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ORIGINAL RESEARCH

Sleep Pattern, Genetic Susceptibility, and Abdominal Aortic Aneurysm in UK Biobank Participants

Large-Scale Cohort Study

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ABSTRACT

BACKGROUND Abdominal aortic aneurysm (AAA) is an important cause of cardiovascular mortality.

OBJECTIVES The authors aimed to explore the associations between sleep patterns and genetic susceptibility to AAA.

METHODS We included 344,855 UK Biobank study participants free of AAA at baseline. A sleep pattern was defined by chronotype, sleep duration, insomnia, snoring, and daytime sleepiness, and an overall sleep score was constructed with a range from 0 to 5, where a high score denotes a healthy sleep pattern. Polygenic risk score based on 22 single nucleotide polymorphisms was categorized into tertiles and used to evaluate the genetic risk for AAA. Cox proportional hazards regression models were used to assess the association between sleep, genetic factors, and the incidence of AAA.

RESULTS During a median of 12.59 years of follow-up, 1,622 incident AAA cases were identified. The HR per 1-point increase in the sleep score was 0.91 (95% CI: 0.86-0.96) for AAA. Unhealthy sleep patterns, defined as a sleep score ranging from 0 to 3, were found to be associated with a higher risk of AAA for the intermediate (HR: 1.18, 95% CI: 1.06-1.31) and poor sleep patterns (HR: 1.40, 95% CI: 1.13-1.73), respectively, compared to the healthy pattern. Participants with poor sleep patterns and high genetic risks had a 2.5-fold higher risk of AAA than those with healthy sleep patterns and low genetic risk.

CONCLUSIONS In this large prospective study, healthy sleep patterns were associated with a lower risk of AAA among participants with low, intermediate, or high genetic risk. (JACC Adv 2024;3:100967) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AAA = abdominal aortic aneurysm

BMI = body mass index

GWAS = genome-wide association study

ICD-10 = International Classification of Diseases-10th Revision

OSA = obstructive sleep apnea

PAF = population attributable fraction

PRS = polygenic risk score

SNP = single nucleotide polymorphism

TDI = Townsend Deprivation Index

Abdominal aortic aneurysm (AAA) is a pathological condition characterized by the dilation of the abdominal aorta. Despite being typically asymptomatic, AAA is prone to rupture,[1] leading to devastating consequences with a mortality rate of nearly 80%.[2,3] The risk of AAA is associated with hypertension, atherosclerosis, smoking, and family history.[4-6] Given the stealthy nature of AAA symptoms and the life-threatening complications associated with it, there is an urgent need for early prevention strategies focusing on modifiable risk factors.

Sleep, due to its vital role in health, has garnered increasing attention.[7-9] Sleep disturbances have emerged as a significant public health issue, with a high prevalence rate that exceeds 10%.[10,11] In a recent study, Lu et al defined a healthy sleep pattern by combining 5 sleep characteristics: sleep duration, chronotype, snoring, insomnia, and excessive daytime sleepiness, and revealed that adherence to a healthy sleep pattern could decrease the risk of coronary heart disease and stroke.[12] Other studies[13-15] have indicated that obstructive sleep apnea (OSA) may influence the development of aortic aneurysms, with severe OSA being associated with rapid AAA progression. In these studies, OSA is typically diagnosed through diagnostic tests such as multichannel polysomnography, with symptoms including excessive daytime sleepiness and loud snoring. However, research on the association between sleep behaviors, such as snoring, insomnia, and daytime sleepiness, and AAA development is limited. The determination of sleep patterns allows for easier identification of individuals at risk for AAA than the clinical diagnosis of OSA. Promoting healthy sleep patterns may help decrease the risk of AAA in high-risk populations, such as individuals with a high genetic risk of AAA.

Over the past few decades, numerous single nucleotide polymorphisms (SNPs) have been identified as being associated with AAA development through genome-wide association studies (GWASs).[16-18] These SNPs provide quantitative measures of genetic susceptibilities and contribute to population stratification. Derek et al[16] found that participants with a 1-SD increase in polygenic risk score (PRS) had a 26% increased risk of AAA.

Therefore, in this study, we aimed to assess the associations of sleep patterns and individual sleep characteristics with AAA risk using data from a large-scale prospective cohort of the UK population. Furthermore, we probed the combined effect of genetic risk and sleep pattern and whether adherence to a healthy sleep pattern could compensate for the nonmodifiable genetic risk of AAA.

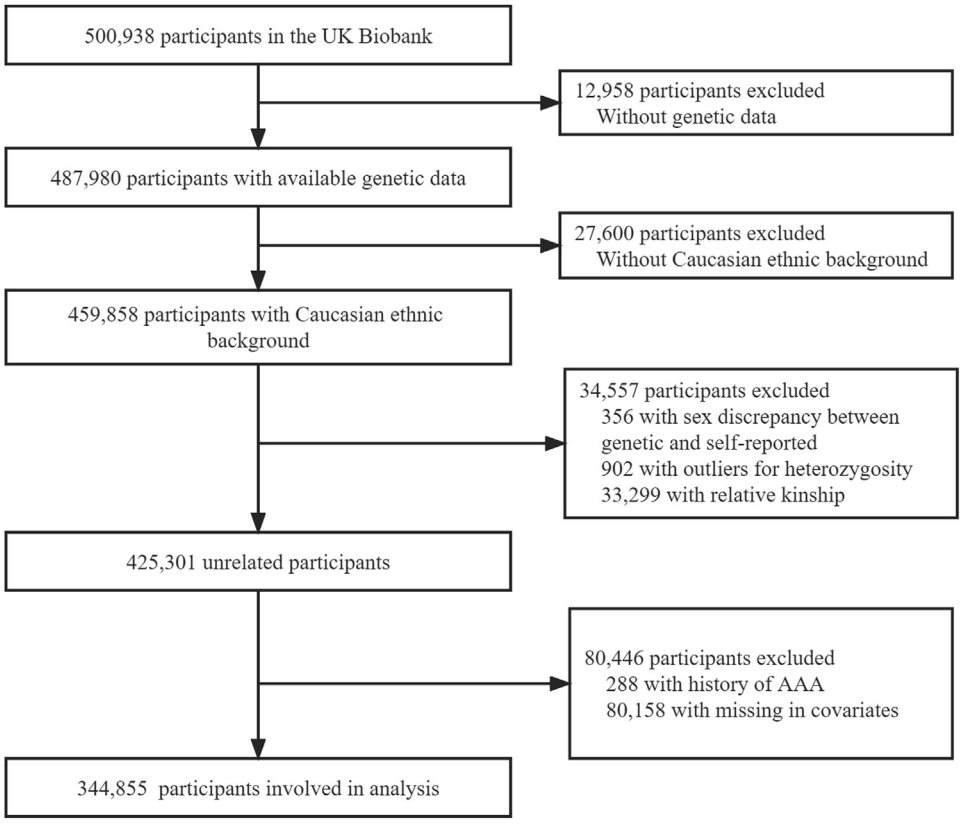
METHODS

STUDY POPULATION. Details of the design and methods of the UK Biobank study have been previously described.[19] Briefly, the UK Biobank is a large-scale biomedical database and research resource that has recruited over 0.5 million adults aged 40 to 69 between 2006 and 2010. The selection of the study participants is shown in **Figure 1**. In the current study, we included all participants with a Caucasian ethnic background and complete data on genetics and covariates and excluded anyone with a history of AAA, self-reported AAA, or AAA diagnosed by a physician.

DEFINITION OF AAA. The AAA status and related conditions were identified based on the inpatient diagnosis and death registry data provided by the UK Biobank at baseline or during follow-up. Briefly, we categorized individuals who had a main/secondary inpatient diagnosis or a postrecruitment diagnosis of an underlying cause of death by application of the International Classification of Diseases, 10th Revision guidelines (ICD-10: I71.3, I71.4) as having incident AAA. Participants with a previous aortic aneurysm (ICD-10: I71) or atherosclerosis (ICD-10: I70) were excluded to ensure that all participants included in this study were free of AAA at baseline, whether self-reported or diagnosed as an inpatient.

ASSESSMENT OF SLEEP BEHAVIORS AND DEFINITION OF SLEEP PATTERNS. All sleep behaviors were obtained from self-reported information based on a baseline questionnaire that included sleep duration, chronotype, snoring, insomnia, and excessive daytime sleepiness. Details of the sleep questionnaire and categories of sleep patterns are presented in Supplemental Table 1. Briefly, we defined low-risk sleep factors as described previously[12]: a sleep duration of 7 to <9 hours/day; morning person of chronotype (answer "morning" or "morning than evening"); no self-reported snoring (answer "no"); self-reported with never/rarely sleeplessness symptoms (answer "never/rarely"); and no regular daytime dozing (answer "never/rarely" or "sometimes"). Participants received a score of 0 if they were classified as high-risk for any of the 5 sleep factors and 1 if they were at low-risk for that factor. A sleep score was generated by adding the 5 component scores, with the sum value ranging from 0 to 5, where higher scores indicate a healthier sleep pattern. We then classified an individual's sleep pattern as "poor" (sleep

FIGURE 1 The Flowchart for the Selection of Study Participants from the UK Biobank Cohort



AAA = abdominal aortic aneurysm.

score ≤1), "intermediate" (2 ≤sleep score ≤3), or "healthy" (sleep score ≥4) based on the sleep score.

ASSESSMENT OF COVARIATES. Our analysis incorporated various covariates associated with AAA to adjust for potential confounding,[12,20,21] including demographic characteristics, clinical conditions, and lifestyle. All covariates were documented using self-reported information gathered through a touchscreen questionnaire during recruitment. Demographic characteristics included age, sex (male/female), and the Townsend Deprivation Index, which served as a measure of socioeconomic status.[22,23] Clinical conditions encompassed an individual's personal history of hypertension (yes/no) and a family history of heart diseases (yes/no). Lifestyle factors incorporated body mass index (kg/m^2), smoking status (ever/never), alcohol intake (high/low), and physical activity, as recommended by the American Heart Association Guidelines.[24] Following the guidelines of the UK Food Standards Agency, the daily intake of pure alcohol, measured in grams, was determined by multiplying the average quantity of alcoholic beverages consumed by the average amount of alcohol contained in each type of drink (Supplemental Table 2). We defined <16 g/day as low alcohol intake in this study. Physical activity was divided into "low," "moderate," and "high" groups depending on weekly exposure level. Details of the categories for these variables are presented in Supplemental Table 3.

GENOTYPE DATA AND POLYGENIC RISK SCORE GENERATION. The genotype data of over 0.48 million participants in the UK Biobank were derived from GWAS chip-based (Affymetrix UK BiLEVE and UK Biobank Axiom arrays) testing of their blood samples. These genotyping data were further imputed using reference panels of the Haplotype Reference Consortium, or UK10K, and 1,000 Genomes Project phase 3.[25] Individuals were excluded due to sex discrepancy (n = 356), sample relatedness (n = 33,299)

TABLE 1 Baseline Characteristics of Study Participants From the UK Biobank

	Sleep Scores				
	0-1 (n = 14,787, 4.29%)	2 (n = 67,831, 19.7%)	3 (n = 132,572, 38.4%)	4 (n = 105,057, 30.5%)	5 (n = 24,608, 7.13%)
Follow up (y)	12.18 ± 2.02	12.26 ± 1.86	12.31 ± 1.78	12.36 ± 1.67	12.39 ± 1.61
Age, y	56.64 ± 7.74	56.84 ± 7.79	56.94 ± 7.88	56.60 ± 8.09	55.20 ± 8.48
Male	7,965 (53.9)	33,964 (50.1)	59,751 (45.1)	44,058 (41.9)	11,349 (46.1)
TDI	−0.99 ± 3.21	−1.35 ± 3.05	−1.57 ± 2.93	−1.74 ± 2.81	−1.77 ± 2.82
Hypertension	9,044 (61.2)	39,046 (57.6)	71,915 (54.2)	53,090 (50.5)	11,359 (46.2)
Family history of heart diseases	7,024 (47.5)	30,784 (45.4)	58,254 (43.9)	44,972 (42.8)	9,579 (38.9)
BMI, kg/m^2	29.59 ± 5.49	28.35 ± 4.98	27.37 ± 4.64	26.60 ± 4.36	26.11 ± 4.17
Ever smoke	10,233 (69.2)	44,804 (66.1)	81,669 (61.6)	60,189 (57.3)	13,145 (53.4)
High alcohol intake	6,217 (42.0)	28,399 (41.9)	51,156 (38.6)	36,975 (35.2)	8,040 (32.7)
Physical activity					
Low	5,881 (39.8)	23,595 (34.8)	41,171 (31.1)	29,436 (28.0)	6,099 (24.8)
Intermediate	7,062 (47.8)	34,965 (51.5)	70,856 (53.4)	57,738 (55.0)	13,867 (56.4)
High	1,844 (12.5)	9,271 (13.7)	20,545 (15.5)	17,883 (17.0)	4,642 (18.9)
Low-risk sleep factors					
No frequent daytime sleepiness	11,548 (78.1)	64,428 (95.0)	130,700 (98.6)	104,784 (99.7)	24,608 (100.0)
No self-report snoring	705 (4.8)	21,430 (31.6)	80,077 (60.4)	89,739 (85.4)	24,608 (100.0)
No frequent insomnia	154 (1.0)	3,661 (5.4)	19,238 (14.5)	36,313 (34.6)	24,608 (100.0)
Sleep 7-8 h/d	642 (4.3)	25,262 (37.2)	88,672 (66.9)	98,637 (93.9)	24,608 (100.0)
Early chronotype	1,005 (6.8)	20,881 (30.8)	79,029 (59.6)	90,755 (86.4)	24,608 (100.0)
PRS					
Low	4,918 (33.3)	22,475 (33.1)	44,268 (33.4)	34,985 (33.3)	8,306 (33.8)
Intermediate	4,976 (33.7)	22,505 (33.2)	44,229 (33.4)	35,039 (33.4)	8,202 (33.3)
High	4,893 (33.1)	22,851 (33.7)	44,075 (33.2)	35,033 (33.3)	8,100 (32.9)

Values are mean ± SD or n (%).
BMI = body mass index; PRS = polygenic risk score; TDI = Townsend Deprivation Index.

determined as kinship >0.088, and outliers of heterozygosity (n = 902). Based on 32 previously reported SNPs associated with AAA identified in GWAS of European populations,[16,17] we selected 22 independent SNP signals (Supplemental Table 4) after quality control, including: 1) minor allele frequency ≥0.05 (one SNP excluded); 2) missing rate <5%; 3) Hardy-Weinberg Equilibrium ≥1.0×10^{-5}; 4) INFO score (information metric) of imputation >0.5; 5) direction of odds ratio (OR) consistent with previous studies (6 SNPs excluded); and 6) linkage disequilibrium $r^2 < 0.5$ (3 SNPs excluded), to construct the final PRS representing genetic risk. For each participant, the PRS was calculated as a weighted sum of these risk alleles, where weights were derived from the OR value of each allele in previous studies. The PRS was then categorized as "low," "intermediate," or "high risk" based on the triple quantile of the distribution among all participants.

STATISTICAL ANALYSIS. The baseline characteristics of participants were described as mean ± SD or frequency (percentages) in each category of sleep scores. The follow-up years were calculated as the time from the recruitment date to the date of outcome diagnosis, death, or end of the follow-up (September 17, 2021), whichever occurred first.

We used multivariate Cox proportional hazards regression models to estimate the HR (95% CI) for genetic and sleep factors associated with AAA risk. The proportional assumption was evaluated the Schoenfeld residuals test, and no violations of the proportional hazard assumptions were found. We evaluated the association of sleep score with AAA using participants with a score ≤1 as the reference group. All 5 sleep factors were simultaneously included in the model to analyze individual sleep factors. In our analysis, 3 different models were developed to avoid the potential confounding effects of known risk factors. Age and sex were adjusted in model 1. Townsend Deprivation Index, history of hypertension, and family history of heart diseases were additionally added to adjust for model 2. Finally, lifestyle factors (body mass index, smoking status, alcohol intake, and physical activity) were further added to model 3 (full model). Individuals with missing values for any covariate were excluded from the analysis.

TABLE 2 Associations of Sleep Factors and Sleep Scores With Incident AAA in the UK Biobank

		Model 1[a]		Model 2[b]		Model 3[c]	
	n (%)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Low-risk sleep factors							
No frequent daytime sleepiness	1,559 (4.64)	0.89 (0.69-1.14)	0.358	0.93 (0.72-1.19)	0.548	0.97 (0.75-1.25)	0.825
No self-report snoring	868 (4.01)	0.91 (0.83-1.01)	0.062	0.92 (0.83-1.01)	0.079	0.97 (0.88-1.07)	0.57
No frequent insomnia	373 (4.44)	**0.83 (0.74-0.94)**	0.002	**0.85 (0.75-0.95)**	0.006	**0.88 (0.79-0.99)**	0.037
Sleep 7-8 h/d	1,038 (4.36)	**0.82 (0.74-0.91)**	<0.001	**0.86 (0.77-0.95)**	0.003	**0.88 (0.80-0.98)**	0.019
Early chronotype	999 (4.62)	**0.83 (0.75-0.92)**	<0.001	**0.84 (0.76-0.93)**	0.001	**0.89 (0.80-0.98)**	0.018
Sleep scores							
0-1	105 (7.10)	*Ref*		*Ref*		*Ref*	
2	375 (5.53)	**0.78 (0.63-0.97)**	0.026	0.81 (0.65-1.01)	0.057	0.85 (0.68-1.05)	0.138
3	654 (4.93)	**0.72 (0.59-0.88)**	0.002	**0.76 (0.62-0.93)**	0.009	0.84 (0.68-1.03)	0.09
4	412 (3.92)	**0.59 (0.48-0.73)**	<0.001	**0.64 (0.52-0.79)**	<0.001	**0.73 (0.59-0.91)**	0.005
5	76 (3.09)	**0.47 (0.35-0.64)**	<0.001	**0.51 (0.38-0.69)**	<0.001	**0.62 (0.46-0.83)**	0.002
Per 1 point (*P* for trend)[d]		**0.85 (0.81-0.89)**	<0.001	**0.87 (0.83-0.91)**	<0.001	**0.91 (0.86-0.96)**	<0.001
Sleep patterns							
Healthy	488 (3.76)	*Ref*		*Ref*		*Ref*	
Intermediate	1,029 (5.13)	**1.30 (1.17-1.45)**	<0.001	**1.26 (1.13-1.41)**	<0.001	**1.18 (1.06-1.31)**	0.003
Poor	105 (7.10)	**1.75 (1.42-2.16)**	<0.001	**1.62 (1.31-2.01)**	<0.001	**1.40 (1.13-1.73)**	0.002
P for trend[d]			<0.001		<0.001		<0.001

Bolding indicates statistical significance. [a]Adjusted for age and sex. [b]Adjusted for variables in model 1, TDI, history of hypertension, and family history of heart diseases. [c]Adjusted for variables in model 2, BMI, smoking status, drinking status, and physical activity. [d]Test for linear trend across categories was performed by modeling the levels of sleep score/sleep pattern as a continuous variable in a separate model.

AAA = abdominal aortic aneurysm; BMI = body mass index; TDI = Townsend Deprivation Index.

We then estimated the strength and direction of the association between risk factors (sleep patterns and PRS) and AAA events in the full model. In addition, ordered multicategorical variables were adapted to perform linear trend tests. Array batches and the significant principal components ($P < 0.05$) were additionally added to adjust the model, including PRS for the impact of population stratification. We also calculated the population attributable fraction (PAF), an estimate of the proportion of events that theoretically would not have occurred if all individuals had been in the low-PRS and healthy sleep pattern groups.[26]

Finally, we calculated the 10-year event rates of AAA according to different genetic risk groups and sleep pattern categories using the Cox regression model that were standardized to the mean of all covariates. Considering the competing risk of non-AAA mortality, we used a Fine and Gray model in sensitivity analysis. All analyses were performed using R 4.2.0 and PRSice-2 2.3.5 software. All *P* values (2-sided) < 0.05 were deemed significant.

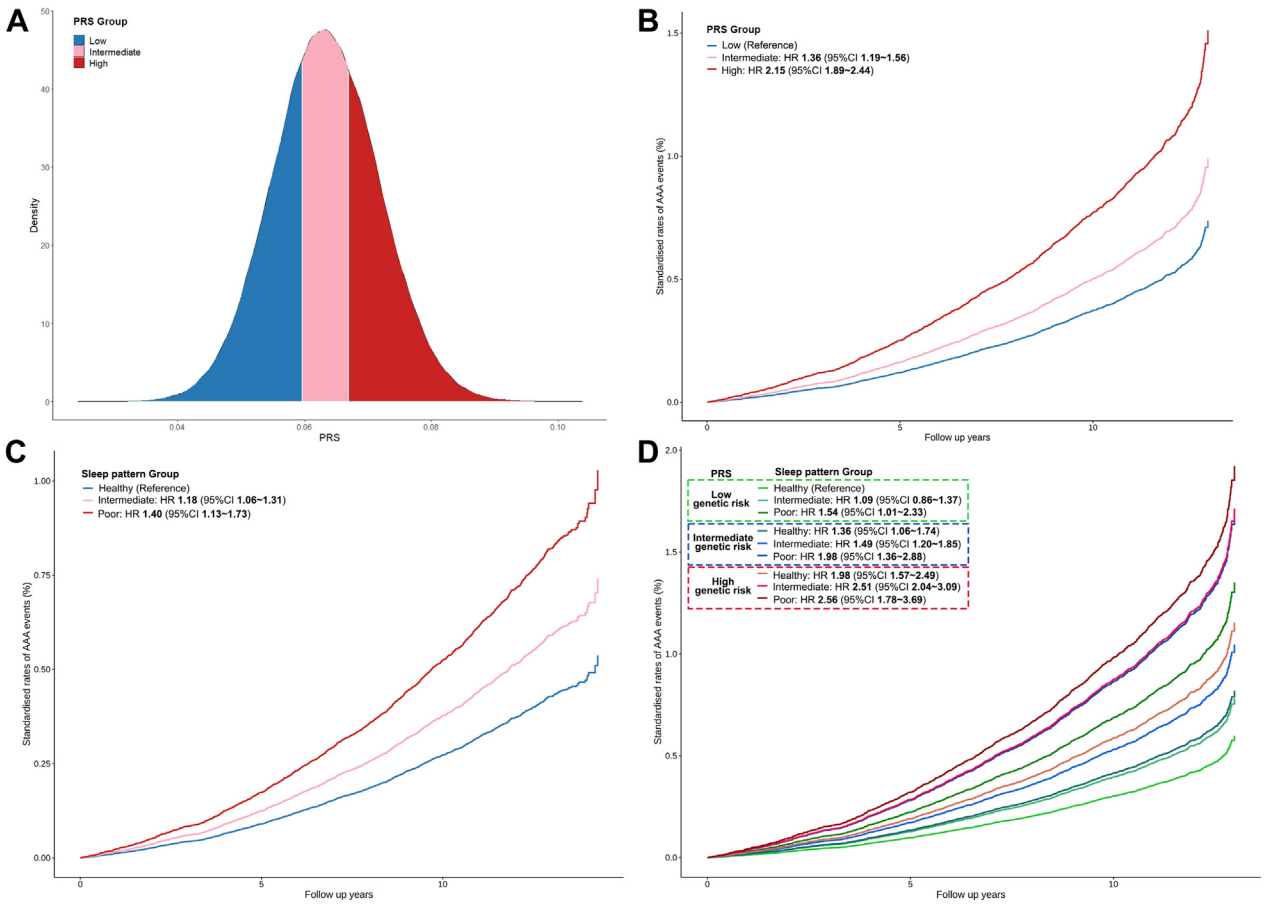
RESULTS

BASIC CHARACTERISTICS. A total of 334,855 individuals were included in this prospective study. In total, 1,622 AAA patients with a mean age of 63.49 ± 4.84 years were confirmed during a median follow-up of 12.59 years (IQR: 11.86-13.29 years), 86.9% of them were males. The comparison between included and excluded participants was provided in Supplemental Table 5. **Table 1** delineates the baseline characteristics of the participants, which have been stratified according to their respective sleep scores. Participants with higher sleep scores tend to exhibit a healthy lifestyle.

A total of 14,787 (4.3%) and 200,403 (58.1%) participants were categorized into poor and intermediate sleep pattern groups, respectively. Baseline characteristics showed significant differences between individuals with and without AAA. Males and older participants were more likely to develop AAA. Individuals without AAA tend to exhibit healthy sleep patterns and lifestyles. Three of the five sleep factors were significantly different between incident AAA and non-AAA cases, suggesting that no frequent daytime sleepiness, no snoring, and sleeping for 7 to 8 hours per day were associated with a lower risk of AAA.

ASSOCIATION OF SLEEP FACTORS WITH INCIDENT AAA CASES. Utilizing multivariate Cox proportional hazards models, the associations between the 5 sleep factors, sleep scores, and AAA risk were estimated, with adjustments considered. Three sleep components, insomnia, sleep duration, and chronotype, were independently associated with the risk of AAA

FIGURE 2 Association of PRS and Sleep pattern with Standardized rates of AAA events in the UK Biobank Cohort

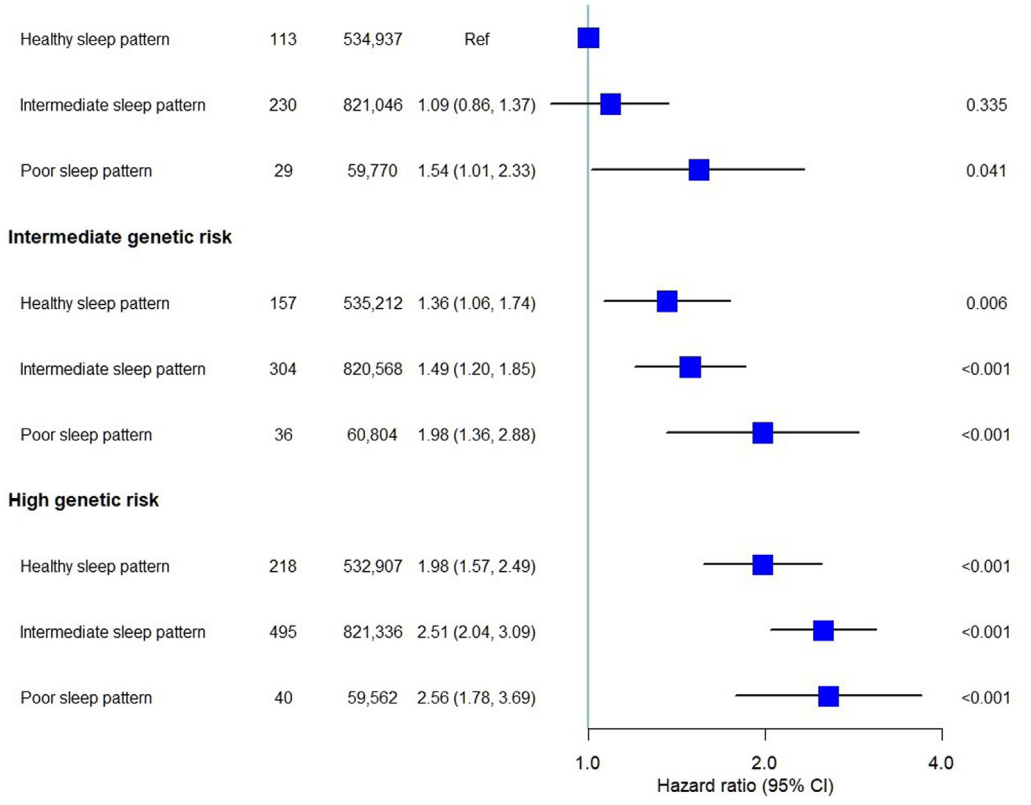


(A) Distribution and category of PRS for AAA; (B) Standardized rate of AAA events in low, intermediate, and high genetic risk group; HRs and CIs were estimated in full model; (C) Standardized rate of AAA events in healthy, intermediate, and poor sleep pattern groups; (D) Cumulative effects of genetic risk and sleep pattern on risk of AAA. AAA = abdominal aortic aneurysm; PRS = polygenic risk score.

across all models (Table 2), exhibiting a lower risk of 17%, 18%, and 17%, respectively. Given that sleep is a composite indicator, all 5 sleep factors were combined into sleep scores. The sleep score was inversely associated with the incidence of AAA, with higher scores correlating with a lower relative risk for the outcome (all P for linear trend <0.001). When compared to the reference group (score 0-1), the HR for AAA was 0.47 (95% CI: 0.35-0.64), 0.51 (95% CI: 0.38-0.69), and 0.62 (95% CI: 0.46-0.83) for participants with a sleep score of 5 across the 3 models, respectively. After adjusting for demographic characteristics, clinical conditions, and lifestyle factors (Model 3), each unit increase in the sleep score was associated with a 9% decrease in the risk of AAA (HR: 0.91, 95% CI: 0.86-0.96). Furthermore, we performed a sensitivity analysis by excluding the 2 insignificant sleep components in calculating sleep scores and found that the association between sleep scores and incident AAA remained robust (Supplemental Table 6). In competing risk analyses, the association between sleep scores and incident AAA remained robust after adjusting for non-AAA mortality (Supplemental Table 7).

Subsequently, the participants were categorized into different sleep pattern groups based on their sleep scores, and the effects of these sleep patterns were estimated. When compared to the group with a healthy sleep pattern (sleep score ≥4), individuals with intermediate (2 ≤sleep score ≤3) and poor (sleep score ≤1) sleep patterns were found to have an increased risk of developing AAA by 18% and 40%, respectively (HR: 1.18, 95% CI: 1.06-1.31 and HR = 1.40, 95% CI: 1.13-1.73, respectively) in the fully adjusted model (Model 3).

FIGURE 3 The Combined Association of Genetic Risk and Sleep Patterns With the Risk of Incident AAA Among 344,855 Participants

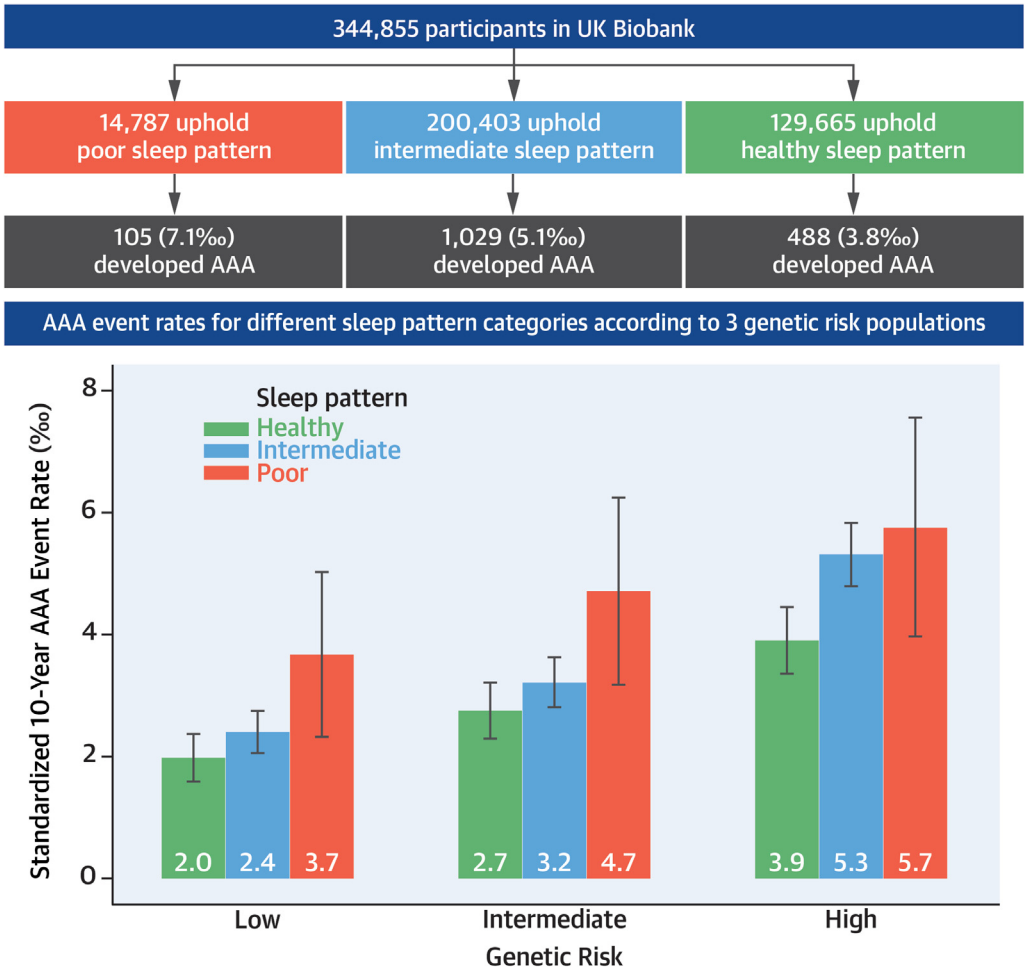


AAA = abdominal aortic aneurysm; PT = total person-years; rciRef = reference group.

ASSOCIATION OF GENETIC RISK WITH INCIDENT AAA CASES. For the PRS analysis, array batches and 10 significant principal components ($P < 0.05$) were added to adjust for the impact of population stratification. The 22 GWAS-identified SNPs (Supplemental Table 4) were used to construct the PRS and to estimate the potential association of genetic factors with AAA risk according to genetic variants. In our cohort, the PRS values approximated a normal distribution (**Figure 2A**) and significantly predicted AAA risk in the UK Biobank cohort (**Figure 2B**). Specifically, there was a gradient of risk across each grade of PRS, and thus participants with high genetic risk (the highest tertile of PRS) had a significantly higher risk of AAA events than those with low genetic risk (the lowest tertile of PRS), with a multivariate adjusted HR of 2.15 (95% CI: 1.89-2.44).

We further analyzed the association of sleep patterns and genetic factors with AAA incidence and assessed the extent to which adherence to a healthy sleep pattern can counteract genetic susceptibility. **Figures 2B and 2C** show the adjusted cumulative incidences of AAA according to sleep patterns and genetic risk, respectively. A joint cumulative effect of sleep patterns and genetic risk was observed for incident AAA events, according to the results of the UK Biobank cohort analysis (**Figure 2D**). **Figure 3** shows that a gradual increase in AAA risk was observed for sleep patterns across all genetic risk groups. Participants with high genetic risk and a poor sleep pattern had a more than 2.5-fold relative risk of AAA in contrast to those with low genetic risk and a healthy sleep pattern (HR: 2.56, 95% CI: 1.78-3.69). Stratification and interaction analyses were performed to assess the association of sleep patterns among genetic risk groups, and no significant interaction between genetic risk and sleep patterns was observed (Supplemental Table 8)

CENTRAL ILLUSTRATION **Ten-Year AAA Event Rates for Different Sleep Pattern Categories According to 3 Genetic Risk Populations**



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Standardized 10-year cumulative AAA event rates in UK Biobank according to sleep pattern and genetic risk. Error bars are 95% CIs. AAA = abdominal aortic aneurysm.

(P = 0.64 for interaction). We then calculated the PAF for sleep patterns and genetic risks, assuming that every participant was in the healthy sleep pattern or low-PRS group, respectively. Sleep pattern was estimated to explain 11.2% (95% CI: 4.62%-17.8%) of the population risk of developing AAA, suggesting that more than 10% of AAA events would have been prevented if all individuals adhered to a healthy sleep pattern. Genetic risk contributed more to AAA risk than sleep pattern, with the PAF value estimated to be 31.5% (95% CI: 25.5%-37.6%).

Further analyses stratified by genetic risk category confirmed that adherence to a healthy sleep pattern was associated with a lower risk of AAA across genetic groups (Central Illustration). Among participants with high genetic risk, 5.7% (95% CI: 3.9%-7.5%) of those with poor sleep patterns and 3.9% (95% CI: 3.3%-4.4%) of those with healthy sleep patterns developed AAA in the 10 years following up. A similar pattern could be observed in populations with low and intermediate genetic risk, where the impact of genetic risk was partially mitigated by adherence to healthy sleep patterns.

DISCUSSION

In this large-scale prospective study, we probed the combined association of genetic risk and 5 sleep behaviors (sleepiness, snoring, insomnia, sleep duration, and chronotype) for AAA risk. We found that healthy sleep factors were inversely associated with the incidence of AAA and that genetic risk and sleep patterns were independently associated with the risk of AAA. Participants with a poor sleep pattern (sleep score 0-1) and high genetic risk had a more than 2.5-fold higher risk of incident AAA than those with low genetic risk and a healthy sleep pattern (sleep score 4-5). Adherence to a healthy sleep pattern was associated with a lower risk of AAA in all genetic risk categories.

These findings lead to several conclusions. First, the analysis results indicated that healthy sleep behaviors, including no frequent insomnia, sleeping 7 to 8 hours/day, and an early chronotype, were associated with a lower AAA risk. This conclusion is similar to the one reported recently by a Mendelian randomization study of insomnia and AAA,[27] though the association was not significant (OR: 1.14, 95% CI: 0.98-1.33), probably due to the small number of cases. Studies on OSA and AAA also suggest an association between sleep behaviors and AAA progression,[13,14] but other features of OSA, such as apnea, may also be associated with AAA. We also compared the distribution of sleep patterns between participants with and without OSA and found that participants with OSA were more likely to have poor sleep patterns (Supplemental Table 9). Considering the correlation of sleep behaviors, we combined all 5 sleep behaviors to generate a sleep pattern as described previously,[12,22] even though some of them were not significantly associated with AAA in our analysis. We found that participants with a healthy sleep pattern had a 40% lower risk of developing AAA. Our results suggest that more than 11% of AAA cases may be prevented if all participants adhered to a healthy sleep pattern (PAF = 11.2%). The precise mechanisms underlying the combined effects of sleep factors on the risk of developing AAA remain unclear. This mechanism may involve the sympathetic nervous system.[13] A previous study showed that shortened sleep may increase the risk of endocrine and metabolic disruption and elevated sympathetic nervous activity.[28,29] From a public health perspective, our findings support the implications of promoting healthy sleep patterns in public health and clinical practice. However, this was an observational study, and further research on sleep should be conducted to investigate the pathophysiology underlying this association.

Similar to previous studies, our study found that male and older participants were more likely to develop AAA, and individuals with a healthy lifestyle, such as no smoking,[30] more physical activity,[31] and a healthy weight,[32] had a lower risk of developing AAA. The known mechanisms by which smoking leads to AAA development include disruption of collagen synthesis, altered expression of metalloproteinases, and response to oxidative stress.[33]

Second, genetic risk and sleep patterns were independently associated with the risk of incident AAA. Numerous studies have highlighted the significance of genetic susceptibility in primary prevention.[16,34-36] In line with previous studies, the current findings suggest that a higher genetic risk increases the risk of AAA. However, while previous studies were more often designed based on case-control studies and a small population, the present study validated the findings of previous GWASs in a large-scale cohort of the European population. In this study, the HR value for the high genetic risk population (top tertile of the PRS) was 2.15, reinforcing the importance of genetic susceptibility in AAA development. With the availability of genome sequencing technology, the application of genetic risk in predicting the occurrence of disease in individuals at the early stages of life has become possible.[37-39] These findings could complement the traditional classification of populations with a high risk of AAA.

Finally, the benefits of a healthy sleep pattern for AAA were observed in all genetic risk categories, indicating that the rise in AAA risk contributed by genetics can be balanced by healthy sleep, at least to some extent. To our knowledge, our study is the first to examine the association between combined healthy sleep behaviors and the risk of AAA and to evaluate the benefits in different genetic risk groups. The relative risk for AAA decreased by more than 30% with healthy sleep patterns compared to poor sleep patterns in the high genetic risk group (3.9% vs 5.7%) (**Central Illustration**), whereas the relative reduction in risk was higher in the moderate and low genetic risk groups, emphasizing the advantages of adhering to a healthy sleep pattern across the population. Similarly, another cohort study found that participants with a sleep score of 5 had a 35% lower risk of cardiovascular disease than those with a score of 0 to 1.[12] These findings further illustrate the implications of healthy sleep patterns in public health and clinical

practice, particularly among individuals with high genetic susceptibility to AAA.

The main strengths of the present study compared to previous studies are that we estimated the associations of sleep patterns and the 5 components of sleep behaviors with AAA and combined sleep patterns and genetic factors to evaluate their combined association with AAA. The design of this large-scale prospective study was based on a UK Biobank study that included data on extensive AAA-related SNPs and the adoption of a standardized information collection protocol.

STUDY LIMITATIONS. Despite these advantages, our study has a few limitations. First, changes in the sleep behaviors of participants after enrollment may affect our results, and our study was conducted under the assumption that sleep habits would not change significantly over time. Second, although the known potential confounders were adjusted in the Cox model, it is possible that unmeasured confounders and biases remained. Third, AAA is a progressive disease, and patients in the early stages often have no obvious symptoms and will not attend the hospital unless they have life-threatening conditions; therefore, its incidence may be underestimated. Fourth, the diagnosis of AAA may overlook certain undiagnosed cases when relying on the ICD-10 guidelines. Additionally, the assessment of covariates and sleep factors was conducted using a questionnaire, which may have introduced some bias. Finally, this study was limited to White British participants aged 39 to 73 years at recruitment; therefore, more research is required to investigate the extent to which these results can be generalized to the populations of other geographic regions in the world.

CONCLUSIONS

In the present study, a healthy sleep pattern was found to be associated with a lower risk of AAA despite the genetic risk, indicating that adherence to a healthy sleep pattern may offset the influence of genetic susceptibility. Our results provide a rationale for developing healthy sleep patterns to prevent AAA. From a public health perspective, our findings can encourage policymakers to focus on primary prevention and lower the risk of AAA by promoting healthy sleep patterns. Further research is needed to explore the mechanisms of sleep factors as well as genetic risk in the development of AAA in the future.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Sleep patterns and genetic risk were associated with the risk of developing AAA. A protective effect of healthy sleep patterns was observed across all genetic risk populations.

TRANSLATIONAL OUTLOOK: Further research is needed to understand the mechanisms by which sleep influences the risk of AAA.

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APPENDIX For supplemental tables, please see the online version of this paper.