatic, psychiatric, and primary care patients, and in the general population [28, 29].

Possible confounders

Information on possible confounders was obtained from the self-report questionnaires in HUNT1 [23]. Age, sex, highest level of education (primary, high school, college or university < 4 years, college or university ≥ 4 years), marital status (unmarried, married, widow/widower, divorced, separated), smoking (never, former, daily smoker), and alcohol consumption during the last 14 days (abstainer/did not drink, 1-10 times, more than 10 times), were identified as potential lifestyle-related confounders in the associations between MVPA and dementia, and distress and dementia. Furthermore, longstanding physical illness or injury which impairs functioning in everyday life (yes, no) was identified as a potential health-related confounder.

Statistical analyses

The initial population in HUNT1 comprised 77,212 participants (mean age 49.5 years; 51.0% women). To avoid reverse causation where level of MVPA could be a marker rather than a risk factor for dementia, participants over the age of 60 years at the time of HUNT1 were excluded. Further, as the risk of dementia is low among individuals younger than 30 years, these participants were also excluded from further analyses. After excluding individuals with missing data, our final sample comprised 28,916 participants (50.2% women) with a mean age of 43.4 years at the time of HUNT1 (Figure 1). A multivariate multiple imputation procedure with 10 imputations was used to replace missing values on possible confounders (0.2-2.2%).

Descriptive statistics were computed for baseline characteristics of the two MVPA groups. The Phi coefficient (φ) was computed to estimate correlation between MVPA and distress. We used adjusted Cox regression models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the independent and joint associations of MVPA and distress with incident dementia. Attained age was used as the time variable in the regression models. Thus, all regression models were finely adjusted for age. Since the cognitive assessment for the hospital-assessed participants did not start until 1995 [24], participants were followed up from January 1st 1995 until dementia diagnosis, death, moving out of the county, or May 1st 2011, whichever occurred first. Mean time from baseline assessment at HUNT1 to end of follow-up was 25.2 (range 9.0-27.2) years. Mean follow-up time from January 1st 1995 was 15.2 (range 0.01-16.3) years.

No weekly MVPA and no distress served as reference categories in the analyses. The Cox regression models were built up in three steps. The first model was adjusted for sex. In the second model, education, marital status, smoking, and alcohol consumption were added. In the third,

fully adjusted model, we added longstanding physical illness. Distress was added to the second model when investigating MVPA independently, and vice versa when investigating distress independently. To calculate the excess number of cases of dementia attributable to not participating in weekly MVPA or to distress, population attributable fraction (PAF) was estimated using the Mantel-Haenszel approach [30]. 95% CI for PAF were estimated using the substitution method [31].

Joint associations of MVPA and distress on dementia were investigated by creating four combination groups: no MVPA distress, no MVPA no distress, MVPA distress, and MVPA no distress. No MVPA distress served as the reference category, and the models were adjusted for the same covariates as above. In order to investigate additive interaction, we calculated relative excess risk due to interaction (RERI) as described by Andersson and colleagues [32]. As the calculation of RERI estimates requires variables to be treated as risk factors [33], the MVPA variable was reverse coded in these calculations.

To test the robustness of the results, we conducted a sensitivity analysis where we excluded the first 5 years of follow-up to reduce the risk of reverse causation. Graphical and statistical methods using Schoenfeld residuals were applied to check the proportional hazards assumption. No violations of proportionality assumptions were observed. All statistical analyses were carried out in IBM SPSS Statistics version 25 for Windows.

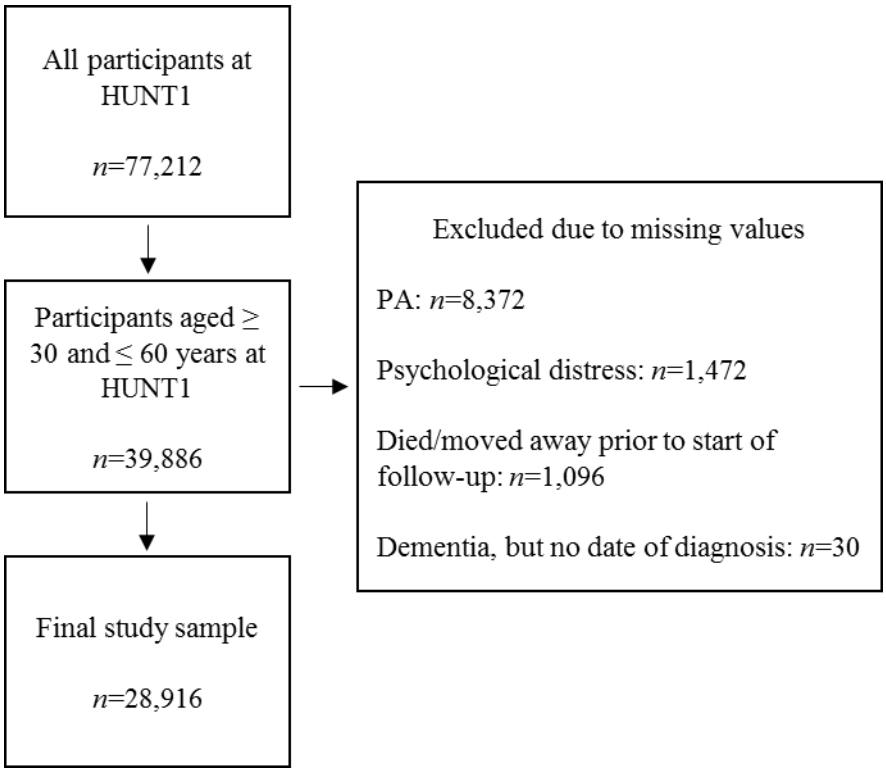

Figure 1. Flowchart of final study sample.

Ethics

The Regional Committee on Medical and Health Research Ethics of Norway (REK sør-øst B 2016/2229) approved the current study.

RESULTS

The final sample in our analyses comprised 28,916 participants aged 30 to 60 years at the time of HUNT1. Participants were younger, had fewer dementia cases, had more distress, were more often MVPA participants, were more likely to be married, smoked more, were less likely to be alcohol abstainers, had higher education, and were less likely to have longstanding physical

illness or impairment than individuals excluded due to missing data. In our final sample, 359 (1.2%) developed dementia during the follow-up period, 9,188 (31.8%) participants took part in MVPA at least once a week, and 4,076 (20.7%) participants were classified as having distress. There was a weak negative correlation between MVPA and distress, $\varphi = -0.08$, $p<0.001$. Table 1 shows baseline characteristics of the study population by MVPA group.

MVPA and dementia

Table 2 shows results from the Cox regression models of MVPA and dementia risk. In the model adjusted for sex (Model 1), engaging in MVPA at least once a week was associated with a reduced risk of dementia (HR 0.77, 95% CI 0.59-1.00) compared to not participating in any weekly MVPA. After additionally adjusting for education, marital status, smoking, alcohol, and distress (Model 2), the association was slightly attenuated, and after adding longstanding physical illness to the model (Model 3), MVPA at least once a week was still associated with a reduced risk of dementia (HR 0.81, 95% CI 0.62-1.06), although the association did not reach statistical significance. Adjusted PAF of dementia attributable to not participating in weekly MVPA was 0.15 (95% CI -0.05-0.33).

Distress and dementia

Compared to no distress, distress was associated with an increased risk of dementia in Model 1 (HR 1.34, 95% CI 1.03-1.74). The association was not attenuated in Model 2, and in Model 3, distress was still associated with an increased risk of dementia (HR 1.30, 95% CI 0.99-1.70) (Table 2), although the association was no longer statistically significant. Adjusted PAF of dementia attributable to distress was 0.04 (95% CI -0.003-0.12).

Joint associations of MVPA and distress on dementia

The results of the combined group analyses are presented in Table 3. In Model 1, compared to no MVPA with distress, no MVPA without distress was associated with a reduced risk of dementia (HR=0.71, 95% CI 0.54-0.94), as was MVPA without distress (HR=0.60, 95% CI 0.42-0.85). MVPA with distress was also associated with a reduced risk of dementia (HR=0.48, 95% CI 0.21-1.11), although the association did not reach statistical significance. The results were similar in model 2, and in model 3 where a reduced risk of dementia was observed in no MVPA participants without distress (HR 0.72, 95% CI 0.54-0.96), MVPA participants with distress (HR 0.50, 95% CI 0.22-1.14), and MVPA participants without distress (HR 0.63, 95% CI 0.44-0.90), when compared to no MVPA participants with distress. In the fully adjusted model, the RERI estimate was 0.69 (95% CI -0.16-1.53), indicating additive interaction between distress and not participating in weekly MVPA on risk of dementia.

Sensitivity analysis

Excluding the first five years of follow-up did not noteworthy change the observed associations (Appendix I).

DISCUSSION

In our study of 28,916 individuals from a general population, we found that midlife weekly MVPA was associated with a decreased risk of incident dementia, whereas distress was associated with an increased dementia risk up to 27 years later. Further, MVPA appeared to reduce the risk of dementia among individuals with as well as without distress.

The findings of an association between MVPA and dementia are in accordance with prior observational studies demonstrating a reduced risk of dementia among individuals participating in PA [4-6]. We show that participants engaging in MVPA at least once a week had a 19% lower risk of incident dementia up to 27 years later, compared to participants not taking part in any weekly MVPA. Although the results in the fully adjusted model did not reach statistical significance, a 19% lower risk may still be considered important for public health [34]. Fifty-four (15%) cases of dementia in our study can be attributed to not participating in weekly MVPA, suggesting that finding effective strategies for promoting MVPA is important when meeting the challenges associated with the aging populations across the world. A longitudinal study of adult twins found that individuals participating in vigorous PA, defined as self-reported PA more strenuous than walking, had a lower risk of dementia mortality when compared to those not participating in any vigorous PA [8]. Our study indicates that even small amounts of MVPA may protect against incident dementia. It thus appears that promoting MVPA at least once a week in middle-aged adults may be crucial for ensuring good public health and healthy aging.

Our results further indicate that distress during midlife increases the risk of dementia. This is in line with prior findings from the HMS [13], and other observational studies suggesting that both anxiety [35, 36] and depression [12, 37] are risk factors for dementia. Sixteen (4.5%) dementia cases in our sample can be attributed to midlife distress. In the combined analyses, when compared to participants who did not take part in MVPA and had distress (reference group), those who did not participate in MVPA and were free from distress had a 28% lower risk of dementia. Further, participants who participated in weekly MVPA and were free from distress had a 37% lower risk of dementia compared to the reference group. The largest risk reduction was observed among participants who took part in weekly MVPA but had distress. This group had a 50% lower risk of dementia compared to the reference group. However, there were only six

dementia cases in this group, providing low precision with wide confidence intervals. Our results nevertheless suggest that MVPA reduces the risk of dementia among individuals with distress, supporting findings from a prospective study in which high intensity PA markedly reduced the risk of dementia-related mortality among individuals with distress [20].

Exercise intervention studies have shown that exercise may increase brain volume [38, 39] and improve cognitive function [40, 41] in older adults. Furthermore, several observational studies have shown that subclinical symptoms of depression and anxiety are associated with smaller brain volume [42, 43] and poorer cognitive function [44, 45]. It is plausible that our results showing a reduced risk of dementia among individuals participating in MVPA at least once a week, despite having distress, stems from MVPA having a protective effect on cognitive and brain structural reserves [46].

Our study has several strengths. HUNT is one of the largest and most comprehensive population-based health surveys ever undertaken [23]. This has provided our study with a large sample size, lengthy follow-up time, validated measures of PA [25] and distress [26], and detailed data on a number of possible confounders. In addition, we were able to assess the risk of reverse causation by limiting our sample with regards to age, and by running a sensitivity analysis where we excluded the first five years of follow-up. However, we also acknowledge that the present study has several limitations. Several of our results did not reach statistical significance, although the estimates still suggest that these results may nevertheless be of relevance for public health [34]. Further, as it is based on subjective experience, self-reported PA may be prone to over- or underrepresentation of intensity and frequency. Similarly, self-report of distress may be sensitive to recent events or daily mood. However, using self-reported distress rather than clinical caseness of depression and/or anxiety makes the results of our study more relevant for the general population, rather than only clinical populations. Our study does not

include longitudinal measures of MVPA and distress, and we thus could not investigate how stability and/or changes in these factors are associated with dementia. However, our results indicate that even a single measure of these factors can predict dementia up to 27 years later. Selection bias may be present due to exclusion of participants who did not answer the PA and/or the distress questions. Included participants were more likely to have distress and to participate in weekly MVPA, and had less incidence of dementia than participants that were excluded. In addition, it is likely that some participants who developed dementia were not discovered and registered in the HMS, and milder cases may have been undercounted. This may have led to the inclusion of dementia cases in the comparison group. Such a misclassification would most likely bias the associations towards the null hypothesis, and it is thus possible that our estimates are lower than what would be expected if all dementia cases had been captured. There were too few cases of dementia to investigate the associations of MVPA and distress with different sub-types of dementia. However, this indicates that our results can be considered relevant for several sub-types of dementia. Further, as the date of diagnosis for the nursing home panel was estimated based on next-of-kin's retrospective report of the first symptoms of dementia, this information could be biased. It is very unlikely that this may have led to reverse causation, as the first reported onset of dementia in our sample is 9 years after the HUNT1 assessment. Finally, there were very few dementia cases (n=6) among participants who took part in MVPA but had distress, making the estimates less precise with wide confidence intervals.

In summary, we found that participating in MVPA at least once a week is associated with a reduced risk of incident dementia, whereas distress is a risk factor for dementia. Importantly, distressed participants who took part in weekly MVPA had a marked lower risk of dementia, suggesting that weekly MVPA reduces the risk of dementia among distressed individuals. Whereas prior studies have investigated the independent associations of distress and PA on

dementia risk, or investigated associations with dementia-related mortality, our study investigated the joint associations of these exposures on incident dementia. We found that MVPA appeared to have a particularly advantageous effect on dementia risk in distressed individuals. Taking part in MVPA at least once a week during midlife exerted benefits on cognitive aging, implying that dementia risk reduction through increased MVPA should be an attainable goal for most people, and should be encouraged by health care professionals.

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Table 1. Characteristics of study sample at HUNT1 by moderate-to-vigorous physical activity (MVPA) group. Table shows means, ranges, proportions, and percentages (%).

	No MVPA N=19,728 Mean (range)/proportion (%)	MVPA N=9,188 Mean (range)/proportion (%)
Age at HUNT1, y	44.2 (30.0-60.0)	41.8 (30.0-60.0)
Age at start of follow-up, y	54.6 (39.0-71.0)	52.3 (40.0-71.0)
Age at exit*, y	69.3 (41.0-87.0)	67.5 (41.0-87.0)
Sex (women)	10,724 (54.4%)	3,800 (41.4%)
Higher education (college or university)†	1,972 (10.0%)	2,047 (22.3%)
Marital status (married)†	16,352 (82.9%)	7,841 (85.3%)
Distress	3,169 (16.1%)	907 (9.9%)
Daily smoking†	8,573 (43.5%)	2,575 (28.0%)
Alcohol consumption ($\geq$ 5 times last 14 days)†	1,244 (6.3%)	621 (6.8%)
Longstanding physical illness†	2,422 (12.3%)	656 (7.1%)
Dementia‡	288 (1.5%)	71 (0.77%)

* Dementia, death, moving out of the county, or May 1st 2011, whichever occurred first.

† Missing values imputed using multiple imputations procedure.

‡ During follow-up from January 1st 1995 until May 1st 2011.

Table 2. Hazard ratios (HR) and 95% confidence intervals (CI) for dementia by moderate-to-vigorous physical activity (MVPA) and psychological distress (distress).

	N	Dementia cases	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Total	28,916	359			
No MVPA	19,728	288	1.00 (ref.)	1.00 (ref.)§	1.00 (ref.)§
MVPA	9,188	71	0.77 (0.59-1.00)	0.81 (0.62-1.06)§	0.81 (0.62-1.06)§
No distress	24,840	290	1.00 (ref.)	1.00 (ref.)¶	1.00 (ref.)¶
Distress	4,076	69	1.34 (1.03-1.74)	1.32 (1.01-1.72)¶	1.30 (0.99-1.70)¶

* Adjusted for sex.

† Adjusted for sex, education, marital status, smoking, and alcohol

‡ Adjusted for sex, education, marital status, smoking, alcohol, and longstanding physical illness.

§ Distress was added to the model.

¶ MVPA was added to the model.

Table 3. Dementia hazard ratios (HR), 95% confidence intervals (CI), and relative risk due to interaction (RERI) by combination groups of moderate-to-vigorous physical activity (MVPA) and psychological distress (distress).

Model	MVPA	No distress			Distress			RERI (95%CI)
		N	Dementia	HR (95% CI)	N	Dementia	HR (95% CI)	
1*	No MVPA	16,559	225	0.71 (0.54-0.94)	3,169	63	1.00 (ref.)	0.81 (-0.05-1.67)
	MVPA	8,281	65	0.60 (0.42-0.85)	907	6	0.48 (0.21-1.11)	
2†	No MVPA	16,559	225	0.71 (0.54-0.94)	3,169	63	1.00 (ref.)	0.75 (-0.07-1.56)
	MVPA	8,281	65	0.61 (0.43-0.88)	907	6	0.49 (0.21-1.14)	
3‡	No MVPA	16,559	225	0.72 (0.54-0.96)	3,169	63	1.00 (ref.)	0.69 (-0.16-1.53)
	MVPA	8,281	65	0.63 (0.44-0.90)	907	6	0.50 (0.22-1.14)	

* Adjusted for sex.

† Adjusted for sex, education, marital status, smoking, and alcohol.

‡ Adjusted for sex, education, marital status, smoking, alcohol, and longstanding physical illness.

Appendix I: Exclusion of first 5 years of follow-up

Supplementary table 1. Hazard ratios (HR) and 95% confidence intervals (CI) for dementia by moderate-to-vigorous physical activity (MVPA) and psychological distress (distress) with follow-up starting in year 2000.

	N	Dementia cases	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Total	28,916	359			
No MVPA	18,987	260	1.00 (ref.)	1.00 (ref.)§	1.00 (ref.)§
MVPA	8,996	64	0.78 (0.59-1.03)	0.83 (0.63-1.11)§	0.84 (0.63-1.11)§
No distress	24,086	265	1.00 (ref.)	1.00 (ref.)¶	1.00 (ref.)¶
Distress	3,897	59	1.25 (0.94-1.66)	1.22 (0.91-1.63)¶	1.20 (0.90-1.61)¶

* Adjusted for sex.

† Adjusted for sex, education, marital status, smoking, and alcohol

‡ Adjusted for sex, education, marital status, smoking, alcohol, and longstanding physical illness.

§ Distress was added to the model.

¶ MVPA was added to the model.

Supplementary table 2. Dementia hazard ratios (HR) and 95% confidence intervals (CI) by combination groups of moderate-to-vigorous physical activity (MVPA) and psychological distress (distress) with follow-up starting in year 2000.

		No distress			Distress		
Model	MVPA	N	Dementia	HR (95% CI)	N	Dementia	HR (95% CI)
1*	No MVPA	15,970	206	0.76 (0.56-1.02)	3,017	54	1.00 (ref.)
	MVPA	8,116	59	0.64 (0.44-0.93)	880	5	0.47 (0.19-1.19)
2†	No MVPA	15,970	206	0.76 (0.56-1.03)	3,017	54	1.00 (ref.)
	MVPA	8,116	59	0.68 (0.46-0.99)	880	5	0.50 (0.20-1.24)
3‡	No MVPA	15,970	206	0.78 (0.57-1.05)	3,017	54	1.00 (ref.)
	MVPA	8,116	59	0.69 (0.47-1.02)	880	5	0.50 (0.20-1.23)

* Adjusted for sex.

† Adjusted for sex, education, marital status, smoking, and alcohol.

‡ Adjusted for sex, education, marital status, smoking, alcohol, and longstanding physical illness.