



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Association between hospital-diagnosed sleep disorders and suicide: A nationwide cohort study

Citation for published version:

Kjær Høier, N, Madsen, T, Spira, AP, Hawton, K, Benros, ME, Nordentoft, M & Erlangsen, A 2022, 'Association between hospital-diagnosed sleep disorders and suicide: A nationwide cohort study', *Sleep*. <https://doi.org/10.1093/sleep/zsac069>

Digital Object Identifier (DOI):

[10.1093/sleep/zsac069](https://doi.org/10.1093/sleep/zsac069)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Sleep

Publisher Rights Statement:

This is the author's peer-reviewed manuscript as accepted for publication.

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



**Association between hospital-diagnosed sleep disorders and suicide:
A nationwide cohort study**

Nikolaj Kjær Høier,^{1,2,3} Trine Madsen,^{1,2}
Adam P. Spira,^{4,5,6} Keith Hawton,^{7,8} Michael Eriksen Benros,^{2,9}
Merete Nordentoft,^{1,2,10} and, Annette Erlangsen^{1,2,4,11}

¹ Danish Research Institute for Suicide Prevention, Mental Health Centre Copenhagen, Denmark

² Copenhagen Research Center for Mental Health – CORE, Mental Health Center Copenhagen, Copenhagen University Hospital

³ Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK.

⁴ Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

⁵ Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

⁶ Johns Hopkins Center on Aging and Health, Baltimore, MD, USA

⁷ Centre for Suicide Research, University of Oxford, Oxford, United Kingdom

⁸ Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, United Kingdom

⁹ Department of Immunology and Microbiology, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

¹⁰ Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

¹¹ Centre for Mental Health Research, Research School of Population Health, The Australian National University, Canberra, Australia

Corresponding author: Nikolaj Kjær Høier, 2f3 46 Moat Street, Edinburgh, EH14 1PH, United Kingdom. Email: Nikolaj.kjaer.hoeier.01@regionh.dk. Telephone: 004542445456

Disclosures and Acknowledgements: Adam Spira has received honoraria for serving as a consultant to Merck and from Springer Nature Switzerland AG for guest editing special issues of *Current Sleep Medicine Reports*.

The other authors report no conflict of interest.

Funding: Lundbeck Foundation Research year scholarship for medicine students was awarded to Nikolaj Kjær Høier to conduct the project.

Abstract

Study objectives: Sleep disorders are related to mental disorders. Yet few studies have examined their association with suicide. We examined whether males and females diagnosed with sleep disorders had higher rates of suicide than individuals not diagnosed with sleep disorders.

Methods: In a cohort study, nationwide data on all males and females aged 15+ years living in Denmark during 1980-2016 were analysed. Sleep disorders were identified through diagnoses recorded during contacts to somatic hospitals. Incidence Rate Ratios (IRR) were estimated using Poisson regression models and adjusted for covariates.

Results:

In all, 3,674,563 males and 3,688,164 females were included, of whom 82,223 (2.2%, mean age: 50.2, SD: 17.5) males and 40,003 (1.1%, mean age: 50.6, SD: 19.9) females had sleep disorder diagnoses. Compared to those with no sleep disorders, the adjusted IRRs for suicide were 1.6 (95% CI, 1.4-1.7) and 2.2 (95% CI, 1.8-2.6) for males and females with sleep disorders, respectively. Excess rates for narcolepsy were found for males (IRR:1.2, 95% CI, 1.0-1.5) and females (IRR:3.3, 95% CI, 3.0-4.1), and for sleep apnea in males (IRR:1.8, 95% CI, 1.5-2.2). A difference with respect to age and sex was observed ($P < 0.001$) between males and females. Males and females had IRRs of 4.1 (95% CI, 3.1-5.5) and 7.0 (95% CI, 4.8-10.1), during the first 6 months after being diagnosed with a sleep disorder.

Conclusions:

Sleep disorders were associated with higher suicide rates even after adjusting for pre-existing mental disorders. Our findings suggest attention towards suicidality in patients with sleep disorders is warranted.

Keywords: Suicide, Suicide Prevention, Sleep disorders, Narcolepsy, Sleep Apnea, Sleep epidemiology

Statement of Significance:

Our findings emphasize that clinicians should pay attention to levels of distress and suicidal thoughts in patients with sleep disorders, particularly if psychiatric comorbidity is present. Furthermore, this study demonstrates associations of suicide amongst patient groups suffering from narcolepsy and sleep apnea, further warranting that clinicians working with these patient groups are aware of early warning signs for suicidal ideation. Screening for psychopathology and suicidal ideation in the process of diagnosing sleep disorders, particularly in somatic settings, might prove to be useful in assessing patients' future suicide risk.

Disclosures:

Financial Disclosures: Adam Spira has received honoraria for serving as a consultant to Merck and from Springer Nature Switzerland AG for guest editing special issues of *Current Sleep Medicine Reports*.

Non-financial Disclosures: None to report.

Accepted Manuscript

Introduction

Every year approximately 700,000 people die by suicide, making it a major public health problem.[1] Suicide has consistently been linked to mental illness,[2] but associations with general medical conditions and sleep disorders have also been demonstrated.[3] Based on survey data, sleep problems may be experienced by 20-27% of the population at any given time.[4]

Sleep disorders, such as insomnia and narcolepsy have been linked to suicidal thoughts and non-fatal suicidal behaviour.[5-7] Yet, only a fraction of people who experience suicidal thoughts or engage in non-fatal attempts will end up dying by suicide.[8] Therefore, evidence, which relates directly to death by suicide is needed, The association by sleep disorders to suicide has previously been examined in a South Korean case-control study.,[9] while sleep apnea has been linked to both death by suicide and self-harm in a recent Danish study.[10] Nocturnal wakefulness has also been linked to death by suicide.[11] Most of these studies lacked adjusting for relevant confounders, such as previous mental disorders.[2] Apart from this, few studies have assessed this association and one meta-analysis concluded that there is a dire need for evidence from studies that account for potential confounding factors.[6,12] Additional limitations include imprecise measures of sleep disorders, such as sleep questionnaires, different methods of observation to determine sleep quality instead of sleep pathology, as well as selected and small study samples, such as veterans, psychiatric patients, or older adults.[12,13] Large, population-based, linkage data with uniform measures of sleep disorders, in the form of hospital diagnoses, could help address these concerns.

Sleep disturbances and disorders are often listed as symptoms of mental disorders, such as depression and anxiety disorders,[14] which in turn are associated with suicide.[2] Although psychiatric patients with sleep disorders have an increased risk of suicidal behavior,[15] the association might not be exclusively be due to mental disorders. However, the associations of sleep and mental disorders with suicide remains to be examined, in particular with regard to timing of disorders as well as how mental disorders might act as a as confounder. Thus a need for deeper looks into associations of suicide risk and timing of mental disorders with respect to sleep disorders is needed to assess the role of mental disorders as confounders. Sleep duration and architecture (i.e., time spent in, and transitions between different sleep stages) are affected by age, sex, habits and environmental factors – thus, certain characteristics, life periods, or events might be important to any risk between sleep disorders and suicidal behaviour. As an example, older adults commonly report a range of different sleep problems[16] and insomnia is more likely to occur in women,[17,18] but it is unclear how these factors interact with hospital diagnosed sleep disorders to alter the risk of death by suicide.

Based on the existing evidence, we hypothesised that sleep disorders are associated with elevated rates of death by suicide. The primary aim of the study was to determine whether males and females with a hospital diagnosis of any sleep disorder had a higher suicide rate than people without such a diagnosis. Secondly, we compared suicide rates with respect to type of sleep disorder, type of patient contact, mode of diagnosis, age group, and presence of mental disorders. We also examined for temporal and dose response associations between sleep disorders and suicide. Utilizing the longitudinal, Danish national registers allowed us to

follow a population of more than 7 million people over 37 years, while accounting for relevant confounders, such as pre-existing mental and chronic medical disorders.

Methods

Data source

A cohort design was applied to national linkage data covering all individuals living in Denmark from Jan 1st, 1980 through Dec 31st, 2016 as listed in the Civil Registration System. Data, including diagnoses and exact dates, on all somatic and psychiatric hospital contacts were obtained from the National Patient Registry (NPR) and Psychiatric Central Registry, respectively. Diagnoses were recorded according to the International Classification of Diseases, Eighth Revision (ICD-8) until January 1, 1994 and the Tenth Revision (ICD-10) thereafter. Individual-level linkage between these nationwide, administrative registers was facilitated using the unique Danish civil registration number assigned at birth or on immigration.

Study population

The study population included all individuals aged 15 years or older. Individuals who turned 15 years of age and immigrants fulfilling the age criterion arriving in the country during the study period were included on the date of the respective event.

Exposure

The NPR was used to identify persons who had been diagnosed with sleep disorders during contact with somatic hospitals. This register contains data on all hospitalizations since 1977, including out-patient and emergency department contacts since 1995 on both somatic and

psychiatric contacts. People were considered to have any sleep disorder from the date when they had first been recorded with one or more of the following diagnoses: ICD-8: 306.4, 780.6, 347 and ICD-10: G47.0, G47.1, G47.2, G47.3, G47.4, G47.8, G47.9, F51.0, F51.1, F51.2, F51.3, F51.4, F51.5, F51.8, F51.9. In addition we separately examined; insomnia (ICD-10: G47.0, F51.0), narcolepsy (ICD-8: 347; ICD-10: G47.4), and sleep apnea (ICD-10: G47.3). Although insomnia was initially included, due to a low number of events (n=12) it was later omitted from separate analysis and added to the exposure of other sleep disorders. Information on type of patient contact and mode of diagnosis was collected based on the most recent contact for sleep disorders.

Outcome

The outcome of interest was death by suicide identified by the following codes: ICD-8: E950-E959; ICD-10: X60-X84, Y87.0, verified where the manner of death was listed as suicide in the Cause of Death Register.

Follow-up

Participants were observed between January 1, 1980, and December 31, 2016. People migrating out of the country or who died were censored on the respective date of these events.

Statistical analysis

We calculated incidence rates per 100,000 by dividing number of events by person-years. Incidence Rate Ratios (IRR) with 95% confidence intervals were estimated using adjusted Poisson regressions, including comparing males and females, respectively, exposed to sleep

disorders with those not exposed. Person-years were calculated based on exact number of person-days. The logarithmic value of these entered in the Poisson regressions as an offset variable to account for time under exposure, i.e., as a denominator of the rates. We also examined IRRs for those only diagnosed with specific sleep disorders (none, sleep apnea, narcolepsy, other or combinations of sleep disorders). In addition, we assessed whether rates varied by type of contact (none, inpatient/emergency department, out-patient) and mode of diagnosis (none, main diagnosis, supplementary diagnosis). Since the examined outcome was death by suicide, we had no problems with the outcome preceding any exposure. We investigated a potential dose-response in relation to number of hospital contacts for sleep disorders (0, 1, ≥ 2) to assess for any risks associated with increase in contact. Similarly, a possible temporal association was examined by calculating IRRs for different categories of time since first sleep disorder diagnosis (none, <6 months, 6 month-2 years, 2-6 years, ≥ 6 years post discharge) and time since last recorded diagnosis of sleep disorder (none, <6 months, 6 month-2 years, 3-6 years, ≥ 6 years post discharge). These intervals were chosen to examine whether proximity to time of diagnosis might be associated with higher IRRs. Stratified models addressed associations with respect to any mental disorder diagnosis made before and during follow-up, following specific disorders: anxiety disorders, bipolar disorder, borderline personality disorder, other personality disorders, post-traumatic stress disorder (PTSD), mood disorders, schizophrenia spectrum disorder, schizophrenia, and substance use disorders, as identified in the Psychiatric Central Registry (eTable 1). Because a mental disorder with an onset after a sleep disorder might be the reason for an increased risk of suicide, IRRs were estimated for persons who had been diagnosed with a mental disorder for the first time after a diagnosis of a sleep disorder in a sub-analysis, which was confined to patients with sleep disorders.

Multivariable regression models were adjusted for: *period* (1980-1989, 1990-1999, 2000-2009, 2010-2016); *age group* (15-29, 30-49, 50-69, ≥70); *living status* (living alone or married/cohabiting); *socio-economic status* (recorded since 1992 and grouped into: working or studying, unemployed, disability pension, retired, missing, cases prior to 1992 were added to missing); *Charlson Comorbidity Index* (a measure of chronic disorders, derived from the NPR and grouped into: 0, 1-3, ≥4 medical conditions); *self-harm diagnosed prior to diagnosis of sleep disorders* (no, yes); and *mental disorder diagnosed prior to diagnosis of sleep disorders* (no, yes), including substance use disorders. Models were analysed separately for males and females after preliminary analysis revealed clear sex differences. We conducted a sensitivity analysis where exposure was defined as having been diagnosed with sleep disorders within the last 6 years before the end of follow-up, in order to assess whether effects persisted when the sample was restricted to those recently exposed between 2011-2016. In a second sensitivity analysis, we examined the association among participants who had not been diagnosed with any mental disorder or recorded with suicide attempts, to examine the association of sleep disorders with suicide independent of mental disorders or prior attempts. Lastly, we examined whether the association between sleep disorders and suicide remained when only using data over the period 1995-2016 to circumvent any major changes related to the transition from ICD-8 to ICD-10. All variables were included as time-varying and updated either on the exact registered date of change or on a yearly basis. Data management and regression analysis were carried out using SAS Institute Inc; version 9.4.

Ethical approval

The project was approved by the Danish Data Protection Agency (P-2020-305).

Results

During the 37 years of follow-up, a total of 3,674,563 males and 3,688,164 females were included, of which 82,223 males (2.2%, mean age at time of diagnosis: 50.2 years, SD: 17.5) and 40,003 females (1.1%, mean age at time of diagnosis: 50.6 years, SD: 19.9) were diagnosed with sleep disorders. It was recorded as the primary diagnosis for 71.2% of males and 66.7% of females who were diagnosed with sleep disorders. Sleep disorders were predominantly diagnosed in outpatient settings (males: inpatients: 24.7%, outpatients: 75.1%, emergency departments patients: 0.2%; females: inpatients: 33.9%, outpatients: 65.8%, emergency departments patients: 0.3%). A total of 23,927 suicides occurred among males, of whom 299 (1.3%) had been diagnosed with a sleep disorder, and out of 11,556 females who died by suicide, a sleep disorder had been diagnosed in 117 (1.01%) (eTable 2a and 2b).

Sleep disorders and suicide

Males with a sleep disorder diagnosis had a suicide rate of 47.4 (95% CI, 42.0-52.7) per 100,000 person-years compared to 29.9 (95% CI, 29.5-30.3) among those not diagnosed with a sleep disorder (Table 1). Females with a sleep disorder had a suicide rate of 42.3 per 100,000 person-years (95% CI, 34.7-50.0) versus 13.9 (95% CI, 13.6-14.1) in those with no sleep disorders. The majority of those who had a sleep disorder and died by suicide, either had a diagnosis of narcolepsy (42% of males; 73.5% of females) or sleep apnea (males: 36%; females: 4.2%).

A 1.6-fold (95% CI, 1.4-1.7) higher suicide rate was found among males with sleep disorders relative to those with none, when adjusting for period, age group, living status, socio-economic status, Charlson Comorbidity Index, previous self-harm and mental disorders. For females, the corresponding IRR was 2.2 (95% CI, 1.8-2.6). With respect to temporality, during the first 6 months after being diagnosed with a sleep disorder for the first time, males had an IRR for suicide of 4.1 (95% CI, 3.1-5.5; $P < 0.0001$) which decreased to 1.2 (95% CI, 1.0-1.5) for those diagnosed more than 6 years previously compared to those with no sleep disorder (Figure 1a). The corresponding IRRs for females were 7.0 (95% CI, 4.8-10.1; $p < 0.0001$) and 2.2 (95% CI, 1.6-2.9; $P < 0.0001$). A higher suicide rate was also found for those who had received their last diagnosis of a sleep disorder within the past 6 months (males: IRR, 3.4; 95% CI, 2.7-4.3; females: IRR, 5.8; 95% CI, 4.1-8.1) versus those last diagnosed more than 6 years previously (males: IRR, 1.2; 95% CI, 1.0-1.5; $P < 0.0001$; females: IRR, 2.3; 95% CI, 1.7-3.1; $P < 0.0001$) (Figure 1b).

When restricting the sample of exposed to those diagnosed within the last 6 years in a sensitivity analyses, males and females with sleep disorders were found to have IRRs of 1.7 (95% CI, 1.5-2.0) and 2.1 (95% CI, 1.7-2.7) respectively, in comparison to those not diagnosed (table not shown). We excluded individuals with previous psychiatric history or suicide attempts in a second analyses, which resulted in IRRs of 2.2 (95% CI, 1.9-2.5) and 4.3 (95% CI, 3.3-5.5) for males and females respectively (eTable 3). In order to exclude impact related to the transition from ICD-8 to ICD-10, we examined the association between sleep disorders and suicide during 1995-2016. IRRs of 1.4 (95% CI, 1.2-1.6) and 1.7 (95% CI, 1.3-2.2) were found for males and females, respectively.

Number of hospital contacts for sleep disorders

When compared to those with no sleep disorder diagnosed, males with one hospital admission or outpatient contact for a sleep disorder had an IRR for suicide of 1.7 (95% CI, 1.4-1.9), while those with two or more hospital contacts had an IRR of 1.3 (95% CI, 1.1-1.6). For females, IRRs of 2.4 (95% CI, 1.9-3.0) and 1.8 (95% CI, 1.3-2.4) were found for those with one and two or more hospital contacts for sleep disorders, respectively.

Specific sleep disorders

Males who had single diagnoses of narcolepsy, or sleep apnea had IRRs for suicide of 1.8 (95% CI, 1.5-2.2; $P < 0.0001$) for narcolepsy, and 1.2 (95% CI, 1.0-1.5; $P < 0.03$) for sleep apnea, when compared to those with no disorders. Those diagnosed with several or other sleep disorders had an IRR for suicide of 2.0 (95% CI, 1.6-2.6; $P < 0.0001$). Females had IRRs for suicide of 3.3 (95% CI, 3.0-4.1; $P < 0.0001$) for narcolepsy, 0.4 (95% CI, 0.2-0.9 $P < 0.02$) for sleep apnea, and 3.8 (95% CI, 3.0-5.6; $P < 0.0001$) for other sleep disorders.

Type of contact and mode of diagnosis

With respect to type of patient, males seen for sleep disorders in inpatient settings, or the emergency department had an IRR of 1.4 (95%CI 1.2-1.7, $p < 0.005$), while those seen in outpatient settings had an IRR of 1.6 (95%CI, 1.4-1.9, $p < 0.005$). Females with inpatient or emergency department contacts for sleep disorders had an IRR of 1.3 (95%CI 0.9-2.0, $p = 0.1$) and those seen in outpatient setting had an IRR of 2.4 (95%CI, 2.0-3.0, $p < 0.005$) when compared to those without a sleep disorder. A higher suicide rate (IRR, 2.9; 95% CI, 2.1-4.1) was found for males where sleep disorders were the main diagnosis than for those where it

was a supplementary diagnosis (IRR, 1.4; 95% CI, 1.2-1.6, $p < 0.005$) when compared to those with no sleep disorders. For females, the IRRs for those with a main and a supplementary diagnosis were 2.1 (95% CI, 1.7-2.6) and 1.9 (95% CI, 1.4-2.6), respectively, in comparison to those with no sleep disorder.

Sleep disorders and age

With respect to age groups, males aged 15-49 years with a sleep disorder had an IRR for suicide of 1.9 (95% CI, 1.6-2.3) for suicide when compared to peers without a sleep disorder (eTable 4). Similarly, an excess suicide rate was noted for males aged 50-69 years with a sleep disorder (IRR, 1.5; 95% CI, 1.3-1.8) when compared to peers without a sleep disorder. An IRR of 4.0 (95% CI, 3.0-5.3) was found for females aged 15-49 years with a sleep disorder when compared to peers without a sleep disorder. Significant differences were noted with respect to age and sex ($p < 0.0001$) when assessed in a joint model (Figure 2).

Sleep disorders and mental disorders

Stratifying analyses by mental disorders, based on a diagnosis at any time before and during follow-up, resulted in an IRR of 1.6 (95% CI, 1.4-1.9) for males diagnosed with sleep disorders but no mental disorder, while an IRR of 5.2 (95% CI, 4.4-6.2) was found for those with both a sleep disorder and a mental disorder compared to those with no disorders (Tables 2). For females, those diagnosed with a sleep disorder alone had an IRR of 3.1 (95% CI, 2.3-4.2) compared with 9.0 (95% CI, 7.2-11.4) in those with both a mental disorder and a sleep disorder. With respect to mood disorders, higher rates were found for those diagnosed with both sleep disorders and mood disorders (males: IRR, 5.0; 95% CI, 4.0-6.2; females: IRR, 6.9; 95% CI, 5.1-9.2) compared with those with sleep disorders only (males: IRR, 1.6; 95%

CI, 1.4-1.8; females: IRR, 2.8; 95% CI, 2.2-3.6) (eTable 5a and 5b). In females, those with a sleep disorder and PTSD had a markedly elevated IRR (13.8, 95% CI 5.2-36.9) compared with those with just a sleep disorder (IRR, 2.3 (95% CI, 1.9-2.7)). However, the estimates for females were based on relatively few suicide deaths.

Males and females who had been diagnosed with a mental disorder prior to their sleep disorder had IRR for suicide of 2.1 (95% CI, 1.6-2.8) and 2.3 (95% CI, 1.5-3.4), respectively, when compared to those individuals who had a sleep disorder but no such history of mental disorders. Both males and females who were first diagnosed with a mental disorder after a sleep disorder diagnosis had substantially greater rate of suicide (males, IRR 6.0; 95% CI, 4.4-8.1; $P < 0.0001$; females, IRR, 4.4; 95% CI, 2.6-7.7; $P < 0.0001$), when compared to those diagnosed with a sleep disorder but with no mental disorder diagnosis.

Discussion

To our knowledge, this is the first study to use sleep disorder diagnosed during hospital contacts to investigate the association between sleep disorders and death by suicide using national and population-based data while adjusting for important confounders, such as previous suicide attempts, previous mental disorders, and socio-economic status. In terms of sex differences, a comparatively high suicide rate was found for females with sleep disorders, considering their baseline suicide rate. In absolute terms, it was at level with the rate for males, which is unusual when considering that males generally outnumber female's suicides some two to three-fold. This was confirmed though elevated IRRs, also when adjusting for differences related to age group and period. Sleep architecture is known to differ between the sexes and previous studies have suggested a higher risk of sleep

disturbances among females.[17,19] A temporal association revealed elevated suicide rates among those recently diagnosed with a sleep disorder versus those among whom the diagnosis was longer ago. People of both sexes diagnosed with narcolepsy and males with sleep apnea had higher suicide rates than those who were not diagnosed with these disorders. Higher suicide rates were also found for people suffering from both sleep disorder and comorbid mental disorders, but people diagnosed with a sleep disorder, but no mental disorder also had higher suicide rates than those with no disorders. Interestingly, individuals were found to have the highest suicide rate at the time of their first hospital contact for a sleep disorder. However, persons with multiple hospital contacts for sleep disorders were also found to have higher suicide rates than those with no contacts. It is possible that people who have attended multiple appointments represent a segment of patients who are more engaged in the treatment, or where the treatment might have begun to show an effect, than those who are seen for the first time. Multiple appointment could also be a marker of severity, but this is seemingly not supported by the findings of this study. Seeking help for sleep problems, in the form of sleep medicine visits, has previously been linked to lower suicide risks.[20] Still, the overlapping confidence intervals revealed that rates could not be assumed to be significantly different from each other.

Narcolepsy and sleep apnea were the most frequently diagnosed types of sleep disorders in Danish hospital settings. Various neurobiological mechanisms have been proposed for the association between different sleep disorders, in particular narcolepsy and sleep apnea, and suicide. Firstly, sleep disturbances of different kind may act as a stressor by having a severe impact on mental well-being and quality of life by increased exhaustion due to lack of sleep.[21] Furthermore, the psychosocial burden and stress placed upon those suffering

from narcolepsy and sleep apnea might affect this group particularly. Other explanations for an association are a disturbance of rapid eye movement (REM) sleep, which is important for emotion regulation, and sleep depth might lead to depressive states and other psychiatric comorbidity, hence linked to an increased risk of suicide.[22] Secondly, neurobiological mechanisms could play a role, as sleep disorders, such as narcolepsy and sleep apnea, are known to affect cognitive functioning, including coping and problem solving, which might lead to emotional instability and a possible risk of suicide.[23] Thirdly, inhibition of sleep depth and enhanced REM sleep pressure has been associated with increased psychiatric comorbidity.[24]

In comparison to previous estimates[4], relatively low prevalence rates of sleep disorders were noted in this study. By only including hospital-diagnosed cases, it is possible that our findings were restricted to more severe cases of sleep disorders, such as narcolepsy and sleep apnea. This could be a contributing explanation to why the majority of those diagnosed with sleep disorders and who died by suicide were recorded with these disorders. Another explanation could relate to the specific characteristics of these disorders. Narcolepsy is characterized by excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis, and disturbed nocturnal sleep,[25] and has a particularly severe impact on daily life as well as links to psychiatric comorbidity.[26] Challenges associated to this conditions such as coping with the disease and mental disorders have previously been linked to suicide.[2]

In addition, sleep apnea has previously been linked to both suicide and self-harm[10] but also neurocognitive impairment.[27] Sleep apnea might cause ischemic harm to the brain as

a result of the recurring hypoxia and sleep fragmentation, which again can affect cognitive functioning, including problem solving, hence potentially leading to an increased suicide risk due to increased stress and mental instability.

As previously mentioned, hypersomnia is a symptom of mood disorders which are associated with suicide. The observed increased rates of suicide among people with sleep disorders might, thus, be a result of an underlying, potentially untreated, mood disorder.[28,29]

The category of “other” sleep disorders might have included more complex cases, for instance persons suffering from more than one type of sleep disorder at the same time, which could explain their higher suicide rate.

We found an elevated suicide rate found among persons diagnosed with a mental disorder prior to any sleep disorder, however, those who developed a mental disorder after being diagnosed with sleep disorders had an even higher rate. This could suggest that sleep disorders might lead to an increased risk of psychiatric comorbidity, which in turn might be the driving force behind the increased suicide rates observed in this study, i.e. that mental disorders might act as a mediator. Still, this does not exclude the possibility that sleep disturbances might be associated with suicide independently of mental disorders.[13] We speculate that the psychosocial burden amongst patients suffering from sleep apnea and narcolepsy is one of the drivers behind the increased suicide risk as well as the psychiatric comorbidity observed in this patient population.

Strengths and limitations

Strengths of the study include a large, longitudinal cohort of more than 7 million participants, a long follow-up period and rigorously analyses, adjusted for a variety of important covariates, such as socio-economic background and previous suicide and mental disorder history. The Civil Registration System is corrected on a continuous basis and the hospital registers have been evaluated to be of high quality. Having complete data and exact dates of hospital admissions, including prior to when the study began, enhanced the quality of the analyses. Our exclusive use of diagnoses given by medical doctors in secondary care settings is likely to have enhanced the robustness of the diagnoses of sleep disorders. Furthermore, since 2003 all contacts to private hospitals have been reported to the National Patient Registry.

However, by only including sleep disorders diagnosed in somatic hospitals, there is a bias away from sleep disorders occurring due to psychiatric disorders. By only including sleep disorders diagnosed in somatic hospitals, we reduced the risk of confounding effects due to sleep disorders occurring as a symptom of a mental disorder. Lastly, the association between hospital diagnosed narcolepsy and death by suicide has seemingly not previously been shown.

This study had several more general limitations. First, data on cases exclusively seen in primary care settings were not available. Thus, sleep disorders, in particular insomnia, were likely under-recorded, which is supported by generally higher prevalence rates than those reported here. Although diagnostic procedures might have changed over time, those identified with sleep disorders in this study likely represented a group with more severe disorders diagnosed in hospital settings. Sleep disorders vary with respect to aetiology and

characteristics, which limits the interpretation of the joint estimate for any sleep disorder, especially as narcolepsy and sleep apnea, are different in pathophysiology when compared to a disorder such as insomnia. Furthermore, date of diagnosis may not represent the exact time of onset of the condition. Also, sleep or mental disorders diagnosed before 1977 and 1969, respectively, were not captured. While we adjusted for mental disorders, we cannot exclude that some people with sleep disorders might have had undiagnosed mental disorders or conditions, which were only diagnosed in primary care. Further, data on medical treatment of sleep disorders were not included. Lastly the risk of type 1 error did exist although all reported results were significant unless otherwise specified and were available with 95% confidence intervals.

Clinical implications

Our findings emphasize that clinicians should pay attention to levels of distress and suicidal thoughts in patients with sleep disorders, particularly if psychiatric comorbidity is present. It is important to ensure that clinicians working with this patient group are aware of early warning signs for suicidal ideation, especially, as these might be communicated as difficulties sleeping and interpreted as just sleep disorders. Screening for psychopathology and suicidal ideation and attempts could be a relevant part of the process of diagnosing sleep disorders in somatic settings, for instance by using the Columbia Suicide Severity Rating Scale.[30] For patients with sleep disorders who are seen in psychiatric settings, medication and behavioural approaches to improve sleep problems might help prevent suicidality[31], especially when sleep disorders are a sign of deterioration of mental health. However, the dangers of self-poisoning with hypnotics needs to be borne in mind[32] as well as the risk of dependence development which might augment suicide risk in this

population.[33] Further research is needed to investigate the relationship between treatment for sleep disorders and its possible effects on suicide risk.

Conclusions

In this national register study, individuals with sleep disorders were found to have an increased suicide rate when compared to those without such disorders. In addition, specific disorders associated with increased suicide rates included narcolepsy, and, in males, sleep apnea. A temporal analysis revealed that the rates of suicide were highest shortly after the time of the sleep disorder diagnosis. The association between sleep disorders and suicide remained significant when adjusted for mental disorders, although presence of these in addition to sleep disorders was linked to elevated rates of suicide, particularly amongst females. The findings from this study illustrate the importance of awareness regarding suicidal ideation when treating patients suffering from sleep disorders and raises the question of whether treating sleep disorders may prevent suicide.

Accepted Manuscript

References

1. WHO. *LIVE LIFE: An implementation guide for suicide prevention in countries*. 2021.
2. Hawton K, van Heeringen K. Suicide. *Lancet*. Apr 18 2009;373(9672):1372-81. doi:10.1016/s0140-6736(09)60372-x
3. Bernert RA, Kim JS, Iwata NG, Perlis ML. Sleep disturbances as an evidence-based suicide risk factor. *Curr Psychiatry Rep*. Mar 2015;17(3):554. doi:10.1007/s11920-015-0554-4
4. Chattu VK, Manzar MD, Kumary S, Burman D, Spence DW, Pandi-Perumal SR. The Global Problem of Insufficient Sleep and Its Serious Public Health Implications. *Healthcare (Basel)*. Dec 20 2018;7(1)doi:10.3390/healthcare7010001
5. Bishop TM, Ashrafioun L, Pigeon WR. The Association Between Sleep Apnea and Suicidal Thought and Behavior: An Analysis of National Survey Data. *J Clin Psychiatry*. Jan/Feb 2018;79(1)doi:10.4088/JCP.17m11480
6. Liu RT, Steele SJ, Hamilton JL, et al. Sleep and suicide: A systematic review and meta-analysis of longitudinal studies. *Clin Psychol Rev*. Nov 2020;81:101895. doi:10.1016/j.cpr.2020.101895
7. Tseng WC, Liang YC, Su MH, Chen YL, Yang HJ, Kuo PH. Sleep apnea may be associated with suicidal ideation in adolescents. *Eur Child Adolesc Psychiatry*. May 2019;28(5):635-643. doi:10.1007/s00787-018-1227-8
8. Hubers AAM, Moaddine S, Peersmann SHM, et al. Suicidal ideation and subsequent completed suicide in both psychiatric and non-psychiatric populations: a meta-analysis. *Epidemiol Psychiatr Sci*. Apr 2018;27(2):186-198. doi:10.1017/s2045796016001049
9. Na EJ, Lee H, Myung W, et al. Risks of Completed Suicide of Community Individuals with ICD-10 Disorders Across Age Groups: A Nationwide Population-Based Nested Case-Control Study in South Korea. *Psychiatry Investig*. Apr 2019;16(4):314-324. doi:10.30773/pi.2019.02.19
10. Udholm N, Fuglsang M, Lundbye-Christensen S, Bille J, Udholm S. Obstructive sleep apnea and risk of suicide and self-harm: a Danish Nationwide Cohort Study. *Sleep*. Feb 14 2022;45(2)doi:10.1093/sleep/zsab286
11. Perlis ML, Grandner MA, Brown GK, et al. Nocturnal Wakefulness as a Previously Unrecognized Risk Factor for Suicide. *J Clin Psychiatry*. Jun 2016;77(6):e726-33. doi:10.4088/JCP.15m10131
12. Pigeon WR, Piquart M, Conner K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *J Clin Psychiatry*. Sep 2012;73(9):e1160-7. doi:10.4088/JCP.11r07586
13. Harris LM, Huang X, Linthicum KP, Bryen CP, Ribeiro JD. Sleep disturbances as risk factors for suicidal thoughts and behaviours: a meta-analysis of longitudinal studies. *Sci Rep*. Aug 17 2020;10(1):13888. doi:10.1038/s41598-020-70866-6
14. Murphy MJ, Peterson MJ. Sleep Disturbances in Depression. *Sleep Med Clin*. Mar 2015;10(1):17-23. doi:10.1016/j.jsmc.2014.11.009
15. Malik S, Kanwar A, Sim LA, et al. The association between sleep disturbances and suicidal behaviors in patients with psychiatric diagnoses: a systematic review and meta-analysis. *Syst Rev*. Feb 25 2014;3:18. doi:10.1186/2046-4053-3-18
16. Foley D, Ancoli-Israel S, Britz P, Walsh J. Sleep disturbances and chronic disease in older adults: results of the 2003 National Sleep Foundation Sleep in America Survey. *J Psychosom Res*. May 2004;56(5):497-502. doi:10.1016/j.jpsychores.2004.02.010
17. Suh S, Cho N, Zhang J. Sex Differences in Insomnia: from Epidemiology and Etiology to Intervention. *Curr Psychiatry Rep*. Aug 9 2018;20(9):69. doi:10.1007/s11920-018-0940-9
18. Krishnan V, Collop NA. Gender differences in sleep disorders. *Curr Opin Pulm Med*. Nov 2006;12(6):383-9. doi:10.1097/01.mcp.0000245705.69440.6a
19. Pengo MF, Won CH, Bourjeily G. Sleep in Women Across the Life Span. *Chest*. Jul 2018;154(1):196-206. doi:10.1016/j.chest.2018.04.005
20. Bishop TM, Walsh PG, Ashrafioun L, Lavigne JE, Pigeon WR. Sleep, suicide behaviors, and the protective role of sleep medicine. *Sleep Med*. Jul 25 2019;doi:10.1016/j.sleep.2019.07.016
21. Kallestad H, Hansen B, Langsrud K, et al. Impact of sleep disturbance on patients in treatment for mental disorders. *BMC Psychiatry*. Oct 29 2012;12:179. doi:10.1186/1471-244x-12-179

22. Palmer CA, Alfano CA. Sleep and emotion regulation: An organizing, integrative review. *Sleep Med Rev*. Feb 2017;31:6-16. doi:10.1016/j.smrv.2015.12.006
23. Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. *Semin Neurol*. Mar 2005;25(1):117-29. doi:10.1055/s-2005-867080
24. Baglioni C, Nanovska S, Regen W, et al. Sleep and mental disorders: A meta-analysis of polysomnographic research. *Psychol Bull*. Sep 2016;142(9):969-990. doi:10.1037/bul0000053
25. Klimova B, Maresova P, Novotny M, Kuca K. A Global View on Narcolepsy - A Review Study. *Mini Rev Med Chem*. Feb 14 2018;18(5):458-464. doi:10.2174/1389557516666160801095630
26. Ruoff CM, Reaven NL, Funk SE, et al. High Rates of Psychiatric Comorbidity in Narcolepsy: Findings From the Burden of Narcolepsy Disease (BOND) Study of 9,312 Patients in the United States. *J Clin Psychiatry*. Feb 2017;78(2):171-176. doi:10.4088/JCP.15m10262
27. Andreou G, Vlachos F, Makanikas K. Effects of chronic obstructive pulmonary disease and obstructive sleep apnea on cognitive functions: evidence for a common nature. *Sleep Disord*. 2014;2014:768210. doi:10.1155/2014/768210
28. Soehner AM, Kaplan KA, Harvey AG. Prevalence and clinical correlates of co-occurring insomnia and hypersomnia symptoms in depression. *J Affect Disord*. 2014;167:93-7. doi:10.1016/j.jad.2014.05.060
29. Dauvilliers Y, Lopez R, Ohayon M, Bayard S. Hypersomnia and depressive symptoms: methodological and clinical aspects. *BMC Med*. Mar 21 2013;11:78. doi:10.1186/1741-7015-11-78
30. Drapeau CW, Nadorff MR, McCall WV, Titus CE, Barclay N, Payne A. Screening for suicide risk in adult sleep patients. *Sleep Med Rev*. Aug 2019;46:17-26. doi:10.1016/j.smrv.2019.03.009
31. McCall WV, Benca RM, Rosenquist PB, et al. Reducing Suicidal Ideation Through Insomnia Treatment (REST-IT): A Randomized Clinical Trial. *Am J Psychiatry*. Nov 1 2019;176(11):957-965. doi:10.1176/appi.ajp.2019.19030267
32. Geulayov G, Ferrey A, Casey D, et al. Relative toxicity of benzodiazepines and hypnotics commonly used for self-poisoning: An epidemiological study of fatal toxicity and case fatality. *J Psychopharmacol*. Jun 2018;32(6):654-662. doi:10.1177/0269881118754734
33. Brandt J, Leong C. Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. *Drugs R D*. Dec 2017;17(4):493-507. doi:10.1007/s40268-017-0207-7

Figure Caption list:

Figure 1. Association between time since first and last recorded diagnosis of sleep disorders and suicide.^{1,2}

a) Time since first diagnosis

¹ Adjusted for period, age group, living status, socio-economic status, Charlson Comorbidity Index, previous self-harm, and previous mental disorders.

² The absolute numbers of suicide for each time period and the person-years and IRR can be observed in Etable 6

b) Time since last diagnosis

Abbreviations: IRR: Incidence Rate Ratio.

¹ Adjusted for period, age group, living status, socio-economic status, Charlson Comorbidity Index, previous self-harm, and previous mental disorders.

² The absolute numbers of suicide for each time period and the person-years and IRR can be observed in Etable 6

Figure 2. Association between sleep disorders and suicide with respect to age group and sex.^{1,2}

Abbreviations: IR: Incidence Rate, IRR: Incidence Rate Ratio.

¹ This is a model examining males and females jointly, the reference group is females with no sleep disorder aged 15-49 years old. Adjusted for period, age group, living status, socio-economic status, Charlson Comorbidity Index, previous self-harm, and previous mental disorders.

² Due to few events age groups 15-29 and 30-49 was merged for these analyses.

Table 1. Associations between sleep disorders and suicide.

	n/N	Unadjusted IRR (CI-95%)	Adjusted IRR ¹ (CI-95%)
Males			
Sleep disorders			
No	23,628/3,592,340	1 [Ref.]	1 [Ref.]
Yes	299/82,223	1.6 (1.4-1.8)	1.6 (1.3-1.7)
Number of hospital contacts for sleep disorders			
None	23,628/3,592,340	1 [Ref.]	1 [Ref.]
1 contact	189/43,247	1.9 (1.6-2.2)	1.7 (1.5-2.0)
2+ contacts	110/38,976	1.3 (1.0-1.5)	1.3 (1.1-1.6)
Type of sleep disorder ²			
None	23,628/3,592,340	1 [Ref.]	1 [Ref.]
Narcolepsia	126/10,436	0.9 (0.8-1.1)	1.2 (1.0-1.5)
Sleep Apnea	110/52,885	3.4 (2.8-4.0)	1.8 (1.5-2.2)
Other sleep disorders	63/18,875	1.8 (1.4-2.3)	2.0 (1.6-2.6)
Mode of diagnosis			
None	11,439/3,648,161	1 [Ref.]	1 [Ref.]
Supplementary diagnosis	265/299	1.5 (1.3-1.7)	1.4 (1.3-1.6)
Main diagnosis	34/299	2.7 (1.9-3.8)	3.0 (2.1-4.1)
Type of patient contact			
None	11,439/3,648,161	1 [Ref.]	1 [Ref.]
Outpatient	142/299	1.1 (0.9-1.3)	1.4 (1.2-1.7)
Inpatient/ED	157/299	2.7 (2.3-3.2)	1.6 (1.4-1.9)
Females			
Sleep disorders			
No	11,439/3,648,161	1 [Ref.]	1 [Ref.]
Yes	117/40,003	3.0 (2.5-3.7)	2.2 (1.8-2.6)
Number of hospital contacts for sleep disorders			
None	11,439/3,648,161	1 [Ref.]	1 [Ref.]
1 contact	80/24,056	3.5 (2.8-4.3)	2.4 (2.0-3.0)
2+ contacts	37/15,947	2.4 (1.7-3.3)	1.8 (1.3-2.5)
Type of disorder ²			
None	11,439/3,648,161	1 [Ref.]	1 [Ref.]
Narcolepsia	86/8,228	6.0 (5.0-8.0)	3.3 (3.0-4.1)
Sleep Apnea	5/18,004	0.3 (0.1-0.7)	0.4 (0.2-0.9)
Other sleep disorders	26/13,771	3.2 (2.2-4.7)	3.8 (3.0-5.6)
Mode of diagnosis			
None	11,439/3,648,161	1 [Ref.]	1 [Ref.]

Supplementary diagnosis	42/299	3.3 (2.4-4.5)	1.9 (1.4-2.6)
Main diagnosis	75/299	2.9 (2.3-3.7)	2.1 (1.7-2.7)
Type of patient contact			
None	11,439/3,648,161	1 [Ref.]	1 [Ref.]
Outpatient	26/117	1.2 (0.8-1.8)	1.3 (0.9-2.0)
Inpatient/ED	91/117	5.4 (4.4-6.6)	2.4 (2.0-3.0)

Abbreviations: IRR: Incidence Rate Ratio. ED: Emergency Department

¹ Adjusted for period, age group, living status, socio-economic status, Charlson Comorbidity Index, previous self-harm and previous mental disorders.

² People who were diagnosed with more than one sleep disorder were assigned to the category of other sleep disorders.

Accepted Manuscript

Table 2. Associations between sleep disorders and mental disorders among males and females.

	n/N	Unadjusted IRR (CI-95%)	Adjusted IRR ¹ (CI-95%)
Males:			
Mental disorders diagnosed before or during follow-up:			
No disorder	15,878/3,592,340	1 [Ref.]	1 [Ref.]
Sleep disorders	148/82,223	1.3 (1.1-1.5)	1.7 (1.4-2.0)
Mental disorders	7,750/3,592,340	8.4 (8.2-8.6)	4.7 (4.5-4.6)
Sleep disorders and mental disorders	151/82,223	7.6 (6.5-8.9)	5.3 (4.5-6.2)
Mental disorders diagnosed before sleep disorder ²			
No prior mental disorders	211/82,223	1 [Ref.]	1 [Ref.]
Prior mental disorders	88/82,223	3.8 (3.0-4.9)	2.1 (1.6-2.8)
Mental disorders diagnosed after sleep disorder ³			
No mental disorders	148/82,223	1 [Ref.]	1 [Ref.]
Mental disorders	63/82,223	7.3 (5.5-9.8)	6.0 (4.4-8.1)
Females:			
Mental disorders given before or during follow-up:			
No disorder	6,140/3,648,161	1 [Ref.]	1 [Ref.]
Sleep disorders	44/40,003	2.6 (1.9-3.5)	3.2 (2.3-4.2)
Mental disorders	5,299/3,648,161	11.6 (11.2-12.0)	6.0 (5.7-6.3)
Sleep disorders and mental disorders	73/40,003	14.5 (11.6-18.3)	9.0 (7.2-11.4)
Mental disorders diagnosed before sleep disorder ²			
No prior mental disorders	64/40,003	1 [Ref.]	1 [Ref.]
Prior mental disorders	53/40,003	4.3 (3.0-6.2)	2.3 (1.5-3.4)
Mental disorders diagnosed after sleep disorder ³			

No mental disorders	44/40,003	1 [Ref.]	1 [Ref.]
Mental disorders	20/40,003	5.4 (3.2-9.2)	4.4(2.6-7.7)

Abbreviations: IRR: Incidence Rate Ratio.

¹ Adjusted for period, age group, living status, socio-economic status, Charlson Comorbidity Index, and previous self-harm.

² This group consisted exclusively of individuals who had been diagnosed with a sleep disorder, the reference group is individuals diagnosed with sleep disorders but no prior mental disorder.

³ This group consisted exclusively of individuals who had been diagnosed with a sleep disorder but had not previous records of mental disorders in order to assess for a possible mediation effect by sleep disorders.

Accepted Manuscript

Figure 1a

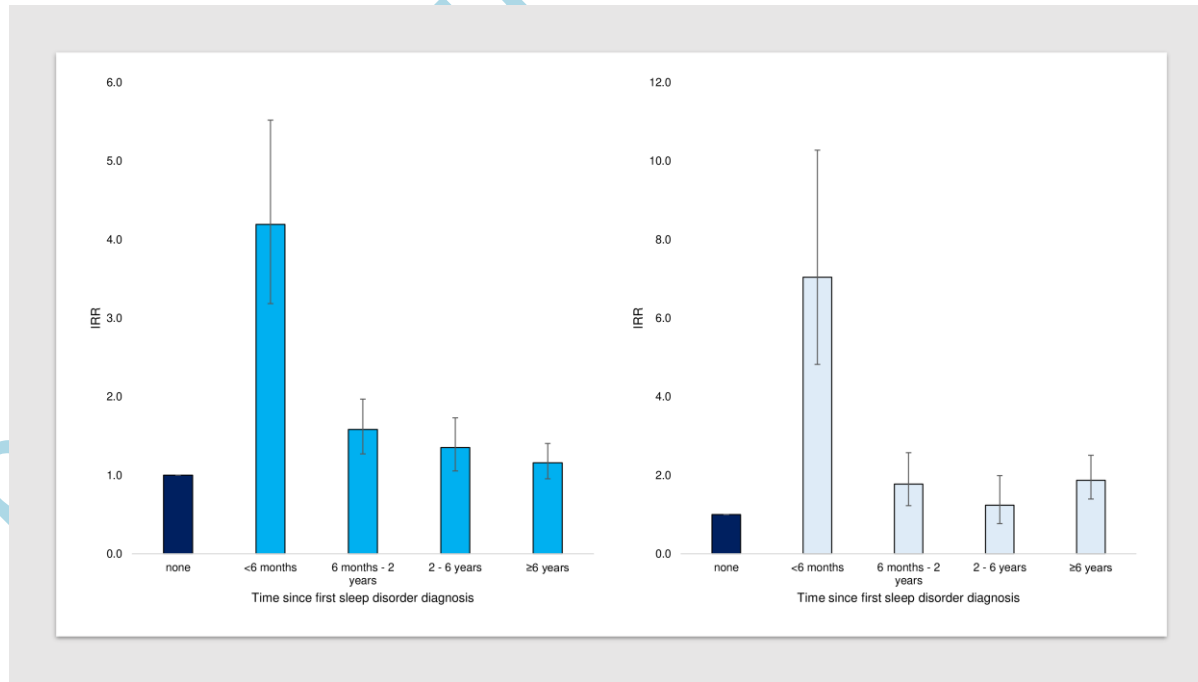


Figure 1b

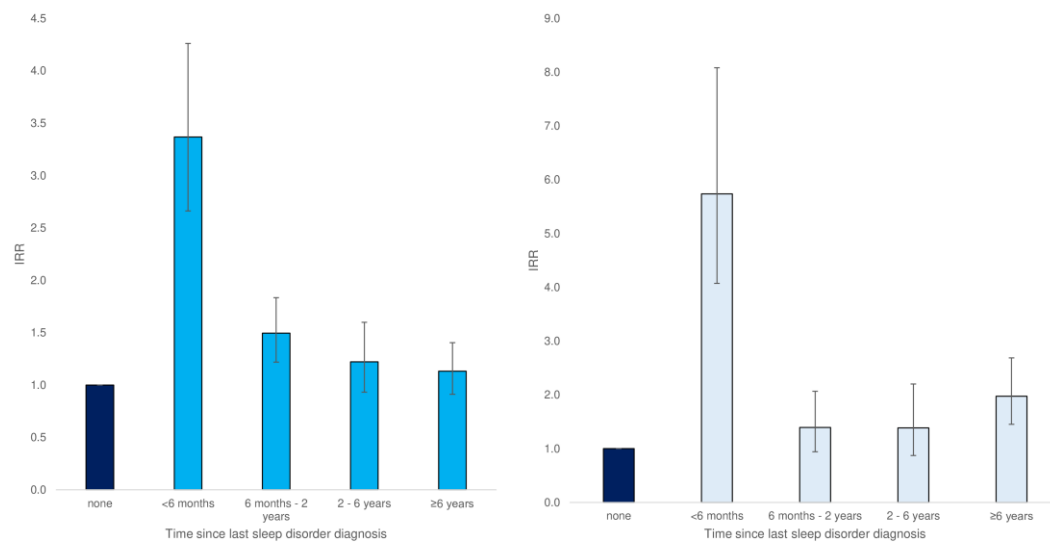
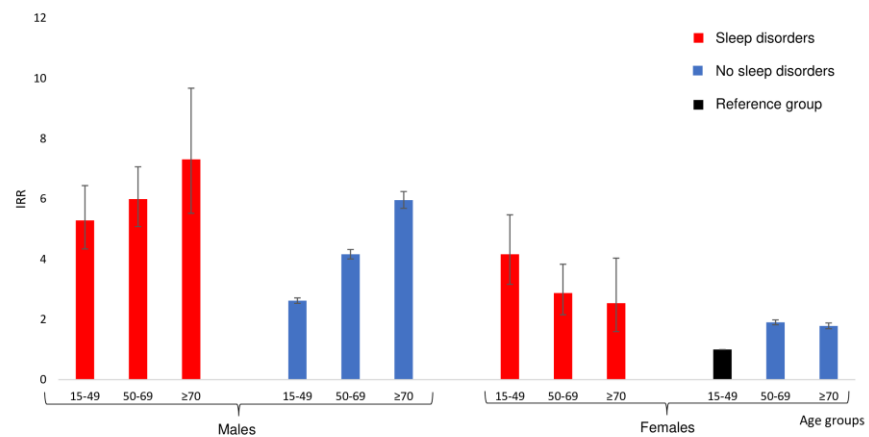


Figure 2



Accer