Cumulative incidence and relative risk of sleep problems among children and adolescents with newly diagnosed neurodevelopmental disorders

A nationwide register-based study

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Title: Cumulative incidence and relative risk of sleep problems among children and adolescents with newly diagnosed neurodevelopmental disorders. A nation-wide register-based study

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We estimated the absolute and relative risk of sleep problems in children and adolescents with newly diagnosed neurodevelopmental disorders. This was a population-based cohort study of individuals born in Denmark 1993-2014 and followed in nationwide registers 2011-2016. We estimated the 5-year cumulative incidence of sleep problems in incident cases of attention deficit/hyperactivity disorder (ADHD; n=12,844), autism spectrum disorder (ASD; n=8,073), oppositional defiant disorder/conduct disorder (ODD/CD; n=2,234) and epilepsy (n=3,709). Hazard ratios (HRs) for sleep problems were estimated by Cox regression. The 5-year risk of sleep problems was highest in ADHD (29.2%; 95% CI: 28.4-30.1), ASD (24.2%; 95% CI: 23.1-25.3) and ODD/CD 27.1% (95% CI: 25.0-29.2%) and lowest in epilepsy (11.3%; 95% CI: 10.2-12.6%). For ADHD and ASD, sleep problems were more common in females than in males. Furthermore, sleep problems were predicted by high parental socioeconomic status and varied with the geographical region of residence, suggesting that different clinical practices exist across Denmark and that sleep problems may be more likely to go undetected in families of lower socioeconomic position. Compared with individuals without these disorders, the likelihood of sleep problems was increased in individuals with ADHD (HR 33.81; 95% CI: 32.78-34.87), ASD (HR 16.77; 95% CI: 16.15-17.41), ODD/CD (HR 14.73; 95% CI: 13.88-15.64) and epilepsy (HR 6.01; 95% CI: 5.67-6.37). After mutual adjustment for comorbidity, HRs were attenuated, especially in ASD, ODD/CD and epilepsy when adjusted for ADHD, suggesting that the increased risk of sleep problems in individuals with ASD, ODD/CD and epilepsy is driven largely by comorbid ADHD.

Introduction
Sleep problems in children with neurodevelopmental disorders are among the most common parental complaints to mental healthcare professionals (Robinson-Shelton, 2016). Sleep problems
mainly include difficulty falling asleep, night awakenings and reduced sleep duration. Such
difficulties are associated with a poor health-related quality of life in the child and the family and
may contribute to aggravation of symptoms of neurodevelopmental disorders (Hvolby, 2008a).

These disorders include attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder
(ASD), oppositional defiant disorder/conduct disorder (ODD/CD) and epilepsy. Studies focusing on
a single disorder have found that sleep problems are common in children with ADHD, where
prevalence rates range from 25% to 66% (Hvolby, 2008a, Corkum, 2016, Hodgkins, 2013), and in
ASD, where prevalence rates of sleep problems range from 40% to 80% (Meltzer, 2008,
Krakowiak, 2008). Other studies have found sleep problems in very young children to be associated
with higher ODD/CD symptom scores (Smedje, 2001). In addition, sleep problems are prevalent in
children with epilepsy. However, these problems may be related to epilepsy itself or be associated
with the use of antiepileptic medications (Katari, 2016).

Several of the studies estimating the prevalence of sleep problems in children and adolescents with
ADHD, ASD, ODD/CD and epilepsy have had various methodological limitations (e.g.
uncontrolled or retrospective studies or studies not accounting for comorbidities), and findings have
been inconsistent. The majority of children and adolescents with ADHD have comorbid mental
disorders, (Kraut, 2013) of which ODD/CD and ASD are among the most common (Bijlenga,
2018). Epilepsy is also associated with the development of ADHD (Bertelsen, 2016). However,
whether the increased risk of sleep disorders in children with ODD/CD, ASD or epilepsy is affected
by the presence of comorbid ADHD remains poorly investigated.

Sleep problems can be an intrinsic characteristic of ADHD, can aggravate ADHD symptoms or be
aggravated by ADHD (Cortese, 2006b, Owens, 2008, Hvolby, 2015). The mechanisms behind this
bidirectional relationship are likely multiple and may involve shifts in the circadian rhythm (Van
der Heijden, 2005), neuroanatomical overlaps (Owens, 2008) and genetic links (Bijlenga, 2018).

Thus, only few studies have been able to estimate the risk of incident sleep problems among
children and adolescents with newly diagnosed ADHD and other neurodevelopmental disorders in a
population-based setting.

The aims of the present study were to a) estimate the five-year cumulative risk of sleep problems
among children and adolescents with newly diagnosed ADHD, ASD, ODD/CD and epilepsy; b)
examine whether sociodemographic characteristics of the child and the family affect the risk of

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developing sleep problems; and c) estimate the relative risk of sleep problems in children with and without these neurodevelopmental disorders.

Materials and Methods

Study population
In this prospective population-based study, we included a cohort of all singletons born in Denmark between 1993 and 2014 with known mothers. All cohortees were alive and living in Denmark on 1 January 2011. We identified the study population using data from the Civil Registration System (Schmidt, 2014), which is considered to have complete coverage of all persons living in Denmark and holds continuously updated information on vital status and place of residence.

Data sources
Information on diagnoses of neurodevelopmental and sleep disorders was obtained from the Psychiatric Central Research Register (Mors, 2011) and the National Patient Register (Schmidt, 2015). These registers contain information on all admissions to psychiatric hospitals (since 1970) and somatic hospitals (since 1977), and on all outpatient and emergency room contacts (since 1995). Diagnostic information is based on the International Classification of Diseases (ICD), 8th revision (ICD-8) until 1993, and on the 10th revision (ICD-10) from 1994 onwards. Statistics Denmark provided information on parental level of education (Jensen, 2011) and paternal income (Baadsgaard, 2011) at the time of delivery of the child. Maternal income was not included as this is affected by maternity leave in the year of giving birth. Information on redeemed prescriptions for medication was obtained from the National Prescription Register (Pottegård, 2016), which holds data on all prescription drugs dispensed at Danish pharmacies since 1994, including the Anatomical Therapeutic Chemical (ATC) code. However, this register has only systematically recorded information on melatonin prescriptions since 2011.

Supplementary eTable 1 shows the ICD-8 and ICD-10 codes used to identify ADHD, ASD, ODD/CD, epilepsy and sleep problems and the ATC codes used to identify ADHD and sleep problems.

Statistical analyses
Individuals in our cohort were followed from birth or 1 January 2011, whichever came later, to death, emigration, onset of sleep problems or end of follow-up on 31 December 2016, whichever came first. Individuals who were diagnosed with ADHD, ASD, ODD/CD or epilepsy before 2011
were not included in the analyses. We estimated the incidence rate and cumulative incidence of sleep problems with 95% confidence intervals (CIs) within the first five years following a first diagnosis of ADHD, ASD, ODD/CD and epilepsy. Cumulative incidences were estimated using competing risks regression, which provides estimates of the absolute risk of sleep problems in the years following onset of the neurodevelopmental disorder while taking into account the risk of dying (Coviello, 2004). We furthermore examined how the 5-year cumulative incidence estimates varied with various socio-demographic characteristics at the time of diagnosis, including sex, age (0-5, 6-11, 12-17 years), highest level of completed maternal and paternal education (primary education, secondary education, undergraduate education, and graduate education), level of paternal income (low (< 20,000 Euro), medium-low (20,000-40,000 Euro), medium (40,000-67,000 Euro), medium-high (67,000-94,000 Euro), and high (≥ 94,000 Euro)), and by administrative region of residence (Capital, Zealand, Southern Denmark, Central Denmark, North Denmark). In individuals with ADHD, we furthermore examined the effect of prior comorbid diagnoses of ASD, ODD/CD and epilepsy (i.e. before the first ADHD diagnosis) on the 5-year cumulative risk of sleep problems after ADHD. Next, we estimated the 5-year cumulative risk of sleep problems in the general population of children, examining all children turning 5, 10, or 15 years old between 1 January 2011 and 31 December 2014 and who had no previous diagnosis of ADHD, ASD, ODD/CD or epilepsy. Finally, we fitted Cox regression models to estimate HRs with 95% CI of sleep problems in children with and without ADHD, ASD, ODD/CD and epilepsy, respectively. For this analysis, all individuals born 1993-2014 were followed from 1 January 2011 to death, emigration, sleep problems or the end of the study on 31 December 2016, whichever came first. Diagnoses of ADHD, ASD, ODD/CD and epilepsy were all treated as time-varying exposures. The age of the child was used as the underlying timescale and sex was treated as a strata variable to allow for different baseline hazards in boys and girls. Proportionality of hazards was evaluated using log-log plots and was satisfied for all main exposures. We fitted three models; Model 1 estimated the crude HR for sleep problems in each of the four neurodevelopmental disorders, separately; Model 2 estimated the HR of sleep problems in each of the four neurodevelopmental disorders adjusting for the effects of the other three; and Model 3 repeated the analyses of Model 2 with additional adjustment for parental educational level, paternal income at birth and parental history of psychiatric disorders and epilepsy.

Results

In a cohort of 1,397,850 children born in Denmark between 1993 and 2014, we identified a total of 25,178 individuals aged 0-17 years with an incident diagnosis of one of the four
neurodevelopmental disorders in the period from 2011 to 2016. After excluding 1,661 children with pre-existing sleep problems (6.6%), we included a total of 23,517 children for the main analyses, including incident cases of ADHD (n=12,844), ASD (n=8,073), ODD/CD (n=2,234) and epilepsy (n=3,709). The socio-demographic characteristics of the population are presented in e-Table 2.

The risk of sleep problems varied between neurodevelopmental disorders. At 5 years of follow-up, the risk of having developed sleep problems was highest in children with ADHD (cumulative incidence 29.2%, 95% CI: 28.4-30.1), ASD (cumulative incidence 24.2%, 95% CI: 23.1-25.3) and ODD/CD (cumulative incidence 27.1%, 95% CI: 25.0-29.2) and lowest in children with epilepsy (cumulative incidence 11.3%; 95% CI: 10.2-12.6%). Figure 1 shows the sex-specific incidence rates and cumulative incidences of sleep problems within the first 5 years following the diagnosis of each disorder. For all four disorders, the incidence of sleep problems peaked within the first year of being diagnosed, which accounted for up to half of the 5-year cumulative risk. In children with ADHD or ASD, the 5-year cumulative incidence of sleep problems was higher in females (33.7%, 95% CI 32.1-35.4% and 29.9%, 95% CI: 27.7-32.2, respectively) than in males (27.1%, 95% CI 26.1-28.2% and 22.1%, 95% CI: 20.8-23.3%, respectively), whereas no such sex difference was observed in children with ODD/CD or epilepsy.

INSERT FIGURE 1

The risk of sleep problems after the onset of a neurodevelopmental disorder was associated with several baseline characteristics of the child and its parents (Figure 2). In epilepsy, sleep problems were more common in those diagnosed before the age of 5 than in those diagnosed after the age of 5. In ASD, the opposite was observed, as sleep problems were more common in those diagnosed after the age of 5. In ADHD and ASD, increasing levels of parental education and income were associated with a higher risk of sleep problems. Furthermore, regional differences in risk of sleep problems were found, with lower risks in individuals with neurodevelopmental disorders diagnosed in the Capital region and the Region of Southern Denmark than in the other three Danish regions (except for epilepsy).

INSERT FIGURE 2

In children with ADHD, we found that having a prior comorbid diagnosis of one of the other neurodevelopmental disorders further increased the 5-year cumulative incidence of sleep problems.
(Table 1), especially prior comorbid ODD/CD (45.0%, 95% CI: 36.5-53.1), compared with those who only had ADHD (28.6%, 95% CI: 27.7-29.5).

In the general population, the 5-year cumulative risk of sleep problems was 1.0% (95% CI: 1.0-1.1%) in children followed from the age of 5, 1.2% (95% CI: 1.2-1.3%) in children followed from the age of 10 and 2.5% (95% CI: 2.4-2.5%) in children followed from the age of 15 (Table 2). In children of young age, sleep problems were more common in boys than in girls. In older children, sleep problems were more common in girls than in boys.

In Cox regression models, (Model 1) ADHD, ASD, ODD/CD and epilepsy were all separately associated with substantially increased likelihoods of developing sleep problems (Table 3). In the crude model, ADHD was associated with the highest increased risk of sleep problems (HR 33.81; 95% CI: 32.78-34.87). Also ASD (HR 16.77; 95% CI: 16.15-17.41), ODD/CD (HR 14.73; 95% CI: 13.88-15.64) and epilepsy (HR 6.01; 95% CI: 5.67-6.37) were associated with a higher likelihood of sleep problems. When mutually adjusted for the other three neurodevelopmental disorders (Model 2), the estimates were attenuated but remained increased; the attenuation after adjustment was modest in ADHD (HR: 22.91, 95% CI: 22.10-23.74) and substantial in ASD (HR: 3.25 95% CI: 3.12-3.39), ODD/CD (HR: 1.34, 95% CI: 1.26-1.42) and epilepsy (HR: 2.75, 95% CI: 2.60-2.92). Further adjustment for sociodemographic characteristics and parental psychiatric disorders and epilepsy produced only minor changes in the estimates (Model 3).

Discussion

In this large population-based study of children and adolescents with newly diagnosed neurodevelopmental disorders, we found that children with ADHD, ASD and ODD/CD had a 25-30% 5-year risk of sleep problems, whereas children with epilepsy had a risk of approximately 12%. The highest incidence of sleep problems was observed within the first year of diagnosis. In children with ADHD and ASD, the risk of sleep problems was higher in females than in males. We furthermore found that the occurrence of sleep problems varied with other socio-demographic

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characteristics of the child and its family, including age at diagnosis, parental socioeconomic indicators and geographical region of residence. In ADHD, comorbidity with each of the three other neurodevelopmental disorders was associated with even higher risks of developing sleep problems. The incidence of sleep problems in children with neurodevelopmental disorders was considerably higher than the relatively low incidence in the general population, where the 5-year risk was 1-3%.

Other studies have shown that sleep problems occur in 25-55% of children with ADHD (Corkum, 2016, Hodgkins, 2013), which correlates well with our finding (29%). In children with ASDs, we identified a 5-year risk of 25%, which is low compared to the risk reported in other studies (Mindell, 2008, Krakowiak, 2008). However, most previous studies of the lifetime prevalence of sleep disorders are retrospective and therefore prone to recall bias. In addition, when including prior sleep problems in the estimates, reversed causation is possible, since sleep problems may result in behaviour mimicking the symptoms of ADHD, ASD or ODD/CD and therefore may lead to the patient being diagnosed with one of these disorders (Smedje, 2001, Hvolby, 2005).

We furthermore found that more females than males with ADHD and ASD developed sleep problems. This is in line with the studies by Becker et al. (Becker, 2018) and Hartley et al. (Hartley, 2009), who found that girls with ADHD or ASD had poorer sleep functioning than boys across most sleep functioning domains.

In children with ADHD and ASD, we found a tendency for the risk of sleep problems to increase with higher levels of parental education and paternal income. In contrast, a study by Meltzer et al (Meltzer, 2014) have suggested that lower maternal perceived economic well-being predicted a shorter sleep duration and a greater variability in sleep onset in children, and a lower sleep efficiency when the caregiver had low educational level (Meltzer, 2014). In contrast, Meltzer et al. found that families with a lower income had fewer follow-up visits at primary care despite persisting sleep problems (Meltzer, 2014). Furthermore, in our study, receiving treatment with melatonin was used as an indicator of sleep problems, and some previous studies have found a high parental income to increase the odds of receiving treatment (Wang, 2005). The difference could therefore be explained in that lower SES parents are less likely to perceive shorter sleep duration etc as a problem than higher SES parents and therefore do not seek treatment.

In addition, we identified significant regional differences in the occurrence of sleep problems in children and adolescents with ADHD, ASD and ODD/CD. The occurrence of sleep problems was generally lower in the region of Southern Denmark and the Capital region than in the other regions.

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This difference may be explained by different clinical practices in general. Thus, the Region of Southern Denmark, in particular, has lower rates of ADHD diagnoses and pharmacotherapy than other Danish regions (Madsen, 2015). Non-pharmacological treatment of sleep problems is more frequently used in these regions (Hvolby, 2011), but data on these interventions are not included in the registers.

Each of the four neurodevelopmental disorders were associated with a substantially increased relative risk of sleep problems. The highest HR was found in ADHD (33-fold risk), and HRs were lower in ASD and ODD/CD (16- and 14-fold risk, respectively) and in epilepsy (6-fold risk) than in children without these disorders. After mutual adjustment for comorbidity with the other three neurodevelopmental disorders, HRs were attenuated, especially in ASD, ODD/CD and epilepsy when adjusted for ADHD; however, the associations remained, also after adjusting for baseline covariates. These findings suggest that the increased relative risk of sleep problems in children with ASD, ODD/CD and epilepsy was driven mainly by comorbid ADHD.

In children with ADHD, we found that comorbid ODD/CD further increased the cumulative incidence of sleep disorders, when compared to those with ADHD and no ODD/CD. This is in contrary with a study (Lycett, 2015) who found an increased risk of sleep problems in ADHD with co-occurring internalizing and externalizing comorbidities but no increased risk of sleep problems when these comorbidities occurred separately. Internalizing comorbidity alone seems to give more sleep anxiety and contrarily they found that children with ADHD and externalising comorbidity alone had less night waking. Previous studies have indicated that sleep problems in children and adolescents with ADHD is mainly associated with comorbid CD (Mick, 2000), and not associated with ADHD alone. Our study suggests the opposite and finds that ADHD (and to a lesser degree ASD) is in itself associated with sleep problems, which was also shown in clinical studies (Hvolby, 2008a, Krakowiak, 2008, Virring, 2016), whereas sleep problems in ODD/CD seem to be related to comorbid ADHD. This could indicate the importance and relevance of screening for ADHD if the primary diagnosis of ASD or ODD/CD also involves comorbid sleeping problems.

In the general population, we found a low incidence of treated or diagnosed sleeping problems. Over a 5-year period, the cumulative risk of sleep problems was only 1-3%, depending on age, which is lower than reported by other studies showing that 7% or even as many as 25-40% of typically developing children are having sleep problems (Meltzer, 2008, Krakowiak, 2008, Hvolby, 2008b). This finding may indicate that sleeping problems without coexisting neurodevelopmental
disorders are generally diagnosed or treated in primary health care (and hence not included in our study).

Limitations
Our study has several limitations. First, the coverage of diagnoses of sleep disorders is low in the Danish health registers (Byrne, 2019). To account for some of this misclassification, we also included data on filled prescriptions for melatonin in order to add cases diagnosed with and treated for sleep disorders in primary care settings (and hence not recorded in the health registers). Even so, we may have underestimated the cumulative risk of sleep problems, which is also reflected in the low risk of sleep disorders we found in typically developing children. Furthermore, we have likely included the more severe forms of sleep problems, which may have made us overestimate the relative risk of sleep problems in children with these neurodevelopmental disorders. In addition, children with neurodevelopmental disorders and comorbid sleep problems may have received non-pharmacological treatment on which the registers include no data. And also, some parents might have got melatonin online without prescription, which the register also do not include. Second, the National Prescription Register holds data on filled prescriptions for melatonin from 2007 onwards, but the register’s coverage prior to 2011 is low. Hence, we may not have identified all individuals treated with melatonin before follow-up was initiated. In contrast, coverage of clinical diagnoses of ADHD, ASD, ODD/CD and epilepsy has been complete since 1970. However, the register included only in-patient contacts from 1970 to 1994, whereas outpatient contacts have also been included since 1994. Indeed, previous studies have found that the clinical diagnoses in the Danish health registries are valid and characterised by high predictive values, including the diagnoses of ADHD (Dalsgaard, 2001, Mohr-Jensen, 2016), ASD (Lauritsen, 2010), epilepsy (Christensen, 2007) and several other disorders (Bock, 2009, Uggerby, 2013).

Third, as in any other study relying on observational data, the findings in the present study infer no causal relationship between neurodevelopmental disorders and sleep problems. Furthermore, we cannot exclude the possibility of residual confounding. Thus, it remains unclear whether neurodevelopmental disorder contributes to the sleep problem or whether certain unmeasured characteristics of children with neurodevelopmental disorders may explain the apparent association with sleep problems.

Conclusion
In this population-based study of children with newly diagnosed neurodevelopmental disorders, we found a high incidence of sleep problems in the first five years following their diagnosis. The occurrence of sleep problems varied with characteristics of the child, including sex and age at diagnosis, and with the sociodemographic characteristics of the family, including parental education, income and geographical region of residence. Our findings give a reason to be more aware on sleep problems in the diagnosing of the neurodevelopmental disorder. It seems that especially children with ADHD or ADHD as a comorbid disorder to other neurodevelopmental disorder have sleep problem. Therefore, there must be an extra attention to ADHD symptoms in other neurodevelopmental disorder, when they also present sleep problems. But we need more research on sleep problem in neurodevelopmental disorder, especially the role of ADHD symptoms.

References


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**Figure 1:** Sex-specific incidence rates and cumulative incidences of sleep problems in the first five years following newly diagnosed ADHD, ASD, ODD/CD and epilepsy among Danish children.
Figure 2: The 5-year cumulative incidence of sleep problems in children with incident diagnoses of ADHD, ASD, ODD/CD and epilepsy, by sociodemographic characteristics of the child and the parents.

Table 1: Cumulative risk of sleep problems 5 years after the diagnosis of ADHD, by other neurodevelopmental comorbidities.

<table>
<thead>
<tr>
<th>Children with ADHD</th>
<th>Children n</th>
<th>Sleep problems n</th>
<th>Cumulative risk of sleep problems at 5 years of follow-up % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>12,844</td>
<td>3,402</td>
<td>29.2 (28.4-30.1)</td>
</tr>
<tr>
<td>With concomitant ASD</td>
<td>665</td>
<td>214</td>
<td>34.7 (30.7-38.6)</td>
</tr>
<tr>
<td>With concomitant conduct disorder</td>
<td>179</td>
<td>72</td>
<td>45.0 (36.5-53.1)</td>
</tr>
<tr>
<td>With concomitant epilepsy</td>
<td>274</td>
<td>82</td>
<td>33.7 (27.3-40.2)</td>
</tr>
<tr>
<td>With neither epilepsy, autism or conduct disorder</td>
<td>11,765</td>
<td>3,046</td>
<td>28.6 (27.7-29.5)</td>
</tr>
</tbody>
</table>

* Groups are not mutually exclusive

Table 2: Cumulative risk of sleep problems at 5 years of follow-up, in all children followed from the age of 5, 10, and 15 years and with no diagnosis of ADHD, ASD, ODD/CD and epilepsy at the beginning of follow-up.

<table>
<thead>
<tr>
<th>Followed from ages</th>
<th>n</th>
<th>Cumulative risk of sleep problems at 5 years of follow-up % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 5</td>
<td>249,779</td>
<td>1.0 (1.0-1.1)</td>
</tr>
<tr>
<td>Age 10</td>
<td>240,659</td>
<td>1.2 (1.2-1.3)</td>
</tr>
<tr>
<td>Age 15</td>
<td>243,804</td>
<td>2.5 (2.4-2.5)</td>
</tr>
<tr>
<td>Girls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 5</td>
<td>121,985</td>
<td>0.7 (0.7-0.8)</td>
</tr>
<tr>
<td>Age 10</td>
<td>119,729</td>
<td>1.3 (1.2-1.4)</td>
</tr>
<tr>
<td>Age 15</td>
<td>121,595</td>
<td>3.2 (3.0-3.3)</td>
</tr>
</tbody>
</table>

Boys

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Table 3: Incidence rates and hazard ratios of sleeping problems among children with and without neurodevelopmental disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>No</th>
<th>Rate of sleep problems per 1,000 person years</th>
<th>Hazard ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>No</td>
<td>2.03 (1.99-2.06)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>ADHD</td>
<td>Yes</td>
<td>74.91 (73.26-76.59)</td>
<td>33.81 (32.78-34.87)</td>
<td>22.91 (22.10-23.74)</td>
<td>20.83 (20.07-21.63)</td>
</tr>
<tr>
<td>ASD</td>
<td>No</td>
<td>2.67 (2.63-2.71)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>ASD</td>
<td>Yes</td>
<td>55.02 (53.24-56.87)</td>
<td>16.77 (16.15-17.41)</td>
<td>3.25 (3.12-3.39)</td>
<td>3.34 (3.20-3.49)</td>
</tr>
<tr>
<td>ODD/CD</td>
<td>No</td>
<td>3.01 (2.96-3.05)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>ODD/CD</td>
<td>Yes</td>
<td>60.93 (57.54-64.52)</td>
<td>14.73 (13.88-15.64)</td>
<td>1.34 (1.26-1.42)</td>
<td>1.27 (1.19-1.36)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>No</td>
<td>3.01 (2.97-3.06)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Yes</td>
<td>22.19 (20.98-23.48)</td>
<td>6.01 (5.67-6.37)</td>
<td>2.75 (2.60-2.92)</td>
<td>2.74 (2.58-2.91)</td>
</tr>
</tbody>
</table>

Model 1: Single-disorder analyses. The neurodevelopmental disorder was treated as a time-varying exposure. The model allows for different baseline hazards for boys and girls.

Model 2: The model was adjusted for comorbidity between the four neurodevelopmental disorders that were all treated as time-varying exposures. The model allowed for different baseline hazards for boys and girls.

Model 3: Same as model 2, but further adjusted for the following covariates: maternal education, paternal education and paternal income measured at birth and parental psychiatric disorders and epilepsy treated as time-varying co-variates.
Table 1: Cumulative risk of sleep problems 5 years after the diagnosis of ADHD, by other neurodevelopmental comorbidities.

<table>
<thead>
<tr>
<th>Children with ADHD</th>
<th>Children(^a)</th>
<th>Sleep problems</th>
<th>Cumulative risk of sleep problems at 5 years of follow-up % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>12,844</td>
<td>3,402</td>
<td>29.2 (28.4-30.1)</td>
</tr>
<tr>
<td>With concomitant ASD</td>
<td>665</td>
<td>214</td>
<td>34.7 (30.7-38.6)</td>
</tr>
<tr>
<td>With concomitant conduct disorder</td>
<td>179</td>
<td>72</td>
<td>45.0 (36.5-53.1)</td>
</tr>
<tr>
<td>With concomitant epilepsy</td>
<td>274</td>
<td>82</td>
<td>33.7 (27.3-40.2)</td>
</tr>
<tr>
<td>With neither epilepsy, autism or conduct disorder</td>
<td>11,765</td>
<td>3,046</td>
<td>28.6 (27.7-29.5)</td>
</tr>
</tbody>
</table>

\(^a\) Groups are not mutually exclusive
**Table 2:** Cumulative risk of sleep problems at 5 years of follow-up, in all children followed from the age of 5, 10, and 15 years and with no diagnosis of ADHD, ASD, ODD/CD and epilepsy at the beginning of follow-up

<table>
<thead>
<tr>
<th>Followed from ages</th>
<th>n</th>
<th>Cumulative risk of sleep problems at 5 years of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>All children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 5</td>
<td>249,779</td>
<td>1.0 (1.0-1.1)</td>
</tr>
<tr>
<td>Age 10</td>
<td>240,659</td>
<td>1.2 (1.2-1.3)</td>
</tr>
<tr>
<td>Age 15</td>
<td>243,804</td>
<td>2.5 (2.4-2.5)</td>
</tr>
<tr>
<td>Girls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 5</td>
<td>121,985</td>
<td>0.7 (0.7-0.8)</td>
</tr>
<tr>
<td>Age 10</td>
<td>119,729</td>
<td>1.3 (1.2-1.4)</td>
</tr>
<tr>
<td>Age 15</td>
<td>121,595</td>
<td>3.2 (3.0-3.3)</td>
</tr>
<tr>
<td>Boys</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 5</td>
<td>127,794</td>
<td>1.4 (1.3-1.4)</td>
</tr>
<tr>
<td>Age 10</td>
<td>120,930</td>
<td>1.2 (1.1-1.3)</td>
</tr>
<tr>
<td>Age 15</td>
<td>122,209</td>
<td>1.8 (1.7-1.9)</td>
</tr>
</tbody>
</table>
Table 3: Incidence rates and hazard ratios of sleeping problems among children with and without neurodevelopmental disorders

<table>
<thead>
<tr>
<th></th>
<th>Rate of sleep problems per 1,000 person years</th>
<th>Model 1 Hazard ratio (95% CI)</th>
<th>Model 2 Hazard ratio (95% CI)</th>
<th>Model 3 Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2.03 (1.99-2.06)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>74.91 (73.26-76.59)</td>
<td>33.81 (32.78-34.87)</td>
<td>22.91 (22.10-23.74)</td>
<td>20.83 (20.07-21.63)</td>
</tr>
<tr>
<td>ASD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2.67 (2.63-2.71)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>55.02 (53.24-56.87)</td>
<td>16.77 (16.15-17.41)</td>
<td>3.25 (3.12-3.39)</td>
<td>3.34 (3.20-3.49)</td>
</tr>
<tr>
<td>ODD/CD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3.01 (2.96-3.05)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>60.93 (57.54-64.52)</td>
<td>14.73 (13.88-15.64)</td>
<td>1.34 (1.26-1.42)</td>
<td>1.27 (1.19-1.36)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3.01 (2.97-3.06)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>22.19 (20.98-23.48)</td>
<td>6.01 (5.67-6.37)</td>
<td>2.75 (2.60-2.92)</td>
<td>2.74 (2.58-2.91)</td>
</tr>
</tbody>
</table>

Model 1: Single-disorder analyses. The neurodevelopmental disorder was treated as a time-varying exposure. The model allows for different baseline hazards for boys and girls.

Model 2: The model was adjusted for comorbidity between the four neurodevelopmental disorders that were all treated as time-varying exposures. The model allowed for different baseline hazards for boys and girls.

Model 3: Same as model 2, but further adjusted for the following covariates: maternal education, paternal education and paternal income measured at birth and parental psychiatric disorders and epilepsy treated as time-varying co-variates.