

Use of Sleep Medications and Mortality: The Hordaland Health Study

Børge Sivertsen^{1,2,3} · Ida E. H. Madsen⁴ · Paula Salo⁵ · Grethe S. Tell⁶ · Simon Øverland¹

Published online: 5 May 2015

© The Author(s) 2015. This article is published with open access at Springerlink.com

Abstract

Background Previous research suggests a possible link between the use of sleep medications and mortality, but findings are mixed and well-controlled community-based studies are lacking.

Objective The aim of the current study was to examine the prospective association between sleep medications and all-cause mortality.

Method Using a cohort design with 13–15 years of follow-up, we linked self-reported medication use and data on possible confounders from the Hordaland Health Study (HUSK $N = 21,826$) obtained over the period 1997–1999 to mortality data from the Norwegian Cause of Death Registry. Users of sleep medications ($n = 159$) were defined as those reporting intake of any prescribed sleep medication (coded according to the Anatomical Therapeutic Chemical [ATC] classification system) on the

day before participation in HUSK. Users of sleep medications were also asked if their intake was on a daily or a non-daily basis. Analyses presented are adjusted for sociodemographic and lifestyle factors, mental and physical health, and other medication use.

Results We found that both type and frequency of sleep medication use were associated with increased general mortality risk. Compared with participants not using sleep medications, those who reported any use had a twofold risk for mortality (95 % confidence interval [CI] 1.1–3.7); the hazard ratio (HR) was 2.9 (95 % CI 1.4–5.9) for daily and 1.1 (95 % CI 0.3–3.4) for non-daily users. Mortality risk was higher for benzodiazepines (HR 3.1; 95 % CI 1.3–7.6), but not significant for short-acting benzodiazepine agonists (HR 1.5; 95 % CI 0.7–3.5).

Conclusion Community dwellers who use sleep medications, particularly benzodiazepines, had a significantly increased risk of dying during the 13–15 years of follow-up. The low numbers of individuals reporting chronic usage indicate that the data should be interpreted with great caution, and more well-controlled studies with registry-based information on sleep medication use are needed to further examine the potential harmful effects of sleep medications.

✉ Børge Sivertsen
borge.sivertsen@fhi.no

¹ Division of Mental Health, Norwegian Institute of Public Health, Kalfarveien 31, 5018 Bergen, Norway

² Regional Centre for Child and Youth Mental Health and Child Welfare, Uni Research Health, Bergen, Norway

³ Department of Psychiatry, Helse Fonna HF, Haugesund, Norway

⁴ National Research Centre for the Working Environment, Copenhagen, Denmark

⁵ Finnish Institute of Occupational Health, Helsinki, Finland

⁶ Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

Key Points

The use of sleep medication is significantly associated with increased mortality risk.

Mortality risk is especially high for benzodiazepines.

1 Introduction

It has been estimated that 6–10 % of the US adult population use hypnotic medication regularly, and corresponding figures have been found in European countries [1, 2]. The association between use of hypnotics and increased mortality has been examined in more than 20 studies [3], and although most studies have found a significant association, several questions remain. For example, investigations of different subgroups of hypnotics are rare, and few studies have examined short-acting benzodiazepine agonists (Z-drugs), which are now more common than the traditional benzodiazepines. Furthermore, studies taking the effect of possible confounders, such as lifestyle behaviours and physical and mental health, into account are lacking. To further the research on this topic, the current study linked information from the Hordaland Health Study (HUSK) to the Norwegian Cause of Death Registry. The aim was to examine whether use of different hypnotics was associated with all-cause mortality over a 13- to 15-year follow-up period.

2 Methods

2.1 Study Population and Data Material

The baseline of the community-based HUSK study was conducted over the period 1997–1999 as a collaboration between the National Health Screening Service, the University of Bergen, and local health services. All individuals born in 1953–1957 who resided in Hordaland County on 31 December 1997 were invited to participate: 29,400 individuals. A total of 18,560 individuals born 1953–1957 answered the first questionnaire or attended a clinical examination, yielding a participation rate of 63 %. Similarly, 3,733 individuals (participation rate of 77 %) born 1950–1951 participated, giving a sample of 22,293 individuals. Of these, 21,826 signed the informed consent and provided valid data on the variables of interest, and thus constitute the study population.

2.2 Measures

2.2.1 Outcome

The Norwegian Cause of Death Registry is held by Statistics Norway and includes information on cause of death for all deceased individuals registered as residents in Norway at the time of death.

2.2.2 Exposure

Use of medication was assessed with the question “Did you take any medication yesterday” (yes/no). Participants who gave a positive response for this item wrote the names of all medications they took, and these were subsequently coded according to the Anatomical Therapeutic Chemical (ATC) classification system [4]. For purposes of the present study, we examined both sleep medications (ATC code N05C) and the following sub-categories of sleep medications: barbiturates (N05CA), benzodiazepine derivatives (N05CD), benzodiazepine-related drugs (N05CF), and other hypnotics and sedatives (N05CM). Participants also indicated whether they used the medication on a daily basis. Only N05CD (benzodiazepines) and N05CF (benzodiazepine-related drugs/Z-drugs) were used in the current study when comparing type of sleep medications, due to the low number of individuals using the N05CA and N05CAM categories (excluded from the analyses).

2.2.3 Covariates

2.2.3.1 Demographic and Lifestyle Factors Level of education was reported in four categories, ranging from <7 years of schooling up to at least 4 years of higher education at college/university. We also used data on marital/cohabitant status, smoking (number of cigarettes smoked daily), and weekly level of exercise: (1) no or easy physical activity 1 h, (2) moderate physical activity 1–2 h, or (3) hard physical activity more than 2 h. Alcohol consumption was categorized according to weekly number of self-reported alcohol units per week (none, 1–2 units, 3–4 units, or ≥ 5 units).

2.2.3.2 Physical Health Questions on somatic diagnoses were framed as follows: “Do you have or have you had (one or more of the following): asthma, myocardial infarction, diabetes, stroke, angina, or multiple sclerosis”. In addition, the physical examination included measurements of height and weight (body mass index [BMI] kg/m^2), blood pressure, and total serum cholesterol. Use of medications other than sleep medications were used as an additional proxy for physical health. Pain was assessed by ten items asking participants if they experienced musculoskeletal pain (yes/no) in ten different body locations. For the current study, a sum score was created (range 0–10).

2.2.3.3 Mental Health Symptoms of mental distress were assessed using the CONOR Mental Health Index (CONOR-MHI), which comprises seven items assessing core symptoms of anxiety and depression. The CONOR-MHI is adapted from the General Health Questionnaire-GHQ [5]

and the Hopkins Symptom Check List (HSCL) [6]. The CONOR-MHI is typically used by summing up the seven individual items, and this continuous variable has been shown to have acceptable psychometric properties [7].

2.3 Statistical Analyses

Cox proportional hazards models were computed to assess the effect of hypnotics on all-cause mortality. Both crude and adjusted models were analysed. In the first model, we adjusted for socio-demographic and lifestyle factors. To explore the relative importance of potential sets of confounders or mediators, we additionally adjusted for physical health (somatic diagnoses, pain and blood pressure), mental distress (CONOR-MHI total score), and use of other medications. Participants were followed from the date of participation in HUSK (1997–1999) to their death or end of follow-up (31 December 2012), at which point they were censored (range of follow-up 13–15 years). Results are presented as hazard ratios (HR) with 95 % confidence intervals (CIs). We evaluated the proportional hazard assumption by inspecting the log minus log plots stratified on the level for each covariate and found no major deviation from a proportional hazard. Cause-specific deaths were not analysed due to statistical power constraints.

2.4 Ethics

The study protocol was approved by the Regional Committee for Medical Research Ethics of Western Norway and approved by the Norwegian Data Inspectorate. Written consent was obtained from all subjects included in this study.

3 Results

3.1 Demographic and Clinical Characteristics

The frequency of sleep medication use on the day before study participation was 0.7 % ($n = 159$), of which 80 participants indicated daily usage. As detailed in Table 1, use of sleep medication was more prevalent among women, individuals with low education, smokers, and those with low physical activity. The number of self-reported somatic diagnoses and use of other medications were also higher among users of sleep medications. Sleep medication use was not associated with alcohol use or BMI (see Table 1 for details).

3.2 Sleep Medication and Mortality Risk

During the follow-up period from 1997–1999 through 2012, a total of 622 of 21,826 (2.8 %) individuals died, of

whom 288/11,750 (2.5 %) were women and 334/10,207 (3.3 %) were men. In the crude analyses, use of any sleep medication was associated with a threefold increase in mortality (HR 3.36; 95 % CI 1.85–6.10; Table 2). Adjustment for demographic and lifestyle factors only slightly reduced the association, and the effect remained after additional adjustment for physical and mental health, as well as use of other medications (HR 1.97; 95 % CI 1.06–3.66).

Mortality risk was higher for daily users of sleep medication (HR 5.25; 95 % CI 2.61–10.55), and this effect also remained in the fully adjusted model (HR 2.87; 95 % CI 1.40–5.91). Non-daily usage was not associated with increased mortality compared with those not using sleep medications. Use of benzodiazepines was more strongly associated with mortality than Z-drugs (HR 6.45 vs. HR 2.43, respectively). Although the effect of benzodiazepines on mortality also remained in the fully adjusted model (HR 3.08), this was not the case for Z-drugs (HR 1.53). As shown in Fig. 1, the mortality risk was especially high among daily users of benzodiazepines (HR 6.7), followed by non-daily users of benzodiazepines (HR 3.9) and daily users of Z-drugs (HR 3.3). Non-daily users of Z-drugs did not exhibit an increased mortality risk.

4 Discussion

In short, while no relation with mortality for intermittent users of Z-drugs was found, the current study showed that use of benzodiazepines and chronic usage of Z-drugs both were associated with increased risk of all-cause mortality. Most of the effect estimates were reduced, but remained significant, after adjusting for confounding factors (except for Z-drugs). However, the low numbers of individuals reporting chronic usage indicate that the data should be interpreted cautiously.

In line with Kripke et al. [3], the strongest effects were found for benzodiazepines, and especially those using benzodiazepines every day. Despite limitations caused by restrained statistical power, the current study also found non-daily users of benzodiazepines and daily users of Z-drugs to significantly predict subsequent mortality in the crude analyses. However, adjusting for mental and physical health reduced the effect of Z-drugs to a non-significant level. Although the exposure measure in the current study was suboptimal and likely to identify extensive use of sleep medications rather than more occasional use, the results support previous notions that benzodiazepines may increase general mortality risk.

Several mechanistic pathways between sleep medication and mortality have been directly or indirectly suggested in previous literature. For example, use of sleep medication has been linked to increased risk both of later depression

Table 1 Baseline demographic and clinical characteristics according to use of sleep medications in the Hordaland Health Study, Norway, 1997–1999

	Non-users	Any sleep medication	Z-drugs	Benzodiazepines
<i>N</i> (%)	21,667 (99.3)	159 (0.7)	112 (70.9)	46 (29.1)
Age, years (SD)**	43.4 (2.3)	43.9 (2.3)	43.9 (2.1)	44.2 (2.7)
Women***	53.7	68.8	72.4	63.0
Education*				
Compulsory	19.4	27.7	24.1	39.1
High school	45.2	42.8	44.8	37.0
College/university	35.5	29.5	31.1	23.9
Married/living with partner***	77.4	50.9	56.3	37.0
Daily smoker***	36.7	64.9	61.1	76.7
Alcohol consumption† (units/week)				
0	27.3	33.3	37.6	25.6
1–2	16.4	9.3	7.3	11.6
3–4	16.3	14.7	13.8	18.6
≥5	39.9	42.7	41.3	44.2
Physical activity***				
No or easy	31.2	45.5	43.5	52.3
Moderate	55.3	45.5	49.6	34.1
Heavy	13.6	9.0	7.0	13.6
Body mass index, kg/m ² (SD)	25.4 (3.8)	25.7 (4.6)	25.3 (4.3)	26.6 (4.8)
Mental distress, MHI total score, (SD)	1.5 (0.4)	2.3 (0.7)	2.3 (0.7)	2.5 (0.7)
Systolic blood pressure, mmHg (SD)*	127.0 (14.7)	124.3 (13.8)	123.4 (14.1)	126.2 (12.9)
Number of somatic diagnoses***				
0	91.8	81.5	85.3	72.7
1	7.8	16.6	13.8	22.7
2 or more	0.4	1.9	0.9	4.5
Number of pain locations, <i>n</i> (SD)***	1.5 (2.2)	4.1 (3.9)	4.3 (3.4)	3.7 (3.3)
Other medication use	45.2	83.0	81.9	89.1

Data are presented as % unless otherwise indicated

MHI Mental Health Index, SD standard deviation

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, contrasting non-users versus any sleep medication users. p values are based on Chi-squared tests (proportions) and independent samples t tests (means)

† 1 unit equals approximately 12 g ethanol

[8] and of suicide [9, 10]. Moreover, it has been shown that both benzodiazepines and Z-drugs are often found in mixed-drug overdoses [11]. Previous studies have also linked sleep medication with cancer [12]. One proposed link between sleep medication and cancer may be infections. For example, a recent meta-analysis reported that patients who were prescribed sleep medications had significantly more infections, particularly in the upper respiratory system [13], and infections in turn may increase the risk of cancer [14]. Moreover, sleep medications induce drowsiness, and, despite label warnings, sleep medication use is linked to increased risk of traffic accidents [15]. Finally, sleep medications may exacerbate symptoms of obstructive sleep apnea, which in turn has been linked to both motor vehicle crashes and cardiovascular deaths [16].

The finding of a link between sleep medication and mortality should be interpreted cautiously due to some important methodological limitations. Most importantly, our exposure measure (sleep medication use) was based on self-report, and the question was phrased in such a manner that only participants reporting taking sleep medication on the day before participating in the study were included in the groups of sleep medication users. Consequently, our exposure measurement is likely to be more representative of those with a high and frequent intake of sleep medication, and many frequent users of sleep medication who did not use the drug that particular night were considered controls. This could again mean that we have a group with more severe sleep problems, and possibly also higher general morbidity, as sleep problems correlate with several

Table 2 Crude and covariate-adjusted hazard ratios of mortality risk associated with sleep medication, during 13–15 years of follow-up of the Hordaland Health Study (1997–1999). Total number of deaths: 622

Exposure	<i>n</i>	Deaths, <i>n</i> (%)	Crude model	Adjusted model ^a	Fully adjusted model ^b
Sleep medication					
Sleep medication use					
No sleep medication	21,667	609 (2.8)	Ref	Ref	Ref
Any sleep medication	159	13 (8.2)	3.36 (1.85–6.10)	2.90 (1.59–5.30)	1.97 (1.06–3.66)
Frequency of sleep medication use					
No sleep medication	21,668	609 (2.8)	Ref	Ref	Ref
Non-daily usage	78	3 (3.8)	1.74 (0.56–5.40)	1.51 (0.49–4.71)	1.08 (0.34–3.41)
Daily usage	80	10 (12.5)	5.25 (2.61–10.55)	4.49 (2.26–9.07)	2.87 (1.40–5.91)
Type of sleep medication					
No sleep medication	21,668	609 (2.8)	Ref	Ref	Ref
Z-drugs	112	7 (6.3)	2.43 (1.09–5.43)	2.17 (0.97–4.88)	1.53 (0.67–3.48)
Benzodiazepines	46	6 (13.0)	6.45 (2.67–15.57)	5.04 (2.08–12.21)	3.08 (1.25–7.58)

Data are presented as *n* (%) or HR (95 % CI)

CI confidence interval, *HR* hazard ratio

^a Adjusted for demographical and lifestyle factors

^b Further adjusted for mental health problems (CONOR MHI), somatic diagnoses, pain, and blood pressure

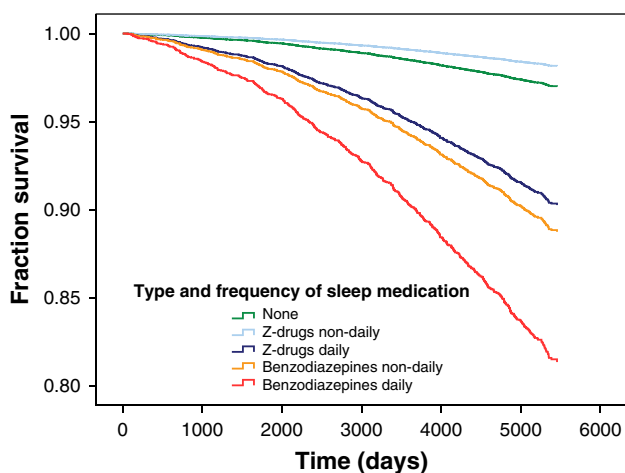


Fig. 1 Kaplan–Meier survival curves (unadjusted) by type and frequency of sleep medication in the Hordaland Health Study (1997–1999)

other conditions [17]. As such, we are likely to have identified stronger associations than would be found for a wider and more modest group of users of sleep medication. As for the possible co-morbidities for the group of high users of sleep medication, this should have partly been accounted for by our adjustment for several health problems and diagnoses. However, residual confounding (e.g., insomnia), imperfect measurements, and specific conditions not requested (e.g., cancer) cannot be ruled out. In relation to this, an important question is whether the discrepancy between the effect of benzodiazepines and Z-drugs is caused by the indication for using the drugs, or

whether the differences can be ascribed to biological effects from the two types of drugs. Adjusting for covariates should theoretically remove some selection by indication, and lead us closer to identifying drug effects. However, given the low statistical power and other limitations of our study, we refrain from drawing any firm conclusion on this issue, and instead encourage future, more robust, studies to address this. Another consequence of the definition of the sleep medication group is that the number of sleep medication users was much smaller than would be expected from national prescription data: according to the Norwegian Prescription Database (www.reseptregisteret.no, which provides data from 2004 onwards), 5.8 % of the population in Hordaland County aged 40–44 years were registered as users of an N05C drug in 2004, which is substantially more than the proportion of users found in the current study (0.7 %). Further, more general register data from Norway show there was a substantial increase in consumption of sleep medication in general from 1997 to 2004 [18, 19]. However, no official data exist on the proportion of daily users or adherence to prescribed sleep medication, and, as such, it is difficult to estimate the accuracy of the self-reported measure used in the current study. The inadequate power of the small numbers is reflected by wide CIs, making the reported estimates less accurate and raising the possibility of missing important but not significant hazards (e.g., the HR 1.5, 95 % CI 0.7–3.5 for zolpidem). A related limitation is that we had no information on dosage or duration of sleep medication use, and we also had no data about use throughout the follow-up period. Furthermore, we had no information on

whether the benzodiazepines were taken for reasons other than as a sleeping pill, and the dosage of intake may differ if the benzodiazepines were taken as medications for a psychiatric disorder. Related to this, although we adjusted for use of other medications, we were unable to further explore the extent to which combinations of several medications (polypharmacy) may have had an impact on the findings. Finally, the limited number of deaths restricts our ability to conduct subgroup analyses. Study strengths include the community-dwelling study population, the complete follow-up with objective register data on mortality, as well as being able to control for several important confounding factors.

Our findings, in line with several previous reviews, indicate a possible increased risk for mortality among users of sleep medication. This should lead to calls for increased efforts in determining whether there is any true causal association involved. To achieve this, we believe further studies examining cause-specific deaths and dose–response relationships are needed.

Conflict of interest The authors report no conflicts of interests.

Open Access This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

- Chong Y, Fryar C, Gu Q. Prescription sleep aid use among adults: United States, 2005–2010. *NCHS Data Brief*. 2013;127:1–8.
- International Narcotics Control Board. Psychotropic substances: statistics for 2008; assessments of annual medical and scientific requirements for substances in schedules II, III and IV of the convention on psychotropic substances of 1971. New York: United Nations; 2010.
- Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open*. 2012;2(1):e000850.
- WHO Collaborating Centre Oslo. ATC/DDD classification. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 2012.
- Goldberg D. The detection of psychiatric illness by questionnaire. Maudsley Monograph No. 21 ed. London: Oxford University Press, 1972; 1972.
- Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci*. 1974;19(1):1–15.
- Søgaard A, Bjelland I, Tell G, Røysamb E. A comparison of the CONOR Mental Health Index to the HSCL-10 and HADS. Measuring mental health status in The Oslo Health Study and the Nord-Trøndelag Health Study. *Nor Epidemiol*. 2003;13(2): 279–84.
- Kripke DF. Greater incidence of depression with hypnotic use than with placebo. *BMC Psychiatry*. 2007;7:42.
- Belleville G. Mortality hazard associated with anxiolytic and hypnotic drug use in the National Population Health Survey. *Can J Psychiatry*. 2010;55(9):558–67.
- Rod NH, Vahtera J, Westerlund H, Kivimaki M, Zins M, Goldberg M, et al. Sleep disturbances and cause-specific mortality: results from the GAZEL cohort study. *Am J Epidemiol*. 2011;173(3):300–9.
- Zosel A, Osterberg EC, Mycyk MB. Zolpidem misuse with other medications or alcohol frequently results in intensive care unit admission. *Am J Ther*. 2011;18(4):305–8.
- Kripke DF. Possibility that certain hypnotics might cause cancer in skin. *J Sleep Res*. 2008;17(3):245–50.
- Joya FL, Kripke DF, Loving RT, Dawson A, Kline LE. Meta-analyses of hypnotics and infections: eszopiclone, ramelteon, zaleplon, and zolpidem. *J Clin Sleep Med*. 2009;5(4):377–83.
- Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer*. 2006;118(12):3030–44.
- Gustavsen I, Bramness JG, Skurtveit S, Engeland A, Neutel I, Morland J. Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam. *Sleep Med*. 2008;9(8):818–22.
- Jean-Louis G, Brown CD, Zizi F, Ogedegbe G, Boutin-Foster C, Gorga J, et al. Cardiovascular disease risk reduction with sleep apnea treatment. *Exp Rev Cardiovasc Ther*. 2010;8(7):995–1005.
- Sivertsen B, Lallukka T, Salo P, Pallesen S, Hysing M, Krokstad S, et al. Insomnia as a risk factor for ill health. Results from the large population-based prospective HUNT study in Norway. *J Sleep Res*. 2014;23:124–32.
- Rønning M. Drug consumption on Norway: 1997–2001. Oslo: Norwegian Institute of Public Health; 2002.
- Rønning M. Drug consumption in Norway: 2000–2004. Oslo: Norwegian Institute of Public Health; 2005.