國立臺灣大學公共衛生學院流行病學與預防醫學研究所

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睡眠至關重要：前瞻性研究探討多面向睡眠表現型對不同心血管疾病類型之影響

Sleep Matters: A Prospective Study of Multidimensional Sleep Phenotypes and Their Differential Impact on Cardiovascular Diseases

李育霖

Yu-Lin Lee

指導教授：郭柏秀 博士

Advisor: Po-Hsiu Kuo, Ph.D.

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本論文係李育霖君（學號 R128490010）在國立臺灣大學流行病學與預防醫學研究所完成之碩士學位論文，於民國 114 年 6 月 25 日承下列考試委員審查通過及口試及格，特此證明。

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中文摘要

引言：

心血管疾病長期位居全球主要死因之首，許多研究致力於識別其風險因子，並將相關發現納入臨床介入指引。而美國心臟協會近年將睡眠納入維護心血管健康的主要因子之一，並依照年齡層提出建議的睡眠時長。然而，健康的睡眠型態本質上是多面向的，涵蓋多種睡眠表現型。現今大部分研究聚焦於單一睡眠表現型對整體心血管疾病風險的影響，且多數依賴問卷調查來獲取主觀的睡眠資訊。因此，本研究旨在全面性的探討主觀及客觀睡眠表現型與各種心血管疾病亞型的關聯，藉此識別與心血管疾病相關性最強的關鍵睡眠表現型，並了解哪些心血管疾病亞型廣泛受到睡眠型態的影響，亦探討需重點介入的易感性族群。

方法：

本研究透過英國人體生物資料庫，以問卷調查取得了 447,183 名參與者的主觀睡眠資料，並進行長期追蹤。部分參與者則進一步配戴腕動計，有 5 天以上客觀睡眠資料的參與者，使用 R 套件 *GGIR* 取得有意義的睡眠參數。心血管疾病亞型則根據住院之 ICD-10 診斷碼及初級照護的病歷紀錄，使用 PheCODE 系統進行亞型分類。統計分析則利用 Cox 比例風險模型評估睡眠表現型與心血管疾病風險的相關性，並進一步計算族群可歸因分率，以量化特定睡眠表現型對疾病風險的貢獻。最後，針對性別及發病年齡進行分層分析，以識別易感性族群。

結果：

在主觀睡眠表現型中，午睡、失眠及晨起困難被發現為顯著的風險因子，且在共 11 種心血管疾病亞型之多重假設檢定經 Bonferroni 校正後（$p < 0.0045$），廣泛影響近半數的亞型。其中，失眠（HR = 1.14-1.30，PAF = 3.35-8.39）及午睡（HR = 1.05-1.20，PAF = 2.1-10.36）展現了相對較強的風險效應。客觀睡眠指標與心血管疾病的相關性則較弱，僅睡眠規律指數對週邊血管疾病呈現顯著的保護作用（HR = 0.71，$p = 0.0029$）。我們也觀察到缺血性心臟病與缺血性中風為最廣泛受到不良睡眠表現型影響的兩大心血管疾病亞型。

除此之外，結合五項主觀睡眠表現型計算的健康睡眠分數對整體心血管疾病、缺血性心臟病及缺血性中風均呈現顯著的保護效果。以健康睡眠分數 3 分以下定

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義為整體睡眠狀況差的參與者增加了 13%整體心血管疾病的風險、22%缺血性心臟病風險以及 12%缺血性中風風險。觀察到較高的族群可歸因分率則進一步表明，同時考量多面向的睡眠型態相較於單一睡眠表現型能更全面的反映睡眠對心血管的影響。而分層分析結果則發現失眠與午睡的風險效應在女性及早發性心血管疾病的參與者中影響更為顯著。

結論：

本研究結果突顯了睡眠在心血管健康中的多面向影響及其重要性。關鍵的睡眠表現型，特別是失眠與日間午睡，在調整其他共變項後，依然廣泛且顯著地提升心血管疾病的發生，尤其是在女性及早發性的群體中更為明顯。而客觀量測的睡眠規律也與週邊血管疾病存在顯著關聯。強調了整合主觀及客觀睡眠特徵以加強我們對睡眠健康理解的重要性，並凸顯在心血管疾病預防中實施更精準的睡眠介入策略的必要性。

關鍵字：

睡眠、失眠、午睡、心血管疾病、世代追蹤研究

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ABSTRACT

Background

Cardiovascular disease (CVD) continues to be the leading global cause of mortality. Although sufficient sleep duration has been recognized as essential for cardiovascular health, sleep health is inherently multidimensional, encompassing a range of sleep phenotypes. To date, most research has examined single sleep traits in relation to total CVD risk, often relying on subjective self-reports. This study aimed to (1) comprehensively assess both subjective and objective sleep phenotypes in relation to various CVD subtypes, (2) identify the key sleep traits most strongly associated with CVD onset and determine the subtypes most influenced by sleep health, also (3) explore population subgroups that may be more susceptible to sleep-related cardiovascular risk.

Materials and Methods

A prospective cohort study of 447,183 UK Biobank participants was conducted with extensive person-years of follow-up. Subjective sleep phenotypes were derived from self-reported questionnaires, while objective measures were extracted from a subset with over 5 days of actigraphy data using the R package *GGIR*. CVD subtypes were classified using the PheCODE system, based on inpatient ICD-10 and primary care records. Cox proportional hazards models were used to evaluate the associations between sleep phenotypes and CVD risk. Additionally, population attributable fraction (PAF) quantified the contribution of specific sleep phenotypes to disease burden. Finally, stratified analyses by age and gender were conducted to identify vulnerable populations.

Results

Among subjective phenotypes, napping, insomnia, and difficulty waking in the morning emerged as significant predictors, broadly influencing nearly half of all CVD subtypes after Bonferroni correction for multiple testing across 11 subtypes ($p < 0.0045$),

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with insomnia (HR = 1.14-1.30, PAF = 3.35-8.39) and napping (HR = 1.05-1.20, PAF = 2.10-10.36) exhibited relatively stronger risk effects. Objectively measured sleep features demonstrated weaker associations, with a significant protective effect only observed for sleep regularity index in relation to peripheral vascular disease (HR = 0.71, p = 0.0029). Additionally, ischemic heart disease and ischemic stroke were identified as the two CVD subtypes most widely affected by adverse sleep profiles.

Notably, a healthy sleep score combining 5 subjective sleep phenotypes showed significant protective effects against total CVD, ischemic heart disease, and ischemic stroke. Participants with poor overall sleep health defined as a healthy sleep score of 3 or lower exhibited a 13% increase in total CVD risk, 22% in ischemic heart disease risk, and 12% in ischemic stroke risk. The higher PAF further suggested that a multidimensional assessment of sleep health better captured the overall impact of sleep on CVD risk. The stratified analyses revealed that the effects of insomnia and napping on CVD subtypes were more pronounced in females and in participants with earlier disease onset age.

Conclusion

Sleep plays a substantial and multidimensional role in cardiovascular health. Key sleep phenotypes, particularly insomnia and daytime napping, contribute broadly and significantly to CVD onset after adjusting for other covariates, especially among women and participants with early disease onset age. Additionally, objectively measured sleep regularity showed a significant association with peripheral vascular disease. These insights show the importance of integrating both subjective and objective sleep characteristics to deepen our understanding of sleep health, and emphasize the need for more targeted sleep interventions in CVD prevention strategies.

Key Words: sleep, insomnia, napping, cardiovascular disease, cohort study

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Chapter 1: Introduction

1.1 Epidemiology of cardiovascular disease and sleep problem

Affecting approximately 640 million people worldwide, predominantly among those aged 50 years and older, cardiovascular disease (CVD) contributes to approximately 33% of all deaths globally [1]. In Europe, CVD poses a significant health and economic burden, costs approximately €282 billion per year, representing 11% of the total EU healthcare expenditure [2].

CVD refers to a wide spectrum of conditions involving the heart and blood system. The most common types including ischemic heart disease, cardiomyopathies, heart failure, cardiac arrhythmias, stroke, and other related conditions [3]. Based on their pathophysiological mechanisms and affected anatomical sites, cardiovascular disease subtypes can be broadly categorized as follows. Cerebrovascular disease, caused by inadequate blood flow to the brain or blood vessel rupture, which can be classified into ischemic stroke and hemorrhagic stroke [4]. Diseases affecting the heart arteries include ischemic heart disease and hypertension, with ischemic heart disease results from heart damage caused by narrowing of the coronary arteries [3]. Other circulatory diseases such as peripheral vascular disease, venous thromboembolic disease, and pulmonary heart disease involve abnormalities in the blood vessels supplying various organs [5]. Finally, cardiac problems directly related to heart structure, function, or electrical activity include heart failure, cardiomyopathy, valvular disease, and arrhythmias.

On the other hand, sleep problems have risen rapidly in the past decade. Approximately 30% of adults experience at least one symptom of nighttime insomnia [6]. Obstructive sleep apnea is the most frequently reported sleep problem, with poor sleep quality, insomnia, and excessive daytime sleepiness occurring subsequently [7]. These

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disturbances impose a substantial socioeconomic burden and related to adverse short and long-term health conditions, further underscore the importance of addressing this issue [8, 9].

1.2 Sleep as a potential risk factor for cardiovascular diseases

Over decades, numerous studies have identified both non-modifiable and modifiable risk factors for cardiovascular disease. Key factors include age, gender, ethnicity, and family history [10], as well as socioeconomic and environmental characteristics such as income, education, and employment [11]. Modifiable factors widely targeted in global prevention efforts, including smoking, physical activity, alcohol consumption, healthy diet, body measurement index (BMI), blood pressure, and cholesterol, were observed remain highly prevalent in the population [12, 13].

In addition to traditional risk factors, sleep health has increasingly been recognized as a critical determinant of cardiovascular outcomes. Among various indicators of sleep health, sleep duration is the most direct and easily measured. Short sleep duration has been consistently linked to both the incidence and mortality of coronary heart disease and stroke in prospective cohort studies [14]. The biological pathways connecting sleep deprivation to increased CVD risk are complex and multifactorial, involving higher levels of inflammation index such as interleukins and C-reactive protein [15], increased oxidative stress leading to endothelial dysfunction [16], impaired insulin sensitivity accompanied by disrupted lipid metabolism [17], and overactivation of the sympathetic nervous system [18]. Together, these pathways lead significantly to the development of CVD.

Therefore, the American Heart Association added sleep as the eighth core component for cardiovascular health in 2022, recommending most adults to sleep for 7 to 9 hours per night [19]. A meta-analysis found that 38.5% of the global population fails to

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meet this sleep recommendation, making insufficient sleep the most prevalent risk factor among all eight components [20]. However, sleep health is inherently multidimensional, influencing body function through various dimensions, mainly including duration, timing, daytime alertness, satisfaction, efficiency or continuity, regularity, and soundness [21, 22]. Since no single aspect of sleep health fully captures its physiological and phenomenological complexity, incorporating multiple dimensions of sleep health and exploring their differential impacts and contributions can offer meaningful insights.

1.3 Relationship between sleep phenotypes and cardiovascular disease

Previous literatures exploring the relationship between sleep and CVD can be divided into two categories based on sleep measurement methods: subjective assessments using questionnaires, and objective assessments using polysomnography or actigraphy.

Using subjective measures in the dimension of duration, one meta-analysis of cohort studies found sleep duration demonstrated a U-shaped association with the risk of total CVD, coronary heart disease, and stroke [23]. Daily 7 hours of sleep showed the lowest risk, compared to this reference, each one-hour decrease related to a 6% higher risk of total CVD, and each one-hour increase was linked to a 13% higher risk. However, another cohort study conducted in China found different results, indicating that increased total CVD risk was related solely to long sleep duration (>9 hours), and only observed in participants more than 50 years old [24]. Regarding sleep timing, a longitudinal study reported that an evening chronotype increased the risk of hemorrhagic stroke [25]. Additionally, meta-analyses have shown that evening chronotypes exhibit worse cardiometabolic profiles, such as higher blood glucose and LDL cholesterol, indicating a potential adverse effect on cardiovascular risk that warrants further investigation [26]. For other sleep dimensions, previous meta-analysis found that daytime sleepiness often assesses by Epworth Sleepiness Scale showed a 28% increased risk for total CVD and

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52% increased risk for stroke, but with high heterogeneity among studies [27]. Genetic evidence suggests that daytime napping has been linked to a higher risk of five CVD subtypes, including heart failure, hypertension, atrial fibrillation, heart arrythmias, and coronary artery disease [28]. However, whether napping is detrimental or protective for CVD remains inconclusive, potentially due to cultural differences in nap duration [29].

On the other hand, research using wearable devices and polysomnography to measure objective sleep parameters has gained increasing attentions these years. A longitudinal study employing in-home polysomnography found that increased sleep duration was linked to a steady decline in CVD mortality, which differed from the J-shape relationship seen with subjective sleep duration [30]. Two additional studies assessed sleep irregularity by sleep duration standard deviation from actigraphy data. One observed a 2.14 times increased risk of CVD among participants with the greatest irregularity [31], and another found a 56% increased risk of essential hypertension with elevated irregularity [32]. However, since sleep duration standard deviation does not capture the full sleep–wake pattern, the sleep regularity index may offer a more comprehensive assessment to consecutively characterize the impact of regularity on CVD risk [33]. Moreover, other objective sleep parameters should also be evaluated for their cardiovascular effects.

1.4 The impact of sleep on cardiovascular diseases in subpopulation

Although lots of studies have reported the significant effect of sleep health on CVD, fewer have explored gender differences. While CVD is a major health concern for both men and women in midlife, one research found that coronary heart disease is more frequently the first manifestation of CVD in men, whereas women more often present initially with cerebrovascular disease or heart failure [34]. From this perspective, the risk factors and mechanisms underlying CVD development may differ between men and

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women. Emerging studies have also highlighted gender-specific differences in sleep patterns, women are more likely to experience poor sleep quality, insomnia, and a morning chronotype, whereas men tend to have lower objective sleep efficiency and an evening chronotype [35]. Given gender differences in sleep patterns, along with gender-specific sociological and environmental factors, additional studies are warranted to explore the impact of gender on the association between sleep health and CVD.

Moreover, meta-analysis also found that risk factor profiles differ between individuals with early-onset coronary heart disease (<65 years) and those with late-onset disease [36], further highlighting the importance of identifying susceptible subgroups for sleep-related cardiovascular risk.

1.5 Study gaps

Previous studies have investigated how sleep health influences CVD using prospective study designs. However, most of these studies have concentrated only on one sleep phenotype and lacked comparisons across different sleep dimensions. Additionally, sleep phenotypes are often measured through subjective self-reported questionnaires for convenience. With the growing use of actigraphy, recent research has begun to utilize objective measurements to assess sleep health, although the majority of studies still primarily focus on objective sleep duration. Furthermore, only a limited number of studies have investigated how sleep health relates to a broad range of CVD subtypes, beyond total CVD, coronary heart disease, and stroke. Lastly, it remains unclear whether the association between sleep and CVD varies among specific population subgroups.

1.6 Specific aims

The study has three main aims. First, to comprehensively assess both subjective and objective sleep phenotypes across multiple dimensions in relation to the risk of various

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CVD subtypes, with subjective sleep phenotypes forming the primary analysis and objective sleep phenotypes serving as a subgroup analysis.

Second, to identify the key sleep phenotypes most strongly and widely associated with CVD subtypes, and compare their relative contributions. Also determine the CVD subtypes most influenced by sleep health, and investigate the multidimensional impact on them.

Third, we conduct stratification analysis by gender and disease onset age, in order to identify the population subgroups that may be particularly susceptible to sleep-related cardiovascular risks.

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Chapter 2: Materials and Methods

2.1 Data source and study participants

Our study participants are from UK Biobank, which is a database recruited over 500,000 participants aged 37 to 70 at baseline from 2006 to 2010. Participants provided informed consent further completed the online touchscreen questionnaire at baseline to capture health-related information not readily available from medical records, such as lifestyle factors, occupational history, chronic pain, mental condition, and more. A subgroup of them also provided blood samples, underwent physical examinations, and wore activity monitors for additional information. Long-term follow-up of their health condition can be conducted through linkage to medical records, including general practice and hospital records, as well as cancer and death records [37].

In order to achieve the aims of our study, participants without any of the subjective sleep phenotype, and those lacked hospital inpatient data or primary care clinical records, were excluded. The final study cohort consisted of 447,183 participants who provided at least one subjective sleep phenotype through the questionnaire, with a subgroup of 82,574 participants having objective sleep phenotype data from wearing the actigraphy for more than five days (**Figure 1**).

2.2 Measurements of subjective sleep phenotypes

2.2.1 Assessment and definition of each subjective sleep phenotype

In the touchscreen questionnaire completed by participants after the assessment between 2006 and 2010, seven subjective sleep phenotypes were collected under the lifestyle section, with the corresponding field IDs and the definition listed in **Table S1**. These subjective sleep phenotypes can be categorized into five common dimensions: duration, represented by sleep duration; timing, captured by chronotype and difficulty

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getting up in the morning; alertness, reflected in dozing and napping; soundness, indicated by snoring; and satisfaction, measured by insomnia [21].

For sleep duration (field 1160), the question is "About how many hours sleep do you get in every 24 hours? (please include naps)." Those who answered no more than 7 hours were classified into short duration group, 7-9 hours into normal duration group, and more than 9 hours into long duration group, according to the suggestion for adults in the guideline of the American Heart Association and the National Sleep Foundation [38]. Chronotype (field 1180) was then categorized into three types: morning, intermediate, and evening. For getting up in the morning (field 1170), participants were divided into two groups base on their responses: those who find it easy to get up and those who find it not easy to get up. Daytime dozing (field 1220) and nap during the day (field 1190) were both classified into two frequency groups: "never/rarely" and "sometimes or usually." For insomnia (field 1200), participants responded to the question, "Do you have trouble falling asleep at night or do you wake up in the middle of the night?", further categorized into two groups based on frequency. Lastly, snoring (field 1210) was determined through question regarding whether they had been noticed or judged by a partner, relative, or friends.

2.2.2 Measurement of multidimension healthy sleep score

Additionally, to account for the concept of multidimensional sleep health, which is typically assessed by aggregating individual sleep phenotypes, some previous studies have created overall sleep health scores by summing the optimal sleep dimensions [39]. Following the approach, five subjective sleep phenotypes (sleep duration, chronotype, daytime dozing, snoring, and insomnia) were assessed to derive a healthy sleep score. Using our previous classification, participants were deemed to have a healthy sleep habit for each phenotype if they exhibited normal sleep duration, morning or intermediate

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chronotype, no snoring, seldom suffer from insomnia, and no daytime dozing. Participants received one point for each healthy sleep habit, and then added up to generate a total 0-5 points, where higher scores reflected healthier sleep. Analyses were conducted using the healthy sleep score as both a continuous measure and a categorical variable, as 0 to 3 points indicating poor overall sleep health and 4 to 5 indicating good overall sleep health.

2.3 Measurements of objective sleep phenotypes in subgroup cohort

2.3.1 Assessment and processing of actigraphy data

Within the UK Biobank participants, a subgroup of 103,688 of them wore the actigraphy (Axivity AX3 wrist-worn triaxial accelerometer) on the dominant hand for a continuous period of 7 days between 2013 and 2016 to measure their sleep and physical activity patterns [40]. The objective sleep raw data were then extracted from the actigraphy (field 90001) and preprocessed using the R package *GGIR* (version 2.3.0) [41] to obtained meaningful sleep parameters.

The data quality control and filtering criteria for the actigraphy were based on Liang's master thesis [42]. The accelerometer data from 10,821 participants were flagged as unreliable in field IDs 90002, 90016, 90017, 90180, 90181, and 90182, based on the UK Biobank quality control procedures. These issues included data file sizes being too large or too small, poor calibration of raw accelerometer data, interrupted recording periods, and data recording errors. Additionally, nights with more than 20% non-wear time during the sleep period were considered imprecise and were therefore excluded. After applying these criteria and matching with the main cohort inclusion criteria, a final of 82,574 participants with five or more nights of valid data were remained for subgroup analysis.

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The process of extracting sleep parameters from the raw data applied the HDCZA algorithm to detect sleep period (SPT-window) [43]. The algorithms utilized arm angles averaged across 5-second epochs, with sustained inactivity defined as absolute changes in z-angle wrist-rotation of ≤5° for more than 5 consecutive minutes. Each day's sleep period was identified as the longest sustained inactivity period exceeding 30 minutes. Sleep characteristics were then derived from the processed *GGIR* output, with final 6 objective sleep phenotypes used in further analysis (**Table S1**), which can also be categorized into four common sleep dimensions: duration, represented by objective sleep duration; timing, captured by objective chronotype based on sleep midpoint; efficiency, reflected in sleep efficiency, wake after sleep onset (WASO) and awake times during sleep period; and regularity, measured by sleep regularity index (SRI) [21].

2.3.2 Definition and classification of each objective sleep phenotype

Objective sleep duration refers to the total duration of sustained inactivity intervals within the SPT-window, averaged over all observed days. Since previous study observed that subjective sleep duration exceeds actigraphy-based sleep duration by approximately an hour [44], and consider the commonly used optimal cut points for objective sleep duration [22], we thus classified participants with less than 6 hours of sleep into short duration group, 6-8 hours into normal duration group, and more than 8 hours into long duration group. According to previous literature, the objective chronotype was defined based on the midpoint of sleep, with participants considered morning type if their median sleep midpoint over all observed days falls before 3:00 AM, intermediate type if sleep midpoint falls in 3 AM to 5 AM, and evening type as those sleep midpoint falls after 5:00 AM [45]. The percentage of actual sleep duration within the SPT window was used to calculate sleep efficiency, with values less than 85% classified as poor sleep efficiency according to the recommendation of National Sleep Foundation [46]. WASO refers to the

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total duration of wakefulness during the SPT-window, with the number of non-sleep episodes experienced during the sleep window period was used to quantify the awake times during the sleep period.

In addition, the R package *SLEEPREG* was used to calculate SRI from *GGIR* output [47]. The concept of SRI is to determine the percentage probability that participants maintain the same sleep or wake circumstances at the same time point across consecutive 24-hours periods, averaged over all days. SRI is calculated with the formula below, where s_i indicates sleep-wake status (1 = awake, 0 = asleep), total number of valid epochs used in the calculation is represented by N_v, and with i denoting each epoch from the beginning of recording to 24 hours prior to its end, C refers to the time lag between epochs within 24 hours on consecutive days. SRI ranges from 0 to 100, with 100 indicates completely consistent sleep-wake patterns across days, and 0 represents random patterns. For quality control, nights with miscalculations were excluded and only participants with data of more than 5 valid nights were included in our study for SRI calculation, following the recommendation. In order to consider the impact of weekend sleep habits on sleep regularity, we also calculated a weekday SRI, excluding Friday and Saturday nights.

$$\boldsymbol{SRI = -100 + 200\left(1 - \frac{1}{N_v}\sum_{i=1}^{N}|s_i - s_{i+C}|\right)}$$

2.4 Definition and classification of cardiovascular disease subtypes

Cardiovascular diseases were defined based on clinical diagnosis, which included the 10th revision of the International Classification of Diseases (ICD-10) from hospital inpatient records (field 41202) and also the primary care data.

UK Biobank primary care data consist of electronic health records collected from general practitioners at local practices, sourced from multiple data providers across the

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United Kingdom. The clinical events file within the dataset contains clinical codes (Read v2 or CTV3), which can be mapped to ICD-10 codes for disease definition [48].

To classify clinically meaningful CVD subtypes, the PheCODE system [49] was used, successfully identified 10 distinct subtypes: hemorrhagic stroke, ischemic stroke, ischemic heart disease, hypertension, peripheral vascular disease, venous thromboembolic disease, pulmonary heart disease, cardiomyopathy, heart valve disorder, and heart arrhythmia. For heart failure, it is more accurately described as a complex clinical syndrome rather than just a single disease, which often caused by ischemic heart disease, hypertension, valvular disease, and myocarditis. Therefore, we followed the typical definitions used in previous literatures and additionally included the codes referring to heart failure caused by other conditions, which involved the following ICD-10 codes: I50.X, I11.0, I13.0, I13.2 [50, 51]. Therefore, we also defined the total cardiovascular disease included all the 11 subtypes. The detail definition of each CVD subtype, along with the corresponding PheCODEs, the exclusion PheCODEs, and ICD-10 codes are presented in **Table S2**.

2.5 The design of follow-up cohort

In order to estimate how various sleep phenotypes influence cardiovascular disease subtypes, separate cohort studies were conducted for each combination, as shown in **Figure 1**. The primary cohorts were based on subjective sleep phenotypes, while subgroup cohorts were conducted for objective sleep phenotypes.

Taking the subjective sleep duration and hemorrhagic stroke cohort as an example, participants were included following these criteria: (1) participants without hemorrhagic stroke diagnosis prior to baseline, which refers to the date the subjective sleep duration data was obtained, (2) participants without hemorrhagic stroke diagnosis within one year of follow-up, to account for subclinical conditions and prevent bias from undiagnosed or

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latent diseases, and (3) participants without any disease diagnosis from the corresponding exclusion PheCODE prior to baseline and within one year of follow-up.

During follow-up, incident hemorrhagic stroke was defined as the first documented occurrence of either a hemorrhagic stroke diagnosis or death attributable to hemorrhagic stroke, based on information from primary care and inpatient hospital records. For participants with information available from both primary care and hospital inpatient records, the earliest recorded date was used as the event date. Censoring occurred at the date of death from causes other than hemorrhagic stroke or at the study endpoint (October 22, 2022) for those who did not experience hemorrhagic stroke. Follow-up time was defined as the period from the baseline assessment to either the first hemorrhagic stroke event or censoring, whichever occurred first.

2.6 Assessment of covariates

Participants provided demographic and lifestyle data through a self-completed touchscreen questionnaire at baseline. Sociodemographic factors included age at recruitment, gender, education, employment status, and Townsend Deprivation Index (TDI). Life style factors included smoking, alcohol intake, physical activity, and diet quality. Additional anthropometric measures and blood biochemical index included BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, and total cholesterol.

The TDI (field 22189) is a commonly used metric in the UK to represent material deprivation in a given area, calculated based on four key factors: unemployment, household overcrowding, non-car ownership, and non-home ownership [52]. Greater TDI indicate higher levels of deprivation. Regarding lifestyle factors, alcohol intake (field 1558) was assessed based on intake frequency and converted into the number of times per month. Smoking status (field 1239) classified participants as current or non-current

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smokers. According to the American Heart Association, regular physical activity refers to ≥150 minutes of moderate or ≥75 minutes of vigorous activity per week, or an equivalent set [53]. Healthy diet was defined as consuming at least 4 out of 7 widely consumed food categories, based on dietary recommendations for cardiometabolic health, assessed through the food frequency questionnaire [54, 55]. A detailed summary of these characteristics in the UK Biobank is provided in **Table S3**.

2.7 Statistical analysis

Incidence rates, expressed per 1,000 person-years, were determined from the number of incident events relative to the total person-years of follow-up within the cohort. To compare the demographic and lifestyle data among different groups, we used Student's t-test, ANOVA, and Chi-squared test. To estimate the correlations among sleep phenotypes and CVD subtypes, Pearson correlation was used for continuous variables, polychoric correlation for categorical variables, and polyserial correlation was applied for the relationship between continuous and categorical variables. A two-sided p-value of less than 0.05 was considered statistically significant.

For main results, Cox proportional hazards regression was applied to evaluate the effect of each sleep phenotype on individual cardiovascular disease subtype. All models were assessed to confirm that the proportional hazards assumption was met. Crude models were first fitted without adjustment for covariates. The basic models were adjusted for age, sex, education level, employment status, TDI, alcohol intake, and smoking status. The fully adjusted models were further adjusted for physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose. For hypertension as the outcome, SBP and DBP were not included in the fully adjusted model. To account for multiple comparisons across 11 cardiovascular disease subtypes, statistical significance was set at $p < 0.0045$, based on a Bonferroni correction (0.05/11).

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After identified the key sleep phenotypes most strongly associated with CVD onset and the CVD subtypes most affected, we quantified the proportion of disease risk in the population that can be attributed to specific sleep phenotype by calculating the population attributable fraction (PAF). PAFs for binary sleep phenotypes were derived using the AFcoxph R package based on fully adjusted Cox models, whereas PAFs for the continuous healthy sleep score were estimated using a counterfactual Cox regression–based framework as described by Chen and Lin [56].

Finally, we conducted stratified analyses by gender and age at disease onset to identify subgroups most susceptible to sleep-related cardiovascular risk. For the age-at-onset stratification analysis, we adopted 65 years as the cutoff in our study. This choice is based on the fact that most epidemiological studies and clinical guidelines use 65 years as the threshold to define the elderly population when analyzing the prevalence of CVD, and a study showed significant differences in risk factors between coronary heart disease patients younger and older than 65 years [36]. Participants who developed CVD were first divided into two groups (< 65 years vs. ≥ 65 years at onset). Those who remained free of CVD by the end of the study were randomly assigned to these two groups in proportion to the observed prevalence ratio (**Table S4**). Effect modification by gender and age group was formally assessed by including multiplicative interaction terms between sleep phenotypes and stratification variables in Cox proportional hazards models. All statistical analyses were performed using R software version 4.3.2 and SAS software version 9.4.

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Chapter 3: Results

3.1 Follow-up cohort and sample characteristics

The main cohort comprised 447,183 participants with baseline subjective sleep phenotype data and was followed for a median of 13.6 years, with slight variations across CVD subtypes. Among participants who met the criteria, 39,567 of them (11.93%) developed total cardiovascular disease. Cumulative incidence of each CVD subtype is shown in **Table S5a**: with hypertension had the highest cumulative incidence as 6.85%, followed by ischemic heart disease, heart arrhythmia, and ischemic stroke. In addition, the subgroup cohort included 82,574 participants with objective sleep data collected between 2013 and 2016 was followed for a median of 7.9 years, with 1,904 of them (3.06%) experienced new-onset total cardiovascular disease (**Table S5b**). The interrelationships among the 11 CVD subtypes are depicted in **Figure S1**.

Table 1 presents the baseline characteristics of the study participants. In the total cohort, the mean age was 56.79, 54.89% were female, 57.75% were employed, and 31.78% held a college degree or higher. The mean TDI was negative, indicating material deprivation below the national average and a generally higher socioeconomic status. All of the variables showed significant difference between participants with and without total CVD. Participants with total CVD were older, less likely to be female or employed, lower education, more deprivation according to TDI, with higher BMI, SBP, DBP, total cholesterol, and fasting glucose. Regarding lifestyle factors, they reported higher alcohol intake frequency, more current smoker, less regular physical activity, and lower adherence to a healthy diet. In addition, participants in the subgroup represented a healthier subset of the main cohort, exhibiting higher socioeconomic status, better physical health

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indicators, and more favorable lifestyle behaviors; nevertheless, significant differences in these variables remained between individuals with and without total CVD.

Table 2 presents the baseline subjective sleep phenotypes of the main cohort and the baseline objective sleep phenotypes of the subgroup participants. For subjective sleep phenotypes, the mean sleep duration was 7.15 hours, with 25.52% classified as short duration and 1.93% as long duration. For chronotype, 9.00% were evening types and 27.26% were morning types. Additionally, 18.18% reported difficulty getting up in the morning, 24.48% reported daytime dozing, 44.50% with napping habit, 37.51% reported snoring, and 29.04% usually suffer from insomnia. For objective sleep phenotypes, mean sleep duration measured by actigraphy was 6.53 hours, with 26.77% of the participants divided into short duration group and 6.07% divided into long duration group. For chronotype based on sleep midpoint, 4.93% were defined as evening type and 32.47% were defined as morning type. Mean sleep efficiency was 0.89 among subgroup population, with 14.23% of them fell into the bad efficiency group. The average WASO was 46.70 minutes, with participants' awaking times during sleep period showed a mean 13.50 times. Finally, the mean sleep regularity index for the whole week was 78.82%, increased to 83.82% when excluded Friday and Saturday nights. Agreement between subjective and objective sleep duration groups was slight (weighted Cohen's $\kappa = 0.1346$), whereas agreement between subjective and objective chronotype was fair (weighted Cohen's $\kappa = 0.2866$). **Table 3** further presents the detailed follow-up characteristic of participants in each subjective and objective sleep group for total CVD events. Owing to the extensive sample size and prolonged follow-up, the study accumulated a substantial number of person-years. Among subjective sleep phenotypes, higher incidence rates are generally observed in participants with short or long sleep duration, in evening types compared with intermediate or morning types, and among individuals reporting easy

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getting up in the morning, dozing, habitual napping, snoring, or usually suffer from insomnia. As for objective sleep phenotypes assessed by actigraphy, higher incidence rates are generally observed among participants with short sleep duration, evening types, and bad sleep efficiency.

To explore how different sleep phenotypes may interact with each other, a correlation matrix was presented in **Figure S2**. Some significant associations were observed, though the correlations were generally moderate. Shorter subjective sleep duration linked to insomnia. Participants not easy getting up in the morning were more likely to be classified as subjective evening chronotypes. Habitual napping was associated with daytime dozing. On the objective side, longer actigraphy-measured objective sleep duration correlated with higher sleep efficiency. As for sleep regularity index, it showed positive correlations with both objective sleep duration and sleep efficiency, and a negative correlation with WASO.

3.2 Differential impacts of sleep phenotypes on CVD subtypes

3.2.1 Main effects of subjective sleep phenotypes

The main objective of this study was to assess the differential impact of subjective sleep phenotypes on the risk of various CVD subtypes using Cox models. The significance levels of all associations, after full adjustment for covariates and considered for Bonferroni correction, are summarized in **Figure 2**. As we first focus on the result of total CVD presented in **Table 4**, all subjective sleep phenotypes demonstrated significantly associations in the crude model. However, after adjusted for other covariates, regarding sleep duration, only short duration showed a significant effect. Other detailed adjusted hazard ratios are also presented in **Table 4**. Specifically, short sleep duration, evening chronotype, not easy getting up in the morning, dozing, napping, snoring, and

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insomnia all increased the risk of total CVD after fully adjusted for all covariates, with the strongest effect observed in insomnia (aHR = 1.1359, $p < 0.0001$).

Figure 3 compares the fully adjusted hazard ratios for all CVD subtypes, with detailed values presented in **Table S6a-k**. Among them, ischemic heart disease was most broadly influenced by sleep, with 6 sleep phenotypes showing significant effects, except for chronotype (**Figure 2**). Ischemic stroke was affected by 5 sleep phenotypes, excluding chronotype and snoring, and the risk associated with sleep duration was observed only in the long duration group (**Figure 2)**. These two CVD subtypes will be further discussed in **Chapter 3.3**. The remaining CVD subtypes were significantly influenced by fewer sleep phenotypes. Hemorrhagic stroke, also classified as a cerebrovascular disease, showed no significant associations with any subjective sleep phenotypes (**Figure 3**). Hypertension, as part of an arterial disease, was significantly associated only with snoring as a risk factor, while difficulty getting up in the morning appeared to have a protective effect (**Figure 3**). Other circulatory diseases were not influenced by any subjective sleep phenotypes, except that short duration, long duration, and insomnia elevated the risk of peripheral vascular disease (**Figure 3**, **Table S6e**, $aHR_{\text{short duration}} = 1.2340$, $aHR_{\text{long duration}} = 1.6019$, $aHR_{\text{insomnia}} = 1.3000$). Regarding cardiac-related diseases, cardiomyopathy showed no significant association with subjective sleep phenotypes, whereas the risks of the other three subtypes were more strongly correlated with not easy getting up in the morning, napping, and insomnia (**Figure 3)**.

From the perspective of various subjective sleep phenotypes, insomnia exerts the broadest influence, affecting 6 of the 11 CVD subtypes, followed by getting up in the morning and napping (**Figure 2**). These three subjective sleep phenotypes will be further discussed in **Chapter 3.4**. Despite the lack of association between long sleep duration

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and total CVD risk, it tended to have the largest effect size among subjective sleep phenotypes, increasing the risk of several CVD subtypes (**Figure 3**).

3.2.2 Effects of objective sleep phenotypes in the subgroup

Figure S3 and **Figure S4** illustrate the heterogeneous associations between objective sleep phenotypes and CVD subtypes in subgroup cohort. Results showed that only sleep regularity index was significantly linked to the risk of peripheral vascular disease, demonstrating a protective effect with every 10-points increase in SRI (**Table S6e**, aHR = 0.7122, p = 0.0029). For other objective sleep phenotypes, although the associations failed to achieve statistical significance, the directions and magnitudes of the effect estimates presented in **Table 4** were generally comparable to those observed for subjective sleep phenotypes, suggesting consistent effect sizes but limited statistical power due to small sample size of the actigraphy subgroup.

3.3 Subjective sleep and healthy sleep score effects on total CVD, ischemic heart disease, and ischemic stroke

Since total CVD and its two subtypes, ischemic heart disease and ischemic stroke, were more broadly influenced by subjective sleep phenotypes, we focused on their associations and calculated the population attributable fraction (PAF). For total CVD, insomnia exhibited the largest effect size among all significantly associated sleep phenotypes, with an adjusted hazard ratio of 1.1359 (**Table 5**, p < 0.0001). Correspondingly, the PAF for insomnia was the highest, explaining 3.35% of the total CVD risk at the population level. For both ischemic heart disease and ischemic stroke, the largest effect sizes were observed in long sleep duration (**Table 5**, $aHR_{\text{long duration | ischemic heart disease}}$ = 1.2551, p < 0.0001; $aHR_{\text{long duration | ischemic stroke}}$ = 1.4190, p < 0.0001). Despite this, the PAF for long sleep duration was relatively small (**Table 5**, $PAF_{\text{long duration | ischemic heart disease}}$ = 0.56%, $PAF_{\text{long duration | ischemic stroke}}$ = 0.99%). Insomnia remained the key

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influential sleep phenotype, accounting for 6.43 % and 4.99% of the risk for ischemic heart disease and ischemic stroke, respectively (**Table 5**). Notably, napping exhibited the highest PAFs for both ischemic heart disease and ischemic stroke (**Table 5**, $PAF_{nap \mid ischemic\ heart\ disease} = 7.68\%$, $PAF_{nap \mid ischemic\ stroke} = 5.36\%$).

Next, to investigate the impact of multidimensional sleep health on CVD subtypes, we calculated the healthy sleep score for these three diseases, with the distribution of baseline characteristics presented in **Table S7a-c**. Approximately 36% of participants scored 0-3 points classified as poor overall sleep health group, 64% scored 4-5 points classified as good overall sleep health group. All subjective sleep phenotypes differed significantly across the two groups, with healthier sleep habits more prevalent in good overall sleep health group. The protective effects of the healthy sleep score are shown in **Table 5**. Each 1 point increases corresponded to a significant reduction of total CVD risk (**Table 5**, aHR = 0.9334, $p < 0.0001$), ischemic heart disease risk (**Table 5**, aHR = 0.8925, $p < 0.0001$), and ischemic stroke risk (**Table 5**, aHR = 0.9470, $p < 0.0001$). Participants with poor overall sleep health had a 13% higher risk of total CVD compared with those with good overall sleep health. The PAF for continuous HSS is 4.67%, indicating that approximately 4.67% of total CVD cases in the study population can potentially be prevented with a one-point improvement in sleep health score across the population. Notably, the PAF estimated using the continuous healthy sleep score was comparable to that derived from the categorical classification of poor and good overall sleep health, supporting the validity of the selected cut-off for defining overall sleep health. Similar findings were observed for ischemic heart disease ($PAF_{HSS\ (Poor\ overall\ sleep\ health)} = 8.05\%$) and ischemic stroke ($PAF_{HSS\ (Poor\ overall\ sleep\ health)} = 4.79\%$), suggesting that considering multidimensional sleep health better explains the overall impact of sleep on CVD risk rather than focusing on individual sleep phenotypes alone.

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3.4 Insomnia, napping, and getting up in the morning effects on CVD subtypes

As discussed in **Chapter 3.2.1**, we found that among all sleep phenotypes, insomnia, napping, and getting up in the morning are the most widely influential in affecting various CVD subtypes. Therefore, we further respectively compared the population attributable fraction (PAF) of these three phenotypes across different CVD subtypes, as shown in **Table 6**. Overall, the PAF for getting up in the morning was relatively small compared to napping and insomnia, with the highest significant impact observed in heart failure (aHR = 1.2274, PAF = 3.41 %), ischemic heart disease (aHR = 1.1936, PAF = 2.63 %), and ischemic stroke (aHR = 1.1605, PAF = 2.35 %). Napping accounted for 7.68 % of ischemic heart disease risk and 5.36 % of ischemic stroke risk, and also showed a higher impact on heart failure and heart valve disorder. As for insomnia, aside from ischemic heart disease and ischemic stroke, it accounted for 8.39 % of peripheral vascular disease risk, 5.45 % of heart failure, 4.80 % of heart valve disorder, and 4.05% of heart arrhythmia. Based on the results, as insomnia and napping being the crucial sleep phenotypes, further stratification analyses will be conducted to explore more about these correlations.

3.5 Exploring gender and disease onset age differences

To identify subgroups more susceptible to sleep-related cardiovascular risk, we conducted stratification analysis by gender and disease onset age group. The disease prevalence by gender is presented in **Table S4**, and the differential effects of napping and insomnia on CVD subtypes by gender are summarized in **Figure 4** and **Table 7**. For napping, the effects on ischemic heart disease and ischemic stroke were both more pronounced in females than in males ($aHR_{\text{ischemic heart disease | males}} = 1.1533$, $aHR_{\text{ischemic heart disease | females}} = 1.2023$, $aHR_{\text{ischemic stroke | males}} = 1.0703$, $aHR_{\text{ischemic stroke | males}} = 1.1690$), with

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a significant interaction involving napping and gender was detected solely for ischemic heart disease. In contrast, the risk effect of napping on heart valve disorder was only observed in males, differing from the other subtypes. As for insomnia, all correlations were more pronounced in females, with significant interactions observed in ischemic heart disease as well.

The results of the disease onset age-stratified analysis are presented in **Figure 5** and **Table 8**. For napping, the impact was slightly more pronounced in participants with disease onset before 65 years old across nearly all CVD subtypes, except ischemic stroke. This age-related difference was even more marked for insomnia, which showed a stronger effect in participants with younger disease onset for almost all CVD subtypes, particularly ischemic heart disease, with the exception of peripheral vascular disease.

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Chapter 4: Discussion

Our study comprehensively evaluated the differential impacts of subjective sleep phenotypes across multiple dimensions on the risk of various CVD subtypes. We found that ischemic heart disease and ischemic stroke were the two subtypes most broadly influenced by nearly all sleep phenotypes, with insomnia and napping showing larger effect sizes and higher population attributable fractions for both two diseases, thereby accounting for a greater proportion of disease risk. From the perspective of sleep phenotypes, insomnia and napping emerged as the key traits affecting the largest number of CVD subtypes as well, along with difficulty getting up in the morning, although the latter accounts for a relatively smaller proportion of the disease risk. Beyond their impact on ischemic heart disease and ischemic stroke, insomnia and napping also highly contribute to the risk of other CVD subtypes, further underscoring the importance. Additionally, the effects of objective sleep phenotypes on multiple CVD subtypes were evaluated, revealing a protective association of sleep regularity index with peripheral vascular disease.

Furthermore, using a healthy sleep score to capture multidimensional sleep health, we demonstrated that individuals classified with three or more healthy sleep behaviors among five common phenotypes experienced a significantly lower likelihood of ischemic heart disease and stroke. Moreover, considering multidimensional sleep health provides a better explanation of the overall impact of sleep health on CVD than focusing on individual sleep phenotypes alone. Finally, our stratified analyses revealed that women and participants with younger disease onset age represent subgroups more susceptible to sleep-related cardiovascular risks. Together, these findings highlight the specific focal

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points within the complex and multifaceted relationship between sleep health and CVD that warrant targeted attention and intervention.

4.1 Prevalence of CVD in the main cohort and the distribution of subjective sleep phenotypes

The prevalence of total CVD in this study was 11.92%, with a median nearly 13 years of follow-up in main cohort (**Table S5a**), which is comparable to the estimated 11.2% (approximately 760 million people) living with CVD in the general UK population in 2022 [57, 58]. The most common CVD subtypes observed in our cohort were hypertension (6.76%), ischemic heart disease (4.68%), heart arrhythmia (2.79%), and stroke (combined ischemic stroke and hemorrhagic stroke at 1.94%), which partially aligns with the prevalence reported in the general UK population, 3.1% for coronary heart disease, 2.1% for atrial fibrillation, and 1.9% for stroke. Nevertheless, it should be noted that UK Biobank participants are predominantly middle-aged and tend to have healthier lifestyles [59]. Given that the prevalence of all CVD subtypes generally increases with age [57, 60, 61], the rates observed in our study may underestimate those in the general population within the same age range.

Regarding subjective sleep phenotypes, the mean sleep duration in our main cohort was 7.15 hours (**Table 2**), which is shorter than the 8.11 hours reported for the UK population in an international survey [62]. The proportion of long sleep duration (**Table 2**, 1.93%) in our cohort was also notably lower compared to a previous study conducted in 2005, which 25.6% of participants were classified as long sleepers [63]. As for chronotype, varying definitions across studies have led to inconsistent proportions of different types; however, chronotype tends to be more stable among older individuals, who generally exhibits a higher proportion of more morning types than evening types [64], a pattern also observed in our study. Furthermore, due to differences in habits and

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cultures across countries, the prevalence of napping varies widely. A study in Sweden reported that 41.4% of people habitually take naps, which is similar to that observed in our cohort (**Table 2**, 44.50%) [65]. The prevalence of other sleep phenotypes varied across studies and countries, with regular snoring reported in 30-40% of the UK general population [66], daytime sleepiness affecting 5-20% of population in European countries [67, 68], and approximately one-third experiencing insomnia [6]. In our study, the proportions of nearly all of the sleep phenotypes fell within these reported ranges, with some risk-related conditions showed slightly higher prevalence. This underscores the importance of these sleep phenotypes in our cohort and highlights their potential impact on health outcomes.

4.2 Effects of subjective sleep phenotypes on CVD

4.2.1 The impact of subjective sleep phenotypes on total CVD

Our findings aligned with previous cross-sectional and longitudinal studies that explored the correlations of subjective sleep phenotypes and total cardiovascular disease, which found short sleep duration less than 7 hours [69, 70], daytime sleepiness or dozing [71, 72], habitual napping regardless of daily length [69], regular snoring [71], and insomnia symptoms [73] are all potential risk factors correlated with total CVD, even after accounting for other protective factors. Since the participants in these studies were all middle-aged, their sleep patterns should be similar to those in our study. However, the main difference is that their definition of total CVD only included coronary heart disease and stroke, while our study considered a broader range of cardiovascular diseases.

Interestingly, long sleep duration showed no significant association with total CVD (**Table 4**). Previous meta-analyses reported high heterogeneity in this relationship [74], along with a Swedish study suggested the U-shaped relationship of sleep duration and cardiovascular health becomes more pronounced only at sleep exceeding 10 hours [65].

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Since few participants in our sample slept more than 10 hours, we may be unable to observe such a relationship. Additionally, it is possible that some cardiovascular disease subtypes included in our study are not affected by long sleep duration.

No study has directly linked difficulty getting up in the morning to total CVD, but it may relate to "sleep inertia"—a common, temporary state of impaired cognition and sleepiness after awakening that lessens with age and varies by chronotype, with evening types experiencing it more on workdays [75]. Importantly, since sleep deprivation is likely a key contributor to difficulty getting up, it may underlie the potential link between difficulty awakening and increased CVD risk found in our study.

As for chronotype, after adjusted for traditional factors, we found that evening type is independently correlated with higher risk of total CVD. Although prior studies did not directly assess chronotype and CVD, they reported higher predicted 10-year CVD risk in evening types based on key risk factors like age, gender, smoking, blood pressure, and cholesterol [76]. Since our study did not adjust for comorbidities, the observed association between chronotype and CVD risk may be partly mediated by comorbid conditions such as diabetes. However, previous research has demonstrated that chronotype exerts a significant direct effect on circulating cardiometabolic proteins, suggesting potential mechanisms beyond traditional risk factors [77].

4.2.2 The greater impact of sleep on ischemic heart disease and ischemic stroke

Given that ischemic heart disease and ischemic stroke emerged as the CVD subtypes most extensively affected by various sleep phenotypes in our analysis, we first focused our subsequent discussion on these two conditions.

Insomnia appears to be the most influential sleep phenotype affecting both ischemic heart disease and ischemic stroke in our study, with larger effect size and higher PAF (**Table 5**). We observed increased risks consistent with a study in China, which reported

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that three insomnia symptoms, which are difficulty falling or maintaining sleep, daytime dysfunction, and earlier morning awakening, were all associated with elevated risks of ischemic heart disease and ischemic stroke [73]. Several interconnected biological pathways may explain these associations. Chronic insomnia leads to overactivation of the sympathetic nervous system, caused elevated heart rate and altered heart rate variability [78], which impose significant strain on the heart and coronary arteries. Moreover, insomnia triggers dysregulation of the HPA axis, thus causes cortisol levels increase which promote inflammation [79]. Supporting this, previous mice study has shown that sleep fragmentation can induce inflammation, structural changes in blood vessels, and endothelial dysfunction, all of which accelerate the progression of atherosclerosis and facilitate plaque formation [80]. Considering the main pathogenesis, this inflammatory state may be a crucial pathway underlying why ischemic heart disease and ischemic stroke are the most affected CVD subtypes.

Aside from insomnia, our study also revealed that another widely influential sleep phenotypes, habitual daytime napping, is associated with an increased risk of both ischemic heart disease and ischemic stroke, exhibiting the largest PAF among various sleep phenotypes (**Table 5**). A German prospective cohort study conducted in a non-Mediterranean population, where napping is not considered a cultural norm, supported with our finding. This study reported that individuals who regularly take long midday naps more than an hour have a 2.12 times risk of coronary artery disease [81]. Similarly, an United States prospective cohort study found that participants nap more than five times per week have a 55% increased risk of stroke, regardless of nap duration [82]. Nevertheless, our study did not collect detailed data on the duration of daytime napping. This limitation restricts our ability to explore dose-response relationships or to identify optimal or harmful nap patterns, which may partly explain the discrepancy with a Chinese

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case-control study that also did not consider nap duration and found a protective effect of daytime napping on stroke [83]. Several potential mechanisms may underlie the increased cardiovascular risk associated with habitual napping. One proposed mechanism involves heightened sympathetic nervous system activity, causing a drop in heart rate and blood pressure during prolonged naps, followed by a stronger rebound upon awakening, which in long term may stress arterial walls and accelerate plaque formation [84]. Another mechanism involves disruption of circadian rhythms, which can impair vascular endothelial function and activate inflammatory pathways—processes that are central pathological mechanisms in ischemic heart disease and ischemic stroke [85].

Although other sleep phenotypes also carry significant risk impacts, we emphasize insomnia and habitual daytime napping as two key sleep phenotypes that markedly influence the risk of ischemic heart disease and ischemic stroke through multiple underlying physiological mechanisms.

4.2.3 The impact of sleep on other CVD subtypes

For other CVD subtypes less broadly influenced by sleep phenotypes, certain associations remained evident, with some interesting findings warranting further discussion.

Although hemorrhagic stroke also belongs to cerebrovascular diseases, our study found no significant associations between any sleep phenotypes and hemorrhagic stroke. Previous studies investigating the impact of sleep on hemorrhagic stroke, primarily conducted in Asian populations, have indicated that the effect of sleep duration on hemorrhagic stroke is less pronounced and remains inconsistent compared to ischemic stroke [86]. Additionally, a cohort study reported that insomnia symptoms were not linked to hemorrhagic stroke, despite an adequate number of hemorrhagic stroke cases being included [73], which is consistent with our findings. The potential heterogeneity of the

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relationship between sleep and stroke subtypes remains unclear. However, since hemorrhagic stroke predominantly arises from the disruption of blood vessels caused by hypertension, head injury, vascular malformations, or aneurysm [87], which are factors less directly related to the mechanistic pathways associated with risky sleep behaviors, this may explain the weaker or absent association.

Our study also found that snoring was the only sleep phenotype increased 15% of hypertension risk (**Table S6d**), consistent with a meta-analysis combining cross-section and prospective cohort studies that reported a significant pooled risk estimate of 1.32 for hypertension associated with snoring [88]. Since snoring is often seen as the main symbol of obstructive sleep apnea (OSA), recent studies have primarily been paying attention on the correlation between OSA and CVD. Although our study did not specifically assess OSA, previous study has demonstrated that snoring independently increases the risk of hypertension, regardless of apnea presence [89], showing the concern of considering snoring as a potential marker.

In addition, with respect to other circulatory diseases, we found that short sleep duration, long sleep duration, and insomnia were significantly linked to an increased peripheral vascular disease risk, with insomnia exhibiting a particularly high PAF (**Table 6**). Despite growing interest in sleep health, research examining its association with peripheral vascular disease remains limited, one comprehensive analysis combining case-control and prospective cohort studies observed a U-shape correlation between sleep duration and peripheral vascular disease risk, using sleep duration of 7-8 hours as the reference [90], which the pattern aligns with our findings. Regarding cardiac-related diseases, we identified heart failure as being more strongly attributed to getting up in the morning, daytime napping, and insomnia (**Table 6**). A Mendelian randomization study also observed genetic evidence that insomnia increased 54% heart failure risk [91].

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Dysregulation of the autonomic nervous system and neuroendocrine pathways may represent credible biological mechanisms linking insomnia to the development of peripheral vascular disease and heart failure. And the higher PAF of insomnia for heart failure in our result may be due to the frequent comorbidity of heart failure with other cardiovascular disease subtypes, including atrial fibrillation, peripheral artery disease, valvular disease, and ischemic heart disease [92]. Consistently, we observed relatively stronger correlations among these conditions within our study cohort (**Table S2**). Overall, our study additionally highlights the equally important influence of sleep on heart failure and peripheral vascular disease, in addition to the major cardiovascular disease subtypes.

4.2.4 The impact of multidimensional healthy sleep on CVD

In our study, beyond examining the individual effect of each sleep phenotype on CVD and identifying the crucial sleep phenotype, we further calculated a healthy sleep score based on 5 subjective sleep phenotypes to investigate the multidimensional effects of sleep. We observed that having more than four sleep phenotypes classified as healthy habit was significantly protective against total CVD, ischemic heart disease, and ischemic stroke. Two cohort studies supported with our finding, demonstrating that every one-point rise in the healthy sleep score was linked to an 11% reduction of CVD mortality, and the favorable sleep pattern with more than 4 points even showed a 42% lower risk [93], also with the protective effect exhibited in coronary heart disease and stroke [94].

Although using the same calculation method, we additionally calculated population attributable fraction (PAF), with results showing participants classified as good overall sleep health with a healthy sleep score more than 4 points exhibited a higher PAF than any individual sleep phenotype alone. This suggests that a multidimensional assessment of sleep health better captures the overall impact of sleep on CVD risk compared to evaluating each sleep phenotype separately. So far, based on the aforementioned

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discussion, lots of studies have explored the impact of individual sleep phenotype on CVD. However, there remains a relative scarcity of literature comprehensively examining multidimensional aspects of sleep to identify people at high risk for CVD. Therefore, further investigations are needed to explore integrated sleep phenotypes and their potential role in prevention and management of CVD.

4.3 Effects of objective sleep phenotypes on CVD

For actigraphy-measured objective sleep phenotypes, we examined their associations with CVD subtypes in a subgroup population. Although actigraphy has become increasingly recognized as a reliable tool for objectively assessing sleep patterns, few studies have directly investigated the relationship with CVD subtypes, most research has instead relied on in-home polysomnography. Some previous cohort studies have reported that actigraphy-measured short duration (< 5 hours) is linked to a 46% to 67% increased risk of CVD mortality with comparison to a sleep duration of 7 hours [95]. Another cohort study conducted in America followed for an average 11 years, observed that polysomnography-measured poor sleep efficiency (<80%), WASO in the highest quartile (>78 minutes), and short sleep duration (<6 hours) increased the risk of adverse cardiovascular events and ischemic stroke [96, 97]. Additionally, a longitudinal observational study comparing health outcomes between participants with regular sleep (SRI ≥ 84.0) and irregular sleep (SRI < 60.8) based on the Sleep Regularity Index, found that greater sleep irregularity group showed higher 10-year risk of CVD and hypertension [98]. However, our study observed comparable effect size but almost no significant correlation between objective sleep phenotypes and CVD subtypes. This discrepancy may be due to the relatively low number of CVD events in our subgroup cohort, likely due to a shorter follow-up period (**Table S5b**), as well as the overall better socioeconomic status and health conditions of participants in the subgroup (**Table 1**).

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Interestingly, the only significant correlation we found was a protective effect of the sleep regularity index on peripheral vascular disease: a 10-point increase in SRI was related to a 23% decrease in disease risk. According to our information, no previous research has directly investigated the impact of sleep regularity on peripheral vascular disease. Only one small sample cross-sectional study conducted in America with undergraduate students aged 18 to 25 calculated sleep regularity based on the SD of sleep duration, and explored its impact on lower-limb vascular function using passive leg movement assessment [99]. The results showed that every 1-hour increase in sleep duration SD, rather than sleep duration itself, significantly reduced 397 mL/min in leg blood flow, indicating poorer peripheral vascular condition. Since sleep duration variability was not associated with flow-mediated dilation (a measure of macrovascular function) in this study, the results align with ours, which found that sleep regularity impacts peripheral vascular disease (microvascular) but not other CVD subtypes involving large blood vessels. This supports the hypothesis that irregular sleep may first affect microvascular function, while macrovascular function remains largely unaffected. Although this study focused on a young population and defined sleep regularity based on sleep duration rather than sleep timing, the results highlight the importance of sleep regularity and its impact on peripheral vascular disease. Also suggests that if irregular sleep patterns persist into older age, the cumulative adverse effects on health may be even greater.

4.4 Stratification analysis results

4.4.1 The impact of insomnia and nap on CVD subtypes by gender

To explore gender differences in sleep-related CVD risk, we conducted a gender-stratified analysis focusing on the two key sleep phenotypes and their associations with the significantly affected CVD subtypes. Results pointed out that the impact of napping

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on ischemic stroke, ischemic heart disease, and other CVD subtypes was slightly more pronounced in females, except for heart valve disorders, with a significant interaction observed only for ischemic heart disease (**Figure 4, Table 7**). Few studies have directly investigated gender differences in the association between napping and CVD risk. One dose-response meta-analysis explore the relationship between napping and incident CVD events thus reported a significant association only in women, with a pooled hazard ratio of 1.31; however, no significant interaction between gender and napping was detected [100].

Regarding insomnia, the impact was more pronounced in females across all CVD subtypes, with significant interactions observed for ischemic heart disease and heart valve disorder (**Figure 4, Table 7**). Our findings aligned with previous cohort studies, women tend to have higher relative risks of myocardial infarction [101] and a slightly increased risk of ischemic heart disease [73] due to insomnia.

The observation that insomnia and daytime napping confer greater risk for developing CVD subtypes in women should be interpreted with caution, as the subtle gender differences may be due to statistical chance. Nonetheless, several studies have proposed potential biological mechanisms underlying these gender differences. For instance, a large community-based study in the United States reported that insomnia symptoms were linked to an 18% greater prevalence of coronary artery calcification (CAC > 0) among women, whereas no corresponding association was detected in men [102]. Additionally, another study investigating gender differences in the relationship between sleep quality and inflammatory biomarkers found that poorer baseline subjective sleep quality was predictive of 5-year elevations in IL-6, CRP, and fibrinogen among women, whereas no such relationship was observed in men [103]. Given that systemic inflammation and plaque formation are key pathological mechanisms linking sleep health

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to CVD subtypes, these findings may help explain the more pronounced effects observed in women. Other factors contributing to gender differences include socioeconomic status [104] and the influence of estrogen on subjective sleep quality [105], further highlighting the importance of identifying susceptible subgroups within the population.

4.4.2 The impact of insomnia and nap on CVD subtypes by disease onset age

To explore the differential impact of sleep on CVD subtypes between younger and older disease onset age groups, we further conducted an onset-age stratified analysis. The results indicated that the effect of napping was generally more pronounced in the younger onset group (age < 65 years) across nearly all CVD subtypes, except ischemic stroke, with all interactions reaching statistical significance. Similarly, the effects of insomnia were more evident in the younger onset group for most CVD subtypes, except peripheral vascular disease, with significant interactions observed for both peripheral vascular disease and heart arrhythmia. However, only one meta-analysis systematically compared the prevalence of risk factors between early- and late-onset coronary heart disease participants. This study found that the early-onset group had higher BMI, cholesterol, triglycerides, as well as a greater prevalence of smoking and family history, though it focused solely on traditional CVD risk factors [36]. As sleep health has recently gained increasing attention, our study can further advance the understanding of risk factors for early- and late-onset CVD subtypes by incorporating sleep phenotypes. These results underscore the significance of addressing sleep health in the prevention and management of CVD across different age groups.

4.5 Strengths and limitations

Our study possesses several notable strengths. First, it comprehensively assessed multiple sleep phenotypes using both subjective and objective measures across various CVD subtypes. This allowed comparison between sleep phenotypes and their differential

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impacts on CVD, unlike prior studies that focused on single correlations and limited comparative analysis. Second, we incorporated a sleep regularity parameter—recently receiving increasing attention—and calculated it with greater precision than prior studies, enabling us to uncover new insights. Third, our study is a prospective cohort study with large sample size and an extensive follow-up time as median 13 years for the main cohort. This enhances the credibility and representative of the findings in this study. Lastly, our study calculated the PAF which can further quantify the contribution of sleep phenotypes to the burden of CVD subtypes after adjusting for other risk factors.

Nonetheless, this study has several limitations. First, we used sleep phenotypes data only collected at baseline, without accounting for changes in sleep patterns over time. Second, the time points at which subjective and objective sleep phenotypes were obtained differed, limiting direct comparisons of their respective impacts. Third, subjective sleep phenotypes were obtained through self-reports, making them inherently prone to recall bias. Fourthly, participants in the UK Biobank are subject to the healthy volunteer effect, potentially introduce selection bias. Lastly, still certain factors such as comorbidities, which have been shown in previous studies to be associated with sleep health and CVD, were not included in our analysis.

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Chapter 5: Conclusion

In conclusion, we comprehensively investigated the differential effects of various sleep phenotypes on the risk of CVD subtypes. Our findings highlight two key subjective sleep phenotypes, insomnia and daytime napping, as the most broadly influential factors demonstrating significant risk effects. Additionally, ischemic heart disease and ischemic stroke emerged as the CVD subtypes most affected by sleep health. Furthermore, we observed a protective effect of a composite healthy sleep score, and revealed that a multidimensional assessment of sleep health better captures the overall impact of sleep on CVD risk compared to evaluating each sleep phenotype individually. Notably, the objectively measured sleep regularity index showed a protective effect specifically on peripheral vascular disease, providing novel insights beyond previous studies. Finally, we observed that sleep-related CVD risk was more pronounced in women and in participants with younger disease onset age, underscoring the importance of targeted sleep interventions in CVD prevention strategies. Future investigations are warranted to consider combinations of sleep characteristics, incorporating both subjective sleep phenotypes and objective sleep parameters, to further advance our understanding.

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Tables

Table 1. Baseline characteristic of the total cohort participants and subgroup participants with actigraphy data in the UK Biobank

	Total participants N=447,183	Total CVD N=39,567 (11.93%)	Non total CVD N=292,229 (88.07%)	P-value	Subgroup with actigraphy N=82,574	Total CVD N=1,904 (3.06%)	Non total CVD N=60,246 (96.94%)	P-value
Demographic and clinical characteristic								
Age at recruitment, mean (SD)	56.79 (±8.08)	58.57 (±7.45)	55.40 (±8.15)	**<0.0001****	56.43 (±7.82)	58.73 (±7.26)	55.65 (±7.90)	**<0.0001****
Townsend deprivation index, mean (SD)	-1.29 (±3.09)	-1.28 (±3.11)	-1.37 (±3.05)	**<0.0001****	-1.72 (±2.82)	-1.78 (±2.83)	-1.72 (±2.82)	0.3455
BMI, mean (SD)	27.53 (±4.85)	28.29 (±4.81)	27.04 (±4.63)	**<0.0001****	26.80 (±4.58)	27.41 (±4.72)	26.47 (±4.43)	**<0.0001****
DBP, mean (SD), mmHg	82.21 (±10.15)	85.17 (±10.66)	81.30 (±9.74)	**<0.0001****	81.64 (±10.01)	83.64 (±10.08)	80.79 (±9.67)	**<0.0001****
SBP, mean (SD), mmHg	137.95 (±18.70)	144.90 (±19.22)	135.20 (±17.69)	**<0.0001****	136.69 (±18.24)	142.30 (±18.46)	134.50 (±17.39)	**<0.0001****
Total cholesterol, mean (SD), mmol/L	5.68 (±1.15)	5.76 (±1.19)	5.75 (±1.11)	**0.0452***	5.72 (±1.12)	5.80 (±1.17)	5.76 (±1.09)	0.1361
Fasting glucose, mean (SD), mmol/L	5.13 (±1.26)	5.19 (±1.38)	5.05 (±1.10)	**<0.0001****	5.06 (±1.07)	5.12 (±1.12)	5.03 (±1.02)	**0.0006***
Female, n (%)	245,470 (54.89%)	17,631 (44.56%)	170,875 (58.47%)	**<0.0001****	46,818 (56.70%)	859 (45.12%)	35,582 (59.06%)	**<0.0001****
Current employment status, n (%)				**<0.0001****				**<0.0001****
Employed	255,822 (57.75%)	20,570 (52.49%)	184,863 (63.86%)		50,939 (62.09%)	1,022 (54.07%)	39,012 (65.16%)	
Retired	154,083 (34.78%)	15,820 (40.37%)	84,327 (29.13%)		26,789 (32.65%)	777 (41.11%)	17,710 (29.58%)	
Unemployed	33,086 (7.47%)	2,801 (7.15%)	20,275 (7.00%)		4,315 (5.26%)	91 (4.81%)	3,148 (5.26%)	
Education above college degree, n (%)	139,554 (31.78%)	11,057 (28.53%)	98,886 (34.43%)	**<0.0001****	34,830 (42.58%)	757 (40.22%)	26,405 (44.26%)	**0.0005***
Lifestyle characteristic								
Alcohol intake, mean (SD), times/month	11.04 (±10.64)	11.26 (±10.84)	11.04 (±10.51)	**0.0001***	12.16 (±10.75)	12.46 (±11.05)	12.10 (±10.68)	0.1568
Current smoker, n (%)	47,779 (10.68%)	4,799 (12.13%)	29,205 (9.99%)	**<0.0001****	5,741 (6.95%)	160 (8.40%)	4,155 (6.90%)	**0.0133***
Regular physical activity, n (%)	238,426 (57.04%)	20,672 (56.17%)	159,780 (58.20%)	**<0.0001****	46,953 (59.08%)	1,090 (59.79%)	34,588 (59.60%)	0.8844
Healthy diet, n (%)	287,561 (65.97%)	24,389 (63.17%)	191,005 (67.01%)	**<0.0001****	58,163 (71.62%)	1,302 (69.22%)	42,612 (71.95%)	**0.0099***

BMI, body Mass Index; DBP, diastolic blood pressure; SBP, systolic blood pressure; Continuous variables: mean (SD); Categorical variables: number of people (%); *p-value <0.05; **p-value <0.0001.

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Table 2. Baseline subjective sleep phenotypes of the total cohort participants and objective sleep phenotypes of the subgroup participants with actigraphy data in the UK Biobank

	Total cohort participants N=447,183		Subgroup cohort participants N=82,574
Subjective sleep phenotypes		**Objective sleep phenotypes**	
Sleep duration, mean (SD), hrs	7.15 (±1.12)	Sleep duration, mean (SD), hrs	6.53 (±1.09)
Short duration (<7hr), n (%)	114,104 (25.52%)	Short duration (<6hr), n (%)	22,102 (26.77%)
Normal duration (7-9hr), n (%)	324,455 (72.56%)	Normal duration (6-8hr), n (%)	55,459 (67.16%)
Long duration (>9hr), n (%)	8,624 (1.93%)	Long duration (>8hr), n (%)	5,013 (6.07%)
Chronotype		Objective chronotype	
Evening type, n (%)	35,672 (9.00%)	Evening type, n (%)	4,075 (4.93%)
Intermediate type, n (%)	252,699 (63.74%)	Intermediate type, n (%)	51,685 (62.59%)
Morning type, n (%)	108,077 (27.26%)	Morning type, n (%)	26,814 (32.47%)
Getting up in the morning		Sleep efficiency, mean (SD)	0.89 (±0.05)
Not easy getting up, n (%)	80,584 (18.18%)	Bad sleep efficiency, n (%)	11,750 (14.23%)
Easy getting up, n (%)	362,695 (81.82%)	Good sleep efficiency, n (%)	70,824 (85.77%)
Dozing (=yes), n (%)	108,893 (24.48%)	WASO, mean (SD), mins	46.70 (±19.82)
Nap (=yes), n (%)	198,684 (44.50%)	Awake times, mean (SD), counts	13.50 (±3.56)
Snore (=yes), n (%)	155,676 (37.51%)	Whole week SRI, mean (SD)	78.82 (±9.36)
Sleeplessness / Insomnia		Weekday only SRI, mean (SD)	83.82 (±8.23)
Usually suffer insomnia, n (%)	129,760 (29.04%)		
Seldom suffer insomnia, n (%)	317,045 (70.96%)		

Continuous variables: mean (SD); Categorical variable: number of people (%); Agreement between subjective and objective sleep duration group was slight (weighted Cohen's $\kappa = 0.1346$, 95% CI 0.1278–0.1415); Agreement between subjective and objective chronotype was fair (weighted Cohen's $\kappa = 0.2866$, 95% CI 0.2799–0.2933).

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Table 3. Follow-up characteristics and incidence of total cardiovascular disease according to subjective and objective sleep phenotypes in the UK Biobank

	Total participants, n	Person-years	Total CVD event number, n (%)	Incidence rate (per 1000 person-years)
Subjective sleep phenotypes				
Sleep duration				
Short duration (<7hr)	83,267	1,042,412	10,715 (12.87%)	10.28
Normal duration (7-9hr)	243,162	3,083,168	28,055 (11.54%)	9.99
Long duration (>9hr)	5,367	66,247	797 (14.85%)	12.03
Chronotype				
Evening type	26,486	332,983	3,271 (12.35%)	9.90
Intermediate type	188,882	2,389,693	21,837 (11.56%)	9.14
Morning type	78,839	989,689	9,802 (12.43%)	9.82
Getting up in the morning				
Not easy getting up	60,724	771,906	6,588 (10.85%)	8.53
Easy getting up	268,019	3,374,851	32,612 (12.17%)	9.66
Dozing				
Yes	75,991	943,736	10,565 (13.90%)	11.19
No	254,244	3,228,864	28,781 (11.32%)	8.91
Nap				
Yes	139,911	1,743,754	19,161 (13.70%)	10.99
No	191,395	2,442,060	20,343 (10.63%)	8.33
Snore				
Yes	112,790	1,743,754	15,473 (13.72%)	8.87
No	196,064	2,442,060	21,201 (10.81%)	8.68
Sleeplessness / Insomnia				
Usually suffer insomnia	92,707	1,160,083	12,093 (13.04%)	10.42
Seldom suffer insomnia	238,811	3,028,337	27,436 (11.49%)	9.06

SRI, sleep regularity index; WASO, wake after sleep onset.

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Table 3. Follow-up characteristics and incidence of total cardiovascular disease according to subjective and objective sleep phenotypes in the UK Biobank (continuous)

	Total participants, n	Person-years	Total CVD event number, n (%)	Incidence rate (per 1000 person-years)
Objective sleep phenotypes				
Sleep duration				
Short duration (<6hr)	16,027	121,721	572 (3.57%)	4.70
Normal duration (6-8hr)	42,364	326,155	1,224 (2.89%)	3.75
Long duration (>8hr)	3,759	28,835	108 (2.87%)	3.75
Objective chronotype				
Evening type	2,866	21,623	97 (3.38%)	4.49
Intermediate type	38,816	297,352	1,233 (3.18%)	4.15
Morning type	20,468	157,737	574 (2.80%)	3.64
Sleep efficiency				
Bad sleep efficiency	8,607	65,544	324 (3.76%)	4.94
Good sleep efficiency	53,543	411,168	1,580 (2.95%)	3.84
WASO	62,150	476,712	1,904 (3.06%)	3.99
Awake times	62,150	476,712	1,904 (3.06%)	3.99
Whole week SRI	53,982	414,126	1668 (3.09%)	4.03
Weekday only SRI	52,883	405,793	1638 (3.97%)	4.04

SRI, sleep regularity index; WASO, wake after sleep onset.

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Table 4. Cox proportional hazards models of sleep phenotypes for total cardiovascular disease

	Crude HR (95%CI)	Crude model P-value	Model 1 aHR (95%CI)	Model 1 P-value	Model 2 aHR (95%CI)	Model 2 P-value
Subjective sleep phenotypes						
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.1252 (1.1004-1.1505)	**<0.0001*****	1.0901 (1.0656-1.1153)	**<0.0001*****	1.0916 (1.0629-1.1211)	**<0.0001*****
Long sleep duration	1.3134 (1.2241-1.4092)	**<0.0001*****	1.0942 (1.0175-1.1767)	0.0151*	1.1273 (1.0348-1.2282)	0.0061*
Evening vs. Morning chronotype	0.9909 (0.9524-1.0309)	0.6505	1.0511 (1.0090-1.0949)	0.0169*	1.0856 (1.0354-1.1382)	**0.0007****
Evening vs. Intermediate chronotype	1.0717 (1.0330-1.1118)	**0.0004****	1.0792 (1.0396-1.1203)	**0.0001****	1.1029 (1.0565-1.1513)	**<0.0001*****
Easy getting up	1.0000 (reference)	-	1.0000 (reference)	-	1.0000 (reference)	-
Not easy getting up	0.8853 (0.8622-0.9090)	**<0.0001*****	1.0673 (1.0384-1.0970)	**<0.0001*****	1.0951 (1.0605-1.1309)	**<0.0001*****
Dozing	1.2475 (1.2200-1.2757)	**<0.0001*****	1.0511 (1.0272-1.0755)	**<0.0001*****	1.0839 (1.0553-1.1134)	**<0.0001*****
Nap	1.3122 (1.2866-1.3383)	**<0.0001*****	1.0498 (1.0284-1.0716)	**<0.0001*****	1.0506 (1.0258-1.0760)	**0.0001****
Snore	1.2898 (1.2633-1.3168)	**<0.0001*****	1.0560 (1.0332-1.0794)	**<0.0001*****	1.0446 (1.0185-1.0714)	**<0.0001*****
Seldom suffer insomnia	1.0000 (reference)	-	1.0000 (reference)	-	1.0000 (reference)	-
Usually suffer insomnia	1.1471 (1.1228-1.1719)	**<0.0001*****	1.1087 (1.0846-1.1334)	**<0.0001*****	1.1359 (1.1072-1.1652)	**<0.0001*****
Objective sleep phenotypes						
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.2427 (1.1253-1.3724)	**<0.0001*****	1.0503 (0.9483-1.1632)	0.3463	1.0306 (0.9182-1.1569)	0.6088
Long sleep duration	0.9952 (0.8175-1.2116)	0.9619	0.9718 (0.7951-1.1878)	0.7800	0.9699 (0.7705-1.2208)	0.7944
Evening vs. Morning chronotype	1.2161 (0.9807-1.5081)	0.0747	0.9893 (0.7908-1.2376)	0.9248	1.0303 (0.8018-1.3237)	0.8157
Evening vs. Intermediate chronotype	1.0706 (0.8707-1.3164)	0.5176	0.9724 (0.7867-1.2018)	0.7953	1.0099 (0.7967-1.2802)	0.9348
Good sleep efficiency	1.0000 (reference)	-	1.0000 (reference)	-	1.0000 (reference)	-
Bad sleep efficiency	1.2837(1.1391-1.4467)	**<0.0001*****	1.1242 (0.9950-1.2703)	0.0603	1.1746 (1.0254-1.3455)	0.0203*
WASO (per 30 mins increase)	1.0894 (1.0201-1.1634)	0.0107*	1.0565 (0.9880-1.1297)	0.1082	1.0534 (0.9768-1.1360)	0.1765
Awake times (per count increase)	0.9672 (0.9549-0.9797)	**<0.0001*****	0.9936 (0.9806-1.0068)	0.3417	0.9972 (0.9824-1.0122)	0.7111
Whole week SRI (per 10 points increase)	0.9227 (0.8780-0.9698)	**0.0015****	0.9512 (0.9036-1.0012)	0.0557	0.9522 (0.8980-1.0095)	0.1006
Weekday SRI (per 10 points increase)	0.9223 (0.8712-0.9764)	0.0054*	0.9700 (0.9137-1.0297)	0.3174	0.9709 (0.9068-1.0395)	0.3967

WASO, wake after sleep onset; SRI, sleep regularity index; aHR, adjusted hazard ratio; 95% CI, confidence interval; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; Model 1 adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status; Model 2 adjusted for Model 1 + physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose.

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Table 5. Hazard ratio and population attributable fraction of subjective sleep phenotypes and healthy sleep score in relation to total cardiovascular disease, ischemic heart disease and ischemic stroke

	Total Cardiovascular Disease			Ischemic Heart Disease			Ischemic Stroke		
	aHR (95%CI)	P-value	PAF % (95%CI)	aHR (95%CI)	P-value	PAF % (95%CI)	aHR (95%CI)	P-value	PAF % (95%CI)
Subjective sleep phenotypes									
Normal sleep duration	1.0000 (reference)	-	-	1.0000 (reference)	-	-	1.0000 (reference)	-	-
Short sleep duration	1.0916 (1.0629-1.1211)	**<0.0001*****	2.03 (1.40-2.66)	1.1880 (1.1458-1.2318)	**<0.0001*****	4.44 (3.48-5.40)	1.0641 (0.9992-1.1333)	0.0530	1.66 (0.84-3.23)
Long sleep duration	1.1273 (1.0348-1.2282)	0.0061*	0.19 (0.05-0.34)	1.2551 (1.1376-1.3848)	**<0.0001*****	0.56 (0.29-0.83)	1.4190 (1.2156-1.6564)	**<0.0001*****	0.99 (0.49-1.50)
Evening vs. Morning	1.0856 (1.0354-1.1382)	**0.0007****	1.86 (0.77-2.95)	1.0267 (0.9618-1.0961)	0.4285	0.61 (-0.91-2.13)	1.0325 (0.9246-1.1531)	0.5699	0.76 (-1.87-3.39)
Evening vs. Intermediate	1.1029 (1.0565-1.1513)	**<0.0001*****	1.12 (0.61-1.63)	1.0755 (1.0129-1.1420)	0.0174*	0.89 (0.14-1.64)	1.0867 (0.9819-1.2027)	0.1080	1.05 (-0.25-2.34)
Easy getting up	1.0000 (reference)	-	-	1.0000 (reference)	-	-	1.0000 (reference)	-	-
Not easy getting up	1.0951 (1.0605-1.1309)	**<0.0001*****	1.33 (0.84-1.81)	1.1936 (1.1420-1.2475)	**<0.0001*****	2.63 (1.95-3.32)	1.1605 (1.0762-1.2514)	**<0.0001*****	2.35 (1.16-3.53)
Dozing	1.0839 (1.0553-1.1134)	**<0.0001*****	1.85 (1.23-2.48)	1.1349 (1.0955-1.1757)	**<0.0001*****	3.57 (2.55-4.59)	1.1136 (1.0489-1.1824)	**0.0004****	3.12 (1.37-4.89)
Nap	1.0506 (1.0258-1.0760)	**0.0001****	2.10 (1.08-3.12)	1.1653 (1.1270-1.2049)	**<0.0001*****	7.68 (6.01-9.35)	1.1109 (1.0502-1.1751)	**0.0002****	5.36 (2.51-8.26)
Snore	1.0446 (1.0185-1.0714)	**<0.0001*****	1.65 (0.69-2.62)	1.0769 (1.0405-1.1146)	**<0.0001*****	3.08 (1.64-4.51)	1.0521 (0.9920-1.1159)	0.0906	2.08 (-0.32-4.49)
Seldom suffer insomnia	1.0000 (reference)	-	-	1.0000 (reference)	-	-	1.0000 (reference)	-	-
Usually suffer insomnia	1.1359 (1.1072-1.1652)	**<0.0001*****	3.35 (2.67-4.04)	1.2444 (1.2024-1.2879)	**<0.0001*****	6.43 (5.40-7.48)	1.1723 (1.1061-1.2425)	**<0.0001*****	4.99 (3.15-6.83)
Healthy sleep score									
Continuous HSS (per point increase)	0.9334 (0.9221-0.9448)	**<0.0001*****	4.67 (4.63-4.72)	0.8925 (0.8779-0.9074)	**<0.0001*****	8.30 (8.23-8.38)	0.9470 (0.9239-0.9705)	**<0.0001*****	5.89 (5.82-5.98)
Good overall sleep health	1.0000 (reference)	-	-	1.0000 (reference)	-	-	1.0000 (reference)	-	-
Poor overall sleep health	1.1336 (1.1044-1.1637)	**<0.0001*****	4.45 (3.51-5.39)	1.2212 (1.1783-1.2656)	**<0.0001*****	8.05 (6.60-9.50)	1.1244 (1.0582-1.1947)	**0.0002****	4.79 (2.29-7.28)

HSS, healthy sleep score; aHR, adjusted hazard ratio; 95% CI, confidence interval; PAF, population attributable fraction; Good overall sleep health indicates participants with 4 to 5 points of HSS, and poor overall sleep health indicates participants with 0 to 3 points of HSS; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; Model adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status, physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose.

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Table 6. Hazard ratio and population attributable fraction of getting up in the morning, napping and insomnia in relation to cardiovascular disease subtypes

	Not easy getting up in the morning			Napping			Insomnia		
	aHR (95%CI)	P-value	PAF % (95%CI)	aHR (95%CI)	P-value	PAF % (95%CI)	aHR (95%CI)	P-value	PAF % (95%CI)
Total Cardiovascular Disease	1.0951 (1.0605-1.1309)	**<0.0001*****	1.33 (0.84-1.81)	1.0506 (1.0258-1.0760)	**0.0001****	2.10 (1.08-3.12)	1.1359 (1.1072-1.1652)	**<0.0001*****	3.35 (2.67-4.04)
Hemorrhagic stroke	1.0331 (0.8723-1.2234)	0.7062	0.49 (-2.06 to 3.03)	1.0417 (0.9220-1.1770)	0.5116	1.98 (-3.85 to 7.81)	0.9949 (0.8720-1.1352)	0.9396	-0.15 (-4.00 to 3.70)
Ischemic Stroke	1.1605 (1.0762-1.2514)	**<0.0001*****	2.35 (1.16-3.53)	1.1109 (1.0502-1.1751)	**0.0002****	5.36 (2.51-8.26)	1.1723 (1.1061-1.2425)	**<0.0001*****	4.99 (3.15-6.83)
Ischemic Heart Disease	1.1936 (1.1420-1.2475)	**<0.0001*****	2.63 (1.95-3.32)	1.1653 (1.1270-1.2049)	**<0.0001*****	7.68 (6.01-9.35)	1.2444 (1.2024-1.2879)	**<0.0001*****	6.43 (5.40-7.48)
Hypertension	0.9469 (0.9131-0.9818)	**0.0032****	-0.86 (-1.43 to -0.30)	1.0213 (0.9943-1.0490)	0.1226	0.97 (-0.27 to 2.22)	1.0406 (1.0114-1.0706)	0.0061*	1.16 (0.32-2.00)
Peripheral Vascular Disease	1.1141 (0.9924-1.2507)	0.0671	1.90 (-0.22 to 4.03)	1.0792 (0.9861-1.1810)	0.0970	3.74 (-0.60 to 8.08)	1.3000 (1.1853-1.4259)	**<0.0001*****	8.39 (5.36-11.41)
Venous thromboembolic disease	1.0725 (0.9709-1.1847)	0.1681	1.16 (-0.53 to 2.85)	1.0266 (0.9519-1.1072)	0.4953	1.29 (-2.40 to 4.97)	1.0895 (1.0060-1.1798)	0.0351*	2.61 (0.15-5.06)
Pulmonary heart disease	1.1162 (1.0013-1.2443)	0.0474*	1.79 (-0.02 to 3.61)	1.0850 (0.9991-1.1783)	0.0526	4.13 (-0.04 to 8.30)	1.0912 (1.0010-1.1895)	0.0474*	2.72 (0.01-5.44)
Heart Failure	1.2274 (1.0818-1.3926)	**0.0015****	3.41 (1.27-5.55)	1.1992 (1.0855-1.3248)	**0.0003****	10.36 (5.04-15.87)	1.1761 (1.0648-1.2990)	**0.0014****	5.45 (2.15-8.74)
Cardiomyopathy	1.1444 (0.9081-1.4422)	0.2530	2.97 (-0.82 to 6.77)	1.2034 (1.0056-1.4401)	0.0433*	7.81 (-0.29 to 15.91)	1.2748 (1.0589-1.5348)	0.0103*	7.66 (2.24-13.08)
Heart Valve Disorder	1.1231 (0.9874-1.2776)	0.0773	1.78 (-0.14 to 3.69)	1.1637 (1.0593-1.2785)	**0.0016****	8.01 (3.25-12.77)	1.1699 (1.0611-1.2898)	**0.0016****	4.80 (1.75-7.85)
Heart Arrhythmia	1.1166 (1.0537-1.1832)	**0.0002****	1.68 (0.79-2.58)	1.0462 (1.0022-1.0920)	0.0392*	2.24 (0.12-4.35)	1.1428 (1.0927-1.1953)	**<0.0001*****	4.05 (2.69-5.42)

aHR, adjusted hazard ratio; 95% CI, confidence interval; PAF, population attributable fraction; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; All models except for hypertension adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status, physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose; Model for hypertension adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status, physical activity, diet quality, total cholesterol and fasting glucose.

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Table 7. Gender-stratified Cox proportion hazards models of napping and insomnia for significantly affected CVD subtypes

CVD Subtypes	Group	Napping			Insomnia		
		aHR (95%CI)	P-value	Interaction P-value	aHR (95%CI)	P-value	Interaction P-value
Total CVD	Male	1.0568 (1.0238-1.0908)	**0.0006***	0.5431	1.1050 (1.0664-1.1450)	**<0.0001****	**0.0116***
	Female	1.0460 (1.0086-1.0848)	**0.0155***		1.1667 (1.1244-1.2105)	**<0.0001****	
Ischemic Stroke	Male	1.0703 (0.9948-1.1515)	0.0688	0.8876	1.1570 (1.0707-1.2503)	**0.0002***	0.4452
	Female	1.1690 (1.0713-1.2755)	**0.0005***		1.2009 (1.0996-1.3116)	**<0.0001****	
Ischemic Heart Disease	Male	1.1533 (1.1076-1.2009)	**<0.0001****	**0.0015***	1.2112 (1.1608-1.2638)	**<0.0001****	**0.0016***
	Female	1.2023 (1.1335-1.2752)	**<0.0001****		1.3127 (1.2375-1.3923)	**<0.0001****	
Peripheral Vascular Disease	Male	-	-	-	1.2617 (1.1088-1.4357)	**0.0004***	0.8959
	Female	-	-		1.3495 (1.1821-1.5406)	**<0.0001****	
Heart Failure	Male	1.1437 (1.0143-1.2896)	**0.0284***	0.1075	1.1629 (1.0309-1.3117)	**0.0141***	0.7742
	Female	1.3568 (1.1403-1.6145)	**0.0006***		1.2099 (1.0175-1.4387)	**0.0311***	
Heart Valve Disorder	Male	1.1899 (1.0523-1.3456)	**0.0056***	0.7581	1.0725 (0.9394-1.2244)	0.3004	**0.0252***
	Female	1.1509 (0.9950-1.3312)	0.0585		1.3109 (1.1328-1.5170)	**0.0003***	
Heart Arrhythmia	Male	-	-	-	1.1326 (1.0664-1.2030)	**0.0001***	0.3170
	Female	-	-		1.1612 (1.0855-1.2422)	**<0.0001****	

aHR, adjusted hazard ratio; 95% CI, confidence interval; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; *Interaction p-value < 0.05; **Interaction p-value < 0.0001; Model adjusted for age, education, employment, TDI, alcohol intake, smoking status, physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose.

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Table 8. Disease onset age-stratified Cox proportion hazards models of nap and insomnia for significantly affected CVD subtypes

CVD Subtypes	Group	Napping			Insomnia		
		aHR (95%CI)	P-value	Interaction P-value	aHR (95%CI)	P-value	Interaction P-value
Total CVD	Onset Age < 65	1.0417 (1.0081-1.0764)	**0.0147***	**<0.0001****	1.2047 (1.1630-1.2479)	**<0.0001****	**0.0387***
	Onset Age ≥ 65	1.0431 (1.0071-1.0804)	**0.0184***		1.0944 (1.0546-1.1357)	**<0.0001****	
Ischemic Stroke	Onset Age < 65	1.0869 (0.9899-1.1933)	0.0805	**<0.0001****	1.2442 (1.1283-1.3721)	**<0.0001****	0.7322
	Onset Age ≥ 65	1.1027 (1.0277-1.1833)	**0.0065***		1.1629 (1.0819-1.2499)	**<0.0001****	
Ischemic Heart Disease	Onset Age < 65	1.1616 (1.1052-1.2208)	**<0.0001****	**<0.0001****	1.3349 (1.2675-1.406)	**<0.0001****	0.7169
	Onset Age ≥ 65	1.1427 (1.0922-1.1955)	**<0.0001****		1.1840 (1.1310-1.2396)	**<0.0001****	
Peripheral Vascular Disease	Onset Age < 65	-	-	-	1.2647 (1.1092-1.4421)	**0.0005***	**0.0122***
	Onset Age ≥ 65	-	-		1.3923 (1.2224-1.5858)	**<0.0001****	
Heart Failure	Onset Age < 65	1.2245 (1.0221-1.4670)	**0.0280***	**0.0016***	1.4312 (1.1935-1.7162)	**0.0001***	0.1494
	Onset Age ≥ 65	1.1794 (1.0474-1.3281)	**0.0064***		1.1150 (0.9911-1.2543)	0.0701	
Heart Valve Disorder	Onset Age < 65	1.2496 (1.0652-1.4658)	**0.0062***	**0.0001***	1.3325 (1.1273-1.5751)	**0.0008***	0.9402
	Onset Age ≥ 65	1.1301 (1.0061-1.2694)	**0.0392***		1.1106 (0.9851-1.2521)	0.0863	
Heart Arrhythmia	Onset Age < 65	-	-	-	1.1946 (1.1122-1.2832)	**<0.0001****	**0.0091***
	Onset Age ≥ 65	-	-		1.1359 (1.0723-1.2032)	**<0.0001****	

aHR, adjusted hazard ratio; 95% CI, confidence interval; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; *Interaction p-value < 0.05; **Interaction p-value < 0.0001; Model adjusted for age, education, employment, TDI, alcohol intake, smoking status, physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose.

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Figures

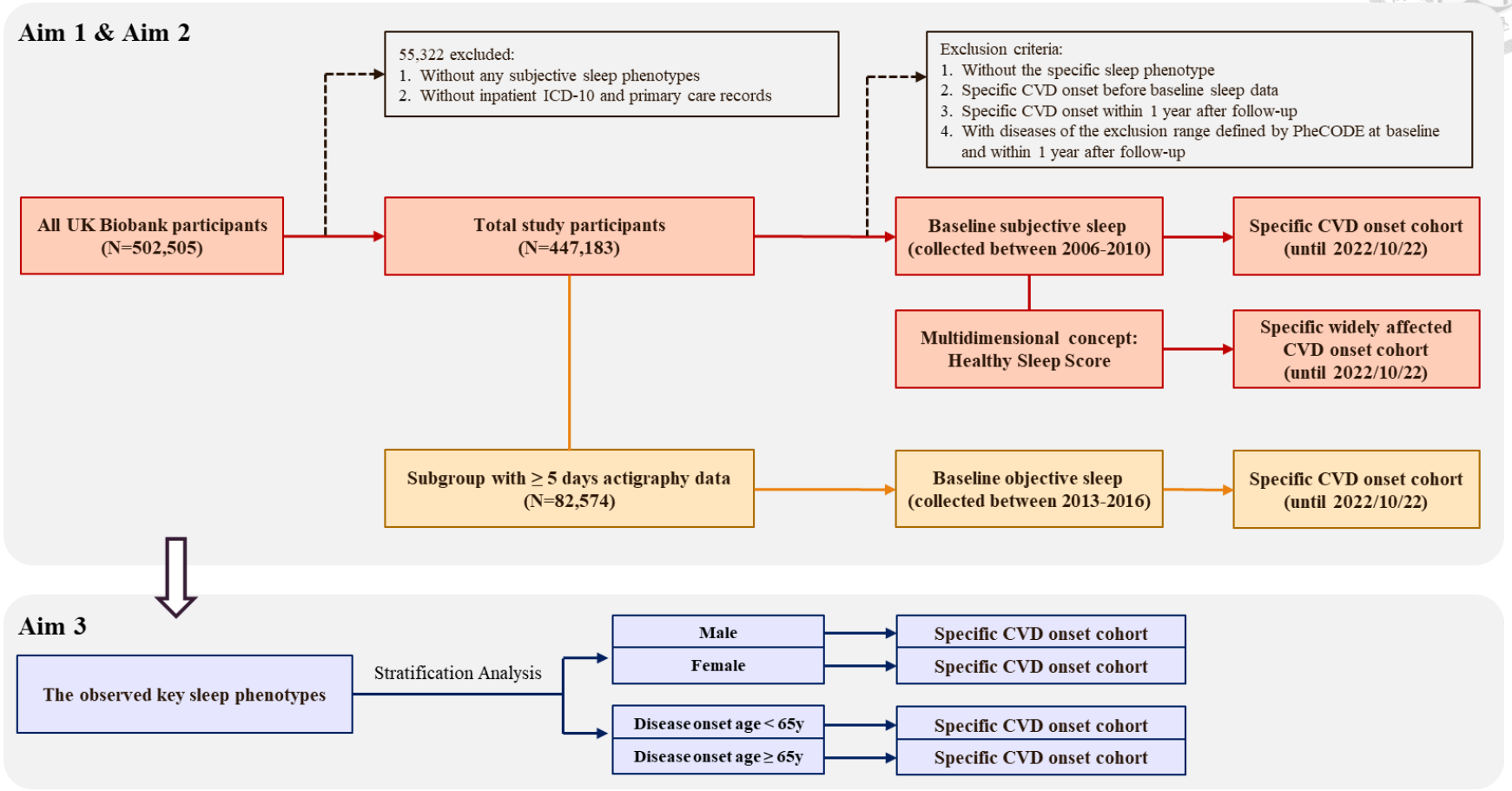

Figure 1. Study flow chart and study design

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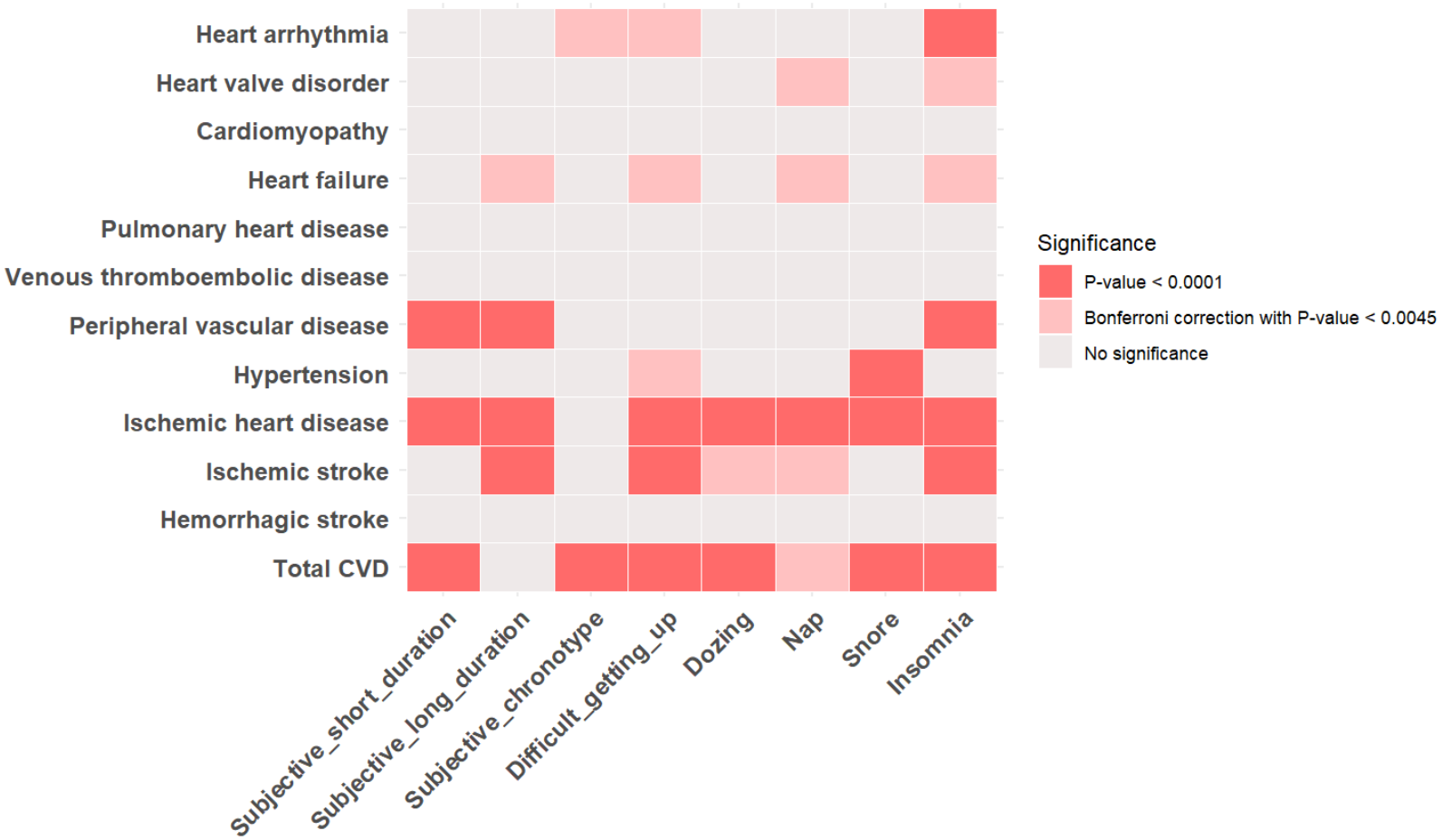

Figure 2. Significance matrix from the Cox model analyzing the impact of subjective sleep phenotypes on cardiovascular disease subtypes

All models except for hypertension adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status, physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose; Model for hypertension adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status, physical activity, diet quality, total cholesterol and fasting glucose.

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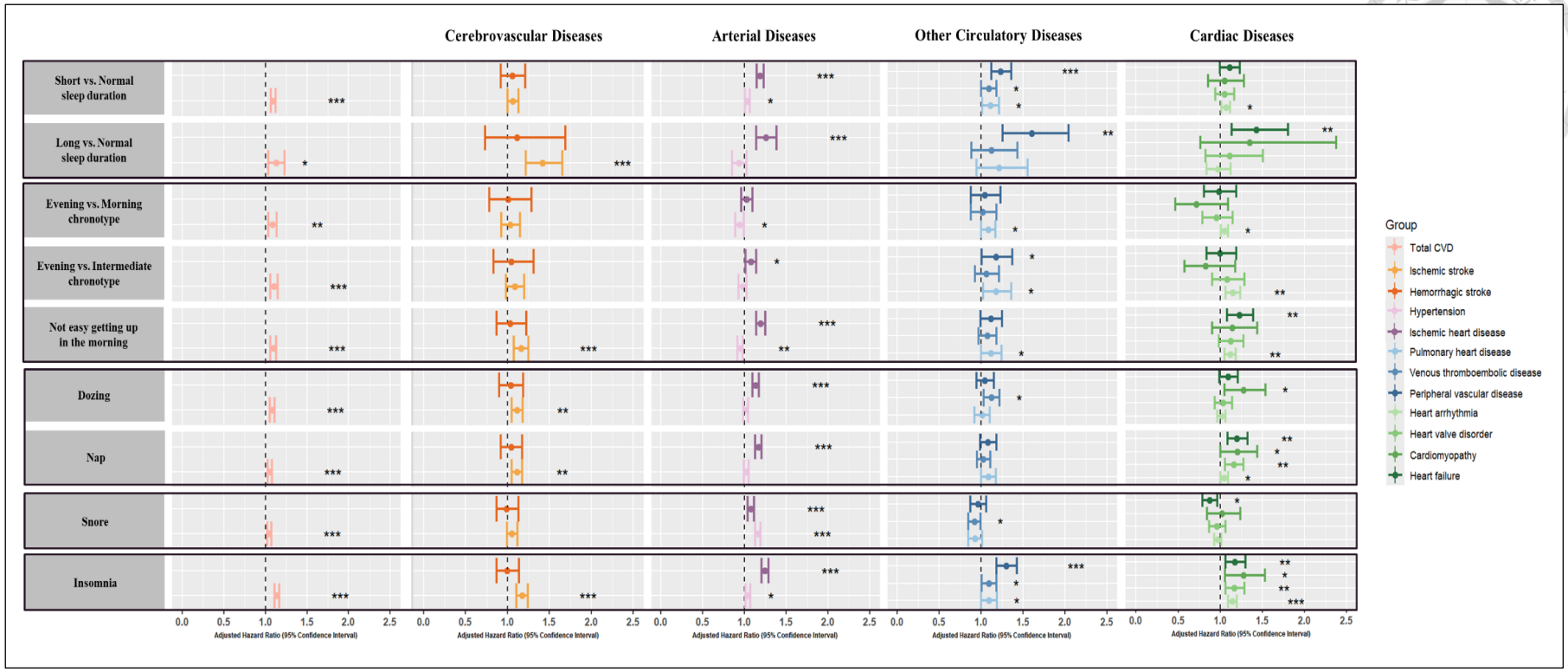

Figure 3. Cox proportional hazards models of subjective sleep phenotypes for cardiovascular disease subtypes

All models except for hypertension adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status, physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose; Model for hypertension adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status, physical activity, diet quality, total cholesterol and fasting glucose; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001

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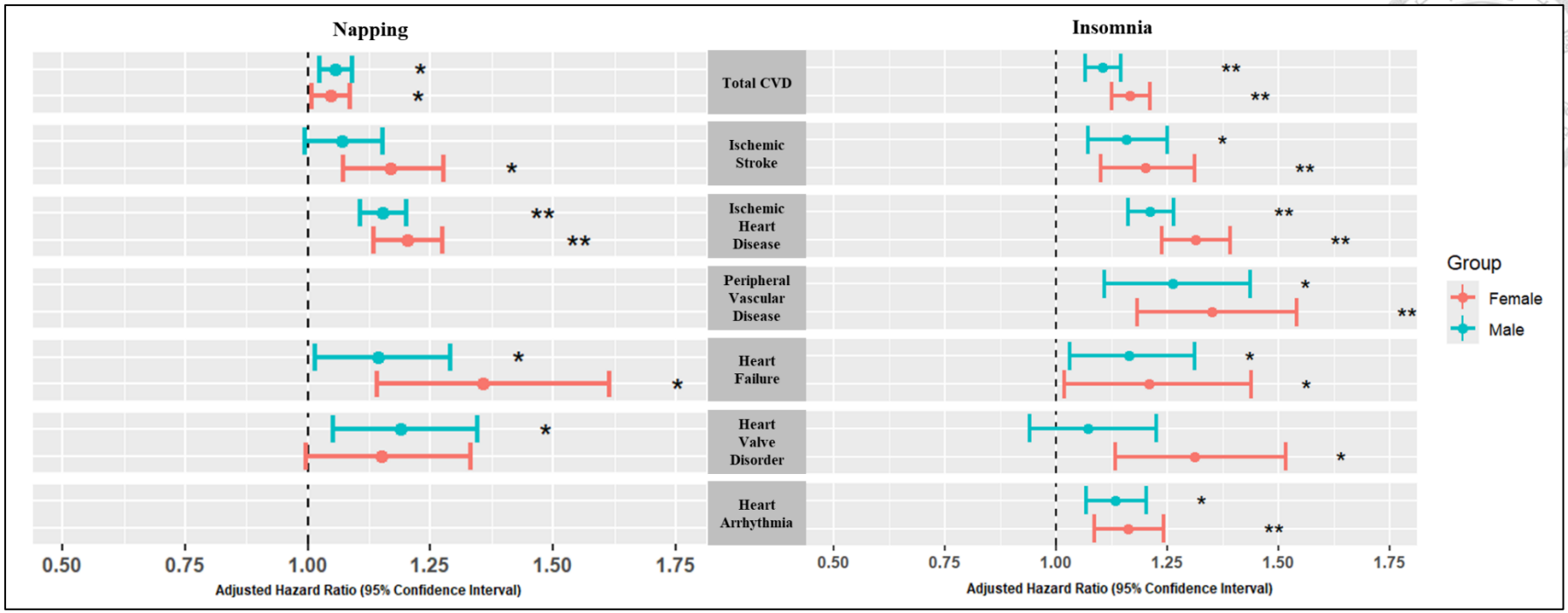

Figure 4. The impact of napping and insomnia in relation to significantly affected cardiovascular disease subtypes by gender

All models adjusted for age, education, employment, TDI, alcohol intake, smoking status, physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose; *p-value <0.05; ***p-value <0.0001

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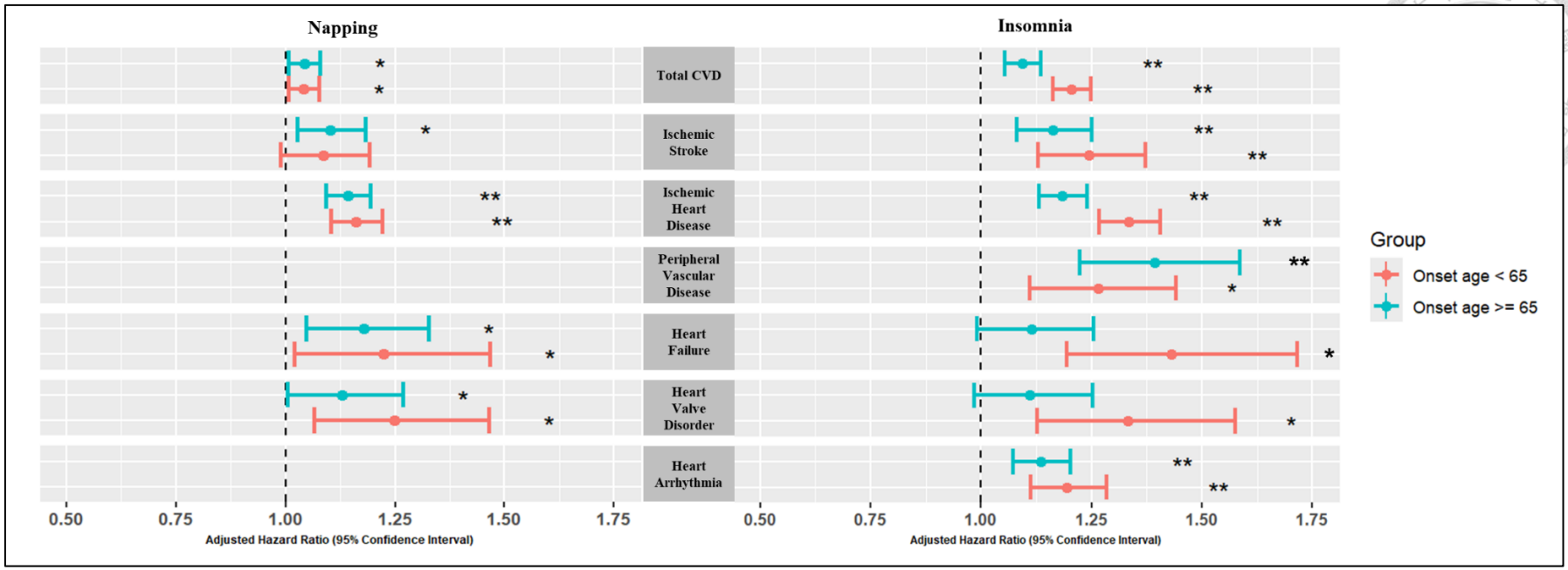

Figure 5. The impact of napping and insomnia in relation to significantly affected cardiovascular disease subtypes by disease onset age group

All model adjusted for age, education, employment, TDI, alcohol intake, smoking status, physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose; *p-value <0.05; ***p-value <0.0001

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Supplementary Materials

Table S1. Definitions of the sleep phenotypes

Variable	Field ID	Description
Subjective sleep duration	1160	Question: “About how many hours sleep do you get in every 24 hours? (please include naps)” Groups: Short sleep duration (<7 hrs), normal sleep duration (7-9 hrs), long sleep duration (>9 hrs)
Subjective chronotype	1180	Question: “Do you consider yourself to be?” Groups: Evening type (definitely an evening person), intermediate type (more an evening person or more a morning person), morning type (definitely a morning person)
Getting up in the morning	1170	Question: “On an average day, how easy do you find getting up in the morning?” Groups: Not easy getting up (not at all easy or not very easy), easy getting up (fairly easy or very easy)
Dozing	1220	Question: “How likely are you to doze off or fall asleep during the daytime when you don't mean to? (e.g. when working, reading or driving)” Groups: Doze (sometimes or often), do not doze (never/rarely)
Nap	1190	Question: “Do you have a nap during the day?” Groups: Nap (sometimes or usually), do not nap (never/rarely)
Snore	1210	Question: “Does your partner or a close relative or friend complain about your snoring?” Groups: Snore, do not snore
Insomnia	1200	Question: “Do you have trouble falling asleep at night or do you wake up in the middle of the night?” Groups: Usually suffer insomnia (usually), seldom suffer insomnia (never/rarely or sometimes)
Objective sleep duration	90001	The total duration of sustained inactivity intervals within the sleep time window Groups: Short sleep duration (<6 hrs), normal sleep duration (6-8 hrs), long sleep duration (>8 hrs)
Objective chronotype	90001	Defined by median sleep midpoint over all observed days Groups: Evening type (before 3 a.m.), intermediate type (3 a.m. to 5 a.m.), morning type (after 5 a.m.)
Sleep efficiency	90001	The percentage of actual sleep duration within the sleep time window Groups: Bad efficiency (≥85%), good efficiency (<85%)
WASO	90001	The total amount of awake time during the SPT-window
Awake times	90001	The number of non-sleep episodes experienced during the sleep time window
Sleep regularity index	90001	The percentage probability that participants are in the same state (sleep or awake) at the same time point every 24 hours apart Calculated the sleep regularity index for the entire week and for weekdays only

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Table S2. Definitions of the cardiovascular disease subtypes

Diseases	PheCODEs	ICD-10 codes	Control Exclusion PheCODEs
Total cardiovascular disease	All the PheCODEs included in the following 11 subtypes	All the ICD-10 codes included in the following 11 subtypes	All the exclusion PheCODEs included in the following 11 subtypes
Hemorrhagic stroke	430: Intracranial hemorrhage 430.1: Subarachnoid hemorrhage 430.2: Intracerebral hemorrhage 430.3: Subdural hemorrhage	I60.X、I61.X、I62.X、S06.4	430-438.99
Ischemic stroke	433: Cerebrovascular disease 433.1: Occlusion and stenosis of precerebral arteries 433.11: Occlusion of cerebral arteries, with cerebral infarction 433.12: Cerebral atherosclerosis 433.2: Occlusion of cerebral arteries 433.21: Cerebral artery occlusion, with cerebral infarction 433.3: Cerebral ischemia 433.31: Transient cerebral ischemia 433.32: Moyamoya disease 433.5: Cerebral aneurysm 433.6: Acute, but ill-defined cerebrovascular disease 433.8: Late effects of cerebrovascular disease	I63.X、I64、I65.X、I66、I67、I671、I672、I675、I676、I677、I678、I679、I68、I680、I682、I688、I69.X、G450、G451、G452、G454、G458、G459、G460、G461、G462、G463、G464、G465、G466、G467、G468	430-438.99
Ischemic heart disease	411: Ischemic heart disease 411.1: Unstable angina (intermediate coronary syndrome) 411.2: Myocardial infarction 411.3: Angina pectoris 411.4: Coronary atherosclerosis 411.41: Aneurysm and dissection of heart 411.8: Other chronic ischemic heart disease, unspecified 411.9: Other acute and subacute forms of ischemic heart disease	I20.X、I21.X、I22.X、I23、I230、I231、I232、I233、I236、I238、I24.X、I25、I251、I252、'I253、I254、I255、I256、I258、I259、I341、I510、I513、Z951、Z955	410-414.99

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Table S2. Definitions of the cardiovascular disease subtypes (continuous)

Diseases	PheCODEs	ICD-10 codes	Control Exclusion PheCODEs
Hypertension	401: Hypertension 401.1: Essential hypertension 401.2: Hypertensive heart and/or renal disease 401.21: Hypertensive heart disease 401.22: Hypertensive chronic kidney disease 401.3: Other hypertensive complications	I10、I11.X、I12.X、I13.X、I15.X、I67.4	401-405.99
Peripheral vascular disease	443: Peripheral vascular disease 443.1: Raynaud's syndrome 443.7: Peripheral angiopathy in diseases classified elsewhere 443.8: Other specified peripheral vascular diseases 443.9: Peripheral vascular disease, unspecified	E10.5、E11.5、E14.5、I73、I73.0、I73.8、 I73.9、I79.1、 I79.2、I79.8	440-449.99
Venous thromboembolic disease	451: Phlebitis and thrombophlebitis 451.2: Phlebitis and thrombophlebitis of lower extremities 452: Other venous embolism and thrombosis 452.1: Iatrogenic pulmonary embolism and infarction 452.2: Deep vein thrombosis [DVT] 452.8: Postphlebitic syndrome	I80.X、I81、I82.X、I87.0	450-457.99
Pulmonary heart disease	415: Pulmonary heart disease 415.1: Acute pulmonary heart disease 415.11: Pulmonary embolism and infarction, acute 415.2: Chronic pulmonary heart disease 415.21: Primary pulmonary hypertension	I26.X、I270、I271、I278、I279、I28.X	415-517.99
Heart failure	428: Congestive heart failure; nonhypertensive 428.1: Congestive heart failure (CHF) NOS 428.2: Heart failure NOS 428.3: Heart failure with reduced EF [Systolic or combined heart failure] 428.4: Heart failure with preserved EF [Diastolic heart failure] 401.21: Hypertensive heart disease 401.2: Hypertensive heart and/or renal disease	I50.0、I50.1、I50.9、I11.0、 I13.0、I13.2	410-405.99、428-429.99

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Table S2. Definitions of the cardiovascular disease subtypes (continuous)

Diseases	PheCODEs	ICD-10 codes	Control Exclusion PheCODEs
Cardiomyopathy	425: Cardiomyopathy 425.1: Primary/intrinsic cardiomyopathies 425.11: Hypertrophic obstructive cardiomyopathy 425.12: Other hypertrophic cardiomyopathy 425.2: Secondary/extrinsic cardiomyopathies 425.8: Other cardiomyopathy	I42.X、I43、I43.8	420-425.99
Heart valve disorder	395: Heart valve disorders 395.1: Nonrheumatic mitral valve disorders 395.2: Nonrheumatic aortic valve disorders 395.3: Nonrheumatic tricuspid valve disorders 395.4: Nonrheumatic pulmonary valve disorders 395.6: Heart valve replaced	I34.X、I35、I359、I36.X、I37、I370、I371、I372、I379、I39、I081、I082、Z952、Z953、Z954	394-399.99
Heart arrhythmia	427: Cardiac dysrhythmias 427.1: Paroxysmal tachycardia, unspecified 427.11: Paroxysmal supraventricular tachycardia 427.12: Paroxysmal ventricular tachycardia 427.2: Atrial fibrillation and flutter 427.21: Atrial fibrillation 427.22: Atrial flutter 427.3: Other specified cardiac dysrhythmias 427.4: Cardiac arrest and ventricular fibrillation 427.41: Ventricular fibrillation and flutter 427.42: Cardiac arrest 427.5: Arrhythmia (cardiac) NOS 427.6: Premature beats 427.61: Supraventricular premature beats 427.7: Tachycardia NOS 427.8: Sinoatrial node dysfunction (Bradycardia) 427.9: Palpitations	I47.X、I49.X、I48、I46、I46.0、I46.9、R00.0、R00.1、R00.2	426-427.99

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Table S3. Definitions of the baseline characteristics

Variable	Field ID	Description
Sociodemographic factors		
Age at recruitment	21022	-
Gender	31	-
Education level	6138	A binary variable categorized participants into with and without university degree
Employment status	6142	Answers with “In paid employment or self-employed” were classified as employed, answers with “Retired” were classified as retired, and the remaining were classified into unemployed
Townsend Deprivation Index	22189	Represent material deprivation in a given area, calculated based on four key factors: unemployment, household overcrowding, non-car ownership, and non-home ownership
Lifestyle factors		
Smoking status	1239	Participants were asked “Do you smoke tobacco now?”, answers with “On most or all days” or “Occasionally” were classified as current smoker, and “No” as not current smoker
Alcohol intake	1558	Intake frequency was transformed into times per month
Physical activity	884, 894, 904, 914	Regular physical activity was defined as at least 150 minutes of moderate activity per week or 75 minutes of vigorous activity per week or an equivalent combination
Diet Quality	1309, 1319, 1289, 1299, 1329, 1339, 1349, 1369, 1379, 1389, 1438, 1448, 1458, 1468	Healthy diet was defined as at least 4 of the following 7 food groups: Fruits: ≥ 3 servings/day, Vegetables: ≥ 3 servings/day, Fish: ≥ 2 servings/week, Processed meats: ≤ 1 serving/week, Unprocessed red meats: ≤ 1.5 servings/week, Whole grains: ≥ 3 servings/day, and Refined grains: ≤ 1.5 servings/day
Anthropometry		
Body mass index	21001	(kg/m²)
Systolic blood pressure	4080.	Take the blood pressure taken at the time of admission (usually two measurements); if there are two, take the average; if there is only one, take that one
Diastolic blood pressure	4079.	Take the blood pressure taken at the time of admission (usually two measurements); if there are two, take the average; if there is only one, take that one
Blood biochemistry		
Fasting glucose	30740	(mmol/L)
Total cholesterol	30690	(mmol/L)

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Table S4. Cardiovascular disease subtypes prevalence by gender and disease onset age group

	Gender group			Disease onset age group		
	Male	**Female**	**Prevalence Ratio (Male : Female)**	**Onset age ≥ 65**	**Onset age < 65**	**Prevalence Ratio (Age ≥ 65 : <65)**
Total Cardiovascular Disease	15.3088 % (21,936/143,290)	9.3530 % (17631/188506)	1.6368	10.9652 % (18,191/165,897)	12.8849 % (21,376/165,899)	0.8510
Ischemic Stroke	2.1857 % (4,375/200,167)	1.3012 % (3179/244318)	1.6798	2.1715 % (4,826/222,242)	1.2275 % (2,728/222,243)	1.9691
Ischemic Heart Disease	7.0702 % (14,191/200,716)	2.7293 % (6692/245191)	2.5905	5.2200 % (11,638/222,953)	4.1466 % (9,245/222,954)	1.2588
Peripheral Vascular Disease	0.7999 % (1,579/197,410)	0.5596 % (1357/242494)	1.4294	0.6574 % (1,446/219,952)	0.6774 % (1,490/219,952)	0.9705
Heart Failure	0.1022 % (1,803/176,156)	0.3888 % (830/221186)	0.2628	0.9282 % (1,844/198,671)	0.3971 % (789/198,671)	2.3371
Heart Valve Disorder	0.7516 % (1,499/199,447)	0.4468 % (1082/242148)	1.6822	0.7636 % (1,686/220,797)	0.4053 % (895/220,798)	1.8838
Heart Arrhythmia	3.5764 % (7,176/200,646)	2.1455 % (5253/244842)	1.6669	3.3011 % (7,353/222,744)	2.2788 % (5,076/222,744)	1.4486

Prevalence presented as: % (number of disease onset people / total people at risk)

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Table S5a. Follow-up cohort of subjective sleep phenotypes to each incident cardiovascular disease subtypes

Exposure	Outcome	Median Follow-up (years)	Cumulative Incidence % (case number / N)
Subjective sleep phenotypes	Total cardiovascular disease	13.59	11.9251 (39,567/331,796)
	Hemorrhagic stroke	13.65	0.3406 (1,502/440,936)
	Ischemic stroke	13.63	1.6995 (7,554/444,485)
	Ischemic heart disease	13.60	4.6833 (20,883/445,907)
	Hypertension	13.56	6.7621 (29,818/440,956)
	Peripheral vascular disease	13.65	0.6674 (2,936/439,904)
	Venous thromboembolic disease	13.65	0.9574 (3,989/416,628)
	Pulmonary heart disease	13.65	0.7453 (3,325/446,104)
	Heart failure	13.66	0.6627 (2,633/397,342)
	Cardiomyopathy	13.65	0.1930 (861/446,149)
	Heart valve disorder	13.65	0.5845 (2,581/441,595)
	Heart arrhythmia	13.62	2.7900 (12,429/445,488)

doi:10.6342/NTU202600551

Table S5b. Follow-up cohort of objective sleep phenotypes to each incident cardiovascular disease subtypes

Exposure	Outcome	Median follow-up (years)	Cumulative Incidence % (case number / N)
Objective sleep phenotypes	Total cardiovascular disease	7.92	3.0636 (1,904/62,150)
	Hemorrhagic stroke	7.96	0.0752 (61/81,065)
	Ischemic stroke	7.95	0.3729 (305/81,788)
	Ischemic heart disease	7.94	1.1745 (963/81,973)
	Hypertension	7.94	1.3324 (1,080/81,059)
	Peripheral vascular disease	7.96	0.1162 (94/80,893)
	Venous thromboembolic disease	7.96	0.2366 (178/75,248)
	Pulmonary heart disease	7.96	0.1956 (161/82,308)
	Heart failure	7.96	0.1008 (73/72,432)
	Cardiomyopathy	7.96	0.0450 (37/82,293)
	Heart valve disorder	7.96	0.1457 (118/80,986)
	Heart arrhythmia	7.95	0.9316 (762/81,795)

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Table S6a. Cox proportional hazards models of sleep phenotypes for hemorrhagic stroke

	Model 1 aHR (95%CI)	Model 1 P-value	Model 2 aHR (95%CI)	Model 2 P-value
Subjective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.0854 (0.9645-1.2215)	0.1737	1.0579 (0.9217-1.2142)	0.4236
Long sleep duration	1.2662 (0.9095-1.7627)	0.1621	1.1138 (0.7335-1.6915)	0.6130
Evening vs. Morning type	1.0258 (0.9222-1.1412)	0.6389	1.0056 (0.7854-1.2876)	0.9646
Evening vs. Intermediate type	1.0261 (0.8440-1.2476)	0.7958	1.0463 (0.8341-1.3126)	0.6953
Easy getting up	1.0000 (reference)	-	1.0000 (reference)	-
Not easy getting up	1.1206 (0.9738-1.2896)	0.1120	1.0331 (0.8723-1.2234)	0.7062
Dozing	1.0960 (0.9760-1.2308)	0.1214	1.0353 (0.9035-1.1862)	0.6175
Nap	1.0885 (0.9790-1.2101)	0.1169	1.0417 (0.9220-1.1770)	0.5116
Snore	1.0124 (0.9036-1.1343)	0.8321	0.9915 (0.8701-1.1300)	0.8987
Seldom suffer insomnia	1.0000 (reference)	-	1.0000 (reference)	-
Usually suffer insomnia	1.0181 (0.9090-1.1404)	0.7559	0.9949 (0.8720-1.1352)	0.9396
Objective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	0.9316 (0.5122-1.6945)	0.8164	0.8632 (0.4331-1.7205)	0.6760
Long sleep duration	0.9112 (0.2805-2.9604)	0.8771	1.2975 (0.3934-4.2799)	0.6689
Evening vs. Morning type	0.5470 (0.1228-2.4360)	0.4285	0.8869 (0.1920-4.0969)	0.8778
Evening vs. Intermediate type	0.6607 (0.1565-2.7896)	0.5728	0.8568 (0.1999-3.6723)	0.8351
Good sleep efficiency	1.0000 (reference)	-	1.0000 (reference)	-
Bad sleep efficiency	1.0058 (0.4882-2.0724)	0.9874	1.3153 (0.6228-2.7782)	0.4725
WASO (per 30 mins increase)	0.8121 (0.5329-1.2378)	0.3332	0.9914 (0.6341-1.5499)	0.9697
Awake times (per count increase)	0.9934 (0.9204-1.0720)	0.8639	1.0296 (0.9452-1.1217)	0.5035
Whole week SRI (per 10 points increase)	1.0912 (0.7939-1.4998)	0.5907	1.0114 (0.7108-1.4392)	0.9498
Weekday SRI (per 10 points increase)	1.1001 (0.7645-1.5830)	0.6074	0.9718 (0.6557-1.4403)	0.8869

WASO, wake after sleep onset; SRI, sleep regularity index; aHR, adjusted hazard ratio; 95% CI, confidence interval; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; Model 1 adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status; Model 2 adjusted for Model 1 + physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose.

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Table S6b. Cox proportional hazards models of sleep phenotypes for ischemic stroke

	Model 1 aHR (95%CI)	Model 1 P-value	Model 2 aHR (95%CI)	Model 2 P-value
Subjective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.0804 (1.0249-1.1390)	**0.0040****	1.0641 (0.9992-1.1333)	0.0530
Long sleep duration	1.4523 (1.2797-1.6481)	**<0.0001*****	1.4190 (1.2156-1.6564)	**<0.0001*****
Evening vs. Morning type	1.0573 (0.9625-1.1613)	0.2449	1.0325 (0.9246-1.1531)	0.5699
Evening vs. Intermediate type	1.0647 (0.9766-1.1608)	0.1550	1.0867 (0.9819-1.2027)	0.1080
Easy getting up	1.0000 (reference)	-	1.0000 (reference)	-
Not easy getting up	1.1731 (1.1019-1.2489)	**<0.0001*****	1.1605 (1.0762-1.2514)	**<0.0001*****
Dozing	1.1161 (1.0612-1.1739)	**<0.0001*****	1.1136 (1.0489-1.1824)	**0.0004****
Nap	1.1141 (1.0625-1.1683)	**<0.0001*****	1.1109 (1.0502-1.1751)	**0.0002****
Snore	1.0266 (0.9764-1.0793)	0.3051	1.0521 (0.9920-1.1159)	0.0906
Seldom suffer insomnia	1.0000 (reference)	-	1.0000 (reference)	-
Usually suffer insomnia	1.1287 (1.0744-1.1858)	**<0.0001*****	1.1723 (1.1061-1.2425)	**<0.0001*****
Objective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.2710 (0.9941-1.6251)	0.0558	1.1979 (0.9074-1.5812)	0.2025
Long sleep duration	1.0606 (0.6528-1.7232)	0.8121	1.0604 (0.6119-1.8377)	0.8343
Evening vs. Morning type	0.9301 (0.5415-1.5975)	0.7928	0.7987 (0.4201-1.5186)	0.4929
Evening vs. Intermediate type	1.0310 (0.6138-1.7316)	0.9082	0.8929 (0.4795-1.6627)	0.7210
Good sleep efficiency	1.0000 (reference)	-	1.0000 (reference)	-
Bad sleep efficiency	1.0103 (0.7389-1.3815)	0.9487	0.9914 (0.6975-1.4091)	0.9617
WASO (per 30 mins increase)	1.0253 (0.8653-1.2149)	0.7727	0.9971 (0.8235-1.2074)	0.9767
Awake times (per count increase)	0.9764 (0.9443-1.0097)	0.1630	0.9761 (0.9400-1.0135)	0.2066
Whole week SRI (per 10 points increase)	0.8619 (0.7646-0.9717)	0.0151*	0.8711 (0.7596-0.9990)	0.0484*
Weekday SRI (per 10 points increase)	0.8600 (0.7495-0.9869)	0.0317*	0.8559 (0.7326-1.0000)	0.0499*

WASO, wake after sleep onset; SRI, sleep regularity index; aHR, adjusted hazard ratio; 95% CI, confidence interval; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; Model 1 adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status; Model 2 adjusted for Model 1 + physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose.

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Table S6c. Cox proportional hazards models of sleep phenotypes for ischemic heart disease

	Model 1 aHR (95%CI)	Model 1 P-value	Model 2 aHR (95%CI)	Model 2 P-value
Subjective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.1925 (1.1561-1.2299)	**<0.0001*****	1.1880 (1.1458-1.2318)	**<0.0001*****
Long sleep duration	1.2663 (1.1660-1.3752)	**<0.0001*****	1.2551 (1.1376-1.3848)	**<0.0001*****
Evening vs. Morning type	1.0140 (0.9859-1.0430)	0.3325	1.0267 (0.9618-1.0961)	0.4285
Evening vs. Intermediate type	1.0835 (1.0285-1.1414)	**0.0025****	1.0755 (1.0129-1.1420)	0.0174*
Easy getting up	1.0000 (reference)	-	1.0000 (reference)	-
Not easy getting up	1.2289 (1.1839-1.2756)	**<0.0001*****	1.1936 (1.1420-1.2475)	**<0.0001*****
Dozing	1.1465 (1.1124-1.1817)	**<0.0001*****	1.1349 (1.0955-1.1757)	**<0.0001*****
Nap	1.1674 (1.1344-1.2014)	**<0.0001*****	1.1653 (1.1270-1.2049)	**<0.0001*****
Snore	1.0641 (1.0329-1.0961)	**<0.0001*****	1.0769 (1.0405-1.1146)	**<0.0001*****
Seldom suffer insomnia	1.0000 (reference)	-	1.0000 (reference)	-
Usually suffer insomnia	1.2552 (1.2187-1.2927)	**<0.0001*****	1.2444 (1.2024-1.2879)	**<0.0001*****
Objective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.1007 (0.9572-1.2659)	0.1783	1.0100 (0.8612-1.1844)	0.9030
Long sleep duration	1.0541 (0.7970-1.3941)	0.7118	1.0068 (0.7309-1.3868)	0.9670
Evening vs. Morning type	1.0429 (0.7776-1.3988)	0.7789	1.0049 (0.7254-1.3922)	0.9765
Evening vs. Intermediate type	1.0235 (0.7762-1.3495)	0.8693	1.0835 (0.7955-1.4757)	0.6110
Good sleep efficiency	1.0000 (reference)	-	1.0000 (reference)	-
Bad sleep efficiency	1.2101 (1.0305-1.4211)	0.0200*	1.2654 (1.0577-1.5140)	0.0101*
WASO (per 30 mins increase)	1.0891 (0.9942-1.1931)	0.0666	1.1094 (1.0020-1.2283)	0.0457*
Awake times (per count increase)	1.0034 (0.9851-1.0221)	0.7148	1.0137 (0.9929-1.0349)	0.1982
Whole week SRI (per 10 points increase)	0.9446 (0.8796-1.0144)	0.1170	0.9526 (0.8784-1.0331)	0.2409
Weekday SRI (per 10 points increase)	0.9502 (0.8750-1.0319)	0.2251	0.9590 (0.8729-1.0537)	0.3838

WASO, wake after sleep onset; SRI, sleep regularity index; aHR, adjusted hazard ratio; 95% CI, confidence interval; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; Model 1 adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status; Model 2 adjusted for Model 1 + physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose.

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Table S6d. Cox proportional hazards models of sleep phenotypes for hypertension

	Model 1 aHR (95%CI)	Model 1 P-value	Model 2 aHR (95%CI)	Model 2 P-value
Subjective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.0368 (1.0100-1.0644)	0.0069*	1.0341 (1.0037-1.0653)	0.0275*
Long sleep duration	0.9310 (0.8581-1.0102)	0.0860	0.9335 (0.8498-1.0254)	0.1507
Evening vs. Morning type	0.9750 (0.9520-0.9986)	0.0379*	0.9417 (0.8924-0.9938)	0.0287*
Evening vs. Intermediate type	0.9805 (0.9382-1.0248)	0.3829	0.9778 (0.9306-1.0273)	0.3724
Easy getting up	1.0000 (reference)	-	1.0000 (reference)	-
Not easy getting up	0.9507 (0.9209-0.9814)	**0.0018****	0.9469 (0.9131-0.9818)	**0.0032****
Dozing	1.0018 (0.9757-1.0286)	0.8931	1.0131 (0.9833-1.0439)	0.3929
Nap	1.0288 (1.0047-1.0535)	0.0188*	1.0213 (0.9943-1.0490)	0.1226
Snore	1.1397 (1.1115-1.1686)	**<0.0001*****	1.1581 (1.1259-1.1912)	**<0.0001*****
Seldom suffer insomnia	1.0000 (reference)	-	1.0000 (reference)	-
Usually suffer insomnia	1.0392 (1.0134-1.0657)	**0.0027****	1.0406 (1.0114-1.0706)	0.0061*
Objective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	0.8881 (0.7721-1.0214)	0.0963	0.8992 (0.7715-1.0480)	0.1738
Long sleep duration	0.8676 (0.6607-1.1393)	0.3070	0.9246 (0.6885-1.2416)	0.6022
Evening vs. Morning type	0.9857 (0.7303-1.3304)	0.9251	1.0219 (0.7348-1.4210)	0.8977
Evening vs. Intermediate type	0.8578 (0.6476-1.1362)	0.2848	0.8438 (0.6202-1.1480)	0.2796
Good sleep efficiency	1.0000 (reference)	-	1.0000 (reference)	-
Bad sleep efficiency	0.8879 (0.7427-1.0615)	0.1919	0.8485 (0.6956-1.0350)	0.1050
WASO (per 30 mins increase)	1.0318 (0.9416-1.1307)	0.5019	1.0066 (0.9098-1.1136)	0.8988
Awake times (per count increase)	1.0054 (0.9880-1.0232)	0.5437	0.9981 (0.9791-1.0175)	0.8447
Whole week SRI (per 10 points increase)	1.0073 (0.9401-1.0793)	0.8357	1.0183 (0.9433-1.0993)	0.6425
Weekday SRI (per 10 points increase)	0.9673 (0.8950-1.0455)	0.4019	0.9766 (0.8960-1.0645)	0.5899

WASO, wake after sleep onset; SRI, sleep regularity index; aHR, adjusted hazard ratio; 95% CI, confidence interval; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; Model 1 adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status; Model 2 adjusted for Model 1 + physical activity, diet quality, total cholesterol and fasting glucose.

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Table S6e. Cox proportional hazards models of sleep phenotypes for peripheral vascular disease

	Model 1 aHR (95%CI)	Model 1 P-value	Model 2 aHR (95%CI)	Model 2 P-value
Subjective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.2063 (1.1116-1.3090)	**<0.0001*****	1.2340 (1.1194-1.3603)	**<0.0001*****
Long sleep duration	1.4582 (1.1837-1.7965)	**0.0004****	1.6019 (1.2572-2.0410)	**0.0001****
Evening vs. Morning type	1.0401 (0.9689-1.1165)	0.2771	1.0406 (0.8777-1.2338)	0.6466
Evening vs. Intermediate type	1.2123 (1.0649-1.3802)	**0.0036****	1.1736 (1.0056-1.3697)	0.0423*
Easy getting up	1.0000 (reference)	-	1.0000 (reference)	-
Not easy getting up	1.1217 (1.0185-1.2354)	0.0197*	1.1141 (0.9924-1.2507)	0.0671
Dozing	1.0964 (1.0092-1.1911)	0.0295*	1.0421 (0.9430-1.1515)	0.4186
Nap	1.0880 (1.0087-1.1735)	0.0289*	1.0792 (0.9861-1.1810)	0.0970
Snore	0.9470 (0.8723-1.0281)	0.1939	0.9622 (0.8729-1.0606)	0.4383
Seldom suffer insomnia	1.0000 (reference)	-	1.0000 (reference)	-
Usually suffer insomnia	1.2231 (1.1310-1.3227)	**<0.0001*****	1.3000 (1.1853-1.4259)	**<0.0001*****
Objective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.6858 (1.0939-2.5982)	0.0180*	1.5780 (0.9696-2.5679)	0.0664
Long sleep duration	0.9917 (0.3961-2.4830)	0.9858	0.7618 (0.2359-2.4599)	0.6491
Evening vs. Morning type	1.6334 (0.7546-3.5359)	0.2130	1.9419 (0.8410-4.4842)	0.1201
Evening vs. Intermediate type	2.3125 (1.1198-4.7753)	0.0235*	2.6182 (1.1995-5.7151)	0.0157*
Good sleep efficiency	1.0000 (reference)	-	1.0000 (reference)	-
Bad sleep efficiency	1.8007 (1.1055-2.9331)	0.0181*	1.6804 (0.9673-2.9191)	0.0655
WASO (per 30 mins increase)	1.1182 (0.8316-1.5035)	0.4598	1.1724 (0.8490-1.6191)	0.3341
Awake times (per count increase)	0.9511 (0.8955-1.0102)	0.1029	0.9467 (0.8849-1.0128)	0.1118
Whole week SRI (per 10 points increase)	0.7685 (0.6237-0.9468)	0.0134*	0.7122 (0.5697-0.8904)	**0.0029****
Weekday SRI (per 10 points increase)	0.7892 (0.6181-1.0075)	0.0574	0.7625 (0.5826-0.9980)	0.0483*

WASO, wake after sleep onset; SRI, sleep regularity index; aHR, adjusted hazard ratio; 95% CI, confidence interval; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; Model 1 adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status; Model 2 adjusted for Model 1 + physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose.

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Table S6f. Cox proportional hazards models of sleep phenotypes for venous thromboembolic disease

	Model 1 aHR (95%CI)	Model 1 P-value	Model 2 aHR (95%CI)	Model 2 P-value
Subjective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.0841 (1.0091-1.1646)	0.0272*	1.0878 (1.0006-1.1825)	0.0483*
Long sleep duration	1.0241 (0.8276-1.2673)	0.8266	1.1241 (0.8806-1.4351)	0.3476
Evening vs. Morning type	1.0026 (0.9395-1.0700)	0.9367	1.0196 (0.8776-1.1846)	0.8001
Evening vs. Intermediate type	1.0373 (0.9203-1.1692)	0.5490	1.0597 (0.9242-1.2151)	0.4060
Easy getting up	1.0000 (reference)	-	1.0000 (reference)	-
Not easy getting up	1.0556 (0.9691-1.1498)	0.2150	1.0725 (0.9709-1.1847)	0.1681
Dozing	1.0948 (1.0198-1.1752)	0.0123*	1.1203 (1.0318-1.2163)	0.0068*
Nap	1.0057 (0.9423-1.0733)	0.8650	1.0266 (0.9519-1.1072)	0.4953
Snore	0.9258 (0.8637-0.9924)	0.0296*	0.9171 (0.8464-0.9938)	0.0347*
Seldom suffer insomnia	1.0000 (reference)	-	1.0000 (reference)	-
Usually suffer insomnia	1.0596 (0.9891-1.1351)	0.0992	1.0895 (1.0060-1.1798)	0.0351*
Objective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.0524 (0.7526-1.4717)	0.7652	1.0181 (0.7069-1.4664)	0.9231
Long sleep duration	1.7192 (1.0144-2.9135)	0.0441*	1.4064 (0.7508-2.6345)	0.2870
Evening vs. Morning type	0.9352 (0.4157-2.1041)	0.8714	0.9568 (0.3946-2.3198)	0.9221
Evening vs. Intermediate type	0.6100 (0.2820-1.3195)	0.2093	0.6518 (0.2838-1.4971)	0.3131
Good sleep efficiency	1.0000 (reference)	-	1.0000 (reference)	-
Bad sleep efficiency	0.8660 (0.5641-1.3294)	0.5107	0.9772 (0.6224-1.5343)	0.9203
WASO (per 30 mins increase)	0.8006 (0.6295-1.0183)	0.0699	0.8182 (0.6302-1.0623)	0.1320
Awake times (per count increase)	0.9760 (0.9345-1.0194)	0.2741	0.9753 (0.9302-1.0227)	0.3016
Whole week SRI (per 10 points increase)	1.1674 (0.9727-1.4011)	0.0963	1.2023 (0.9790-1.4766)	0.0789
Weekday SRI (per 10 points increase)	1.1859 (0.9603-1.4645)	0.1133	1.1885 (0.9395-1.5036)	0.1500

WASO, wake after sleep onset; SRI, sleep regularity index; aHR, adjusted hazard ratio; 95% CI, confidence interval; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; Model 1 adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status; Model 2 adjusted for Model 1 + physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose.

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Table S6g. Cox proportional hazards models of sleep phenotypes for pulmonary heart disease

	Model 1 aHR (95%CI)	Model 1 P-value	Model 2 aHR (95%CI)	Model 2 P-value
Subjective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.0879 (1.0060-1.1766)	0.0349*	1.1061 (1.0100-1.2112)	0.0296*
Long sleep duration	1.2432 (1.0123-1.5268)	0.0378*	1.2125 (0.9456-1.5549)	0.1288
Evening vs. Morning type	1.2372 (1.0809-1.4160)	**0.0020****	1.0834 (1.0016-1.1718)	0.0456*
Evening vs. Intermediate type	1.1965 (1.0586-1.3524)	**0.0041****	1.1771 (1.0211-1.3569)	0.0246*
Easy getting up	1.0000 (reference)	-	1.0000 (reference)	-
Not easy getting up	1.1639 (1.0621-1.2754)	**0.0012****	1.1162 (1.0013-1.2443)	0.0474*
Dozing	1.0259 (0.9494-1.1085)	0.5180	1.0099 (0.9227-1.1054)	0.8307
Nap	1.0700 (0.9964-1.1490)	0.0626	1.0850 (0.9991-1.1783)	0.0526
Snore	0.9072 (0.8411-0.9785)	0.0117*	0.9251 (0.8479-1.0094)	0.0803
Seldom suffer insomnia	1.0000 (reference)	-	1.0000 (reference)	-
Usually suffer insomnia	1.0747 (0.9976-1.1579)	0.0580	1.0912 (1.0010-1.1895)	0.0474*
Objective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.1180 (0.7899-1.5825)	0.5292	1.4138 (0.9542-2.0948)	0.0843
Long sleep duration	1.6489 (0.9389-2.8958)	0.0818	2.0512 (1.1050-3.8075)	0.0228*
Evening vs. Morning type	1.2832 (0.5763-2.8570)	0.5415	1.5884 (0.6623-3.8094)	0.2998
Evening vs. Intermediate type	0.6854 (0.3314-1.4177)	0.3084	0.8679 (0.3976-1.8946)	0.7220
Good sleep efficiency	1.0000 (reference)	-	1.0000 (reference)	-
Bad sleep efficiency	1.0634 (0.6937-1.6299)	0.7780	1.0359 (0.6294-1.7050)	0.8896
WASO (per 30 mins increase)	0.9961 (0.9879-1.0044)	0.3561	0.8750 (0.6565-1.1662)	0.3624
Awake times (per count increase)	0.9741 (0.9301-1.0201)	0.2646	0.9687 (0.9185-1.0217)	0.2420
Whole week SRI (per 10 points increase)	1.0626 (0.8868-1.2733)	0.5105	0.9864 (0.8060-1.2072)	0.8941
Weekday SRI (per 10 points increase)	1.1214 (0.9061-1.3878)	0.2921	1.0179 (0.8026-1.2901)	0.8859

WASO, wake after sleep onset; SRI, sleep regularity index; aHR, adjusted hazard ratio; 95% CI, confidence interval; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; Model 1 adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status; Model 2 adjusted for Model 1 + physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose.

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Table S6h. Cox proportional hazards models of sleep phenotypes for heart failure

	Model 1 aHR (95%CI)	Model 1 P-value	Model 2 aHR (95%CI)	Model 2 P-value
Subjective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.1641 (1.0656-1.2718)	**0.0008****	1.1099 (0.9971-1.2354)	0.0566
Long sleep duration	1.7330 (1.4419-2.0828)	**<0.0001*****	1.4310 (1.1340-1.8059)	**0.0025****
Evening vs. Morning type	1.1128 (0.9508-1.3023)	0.1829	0.9818 (0.8091-1.1914)	0.8524
Evening vs. Intermediate type	1.0690 (0.9249-1.2354)	0.3665	0.9974 (0.8361-1.1899)	0.9773
Easy getting up	1.0000 (reference)	-	1.0000 (reference)	-
Not easy getting up	1.3323 (1.2021-1.4767)	**<0.0001*****	1.2274 (1.0818-1.3926)	**0.0015****
Dozing	1.1311 (1.0401-1.2300)	**0.0040****	1.0950 (0.9899-1.2111)	0.0779
Nap	1.2702 (1.1693-1.3797)	**<0.0001*****	1.1992 (1.0855-1.3248)	**0.0003****
Snore	0.8527 (0.7825-0.9292)	**0.0003****	0.8731 (0.7876-0.9677)	0.0097*
Seldom suffer insomnia	1.0000 (reference)	-	1.0000 (reference)	-
Usually suffer insomnia	1.2198 (1.1231-1.3247)	**<0.0001*****	1.1761 (1.0648-1.2990)	**0.0014****
Objective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.1378 (0.6906-1.8744)	0.6123	0.9789 (0.5593-1.7134)	0.9405
Long sleep duration	0.5383 (0.1300-2.2285)	0.3929	0.6122 (0.1470-2.5498)	0.5003
Evening vs. Morning type	0.5216 (0.1507-1.8058)	0.3043	0.3540 (0.0782-1.6012)	0.1775
Evening vs. Intermediate type	0.6187 (0.1885-2.0299)	0.4283	0.5707 (0.1351-2.4106)	0.4454
Good sleep efficiency	1.0000 (reference)	-	1.0000 (reference)	-
Bad sleep efficiency	0.7719 (0.3918-1.5207)	0.4542	0.7556 (0.3550-1.6085)	0.4673
WASO (per 30 mins increase)	0.7943 (0.5432-1.1615)	0.2349	0.8284 (0.5503-1.2468)	0.3667
Awake times (per count increase)	0.9026 (0.8406-0.9692)	0.0048*	0.9127 (0.8446-0.9863)	0.0210*
Whole week SRI (per 10 points increase)	1.0077 (0.7719-1.3156)	0.9549	1.1323 (0.8279-1.5487)	0.4366
Weekday SRI (per 10 points increase)	1.0367 (0.7600-1.4141)	0.8199	1.1709 (0.8133-1.6857)	0.3962

WASO, wake after sleep onset; SRI, sleep regularity index; aHR, adjusted hazard ratio; 95% CI, confidence interval; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; Model 1 adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status; Model 2 adjusted for Model 1 + physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose.

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Table S6i. Cox proportional hazards models of sleep phenotypes for cardiomyopathy

	Model 1 aHR (95%CI)	Model 1 P-value	Model 2 aHR (95%CI)	Model 2 P-value
Subjective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.0581 (0.8934-1.2532)	0.5131	1.0503 (0.8589-1.2844)	0.6323
Long sleep duration	1.6899 (1.0931-2.6126)	0.0183*	1.3498 (0.7664-2.3774)	0.2989
Evening vs. Morning type	1.0221 (0.7301-1.4309)	0.8987	0.7144 (0.4659-1.0953)	0.1229
Evening vs. Intermediate type	0.9514 (0.7164-1.2634)	0.7304	0.8257 (0.5772-1.1814)	0.2947
Easy getting up	1.0000 (reference)	-	1.0000 (reference)	-
Not easy getting up	1.2828 (1.0643-1.5460)	0.0089*	1.1444 (0.9081-1.4422)	0.2530
Dozing	1.1925 (1.0138-1.4027)	0.0336*	1.2747 (1.0543-1.5412)	0.0122*
Nap	1.2513 (1.0771-1.4538)	**0.0034****	1.2034 (1.0056-1.4401)	0.0433*
Snore	1.0086 (0.8599-1.1831)	0.9161	1.0240 (0.8471-1.2377)	0.8066
Seldom suffer insomnia	1.0000 (reference)	-	1.0000 (reference)	-
Usually suffer insomnia	1.2432 (1.0646-1.4518)	0.0059*	1.2748 (1.0589-1.5348)	0.0103*
Objective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.6505 (0.8437-3.2288)	0.1433	1.4926 (0.6990-3.1873)	0.3008
Long sleep duration	Sample size too small	-	Sample size too small	-
Evening vs. Morning type	0.7737 (0.0941-6.3606)	0.8114	Sample size too small	-
Evening vs. Intermediate type	0.4297 (0.0574-3.2147)	0.4107	Sample size too small	-
Good sleep efficiency	1.0000 (reference)	-	1.0000 (reference)	-
Bad sleep efficiency	0.9412 (0.3619-2.4473)	0.9010	0.9805 (0.3368-2.8540)	0.9712
WASO (per 30 mins increase)	1.0919 (0.6730-1.7716)	0.7217	1.0505 (0.6070-1.8182)	0.8602
Awake times (per count increase)	1.0021 (0.9114-1.1017)	0.9659	0.9695 (0.8717-1.0781)	0.5672
Whole week SRI (per 10 points increase)	0.7420 (0.5341-1.0306)	0.0751	0.7453 (0.5188-1.0706)	0.1116
Weekday SRI (per 10 points increase)	0.9491 (0.6140-1.4672)	0.8142	0.9630 (0.5921-1.5663)	0.8793

WASO, wake after sleep onset; SRI, sleep regularity index; aHR, adjusted hazard ratio; 95% CI, confidence interval; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; Model 1 adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status; Model 2 adjusted for Model 1 + physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose.

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Table S6j. Cox proportional hazards models of sleep phenotypes for heart valve disorder

	Model 1 aHR (95%CI)	Model 1 P-value	Model 2 aHR (95%CI)	Model 2 P-value
Subjective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.0371 (0.9469-1.1359)	0.4329	1.0500 (0.9444-1.1673)	0.3671
Long sleep duration	1.1508 (0.8951-1.4794)	0.2733	1.1143 (0.8231-1.5086)	0.4838
Evening vs. Morning type	0.9777 (0.9006-1.0613)	0.5900	0.9528 (0.7881-1.1518)	0.6173
Evening vs. Intermediate type	1.0651 (0.9137-1.2417)	0.4199	1.0808 (0.9060-1.2892)	0.3881
Easy getting up	1.0000 (reference)	-	1.0000 (reference)	-
Not easy getting up	1.1628 (1.0427-1.2967)	0.0067*	1.1231 (0.9874-1.2776)	0.0773
Dozing	1.0466 (0.9589-1.1423)	0.3077	1.0343 (0.9341-1.1452)	0.5165
Nap	1.1749 (1.0836-1.2739)	**0.0001****	1.1637 (1.0593-1.2785)	**0.0016****
Snore	0.9280 (0.8517-1.0112)	0.0881	0.9610 (0.8705-1.0610)	0.4309
Seldom suffer insomnia	1.0000 (reference)	-	1.0000 (reference)	-
Usually suffer insomnia	1.1500 (1.0571-1.2510)	**0.0011****	1.1699 (1.0611-1.2898)	**0.0016****
Objective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.3399 (0.9056-1.9824)	0.1432	1.4671 (0.9313-2.3110)	0.0983
Long sleep duration	0.5929 (0.2164-1.6248)	0.3095	0.6545 (0.2037-2.1029)	0.4765
Evening vs. Morning type	0.6913 (0.2084-2.2929)	0.5462	1.1570 (0.3344-4.0034)	0.8179
Evening vs. Intermediate type	0.4693 (0.1472-1.4960)	0.2009	0.6111 (0.1899-1.9667)	0.4089
Good sleep efficiency	1.0000 (reference)	-	1.0000 (reference)	-
Bad sleep efficiency	1.2840 (0.7941-2.0760)	0.3080	1.3234 (0.7610-2.3013)	0.3209
WASO (per 30 mins increase)	0.8798 (0.6570-1.1783)	0.3903	0.8982 (0.6410-1.2585)	0.5327
Awake times (per count increase)	0.9753 (0.9236-1.0298)	0.3667	0.9834 (0.9229-1.0478)	0.6043
Whole week SRI (per 10 points increase)	0.9071 (0.7460-1.1030)	0.3285	0.9225 (0.7318-1.1629)	0.4948
Weekday SRI (per 10 points increase)	0.8590 (0.6897-1.0699)	0.1748	0.8639 (0.6678-1.1174)	0.2650

WASO, wake after sleep onset; SRI, sleep regularity index; aHR, adjusted hazard ratio; 95% CI, confidence interval; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; Model 1 adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status; Model 2 adjusted for Model 1 + physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose.

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Table S6k. Cox proportional hazards models of sleep phenotypes for heart arrhythmia

	Model 1 aHR (95%CI)	Model 1 P-value	Model 2 aHR (95%CI)	Model 2 P-value
Subjective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.0729 (1.0298-1.1178)	**0.0008****	1.0671 (1.0171-1.1196)	0.0080*
Long sleep duration	1.0426 (0.9241-1.1762)	0.4980	0.9715 (0.8373-1.1273)	0.7035
Evening vs. Morning type	1.0370 (1.0003-1.0750)	0.0481*	1.0514 (1.0082-1.0966)	0.0193*
Evening vs. Intermediate type	1.1333 (1.0606-1.2110)	**0.0002****	1.1495 (1.0647-1.2411)	**0.0004****
Easy getting up	1.0000 (reference)	-	1.0000 (reference)	-
Not easy getting up	1.1476 (1.0929-1.2051)	**<0.0001*****	1.1166 (1.0537-1.1832)	**0.0002****
Dozing	1.0258 (0.9853-1.0680)	0.2151	1.0119 (0.9653-1.0608)	0.6221
Nap	1.0690 (1.0304-1.1091)	**0.0004****	1.0462 (1.0022-1.0920)	0.0392*
Snore	0.9540 (0.9175-0.9919)	0.0178*	0.9711 (0.9282-1.0159)	0.2025
Seldom suffer insomnia	1.0000 (reference)	-	1.0000 (reference)	-
Usually suffer insomnia	1.1621 (1.1184-1.2076)	**<0.0001*****	1.1428 (1.0927-1.1953)	**<0.0001*****
Objective sleep phenotypes				
Normal sleep duration	1.0000 (reference)	-	1.0000 (reference)	-
Short sleep duration	1.1303 (0.9660-1.3225)	0.1264	1.1866 (0.9972-1.4119)	0.0537
Long sleep duration	0.8671 (0.6174-1.2177)	0.4104	0.9190 (0.6292-1.3424)	0.6623
Evening vs. Morning type	0.9436 (0.6603-1.3484)	0.7499	0.9452 (0.6395-1.3968)	0.7772
Evening vs. Intermediate type	0.8960 (0.6385-1.2573)	0.5253	0.9610 (0.6629-1.3931)	0.8337
Good sleep efficiency	1.0000 (reference)	-	1.0000 (reference)	-
Bad sleep efficiency	1.1505 (0.9534-1.3884)	0.1436	1.2495 (1.0192-1.5318)	0.0321*
WASO (per 30 mins increase)	1.0234 (0.9200-1.1384)	0.6707	1.0899 (0.9711-1.2234)	0.1439
Awake times (per count increase)	0.9911 (0.9706-1.0121)	0.4038	1.0017 (0.9787-1.0252)	0.8881
Whole week SRI (per 10 points increase)	0.9746 (0.8991-1.0565)	0.5318	0.9592 (0.8769-1.0491)	0.3621
Weekday SRI (per 10 points increase)	0.9809 (0.8933-1.0770)	0.6854	0.9726 (0.8762-1.0796)	0.6015

WASO, wake after sleep onset; SRI, sleep regularity index; aHR, adjusted hazard ratio; 95% CI, confidence interval; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001; Model 1 adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status; Model 2 adjusted for Model 1 + physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose.

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Table S7a. Baseline characteristic and subjective sleep phenotypes among participants with different healthy sleep scores for total cardiovascular disease

	Poor Overall Sleep Health (HSS: 0-3 points)	Good Overall Sleep Health (HSS: 4-5 points)
Number of participants, n (%)	98,319 (35.89%)	175,621 (64.11%)
Age at recruitment, mean (SD) **	56.42 (±7.86)	55.34 (±8.26)
Townsend deprivation index, mean (SD)**	-1.18 (±3.15)	-1.60 (±2.91)
BMI, mean (SD) **	28.09 (±4.99)	26.64 (±4.35)
DBP, mean (SD), mmHg **	82.38 (±9.97)	81.35 (±9.86)
SBP, mean (SD), mmHg **	137.30 (±17.92)	135.70 (±18.26)
Total cholesterol, mean (SD), mmol/L	5.76 (±1.14)	5.76 (±1.10)
Fasting glucose, mean (SD), mmol/L **	5.12 (±1.24)	5.03 (±1.03)
Female, n (%) **	52,911 (53.82%)	104,439 (59.47%)
Current employment status, n (%) **		
Employed	57,925 (59.42%)	113,215 (64.96%)
Retired	8,519 (8.74%)	9,768 (5.60%%)
Unemployed	31,038 (31.84%)	51,310 (29.44%)
Education above college degree, n (%) **	29,452 (30.24%)	62,640 (35.92%)
Alcohol intake, mean (SD), times/month **	11.03 (±10.72)	11.34 (±10.47)
Current smoker, n (%) **	12,986 (12.29%)	15,694 (8.94%)
Regular physical activity, n (%) **	50,847 (54.86%)	102,173 (60.86%)
Healthy diet, n (%) **	60,521 (62.29%)	119,260 (69.06%)
Subjective sleep phenotypes		
Sleep duration **		
Short duration (<7hr), n (%)	53,059 (53.97%)	13,797 (7.86%)
Normal duration (7-9hr), n (%)	42,050 (42.77%)	160,722 (91.52%)
Long duration (>9hr), n (%)	3,210 (3.26%)	1,102 (0.63%)
Usually suffer insomnia, n (%) **	57,521 (58.50%)	18,457 (10.51%)
Chronotype **		
Evening type, n (%)	17,815 (18.12%)	6,408 (3.65%)
Intermediate type, n (%)	54,845 (55.78%)	121,529 (69.20%)
Morning type, n (%)	25,659 (26.10%)	47,684 (27.15%)
Snore (=yes), n (%) **	58,431 (59.43%)	41,296 (23.51%)
Dozing (=yes), n (%) **	46,456 (47.25%)	16,245 (9.25%)

Continuous variables: mean (SD); categorical variable: number of people (%); *p-value <0.05; **p-value <0.0001

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Table S7b. Baseline characteristic and subjective sleep phenotypes among participants with different healthy sleep scores for ischemic stroke

	Poor Overall Sleep Health (HSS: 0-3 points)	Good Overall Sleep Health (HSS: 4-5 points)
Number of participants, n (%)	137,021 (37.45%)	228,819 (62.55%)
Age at recruitment, mean (SD) **	57.40 (±7.78)	56.31 (±8.24)
Townsend deprivation index, mean (SD)**	-1.10 (±3.18)	-1.56 (±2.93)
BMI, mean (SD) **	28.46 (±5.18)	26.92 (±4.49)
DBP, mean (SD), mmHg **	82.73 (±10.19)	81.85 (±10.07)
SBP, mean (SD), mmHg **	138.70 (±18.45)	137.40 (±18.83)
Total cholesterol, mean (SD), mmol/L **	5.67 (±1.17)	5.71 (±1.13)
Fasting glucose, mean (SD), mmol/L **	5.20 (±1.39)	5.08 (±1.13)
Female, n (%) **	71,562 (52.23%)	131,965 (57.67%)
Current employment status, n (%) **		
Employed	74,055 (54.50%)	138,087 (60.81%)
Retired	12,710 (9.35%)	12,972 (5.71%)
Unemployed	49,122 (36.15%)	76,021 (33.48%)
Education above college degree, n (%) **	38,410 (28.32%)	77,554 (34.16%)
Alcohol intake, mean (SD), times/month**	10.92 (±10.78)	11.38 (±10.56)
Current smoker, n (%) **	17,265 (12.60%)	21,223 (9.28%)
Regular physical activity, n (%) **	69,209 (53.83%)	131,555 (60.32%)
Healthy diet, n (%) **	83,479 (62.29%)	154,534 (68.69%)
Subjective sleep phenotypes		
Sleep duration **		
Short duration (<7hr), n (%)	72,793 (53.13%)	17,884 (7.82%)
Normal duration (7-9hr), n (%)	59,010 (43.07%)	209,284 (91.46%)
Long duration (>9hr), n (%)	5,218 (3.81%)	1,651 (0.72%)
Usually suffer insomnia, n (%) **	80,623 (58.84%)	24,469 (10.69%)
Chronotype **		
Evening type, n (%)	24,200 (17.66%)	8,106 (3.54%)
Intermediate type, n (%)	76,301 (55.69%)	157,572 (68.86%)
Morning type, n (%)	36,520 (26.65%)	63,141 (27.59%)
Snore (=yes), n (%) **	81,907 (59.78%)	54,907 (24.00%)
Dozing (=yes), n (%) **	66,610 (48.61%)	22,273 (9.73%)

Continuous variables: mean (SD); categorical variable: number of people (%); *p-value <0.05; **p-value <0.0001

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Table S7c. Baseline characteristic and subjective sleep phenotypes among participants with different healthy sleep scores follow up for ischemic heart disease

	Poor Overall Sleep Health (HSS: 0-3 points)	Good Overall Sleep Health (HSS: 4-5 points)
Number of participants, n (%)	137,499 (37.47%)	229,496 (62.53%)
Age at recruitment, mean (SD) **	57.41 (±7.78)	56.32 (±8.24)
Townsend deprivation index, mean (SD)**	-1.10 (±3.18)	-1.56 (±2.93)
BMI, mean (SD) **	28.46 (±5.17)	26.92 (±4.49)
DBP, mean (SD), mmHg **	82.74 (±10.19)	81.86 (±10.07)
SBP, mean (SD), mmHg **	138.70 (±18.45)	137.40 (±18.83)
Total cholesterol, mean (SD), mmol/L **	5.66 (±1.17)	5.71 (±1.13)
Fasting glucose, mean (SD), mmol/L **	5.20 (±1.38)	5.08 (±1.13)
Female, n (%) **	71,873 (52.27%)	132,372 (57.68%)
Current employment status, n (%) **		
Employed	74,172 (54.39%)	138,342 (60.74%)
Retired	12,801 (9.39%)	13,041 (5.73%)
Unemployed	49,392 (36.22%)	76,367 (33.53%)
Education above college degree, n (%) **	38,495 (28.29%)	77,714 (34.13%)
Alcohol intake, mean (SD), times/month**	10.92 (±10.78)	11.37 (±10.56)
Current smoker, n (%) **	17,358 (12.62%)	21,310 (9.29%)
Regular physical activity, n (%) **	69,409 (53.79%)	131,865 (60.29%)
Healthy diet, n (%) **	83,749 (62.28%)	154,973 (68.68%)
Subjective sleep phenotypes		
Sleep duration **		
Short duration (<7hr), n (%)	73,031 (55.11%)	17,938 (7.82%)
Normal duration (7-9hr), n (%)	59,198 (43.05%)	209,896 (91.46%)
Long duration (>9hr), n (%)	5,270 (3.83%)	1,662 (0.72%)
Usually suffer insomnia, n (%) **	80,940 (58.87%)	24,549 (10.70%)
Chronotype **		
Evening type, n (%)	24,274 (17.65%)	8,121 (3.54%)
Intermediate type, n (%)	76,578 (55.69%)	158,033 (68.86%)
Morning type, n (%)	36,647 (26.65%)	63,342 (27.60%)
Snore (=yes), n (%) **	82,159 (59.75%)	55,072 (24.00%)
Dozing (=yes), n (%) **	66,873 (48.64%)	22,358 (9.74%)

Continuous variables: mean (SD); categorical variable: number of people (%); *p-value <0.05; **p-value <0.0001

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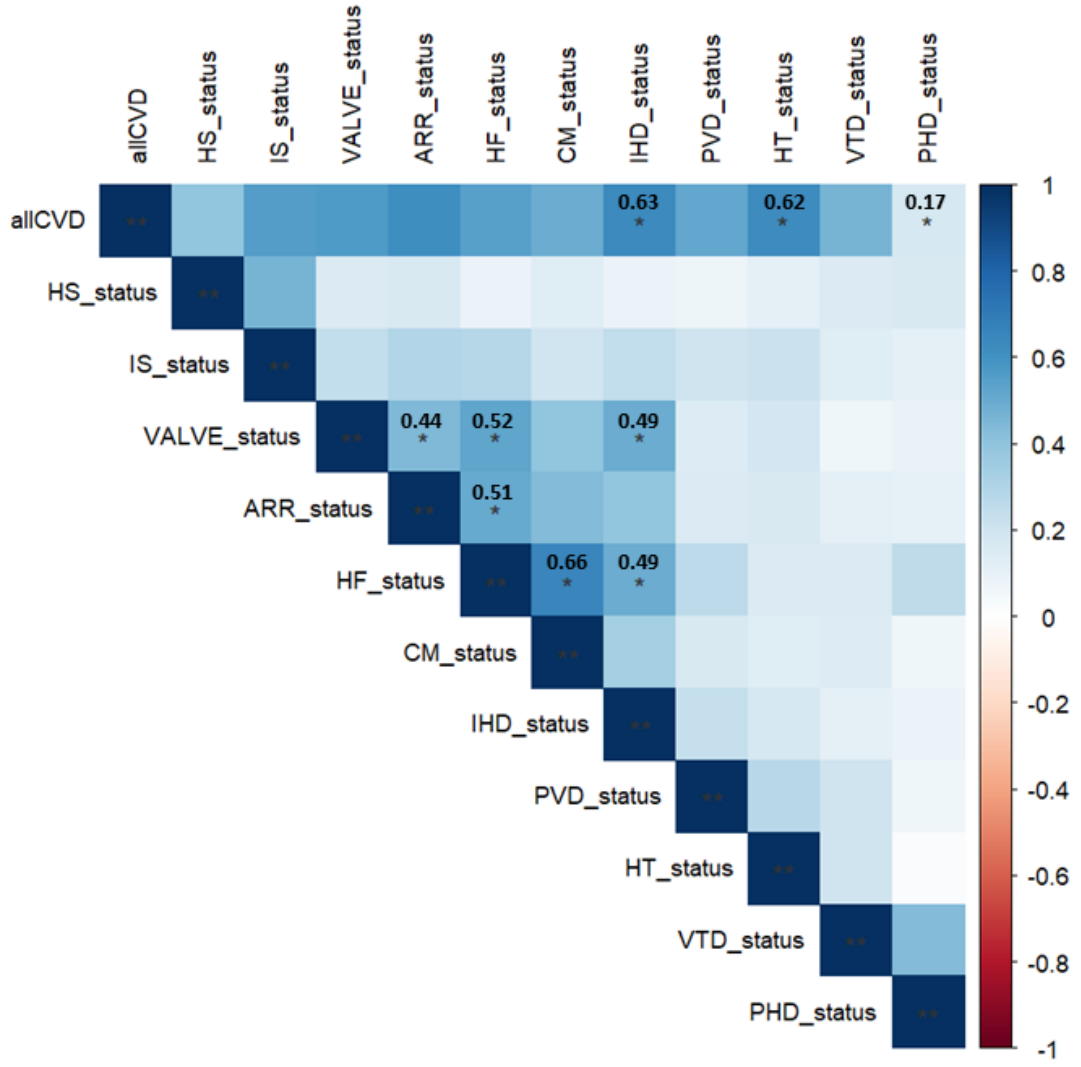

Figure S1. Correlation matrix of cardiovascular disease subtypes

allCVD, total cardiovascular disease; HS, hemorrhagic stroke; IS, ischemic stroke; VALVE, heart valve disorder; ARR, heart arrhythmia; HF, heart failure; CM, cardiomyopathy; IHD, ischemic heart disease; PVD, peripheral vascular disease; HT, hypertension; VTD, venous thromboembolic disease; PHD, pulmonary heart disease; *p-value <0.05; **p-value <0.0001

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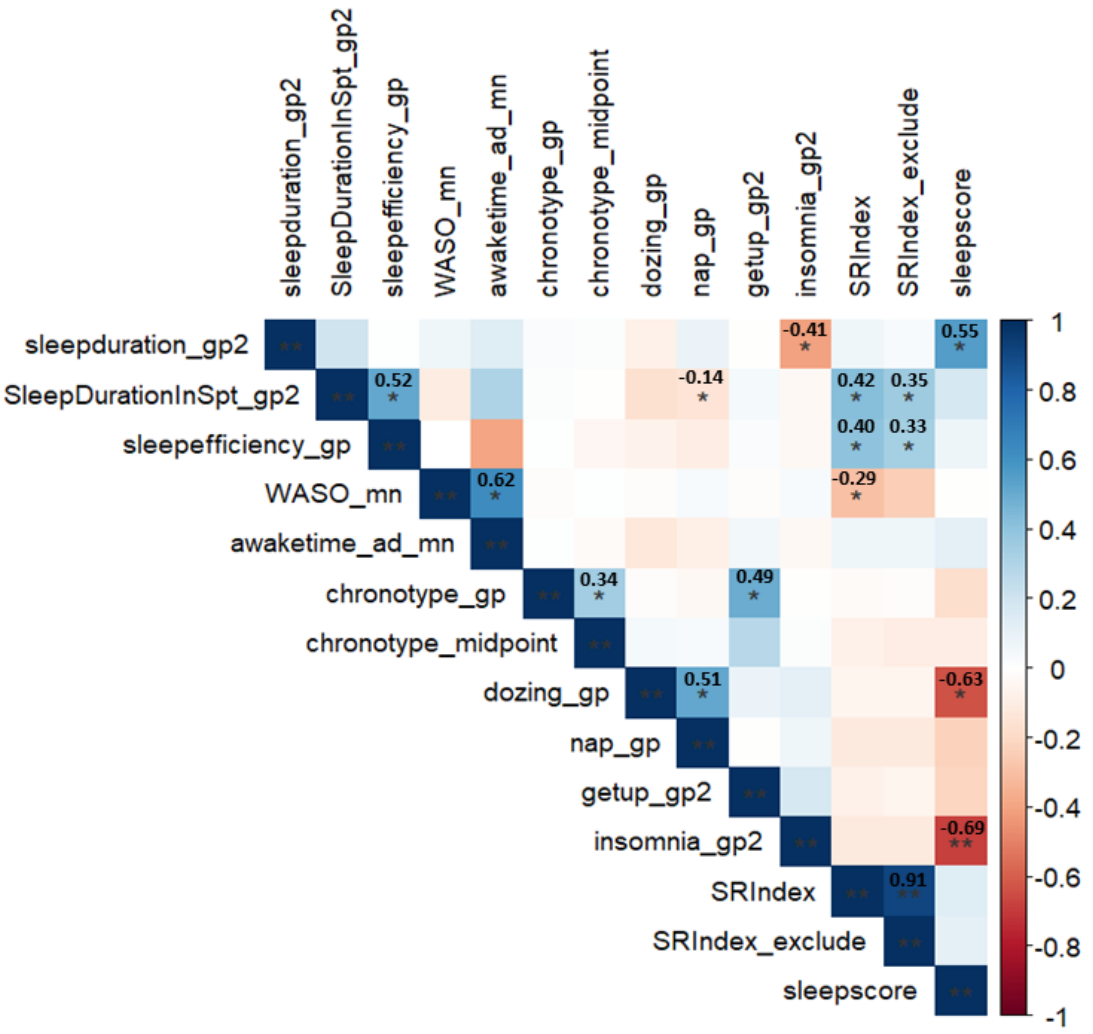

Figure S2. Correlation matrix of baseline sleep phenotypes

sleepduration, subjective sleep duration; SleepDurationInSpt, objective sleep duration; chronotype, subjective chronotype; chronotype_midpoint, objective chronotype; SRIndex, sleep regularity index; SRIndex_exclude, weekday only sleep regularity index; sleepscore, healthy sleep score; *p-value <0.05; **p-value <0.0001

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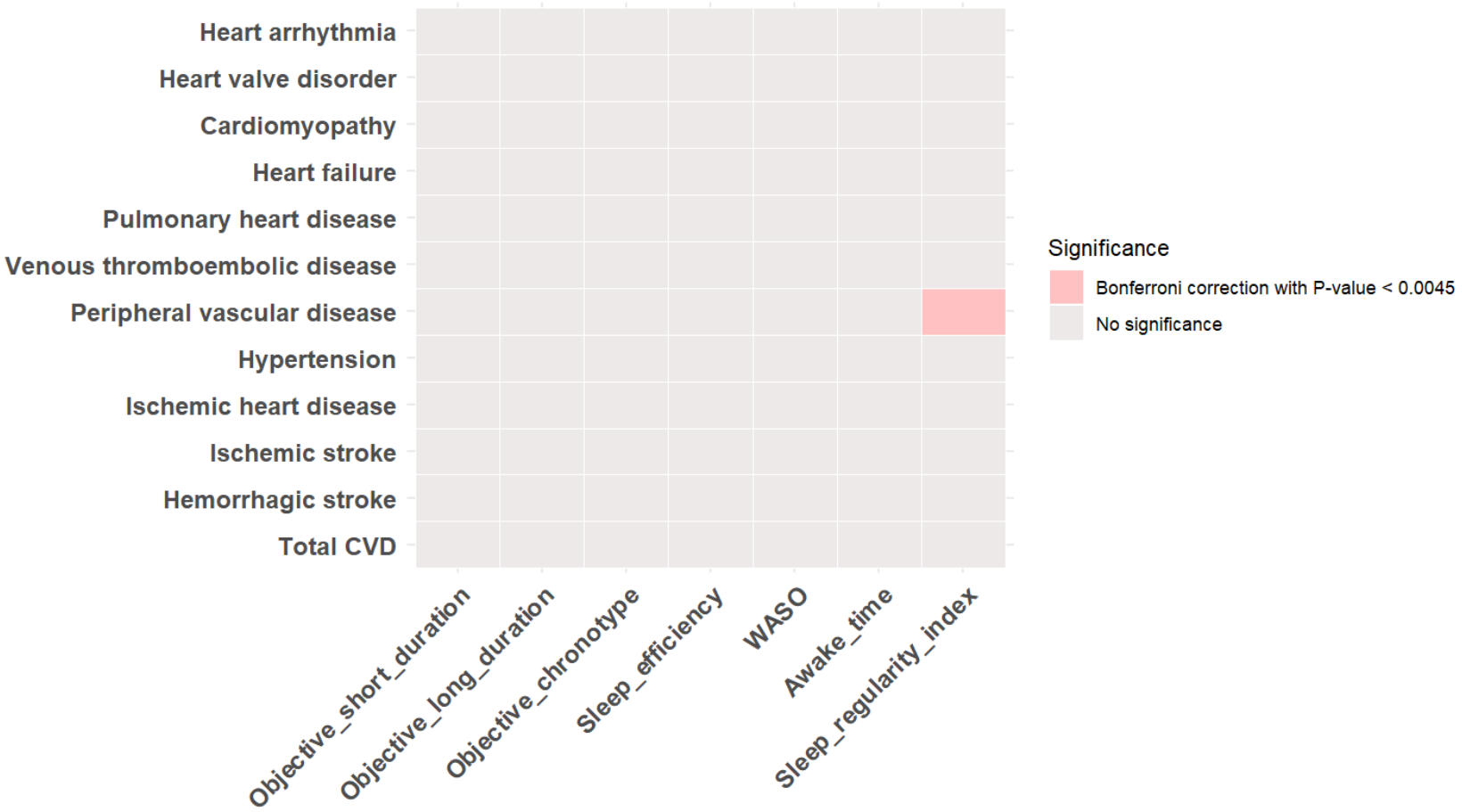

Figure S3. Significance matrix from the Cox model analyzing the impact of objective sleep phenotypes on cardiovascular disease subtypes

All models except for hypertension adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status, physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose; Model for hypertension adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status, physical activity, diet quality, total cholesterol and fasting glucose.

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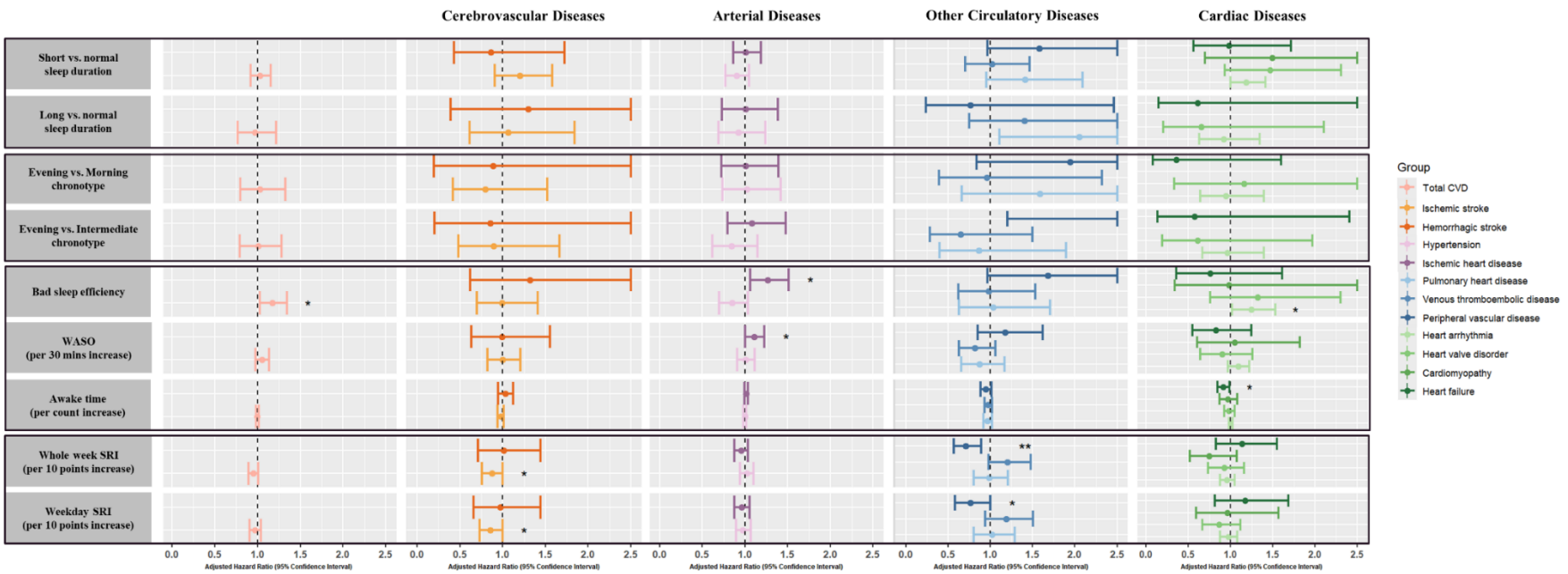

Figure S4. Cox proportional hazards models of objective sleep phenotypes for cardiovascular disease subtypes

All models except for hypertension adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status, physical activity, diet quality, DBP, SBP, total cholesterol and fasting glucose; Model for hypertension adjusted for age, sex, education, employment, TDI, alcohol intake, smoking status, physical activity, diet quality, total cholesterol and fasting glucose; *p-value <0.05; **p-value <0.0045 after Bonferroni correction; ***p-value <0.0001

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