Onset of Impaired Sleep and Cardiovascular Disease Risk Factors: A Longitudinal Study

Alice Jessie Clark, PhD[1,2]; Paula Salo, PhD[3,4]; Theis Lange, PhD[5]; Poul Jennum, PhD[6,7]; Marianna Virtanen, PhD[3]; Jaana Pentti, BSc[3]; Mika Kivimäki, PhD[8,9]; Naja Hulvej Rod, DMSc[*1,2]; Jussi Vahtera, PhD[*3,10]

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[1]Section of Social Medicine, Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [2]The Copenhagen Stress Research Center, University of Copenhagen, Copenhagen, Denmark; [3]Finnish Institute of Occupational Health, Helsinki and Turku, Finland; [4]Department of Psychology, University of Turku, Turku, Finland; [5]Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [6]The Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, Glostrup University Hospital, Copenhagen, Denmark; [7]Center for Healthy Aging, University of Copenhagen, Copenhagen, Denmark; [8]Department of Public Health, University of Helsinki, Helsinki, Finland; [9]Department of Epidemiology and Public Health, University College London, London, UK; [10]Department of Public Health, University of Turku and Turku University Hospital, Turku, Finland; [*]Joint last authors

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Address correspondence to: Alice Clark, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, 1014 Copenhagen K, P.O. box 2099, Denmark;

Tel: (+45) 35326737; Fax: (+45) 35351181; Email: alcl@sund.ku.dk

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ABSTRACT

Study Objectives: Impaired sleep has been linked to increased risk of cardiovascular disease (CVD), but the underlying mechanisms are still unsettled. We sought to determine how *onset* of impaired sleep affects the risk of established physiological CVD risk factors (i.e., hypertension, diabetes, and dyslipidemia).

Methods: In a longitudinal cohort study with 3 survey waves (2000, 2004, 2008) from the Finnish Public Sector study we used repeated information on sleep duration and disturbances to determine *onset* of impaired sleep. Information on development of CVD risk factors, as indicated by initiation of medication for hypertension, diabetes, and dyslipidemia was derived from electronic medical records within 8 years of follow-up. Data on 45,647 participants was structured as two data-cycles to examine the effect of change in sleep (between two waves) on incident CVD events. We applied strict inclusion and exclusion criteria to determine temporality between changes in sleep and the outcomes.

Results: While we did not find consistent effects of onset of short or long sleep, we found onset of disturbed sleep to predict subsequent risk of hypertension (hazard ratio = 1.22, 95% CI: 1.04-1.44) and dyslipidemia (HR = 1.17, 95% CI: 1.07-1.29) in fully adjusted analyses.

Conclusion: Results suggest that onset of sleep disturbances rather than short or long sleep mark an increase in physiological risk factors, which may partly explain the higher risk of CVD observed among impaired sleepers.

Keywords: diabetes; dyslipidemia; hypertension; impaired sleep; longitudinal study; mechanisms.

STATEMENT OF SIGNIFICANCE

Impaired sleep is among the most frequent complaints at the general practitioner. While a growing body of evidence an association between impaired sleep and cardiovascular health, less attention has been directed at detangling the underlying mechanisms, which is imperative for early preventive strategies.

We found onset of disturbed sleep to predict physiological CVD risk factors, which may partly explain the higher risk of CVD observed among impaired sleepers. Evaluation of habitual sleeping patterns may provide additional information in clinical cardiovascular risk assessment; by identifying people at higher risk of CVD.

Further, future studies could benefit from a larger focus on the importance of timing and changes in sleep in the likely didirectional assocaitions between sleep and disease.

INTRODUCTION

Cardiovascular disease (CVD) is the primary cause of death worldwide,[1] making identification of new modifiable risk factors a public health priority. While evidence supports an association between impaired sleep and CVD,[2] the underlying mechanisms are still unclear. It has been hypothesized that impaired sleep affects cardiac health through the development of diabetes, hypertension, and dyslipidemia,[3] conditions which themselves are associated with reduced quality of life and increased costs for the individual and society as a whole.[4-6]

Short-term experiments and cross-sectional studies have indicated adverse effects of impaired sleep on regulation of multiple body systems with detectable changes in glucose sensitivity,[7,8] blood pressure,[9,10] and blood lipid levels.[2] Prospective studies also generally support a higher risk of diabetes and hypertension among short sleepers,[8,10,11] while findings for blood lipids are scarce and conflicting.[2] A major limitation of these previous studies is that measures of sleep were only obtained once, not allowing direct assessment of the effect of *onset* of impaired sleep on *subsequent* risk of hypertension, diabetes, and dyslipidemia. Such temporal distinction is particularly important as the relationship between impaired sleep and these disorders may be bidirectional.

Our aim is to determine how *onset* of impaired sleep affects subsequent risk of hypertension, diabetes, and dyslipidemia building on repeated information on sleep and applying strinct predefined inclusion and exclusion criteria to ensure temporality between sleep and the outcomes.

MATERIALS AND METHODS

Study Population

Participants were derived from the Finnish Public Sector Study survey-cohort (FPSS), initiated in 1997-98 among public sector employees from 10 towns and 5 hospital districts, described in detail elsewhere.[12,13] Participants are continuously linked to comprehensive national drug reimbursement, health, and retirement registers through unique

personal identification codes assigned to all permanent Finnish residents. At approximately 4-year intervals, all employees working at the target organizations, and previous participants who have left the organizations, are invited to the survey-cohort. In 2000-02, the survey included items on sleep for the first time, and these have been included in every wave since. Our study includes information on participants from waves 2000-02 (response rate 68%), 2004-05 (response rate 67%), and 2008-09 (response rate 69%). The Ethics committees of Helsinki University Hospital and the Finnish Institute of Occupational Health approved the study protocol, and participants provided informed consent.

Study Design

To determine the effect of *onset* of impaired sleep, we examined the effect of changes in sleeping patterns between two successive waves. Development of hypertension, diabetes, and dyslipidemia was assessed between the second wave and end of follow-up December 31, 2011, from the registries. The three FPSS waves available enabled the construction of two data-cycles for analyses as depicted in Figure 1. Participants with data from all three waves could thus contribute observations to both data-cycles if they fulfilled the eligibility criteria presented below. Our approach is similar to those previously used to model HIV-progression, hormone therapy initiation, and lifestyle changes.[14-16]

At the beginning of each data-cycle we mimicked the selection procedure of eligible study participants applied in a clinical trial to assure that a change in sleep preceded development of the disease:

- *Inclusion criteria*: Participation in at least 2 successive waves and normal sleep at the first time-point. Normal sleep duration was defined as 7-8 h/night. In analyses of disturbed sleep, we defined normal sleep as having sleep complaints no more than once a week on average.
- *Exclusion criteria*: Having been hospitalised with a diagnosis of sleep apnea (Finnish ICD-9 code 3472A; ICD-10 G47.3) or having been hospitalized or treated for coronary heart disease or stroke (ICD10 I20.0, I21, I22, I46 and I60-I69) within 7 years of the

second time-point, T_{x+1}. In addition, we excluded those having been reimbursed for hypertension, diabetes, or medication for dyslipidemia within 7 years of the second time-point, T_{x+1}, in analysis of these outcomes, respectively. Participants with missing information on sleep or any of the covariates were also excluded.

This left us with a total study population of 37,486 women and 8,161 men, who contributed to one or both data-cycles. Non-responders of the FPSS survey-cohort were younger and more likely to be male and manual workers than participants.[12,13] These characteristics were shared by participants of only a single wave, who were not eligible for our study. In addition, single wave participants were less likely to have a normal sleep duration and undisturbed sleep than eligible participants of 2 successive waves.

Onset of Impaired Sleep

Habitual sleep duration was assessed from the surveys as the average hours of sleep in half-hour intervals (from ≤6 to ≥10). Sleep disturbances were assessed by the frequently used validated Jenkins Sleep Problem Scale,[17] including the average frequency (from 1 = never to 6 = every night) of: difficulties falling asleep, difficulties maintaining sleep, early morning awakenings, and non-restorative sleep. All symptoms correspond to the insomnia-symptoms specified by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Onset of disturbed sleep was assessed by creating an index (range 1-6) of the average frequency of the included sleep complaints. Due to the inclusion criteria, all participants had normal sleep at the first time-point, T_x, and onset of the various aspects of impaired sleep was defined as:

- *Onset of short sleep duration*: sleeping <7 h/night at time T_{x+1}.
- *Onset of long sleep duration*: sleeping ≥9 h/night at time T_{x+1}.
- *Onset of disturbed sleep*: reporting an average frequency of sleep complaints more than once weekly (index score ≥4) at time T_{x+1}, reflecting a clinically significant level of disturbed sleep.[18,19]

Hypertension, Diabetes, and Dyslipidemia

Using unique personal identification codes, participants were linked to the nationwide Prescription Register, which holds automated dispensing data on all outpatient reimbursed purchases of prescribed drugs in every Finnish pharmacy ensuring complete coverage for these records (excluding inpatient admissions).[20] The Finnish National Sickness Insurance scheme provides special reimbursement for many chronic diseases, including hypertension and diabetes. Entitlement is based on a detailed medical statement prepared by the treating physician confirming that the patient meet explicitly predefined diagnostic criteria.[21] Information on grated reimbursement is stored in the Central Reimbursement Register.

HYPERTENSION

We defined cases of hypertension at the time they were listed in the Central Reimbursement Register as being granted special reimbursement for treatment of chronic hypertension during follow-up. Entitlement was based on: repeated evidence of diastolic blood pressure >105 mm Hg, or diastolic pressure >95 mm Hg with cardiovascular comorbidities or signs of complications; or systolic pressure >200 mm Hg, after 6-month follow-up without pharmacological treatment and subsequent 6 months' pharmacological treatment.[21]

TYPE 2 DIABETES

Diabetes cases were defined at date of being granted special reimbursement for treatment for type-2 diabetes during follow-up. Confirmation of diabetes requires physician documented evidence of a fasting plasma glucose of ≥7.0 mmol/L, or a non-fasting plasma glucose of ≥11.1 mmol/L and symptoms of diabetes, e.g., polyuria, polydipsia, or glucosuria.[21]

DYSLIPIDEMIA

Treatment initiation of statins (ATC code C10AA) – the primary treatment for dyslipidemia – was used to identify cases of dyslipidemia at the date of first dispensed prescription during follow-up. In Finland, statins are available by prescription only.

Participants were linked to electronic medical records and followed from the second time-point until the date of the outcome of interest, death, or end of follow-up on December 31, 2011.

Covariates

Employers' records and national registers provided information on sociodemographic characteristics: sex, age, retirement, and occupational status (based on the International Standard Classification of Occupations-88).[22] Shift work was obtained by survey only for employees at the target organizations. Cohabitation and lifestyle factors were obtained by survey. Respiratory disorders (chronic obstructive pulmonary disease [COPD] and asthma) were defined as a primary diagnosis at hospitalization or granted special reimbursement for treatment within three years prior to the first time-point in each data-cycle. Cancer diagnoses were obtained from the Finnish Cancer Registry within 5 years prior to the first time-point in each data-cycle. Depression was obtained as a self-reported doctor-diagnosed depression and/ or a record of purchases of more than 30 defined daily doses (DDD) of antidepressant medication (ATC-code N06A) within 3 years prior to the first time-point in each data-cycle. Psychological distress was defined as ≥4 symptoms on the 12-item version of the General Health Questionnaire.[23] The 6-item Trait Anxiety Inventory was used to quantify subjective symptoms of anxiety.[24]

Statistical Analyses

With the FPSS-waves structured as 2 data-cycles, results of these were pooled to increase statistical power. We modelled the hazard ratio (HR) and corresponding 95% confidence intervals (CI) of the individual outcomes associated with onset of impaired sleep duration and disturbances in separate models (as shown in Fig. 2). Clustered proportional hazards Cox models with participant ID as the cluster variable were used to account for within-person correlation across data-cycles. Due to similarity of effects between the genders (Appendix 1) and the limited power to address effects among men, analyses were performed for

men and women together. Participants were followed from the date of the second time-point, T_{x+1}, until granted reimbursement for treatment of hypertension, diabetes, or filled prescription for statins, death, or end of follow-up in each data-cycle with "follow-up time," i.e., time from the second time-point as the underlying time-scale.

We tried to account for the lack of exchangeability between those with persistent normal sleep and those who experienced onset of impaired sleep between two waves by adjusting for potential confounders from the first time-point in each data-cycle. First, models including age (continuous) and sex were carried out. Second, additional potential confounders were added: cohabitation (yes/ no), occupational status (upper-grade non-manual, lower-grade non-manual, and manual workers), retirement (working, disability retirees, statutory retirees), smoking (never smoker, ex-smoker, smoker of 1-14 cigarettes/ day, 15-24 cigarettes/ day, >24 cigarettes/ day), alcohol consumption (abstainer, 1-16 units/ week, 17-24 units/week, >24 units/week), physical activity (>2 metabolic equvivalent task [MET] hours/day, ≤2 MET h/day), BMI (<18.5, 18.5-25, 25-30, ≥30), respiratory disease (no/ yes), and cancer (no/ yes). Lastly, models were further adjusted for psychological distress (no/ yes), depression (no/ yes), and anxiety (as the average response-category 1-4 continuously). Confounders were identified according to prior knowledge and the methods of directed acyclic graphs.[25]

In sensitivity analyses, we restricted the analyses to a healthy subsample without any of the outcomes or COPD, asthma, or cancer within 7 years prior to the second time-point, in order to reduce confounding arising from the effects of chronic disorders on both sleeping patterns and risk of subsequent disease. Similarly, we excluded participants with depression in a separate analysis. Reimbursement for chronic hypertension and diabetes requires repeated evidence of dysregulation and up to one year of lifestyle and pharmacological interventions, and analyses including a one-year lag-time were carried out to further reduce the risk of reverse causation. Since shift work (no/ yes) was not collected for participants who had left the study organizations adjustment for this was only performed in a sensitivity analysis. To minimize the effect of clinical sleep disorders, we further excluded participants using sleep medication

(ATC-code N05C) in a sensitivity analysis. As people may be prescribed sleep medication for purposes other than impaired sleep, e.g., for psychiatric disorders, and because they may experience impaired sleep despite taking sleep medication, these exclusion criteria were not applied in the main analysis. Lastly, to accommodate the potential effect of changing sleep duration irrespective of initial sleep duration, we conducted a sensitivity analysis examining the effect of shortening or prolonging sleep by ≥2 h/night, also including shifts to the extreme response categories of sleep duration (≤6 h/night and ≥10 h/night).

RESULTS

The study included 45,647 participants of at least 2 successive waves between 2000 and 2009. Data-cycle 1 included observations from 32,038 participants. The majority of these (n = 24,402) also contributed with observations to Data-cycle 2, which included a total of 38,011 participant-observations. This combined into a total of 70,049 participant-observations eligible for analyses.

The mean follow-up was 7 years in Data-cycle 1 and 3 years in Data-cycle 2. Among those with normal sleep duration at the first time-point, 13% experienced onset of short sleep and 3% onset of long sleep at the second time-point. Further, 10% of undisturbed sleepers experienced onset of disturbed sleep at the subsequent wave. During follow-up, 3% without prior hypertension were reimbursed for the disorder, 2% of non-diabetics were reimbursed for treatment of diabetes, and 9% without prior statin treatment filled at least one prescription for statins. Table 1 shows the baseline characteristics of the study population. The majority of participants were female (83%), reflecting the gender distribution of the source population, comprising Finnish public sector and hospital employees (77% women). Participants were between 18 and 69, with a smaller proportion of those with onset of short or disturbed sleep being younger than 40 years of age compared to persistent normal sleepers. Meanwhile, onset of long sleep was associated with a higher likelihood of being either younger than 40 years or 60 years or older. Compared to persistent normal sleepers, those with onset of impaired sleep

were more often manual workers, worked shifts, and had adverse lifestyle factors and more existing disorders.

Onset of Impaired Sleep and Risk of Hypertension

In age- and sex-adjusted analyses, onset of short sleep was associated with a higher risk of hypertension (HR=1.25, 95% CI: 1.06-1.47), as seen in Table 2. Additional adjustments for confounders, in particular BMI and lifestyle factors, attenuated this association. Compared to participants with persistent undisturbed sleep, those with onset of disturbed sleep had approximately 20% higher risk of developing hypertension within the following 8 years (HR = 1.22: 1.04-1.44 in the fully adjusted analysis). Onset of long sleep was not associated with later risk of hypertension (HR = 0.80: 0.55-1.17).

Onset of Impaired Sleep and Risk of Diabetes

Onset of impaired sleep did not markedly affect the risk of diabetes in fully adjusted analyses, and a higher risk associated with **onset of disturbed sleep** in the age- and sex-adjusted analyses **(HR=1.29, 95% CI: 1.09-1.53) was weakened and no longer apparent upon further adjustments (Table 2).** Similarly, the suggestive higher risks after onset of short or long sleep seen in the age- and sex-adjusted analyses disappeared upon further adjustment for confounders.

Onset of Impaired Sleep and Risk of Dyslipidemia

Compared to persistent normal sleep, onset of short or long sleep was not associated with the risk of dyslipidemia as seen in Table 2. Meanwhile, onset of disturbed sleep compared to persistent undisturbed sleep was assocated with a higher risk of dyslipidemia in the fully adjusted analysis (HR = 1.17: 1.07-1.29).

Sensitivity Analyses

Restricting the analyses to a healthy subsample did not alter the associations with of onset of disturbed sleep (Table 3). The results were also robust to: exclusion of participant-

observations with depression, exclusion of participants filling prescriptions for sleep medication, additional adjustment for shift-work and inclusion of a one-year lag-time (Table 4). Assessing at the effects of shortening or prolonging sleep by ≥2 h yielded results similar to the main analyses, except for a higher risk of diabetes after prolonging sleep (HR = 1.42: 0.99-2.03), which was not seen in the analysis looking at onset of long sleep (Appendix 2).

DISCUSSION

We analysed longitudinal observational data with strict temporal requirements in order to determine associations between *onset* of impaired sleep and *subsequent* risk of hypertension, diabetes, and dyslipidemia. We found onset of disturbed sleep to be associated with a higher risk of hypertension and dyslipidemia, while the associations observed with onset of short sleep was explained by BMI and underlying ill health. There were no clear associations between onset of impaired sleep and diabetes.

A recent randomized pilot trial showed that a nightly one-hour sleep extension among short sleepers over a six-week period resulted in lower blood pressure among 13 hypertensive patients.[26] We therefore hypothesized that onset of habitual short or long sleep might also affect risk of hypertension among healthy people. However, we found no effect of changes in sleep duration on hypertension, which is also in contrast with recent reviews supporting a cross-sectional association between sleep duration and hypertension.[9-11] This inconsistency may be due to problems with reversed causality in cross-sectional studies and the importance of strict temporal requirements as those applied in our study should be emphasized. On the other hand, we found a higher risk of hypertension among those with onset of disturbed sleep. In line with this, associations between symptoms of disturbed sleep and hypertension are generally supported in the literature – especially in combination with short sleep.[10,27-29]

Experimental studies generally support a negative effect of short-term sleep deprivation on glucose metabolism and insulin sensitivity.[7] Evidence of a U-shaped association between sleep duration and incidence of diabetes is supportet in previous meta-analyses.[8, 30] This association seems stronger in studies with a longer follow-up, and may be confined to

men.[8] However, these meta-analyses include studies with information on sleep at one time-point only, which hampers assessment of the effect of *changes* in sleep on diabetes risk. Looking at onset of impaired sleep, we found no convincing evidence of a relation between sleep and diabetes. These findings are in line with a recently published study from the Whitehall cohort, where a decrease in sleep duration was not associated with diabetes risk.[31] In a sensitivity analysis, we found a higher risk of diabetes among those who prolonged their sleep by at least 2 hours, suggesting effects of larger shifts in sleep duration rather than movements across a predefined cutoff for long sleep. This is also in agreement with findings from the Whitehall study, similarly showing a higher risk of diabetes in association with a ≥2-hour/ night increase in sleep duration. The results of our study may differ from previous findings due to the gender distribution of our study, comprising 84% women, which hampers direct assessment of gender differences supported in previous studies.[8] Further, the mean follow-up in our study was just 4.8 years. If effects of impaired sleep are indeed stronger with longer follow-up, we may have had insufficient power to detect weaker associations within a shorter timeframe. Our definition of impaired sleep as *onset* rather than prevalent impaired sleep may also have yielded insufficient induction time for effects of impaired sleep on diabetes risk.

Evidence on the association between impaired sleep and dyslipidemia is scant. Experimental studies generally show adverse effects of sleep restriction and fragmentation on lipid profiles in healthy volunteers.[32,33] Results from population studies have been conflicting and mostly comprised restricted samples.[2,32,34-37] We found a higher risk of dyslipidemia among participants with onset of disturbed sleep, while onset of short and long sleep did not predict dyslipidemia in fully adjusted analyses. In contrast to our findings, two cross-sectional studies have previously shown adverse lipid levels[38] and self-reported hypercholestrolemia[39] in women, but not men, with short or long sleep.

Limitations and Strengths

Systematic measurement of blood pressure, insulin sensitivity, and blood lipids in all participants would have been preferable, but is seldom attainable in large longitudinal studies.

However, legislation and economic incentives promote a high degree of completeness and accuracy of the recordings of dispensed prescription drugs.[20] Further, reimbursements for chronic hypertension and diabetes follow explicit protocols of clinical assessment, which reduce the risk of false-positives. Conversely, while strict clinical requirements ensure a high degree of specificity, sensitivity is comparatively low. Examination by a physician is required to be diagnosed, and diagnosed patients need to actively apply for reimbursement. Further, the partial out of pocket payment for statins may have precluded some patients from following assigned treatment. Hence, undiagnosed, untreated, and/ or unreimbursed cases will not be identified when relying solely on the register information. Further, detection may be socioeconomically patterned. If we assume that lower socioeconomic status is associated with onset of impaired sleep (as suggested in Table 1) and also with a lower likelihood of seeking medical assistance and subsequent reimbursement as well as being less likely to purchase prescribed medication, this misclassification may have resulted in conservative estimates of the relations.

Another source of detection bias may occur if participants with impaired sleep are more likely to see a doctor and consequently of having an underlying condition detected. If so, the causal relation may be weaker than reflected in our analyses. Whereas reimbursement for hypertension and diabetes rely on specific diagnostic criteria, the information on statins does not include the indication for prescription, which is not limited to dyslipidemia. Rather, statins are prescribed as a general precaution for individuals considered at high risk of CVD.[40] So, while the use of the universal drug reimbursement system in Finland and availability of statins by prescription only ensures comprehensive data on statin purchases,[41] perhaps this betters reflects a more general cardiac risk marker than dyslipidemia per se.[4] However, being among the first large-scale studies on the association between impaired sleep and dyslipidemia, our study provides new information which adds to current cardiovascular sleep research.

We assessed sleep using self-report, which is the most common method in large-scale research; self-reported information on sleep also forms the basis for diagnosing insomnia in

sleep clinics.[18] While objective sleep recordings using, e.g., polysomnography would have yielded more accurate measures of sleep duration, these are seldom available in large cohort studies, such as ours. There is great heterogeneity concerning the operationalization of disturbed sleep across studies. We applied insomnia-related symptoms to reflect a clinically significant level of impaired sleep.[18,19] In the FPSS, a strong correlation between self-reported disturbed sleep and prescribed sleep medication (ATC-code N05C) has previously been reported.[12] Meanwhile, other studies have used more global questions of general sleep quality or sleep dissatisfaction, which may contribute to differences in results across studies. Similarly, some studies have examined associations with more extreme levels of short and long sleep than applied here, and stronger associations may have been expected had we addressed more severe levels of impaired sleep.

Participants with underlying sleep disorders may be of concern, and although we excluded participants hospitalized with sleep apnea, this is an underdiagnosed disorder and only a fraction of cases are hospitalized.[42] To address this issue, we further excluded participants taking sleep medication. This did not materially alter the results, and we doubt that underlying sleep disorders explain the associations seen in our study. Another matter concerns our operationalization of normal sleep. While our operationalisation of disturbed sleep is based on established definitions of insomnia,[18,19] the choice to define the optimal sleep duration as 7-8 hours/night can be debated. There is no clinically agreed upon optimal sleep duration, although the lowest risk of cardiovascular disease is often observed in this sleep range.[43] While the majority of study participants report sleep duration within this range, there will be individuals for whom shorter or longer sleep duration would reflect an optimal sleep length. As determination of the optimal sleep duration at an individual level is not feasible we relied on 7-8 hours/night as being the range most likely to capture the optimal sleep duration for the majority of study participants. To capture the effect of changing sleep duration for the normal short and long sleepers, we conducted a sensitivity analysis looking at the effect of shortening and prolonging sleep duration at least 2 hours, irrespective of initial sleep duration. These

results proved very similar to those of the main analysis, except for the higher risk of diabetes followed by prolonging sleep, which was not apparent in the main analyses.

The major strengths of our study comprise the high statistical power and the use of repeat measurements of sleep, enabling determination of the association with *onset* of impaired sleep. Further, use of nationwide registers to determine initiation of treatment for chronic hypertension and diabetes as well statins initiation, confer strengths of our study.

Conclusion

We found *onset* of disturbed sleep to be associated with a higher risk of hypertension and dyslipidemia within seven years of follow-up. Meanwhile modest or no associations with hypertension, diabetes, and dyslipidemia were observed for onset of short or long sleep. This suggests that onset of sleep disturbances rather than short or long sleep mark an increase in physiological risk factors for CVD.

Figure legends

Figure 1. Measurement time-points for the two data-cycles. T_x, Participants with normal sleep and without the preexisting outcome in question; T_{x+1}. Onset of impaired sleep was measured and participants were still without the outcome in question.

Figure 2. Flowchart showing the selection of eligible participant-observations for the individual analyses *Participants from the town of Tampere are not linked to the prescription register, hence no information on statins. Observations in the white boxes are those that are excluded and shaded boxes those who are included in the analyses.

Abbreviations

ATC: Anatomical Therapeutic Chemical Classification System

BMI: Body mass index

CI: Confidence interval

COPD: Chronic obstructive pulmonary disease

CVD: Cardiovascular disease

DDD: Defined daily doses

FPSS: Finnish Public Sector Study

H: hours

HR: Hazard ratio

ICD: International Classification of Diseases

IR: Incidence rate

MET: Metabolic equivalent task

mm Hg: millimeter of mercury

n: number

OSA: Obstructive sleep apnea syndrome

SD: Standard deviation

yrs: years

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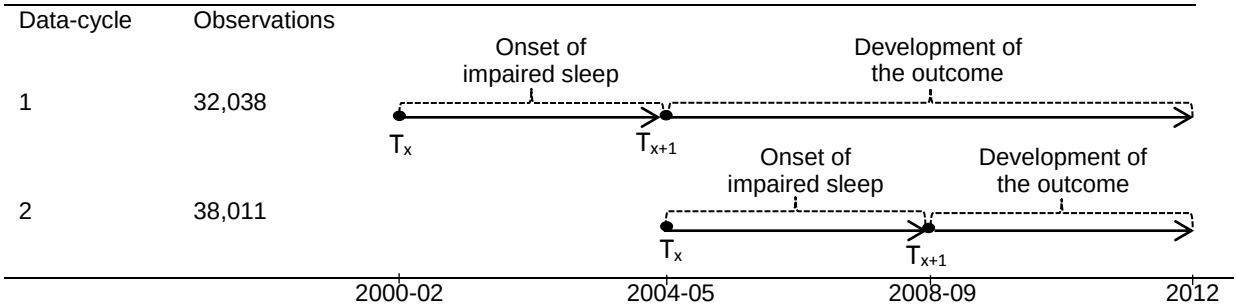

Figure 1 Measurement time-points for the two data-cycles. T_x, Participants with normal sleep and without the pre-existing outcome in question; T_{x+1}, Onset of impaired sleep was measured and participants were still without the outcome in question.

Table 1. Baseline characteristics of the 70,049 participant-observations from the Finnish Public Sector Study according to sleep duration and disturbed sleep

	All observations	Sleep duration			Disturbed sleep	
		Onset of short sleep (<7 h/night)	Persistent normal sleep (7-8 h/night)	Onset of long sleep (≥9 h/night)	No	Onset of disturbed sleep
	70,049	6,641	43,235	1,616	53,955	6,008
Women, n (%)	57,947 (83)	5,421 (82)	36,120 (84)	1,414 (88)	44,197 (82)	5,154 (86)
Age <40, n (%)	18,504 (26)	1,594 (24)	12,455 (29)	503 (31)	15,601 (29)	1,259 (21)
Age 40-60, n (%)	47,723 (68)	4,764 (72)	28,521 (66)	968 (60)	35,510 (66)	4,480 (75)
Age ≥ 60, n (%)	3,822 (5)	283 (4)	2,259 (5)	145 (9)	2,844 (5)	269 (4)
Shift work[a], n (%)	21,686 (33)	2,161 (34)	12,620 (31)	592 (39)	16,423 (32)	1,974 (35)
Manual workers, n (%)	9,292 (13)	1,081 (16)	4,856 (11)	202 (13)	6,745 (13)	923 (15)
Living alone, n (%)	16,320 (23)	1,585 (24)	9,511 (22)	434 (27)	12,187 (23)	1,462 (24)
Stress[b], n (%)	17,136 (24)	1,794 (27)	9,032 (21)	396 (25)	9,808 (18)	1,818 (30)
Depression[c], n (%)	9,411 (13)	919 (14)	5,093 (12)	329 (20)	5,378 (10)	1,059 (18)
Mean trait anxiety (SD)	1.9 (0.6)	2.0 (0.6)	1.9 (0.5)	1.9 (0.6)	1.8 (0.5)	2.0 (0.5)
Physically inactive[d], n (%)	16,558 (24)	1,591 (24)	9,464 (22)	421 (26)	12,109 (22)	1,564 (26)
Smokers, n (%)	10,926 (16)	1,191 (18)	6,002 (14)	221 (14)	8,152 (15)	1,079 (18)
High risk alcohol intake[e], n (%)	5,792 (8)	580 (9)	3,412 (8)	135 (8)	4,124 (8)	567 (9)
Obese[f], n (%)	8,403 (12)	880 (13)	4,659 (11)	221 (14)	6,047 (11)	802 (13)
Previous hypertension, n (%)	6,350 (9)	649 (10)	3,478 (8)	173 (11)	4,367 (8)	634 (11)
Previous diabetes, n (%)	1,363 (2)	141 (2)	745 (2)	46 (3)	965 (2)	131 (2)
Previous dyslipidaemia[g], n (%)	5,728 (10)	511 (9)	3,275 (9)	184 (13)	9,988 (9)	537 (11)
Respiratory disorders[h], n (%)	2,624 (4)	259 (4)	1,524 (4)	96 (6)	1,845 (3)	271 (5)
Cancer, n (%)	1,283 (2)	118 (2)	765 (2)	42 (3)	909 (2)	156 (3)

[a]Among the 64,275 participants working at the target organizations at baseline. [b]≥4 symptoms on the 12-item General Health Questionnaire. [c]Self-reported diagnosis of depression and/or register record of > 30 defined daily doses of anti-depressant medication (ATC codes N06A) in the 3 years prior to baseline. [d]≤2 metabolic equivalent task hours/day. [e]>16 units/week for women and >24 units/week for men. [f]Body mass index≥30. [g]Among the 59,336 participants with information on statins. [h]Asthma and/or chronic obstructive pulmonary disease. n, number; SD, standard deviation.

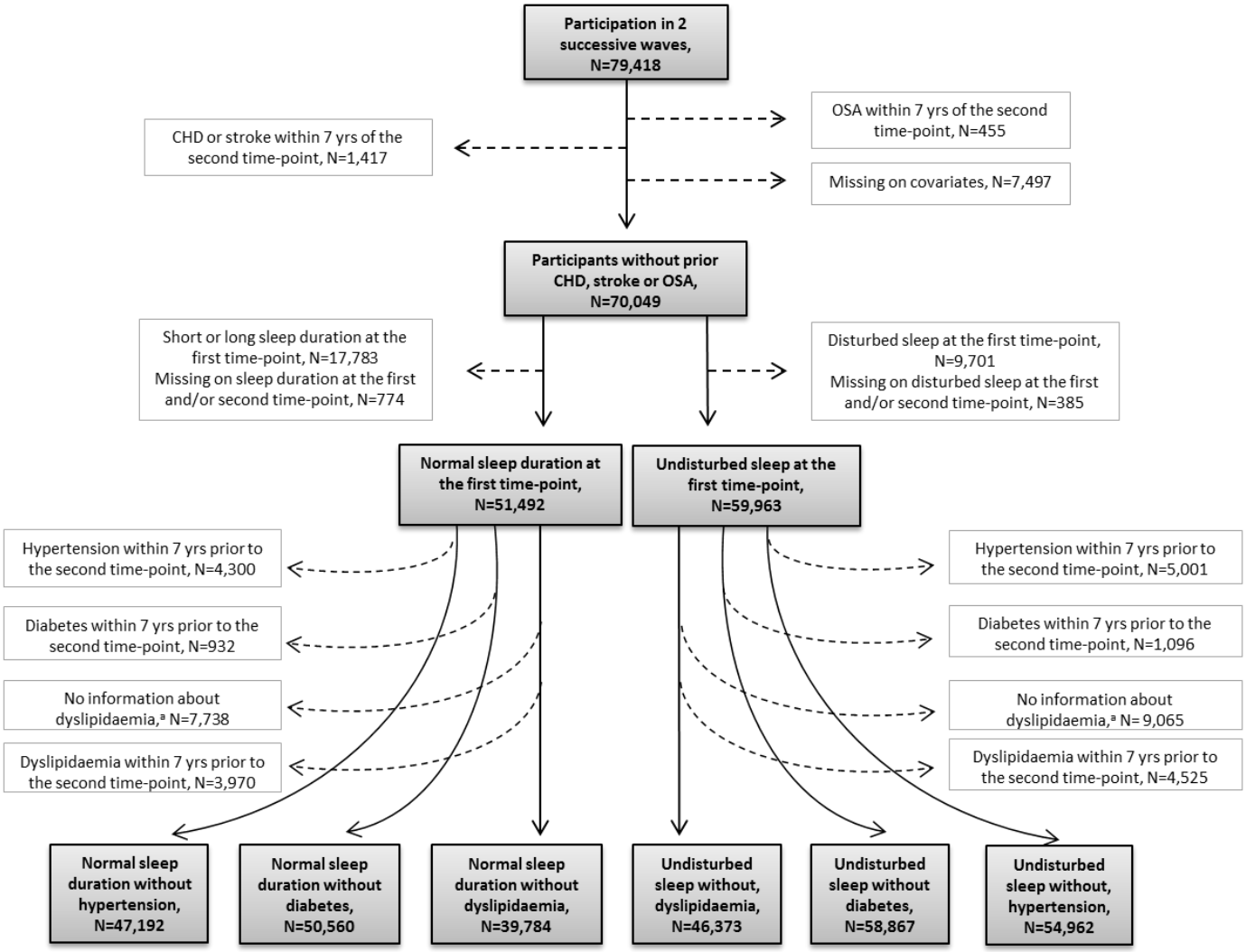

Figure 2 – Flowchart showing the selection of eligible participant-observations for the individual analyses. Observations in the white boxes are those that are excluded and shaded boxes those who are included in the analyses. [a] Participants from the town of Tampere are not linked to the prescription register, hence no information on statins.

Table 2. Onset of impaired sleep and hazard ratios for hypertension, diabetes, and dyslipidemia among 70,049 participant-observations

	Number of cases	IR/ 100,000 yr.	Age- & sex-adjusted HR (95% CI)	Multiple Adjusted[a] HR (95% CI)	+ Mental health adjusted[b] HR (95% CI)
Hypertension					
Sleep duration					
Onset of short sleep (<7 h/night)	177	622	1.25 (1.06-1.47)	1.15 (0.98-1.35)	1.13 (0.96-1.33)
Persistent normal sleep (7-8 h/night)	924	484	1 (ref.)	1 (ref.)	1 (ref.)
Onset of long sleep (≥9 /night)	28	411	0.87 (0.60-1.27)	0.80 (0.55-1.17)	0.80 (0.55-1.17)
Disturbed sleep					
No	1,165	489	1 (ref.)	1 (ref.)	1 (ref.)
Onset of disturbed sleep	180	687	1.35 (1.16-1.59)	1.26 (1.07-1.47)	1.22 (1.04-1.44)
Diabetes					
Sleep duration					
Onset of short sleep (<7 h/night)	157	504	1.15 (0.97-1.37)	1.01 (0.85-1.20)	0.99 (0.83-1.18)
Persistent normal sleep (7-8 h/night)	850	414	1 (ref.)	1 (ref.)	1 (ref.)
Onset of long sleep (≥9 h/night)	40	540	1.34 (0.97-1.85)	1.13 (0.82-1.57)	1.11 (0.80-1.54)
Disturbed sleep					
No	1,053	411	1 (ref.)	1 (ref.)	1 (ref.)
Onset of disturbed sleep	161	555	1.29 (1.09-1.53)	1.15 (0.97-1.36)	1.12 (0.95-1.33)
Dyslipidaemia					
Sleep duration					
Onset of short sleep (<7 h/night)	511	2,173	1.08 (0.98-1.19)	1.03 (0.94-1.14)	1.02 (0.93-1.12)
Persistent normal sleep (7-8 h/night)	2,958	1,914	1 (ref.)	1 (ref.)	1 (ref.)
Onset of long sleep (≥9 h/night)	120	2,082	1.10 (0.91-1.32)	1.05 (0.88-1.26)	1.03 (0.85-1.23)
Disturbed sleep					
No	3,631	1,868	1 (ref.)	1 (ref.)	1 (ref.)
Onset of disturbed sleep	545	2,559	1.27 (1.16-1.39)	1.21 (1.10-1.32)	1.17 (1.07-1.29)

[A]Adjusted for age, sex, cohabitation, occupational class, retirement, smoking, alcohol, BMI, physical activity, respiratory disorders (COPD and asthma) and cancer. [b]+ Additional adjustment for stress, depression, and anxiety. CI, confidence interval; HR, hazard ratio; IR, incidence rate; ref., reference; yr, year.

Table 3. Onset of impaired sleep and hazard ratios for hypertension, diabetes, and dyslipidemia in a healthy subsample[a] of 45,954 participant-observations

	Number of cases	IR/ 100,000 yr.	Age- & sex-adjusted HR (95% CI)	Multiple adjusted[b] HR (95% CI)	+ Mental health adjusted[c] HR (95% CI)
Hypertension					
Sleep duration					
Onset of short sleep (<7 h/night)	107	517	1.23 (1.00-1.51)	1.14 (0.93-1.40)	1.12 (0.91-1.38)
Persistent normal sleep (7-8 h/night)	571	407	1 (ref.)	1 (ref.)	1 (ref.)
Onset of long sleep (≥9 h/night)	20	396	1.02 (0.65-1.59)	0.95 (0.61-1.49)	0.95 (0.61-1.49)
Disturbed sleep					
No	732	416	1 (ref.)	1 (ref.)	1 (ref.)
Onset of disturbed sleep	111	590	1.35 (1.11-1.65)	1.28 (1.04-1.56)	1.24 (1.01-1.53)
Diabetes					
Sleep duration					
Onset of short sleep (<7 h/night)	60	287	1.12(0.85-1.48)	0.99 (0.75-1.30)	0.97 (0.74-1.28)
Persistent normal sleep (7-8 h/night)	341	241	1 (ref.)	1 (ref.)	1 (ref.)
Onset of long sleep (≥9 h/night)	13	255	1.16 (0.67-2.03)	0.98 (0.56-1.73)	0.97 (0.55-1.71)
Disturbed sleep					
No	447	252	1 (ref.)	1 (ref.)	1 (ref.)
Onset of disturbed sleep	54	283	1.06 (0.80-1.41)	0.97 (0.73-1.29)	0.96 (0.72-1.28)
Dyslipidaemia					
Sleep duration					
Onset of short sleep (<7 h/night)	366	1,837	1.04 (0.93-1.16)	1.00 (0.90-1.12)	0.99 (0.88-1.10)
Persistent normal sleep (7-8 h/night)	2,274	1,675	1 (ref.)	1 (ref.)	1 (ref.)
Onset of long sleep (≥9 h/night)	88	1,799	1.11 (0.90-1.38)	1.07 (0.86-1.33)	1.04 (0.84-1.29)
Disturbed sleep					
No	2,770	1,623	1 (ref.)	1 (ref.)	1 (ref.)
Onset of disturbed sleep	400	2,233	1.26 (1.14-1.41)	1.21 (1.08-1.34)	1.16 (1.04-1.30)

[a]Without prior diabetes, hypertension, dyslipidaemia, respiratory disorders, or cancer, also excluding participants from Tampera witout information on statins. [b]Adjusted for age, sex, cohabitation, occupational class, retirement, smoking, alcohol, BMI, and physical activity. [c]+ Additional adjustment for stress, depression, and anxiety. CI, confidence interval; HR, hazard ratio; IR, incidence rate; ref., reference; yr, year.

Table 4. Sensitivity Analyses – onset of impaired sleep and hazard ratios for hypertension, diabetes, and dyslipidemia

	Sleep duration			Disturbed sleep	
	Onset of short sleep (<7 h/night)	Persistent normal sleep (7-8 h/night)	Onset of long sleep (≥9 h/night)	No	Onset of disturbed sleep
Participants without depression[a]					
Hypertension					
No. of cases	155	798	23	1,037	149
IR/100,000 years	629	470	409	479	684
Adjusted[b] HR (95% CI)	1.17 (0.99-1.40)	1 (ref.)	0.84 (0.55-1.27)	1 (ref.)	1.25 (1.05-1.49)
Diabetes					
No. of cases	134	708	27	922	126
IR/100,000 years	496	388	444	397	524
Adjusted[b] HR (95% CI)	1.05 (0.87-1.27)	1 (ref.)	1.05 (0.71-1.56)	1 (ref.)	1.13 (0.94-1.37)
Dyslipidemia					
No. of cases	414	2,496	86	3,148	439
IR/100,000 years	2,025	1,810	1,791	1,781	2,483
Adjusted[b] HR (95% CI)	1.01 (0.91-1.12)	1 (ref.)	0.98 (0.79-1.22)	1 (ref.)	1.21 (1.09-1.34)
Participants without prescription of sleep medication[c]					
Hypertension					
No. of cases	173	891	28	1,139	174
IR/100,000 years	632	480	427	487	701
Adjusted[d] HR (95% CI)	1.16 (0.98-1.36)	1 (ref.)	0.83 (0.57-1.22)	1 (ref.)	1.26 (1.06-1.48)
Diabetes					
No. of cases	146	810	39	1,022	151
IR/100,000 years	487	407	549	407	551
Adjusted[d] HR (95% CI)	0.97 (0.81-1.16)	1 (ref.)	1.16 (0.83-1.62)	1 (ref.)	1.14 (0.95-1.35)
Dyslipidaemia					
No. of cases	483	2,799	110	3,498	496
IR/100,000 years	2,146	1,868	1,990	1,839	2,476
Adjusted[d] HR (95% CI)	1.04 (0.94-1.15)	1 (ref.)	1.01 (0.84-1.23)	1 (ref.)	1.16 (1.05-1.28)
Working population with additional adjustment for shift-work[e]					
Hypertension					
No. of cases	170	897	28	1,131	172
IR/100,000 years	627	494	436	497	685
Adjusted[f] HR (95% CI)	1.12 (0.95-1.32)	1 (ref.)	0.83 (0.57-1.21)	1 (ref.)	1.20 (1.01-1.41)
Diabetes					
No. of cases	149	798	38	989	156
IR/100,000 years	502	409	546	404	561
Adjusted[f] HR (95% CI)	1.01 (0.84-1.20)	1 (ref.)	1.17 (0.84-1.64)	1 (ref.)	1.15 (0.97-1.37)
Dyslipidaemia					
No. of cases	488	2,787	110	3,438	524
IR/100,000 years	2,192	1,906	2,028	1,864	2,580
Adjusted[f] HR (95% CI)	1.04 (0.94-1.14)	1 (ref.)	1.00 (0.82-1.21)	1 (ref.)	1.17 (1.07-1.29)
Including a 1 yr lag-time					
Hypertension					
No. of cases	142	705	18	903	139
IR/100,000 years	632	467	335	478	666
Adjusted[b] HR (95% CI)	1.20 (1.00-1.44)	1 (ref.)	0.68 (0.42-1.09)	1 (ref.)	1.23 (1.02-1.48)
Diabetes					
No. of cases	138	739	35	912	141
IR/100,000 years	559	454	599	448	609
Adjusted[b] HR (95% CI)	1.00 (0.83-1.21)	1 (ref.)	1.14 (0.80-1.61)	1 (ref.)	1.14 (0.95-1.37)
Dyslipidaemia					
No. of cases	386	2,296	94	2,810	427
IR/100,000 years	2,095	1,890	2,074	1,837	2,544
Adjusted[b] HR (95% CI)	1.00 (0.89-1.11)	1 (ref.)	1.06 (0.86-1.30)	1 (ref.)	1.18 (1.06-1.31)

[a]Excluding participant-observations with self-reported doctor-diagnosed depression and/or a national health register record of purchases of more than 30 defined daily doses of anti-depressant medication (ATC codes N06A) in the three years prior to baseline. [b]Adjusted for age, sex, pseudo-trial no., follow-up, cohabitation, occupational class, retirement, smoking, alcohol, BMI, physical activity, respiratory disorders (COPD and asthma), cancer, stress, depression, and anxiety. [c]Excluding participants with ≥30 defined daily doses of sleep medication within 3 years of baseline. [d]Adjusted for age, sex, pseudo-trial no., follow-up, cohabitation, occupational class, retirement, smoking, alcohol, BMI, physical activity, stress, and anxiety. [e]Excluding retired participants and participants no longer employed at the project organizations. [f]Adjusted for age, sex, pseudo-trial no., follow-up, cohabitation, occupational class, smoking, alcohol, BMI, physical activity, stress, depression, anxiety, and shift work. CI, confidence interval; HR, hazard ratio; IR, incidence rate; No., number; ref., reference.

Appendix 1. Onset of impaired sleep and hazard ratios for hypertension, diabetes, and dyslipidemia among 12,102 male and 57,947 female participant-observations

	Sleep duration			Disturbed sleep	
	Onset of short sleep (<7 h/night)	Persistent normal sleep (7-8 h/night)	Onset of long sleep (≥9 h/night)	No	Onset of disturbed sleep
Women					
Hypertension					
No. of cases	125	717	21	874	142
IR/100,000 years	533	446	345	443	623
Adjusted[a] HR (95% CI)	1.05 (0.87-1.28)	1 (ref.)	0.70 (0.45-1.09)	1 (ref.)	1.17 (0.98-1.41)
Diabetes					
No. of cases	110	668	29	770	126
IR/100,000 years	430	388	340	364	503
Adjusted[a] HR (95% CI)	0.92 (0.75-1.12)	1 (ref.)	0.95 (0.65-1.39)	1 (ref.)	1.15 (0.95-1.40)
Dyslipidemia					
No. of cases	403	2,340	103	2,819	458
IR/100,000 years	2,045	1,757	1,964	1,711	2,428
Adjusted[a] HR (95% CI)	1.04 (0.93-1.16)	1 (ref.)	1.04 (0.85-1.27)	1 (ref.)	1.10 (0.87-1.38)
Men					
Hypertension					
No. of cases	52	207	7	291	38
IR/100,000 years	1046	690	958	704	1113
Adjusted[a] HR (95% CI)	1.37 (1.00-1.88)	1 (ref.)	1.29 (0.60-2.78)	1 (ref.)	1.41 (0.99-2.03)
Diabetes					
No. of cases	47	182	11	283	35
IR/100,000 years	840	553	1361	629	888
Adjusted[a] HR (95% CI)	1.24 (0.89-1.72)	1 (ref.)	1.78 (0.87-3.64)	1 (ref.)	1.03 (0.72-1.48)
Dyslipidaemia					
No. of cases	108	618	17	812	87
IR/100,000 years	2,837	2,893	3,263	2,740	3,574
Adjusted[a] HR (95% CI)	0.94 (0.76-1.17)	1 (ref.)	1.01 (0.64-1.60)	1 (ref.)	1.18 (1.07-1.31)

[A]Adjusted for age, cohabitation, occupational class, retirement, smoking, alcohol, BMI, physical activity, respiratory disorders (COPD and asthma), cancer, stress, depression, and anxiety. CI, confidence interval; HR, hazard ratio; IR, incidence rate; ref., reference; yr, year.

Appendix 2. ≥2 hour/night change in sleep and hazard ratios for hypertension, diabetes, and dyslipidemia among 70,049 participant-observations

	Number of cases	IR/ 100,000 yr.	Age- & sex-adjusted HR (95% CI)	Multiple Adjusted[a] HR (95% CI)	+ Mental health adjusted[b] HR (95% CI)
Hypertension					
Shortening sleep[c]	116	659	1.28 (1.06-1.54)	1.16 (0.96-1.40)	1.14 (0.95-1.38)
Stable sleep duration	1340	503	1 (ref.)	1 (ref.)	1 (ref.)
Prolonging sleep[d]	18	525	0.99 (0.62-1.58)	0.88 (0.55-1.40)	0.86 (0.54-1.38)
Diabetes					
Shortening sleep[c]	107	547	1.19 (0.98-1.45)	1.00 (0.82-1.22)	0.99 (0.81-1.20)
Stable sleep duration	1261	438	1 (ref.)	1 (ref.)	1 (ref.)
Prolonging sleep[d]	31	838	1.85 (1.30-2.64)	1.46 (1.02-2.10)	1.42 (0.99-2.03)
Dyslipidaemia					
Shortening sleep[c]	333	2,263	1.10 (0.98-1.23)	1.03 (0.92-1.15)	1.01 (0.91-1.14)
Stable sleep duration	4,253	1,969	1 (ref.)	1 (ref.)	1 (ref.)
Prolonging sleep[d]	72	2,677	1.24 (0.98-1.58)	1.18 (0.93-1.50)	1.12 (0.88-1.42)

[A]Adjusted for age, sex, cohabitation, occupational class, retirement, smoking, alcohol, BMI, physical activity, respiratory disorders (COPD and asthma) and cancer. [b]+ Additional adjustment for stress, depression, and anxiety. [c] ≥ 2 hours/night from the first to the second time-ponit, also including shifts to the extreme response category of short sleep duration (≤6 hours/night). [d] ≥2 hours/night from the first to the second time-ponit, also including shifts to the extreme category of long sleep duration (≥10 hours/night). CI, confidence interval; HR, hazard ratio; IR, incidence rate; ref., reference; yr, year.