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Replacement of sedentary behavior with various physical activities and the risk of all-cause and cause-specific mortality

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Abstract

Background Sedentary behavior (SB) has emerged as a significant health concern that deserves attention. This study aimed to examine the associations between prolonged sedentary behavior and the risk of all-cause and cause-specific mortality as well as to explore desirable alternatives to sitting in terms of physical activity (PA).

Methods Two prospective cohort investigations were conducted using the UK Biobank and NHANES datasets, with a total of 490,659 and 33,534 participants, respectively. Cox proportional hazards regression models were used to estimate the associations between SB and the risk of all-cause and cause-specific mortality due to cancer, cardiovascular disease (CVD), respiratory diseases, and digestive diseases. In addition, we employed isotemporal substitution models to examine the protective effect of replacing sitting with various forms of PA.

Results During the average follow-up times of 13.5 and 6.7 years, 36,109 and 3057 deaths were documented in the UK Biobank and NHANES, respectively. Both cohorts demonstrated that, compared with individuals sitting less than 5 h per day, individuals with longer periods of sitting had higher risks of all-cause and cause-specific mortality due to cancer, CVD, and respiratory diseases but not digestive diseases. Moreover, replacing SB per day with PA, even substituting 30 min of walking for pleasure, reduced the risk of all-cause mortality by 3.5% (hazard ratio [HR] 0.965, 95% confidence interval [CI] 0.954–0.977), whereas cause-specific mortality from cancer, CVD, and respiratory diseases was reduced by 1.6% (HR 0.984, 95% CI 0.968–1.000), 4.4% (HR 0.956, 95% CI 0.930–0.982), and 15.5% (HR 0.845, 95% CI 0.795–0.899), respectively. Furthermore, the protective effects of substitution became more pronounced as the intensity of exercise increased or the alternative duration was extended to 1 h.

Conclusions SB was significantly correlated with substantially increased risks of all-cause mortality and cause-specific mortality from cancer, CVD, and respiratory diseases. However, substituting sitting with various forms of PA, even for short periods involving relatively light and relaxing physical activity, effectively reduced the risk of both overall and cause-specific mortality.

Keywords Sedentary behavior, Physical activity, Mortality, UK Biobank, NHANES

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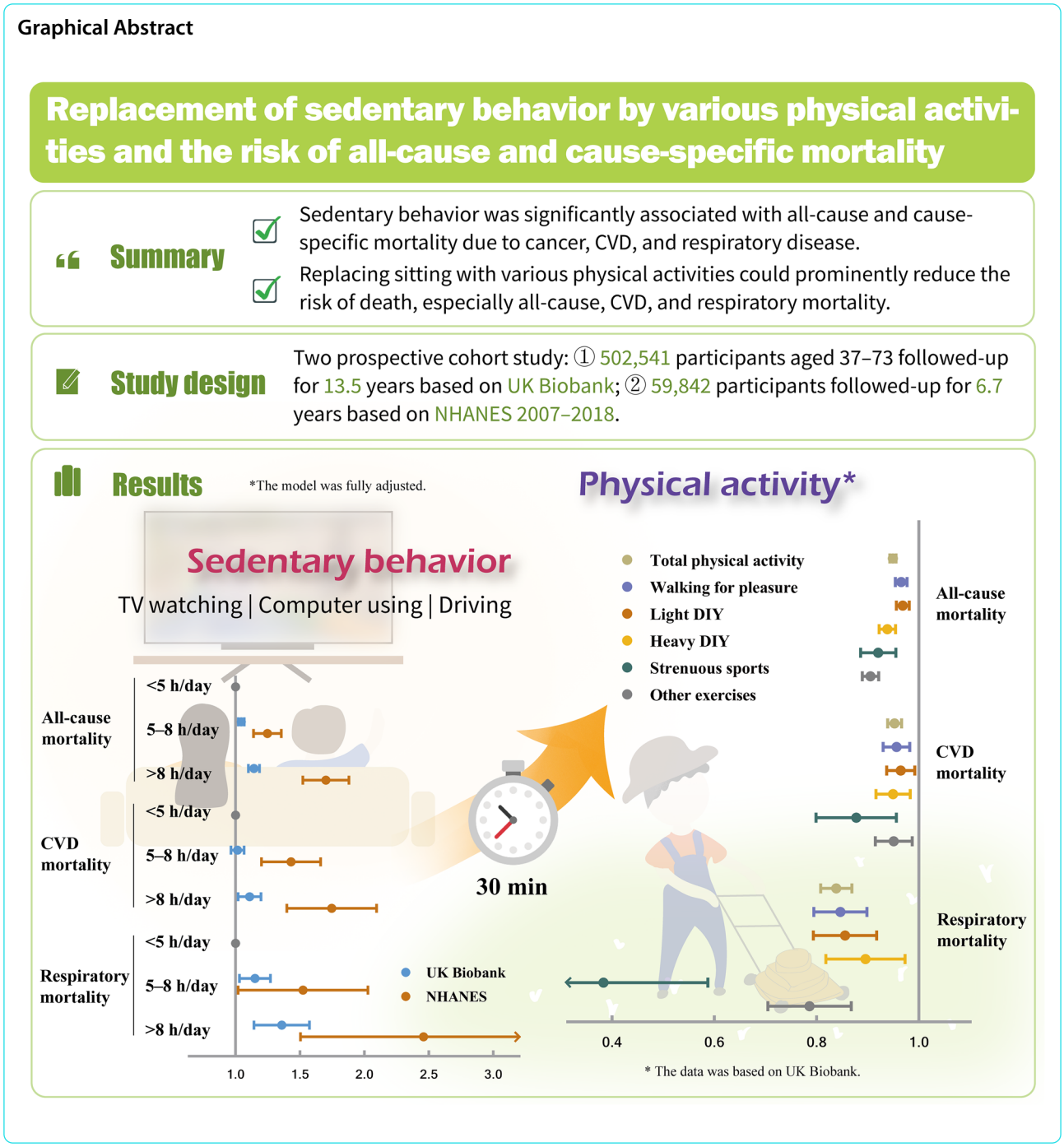
Graphical Abstract



Background

Sedentary behavior (SB) has invasively dominated the lives of contemporary individuals, and the resulting health issues are likewise becoming a growing concern [1]. SB is defined as "any waking behavior characterized by an energy expenditure of 1.5 metabolic equivalents (METs) or lower while sitting, reclining, or lying," according to the World Health Organization 2020 guidelines on physical activity (PA) and SB [2].

The associations between SB and various diseases as well as mortality have been extensively demonstrated in prior researches [3–6]. A meta-analysis incorporating 34 studies with a total of 1,331,468 participants indicated that sitting for more than 6–8 h per day was

associated with an increased risk of all-cause and cardiovascular disease (CVD) mortality [7]. PA has often been shown to partially mitigate this risk. Another meta-analysis, encompassing 8 cohort studies that used accelerometers to assess PA and SB time, revealed that reduced SB time and higher overall activity levels were associated with lower all-cause mortality risk [8]. The Prospective Urban Rural Epidemiology study, involving 167,082 participants from 21 countries, demonstrated that increasing PA levels were correlated with a decreased risk of CVD incidence and mortality associated with prolonged sitting [9]. Nevertheless, given that the daily schedules of individuals consist of sleep, sedentary, and active activities, any increase in one time segment results in a decrease in another. As a result, the isotemporal substitution model (ISM) was introduced as a relatively ideal approach to investigate the effect of replacing one activity with another for an equal duration of time [10].

The use of accelerometers for monitoring PA is more precise; however, it is limited to assessing the intensity and duration of PA. A cohort study conducted by the Toledo Study of Health Ageing revealed that substituting moderate-vigorous physical activity (MVPA) for SB could significantly reduce the incidence of sarcopenia, and the effect became more pronounced as the length of the substitution increased [11]. Moreover, replacing SB with vigorous physical activity (VPA) was also shown to be related to a lower risk of all-cause mortality among individuals with a SB time > 6 h/day in an Australian cohort involving 267,119 individuals during a median follow-up period of 8.9 years [12]. Nevertheless, there is less evidence on which specific types of PA are ideal alternatives to SB in terms of decreasing the risk of all-cause and cause-specific mortality, particularly lighter and more daily activities. Light and heavy do-it-yourself (DIY) activities were only found to reduce the likelihood of developing dementia and its specific mortality [13], as well as the incidence of type 2 diabetes [14], when replacing the same duration of sedentary time.

Therefore, our study explored the relationship between SB and the risk of all-cause and cause-specific mortality on the basis of two prospective cohorts from the UK Biobank and NHANES. Furthermore, the ISM was applied to investigate the appropriate types of PA to replace SB, which has a better protective effect on the risk of all-cause and cause-specific mortality.

Methods

Study design and population

The UK Biobank [15] is the largest repository of genetic and environmental factors related to disease pathogenesis or prevention in the United Kingdom to date (www.ukbiobank.ac.uk/). Invitations were mailed to 9.2 million individuals aged 37 to 73 years who were registered with the National Health Service (NHS) in the UK and resided within a short travel distance of one of 22 dedicated assessment centers (typically approximately 25 miles). Between 2006 and 2010, the UK Biobank recruited 502,000 participants (5.5% of those invited); collected their genetic information, blood samples, lifestyle, and environmental exposure data; and subsequently tracked their health and medical records for several decades. The UK Biobank program was approved by the Northwest Multicenter Research Ethics Committee (16/NW/0274). Informed consent was obtained from all the participants. This study was conducted based on data under application number 90060.

The National Health and Nutrition Examination Survey (NHANES) [16] is an ongoing health and nutritional survey program in the U.S. for adults and children conducted by the National Center for Health Statistics (NCHS) in the United States since 1999 (www.cdc.gov/nchs/nhanes/about_nhanes.htm/). The survey annually reviews a nationally representative sample of approximately 5000 individuals, which are located across counties nationwide. The NHANES interview component covers demographic, socioeconomic, dietary, and health-related questions, and the examination component includes physiological measurements, laboratory tests, etc. The NHANES employs a complex, multistage probability sampling design to select participants representing the civilian, noninstitutionalized U.S. population. Oversampling of certain demographic subgroups is conducted to increase the reliability and precision of health indicator estimates for these specific subgroups. The NHANES data are released biennially, and we utilized survey data from six survey cycles, namely, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018, supplemented by public-use linked mortality files (LMFs) updated to 2019. Because the public-use LMFs do not provide data on respiratory mortality after 2015, we used data from the first four cycles when studying respiratory mortality.

Assessment of SB and PA

The SB time from the UK Biobank was defined as the total time the participants spent watching TV, using a computer, or driving. They were asked how many hours they spent on these activities in a typical day. For participants whose sedentary time varied greatly in the last 4 weeks, they were required to provide the average amount of time. In the NHANES cohort, the SB time was based on the participants' self-assessment [17]; they were asked how much time they usually spent sitting or reclining in a typical day, except for time spent sleeping. The answer

range was limited to 0–24 h, and answers > 18 h required confirmation. We then categorized sedentary time into three levels according to the relevant literature: < 5 h/day, 5–8 h/day, and > 8 h/day [13, 18].

In the UK Biobank, participants reported 5 types of PA: walking for pleasure (not as a means of transport), light DIY (e.g., pruning, watering the lawn), heavy DIY (e.g., weeding, lawn mowing), strenuous sports (defined as inducing sweating and hard breathing), and other exercises (e.g., swimming, cycling). In the NHANES cohort, PA was classified as work activity (defined as paid or unpaid work, household chores, and yard work) and recreational activity, which, according to the degree of increase in breathing or heart rate, was divided into vigorous and moderate activity. Walking or bicycling (for transportation) was also included in the NHANES questionnaire. The participants reported the frequency and average duration of engagement in each activity per week. Using this information, we calculated the average daily duration of each activity.

Assessment of outcomes

The death data for the UK Biobank cohort was obtained from the NHS Information Centre and NHS Central Register. The NHANES linked data was collected from several NCHS population surveys with death certificate records from the National Death Index. The duration of follow-up was determined based on the earliest occurrence among the following endpoints: death, loss to follow-up, or May 25, 2022, for the UK Biobank, and December 31, 2019, for the NHANES. According to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), the following specific causes of death were defined: cancer (C00–D48 for the UK Biobank; C00–C97 for the NHANES), CVD (I00–I79 for the UK Biobank; I00–I09, I11, I13, I20–I51 for the NHANES), respiratory diseases (J09–J18, J40–J47 for both the UK Biobank and the NHANES), and digestive diseases (K20–K93 for the UK Biobank).

Assessment of covariates

For both the UK Biobank and NHANES cohorts, we adjusted for critical covariates as follows: age, sex, race, socioeconomic status, education level, employment status, body mass index (BMI), smoking status, alcohol consumption frequency, dietary habits, overall health rating, and sleep duration. Owing to differences in questionnaire formats, methods of classifying covariates were slightly different between the two cohorts, and the details are shown in Additional file 1: Table S1–S2. In terms of dietary habit covariates, vegetable and fruit intake, and processed meat intake were adjusted for in the UK Biobank cohort, whereas in the NHANES, dietary quality from 24-h dietary recalls was used to determine healthy eating index (HEI) scores [19].

Statistical analysis

According to the sedentary time categories, we conducted descriptive statistics of the population characteristics. For categorical variables, systematic missing values and responses of "do not know" or "prefer not to answer" were consolidated into the "missing" category. Percentages were employed for descriptive purposes, and the chi-square test was used to examine the differences between groups. For continuous variables, absent values were imputed with the median. Variables conforming to a normal distribution were described using the mean and standard deviation (SD), while those deviating from normality were characterized by the median and interquartile range (IQR). The Kruskal–Wallis rank sum test was employed to assess variations between groups.

Our study included two retrospective analyses of longitudinal cohorts from the UK Biobank and NHANES. A Cox proportional hazards model was used to estimate the relationship between SB and the risk of all-cause and cause-specific mortality, with hazard ratios (HRs) and 95% confidence intervals (CIs) used to describe the results. All variables met the proportional hazards assumption via the Schoenfeld residual method (Additional file 1: Fig. S1). Restricted cubic spline models were employed to evaluate potential nonlinear relationships between the daily sedentary time and the risk of all-cause and cause-specific mortality. This analysis excluded individuals whose sedentary time fell outside the 0.5th–99.5th percentile.

On the basis of the assumption that the total daily discretionary time remains unchanged, we subsequently used ISM to estimate the effect of replacing SB with a certain type of PA on mortality. In the UK Biobank cohort, the model was as follows: $h(t) = h_0(t)\ exp\ (\beta_1\ walking\ for\ pleasure + \beta_2\ light\ DIY + \beta_3\ heavy\ DIY + \beta_4\ strenuous\ exercise + \beta_5\ other\ exercises + \beta_6\ total\ discretionary\ time + \beta_7\ covariates)$. For the NHANES cohort, the model was follows: $h(t) = h_0(t)\ exp\ (\beta_1\ walk\ or\ bicycle + \beta_2\ moderate\ work\ activity + \beta_3\ vigorous\ work\ activity + \beta_4\ moderate\ recreational\ activity + \beta_5\ vigorous\ recreational\ activity + \beta_6\ total\ discretionary\ time + \beta_7\ covariates)$. The total discretionary time was the sum of the sedentary time and total PA time. $h(t)$ represents the hazard function of the Cox model, where $h_0(t)$ denotes the baseline hazard. Coefficients β_1 to β_6 represent the effects of different types of PA replacing 30 or 60 min of SB. Furthermore, subgroup analyses in this

study were based on sex, age, BMI, smoking status, and sleep duration.

We also conducted several sensitivity analyses to confirm the reliability of the main findings as follows: (1) excluding death cases within the first 2 years of follow-up, (2) using chained equations with five imputations for critical missing values, and (3) using the Fine–Grey competitive risk model to re-estimate the cause-specific mortality risk. In competing risk models, for cause-specific mortality, competing events refer to deaths from other specified causes, excluding the primary cause under consideration.

The statistical analyses in this study were performed using the R-4.3.0 software (R Foundation for Statistical Computing, Vienna, Austria), IBM SPSS Statistics 26 (IBM Corporation, Armonk, NY, USA), and Stata MP 17 (StataCorp LP, College Station, USA). A two-sided *P* value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the participants

After excluding individuals lacking information on SB, PA, and critical covariates, including sex, age, BMI, smoking status, and sleep duration, a total of 490,659 participants from the UK Biobank cohort and 33,534 individuals from the NHANES cohort were included in the study (Fig. 1). The numbers and percentages censored for various reasons were shown in Additional file 1: Table S3. During the average follow-up of 13.5 and 6.7 years (8.5 years for respiratory mortality), 36,109 and 3057 deaths were recorded in the UK Biobank and NHANES cohorts, respectively. The Kaplan–Meier curves in Additional file 1: Fig. S2 clearly showed that in UK Biobank cohort, the cumulative mortality risk associated with all-cause and four specific causes increased with increasing SB time, and the survival curves did not intersect among the three categories of sedentary time. Distinct

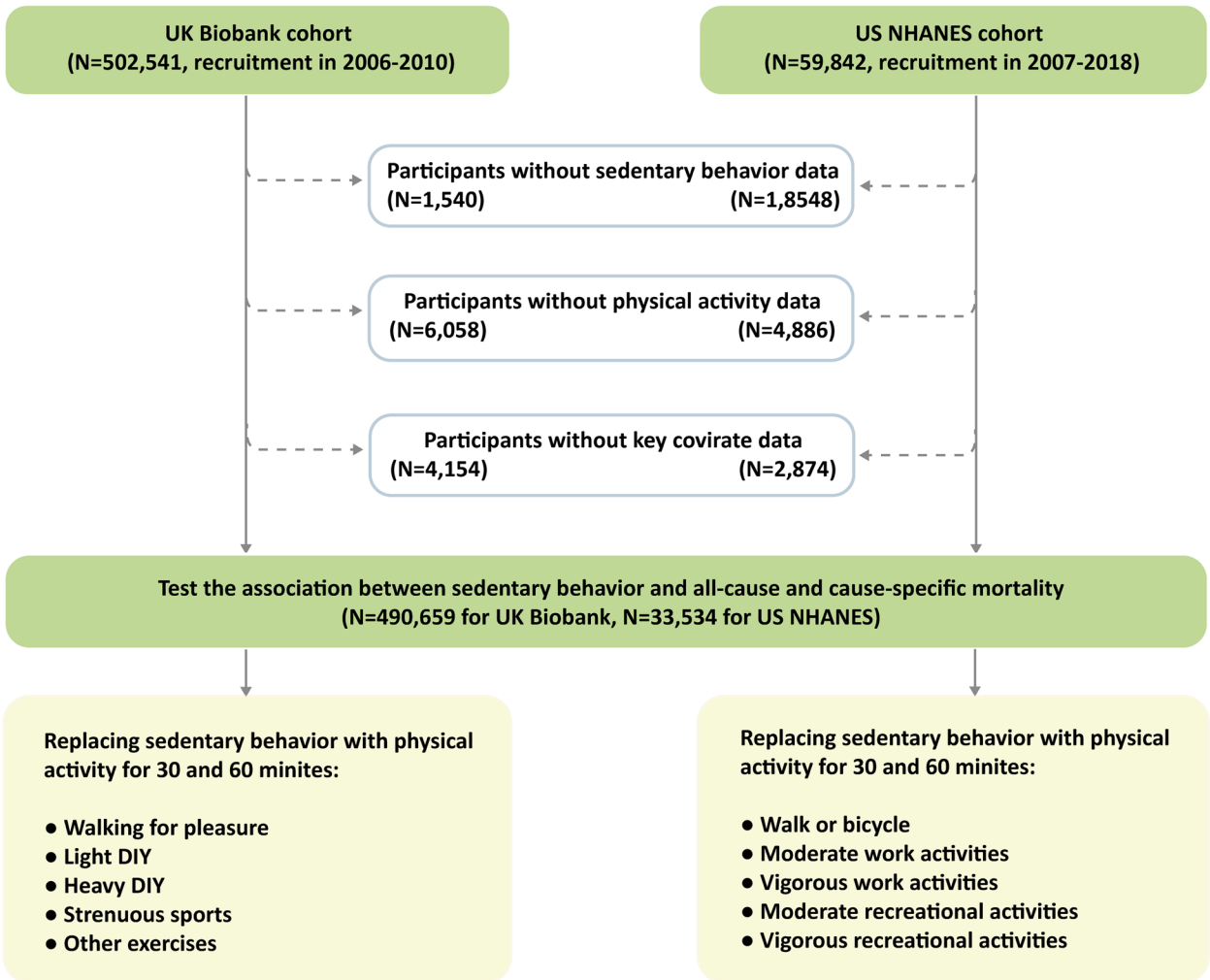


Fig. 1 Flowchart of the participants

demographic characteristics and lifestyle factors were observed across the sedentary categories (Table 1; Additional file 1: Table S4). Individuals with longer sedentary times were more likely to be male, obese, and non-white and to have a reduced likelihood of smoking and drinking alcohol. Nevertheless, discrepancies in population characteristics were observed between the UK Biobank and NHANES cohorts. In the UK Biobank cohort, individuals with prolonged sitting had lower levels of education and lower socioeconomic status, as well as poorer health status, whereas the different distribution was observed in the NHANES cohort.

SB and all-cause and cause-specific mortality

As shown in Fig. 2, sedentary time was linearly or non-linearly positively associated with all-cause mortality and cause-specific mortality. Both the UK Biobank and NHANES cohorts indicated that individuals sitting for more than 8 h per day had a substantially increased risk for all-cause mortality (HR 1.412, 95% CI 1.100–1.186 for the UK Biobank; HR 1.695, 95% CI 1.525–1.883 for the NHANES) compared with those sitting less than 5 h per day. For cause-specific mortality, the greatest detrimental effect was shown by the increase in the risk of respiratory mortality (HR 1.347, 95% CI 1.149–1.579 for the UK Biobank; HR 2.355, 95% CI 1.517–3.468 for the NHANES), followed by the increased risk of CVD mortality (HR 1.106, 95% CI 1.021–1.199 for the UK Biobank; HR 1.723, 95% CI 1.410–2.106 for the NHANES), and the risk of cancer mortality (HR 1.106, 95% CI 1.047–1.167 for the UK Biobank) (Table 2).

Replacement effects of SB with PA

Both cohorts provided evidence that substituting SB with PA yielded a substantially significant decrease in the risk of all-cause and cause-specific mortality (Table 3; Fig. 3). Even replacing SB with 30 min of total PA reduced the risk of all-cause mortality by 5.1% (HR 0.949, 95% CI 0.943–0.955) in the UK Biobank and 5.5% (HR 0.945, 95% CI 0.933–0.957) in the NHANES. In the assessment of cause-specific mortality, the risk reductions associated with replacing SB with 30 min of PA ranged from 6.1 to 29.8% for the UK Biobank cohort and from 5.7 to 24.6% for the NHANES cohort. Furthermore, the aforementioned protective effects were enhanced through an extended replacement duration of 1 h of exercise (Table 3).

In addition, as shown in Table 3 and Fig. 3, different types and intensities of PA may play a role in its effects on mortality from any or specific cause. From the UK Biobank, we identified that even replacing 30 min of SB with walking for pleasure could reduce the risk of all-cause (HR 0.965, 95% CI 0.954–0.977), cancer (HR 0.984, 95% CI 0.968–1.000), CVD (HR 0.956, 95% CI 0.930–0.982), and respiratory disease (HR 0.845, 95% CI 0.795–0.899) mortality. As the activity intensity increased, the effect of substitution increased, particularly for the effect of strenuous sports, which was related to decreased risks of 8%, 12.5%, and 65.3% mortality due to all-cause, CVD, and respiratory diseases, respectively. In the NHANES cohort, substituting 30 min of SB with walking or bicycling also reduced the risks of all-cause (HR 0.935, 95% CI 0.900–0.972) and respiratory disease (HR 0.658, 95% CI 0.470–0.920) mortality. In contrast to the findings of the UK Biobank, the protective effect against mortality did not increase proportionally with the intensity of exercise—it ceased to be statistically significant as the intensity of activity increased to vigorous work activities ($P > 0.05$). Notably, when only recreational activities were considered, an increase in activity intensity corresponded to a heightened protective effect. Similarly, the protective effects were slightly amplified when exercise replacement was prolonged to 1 h.

Subgroup and sensitivity analyses

Subgroup analyses, as shown in Additional file 1: Table S5, demonstrated that the relationships between SB for more than 8 h per day and all-cause mortality were more pronounced among women (HR 1.272, 95% CI 1.186–1.365), individuals with a normal BMI (HR 1.257, 95% CI 1.155–1.367), and participants with a sleep duration of less than 7 h per day (HR 1.221, 95% CI 1.142–1.306). The protective effects of total PA replacement on all-cause mortality were not modified by sex, age, BMI, smoking status, or sleep duration (Additional file 1: Table S6–S7). Nevertheless, there were specific variations in the impacts of different forms of PA on reducing mortality risk. For example, women were found to have a lower risk of all-cause mortality from engaging in daily life activities, whereas men (HR 0.903, 95% CI 0.864–0.944), obese people (HR 0.855, 95% CI 0.777–0.941), and current smokers (HR 0.789, 95% CI 0.697–0.893) derived greater benefits from vigorous sports.

In the sensitivity analyses, our primary findings remained robust after excluding individuals who died within the initial 2 years of follow-up, employing multiple imputations, or utilizing a competitive risk model for estimation (Additional file 1: Table S8–S13).

Discussion

Drawing upon two distinct cohorts from disparate populations, our investigation revealed that increased sedentary time was related to an elevated risk of all-cause mortality and cause-specific mortality due to cancer, CVD, and respiratory diseases. Moreover, substituting

Table 1 Baseline characteristics of the UK Biobank participants according to hours of sedentary behaviour (*n*=490,659)

	Sedentary behaviour (h/day)			*P* value
	<5	5–8	>8	
Number (%)	267,589 (54.5)	185,659 (37.9)	37,411 (7.6)	
Age (years), mean ± SD	56.1 ± 8.1	57.4 ± 8.0	55.3 ± 8.1	<0.001
Sex, N (%)				<0.001
Male	102,726 (38.4)	95,749 (51.6)	25,023 (66.9)	
Female	164,863 (61.6)	89,910 (48.4)	12,388 (33.1)	
Race, N (%)				<0.001
White	253,213 (94.6)	176,136 (94.9)	34,067 (91.1)	
Nonwhite	13,448 (5.0)	8,959 (4.8)	3,912 (8.5)	
Missing	928 (0.3)	564 (0.3)	152 (0.4)	
Townsend deprivation index, median (IQR)	-2.2 (4.1)	-2.2 (4.1)	-1.5 (5.0)	<0.001
Education level, N (%)				<0.001
College or university degree	101,971 (38.1)	48,898 (26.3)	8,875 (23.7)	
Professional qualifications	32,030 (12.0)	19,282 (10.4)	3,503 (9.4)	
A levels/AS levels or equivalent	54,023 (20.2)	41,984 (22.6)	8,099 (21.6)	
O levels/GCSEs or equivalent	39,972 (14.9)	36,060 (19.4)	8,276 (22.1)	
Missing	39,593 (14.8)	39,435 (21.2)	8,658 (23.1)	
Employment status, N (%)				<0.001
Working	162,646 (60.8)	96,325 (51.9)	23,413 (62.6)	
Retired	82,667 (30.9)	71,631 (38.6)	8,979 (24.0)	
Others	19,863 (7.4)	16,059 (8.6)	4,632 (12.4)	
Missing	2,413 (0.9)	1,644 (0.9)	387 (1.0)	
BMI, N (%)				<0.001
Normal (<25.0 kg/m^2)	108,348 (40.5)	47,163 (25.4)	7,052 (18.9)	
Overweight (25.0–29.9 kg/m^2)	109,317 (40.9)	83,631 (45.0)	15,755 (42.1)	
Obese (≥30 kg/m^2)	49,924 (18.7)	54,865 (29.6)	14,604 (39.0)	
Smoking status, N (%)				<0.001
Current smoker	156,898 (58.6)	94,773 (51.0)	17,227 (46.0)	
Never smoker	86,575 (32.4)	69,572 (37.5)	14,078 (37.6)	
Previous smoker	24,116 (9.0)	21,314 (11.5)	6,106 (16.3)	
Ideal drinking, N (%)				<0.001
Yes	211,781 (79.1)	147,947 (79.7)	30,372 (81.2)	
No	55,526 (20.8)	37,543 (20.2)	6,983 (18.7)	
Missing	282 (0.1)	169 (0.1)	56 (0.1)	
Vegetable and fruit intake (serves/day), mean ± SD	8.2 ± 4.7	7.7 ± 4.7	7.4 ± 5.2	<0.001
Processed meat intake, N (%)				<0.001
Never	29,277 (10.9)	13,638 (7.3)	2,620 (7.0)	
Less than once a week	87,261 (32.6)	52,821 (28.5)	9,254 (24.7)	
Once a week	77,711 (29.0)	54,867 (29.6)	10,309 (27.9)	
2–4 times a week	64,093 (24.0)	55,863 (30.1)	12,619 (33.7)	
5–6 times a week	6,888 (2.6)	6,533 (3.5)	1,937 (5.2)	
Once or more daily	1,744 (0.7)	1,654 (0.9)	576 (1.5)	
Missing	615 (0.2)	283 (0.2)	96 (0.3)	
Overall health rating, N (%)				<0.001
Excellent or good	210,471 (78.7)	131,550 (70.9)	22,962 (61.4)	
Fair or poor	55,906 (20.9)	53,328 (28.7)	14,249 (38.1)	
Missing	1,212 (0.5)	781 (0.4)	200 (0.5)	
Sleep duration (hours), mean ± SD	7.8 ± 7.4	7.6 ± 6.3	7.6 ± 6.8	<0.001
Sedentary behaviour (h/day), mean ± SD				<0.001

Table 1 (continued)

	Sedentary behaviour (h/day)			*P* value
	<5	5–8	>8	
Watching TV	1.9 ± 1.0	3.6 ± 1.4	4.6 ± 2.6	
Computer use	0.6 ± 0.6	1.3 ± 1.2	3.4 ± 2.8	
Driving	0.6 ± 0.6	1.1 ± 1.0	2.7 ± 2.9	
Physical activity (min/day), median (IQR)	38.6 (63.2)	30.0 (60.0)	19.3 (51.4)	<0.001
Walking for pleasure	8.6 (25.7)	4.3 (25.7)	2.1 (12.9)	
Light DIY	0.5 (10.7)	0.0 (8.6)	0.0 (4.3)	
Heavy DIY	0.0 (4.3)	0.0 (4.3)	0.0 (2.1)	
Strenuous sports	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	
Other exercises	1.1 (21.4)	0.0 (12.9)	0.0 (8.6)	

Abbreviation:N Numbers, *SD* Standard deviation, *IQR* Interquartile range, *BMI* Body mass index, *DIY* Do-it-yourself

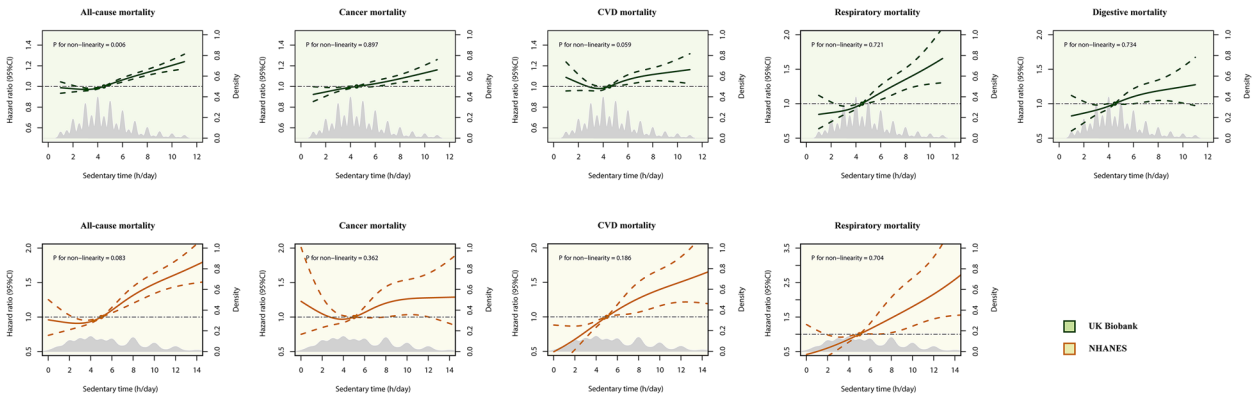


Fig. 2 Associations of the sedentary behavior time with all-cause and cause-specific mortality. The solid line represents the hazard ratio modeled via a restricted cubic spline with 4 knots, and the dashed lines represent the 95% confidence intervals for the hazard ratios. The hazard ratios are adjusted for age, sex, race (white, nonwhite, missing), Townsend deprivation index (continuous), education level (college or university degree, professional qualifications, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, missing), employment status (working, retired, others, missing), BMI (normal, overweight, obese), smoking status (current smoker, never smoker, previous smoker), ideal drinking (yes, no, missing), vegetable and fruit intake (continuous), processed meat intake (never, less than once a week, once a week, 2–4 times a week, 5–6 times a week, once or more daily, missing), overall health rating (excellent or good, fair or poor, missing), and sleep duration (continuous). In the NHANES cohort, the model was adjusted for age, sex, race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other race), income level (< $25 k, $25 k to < $75 k, ≥ $75 k, missing), education level (less than high school, high school, college or above, missing), employment status (working, unemployed, missing), BMI (normal, overweight, obese), smoking status (current or previous smoker, never smoker), alcohol consumption frequency (more than once a week, more than once a month, less than once a month, never, missing), healthy diet (quartiles), overall health rating (excellent or good, fair or poor, missing), and sleep duration (continuous)

sedentary time with equal amounts of time engaging in PA, even a short period of light and daily life activities, could reduce the risk of all-cause, cancer, CVD, and respiratory disease mortality.

SB has been proven to be associated with an elevated risk of all-cause mortality in previous investigations; however, for cancer and CVD mortality, the findings have been far from consistent. Moreover, the relationship between SB and mortality from respiratory and digestive diseases has been the subject of few studies. According to a meta-analysis of six studies, an extended duration of sedentary time substantially increased the risk of all-cause and CVD mortality after adjusting for physical activity but not for cancer mortality [7]. Furthermore, an additional 5.3-year follow-up prospective cohort study revealed a correlation between increased total sedentary time and a higher risk of cancer mortality [5]. Nevertheless, a longitudinal study conducted

Table 2 Association between sedentary behaviour time and all-cause and cause-specific mortality

Sedentary time (h/day)	UK Biobank[a] (*n*=490,659)		NHANES[b] (*n*=33,407)	
	Events, N (%)	HRs	Events, N (%)	HRs
All-cause mortality				
<5	16,751 (6.3)	Ref.	1,028 (7.5)	Ref.
5–8	15,788 (8.5)	1.044 (1.021, 1.068)	1,334 (10.1)	1.244 (1.141, 1.357)
>8	3,570 (9.5)	1.142 (1.100, 1.186)	695 (10.7)	1.695 (1.525, 1.883)
P for trend		<0.001		<0.001
Per 1 SD increase		1.040 (1.029, 1.051)		1.246 (1.199, 1.294)
Cancer mortality				
<5	8,925 (3.3)	Ref.	274 (2.0)	Ref.
5–8	7,846 (4.2)	1.034 (1.002, 1.066)	330 (2.5)	1.072 (0.904, 1.271)
>8	1,633 (4.4)	1.106 (1.047, 1.167)	141 (2.2)	1.216 (0.977, 1.513)
P for trend		0.001		0.215
Per 1 SD increase		1.032 (1.017, 1.048)		1.087 (1.003, 1.179)
CVD mortality				
<5	3,136 (1.2)	Ref.	273 (2.0)	Ref.
5–8	3,204 (1.7)	1.014 (0.964, 1.066)	424 (3.2)	1.418 (1.207, 1.667)
>8	800 (2.1)	1.106 (1.021, 1.199)	196 (3.0)	1.723 (1.410, 2.106)
P for trend		0.045		<0.001
Per 1 SD increase		1.028 (1.005, 1.052)		1.305 (1.216, 1.400)
Respiratory mortality				
<5	693 (0.3)	Ref.	64 (0.5)	Ref.
5–8	792 (0.4)	1.146 (1.033, 1.273)	93 (0.7)	1.468 (1.050, 2.053)
>8	214 (0.6)	1.347 (1.149, 1.579)	53 (0.8)	2.335 (1.571, 3.468)
P for trend		0.001		<0.001
Per 1 SD increase		1.101 (1.056, 1.148)		1.414 (1.233, 1.622)
Digestive mortality				
<5	604 (0.2)	Ref.		
5–8	625 (0.3)	1.055 (0.940, 1.183)		
>8	156 (0.4)	1.081 (0.901, 1.297)		
P for trend		0.570		
Per 1 SD increase		1.045 (0.995, 1.097)		

[a] The model was adjusted for age, sex, race (white, nonwhite, missing), Townsend deprivation index (continuous), education level (college or university degree, professional qualifications, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, missing), employment status (working, retired, others, missing), BMI (normal, overweight, obese), smoking status (current smoker, never smoker, previous smoker), ideal drinking (yes, no, missing), vegetable and fruit intake (continuous), processed meat intake (never, less than once a week, once a week, 2–4 times a week, 5–6 times a week, once or more daily, missing), overall health rating (excellent or good, fair or poor, missing), and sleep duration (continuous).

[b] The model was adjusted for age, sex, race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other race), income level (<$25k, $25k to <$75k, ≥$75k, missing), education level (less than high school, high school, college or above, missing), employment status (working, unemployed, missing), BMI (normal, overweight, obese), smoking status (current or previous smoker, never smoker), alcohol consumption frequency (more than once a week, more than once a month, less than once a month, never, missing), healthy diet (quartiles), overall health rating (excellent or good, fair or poor, missing), and sleep duration (continuous).

Abbreviations: *SD* standard deviation, *CVD* cardiovascular disease, *HR* hazard ratio, *BMI* body mass index

in Australia with 149,077 participants revealed no significant correlation between SB and the risk of CVD-related mortality [12]. Our analysis, which was grounded in large datasets from the UK Biobank and NHANES cohorts, strengthened the association between SB and the risk of all-cause mortality identified in the majority of previous studies. More importantly, we provided support for the relationship between SB and the risk of CVD mortality, and we identified the detrimental effect of SB on cancer mortality in the UK Biobank cohort. Notably, our investigation was also the first to examine the positive correlation between SB and mortality resulting from respiratory diseases, but not from digestive diseases.

Many studies have shown that appropriate PA benefits population health [20]. However, previous studies

Table 3 Multivariate HRs of the isotemporal substitution analysis examining the theoretical effects of replacing sedentary time with physical activity for 30 and 60 min on all-cause and cause-specific mortality

UK Biobank[a]	Total physical activity	Walking for pleasure	Light DIY	Heavy DIY	Strenuous sports	Other exercises
All-cause mortality						
30 min	0.949 (0.943, 0.955)	0.965 (0.954, 0.977)	0.968 (0.956, 0.981)	0.938 (0.922, 0.954)	0.920 (0.886, 0.955)	0.905 (0.889, 0.921)
60 min	0.901 (0.889, 0.913)	0.931 (0.909, 0.954)	0.938 (0.914, 0.962)	0.880 (0.851, 0.909)	0.846 (0.785, 0.912)	0.819 (0.790, 0.848)
Cancer mortality						
30 min	0.969 (0.960, 0.978)	0.984 (0.968, 1.000)	0.993 (0.976, 1.010)	0.953 (0.932, 0.975)	0.961 (0.915, 1.008)	0.917 (0.895, 0.940)
60 min	0.939 (0.922, 0.956)	0.968 (0.936, 1.000)	0.986 (0.952, 1.021)	0.909 (0.868, 0.951)	0.923 (0.838, 1.017)	0.841 (0.802, 0.883)
CVD mortality						
30 min	0.952 (0.939, 0.966)	0.956 (0.930, 0.982)	0.964 (0.937, 0.992)	0.949 (0.916, 0.983)	0.875 (0.800, 0.957)	0.950 (0.915, 0.987)
60 min	0.907 (0.882, 0.934)	0.913 (0.865, 0.964)	0.929 (0.877, 0.984)	0.900 (0.839, 0.966)	0.765 (0.640, 0.915)	0.903 (0.836, 0.975)
Respiratory mortality						
30 min	0.838 (0.808, 0.869)	0.845 (0.795, 0.899)	0.854 (0.794, 0.918)	0.893 (0.819, 0.974)	0.347 (0.199, 0.603)	0.783 (0.706, 0.869)
60 min	0.702 (0.652, 0.755)	0.714 (0.632, 0.808)	0.729 (0.630, 0.843)	0.798 (0.671, 0.949)	0.120 (0.040, 0.364)	0.613 (0.498, 0.755)
Digestive mortality						
30 min	0.913 (0.882, 0.946)	0.968 (0.911, 1.029)	0.947 (0.882, 1.016)	0.841 (0.760, 0.930)	0.919 (0.741, 1.141)	0.820 (0.740, 0.910)
60 min	0.834 (0.777, 0.896)	0.937 (0.830, 1.058)	0.897 (0.778, 1.033)	0.707 (0.578, 0.865)	0.845 (0.549, 1.302)	0.673 (0.548, 0.828)
NHANES[b]	Total physical activity	Walking or bicycling	Moderate work activity	Vigorous work activity	Moderate recreational activity	Vigorous recreational activity
All-cause mortality						
30 min	0.945 (0.933, 0.957)	0.935 (0.900, 0.972)	0.953 (0.933, 0.973)	0.977 (0.952, 1.004)	0.833 (0.787, 0.882)	0.806 (0.709, 0.916)
60 min	0.893 (0.871, 0.916)	0.874 (0.810, 0.944)	0.908 (0.871, 0.947)	0.955 (0.906, 1.007)	0.695 (0.620, 0.779)	0.650 (0.503, 0.840)
Cancer mortality						
30 min	0.971 (0.949, 0.993)	0.968 (0.904, 1.037)	0.975 (0.938, 1.014)	0.972 (0.923, 1.024)	0.942 (0.859, 1.034)	0.998 (0.834, 1.193)
60 min	0.943 (0.901, 0.987)	0.937 (0.817, 1.075)	0.951 (0.880, 1.029)	0.945 (0.852, 1.048)	0.888 (0.737, 1.070)	0.996 (0.696, 1.424)
CVD mortality						
30 min	0.932 (0.908, 0.956)	0.933 (0.866, 1.005)	0.947 (0.909, 0.986)	0.954 (0.900, 1.012)	0.852 (0.768, 0.944)	0.576 (0.399, 0.832)
60 min	0.868 (0.825, 0.914)	0.870 (0.750, 1.010)	0.896 (0.826, 0.973)	0.911 (0.809, 1.024)	0.725 (0.590, 0.891)	0.332 (0.159, 0.692)
Respiratory mortality						
30 min	0.868 (0.808, 0.932)	0.658 (0.470, 0.920)	0.954 (0.877, 1.061)	0.914 (0.787, 1.061)	0.469 (0.317, 0.693)	0.744 (0.393, 1.411)
60 min	0.754 (0.653, 0.869)	0.432 (0.221, 0.847)	0.911 (0.770, 1.078)	0.835 (0.619, 1.125)	0.220 (0.100, 0.480)	0.554 (0.154, 1.991)

[a] The model was adjusted for age, sex, race (white, nonwhite, missing), Townsend deprivation index (continuous), education level (college or university degree, professional qualifications, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, missing), employment status (working, retired, others, missing), BMI (normal, overweight, obese), smoking status (current smoker, never smoker, previous smoker), ideal drinking (yes, no, missing), vegetable and fruit intake (continuous), processed meat intake (never, less than once a week, once a week, 2–4 times a week, 5–6 times a week, once or more daily, missing), overall health rating (excellent or good, fair or poor, missing), and sleep duration (continuous)

[b] The model was adjusted for age, sex, race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other race), income level (< $25 k, $25 k to < $75 k, ≥ $75 k, missing), education level (less than high school, high school, college or above), employment status (working, unemployed, missing), BMI (normal, overweight, obese), smoking status (current or previous smoker, never smoker), alcohol consumption frequency (more than once a week, more than once a month, less than once a month, never, missing), healthy diet (quartiles), overall health rating (excellent or good, fair or poor, missing), and sleep duration (continuous)

Abbreviations: *DIY* Do-it-yourself, *HR* Hazard ratio, *CVD* Cardiovascular disease, *BMI* Body mass index

that examined PA primarily utilized classifications based on the activity intensity [21], such as MVPA and VPA, rather than placing emphasis on distinctions according to the activity type. This may result in an overemphasis on the intensity of the exercise and an underestimation of the effects of milder forms of exercise, thereby limiting the individualization of exercise and simplifying the exercise form. To more precisely estimate the protective effect of the substitution of various forms of PA for SB on mortality, we applied ISM analysis. ISM provides a better estimation of the tangible consequences of both prolonged PA time and reduced SB time, in contrast to conventional and classical time models, which neglect to account for the competitive environment [10]. Using this strategy, we found that all forms of PA, even walking for pleasure, substantially decreased the risk of all-cause, CVD, and respiratory disease mortality. Another NHANES study revealed that a greater number of daily steps was significantly associated with lower all-cause mortality, independent of the step intensity [22].

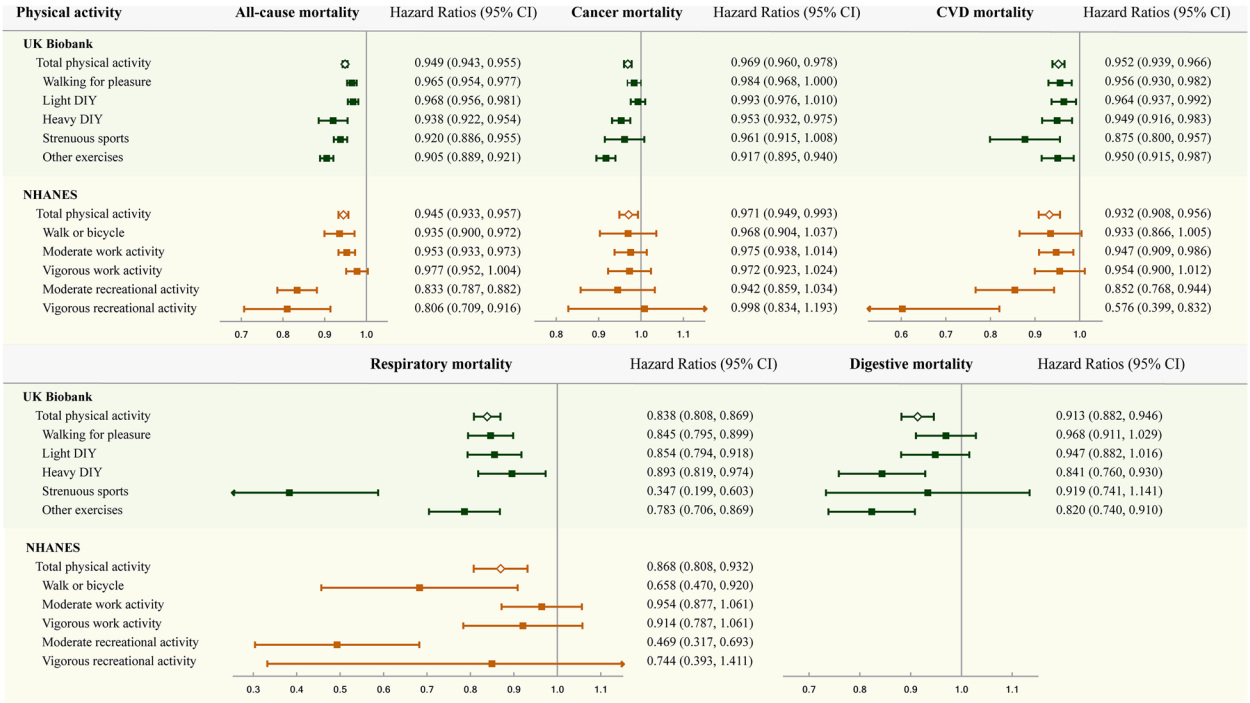


Fig. 3 Thirty minutes/day of sedentary behavior was replaced with different types of physical activity. In the UK Biobank, the model was adjusted for age, sex, race (white, nonwhite, missing), Townsend deprivation index (continuous), education level (college or university degree, professional qualifications, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, missing), employment status (working, retired, others, missing), BMI (normal, overweight, obese), smoking status (current smoker, never smoker, previous smoker), ideal drinking (yes, no, missing), vegetable and fruit intake (continuous), processed meat intake (never, less than once a week, once a week, 2–4 times a week, 5–6 times a week, once or more daily, missing), overall health rating (excellent or good, fair or poor, missing), and sleep duration (continuous). In the NHANES cohort, the model was adjusted for age, sex, race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other race), income level (< $25 k, $25 k to < $75 k, ≥ $75 k, missing), education level (less than high school, high school, college or above, missing), employment status (working, unemployed, missing), BMI (normal, overweight, obese), smoking status (current or previous smoker, never smoker), alcohol consumption frequency (more than once a week, more than once a month, less than once a month, never, missing), healthy diet (quartiles), overall health rating (excellent or good, fair or poor, missing), and sleep duration (continuous). Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index

Furthermore, substituting even 30 min of SB with equal PA time effectively decreased the mortality risk, and the protective effects were slightly amplified when the exercise duration was prolonged to 1 h. Although the effect of light PA during leisure time is not as pronounced as that of vigorous PA, its effect appears to be more beneficial during work activities. Previous studies have also indicated that excessive occupational physical activity does not necessarily confer health benefits to the general public [23, 24]. Although previous studies have demonstrated the mitigating effect of light PA such as household chores, on the risk of mortality [25, 26], we conducted the first validation using large-scale population data and ISM, highlighting the significance of light PA in improving the sedentary lifestyle of populations. In terms of the form of PA during leisure time, engaging in structured exercise facilitates the integration of all body parts and the adjustment of internal tissue structures, allowing each part to perform at its maximum capacity. However, this type of exercise generally demands more time and space, while performing daily life activities is more habitual, less demanding, and easier to persist, especially for individuals with compromised conditions. Therefore, exercise may be individualized according to the patient's physical condition, which could serve to emphasize its benefits more effectively.

In addition, through subgroup analyses, we identified population-specific patterns of both the detrimental effect of SB and the advantageous effects of PA as an alternative to SB on the risk of all-cause mortality. In contrast to men, women presented an increased association between SB and an increased risk of all-cause mortality. Moreover, women demonstrated a more constrained benefit from strenuous sports while exhibiting a comparatively enhanced protective effect from daily life activities. The variations in the duration of SB between sexes, as well as the distinctions in personality traits and occupational factors, might be possible reasons for these

findings. Moreover, strenuous sports may lead to various metabolic disorders, osteoporosis, and injury to the pelvic floor muscle in women [27, 28]. Furthermore, the greater effect of SB on all-cause mortality among the population sleeping < 7 h/day may be partially explained by the hypothesis that SB has been established as a risk factor for sleep disorders [29] and that sleeping < 7 h/day is associated with a greater likelihood of mortality [30]. In addition, individuals who are obese or currently smoke derive greater benefits from strenuous sports, which may be related to an overall reduction in free radical production [31, 32]. In total, our study emphasized that different types of PA were more suitable as alternatives to SB for different populations.

In our analysis, the risk of death from a variety of diseases was increased by SB; however, replacing SB with an equal amount of PA decreased mortality risk, especially the risk of CVD and respiratory disease mortality, which benefited from a wider variety of PA types. Excessive SB can lead to insulin resistance, vascular dysfunction, a shift in substrate use towards carbohydrate oxidation, reduced cardiorespiratory fitness, loss of muscle mass, strength and bone mass, increased blood lipid concentrations, and inflammation [33]. An increasing body of evidence suggests that PA plays a central role in preventing CVD incidence and death at the individual and population levels [34]. The possible mechanism by which PA may exert its effect involves significantly decreasing low-density lipoprotein levels, increasing high-density lipoprotein levels [35], and reducing systolic blood pressure [36]. Previous investigations revealed a correlation between appropriate levels of PA and increased lung function, as well as a decreased risk of acute respiratory infections [37], asthma [38], chronic obstructive pulmonary disease (COPD), and COPD mortality [39]. Nevertheless, exercise training interventions could significantly improve the quality of life of individuals diagnosed with pulmonary cystic fibrosis [40] and COPD [41]. The mechanism might stem from the enhancement of immunity and the regulation of inflammatory reactions [42, 43]. In addition, PA has been shown to have a preventive effect on the development of various cancers, including bladder, breast, colon, endometrial, and gastric cardia [44]. The underlying biological mechanism has not yet been clarified, and potential avenues for future research may include telomere lengthening [45] and antioxidant defense [46]. Replacing SB with PA has been shown to reduce the risk of incident irritable bowel syndrome [18]. Nevertheless, the effects of PA on the gastrointestinal tract are controversial, particularly with respect to strenuous exercise inducing symptoms such as nausea, vomiting, and even gastrointestinal bleeding [47].

Strengths and limitations

To the best of our knowledge, this is the most extensive investigation into the correlation between SB and the risk of all-cause and cause-specific mortality. Simultaneously, we innovatively utilized ISM to examine the relationships between substituting various forms of PA for SB and all-cause and cause-specific mortality. In addition, to validate the results, we analyzed two cohorts of distinct nationalities and ethnic backgrounds via a comparable methodology. Nevertheless, our study has several limitations. First, there was a notable divergence in the number of participants between the two cohorts, a factor that could influence the contrasting results. Second, a questionnaire survey was used to assess the SB and PA time of the participants, which could introduce potential memory bias. Third, because data regarding exposure factors were collected at baseline, any changes that may have occurred during follow-up were not documented. Moreover, although as many covariates as possible have been adjusted, bias caused by residual confounders may still exist. Finally, even though ISM outperforms traditional time models, its substitution effect remains a theoretical construct that requires further validation through randomized controlled studies.

Conclusions

This study revealed that prolonged sedentary time was related to a substantially increased risk of all-cause, cancer, CVD, and respiratory disease mortality. However, substituting sitting with various forms of PA, even for short periods of time involving relatively light and relaxing physical activity, can effectively reduce the risk of both overall and cause-specific mortality; therefore, exercise may be individualized according to the personal physical conditions, which could serve to emphasize its benefits more effectively.

Abbreviations

BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DIY	Do-it-yourself
HEI	Healthy eating index
HR	Hazard ratio
ICD-10	10Th revision of the International Statistical Classification of Diseases and Related Health Problems
IQR	Interquartile range
ISM	Isotemporal substitution model
LMFs	Linked mortality files
METs	Metabolic equivalents
MVPA	Moderate-vigorous physical activity
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
PA	Physical activity
SB	Sedentary behavior
SD	Standard deviation
VPA	Vigorous physical activity

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03599-2.

Additional file 1: Table S1. The resource and definition of the selected covariates. Table S2. Classification methods for categorical covariates. Table S3. Numbers and percentage censored for the various reasons in UK Biobank and NHANES cohort. Table S4. Baseline characteristics of NHANSE participants according to hours of sedentary behaviour. Table S5. The stratified analysis according to sex, age, BMI, smoking status, and sleep duration between sedentary behaviour time and all-cause mortality in a multi-variable adjusted model in UK Biobank.. Table S6. Multivariate HRs of isotemporal substitution analysis examining the theoretical effects of replacing sedentary time with physical activities for 30 min on all-cause mortality stratified by sex, age, BMI, smoking status, sedentary behaviour time and sleep duration in UK Biobank. Table S7. Multivariate HRs of isotemporal substitution analysis examining the theoretical effects of replacing sedentary time with physical activities for 60 min on all-cause mortality stratified by sex, age, BMI, smoking status, sedentary behaviour time and sleep duration in UK Biobank. Table S8. Sensitivity analysis 1: Multivariate HRs of isotemporal substitution analysis examining the theoretical effects of replacing sedentary time with physical activities for 30 and 60 min on all-cause mortality after excluding death cases within the first two years of follow-up. Table S9. Sensitivity analysis 2: Multivariate HRs of isotemporal substitution analysis examining the theoretical effects of replacing sedentary time with physical activities for 30 and 60 min on all-cause mortality after performing multiple imputations for missing covariates. Table S10. Sensitivity analysis 3: Multivariate HRs of isotemporal substitution analysis examining the theoretical effects of replacing sedentary time with physical activities for 30 and 60 min on cause-specific mortality using Fine-Gray competitive risk model. Table S11. Sensitivity analysis 1: Association between sedentary behaviour time and all-cause and cause-specific mortality after excluding death cases within the first two years of follow-up. Table S12. Sensitivity analysis 2: Association between sedentary behaviour time and all-cause and cause-specific mortality after performing multiple imputations for missing covariates. Table S13. Sensitivity analysis 3: Association between sedentary behaviour time and cause-specific mortality using Fine-Gray competitive risk model. Fig. S1. Kaplan-Meier curves for all-cause mortality, cancer mortality, CVD mortality, respiratory mortality, and digestive mortality according to sedentary behaviour time in the UK Biobank. Fig. S2. Schoenfeld residual diagram of main Cox proportional hazards model of UK Biobank cohort

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Authors' contributions
Conceptualisation: YZ 2 and PP; Data curation: YZ 2; Formal analysis: QC and YZ 1; Funding acquisition: YZ 2 and PP; Investigation: ZL and JC; Methodology: JC; Project administration: HL; Resources: YZ 2; Software: FL; Supervision: DL; Validation: JP; Visualisation: JP; Writing-original draft: QC and YZ 1; Writing-review & editing: YZ 2 and JC. QC, YZ 1 and JC are joint first authors. YZ is the study guarantor. All the authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated during the current study are available in the UK Biobank and NHANES repository: https://www.ukbiobank.ac.uk/ and https://www.cdc.gov/nchs/nhanes/about_nhanes.html/.

Declarations

Ethics approval and consent to participate
The study was approved by the Northwest Multicenter Research Ethics Committee (16/NW/0274). Informed consent was obtained from all the participants.

Competing interests
The authors declare no competing interests.

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