

Insomnia as a risk factor for ill health: results from the large population-based prospective HUNT Study in Norway

BØRGE SIVERTSEN^{1,2,3}, TEA LALLUKKA^{4,5}, PAULA SALO^{4,6}, STÅLE PALLESEN^{7,8}, MARI HYSING⁹, STEINAR KROKSTAD^{10,11} and SIMON ØVERLAND^{1,8}

¹Division of Mental Health, Norwegian Institute of Public Health, Bergen, Norway, ²Uni Health, Uni Research, Bergen, Norway, ³Department of Psychiatry, Helse Fonna HF, Haugesund, Norway, ⁴Finnish Institute of Occupational Health, Helsinki, Finland, ⁵Department of Public Health, Hjelt Institute, University of Helsinki, Helsinki, Finland, ⁶Department of Psychology, University of Turku, Turku, Finland, ⁷Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen, Norway, ⁸Faculty of Psychology, University of Bergen, Bergen, Norway, ⁹Regional Centre for Child and Youth Mental Health and Child Welfare, Uni Health, Uni Research, Bergen, Norway, ¹⁰Levanger Hospital, Nord-Trøndelag Health Trust, Levanger, Norway and ¹¹HUNT Research Centre, Norwegian University of Technology and Science, Levanger, Norway

Keywords

epidemiology, health, insomnia, risk factor, prospective

Correspondence

Børge Sivertsen, PhD, Division of Mental Health, Norwegian Institute of Public Health, Bergen, Norway, Kalfarveien 31, 5018 Bergen, Norway.

Tel.: +47-53-20-41-01;

fax: +47-53-20-40-01;

e-mail: borge.sivertsen@fhi.no

Accepted in revised form 15 September 2013; received 21 June 2013

DOI: 10.1111/jsr.12102

SUMMARY

Insomnia co-occurs with many health problems, but less is known about the prospective associations. The aim of the current study was to investigate if insomnia predicts cumulative incidence of mental and physical conditions. Prospective population-based data from the two last Nord-Trøndelag Health Studies (HUNT2 in 1995–97 and HUNT3 in 2006–08), comprising 24 715 people in the working population, were used to study insomnia as a risk factor for incidence of physical and mental conditions. Insomnia was defined according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Insomnia at HUNT2 was a significant risk factor for incidence of a range of both mental and physical conditions at HUNT3 11 years later. Most effects were only slightly attenuated when adjusting for confounding factors, and insomnia remained a significant risk factor for the following conditions in the adjusted analyses: depression [odds ratio (OR): 2.38, 95% confidence interval (CI): 1.91–2.98], anxiety (OR: 2.08, 95% CI: 1.63–2.64), fibromyalgia (OR: 2.05, 95% CI: 1.51–2.79), rheumatoid arthritis (OR: 1.87, 95% CI: 1.29–2.52), whiplash (OR: 1.71, 95% CI: 1.21–2.41), arthrosis (OR: 1.68, 95% CI: 1.43–1.98), osteoporosis (OR: 1.52, 95% CI: 1.14–2.01), headache (OR: 1.50, 95% CI: 1.16–1.95), asthma (OR: 1.47, 95% CI: 1.16–1.86 and myocardial infarction (OR: 1.46, 95% CI: 1.06–2.00). Insomnia was also associated significantly with incidence of angina, hypertension, obesity and stroke in the crude analyses, but not after adjusting for confounders. We conclude that insomnia predicts cumulative incidence of several physical and mental conditions. These results may have important clinical implications, and whether or not treatment of insomnia would have a preventive value for both physical and mental conditions should be studied further.

INTRODUCTION

There is ample evidence linking insomnia to ill health. Insomnia is associated strongly with a wide range of conditions and diseases, including cardiac diseases, hypertension, neurological disease, cancer, diabetes and asthma

(Vgontzas *et al.*, 2009a,b). Insomnia is also a common symptom in a variety of musculoskeletal pain conditions, including rheumatoid arthritis, osteoporosis and fibromyalgia (Moldofsky, 2001; Sivertsen *et al.*, 2009a). Furthermore, insomnia typically co-occurs with several mental disorders, especially anxiety and depression. Most of the evidence on

these associations is derived from cross-sectional studies, but also longitudinal studies have suggested that insomnia is a significant risk factor for the development of depression (Baglioni *et al.*, 2011; Sivertsen *et al.*, 2012), anxiety (Morphy *et al.*, 2007; Neckelmann *et al.*, 2007), musculoskeletal pain (Morphy *et al.*, 2007), coronary heart disease (Chandola *et al.*, 2010) and myocardial infarction (Laugsand *et al.*, 2011). Beyond prospective links to a variety of health outcomes, several recent studies have demonstrated that insomnia predicts subsequent work disability certified medically for mental or physical conditions, such as diseases of the musculoskeletal, circulatory and nervous system, and injuries and poisonings (Lallukka *et al.*, 2011; Salo *et al.*, 2012a). In a non-depressed occupational cohort, insomnia predicts onset of treatment for depression (Salo *et al.*, 2012b). In addition, a recent study demonstrated that insomnia in combination with short sleep duration may be a risk factor for subsequent hypertension (Fernandez-Mendoza *et al.*, 2012). Nevertheless, there is a paucity of studies examining the longitudinal association between insomnia and subsequent onset of different physical and mental disorders or conditions. Furthermore, most of these studies have focused on one condition at a time, and few have examined relative strengths in a prospective design with proper control for confounders.

The aim of the current study was to examine to what extent insomnia represents a risk factor for developing a range of physical and mental conditions. Data stem from the two most recent waves of a large prospective population-based study—the Nord-Trøndelag Health Studies (HUNT2 and HUNT3) conducted 11 years apart.

MATERIALS AND METHODS

Participants

The HUNT Study is a large population database for medical and health-related research. So far, three health surveys (HUNT1–HUNT3) of the general adult population in the Nord-Trøndelag County, Norway have been completed. The current study uses data from the two most recent surveys, the HUNT2 conducted in the period 1995–97 and HUNT3 conducted in the period 2006–08. In all the HUNT surveys, the data were collected in each of the 24 municipalities in the county by using temporarily located health examination sites staffed by certified fieldwork teams. Invitation files for the HUNT surveys were created from monthly updated national census data. The invitation letter was sent by post and included the first questionnaire (Q1) and an information pamphlet. The participants delivered Q1 and written consent when they attended the health examination sites. After the clinical examination, a second questionnaire (Q2) was handed out to everyone.

In all, 92 100 individuals aged 20–89 years received an initial questionnaire and a personal invitation to participate in HUNT2 (1995–97) (Krokstad *et al.*, 2012). Of these, 65 648

(71%) attended a physical examination, where they also received a second questionnaire (including questions on sleep and health conditions), which 52 814 (80%) participants completed. Valid ratings on the variables for the purposes of the current study were obtained from 43 045 participants, 82% of those who completed the questionnaire or 66% of those who attended the examination. In HUNT3 (2006–08), 93 010 individuals aged 20–89 years were invited based on the same procedure as in HUNT2, and 50 625 (54%) participated. Of these, 49 797 received a second set of questionnaires when they attended the clinical examination (including questions on sleep and health conditions), and 41 162 (83%) completed the questionnaire. Due to the 11-year lag between the two surveys, participants aged between 20 and 31 years were excluded from the HUNT3, as also were participants older than 67 years in HUNT2 due to age-based retirement (as one of the insomnia questions assessed impaired work performance). Thus, the final data set for the current study comprised measurements from a total of 24 715 individuals in the working population (aged 32–66 years) who provided complete information on all study variables.

Measures

Insomnia (HUNT2)

The DSM-IV criteria for insomnia include difficulty initiating or maintaining sleep or experiencing non-restorative sleep for a period of 1 month or more. In addition, it is a prerequisite that the symptoms result in significant impairment in daily functioning. In the HUNT2 study, a proxy for the insomnia diagnosis according to the fourth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) was based on three items, encompassing people endorsing sleep onset or terminal/late insomnia (unable to get back to sleep after an awakening) ‘often’ or ‘almost every night’ in the preceding month, in addition to reporting impaired work performance caused by insomnia during the preceding year. This operationalization has also been applied in previous studies (Sivertsen *et al.*, 2012). No information was available concerning the duration of insomnia which, according to the DSM-IV and Research Diagnostic Criteria (Edinger *et al.*, 2004), would be formally required to fulfil the criteria for insomnia syndrome.

Physical and mental health (HUNT2 and HUNT3)

Physical and mental conditions were assessed by self-reported diagnoses. The diagnoses were categorized into physical conditions (angina, arthrosis, asthma, ankylosing spondylitis, cancer, diabetes (type 2), fibromyalgia, headache, hypertension, myocardial infarction, osteoporosis, rheumatoid arthritis, stroke and whiplash) and mental conditions (anxiety and depression). This operationalization has been used in previous studies from the same health survey

(Sivertsen *et al.*, 2009a). Body height and weight were measured during the clinical examinations at HUNT2 and HUNT3. Body mass index (BMI) was calculated from body weight (kg) divided by height squared (m²). Obesity was defined as BMI \geq 30, as recommended by the World Health Organization (WHO). (2013).

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) was used to assess self-reported symptoms of anxiety and depression in both HUNT2 and HUNT3. The HADS comprises 14 items each scored on a 4-point scale. Seven of the 14 items reflect symptoms of anxiety (HADS-A) and a further seven depict symptoms of depression (HADS-D), respectively. No items concerning vegetative symptoms or sleep difficulties are included in the HADS. A cut-off score of 8 on both subscales has been shown to give an optimal balance between sensitivity and specificity at approximately 0.80 for depression, according to the third and fourth versions of the Statistical Manual of Mental Disorders (DSM-III and -IV), as well as according to the 8th and 9th editions of the International Classification of Disorders (ICD-8 and -9). For the present study, we used the dichotomous measure of anxiety and depression. In addition, we included a single item where participants were asked if they had ever had a mental problem for which they had sought help. This item was coded 'yes' or 'no'. The frequency

of the conditions included in the study can be seen in Table 1.

Sociodemographic variables

Data on age and gender were obtained from the national population registry of Norway. Self-reported educational level was coded as 'primary', 'secondary' or 'college/university'.

Statistics

IBM SPSS statistics, version 21 for Mac (SPSS Inc., Chicago, IL, USA), was used to run block-wise logistic regression analyses to examine relationships between insomnia at HUNT2 and physical and mental health problems in HUNT3. To investigate the effect of insomnia on the incident of these conditions, the logistic regression analyses were repeated excluding those participants reporting that specific disorder/condition at HUNT2. To identify the unique association between insomnia and each condition, both bivariate and multivariate logistic regression analyses were conducted to control for demographics as well as physical or mental conditions. For example, in the fully adjusted model concerning the association between insomnia and angina, we controlled for demographics, as well as all conditions listed

Table 1 Frequency of conditions at HUNT2 and HUNT3

	Total N*	HUNT2		HUNT3		New onset at HUNT3 [†]	
		n	%	n	%	n	%
Insomnia	44 270	2501	5.6				
Physical conditions							
Angina	29 897	530	1.8	1060	3.5	671	2.3
Arthrosis	27 001	1860	6.9	4447	16.5	3157	12.6
Asthma	29 887	2252	7.5	2600	8.1	1037	3.8
Ankylosing spondylitis	27 116	514	1.9	452	1.7	107	0.4
Cancer	29 144	741	2.5	1705	5.9	1188	4.2
Diabetes (type 2)	29 923	421	1.4	1416	4.7	1029	3.5
Fibromyalgia	27 222	1000	3.7	1165	4.3	488	1.9
Headache	24 463	10 454	42.7	8326	24.0	2214	15.8
Hypertension	29 913	2033	6.8	7189	24.0	5259	18.9
Myocardial infarction	29 924	349	1.2	988	3.3	684	2.3
Obesity (BMI > 30)	29 771	4135	13.9	6816	22.9	3278	12.8
Osteoporosis	27 411	375	1.4	871	3.2	685	2.5
Rheumatoid arthritis	27 138	560	2.1	962	3.5	618	2.3
Stroke	29 904	190	0.6	801	2.7	661	2.2
Whiplash	26 613	755	2.8	944	3.5	473	1.8
Mental conditions							
Anxiety	25 608	3795	14.8	3456	13.5	1757	8.1
Depression	25 750	2302	8.9	2430	9.4	1506	6.4
Mental disorder (seeking help for)	27 768	3171	11.4	3606	13.0	1774	7.2

BMI, body mass index; HUNT, Nord-Trøndelag Health Studies.

*Total N refers to number of participants in the longitudinal sample with valid responses on the insomnia items (at HUNT2) and the questions pertaining to the specific conditions (at HUNT2 and HUNT3).

[†]Percentage calculated from participants not reporting that condition at HUNT2.

under 'Mental disorders' in Table 2. Similarly, we controlled for both demographics and all conditions listed under 'Physical conditions' in Table 2 in order to examine the independent effect of insomnia on anxiety. Results are presented as odds ratios (OR) with 95% confidence intervals (95% CI).

Ethics

This study was approved by the Regional Committee for Medical and Health Research Ethics. After providing a description of the study to the subjects, written informed consent was obtained.

RESULTS

Sample characteristics

The mean age for the sample used in the current study was 45.3 years at HUNT2 (range 19–67) and 56.1 years (range 29–80) at HUNT3. The sample included more females

(56.9%) than males (43.1%). Twenty-five per cent had education beyond high school level, and the sample was predominantly Caucasian.

Insomnia and observed physical and mental conditions 11 years later

As detailed in Table 2, insomnia at HUNT2 was associated with all physical and mental conditions observed 11 years later at HUNT3, with the exception of diabetes (type 2). The strongest associations were found with musculoskeletal conditions; for example, fibromyalgia, osteoporosis and rheumatoid arthritis (ORs ranging from 2.4 to 5.9), whereas the estimates were smaller, but still significant, for other physical diagnoses such as cancer, myocardial infarction and stroke (ORs ranging from 1.3 to 1.7). All associations remained significant after adjustment for demographics. After further adjustment for anxiety and depression at baseline, the majority of associations remained significant in the fully adjusted model (adjusted ORs ranging from 1.3 to 3.8). However, the associations between insomnia and cancer,

Table 2 Insomnia at HUNT2 as a risk factor for reporting conditions/disorders 11 years later at HUNT3

Disorder/condition (HUNT3)	Risk factor: Insomnia at HUNT2					
	Unadjusted model		Adjusted model*		Adjusted model†	
	OR	95% CI	OR	95% CI	OR	95% CI
Physical conditions						
Angina	1.72	1.38–2.14	1.75	1.39–2.20	1.52	1.19–1.94
Arthrosis	2.45	2.19–2.75	2.10	1.85–2.37	1.83	1.61–2.08
Asthma	1.70	1.47–1.98	1.68	1.44–1.95	1.46	1.25–1.71
Ankylosing spondylitis	1.94	1.42–2.66	1.96	1.43–2.70	1.68	1.20–2.36
Cancer	1.32	1.09–1.60	1.15	0.94–1.39	1.20	0.98–1.47
Diabetes (type 2)	1.12	0.90–1.41	1.04	0.83–1.31	0.99	0.77–1.26
Fibromyalgia	5.91	5.09–6.85	5.16	4.42–6.02	3.76	3.19–4.45
Headache	1.93	1.72–2.15	2.20	1.96–2.47	1.86	1.64–2.10
Hypertension	1.28	1.15–1.44	1.09	0.97–1.23	1.04	0.92–1.18
Myocardial infarction	1.30	1.01–1.68	1.42	1.09–1.85	1.35	1.02–1.78
Obesity (BMI > 30)	1.23	1.10–1.38	1.18	1.06–1.33	1.09	0.97–1.24
Osteoporosis	2.55	2.08–3.12	1.86	1.50–2.30	1.61	1.28–2.03
Rheumatoid arthritis	2.45	2.01–2.97	2.17	1.79–2.64	1.91	1.55–2.36
Stroke	1.72	1.33–2.21	1.50	1.24–2.07	1.33	1.02–1.75
Whiplash	2.35	1.92–2.87	2.45	2.00–3.00	1.92	1.54–2.38
					<i>Adjusted model‡</i>	
	<i>OR</i>	<i>95% CI</i>	<i>OR</i>	<i>95% CI</i>	<i>OR</i>	<i>95% CI</i>
Mental disorders						
Anxiety	3.81	3.38–4.28	3.75	3.33–4.23	3.07	2.67–3.55
Depression	3.17	2.78–3.63	3.12	2.73–3.57	2.68	2.28–3.14
Mental disorder (seeking help for)	3.60	3.45–4.33	3.80	3.38–4.26	3.05	2.64–3.52

BMI, body mass index; HUNT, Nord-Trøndelag Health Studies; CI, confidence interval; OR, odds ratio.

Statistically significant associations highlighted in bold type.

*Adjusted for demographics (age, gender and education).

†Adjusted for demographics + anxiety and depression at baseline.

‡Adjusted for demographics + angina, arthrosis, asthma, ankylosing spondylitis, cancer, diabetes (type 2), fibromyalgia, headache, hypertension, myocardial infarction, obesity (BMI > 30), osteoporosis, rheumatoid arthritis, stroke and whiplash at baseline.

headache, hypertension and obesity were attenuated to a non-significant level.

Insomnia at HUNT2 was also associated significantly with reporting anxiety and depression at HUNT3, both in the crude analyses (ORs: 3.6–3.8) and after adjusting for demographics and physical conditions (adjusted ORs: 2.7–3.1). Insomnia at baseline was also associated with reporting help-seeking for a mental condition in HUNT3 (adjusted OR: 3.1).

Insomnia as a risk factor for incident of physical and mental conditions 11 years later

To examine the risk of insomnia on the onset (cumulative incidence) of physical and mental conditions in HUNT3, we repeated the analyses, having excluded all participants with the corresponding condition of interest at HUNT2. In the crude analyses, insomnia was a significant risk factor for the incidence of most conditions, including angina, arthrosis, asthma, fibromyalgia, headache, hypertension, myocardial infarction, obesity, osteoporosis, rheumatoid arthritis, stroke and whiplash, with ORs ranging from 1.2 to 3.1 (see Table 3

for details). The effects were strongest for fibromyalgia (OR: 3.1), osteoporosis and rheumatoid arthritis (both OR: 2.3). Notably, no associations were found between insomnia and cancer or diabetes (type 2). The associations were only slightly attenuated when adjusting for sociodemographics, and further adjustment for mental conditions left most associations still statistically significant, with the exception of angina, obesity and stroke.

As detailed in Table 3, insomnia at baseline was also associated with more than twice the odds for incident of anxiety, depression and help-seeking for a mental condition 11 years later (all crude ORs: 2.6). Adjusting for demographics did not reduce these associations, and further adjustment for physical conditions only slightly attenuated the effects (adjusted ORs ranging from 2.1 to 2.4).

DISCUSSION

This study sought to examine the prospective associations between insomnia and subsequent physical and mental conditions. By linking data from two waves of a large

Table 3 Insomnia at HUNT2 as a risk factor for onset* of conditions/disorders 11 years later at HUNT3

Disorder/condition (HUNT3)	Risk factor: insomnia at HUNT2					
	Unadjusted model		Adjusted model [†]		Adjusted model [‡]	
	OR	95% CI	OR	95% CI	OR	95% CI
Physical conditions						
Angina	1.53	1.14–2.04	1.52	1.28–2.04	1.35	0.99–1.84
Arthrosis	2.14	1.85–2.48	1.92	1.64–2.24	1.68	1.43–1.98
Asthma	1.93	1.55–2.40	1.84	1.47–2.29	1.47	1.16–1.86
Ankylosing spondylitis	1.66	0.81–3.43	1.77	0.86–3.66	1.25	0.56–2.78
Cancer	1.17	0.91–1.51	1.05	0.81–1.35	1.09	0.84–1.42
Diabetes (type 2)	1.24	0.97–1.61	1.14	0.88–1.48	1.07	0.82–1.41
Fibromyalgia	3.11	2.34–4.13	2.99	2.25–3.99	2.05	1.51–2.79
Headache	1.35	1.06–1.72	1.68	1.31–2.14	1.50	1.16–1.95
Hypertension	1.21	1.06–1.38	1.03	0.91–1.19	0.99	0.86–1.14
Myocardial infarction	1.40	1.04–1.88	1.46	1.08–1.97	1.46	1.06–2.00
Obesity (BMI > 30)	1.21	1.03–1.41	1.22	1.04–1.43	1.13	0.96–1.33
Osteoporosis	2.31	1.79–2.98	1.73	1.32–2.25	1.52	1.14–2.01
Rheumatoid arthritis	2.25	1.71–2.96	2.08	1.58–2.74	1.87	1.29–2.52
Stroke	1.64	1.23–2.17	1.52	1.14–2.03	1.29	0.95–1.75
Whiplash	1.95	1.40–2.69	2.09	1.51–2.91	1.71	1.21–2.41
<i>Adjusted model[§]</i>						
	OR	95% CI	OR	95% CI	OR	95% CI
Mental disorders						
Anxiety	2.59	2.19–3.17	2.56	2.08–3.14	2.08	1.63–2.64
Depression	2.60	2.14–3.15	2.58	2.13–3.13	2.38	1.91–2.98
Mental disorder (seeking help for)	2.53	2.09–3.06	2.62	2.16–3.17	2.10	1.65–2.66

BMI, body mass index; HUNT, Nord-Trøndelag Health Studies; CI, confidence interval; OR, odds ratio.

Statistically significant associations highlighted in bold type.

*Analyses conducted on participants not reporting that condition at HUNT2.

[†]Adjusted for demographics (age, gender and education).

[‡]Adjusted for demographics + anxiety and depression at baseline.

[§]Adjusted for demographics + angina, arthrosis, asthma, ankylosing spondylitis, cancer, diabetes (type 2), fibromyalgia, headache, hypertension, myocardial infarction, obesity (BMI > 30), osteoporosis, rheumatoid arthritis, stroke and whiplash at baseline.

population study, conducted 11 years apart (the HUNT studies), we found that insomnia at HUNT2 was a significant risk factor for the incidence of a range of both physical and mental conditions at HUNT3, even after adjusting for confounding factors.

Insomnia as a risk factor for physical conditions

The current study found insomnia to be a risk factor for a range of physical conditions and illnesses 11 years later. The strongest effects were found for musculoskeletal pain conditions (e.g. fibromyalgia, rheumatoid arthritis and headache), which also remained significant after adjusting for sociodemographics and mental conditions. Although the link between insomnia and pain conditions has been demonstrated previously (Sivertsen *et al.*, 2009a; Taylor *et al.*, 2007), only a few epidemiological studies have explored the association using a cohort design. In a study by Morphy *et al.* (2007), insomnia predicted onset of widespread pain 12 months after baseline. The finding that insomnia predicted incidence of whiplash is particularly noteworthy, but perhaps not unexpected, as sleep problems, daytime sleepiness and residual effects of sleep medication all increase the risk of being exposed to accidents (Pandi-Perumal *et al.*, 2006) and also coping with health problems after accidents.

We found insomnia to predict incidence of myocardial infarction. Although the association between insomnia and cardiovascular risk has been studied extensively, the findings have been mixed. A review from 2003 (Taylor *et al.*, 2003) identified four prospective studies on this topic, of which the three community studies found no significant association between insomnia and cardiovascular disease (CVD) (Schwartz *et al.*, 1998). In contrast, two recent Norwegian epidemiological studies ($n = 52000+$) linked to hospital records or the National Cause of Death Registry found symptoms of insomnia to be associated with an increased risk of both incident heart failure (Laugsand *et al.*, 2013) and acute myocardial infarction (Laugsand *et al.*, 2011). Also in an occupational cohort, insomnia symptoms have been shown to predict work disability due to CVDs (Salo *et al.*, 2010). In those studies, however, the authors did not combine the items on insomnia symptoms to investigate DSM-IV defined insomnia as was conducted in this study. In addition to the increased risk for incident myocardial infarction, the current study also suggested a link between insomnia and onset of angina, albeit only borderline significant in the fully adjusted model.

Previous studies have linked self-reported sleep duration to both diabetes (type 2) (Vgontzas *et al.*, 2009b) and obesity (Gangwisch *et al.*, 2005), and although the current study found crude associations between obesity and insomnia this effect was not significant when adjusting for anxiety and depression. Further, no significant relationship was found between insomnia and diabetes (type 2). The failure to replicate these associations may be explained partly by the current study focusing on subjective insomnia, as opposed to

actual sleep deprivation. To our knowledge, all studies concerning the prospective link between sleep variables and both diabetes (type 2) and obesity have linked these conditions with sleep loss or short sleep duration, which may overlap with insomnia (Sivertsen *et al.*, 2009b). Thus, the effects of sleep loss and short sleep are not necessarily similar to the effects of insomnia. For example, data from the Penn-State cohort illustrate the importance of assessing insomnia as well as sleep duration, as both consequences and treatment approaches have been suggested to depend upon sleep duration of the insomniacs (Vgontzas and Fernandez-Mendoza, 2013).

While the current study supports insomnia as a risk indicator of later physical ill health, the mechanisms or processes involved are not certain. The consistent relation demonstrated across health conditions could suggest that there are some common aetiological factors driving the association. However, insomnia as a prodromal syndrome or risk indicator of other confounding conditions cannot be ruled out. Some possible pathways between insomnia and health have been proposed, including medication effects, inflammation, immune function and pathophysiological processes such as autonomic hyperarousal. A possible pathophysiological pathway was exemplified by observed blood pressure changes and hyperactivity of the central nervous system in chronic insomniacs (Lanfranchi *et al.*, 2009). This stressor evoked blood pressure reactivity, and central autonomic activity may be a response to inflammation, which has been found to be a risk factor common for both depression and CVD (Harrison *et al.*, 2013). Experimental studies have demonstrated a link between insomnia and inflammation, especially interleukin (IL)-6 (Burgos *et al.*, 2006; Vgontzas *et al.*, 2002), which is also interesting with regard to developing novel approaches in the treatment of chronic insomnia.

Interestingly, several of the associations between insomnia and physical conditions (e.g. obesity) were reduced to a non-significant level when adjusting for anxiety and depression, suggesting that psychological factors mediate these associations. This is in line with the conclusion in a study by Vgontzas *et al.* (2008) who also emphasized the importance of emotional stress in explaining the link between sleep disturbances and obesity.

Insomnia as a risk factor for mental conditions

In sum, our findings show that insomnia is associated most strongly with conditions characterized by some level of psychological or psychosomatic aspects (e.g. anxiety, depression and fibromyalgia), which is in line with previous cross-sectional research in this field (Sivertsen *et al.*, 2009a). The present findings are in accordance with most of the existing studies concerning insomnia as a significant and independent risk factor for subsequent onset of depression. Although it is difficult to compare effect sizes across studies due to differences in age span, operationalization of exposure and outcome variables, follow-up time, etc., our result

showing that insomnia increases the risk of later depression is in accordance with a recent meta-analysis by Baglioni *et al.* (2011) on 21 single prospective studies. For anxiety, a previous study (Neckelmann *et al.*, 2007) linking data from HUNT1 and HUNT2 found insomnia to predict anxiety 11 years later, although that study did not investigate if insomnia predicted onset of anxiety. To our knowledge, the only previous longitudinal epidemiological study investigating the effect of insomnia on the incidence of anxiety was a study from the United Kingdom, where a risk ratio of 2.3 was found after adjusting for confounding factors (sociodemographics, depression and pain). As such, the current study confirms the shift in the view of insomnia from being an epiphenomenon of mental disorders towards insomnia as a co-occurring condition related to both functional outcome and treatment prognosis of co-occurring anxiety or depression (Harvey, 2001). There is now much evidence that insomnia may also function as an independent risk factor for the development of mental disorders. However, both these and the current findings do not rule out reverse causality or a bidirectional association, which was indeed demonstrated in a recent study based on a similar design (Sivertsen *et al.*, 2012).

There are several possible mechanisms that may explain our finding that insomnia increases the risk of mental illnesses. As demonstrated by Harvey and colleagues, sleep disturbances seem to be an important transdiagnostic process across mental illness (Harvey *et al.*, 2011). For example, insomnia has been shown to be linked aetiologically to psychopathology via its reciprocal relation to emotion regulation and the interplay between, for example, the dopamine and serotonin systems across sleep disturbances and several psychiatric disorders (Harvey *et al.*, 2011). Similarly, Baglioni *et al.* (2010) have shown how dysfunctional emotional reactivity may mediate the association between insomnia and mental health problems. Another possible explanation on how insomnia may lead to depression was suggested recently by Riemann *et al.* (2012) who hypothesize that fragmentation of rapid eye movement (REM) sleep may lead to dysfunction in emotional neural networks which, again, may contribute to emotional and cognitive alterations, increasing the risk of developing depression.

Methodological considerations

This is one of the first studies to explore the effect of insomnia on subsequent physical and mental conditions using a prospective cohort design in a large general population sample. As the data were collected in a general health survey, neither researchers nor participants were aware of the research hypothesis during data collection, ruling out some potential sources of design-related and reporting bias. The follow-up time between the two data collections was 11 years. The HUNT Study aims to follow the health of the county population approximately every decade, and consequently the interval was not chosen specifically for the present study. The appropriate length of a follow-up depends upon the causal

mechanisms and processes between the entities involved, thus the ideal time for studying the relationship between insomnia and other conditions is not given. An advantage of this long follow-up is that it enables us to examine some chronic diseases that take a long time to develop. Also, insomnia has been shown previously to be a persistent and recurrent condition (Morin *et al.*, 2009). During 11 years, both insomnia and the other conditions might fluctuate, but we have no information about this in the data from the HUNT Study. Although the magnitude of the associations in studies with different follow-ups does not seem to differ significantly (Baglioni *et al.*, 2011), longer follow-ups generally require more careful consideration of potential confounding factors which are more likely to influence the outcome over time. In the current study, a somewhat long list of conditions and complaints was therefore controlled for. However, adjustments in the final analyses have most probably not captured and fully attenuated all possible confounding effects from chronic physical or psychiatric conditions. If such diagnoses and symptoms are under-reported the relationships found may, in turn, have been overestimated. Also, we have no information as to the severity of the eventual diseases. However, non-participants have higher mortality in the HUNT Study (Langhammer *et al.*, 2012) and it is commonly held that ill health increases risk of non-attendance in epidemiological studies, thus limiting the potential problem of other forms of health problems not being registered by the procedures used in the current study. Previous studies of non-responders in the HUNT studies have also shown that the prevalence rates of CVD, hypertension, diabetes and psychiatric disorders are higher among non-participants, and according to the register data the non-participants also have lower socioeconomic status (Krokstad *et al.*, 2012). Therefore, possible selection bias cannot be ruled out. The same mechanisms, allowed to operate twice over an 11-year gap, are likely to result in bias towards a healthier sample. The fact that only working participants were included in the present study (due to the operationalization of insomnia) may also have resulted in a healthier sample. This may result in underestimated prevalence rates, but also fewer cases with both insomnia and the other conditions. However, the prevalence rate of insomnia in HUNT2 was found to be 5.6%, which is in line with previous studies reporting the prevalence of insomnia based on the DSM-IV criteria (Ohayon, 1997). In line with this, no item on insomnia duration was included, thus the insomnia group comprised both chronic and non-chronic insomniacs. This may explain why some of the associations were small and became non-significant after adjustment for confounders (e.g. hypertension). Also, the use of objective measures of sleep (polysomnography) would most probably have detected more severe insomniacs, which would have impacted upon the magnitude of risk of developing ill health (Vgontzas *et al.*, 2009a, 2013). Finally, it should be noted that all mental and most physical conditions in the current study were self-reported (except obesity, which was based upon height and weight measurements at the clinical examinations), and thus not verified by a clinician.

Clinical implications

The key finding in this study was a prospective association between insomnia and several physical and mental conditions over a time-span of 11 years. Although strong causal conclusions based on epidemiological data cannot be made, our results lend some support to previous studies indicating that treatment of the first-occurring disorder may prevent the development of the subsequent condition. Eaton *et al.* (1995) estimated, for example, that eliminating insomnia at baseline could prevent 47% of new cases with depression during the following year. If similar well-controlled studies confirm that early treatment of insomnia also helps to prevent other conditions, it adds to the importance of detecting and treating insomnia. General practice would be one relevant arena, as a large majority of primary insomniacs remains undetected and untreated. In addition, prevention of new disorders is important as comorbidity in general is associated with poorer prognosis, perhaps leaving both disorders more difficult to treat. There is ample evidence of a strong and lasting effect of cognitive behavioural therapy for insomnia (CBT-I). However, despite being highly effective, individual CBT-I is both expensive and time-consuming and, perhaps even more importantly, it is not readily available for the majority of the population. New evidence on the effect of internet-delivered interventions based on CBT-I, e.g. the SLEEPIO and SHUTi-programs (Espie *et al.*, 2012; Ritterband *et al.*, 2009), points to an important future direction for improving public dissemination and the implementation of efficacious and cost-effective insomnia treatments.

CONCLUSION

Bearing in mind the methodological limitations stemming from observational epidemiological data, our study indicates that insomnia is a risk factor for several physical and mental disorders. It can be considered supportive of the clinical implication that treatment of insomnia may contribute to the prevention of both physical and mental disorders. However, more research is needed to support this hypothesis.

ACKNOWLEDGEMENTS

The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between the HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology NTNU), Central Norway Regional Health Authority, Nord-Trøndelag County Council and the Norwegian Institute of Public Health.

CONFLICT OF INTEREST

No conflicts of interest declared.

REFERENCES

Baglioni, C., Spiegelhalter, K., Lombardo, C. and Riemann, D. Sleep and emotions: a focus on insomnia. *Sleep Med. Rev.*, 2010, 14: 227–238.

- Baglioni, C., Battagliese, G., Feige, B. *et al.* Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J. Affect. Disord.*, 2011, 135: 10–19.
- Burgos, I., Richter, L., Klein, T. *et al.* Increased nocturnal interleukin-6 excretion in patients with primary insomnia: a pilot study. *Brain Behav. Immun.*, 2006, 20: 246–253.
- Chandola, T., Ferrie, J. E., Perski, A., Akbaraly, T. and Marmot, M. G. The effect of short sleep duration on coronary heart disease risk is greatest among those with sleep disturbance: a prospective study from the Whitehall II cohort. *Sleep*, 2010, 33: 739–744.
- Eaton, W. W., Badawi, M. and Melton, B. Prodromes and precursors: epidemiologic data for primary prevention of disorders with slow onset. *Am. J. Psychiatry*, 1995, 152: 967–972.
- Edinger, J. D., Bonnet, M. H., Bootzin, R. R. *et al.* Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. *Sleep*, 2004, 27: 1567–1596.
- Espie, C. A., Kyle, S. D., Williams, C. *et al.* A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. *Sleep*, 2012, 35: 769–781.
- Fernandez-Mendoza, J., Vgontzas, A. N., Liao, D. *et al.* Insomnia with objective short sleep duration and incident hypertension: the Penn State Cohort. *Hypertension*, 2012, 60: 929–935.
- Gangwisch, J. E., Malaspina, D., Boden-Albala, B. and Heymsfield, S. B. Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. *Sleep*, 2005, 28: 1289–1296.
- Harrison, N. A., Cooper, E., Voon, V., Miles, K. and Critchley, H. D. Central autonomic network mediates cardiovascular responses to acute inflammation: relevance to increased cardiovascular risk in depression? *Brain Behav. Immun.*, 2013, 31: 189–196.
- Harvey, A. G. Insomnia: symptom or diagnosis? *Clin. Psychol. Rev.*, 2001, 21: 1037–1059.
- Harvey, A. G., Murray, G., Chandler, R. A. and Soehner, A. Sleep disturbance as transdiagnostic: consideration of neurobiological mechanisms. *Clin. Psychol. Rev.*, 2011, 31: 225–235.
- Krokstad, S., Langhammer, A., Hveem, K. *et al.* Cohort profile: the HUNT Study, Norway. *Int. J. Epidemiol.*, 2012, 42: 968–977.
- Lallukka, T., Haaramo, P., Lahelma, E. and Rahkonen, O. Sleep problems and disability retirement: a register-based follow-up study. *Am. J. Epidemiol.*, 2011, 173: 871–881.
- Lanfranchi, P. A., Pennestri, M. H., Fradette, L., Dumont, M., Morin, C. M. and Montplaisir, J. Nighttime blood pressure in normotensive subjects with chronic insomnia: implications for cardiovascular risk. *Sleep*, 2009, 32: 760–766.
- Langhammer, A., Krokstad, S., Romundstad, P., Heggland, J. and Holmen, J. The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. *BMC Med. Res. Methodol.*, 2012, 12: 143.
- Laugsand, L. E., Vatten, L. J., Platou, C. and Janszky, I. Insomnia and the risk of acute myocardial infarction: a population study. *Circulation*, 2011, 124: 2073–2081.
- Laugsand, L. E., Strand, L. B., Platou, C., Vatten, L. J. and Janszky, I. Insomnia and the risk of incident heart failure: a population study. *Eur. Heart J.*, 2013, doi: 10.1093/eurheartj/ehd019. [E-pub ahead of print].
- Moldofsky, H. Sleep and pain. *Sleep Med. Rev.*, 2001, 5: 385–396.
- Morin, C. M., Belanger, L., Leblanc, M. *et al.* The natural history of insomnia: a population-based 3-year longitudinal study. *Arch. Intern. Med.*, 2009, 169: 447–453.
- Morphy, H., Dunn, K. M., Lewis, M., Boardman, H. F. and Croft, P. R. Epidemiology of insomnia: a longitudinal study in a UK population. *Sleep*, 2007, 30: 274–280.
- Neckelmann, D., Mykletun, A. and Dahl, A. A. Chronic insomnia as a risk factor for developing anxiety and depression. *Sleep*, 2007, 30: 873–880.

- Ohayon, M. M. Prevalence of DSM-IV diagnostic criteria of insomnia: distinguishing insomnia related to mental disorders from sleep disorders. *J. Psychiatr. Res.*, 1997, 31: 333–346.
- Pandi-Perumal, S. R., Verster, J. C., Kayumov, L. et al. Sleep disorders, sleepiness and traffic safety: a public health menace. *Braz. J. Med. Biol. Res.*, 2006, 39: 863–871.
- Riemann, D., Spiegelhalter, K., Nissen, C., Hirscher, V., Baglioni, C. and Feige, B. REM sleep instability—a new pathway for insomnia? *Pharmacopsychiatry*, 2012, 45: 167–176.
- Ritterband, L. M., Thorndike, F. P., Gonder-Frederick, L. A. et al. Efficacy of an internet-based behavioral intervention for adults with insomnia. *Arch. Gen. Psychiatry*, 2009, 66: 692–698.
- Salo, P., Oksanen, T., Sivertsen, B. et al. Sleep disturbances as a predictor of cause-specific work disability and delayed return to work. *Sleep*, 2010, 33: 1323–1331.
- Salo, P., Sivertsen, B., Oksanen, T. et al. Insomnia symptoms as a predictor of incident treatment for depression: prospective cohort study of 40,791 men and women. *Sleep Med.*, 2012a, 13: 278–284.
- Salo, P., Vahtera, J., Hall, M. et al. Using repeated measures of sleep disturbances to predict future diagnosis-specific work disability: a cohort study. *Sleep*, 2012b, 35: 559–569.
- Schwartz, S. W., Conroni-Huntley, J., Cole, S. R., Hays, J. C., Blazer, D. G. and Schocken, D. D. Are sleep complaints an independent risk factor for myocardial infarction? *Ann. Epidemiol.*, 1998, 8: 384–392.
- Sivertsen, B., Krokstad, S., Overland, S. and Mykletun, A. The epidemiology of insomnia: associations with physical and mental health. The HUNT-2 study. *J. Psychosom. Res.*, 2009a, 67: 109–116.
- Sivertsen, B., Overland, S., Pallesen, S. et al. Insomnia and long sleep duration are risk factors for later work disability. The Hordaland Health Study. *J. Sleep Res.*, 2009b, 18: 122–128.
- Sivertsen, B., Salo, P., Mykletun, A. et al. The bidirectional association between depression and insomnia: the HUNT study. *Psychosom. Med.*, 2012, 74: 758–765.
- Taylor, D. J., Lichstein, K. L. and Durrence, H. H. Insomnia as a health risk factor. *Behav. Sleep Med.*, 2003, 1: 227–247.
- Taylor, D. J., Mallory, L. J., Lichstein, K. L., Durrence, H. H., Riedel, B. W. and Bush, A. J. Comorbidity of chronic insomnia with medical problems. *Sleep*, 2007, 30: 213–218.
- Vgontzas, A. N. and Fernandez-Mendoza, J. Objective measures are useful in subtyping chronic insomnia. *Sleep*, 2013, 36: 1125–1126.
- Vgontzas, A. N., Zoumakis, M., Papanicolaou, D. A. et al. Chronic insomnia is associated with a shift of interleukin-6 and tumor necrosis factor secretion from nighttime to daytime. *Metabolism*, 2002, 51: 887–892.
- Vgontzas, A. N., Lin, H. M., Papaliaga, M. et al. Short sleep duration and obesity: the role of emotional stress and sleep disturbances. *Int. J. Obes. (Lond.)*, 2008, 32: 801–809.
- Vgontzas, A. N., Liao, D., Bixler, E. O., Chrousos, G. P. and Vela-Bueno, A. Insomnia with objective short sleep duration is associated with a high risk for hypertension. *Sleep*, 2009a, 32: 491–497.
- Vgontzas, A. N., Liao, D., Pejovic, S., Calhoun, S., Karataraki, M. and Bixler, E. O. Insomnia with objective short sleep duration is associated with type 2 diabetes: a population-based study. *Diabetes Care*, 2009b, 32: 1980–1985.
- Vgontzas, A. N., Fernandez-Mendoza, J., Liao, D. and Bixler, E. O. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. *Sleep Med. Rev.*, 2013, 17: 241–254.
- World Health Organization (WHO). *The WHO Body Mass Index Classification*. World Health Organization, Geneva, 2013.
- Zigmond, A. S. and Snaith, R. P. The hospital anxiety and depression scale. *Acta Psychiatr. Scand.*, 1983, 67: 361–370.