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Epidemiological differences in levels of depressive signs among nocturnal symptoms of insomnia; results from the HUNT study

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Abstract

Background: Insomnia is a sleep disorder characterized by multiple nocturnal symptoms (sleep onset, maintenance and terminal insomnia). However, these symptoms are assumed to have the same weight in the diagnosis and consequences of insomnia. In particular, little is known regarding whether these nocturnal symptoms are equally related to depression. In this study, we compared level of depressive signs among individuals reporting different patterns of nocturnal symptoms of insomnia.

Methods: We used data from the large population-based HUNT3 study. The final sample included 7933 individuals (4317 cases, 3616 controls). Signs of depression were measured using the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D), while the three nocturnal symptoms of insomnia were assessed using a Likert-like scale ("Never", "Sometimes", "Several times a week"). Individuals reporting to experience at least one symptom of insomnia "Several times a week" were grouped according to their pattern of reported symptoms and their HADS-D levels compared.

Results: Participants reporting sleep onset insomnia combined with terminal insomnia had the highest depression score (M = 5.4, SD = 3.4), but reporting maintenance insomnia in addition does not increase the HADS-D scores any further (M = 5.2, SD = 3.6). Accordingly, sleep maintenance insomnia alone had the lowest score (M = 3.4, SD = 2.9).

Conclusions: We found several differences among patterns of symptoms of insomnia but not all of them are clinically relevant. Further studies in clinical samples may help reveal relevant differences among patterns of symptoms, which may aid in refining interventions for concomitant depression and insomnia.

Keywords: HUNT study, Insomnia, Depression, Sleep onset insomnia, Maintenance insomnia, Early morning awakenings

Introduction

According to the fifth edition of Diagnostic and Statistical Manual of psychiatric diseases, (DSM-5) (American Psychiatric Association, 2013), the night-time symptoms of insomnia are difficulties initiating sleep (sleep onset insomnia), several awakenings during the night (maintenance insomnia) and early morning awakenings (terminal insomnia). These three symptoms are weighed equally in clinical diagnosis and few published studies report only scarce characterization of the three symptoms rather than focusing on the validity of this assumption. This may lead to the understanding that different symptoms of insomnia should not differ in their relationship to ills that are commonly coexisting with insomnia, such as depression or anxiety, as well as to social and economic consequences.

As most studies in the field of insomnia research focuses on the final clinical diagnosis, detailed analysis of findings according to the different symptoms is rare.

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Considered the complexity of the possible combinations of symptoms, published research does not make it easier to evaluate the symptoms individually. In order to have a better understanding of the individual symptoms and their significance in the diagnosis, more research on the characterization of symptoms of insomnia and their consequences is required.

Although few, some studies investigated how these symptoms might have different implications and consequences. Previous studies have shown how individuals experiencing trouble with sleep onset were about three times more likely than good sleepers to receive a disability pension due to a mental condition. This risk was higher than for other nocturnal symptoms of insomnia (Canivet et al., 2014). In a recent study we reported that difficulties initiating sleep alone plays a leading role in rising anxiety levels and different combinations of symptoms concur with different strengths of anxiety symptoms (Bragantini et al., 2019). Moreover, magnetic resonance imaging (MRI) studies seems to support biological differences for individual insomnia symptoms, as orbitofrontal grey matter appeared reduced only in patients experiencing early morning awakenings (Stoffers et al., 2012). The DSM-5 report specifically this nocturnal symptom of insomnia among the diagnostic criteria for melancholic depression and indeed patients with comorbid depression and insomnia show also reduced grey matter in the OFC (Yu et al., 2018).

As in case of anxiety, individuals experiencing insomnia are more likely to present depressive symptoms and develop depression (Alvaro et al., 2013; Lichstein et al., 2017). Several studies have demonstrated that the relationship between the two conditions is likely bi-directional (Jansson-Frojmark & Lindblom, 2008; Sivertsen et al., 2012), but some studies report insomnia as increasing the risk for depression but not the opposite (Johnson et al., 2006). Evidence regarding depression and its relationship with individual nocturnal symptoms of insomnia is conflicting. Cervena et al. reported higher levels of depression in individuals experiencing sleep maintenance problems in comparison to good sleepers (Cervena et al., 2014), whereas this was not the case for other insomnia symptoms. In contrast, experiencing sleep onset problems in combination with sleep maintenance problems was associated with higher depression levels in another study (Taylor et al., 2005). Conversely, a third study found no differences in depression severity between individuals experiencing sleep onset and maintenance problems (Pillai et al., 2015). However, these studies had some methodological shortcoming: 1) they did not investigate different patterns/combinations of the nocturnal symptoms of insomnia; and 2) they had generally small study samples.

Identifying differences in severity of depressive symptoms among patterns of symptoms of insomnia in a large cohort may improve our understanding of the interrelationships between insomnia and depression and help refining therapeutic interventions. Based on these considerations, the aim of this study was to assess the level of self-reported depressive signs in subjects reporting also nocturnal symptoms of insomnia, considering all existing patterns and using data from a general population, the HUNT 3 cohort.

Examining the relationship among the individual nocturnal symptoms of insomnia and depressive symptoms more closely may promote our understanding of symptoms of insomnia. This will help evaluate the weight of individual symptoms to the diagnosis and burden of insomnia.

Methods

The individuals in this study were participants in the Nord-Trøndelag Health Study (the HUNT study, Norway). The present study is based on data from 50, 807 citizens collected during the third cohort (2006–08). All citizens ($N = 93,860$) from the region of Nord-Trøndelag, in Norway who were at least 20 years old were asked to complete a questionnaire providing health information and biological samples. Krokstad et al. (Krokstad et al., 2013) summarized in detail all information about the HUNT study.

The selection work-flow of this study can be found here (Bragantini et al., 2019). Of the total HUNT 3 participants, five individuals had no valid answers for the variables relevant for this study. Of the remaining 50,802 those who answered "Never/Seldom" ($N = 18,606$, 36.6%) to questionnaire items regarding the frequency of snoring or interrupted breathing during the sleep (i.e. possible proxy for sleep apnoea) during the past month were selected. A total of 18,473 (97.3%) participants presented complete data for all three symptoms of insomnia and were selected to form the sample investigated in this study.

Nocturnal symptoms of insomnia

The frequency of occurrence of the three nocturnal symptoms of insomnia were determined using participant's answers to the Questionnaire 2 (Sleep section) of the HUNT 3 study:

"How often in the last 3 months have you:

Had difficulty falling asleep at night?

Woken up repeatedly during the night?

Woken too early and couldn't get back to sleep?"

"Never/seldom", "Sometimes", "Several times a week" were the possible response options.

Participant who reported to experience at least one symptoms with a frequency of "Several times a week", were classified as cases ($N = 4317$). Participants who answered "Never/seldom" to all questions were defined as controls ($N = 3616$). Answering "Sometimes" to at least one question and "Several times a week" to none of them determined the exclusion from the study. Cases were further divided according to the pattern of symptoms they presented into seven subgroups.

Measure of depressive signs

The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) is a validated (Bjelland et al., 2002) 14-items questionnaire used to evaluate symptoms of depression and anxiety. Here, we used the sum of the seven items related to depression (HADS-D), giving a score in the range from zero to 21. Cronbach's alpha coefficient of internal consistency for HADS-D ranges between 0.67 to 0.90 (mean score 0.82) (Bjelland et al., 2002).

Participants were also classified in four groups by increasing HADS-D score: normal (0–7), mild (8–10), moderate (11–14) and severe (15–21) (Zigmond & Snaith, 1983).

Statistical analyses

In the sample we selected, 268 subjects (2.6%) had missing data for one or more HADS-D items. These were singly imputed using the Expectation-Maximization algorithm. The imputation model included the HADS-D items and age.

First, we used Student's t-test to compare HADS-D scores between insomnia cases and controls. Secondly, we performed a linear regression with HADS-D as the dependent variable and type of sleep symptoms as an eight-category independent variable, adjusting for sex and age. Differences in HADS-D scores symptoms patterns were compared using Bonferroni's adjustment accounting for all the pairwise comparison between the seven groups. We used bootstrapping with 1000 bootstrap samples, as the data were not normally distributed. Separate analyses for males and females were conducted in the same way.

Frequencies of the insomnia symptoms and their combination were examined across the four HADS-D groups of increasing severity using a chi-squared test. We compared HADS-D scores and age between cases, controls and excluded subjects using ANOVA with 1000 bootstrap samples. A chi-squared test was used to examine differences in distribution of sexes among the three groups. All analyses were conducted using IBM SPSS 25 (SPSS Inc., Chicago, IL, USA).

Results

In our sample ($N = 7933$) 66.2% were females. Of these 64% percent reported symptoms of insomnia as compared to 48.2% of males ($\chi(1) = 144$, 6, $p < 0.001$). Mean age for the sample was 49.7 years, (SD = 16.2, range: 19.2 to 96.8). The mean age for cases was 54 years while for controls it was significantly lower by 9 years, ($t(7931) = 26.29$, $p < 0.001$). HADS-D score was significantly higher in cases (M = 4.1, SD = 3.2) than controls (M = 1.9, SD = 2.2), ($t(7931) = 35.66$, $p = 0.001$).

HADS-D scores were significantly higher for males than females in both cases (M = 4.7 vs 3.9) ($t(1945) = -7.25$, $p < 0.001$) and controls (M = 2.2 vs 1.7) ($t(3123.5) = -6.18$, $p < 0.001$). Among cases, HADS-D was higher for males independently from the pattern of symptoms experienced (Table 1).

The regression results showed that the HADS-D scores differed significantly among the types of insomnia symptoms ($F(6, 4317) = 27.35$, $p < 0.001$). Table 2 shows the results for Bonferroni-corrected group comparisons. Participants reporting all three insomnia symptoms had the highest depression score (M = 5.2, SD = 3.6), followed in decreasing order by sleep onset problems with terminal insomnia (M = 5, SD = 3.4), sleep onset insomnia with sleep maintenance insomnia (M = 4.6, SD = 3.2), sleep maintenance insomnia with terminal insomnia (M = 4.3, SD = 3.1), terminal insomnia (M = 4.1, SD = 3), sleep onset insomnia only (M = 4, SD = 3.2), and sleep maintenance insomnia only (M = 3.4, SD = 2.9). Mean HADS-D score was significantly lower for maintenance insomnia than for all other patterns of symptoms. Other groups significantly different from one another are reported in Table 2. Inclusion of sex and age as covariates $F(6, 4317) = 28.7$, $p < 0.001$) did not significantly change the mean differences among the groups as shown in Table 3 by the 95% CI.

The pattern of results was different when conducting separate analyses for men and women. In particular, men experiencing sleep onset and terminal insomnia simultaneously had HADS-D scores that are significantly higher than men reporting any other patterns of symptoms (mean difference of 3 points). In females, the same combination of sleep onset insomnia and terminal insomnia differed significantly only from sleep maintenance insomnia ($p = 0.004$, mean difference = 1.12 95%CI [0.01 to 2.23]) (Table 4).

The distribution of insomnia symptoms according to the four HADS-D levels is shown in Fig. 1. The percentage of people experiencing sleep maintenance problems were significantly higher in the "Normal" HADS-D group (33%) than all the others ($p < 0.001$). Regarding all three symptoms of insomnia, only 13% in the "Normal" group experienced this pattern while much higher proportions in the other groups with a peak of 41% in the "Severe" group.

The 10,540 subjects excluded from the study had a mean HADS-D score of (M = 2.9), which is between controls

Table 1 Descriptive statistics for the sample we investigated in this study

		Sleep onset (SOI)	Maintenance (MI)	Terminal (TI)	SOI + MI	MI + TI	SOI + TI	All symptoms	Tot. Cases	Controls	Total
N		*733*	*1333*	*470*	*516*	*527*	*96*	*642*	*4317*	*3616*	*7933*
Females %		*72*	*71.6*	*62.1*	*80.8*	*69.6*	*80.2*	*81.9*	*73.2**	*57.9*	*66.2*
Age M (SD)		*49.5 (17.8)*	*53.3 (16.3)*	*57.9 (15.2)*	*52.6 (15.3)*	*56.2 (14.2)*	*59.7 (18.1)*	*56.1 (15.4)*	*53.9 (16.2)**	*44.6 (14.7)*	*49.7 (16.2)*
HADS-D M (SD)	**Tot.**	*4.0 (3.2)*	*3.4 (2.9)*	*4.1 (3.0)*	*4.6 (3.2)*	*4.3 (3.1)*	*5 (3.4)*	*5.2 (3.6)*	*4.1 (3.2)**	*1.9 (2.1)*	*3.2 (2.8)*
	Females	*3.7*[a]	*3.2*[a]	*3.9*[a]	*4.4*[a]	*4.0*[a]	*4.3*[a]	*5.0*[a]	*3.9*[a]	*1.7*[a]	*2.8*[a]
	Males	*4.5*	*4.1*	*4.6*	*5.3*	*5.0*	*8.1*	*6.2*	*4.7*	*2.2*	*3.3*

*significantly different (α = 0.05) between cases and controls
[a]significantly lower (α = 0.05) than in males

(M = 1.9) and cases (M = 4.2). Age followed a different trend, with excluded participants presenting the highest mean age (M = 54), followed by cases (M = 52) and controls (M = 45). Finally, excluded subjects showed a percentage of females than is higher (73.2%), than the others groups (66.3% in cases and 58% in controls).

Discussion

In this study, we analysed differences in levels of depressive signs among individuals reporting different patterns of nocturnal symptoms of insomnia. We found HADS-D scores to be lower in controls compared to insomnia cases and there were several statistically significant differences between patterns of symptoms. These differences were greater for men than women.

Individuals reporting symptoms of insomnia scored an average of 2.2 points higher than controls. This difference was statistically significant and can be considered meaningful as it is over the minimal important difference (MID) for HADS-D, estimated to be between 1.9 to 2.3 points (Chan et al., 2016). Moreover, these results are in line with the notion that insomnia is associated

Table 2 Pairwise comparison of mean HADS-D for each combination of symptoms

Pairwise comparison		Mean difference	95% CI	*p*-value *
Onset	**Maintenance**	0.5	[0.1 to 1]	**0.009**
	Terminal	− 0.2	[− 0.8 to 0.4]	1.000
	Onset + Maintenance	−0.6	[−1.2 to − 0.1]	**0.007**
	Maintenance + Terminal	− 0.3	[− 0.9 to 0.2]	1.000
	Onset + Terminal	− 1.1	[− 2.1 to − 0.1]	**0.030**
	Onset + Maintenance + Terminal	− 1.3	[− 1.8 to − 0.8]	**< 0.001**
Maintenance	**Terminal**	− 0.7	[− 1.2 to − 0.2]	**0.001**
	Onset + Maintenance	− 1.2	[− 1.7 to − 0.7]	**< 0.001**
	Maintenance + Terminal	− 0.9	[− 1.4 to − 0.4]	**< 0.001**
	Onset + Terminal	− 1.6	[− 2.6 to − 0.6]	**< 0.001**
	Onset + Maintenance + Terminal	− 1.8	[− 2.2 to − 1.3]	**< 0.001**
Terminal	**Onset + Maintenance**	− 0.5	[− 1.1 to 0.2]	0.469
	Maintenance + Terminal	− 0.2	[− 0.8 to 0.4]	1.000
	Onset + Terminal	− 0.9	[− 2 to 0.2]	0.228
	Onset + Maintenance + Terminal	− 1.1	[− 1.7 to − 0.5]	**< 0.001**
Onset + Maintenance	**Maintenance + Terminal**	0.3	[− 0.3 to 0.9]	1.000
	Onset + Terminal	−0.4	[− 1.5 to 0.6]	1.000
	Onset + Maintenance + Terminal	− 0.6	[− 1.2 to − 0.1]	**0.018**
Maintenance + Terminal	**Onset + Terminal**	−0.7	[− 1.8 to 0.3]	0.718
	Onset + Maintenance + Terminal	− 0.9	[− 1.5 to − 0.4]	**< 0.001**
Onset + Terminal	**Onset + Maintenance + Terminal**	−0.2	[− 1.2 to 0.9]	1.000

*Bonferroni corrected for 21 comparisons
N.B.: Differences in mean values can be considered as effect measure for the pairwise comparisons (Baguley, 2009)

Table 3 Pairwise comparison for mean HADS-D scores among pattern of symptoms with sex and age as covariates

Pairwise comparisons		Difference in HADS-D mean	95% CI	*p*-value *
Onset	**Maintenance**	0.7	[0.2 to 1.1]	**0.001**
	Terminal	0.2	[−0.4 to 0.8]	1.000
	Onset + Maintenance	−0.6	[− 1.3 to 0.0]	0.108
	Maintenance + Terminal	−0.1	[− 0.8 to 0.5]	1.000
	Onset + Terminal	− 1.7	[−3 to − 0.5]	**0.001**
	Onset + Maintenance + Terminal	− 1.3	[− 1.9 to − 0.7]	**< 0.001**
Maintenance	**Terminal**	− 0.5	[− 1.0 to 0.0]	0.100
	Onset + Maintenance	− 1.3	[− 1.9 to − 0.7]	**< 0.001**
	Maintenance + Terminal	− 0.8	[− 1.3 to − 0.3]	**< 0.001**
	Onset + Terminal	−2.4	[− 3.6 to − 1.1]	**< 0.001**
	Onset + Maintenance + Terminal	− 1.9	[− 2.5 to − 1.4]	**< 0.001**
Terminal	**Onset + Maintenance**	− 0.8	[− 1.5 to − 0.9]	**0.015**
	Maintenance + Terminal	− 0.3	[− 0.9 to 0.3]	1.000
	Onset + Terminal	− 1.9	[− 3.2 to − 0.6]	**< 0.001**
	Onset + Maintenance + Terminal	− 1.4	[− 2.1 to − 0.8]	**< 0.001**
Onset + Maintenance	**Maintenance + Terminal**	0.5	[− 0.2 to 1.2]	0.731
	Onset + Terminal	− 1.1	[− 2.4 to 0.2]	0.191
	Onset + Maintenance + Terminal	− 0.6	[− 1.4 to 0.1]	0.112
Maintenance + Terminal	**Onset + Terminal**	− 1.6	[− 2.9 to − 0.3]	**0.003**
	Onset + Maintenance + Terminal	− 1.1	[− 1.8 to − 0.5]	**< 0.001**
Onset + Terminal	**Onset + Maintenance + Terminal**	0.5	[− 0.8 to 1.8]	1.000

*Bonferroni corrected for 21 comparisons
N.B.: Differences in mean values can be considered as effect measure for the pairwise comparison (Baguley, 2009)

with depression as reported by, among others, a meta-analysis from 2016 (Li et al., 2016).

HADS-D results were statistically different also among several patterns of symptoms. Experiencing terminal insomnia alone (M = 4.1), did not differ in HADS-D score significantly from experiencing only sleep onset problems (M = 4.0). However experiencing these two symptoms at the same time produced significantly higher average HADS-D score (M = 5.0). As previously suggested (Bragantini et al., 2019), this combination of symptoms might affect sleep length more than other patterns and therefore produce more severe consequences (Vgontzas et al., 2013). In a previous article, we reported a similar results also for the anxiety subscale of HADS (HADS-A) (Bragantini et al., 2019). This suggests that experiencing sleep onset problems together with terminal insomnia reflects a more severe psychological distress than for other patterns of symptoms.

This combination of symptom may be the result of a peculiar etiopathology or of the presence of different, concomitant factors. Previous studies reported sleep onset insomnia increasing the risk for debilitating mental problems (Canivet et al., 2014) while neuroimaging brings evidence of a connection between early morning awakenings and depression (Stoffers et al., 2012; Yu et al., 2018). Speculatively, it is possible that the two insomnia symptoms and depression are connected in a consecutive and escalating manner. Early morning awakening may be a symptom of depression from the beginning due to functional changes in the OFC while sleep onset could emerge when depression exacerbate.

Surprisingly, experiencing also the third symptom, maintenance problems, did not significantly increase the HADS-D score (M = 5.2). This is consistent with the fact that maintenance insomnia has the lowest HADS-D score (3.4 points), which was the lowest score among the patterns of symptoms. However, the difference among maintenance insomnia and other single symptoms was statistically significant but not meaningful, as it was only 0.5 point with sleep onset insomnia and 0.7 point with terminal insomnia. This is in agreement with previous studies in which single nocturnal symptoms of insomnia did not differ in measure of depression (Taylor et al., 2005; Pillai et al., 2015).

Analysing the data in another perspective gave a similar view. When participants were divided into four groups according to increasing HADS-D scores, among people in the "Normal" group, 33% reported maintenance insomnia. This percentage was significantly higher than for all other groups. On the other hand, the

Table 4 Post-hoc analyses for differences among pattern of symptoms in HADS-D scores stratified by gender

Pairwise comparisons		Women			Men		
		Mean Difference	95% CI	*p*-value	Mean Difference	95% CI	*p*-value
Onset	**Maintenance**	0.571*	[0.06 to 1.08]	0.01	0.37	[−0.49 to 1.23]	1.00
	Terminal	−0.157	[−0.84 to 0.52]	1.00	−0.05	[− 1.07 to 0.97]	1.00
	Onset + Maintenance	−0.693*	[− 1.3 to − 0.08]	0.01	− 0.82	[− 2.04 to 0.39]	0.84
	Maintenance + Terminal	−0.27	[− 0.9 to 0.36]	1.00	− 0.47	[− 1.52 to 0.58]	1.00
	Onset + Terminal	− 0.55	[− 1.69 to 0.59]	1.00	− 3.60*a	[− 5.99 to − 1.22]	0.00
	Onset + Maintenance + Terminal	−1.28*	[− 1.86 to − 0.71]	0.00	− 1.65*	[− 2.81 to − 0.5]	0.00
Maintenance	**Terminal**	− 0.73*	[− 1.35 to − 0.1]	0.01	−0.42	[−1.32 to 0.49]	1.00
	Onset + Maintenance	−1.26*	[−1.81 to −0.72]	0.00	− 1.19*	[− 2.31 to − 0.07]	0.03
	Maintenance + Terminal	− 0.84*	[−1.41 to − 0.27]	0.00	−0.84	[− 1.78 to 0.1]	0.13
	Onset + Terminal	− 1.12*	[− 2.23 to − 0.01]	0.04	− 3.97*	[− 6.31 to − 1.63]	0.00
	Onset + Maintenance + Terminal	−1.85*	[− 2.36 to − 1.35]	0.00	− 2.02*	[− 3.08 to − 0.97]	0.00
Terminal	**Onset + Maintenance**	− 0.54	[−1.25 to 0.18]	0.46	− 0.77	[− 2.02 to 0.47]	1.00
	Maintenance + Terminal	− 0.11	[− 0.85 to 0.62]	1.00	− 0.42	[− 1.51 to 0.66]	1.00
	Onset + Terminal	− 0.39	[− 1.59 to 0.8]	1.00	−3.55*a	[−5.95 to − 1.16]	0.00
	Onset + Maintenance + Terminal	−1.13*	[− 1.81 to − 0.44]	0.00	−1.60*	[− 2.79 to − 0.42]	0.00
Onset + Maintenance	**Maintenance + Terminal**	0.42	[−0.25 to 1.09]	1.00	0.35	[−0.92 to 1.62]	1.00
	Onset + Terminal	0.14	[−1.01 to 1.3]	1.00	−2.78*a	[− 5.27 to −0.29]	0.01
	Onset + Maintenance + Terminal	−0.59	[− 1.2 to 0.02]	0.07	− 0.83	[− 2.19 to 0.53]	1.00
Maintenance + Terminal	**Onset + Terminal**	− 0.28	[− 1.45 to 0.89]	1.00	− 3.13*a	[− 5.54 to − 0.72]	0.00
	Onset + Maintenance + Terminal	−1.01*	[− 1.65 to − 0.38]	0.00	−1.18	[− 2.39 to 0.03]	0.07
Onset + Terminal	**Onset + Maintenance + Terminal**	− 0.73	[−1.87 to 0.41]	1.00	1.95	[−0.51 to 4.41]	0.34

N.B.: Differences in mean values can be considered as effect measure for the pairwise comparisons (Baguley, 2009)
*p-value <0.05
[a]statistically different (p<0.05)

percentage of people reporting all three symptoms of insomnia was significantly lower in the HADS-D "Normal" group (13%).

In general, maintenance insomnia seems to be a more common complaint than other symptoms (Canivet et al., 2014; Bragantini et al., 2019; Taylor et al., 2005) but is associated to lower psychological distress in this and our previous study on anxiety (Bragantini et al., 2019). Accordingly, artificially produced sleep fragmentation seems to have only a limited effect on increasing cortisol levels both at night and the morning after (Späth-Schwalbe et al., 1991; Hucklebridge et al., 2000). After an initial burst of cortisol at the introduction of sleep disruption, the individuals seems to habituate and cortisol levels decrease at following interruptions. These differences could be related to the phase in which sleep is disrupted (i.e. N-REM or REM) or to accumulation of sleep time counterbalancing the stress of the interruptions (Späth-Schwalbe et al., 1991).

Alternatively, this symptom may be the manifestation of other organic sleep disorders rather than correlate of psychological distress. Conditions such as sleep apnoea (SA), restless leg syndrome (RLS) and other disorders may disrupt sleep several times during the night (Bonnet & Arand, 2003) without leading to severe depression or anxiety.

Previous studies found that individuals reporting "combined insomnia" (i.e. sleep onset and maintenance insomnia) scored significantly higher than those with single symptoms in measures of depression (Taylor et al., 2005; Pillai et al., 2015). Similarly, in our study, participants reporting combined sleep onset and maintenance/terminal insomnia had higher scores, which was statistically significant, than respondents with only one

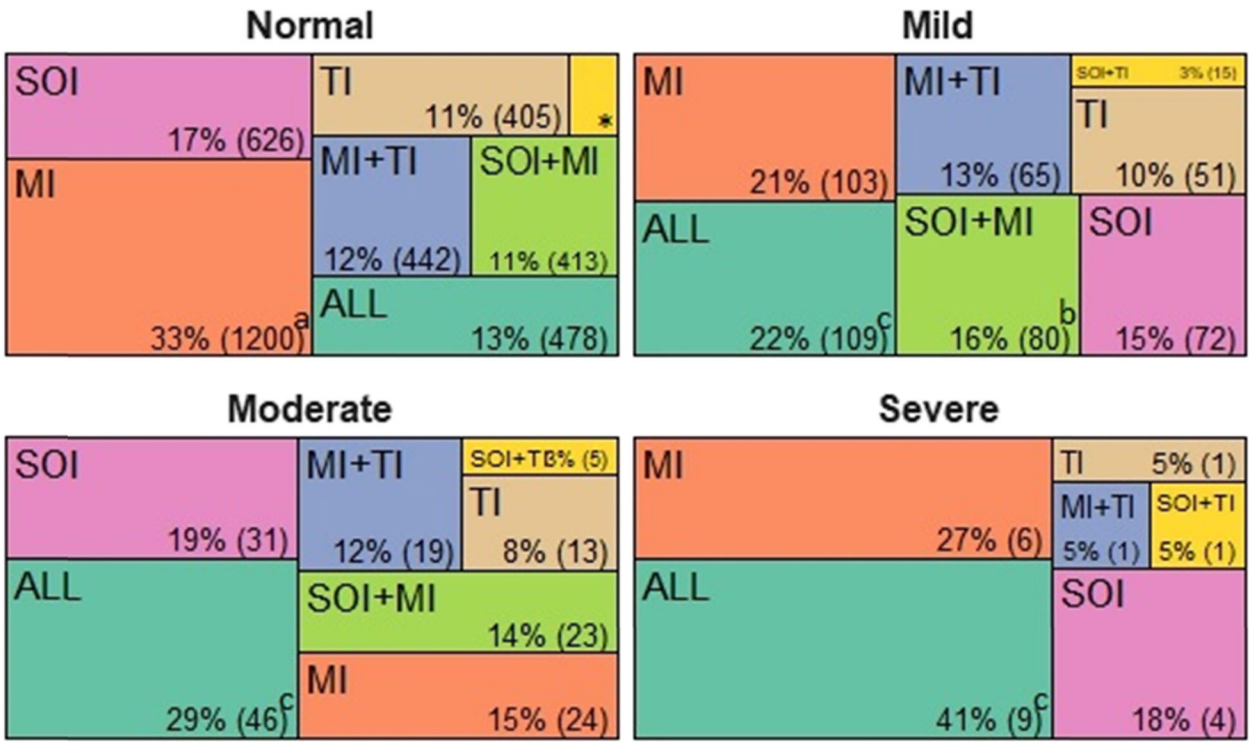

Fig. 1 Comparison of the distribution of patterns of symptoms of insomnia among the HADS-D subgroups. [a] = $p < 0.05$ for comparison of percentages within all other HADS-D groups. [b] = $p < 0.05$ for comparison of percentage of individuals experiencing Onset + Maintenance in HADS-D group "Normal". [c] = $p < 0.05$ for comparison of percentage of individuals experiencing Onset + Maintenance + Terminal in HADS-D group "Normal". **SOI + TI*, 2%

symptom, except for terminal insomnia. This may indicate that the burden of sleep onset insomnia is somehow magnified only in the presence of another symptom. As discussed earlier, maintenance insomnia may be the result of somatic diseases. The relatively low psychological burden of these conditions could interact negatively with the one provoked by concomitant sleep onset insomnia, intensifying symptoms of depression.

In contrast to previous findings, in our sample, men had more pronounced HADS-D scores (M = 3.3). A meta-analysis from 2017 showed that women are two times more likely than men to be diagnosed with Major Depressive Disorder (MDD) and 1.6 times to have depressive symptoms (Salk et al., 2017). Even so, the inverted trend of HADS-D scores have been described before and appear to be a peculiarity of the HUNT cohort. Reasons for this are not clear, but the lack of questions about somatic symptoms of depression in HADS-D, which are more frequent in women, are hypothesized to be the cause for this unusual trend (Langvik et al., 2016).

The lack of somatic symptoms of depression in HADS-D questionnaire results in an over-representation of the anhedonic symptoms. These are typical of the melancholic depression sub-type (Fletcher et al., 2015), characterized also by sleep difficulties, specifically in the form of early morning awakenings (American Psychiatric Association, 2013). From our results we cannot confirm this notion which seems to emerge from clinical practice more than scientific literature. Future studies could deepen the knowledge on the relationship between insomnia and depression by including also measures for single symptoms of depression. This approach could bring clarity over which symptoms of depression and which symptoms of insomnia are more tightly correlated.

Strengths, limitations and future prospective

In this study, we were able to analyse all possible patterns of nocturnal symptoms of insomnia thanks to the use of data from the HUNT study. Moreover, free healthcare and strong welfare measures in the Norway reduced the confounder potential of socioeconomic factors.

The HUNT3 study sleep questionnaire presented only the three aforementioned questions on nocturnal symptoms of insomnia. Sleep length, sleep satisfaction and duration of the sleep problems, were not present in the HUNT dataset and therefore we could not produce a more defined definition of the three nocturnal symptoms of insomnia.

Even if we did not find large differences in HADS-D among people experiencing different patterns of

symptoms of insomnia, the picture may be different in a clinical sample. In future studies, focusing on patients diagnosed with insomnia using tools with higher resolution may highlight these differences.

The approach of stratifying results of studies on insomnia by nocturnal symptoms could improve the knowledge on insomnia on several levels. In particular, identifying the specific psychopathological characteristics of the symptoms and integrating them with findings from sleep research could help elucidate the neurobiological mechanisms that link insomnia and depression. Moreover, identifying which symptoms of insomnia are more likely to be accompanied by severe depressive symptoms may be a useful information in the clinic. For example, patients reporting the nocturnal symptoms associated with more depressive symptoms could be monitored more closely for depression. At the same time, the therapeutic offer could also be tailored to the reported symptoms of insomnia to include interventions that target depression.

Conclusions

Different patterns of nocturnal symptoms of insomnia are associated with different levels of depression. Of relevance, people with sleep onset insomnia combined with terminal insomnia had the highest depression levels, but reporting maintenance insomnia in addition did not increase the HADS-D scores any further. Overall, individuals experiencing maintenance insomnia alone had the lowest scores on the HADS-D. This suggests that the relationship between depression and insomnia may vary according to the pattern of symptoms experienced. Further studies in clinical samples may help reveal relevant differences among patterns of symptoms, which may aid in refining interventions for concomitant depression and insomnia.

Abbreviations

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; FDR: False Discovery Rate; HADS: Hospital Anxiety and Depression Scale; HUNT: Helse Undersøkelse Nørd-Trøndelag (Nord-Trøndelag Health Study); MDD: Major Depressive Disorder; MID: Minimal important difference; MRI: Magnetic Resonance Imaging

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Authors' contributions

DB: analysis of the data and draft of the manuscript; BS: supervision of the study; PG: critical reading and discussion of manuscript; SL: design and interpretation of the statistical methodology and results; ICG: design and supervision of the study; All authors: critical revision of the manuscript and contribution to the intellectual content of the work. The authors read and approved the final manuscript.

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Availability of data and materials

The data used in this study are available on request to the HUNT databank.

Ethics approval and consent to participate

This study was approved by the Regional Committee for Medical and Health Research Ethics of South-East Norway (reference number 2016/672) on date 04.27.2016. All partakers in the HUNT study signed a written informed consent form allowing the use of their data and samples for research purposes. Participants can request to withdraw their data from the HUNT database at any given moment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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