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The Interaction Between Genetic Factors and Sleep Duration Associated with Coronary Artery Disease

By

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Degree to be awarded: Master of Public Health

Epidemiology

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The Interaction Between Genetic Factors and Sleep Duration Associated with Coronary Artery Disease

By

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Bachelor of Medicine and Bachelor of Surgery
Kwame Nkrumah University of Science and Technology
2017

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Abstract

The Interaction Between Genetic Factors and Sleep Duration Associated with Coronary Artery Disease
By Jeffery Osei

Background: Although genetic and lifestyle factors such as sleep duration contribute to the development of coronary artery disease (CAD), it is unclear whether sleep duration modifies the effect of genetic predisposition on CAD outcomes.

Methods: We examined the relationship between several polygenic risk scores (comprehensive CAD PRS, and PRSs of three risk factors) and CAD outcomes, as well as the interaction with sleep duration, in 354,845 participants of European ancestry in the UK Biobank. We fitted cox proportional hazard and Fine-Gray competing risk models and assessed PRS-sleep duration interaction on both additive and multiplicative scales.

Results: After excluding 14, 283 participants who had prevalent CAD at baseline, 354,845 people were followed for up to 12.0 (11.2-12.8) years. Out of this, 82,568 (23.2%), 266,745 (75.2%), and 5,532 (1.6%) had less than 7 hours of sleep/day, 7-9 hours of sleep/day, and more than 9 hours of sleep/day, respectively. We found a significant multiplicative gene-sleep duration interaction (PRS_{CAD}×Sleep) for new onset CAD. The risk was highest among participants with 7-9 hours of sleep/day (hazard ratio [HR] for 1 SD increase in genetic risk 1.39 [95% CI, 1.37-1.41]; compared with low genetic risk, HR for intermediate genetic risk 1.56 [95% CI, 1.49-1.64] and HR for high genetic risk 2.51 [95% CI, 2.39-2.64]). Participants with more than 9 hours of sleep/day had the lowest risk (HR for 1 SD increase in genetic risk 1.24 [95% CI, 1.15-1.34]; compared with low genetic risk, HR for intermediate genetic risk 1 .31 [95% CI, 1.06-1.64] and HR for high genetic risk 1.75 [95% CI, 1.37-2.23]). However, on the additive scale, there was no evidence of interaction. Additionally, Among the PRSs of three risk factors, we found a significant antagonistic interaction between hypertension-based PRS (PRS_{HTN}) and sleep duration for CAD death at both additive and multiplicative scales.

Conclusions: Further validation of the interaction between genetic factors and sleep duration associated with CAD is warranted. The assessment of gene-environment interaction on both multiplicative and additive scales could aid in understanding the complex interplay between risk factors and mechanisms underlying CAD. Robust gene-environment interaction effects would guide future public health preventive strategies of CAD.

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1.0 INTRODUCTION

Coronary artery disease (CAD) is the most common form of heart disease and remains the leading cause of death in the US and globally[1,2]. Globally, an estimated 9.4 million deaths and 185 million disability-adjusted life years were caused by CAD in 2021[3]. In the US, approximately 20 million adults aged 20 years and above were found to be living with CAD in 2020, with about 380,000 people dying from CAD[2]. According to a report from the American Heart Association, it is estimated that for every 40 seconds, a person in the US suffers a heart attack, a common clinical presentation of CAD[2]. In addition to increasing mortality and negatively affecting people's quality of life, CAD has a significant negative economic impact both internationally and locally in the US[4,5]. On average, about $219 billion is spent on CAD and other heart diseases in the US each year[6]. The national expenditure of CAD is projected to double from $187.9 billion in 2015 to $365.8 billion in 2035[7]. The overall burden of CAD continues to pose a serious threat to public health despite significant advances in CAD preventive measures. Thus, it is critical to understand the biological mechanism underlying the development of CAD and take early action against risk factors.

CAD is a complex multifactorial disease that results in an interplay between both genetic and environmental factors. The hallmark of the pathogenesis of CAD involves the formation of atherosclerotic plaque in the coronary arteries, eventually leading to an impairment of blood flow and oxygen to the heart. Atherosclerosis is an inflammatory process of the arteries predominantly driven by lipid deposition and other metabolic alterations brought on by a number of risk factors[8,9]. Genetic predisposition accounts for about 30-40% of the risk for CAD based on recent large-scale multi-population genetic studies[10]. This is lower than estimates previously reported in family and twin studies[11–13]. Previous genetic epidemiologic investigations have shown that CAD is polygenic and strongly driven by multiple genetic

variants, unlike mendelian diseases[14,15]. Over the past century, identifying these genetic variations has advanced slowly. Following the completion of the International HapMap Project in 2007[16], and recent development in high-throughput single nucleotide polymorphism (SNP) genotyping technologies, genome-wide association studies (GWAS) have been used to identify several genetic loci of relatively small effect size, associated with CAD[10,17–21].There have been several well-powered GWAS performed on CAD in predominantly European populations. The majority of these genetic variants discovered in European populations have also been replicated in Asians, and more recently, in Black and Hispanic populations[10]. Currently, over 270 genome-wide significant loci have been associated with CAD[21]. Although various pathophysiological pathways in CAD have been linked to these genetic variants, to date, the exact mechanism leading to the disease remains unknown. According to available evidence, these variants, when combined into a polygenic risk score (PRS), may better identify individuals at risk for CAD regardless of their family history of the disease[22]. Hence PRS of CAD can be used as a quantitative measure of genetic predisposition and a risk prediction tool for incident CAD outcomes.

The individual genetic variants discovered by GWAS only account for less than 15% of the estimated heritability of CAD[23]. Thus, the need to investigate additional genetic effects, such as those resulting from gene-environment interactions and CAD risk factors like body mass index (BMI), hypertension (HTN), and low-density lipoprotein (LDL) cholesterol. Some of the CAD genetic variants exhibit pleiotropy with traditional risk factors such as blood pressure phenotypes, BMI, and LDL cholesterol levels[24]. However, little is known about how the genetic effects of these risk factors interact with environmental factors such as sleep duration to contribute to the development of CAD, given that they have different molecular pathways.

A large proportion of the burden associated with CAD is attributable to modifiable health behavior including unhealthy sleep duration, smoking, and physical inactivity[3]. Getting enough sleep every day is important to our health, especially our mental and cardiovascular health. According to the American Academy of Sleep Medicine and Sleep Research Society, 7 hours or more of nighttime sleep is considered optimal for adults, even more than 9 hours for young adults, individuals with illness, and those recovering from a sleep deficit[25]. In contrast, from this same joint consensus statement, sleeping less than 7 hours every night is said to be associated with several detrimental health effects such as heart disease, stroke, and diabetes[25]. In spite of this, evidence from multiple epidemiological studies also suggests that too much sleep or too little sleep are both associated with an increased risk of coronary events[26,27]. For example, Krittanawong et al. in a systematic review and meta-analysis showed a U-shaped association between sleep duration and CAD[28]. Short sleep duration is linked to an increase in inflammatory markers, according to results of experimental studies conducted on humans and animals[29]. Also, inflammation, coagulation, and arterial stiffness are some of the hypothesized mechanisms underlying the association between too much sleep and CAD[30–33]. Despite these, several meta-analyses and Mendelian Randomization studies, have consistently reported evidence supporting a causal relationship between short sleep duration and CAD[26], whereas, findings from studies on the association between long sleep duration and CAD outcomes have been inconsistent.

The development of CAD is influenced by both genetic and lifestyle factors, thus previous studies have sought to understand if their interactions affect CAD. For instance, Khera et al.[34] in 2016 and Said et al.[35] in 2018 showed that a combination of genetic variations and unhealthy behavior increased the risk of cardiovascular diseases such as CAD and

hypertension. Since the introduction of large population-based consorts such as the UK Biobank, gene-environment interaction studies have been conducted on cardiovascular outcomes/traits such as CAD, blood pressure, lipid levels, considering environmental factors such as smoking, diet, and air pollution[36–40]. However, no large scale studies have been conducted to investigate gene-sleep interaction for CAD. Previous studies on sleep, genetic susceptibility, and the risk of CAD outcomes have predominantly focused on the joint effects of sleep duration and other sleep characteristics such as sleep pattern, quality of sleep, and daytime sleepiness[41–43]. However, little has been done to evaluate the complex interaction between sleep duration alone and genetics on the risk of CAD outcomes. Whether the effect of genetic predisposition on CAD outcomes may be modified by an individual's sleep duration remains largely unknown. Gene-environment interactions are likely to enhance our understanding of the pathophysiology and genetic susceptibility of cardiovascular diseases, which could also have significant clinical implications. Additionally, understanding how sleep duration and genetics interact to affect the risk of coronary artery disease (CAD) could aid in the risk stratification and even therapeutic strategies, and prevention of CAD given that sleep duration is a modifiable lifestyle behavior.

In this study, we investigated whether the effect of genetic predisposition on CAD outcomes is modified by sleep duration in a large population of European ancestry. The secondary aim was to investigate how the genetic predisposition to CAD outcomes driven by three risk factors is modified by sleep duration.

2.0 METHODS

2.1 Study population

The study population was drawn from the UK Biobank (UKB). The UKB is a large prospective study with more than 500,000 individuals, aged 40-69 years, enrolled between 2006 and 2010 from 22 assessment centers across the United Kingdom[44]. All participants

provided informed consent for the study. Phenotypic and health-related data, including laboratory biomarkers and lifestyle indicators, were collected during the baseline visit through standardized questionnaires, physical assessments, and interviews. For our study, only individuals of European ancestry were used. The research ethics committee at UKB gave its approval for our study, which was carried out under application number 34032. Detailed information on the study design and population is presented in figure 1. Additional information on data collection can be found here: https://www.ukbiobank.ac.uk/

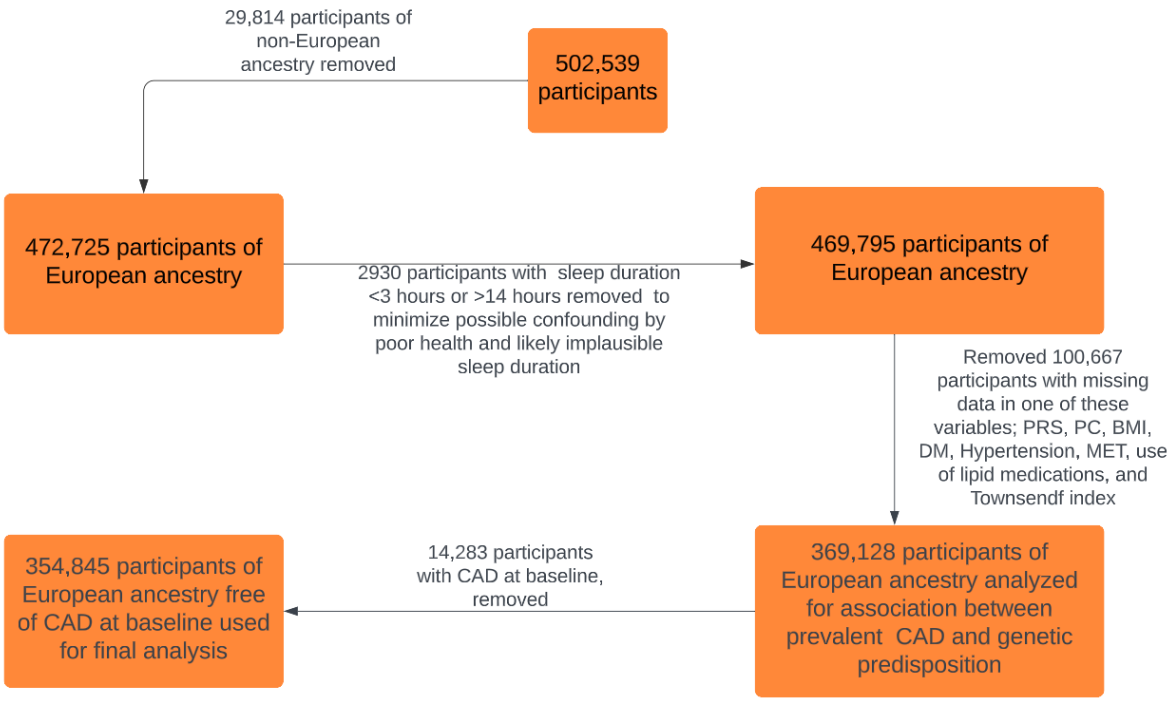


Figure 1.0 Flow chart of the study population inclusion/exclusion criteria used for this study

2.2 Ascertainment of outcome

The outcomes for this study were defined as primary events of incident CAD and CAD mortality. Hence, participants with no known CAD events before enrollment were used for this project. Using both data from the national health registry and inpatient hospital records, we identified incident CAD cases and death due to CAD after baseline. CAD case and death were defined as a person with at least one occurrence of CAD events or procedures as listed

in the International Classification of Disease, 10th edition (ICD-10) codes I20- I25 and Office of Population censuses and Survey Classification of Interventions and Procedures (K40-K46, K49, K50 or K75). The date of CAD events was recorded according to the earliest documented date of incident CAD or death diagnosis or the censoring date.

2.3 PRS construction

Polygenic risk scores for CAD and three risk factors (hypertension, BMI, and LDL-cholesterol) were developed in the UK Biobank[45]. Recently, the UKB released two sets of PRS for 53 traits in the cohort: a standard PRS generated from a meta-analysis of multiple external GWAS studies for all individuals in the cohort and an Enhanced PRS generated for a testing subgroup of 104,231 UKB participants[45]. In our study, we used the Standard PRS Set. Individual PRS values were calculated using a weighted PRS approach, after which a centering and standardization step was applied. Performance evaluation was done for the PRS in a multi-ancestry testing subgroup in UKB and other evaluation cohorts. A thorough description of the method used in constructing the scores including genetic data processing and supplementary tables can be found here:

https://www.medrxiv.org/content/10.1101/2022.06.16.22276246v2.supplementary-material

2.4 Ascertainment of sleep duration and other covariates

Sleep duration was self-reported and has been recorded as the number of hours of total night sleep. Given that the association between sleep duration and CAD has been described as U-shape, sleep duration was categorized as <7 hours/day, 7-9 hours/day, and >9 hours/day as has been used in the literature[46]. Potential confounders as seen in prior studies include age, sex, BMI, education (school leaving age <15 years vs. ≥15 years), smoking status, diabetes status, hypertension status, alcohol status, the use of lipid-lowering medications, socioeconomic status (measured as the Townsend deprivation index) and physical activity (<600 metabolic equivalent of task-min/week vs. ≥600 metabolic equivalent of task-min/week). Metabolic equivalent of task (MET) is a practical and objective means of

assessing energy expenditure during physical activities. It is a ratio of the rate of energy consumed during an activity to the rate of energy consumed at rest, which is about 3.5 ml of oxygen per kilogram body weight per minute[47–50]. Information on these confounders was collected using questionnaires and physical assessment at baseline enrollment.

2.5 Statistical analyses

We compared the baseline characteristics of the study participants by sleep duration groups using chi-square tests for categorical variables and ANOVA for continuous variables. PRS for CAD and the three risk factors were categorized into quintiles and divided into low (lowest quintile), intermediate (quintiles 2-4), and high (highest quintile) genetic risk groups. Additionally, PRSs were converted into Z-scores and modeled as continuous variables. Before excluding participants with prevalent CAD from the study population, we used logistic regression to evaluate the association of PRSs and prevalent CAD at baseline as well as effect modification by sleep duration. We then excluded participants who had prevalent CAD at baseline and used a cox proportional hazard model to examine the relationship of PRSs with incident CAD cases as well as the interactions between PRSs and sleep duration. The PH assumption was assessed using the Goodness of fit test. For variables that violated the assumption, stratified cox models were used. We adjusted for the following covariates in our final model: age, sex, BMI, education, smoking status, diabetes status, hypertension status, alcohol status, the use of lipid-lowering medications, socioeconomic status (Townsend index), physical activity (MET-min/week), and top 10 principal components of the GWAS. For analysis involving risk factor-based PRS, the corresponding risk factor was removed from the model. For example, in an analysis involving PRS_{BMI}, BMI was removed as a covariate from the model. For the secondary analysis, we used a competing risk model proposed by Fine and Gray to evaluate the association between PRSs and CAD death[51]. We also created composite CAD outcomes (non-fatal CAD/incident CAD and CAD death) and evaluated its association with PRS using the Fine and Gray competing risk model.

For these models, non-CAD death was treated as a competing event. Interaction was assessed on both a multiplicative and additive scale. For interaction on the multiplicative scale, we included the product terms in the cox model and conducted a likelihood ratio tests on them. We assessed additive interaction by calculating the relative excess risk due to interaction (RERI) on the hazard ratio estimates[52]. Confidence interval of the RERI estimates was calculated using the variance recovery method[53].

3.0 RESULTS

3.1 Population Characteristics

Out of the 469,795 participants of European ancestry, 100,667 participants were excluded because of missing data on PRS, BMI, diabetes status, hypertension status, MET, use of lipid medications, principal components, or Townsend index (Figure 1). 14,283 participants (69% of whom had 7-9 hours of sleep/day) with prevalent CAD at baseline were also excluded, leaving 354,845 participants for the final analysis (Figure 1). Table 1 shows the baseline characteristics of the study participants across the different sleep duration groups. During a median (interquartile range) follow-up of 12.0 (11.2-12.8) years, 25,316 (7.1%) had incident CAD and 2,780 (0.8%) died from CAD. Among all participants, 82,568 (23.2%), 266,745 (75.2%), and 5,532 (1.6%) had less than 7 hours of sleep/day, 7-9 hours of sleep/day, and more than 9 hours of sleep/day at baseline, respectively. At enrolment, the average age and BMI were 56.3 years old and 27.2 kg/m^2, respectively. In all sleep duration categories, there were more females than males. Compared with individuals with 7-9 hours of sleep per day, those with sleep duration of fewer than 7 hours had a higher incident CAD rate; were less active and had higher BMI; less educated; more likely to be smokers, hypertensive and diabetic; and less likely to drink alcohol. Additionally, among all three sleep duration groups, individuals with more than 9 hours of sleep had the highest incident CAD rate; were the oldest; had the highest BMI, and were less active; less likely to drink alcohol and less educated; more likely to be diabetic and hypertensive.

Table 1. Baseline characteristics of 354,845 UK Biobank participants of European Ancestry by Sleep Duration

	Mean (SD) or n (%)			
	<7 hrs/day (82568)	7-9 hrs/day (266745)	>9 hrs/day (5532)	Total (354845)
Incident CAD cases	6700 (8.1%)	17939 (6.7%)	677 (12.2%)	25316 (7.1%)
CAD death	722 (0.9%)	1943 (0.7%)	115 (2.1%)	2780 (0.8%)
Female	42954 (52.0%)	142929 (53.6%)	3110 (56.2%)	188993 (53.3%)
Age (years)	56.2 (7.79)	56.3 (8.14)	57.9 (8.13)	56.3 (8.06)
BMI (kg/mm)	27.8 (4.97)	27.0 (4.50)	28.8 (5.57)	27.2 (4.65)
Alcohol consumption				
Current	76599 (92.8%)	251690 (94.4%)	4776 (86.3%)	333065 (93.9%)
Past	3237 (3.9%)	7663 (2.9%)	400 (7.2%)	11300 (3.2%)
Never	2732 (3.3%)	7392 (2.8%)	356 (6.4%)	10480 (3.0%)
Diabetes	3762 (4.6%)	10288 (3.9%)	564 (10.2%)	14614 (4.1%)
Smoking Status				
Current	9973 (12.1%)	24702 (9.3%)	839 (15.2%)	35514 (10.0%)
Past	29273 (35.5%)	93274 (35.0%)	2042 (36.9%)	124589 (35.1%)
Never	43322 (52.5%)	148769 (55.8%)	2651 (47.9%)	194742 (54.9%)
Physical activity				
Ideal (≥600 MET-min/week)	66232 (80.2%)	220043 (82.5%)	3890 (70.3%)	290165 (81.8%)
Poor (<600 MET-min/week)	16336 (19.8%)	46702 (17.5%)	1642 (29.7%)	64680 (18.2%)
Townsend index	-1.23 (3.10)	-1.67 (2.86)	-0.666 (3.36)	-1.55 (2.93)
Lipid medication use	12247 (14.8%)	36501 (13.7%)	1354 (24.5%)	50102 (14.1%)
Hypertension	21297 (25.8%)	61050 (22.9%)	1759 (31.8%)	84106 (23.7%)
Education (years)				
School leaving Age < 15	1379 (1.7%)	3117 (1.2%)	210 (3.8%)	4706 (1.3%)
School leaving age 15 or more	81189 (98.3%)	263628 (98.8%)	5322 (96.2%)	350139 (98.7%)

CAD = coronary artery disease; BMI = Body Mass Index; MET= Metabolic Equivalents of Task.

3.2 Association between genetic susceptibility and prevalent CAD

In the multivariable-adjusted logistic regression and cox models, both comprehensive CAD (PRS_{CAD}) and the three risk factor-based PRSs were found to be significantly associated with prevalent CAD at baseline, incident CAD, CAD mortality, and composite CAD outcomes (both fatal and non-fatal CAD) after enrollment (Overall column in tables 2, 3, 4 and 5). Combined associations of all PRSs and sleep duration groups with prevalent CAD at baseline are shown in table 2. The overall odds of prevalent CAD increased significantly with each standard deviation increase in genetic risk (both comprehensive CAD and risk factor-based PRSs). However, this association was stronger with PRS_{CAD} compared with the three PRSs of

risk factors (PRS_{CAD} - OR 1.45 [95% CI, 1.42-1.48] vs PRS_{BMI}- OR 1.09 [95% CI,1.07-1.11] vs PRS_{HTN}- OR 1.15 [95% CI,1.12-1.17] vs PRS_{LDL}- OR 1.19 [95% CI,1.17-1.21]). Compared with the low comprehensive CAD risk group, the overall odds of prevalent CAD at baseline was 54% higher in the intermediate risk group (OR 1.54 [95% CI, 1.45-1.64]) and over 2.5 fold higher in the high-risk group (OR 2.77 [95% CI, 2.59-2.96]). For the categorized genetic risk groups, we observed a significant interaction with sleep duration on the multiplicative scale (p-value 0.04). For a given level of genetic risk, the odds of CAD at baseline was highest among participants with sleep duration more than 9 hours (Table 2.0). Among the three risk factor-based PRSs, PRS_{LDL} had the strongest association with prevalent CAD; compared with low genetic risk group, the overall odds of prevalent CAD at baseline was 33% higher in the intermediate risk group (OR 1.33 [95% CI, 1.27-1.40]) and 65% higher in the high-risk group (OR 1.65 [95% CI, 1.56-1.75]). Additionally, in the analysis involving the three risk factor-based PRSs, there was no significant interaction with sleep duration in the association between genetic predisposition and prevalent CAD at baseline.

3.3 Association of sleep duration and genetic susceptibility with incident CAD

For incident CAD, one standard deviation increase in comprehensive CAD genetic risk was associated with a 37% increase in risk (HR 1.37 [95% CI, 1.35-1.39]). Compared to participants with low CAD genetic risk, the overall risk of incident CAD moved from 53% in the intermediate risk group (HR 1.53 [95% CI, 1.47-1.59]) to over 2-folds in the high genetic risk groups (HR 2.39 [95% CI, 2.29-2.49]). We observed a relatively weaker association in the analysis for the three risk factor-based PRSs (Table 3). However, unlike prevalent CAD at baseline, PRS_{HTN} had the strongest association with incident CAD (HR for 1 SD increase in genetic risk 1.15 [95% CI, 1.13-1.16]; compared with low genetic risk, HR for intermediate genetic risk 1.24 [95% CI, 1.20-1.29]; compared with low genetic risk, HR for high genetic risk 1.49 [95% CI, 1.43-1.55]) among the three risk factors.

Table 2. Association of comprehensive CAD-PRS and three risk factor-based PRSs with prevalent CAD in the UK Biobank

	Overall	Sleep Duration			P value for interaction on multiplicative scale
		<7 hrs/day	7-9 hrs/day	>9 hrs/day	
Genetic predisposition*	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	
PRS_{CAD}[1]					
Per SD increase	1.45 (1.42, 1.48)	1.41 (1.35, 1.46)	1.47 (1.43, 1.50)	1.51 (1.36, 1.69)	0.13
Intermediate	1.54 (1.45, 1.64)	1.31 (1.16, 1.48)	1.63 (1.51, 1.76)	1.74 (1.23, 2.46)	0.04
High	2.77 (2.59, 2.96)	2.38 (2.09, 2.70)	2.92 (2.70, 3.17)	3.23 (2.24, 4.68)	
PRS_{BMI}[2]					
Per SD increase	1..09 (1.07, 1.11)	1.08 (1.04, 1.12)	1.09 (1.07, 1.12)	1.16 (1.04, 1.29)	0.44
Intermediate	1.15 (1.09, 1.21)	1.09 (0.98, 1.20)	1.16 (1.09, 1.24)	1.30 (0.97, 1.76)	0.68
High	1.28 (1.20, 1.36)	1.24 (1.10, 1.40)	1.28 (1.19, 1.38)	1.49 (1.06, 2.10)	
PRS_{HTN}[3]					
Per SD increase	1.15 (1.12, 1.17)	1.13 (1.09, 1.17)	1.15 (1.12, 1.17)	1.21 (1.09, 1.33)	0.44
Intermediate	1.24 (1.17, 1.31)	1.32 (1.18, 1.47)	1.20 (1.13, 1.28)	1.36 (1.01, 1.84)	0.51
High	1.50 (1.41, 1.59)	1.54 (1.37, 1.74)	1.48 (1.38, 1.59)	1.68 (1.21, 2.34)	
PRS_{LDL}[4]					
Per SD increase	1.19 (1.17, 1.21)	1.19 (1.15, 1.23)	1.19 (1.17, 1.22)	1.18 (1.08, 1.30)	0.98
Intermediate	1.33 (1.27, 1.40)	1.36 (1.23, 1.49)	1.33 (1.25, 1.41)	1.19 (0.92, 1.53)	0.84
High	1.65 (1.56, 1.75)	1.64 (1.47, 1.83)	1.67 (1.56, 1.79)	1.47 (1.09, 1.98)	

PRS_{CAD} = Polygenic risk score for coronary artery disease; PRS_{BMI} = Polygenic risk score for Body mass index; PRS_{HTN} = Polygenic risk score for Hypertension; PRS_{LDL} = Polygenic risk score for Low-density lipoprotein; SD = standard deviation.
*For categorized PRS scores, participants with low genetic risk (quintile 1) was used as reference.
1. We adjusted for age, sex, BMI, education, hypertension, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, use of lipid medications and top 10 principal components of GWAS.
2. We adjusted for age, sex, education, hypertension, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, use of lipid medications and top 10 principal components of GWAS.
3. We adjusted for age, sex, BMI, education, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, use of lipid medications and top 10 principal components of GWAS.
4. We adjusted for age, sex, BMI, education, hypertension, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, and top 10 principal components of GWAS.

We next assessed potential effect modification of the association between genetic predisposition and incident CAD by sleep duration on both multiplicative and additive scales. There was evidence of effect modification on the multiplicative scale between sleep duration and comprehensive CAD genetic risk with incident CAD (Table 3, p value when PRS was modeled as a continuous variable - 0.0007 and p-value for categorized PRS risk - 0.001). For

a given level of CAD genetic risk (PRS_{CAD}, both continuous variable and categorized genetic risk), the risk of incident CAD was highest among participants with sleep duration of 7 to 9 hours/day (HR for 1 SD increase in genetic risk 1.39 [95% CI, 1.37-1.41]; compared with low genetic risk, HR for intermediate genetic risk 1.56 [95% CI, 1.49-1.64]; compared with low genetic risk, HR for high genetic risk 2.51 [95% CI, 2.39-2.64]). Participants with more than 9 hours of sleep duration had the lowest risk of incident CAD among the 3 sleep duration groups (HR for 1 SD increase in genetic risk 1.24 [95% CI, 1.15-1.34]; compared with low genetic risk, HR for intermediate genetic risk 1.31 [95% CI, 1.06-1.64]; compared with low genetic risk, HR for high genetic risk 1.75 [95% CI, 1.37-2.23]). In the risk factor-based PRS analyses, we observed similar patterns for PRS_{HTN} and PRS_{LDL} (Table 3). However, we found no evidence of interaction on the multiplicative scale between sleep duration and the three risk factor-based PRSs with incident CAD (Table 3).

On the additive scale, effect modification of the association between genetic predisposition and incident CAD by sleep duration was done by estimating the relative excess risk due to interaction (RERI) for each PRS (Figure 2). We observed an antagonistic relationship between the comprehensive CAD genetic risk and sleep duration suggesting that the absolute risk of PRS_{CAD} and sleep duration was smaller than the sum of the risk due to each exposure. However, in contrast to interaction on the multiplicative scale, none of these RERI estimates was statistically significant (Figure 2). Hence, there was no evidence of interaction on the additive scale. Most of the RERI estimates in the analyses involving the three risk factor-based PRSs showed a synergistic relationship between genetic risk and sleep duration (Figure 2), but, as with the interaction on the multiplicative scale, none of these RERI estimates was statistically significant

Table 3. Combined association of genetic predisposition (PRSs) and sleep duration with incident CAD in the UK Biobank

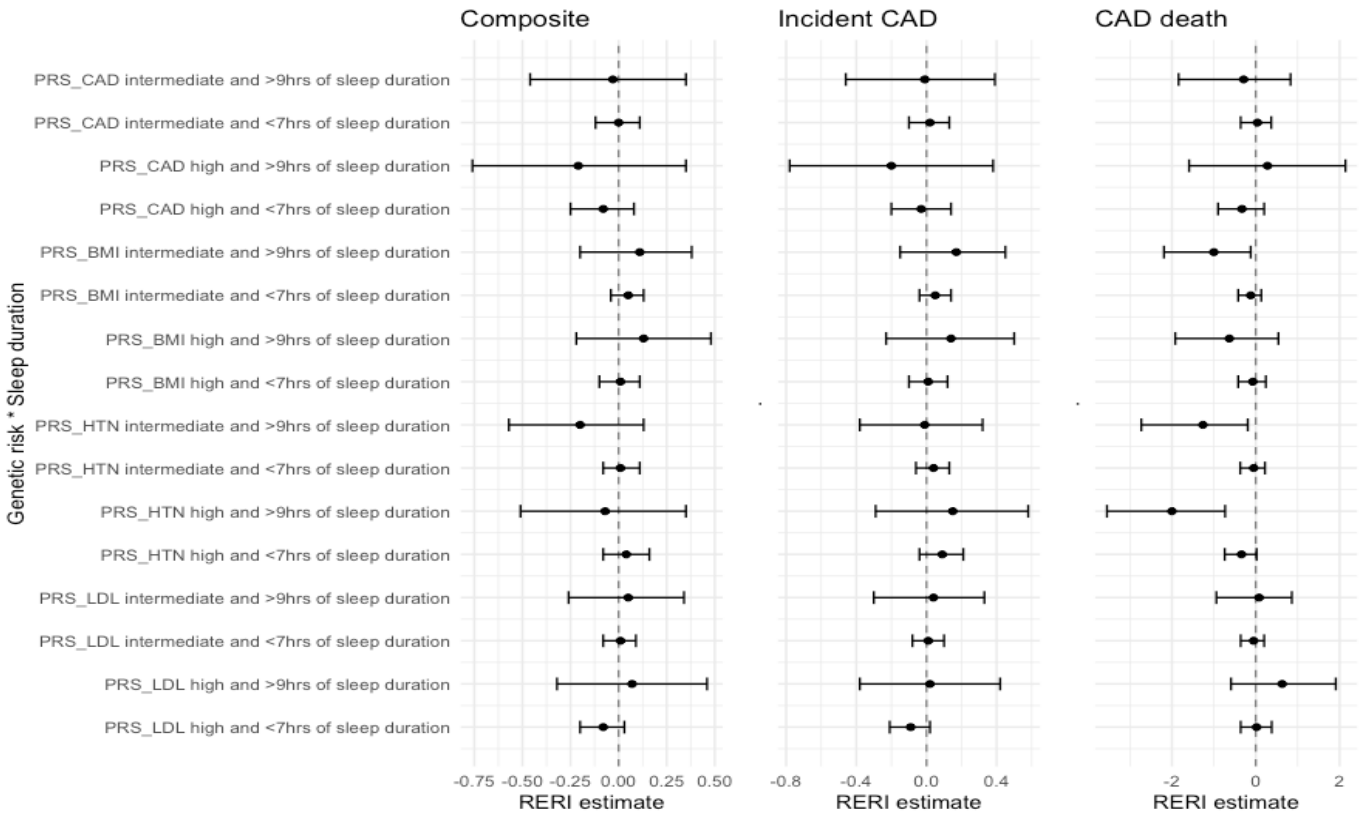
	Overall	Sleep Duration			P value for interaction on multiplicative scale
		<7 hrs/day	7-9 hrs/day	>9 hrs/day	
Genetic predisposition*	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
PRS_{CAD}[1]					
Per SD increase	1.37 (1.35, 1.39)	1.33 (1.30, 1.36)	1.39 (1.37, 1.41)	1.24 (1.15, 1.34)	0.0007
Intermediate	1.53 (1.47, 1.59)	1.46 (1.35, 1.57)	1.56 (1.49, 1.64)	1.31 (1.06, 1.64)	0.001
High	2.39 (2.29, 2.49)	2.16 (2.00, 2.34)	2.51 (2.39, 2.64)	1.75 (1.37, 2.23)	
PRS_{BMI}[2]					
Per SD increase	1.05 (1.04, 1.06)	1.04 (1.01, 1.06)	1.05 (1.04, 1.07)	1.05 (0.97, 1.13)	0.65
Intermediate	1.04 (1.01, 1.08)	1.07 (1.00, 1.14)	1.03 (1.99, 1.07)	1.15 (0.93, 1.41)	0.55
High	1.12 (1.07, 1.16)	1.11 (1.03, 1.20)	1.12 (1.07, 1.17)	1.19 (0.93, 1.51)	
PRS_{HTN}[3]					
Per SD increase	1.15 (1.13, 1.16)	1.15 (1.12, 1.17)	1.15 (1.13, 1.16)	1.13 (1.05, 1.22)	0.94
Intermediate	1.24 (1.20, 1.29)	1.24 (1.16, 1.33)	1.25 (1.20, 1.30)	1.16 (0.93, 1.44)	0.97
High	1.49 (1.43, 1.55)	1.49 (1.38, 1.61)	1.49 (1.42, 1.56)	1.49 (1.38, 1.61)	
PRS_{LDL}[4]					
Per SD increase	1.09 (1.08, 1.11)	1.07 (1.05, 1.10)	1.10 (1.08, 1.12)	1.06 (0.98, 1.14)	0.21
Intermediate	1.14 (1.11, 1.18)	1.13 (1.06, 1.21)	1.15 (1.10, 1.19)	1.13 (0.92, 1.38)	0.13
High	1.27 (1.22, 1.32)	1.18 (1.09, 1.27)	1.31 (1.25, 1.37)	1.23 (0.97, 1.55)	

PRS_{CAD} = Polygenic risk score for coronary artery disease; PRS_{BMI} = Polygenic risk score for Body mass index; PRS_{HTN} = Polygenic risk score for Hypertension; PRS_{LDL} = Polygenic risk score for Low-density lipoprotein; SD = standard deviation.

*For categorized PRS scores, participants with low genetic risk (quintile 1) was used as reference.

1. We adjusted for age, sex, BMI, education, hypertension, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, use of lipid medications and top 10 principal components of GWAS.
2. We adjusted for age, sex, education, hypertension, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, use of lipid medications and top 10 principal components of GWAS.
3. We adjusted for age, sex, BMI, education, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, use of lipid medications and top 10 principal components of GWAS.
4. We adjusted for age, sex, BMI, education, hypertension, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, and top 10 principal components of GWAS.

Figure 2. Relative excess risk due to interaction (RERI) for CAD polygenic risk scores and sleep duration on CAD outcomes. (Reference group is low PRS with 7-9 hours of sleep/day)



3.4 Association of sleep duration and genetic susceptibility with CAD death

We also explored the association between genetic susceptibility and CAD death and its interaction with sleep duration. In the Fine-Gray models treating non-CAD death as a competing risk, both comprehensive CAD genetic risk and the three risk factor-based PRSs were associated with CAD death (Table 4). However, we observed a stronger association for PRS_{CAD}, compared with the three risk factor-based PRSs. For example, one standard deviation increase in PRS_{CAD} was associated with a 42% increase in the risk of CAD death (HR 1.42 [95% CI, 1.36-1.47]) compared to a 6%, 12%, and 13% increased risk for PRS_{BMI}, PRS_{HTN}, and PRS_{LDL} respectively (Table 4). Also, compared with low PRS_{CAD} group, CAD mortality was 63% higher in the intermediate PRS_{CAD} group (HR 1.63 [95% CI, 1.44-1.83]) and more than 2.5 times higher in the high PRS_{CAD} group (HR 2.56 [95% CI, 2.25-2.91]). Among the three risk factor-based PRS analyses, we found the strongest association with

PRS_{LDL} (compared with low genetic risk, HR for intermediate genetic risk 1.25 [95% CI, 1.12-1.38]; compared with low genetic risk, HR for high genetic risk 1.40 [95% CI, 1.24-1.58]) and the weakest with PRS_{BMI} (compared with low genetic risk, HR for intermediate risk 0.99 [95% CI, 0.90-1.10]; HR for high risk 1.14 [95% CI, 1.01-1.28]).

The only significant multiplicative interaction we found between sleep duration and genetic predisposition to CAD death among all four PRS groups was for PRS_{HTN}. (Table 4).

Similarly, on the additive scale, we found an antagonistic interaction between PRS_{HTN} and sleep duration for two subgroups (a. participants with intermediate PRS_{HTN} genetic risk and sleep duration greater than 9 hours; RERI was -1.26 [95% CI: -2.73, -0.19] b. participants with high PRS_{HTN} genetic risk and sleep duration greater than 9 hours; RERI was -2.0 [95% CI: -3.55, -0.73]). This suggests that the absolute risk of PRS_{HTN} (intermediate and high risk) and long sleep duration was smaller than the sum of the risks due to each exposure alone. We also observed antagonistic additive interactions of PRS_{BMI} with sleep duration for one subgroup (participants with intermediate PRS_{BMI} and sleep duration greater than 9 hours; RERI was -1.0 [95% CI: -2.19, -0.12]).

3.5 Association of sleep duration and genetic susceptibility with composite CAD outcomes

Lastly, we evaluated the association between genetic susceptibility and composite CAD outcomes (both non-fatal CAD and fatal CAD) and its interaction with sleep duration. Here, the effect sizes and trends in effect modification were similar to those seen for incident CAD (Table 3 vs Table 5). For example, one standard deviation increase in comprehensive CAD genetic risk was associated with a 37% increase in risk of composite CAD outcomes (HR 1.37 [95% CI, 1.36-1.39]). Also, compared to participants with low CAD risk, the overall risk of composite CAD was 53% higher in the intermediate risk group (HR 1.53 [95% CI, 1.47-1.59]) and about 2.4 folds higher in the high genetic risk groups (HR 2.40 [95% CI, 2.30-

2.50]). PRS_{BMI} and PRS_{HTN} had the weakest and strongest associations with composite CAD outcomes among the three risk factors, respectively (Table 5).

Similar to incident CAD, we found evidence of effect modification on the multiplicative scale between sleep duration and PRS_{CAD} with composite CAD outcomes among the four PRS groups (p-value when PRS_{CAD} was modeled as a continuous variable - 0.0002 and p-value for categorized PRS_{CAD} risk - 0.001). For a given level of CAD genetic risk (PRS_{CAD}), the risk of composite CAD outcomes was highest for participants with 7-9 hours sleep/day (HR for 1 SD increase in genetic risk 1.39 [95% CI, 1.37-1.41]; compared with low genetic risk, HR for intermediate genetic risk 1.57 [95% CI, 1.50-1.64]; compared with low genetic risk, HR for high genetic risk 2.54 [95% CI, 2.42-2.66]) and lowest for participants with more than 9 hours of sleep/day (HR for SD increase in genetic risk 1.25 [95% CI, 1.16-1.35]; compared with low genetic risk, HR for intermediate genetic risk 1.30 [95% CI, 1.05-1.61]; compared with low genetic risk, HR for high genetic risk 1.75 [95% CI, 1.38-2.22]). However, there was no evidence of statistically significant interaction in the analyses involving the three risk factor-based PRSs.

On the additive scale, even though we observed an antagonistic relationship between PRS_{CAD} and sleep duration, none of the RERI estimates was statistically significant (Figure 2). Among the three risk factor-based PRSs, just like interaction on the multiplicative scale, interaction on the additive scale was not statistically significant (Figure 2).

Table 4. Combined association of genetic predisposition (PRSs) and sleep duration with CAD death in the UK Biobank

	Overall	Sleep Duration			P value for interaction on multiplicative scale
		<7 hrs/day	7-9 hrs/day	>9 hrs/day	
Genetic predisposition*	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
PRS_{CAD}[1]					
Per SD increase	1.42 (1.36, 1.47)	1.39 (1.29, 50)	1.44 (1.37, 1.50)	1.24 (1.02, 1.52)	0.27
Intermediate	1.63 (1.44, 1.83)	1.58 (1.25, 1.99)	1.68 (1.45, 1.94)	1.18 (0.68, 2.05)	0.22
High	2.56 (2.25, 2.91)	2.16 (1.67, 2.78)	2.77 (2.37, 3.23)	1.94 (1.07, 3.52)	
PRS_{BMI}[2]					
Per SD increase	1.06 (1.03, 1.10)	1.04 (0.97, 1.12)	1.08 (1.03, 1.12)	0.98 (0.80, 1.21)	0.55
Intermediate	0.99 (0.90, 1.10)	0.94 (0.77, 1.14)	1.05 (0.93, 1.18)	0.61 (0.39, 0.96)	0.25
High	1.14 (1.01, 1.28)	1.09 (0.87, 1.36)	1.18 (1.03, 1.36)	0.81 (0.49, 1.37)	
PRS_{HTN}[3]					
Per SD increase	1.12 (1.08, 1.17)	1.03 (0.96, 1.11)	1.18 (1.12, 1.23)	0.88 (0.74, 1.04)	0.0002
Intermediate	1.14 (1.02, 1.26)	1.12 (0.91, 1.37)	1.19 (1.05, 1.35)	0.64 (0.41, 1.00)	0.002
High	1.32 (1.17, 1.49)	1.12 (0.88, 1.42)	1.48 (1.28, 1.71)	0.49 (0.27, 0.88)	
PRS_{LDL}[4]					
Per SD increase	1.13 (1.09, 1.17)	1.15 (1.07, 1.24)	1.11 (1.07, 1.17)	1.22 (1.00, 1.48)	0.53
Intermediate	1.25 (1.12, 1.38)	1.19 (0.97, 1.45)	1.27 (1.12, 1.44)	1.21 (0.73, 2.01)	0.9
High	1.40 (1.24, 1.58)	1.36 (1.08, 1.72)	1.41 (1.22, 1.63)	1.63 (0.91, 2.90)	

PRS_{CAD} = Polygenic risk score for coronary artery disease; PRS_{BMI} = Polygenic risk score for Body mass index; PRS_{HTN} = Polygenic risk score for Hypertension; PRS_{LDL} = Polygenic risk score for Low-density lipoprotein; SD = standard deviation.

*For categorized PRS scores, participants with low genetic risk (quintile 1) was used as reference.

1. We adjusted for age, sex, BMI, education, hypertension, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, use of lipid medications and top 10 principal components of GWAS.
2. We adjusted for age, sex, education, hypertension, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, use of lipid medications and top 10 principal components of GWAS.
3. We adjusted for age, sex, BMI, education, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, use of lipid medications and top 10 principal components of GWAS.
4. We adjusted for age, sex, BMI, education, hypertension, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, and top 10 principal components of GWAS.

Table 5. Combined association of genetic predisposition (PRSs) and sleep duration with composite CAD outcomes* in the UK Biobank

	Overall	Sleep Duration			P value for interaction on multiplicative scale
		<7 hrs/day	7-9 hrs/day	>9 hrs/day	
Genetic predisposition**	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
PRS_{CAD}[1]					
Per SD increase	1.37 (1.36, 1.39)	1.33 (1.30, 1.36)	1.39 (1.37, 1.41)	1.25 (1.16, 1.35)	0.0002
Intermediate	1.53 (1.47, 1.59)	1.45 (1.35, 1.55)	1.57 (1.50, 1.64)	1.30 (1.05, 1.61)	0.001
High	2.40 (2.30, 2.50)	2.13 (1.97, 2.30)	2.54 (2.42, 2.66)	1.75 (1.38, 2.22)	
PRS_{BMI}[2]					
Per SD increase	1.05 (1.03, 1.06)	1.04 (1.01, 1.06)	1.05 (1.04, 1.07)	1.05 (0.98, 1.13)	0.51
Intermediate	1.04 (1.01, 1.07)	1.07 (1.00, 1.14)	1.03 (0.99, 1.07)	1.10 (0.90, 1.34)	0.64
High	1.11 (1.07, 1.15)	1.10 (1.02, 1.19)	1.11 (1.06, 1.16)	1.18 (0.93, 1.49)	
PRS_{HTN}[3]					
Per SD increase	1.14 (1.13, 1.16)	1.13 (1.11, 1.16)	1.15 (1.13, 1.16)	1.10 (1.02, 1.18)	0.38
Intermediate	1.23 (1.19, 1.28)	1.22 (1.14, 1.30)	1.25 (1.20, 1.30)	1.03 (0.84, 1.27)	0.47
High	1.47 (1.42, 1.53)	1.45 (1.34, 1.56)	1.49 (1.42, 1.56)	1.25 (0.99, 1.57)	
PRS_{LDL}[4]					
Per SD increase	1.09 (1.08, 1.11)	1.08 (1.05, 1.10)	1.10 (1.08, 1.12)	1.07 (1.00, 1.15	0.26
Intermediate	1.15 (1.11, 1.19)	1.14 (1.07, 1.21)	1.16 (1.11, 1.20)	1.14 (0.94, 1.38)	0.15
High	1.28 (1.23, 1.32)	1.19 (1.10, 1.28)	1.32 (1.26, 1.38)	1.25 (1.00, 1.58)	

PRS_{CAD} = Polygenic risk score for coronary artery disease; PRS_{BMI} = Polygenic risk score for Body mass index; PRS_{HTN} = Polygenic risk score for Hypertension; PRS_{LDL} = Polygenic risk score for Low-density lipoprotein; SD = standard deviation.
*Composite CAD outcomes = non-fatal CAD and fatal CAD
**For categorized PRS scores, participants with low genetic risk (quintile 1) was used as reference.
1. We adjusted for age, sex, BMI, education, hypertension, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, use of lipid medications and top 10 principal components of GWAS.
2. We adjusted for age, sex, education, hypertension, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, use of lipid medications and top 10 principal components of GWAS.
3. We adjusted for age, sex, BMI, education, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, use of lipid medications and top 10 principal components of GWAS.
4. We adjusted for age, sex, BMI, education, hypertension, diabetes, smoking status, alcohol status, socioeconomic status, physical activity, and top 10 principal components of GWAS.

4.0 DISCUSSION

In this large prospective cohort study of individuals of European ancestry, using standard PRSs from the UK Biobank, we found the following: (a) a higher genetic risk (both comprehensive CAD and three risk factor-based PRSs) was associated with increased risk of prevalent CAD, new onset CAD, CAD death and composite CAD outcomes; (b) among the PRSs of the three risk factors, a significant gene-sleep duration antagonistic additive and

multiplicative interaction for hypertension-based PRS (PRS_{HTN}) for CAD death (but not for prevalent, incident CAD and composite CAD outcomes); (c) a significant gene-sleep duration (comprehensive CAD genetic risk or PRS_{CAD}) multiplicative interaction for new onset CAD and composite CAD outcomes (but not for prevalent CAD and CAD death), where the risk of these outcomes was highest among participants with 7-9 hours sleep/day and least among participants with more than 9 hours of sleep/day. Most importantly, we did not find evidence of additive interaction between genetic predisposition to CAD (PRS_{CAD}) and sleep duration on CAD incidence and composite CAD outcomes although we observed a significant multiplicative interaction. Based on the findings of these statistical interactions, genetic predisposition, and sleep duration may be independent in the causation of CAD[54–56]. However, these findings need further validation.

Our study demonstrated how genetic effects from intermediate traits such as hypertension, BMI, and LDL-Cholesterol levels drive the incidence of CAD outcomes, and how this association is modified by sleep duration. When compared to BMI and LDL-cholesterol levels, the genetic effect of hypertension was associated with a higher risk of CAD incidence. This is consistent with the previously established link between hypertension and CAD[57–59]. Thus, genetically-driven hypertension pathway may be an important one to consider in the pathogenesis of CAD. And could be added to other pathophysiologic mechanisms underlying the association between hypertension and CAD, such as the direct effect of hypertension on arterial wall and endothelium; a reduction in coronary reserve due to coronary artery remodeling; and an increase in myocardial oxygen demand due to left ventricular hypertrophy[58]. Contrary to previous studies (where either sleep duration was used in combination with other health behaviors or the outcome was just one subtype of CAD), [26,43,60] our study did not find the U or J shape association between sleep and CAD after adjustment of other CAD risk factors[26,43,60]. Rather, the present study suggests that, for a given level of

genetic risk, individuals with optimal sleep duration (7-9 hours/day, as defined by the American Academy of Sleep Medicine and Sleep Research Society) have the highest risk for both fatal and non-fatal CAD.

Interaction on the additive scale has not been evaluated in previous gene-sleep interaction[42,60] and gene-lifestyle behaviors studies[34,35]. The majority of these studies assessed multiplicative interaction, though, additive interaction is said to have a greater potential impact on public health and is more directly related to tests for mechanistic interaction[61]. We found evidence of an antagonistic additive interaction between genetic predisposition for hypertension and long sleep duration on CAD death in our study, with the absolute risk reduction due to long sleep duration being stronger in the high genetic risk group than the intermediate genetic risk group. This shows that contrary to what we know about the effect of long sleep duration on hypertension, the combined effect of these exposures reduces the risk of CAD death. Despite the fact that all of the other additive interaction estimates found in our study were not statistically significant, these findings could serve as the starting point for future exploratory research on the relationship between sleep duration and CAD outcomes. Through this, new hypotheses on the potentially different mechanisms between sleep duration and its effect on CAD onset can be generated. The biological mechanisms that drive the association between sleep-related factors and CAD outcomes are complex and need more research. Hence, the use of sleep duration alone can be a starting point for such studies. Our study focused on sleep duration alone because of this reason and the fact that sleep duration can be easily modified as compared to other sleep behaviors and patterns.

Our study has several limitations. First of all, we only included people of European ancestry in our final analysis and this poses a potential threat to the generalizability of our findings. Secondly, there is the risk of residual confounding and misclassification due to imperfect covariate measurements because we used self-reported rather than objective assessment of

most variables, including sleep duration. Also, according to the UK biobank PRS release statement, the enhanced PRS is more powerful than almost all other PRSs previously issued, including the standard PRS. Hence the use of the standard PRS as seen in our study may have resulted in biased effect sizes. Finally, in our study, outcomes were defined based on data from in-hospital records and this could lead to the misclassification of outcomes and loss of potential cases that might have been reported in outpatient settings.

5.0 CONCLUSION

In conclusion, we found evidence of a multiplicative but not additive interaction between genetic predisposition to CAD and sleep duration on the risk of CAD development. We also found evidence of an antagonistic interaction (both multiplicative and additive) between genetic predisposition to hypertension and sleep duration on the risk of CAD death. Further validation of the interaction between genetic factors and sleep duration associated with CAD is warranted. Our findings emphasize the importance of the assessment of gene-environment interactions on both multiplicative and additive scales. Findings from robust gene-environment interaction studies could help us better understand the risk factors and mechanisms underlying cardiovascular diseases like CAD, as well as guide future public health preventive strategies.

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