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Beyond Universal Guidelines: Sleep-Stratified Isotemporal Substitution of 24-Hour Movement Behaviors and Cardiovascular Risk

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Abstract

Objectives

To investigate whether baseline sleep duration modifies the cardiovascular benefits of reallocating time among sedentary behavior, sleep, and physical activity.

Design

Prospective cohort study.

Method

We analyzed 92,562 UK Biobank adults. Sleep-stratified isotemporal substitution models (short: ≤6 hours, normal: 7–8 hours, long: ≥9 hours) evaluated the theoretical impact of reallocating 30 minutes/day between TV viewing (sedentary surrogate), sleep, and moderate-to-vigorous physical activity (MVPA) on incident major adverse cardiovascular events (MACE).

Results

Over a 13.03-year median follow-up, 6,522 MACE cases occurred. While replacing TV viewing with MVPA generally conferred cardiovascular protection across all groups, sleep-stratified substitutions revealed pronounced heterogeneity. For short sleepers, prioritizing sleep recovery (replacing TV viewing with sleep) optimized risk reduction (Hazard Ratio [HR]: 0.93, 95% CI: 0.90–0.96), whereas modeling the replacement of sleep with MVPA was potentially detrimental (HR: 1.04, 95% CI: 1.01–1.07). For normal sleepers, displacing TV viewing with MVPA remained the primary protective driver. For long sleepers, replacing prolonged sleep with MVPA yielded the greatest theoretical risk reduction (HR: 0.90, 95% CI: 0.87–0.94).

Conclusion

The theoretical cardiovascular efficacy of modifying 24-hour movement behaviors is highly heterogeneous and fundamentally constrained by an individual's baseline sleep duration. These findings challenge the "one-size-fits-all" physical activity guidelines, underscoring the necessity for sleep-stratified, context-specific behavioral prescriptions.

Introduction

Cardiovascular disease (CVD) remains the leading cause of global morbidity and mortality, yet this profound public health burden is not distributed equitably [1]. Socioeconomically disadvantaged populations consistently bear a disproportionately higher risk of cardiovascular events and premature death [2]. Driven by structural barriers, chronic psychosocial stress, and limited healthcare access, these vulnerable groups face immense challenges in maintaining cardiometabolic health. Consequently, identifying accessible, cost-effective, and highly modifiable lifestyle interventions—rather than relying solely on pharmacological management—is an urgent public health imperative for socioeconomically deprived populations [3].

Within the framework of cardiovascular prevention, the epidemiological paradigm has shifted toward the 24-hour movement behavior spectrum, encompassing sleep, sedentary behavior (e.g., television viewing), and moderate-to-vigorous physical activity (MVPA) [4, 5]. Traditional studies have robustly established that insufficient sleep, prolonged sitting, and physical inactivity independently drive cardiovascular risk. However, because the daily time budget is strictly constrained to 24 hours, these behaviors are intrinsically co-dependent; time spent in one domain perfectly displaces time available for another. Traditional analytical approaches often fail to account for this finite compositional nature [6], yielding an incomplete understanding of how real-world behavioral modifications translate into cardiovascular benefits. Isotemporal substitution analysis (ISA) has emerged as a robust statistical framework to overcome this limitation, estimating the theoretical health effects of reallocating a specific duration from one behavior to another while holding total time constant [7].

While previous ISA studies have unequivocally advocated for replacing sedentary time with MVPA to reduce mortality and CVD risk [8], current behavioral guidelines predominantly operate on a precarious "one-size-fits-all" assumption. They implicitly presume that the cardiovascular yield of behavioral reallocation is uniform, rarely considering the modifying effect of an individual's baseline sleep phenotype. This oversight is particularly critical—and potentially detrimental—for socioeconomically disadvantaged individuals. Compared to affluent counterparts, marginalized populations experience significantly higher prevalences of pathological sleep phenotypes, including severe sleep deprivation and prolonged, fragmented sleep [9, 10, 11]. For a chronically sleep-deprived manual worker, reallocating sleep time to exercise might inadvertently exacerbate physiological stress rather than confer cardiovascular protection.

We hypothesize that the cardiovascular benefits of behavioral reallocation are highly heterogeneous and fundamentally dependent on an individual's baseline sleep duration [12]. To address this critical knowledge gap, the present study investigates the dose-response relationships between 24-hour movement behaviors and the incidence of major adverse cardiovascular events (MACE) in a socioeconomically disadvantaged adult cohort (defined by a Townsend Deprivation Index > 0). Furthermore, we utilize sleep-stratified isotemporal substitution models to estimate the precise cardiovascular impacts of reallocating time among sleep, TV viewing, and MVPA across short, normal, and long sleep phenotypes. By dismantling the "one-size-fits-all" approach, this study seeks to provide

actionable, phenotype-tailored evidence to refine cardiovascular prevention guidelines for the most vulnerable populations.

Methods

Study design and participants

This prospective cohort study uses data from the UK Biobank (UKB), a large-scale biomedical database and research resource. The UKB recruited over 500,000 UK adults aged 40–69 years between 2006 and 2010. Detailed lifestyle, environmental, and medical history details were collected at the baseline assessment center visits via touch-screen questionnaires, physical measurements, and biological sampling (described in detail on the study website: https://www.ukbiobank.ac.uk/**).** Follow-up for the occurrence of health outcomes is ongoing through linkage to national health registries.

For the current study, participants were excluded if they had prevalent cardiovascular disease (including myocardial infarction, heart failure, or stroke) or cancer at baseline. We further excluded individuals with missing data on core movement behaviors (sleep duration, TV viewing, and moderate-to-vigorous physical activity [MVPA]) and essential covariates. The final analytical sample comprised 92,562 participants. The detailed sample selection process from the total UKB cohort is displayed in Fig. 1.

Consent statement

All UKB participants provided written informed consent to participate in the study. The UK Biobank has approval from the North West Multi-Centre Research Ethics Committee (REC reference: 11/NW/0382). The present study operates under the approved UKB application. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Measurement of 24-h movement behaviors

Information on 24-hour movement behaviors, including sleep duration, sedentary behavior (surrogated by TV viewing time), and physical activity, was collected at baseline via a validated self-reported touch-screen questionnaire.

Sleep duration: Participants were asked, "About how many hours sleep do you get in every 24 hours? (please include naps)." Based on consensus recommendations and restricted cubic spline analyses, sleep duration was categorized into three distinct phenotypes for stratified analysis: short sleepers (≤ 6 h/day), normal sleepers (7–8 h/day), and long sleepers (≥ 9 h/day).

Sedentary behavior: Daily TV viewing time was used as the primary indicator for domain-specific sedentary behavior, assessed by the question, "In a typical day, how many hours do you spend watching

TV?"

MVPA: Time spent in moderate and vigorous physical activity was calculated based on the frequency (days/week) and duration (minutes/day) of walking, moderate, and vigorous activities, as adapted from the International Physical Activity Questionnaire (IPAQ). The total weekly MVPA volume was calculated in minutes per week. To facilitate the isotemporal substitution modeling, time spent in TV viewing, sleep, and MVPA were all mathematically harmonized into consistent 30-minute (0.5 hour) daily units.

Outcome ascertainment

The primary outcome was incident Major Adverse Cardiovascular Events (MACE), defined as a composite of non-fatal myocardial infarction, non-fatal ischemic stroke, and cardiovascular death. Incident events and mortality dates were ascertained through deterministic linkage to the Hospital Episode Statistics (HES) for England, Scottish Morbidity Record, Patient Episode Database for Wales, and national death registries using the International Classification of Diseases, Tenth Revision (ICD-10) codes. Follow-up time was calculated from the date of the baseline assessment to the date of the first MACE occurrence, death, loss to follow-up, or the end of the current follow-up period, whichever occurred first.

Data analysis

Baseline characteristics of the study population were summarized and stratified by the three sleep duration phenotypes. Categorical variables were presented as frequencies and percentages, and continuous variables as means and standard deviations (SD).

To flexibly model the continuous dose-response relationships of sleep duration, TV viewing time, and MVPA with the risk of MACE, restricted cubic spline (RCS) models with four knots (located at the 5th, 35th, 65th, and 95th percentiles) were constructed. Nonlinearity was evaluated using the Wald test.

Isotemporal substitution modeling We employed an isotemporal substitution framework to estimate the hypothetical effects of reallocating 30 minutes per day from one movement behavior to another. First, a total activity time pool was created by summing the 30-minute units of TV viewing, sleep, and MVPA. We then fitted multivariable Cox proportional hazards models comprising the total activity pool and two of the three behaviors. In this model, the hazard ratio (HR) and 95% confidence interval (CI) associated with each included behavior represent the estimated effect of substituting 30 minutes of the omitted behavior with the respective included behavior, while keeping total time constant. Crucially, recognizing the heterogeneous physiological needs across different sleep patterns, these substitution models were strictly stratified by the three baseline sleep phenotypes (≤ 6 h, 7–8 h, ≥ 9 h).

All models were comprehensively adjusted for age at recruitment, sex, Townsend deprivation index, body mass index (BMI), smoking status, and alcohol frequency.

Sensitivity analyses

To rigorously validate our findings, two sensitivity analyses were conducted. First, considering the long follow-up duration, we performed a competing risk analysis using the Fine-Gray subdistribution hazard model. Non-cardiovascular death (i.e., participants who died before experiencing a MACE) was treated as a competing event to ensure that the primary substitution effects were not upwardly biased by competing mortality. Second, to mitigate the risk of reverse causation (where subclinical disease at baseline might alter movement behaviors and independently predict near-term MACE), we conducted a landmark analysis by excluding participants who experienced a MACE event or died within the first two years of follow-up.

All statistical analyses were performed using R software (version 4.x.x, R Foundation for Statistical Computing). A two-sided *P*-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics of Participants

The participant selection process is detailed in Fig. 1. Among the initial 502,409 adults enrolled in the UK Biobank, we first excluded 357,481 individuals with a baseline Townsend Deprivation Index (TDI) ≤ 0 to strictly focus on the socioeconomically disadvantaged population, leaving 144,928 participants. We subsequently excluded individuals with missing data on core behavioral exposures, including television (TV) viewing time (N = 9,651), sleep duration (N = 1,130), and moderate-to-vigorous physical activity (MVPA) (N = 17,041). To minimize the potential for reverse causality, we further excluded participants with a history of severe pre-existing conditions at baseline, specifically myocardial infarction (N = 3,893), stroke (N = 2,141), heart failure (N = 382), and cancer (N = 16,667). Finally, after excluding those with missing data on essential covariates—such as BMI (N = 994), smoking status (N = 351), and alcohol intake (N = 116)—the final analytical cohort comprised 92,562 socioeconomically disadvantaged adults.

The baseline characteristics of the final cohort, both overall and stratified by sleep duration phenotypes, are summarized in Table 1. The median age of the participants was 55 years (interquartile range [IQR], 48–62 years), and 51.5% (N = 47,684) were female. Participants were categorized into three sleep phenotypes: short sleepers (≤ 6 h/day, N = 26,535), normal sleepers (7–8 h/day, N = 58,620), and long sleepers (≥ 9 h/day, N = 7,407). Significant baseline heterogeneities were observed across the three sleep groups (all $P < 0.001$). Over a median follow-up period of 13.03 years (IQR, 12.24–13.86 years), a total of 6,522 (7.0%) incident MACE occurred.

Compared to normal sleepers, participants reporting short sleep were more likely to be male (51% vs. 48%) and current smokers (20% vs. 15%), and they had a higher median BMI (27.7 vs. 26.9 kg/m²). Conversely, individuals with a long sleep duration were generally older (median age 58 vs. 55 years),

experienced the highest absolute incidence of MACE (9.7%), and engaged in the lowest weekly MVPA volume (median 144 vs. 210 minutes/week) among the three groups (all $P < 0.001$).

Non-linear Dose-Response Associations

Restricted cubic spline (RCS) models revealed significant non-linear relationships for sleep duration and moderate-to-vigorous physical activity (MVPA) with the incidence of MACE (both P for non-linearity < 0.001). As depicted in Fig. 2A, sleep duration exhibited a classic U-shaped association with cardiovascular risk. The nadir of MACE risk (Hazard Ratio [HR] = 1.0) was observed at exactly 7.0 hours per day, with the risk increasing progressively for both shorter and longer sleep durations. This biologically plausible U-shaped dose-response curve robustly validates our rationale for stratifying the subsequent substitution analyses by the three distinct sleep phenotypes.

Regarding waking behaviors, MVPA displayed a pronounced L-shaped protective association (Fig. 2B). The risk of MACE declined steeply with initial increases in physical activity and subsequently reached a nadir at approximately 200 minutes per week, beyond which the protective effect plateaued. This indicates that transitioning from complete inactivity to even moderate volumes of MVPA yields substantial cardiovascular benefits. Conversely, the association between daily TV viewing time and MACE did not demonstrate significant non-linearity (P for non-linearity = 0.117). Instead, it exhibited a dose-dependent, primarily linear detrimental association, where the cardiovascular risk increased steadily with prolonged daily viewing hours, particularly accelerating past the 3.0-hour mark (Fig. 2C).

Table 1
Baseline characteristics of the study population, overall and stratified by sleep duration phenotypes

Characteristic	Overall N = 92,562	Short (≤ 6 h) N = 26,535	Normal (7–8 h) N = 58,620	Long (≥ 9 h) N = 7,407	p-value
Age (years)	55 (48, 62)	55 (48, 61)	55 (47, 62)	58 (49, 64)	< 0.001
Sex, n (%)					< 0.001
Female	47,684 (52%)	13,086 (49%)	30,638 (52%)	3,960 (53%)	
Male	44,878 (48%)	13,449 (51%)	27,982 (48%)	3,447 (47%)	
TDI	2.32 (1.02, 4.08)	2.56 (1.14, 4.39)	2.21 (0.97, 3.91)	2.44 (1.07, 4.35)	< 0.001
BMI (kg/m²)	27.1 (24.3, 30.6)	27.7 (24.7, 31.3)	26.9 (24.1, 30.2)	27.8 (24.7, 31.6)	< 0.001
Smoking Status, n (%)					< 0.001
Never	45,103 (49%)	12,729 (48%)	29,004 (49%)	3,370 (45%)	
Previous	31,670 (34%)	8,557 (32%)	20,539 (35%)	2,574 (35%)	
Current	15,789 (17%)	5,249 (20%)	9,077 (15%)	1,463 (20%)	
Alcohol Intake, n (%)					< 0.001
Never or Rarely	34,903 (38%)	11,100 (42%)	20,603 (35%)	3,200 (43%)	
Weekly	40,671 (44%)	11,036 (42%)	26,775 (46%)	2,860 (39%)	
Daily/Almost daily	16,988 (18%)	4,399 (17%)	11,242 (19%)	1,347 (18%)	
TV Viewing Time (hours/day)	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	3.00 (2.00, 5.00)	< 0.001
Actual Sleep Duration (hours/day)	7.00 (6.00, 8.00)	6.00 (5.00, 6.00)	7.00 (7.00, 8.00)	9.00 (9.00, 10.00)	< 0.001
MVPA (mins/week)	195 (30, 540)	180 (20, 540)	210 (40, 540)	144 (10, 450)	< 0.001
Follow-up Duration (years)	13.03 (12.24, 13.86)	12.99 (12.22, 13.85)	13.05 (12.27, 13.86)	12.97 (12.13, 13.83)	< 0.001

Characteristic	Overall N = 92,562	Short (≤ 6 h) N = 26,535	Normal (7–8 h) N = 58,620	Long (≥ 9 h) N = 7,407	p-value
Incident MACE Events, n (%)					< 0.001
No MACE	86,040 (93%)	24,401 (92%)	54,949 (94%)	6,690 (90%)	
Incident MACE	6,522 (7.0%)	2,134 (8.0%)	3,671 (6.3%)	717 (9.7%)	

Notes: Data are presented as median (interquartile range, Q1-Q3) for continuous variables and as number (percentage) for categorical variables. P-values represent the overall statistical significance of differences across the three sleep duration groups (Short, Normal, and Long sleepers), calculated using the Kruskal-Wallis rank-sum test for non-normally distributed continuous variables and Pearson's Chi-squared test for categorical variables.

Abbreviations: BMI, Body Mass Index; MACE, Major Adverse Cardiovascular Events; MVPA, Moderate-to-Vigorous Physical Activity; TDI,Townsend Deprivation Index; Q1, First Quartile; Q3, Third Quartile; TV, Television.

Isotemporal Substitution Analysis Stratified by Sleep Phenotypes

To explore the theoretical cardiovascular benefits of reallocating time between different daily behaviors, we performed an isotemporal substitution analysis, modeling the effect of replacing 30 minutes per day of one behavior with another across the three distinct sleep phenotypes (Table 2, illustrated as a forest plot in Fig. 3).

A universal finding across all sleep durations was the consistent cardiovascular benefit of replacing sedentary television viewing with MVPA. Reallocating 30 minutes from TV viewing to MVPA yielded a significant reduction in MACE risk across short (HR = 0.97, 95% CI: 0.95–0.98), normal (HR = 0.97, 95% CI: 0.96–0.98), and long sleepers (HR = 0.96, 95% CI: 0.94–0.99). Conversely, replacing MVPA with TV viewing was universally detrimental.

Crucially, our stratification revealed substantial heterogeneity regarding the reallocation of sleep time. For **short sleepers (≤ 6h)**, sleep prioritization emerged as the optimal strategy. Replacing 30 minutes of TV viewing with sleep significantly reduced MACE risk by 7% (HR = 0.93, 95% CI: 0.90–0.96). Notably, sacrificing sleep for exercise was detrimental in this group, as replacing 30 minutes of sleep with MVPA was associated with a 4% increased risk (HR = 1.04, 95% CI: 1.01–1.07).

For **normal sleepers (7-8h)**, substituting sleep with either TV viewing or MVPA yielded no significant changes in cardiovascular risk (all $P > 0.05$). This underscores that for socioeconomically disadvantaged adults with adequate sleep, displacing sedentary time with activity remains the primary driver of cardiovascular health.

In stark contrast, for **long sleepers (≥ 9h)**, reducing sleep duration conferred the greatest protective benefits, regardless of the replacement behavior. Reallocating 30 minutes of sleep to MVPA resulted in a striking 10% reduction in MACE risk (HR = 0.90, 95% CI: 0.87–0.94), the largest benefit observed in any substitution model. Remarkably, even replacing 30 minutes of prolonged sleep with sedentary TV viewing was associated with a 6% risk reduction (HR = 0.94, 95% CI: 0.91–0.97). Conversely, replacing TV viewing with additional sleep in this cohort exacerbated the risk (HR = 1.07, 95% CI: 1.03–1.10), emphatically highlighting the adverse cardiometabolic effects of extended time in bed for this phenotype.

Table 2
Estimated hazard ratios for incident MACE associated with the isotemporal substitution of 30 minutes/day of daily behaviors, stratified by sleep duration phenotypes

		Short Sleepers (≤ 6h)		**Normal Sleepers (7-8h)**		**Long Sleepers (≥ 9h)**	
Group	**Characteristic**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Substituting 30m of TV Viewing with:	→ to MVPA	0.97 (0.95 to 0.98)	**< 0.001**	0.97 (0.96 to 0.98)	**< 0.001**	0.96 (0.94 to 0.99)	**0.012**
	→ to Sleep	0.93 (0.90 to 0.96)	**< 0.001**	0.99 (0.95 to 1.02)	0.40	1.07 (1.03 to 1.10)	**< 0.001**
Substituting 30m of Sleep with:	→ to MVPA	1.04 (1.01 to 1.07)	**0.014**	0.98 (0.95 to 1.02)	0.37	0.90 (0.87 to 0.94)	**< 0.001**
	→ to TV Viewing	1.08 (1.04 to 1.11)	**< 0.001**	1.01 (0.98 to 1.05)	0.40	0.94 (0.91 to 0.97)	**< 0.001**
Substituting 30m of MVPA with:	→ to Sleep	0.96 (0.93 to 0.99)	**0.014**	1.02 (0.98 to 1.05)	0.37	1.11 (1.07 to 1.15)	**< 0.001**
	→ to TV Viewing	1.04 (1.02 to 1.05)	**< 0.001**	1.03 (1.02 to 1.04)	**< 0.001**	1.04 (1.01 to 1.07)	**0.012**

All Cox proportional hazards models were adjusted for age at recruitment, sex, Townsend Deprivation Index, body mass index (BMI), smoking status, and alcohol frequency. In accordance with the isotemporal substitution framework, each model inherently held the total duration of the interacting behaviors constant. A Hazard Ratio (HR) < 1 indicates a protective effect (decreased risk of MACE), whereas an HR > 1 indicates a detrimental effect (increased risk of MACE).

Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; MACE, Major Adverse Cardiovascular Events; MVPA, Moderate-to-Vigorous Physical Activity; TV, Television.

Subgroup Analyses

To investigate potential heterogeneities in the effects of behavioral reallocation, we performed stratified analyses by age (< 60 vs. ≥ 60 years) and sex (male vs. female), calculating interaction *P*-values to assess modifying effects (**Supplementary Tables S1-S2 and Supplementary Figures S1-S2**).

The core protective strategies identified in the main analysis demonstrated remarkable robustness across all subgroups. For instance, prioritizing sleep by replacing 30 minutes of TV viewing with sleep in short sleepers was universally protective regardless of age or sex. Similarly, for long sleepers, the substantial cardiovascular benefit of reducing sleep duration in favor of MVPA remained highly consistent and significant across both age strata and sexes (all $P < 0.05$, without significant interactions).

However, significant modifying effects were observed within specific behavioral substitutions. When stratifying by age, replacing 30 minutes of sleep with MVPA was significantly detrimental for younger short sleepers (< 60 years: HR = 1.04, 95% CI: 1.00-1.09) but lost its harmful effect in the older cohort (*P*-interaction = 0.028). For normal sleepers, replacing sleep with MVPA showed a trend towards cardiovascular protection only in younger adults (*P*-interaction = 0.026).

When stratifying by sex, a consistent pattern emerged regarding the transition from sedentary behavior to physical activity. While replacing 30 minutes of TV viewing with MVPA was protective for both sexes, the magnitude of the cardiovascular benefit was significantly more pronounced in females than in males among both short sleepers (Female HR = 0.94 vs. Male HR = 0.97; *P*-interaction = 0.043) and normal sleepers (Female HR = 0.94 vs. Male HR = 0.98; *P*-interaction = 0.007).

Sensitivity Analyses

To test the robustness of our primary findings, we conducted two sensitivity analyses. First, to minimize potential reverse causality, we excluded participants who developed incident MACE within the first two years of follow-up (Supplementary Table S4). Second, to account for the competing risk of non-cardiovascular death, we repeated the analyses using Fine-Gray proportional subdistribution hazards models (Supplementary Table S3). In both sensitivity analyses, the core findings regarding the sleep-stratified behavioral reallocation strategies remained robust and virtually unchanged, confirming the stability of our main results.

Discussion

In this large-scale prospective cohort study of socioeconomically disadvantaged adults, we comprehensively evaluated the dose-response associations and isotemporal substitution effects of 24-hour movement behaviors on incident MACE. Our findings challenge the conventional "one-size-fits-all" approach to lifestyle recommendations by demonstrating that the cardiovascular associations of modeled behavioral reallocation vary profoundly depending on an individual's baseline sleep phenotype. Specifically, for short sleepers (≤ 6 h), theoretical replacement of sedentary television viewing with sleep was associated with the lowest MACE risk, whereas modeling the replacement of sleep with exercise

yielded a potentially detrimental association. Conversely, for long sleepers (≥ 9 h), lower theoretical risk was observed when sleep duration was modeled to be replaced by MVPA. For individuals with normal sleep duration (7–8 h), the traditional paradigm of replacing sedentary time with MVPA remains the primary driver of cardiovascular health. Furthermore, our subgroup analyses revealed a novel sex-specific pattern, indicating that females derive significantly greater cardiovascular benefits than males when reallocating sedentary TV viewing to MVPA.

Our study significantly advances the current understanding of 24-hour movement behaviors and cardiovascular health. Previous isotemporal substitution studies have largely focused on the universal benefits of replacing sedentary behavior with physical activity [13, 14]. While our findings in normal sleepers align with these established guidelines, applying such uniform recommendations to individuals with abnormal sleep durations may be suboptimal or even harmful. Prior meta-analyses have firmly established a U-shaped association between sleep duration and cardiovascular mortality [15], a non-linear trend robustly replicated in our restricted cubic spline models. However, our study is among the first to translate this epidemiological observation into actionable, sleep-stratified time-reallocation strategies using isotemporal substitution models, particularly within a socioeconomically vulnerable population.

The heterogeneous risk profiles observed in our substitution models may be underpinned by distinct physiological and socio-environmental mechanisms. For socially disadvantaged short sleepers, sleep curtailment is frequently driven by external stressors such as shift work, economic insecurity, or long commuting times, which are fundamental drivers of cardiovascular disparities [16]. In this state of chronic allostatic load and sustained sympathetic activation [17], mathematically imposing an additional physical stressor (MVPA) at the expense of sleep may hypothetically exacerbate systemic inflammation, offsetting the traditional cardiovascular benefits of exercise [18]. Conversely, the cardiovascular harm associated with prolonged sleep (≥ 9 h) is increasingly recognized to be linked with sleep fragmentation, reduced metabolic rate, and underlying low-grade inflammation [19]. By reducing excessive time in bed and replacing it with physical activity, long sleepers effectively disrupt this prolonged state of physical inactivity, simultaneously improving insulin sensitivity, enhancing cardiorespiratory fitness, and mitigating the detrimental effects of excessive sedentary-like resting time [20].

Furthermore, our finding that females exhibit a significantly greater reduction in MACE risk than males when replacing TV viewing with MVPA highlights an important sex dimorphism in cardiovascular exercise physiology. Recent evidence suggests that women may require less volume of MVPA to achieve the same or greater cardiovascular mortality benefits compared to men [21]. This may be attributed to sex-based differences in body fat distribution, varying endocrine responses to moderate-to-vigorous exertion, and differences in baseline types of non-leisure physical activities (such as domestic labor), which may prime the female cardiovascular system to respond more robustly to structured MVPA [21, 22].

These findings carry significant implications for refining public health messaging, particularly for socioeconomically disadvantaged populations facing systemic barriers to health. Rather than prescribing a blanket recommendation to increase MVPA, our theoretical models suggest that cardiovascular prevention strategies should be context-dependent. For sleep-deprived individuals in highly deprived areas, prioritizing sleep recovery and minimizing passive sedentary behaviors (e.g., prolonged TV viewing) may be a more appropriate initial target than aggressively promoting physical activity. These mathematically derived reallocation strategies provide a vital framework that warrants rigorous testing in future multi-component behavioral randomized controlled trials.

The strengths of this study include the large sample size, the specific focus on a highly relevant but understudied socioeconomically disadvantaged population, and the use of robust statistical methodologies, including Fine-Gray competing risk models and lag-time sensitivity analyses to minimize reverse causality. However, several critical limitations must be acknowledged. First, the isotemporal substitution approach mathematically models between-person variance rather than true longitudinal within-person behavioral changes. Consequently, the modeled 'substitutions' represent theoretical population-level shifts, and we cannot definitively conclude that an individual actively changing their behavior will experience the exact magnitude of risk reduction estimated in our models. Second, we utilized TV viewing as a surrogate for total domain-specific sedentary behavior. TV viewing is a highly specific leisure-time behavior heavily confounded by socioeconomic distress, unmeasured dietary habits (e.g., concurrent consumption of ultra-processed foods), and psychological status[23]. Replacing 'TV viewing' in our models may simultaneously capture the cessation of these unmeasured confounding behaviors, potentially overestimating the physiological effect of displacing sedentary time itself. Third, while our cohort was explicitly restricted to socioeconomically disadvantaged adults, our models lacked granular adjustments for occupational physical activity and shift work. In this demographic, employment characteristics frequently dictate both sleep architecture and baseline MVPA, leaving our estimates vulnerable to residual confounding by occupational status, a limitation heavily underscored by the "physical activity paradox," wherein occupational labor confers cardiovascular harm rather than benefit [24]. Finally, relying on self-reported baseline questionnaires introduces potential misclassification; future studies utilizing accelerometer-derived 24-hour compositional data, coupled with clinical screening for obstructive sleep apnea (OSA), are essential to validate these findings.

Conclusion

In conclusion, the theoretical reallocation of 24-hour movement behaviors demonstrates highly heterogeneous associations with cardiovascular risk in socioeconomically disadvantaged adults, contingent upon their baseline sleep phenotypes. These findings highlight the limitations of universal behavioral guidelines and provide an epidemiological rationale for developing context-specific, sleep-stratified health interventions for vulnerable populations.

Abbreviations

MACE Major adverse cardiovascular events

HR Hazard ratio

CI Confidence interval

MVPA Moderate-to-vigorous physical activity

TV Television

BMI Body mass index

RCS Restricted cubic spline

TDI Townsend Deprivation Index

SHR Subdistribution hazard ratio

UKB UK Biobank

OSA Obstructive sleep apnea

CVD Cardiovascular disease

Declarations

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Authors' contributions

Y.W., S.C., and L.Z. conceived and designed the study. S.R., J.Z., and Z.W. were responsible for data curation, harmonization, and preprocessing. Z.L., A.X., and W.Q. conducted statistical analyses and developed the data visualization framework. J.W., T.Z., and Y.H. contributed to validation, results interpretation, and sensitivity analysis. Z.J., L.L., assisted in software implementation, computational modeling, and algorithm optimization. D.L. participated in literature review, data verification, and quality control. L.Z. provided methodological supervision and critical input on study design. L.Z. supervised the overall research process, provided conceptual guidance, and critically revised the manuscript. All authors contributed to drafting and reviewing the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

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Availability of data and materials

The data are available from the UK Biobank (https://biobank.ctsu.ox.ac.uk/), but the use of these data is subject to the UK Biobank's rigorous approval process and therefore they are not publicly available.

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The UK biobank was approved by the Northwest Multicenter Research Ethics Committee (11/NW/0382), and all participants agreed to their inclusion, and signed written informed consent forms.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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Figures

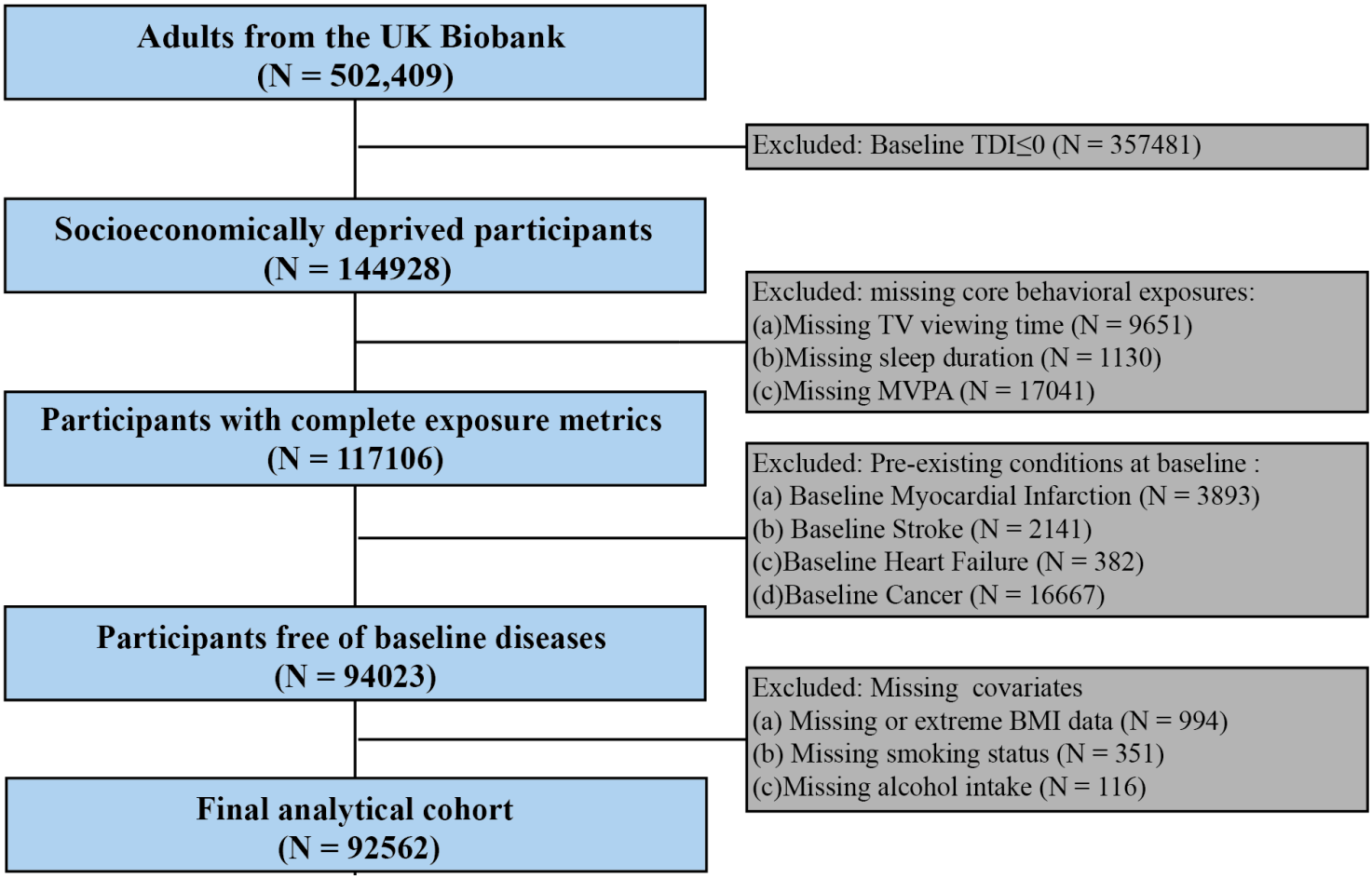


Figure 1

Flowchart of participant selection in the UK Biobank.

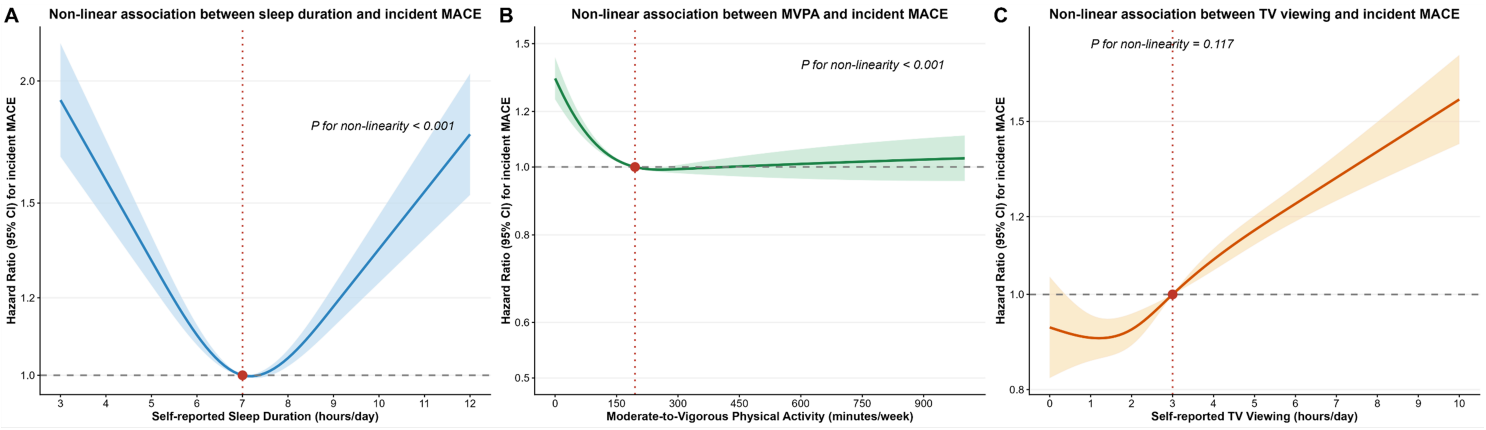


Figure 2

Non-linear dose-response associations between 24-hour movement behaviors and incident MACE. Restricted cubic spline (RCS) curves illustrating the relationships of (A) sleep duration, (B) moderate-to-vigorous physical activity (MVPA), and (C)television (TV) viewing time with incident MACE in socioeconomically disadvantaged adults. Solid lines represent the estimated Hazard Ratios (HRs), and shaded areas indicate 95% confidence intervals (CIs). The horizontal dashed gray lines represent the reference HR of 1.0, with red dots marking the reference nadir points. Significant non-linearity was observed for sleep duration and MVPA (both *P* < 0.001), while TV viewing demonstrated a primarily dose-dependent linear trend (*P* = 0.117). All models were adjusted for age, sex, Townsend Deprivation Index, BMI, smoking status, and alcohol frequency.

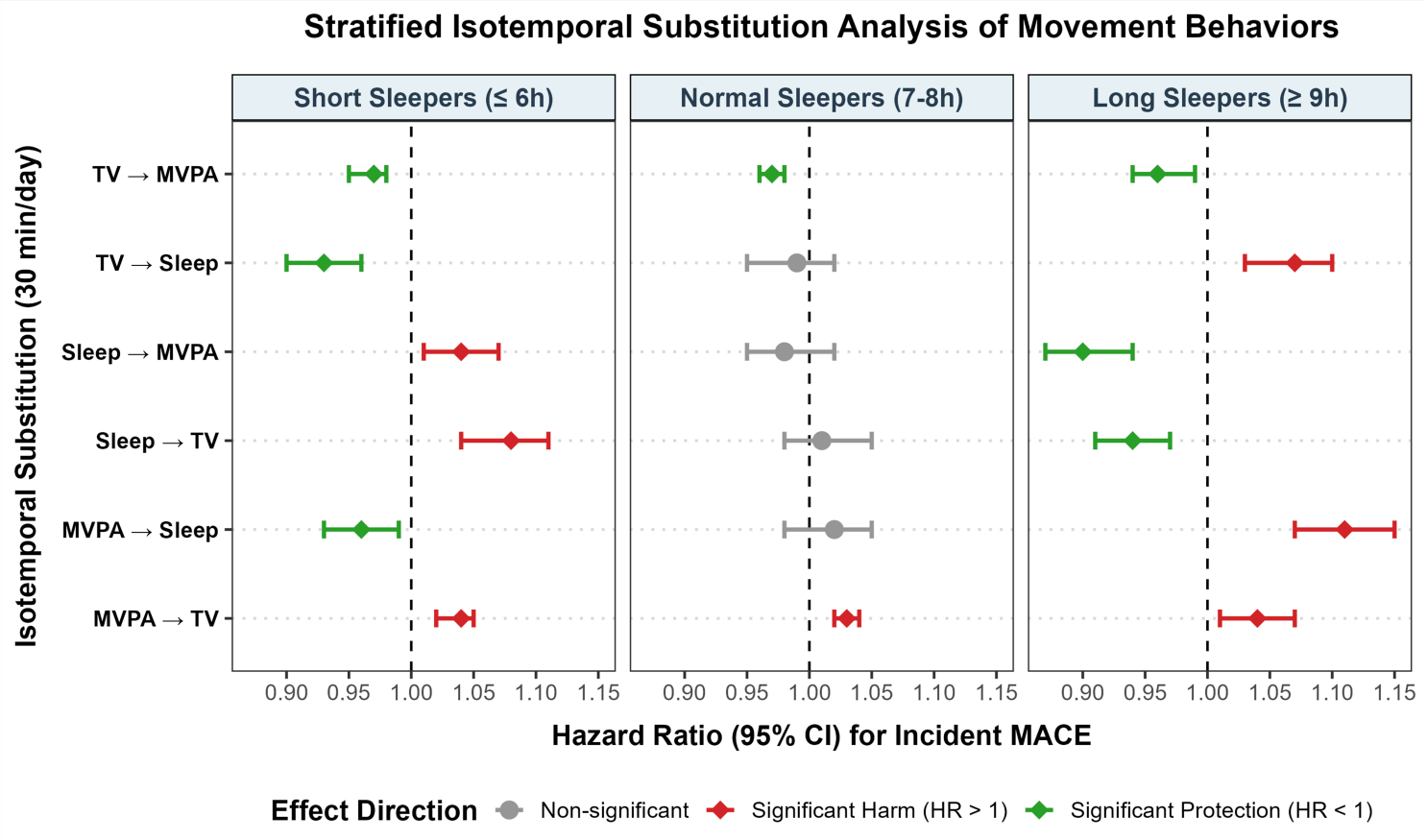


Figure 3

Stratified isotemporal substitution analysis of 24-hour movement behaviors and incident MACE in socioeconomically disadvantaged adults. Forest plot illustrating the estimated Hazard Ratios (HRs) and 95% confidence intervals (CIs) for incident MACE associated with reallocating 30 minutes/day between baseline behaviors. Analyses were stratified by short (≤6 h/day), normal (7-8 h/day), and long (≥9 h/day) sleep phenotypes. Green diamonds indicate significant cardiovascular protection (HR < 1.0), red indicates significant harm (HR > 1.0), and gray denotes non-significant associations. All models were adjusted for age, sex, Townsend Deprivation Index, BMI, smoking status, and alcohol frequency.

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