

Supplemental Online Content

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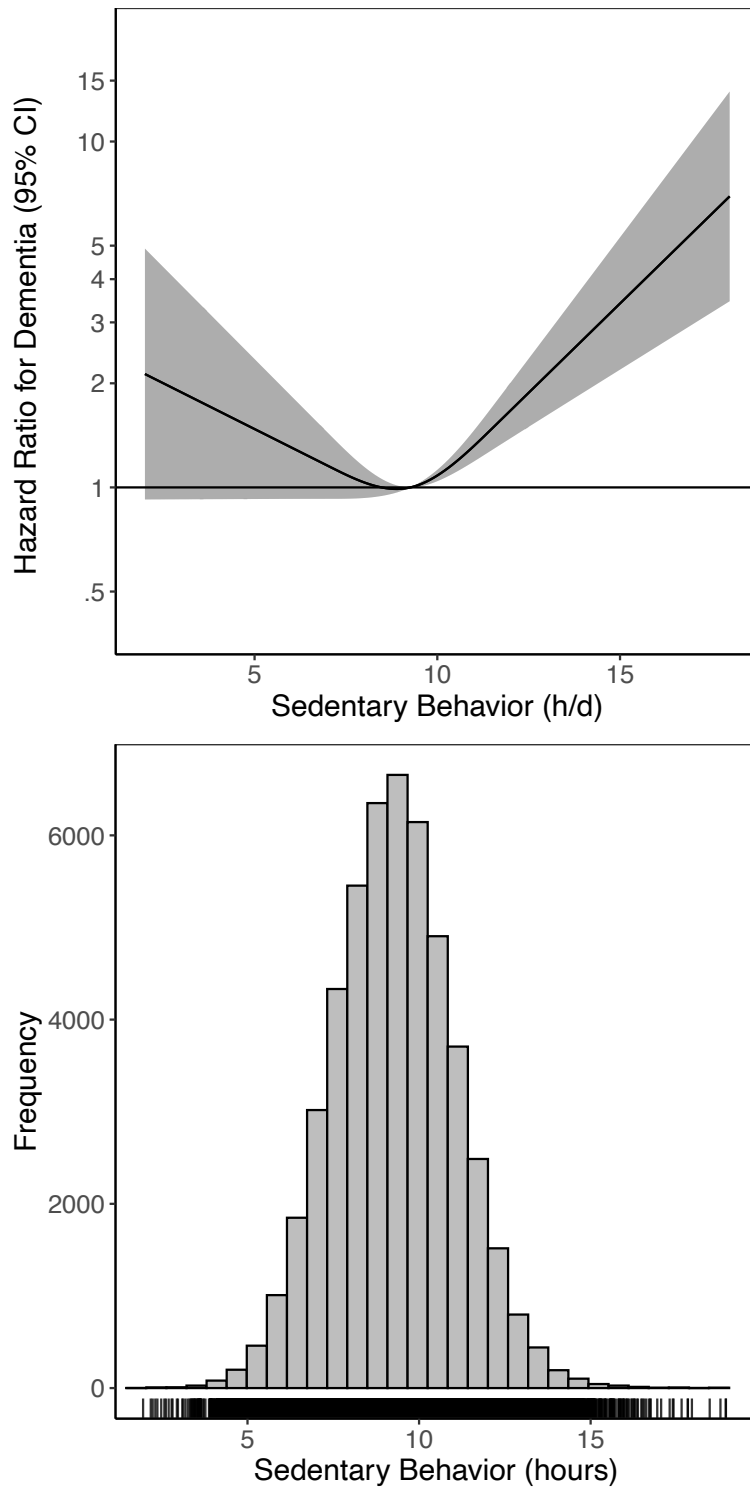
This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

In fully adjusted models, we included the following covariates and provide further description here. Education was coded as having a college or university degree vs. no college or university degree. Socioeconomic status was assessed by the Townsend deprivation index. The index is calculated using four key variables obtained from census data: unemployment rate, non-car ownership, non-home ownership, and household overcrowding. These variables are combined to create a single composite score, which is then standardized to have a mean of zero and a standard deviation of one. Higher scores on the Townsend Deprivation Index indicate higher levels of socioeconomic deprivation, while lower scores represent lower levels of deprivation. Presence of the *APOE* $\epsilon 4$ allele (genetic risk factor for dementia) was determined as present or absent. The study considered ethnicity as a potential confounder when assessing the association between sedentary behavior and the incidence of dementia, and the data were obtained from self-report using a set of sequential branching questions with fixed categories. Ethnicity was scored as white or non-white in models. Chronic conditions were scored as whether or not a physician had diagnosed vascular or heart problems (heart attack, angina, stroke, or high blood pressure), diabetes, or cancer. General health was self-reported as excellent, good, fair, or poor. Smoking status was self-reported as never smoker, former smoker, or current smoker. Alcohol use was determined following from Lourida et al.¹. Using self-reported alcohol consumption, the volume of alcohol consumed was multiplied by the alcohol content (percent) and then divided by 0.6 ounces of alcohol per drink-equivalent. This value was then converted to grams where 1 drink equivalent contained 14g of alcohol. Moderate consumption was considered >0 to ≤ 14 g/day for women and >0 and ≤ 28 g/day for men and we coded alcohol consumption as: never, moderate, or excessive. Body mass index (BMI) was included in fully adjusted models. Depression was based on a self-reported questionnaire ("Over the past two weeks, how often have you felt down, depressed or hopeless?"). Adherence to a healthy diet was calculated following Lourida et al.¹. A healthy diet was considered one that included at least 4 of the following 7 categories: 1) ≥ 3 servings/day of fruit; 2) ≥ 3 servings/day of vegetables; 3) ≥ 2 servings/week of fish; 4) ≤ 1.5 servings/week of unprocessed red meats; 5) ≤ 1 serving/week of processed meats; 6) ≥ 3 servings/day of whole grains; 7) ≤ 1.5 servings/day of refined grains. For sensitivity analyses including sleep, we included self-reported sleep as hours of sleep (self-reported from the question: "About how many hours sleep do you get in every 24 hours? [please include naps]"). We additionally included sleep derived from the machine learning algorithm based on wrist-worn accelerometers in a sensitivity analysis.

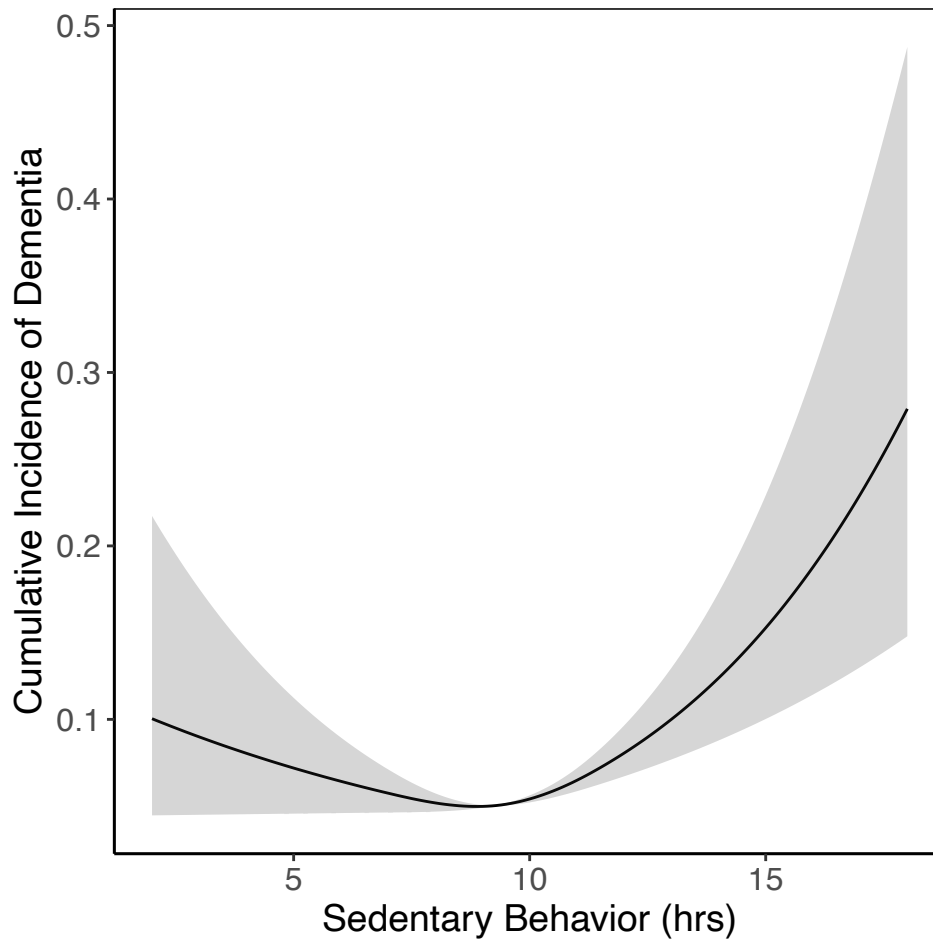
For the non-linear model of average daily sedentary behavior time and risk of dementia, we used the RMS package in R (version 3.6.3). Restricted cubic spline terms were included in the model, and knots were positioned at 7.035, 9.265, 11.553 hrs of SB per day which are the 10th, 50th, and 90th percentiles.

Supplementary figures for sensitivity analyses

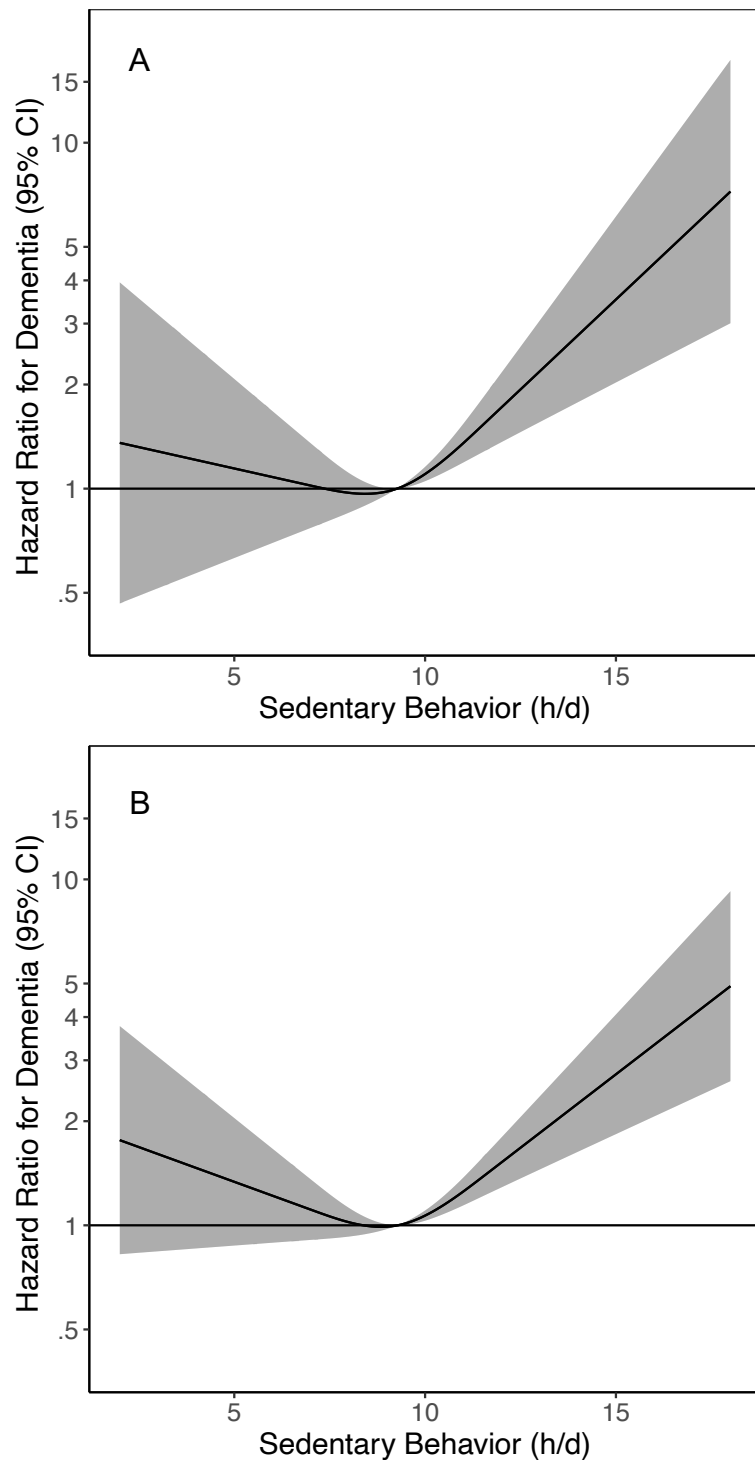


eFigure 1. Associations of sedentary behavior time and incident dementia in the full sample including individuals with average daily sedentary behavior times greater than 18 hours/day. Model shown here is fully adjusted for the following covariates: age, sex, education, townsend

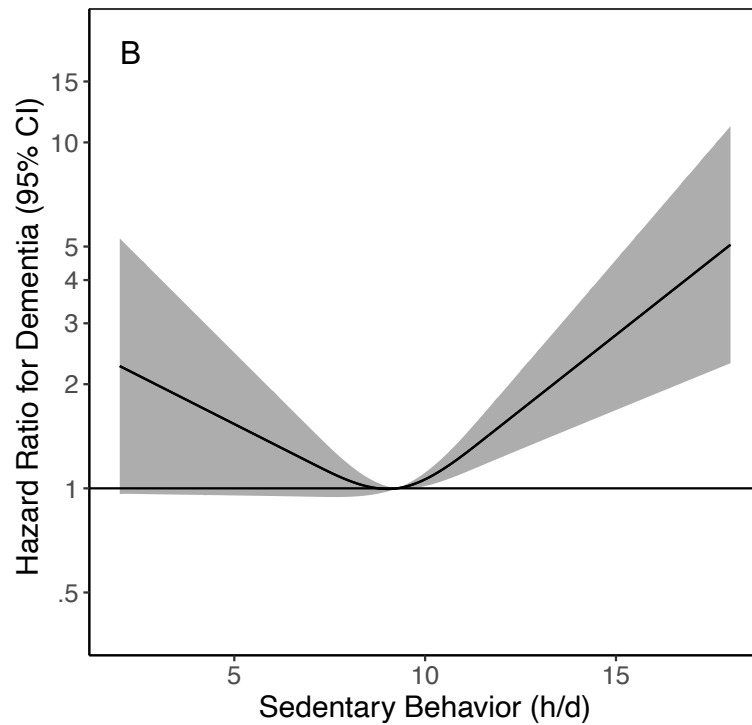
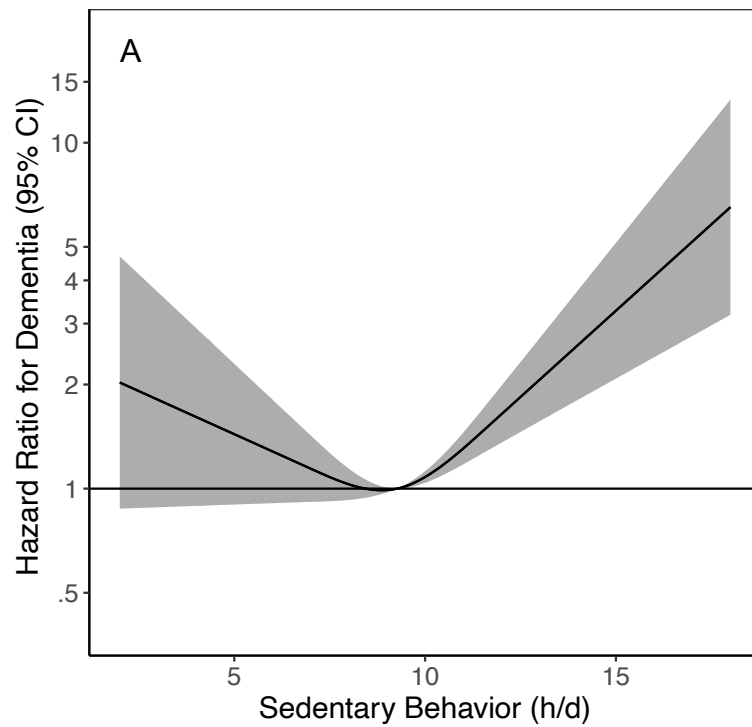
deprivation index, presence of APOE ϵ 4 allele, ethnicity, chronic conditions (heart/vascular disease, diabetes, cancer), self-reported general health, smoking status, alcohol consumption, diet, body mass index, depression, and time spent in moderate-to-vigorous physical activity.



eFigure 2. Cumulative incidence of dementia across mean daily sedentary behavior times (hrs). Model shown here is fully adjusted for the following covariates: age, sex, education, townsend deprivation index, presence of APOE ϵ 4 allele, ethnicity, chronic conditions (heart/vascular disease, diabetes, cancer), self-reported general health, smoking status, alcohol consumption, diet, body mass index, depression, and time spent in moderate-to-vigorous physical activity.

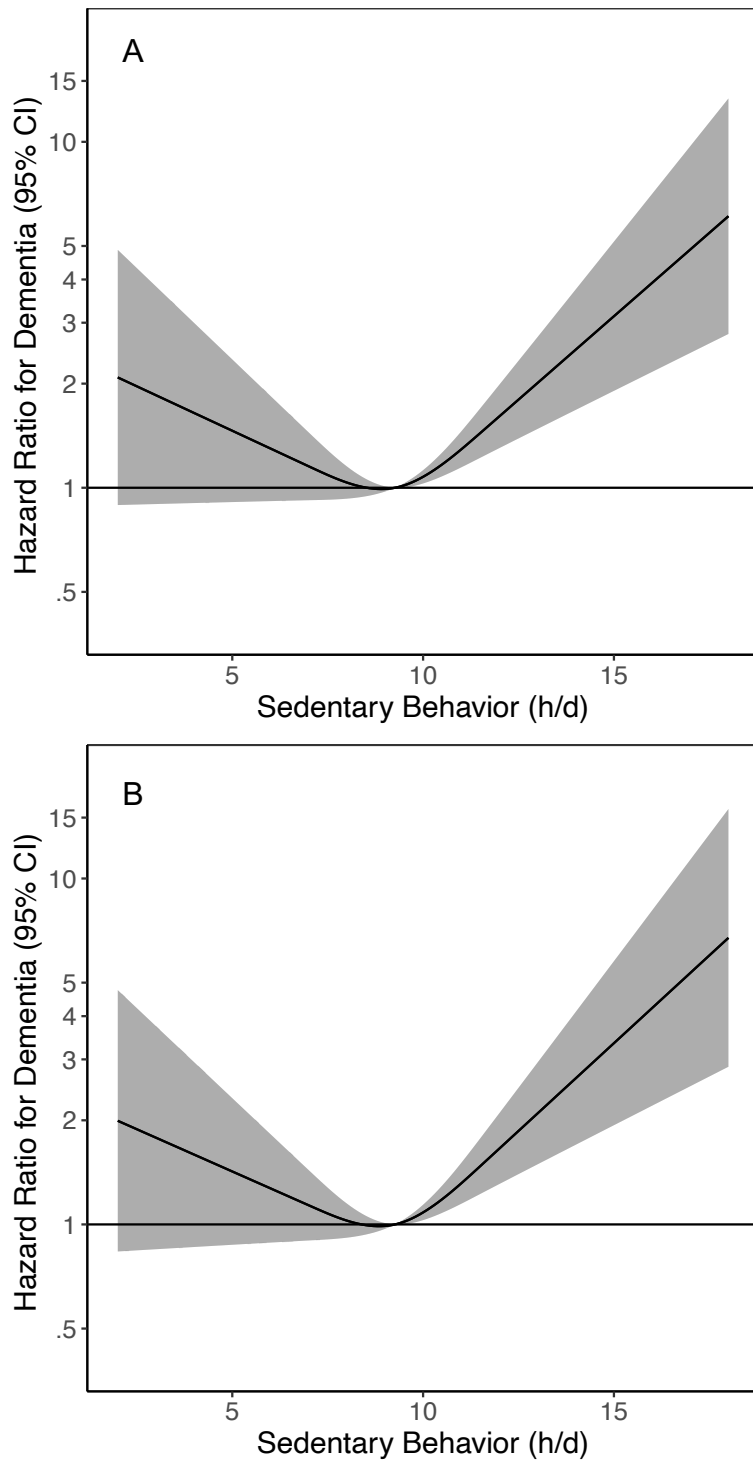


eFigure. 3. Association between sedentary behavior time and incident dementia for landmark analysis moving the start of follow-up to four years after accelerometer wear time (A) and when using imputed data (B). Hazard ratios plotted on logged axes. Models are fully adjusted (see methods for full list of covariates). For landmark analysis where start of follow-up began 4 years after accelerometer wear, (A), there were 47,944 controls and 284 dementia cases. For imputed dataset (B), there were 57,960 controls and 495 dementia cases.



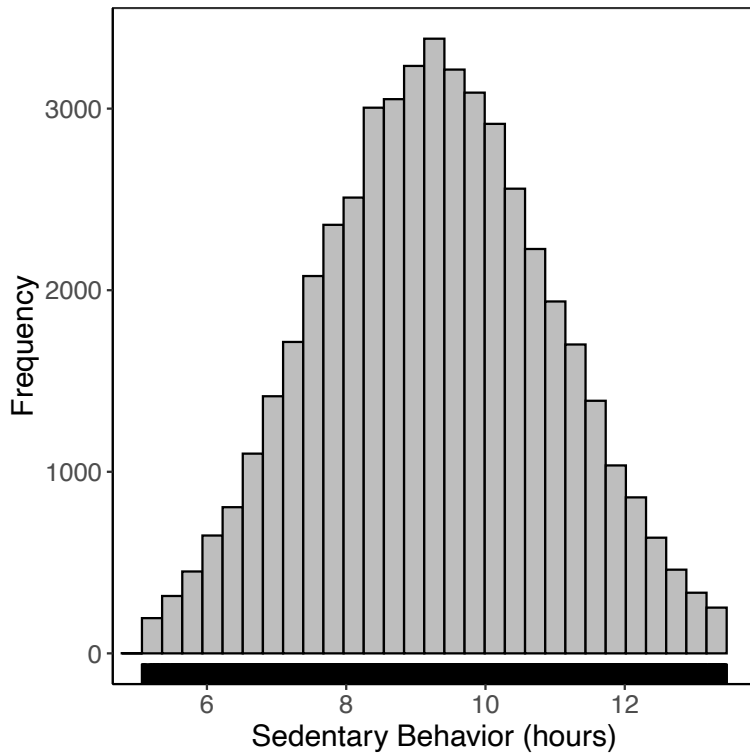
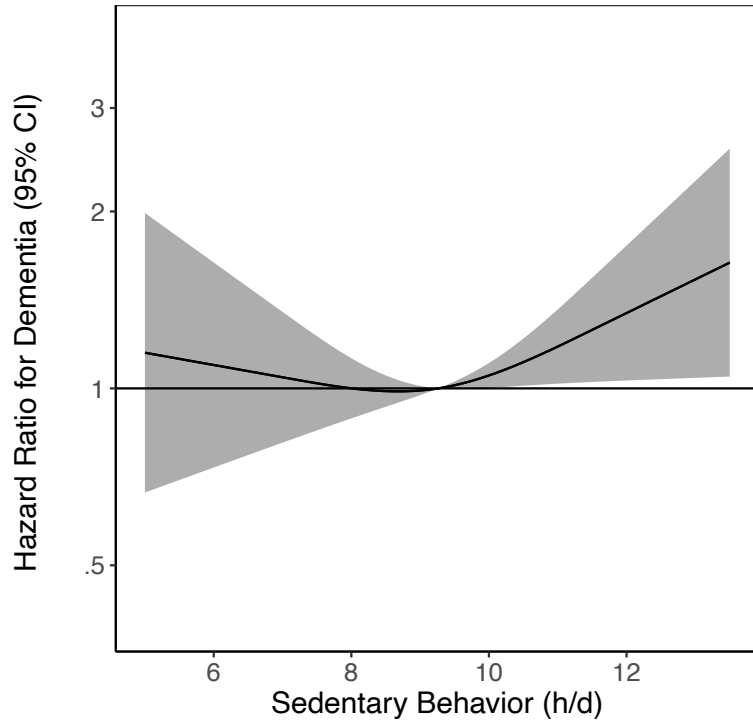
eFigure 4. Association between average daily sedentary behavior time and incident dementia when including additional adjustment for A) self-reported sleep, and B) device measured sleep calculated from the machine learning algorithm. Models shown here are fully adjusted for the following covariates: age, sex, education, Townsend deprivation index, presence of APOE ϵ 4 allele, ethnicity, chronic conditions (heart/vascular disease, diabetes, cancer), self-reported

general health, smoking status, alcohol consumption, diet, body mass index, depression, and time spent in moderate-to-vigorous physical activity.



eFigure 5. Associations of sedentary behavior time and incident dementia when including an additional adjustment for A) mean sedentary bout length (hrs/day) and B) maximum sedentary bout length (hrs/day). Models shown here are fully adjusted for the following additional covariates:

age, sex, education, Townsend deprivation index, presence of APOE ϵ 4 allele, ethnicity, chronic conditions (heart/vascular disease, diabetes, cancer), self-reported general health, smoking status, alcohol consumption, diet, body mass index, depression, and time spent in moderate-to-vigorous physical activity.



eFigure 6. Association between average daily sedentary behavior time and incident dementia excluding extreme values of sedentary behavior using the median absolute deviation method (MAD). In this analysis, there were 48,496 controls and 389 dementia cases. Model shown here is fully adjusted for the following covariates: age, sex, education, Townsend deprivation index, presence of APOE ϵ 4 allele, ethnicity, chronic conditions (heart/vascular disease, diabetes, cancer), self-reported general health, smoking status, alcohol consumption, diet, body mass index, depression, and time spent in moderate-to-vigorous physical activity.

Supplementary tables

eTable 1. ICD 9 and ICD 10 codes used by the UK Biobank for determining all-cause dementia diagnoses

Disease	ICD-9 codes	ICD-10 codes
AD	331.0	F00, F00.0, F00.1, F00.2, F00.9, G30, G30.0, G30.1, G30.8, G30.9
VaD	290.4	F01, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, I67.3
FTD	331.1	F02.0, G31.0
All-Cause dementia	290.2, 290.3, 291.2, 294.1, 331.2, 331.5	A81.0, F02, F02.1, F02.2, F02.3, F02.4, F02.8, F03, F05.1, F10.6, G31.1, G31.8

eTable 2. Cohort characteristics by sedentary behavior quartile

Variables	Q1 (1.96 to < 8.08 hrs/day)	Q2 (8.08 to < 9.27 hrs/day)	Q3 (9.27 to < 10.44 hrs/day)	Q4 (\geq 10.44 hrs/day)
	Median (IQR) or n (%)	Median (IQR) or n (%)	Median (IQR) or n (%)	Median (IQR) or n (%)
Dementia cases	82	82	96	154
Age (years)	67 (63,70)	67 (64,71)	67 (64,70)	67 (64,71)
Female	8096 (65)	7356 (59)	6557 (52.6)	5231 (42)
Male	4365 (35)	5104 (41)	5903 (47.4)	7229 (58)
Education (college or higher)	4585 (36.8)	5023 (40.3)	5484 (44)	5653 (45.4)
Townsend deprivation index	-2.7 (-4,-0.9)	-2.7 (-3.9,-0.8)	-2.7 (-3.9,-0.6)	-2.5 (-3.8,-0.2)
Ethnicity				
<i>white</i>	12224 (98.1)	12258 (98.4)	12251 (98.3)	12251 (98.3)
<i>asian</i>	99 (0.8)	88 (0.7)	77 (0.6)	104 (0.8)
<i>black</i>	43 (0.3)	36 (0.3)	36 (0.3)	26 (0.2)
<i>multiethnic</i>	35 (0.3)	36 (0.3)	36 (0.3)	40 (0.3)
<i>other</i>	60 (0.5)	42 (0.3)	60 (0.5)	39 (0.3)
ApoE status				
1 ϵ 4 allele	3000 (24.1)	2961 (23.8)	2950 (23.7)	2911 (23.4)
2 ϵ 4 alleles	299 (2.4)	257 (2.1)	264 (2.1)	287 (2.3)
BMI (kg/m ²)	25.1 (23,27.6)	25.8 (23.5,28.5)	26.3 (24,29.1)	27.5 (24.9,30.7)
Smoking status				
<i>current</i>	4823 (38.7)	4945 (39.7)	5059 (40.6)	5221 (41.9)
<i>former</i>	571 (4.6)	625 (5)	653 (5.2)	854 (6.9)
<i>never</i>	7067 (56.7)	6890 (55.3)	6748 (54.2)	6385 (51.2)
Alcohol				
<i>excessive</i>	3712 (29.8)	3757 (30.2)	3827 (30.7)	3740 (30)
<i>moderate</i>	5677 (45.6)	5822 (46.7)	5866 (47.1)	5904 (47.4)
<i>never</i>	3072 (24.7)	2881 (23.1)	2767 (22.2)	2816 (22.6)
Any chronic condition (present)	4055 (32.5)	4442 (35.7)	4686 (37.6)	5391 (43.3)
General health				
<i>excellent</i>	2945 (23.6)	2844 (22.8)	2722 (21.8)	2291 (18.4)
<i>good</i>	7801 (62.6)	7840 (62.9)	7840 (62.9)	7720 (62)
<i>fair</i>	1534 (12.3)	1577 (12.7)	1785 (14.3)	2378 (19.1)
<i>poor</i>	181 (1.5)	199 (1.6)	233 (1.9)	425 (3.4)
Depression (yes)	2233 (17.92)	2166 (17.38)	2131 (17.10)	2216 (17.78)
Healthy diet score (yes)	7719 (61.9)	7438 (59.7)	7122 (57.2)	6501 (52.2)
Sedentary Behavior (hrs/day)	7.2 (6.6,7.7)	8.7 (8.4,9)	9.8 (9.5,10.1)	11.3 (10.8,12)
Number of bouts	17.3 (15.2,40.7)	17.8 (15.7,44)	17.8 (15.5,44.3)	17.2 (14.7,41.7)
Mean bout length (hrs/day)	0.4 (0.2,0.5)	0.5 (0.2,0.6)	0.6 (0.2,0.6)	0.7 (0.3,0.8)

Maximum bout length (hrs/day)	1.4 (1.1,1.7)	1.8 (1.4,2.1)	2 (1.6,2.4)	2.5 (2,3)
Moderate to Vigorous Physical Activity (hrs/day)	0.7 (0.4,1.2)	0.6 (0.3,1)	0.5 (0.3,0.9)	0.4 (0.2,0.7)

Note: n=12,461 for quartile 1, and n=12,460 for quartiles 2-4. See notes in for Table 1 for further description of variables.

eTable 3. Associations between sedentary behavior patterns and incident dementia in the full sample including participants with average daily sedentary behavior times greater than 18 hours.

Model	Variable	HR	lower 95	upper 95	p value
Minimally adjusted	Sedentary Bouts per day	1.00	0.99	1.00	0.71
	Mean daily bout length	1.83	1.24	2.69	0.002
	Maximum daily bout length	1.23	1.09	1.39	0.001
	Sitting time quartile 1	1.11	0.82	1.51	0.50
	Sitting time quartile 3	1.14	0.85	1.53	0.38
	Sitting time quartile 4	1.74	1.33	2.28	<0.001
Fully adjusted	Sedentary Bouts per day	1.00	0.99	1.01	0.88
	Mean daily bout length	1.55	1.04	2.29	0.03
	Maximum daily bout length	1.16	1.02	1.31	0.02
	Sitting time quartile 1	1.14	0.83	1.55	0.42
	Sitting time quartile 3	1.09	0.81	1.47	0.57
	Sitting time quartile 4	1.51	1.15	2.00	0.003

eTable 4. Associations between sedentary behavior patterns and incident dementia in landmark analysis.

Model	Variable	HR	lower 95	upper 95	p value
Minimally adjusted	Sedentary Bouts per day	1.00	0.99	1.01	0.69
	Mean daily bout length	1.87	1.17	2.99	0.01
	Maximum daily bout length	1.25	1.08	1.44	0.003
	Sitting time quartile 1	1.10	0.75	1.61	0.62
	Sitting time quartile 3	1.27	0.89	1.81	0.19
	Sitting time quartile 4	1.82	1.31	2.53	<0.001
Fully adjusted	Sedentary Bouts per day	1.00	0.99	1.01	0.86
	Mean daily bout length	1.59	0.99	2.56	0.06
	Maximum daily bout length	1.18	1.02	1.37	0.03
	Sitting time quartile 1	1.12	0.77	1.64	0.56
	Sitting time quartile 3	1.22	0.85	1.74	0.28
	Sitting time quartile 4	1.60	1.14	2.25	0.007

Notes: Results reported for minimally (adjusted for age and sex) and fully adjusted models (see methods for list of covariates) which included 47,944 controls and 284 dementia cases.

eTable 5. Associations between sedentary behavior patterns and incident dementia with further adjustment for sleep

Model	Variable	HR	lower 95	upper 95	p value
Fully adjusted self-report sleep	Sedentary Bouts per day	1.00	0.99	1.01	0.88
	Mean daily bout length	1.53	1.03	2.28	0.03
	Maximum daily bout length	1.16	1.02	1.31	0.02
	Sitting time quartile 1	1.14	0.84	1.55	0.41
	Sitting time quartile 3	1.09	0.81	1.47	0.55
	Sitting time quartile 4	1.52	1.15	2.01	0.003
Fully adjusted device-measured sleep	Sedentary Bouts per day	1.00	0.99	1.01	0.92
	Mean daily bout length	1.38	0.92	2.06	0.12
	Maximum daily bout length	1.11	0.97	1.26	0.12
	Sitting time quartile 1	1.18	0.87	1.61	0.30
	Sitting time quartile 3	1.05	0.78	1.42	0.73
	Sitting time quartile 4	1.37	1.02	1.83	0.04

Note: Results reported for fully adjusted models (see methods for list of covariates)

eTable 6. Dose-response for patterns of average daily sedentary behavior using imputed dataset.

Model	Variable	HR	lower 95	upper 95	p value
Minimally adjusted	Sedentary Bouts per day	1.00	0.99	1.00	0.37
	Mean daily bout length	1.68	1.21	2.33	0.002
	Maximum daily bout length	1.21	1.09	1.35	<0.001
	Sitting time quartile 1	1.03	0.78	1.36	0.83
	Sitting time quartile 3	1.03	0.79	1.36	0.79
	Sitting time quartile 4	1.61	1.27	2.06	<0.001
Fully adjusted	Sedentary Bouts per day	1.00	0.99	1.00	0.64
	Mean daily bout length	1.43	1.01	2.02	0.05
	Maximum daily bout length	1.15	1.03	1.28	0.01
	Sitting time quartile 1	1.05	0.79	1.39	0.73
	Sitting time quartile 3	1	0.76	1.31	0.99
	Sitting time quartile 4	1.44	1.12	1.85	0.005

Notes: For imputed dataset, there were 57,960 controls and 495 dementia cases. Results reported for minimally (adjusted for age and sex) and fully adjusted models (see methods for list of covariates)

eTable 7. Associations between sedentary behavior patterns and incident dementia adjusted for average daily sedentary behavior time

Model	Variable	HR	lower 95	upper 95	p value
Fully adjusted	Sedentary Bouts per day	1.00	0.99	1.01	0.95
	Mean daily bout length	1.15	0.74	1.79	0.53
	Maximum daily bout length	1.02	0.87	1.20	0.83

Note: Results reported for fully adjusted models (see methods for list of covariates)

eTable 8. Associations between SB patterns and incident dementia excluding extreme values of sedentary behavior using MAD method (see methods for further description).

Model	Variable	HR	lower 95	upper 95	p value
Minimally adjusted	Sedentary Bouts per day	1.00	0.99	1.01	0.95
	Mean daily bout length	1.28	0.83	1.97	0.26
	Maximum daily bout length	1.06	0.92	1.23	0.39
	Sitting time quartile 1	1.09	0.80	1.48	0.60
	Sitting time quartile 3	1.14	0.85	1.53	0.38
	Sitting time quartile 4	1.57	1.19	2.08	0.001
Fully adjusted	Sedentary Bouts per day	1.00	0.99	1.01	0.85
	Mean daily bout length	1.15	0.74	1.80	0.54
	Maximum daily bout length	1.02	0.89	1.18	0.75
	Sitting time quartile 1	1.12	0.82	1.53	0.47
	Sitting time quartile 3	1.10	0.82	1.48	0.52
	Sitting time quartile 4	1.42	1.07	1.89	0.02

Note: In this analysis, there were 48,496 controls and 389 dementia cases. Results reported for minimally (adjusted for age and sex) and fully adjusted models (see methods for list of covariates)

eReferences

1. Lourida I, Hannon E, Littlejohns TJ, et al. Association of lifestyle and genetic risk with incidence of dementia. *JAMA*. 2019;322(5):430-437.