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FULL RESEARCH PAPER
Cardiovascular disease

Combined variations in sleep, physical activity, and nutrition and the risk of major adverse cardiovascular events

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Aims Sleep, physical activity, and nutrition (SPAN) are major lifestyle behaviours that influence cardiovascular disease risk. We examined the multi-behaviour associations of SPAN with risk of major adverse cardiovascular events (MACE) and its subtypes (myocardial infarction (MI), heart failure (HF), and stroke).

Methods and results This prospective cohort analysis included 53 242 participants from the UK Biobank (median age: 63.0 years; 56.8% male). Wearable-measured sleep (h/day) and moderate to vigorous physical activity (MVPA; min/day) were calculated using a machine learning-based algorithm, and diet was assessed using a 10-item diet quality score (DQS). Major adverse cardiovascular event risk was estimated across 27 joint tertile combinations of SPAN behaviours, and dose–response associations of SPAN with MACE were examined using a composite score (0–100). Synergistic relationships were examined using the relative excess risk due to interaction (RERI), attributable proportion (AP), and the synergy index (S). Over the 8.0-year follow-up, 2034 MACE events occurred, including 932 MI, 584 strokes, and 518 HF events. Compared with the lowest tertile for all SPAN behaviours, the optimal SPAN combination of 8.0–9.4 h/day sleep, 42–104 min/day MVPA, and a DQS of 32.5–50.0 was associated with a 57% lower risk of MACE (HR: 0.43; 95% CI: 0.30, 0.62). A median SPAN score (52.8) was associated with a 41% lower risk of MACE (HR: 0.59; 95% CI: 0.49, 0.70). The median SPAN score corresponded to an HR of 0.53 (0.38, 0.75) for HF, 0.65 (95% CI: 0.50, 0.84) for MI, and 0.52 (95% CI: 0.38, 0.71) for stroke. A minimum combined variation of an additional 11 min/day of sleep, 4.5 min/day MVPA, and 3 DQS points was associated with 10% lower MACE risk (HR: 0.90; 0.88, 0.94). No synergistic interaction was observed between the SPAN behaviours and MACE (RERI = 0.003; 95% CI: −0.03, 0.04; AP = 0.4%; 95% CI: −6 to 7%; S = 1.03; 95% CI: −3.32, 5.29).

Conclusion Modest differences in combined SPAN behaviour levels were associated with meaningful reductions in MACE risk.

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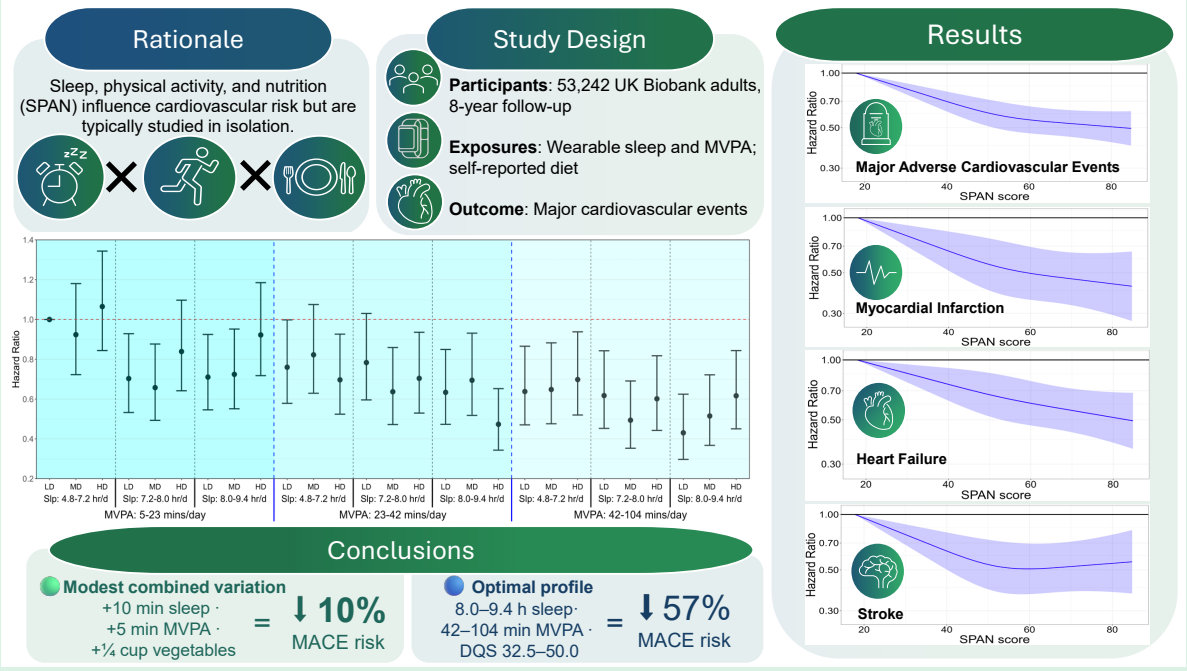
Lay summary

Sleep, physical activity, and nutrition are major lifestyle behaviours that influence cardiovascular disease risk, yet they are often studied in isolation despite their behavioural interdependence in daily life. The minimum combined between-individual variation necessary for clinically meaningful lower cardiovascular risk is also unclear. In this prospective cohort of 53 242 adults, we provide the first investigation examining the multi-behaviour associations of SPAN with risk of MACE, including MI, HF, and stroke. Sleep (h/day) and MVPA (min/day) were estimated using wearable devices and a machine learning-based algorithm. Diet was assessed using a 10-item DQS. Our findings suggest that when SPAN are targeted concurrently, even subtle variations may be associated with significant long-term cardiovascular benefits. Combined behavioural targets may offer substantial cardiovascular health potential while minimizing the burden of change on any single behaviour. This has potential to create opportunities for more feasible and behaviourally sustainable intervention strategies. Our findings should be interpreted cautiously, as they reflect theoretical relationships from observational data rather than effects from behavioural interventions.

- The optimal SPAN combination of approximately 8.0–9.5 h/day sleep, 40–105 min/day MVPA, and a DQS of 33–50 was associated with 57% lower risk of MACE (HR: 0.43; 95% CI: 0.30, 0.62).
- A minimum between-individual increase of approximately 10 min/day of sleep, 5 min/day MVPA, and 3 DQS points (one-fourth cup of vegetables per day) was associated with 10% lower MACE risk (HR: 0.90; 95% CI: 0.88, 0.94).

Graphical Abstract



Keywords Sleep • Nutrition • Diet • Physical activity • Exercise • Lifestyle risk factors • Cardiovascular disease • Major adverse cardiovascular events • Heart failure • Stroke • Myocardial infarction

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide,[1] which contributes to an increasingly unsustainable burden on healthcare systems from major clinical events, such as myocardial infarction (MI), heart failure (HF), and stroke.[2] Lifestyle behaviours, including SPAN, are key modifiable risk factors that physiologically underpin the development of CVD.[3] Short or long sleep, physical inactivity, and low diet quality have many shared cardiometabolic pathways that may predispose individuals to CVD, including impaired glucose homeostasis, endothelial dysfunction, elevated blood pressure, chronic low-grade inflammation, and obesity.[4–10]

Traditionally, these behaviours have been explored as individual fields or disciplinary siloes. However, these behaviours are uniquely interdependent and have bidirectional impacts on

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one another. For example, poor sleep can disrupt the normal neurotransmission of appetite hormones, influencing food selection and driving an increase in total energy intake.[7] Physical activity is also bidirectionally associated with sleep, where physical activity may improve sleep quality, while poor sleep may limit functional capacity due to fatigue.[11,12] Diet quality is also interlinked, demonstrating a relationship with sleep onset and wake time as well as energy and regulation for normal physical activity. Despite several studies examining distinct pairs of these behaviours,[13,14] few studies have explored all three behaviours in combination and the clinically relevant variations needed for CVD prevention. A recent study exploring the combination of SPAN[15] revealed unique synergies between the behaviours, suggesting that a minimum variation of an additional 15 min of sleep, 1.5 min of MVPA, and one-half serving of vegetables per day was associated with a clinically meaningful 10% lower risk of all-cause mortality.

Previous intensive lifestyle interventions[16–18] and population-level studies[19–21] have largely focused on achieving broad, self-reported lifestyle targets, such as completing 150–300 min per week of moderate to vigorous physical activity (MVPA), meeting general dietary quality goals, or substantial caloric restriction. These one-size-fits-all approaches may discourage some individuals and hinder the initiation and sustainability of behaviour change.[22] Integrating simultaneous change across all three SPAN behaviours also has significant public health advantages as it reduces the required changes needed in any one behaviour to achieve meaningful clinical improvements,[15] likely resulting in more achievable lifestyle recommendations. Emerging clinical practice and research[23–25] is shifting towards high-resolution personalized combined lifestyle approaches, yet limited evidence exists of clinically meaningful lifestyle targets for the general population.

This study aims to address this gap by exploring the association between combined SPAN variations and major adverse cardiovascular events (MACE) and to identify the minimum and incremental variations necessary to achieve a clinically meaningful lower MACE risk.

Methods

Study population

We used data from the UK Biobank accelerometry sub-study,[26] part of a wider cohort study of 502 629 adults aged 40–69 who were recruited from 2006 to 2010. All participants completed informed consent, and ethical approval was obtained by the UK National Health Service (NHS) and National Research Ethics Service for the UK (No. 11/NW/0382). Additional details of the study sample and study design are provided in Supplementary material online, *Methods S1*.

Outcome ascertainment

Due to the nature of rolling updates for data linkage, participants were followed through 30 November 2022, where the date and cause of death were identified using the data linkage programme with the National Health Service (NHS) Digital of England and Wales and the NHS Central Register and National Records of Scotland. Inpatient hospitalization data were provided by either the Hospital Episode Statistics for England, the Patient Episode Database for Wales, or the Scottish Morbidity Record for Scotland. Instances of MACE were defined using the International Classification of Diseases Version 10 codes, including CVD death (I0, I11, I13, I20-I51, I60-I69), incidence of ST-elevated or non-ST-elevated MI (I21, I23, I24.1, I25.2), stroke (I60, I61, I63, I64), and HF (I50).[27–31] Participants with an event in the first year of follow-up or previous diagnosis of major CVD (defined as disease of the circulatory system, arteries, and lymph, excluding hypertension derived from self-report and hospitalization records) were excluded from the analysis.

Assessment of SPAN behaviours

Sleep and physical activity information was derived from wrist accelerometry data. All accelerometers were calibrated and initialized to 100 Hz, and participants were instructed to wear the device on their dominant wrist for 7 consecutive days.[26] Sleep was defined as the average daily duration of sleep (h/day), calculated using a validated algorithm based on relative changes in wrist tilt angle between successive 5-s windows.[32,33] We used time in MVPA as the main physical activity indicator in these analyses, estimated using a validated two-stage machine learning schema[27,29,34–37] that categorizes activities into light, moderate, or vigorous physical activity in 10-s epochs.[27,29,34–37] Additional details regarding the development, validation, and performance of this schema are provided in Supplementary material online, *Methods S2*.

A single food frequency questionnaire (FFQ) was collected during the baseline assessments to assess dietary intake. From the recorded FFQ dietary information, we calculated a previously established DQS, which emphasizes a higher intake of vegetables, fruits, fish, dairy, whole grains, and vegetable oils and a lower intake of refined grains, processed meats, unprocessed red meats, and sugar-sweetened beverages (see Supplementary material online, *Table S1*).[15,38] This score rates the intake of each category on a scale from 0 (unhealthiest) to 10 (healthiest) for a total of 100 points, where higher values equate to a higher diet quality.

Analysis of combined sleep, physical activity, and nutrition

As per our previous work,[15,39] we first created 27 mutually exclusive groups of combined SPAN exposure (i.e. low, medium, high). This categorization approach employed a data-driven rather than guideline-based approach to ensure adequate sample size and sufficient event numbers across exposure groups. The specific ranges for each exposure included sleep duration as 4.9–7.2 h/day (low), 7.2–8.0 h/day (medium), and 8.0–9.4 h/day (high); MVPA measurements as 5–23 min/day (low), 23–43 min/day (medium), and 43–104 min/day (high); and diet quality using the DQS as 32.5–50.0 (low), 50.0–57.5 (medium), and 57.5–72.5 (high). We used Cox proportional hazards models to assess the joint associations with MACE risk using follow-up time from the point of accelerometry measure as the time scale.[27,30] To account for competing risks from non-cardiovascular events, we employed a Fine–Gray sub-distribution hazards model.[27,29,30,40] We visualized the multivariable-adjusted associations of SPAN exposures with MACE by plotting each of the 27 categories as a forest plot with the lowest tertile of each exposure used as the reference point (*Figure 1*). Models were adjusted for age, sex, ethnicity (White, Other), smoking (never, past, current), education [General Certificate of Secondary Education (GCSE), National Vocational Qualifications (NVQ), Higher National Diploma (HND), Higher National Certificate (HNC)], Townsend Deprivation Index, alcohol (units per day), discretionary screen time (time spent watching TV or using the computer outside of work), light intensity physical activity, medication (yes/no for blood pressure, insulin, and cholesterol), previous diagnosis of cancer (yes/no), and familial history of CVD and cancer (yes/no).[15] Further

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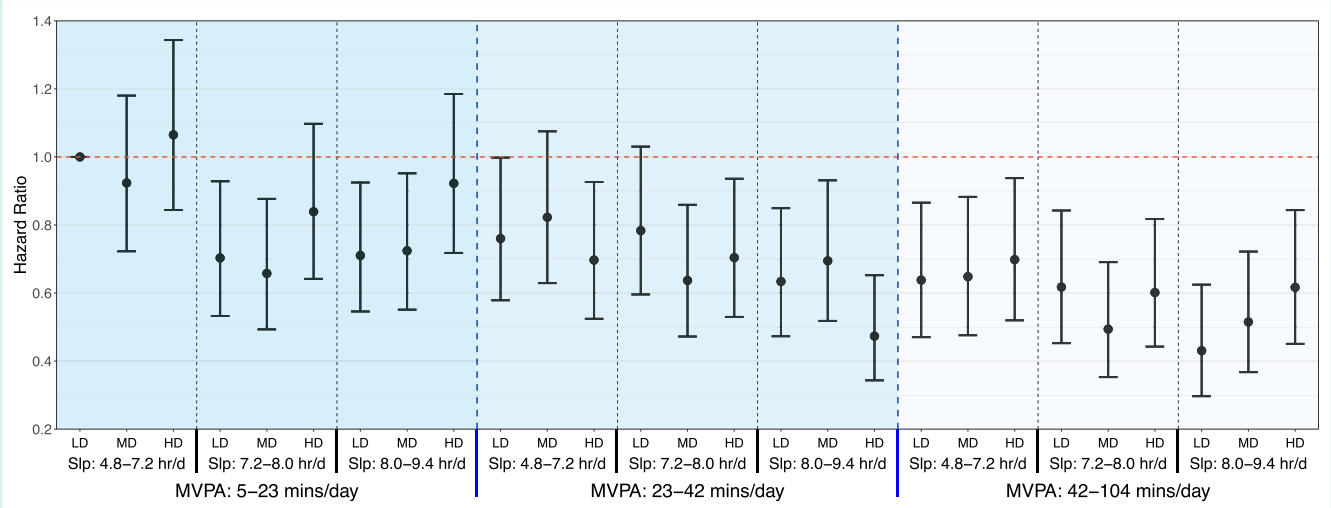

Figure 1 Multivariable-adjusted associations of combined sleep, physical activity, and nutrition with MACE risk (n = 53 242; events = 2034). Model is adjusted for age, sex, ethnicity, smoking, education, Townsend Deprivation Index, alcohol, discretionary screen time (time spent watching TV or using the computer outside of work), light intensity physical activity, medication (blood pressure, insulin, and cholesterol), previous diagnosis of cancer, and familial history of CVD and cancer. Sleep (h/day), physical activity [moderate to vigorous intensity (MVPA) minutes/day], and nutrition [Dietary Quality Score (DQS)] were included in the model as a joint term. Participants with a previous diagnosis of major CVD (defined as disease of the circulatory system, arteries, and lymph, excluding hypertension) were excluded from the analysis. The specific ranges for each exposure included sleep duration as 4.8–7.2 h/day (low), 7.2–8.0 h/day (medium), and 8.0–9.4 h/day (high); MVPA measurements as 5–23 min/day (low), 23–42 min/day (medium), and 42–104 min/day (high); and diet quality using the DQS as 32.5–50.0 (low), 50.0–57.5 (medium), and 57.5–72.5 (high). Categorical differences for diet should be interpreted with caution given the differences in measurement (self-report) compared with sleep and physical activity (wearable-derived). The lowest tertiles for all three exposures (sleep, MVPA, and DQS) were considered the reference group. Dashed blue lines separate tertiles of MVPA and dashed black lines separate tertiles of sleep. Sleep (Slp); Low Diet Quality (LD); Medium Diet Quality (MD); High Diet Quality (HD).

details on the covariates are provided in Supplementary material online, *Table S2*. All models satisfied proportional hazards assumptions using Schoenfeld residuals. We examined the potential synergistic effects of SPAN behaviours using the relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and the synergistic effects index (S)[28,41] for MACE and its corresponding subtypes. These three indices estimate the contribution of synergistic interactions between exposures where an RERI or AP of 0 and an S value of 1 denote no interaction effect.

Continuous sleep, physical activity, and nutrition score

We further examined the dose–response relationship between the combined and individual SPAN components using a continuous composite SPAN score (range: 0–100), with higher scores indicating healthier collective SPAN behaviours and each behaviour weighted equally. Higher scores reflect closer alignment to the theoretically optimal dose identified from the dose–response relationship with MACE.[42,43] For example, a U-shaped relationship was observed for sleep, whereby the nadir of the curve (i.e. theoretically most optimal amount of sleep) received the highest number of points, while under- or over-sleeping contributed a lower number of points to the SPAN score. The overall contribution of each behaviour was then interpreted using the hazard ratio estimates from the joint tertile-based SPAN model with MACE. The model estimates were used to derive behaviour-specific weights, which were then applied to transform the SPAN score into the incremental variations needed for clinically meaningful associations with MACE risk. We defined clinically meaningful as increments of 10% lower risk for MACE or its corresponding subtypes.[15,44] The point of clinical meaningfulness was defined based on thresholds commonly used in clinical trials[44] and to avoid using more trivial estimations, which may be more susceptible to residual confounding or regression dilution bias. To further evaluate the clinically meaningful variations of SPAN with MACE risk, we created a heat map correlogram that uses the fifth percentile of all three exposures as a reference[15] while providing the corresponding MACE risk associated with combined SPAN increments.

Sensitivity analyses

We completed a series of sensitivity analyses to examine how results vary by different analysis assumptions:

- To account for alternative sleep characteristics, we created a model that adjusted for self-reported insomnia, snoring, chronotype (morning/evening person), and daytime sleepiness.[14]
- To ensure findings were robust to the choice of dietary indicator, we repeated the primary analyses using the proportion of dietary ultra-processed food as a marker of diet quality (see Supplementary material online, *Table S3*).[45,46]
- We also completed an analysis adjusting the model for total energy intake and excluded participants with sex-specific implausible ranges.[47,48]
- To minimize the influence of reverse causation, we repeated the core analyses after excluding participants who self-reported poor health, current smokers, those in the top 20th percentile of the Frailty Index, and those with an underweight BMI (<18.5).

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- We repeated the main analysis excluding those with a MACE event in the first 2 years of follow-up to assess potential reverse causation.[49]
- To account for the potential mediating role of BMI[50–52] in the associations between SPAN exposures and MACE, we repeated the main analyses adjusted for BMI.
- We repeated the main analyses using age as the time scale in the Cox proportional hazards model rather than follow-up time from accelerometry assessment.

We undertook all statistical analyses and visualizations using the survival, rms, ggplot2 packages of R (version 4.4.2). We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (see Supplementary material online, *Table S4*).

Results

Sample

The final analytical sample in this study included 53 242 participants [median age (IQR): 63 (56, 68) years; 56.8% male; Supplementary material online, *Figure S1*]. Over the 8.0-year follow-up period, 2034 MACE events occurred, comprising 932 MI, 584 strokes, and 518 HF events. We present baseline characteristics across tertiles of SPAN behaviours in *Table 1*.

Combined SPAN associations with MACE risk

In the overall gradient of behaviours, MVPA contributed the most to the association with MACE, followed by sleep and diet (*Figure 1*). Compared with the referent category (i.e. theoretically least healthy of all three behaviours), low MVPA, moderate sleep, and moderate diet were associated with a 34% lower MACE risk (HR: 0.66; 95% CI: 0.49, 0.88). Moderate MVPA, moderate sleep, and moderate DQS were associated with 36% lower risk of MACE (HR: 0.64; 95% CI: 0.47, 0.86). The lowest risk group associated with MACE was the high MVPA, high sleep, and low DQS (HR: 0.43; 95% CI: 0.30, 0.62), although a similar level of risk was observed in the moderate MVPA, high sleep, and high DQS category (HR: 0.47; 95% CI: 0.34, 0.62).

Assessment of the interaction between SPAN behaviours and MACE risk

We observed a nonstatistically significant positive interaction between SPAN behaviours for overall MACE risk (RERI = 0.003; 95% CI: −0.03, 0.04; AP = 0.4%; 95% CI: −6 to 7%; S = 1.03; 95% CI: −3.32, 5.29; Supplementary material online, *Figure S2*). Similar nonsignificant results were found for HF (RERI = −0.02; 95% CI: −0.11, 0.07; AP = −2.6%; 95% CI: −24 to 18%; S = 1.07; 95% CI: −4.46, 6.59) and MI (RERI = −0.003; 95% CI: −0.05, 0.04; AP = −0.3%; 95% CI: −8 to 8%; S = 1.03; 95% CI: 0.18, 1.89). We observed a weaker, nonstatistically significant positive interaction for stroke (RERI = 0.038; 95% CI: −0.07, 0.15; AP = 6%; 95% CI: −40 to 51%; S = 0.90; 95% CI: 0.57, 1.22).

Dose–response relationship of SPAN behaviours with MACE risk

The dose–response relationship for the individual SPAN behaviours with MACE risk and the corresponding subtypes is shown in Supplementary material online, *Figure S3*. Sleep displayed an L-shaped relationship for MACE, MI, and stroke, while a linear dose–response relationship was observed for HF. We observed an L-shaped relationship with physical activity for all outcomes, while nutrition displayed a subtle, nonstatistically significant association.

We present the dose–response associations of the combined continuous composite SPAN score with MACE, MI, HF, and stroke risk in *Figure 2*. There was a near-linear inverse relationship between SPAN score and MACE risk, wherein compared with the fifth percentile of the SPAN score, the median (52.8) and maximum SPAN score (85.2) were associated with a 41% (HR: 0.59; 95% CI: 0.49, 0.70) and 50% lower risk (HR: 0.50; 95% CI: 0.40, 0.62) of MACE, respectively. We found a linear relationship of the SPAN score with HF and MI, with median values corresponding to an HR of 0.53 (95% CI: 0.38, 0.75) and 0.65 (95% CI: 0.50, 0.84), respectively. There was an L-shaped relationship between SPAN score and stroke risk, with a median SPAN score associated with an HR of 0.52 (95% CI: 0.38, 0.71).

Clinically meaningful combined thresholds of SPAN behaviours associated with MACE risk

We present the minimum and incremental clinically meaningful variations (10–60%) of combined SPAN behaviours for MACE, HF, MI, and stroke risk in *Table 2*. The rows indicate variations of both combined and individual SPAN behaviours associated with 10% lower risk for each outcome. Compared with the fifth percentile of sleep (5.5 h per day), physical activity (7.9 min per day of MVPA), and diet (37.2 DQS points), a combined increase of 11 min/day of sleep, 4.5 min of MVPA, and 3 DQS points was associated with a 10% lower risk of MACE. A similar minimum variation of combined SPAN behaviours was observed for HF (additional 9 min/day sleep, 3.7 min/day MVPA, 2 DQS; HR: 0.91; 95% CI: 0.86, 0.96), MI (additional 15 min/day sleep, 6 min/day MVPA, and 4 DQS; HR: 0.90; 95% CI: 0.84, 0.97), and stroke (additional 9 min/day sleep, 4.9 min/day MVPA, and 2 DQS; HR: 0.90; 95% CI: 0.86, 0.95). Higher variations, such as 62 min of additional sleep per day, 24.6 min/day MVPA, and 16 additional DQS points, were associated with a 40% lower risk of MACE (HR: 0.60; 95% CI: 0.50, 0.71). We provide an additional visualisation of combined SPAN behaviour variations and corresponding MACE risk as a heat map in *Figure 3* (MACE subtypes are presented in see Supplementary material online, *Figure S4–S6*).

Sensitivity analyses

Excluding individuals who had poor health at baseline (n = 50 787; events = 1907) or those with an event in the first 2 years of follow-up resulted in no major changes in our findings (see Supplementary material online, *Figure S7* and S8). Additional adjustments for BMI (n = 52 744; events = 2004) or additional sleep characteristics (n = 33 518; events = 1241) did not impact the results (see Supplementary material online, *Figure S9* and S10). We also observed no materially different results when using the proportion of diet from ultra-processed foods as an alternative dietary quality index (n = 39 533; events = 1462) or adjusting for total energy intake (n = 38 921; events = 1441; Supplementary material online, *Figure S11* and S12). There were minimal differences in the results when using age as the

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Table 1 Distribution of SPAN exposures across participant characteristics

	Overall	Sleep			Physical activity			Nutrition		
		Low	Medium	High	Low	Moderate	High	Low	Moderate	High
Sample	53 242	17 749	17 746	17 747	17 748	17 747	17 747	18 889	17 617	16 736
Events, *n*	2034 (3.8%)	829 (4.7%)	608 (3.4%)	597 (3.4%)	914 (5.1%)	639 (3.6%)	481 (2.7%)	692 (3.7%)	630 (3.6%)	712 (4.3%)
Follow-up, years [median (IQR)]	8.04 [7.47, 8.56]	8.04 [7.45, 8.55]	8.06 [7.49, 8.58]	8.04 [7.49, 8.58]	8.04 [7.43, 8.59]	8.04 [7.49, 8.57]	8.06 [7.49, 8.55]	8.05 [7.47, 8.57]	8.05 [7.47, 8.59]	8.03 [7.46, 8.55]
Age, years [median (IQR)]	63.00 [56.00, 68.00]	64.00 [56.00, 69.00]	63.00 [56.00, 68.00]	64.00 [57.00, 68.00]	65.00 [59.00, 70.00]	63.00 [56.00, 68.00]	61.00 [54.00, 67.00]	62.00 [54.00, 67.00]	64.00 [57.00, 68.00]	65.00 [58.00, 69.00]
Male, *n* (%)	30 243 (56.8%)	8283 (46.7%)	7659 (43.2%)	7057 (39.8%)	7072 (39.8%)	7762 (43.7%)	8165 (46.0%)	9172 (48.6%)	6982 (39.6%)	6845 (40.9%)
Sleep, h/day [median (IQR)]	7.63 [6.90, 8.26]	6.53 [5.95, 6.90]	7.63 [7.42, 7.83]	8.52 [8.26, 8.89]	7.60 [6.80, 8.30]	7.66 [6.94, 8.28]	7.62 [6.96, 8.22]	7.61 [6.88, 8.25]	7.63 [6.92, 8.26]	7.65 [6.91, 8.28]
Moderate to vigorous physical activity, min/day [median (IQR)]	32.04 [19.14, 49.93]	31.07 [18.26, 49.05]	33.81 [20.38, 52.31]	31.29 [18.86, 48.43]	14.93 [10.19, 19.14]	32.05 [27.53, 37.12]	59.67 [49.93, 75.86]	31.41 [18.95, 49.05]	32.31 [19.26, 50.17]	32.57 [19.24, 50.69]
Diet quality score [median (IQR)]	54.01 [47.50, 60.00]	53.93 [47.50, 60.00]	53.93 [47.50, 60.00]	54.64 [47.50, 60.00]	53.93 [47.50, 60.00]	53.93 [47.50, 60.00]	54.37 [47.50, 60.00]	45.00 [40.00, 47.50]	55.00 [52.50, 56.79]	62.50 [60.00, 67.50]
Light physical activity, min/day [median (IQR)]	103.54 [70.67, 158.91]	107.48 [72.88, 163.39]	105.91 [72.31, 162.76]	97.29 [67.24, 150.34]	84.86 [60.69, 119.84]	108.15 [73.55, 158.40]	131.39 [81.79, 196.71]	101.57 [69.55, 156.31]	104.43 [71.69, 159.39]	104.67 [70.95, 160.73]
Discretionary screen time, h/day [median (IQR)]	3.50 [2.50, 5.00]	3.50 [2.50, 5.00]	3.50 [2.50, 5.00]	3.50 [2.50, 5.00]	4.00 [2.50, 5.00]	3.50 [2.50, 5.00]	3.00 [2.00, 4.50]	3.50 [2.50, 5.00]	3.50 [2.50, 5.00]	3.50 [2.50, 5.00]
Smoking history, *n* (%)		—	—	—	—	—	—	—	—	—
Never	31 199 (58.6%)	10 044 (56.6%)	10 502 (59.2%)	10 653 (60.0%)	9970 (56.2%)	10 515 (59.2%)	10 714 (60.4%)	10 972 (58.1%)	10 444 (59.3%)	9783 (58.5%)
Former	18 747 (35.2%)	6394 (36.0%)	6199 (34.9%)	6154 (34.7%)	6428 (36.2%)	6211 (35.0%)	6108 (34.4%)	6358 (33.7%)	6239 (35.4%)	6150 (36.7%)
Current	3296 (6.2%)	1311 (7.4%)	1045 (5.9%)	940 (5.3%)	1350 (7.6%)	1021 (5.8%)	925 (5.2%)	1559 (8.3%)	934 (5.3%)	803 (4.8%)
Alcohol consumption, units/week [median (IQR)]	9.75 [1.81, 19.50]	9.50 [1.14, 19.50]	9.75 [2.50, 19.50]	9.75 [2.27, 19.50]	8.77 [0.81, 18.54]	9.75 [2.31, 19.50]	10.42 [3.17, 20.42]	9.75 [1.31, 19.80]	9.75 [2.50, 19.50]	9.75 [1.95, 19.50]
Total energy intake, kcal/day [median (IQR)]	2018 [1,651, 2443]	2056 [1,676, 2500]	2026 [1,662, 2441]	1975 [1,617, 2392]	1965 [1,607, 2382]	2011 [1,649, 2435]	2075 [1,699, 2511]	2045 [1,677, 2490]	2017 [1,652, 2433]	1989 [1,620, 2413]
Townsend Deprivation Index, (median [IQR])	−2.50 [−3.84, −0.26]	−2.33 [−3.76, 0.13]	−2.50 [−3.84, −0.33]	−2.64 [−3.92, −0.60]	−2.41 [−3.78, −0.14]	−2.54 [−3.88, −0.32]	−2.52 [−3.85, −0.32]	−2.44 [−3.82, −0.10]	−2.53 [−3.86, −0.39]	−2.52 [−3.85, −0.33]
Education, *n* (%)	—	—	—	—	—	—	—	—	—	—

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Table 1 *Continued*

	Overall	Sleep			Physical activity			Nutrition		
		Low	Medium	High	Low	Moderate	High	Low	Moderate	High
College/university	23 536 (44.2%)	7953 (44.8%)	8144 (45.9%)	7439 (41.9%)	7512 (42.3%)	8015 (45.2%)	8009 (45.1%)	7933 (42.0%)	8062 (45.8%)	7541 (45.1%)
A/AS	7064 (13.3%)	2397 (13.5%)	2307 (13.0%)	2360 (13.3%)	2326 (13.1%)	2392 (13.5%)	2346 (13.2%)	2502 (13.2%)	2446 (13.9%)	2116 (12.6%)
O levels	10 798 (20.3%)	3494 (19.7%)	3512 (19.8%)	3792 (21.4%)	3690 (20.8%)	3562 (20.1%)	3546 (20.0%)	3983 (21.1%)	3515 (20.0%)	3300 (19.7%)
CSE	2042 (3.8%)	665 (3.7%)	662 (3.7%)	715 (4.0%)	583 (3.3%)	635 (3.6%)	824 (4.6%)	859 (4.5%)	618 (3.5%)	565 (3.4%)
NVQ/HND/HNC	2801 (5.3%)	931 (5.2%)	925 (5.2%)	945 (5.3%)	961 (5.4%)	953 (5.4%)	887 (5.0%)	1084 (5.7%)	856 (4.9%)	861 (5.1%)
Other	7001 (13.1%)	2309 (13.0%)	2196 (12.4%)	2496 (14.1%)	2676 (15.1%)	2190 (12.3%)	2135 (12.0%)	2528 (13.4%)	2120 (12.0%)	2353 (14.1%)
Parental history of CVD, *n* (%)	29 287 (55.0%)	9767 (55.0%)	9707 (54.7%)	9813 (55.3%)	10 098 (56.9%)	9759 (55.0%)	9430 (53.1%)	9860 (52.2%)	9815 (55.7%)	9612 (57.4%)
Parental history of cancer, *n* (%)	16 797 (31.5%)	5608 (31.6%)	5560 (31.3%)	5629 (31.7%)	5624 (31.7%)	5651 (31.8%)	5522 (31.1%)	5902 (31.2%)	5618 (31.9%)	5277 (31.5%)
Previous cancer, *n* (%)	4365 (8.2%)	1413 (8.0%)	1434 (8.1%)	1518 (8.6%)	1709 (9.6%)	1460 (8.2%)	1196 (6.7%)	1440 (7.6%)	1505 (8.5%)	1420 (8.5%)
Ethnicity, *n* (%)	—	—	—	—	—	—	—	—	—	—
Other	3290 (6.2%)	1433 (8.1%)	1026 (5.8%)	831 (4.7%)	1061 (6.0%)	1083 (6.1%)	1146 (6.5%)	1166 (6.2%)	1085 (6.2%)	1039 (6.2%)
White	49 952 (93.8%)	16 316 (91.9%)	16 720 (94.2%)	16 916 (95.3%)	16 687 (94.0%)	16 664 (93.9%)	16 601 (93.5%)	17 723 (93.8%)	16 532 (93.8%)	15 697 (93.8%)
Medication use, *n* (%)		—	—	—	—	—	—	—	—	—
Cholesterol	6442 (12.1%)	2410 (13.6%)	1969 (11.1%)	2063 (11.6%)	2884 (16.2%)	2056 (11.6%)	1502 (8.5%)	1963 (10.4%)	2044 (11.6%)	2435 (14.5%)
Blood pressure	4637 (8.7%)	1702 (9.6%)	1448 (8.2%)	1487 (8.4%)	1991 (11.2%)	1500 (8.5%)	1146 (6.5%)	1523 (8.1%)	1500 (8.5%)	1614 (9.6%)
Insulin	64 (0.1%)	17 (0.1%)	27 (0.2%)	20 (0.1%)	22 (0.1%)	25 (0.1%)	17 (0.1%)	20 (0.1%)	16 (0.1%)	28 (0.2%)
Frailty Index >3, *n* (%)	148 (0.3%)	68 (0.4%)	39 (0.2%)	41 (0.2%)	105 (0.6%)	20 (0.1%)	23 (0.1%)	69 (0.4%)	43 (0.3%)	36 (0.2%)
Self-rated health, *n* (%)	—	—	—	—	—	—	—	—	—	—
Excellent	11 821 (23.3%)	10 082 (59.6%)	10 388 (61.3%)	4040 (23.9%)	10 273 (60.7%)	4065 (24.0%)	4775 (28.2%)	10 802 (60.1%)	3999 (23.8%)	3992 (25.0%)
Good	30 893 (60.8%)	2769 (16.4%)	2146 (12.7%)	10 423 (61.6%)	3138 (18.5%)	10 457 (61.8%)	10 163 (60.0%)	2871 (16.0%)	10 373 (61.6%)	9718 (60.8%)
Fair	7080 (13.9%)	401 (2.4%)	250 (1.5%)	2165 (12.8%)	508 (3.0%)	2136 (12.6%)	1806 (10.7%)	430 (2.4%)	2186 (13.0%)	2023 (12.6%)
Poor	927 (1.8%)	26 (0.2%)	20 (0.1%)	276 (1.6%)	29 (0.2%)	252 (1.5%)	167 (1.0%)	26 (0.1%)	248 (1.5%)	249 (1.6%)
Body mass index, kg/m^2 [median (IQR)]	25.90 [23.50, 28.80]	26.50 [24.00, 29.60]	25.70 [23.40, 28.60]	25.50 [23.20, 28.30]	27.00 [24.40, 30.30]	25.80 [23.50, 28.60]	25.10 [22.90, 27.50]	26.20 [23.80, 29.30]	25.80 [23.50, 28.70]	25.70 [23.30, 28.50]

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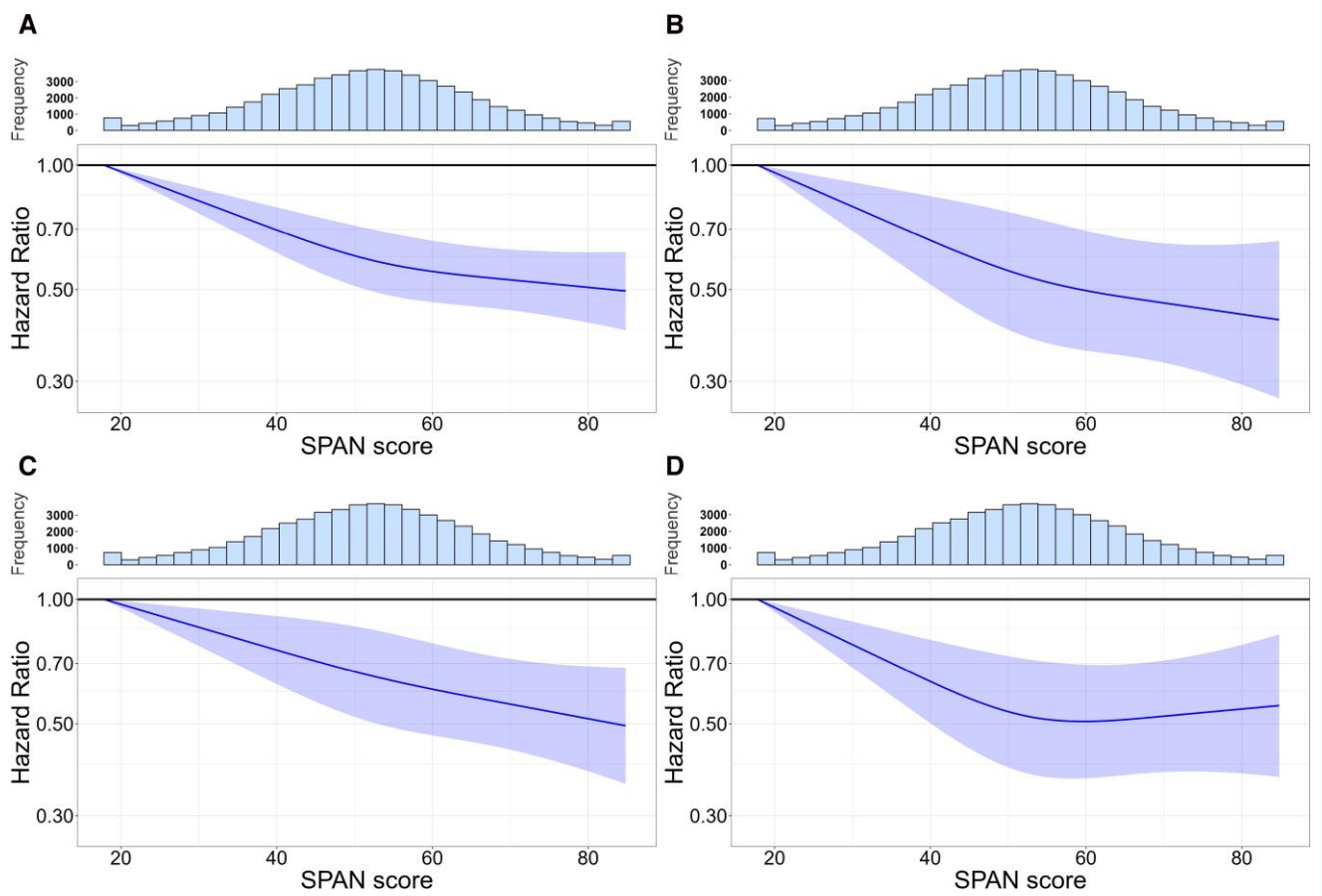

Figure 2 Multivariable-adjusted associations of combined sleep, physical activity, and nutrition with risk of (*A*) MACE, (*B*) heart failure, (*C*) myocardial infarction, and (*D*) stroke (n = 53 242; events = 2034). Model is adjusted for age, sex, ethnicity, smoking, education, Townsend Deprivation Index, alcohol, discretionary screen time (time spent watching TV or using the computer outside of work), light intensity physical activity, medication (blood pressure, insulin, and cholesterol), previous diagnosis of cancer, and familial history of CVD and cancer. Participants with a previous diagnosis of major CVD (defined as disease of the circulatory system, arteries, and lymph, excluding hypertension) were excluded from the analysis. A combined SPAN score ranging from 0 to 100 was developed by assigning equal weights (33.33 points) to three lifestyle components: sleep (h/day), physical activity (MVPA minutes/day), and diet quality (Dietary Quality Score, DQS). Scoring for each component was based on the observed sample range. For physical activity, participants with the lowest MVPA received a score of 0, while those with the highest MVPA scored 33.33, with intermediate values scaled proportionally. Diet quality was scored similarly, from 0 for the lowest DQS to 33.33 for the highest. However, because sleep duration had a U-shaped association with MACE, a score of 33.33 was assigned to the optimal sleep duration of 7.9 h/day. Sleep durations above and below 7.9 h were scored proportionally lower, tapering symmetrically on either side of this nadir.

time scale in the Cox proportional hazards model (see Supplementary material online, *Figure S13*).

Discussion

Main findings

This study presents the first investigation into clinically relevant combined variations of SPAN behaviours in relation to MACE risk. We apply a novel multi-behaviour framework[15] and a large wearable sub-study from the UK Biobank to examine the association of combined SPAN behaviour variations with MACE and its subtypes. We show that when compared with the lowest tertile of all exposures, the optimal combinations of SPAN behaviours consisted of 8.0–9.4 h per day of sleep, 42–104 min per day of MVPA, and a DQS score of 32.50–50.0, which was associated with a 57% lower risk of MACE (HR: 0.43; 95% CI: 0.30–0.62). We also identified clinically relevant between-individual levels of the behaviours, which in combination yielded significantly lower MACE risk through relatively modest combined variations. For example, an approximate minimum combined variation of an additional 10 min/day of sleep, 5 min/day of MVPA, and 3 DQS (equivalent to an extra one-fourth cup of vegetables) was associated with a 10% lower risk of MACE.

Previous studies[53–55] involving lifestyle behaviours and CVD risk have primarily used broad-level self-reported categories of behaviours, such as dichotomously categorizing participants as healthy or unhealthy. Studies often provide general suggestions such that improving a combination of lifestyle behaviours, including alcohol, smoking, obesity, sleep, physical, activity and

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Table 2 Clinically meaningful combined variations of sleep, physical activity, and nutrition associated with MACE, heart failure, myocardial infarction, and stroke risk

Clinically meaningful increments of risk[a]	Additional SPAN score	Additional sleep (min/day)	Additional moderate to vigorous physical activity (min/day)	Additional nutrition (DQS points)	Additional sleep[b] (min/day)	Additional moderate to vigorous physical activity (min/day)	Additional nutrition (DQS points)
MACE			**Combined SPAN**			**Individual SPAN**	
10% lower risk (HR: 0.91; 95% CI: 0.88, 0.94)	6	11	4.5	3	30	6.6	15[b]
20% lower risk (HR: 0.80; 95% CI: 0.74, 0.86)	14	26	10.5	7	66	14	—
30% lower risk (HR: 0.70; 95% CI: 0.58, 0.84)	22	41	16.4	11	174	24.6	—
40% lower risk (HR: 0.60; 95% CI: 0.50, 0.71)	33	62	24.6	16	—	50.6	—
50% lower risk (HR: 0.50; 95% CI: 0.41, 0.62)	63	119	47.8	30	—	—	—
Heart failure			**Combined SPAN**			**Individual SPAN**	
10% lower risk (HR: 0.91; 95% CI: 0.86, 0.96)	5	9	3.7	2	32	4.5	13*
20% lower risk (HR: 0.80; 95% CI: 0.70, 0.91)	12	22	9.0	6	62	10.0	—
30% lower risk (HR: 0.70; 95% CI: 0.57, 0.86)	19	35	14.2	9	104	16.0	—
40% lower risk (HR: 0.60; 95% CI: 0.45, 0.81)	27	50	20.2	13	182	25.0	—
50% lower risk (HR: 0.50; 95% CI: 0.36, 0.70)	41	76	30.6	20	—	54.0	—
60% lower risk (HR: 0.42; 95% CI: 0.28, 0.65)	67	125	50.02	32	—	—	—
Myocardial infarction			**Combined SPAN**			**Individual SPAN**	
10% lower risk (HR: 0.90; 95% CI: 0.84, 0.97)	8	15	6.0	4	49	6.0	16*
20% lower risk (HR: 0.80; 95% CI: 0.68, 0.93)	18	34	13.4	9	103	12.5	
30% lower risk (HR: 0.70; 95% CI: 0.56, 0.89)	28	52	20.9	13	—	21.0	—
40% lower risk (HR: 0.60; 95% CI: 0.47, 0.78)	43	80	32.1	20	—	36.5	—

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Table 2 *Continued*

Clinically meaningful increments of risk[a]	Additional SPAN score	Additional sleep (min/day)	Additional moderate to vigorous physical activity (min/day)	Additional nutrition (DQS points)	Additional sleep[b] (min/day)	Additional moderate to vigorous physical activity (min/day)	Additional nutrition (DQS points)
50% lower risk (HR: 0.50; 95% CI: 0.37, 0.69)	66	123	49.3	31	—	—	—
Stroke			**Combined SPAN**			**Individual SPAN**	
10% lower risk (HR: 0.90; 95% CI: 0.86, 0.95)	5	9	4.9	2	26	13.0	7.0*
20% lower risk (HR: 0.80; 95% CI: 0.71, 0.89)	11	21	10.8	5	50	30.5	16*
30% lower risk (HR: 0.70; 95% CI: 0.59, 0.84)	17	32	16.7	8	80	71.5	—
40% lower risk (HR: 0.60; 95% CI: 0.46, 0.78)	25	46	24.5	11.9	—	—	—
50% lower risk (HR: 0.50; 95% CI: 0.37, 0.71)	38	70.8	37.2	18.1	—	—	—

Table 2 displays the clinically meaningful concurrent variations of sleep, physical activity, and nutrition associated with MACE risk compared with individual SPAN exposures. The combined columns show the SPAN combinations and corresponding MACE risk compared with the fifth percentile of sleep (5.5 h/day), moderate to vigorous physical activity (7.9 min/day), nutrition (37.2 DQS), and composite SPAN score (17.8) in increments of 10%. For comparison, the variation needed for individual SPAN exposures is shown on the right. Empty cells denote that the individual SPAN exposure could not achieve that level of risk reduction in isolation. All models were adjusted for age, sex, ethnicity, smoking, education, Townsend Deprivation Index, alcohol, discretionary screen time (time spent watching TV or using the computer outside of work), light intensity physical activity, medication (blood pressure, insulin, and cholesterol), previous diagnosis of cancer, and familial history of CVD and cancer. Participants with a previous diagnosis of major CVD (defined as disease of the circulatory system, arteries, and lymph, excluding hypertension) were excluded from the analysis. Moderate to vigorous physical activity, MVPA; diet quality score, DQS; hazard ratio, HR. Each exposure was adjusted by the median value of the other two SPAN exposures.

[a]95% CI is based on the combined SPAN model.

[b]Values were nonsignificant.

diet, is associated with a 58–62% lower risk of CVD.[53–55] However, this broad level of recommendation limits the ability to generate consumer-friendly, translatable public health messaging. For example, physical activity guidelines often recommend achieving 150 min/week of MVPA;[56] however, these recommendations lack the specificity needed to initiate and sustain behaviour change while taking into consideration other behaviours. Similar one-size-fits-all recommendations exist for sleep (e.g. optimal sleep of 7–8 h per night for older adults)[57] or the UK Eatwell Guide,[58] which recommends general serving food groups and portion goals. However, understanding the incremental variations needed to achieve clinically meaningful lower cardiovascular risk is necessary for the implementation of more tailored and sustainable holistic lifestyle recommendations.[24,59]

Sleep, physical activity, and nutrition have been almost exclusively examined as individual behaviours or as joint pairwise behaviours.[13,14,60–63] This narrow unidisciplinary approach fails to account for the many unique biological and behavioural interdependencies that exist between these behaviours.[62,64–68] For example, recent evidence[15] suggests the unique collective synergies of these behaviours for the risk of all-cause mortality, whereby in combination, they offer clinically meaningful changes in risk with relatively modest combined variations. The present findings align with this previous work, suggesting that individual behaviours require substantially higher levels to achieve the same level of risk reduction. For example, we show that in isolation, sleep would require three times the amount (30 min) to achieve a 10% lower risk of MACE when compared with more modest amounts of sleep (≈10 min) in combination with physical activity (≈5 additional minutes MVPA per day) and nutrition (additional one-fourth cup of vegetables per day).

Notably, we observed a unique heterogeneity for the SPAN relationship across MACE subtypes. The greatest overall benefit of SPAN was observed for HF with a linear dose–response relationship associated with 69% lower risk at the maximum observed SPAN score, compared with 49% for MI and 53% for stroke. Among the individual behaviours, sleep displayed the most pronounced differential relationship, whereby we observed a beneficial relationship with HF linearly compared with the L- and U-shaped relationship observed for MI and

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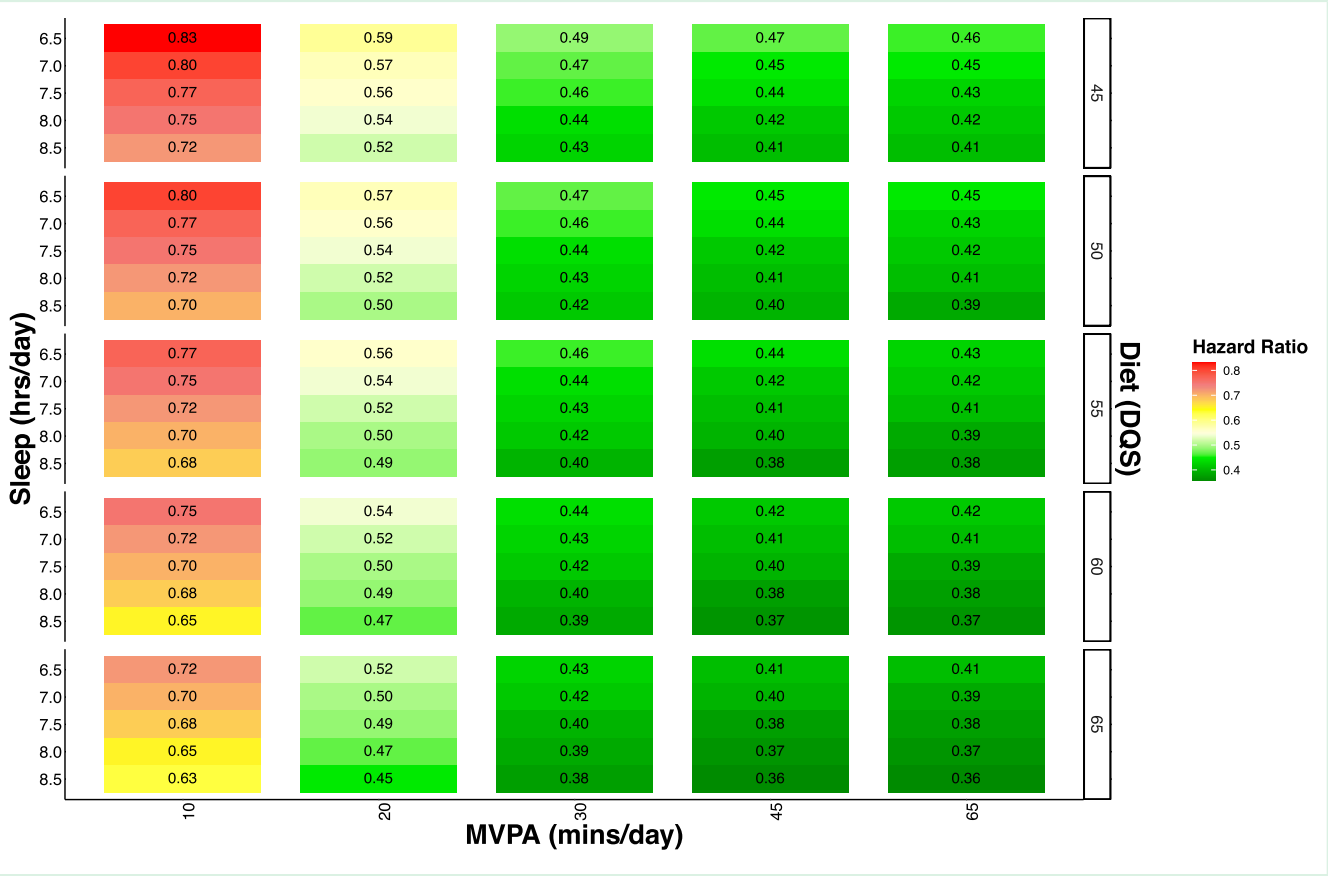

Figure 3 Multivariable adjusted MACE risk associated with concurrent variations in sleep, physical activity, and nutrition (n = 53 242; events = 2034). The correlogram displays changes in sleep (h/day), physical activity [moderate to vigorous intensity (MVPA) minutes/day], nutrition [Dietary Quality Score (DQS)] and corresponding MACE risk with the reference being the fifth percentile of sleep (5.5 h/day), physical activity (7.9 min/day), and nutrition (37.2 DQS). Sleep, physical activity, and nutrition are included as independent terms in the model to allow for more granular predictions. Each square on the grid represents the hazard ratio for MACE associated with a combination of behaviours, as defined by the x-axis (physical activity), y-axis (sleep), and z-axis (nutrition). The colour corresponds to the hazard ratio where red indicates a higher risk of MACE and green indicates a lower risk of MACE. Model is adjusted for age, sex, ethnicity, smoking, education, Townsend Deprivation Index, alcohol, discretionary screen time (time spent watching TV or using the computer outside of work), light intensity physical activity, medication (blood pressure, insulin, and cholesterol), previous diagnosis of cancer, and familial history of CVD and cancer. Participants with a previous diagnosis of major CVD (defined as disease of the circulatory system, arteries, and lymph, excluding hypertension) were excluded from the analysis.

stroke, respectively. For all subtypes, increased risk from insufficient sleep is mechanistically supported by increased sympathetic nervous system activity, endothelial dysfunction, blood pressure, and inflammation.[69] Longer sleep periods may confer unique physiological benefits for HF through the restoration and maintenance of autonomic balance, the renin–angiotensin–aldosterone system, and blood pressure regulation.[70] In contrast, the detrimental association observed for longer sleep with MI and stroke may be partially explained by circadian dysregulation, which can increase pro-thrombotic triggering processes, including increased platelet aggregation, reduced fibrinolysis, and abnormal blood pressure surges.[71,72] The differing dose–response patterns, whereby MI demonstrated an L-shaped relationship, may suggest that no additional benefit is conferred beyond sufficient sleep duration, whereas the U-shaped relationship observed for stroke may indicate a stronger link to circadian and haemodynamic abnormalities associated with prolonged sleep periods. In line with these findings, there is a growing recognition of sleep as a relevant lifestyle characteristic, as evidenced by its recent addition to the American Heart Association's Essential 8 behaviours for the prevention and management of CVD.[3]

This study highlights the combined potential of SPAN behaviours in reducing MACE risk, with significant clinical and public health implications. For many individuals, meeting guideline-based targets, such as 150–300 min/week of MVPA, sufficient sleep, or recommended fruit and vegetable intake, can be challenging and is often met with feasibility concerns. Our results suggest that focusing on the combination of behaviours, rather than strict adherence to broad behavioural targets, may yield substantial health benefits while minimising the burden of change on any single behaviour. We note that the behavioural categories used in this study were derived using a data-driven approach and were not intended to reflect established clinical

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guidelines. For example, the optimal sleep category ranged from 7.2 to 9.4 h per day, extending beyond current recommendations of 7–9 h of sleep per night for adults.[3,57] Importantly, although benefits were observed with combinations of behaviours, we observed a weak synergistic relationship between behaviours, and these findings should not be interpreted as a biological interaction. However, by exploring the incremental between-individual variations of SPAN needed for clinically meaningful shifts in MACE risk, these findings can help shape more holistic and behaviourally sustainable lifestyle recommendations with clear and translatable lifestyle targets, which is a fundamental tenet of sustainable behaviour change.[24]

Strengths and limitations

A core strength of the study is a novel multi-behavioural analytical approach[15] which enabled us to explore combined, clinically meaningful variations of SPAN behaviours for MACE risk. Wearable-based metrics and machine learning approaches for these behaviours allowed us to explore incremental variations of these behaviours at a higher resolution than self-reported research, which typically characterizes the behaviour in crude terms (i.e. >10-minute chunks) of physical activity[73] and hourly increments of sleep.[74] For physical activity in particular, this resolution of wearables data offers a major advantage in this study, as the self-report surveys fail to capture the brief periods of movement that contribute to CVD risk.[27,29,73,75,76]

However, a potential limitation of this study is the differing methods used to assess SPAN. Sleep and physical activity were collected using wearable devices while nutrition was self-reported using a validated FFQ. This methodological discrepancy may partially explain the subtle, nonsignificant relationship between diet and MACE which differs from existing literature.[10,77] Due to the limitations of self-reported dietary assessment, dietary behaviours in the UK Biobank are also more significantly affected by regression dilution bias.[78] This is evident in some categorical associations with diet, where the patterns in certain categories appear counterintuitive, including some groups where lower diet quality was associated with a lower risk of MACE. In the UK Biobank,[26,79] there is also a median of 5.5 years' lag between the data collection of self-reported dietary data and the wearable device measures of sleep and physical activity which could have further contributed to exposure misclassification. In sensitivity analyses considering the consumption of ultra-processed foods derived from 24-hour dietary recalls, which were collected after the FFQ (3-year lag time between accelerometry measure), similar diet associations were observed with MACE risk. Nonetheless, it cannot be dismissed that the combination of measurement error, regression dilution bias, and temporal misalignment may have attenuated the association towards the null, resulting in a potential underestimation of the true association between diet and MACE risk. Despite a range of conducted sensitivity analyses undertaken in the present study, the risk of reverse causation and residual confounding inherent to this observational design cannot be ruled out. While we estimate the minimum changes needed of SPAN behaviours, these represent theoretical extrapolations from a restricted cubic spline model, and caution is warranted for interpreting them as prescriptive targets, and the true effects of a behaviour change intervention may differ. For example, the minimum variation for diet was derived with the DQS and translated (e.g. one-fourth cup of vegetables per day) as an approximate illustration and not a calibrated equivalence. Further research is needed to explore the length of time under behaviour change needed to elicit health benefits and how sustainable these are across diverse populations. Future work may benefit by considering these relationships with more detailed cardiovascular outcomes including distinction between ST elevation MI (STEMI) and non-ST elevation MI (NSTEMI), Type 1 and Type 2 MI, or MI with non-obstructive coronary arteries (MINOCA). The UK Biobank cohort is also known to be healthier than the general UK population, including lower prevalence of smoking, alcohol intake, obesity, and less likely to live in socioeconomically disadvantaged areas which may affect the generalizability of these results.[80] However, previous work by our group has shown that the lack of cohort representativeness does not materially distort the relationship between physical activity and diet with cardiovascular mortality.[81] Lastly, although we explored the combined associations of SPAN, substance-use behaviours such as smoking and alcohol use should be explored as a part of future studies as they also contribute to overall lifestyle patterns and cardiovascular risk.

Conclusions

We show that even modest combined between-individual variations, including approximately 10 additional minutes per day of sleep, 5 additional minutes per day of MVPA, and an additional one-fourth cup of vegetables per day, were associated with a 10% lower risk of MACE. In combination, larger concurrent variations were associated with substantially lower risk than any single behaviour in isolation. These findings highlight the need for integrated multi-behaviour lifestyle prevention trials to evaluate the effectiveness of small, achievable lifestyle changes for MACE prevention.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Acknowledgements

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Authors' contributions

Nicholas A. Koemel (Writing—original draft, Conceptualization, Formal Analysis [lead]), Raaj Kishore Biswas (Writing—review & editing, Conceptualization, Formal Analysis [equal]), Stephen J. Simpson (Writing—review & editing [equal]), Leandro F. M. Rezende (Writing—review & editing [equal]), Tian Wang (Writing—review & editing [equal]), Adrian Bauman (Writing—review & editing [equal]), David Raubenheimer (Writing—review & editing [equal]), Margaret Allman-Farinelli (Writing—review & editing [equal]), Peter A. Cistulli (Writing—review & editing [equal]), Matthew N. Ahmadi (Writing—review & editing, Conceptualization,

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Supervision [equal]), and Emmanuel Stamatakis (Writing—review & editing, Conceptualization, Supervision [equal]).

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Conflict of interest: E.S. is a paid consultant for Complement 1, a US-based company whose products and services relate to healthy lifestyles. All other authors disclose no conflict of interest for this work.

Data availability

The data that support the findings of this study are available from the UK Biobank, but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with the permission of the UK Biobank.

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