

## **Physical Activity, Cognitive Decline and Risk of Dementia: 28-year Follow-Up of the Whitehall II Study**

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## **Supplementary Methods**

### **Sensitivity analysis for trajectories of physical activity preceding dementia using a case-control approach**

We used a case-control approach in order to better adjust for confounders, and period effects inherent in the diagnosis of dementia. Index year for dementia cases and their matched controls was year of the first record of dementia diagnosis. Each case was individually matched to 6 controls drawn randomly from the study population using the following criteria: age (5-year age-group at the index year), sex, education, being alive at the index date, and without a diagnosis of dementia at the end of follow-up. The analytic strategy was similar to that in the main analysis, mixed models with a backward scale were used to compare trajectories of physical activity between dementia cases and their matched controls.

## Equations

### (1) Association of physical activity with cognitive performance at age 50, 60, 70, and 80

$$\text{years } \text{Cognition}_{ij} = \beta_0 + \beta_1 \text{age}_{ij} + \beta_2 \text{age}_{ij}^2 + \beta_3 \text{PA}_{ij} + \beta_4 X_i + \beta_5 Z_{ij} + \beta_6 C_i + \beta_7 \text{PA}_{ij} \text{age}_{ij} + \beta_8 X_i \text{age}_{ij} + \beta_9 \text{PA}_{ij} \text{age}_{ij}^2 + \beta_{10} X_i \text{age}_{ij}^2 + U_{0i} + U_{1i} \text{age}_{ij} + e_{ij}$$

where  $\text{Cognition}_{ij}$  is the cognitive score of the  $i^{\text{th}}$  participant at the  $j^{\text{th}}$  occasion,  $\text{age}_{ij}$  is the age (centred at mean age (65 years) over the follow-up period) of the  $i^{\text{th}}$  participant at the  $j^{\text{th}}$  occasion,  $\text{PA}_{ij}$  is the physical activity variable for the  $i^{\text{th}}$  participant at the  $j^{\text{th}}$  occasion,  $C_i$  is the 5-year birth cohort of  $i^{\text{th}}$  participant,  $X_i$  is the vector of time independent covariates (sex, education, ethnicity) of  $i^{\text{th}}$  participant,  $Z_{ij}$  is the vector of time-varying covariates (occupational position, marital status, health behaviours and health-related variables) of  $i^{\text{th}}$  participant at the  $j^{\text{th}}$  occasion,  $U_{0i}$  is the random intercept,  $U_{1i}$  is the random slope, and  $e_{ij}$  is the residual.

### (2) Association of physical activity in 1997/99 with cognitive decline over 15 years (1997/99 to 2012/13)

$$\text{Cognition}_{ij} = \beta_0 + \beta_1 \text{time}_{ij} + \beta_2 \text{time}_{ij}^2 + \beta_3 \text{PA}_i + \beta_4 \text{age}_i + \beta_5 X_i + \beta_6 \text{PA}_i \text{time}_{ij} + \beta_7 \text{age}_i \text{time}_{ij} + \beta_8 X_i \text{time}_{ij} + \beta_9 \text{age}_i \text{time}_{ij}^2 + U_{0i} + U_{1i} \text{time}_{ij} + e_{ij}$$

where  $\text{Cognition}_{ij}$  is the cognitive score of the  $i^{\text{th}}$  participant at the  $j^{\text{th}}$  occasion,  $\text{time}_{ij}$  is the delay since 1997/99 for the  $i^{\text{th}}$  participant at the  $j^{\text{th}}$  occasion,  $\text{PA}_i$  is the physical activity variable of the  $i^{\text{th}}$  participant in 1997/99,  $\text{age}_i$  is the age of the  $i^{\text{th}}$  participant in 1997/99 (centred at mean age (55 years)),  $X_i$  is the vector of covariates in 1997/99 (sex, education, occupational position, marital status, health behaviours, and health-related variables)  $U_{0i}$  is the random intercept,  $U_{1i}$  is the random slope, and  $e_{ij}$  is the residual.

### (3) Association between physical activity and dementia

$$\lambda(a | j, z) = \lambda_{0,j}(a) \exp(\beta' Z)$$

where  $\lambda$  is the hazard of dementia at age  $a$  for an individual with the vector of covariates  $Z$  in 1985/88 and  $\lambda_{0,j}$  is the baseline hazard for participants born in the  $j^{\text{th}}$  5-year birth cohort.

#### (4) Trajectories of physical activity (hours/week) over 28 years preceding dementia

$$PA_{ij} = \beta_0 + \beta_1 time_{ij} + \beta_2 time_{ij}^2 + \beta_3 time_{ij}^3 + \beta_4 Dementia_i + \beta_5 C_i + \beta_6 age_i + \beta_7 X_i + \beta_8 Z_{ij} + \beta_9 Dementia_i time_{ij} + \beta_{10} age_i time_{ij} + \beta_{11} X_i time_{ij} + \beta_{12} Dementia_i time_{ij}^2 + \beta_{13} age_i time_{ij}^2 + \beta_{14} X_i time_{ij}^2 + \beta_{15} Dementia_i time_{ij}^3 + \beta_{16} age_i time_{ij}^3 + \beta_{17} X_i time_{ij}^3 + U_{0i} + U_{1i} time_{ij} + e_{ij}$$

where  $PA_{ij}$  is the physical activity variable for the  $i^{th}$  participant at the  $j^{th}$  occasion,

$time_{ij}$  is the delay (negative value) between the time when physical activity was measured

for the  $i^{th}$  participant at the  $j^{th}$  occasion and the index date (year=0, corresponding to dementia

diagnosis for cases, year of death for those who died, and March 31<sup>st</sup> 2015 for all others),

$Dementia_i$  is the dementia status at the end of follow-up (0=non-cases, 1=cases),

$C_i$  is the 5-year birth cohort of  $i^{th}$  participant,

$age_i$  is the age of the  $i^{th}$  participant at the index year (centred at mean age of dementia diagnosis (75 years)),

$X_i$  is the vector of time-independent covariates at Year 0 (sex, education, ethnicity)

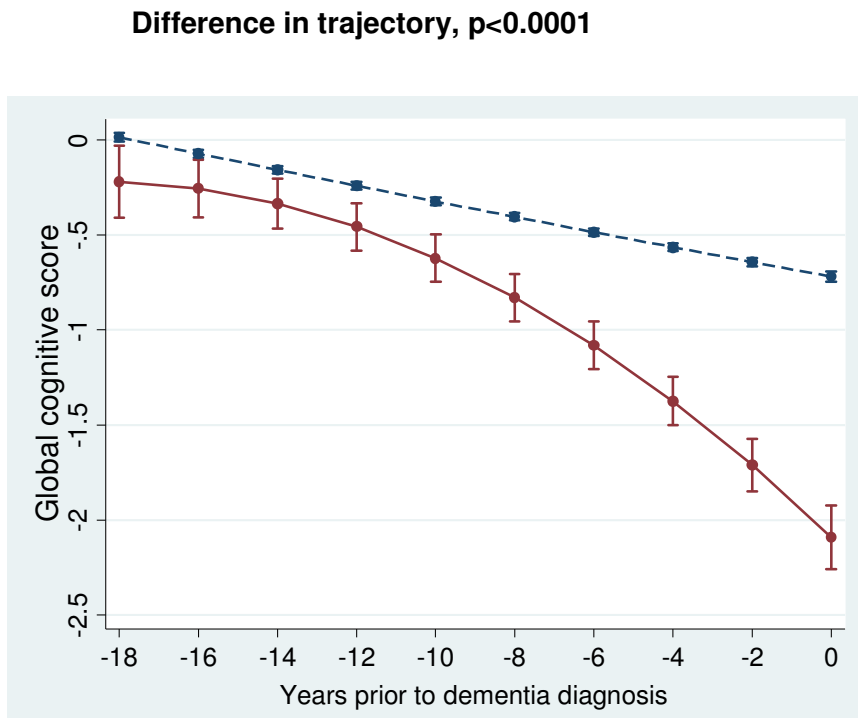
of the  $i^{th}$  participant,

$Z_{ij}$  is the vector of time-varying covariates (occupation position, marital status, and behavioural

factors) of  $i^{th}$  participant at the  $j^{th}$  occasion,

$U_{0i}$  is the random intercept,  $U_{1i}$  is the random slope, and  $e_{ij}$  is the residual.

**Figure A. Trajectory of global cognitive score in dementia cases and all other participants in the years leading to dementia diagnosis.**



	<b>Number of observations in the analysis</b>				
<b>Years</b>	-18 to -16	-16 to -12	-12 to -8	-8 to -4	-4 to 0
<b>Dementia free (N=7311)</b>	5192	2489	3714	5938	4777
<b>Dementia cases (N=195)</b>	31	81	119	110	89

**Legend** - - - - Dementia free — Dementia cases

**Figure B. Study flow chart of sample selection, Whitehall II Study.**

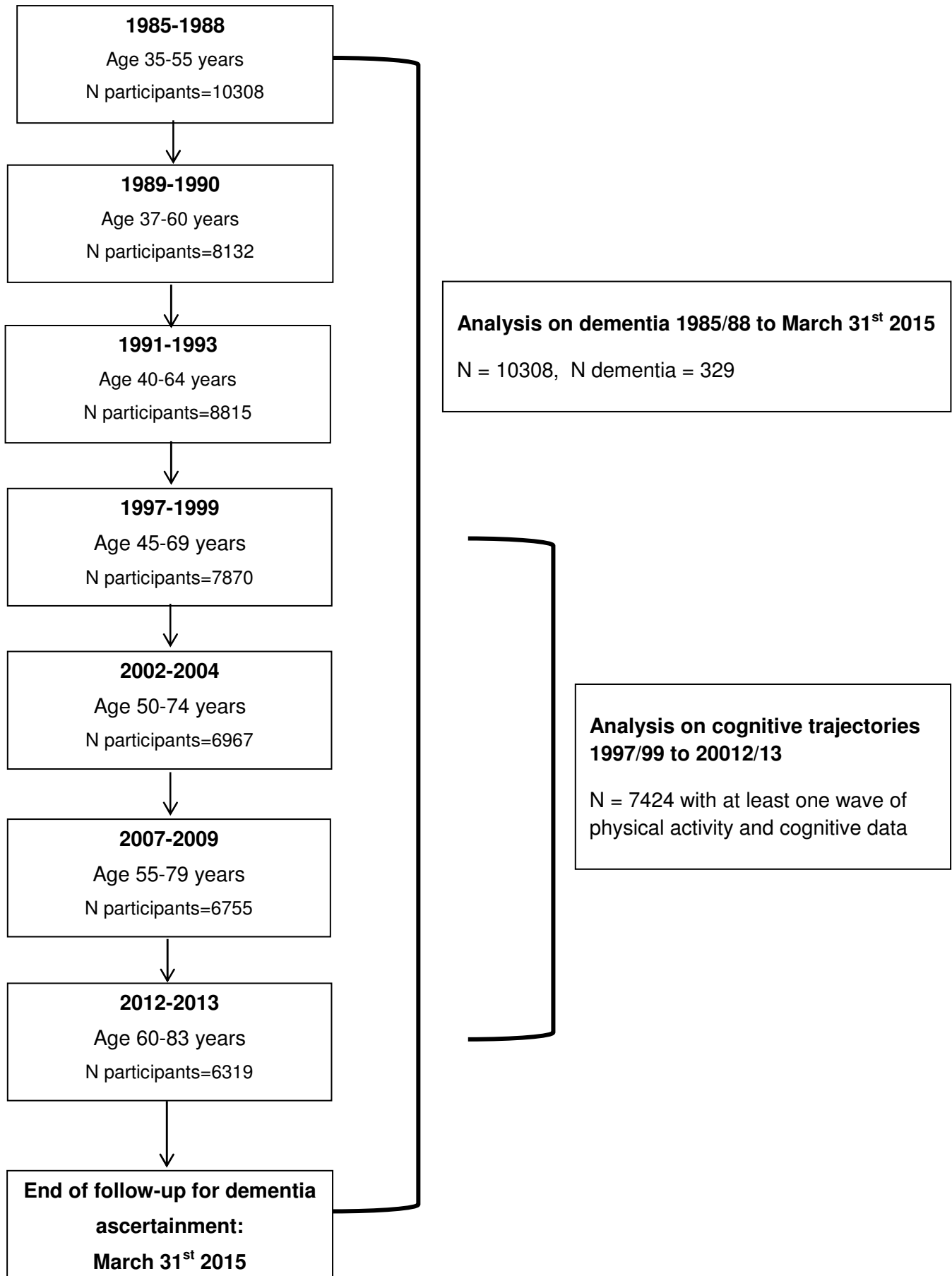
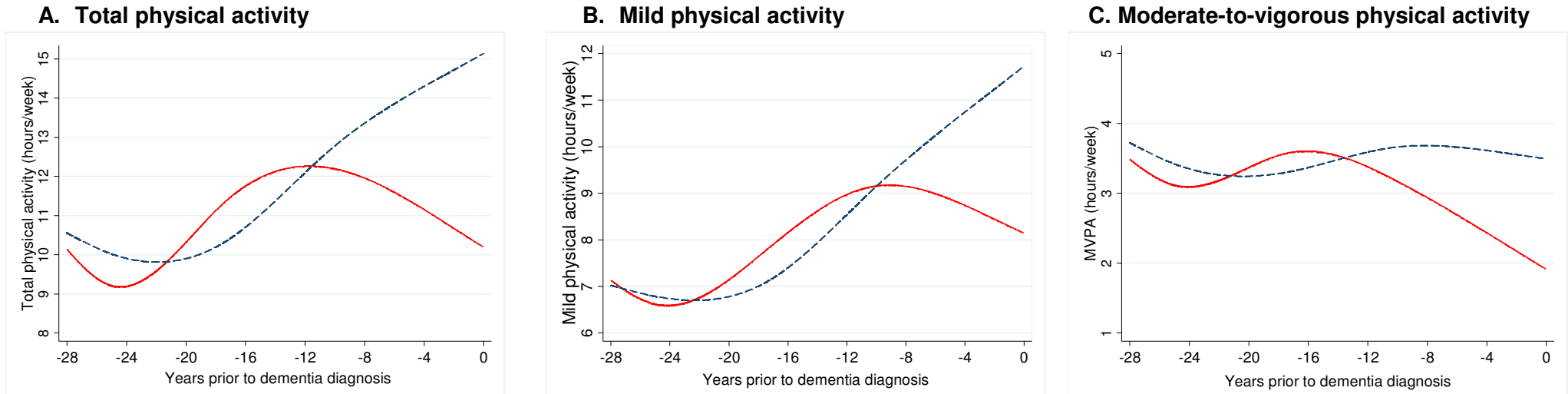




Figure C. Trajectories of physical activity (hours/week) preceding dementia using cubic regression splines

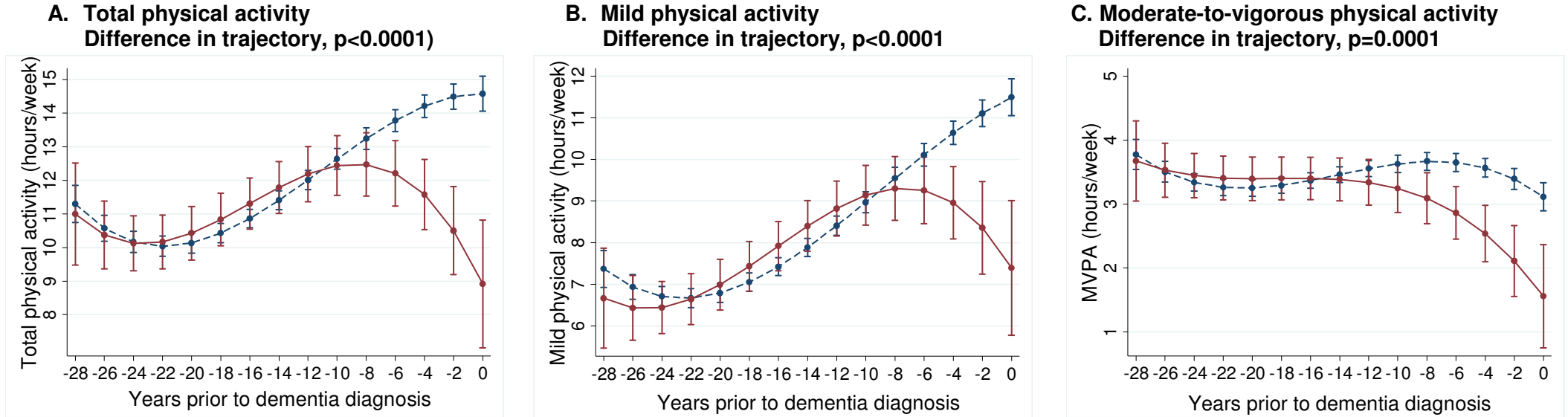


**Legend**    - - - - Dementia free    ——— Dementia cases

Abbreviation: MVPA, moderate-to-vigorous physical activity.

Figure D. Trajectories of physical activity (hours/week) prior to dementia diagnosis using a case-control approach

Legend —•— Controls —•— Dementia cases

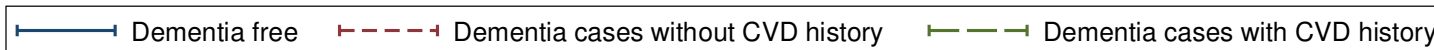


	Number of observations in the analysis																							
Years	-28 to -24	-24 to -20	-20 to -16	-16 to -12	-12 to -8	-8 to -4	-4 to 0		-28 to -24	-24 to -20	-20 to -16	-16 to -12	-12 to -8	-8 to -4	-4 to 0		-28 to -24	-24 to -20	-20 to -16	-16 to -12	-12 to -8	-8 to -4	-4 to 0	
<b>Controls (N=1974)</b>	1822	2260	1347	1186	1313	1148	1509		1822	2260	1347	1186	1313	1148	1509		1822	2260	1347	1186	1313	1148	1509	
<b>Dementia cases (N=329)</b>	256	298	195	163	168	137	118		256	298	195	163	168	137	118		256	298	195	163	168	137	118	

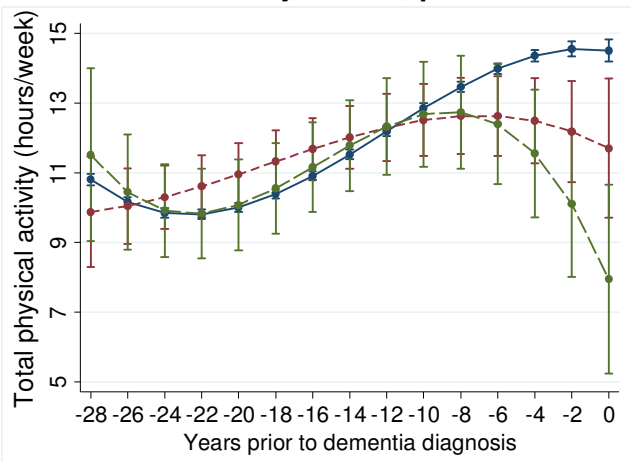
See accompanying table in appendix table S9. Abbreviation: MVPA, moderate-to-vigorous physical activity.

**Figure E. Trajectories of physical activity (hours/week) over 28 years preceding dementia with or without CVD history**

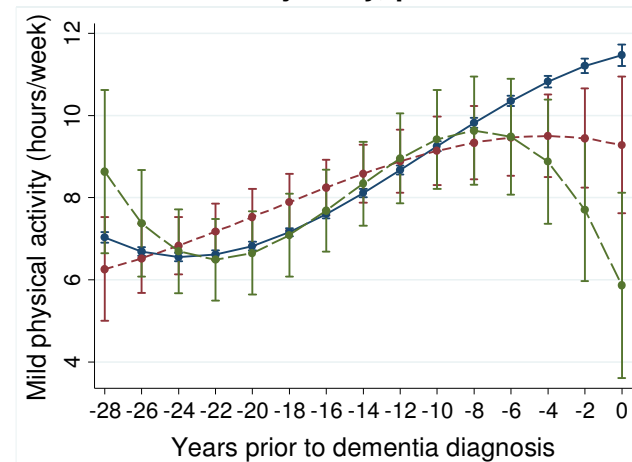
**Legend**



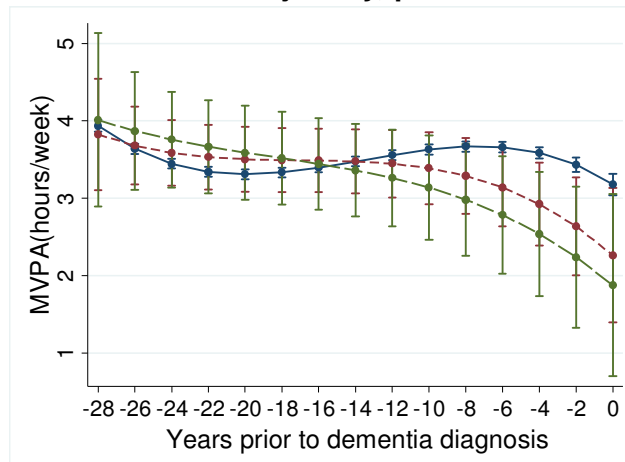
**A. Total physical activity**  
Difference in trajectories,  $p < 0.0001$



**B. Mild physical activity**  
Difference in trajectory,  $p < 0.0001$



**C. Moderate-to-vigorous physical activity**  
Difference in trajectory,  $p = 0.01$



	Number of observations in the analysis																							
Years	-28 to -24	-24 to -20	-20 to -16	-16 to -12	-12 to -8	-8 to -4	-4 to 0		-28 to -24	-24 to -20	-20 to -16	-16 to -12	-12 to -8	-8 to -4	-4 to 0		-28 to -24	-24 to -20	-20 to -16	-16 to -12	-12 to -8	-8 to -4	-4 to 0	
<b>Dementia free (N=9979)</b>	10893	7856	6958	2456	5237	6937	6756		10893	7856	6958	2456	5237	6937	6756		10893	7856	6958	2456	5237	6937	6756	
<b>Dementia cases with CVD history (N=111)</b>	78	93	59	52	54	39	32		78	93	59	52	54	39	32		78	93	59	52	54	39	32	
<b>Dementia cases without CVD history (N=218)</b>	178	205	136	111	114	98	86		178	205	136	111	114	98	86		178	205	136	111	114	98	86	

**Table A. Association of physical activity with performance on the global cognitive z-score at age 50, 60, 70, and 80 years, adjusted for socio-demographic and behavioural factors.**

	<b>AGE 50</b>	<b>AGE 60</b>	<b>AGE 70</b>	<b>AGE 80</b>	<b><i>P for interaction with age</i></b>
	<b>Difference in cognitive function* (95% CI)</b>	<b>Difference in cognitive function* (95% CI)</b>	<b>Difference in cognitive function* (95% CI)</b>	<b>Difference in cognitive function* (95% CI)</b>	
<b>Total physical activity</b>					<i>&lt;0.0001</i>
<b>&lt;8 hours/week</b>	Ref	Ref	Ref	Ref	
<b>8-12 hours/week</b>	0.01 (-0.03 to 0.05)	0.00 (-0.03 to 0.02)	0.06 (0.03 to 0.09)	0.20 (0.13 to 0.28)	
<b>≥12 hours/week</b>	0.02 (-0.03 to 0.06)	0.01 (-0.01 to 0.03)	0.06 (0.04 to 0.09)	0.18 (0.11 to 0.25)	
<b>Mild physical activity</b>					<i>0.02</i>
<b>&lt;5 hours/week</b>	Ref	Ref	Ref	Ref	
<b>5-9 hours/week</b>	0.01 (-0.03 to 0.05)	0.00 (-0.02 to 0.03)	0.05 (0.02 to 0.08)	0.14 (0.06 to 0.22)	
<b>≥9 hours/week</b>	0.00 (-0.05 to 0.04)	0.01 (-0.02 to 0.03)	0.05 (0.02 to 0.08)	0.12 (0.04 to 0.19)	
<b>Moderate-to-vigorous physical activity</b>					<i>&lt;0.0001</i>
<b>&lt;2 hours/week</b>	Ref	Ref	Ref	Ref	
<b>2-4 hours/week</b>	0.02 (-0.02 to 0.06)	0.02 (-0.01 to 0.04)	0.06 (0.04 to 0.09)	0.16 (0.09 to 0.23)	
<b>≥4 hours/week</b>	0.04 (0.01 to 0.09)	0.01 (-0.01 to 0.03)	0.06 (0.03 to 0.08)	0.18 (0.11 to 0.24)	
<b>Physical activity recommendations<sup>†</sup></b>					<i>&lt;0.0001</i>
<b>MVPA &lt;2.5 hours/week</b>	Ref	Ref	Ref	Ref	
<b>MVPA ≥2.5 hours/week</b>	0.03 (0.01 to 0.07)	0.00 (-0.02 to 0.02)	0.04 (0.02 to 0.06)	0.15 (0.10 to 0.21)	

\* Estimated differences (expressed in standard deviations using the distribution of the first wave of cognitive data in 1997/99) in cognitive function at age 50, 60, 70, and 80 years drawn from a single longitudinal model using age at the time scale.

Models are adjusted for ethnicity, education, 5-year birth cohort, and time-dependent occupational position, marital status, smoking status, alcohol consumption, and fruit and vegetable consumption.

<sup>†</sup>Recommended level corresponds to Moderate-to-Vigorous Physical Activity (MVPA) ≥2.5 hours/week.

**Table B. Association of physical activity with the MEMORY z-score at age 50, 60, 70, and 80 years**

	<b>AGE 50</b>	<b>AGE 60</b>	<b>AGE 70</b>	<b>AGE 80</b>	<i><b>P for interaction with age</b></i>
	<b>Difference in cognitive function* (95% CI)</b>	<b>Difference in cognitive function* (95% CI)</b>	<b>Difference in cognitive function* (95% CI)</b>	<b>Difference in cognitive function* (95% CI)</b>	
<b>Total physical activity</b>					<i>0.007</i>
<b>&lt;8 hours/week</b>	Ref	Ref	Ref	Ref	
<b>8-12 hours/week</b>	-0.01 (-0.07 to 0.06)	-0.01 (-0.05 to 0.02)	0.05 (0.01 to 0.09)	0.19 (0.07 to 0.31)	
<b>≥12 hours/week</b>	0.05 (-0.02 to 0.12)	-0.02 (-0.06 to 0.02)	0.01 (-0.03 to 0.05)	0.15 (0.04 to 0.26)	
<b>Mild physical activity</b>					<i>0.42</i>
<b>&lt;5 hours/week</b>	Ref	Ref	Ref	Ref	
<b>5-9 hours/week</b>	0.02 (-0.04 to 0.09)	-0.01 (-0.04 to 0.03)	0.03 (-0.01 to 0.07)	0.13 (0.01 to 0.26)	
<b>≥9 hours/week</b>	0.00 (-0.08 to 0.08)	-0.03 (-0.07 to 0.01)	-0.01 (-0.05 to 0.04)	0.08 (-0.04 to 0.20)	
<b>Moderate-to-vigorous physical activity</b>					<i>0.28</i>
<b>&lt;2 hours/week</b>	Ref	Ref	Ref	Ref	
<b>2-4 hours/week</b>	0.03 (-0.04 to 0.09)	0.00 (-0.03 to 0.04)	0.02 (-0.02 to 0.06)	0.08 (-0.03 to 0.18)	
<b>≥4 hours/week</b>	0.09 (0.02 to 0.16)	0.02 (-0.02 to 0.05)	0.02 (-0.02 to 0.06)	0.10 (0.00 to 0.21)	
<b>Physical activity recommendations<sup>†</sup></b>					<i>0.05</i>
<b>MVPA &lt;2.5 hours/week</b>	Ref	Ref	Ref	Ref	
<b>MVPA ≥2.5 hours/week</b>	0.06 (0.01 to 0.12)	0.00 (-0.03 to 0.03)	0.02 (-0.02 to 0.05)	0.11 (-0.02 to 0.20)	

\* Estimated differences (expressed in standard deviations using the distribution of the first wave of cognitive data in 1997/99) in cognitive function at age 50, 60, 70, and 80 years drawn from a single longitudinal model using age at the time scale.

Models are adjusted for ethnicity, education, 5-year birth cohort, and time-dependent occupational position, marital status, smoking status, alcohol consumption, fruit and vegetable consumption, hypertension, diabetes, BMI, GHQ score, CVD, CVD medication and the SF-36 physical component score.

<sup>†</sup>Recommended level corresponds to Moderate-to-Vigorous Physical Activity (MVPA) ≥2.5 hours/week.

**Table C. Association of physical activity with the REASONING z-score at age 50, 60, 70, and 80 years**

	<b>AGE 50</b>	<b>AGE 60</b>	<b>AGE 70</b>	<b>AGE 80</b>	<i><b>P for interaction with age</b></i>
	<b>Difference in cognitive function* (95% CI)</b>	<b>Difference in cognitive function* (95% CI)</b>	<b>Difference in cognitive function* (95% CI)</b>	<b>Difference in cognitive function* (95% CI)</b>	
<b>Total physical activity</b>					<i>0.03</i>
<b>&lt;8 hours/week</b>	Ref	Ref	Ref	Ref	
<b>8-12 hours/week</b>	0.01 (-0.03 to 0.04)	0.00 (-0.03 to 0.02)	0.02 (0.00 to 0.05)	0.09 (0.02 to 0.15)	
<b>≥12 hours/week</b>	-0.02 (-0.06 to 0.02)	0.01 (-0.01 to 0.03)	0.03 (0.01 to 0.06)	0.06 (0.00 to 0.12)	
<b>Mild physical activity</b>					<i>0.03</i>
<b>&lt;5 hours/week</b>	Ref	Ref	Ref	Ref	
<b>5-9 hours/week</b>	0.00 (-0.04 to 0.03)	-0.01 (-0.03 to 0.01)	0.01 (-0.01 to 0.03)	0.07 (-0.01 to 0.14)	
<b>≥9 hours/week</b>	-0.02 (-0.06 to 0.02)	0.02 (-0.01 to 0.04)	0.03 (0.01 to 0.06)	0.03 (-0.03 to 0.10)	
<b>Moderate-to-vigorous physical activity</b>					<i>0.001</i>
<b>&lt;2 hours/week</b>	Ref	Ref	Ref	Ref	
<b>2-4 hours/week</b>	0.01 (-0.03 to 0.04)	0.02 (0.00 to 0.04)	0.05 (0.03 to 0.07)	0.10 (0.04 to 0.16)	
<b>≥4 hours/week</b>	0.00 (-0.03 to 0.04)	-0.02 (-0.04 to 0.00)	0.01 (-0.01 to 0.04)	0.11 (0.05 to 0.16)	
<b>Physical activity recommendations<sup>†</sup></b>					<i>0.008</i>
<b>MVPA &lt;2.5 hours/week</b>	Ref	Ref	Ref	Ref	
<b>MVPA ≥2.5 hours/week</b>	0.01 (-0.02 to 0.04)	-0.01 (-0.03 to 0.01)	0.01 (-0.01 to 0.03)	0.08 (0.03 to 0.13)	

\* Estimated differences (expressed in standard deviations using the distribution of the first wave of cognitive data in 1997/99) in cognitive function at age 50, 60, 70, and 80 years drawn from a single longitudinal model using age at the time scale.

Models are adjusted for ethnicity, education, 5-year birth cohort, and time-dependent occupational position, marital status, smoking status, alcohol consumption, fruit and vegetable consumption, hypertension, diabetes, BMI, GHQ score, CVD, CVD medication and the SF-36 physical component score.

<sup>†</sup>Recommended level corresponds to Moderate-to-Vigorous Physical Activity (MVPA) ≥2.5 hours/week.

**Table D. Association of physical activity with the FLUENCY z-score at age 50, 60, 70, and 80 years**

	<b>AGE 50</b>	<b>AGE 60</b>	<b>AGE 70</b>	<b>AGE 80</b>	<i><b>P for interaction with age</b></i>
	<b>Difference in cognitive function* (95% CI)</b>	<b>Difference in cognitive function* (95% CI)</b>	<b>Difference in cognitive function* (95% CI)</b>	<b>Difference in cognitive function* (95% CI)</b>	
<b>Total physical activity</b>					<i>0.003</i>
<b>&lt;8 hours/week</b>	Ref	Ref	Ref	Ref	
<b>8-12 hours/week</b>	0.01 (-0.04 to 0.05)	-0.01 (-0.04 to 0.02)	0.03 (0.00 to 0.06)	0.14 (0.05 to 0.22)	
<b>≥12 hours/week</b>	-0.03 (-0.08 to 0.02)	0.00 (-0.03 to 0.03)	0.05 (0.02 to 0.08)	0.12 (0.04 to 0.19)	
<b>Mild physical activity</b>					<i>0.38</i>
<b>&lt;5 hours/week</b>	Ref	Ref	Ref	Ref	
<b>5-9 hours/week</b>	-0.01 (-0.06 to 0.04)	0.02 (-0.01 to 0.05)	0.05 (0.02 to 0.08)	0.07 (-0.02 to 0.15)	
<b>≥9 hours/week</b>	0.00 (-0.05 to 0.06)	0.02 (-0.01 to 0.05)	0.04 (0.01 to 0.07)	0.06 (-0.02 to 0.14)	
<b>Moderate-to-vigorous physical activity</b>					<i>0.003</i>
<b>&lt;2 hours/week</b>	Ref	Ref	Ref	Ref	
<b>2-4 hours/week</b>	0.02 (-0.03 to 0.06)	0.00 (-0.02 to 0.03)	0.04 (0.01 to 0.07)	0.14 (0.06 to 0.21)	
<b>≥4 hours/week</b>	0.01 (-0.04 to 0.05)	0.00 (-0.02 to 0.03)	0.05 (0.02 to 0.08)	0.16 (0.07 to 0.22)	
<b>Physical activity recommendations<sup>†</sup></b>					<i>0.002</i>
<b>MVPA &lt;2.5 hours/week</b>	Ref	Ref	Ref	Ref	
<b>MVPA ≥2.5 hours/week</b>	0.01 (-0.03 to 0.05)	0.00 (-0.02 to 0.02)	0.03 (0.01 to 0.06)	0.12 (0.06 to 0.18)	

\* Estimated differences (expressed in standard deviations using the distribution of the first wave of cognitive data in 1997/99) in cognitive function at age 50, 60, 70, and 80 years drawn from a single longitudinal model using age at the time scale.

Models are adjusted for ethnicity, education, 5-year birth cohort, and time-dependent occupational position, marital status, smoking status, alcohol consumption, fruit and vegetable consumption, hypertension, diabetes, BMI, GHQ score, CVD, CVD medication and the SF-36 physical component score.

<sup>†</sup>Recommended level corresponds to Moderate-to-Vigorous Physical Activity (MVPA) ≥2.5 hours/week.

**Table E. Association of physical activity in 1997/99 with decline over 15 years (1997/99 to 2012/13) in the MEMORY z-score.**

	Adjusted for age and sex		Adjusted for socio-demographic and behavioural factors*		Fully adjusted†	
	15-y cognitive decline‡ (95% CI)	p§	15-y cognitive decline‡ (95% CI)	p§	15-y cognitive decline‡ (95% CI)	p§
<b>Total physical activity</b>						
<8 hours/week	-0.48 (-0.53 to -0.43)	Ref	-0.49 (-0.55 to -0.44)	Ref	-0.49 (-0.55 to -0.44)	Ref
8-12 hours/week	-0.45 (-0.50 to -0.40)	0.48	-0.46 (-0.51 to -0.40)	0.33	-0.46 (-0.51 to -0.41)	0.24
≥12 hours/week	-0.47 (-0.52 to -0.42)	0.88	-0.47 (-0.52 to -0.42)	0.57	-0.47 (-0.52 to -0.42)	0.56
<b>Mild physical activity</b>						
<5 hours/week	-0.46 (-0.52 to -0.41)	Ref	-0.48 (-0.54 to -0.43)	Ref	-0.48 (-0.54 to -0.42)	Ref
5-9 hours/week	-0.49 (-0.53 to -0.44)	0.54	-0.49 (-0.53 to -0.44)	0.89	-0.49 (-0.53 to -0.44)	0.85
≥9 hours/week	-0.45 (-0.50 to -0.40)	0.71	-0.45 (-0.50 to -0.40)	0.46	-0.45 (-0.51 to -0.40)	0.50
<b>Moderate-to-vigorous physical activity</b>						
<2 hours/week	-0.44 (-0.48 to -0.39)	Ref	-0.45 (-0.49 to -0.40)	Ref	-0.44 (-0.49 to -0.40)	Ref
2-4 hours/week	-0.48 (-0.54 to -0.42)	0.27	-0.48 (-0.54 to -0.43)	0.30	-0.49 (-0.55 to -0.43)	0.24
≥4 hours/week	-0.49 (-0.54 to -0.44)	0.11	-0.50 (-0.55 to -0.45)	0.16	-0.50 (-0.55 to -0.45)	0.14
<b>Physical activity recommendations#</b>						
MVPA <2.5 hours/week	-0.45 (-0.50 to -0.41)	Ref	-0.46 (-0.51 to -0.42)	Ref	-0.46 (-0.50 to -0.42)	Ref
MVPA ≥2.5 hours/week	-0.48 (-0.52 to -0.44)	0.38	-0.48 (-0.53 to -0.44)	0.47	-0.48 (-0.53 to -0.44)	0.45

\* Adjusted for age, sex, ethnicity, education, occupational position, marital status, smoking status, alcohol consumption, and fruit and vegetable consumption.

† Additionally adjusted for hypertension, diabetes, BMI, GHQ score, CVD, CVD medication, and physical component score.

‡ Estimated cognitive decline over 15 years (expressed in standard deviations using the distribution of the first wave of cognitive data in 1997/99) as a function of physical activity..

§ p for difference in decline in the global cognitive score over 15 years by physical activity groups (drawn from a test of interaction between physical activity categories and time since baseline).

# Recommended level corresponds to Moderate-to-Vigorous Physical Activity (MVPA) ≥2.5 hours/week.



**Table F. Association of physical activity in 1997/99 with decline over 15 years (1997/99 to 2012/13) in the REASONING z-score.**

	Adjusted for age and sex		Adjusted for socio-demographic and behavioural factors*		Fully adjusted†	
	15-y cognitive decline‡ (95% CI)	p§	15-y cognitive decline‡ (95% CI)	p§	15-y cognitive decline‡ (95% CI)	p§
<b>Total physical activity</b>						
<8 hours/week	-0.41 (-0.44 to -0.38)	Ref	-0.41 (-0.44 to -0.38)	Ref	-0.41 (-0.44 to -0.38)	Ref
8-12 hours/week	-0.41 (-0.44 to -0.39)	0.73	-0.42 (-0.44 to -0.39)	0.76	-0.42 (-0.45 to -0.39)	0.65
≥12 hours/week	-0.44 (-0.46 to -0.41)	0.15	-0.44 (-0.46 to -0.41)	0.15	-0.44 (-0.47 to -0.42)	0.10
<b>Mild physical activity</b>						
<5 hours/week	-0.42 (-0.45 to -0.39)	Ref	-0.43 (-0.46 to -0.40)	Ref	-0.43 (-0.46 to -0.40)	Ref
5-9 hours/week	-0.40 (-0.43 to -0.38)	0.27	-0.41 (-0.43 to -0.38)	0.23	-0.41 (-0.43 to -0.38)	0.26
≥9 hours/week	-0.44 (-0.47 to -0.41)	0.44	-0.44 (-0.47 to -0.42)	0.47	-0.45 (-0.47 to -0.42)	0.43
<b>Moderate-to-vigorous physical activity</b>						
<2 hours/week	-0.42 (-0.44 to -0.39)	Ref	-0.42 (-0.44 to -0.39)	Ref	-0.41 (-0.44 to -0.39)	Ref
2-4 hours/week	-0.41 (-0.44 to -0.38)	0.64	-0.41 (-0.44 to -0.38)	0.77	-0.41 (-0.44 to -0.38)	0.96
≥4 hours/week	-0.44 (-0.46 to -0.41)	0.32	-0.44 (-0.47 to -0.41)	0.28	-0.44 (-0.47 to -0.41)	0.17
<b>Physical activity recommendations#</b>						
MVPA <2.5 hours/week	-0.42 (-0.44 to -0.39)	Ref	-0.42 (-0.44 to -0.39)	Ref	-0.41 (-0.44 to -0.39)	Ref
MVPA ≥2.5 hours/week	-0.43 (-0.45 to -0.40)	0.55	-0.43 (-0.45 to -0.41)	0.46	-0.43 (-0.45 to -0.41)	0.29

\* Adjusted for age, sex, ethnicity, education, occupational position, marital status, smoking status, alcohol consumption, and fruit and vegetable consumption.

† Additionally adjusted for hypertension, diabetes, BMI, GHQ score, CVD, CVD medication, and the SF-36 physical component score.

‡ Estimated cognitive decline over 15 years (expressed in standard deviations using the distribution of the first wave of cognitive data in 1997/99) as a function of physical activity.

§ p for difference in decline in the global cognitive score over 15 years by physical activity groups (drawn from a test of interaction between physical activity categories and time since baseline).

# Recommended level corresponds to Moderate-to-Vigorous Physical Activity (MVPA) ≥2.5 hours/week.

**Table G. Association of physical activity in 1997/99 with decline over 15 years (1997/99 to 2012/13) in the FLUENCY z-score.**

	Adjusted for age and sex		Adjusted for socio-demographic and behavioural factors*		Fully adjusted†	
	15-y cognitive decline‡ (95% CI)	p§	15-y cognitive decline‡ (95% CI)	p§	15-y cognitive decline‡ (95% CI)	p§
<b>Total physical activity</b>						
<8 hours/week	-0.55 (-0.59 to -0.52)	Ref	-0.57 (-0.61 to -0.53)	Ref	-0.57 (-0.61 to -0.53)	Ref
8-12 hours/week	-0.59 (-0.63 to -0.56)	0.14	-0.59 (-0.63 to -0.56)	0.44	-0.60 (-0.63 to -0.56)	0.37
≥12 hours/week	-0.58 (-0.61 to -0.55)	0.29	-0.59 (-0.62 to -0.55)	0.60	-0.59 (-0.62 to -0.55)	0.54
<b>Mild physical activity</b>						
<5 hours/week	-0.54 (-0.58 to -0.51)	Ref	-0.56 (-0.60 to -0.52)	Ref	-0.56 (-0.60 to -0.52)	Ref
5-9 hours/week	-0.59 (-0.62 to -0.56)	0.06	-0.59 (-0.63 to -0.56)	0.14	-0.60 (-0.63 to -0.56)	0.14
≥9 hours/week	-0.58 (-0.62 to -0.55)	0.16	-0.59 (-0.63 to -0.56)	0.18	-0.60 (-0.64 to -0.56)	0.15
<b>Moderate-to-vigorous physical activity</b>						
<2 hours/week	-0.57 (-0.60 to -0.54)	Ref	-0.59 (-0.62 to -0.55)	Ref	-0.59 (-0.62 to -0.55)	Ref
2-4 hours/week	-0.58 (-0.62 to -0.54)	0.70	-0.58 (-0.62 to -0.54)	0.97	-0.59 (-0.63 to -0.55)	0.99
≥4 hours/week	-0.58 (-0.62 to -0.55)	0.55	-0.58 (-0.62 to -0.54)	0.85	-0.59 (-0.62 to -0.55)	0.99
<b>Physical activity recommendations#</b>						
MVPA <2.5 hours/week	-0.57 (-0.61 to -0.54)	Ref	-0.59 (-0.62 to -0.56)	Ref	-0.59 (-0.62 to -0.56)	Ref
MVPA ≥2.5 hours/week	-0.58 (-0.61 to -0.55)	0.92	-0.58 (-0.61 to -0.55)	0.61	-0.58 (-0.61 to -0.55)	0.70

\* Adjusted for age, sex, ethnicity, education, occupational position, marital status, smoking status, alcohol consumption, and fruit and vegetable consumption.

† Additionally adjusted for hypertension, diabetes, BMI, GHQ score, CVD, CVD medication, and the SF-36 physical component score.

‡ Estimated cognitive decline over 15 years (expressed in standard deviations using the distribution of the first wave of cognitive data in 1997/99) as a function of physical activity..

§ p for difference in decline in the global cognitive score over 15 years by physical activity groups (drawn from a test of interaction between physical activity categories and time since baseline).

# Recommended level corresponds to Moderate-to-Vigorous Physical Activity (MVPA) ≥2.5 hours/week.

**Table H. Difference in Physical Activity (hours/week) between dementia cases and all others in the years preceding dementia diagnosis**

Year	Total physical activity		Mild physical activity		Moderate-to-vigorous physical activity	
	Difference in hours	<i>p</i>	Difference in hours	<i>p</i>	Difference in hours	<i>p</i>
-28	-0.42	0.54	-0.06	0.91	-0.05	0.86
-27	-0.21	0.71	0.00	1.00	0.03	0.91
-26	-0.02	0.97	0.06	0.87	0.10	0.65
-25	0.15	0.72	0.13	0.69	0.15	0.43
-24	0.30	0.45	0.19	0.52	0.19	0.29
-23	0.42	0.27	0.26	0.38	0.22	0.23
-22	0.52	0.17	0.32	0.28	0.23	0.20
-21	0.60	0.12	0.38	0.20	0.23	0.20
-20	0.66	0.09	0.43	0.15	0.22	0.22
-19	0.69	0.07	0.46	0.12	0.20	0.27
-18	0.69	0.07	0.49	0.10	0.17	0.35
-17	0.67	0.08	0.50	0.09	0.13	0.47
-16	0.63	0.10	0.50	0.09	0.08	0.64
-15	0.55	0.15	0.48	0.11	0.03	0.87
-14	0.45	0.24	0.44	0.15	-0.03	0.86
-13	0.32	0.42	0.37	0.24	-0.10	0.59
-12	0.16	0.69	0.28	0.39	-0.17	0.37
-11	-0.02	0.96	0.17	0.62	-0.24	0.21
-10	-0.24	0.59	0.02	0.95	-0.32	0.11
-9	-0.49	0.29	-0.15	0.68	-0.39	0.05
-8	-0.77	0.10	-0.36	0.35	-0.47	0.03
-7	-1.08	0.03	-0.60	0.13	-0.55	0.01
-6	-1.42	0.004	-0.88	0.03	-0.63	0.004
-5	-1.80	0.0004	-1.20	0.004	-0.70	0.002
-4	-2.21	<0.0001	-1.56	0.0003	-0.78	0.0008
-3	-2.65	<0.0001	-1.97	<0.0001	-0.85	0.0005
-2	-3.13	<0.0001	-2.42	<0.0001	-0.91	0.0007
-1	-3.65	<0.0001	-2.91	<0.0001	-0.98	0.002
0	-4.20	<0.0001	-3.46	<0.0001	-1.03	0.005
<i>P for difference in trajectories</i>		<0.0001	<0.0001		0.001	

Model adjusted for age (age was entered as time scale in the model), sex, ethnicity, education, and time-dependent occupational position, marital status, smoking status, alcohol consumption, and fruit and vegetable consumption.

**Table I. Difference in Physical Activity (hours/week) between dementia cases and controls in the years preceding dementia diagnosis**

Year	Total physical activity		Mild physical activity		Moderate-to-vigorous physical activity	
	Difference in hours	<i>p</i>	Difference in hours	<i>p</i>	Difference in hours	<i>p</i>
-28	-0.31	0.71	-0.70	0.28	-0.10	0.76
-27	-0.26	0.69	-0.61	0.24	-0.03	0.91
-26	-0.20	0.71	-0.50	0.23	0.03	0.91
-25	-0.13	0.79	-0.39	0.29	0.07	0.72
-24	-0.04	0.92	-0.27	0.43	0.11	0.57
-23	0.04	0.92	-0.14	0.66	0.13	0.47
-22	0.13	0.76	-0.02	0.94	0.15	0.43
-21	0.21	0.62	0.09	0.78	0.15	0.42
-20	0.29	0.50	0.20	0.55	0.15	0.44
-19	0.35	0.41	0.30	0.37	0.13	0.48
-18	0.40	0.34	0.38	0.24	0.11	0.56
-17	0.44	0.30	0.45	0.16	0.07	0.69
-16	0.44	0.28	0.50	0.12	0.03	0.86
-15	0.43	0.30	0.52	0.11	-0.02	0.92
-14	0.38	0.37	0.51	0.12	-0.08	0.67
-13	0.30	0.49	0.48	0.16	-0.14	0.45
-12	0.17	0.70	0.41	0.25	-0.22	0.26
-11	0.01	0.98	0.31	0.40	-0.30	0.14
-10	-0.20	0.68	0.17	0.66	-0.38	0.06
-9	-0.46	0.36	-0.01	0.97	-0.48	0.02
-8	-0.77	0.13	-0.24	0.56	-0.58	0.008
-7	-1.14	0.03	-0.52	0.22	-0.68	0.002
-6	-1.57	0.003	-0.85	0.05	-0.79	0.0004
-5	-2.07	0.0001	-1.24	0.005	-0.91	0.0001
-4	-2.63	<0.0001	-1.68	0.0003	-1.03	<0.0001
-3	-3.27	<0.0001	-2.18	<0.0001	-1.15	<0.0001
-2	-3.98	<0.0001	-2.75	<0.0001	-1.29	<0.0001
-1	-4.78	<0.0001	-3.39	<0.0001	-1.42	0.0001
0	-5.66	<0.0001	-4.10	<0.0001	-1.56	0.0003
<i>P for difference in trajectories</i>		<0.0001	<0.0001		0.0001	

Model adjusted for age (age was entered as time scale in the model), sex, ethnicity, education, and time-dependent occupational position, marital status, smoking status, alcohol consumption, and fruit and vegetable consumption.

**Table J. Association between physical activity and risk of dementia with history of CVD.**

Physical activity in 1985-88 (mean FU=26.6y)	N cases/ N total	Adjusted for age and sex		Adjusted for socio-demographic and behavioural factors*		Fully adjusted <sup>†</sup>	
		Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
<b>Total physical activity</b>							
<8 hours	46/4285	1.00	Ref	1.00	Ref	1.00	Ref
8-12 hours	24/2451	0.91 (0.55 to 1.49)	0.70	1.08 (0.65 to 1.79)	0.77	1.15 (0.69 to 1.92)	0.59
≥12 hours	41/2572	1.14 (0.75 to 1.74)	0.55	1.26 (0.81 to 1.94)	0.31	1.28 (0.82 to 2.00)	0.27
<i>Per 1 hour/week</i>	<i>111/10308</i>	<i>1.00 (0.98 to 1.02)</i>	<i>0.95</i>	<i>1.00 (0.98 to 1.02)</i>	<i>0.91</i>	<i>1.00 (0.98 to 1.02)</i>	<i>0.93</i>
<b>Mild physical activity</b>							
<5 hours	43/4266	1.00	Ref	1.00	Ref	1.00	Ref
5-9 hours	35/3211	1.11 (0.71 to 1.73)	0.66	1.33 (0.84 to 2.10)	0.23	1.39 (0.87 to 2.21)	0.17
≥9 hours	33/2831	1.16 (0.73 to 1.84)	0.52	1.16 (0.72 to 1.87)	0.54	1.18 (0.73 to 1.92)	0.50
<i>Per 1 hour/week</i>	<i>111/10308</i>	<i>1.01 (0.99 to 1.03)</i>	<i>0.41</i>	<i>1.00 (0.98 to 1.02)</i>	<i>0.93</i>	<i>1.00 (0.98 to 1.02)</i>	<i>0.88</i>
<b>Moderate-to-vigorous physical activity</b>							
<2 hours	40/3225	1.00	Ref	1.00	Ref	1.00	Ref
2-4 hours	32/3078	0.96 (0.60 to 1.53)	0.85	1.42 (0.87 to 2.32)	0.16	1.39 (0.85 to 2.29)	0.19
≥4 hours	39/4005	0.96 (0.61 to 1.51)	0.85	1.34 (0.84 to 2.14)	0.22	1.35 (0.84 to 2.16)	0.21
<i>Per 1 hour/week</i>	<i>111/10308</i>	<i>1.00 (0.96 to 1.05)</i>	<i>0.97</i>	<i>1.01 (0.97 to 1.05)</i>	<i>0.54</i>	<i>1.01 (0.97 to 1.05)</i>	<i>0.52</i>
<b>Physical activity recommendations<sup>‡</sup></b>							
MVPA <2.5 hours/week	57/4961	1.00	Ref	1.00	Ref	1.00	Ref
MVPA ≥2.5 hours/week	54/5347	1.01 (0.69 to 1.47)	0.97	1.30 (0.88 to 1.92)	0.19	1.32 (0.89 to 1.95)	0.17

\*Adjusted for age, sex, ethnicity, education, occupational position, marital status, smoking status, alcohol consumption, and fruit and vegetable consumption.

<sup>†</sup>Additionally adjusted for hypertension, diabetes, BMI, GHQ score, CVD, and CVD medication.

<sup>‡</sup>Recommended level corresponds to Moderate-to-Vigorous Physical Activity (MVPA) ≥2.5 hours/week.

**Table K. Association between physical activity and risk of dementia without history of CVD.**

Physical activity in 1985-88 (mean FU=26.6y)	N cases/ N total	Adjusted for age and sex		Adjusted for socio-demographic and behavioural factors*		Fully adjusted <sup>†</sup>	
		Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
<b>Total physical activity</b>							
<8 hours	96/4285	1.00	Ref	1.00	Ref	1.00	Ref
8-12 hours	47/2451	0.88 (0.62 to 1.25)	0.47	0.89 (0.63 to 1.27)	0.54	0.90 (0.63 to 1.28)	0.55
≥12 hours	75/2572	0.98 (0.72 to 1.32)	0.88	0.98 (0.72 to 1.33)	0.89	0.97 (0.71 to 1.32)	0.85
<i>Per 1 hour/week</i>	<i>218/10308</i>	<i>0.99 (0.98 to 1.01)</i>	<i>0.39</i>	<i>0.99 (0.98 to 1.01)</i>	<i>0.32</i>	<i>0.99 (0.97 to 1.01)</i>	<i>0.28</i>
<b>Mild physical activity</b>							
<5 hours	88/4266	1.00	Ref	1.00	Ref	1.00	Ref
5-9 hours	73/3211	1.12 (0.82 to 1.53)	0.40	1.14 (0.83 to 1.56)	0.43	1.13 (0.83 to 1.56)	0.44
≥9 hours	57/2831	0.92 (0.66 to 1.29)	0.64	0.91 (0.65 to 1.29)	0.61	0.89 (0.63 to 1.27)	0.53
<i>Per 1 hour/week</i>	<i>218/10308</i>	<i>0.99 (0.98 to 1.01)</i>	<i>0.62</i>	<i>0.99 (0.97 to 1.01)</i>	<i>0.56</i>	<i>0.99 (0.97 to 1.01)</i>	<i>0.50</i>
<b>Moderate-to-vigorous physical activity</b>							
<2 hours	83/3225	1.00	Ref	1.00	Ref	1.00	Ref
2-4 hours	57/3078	0.84 (0.60 to 1.19)	0.33	0.88 (0.62 to 1.25)	0.49	0.87 (0.61 to 1.24)	0.44
≥4 hours	78/4005	0.97 (0.71 to 1.34)	0.86	1.00 (0.72 to 1.38)	0.99	0.99 (0.71 to 1.37)	0.94
<i>Per 1 hour/week</i>	<i>218/10308</i>	<i>0.99 (0.95 to 1.02)</i>	<i>0.46</i>	<i>0.98 (0.95 to 1.02)</i>	<i>0.37</i>	<i>0.98 (0.95 to 1.02)</i>	<i>0.38</i>
<b>Physical activity recommendations<sup>‡</sup></b>							
<b>MVPA &lt;2.5 hours/week</b>	115/4961	1.00	Ref	1.00	Ref	1.00	Ref
<b>MVPA ≥2.5 hours/week</b>	103/5347	0.99 (0.76 to 1.30)	0.96	1.01 (0.77 to 1.33)	0.94	0.99 (0.75 to 1.31)	0.93

\*Adjusted for age, sex, ethnicity, education, occupational position, marital status, smoking status, alcohol consumption, and fruit and vegetable consumption.

<sup>†</sup>Additionally adjusted for hypertension, diabetes, BMI, GHQ score, CVD, and CVD medication.

<sup>‡</sup>Recommended level corresponds to Moderate-to-Vigorous Physical Activity (MVPA) ≥2.5 hours/week.

**Table L. Association between physical activity and dementia: sensitivity analysis on the influence of dementia misclassification\***

<b>Following vs not following physical activity recommendations</b>	<b>Correlation between classification indices</b>	<b>Odds ratio for dementia (95% CI) Adjusted for age and sex</b>
<b>Observed data</b>	NA	1.02 (0.81 to 1.29)
<b>Simulated data: scenario 1</b>	0.8	0.82 (0.10 to 1.92)
<b>Simulated data: scenario 2</b>	0.6	0.83 (0.08 to 2.60)

\*Simulated data were generated assuming sensitivity range between 50% and 80% and specificity range between 97% and 100% with a trapezoidal probability density function. This simulation makes the hypothesis of differential dementia misclassification (i.e. the hypothesis that probability of dementia misclassification depends on physical activity). We simulated two scenarios: first where the correlation between the sensitivity distribution in those following recommendations and the sensitivity distribution in all others was 0.8 and then 0.6 (and similarly for the correlations of the specificity distributions); note that a correlation of 1 corresponds to non-differential misclassification.

Abbreviation: NA, not applicable.