ORIGINAL ARTICLE

Full manuscript title

The contribution of sleep to social inequalities in cardiovascular disorders: a multi-cohort study

Short title

The role of sleep in social differences in CVD

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Abstract

Aims

Sleep disturbances exhibit a strong social patterning, and inadequate sleep has been associated with adverse health outcomes, including cardiovascular disorders (CVD). However, the contribution of sleep to socioeconomic inequalities in CVD is unclear. This study pools data from eight European cohorts to investigate the role of sleep duration in the association between life-course socioeconomic status (SES) and CVD.

Methods and Results

We used cross-sectional data from eight European cohorts, totaling 111,205 participants. Life-course SES was assessed using father's and adult occupational position. Self-reported sleep duration was categorized into recommended (6h-8.5h/night), long (>8.5h/night), and short (<6h/night). We examined two cardiovascular outcomes: coronary heart disease (CHD) and stroke. Main analyses were conducted using pooled data and examined the association between life-course SES and CVD, and the contribution of sleep duration to this gradient using counterfactual mediation. Low father's occupational position was associated with an increased risk of CHD (men: OR=1.19, 95% CI [1.04;1.37]; women: OR=1.25, 95% CI [1.02;1.54]), with marginal decrease of the gradient after accounting for adult occupational position (men: OR=1.17, 95% CI [1.02;1.35]; women: OR=1.22, 95% CI [0.99;1.52]), and no mediating effect by short sleep duration. Low adult occupational position was associated with an increased risk of CHD in both men and women (men: OR=1.48, 95% CI [1.14;1.92]; women: OR=1.53, 95% CI [1.04;2.21. Short sleep duration meaningfully contributed to the association between adult occupational position and CHD in men, with 13.4% mediation. Stroke did not exhibit a social patterning with any of the variables examined.

Conclusion

This study suggests that inadequate sleep accounts to a meaningful proportion of the association between adult occupational position and coronary heart disease, at least in men. With sleep increasingly being considered an important cardiovascular risk factor in its own terms, our study additionally points to its potential role in social inequalities in cardiovascular disease.

Translational perspective

This study, including data on 111,205 participants from eight cohorts in four European countries, suggests that inadequate sleep accounts for a meaningful proportion of the socioeconomic gradient in coronary heart disease, at least in men. With inadequate sleep increasingly being considered an important cardiovascular risk factor in its own terms, our study additionally points to its potential role in social inequalities in cardiovascular disease, and should encourage health professionals to consider these factors as major contributors to the pathophysiology of coronary heart disease.

1 Introduction

Individuals experiencing adverse socioeconomic circumstances across the life-course are disproportionately affected by cardiovascular disorders (CVD), including coronary heart disease and stroke [1, 2]. Social differences in cardiovascular disorders are partly explained by behavioral or psychosocial factors [3, 4]. However, a significant part of the socioeconomic gradient in cardiovascular disease remains unexplained [4].

Among the factors that may potentially link social disadvantage to CVD is inadequate sleep. First, individuals who experienced social adversity across the life-course report sleep-related problems more frequently than those with more advantaged experiences [5-7]. In particular, people working in shifts, living in deprived neighborhoods, or who have experienced adversity in childhood show an increased prevalence of sleep-related disorders [6, 8-12].

Second, inadequate sleep has been associated with an increased risk of cardiovascular disease [13-15]. Chronic sleep deprivation disrupts the function of several physiological systems including the dysregulation of key endocrine and metabolic processes, which may lead to an aberrant activation of the autonomous nervous system, and the impairment of immunity and inflammatory processes, altogether leading to an increased cardiovascular risk [13, 16, 17]. Excessively long sleep has also been associated with adverse cardiovascular health outcomes, although reverse causation processes whereby individuals sleep longer cannot be excluded [18-21]. To date, however, no large population-based study has assessed the contribution of sleep to the social gradient in CVD [8, 22].

In this study, we examine the associations between indicators of socioeconomic status (SES) across the life-course and cardiovascular disorders, namely coronary heart disease (CHD) and stroke, by using cross-sectional data from eight cohort studies from four European countries.

Further, we assess to what extent the associations between life-course SES and CVD are explained by sleep duration by applying the counterfactual mediation model.

2 Methods

2.1 Study population

This study is part of the Lifepath project [23] and uses cross-sectional data from eight cohorts: the French Constances (study period 2012-2016; N=65,843), E3N (2005-2006; N=51,841) and GAZEL (2014; N=10,203), the English Whitehall II (1997-1998; N=6,359) and ELSA (2012; N=5,083), the Swiss COLAUS (2009-2011; N=4,147) and SKIPOGH (2013-2016; N=979) and the Portuguese EPIPORTO (2005-2009; N=2,410) [11, 24-30]. While five cohorts included adults from the general population, E3N, GAZEL and Whitehall II were occupational cohorts and included women working in the French national education sector, employees of the French national gas and electricity company and British civil servants, respectively. All participants underwent a clinical examination and filled a questionnaire collecting data on demographic characteristics, health, medication, education, work, lifestyle and sleep characteristics.

2.1.1 Ethics statement

Each study was approved by relevant local or national ethics committees and all procedures performed in these studies were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All participants gave written informed consent. This study does not contain any studies with animals performed by any of the authors.

2.2 Measures

2.2.1 Life-course socioeconomic status

We used father's occupational position and last known adult occupational position as measures of SES across the life-course. Father's occupational position is a common indicator of SES in early life, whereas adult occupational position is the most used SES indicator in adulthood [31]. Both variables capture multiple dimensions of SES, including education, social prestige, wealth, and retirement benefits, and have been widely used in former studies exploring socioeconomic differences in health [32]. While father's occupational position was self-reported by study participants in all cohorts, adult occupational position was retrieved through work registries in GAZEL and Whitehall II studies, and self-reported in the six other cohorts (Supplementary table 15). Both SES indicators were coded according to the nine categories of the European Socio-economic Classification system (ESeC), which is a standard system for classifying professions in social epidemiology, and further grouped in three main categories: "High" (higher professionals/managers, lower professionals/managers, higher clerical), "Middle" (small employers and self-employed, farmers, lower supervisors and technicians) and "Low" (lower clerical, sales workers, skilled/unskilled workers) [33].

2.2.2 Cardiovascular disorders

Two cardiovascular disorders were considered as outcomes: coronary heart disease (CHD) and stroke. CHD was defined as reporting ischemic artery disease, angina pectoris, or myocardial infarction, whereas stroke was defined as reporting an ischemic or hemorrhagic stroke. The history of CVD events was based on self-report in GAZEL, ELSA, COLAUS, SKIPOGH and EPIPORTO studies, whereas an objective assessment of cardiovascular outcomes was available in Constances, E3N and Whitehall II cohorts, as these studies included thorough cardiological examinations at interview or had access to participant's medical records (Supplementary Table 15).

2.2.3 Sleep duration

Our study focused on sleep duration as this measure has previously been related to both SES and CVD and was available in all eight cohorts [13, 34]. Sleep duration was self-reported in all eight cohorts as the average number of hours of sleep per night and subsequently categorized into recommended or normal sleep (6-8.5 h/night), short sleep (<6h/night) and long sleep (>8.5h/night). These thresholds were chosen from clinical practice which found that short sleep (<6h/night) was associated with an increased risk of CVD [14, 35], whereas long sleep (>8.5h/night) was related with preexistent conditions, such as depression [19, 36].

2.2.4 Other covariates

Potential confounders we considered included cohort, study period, health behaviors, and flexible working hours. Health behaviors were self-reported in all eight cohorts and included smoking, sedentary behavior and alcohol intake. Smoking status was categorized as current vs. former/never smoker, sedentary behavior was categorized as sedentary vs. non-sedentary based on the amount, frequency, and type of physical activity, whereas alcohol intake was categorized as hazardous intake (>3 daily alcohol units for men, >2 daily alcohol units for women) vs. non-hazardous intake. Flexible working hours were based on the ESeC classification of professions and were categorized as flexible (higher professionals and managers, lower professionals and managers; higher clerical, services and sales workers) and non-flexible (small employers and self-employed; farmers; lower supervisors; technicians; lower clerical, services and sales workers, skilled and unskilled workers).

2.3 Statistical analyses

We tested the association between adult or father's occupational position (main exposure variables) and sleep duration (outcome), using a multinomial logistic regression model adjusted for age, cohort, study period, health behaviors, and flexible working hours. To account for the effect of adult occupational position in analyses using father's occupational

position as the main exposure, we implemented an additional model that was further adjusted for adult occupational position [37]. We used the same set of covariates for the logistic model assessing the association between sleep duration (exposure) and CVD (outcome). We tested the associations between SES indicators and cardiovascular disorders and the mediating effect of each level of sleep duration by applying the counterfactual mediation method, using the same sets of covariates. The counterfactual mediation method is based on two regression models (Annex 1): a first model predicting the outcome (CHD, stroke) based on the main exposure variable (SES), the mediator (sleep duration), an interaction term between the main exposure and the mediator, and confounders, and a second regression model predicting the mediator based on the main exposure and confounders. The regression coefficients from the two models are subsequently used to compute counterfactual mediation estimates (Figure 1), namely the natural direct effects (NDE(odds ratio): effect of exposure on the outcome via pathways that do not involve the mediator), natural indirect effects (NIE(odds ratio): effect of exposure on the outcome operating through the mediator), marginal total effects (MTE(odds ratio)=NIE+NDE, total effect of the exposure on the outcome), and the proportion of the association between the exposure and the outcome which is mediated by the mediator (Proportion mediated-PM) [38]. Confidence intervals for MTE, NDE, NIE and PM parameters were computed through bootstrap procedure (random sample with replacement - 10,000 simulations). The main statistical analyses were conducted using Stata v.14 (Stata Corp, TX, USA). Statistical significances were set at p-value <0.05.

2.4 Individual cohort associations

To investigate for potential differences between individual cohorts, we repeated the associations between SES and sleep duration, sleep duration and CVD, and the counterfactual mediation models between SES, sleep duration and CVD, cohort by cohort. We also

performed a meta-analysis of the eight individual cohorts to examine which studies contributed the most to the pooled data associations, and to explore the inter-study heterogeneity by computing the I2 coefficient.

2.5 Additional sensitivity analyses

2.5.1 Cox regression models for time-to-event event longitudinal analyses

To examine whether the cross-sectional approach could have biased the main findings, we also conducted a series of longitudinal analyses using Cox regression models for the associations between SES at baseline and CVD occurrence, and between sleep duration at baseline and CVD occurrence, using time-to-event data from Whitehall II study through waves 1 to 8 (w1 1985-1988, w2 1989-1990, w3 1991-1993, w4 1995-1996, w5 1997-1999, w6 2001, w7 2003-2004, w8 2006)[27]. We included 6805 individuals with complete data at waves 1-8, and tested the proportional hazard assumptions for Cox regression models by using log-log plots (not violated).

2.5.2 Multiple imputation for missing data for health behaviors

To test for bias that would result from missing values, we imputed missing data for health behaviors (confounding factors) using chained equations based on SES, cardiovascular disorders and major confounders (Stata procedure "mi") [39].

2.5.3 Confounding by sleep quality indicators and other cardiometabolic disorders

We further explored potential confounding effects by four binary sleep quality indicators, namely "Difficulty falling asleep", "Difficulty waking up in the morning", "Waking up during the night", and "Waking up too early", by including them as covariables in counterfactual mediation analyses between SES indicators, sleep duration, and CVD (Annex 1). We also explored the potential confounding/contribution to the main associations by further adjusting

for two major cardiometabolic disorders, namely type 2 diabetes (T2D), and obesity (Annex 2).

2.5.4 Comparison of studies using objective assessment vs. self-reported data

To investigate whether the methodology of data acquisition could have affected our findings, we compared the gradients for the associations between SES and sleep duration, sleep duration and CVD, and the mediation by sleep duration to the SES gradient in CVD, between cohorts that either used an objective assessment of the data for the main endpoints (Constances, E3N, Whitehall II) cohorts that were based on self-report (GAZEL, ELSA, COLAUS, SKIPOGH, EPIPORTO).

2.5.5 Education as the main SES indicator

In addition to father's and adult occupational position, we also used education as the main exposure variable, in order to examine the association between education and sleep duration, and to assess the contribution of sleep duration to the educational gradient in CVD.

2.5.6 Extreme sleep duration thresholds

Finally, we repeated the associations between SES and sleep duration, sleep duration and CVD, and the contribution of sleep duration to the SES gradient in CVD using extreme sleep duration thresholds, namely 0h-5h for short sleep duration, and >10h for long sleep duration.

3 Results

From the initial 188,238 participants from the eight cohorts, 37,682 were excluded due to missing information on health behaviors, 3,691 for missing sleep duration, 17,328 for missing adult occupational position, and 18,332 participants for missing father's occupational position, leaving a total of 111,205 participants to be included in the study. Excluded

participants were more frequently women (73% vs. 67%) and had a lower adult occupational position than those included in the study (20% vs. 26% in the high occupation group).

3.1 Sample characteristics

We report the characteristics of the study population in **Table 1**. In the majority of the cohorts, low and middle father's occupational positions were the most prevalent, whereas the distribution of adult occupational position varied among studies and countries, with high and middle adult SES groups being generally more prevalent in English cohorts, and low and middle adult SES groups being more common in Southern European cohorts. The prevalence of short sleep ranged between 3% and 14% (6% for pooled data) and was higher in ELSA (14%) and lower in E3N and EPIPORTO (3% and 5%, respectively), while the prevalence of long sleep ranged between 9% and 27%, and was lower in Whitehall II, SKIPOGH and COLAUS (2%-5%), and higher in EPIPORTO (27%). The distribution of detrimental health behaviors varied substantially across the cohorts, and prevalence estimates ranged between 7% and 26% for current smoking, between 8% and 42% for hazardous alcohol intake, and between 6% and 81% for sedentary behavior. The prevalence of CHD ranged between 1% and 13%, with highest prevalence estimates being observed in Whitehall II and ELSA (13%), while the prevalence of stroke ranged between 1% and 5%, with highest prevalence being in ELSA.

3.2 Association between life-course SES indicators and sleep duration

We show the association between life-course SES indicators and sleep duration using pooled data in **Table 2**. We found a U-shaped association between father's occupational position and sleep duration, with low SES being more strongly associated with short sleep (A. Odds Ratio(OR)=1.18, 95% Confidence Interval(CI)[1.07;1.31], women: OR=1.31, 95% CI [1.20;1.44]), than long sleep (A. OR=1.01, 95% CI [0.92;1.11], women: OR=1.07, 95% CI

[1.01;1.14]). The association between father's occupational position and sleep duration persisted after accounting for adult SES. Larger effect size and stronger associations were observed for the association between adult occupational position and sleep duration, with stronger associations in men than in women. As for father's occupational position, however, we found stronger associations for short sleep (men: OR=2.22, 95% CI [1.85;2.66], women: OR=2.12, 95% CI [1.82;2.47]), than for long sleep (men: OR=1.88, 95% CI [1.59;2.23], women: OR=1.14, 95% CI [1.03;1.27]).

3.3 Association between sleep duration and cardiovascular disorders

The association between sleep duration and cardiovascular disorders is presented in **Table 3**. Short sleep was associated with an increased risk of CHD in both sexes (CHD-men: OR=1.65, 95% CI [1.41;1.92]; women: OR=1.59, 95% CI [1.28;1.97]), whereas it was associated with an increased risk of stroke in women but not in men (Stroke-men: OR=1.16, 95% CI [0.84;1.60]; women: OR=1.31, 95% CI [1.03;1.66]). We also observed a higher risk of stroke in participants with long sleep (men: OR=1.51, 95% CI [1.17;1.95]; women: OR=1.24, 95% CI [1.06;1.49]), while long sleep was also associated with an increased risk of CHD in women (OR=1.24, 95% CI [1.03;1.43]).

3.4 Association between life-course SES indicators and CVD, and the contribution of sleep duration

In **Table 4**, we present the counterfactual mediation models for the associations between SES indicators and cardiovascular disorders, mediated by short sleep duration. We observed an inverse association between father's occupational position and CHD in both men and women (A. men: marginal total effect (MTE – OR scale)=1.19 95% CI [1.04;1.37], women: MTE (OR) = 1.25 95% CI [1.02;1.55]). Upon accounting for the effect of adult occupational

position, the gradient between father's occupational position and CHD was marginally decreased (B. men: MTE (OR)=1.17 95% CI [1.02;1.35], women: MTE (OR) = 1.22 95% CI [0.99;1.51]). Sleep did not mediate the association between father's occupational position and stroke. We found a strong inverse association between adult occupational position and CHD risk in both sexes (C. men: MTE (OR)=1.45 95% CI [1.13;1.86], women: MTE (OR) = 1.52 95% CI [1.07;2.11]), with 13.4% mediation of this association by short sleep duration in men. We also evaluated the contribution of *long* sleep duration to the life-course socioeconomic gradient in cardiovascular disorders, but found no meaningful mediation **(Supplementary Table 1)**.

3.5 Individual cohort associations

We further examined the associations between SES and sleep duration, sleep duration and cardiovascular disorders, and the mediating effect of short sleep duration to the association between SES and cardiovascular disorders on each cohort separately **(Supplementary tables 2-8)**. Overall, we found that low adult occupational position was associated with an increased risk of short and long sleep duration in the majority of cohorts (Constances, E3N, Whitehall II, ELSA, COLAUS, SKIPOGH, EPIPORTO), with generally stronger odds ratios for short sleep than long sleep, whereas there were fewer associations between father's occupational position and sleep duration, with stronger associations in the model unadjusted for adult occupational position. We also found associations between short sleep duration and an increased risk of CHD, with significant associations being observed in Constances, GAZEL, E3N and Whitehall II cohorts, whereas there were fewer associations between sleep duration and stroke, in both unadjusted and adjusted models for adult occupational position. Furthermore, in most of the studies, results from mediation analyses were uninformative and yielded non-significant estimates for the mediation by short sleep duration due to low

statistical power, the few exceptions being the inverse associations between father's occupational position and CHD in Constances and Whitehall II studies (**Supplementary tables 6-7**), and a strong inverse association between adult occupational position and CHD in Whitehall II (**Supplementary table 8**). Finally, we performed a meta-analysis using adult occupational position, sleep duration, and CHD, in order to examine which cohorts contributed the most to the pooled data associations (weights), and to examine the degree of heterogeneity across the cohorts (Supplementary Figure 1). We found a high inter-study heterogeneity for the SES-sleep duration gradient, while there were more consistent gradients for the associations between sleep duration and CHD, the adult occupational gradient in CHD (MTE), and the mediating effect by sleep duration (NIE) across the cohorts. The observed heterogeneity for the SES-sleep duration gradient may be explained by the different gradients found in GAZEL, SKIPOGH, and EPIPORTO studies when compared to the other cohorts. A possible explanation for these differences may be the lack of statistical power, as well as a weaker socioeconomic patterning of sleep duration in these studies.

3.6 Additional sensitivity analyses

3.6.1 Cox regression models for time-to-event event longitudinal analyses

As there is currently no methodology allowing to apply counterfactual mediation modelling to time-to-event longitudinal analysis, main analyses presented in this study were performed cross-sectionally. To assess whether this may have biased our findings for the main associations examined, the one between adult SES and CVD and the one between sleep duration and CVD, we repeated the analysis using a longitudinal design in a cohort where repeated data was available (Whitehall II). Using time-to-event analyses fitted through Cox regression models, we observed that low occupational position and short sleep (baseline, wave 1) were systematically associated with a higher risk of CHD events through waves 1 to

8 when compared to higher adult occupational position, and normal or long sleep duration. There were no clear gradients in women and for stroke, likely due to lack of statistical power and insufficient number of events (Supplementary Tables 9-10; Supplementary Figures 2-3).

3.6.2 Multiple imputation for missing data for health behaviors

We performed further sensitivity analyses by imputing missing values for confounders using chained equations, and by investigating the potential confounding effects of four sleep quality indicators in the cohorts where this information was available. We observed that there were no important differences between the associations using the complete case data from those using imputed data (**Supplementary tables 11-12, Tables 2-3**).

3.6.3 Confounding by sleep quality indicators

We also found that sleep quality indicators could act as potential confounders of the association between life-course SES, sleep duration, and CVD, as they were simultaneously associated with sleep duration and CVD in the counterfactual models (**Supplementary tables 13-14**).

3.6.4 Comparison of studies using objective assessment vs. self-reported data

We further investigated whether the fact that several data were self-reported could have biased our results by comparing the associations between SES and sleep duration, sleep duration and CHD, the association between SES and CHD (MTE), and the mediation of this association by sleep duration between cohorts that used objective assessment of CHD and those with self-reported data (**Supplementary tables 16-18**). Results from cohorts that used objectively assessed data provided systematically stronger gradients than cohorts that were based on self-report, including meaningful mediation by short sleep duration (11.1%). However, we cannot conclude that these differences are exclusively attributed to the

assessment method of CHD, as there were major regional differences between the two groups of cohorts.

3.6.5 Education as the main SES indicator

We also investigated to what extent education was associated with sleep duration, and whether the educational gradient in CVD outcomes was mediated by short sleep duration (**Supplementary tables 19-20**). We observed that low education was associated with an increased risk of short sleep duration and a higher risk for CHD, and that this association was significantly mediated by short sleep duration (9.2%). These associations and mediation were systematically weaker than those involving adult occupational position, and somewhat higher compared to associations using father's occupational position as main exposure.

3.6.6 Confounding/contribution by cardiometabolic disorders

Moreover, we also performed a series of additional analyses where associations between adult occupational position, sleep duration, and CHD were further adjusted for type 2 diabetes and obesity (**Supplementary tables 21-23**). We observed that the associations between adult SES and short sleep, and between short sleep and CHD were attenuated upon adjustment for type 2 diabetes (T2D) and obesity, whereas the association between SES and CHD and the contribution of short sleep duration to this association were no longer significant.

3.6.7 Extreme sleep duration thresholds

Finally, we also examined the associations between adult SES, sleep duration, and CHD, using more extreme thresholds for sleep duration; 0h-5h for short sleep duration, and >10h for long sleep duration (**Supplementary tables 24-26**). We generally found stronger gradients for the association between adult SES and extreme sleep duration, and for extreme sleep duration and CHD, in particular for the 0h-5h sleep duration category. These findings indicate that

extreme sleep patterns are more prevalent among socially disadvantaged individuals, and that they have stronger effects on cardiovascular outcomes. Furthermore, we also observed that there was a somewhat weaker mediation by extreme short sleep duration (0h-5h) when compared to the former threshold (0h-6h), which was due to a weaker indirect effect (NIE).

4 Discussion

In this study, we found that both father's and adult occupational position were associated with abnormal sleep duration patterns, with stronger associations for adult than for early life SES, and for short sleep than for long sleep. Furthermore, abnormal sleep duration was associated with an increased risk of cardiovascular disorders, with stronger associations for short sleep than for long sleep. Finally, we observed that there were inverse associations between both life-course SES indicators and CHD, and that the association between adult occupational position and CHD was partly explained by short sleep duration, at least in men.

Our results on life-course socioeconomic gradient in short sleep duration tend to be in line with previous studies [6, 12, 34]. Former research has reported that adverse socioeconomic circumstances in childhood affect sleep health in adulthood through a latent effect, and that this association may be related to the fact that stressful childhood experiences lead to disrupted emotion regulation in adulthood, which in turn has a negative impact on adult sleep [12, 40]. The adult occupational gradient in sleep duration may be related to the fact that individuals with lower grade occupations often have to combine several jobs, work in shifts, and live in noisy environments, thus experiencing greater levels of stress, altogether leading to sleep deprivation [5, 11, 22]. The stronger association between adult occupational position and short sleep duration when compared with father's occupational position and education may be related to the fact that adult occupational position directly acts on proximal exposures which affect sleep, such as poor housing, work stress, and recent psychosocial exposures, whereas

father's occupational position and education likely act through more indirect effects that have occurred in early life [7, 40, 41]. Interestingly, we also observed that individuals with low father's and adult occupational position were more likely to have excessively long sleep duration, when compared to high SES individuals. However, while short sleep duration is more probably the consequence of adverse socioeconomic circumstances, later leading to adverse health outcomes, long sleep duration more probably results from preexisting conditions, such as depression, that affect socially disadvantaged individuals more [18-21, 35].

Our study also confirms the relationship between short sleep duration and an increased risk of CHD and stroke [13]. Mechanistic studies suggest that chronic sleep deprivation may result in hypertension, elevated inflammation, and atherosclerosis through an aberrant activation of the sympathetic nervous system, as well as to an increased risk of type 2 diabetes (T2D) and obesity, altogether leading to cardiovascular events [13, 15, 42]. In a series of sensitivity analyses additionally adjusted for T2D and obesity, we observed that the association between adult SES and CHD, and the contribution of sleep duration were no longer significant, which may be attributed to potential confounding or even mediation, whereby T2D and obesity could constitute an additional intermediate step between chronic sleep deprivation, and the eventual occurrence of CHD or stroke. The potential role of inappropriate nutrition as an additional step in this chain of causation could not be investigated in our study and shall be the subject of additional research.

We also found that long sleep duration is associated with an increased CVD risk, but to a lesser extent than short sleep, which is line with previous studies reporting that an excessively long sleep duration is also associated with adverse health outcomes, including CVD [21]. Nevertheless, the underlying mechanisms linking sleep duration and CVD are not the same for short and long sleep duration, and long sleep duration is often mentioned as a consequence of preexisting illnesses rather than a cause [18-21]. While there is no clear evidence that sleeping

more than eight hours per night could lead to adverse health outcomes in healthy individuals, former research has often reported that major depressive disorder is a strong predictor of excessive sleeping, suggesting that depression may confound the associations between long sleep and adverse health-related outcomes[18].

Our study found that there was an inverse association between adult occupational position and CHD in both men and women, which is in line with previous research [43]. We also observed that short sleep duration significantly contributed to the adult occupational gradient in CHD in men, but not in women. The absence of mediation by short sleep duration in women may be related to the fact that there was a weaker adult occupational gradient in short sleep duration in women than in men. Overall, these gender-related differences may be explained by additional sociodemographic and socioeconomic factors, such as the fact that low SES women often have to combine the physical and psychosocial strain of manual, less paid jobs to that of numerous household responsibilities and stress, which eventually negatively affects their sleep and its health-restoring effects when compared to men [11]. Furthermore, we found an inverse association between father's occupational position and CHD, which was only marginally decreased upon accounting for adult occupational position. These findings indicate that father's occupational position likely affects CHD through latent mechanisms, whereby adverse socioeconomic circumstances in early life have left permanent biological imprints that translate into higher CHD risk in later life [37, 44]. Finally, we also observed that there were no associations between both life-course SES indicators and stroke, which may be related to a differential socioeconomic patterning, and different pathophysiology and risk factors for these two cardiovascular disorders [45, 46] . Another explanation may be related to a lack of statistical power, as the occurrence of stroke was much lower than the occurrence of CHD events throughout the included cohorts.

4.1 Strengths and limitations

Our study has several strengths. First, to our knowledge this is the first study to investigate the contribution of sleep duration to the association between life-course socioeconomic status and cardiovascular disorders. Second, we used data from eight cohorts conducted in four European countries, involving more than 111,000 participants. Our study also has some limitations to acknowledge. First, the demographic, epidemiological and methodological differences between the eight cohorts represent a vast challenge in terms of data harmonization, and may result in important heterogeneity, particularly concerning the occurrence and assessment of cardiovascular outcomes. While the difference in CHD prevalence between the Northern (Whitehall II, ELSA) and the Southern European cohorts (Constances, E3N, GAZEL, SKIPOGH, COLAUS) may be attributed to the well-established North-South gradient in CHD prevalence in Europe [47], potential bias resulting from a differential reporting of cardiovascular outcomes cannot be excluded. In particular, the absence of objectively assessed health-related outcomes and the lack of access to medical records may result in important self-report and recall biases, eventually yielding differential SES-CVD and sleep duration-CVD gradients across included studies [48, 49]. These types of systematic errors represent an important issue in epidemiological studies, especially given the fact that factors such as education and other SES variables were found to influence recall bias in retrospective cohorts[48]. Furthermore, another limitation related to procurement methodology is the systematic difference observed between self-reported and objectively measured sleep duration, which could not be accounted for in the present analyses[50]. Additional issues may be related to the statistical methodology applied in this study. In particular, cross-sectional analyses do not allow determining the causal direction of associations, which can be a particular issue for analyses involving sleep disturbances and health-related outcomes, as the relation between these two factors is not exclusively unidirectional. However, we managed to address this issue by performing a series of

longitudinal analyses in Whitehall II study. Furthermore, apart from the contribution of sleep duration, we must acknowledge the role of other potential confounders or mediators of the socioeconomic gradient in cardiovascular disorders, including hypertension, hyperlipidemia, life-related factors, working hours, psychosocial exposures, and environmental factors, whose contribution was not examined in this multi-cohort study. Finally, the lack of information on objectively measured sleep disorders (i.e. sleep-disordered breathing) as well as sleep quality indicators in the majority of cohorts may be another limiting factor in this study, as sleep apnea and sleep quality have been found to be associated with CVD risk as well as sleep duration, and could potentially confound the causal pathways involving SES, sleep duration, and cardiovascular disorders [51-53].

4.2 Conclusion

In summary, this large pan-European analysis suggests that short sleep duration is a potential mechanism underlying the association between adult occupational position and CHD. Additional longitudinal analyses shall be conducted to further investigate the causal relationship between SES, sleep duration and CVD. Finally, the role of other sleep features, in particular sleep quality, shall further be investigated as potential confounders of the associations between SES, sleep duration, and CVD.

5 Author's contributions

SS, DP, CC and MCH designed the study. JHR, MK-I, PVi, MK, MG, FR, AD'E, MB, PVo, HB, SF, MG, MZ, AS, CD, RH, and SS actively contributed to data acquisition and harmonization. DP, SN, SS, CC, MCH analyzed the data. DP, SS, CC, MCH, JHR, CDM, MK-I, PVi, MK, SN, MG, FR, AD'E, MB, PVo, HB, SF, MG, MZ, AS, CD, RH critically revised the manuscript.

6 LIFEPATH Consortium

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9 Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

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Table 1: General characteristics of included participants by cohort

	Constances	GAZEL	E3N	Whitehall II	ELSA	COLAUS	SKIPOGH	EPIPORTO	Pooled data
	N=50,463	N=8,760	N=39,258	N=4,356	N=3,838	N=2,228	N=854	N=1,448	N=111,205
% Women	26437 (52%)	2059 (24%)	39258 (100%)	1239 (28%)	2144 (56%)	1149 (52%)	432 (51%)	864 (60%)	73582 (66%)
Age (mean±SD, y)	48.4 (±13)	68.9 (±3.4)	64 (±6.3)	55.7 (±6)	72 (±8.7)	53 (±8)	50.3 (±16.2)	52 (±13.3)	56.8 (±13.1)
Father's occupationnal position (N, %)									
High	10933 (22%)	3251 (37%)	6303 (16%)	426 (10%)	396 (10%)	718 (32%)	215 (25%)	195 (13%)	22437 (20%)
Middle	20504 (41%)	1930 (22%)	16805 (43%)	1335 (31%)	1476 (38%)	848 (38%)	406 (48%)	306 (21%)	43610 (39%)
Low	19026 (38%)	3579 (41%)	16150 (41%)	2595 (60%)	1966 (51%)	662 (30%)	233 (27%)	947 (65%)	45158 (41%)
Adult occupational position (N, %)									
High	17041 (34%)	2527 (29%)	5041 (13%)	2412 (55%)	1118 (29%)	352 (16%)	187 (22%)	310 (21%)	28988 (26%)
Middle	16402 (33%)	4649 (53%)	28411 (72%)	1350 (31%)	1679 (44%)	818 (37%)	293 (34%)	313 (22%)	53915 (48%)
Low	17020 (34%)	1584 (18%)	5806 (15%)	594 (14%)	1041 (27%)	1058 (47%)	374 (44%)	825 (57%)	28302 (25%)
Flexible working hours (N, %)	17041 (34%)	2527 (29%)	5041 (13%)	3762 (86%)	1118 (29%)	352 (16%)	185 (22%)	310 (21%)	30336 (27%)
Sleep duration (mean±SD, h/n)	7.2 (±1.2)	7.3 (±1.1)	7.6 (±1.1)	6.7 (±1)	6.9 (±1.3)	6.9 (±1)	6.9 (±1.1)	7.8 (±1.5)	7.3 (±1.2)
Sleep duration (N, %)									
Normal sleep (6h-8.5h/n)	40382 (80%)	6676 (76%)	31532 (80%)	3960 (91%)	2962 (77%)	1953 (88%)	728 (85%)	996 (69%)	89189 (80%)
Long sleep (>8.5h/n)	5934 (12%)	1376 (16%)	6670 (17%)	66 (2%)	325 (8%)	80 (4%)	42 (5%)	385 (27%)	14878 (13%)
Short sleep (<6h/n)	4147 (8%)	708 (8%)	1056 (3%)	330 (8%)	551 (14%)	195 (9%)	84 (10%)	67 (5%)	7138 (6%)
Health-related behaviors (N, %)									
Current smoking	9696 (19%)	635 (7%)	2639 (7%)	452 (10%)	354 (9%)	496 (22%)	224 (26%)	327 (23%)	14823 (13%)
Hazardous alcohol consumption [a]	5847 (12%)	2468 (28%)	16601 (42%)	1731 (40%)	1057 (28%)	401 (18%)	72 (8%)	475 (33%)	28652 (26%)
Sedentary behavior	11689 (23%)	2884 (33%)	7874 (20%)	259 (6%)	1280 (33%)	611 (27%)	337 (39%)	1169 (81%)	26103 (23%)
Diabetes (N, %)	1683 (3%)	1155 (13%)	***	204 (5%)	303 (12%)	176 (8%)	46 (5%)	165 (11%)	3732 (5%)
Obesity (N, %)	5676 (11%)	1177 (14%)	2660 (7%)	596 (18%)	945 (29%)	297 (13%)	123 (14%)	312 (22%)	11786 (11%)
Cardiovascular disorders									
CHD (N, %)	660 (1%)	518 (6%)	460 (1%)	574 (13%)	445 (13%)	93 (4%)	21 (2%)	92 (6%)	2863 (3%)
Stroke (N, %)	400 (1%)	99 (1%)	878 (2%)	18 (0%)	190 (5%)	24 (1%)	10 (1%)	36 (2%)	1655 (2%)

CHD, coronary heart disease; h/n, hours per night

[a] Hazardous alcohol consumption was defined as having >3 alcoholic drinks per day for men and >2 alcoholic drinks per day in women

*** This outcome was not assessed in the E3N cohort

Table 2: Association between SES indicators and sleep duration based on pooled cohort data

Men		**OR (95 %CI)**	***P*-value**	**N**
A. Father's occupational position (unadj. adult occ.)	Short sleep (0h-6h)	1.18 [1.07;1.31]	0.002	37623
(High: 7.15h; Mid: 7.13h; Low: 7.07h) [d]	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	1.01 [0.92;1.11]	0.805	
B. Father's occupational position (adj. adult occ.)	Short sleep (0h-6h)	1.12 [1.01;1.24]	0.036	37623
(High: 7.15h; Mid: 7.13h; Low: 7.07h) [d]	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	0.97 [0.89;1.07]	0.560	
C. Adult occupational position	Short sleep (0h-6h)	2.22 [1.85;2.66]	<0.001	37623
(High: 7.11h; Mid: 7.12h; Low: 7.09h) [d]	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	1.88 [1.59;2.23]	<0.001	
Women				
A. Father's occupational position (unadj. adult occ.)	Short sleep (0h-6h)	1.31 [1.20;1.44]	<0.001	73582
(High: 7.37h; Mid: 7.41h; Low: 7.37h) [d]	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	1.07 [1.01;1.14]	0.014	
B. Father's occupational position (adj. adult occ.)	Short sleep (0h-6h)	1.24 [1.13;1.36]	<0.001	73582
(High: 7.37h; Mid: 7.41h; Low: 7.37h) [d]	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	1.07 [1.01;1.13]	0.028	
C. Adult occupational position	Short sleep (0h-6h)	2.12 [1.82;2.47]	<0.001	73582
(High: 7.33h; Mid: 7.46h; Low: 7.27h) [d]	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	1.14 [1.03;1.27]	0.014	

OR, odds ratio; CI, confidence interval

A. Multinomial logistic regression for the association between father's occupational position (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night), adjusted for age, cohort, study period, flexible working hours and health behaviors

B. Multinomial logistic regression for the association between father's occupational position (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night), adjusted for age, adult occupational position, cohort, study period, flexible working hours and health behaviors

C. Multinomial logistic regression for the association between adult occupational position (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night), adjusted for age, cohort, study period, flexible working hours and health behaviors

[d] Average sleep duration per SES categories

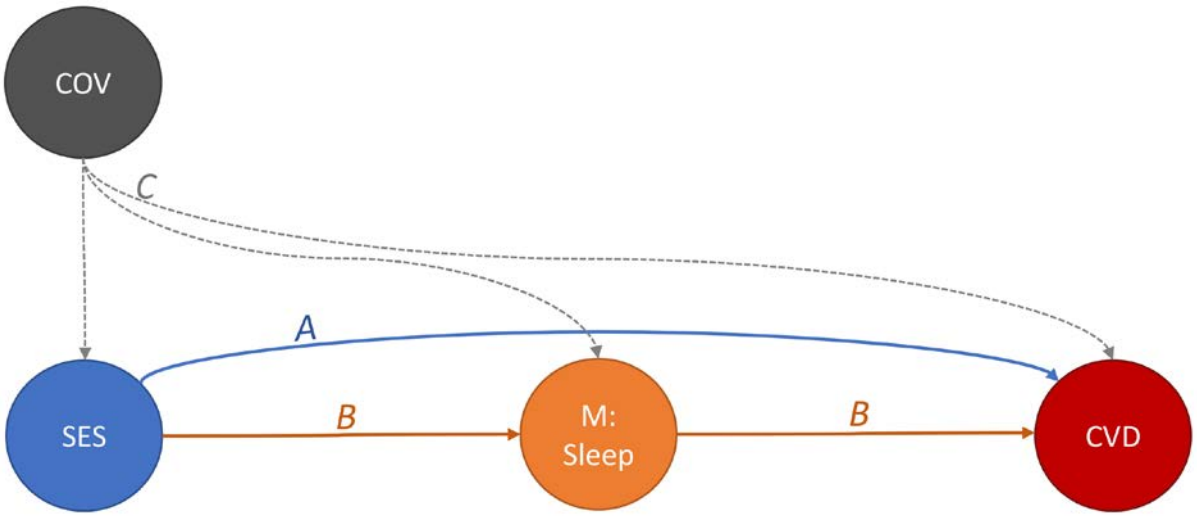
Table 3: Association between sleep duration and cardiovascular disorders based on pooled cohort data

			OR (95% CI) [a]	P-value	N
Men	Short sleep (0h-6h)	CHD	1.65 [1.41;1.92]	<0.001	36987
	Normal sleep (6h-8.5h) (ref. predictor)		1.00		
	Long sleep (>8.5h)		1.02 [0.87;1.19]	0.825	
	Short sleep (0h-6h)	Stroke	1.16 [0.84;1.60]	0.381	36759
	Normal sleep (6h-8.5h) (ref. predictor)		1.00		
	Long sleep (>8.5h)		1.51 [1.17;1.95]	0.001	
Women	Short sleep (0h-6h)	CHD	1.59 [1.28;1.97]	<0.001	72863
	Normal sleep (6h-8.5h) (ref. predictor)		1.00		
	Long sleep (>8.5h)		1.24 [1.03;1.49]	0.024	
	Short sleep (0h-6h)	Stroke	1.31 [1.03;1.66]	0.028	72819
	Normal sleep (6h-8.5h) (ref. predictor)		1.00		
	Long sleep (>8.5h)		1.24 [1.06;1.43]	0.005	

OR, odds ratio; CI, confidence interval; CHD, coronary heart disease

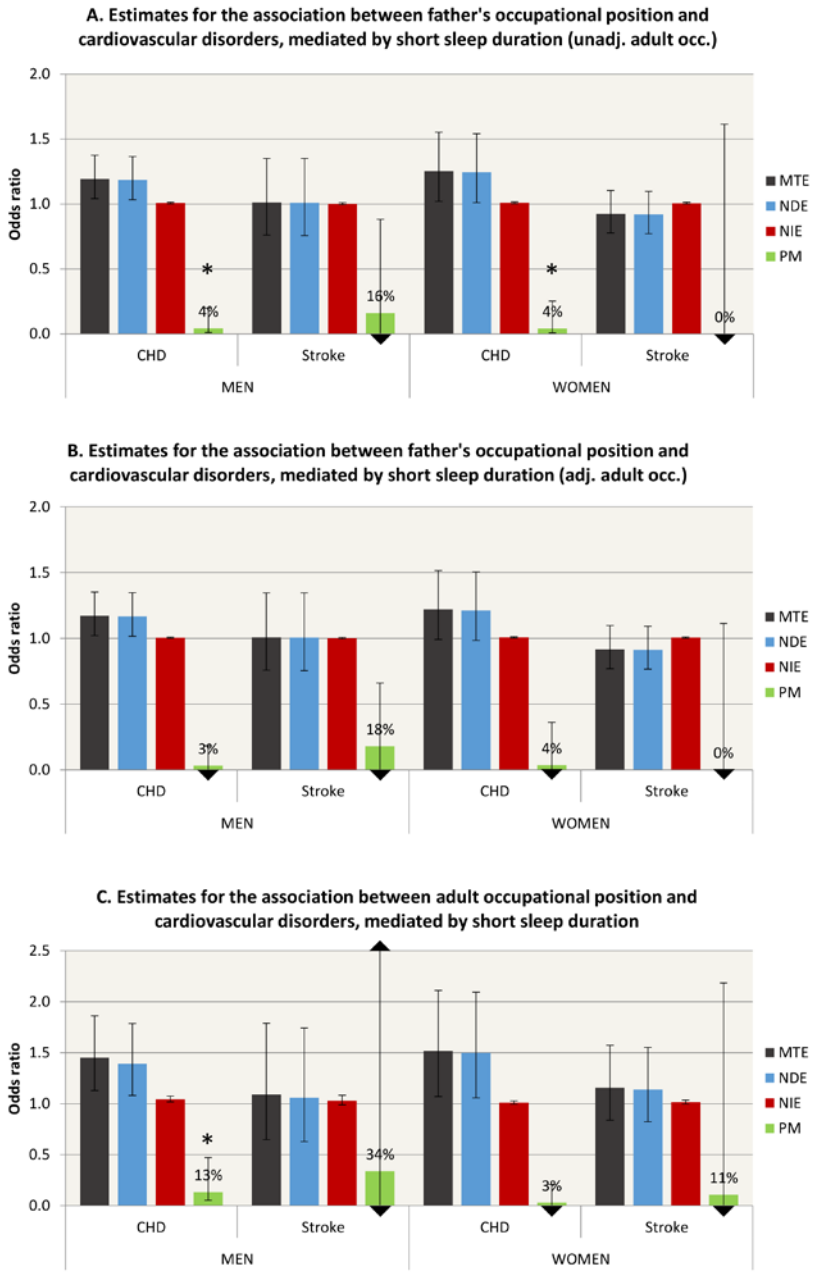
[a] Logistic regression for the association between three category sleep duration (categorical predictor-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night) and cardiovascular disorders (outcome), adjusted for age, cohort , study period, flexible working hours, and health behaviors

Figure 1: Directed acyclic graphs representing the counterfactual mediation model for the association between SES indicators and cardiovascular outcomes, mediated by sleep duration



COV: Covariates (age, cohort, study period, health behaviors, flexible working hours); SES: (Adult/Father's occupational position); M: mediator – sleep duration; CVD (cardiovascular disorders)
A: NDE, Natural direct effect: Effect of the predictor (SES) on the main outcome (CVD), through pathways which do not involve the mediator (sleep duration)
B: NIE: Natural indirect effect: Effect of the predictor (SES) on the main outcome (CVD), through pathways which involve the mediator (sleep duration)
C: Confounding effects by covariates
MTE: Marginal total effect of the predictor (SES) on the main outcome (CVD): NDE + NIE (not represented)
This figure was realized with MS Office-Excel.

Figure 2: Counterfactual mediation estimates for the association between SES indicators and cardiovascular disorders, mediated by short sleep duration (<6h/n), using pooled cohort data



CHD, coronary heart disease

A. Association between father's occupational position and CVD, adjusted for age, cohort, study period, flexible working hours and health behaviors.

B. Association between father's occupational position and CVD, adjusted for age, adult occupational position, cohort, study period, flexible working hours and health behaviors

C. Association between adult occupational position and CVD, adjusted for age, cohort, study period, flexible working hours and health behaviors.

Sample size (A, B, C): Men: N=36987 CHD, N=36759 stroke ; Women: N=72863 CHD, N=72819 stroke

MTE: Marginal total effect (OR95% CI); NDE: Natural direct effect (OR 95% CI); NIE: Natural indirect effect (OR 95% CI); PM: Proportion of the association between occupational position and cardiovascular disorders which is mediated by short sleep duration (*****, significant mediation; Lower ▾ and upper ▴ arrow indicate that CIs extend beyond the limits of the graph)

This figure was realized with MSOffice-Excel.