Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Public Health and Nursing

Samir Chalise

THE JOINT EFFECT OF INSOMNIA WITH SHORT SLEEP DURATION AND LEISURE-TIME PHYSICAL ACTIVITY ON THE RISK OF CARDIOVASCULAR AND ALL-CAUSE MORTALITY (THE HUNT STUDY)

Master's thesis in Msc. Global Health
Supervisor: Eivind Schjelderup Skarpsno
Co-supervisor: Mats Flaaten
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Samir Chalise

ABSTRACT

Introduction: Previous studies indicate that insomnia with short sleep duration is associated with a significantly increased risk of all-cause and cardiovascular mortality. However, no previous study has investigated whether leisure-time physical activity modifies this association. The aim of this study was therefore to investigate if leisure-time physical activity modifies the association between insomnia with short sleep duration and all-cause and cardiovascular mortality.

Methods: This prospective study included 40,368 adults who participated in the second survey of the HUNT study in 1995-1997. The study population comprised adults aged ≥20 years who responded to questionnaires on lifestyle, socio-demographics, insomnia symptoms, and sleep duration. Cox regression was used to estimate adjusted hazard risks (HRs) with 95% confidence interval (CI) for the association of insomnia, sleep duration, and leisure-time physical activity with all-cause and cardiovascular mortality.

Results: Among 40,376 adult participants included in the study, 5,223 (12.9%) had insomnia symptoms and 6.9% reported short sleep duration. During a 17-year follow-up period, 6686 participants died (2575 due to cardiovascular disease). Compared to the reference category of physically active people without insomnia symptoms and normal sleep duration, people with insomnia with short sleep had an HR for all-cause mortality of 1.86 (95% CI 1.38-2.50) if they were physically inactive and an HR of 1.19 (95% CI 0.94-1.29) if they were physically active. Physically inactive people without insomnia and normal sleep duration had an HR of 1.16 (95% CI 1.02-1.34). The corresponding HRs for cardiovascular mortality were 1.78 (95% CI: 1.10-2.41), 1.26 (95% CI: 0.69-1.87), and 1.05 (95% CI 0.53-1.68); respectively.

Conclusion: This study shows that meeting recommended levels of physical activity modified some of the increased risks of all-cause and cardiovascular mortality among participants with insomnia accompanied by short sleep duration. These findings suggest that promoting physical activity could reduce adverse health effects outcomes of insomnia with short sleep duration.

Keywords: insomnia; sleep duration; leisure-time physical activity; all-cause mortality; cardiovascular mortality

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ABBREVIATIONS

BMI	Body Mass Index
CHD	Coronary Heart Diseases
CI	Confidence Interval
CVD	Cardiovascular Disease
DAG	Directed Acyclic Graph
EM	Expectation Maximization Method
HUNT	The Trøndelag Health Study
HUNT2	Second Trøndelag Health Study
HPA	Hypothalamic-Pituitary Axis
HADS	Hospital Anxiety and Depression Scale
HR	Hazard Ratio
ICSD	International Classification of Sleep Disorders criteria
ICD-10	International Classification of Disease, Tenth Revision
LTPA	Leisure-Time Physical Activity
REK	Regionale komiteer for medisinsk og helsefaglig forskningsetikk
SPSS	Statistical Package for Social Sciences
UK	United Kingdom
US	United States

1. INTRODUCTION

1.1 Background

1.1.1 Definition and prevalence of Insomnia

Insomnia is defined as the subjective perception of difficulty with sleep initiation or maintaining sleep, which occurs despite adequate opportunity for sleep, and results in some form of daytime impairment. (1). Insomnia is linked to significant reductions in a person's quality of life (2) and could be a sign of a variety of psychiatric, medical, and/or other sleep conditions (3). International Classification of Sleep Disorders criteria (ICSD-3) published in 2014 is the most widely used guide for diagnosing sleep disorders, which classifies insomnia into two categories: short-term insomnia disorders and chronic insomnia disorders (1). Short-term (acute) insomnia may cause increased stress responsivity, reduced quality of life, mood disruption, and difficulties with concentration and memory (4). Chronic insomnia may cause even more adverse health effects such as mood disorders, cardiovascular disease (CVD), chronic pain, pulmonary disease, and gastrointestinal disorders (5).

Insomnia is more common in the elderly (6), women (7), and people who have physical or mental health problems (8). Even though chronic insomnia is common, studies on its actual prevalence have yielded variable estimates. Epidemiological studies show that 20% to 35% of the general population report insomnia symptoms, with 10% to 20% having clinically significant insomnia symptoms (5). Not surprisingly, the prevalence appears to be higher in clinical settings with more than half of the patients visiting their general practitioner reporting insomnia symptoms (9). Recent data from Norway, the United Kingdom (UK), and Germany show that the prevalence of insomnia is around 10% (8). Due to differing definitions of insomnia and standardized diagnostic and screening methods, the estimate for prevalence varies among epidemiologic studies.

1.1.2 Insomnia symptoms on risk of cardiovascular mortality

The Trøndelag health study (HUNT) was one of the first large prospective population studies to link insomnia symptoms with CVDs: heart failure (10), coronary heart disease (CHD) (11), and hypertension (12). Prospective data demonstrate that there is a higher incidence risk of subclinical CVD (13) and cardiovascular mortality (14, 15) among patients with insomnia. A 10-year cohort study on 500,000 thousand million adults in China suggests that insomnia symptoms are associated with an increased risk of CVD (16). Several potential mechanisms underpin the relationship between insomnia symptoms and CVD. For instance, some evidence suggests that insomnia symptoms have an integral role in intermediary processes of CVD, such as increases in pro-inflammatory biomarkers (17) and systematic inflammation (18), and downregulation of the hypothalamic-pituitary axis (HPA) (19, 20) Chronic insomnia is thought to be linked to increases in sympathetic nervous system activity and hormones such as cortisol, which is responsible for hyperarousal and sleeplessness which in the long-term raises the risk of death (21, 22). Another explanation could be linked to the close interplay between insomnia symptoms and mental illness. Various findings suggest that sleep-related symptoms that occur before, during, or after a depressive episode are potentially modifiable factors that can help people achieve and maintain depression remission (23). For instance, although insomnia is sometimes thought to be a side effect of depression or other affective disorders, there is evidence that chronic activation of HPA due to insomnia may also play a role in incident depression (24), which can contribute to enhancing CVD risk on its own (25).

Despite consistent links between insomnia and subsequent health conditions, evidence on the association between different insomnia symptoms and mortality is diverse and inconsistent. Most population-based studies have established the longitudinal association of insomnia with mortality risk (26-29). In some studies, a weaker association was observed, or the associations were reduced after adjustments (30, 31). A meta-analysis of 13 prospective cohort studies showed

that insomnia was associated with an approximately 45% increased risk of dying from cardiovascular disease (28). Another meta-analysis of 17 cohort studies found that people with insomnia had a 33 percent higher relative risk of cardiovascular death (32).

1.1.3 Sleep duration on risk of all-cause and cardiovascular mortality

The effect of sleep duration on mortality has been the main finding of a few prospective studies, which have shown a U-shaped relationship between sleep duration and all-cause mortality (30, 33-35). Other studies, on the other hand, have found inconsistent results (36, 37) or no link at all (38). A number of these studies have looked at the relationship between sleep duration and cardiovascular mortality (30, 36, 37). A large prospective study done on women showed that sleeping for less than 6 hours or more than 7 hours is linked to a higher risk of death (39). Data from a cohort of working Scottish men and women recruited between 1970 and 1973 suggests that short sleep (less than 7 hours of sleep in every 24 hrs) over a prolonged period can be associated with an increased risk of all-cause mortality (36).

1.1.4 Insomnia with short sleep duration and its associated risk

Most studies have conceptualized insomnia and sleep duration as different traits, without considering the close overlap between these sleep traits. Insomnia with short sleep duration has been associated with cardiovascular and cerebrovascular disease (35, 40, 41), type 2 diabetes (42, 43), hypertension (21, 44, 45), respiratory disorders (46), poor self-rated health (47), and may increase the risk of mortality (48). In patients with insomnia, both adrenocorticotropic hormone and cortisol secretion are elevated, especially in those with objectively short sleep duration, implying increased HPA activity (17, 19, 20) and increased neurocognitive–physiological arousal (17, 19, 49), which is particularly accountable to CVD. Most epidemiological studies have looked at each exposure separately, but some research suggests that the co-occurrence of insomnia and objectively short sleep duration is the biologically most severe phenotype of insomnia disorder

(50). A handful of studies have looked at the combined effect of insomnia with sleep duration on mortality risk (51-54). Vgontzas et al. showed that chronic insomnia in men with objectively measured short sleep duration is linked to an increased risk of all-cause death (52). This was supported by findings from the Whitehall II Cohort Study showing that the joint effect of short and disturbed sleep was associated with a higher risk of CVD mortality among women (51). A Sleep Heart Health Study from the US established that insomnia or poor sleep with objectively short sleep was linked to an increased risk of incident CVD but not for all-cause mortality(53). In contrast, a smaller study done on middle-aged Chinese adults showed that frequent insomnia was linked to a higher risk of all-cause mortality among those sleeping more than 9 hours per night, but not among those with short sleep duration (54). Some of the disparity in the results could be explained by a difference in the measurement of insomnia and sleep duration (subjective vs polysomnography) (55)

1.1.5 Potential modifying role of leisure-time physical activity on the associated risks

Physical inactivity has been linked to an increased risk of several chronic diseases, including CVD, type 2 diabetes, and certain cancers (56). Self-reported leisure-time physical activity (LTPA) does have an inverse dose-response relationship with all-cause and cardiovascular mortality (57). A prospective study showed that a high level of physical activity improves cardiovascular health by lowering the overall risk of CHD and stroke in men and women by 20 to 30% (58). Increased physical activity has repeatedly been associated with reduced mortality and cardiovascular disease (59, 60).

Physical activity and sleep are believed to have a bidirectional relationship, whereas both acute and regular physical activity can improve sleep where as appropriate sleep duration and quality may likewise influence physical activity behavior (61). Variations in body temperature and glucose metabolism, autonomic nervous system activity, mood, and cardiorespiratory fitness are

some mechanisms affected by physical activity which are thought to affect sleep (62, 63). Few studies have hinted at the possible synergistic interaction between two closely associated behaviors like physical activity and sleep on all-cause and cardiovascular mortality(64, 65). Findings from a Finnish cohort study indicate that people with short sleep and inadequate LTPA have an increased risk of cardiovascular mortality (58). There is also evidence indicating that regular physical activity improves sleep quality, which in turn may reduce the risk of other adverse health outcomes (65-67). Some studies have hinted at the mediating effect of physical activity on the relationship between short sleep and CVD and all-cause mortality (68, 69) but the interrelationship between physical activity and insomnia with short sleep duration on mortality has not been considered till date. Thus, this is the first study to explore if leisure time physical activity modifies the adverse effect of insomnia with short sleep duration on the risk of all-cause and cardiovascular mortality.

1.2 Objectives and research questions

This study aims to investigate the effects of insomnia symptoms with subjective sleep duration on the risk of mortality and to explore whether leisure-time physical activity modifies these associations. In specific, the research questions for this master's thesis are:

1. Is the joint effect of leisure-time physical activity with insomnia with short sleep duration associated with all-cause and cardiovascular mortality?

2. Does meeting recommended levels of leisure-time physical activity modifies some of the increased risks of all-cause and cardiovascular mortality among participants with insomnia accompanied by short sleep duration?

2. MATERIALS & METHODS

2.1 Study population & data collection

This study utilizes data from a large comprehensive population-based research project in Nord-Trøndelag County, Norway called the Trøndelag Health Study (the HUNT Study) (70, 71). Data from the second survey of the HUNT study (HUNT2) which took place in 1995-97 was used for this study. The reason for selecting HUNT2 in our study was because the information on sleep duration was not available in other surveys of HUNT study. All residents above the age of 20 were invited to take part in the survey. Of the approximately 93,000 individuals invited to participate in the HUNT2 survey, 65,393 took part in the study (response rate: 70%).

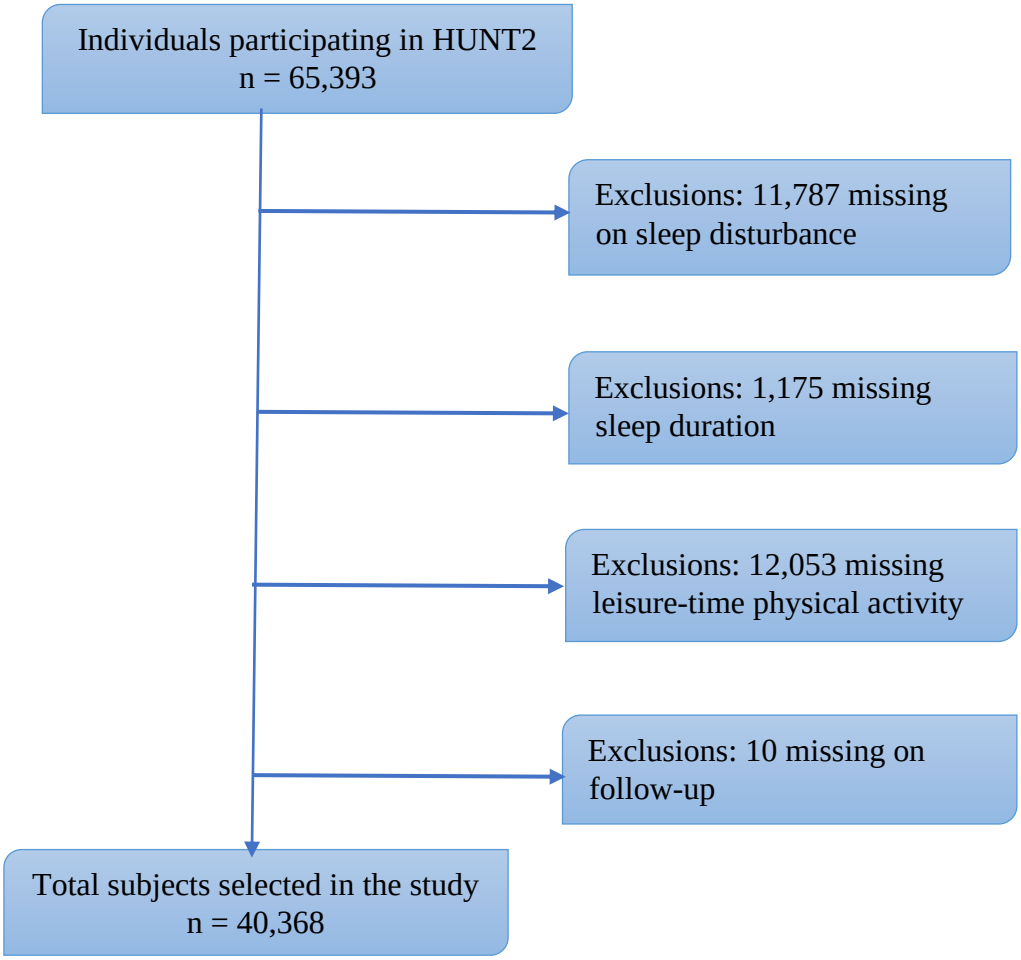

Figure 1 Selection of the study population in HUNT2

Participants in this study were chosen based on their attendance and completion of the questionnaire. Data collection and clinical examinations (height and body weight) were performed by trained health professionals (71). The study population comprised participants with complete information on sleep difficulty assessment, self-reported sleep measurements, and subjective leisure-time physical activity measures. 25,025 participants were excluded from the study due to their missing information (11,787 participants on sleep disturbance, 1,175 participants on sleep duration, 12,053 participants on leisure-time physical activity, and 10 participants on follow-up). Data collection was done in two separate questionnaires which may be the reason for many missing data. As a result, this prospective analysis uses data from 40,368 participants. **(Figure 1)**

2.2 Insomnia and sleep duration as an exposure variable

Insomnia symptoms in our study were accessed by two questions related to persistent sleep difficulty which were asked during the HUNT2 survey. (1) 'How often during the last month have you had difficulty falling asleep at night?' and (2) 'How often during the last month have you woken too early and couldn't get back to sleep?' These two questions had the response options 'never', 'occasionally', 'often', and 'almost every night. Participants were classified with 'insomnia' if they answered 'often/almost every night' on at least one of the questions. Those who answered 'never/occasionally' were classified as having 'no insomnia'.

Sleep duration in HUNT2 was accessed by the question 'How many hours do you usually spend lying down for 24 hours (e.g., sleeping, napping)?' Sleep duration was classified into three categories based on the previous literature and studies (72): ≤ 6 hours (short sleep), 7-8 hours (normal sleep), and ≥ 9 hours (long sleep) with the extremes representing short and long sleep duration. We determined 7-8 hours (normal sleep) as the reference category in our study, which was identified as the most-used reference category in the systematic review by Cappuccio et al (72).

2.3 Leisure time physical activity in HUNT2

At HUNT2, the following question was used to measure LTPA: ‘How much of your leisure time have you been physically active during the last year (think of a weekly average for the year)?'. Participants were asked to provide a weekly average number of hours of light physical activity and/or hard physical activity while answering this question with the response options: 'none', 'less than 1 hr, '1–2 hr', and '≥3 hr' separately for light and hard activity. Participants were categorized into two levels of leisure-time physical activity (i.e., 'inactive’ and ‘active’) according to the recommended guideline for physical activity in HUNT2 (73), i.e., Accumulation of ≥ 150 min/week (≥3 h) of moderate physical activity or ≥ 60 min/week of vigorous physical activity (1–2 h) was defined as meeting recommended physical activity and categorized as ‘active’ while not achieving these recommendations was categorized as ‘inactive’.

2.4 Assessment of covariates

All covariates’ data were collected during baseline in HUNT2. Body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2) using standardized measurements of height and weight from the clinical examination. Smoking status was assessed by questions about past or present use of cigarettes/pipe/cigars and divided into three categories: ‘never smoked’, ‘former smoker’, and ‘current smoker’. Education was assessed by the question: 'What is your highest level of education?', and divided into '< 10 years', '10 to 12 years, and '≥13 years'. Alcohol consumption was assessed by the question: 'How many units of beer, wine or spirits do you usually drink over 14 days?'. Participants were then divided into three groups: '0 units', '1–4 units', and '≥5 units. Symptoms of anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS) with a cut-off score of ≥ 8 on both anxiety and depression. As recommended, the cut-off score was set to ≥8 on both anxiety and depression to indicate the presence of anxiety and/or depression (74). Anxiety and/or depression were then divided into two

categories: ‘yes’ for participants with anxiety and/or depression’ and ‘no’ for participants without both anxiety and depression. History of CVD was assessed by questions if they answered, ‘yes’ on at least one of the questions ‘do you have or have you had any of the following diseases: myocardial infarction, stroke and/or angina’. History of diabetes was assessed by questions on if they answered, 'yes' to the question ‘do you have or have you had any of the diabetes Mellitus. History of hypertension was accessed by the question ‘are you currently taking, or have you previously taken any medication for high blood pressure?’ and divided into two groups; ‘yes’ and ‘no’. Occupational physical activity was defined based on the self-reported description of work demands and was categorized into four groups: ‘sedentary work’, ‘much walking, ‘much walking or lifting’, and ‘heavy physical work’. Shift work was defined as ‘do you work shifts, at night, or on call’ and was divided into two groups: ‘no’, and ‘yes’.

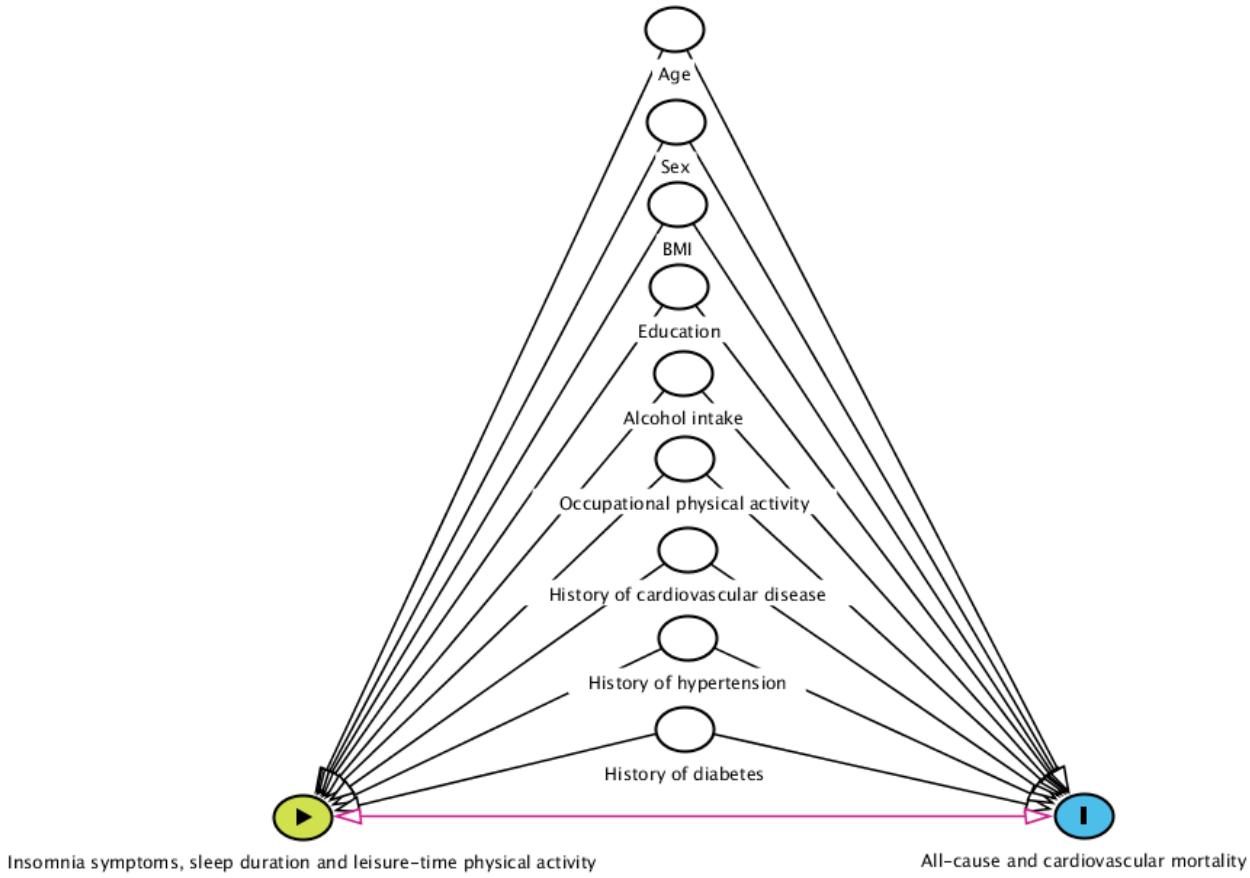

Figure 2: A directed acyclic graph (DAG) depicts the relationship between exposure and outcome, considering possible covariate confounding.

2.5 Outcome variables

Participants in the HUNT Study were linked to Statistics Norway's, Norwegian Cause of Death Registry to examine incident cases of death in the cohort prospectively. Underlying causes of death were coded according to the International Classification of Disease, Tenth Revision (ICD-10). and the number of fatalities from CVD (ICD-10 codes: I00-I99) was determined (75). From the start of HUNT2 until death, emigration, or the end of follow-up on December 31st, 2013, each participant contributed person-years. In the analyses of cardiovascular mortality, participants were censored at the end of the trial as well as at the date of death from other causes. A summary of both exposure and outcome variables used in the analysis of this study with their definition and description is given in **supplementary table 1**.

2.6 Statistical analysis

Descriptive statistics were calculated for the analytical sample of total participants (n = 40,368) and stratified by insomnia symptoms. Data were analysed using Cox regression models to estimate hazard ratios (HR) to estimate the association of insomnia and sleep duration with all-cause and cardiovascular mortality. We also looked at their joint effect with LTPA. 95% confidence intervals (CI) were used to assess the precision of HR. Physically active participants without insomnia symptoms and normal sleep duration served as the reference category in the analysis. Using directed acyclic graphs, potential confounders were identified based on existing knowledge of risk factors for sleep disturbance and premature death. All associations were adjusted for age (using age as the time scale in the model), sex, BMI, education, smoking status, alcohol intake, occupational physical activity, history of CVD, history of hypertension, and history of diabetes due to their plausible confounding relationship with exposure and outcome variables **(Figure 1)**.

To ensure that the findings were reliable, sensitivity analyses were performed: first, we excluded the first three years of follow-up to avoid potential death events occurring due to pre-existing illness (reverse causation). Second, we excluded participants with a history of CVD at baseline (for cardiovascular mortality only) to avoid reverse causation. Third, we conducted complete case analyses where missing data on possible confounders were imputed. We used the Expectation Maximization Method (EM) for data imputation. Anxiety and/or depression and shift work were left out of the main analyses because they are assumed to have a mediator effect and could induce interaction bias in the association between insomnia and mortality, these variables were adjusted in sensitivity analysis, Lastly, we ran the analysis for the association of sleep duration with all-cause and cardiovascular mortality by categorizing sleep duration into eight categories based on one-hour sleep difference to ensure that the cut-offs used in this study were reasonable **(Supplementary tables 3-6)**. The proportional hazards assumption was tested using Kaplan-Meier estimation and graphical inspection of log-log plots which showed no obvious violations violation of the proportional hazard assumption for the variables. All statistical analyses were performed using SPPS statistics for Windows, version 27.

2.7 Ethical considerations

Before participation, all individuals signed a written informed consent form. The research was carried out as a sub-study with the permission of the Regional Committee for Medical Research Ethics (REK 2014/1116). Data was received from the HUNT Research Centre after the agreement for the use of HUNT data. When the data was received, it was anonymized by removing personal identifying numbers and names. Because the HUNT Research Centre had all the data needed for the current analysis, no HUNT participants were contacted for extra data collection (see **Appendix B**).

3. RESULTS

3.1 Baseline characteristics of the study population

Among 40,368 participants who were included in this study, 20,955 (51.9%) of them were female. The mean age and mean BMI of the study participants were 47.3±16.3 years and 26.2±3.9 kg/m^2, respectively. The total number of deaths that occurred during 17 years of follow-up (655,463 person-years) was 6,686 The mortality rate was higher among males (20.2%) as compared to females (13.2%). Among total events, 2,575 of them died due to underlying CVD (38.5% of total deaths) and 2,050 died of cancer.

Table 1 shows the baseline characteristics of the study population stratified by the presence of insomnia symptoms (insomnia and no insomnia). From the table, 5,223 of the total participants had reported insomnia symptoms. Most participants reported having normal sleep (68.2%) followed by long sleep (24.9%) and short sleep (6.9%) **(supplementary table 2)**.

3.2 Combined association of exposures with mortality

Table 2 shows the joint association of insomnia and sleep duration with all-cause and cardiovascular mortality. The reference group comprised participants with no insomnia and normal sleep duration. Compared to the reference group, participants with insomnia had an HR of dying from all-cause mortality of 1.43 (96% CI: 1.25-1.62) if they reported short sleep and an HR of 1.20 (95% CI: 1.05-1.30) if they reported long sleep duration. The corresponding HRs for cardiovascular mortality were 1.34 (95% CI: 1.08-1.60) for participants reporting short sleep and 1.19 (95% CI: 1.01-1.40) for long sleep.

3.3 Modifying role of physical activity

Table 3 shows the combined effect of insomnia, sleep duration, and LTPA on all-cause and cardiovascular mortality. Physically active participants without insomnia symptoms and normal

sleep served as the reference category. Compared to this reference category, people with insomnia with short sleep had an HR of all-cause mortality of 1.86 (95% CI 1.38-2.50) if they were inactive and an HR of 1.19 (95% CI 0.94-1.46) if they were physically active. Physically inactive people without insomnia and normal sleep duration had an HR of 1.16 (95% CI 1.02-1.34). The HR estimates for all-cause deaths among people with insomnia with long sleep were 1.49 (95% CI 1.28-1.80) if they were inactive and 1.20 (95% CI 0.68-1.74) if they were active.

As compared with reference subjects, participants with insomnia with short sleep were associated with cardiovascular mortality with HR of 1.78 (95% CI: 1.10-2.41) among inactive participants and HR of 1.26 (95% CI: 0.69-1.87) among active participants during the study follow-up. Physically inactive people without insomnia and normal sleep duration had an HR of 1.05 (95% CI 0.53-1.68). The HR estimates for cardiovascular mortality among people with insomnia with long sleep were 1.31 (95% CI 1.01-1.72) if they were inactive and 1.17 (95% CI 0.55-1.84) if they were active. We observed significant p-values for the interaction between leisure-time physical activity and all-cause and cardiovascular mortality ($p<0.001$ and $p<0.001$; respectively). Hence, we observed effect modification by leisure-time physical activity on the risk of all-cause and cardiovascular mortality caused by insomnia with short sleep duration

-

Table 1: Baseline characteristics of participants with and without insomnia symptoms

Characteristics	Overall	Insomnia	
		No	Yes
Participants, n (%)	40,368	35,145 (87.1)	5223 (12.9)
Female, n (%)	20955 (48.1)	17861 (50.8)	2129 (40.8)
Age (years), mean (SD)	47.3(16.3)	46.3(16.1)	53.5(16.6)
BMI (kg/m^2), mean (SD)	26.2(3.9)	26.1(3.9)	26.4(4.2)
13+ years of education, n (%)	9396 (23.3)	8527 (24.3)	869 (16.6)
Current smoker, n (%)	10952 (27.4)	9303 (26.8)	1649 (32.0)
≥5 units of alcohol intake, n (%)	6891 (28.7)	6107 (29.0)	784 (26.6)
History of CVD, n (%)	2597 (6.4)	1968 (5.6)	629 (12.0)
History of diabetes, n (%)	967 (2.4)	774 (2.2)	193 (3.7)
History of hypertension, n (%)	4618 (11.4)	3652 (10.4)	966 18.5)
Anxiety and/or depression, n (%)	5273 (14.3)	3649 (11.3)	1624 (35.3)
Sedentary work, n (%)	10572 (26.2)	9312 (26.5)	1260 (24.1)
Shift work, n (%)	6480 (21.3)	5781 (21.4)	699 (20.6)

*Data are given as a total number of subjects (column percentage) or mean ± standard deviation.

Table 2: Joint association between insomnia and sleep duration with all-cause and cardiovascular mortality over 17 years of follow-up

Exposures	Person years	Death	Age-adjusted, HR	Multi-adjusted HR* (95% CI)
All-cause mortality				
No insomnia				
7-8h sleep	406693	2771	1.00 (Reference)	1.00 (Reference)
≤6h sleep	36374	244	1.06 (0.92-1.20)	1.05 (0.86-1.23)
≥9h sleep	131057	2296	1.17 (1.10-1.24)	1.16 (1.07-1.26)
Insomnia				
7-8h sleep	50170	643	1.07 (0.97-1.16)	1.06 (0.93-1.21)
≤6h sleep	9125	140	1.51 (1.27-1.79)	1.43 (1.25-1.62)
≥9h sleep	21044	592	1.23 (1.12-1.34)	1.20 (1.05-1.30)
Cardiovascular mortality				
No insomnia				
7-8h sleep	406693	992	1.00 (Reference)	1.00 (Reference)
≤6h sleep	36374	73	0.84 (0.66-1.07)	0.83 (0.65-1.06)
≥9h sleep	131057	970	1.17 (1.07-1.29)	1.14 (1.06-1.22)
Insomnia				
7-8h sleep	50170	241	1.03 (0.89-1.18)	1.07 (0.87-1.30)
≤6h sleep	9125	53	1.48 (1.12-1.95)	1.34 (1.08-1.66)
≥9h sleep	21044	247	1.16 (1.00-1.33)	1.19 (1.01-1.60)

HR: Hazard ratio, CI: confidence interval

*Adjusted for age, sex, BMI, education, smoking status, alcohol intake, LTPA, history of diabetes, history of CVD, history of hypertension, and occupational physical activity

Table 3: Joint association between insomnia and sleep duration with all-cause and cardiovascular mortality and effect modification by LTPA over 17 years of follow-up

Exposures	Leisure-time physical activity								P-value
	Active				Inactive				
	Person years	Death	Age-adjusted HR	Multi-adjusted* HR [a] (95% CI)	*Person year*	Death	Age-adjusted HR	Multi-adjusted* HR (95% CI)	
All-cause mortality									
No insomnia + 7-8h sleep	237680	1565	1.00 (Reference)	1.00 (Reference)	169013	1208	1.30 (0.99-1.69)	1.16 (1.02-1.34)	
No insomnia + ≤6h sleep	20512	108	0.97 (0.80-1.19)	0.94 (0.70-1.23)	15862	136	1.18 (1.03-1.52)	1.39 (1.17-1.61)	<0.001
No insomnia + ≥9h sleep	74723	1108	1.16 (1.07-1.24)	1.16 (1.03-1.28)	56334	1188	1.40 (1.30-1.52)	1.36 (1.22-1.52)	
Insomnia + 7-8h sleep	27423	330	1.12 (1.03-1.20)	1.10 (0.93-1.23)	22747	313	1.20 (1.06-1.35)	1.21 (1.02-1.45)	
Insomnia + ≤6h sleep	4821	56	1.08 (0.95-1.20)	1.19 (0.94-1.46)	4303	84	1.90 (1.52-2.31)	1.86 (1.38-2.50)	
Insomnia + ≥9h sleep	10106	224	1.27 (1.07-1.51)	1.20 (0.68-1.74)	10939	368	1.40 (1.24-1.57)	1.49 (1.28-1.80)	
CVD-mortality									
No insomnia + 7-8h sleep	237680	557	1.00 (Reference)	1.00 (Reference)	169013	435	1.17 (0.90-1.41)	1.05 (0.53-2.34)	
No insomnia + ≤6h sleep	20512	34	0.89 (0.62-1.23)	0.91 (0.62-1.25)	15862	39	0.94 (1.28-1.64)	0.88 (0.86-1.61)	<0.001
No insomnia + ≥9h sleep	74723	441	1.09 (1.04-1.33)	1.05 (0.87-1.24)	56334	529	1.45 (1.28-1.64)	1.41 (1.16-1.64)	
Insomnia + 7-8h sleep	27423	108	0.93 (0.75-1.14)	0.92 (0.88-1.26)	22747	133	1.33 (1.07-1.57)	1.31 (1.01-1.73)	
Insomnia + ≤6h sleep	4821	18	1.15 (0.68-1.30)	1.26 (0.69-1.23)	4303	35	2.03 (1.44-2.86)	1.78 (1.10-2.41)	
Insomnia + ≥9h sleep	10106	86	1.16 (0.69-1.78)	1.17 (0.55-1.42)	10939	181	1.33 (1.10-1.58)	1.31 (1.01-1.72)	

HR: Hazard ratio, CI: confidence interval

*Adjusted for age, sex, BMI, education, smoking status, alcohol intake, history of diabetes, history of CVD, history of hypertension, and occupational physical activity

3.5 Sensitivity analysis

In the additional analyses, when we excluded individuals who died during the first 3 years of follow-up, we observed some changes to some of the estimates. A small increment in the risk estimates was seen, particularly with the association of cardiovascular mortality. Excluding individuals with a history of cardiovascular disease at baseline increased the estimates for cardiovascular mortality marginally. In complete case analyses, where missing data were imputed, we observed some minor changes in the risk estimates. When adjusting for anxiety and/or depression and work shift, we observed essentially small changes to the estimates**.** We ran the analysis by categorizing sleep duration into one-hour cut-offs and observed the risk of dying from all-cause and cardiovascular mortality was highest among the participants who reported long sleep of >11 hours **(Supplementary Table 3-7)**

4. DISCUSSION

4.1 Main findings

This large prospective study examined the joint effect of insomnia, sleep duration and physical activity on all-cause and cardiovascular mortality. Insomnia with short sleep duration was associated with an increased risk of all-cause and cardiovascular mortality, but the risk was modified by LTPA. These findings suggest that meeting recommended levels of physical activity modifies some of the increased risks of all-cause and cardiovascular mortality among participants with insomnia accompanied by short sleep duration.

4.2 Comparison to past literature

4.2.1 Independent and joint association of insomnia and sleep duration with mortality

Several population-based studies have investigated the longitudinal association of insomnia with total mortality risk (51, 54, 76-78). Our results were consistent with the findings from a meta-analysis of twenty-nine prospective cohort studies study in which having insomnia was associated with a moderate risk of all-cause mortality among adults (79). We observed a weaker association of insomnia with cardiovascular mortality. The link between insomnia symptoms and mortality can be explained by some underlying mechanism where insomnia symptoms can raise the level of c-reactive protein in the liver, causing systemic inflammation and leading to mortality risk in a long-term course (18, 80).

Our study indicates that insomnia symptoms with subjective short sleep duration are associated with a particularly increased risk of all-cause and cardiovascular mortality. Our findings are supported by a cohort study done in the UK, which found that short sleep with disturbed sleep was linked to a higher risk of CVD mortality in women (51). Moreover, another study showed that insomnia with objective short sleep duration was associated with an increased risk of mortality (52). In contrast, a study based on polysomnographic measures of sleep found no association between insomnia or poor sleep with objective short sleep and mortality (53). The mechanism behind the increased risk of death among participants with insomnia with shorter sleep may be related to an increase in comorbidities, caused by increased HPA activity and increased neurocognitive–physiological arousal which is particularly accountable to CVD (81). Interestingly, when we considered short sleep as an independent exposure to cardiovascular mortality risk, we found no increased risk. However, when we examined the joint association between insomnia symptoms and short sleep, we found a strong association. Additionally,

insomnia with long sleep duration was associated with a moderate risk of all-cause and CVD mortality.

4.2.2 Modifying role of leisure-time physical activity

Our study is the first study to examine the potential effect of modification by leisure-time physical activity on the risk of all-cause and cardiovascular mortality caused by insomnia with short sleep duration. Most research has shown that increasing physical activity or fitness levels over time lowers the risk of cardiovascular and all-cause mortality (57-60). Compared to participants meeting recommended level of physical activity, we found that participants with 'insomnia and short sleep' were 86% and 78% more likely to die from all-cause and CVD, respectively, if they reported being physically inactive. In contrast, people with 'insomnia and short sleep' were a 19% and 26% increased risk of all-cause and CVD mortality if they reported being physically active. Our findings are the first to show that physical inactivity may exacerbate the risks of short sleep duration and insomnia symptoms on mortality. A 15-year follow-up cohort study manifested that physical activity has a crucial role in reducing some of the mortality risks associated with sleep difficulty (82). Our finding is backed up by a large population-based Australian cohort that looked at the relationship between sleep and mortality risk and considered potential interaction by lifestyle behaviors such as physical inactivity and sedentary behavior. Their results showed that when sleep was the only factor considered, short sleep was found to be marginally linked to all-cause mortality but when potential effect modification by physical inactivity was considered, short sleep duration was strongly linked to all-cause and cardiovascular mortality (83).

These findings suggest that meeting recommended levels of physical activity (≥ 150 min/week of moderate-to-vigorous physical activity or ≥ 60 min/week of vigorous physical activity) may help to mitigate the negative health effects of irregular sleeping insomnia with short sleep. It has been established that insufficient sleep duration is linked to obesity, inflammation, and negative

cardiovascular outcomes (72, 84, 85) and sleep disturbances are risk factors for depression and dementia (23-25). While it is also known that higher levels of physical activity, on the other hand, are linked to lower rates of depression, cognitive decline, obesity, and CVD (56, 58, 86). The reason behind the modifying risk of LTPA on the associated risk of mortality among participants with insomnia with short sleep may be related to health-related benefits of physical activity which can reduce some of the mortality risks associated with poor sleep patterns, while physical inactivity may increase the risks associated with short sleep duration.

When we considered the interplay of LTPA on the association between insomnia with long sleep duration and all-cause and cardiovascular mortality, not meeting recommended levels of activity interacted with these associations and alleviated risk estimates particularly of all-cause mortality. Although, being physically active during leisure time had minimum interaction with these associations. From the results, we found that insomnia with long sleep duration is associated with an increased risk of all-cause and CVD mortality. Several studies have shown that insomnia with longer sleep duration seems to be is associated with a higher risk of all-cause mortality (33-35, 40). Although, publications explaining the mediating effect of physical inactivity on the association between insomnia with long sleep duration and all-cause mortality have not been published. The potential explanation for increased risk among people with insomnia with a long sleep and physical inactivity may be detrimental effects resulting from inactivity during leisure time which may have exacerbated these associations. Another explanation could be associated with residual confounding and comorbidities associate with longer periods of sleep (87), which can partly explain the exaggerated risk of all-cause mortality when confound with low physical activity (87).

4.3 Strengths and limitations of the study

The strengths of the current study include the large sample size that enabled us to carry out joint analyses of insomnia symptoms, sleep duration, and physical activity; linkage to the Norwegian Cause of Death Registry which contains information on all deaths; the long follow-up period with few losses to follow-up; and the possibility to adjust for several confounders.

The study has several limitations: we cannot rule out the possibility of residual confounding from factors that were unmeasured or poorly measured. People had to be alive, residing in their homes, and be willing to participate to provide data on long-term changes in sleep and leisure-time physical activity, and some of these selection mechanisms may have resulted in a healthy participant bias. Another limitation is the assessment of self-reported physical activity which is subjected to measurement error and misclassification. Nonetheless, self-reported data is thought to be sufficient for categorizing people into broad categories such as inactive/active (88). Another limitation may be related to the misclassification of insomnia symptom because insomnia symptom at HUNT2 was accessed by the two questions related to persistent sleep difficulty. No information about the frequency or severity criteria of insomnia, frequent nocturnal awakenings, and daytime impairment or distress was available at HUNT2. Moreover, we were unable to include objective sleep duration and polysomnographic measurements of sleep. Previous research, on the other hand, suggests that self-reported sleep duration and polysomnography measurements are in good agreement (86). We could not control for obstructive sleep apnoea and restless legs syndrome, sleep disorders with a well-established link to medical morbidity and mortality. Finally, we observed very few cases in some of the categories of insomnia with sleep duration. It may be difficult to decide whether these associations are sufficient to trust its statistical power and the confidence interval of risk estimates.

5. CONCLUSION

This study shows that meeting recommended levels of physical activity modifies some of the increased risk of all-cause and cardiovascular mortality among participant with insomnia accompanied by short sleep duration. Thus, these findings suggest that there is an effect modification by leisure-time physical activity on the association of sleep-related behaviors with mortality. These findings suggest that physical activity should receive particular attention in clinical sleep interventions and public health guidelines.

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7. SUPPLEMENTARY TABLES

Summary of exposure and outcome variables

Supplementary table 1: Summary of exposure and outcome variables

Variables	Definition	Description
Insomnia symptoms*	No insomnia (responded with 'never' and 'occasionally' on persistent sleep difficulty for last month)	Independent variable (Exposure)
	Insomnia (responded 'often', and 'almost every night' on persistent sleep difficulty for last month)	
Sleep duration (categorical variable)	Short sleep (≤6 hrs) Average sleep (7 to 8 hrs) Long sleep (≥9 hrs)	Independent variable (Exposure)
Leisure-time physical activity	Active (achieving recommended level i.e., minimum 150 minutes moderate-intensity/week, or vigorous-intensity activity of 60 minutes/week)	Independent variable (Exposure)
	Inactive (not achieving recommended level i.e., minimum 150 minutes moderate-intensity/week, or vigorous-intensity activity of 60 minutes/week)	
All-cause mortality (Total death)	Total death event from the end of study (HUNT2) to follow up in 2013	Dependent variable (Outcome)
Cardiovascular mortality	Total death events due to CVD from the end of study (HUNT2) to follow up in 2013	Dependent variable (Outcome)

Accessed at baseline HUNT2

***Supplementary table 2*: Baseline characteristics of participants stratified by self-reported sleep duration**

Characteristics	Sleep duration (hours/day)		
	Short (≤6h)	**Normal (7 - 8h)**	**Long (≥9h)**
Participants, n (%)	2780 (6.9)	27544 (68.2)	10044 (24.9)
Female, n (%)	1183 (42.6)	14045 (51.0)	5727 (57.0)
Age, mean (SD)	45.1 (15.3)	45.7 (14.9)	52.2 (19.4)
BMI, mean (SD)	26.3 (4.0)	26.1 (3.9)	26.4 (4.2)
13+ years of Education, n (%)	499 (17.9)	7098 (25.8)	1799 (17.9)
Current smoker, n (%)	975 (35.4)	7478 (27.4)	2599 (25.3)
≥5 units of alcohol intake, n (%)	511 (30.6)	4951 (29.9)	1429 (24.7)
History of CVD, n (%)	142 (5.1)	1267 (4.6)	188 (11.8)
History of diabetes, n (%)	70 (2.5)	501 (1.8)	396 (4.0)
History of hypertension, n (%)	241 (8.7)	2627 (9.6)	1750 (12.4)
Anxiety and/or depression, n (%)	482 (19.0)	3329 (13.1)	1462 (16.6)
Sedentary work, n (%)	712 (25.6)	7698 (27.9)	2162 (21.5)
Shift work, n (%)	556 (25.6)	4682 (21.3)	1242 (19.9)

*Data are given as the number of subjects (column percentage) or mean ± standard deviation.

***Supplementary table 3*: Independent association between insomnia and sleep duration with all-cause and cardiovascular mortality over 17 years of follow-up**

Exposures	Person years	Death	Age-adjusted, HR	Multi-adjusted HR [a] (95% CI)
All-cause mortality				
Insomnia				
No	574125	5311	1.00 (Reference)	1.00 (Reference)
Yes	80338	1375	1.09 (1.02-1.15)	1.08 (1.07-1.18)
Sleep duration				
7-8h sleep	456893	3414	1.00 (Reference)	1.00 (Reference)
≤6h sleep	45499	384	1.18 (1.05-1.30)	1.15 (0.99-1.33)
≥9h sleep	152102	2888	1.17 (1.11-1.23)	1.16 (1.12-1.21)
Cardiovascular mortality				
Insomnia				
No	574125	2035	1.00 (Reference)	1.00 (Reference)
Yes	80338	541	1.05 (0.98-1.11)	1.03 (0.92-1.12)
Sleep duration				
7-8h sleep	456893	1233	1.00 (Reference)	1.00 (Reference)
≤6h sleep	45499	126	1.05 (0.86-1.22)	1.04 (0.81-1.35)
≥9h sleep	152102	1217	1.16 (1.07-1.26)	1.17 (1.04-1.32)

HR: Hazard ratio, CI: confidence interval

*Adjusted for age, sex, BMI, education, smoking status, alcohol intake, LTPA, history of diabetes, history of CVD, history of hypertension, and occupational physical activity

Supplementary table 4: **Self-reported sleep duration categorized into eight categories**

Association between sleep duration with all-cause and cardiovascular mortality over 17 years of follow-up

Sleep duration categories	All-cause mortality				CVD mortality			
	Person years	Deaths	Age adjusted HR	Multi-adjusted HR*	Person years	Deaths	Age adjusted HR	Multi-adjusted HR*
7-8 h	272887	2395	1.00	1.00 (Reference)	272887	905	1.00	1.00 (Reference)
<5 h	7678	119	1.08	1.04 (0.79-1.34)	7678	41	0.91	0.87 (0.55-1.37)
5-6 h	37800	265	1.20	1.23 (1.04-1.44)	37800	85	1.03	1.07 (0.79-1.45)
6-7 h	178975	1019	0.96	0.96 (0.70-1.36)	178975	328	0.86	0.80 (0.67-1.96)
8-9 h	100822	1427	1.04	1.07 (0.80-1.48)	100822	574	0.99	1.05 (0.91-1.22)
9-10 h	40484	999	1.22	1.20 (1.04-1.44)	40484	430	1.17	1.10 (0.93-1.30)
10-11 h	4409	169	1.40	1.22 (0.80-1.58)	4409	75	1.36	1.18 (0.85-1.64)
>11 h	6385	303	1.89	1.86(1.04-2.78)	6385	138	1.69	1.80 (1.25-2.71)

HR: Hazard ratio, CI: confidence interval

*Adjusted for age, sex, BMI, education, smoking status, alcohol intake, LTPA, history of diabetes, history of CVD, history of hypertension and occupational physical activity

Supplementary table 5: **Excluded individuals who died during the first three years of follow-up**

Joint association between insomnia and sleep duration with all-cause and cardiovascular mortality and effect modification by LTPA over 17 years of follow-up

Exposures	Leisure-time physical activity							
	Active				Inactive			
	Person years	Death	Age-adjusted HR	Multi-adjusted* HR [a] (95% CI)	*Person year*	Death	Age-adjusted HR	Multi-adjusted* HR (95% CI)
All-cause mortality								
No insomnia + 7-8h sleep	237427	1423	1.00	1.00 (Reference)	168817	1093	1.17	1.16 (1.02-1.31)
No insomnia + ≤6h sleep	20497	101	0.99	0.96 (0.70-1.23)	15831	118	1.26	1.38 (1.17-1.65)
No insomnia + ≥9h sleep	74562	1016	1.23	1.18 (1.03-1.28)	56045	1010	1.37	1.35 (1.22-1.52)
Insomnia + 7-8h sleep	27388	308	1.16	1.14 (0.96-1.35)	22662	268	1.15	1.14 (0.95-1.39)
Insomnia + ≤6h sleep	4803	46	1.18	1.13 (0.73-1.59)	4283	71	1.89	1.86 (1.38-2.56)
Insomnia + ≥9h sleep	16061	119	1.17	1.18 (0.97-1.43)	10871	326	1.51	1.59 (1.35-1.91)
CVD-mortality								
No insomnia + 7-8h sleep	237427	493	1.00	1. (Reference)	169013	383	1.18	1.04 (0.53-2.34)
No insomnia + ≤6h sleep	20497	32	0.93	0.92 (0.62-1.56)	15862	33	0.98	1.01 (0.84-1.64)
No insomnia + ≥9h sleep	168817	400	1.14	1.07 (0.87-1.30)	56334	440	1.45	1.47 (1.25-1.78)
Insomnia + 7-8h sleep	74562	96	0.95	0.93 (0.90-1.31)	22747	109	1.24	1.22 (0.86-1.59)
Insomnia + ≤6h sleep	27388	33	0.99	1.28 (0.69-1.26)	4303	30	2.15	2.09 (1.26-3.39)
Insomnia + ≥10h sleep	15831	76	1.17	1.16 (0.59-1.38)	10939	141	1.44	1.41 (1.06-1.88)

HR: Hazard ratio, CI: confidence interval *Adjusted for age, sex, BMI, education, smoking status, alcohol intake, history of diabetes, history of CVD, history of hypertension and occupational physical activity

Supplementary table 6 **Excluded individuals with cardiovascular disease (CVD) at baseline**

Joint association between insomnia and sleep duration with cardiovascular mortality and effect modification by LTPA over 17 years of follow-up

Exposures	Leisure-time physical activity							
	Active				Inactive			
	Person years	Death	Age-adjusted HR	Multi-adjusted* HR [a] (95% CI)	*Person year*	Death	Age-adjusted HR	Multi-adjusted* HR (95% CI)
CVD-mortality								
No insomnia + 7-8h sleep	230072	384	1.00	1. (Reference)	163838	307	1.25	1.08 (0.53-2.34)
No insomnia + ≤6h sleep	20|136	25	0.98	1.01 (0.62-1.42)	15326	26	0.92	0.75 (0.54-1.08)
No insomnia + ≥9h sleep	69466	286	1.09	1.04 (0.87-1.35)	51842	324	1.44	1.45 (1.15-1.78)
Insomnia + 7-8h sleep	25506	64	0.88	0.89 (0.63-1.28)	21124	78	1.24	1.22 (0.86-1.59)
Insomnia + ≤6h sleep	4580	12	1.10	1.59 (0.39-3.42)	3827	17	1.89	1.88 (1.26-3.39)
Insomnia + ≥10h sleep	8886	50	1.09	1.14 (0.79-1.43)	9295	85	1.35	1.33 (0.86-1.88)

HR: Hazard ratio, CI: confidence interval

**Adjusted for age, sex, BMI, education, smoking status, alcohol intake, history of diabetes, history of hypertension and occupational physical activity*

Supplementary table 7: **Complete case**

Table 5: *Joint association between insomnia and sleep duration with all-cause and cardiovascular mortality and effect modification by LTPA over 17 years of follow-up*

Exposures	Leisure-time physical activity							
	Active				Inactive			
	Person years	Death	Age-adjusted HR	Multi-adjusted* HR [a] (95% CI)	*Person year*	Death	Age-adjusted HR	Multi-adjusted* HR (95% CI)
All-cause mortality								
No insomnia + 7-8h sleep	140391	811	1.00	1.00 (Reference)	140239	641	1.17	1.16 (1.02-1.31)
No insomnia + ≤6h sleep	12298	53	0.93	0.92 (0.70-1.23)	3698	76	1.29	1.37 (1.17-1.65)
No insomnia + ≥9h sleep	43057	571	1.10	1.15 (1.03-1.32)	33241	605	1.41	1.36 (1.12-1.52)
Insomnia + 7-8h sleep	15815	179	1.08	1.09 (0.96-1.35)	13495	155	1.20	1.18 (1.05-1.39)
Insomnia + ≤6h sleep	2778	25	1.29	1.19 (0.83-1.59)	2569	50	1.90	1.86 (1.28-2.56)
Insomnia + ≥9h sleep	5463	113	1.20	1.21 (0.97-1.47)	5760	175	1.48	1.50 (1.35-1.91)
CVD-mortality								
No insomnia + 7-8h sleep	140391	292	1.00	1. (Reference)	140239	297	1.19	1.06 (0.53-2.34)
No insomnia + ≤6h sleep	12298	18	0.90	0.90 (0.62-1.56)	3698	19	0.93	0.84 (0.84-1.64)
No insomnia + ≥9h sleep	43057	211	1.09	1.05 (0.87-1.30)	33241	279	1.47	1.42 (1.25-1.78)
Insomnia + 7-8h sleep	15815	57	0.93	0.91 (0.90-1.31)	13495	66	1.31	1.29 (1.06-1.59)
Insomnia + ≤6h sleep	2778	10	1.28	1.26 (0.69-1.26)	2569	19	2.03	1.79 (1.26-3.39)
Insomnia + ≥10h sleep	5463	46	1.33	1.18 (0.59-1.38)	5760	72	1.34	1.33 (1.06-1.88)

HR: Hazard ratio, CI: confidence interval *Adjusted for age, sex, BMI, education, smoking status, alcohol intake, history of diabetes, history of CVD, history of hypertension and occupational physical activity

Supplementary table 8: **Adjusted for anxiety and/or depression and work shift**

Joint association between insomnia and sleep duration with all-cause and CVD mortality and effect modification by LTPA over 17 years of follow-up

Exposures	Leisure-time physical activity							
	Active				Inactive			
	Person years	Death	Age-adjusted HR	Multi-adjusted* HR [a] (95% CI)	*Person year*	Death	Age-adjusted HR	Multi-adjusted* HR (95% CI)
All-cause mortality								
No insomnia + 7-8h sleep	169013	1565	1.00	1.00 (Reference)	169013	1208	1.30	1.19 (1.02-1.39)
No insomnia + ≤6h sleep	15862	108	0.97	0.92 (0.70-1.23)	15862	136	1.18	1.47 (1.17-1.79)
No insomnia + ≥9h sleep	56335	1108	1.16	1.19 (1.03-1.28)	56334	1188	1.40	1.38 (1.22-1.52)
Insomnia + 7-8h sleep	22747	330	1.12	1.18 (0.93-1.23)	22747	313	1.20	1.28 (0.92-1.75)
Insomnia + ≤6h sleep	4303	56	1.08	1.31 (0.94-1.68)	4303	84	1.90	1.67 (1.38-2.50)
Insomnia + ≥9h sleep	10939	224	1.27	1.21 (0.68-1.74)	10939	368	1.40	1.31 (0.98-1.64)
CVD-mortality								
No insomnia + 7-8h sleep	237680	557	1.00	1. (Reference)	169013	435	1.17	1.02 (0.53-2.34)
No insomnia + ≤6h sleep	20512	34	0.89	0.80 (0.62-1.25)	15862	39	0.94	1.05 (0.53-2.08)
No insomnia + ≥9h sleep	74723	441	1.09	1.05 (0.87-1.24)	56334	529	1.45	1.34 (0.86-1.84)
Insomnia + 7-8h sleep	27423	108	0.93	0.67 (0.88-1.26)	22747	133	1.33	1.45 (0.91-2.04)
Insomnia + ≤6h sleep	4821	18	1.15	1.01 (0.69-1.23)	4303	35	2.03	1.89 (0.87-4.13)
Insomnia + ≥10h sleep	10106	86	1.16	1.44 (0.55-1.42)	10939	181	1.33	0.97 (0.58-1.64)

HR: Hazard ratio, *CI*: confidence interval

*Adjusted for age, sex, BMI, education, smoking status, alcohol intake, history of diabetes, history of CVD, history of hypertension, occupational physical activity, anxiety and/or depression and work shif

APPENDIX A: HUNT Contract

NTNU

Fakultet for medisin og helsevitenskap
Institutt for samfunnsmedisin og sykepleie
HUNT forskningssenter

Vår dato	Vår referanse
18.01.2022	2021/46772
Deres dato	Deres referanse

AVTALE

HUNT forskningssenter, Institutt for samfunnsmedisin og sykepleie, Fakultet for medisin og helsevitenskap, NTNU og **Institutt for samfunnsmedisin og sykepleie, Fakultet for medisin og helsevitenskap, NTNU**

inngår med dette en avtale om bruk av forskningsmateriale fra Helseundersøkelsen i Trøndelag (HUNT) til studentoppgave for Samir Chalise med Eivind Schjelderup Skarpsno som prosjektleder.

Prosjekttittel: The effect of long-term poor sleep quality on risk of cardiovascular mortality and the modifying role of physical activity, 2021/46772.

Denne avtalen er i to deler; del I er hovedavtalen med HUNT forskningssenter og del II er dataoverføringsavtale. Ved signering godkjennes begge deler av avtalen.

DEL I – Hovedavtalen med HUNT forskningssenter:

Grunnlag for avtalen
Avtalen bygger på prosjektbeskrivelse med protokoll datert 20.08.2021. Avtalen bygger også på godkjenning i Regional komite for medisinsk og helsefaglig forskningsetikk REK, referanse 9468 datert 18.06.2021.

Veileder er ansvarlig for at forskningsarbeidet skjer i henhold til gjeldende lov- og regelverk, spesielt Helseforskningsloven når det gjelder et helseforskningsprosjekt, og Personopplysningsloven når en ikke-anonym datafil blir utlevert. Videre har veileder ansvar for at forskningsmaterialet blir brukt kun til de oppgitte formål som beskrevet i søknad og protokoll tilhørende prosjektet.

Avtalen gjelder for følgende studentoppgave:

- The effect of long-term poor sleep quality on risk of cardiovascular mortality and the modifying role of physical activity.

Forskningsmateriale
HUNT forskningssenter skal levere ut forskningsmateriale som spesifisert i vedlegg 1 til studentens veileder.

For data som befinner seg i HUNT databank er estimert dato for utlevering av datafilen innen 3 uker etter at signert avtale er mottatt ved HUNT forskningssenter.

APPENDIX B: REK Approval

REK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK midt	Ramunas Kazakauskas	73597510	18.06.2021	9468

Tom Ivar Lund Nilsen

Prosjektsøknad: Livsløpstudier av fysisk inaktivitet og risiko for kardiovaskulær sykdom og død
Søknadsnummer: 2014/1116
Forskningsansvarlig institusjon: Norges teknisk-naturvitenskapelige universitet
Samarbeidende forskningsansvarlige institusjoner: Norges teknisk-naturvitenskapelige universitet

Prosjektsøknad: Endring godkjennes.

Søkers beskrivelse

Fysisk inaktivitet er en betydningsfull risikofaktor for kardiovaskulær sykdom. Likevel vet vi lite om hva som predikerer fysisk inaktivitet gjennom livssløpet. Vi vet heller ikke hvordan en fysisk inaktiv livsstil over flere tiår påvirker risiko for kardiovaskulær sykdom og død. Vi vil utnytte longitudinelle data fra Helseundersøkelsene i Nord-Trøndelag koblet til nasjonale registre for å studere:
1. om sosioøkonomiske, livsstils- og helserelaterte faktorer i tidlig voksenliv/ungdomstid predikerer senere fysisk inaktivitet
2. om endringer i fysisk aktivitet gjennom livsløpet gjenspeiles i tilsvarende endringer i risikofaktorer for hjerte- og karsykdommer
3. hvordan vedvarende inaktivitet gjennom livet påvirker risikoen for kardiovaskulær sykdom og kardiovaskulær død
Prosjektet vil gi økt kunnskap om faktorer som predikterer fysisk inaktivitet, samt hvilke konsekvenser fysisk inaktivitet over flere år har på kardiovaskulær helse og sykdomsrisiko.

Vi mottok din søknad om prosjektendring 18.05.2021. Søknaden er behandlet av sekretariat for REK midt på delegert fullmakt fra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

REKs vurdering

Du søker om å registrere en ny prosjektmedarbeider (Samir Chalise) som skal skrive en masteroppgave basert på prosjektdata. Mastergradprosjektet dreier seg om å "undersøke om det er synergistiske effekter av endringer i fysisk aktivitet og søvnkvalitet på dødeligheten av hjertekarsykdommer".

REK midt **Telefon**:73 59 75 11 | **E-post**:rek-midt@ntnu.no
Besøksadresse: Øya Helsehus, 3. etasje, Mauritz Hansens gate 2, Trondheim **Web**:https://rekportalen.no

Vi har vurdert søknad om prosjektendring. Vi ber deg om å sende inn en forskningsprotokoll for mastergradprosjektet til orientering. Vi har ellers ingen forskningsetiske innvendinger mot endringen av prosjektet. Endringen ligger innenfor de rammer som er lagt for Helseundersøkelsen i Nord-Trøndelag (HUNT), og innenfor det samtykke som deltakerne har gitt til bruk av dette materialet. Hensynet til deltakernes velferd og integritet er fremdeles godt ivaretatt. Vi minner om at prosjektet må gjennomføres i henhold til tidligere vedtak i saken.

Vennligst send inn forskningsprotokollen gjennom skjemaet «Endring og/eller henvendelse».

Vedtak

Godkjent.

Sluttmelding
Prosjektleder skal sende sluttmelding til REK på eget skjema via REK-portalen senest senest 6 måneder etter sluttdato 31.12.2024, jf. helseforskningsloven § 12. Dersom prosjektet ikke starter opp eller gjennomføres meldes dette også via skjemaet for sluttmelding.

Søknad om endring
Dersom man ønsker å foreta vesentlige endringer i formål, metode, tidsløp eller organisering må prosjektleder sende søknad om endring via portalen på eget skjema til REK, jf. helseforskningsloven § 11.

Klageadgang
Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar av dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

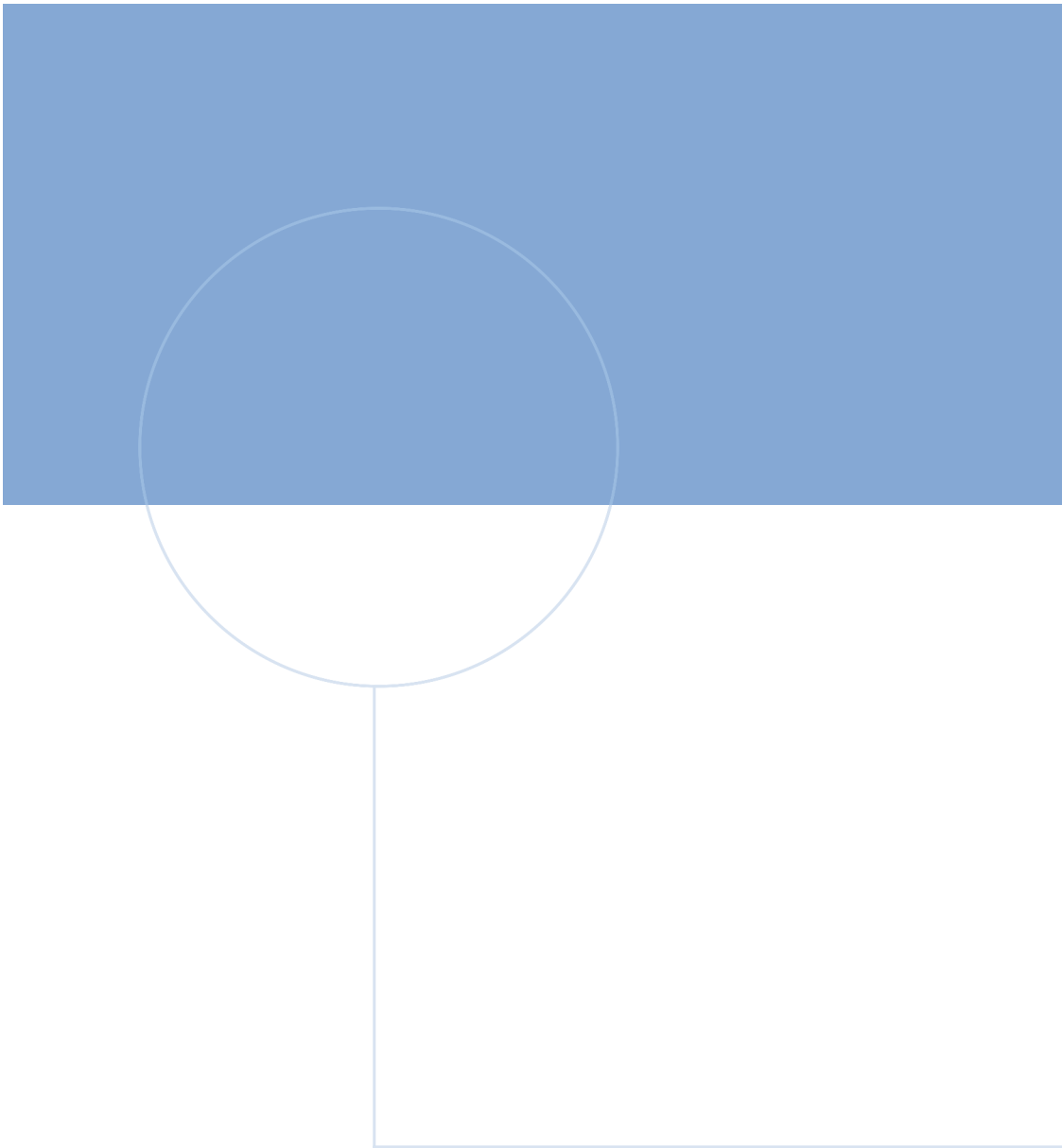
Med vennlig hilsen

Hilde Eikemo
Sekretariatsleder

Ramunas Kazakauskas
Rådgiver

Kopi til:

Norges teknisk-naturvitenskapelige universitet
Norges teknisk-naturvitenskapelige universitet



NTNU

Norwegian University of
Science and Technology