Received: 16 November 2020 | Revised: 10 January 2021 | Accepted: 15 January 2021

DOI: 10.1111/jsr.13299

REGULAR RESEARCH PAPER

Journal of Sleep Research

Insomnia symptoms and subclinical myocardial injury: Data from the Nord-Trøndelag Health (HUNT) study

Fjola D. Sigurdardottir[1,2] | Magnus N. Lyngbakken[1,2] | Kristian Hveem[3] | Harald Hrubos Strøm[4,5] | Helge Røsjø[2,6] | Susan Redline[7] | Torbjørn Omland[1,2]

[1]Department of Cardiology, Akershus University Hospital, Lørenskog, Norway

[2]Cardiovascular Research Group, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[3]HUNT Research Centre, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Levanger, Norway

[4]Division of Surgery, Department of Ear, Nose and Throat, Akershus University Hospital, Lørenskog, Norway

[5]Medical Faculty, Department of behavioural sciences, Institute of basic Medical Sciences, University of Oslo, Oslo, Norway

[6]Division of Research and Innovation, Akershus University Hospital, Lørenskog, Norway

[7]Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Correspondence
Torbjørn Omland, Professor of Medicine, Division of Medicine, Akershus University Hospital, University of Oslo, NO-1478 Lørenskog, Norway.
Email: torbjorn.omland@medisin.uio.no

Funding information
Foundation for the National Institutes of Health, Grant/Award Number: NHLBI R35 135818; Helse Sør-Øst RHF

Summary

Insomnia symptoms are associated with increased risk of heart failure (HF) and cardiovascular (CV) mortality. We hypothesised that insomnia symptoms are cross-sectionally associated with increased cardiac troponin I (cTnI), a biomarker of subclinical myocardial injury, and that phenotyping by insomnia symptoms and cTnI enhances longitudinal risk stratification in the general population. In a population-based study, cTnI was measured in 8,398 participants (median age 49 years, 55% women), who had answered questionnaires regarding insomnia symptoms. Association between cTnI and insomnia symptoms was assessed by linear regression analysis for each response category of a sleep questionnaire. Insomnia symptoms were defined as having difficulty falling asleep almost every night, difficulty maintaining sleep almost every night, and/or non-restorative sleep once a week or more. The primary outcome measure was a composite endpoint of CV mortality or first admission for HF. In all, 844 participants reported insomnia symptoms, 585 (69%) were women. Those with insomnia symptoms had marginally, but significantly higher median cTnI than those without insomnia symptoms, (median [interquartile range] 3.4 [2.4–5.2] ng/L versus 3.2 [2.2–4.9] ng/L; $p = .014$), but there was no association between any insomnia symptom and cTnI in unadjusted linear regression models (β 0.06, 95% confidence interval [CI] −0.01 to 0.12). In adjusted analyses, participants with insomnia symptoms and increased cTnI were at increased risk of the composite endpoint (hazard ratio 1.71, 95% CI 1.04–2.79) compared to participants with insomnia symptoms and low cTnI. In the general population, insomnia symptoms are not associated with biochemical evidence of subclinical myocardial injury.

KEYWORDS
biomarkers, cardiac troponin I, cardiovascular disease, cardiovascular risk, heart failure, insomnia symptoms

1 | INTRODUCTION

Insomnia symptoms, characterised by difficulty falling and/or staying asleep, is a common but treatable condition with prevalence up to 36% in the general population and 45% in patients with coronary heart disease (CHD) (Frøjd et al., 2021; Ohayon, 2002). Insomnia symptoms are associated with increased risk of hypertension, heart failure (HF), and cardiovascular (CV) disease (CVD) (Laugsand

et al., 2014; Meng et al., 2013; Sofi et al., 2014). However, a more recent meta-analysis reported no overall association with CV mortality (Ge et al., 2019). Accordingly, insomnia symptoms are not considered an established risk factor for CVD, also due to the lack of mechanistic insight into how insomnia symptoms influence CV risk (St-Onge et al., 2016).

Insomnia diagnosis has been associated with increased levels of noradrenaline in blood, a vasoconstrictive that has an excitatory effect on the hypothalamic–pituitary–adrenal axis (HPA axis) (Feldman & Weidenfeld, 2004; Irwin et al., 2003). Sympathetic hyperactivity may contribute to diffuse myocardial fibrosis, development of left ventricular dysfunction and increased risk of CVD (Grassi et al., 2009), and these pathophysiological processes are closely associated with higher cardiac troponin concentrations (Omland et al., 2009, 2013; Seliger et al., 2017). Potential mechanisms linking insomnia symptoms to increased CV risk therefore include increased sympathetic nervous system activity and dysregulation of the HPA axis, possibly promoting hypertension and subclinical myocardial injury (Javaheri and Redline 2017).

Cardiac troponin I (cTnI) is an organ-specific marker of myocardial injury and a standard diagnostic tool in the evaluation of acute myocardial infarction (McCarthy et al., 2019). With the introduction of high-sensitivity assays, very low concentrations of cTnI can be measured in patients with subclinical CVD, as well as in large proportions of apparently healthy individuals (Apple & Collinson, 2012; Apple et al., 2012; Seliger et al., 2017). Concentrations of cTnI measured with high-sensitivity assays are specific and sensitive markers of subclinical myocardial injury and predict the risk of HF and CV mortality among asymptomatic individuals and individuals with stable CHD (Everett et al., 2015; Farmakis et al., 2020; Omland et al., 2013). cTnI concentrations are generally higher in men, but the association between cTnI and risk of CV mortality is stronger in women, both in the general population and in individuals with obstructive sleep apnea (Omland et al., 2015; Roca et al., 2015). There are currently no published reports on the association between insomnia symptoms and subclinical myocardial injury as assessed by cTnI. We hypothesised that subclinical myocardial injury is a possible link between insomnia symptoms and increased risk of CVD. The aims of the present study were therefore to investigate whether insomnia symptoms are cross-sectionally associated with higher concentrations of circulating cTnI, and whether phenotyping by insomnia symptoms and concentrations of cTnI may enhance risk stratification for CV morbidity and death in the general population.

2 | METHODS

2.1 | Study design and participants

A detailed description of the Trøndelag Health (HUNT) Study, a large prospective population study carried out in the county of Nord-Trøndelag in Norway, has previously been published (Holmen et al., 2003). The second wave of the study (HUNT2) was carried out from August 1995 to June 1997, where 93,898 residents of the county aged ≥ 20 years were invited to participate and 69% (65,237) accepted this invitation. The conduct of the second wave of the study was set up by the HUNT Research Centre and was both a new cross-sectional survey and a follow-up of the first wave (HUNT1) of the study. The participants included in this study were part of a biomarker substudy encompassing four out of 24 municipalities in the county. Blood samples in the substudy were collected at the same time as the questionnaire data on insomnia symptoms. Participants with missing data on all sleep questionnaires (n = 1,357) and those who had missing cTnI measurements (298) were excluded, leaving 8,398 participants who were included in the present analysis. Participants with missing data on sleep questionnaires were more likely to be younger, male and did not have significantly different cTnI levels compared to those with data on insomnia symptoms (Table S1). A total of 1,476 individuals did not answer all sleep questionnaires and were therefore not included in the analysis for association of cTnI and number of insomnia symptoms.

2.2 | Insomnia symptoms

Participants completed questionnaires concerning health status, medical history, and lifestyle factors. This included three questions regarding insomnia symptoms: “Have you had difficulties falling asleep in the last month?”, with the response options “never, occasionally, often, almost every night”; “During the last month, have you woken up too early and not been able to get back to sleep?”, with the response options “never, occasionally, often, almost every night”; “How often do you suffer from non-restorative sleep?”, with the response options “never or a few times a year, one to two times per month, about once a week, more than once a week”. Only individuals aged 20–69 years received the last question.

2.3 | Clinical variables

Blood samples were drawn from the participants by trained nurses who also performed a physical examination with a standardised collection of clinical data. The data collection included height, weight, waist and hip circumference, and systolic and diastolic blood pressure. An automated blood pressure device (Dinamap 845 XT, Criticon) was used for all blood pressure measurements. History of CVD was defined as self-reported history of angina, myocardial infarction, and/or stroke. History of diabetes was defined as having a self-reported history of previous and/or current diabetes. The Hospital Anxiety and Depression Scale (HADS) questionnaire was used to screen for symptoms of depression and/or anxiety (Eriksen et al. 2019; Zigmond & Snaith, 1983). The HADS has previously been described to fulfil reliability and validity

criteria for anxiety and depression screening in the general population (Bjelland et al., 2002).

2.4 | Biochemical analysis

Non-fasting venous blood samples were collected, centrifuged at room temperature and frozen down to −80°C. For cTnI analysis, samples that had previously been thawed, re-frozen in 2008 and stored at −20°C were shipped on dry ice to Akershus University Hospital, Lørenskog, Norway. Samples were centrifuged for 30 min at 3,500 ***g*** before analysis with the Abbott Diagnostics Architect STAT High Sensitive Troponin assay (Omland et al., 2013). The cTnI analysis was performed in 2014 (Lyngbakken et al., 2019). The limit of detection for this assay is 1.2 ng/L (range 0–50 000 ng/L), with a coefficient of variation of 10% at a concentration of 3.0 ng/L (Apple & Collinson, 2012). With control material from the producer, a coefficient of variation of 4.1% was found in the high concentration range (1,500 ng/L), 4.4% in the medium concentration range (200 ng/L), and 6.3% in the low concentration range (20 ng/L). All measurements below the detection limit were assigned a value corresponding to 50% of the limit of detection (i.e. 0.6 ng/L). Other biochemical analyses such as concentrations of total cholesterol, high-density lipoprotein cholesterol, triglycerides, and creatinine in serum were measured by routine laboratory methods (Krokstad et al., 2013). Estimated glomerular filtration rate (eGFR) was calculated with the four-variable Modification of Diet in Renal Disease equation (Levey et al., 2009).

2.5 | Endpoints

Data on admissions for HF were obtained from hospital records and defined as primary diagnosis International Classification of Diseases (ICD) codes 428 (ninth revision) or I50 (10th revision). The Cause of Death Registry of Statistics Norway provides the diagnoses stated as the primary cause of death on the death certificate. CV death was defined as the primary cause of death registered as ICD codes 390–459 (ninth revision) or I00-I99 (10th revision). All survival data were obtained from the participation date of the second wave through to 31 December 2016.

2.6 | Statistical analysis

Descriptive statistics are reported as absolute numbers with percentages or medians with interquartile range (quartile one to quartile 3 [IQR]). Categorical variables were compared with the chi-square test and continuous variables with the Mann–Whitney *U*-test. The cTnI measurements were log transformed for further statistical analysis due to their skewed distribution. To assess the association between insomnia symptoms and cTnI, we included each symptom using the original response categories in five different models of linear regression analysis. Individuals who had not responded to all questions regarding insomnia symptoms were not included in the analyses for the association of cTnI and the increasing number of insomnia symptoms. For the prognostic analyses, we created a composite endpoint of CV death or hospitalisation due to HF. Subjects who reported almost nightly problems with either difficulty falling asleep, difficulty maintaining sleep or having non-restorative sleep more than once a week were categorised as having insomnia symptoms (Laugsand et al., 2014). We categorised participants into different phenotypes according to prevalent insomnia symptoms and circulating cTnI concentrations above/below sex-specific cut-offs (≥4 ng/L for women and ≥6 ng/L for men (Sigurdardottir et al., 2018): (a) insomnia symptoms and cTnI below the sex-specific cut-off (reference category), (b) insomnia symptoms and cTnI above the sex-specific cut-off. Cox proportional hazard regression models were generated to test the relationship between insomnia symptoms with or without cTnI ≥4 ng/L or ≥6 ng/L and time to events. Additional Cox proportional hazard regression models were generated for the subgroup of subjects without prevalent insomnia symptoms, comparing subjects with concentrations of cTnI above/below the sex-specific cut-offs. For all the regression models, Model 1 was unadjusted, Model 2 was adjusted for age and sex, Model 3 was adjusted for smoking in addition to Model 2, Model 4 was adjusted for serum cholesterol and eGFR in addition to Model 3, and Model 5 was adjusted for depression and anxiety in addition to Model 4. As prior studies have suggested a stronger association between cardiac troponins and outcome in women (Omland et al., 2015) a test for interaction by sex was performed. However, no significant interaction was observed and no subgroup analyses by sex were conducted. STATA 15.1 (StataCorp LP) was used to conduct the statistical analysis.

2.7 | Ethics approval

All participants provided written informed consent and both the study was approved by the Regional Ethics Committee (REC 2012/859).

3 | RESULTS

3.1 | Participant characteristics

cTnI was measured in 8,398 individuals, 3,784 men and 4,614 women, who had answered questions on difficulty initiating sleep, maintaining sleep and/or having symptoms of non-restorative sleep. Of those, 259 men (7%) and 585 women (15%) reported significant insomnia symptoms, i.e. 844 in total. Participants with insomnia symptoms were more frequently women, current smokers, and had a higher frequency of history of CVD, hypertension, and diabetes. Additionally, participants with insomnia symptoms had higher body mass index (BMI), higher blood pressure, serum lipids, C-reactive protein (CRP), and a higher score on the HADS (Table 1).

TABLE 1 Baseline characteristics of individuals with and without insomnia symptoms

	No insomnia		Insomnia		
Variable	***N***	**Value**	***N***	**Value**	***p***
Sex, women, *n* (%)	7,554	4,029 (53.3)	844	585 (69.3)	<.001
Age, years, mean (*SD*)	7,554	49.8 (16.8)	844	55.8 (15.3)	<.001
Weight, kg, mean (*SD*)	7,527	76.5 (13.7)	839	74.6 (14.4)	<.001
Body mass index, kg/m^2, mean (*SD*)	7,527	26.3 (4.0)	839	26.7 (4.3)	.002
Current smoker, *n* (%)	7,489	1993 (26.6)	832	298 (35.8)	<.001
History of cardiovascular disease, *n* (%)	7,550	522 (6.9)	841	96 (11.4)	<.001
History of hypertension, *n* (%)	7,519	3,191 (42.4)	840	416 (49.5)	<.001
History of diabetes mellitus, *n* (%)	7,538	201 (2.7)	842	39 (4.6)	<.001
Shift work, *n* (%)	7,441	1,033 (19.1)	481	94 (19.5)	.81
Systolic blood pressure, mmHg, mean (*SD*)	7,523	136.4 (21.8)	840	138.4 (22.4)	.012
Diastolic blood pressure, mmHg, mean (*SD*)	7,523	80.3 (12.1)	840	81.4 (12.7)	.010
Glucose non-fasting, mmol/L, mean (range)	7,554	5.2 (4.8–5.8)	844	5.3 (4.8–5.8)	.006
Triglycerides non-fasting, mmol/L, mean (range)	7,554	1.4 (1.0–2.1)	844	1.5 (1.1, 2.2)	.001
Total cholesterol, mmol/L, mean (range)	7,554	5.7 (5.0–6.6)	844	6.1 (5.2, 7.0)	<.001
HDL cholesterol, mmol/L, mean (range)	7,552	1.3 (1.1–1.6)	844	1.4 (1.2, 1.7)	.001
eGFR, mL/min/1.73 m^2, mean (range)	7,554	75.7 (68.1–84.0)	844	74.8 (66.7–82.6)	<.001
Framingham cardiovascular disease score, mean (*SD*)	7,426	15.3 (17.6)	825	18.2 (17.1)	<.001
HADS depression, total score, mean (range)	7,004	2.0 (1.0–5.0)	738	5.0 (2.0–7.0)	<.001
HADS anxiety, total score, mean (range)	6463	3.0 (2.0–6.0)	639	6.0 (4.0–10.0)	<.001
CRP, mg/L, mean (range)	7,548	1.0 (0.4–2.5)	843	1.3 (0.5–3.0)	<.001
cTnI, ng/L, mean (range)	7,554	3.2 (2.2–4.9)	844	3.4 (2.4–5.2)	.014
cTnI over sex specific cut-offs (4 ng/L and 6 ng/L), *n* (%)	7,554	1929 (25.5)	844	276 (32.7)	<.001
cTnI >99th percentile, *n* (%)	7,554	149 (2.0)	844	21 (2.5)	.31

CRP, C-reactive protein; cTnI, cardiac troponin I; eGFR, estimated glomerular filtration rate; HADS, Hospital Anxiety and Depression Scale; HDL, high-density lipoprotein.

3.2 | Insomnia symptoms and cardiac troponins

Participants with insomnia symptoms were more likely to have cTnI concentrations above the sex-specific cut-offs previously associated with increased risk, 4 ng/L for women and 6 ng/L for men (Table 1). Individuals with insomnia symptoms had higher concentrations of cTnI than those without (median [IQR] 3.4 [2.4–5.2] ng/L versus 3.2 [2.2–4.9] ng/L; $p = .01$), but there was no association between insomnia symptoms and cTnI in a linear regression model (β 0.06, 95% confidence interval [CI] −0.01 to 0.12) (Table 2). We also assessed the associations of cTnI and each individual symptom of insomnia: difficulty initiating sleep, difficulty maintaining sleep, and non-restorative sleep. In unadjusted models, we observed an association between concentrations of cTnI and difficulty falling asleep (β 0.18, 95% CI 0.09–0.27; $p < .001$), problems maintaining sleep (β 0.33, 95% CI 0.23–0.44; $p < .001$), and non-restorative sleep once a week or more (β 0.06, 95% CI 0.00–0.12; $p = .04$). In adjusted models for age and sex, there was no association between concentrations of cTnI and difficulty falling asleep (β 0.00; 95% CI −0.07 to 0.08), difficulty maintaining sleep (β 0.01, 95% CI −0.08 to 0.10) or non-restorative sleep (β 0.00, 95% CI −0.05 to 0.05). There was no significant association between an increasing number of insomnia symptoms and concentrations of cTnI compared with those with no insomnia symptoms in a linear regression analysis (Table 2).

3.3 | Cardiac troponin, insomnia symptoms and CV death

After a median follow-up of 19.6 years, a total of 948 individuals (11.3%) reached the composite endpoint of CV mortality or HF hospitalisation (474 [50.0%] women, Table 3). Subjects with insomnia symptoms were at increased CV risk after adjusting for age and sex (hazard ratio [HR] 1.26, 95% CI 1.06–1.51; $p = .01$), but this association was attenuated in fully adjusted models (HR 1.14, 95% CI 0.89–1.45; $p = .31$). Subjects with insomnia symptoms and higher concentrations of cTnI were at higher risk of HF and CV death

TABLE 2 Associations of cardiac troponin I with a number of insomnia symptoms

Insomnia symptoms, *n*	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)	Model 4 β (95% CI)	Model 5 β (95% CI)
0	Ref	Ref	Ref	Ref	Ref
1	0.06 (−0.01, 0.12)	0.02 (−0.03, 0.08)	0.03 (−0.04, 0.08)	0.01 (−0.05, 0.07)	0.03 (−0.03, 0.10)
2	0.02 (−0.08, 0.13)	−0.03 (−0.13, 0.06)	−0.03 (−0.12, 0.06)	−0.02 (−0.11, 0.07)	0.01 (−0.09, 0.11)
3	0.08 (−0.16, 0.31)	−0.03 (−0.24, 0.18)	−0.03 (−0.24, 0.18)	−0.09 (−0.30, 0.12)	−0.03 (−0.26, 0.20)
N	6,922	6,922	6,872	6,862	6,022
p for trend	0.142	0.856	0.902	0.569	0.589

Model 1 unadjusted; Model 2, adjusted for age and sex; Model 3, adjusted for age, sex and smoking; Model 4, adjusted for model 3, cholesterol and estimated glomerular filtration rate; Model 5, adjusted for model 4 and depression and anxiety. Being categorised as having an insomnia symptom required difficulty falling asleep and early awakenings to be prevalent almost every night and non-restorative sleep more than once a week. Individuals with three insomnia symptoms therefore answered that they had difficulty falling asleep and maintaining sleep almost every night in addition to having non-restorative sleep more than once a week.

TABLE 3 Cardiovascular (CV) mortality and heart failure (HF) events according to insomnia symptoms

Events	No insomnia, *N*	*n* (%)	Insomnia *N*	*n* (%)	*p*
CV mortality	7,554	695 (9.2)	844	116 (13.7)	<.001
HF	7,554	227 (3.0)	844	45 (5.3)	<.001
Composite endpoint	7,554	811 (10.7)	844	137 (16.2)	<.001
Women					
CV mortality	4,029	332 (8.2)	585	74 (12.6)	<.001
HF	4,029	113 (2.8)	585	34 (5.8)	<.001
Composite endpoint	4,029	384 (9.5)	585	90 (15.4)	<.001
Men					
CV mortality	3,525	363 (10.3)	259	42 (16.2)	.003
HF	3,525	114 (3.2)	259	11 (4.2)	.38
Composite endpoint	3,525	427 (12.1)	259	47 (18.1)	.005

($p < .001$ by log-rank test, Figure 1). In adjusted analyses, participants with insomnia symptoms and cTnI over the sex-specific cut-offs were at increased risk of the composite endpoint (HR 1.71, 95% CI 1.04–2.79; $p = .03$ (Table 4)) compared to participants with insomnia symptoms and low cTnI.

4 | DISCUSSION

In a large cohort of subjects from the general population, there was no significant association between the presence of frequent insomnia symptoms and higher cTnI concentrations or increased CV risk in adjusted models. This suggests no independent association between prevalent insomnia symptoms and subclinical myocardial injury quantified by circulating concentrations of cTnI. However, in accordance with previously reported data, we observed that individuals with cTnI above the sex-specific cut-offs had increased CV risk regardless of insomnia symptoms. In individuals with insomnia symptoms, those with higher cTnI concentrations were at a higher CV risk.

4.1 | Insomnia symptoms and CV risk

Insomnia symptoms have been associated with an increased risk of CVD in a number of epidemiological studies (Ge et al., 2019; Sofi et al., 2014). More recently, genome-wide association studies with Mendelian randomisation have suggested a direct effect of insomnia symptoms on BMI, diabetes Type 2, and coronary artery disease (Jansen et al., 2019; Lane et al. 2019; Larsson &

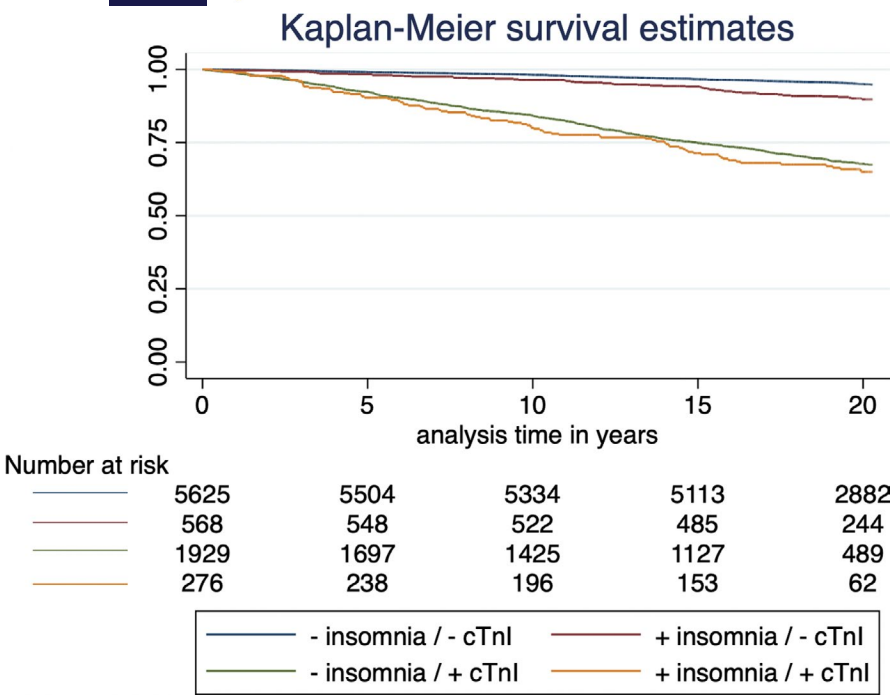

FIGURE 1 Kaplan–Meier survival curves for the endpoint of cardiovascular mortality or heart failure events according to insomnia symptoms and cardiac troponin I (cTnI) concentrations

TABLE 4 Associations between cardiac troponin I (cTnI) concentrations and cardiovascular mortality and heart failure events in participants with and without insomnia symptoms

	Participants with insomnia		Participants without insomnia	
	N	cTnI ≥4.0 ng/L for women and ≥6ng/L for men, HR (95% CI)	*N*	cTnI ≥4.0 ng/L for women and ≥6ng/L for men, HR (95% CI)
Model 1	844	4.23 (2.99, 5.97)*	7,554	7.75 (6.69, 8.97)*
Model 2	844	1.49 (1.03, 2.16)*	7,554	2.09 (1.78, 2.44)*
Model 3	832	1.53 (1.04, 2.25)*	7,554	2.09 (1.78, 2.45)*
Model 4	832	1.54 (1.05, 2.26)*	7,554	2.11 (1.80, 2.48)*
Model 5	615	1.71 (1.04, 2.79)*	7,554	1.95 (1.61, 2.35)*

HR, *hazard ratio;*: Model 1, unadjusted; Model 2, adjusted for age and sex; Model 3, adjusted for age, sex and smoking; Model 4, adjusted for model 3, cholesterol and estimated glomerular filtration rate; Model 5, adjusted for model 4 and depression and anxiety.

*$p < .05$.

Markus, 2019). Despite this, insomnia symptoms are not recognised as an established risk factor for CVD, both due to a lack of understanding of the mechanisms linking insomnia symptoms to CV risk and inconsistencies in previous studies on the association between insomnia symptoms and CVD (Ge et al., 2019; Javaheri and Redline 2017). Insomnia is a state of hyper-arousal and a possible link between insomnia and CVD is an increase in sympathetic nervous system activity (Zhang et al., 2011). Experimental physiological studies in humans have indeed suggested that both insomnia diagnosis and lack of normal sleep is associated with persistent high sympathetic activity and an increase in circulating noradrenaline and adrenaline (Irwin et al., 2003; Redwine et al., 2000; Spiegel et al., 1999). Similar hyperactivity of the sympathetic nervous system is seen in HF, where it might contribute to diffuse myocardial fibrosis, development of left ventricular dysfunction, and increased risk of CVD (Grassi et al., 2009). HF is independently associated with increased concentrations of circulating cTnI (Januzzi et al., 2012).

In the present study, we did not find an independent association between insomnia symptoms and concentrations of cTnI, which suggests that in most cases, insomnia symptoms are not associated with subclinical myocardial injury and subsequent increased risk of HF and CV death. Our present findings did not change after removing the question regarding non-restorative sleep from the analysis and were therefore the same regardless of whether the older or newer guidelines for insomnia symptoms were used. This inference was corroborated by the observation that having insomnia symptoms was associated with a modest and non-significant increase in CV risk in the present population after adjustment for potential confounders. Indeed, individuals with insomnia symptoms had a number of known comorbidities that increase the risk of HF and CV mortality, such as tobacco smoking, higher BMI, and prevalent diabetes and hypertension that could confound the association between insomnia symptoms and CV risk. Individuals with insomnia symptoms and increased cTnI had an increased risk of a composite endpoint in crude analysis (Table 4). In an explorative analysis of the associations between cTnI

and the specific endpoints of CV death, HF hospitalisation and acute myocardial infarction (AMI), the association appeared to be stronger for the endpoint CV mortality than for HF hospitalisation or AMI (Table S2).

Despite a possible causal association of insomnia symptoms on coronary artery disease in a Mendelian randomisation study from the UK biobank, (Lane et al. 2019) a meta-analysis of 29 cohort studies found the association between insomnia symptoms and CV mortality to be non-significant (Ge et al., 2019). Additionally, the meta-analysis found that although insomnia symptoms were not associated with CV mortality (low-to-moderate certainty), difficulty falling asleep and non-restorative sleep were significantly associated with increased CV mortality (Ge et al., 2019). These conflicting observations underscore the heterogeneity of insomnia symptoms and that risk of coronary artery disease may not translate into moderate or high risk of subclinical myocardial injury or CV death. Additionally, inconsistent adjustment for potential confounding factors and variability in measurements of insomnia symptoms further complicate the interpretation of observational studies and meta-analysis based on these. Although insomnia symptoms were not independently associated with increased levels of cTnI, higher levels of cTnI might identify individuals with insomnia symptoms in the general population at a significantly increased risk of HF and CV mortality. Measuring the severity of insomnia symptoms and how they might affect CVD is challenging as the diagnosis of insomnia is based on subjective criteria. Using existing serum biomarkers for subclinical myocardial injury can present a useful objective tool to help sleep clinicians stratify CV risk in their patients with insomnia symptoms.

4.2 | Strengths and limitations

Major strengths of the present study include a substantial sample size, measurement of cTnI with one of the most sensitive assays currently available, and long-term follow-up of clinical endpoints from the HUNT2 study. The main reason for using HUNT2 data was to obtain optimal statistical power. The number of cTnI measurements in HUNT2 was almost twice that of HUNT3; in addition, the follow-up time was almost 10 years longer. HUNT4 was performed in 2018–2019 and to date, follow-up data are not available. However, several important limitations are worth mentioning. First of all, data on the prevalence of insomnia diagnosis, sleep latency, efficiency, sleep stage distributions, sleep disordered breathing, and sleep length were not available for our present cohort, barring us from making further phenotyping based on these characteristics. The main limitation of not having polysomnographic data is that we cannot assert whether any of the study participants fulfilled diagnostic criteria for obstructive sleep apnea. However, polysomnography and/or other objective measurements of sleep are not the standard in the current diagnosis and treatment of insomnia without clinical suspicion of other sleep disorders (Riemann et al., 2017). Second, the sleep questionnaires are subject to recall and response bias. Additionally, the present cross-sectional data did not include follow-up information on the duration of insomnia symptoms, and we were therefore unable to evaluate whether the participants had transient or chronic insomnia symptoms. This limitation may have obscured an association between chronic insomnia and the risk of subclinical myocardial injury and/or CV events.

Insomnia symptoms can vary in prevalence and intensity over time, and menopausal status is related to both risk of disturbed sleep and CV events (Xu & Lang, 2014). It is a limitation of the present study that we could not account for the progression of insomnia symptoms or the effect of menopause on cTnI in women with insomnia symptoms. Another major limitation of the present study is a lack of imaging data to detect subclinical atherosclerosis and/or scarring of myocardial tissue in individuals with increased circulating cTnI. The study cohort is also ethnically homogenous with predominantly Caucasians of North-European descent, limiting generalisability to other ethnic groups.

4.3 | Clinical implications

Insomnia is a common but heterogeneous sleep disorder that is prevalent in both younger and older adults, both with and without objective short sleep duration (Bonnet et al., 2014). Although insomnia symptoms have been associated with adverse CV outcomes, the association with CV risk is modest. Moreover, randomised controlled trials (RCTs) are best suited to control for confounding factors, but there is a lack of RCTs investigating the impact of treatment for insomnia on CVD endpoints (Larsson & Markus, 2019). However, a newly published RCT assessed the short-term effect of cognitive behavioural therapy for insomnia (CBT-I) on CV risk factors such as 24-hr ambulatory blood pressure, heart rate, CRP and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in 46 individuals without CVD before and after 8 weeks of CBT-I therapy. The study found no significant treatment effects on these markers of CVD in those receiving treatment or randomised to waitlist control (Johann et al., 2020). That study did not include individuals at increased risk of CVD or elevated cTnI in their analysis, but reaches the same conclusion as a previous study published in 2017 that CBT-I did not lower blood pressure in individuals free of known CVD (Mcgrath et al., 2017).

With regard to CV risk prediction, evidence is accumulating for the use of cardiac troponin as an index of CV health (Welsh et al., 2019). In patients with increased serum cholesterol, statin therapy attenuates both CV risk and concentrations of cardiac troponin, with especially strong reductions in CV risk in patients with high baseline concentrations of cardiac troponin (Everett et al., 2015; Ford et al., 2016). A similar approach could be undertaken in individuals with insomnia symptoms, with the reassurance of individuals with insomnia symptoms and low cTnI concentrations and targeted CVD preventive therapy in patients with insomnia symptoms and increased CV risk, as assessed by higher concentrations of cardiac troponin. However, our present findings would first need to be

confirmed by studies that also assess objective sleep measurements and the duration of insomnia symptoms. For individuals with sleep disorders, measurement of cTnI would be especially appealing, as the specificity and sensitivity of cTnI does not seem to be affected by diurnal variations (Wildi et al., 2018). If our present findings are confirmed in other cohorts, cTnI could be a useful tool to evaluate CV risk in individuals with insomnia symptoms, (Farmakis et al., 2020) and help clinicians identify individuals with insomnia symptoms that are at a particularly low risk of developing CVD. Being able to identify individuals with a low risk of CVD in this common but heterogeneous disorder could be a valuable tool to avoid overtreatment and extensive use of clinical resources for CVD risk reduction in a population unlikely to develop HF or CVD. The same resources, testing and targeted therapy could then be focussed on individuals with high CVD risk.

5 | CONCLUSIONS

Although insomnia symptoms were not independently associated with subclinical myocardial injury, cTnI remains a potentially useful CV biomarker in sleep medicine that can stratify individuals with insomnia symptoms into groups at high and low CV risk.

ACKNOWLEDGEMENTS

The Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU), Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health. SR reported support from the NIH NHLBI R35 135818. FDSs PhD fellowship was supported by the Southern and Eastern Norway Regional Health Authority.

CONFLICT OF INTEREST

Torbjørn Omland has received consultant and/or speaker honoraria from Abbott Diagnostics, Bayer, Roche Diagnostics, Novartis, and CardiNor and has received research support from AstraZeneca, Abbott Diagnostics, Roche Diagnostics and SomaLogic via Akershus University Hospital. cTnI analysis was supported by Abbott Laboratories, Abbott Park, II, USA.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work. KH contributed to data and analysis tools. Data analysis was performed by FDS and MNL. Figures and tables were prepared by FDS, MNL and TO. All authors interpreted data and contributed to drafting the main manuscript text and revision. All authors approved the final submitted version of this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from HUNT Databank. Restrictions apply to the availability of these data, which were used under license for this study. Data are available at https://www.ntnu.edu/hunt/data by request.

ORCID

Fjola D. Sigurdardottir https://orcid.org/0000-0002-3497-2698

REFERENCES

Apple, F. S., & Collinson, P. O. (2012). Analytical characteristics of high-sensitivity cardiac troponin assays. *Clinical Chemistry*, *58*(1), 54–61. https://doi.org/10.1373/clinchem.2011.165795

Apple, F. S., Ler, R., & Murakami, M. M. (2012). Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. *Clinical Chemistry*, *58*(11), 1574–1581. https://doi.org/10.1373/clinchem.2012.192716

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale: An updated literature review. *Journal of Psychosomatic Research*, *52*(2), 69–77. https://doi.org/10.1016/S0022-3999(01)00296-3

Bonnet, M. H., Burton, G. G., & Arand, D. L. (2014). Physiological and medical findings in insomnia: Implications for diagnosis and care. *Sleep Medicine Reviews*, *18*(2), 111–122. https://doi.org/10.1016/j.smrv.2013.02.003

Eriksen, S., Bjørkløf, G. H., Helvik, A.-S., Larsen, M., & Engedal, K. (2019). The validity of the hospital anxiety and depression scale and the geriatric depression scale-5 in home-dwelling old adults in Norway☆. *Journal of Affective Disorders*, *256*, 380–385. https://doi.org/10.1016/j.jad.2019.05.049

Everett, B. M., Zeller, T., Glynn, R. J., Ridker, P. M., & Blankenberg, S. (2015). High-sensitivity cardiac troponin I and B-type natriuretic peptide as predictors of vascular events in primary prevention impact of statin therapy. *Circulation*, *131*(21), 1851–1860. https://doi.org/10.1161/CIRCULATIONAHA.114.014522

Farmakis, D., Mueller, C., & Apple, F. S. (2020). High-sensitivity cardiac troponin assays for cardiovascular risk stratification in the general population. *European Heart Journal*, *41*, 1–8. https://doi.org/10.1093/eurheartj/ehaa083

Feldman, S., & Weidenfeld, J. (2004). Involvement of Endogeneous Glutamate in the Stimulatory Effect of Norepinephrine and Serotonin on the Hypothalamo-Pituitary-Adrenocortical Axis. *Neuroendocrinology*, *79*(1), 43–53. https://doi.org/10.1159/000076044

Ford, I., Shah, A. S. V., Zhang, R., McAllister, D. A., Strachan, F. E., Caslake, M., Newby, D. E., Packard, C. J., & Mills, N. L. (2016). High-Sensitivity Cardiac Troponin, Statin Therapy, and Risk of Coronary Heart Disease. *Journal of the American College of Cardiology*, *68*(25), 2719–2728. https://doi.org/10.1016/j.jacc.2016.10.020

Frøjd, L. A., Munkhaugen, J., Moum, T., Sverre, E., Nordhus, I. H., Papageorgiou, C., & Dammen, T. (2021). Insomnia in patients with coronary heart disease: Prevalence and correlates. *Journal of Clinical Sleep Medicine*, *17*. [Online ahead of print]. https://doi.org/10.5664/jcsm.9082

Ge, L., Guyatt, G., Tian, J., Pan, B., Chang, Y., Chen, Y., Li, H., Zhang, J., Li, Y., Ling, J., & Yang, K. (2019). Insomnia and risk of mortality from all-cause, cardiovascular disease, and cancer: Systematic review and meta-analysis of prospective cohort studies. *Sleep Medicine Reviews*, *48*, 101215. https://doi.org/10.1016/j.smrv.2019.101215

Grassi, G., Seravalle, G., Quarti-Trevano, F., Dell'Oro, R., Arenare, F., Spaziani, D., & Mancia, G. (2009). Sympathetic and baroreflex cardiovascular control in hypertension-related left ventricular dysfunction. *Hypertension*, *53*(2), 205–209. https://doi.org/10.1161/HYPERTENSIONAHA.108.121467

Holmen, J., Midthjell, K., Krüger, Ø., Langhammer, A., Holmen, T. L., Bratberg, G. H., Vatten, L., & Lund-larsen, P. G. (2003). The Nord-Trøndelag Health Study 1995–97 (HUNT 2): Objectives, contents, methods and participation. *Norsk Epidemiology*, *13*(1), 19–32.

Irwin, M., Clark, C., Kennedy, B., Gillin, J. C., & Ziegler, M. (2003). Nocturnal catecholamines and immune function in insomniacs, depressed patients, and control subjects. *Brain, Behavior, and Immunity*, *17*(5), 365–372. https://doi.org/10.1016/S0889-1591(03)00031-X

Jansen, P. R., Watanabe, K., Stringer, S., Skene, N., Bryois, J., Hammerschlag, A. R., de Leeuw, C. A., Benjamins, J. S., Muñoz-Manchado, A. B., Nagel, M., Savage, J. E., Tiemeier, H., White, T., Tung, J. Y., Hinds, D. A., Vacic, V., Wang, X., Sullivan, P. F., van der Sluis, S., … Posthuma, D. (2019). Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. *Nature Genetics*, *51*(3), 394–403. https://doi.org/10.1038/s41588-018-0333-3

Januzzi, J. L., Filippatos, G., Nieminen, M., & Gheorghiade, M. (2012). Troponin elevation in patients with heart failure: On behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section. *European Heart Journal*, *33*(18), 2265–2271. https://doi.org/10.1093/eurheartj/ehs191

Javaheri, S., & Redline, S. (2017). Insomnia and risk of cardiovascular disease. *Chest*, *934*, 435. https://doi.org/10.1016/j.chest.2017.01.026

Johann, A. F., Hertenstein, E., Feige, B., Akram, U., Holub, F., Baglioni, C., Domschke, K., Schramm, E., Nissen, C., Kyle, S. D., Riemann, D., Biermann, J., & Spiegelhalder, K. (2020). Cognitive behavioural therapy for insomnia does not appear to have a substantial impact on early markers of cardiovascular disease: A preliminary randomized controlled trial. *Journal of Sleep Research*, *29*, 5. https://doi.org/10.1111/jsr.13102

Krokstad, S., Langhammer, A., Hveem, K., Holmen, T. L., Midthjell, K., Stene, T. R., Bratberg, G., Heggland, J., & Holmen, J. (2013). Cohort profile: The HUNT study, Norway. *International Journal of Epidemiology*, *42*(4), 968–977. https://doi.org/10.1093/ije/dys095

Lane, J. M., Jones, S. E., Dashti, H. S., Wood, A. R., Aragam, K. G., van Hees, V. T., Strand, L. B., Winsvold, B. S., Wang, H., Bowden, J., Song, Y., Patel, K., Anderson, S. G., Beaumont, R. N., Bechtold, D. A., Cade, B. E., Haas, M., Kathiresan, S., Little, M. A., Saxena, R. (2019). Biological and clinical insights from genetics of insomnia symptoms. *Nature Genetics*, *51*(3), 387–393. https://doi.org/10.1038/s41588-019-0361-7

Larsson, S. C., & Markus, H. S. (2019). Genetic Liability to Insomnia and Cardiovascular Disease Risk. *Circulation*, *140*(9), 796–798. https://doi.org/10.1161/circulationaha.119.041830

Laugsand, L. E., Strand, L. B., Platou, C., Vatten, L. J., & Janszky, I. (2014). Insomnia and the risk of incident heart failure: A population study. *European Heart Journal*, *35*(21), 1382–1393. https://doi.org/10.1093/eurheartj/eht019

Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y. L., Castro, A. F., Feldman, H. I., Kusek, J. W., Eggers, P., Van Lente, F., Greene, T., Coresh, J., & CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). (2009). A new equation to estimate glomerular filtration rate. *Annals of Internal Medicine*, *150*(9), 604–612. https://doi.org/10.7326/0003-4819-150-9-200905050-00006

Lyngbakken, M. N., Røsjø, H., Holmen, O. L., Dalen, H., Hveem, K., & Omland, T. (2019). Temporal changes in cardiac troponin i are associated with risk of cardiovascular events in the general population: The nord-trøndelag health study. *Clinical Chemistry*, *65*(7), 871–881. https://doi.org/10.1373/clinchem.2018.301069

McCarthy, C. P., Raber, I., Chapman, A. R., Sandoval, Y., Apple, F. S., Mills, N. L., & Januzzi, J. L. (2019). Myocardial Injury in the Era of High-Sensitivity Cardiac Troponin Assays. *JAMA Cardiology*, *4*(10), 1–9. https://doi.org/10.1001/jamacardio.2019.2724

Mcgrath, E. R., Espie, C. A., Power, A., Murphy, A. W., Newell, J., Kelly, C., Duffy, N., Gunning, P., Gibson, I., Bostock, S., & O'donnell, M. J. (2017). Sleep to Lower Elevated Blood Pressure: A Randomized Controlled Trial (SLEPT). *American Journal of Hypertension*, *30*(3), 319. https://doi.org/10.1093/ajh/hpw132

Meng, L., Zheng, Y., & Hui, R. (2013). The relationship of sleep duration and insomnia to risk of hypertension incidence: A meta-analysis of prospective cohort studies. *Hypertension Research*, *36*(11), 985–995. https://doi.org/10.1038/hr.2013.70

Ohayon, M. M. (2002). Epidemiology of insomnia: What we know and what we still need to learn. *Sleep Medicine Reviews*, *6*(2), 97–111. https://doi.org/10.1053/smrv.2002.0186

Omland, T., de Lemos, J. A., Sabatine, M. S., Christophori, C. A., Rice, M., Jablonski, K. A., Tjora, S., Domanski, M. J., Gersh, B. J., Rouleau, J. L., Pfeffer, M. A., & Braunwald, E. (2009). A Sensitive Cardiac Troponin T Assay in Stable Coronary Artery Disease. *The New England Journal of Medicine*, *361*(1478), 2538–2547. https://doi.org/10.1056/NEJMoa0805299.A

Omland, T., De Lemos, J. A., Holmen, O. L., Dalen, H., Benth, J. Š., Nygård, S., Hveem, K., & Røsjø, H. (2015). Impact of sex on the prognostic value of high-sensitivity cardiac troponin I in the general population: The HUNT study. *Clinical Chemistry*, *61*(4), 646–656. https://doi.org/10.1373/clinchem.2014.234369

Omland, T., Pfeffer, M. A., Solomon, S. D., De Lemos, J. A., Røsjø, H., Benth, J. Š., Maggioni, A., Domanski, M. J., Rouleau, J. L., Sabatine, M. S., & Braunwald, E. (2013). Prognostic value of cardiac troponin i measured with a highly sensitive assay in patients with stable coronary artery disease. *Journal of the American College of Cardiology*, *61*(12), 1240–1249. https://doi.org/10.1016/j.jacc.2012.12.026

Redwine, L., Hauger, R. L., Gillin, J. C., & Irwin, M. (2000). Effects of sleep and sleep deprivation on interleukin-6, growth hormone, cortisol, and melatonin levels in humans. *Journal of Clinical Endocrinology and Metabolism*, *85*(10), 3597–3603. https://doi.org/10.1210/jc.85.10.3597

Riemann, D., Baglioni, C., Bassetti, C., Bjorvatn, B., Dolenc Groselj, L., Ellis, J. G., Espie, C. A., Garcia-Borreguero, D., Gjerstad, M., Gonçalves, M., Hertenstein, E., Jansson-Fröjmark, M., Jennum, P. J., Leger, D., Nissen, C., Parrino, L., Paunio, T., Pevernagie, D., Verbraecken, J., … Spiegelhalder, K. (2017). European guideline for the diagnosis and treatment of insomnia. *Journal of Sleep Research*, *26*(6), 675–700. https://doi.org/10.1111/jsr.12594

Roca, G. Q., Redline, S., Claggett, B., Bello, N., Ballantyne, C. M., Solomon, S. D., & Shah, A. M. (2015). Sex-specific association of sleep apnea severity with subclinical myocardial injury, ventricular hypertrophy, and heart failure risk in a community-dwelling cohort. *Circulation*, *132*(14), 1329–1337. https://doi.org/10.1161/CIRCULATIONAHA.115.016985

Seliger, S. L., Hong, S. N., Christenson, R. H., Kronmal, R., Daniels, L. B., Lima, J. A. C., De Lemos, J. A., Bertoni, A., & Defilippi, C. R. (2017). High-Sensitive Cardiac Troponin T as an Early Biochemical Signature for Clinical and Subclinical Heart Failure: MESA (Multi-Ethnic Study of Atherosclerosis). *Circulation*, *135*(16), 1494–1505. https://doi.org/10.1161/CIRCULATIONAHA.116.025505

Sigurdardottir, F. D., Lyngbakken, M. N., Holmen, O. L., Dalen, H., Hveem, K., Røsjø, H., & Omland, T. (2018). Relative Prognostic Value of Cardiac Troponin I and C-Reactive Protein in the General Population (from the Nord-Trøndelag Health [HUNT] Study). *The American Journal of Cardiology*, *121*(8), 949–955. https://doi.org/10.1016/j.amjcard.2018.01.004

Sofi, F., Cesari, F., Casini, A., Macchi, C., Abbate, R., & Gensini, G. F. (2014). Insomnia and risk of cardiovascular disease: A meta-analysis. *European Journal of Preventive Cardiology*, *21*(1), 57–64. https://doi.org/10.1177/2047487312460020

Spiegel, K., Leproult, R., & Van Cauter, E. (1999). Impact of sleep debt on metabolic and endocrine function. *Lancet*, *354*(9188), 1435–1439. https://doi.org/10.1016/S0140-6736(99)01376-8

St-Onge, M.-P., Grandner, M. A., Brown, D., Conroy, M. B., Jean-Louis, G., Coons, M., & Bhatt, D. L. (2016). Sleep Duration and Quality: Impact on Lifestyle Behaviors and Cardiometabolic Health: A Scientific Statement From the American Heart Association. *Circulation*, *134*, 18. https://doi.org/10.1161/CIR.0000000000000444

Welsh, P., Preiss, D., Hayward, C., Shah, A. S. V., Mcallister, D., Briggs, A., Boachie, C., Mcconnachie, A., Padmanabhan, S., & Welsh, C. (2019). Cardiac Troponin T and Troponin I in the General Population

: Comparing and Contrasting their Genetic Determinants and Associations with Outcomes. *Circulation*, *139*(24), 2754–2764. https://doi.org/10.1161/CIRCULATIONAHA.118.038529

Wildi, K., Singeisen, H., Twerenbold, R., Badertscher, P., Wussler, D., Klinkenberg, Ljj, Meex, Sjr, Nestelberger, T., Boeddinghaus, J., Miró, Ò., Martin-Sanchez, Fj, Morawiec, B., Muzyk, P., Parenica, J., Keller, Di, Geigy, N., Potlukova, E., Sabti, Z., Kozhuharov, N., Puelacher, C., du Fay de Lavallaz, J., Rubini Gimenez, M., Shrestha, S., Marzano, G., Rentsch, K., Osswald, S., Reichlin, T., & Mueller, C. (2018). Circadian rhythm of cardiac troponin I and its clinical impact on the diagnostic accuracy for acute myocardial infarction. *International Journal of Cardiology*, *270*, 14–20. https://doi.org/10.1016/j.ijcard.2018.05.136

Xu, Q., & Lang, C. P. (2014). Examining the relationship between subjective sleep disturbance and menopause. *Menopause*, *21*(12), 1301–1318. https://doi.org/10.1097/GME.0000000000000240

Zhang, J., Ma, R. C. W., Kong, A. P. S., So, W. Y., Li, A. M., Lam, S. P., Li, S. X., Yu, M. W. M., Ho, C. S., Chan, M. H. M., Zhang, B., & Wing, Y. K. (2011). Relationship of sleep quantity and quality with 24-hour urinary catecholamines and salivary awakening cortisol in healthy middle-aged adults. *Sleep*, *34*(2), 225–233. https://doi.org/10.1093/sleep/34.2.225

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Sigurdardottir FD, Lyngbakken MN, Hveem K, et al. Insomnia symptoms and subclinical myocardial injury: Data from the Nord-Trøndelag Health (HUNT) study. *J Sleep Res*. 2021;30:e13299. https://doi.org/10.1111/jsr.13299