Universidad de Alcalá

FACULTAD DE MEDICINA

Programa de doctorado en Ciencias de la Salud

Insomnia in obsessive-compulsive disorder and body dysmorphic disorder

Insomnio en el trastorno obsesivo-compulsivo y trastorno dismórfico corporal

Tesis Doctoral presentada por:

Laura María Sevilla Cermeño

Directores:

Dra. Lorena Fernández de la Cruz

Dr. Guillermo Lahera Forteza

Alcalá de Henares, 2021

Agradecimientos

En primer lugar me gustaría agradecer la inestimable ayuda de mis directores de tesis. Gracias Lorena Fernández de la Cruz por tu supervisión continuada, tu trabajo incansable y por todos tus consejos. Gracias Guillermo Lahera por tu disponibilidad y amabilidad, y por todas tus enseñanzas. Gracias a la Universidad de Alcalá por facilitarme la elaboración de esta tesis. Le agradezco a David Mataix-Cols su apoyo incondicional durante mi estancia en Karolinska Institutet, así como su supervisión que me proporcionó conocimientos inigualables. Gracias a todos mis compañeros del equipo sueco, en especial a Alba, Ana y a Kayoko, pero por supuesto también a Eva Hesselmark, Elles, TianYang, Gustaf, Per, Daniel, Anna, Josef, Caroline, Eva Serlachius, Fabian y a todos los compañeros psicólogos y psiquiatras que hacen un trabajo fantástico en la clínica BUP-OCD de Estocolmo, Suecia. Le agradezco también a la Fundación Alicia Koplowitz la oportunidad que me brindó de formarme en un sitio de excelencia gracias a la beca de la que fui beneficiaria. Gracias, a su vez, a todos mis compañeros del Servicio de Psiquiatría Infanto-Juvenil del Hospital General Universitario Gregorio Marañón, que me han acompañado en la segunda etapa de elaboración de esta tesis doctoral.

Gracias por supuesto a toda mi familia. A mis padres, Pilar y Domingo, por apoyarme y aconsejarme siempre. A mis abuelos y tíos y, en especial, a mi abuelo Juan por todas sus cartas de ánimo y cariño enviadas a Suecia; descansa en paz abuelo.

A ti Miguel, gracias por acompañarme y apoyarme siempre, sobre todo, en los momentos más difíciles. Gracias también a Elena, Luis, Quique y a toda tu familia por todo el apoyo que me han brindado durante este camino.

Y por ultimo, pero no menos importante, gracias a todos mis amigos y compañeros, que de una forma u otra, me han ayudado durante el camino de elaboración de esta tesis doctoral.

LIST OF SCIENTIFIC PAPERS INCLUDED IN THIS THESIS

1. **Sevilla-Cermeño L**, Isomura K, Larsson H, Akerstedt T, Vilaplana-Pérez A, Lahera G, et al. Insomnia in obsessive-compulsive disorder: A Swedish population-based cohort study. J Affect Disord. 2020;266: 413-6.

2. **Sevilla-Cermeño L**, Andrén P, Hillborg M, Silverberg-Morse M, Mataix-Cols D, Fernández de la Cruz L. Insomnia in pediatric obsessive-compulsive disorder: Prevalence and association with multimodal treatment outcomes in a naturalistic clinical setting. Sleep Med. 2019;56:104-10.

3. **Sevilla-Cermeño L**, Rautio D, Andrén P, Hillborg M, Siveberg-Morse M, Lahera G, et al. Prevalence and impact of insomnia in children and adolescents with body dysmorphic disorder undergoing multimodal specialist treatment. Eur Child Adolesc Psychiatry. 2020;29(9):1289-1299.

LIST OF OTHER SCIENTIFIC PAPERS CO-AUTHORED BY THE PH.D. CANDIDATE, NOT INCLUDED IN THIS THESIS

1. Zhang T, Sidorchuk A, **Sevilla-Cermeño L**, Vilaplana-Perez A, Chang Z, Larsson H, et al. Association of Cesarean Delivery with Risk of Neurodevelopmental and Psychiatric Disorders in the Offspring: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(8): e1910236.

2. Rautio D, Jassi A, Krebs G, Andrén P, Monzani B, Gumpert M, Lewis A, Peile L, **Sevilla-Cermeño L**, et al. Clinical characteristics of 172 children and adolescents with body dysmorphic disorder. European Child & Adolescent Psychiatry. 2020.

3. Vilaplana-Pérez A, Sidorchuk A, Pérez-Vigil A, Brander G, Isoumura K, Hesselmark E, **Sevilla-Cermeño L**, et al. Assessment of Posttraumatic Stress Disorder and Educational Achievement in Sweden. JAMA network open [Internet]. 2020 2020/12//; 3(12):[e2028477 p.].

Table of Contents

1. INTRODUCTION
    1.1. Obsessive-compulsive disorder
        1.1.1. Diagnosis and clinical characteristics
        1.1.2. Impairment
        1.1.3. Current evidence-based treatment
    1.2. Body dysmorphic disorder
        1.2.1. Diagnosis and clinical characteristics
        1.2.2. Impairment
        1.2.3. Current evidence-based treatment
    1.3. Insomnia
        1.3.1. Insomnia and mental disorders
        1.3.2. Insomnia in obsessive-compulsive disorder
        1.3.3. Insomnia in body dysmorphic disorder
2. AIMS AND HYPOTHESES
    2.1. Aims
    2.2. Hypotheses
3. SCIENTIFIC PUBLICATIONS
    3.1. STUDY 1: Insomnia in obsessive-compulsive disorder: A Swedish population-based cohort study
    3.2. STUDY 2: Insomnia in pediatric obsessive-compulsive disorder: prevalence and association with multimodal treatment outcomes in a naturalistic clinical setting
    3.3. STUDY 3: Prevalence and impact of insomnia in children and adolescents with body dysmorphic disorder undergoing multimodal specialist treatment

4. DISCUSSION

4.1. General discussion of the main findings

4.2. Limitations

4.3. Clinical implications

4.4. Research implications

5. CONCLUSIONS

6. SUMMARY IN SPANISH

6.1. Introducción

6.2. Métodos y resultados

6.2.1 Estudio 1

6.2.2 Estudio 2

6.2.3 Estudio 3

6.3. Conclusiones

7. REFERENCES

1. INTRODUCTION

1.1.Obsessive-compulsive disorder

1.1.1. Diagnosis and clinical characteristics

Obsessive-compulsive disorder (OCD) is a psychiatric condition classified under an obsessive-compulsive and related disorders (OCRDs) category in the current main classificatory systems. Interestingly, the placement of OCD in these diagnostic manuals has changed only recently. Classically considered an anxiety disorder both in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and in the International Classification of Diseases (ICD), OCD is now the main diagnostic entity in a newly created OCRDs chapter in the 5th edition of the DSM (DSM-5), published earlier this decade (1), and in the 11th version of the ICD (ICD-11), published last year (2). In the DSM-5, the corresponding OCRDs chapter also includes body dysmorphic disorder (BDD), trichotillomania (hair pulling disorder), excoriation disorder (skin-picking), and hoarding disorder, whereas in the ICD-11, these disorders are also included, together with olfactory reference disorder and hypochondriasis, highlighting the similarities of these disorders across a variety of validators (3, 4). This new clustering of OCRDs both in DSM-5 and ICD-11 is based on the increasing evidence of related neurobiological and neurocognitive processes shared by them (1, 3, 4).

OCD is characterised by the occurrence of either obsessions, compulsions or both that are time-consuming and cause great impairment in a variety of areas of functioning (1). Obsessions are recurrent and persistent thoughts, urges or impulses that are experienced as intrusive and unwanted (e.g., fear of being contaminated by germs or dirt or fear of contaminating others, intrusive sexually explicit or violent thoughts and images), causing marked distress. Compulsions are repetitive behaviours (e.g., hand washing, ordering or checking) or mental acts (e.g., counting, praying or repeating words silently) that the affected individual feels compelled to perform in response to an

obsession or according to rules that must be followed rigidly. Compulsions are aimed at preventing or reducing the distress caused by the obsessions or preventing some dreaded situation. However, these behaviours are not connected in a realistic way with what they are meant to neutralize or they are evidently excessive (1).

To fulfil diagnostic criteria for OCD, according to the DSM-5, symptoms must not be attributable to the effects of a substance or another medical condition, and they cannot be better explained by the presence of another mental disorder (1). The definition of OCD in DSM-5 has also two specifiers: the degree of insight (ranging from good or fair to absent or delusional) and the presence or absence of tics (1). The definition of OCD in the ICD-11 is similar to the diagnostic criteria in the DSM-5, stressing the presence of recurrent obsessions and compulsions and their repercussion in personal, family, social, educational, occupational or other areas of functioning (4).

OCD has a lifetime prevalence of 2–3% in the general population (5), with higher rates in women, compared to men, across the lifespan (6), although paediatric clinical samples have been found to be predominantly male (7). The age of onset of OCD shows a bimodal distribution, with one peak in preadolescent childhood and another peak in early adulthood (8) and with boys, compared to girls, tending to have an earlier onset (5). The childhood onset of the disorder seems to be associated with an increased risk for familiar transmission of OCD and with the comorbidity with tic disorders and attention-deficit hyperactivity disorder (ADHD) (8). If untreated, OCD is typically chronic, following a waxing and waning course (9). Individuals with OCD also tend to have other lifetime comorbid psychiatric conditions, with the most common being anxiety disorders, followed by mood disorders, impulse-control disorders, and substance use disorders (10). The pattern of psychiatric comorbidity in paediatric OCD

is similar to that of adults, with a distinct association with tic disorders, ADHD, oppositional defiant disorder, and pervasive developmental disorders (7).

Regarding the aetiology of the disorder, family studies and twin studies have shown that genetic factors are relevant in the manifestation of OCD (specifically, additive genetic factors account for approximately 47% of the familiar risk for OCD) and that non-genetic, non-shared environmental factors also have an influence on the development of OCD, accounting for the rest of the variance, probably through epigenetic mechanisms (11, 12). Although the environmental factors implicated in OCD are still deficiently understood, a range of potential environmental risk factors for OCD have been proposed including a number of perinatal factors (13), reproductive cycle events, and stressful or traumatic life events (14).

1.1.2. Impairment

OCD is associated with great impairment across a broad range of functional and health-related quality of life domains, with a negative association between symptom severity and functional impairment (15). Two population-based studies concluded that individuals with OCD experience a profound decrease in educational attainment across their lifespan (16) and marked difficulties to participate in the labour market (17).

The disorder has also been linked with somatic health problems. For example, OCD has been associated with a 45% increased risk of metabolic and cardiovascular complications (18) and a 43% increased risk of autoimmune diseases, compared to unaffected individuals from the general population (19). Furthermore, OCD has been associated with a significantly increased mortality risk, particularly in the presence of comorbid anxiety disorders, depression or substance use disorders (20).

Despite the traditional conception of OCD being associated with a relatively low risk of suicidality, recent evidence has shown that individuals with OCD are at an increased risk of both death by suicide and suicide attempts (20, 21).

1.1.3. Current evidence-based treatment

The evidence-based treatment for OCD includes both cognitive behavioural therapy (CBT) and pharmacotherapy (specifically, selective serotonin reuptake inhibitors [SSRIs] and clomipramine) for both children and adults (22, 23). Of note, the number of controlled treatment studies is smaller in children and young people with OCD, compared to adults.

The evidence-based CBT technique in the treatment of OCD is exposure and response prevention (ERP), although different variants of cognitive therapy or a combination of ERP and cognitive therapy are also applied. Most research has been conducted on individual or group face-to-face treatments, although the efficacy of internet-based CBT for children and adolescents and adults with OCD has also been shown (24-26).

Regarding pharmacological treatment, SSRIs are generally also effective, with no evidence to support that one medication is better than the others. The current recommendation is to use SSRIs rather than clomipramine as first-line pharmacological treatment and, although antipsychotics are not effective on their own, they can play a role as agents of augmentation when the response to SSRIs is partial (27).

Neurosurgical procedures have been used for the most severe and treatment-refractory patients. Ablative techniques or deep-brain stimulation on specific neural

structures implicated in OCD have shown to enhance treatment outcomes in some individuals with OCD presenting with very refractory symptoms (28).

1.2. Body Dysmorphic Disorder

1.2.1. Diagnosis and clinical characteristics

BDD is a psychiatric disorder, classified under the OCRDs chapter both in DSM-5 and ICD-11 (1, 2), characterised by the excessive and persistent preoccupation with perceived defects or flaws in one's appearance that are not observable or appear slight to others. These symptoms produce important distress or impairment to the sufferer (1). Individuals with BDD are most frequently concerned about the appearance of their hair, skin, nose, and stomach (29). The presence of repetitive behaviours (e.g., mirror checking or camouflaging) or mental acts (e.g., comparing own appearance with that of others) in response to the appearance concerns at some point during the course of the disorder is necessary to fulfil diagnostic criteria for BDD. The preoccupation about the appearance should not be better explained by concerns with body weight in an individual whose symptoms meet diagnostic criteria for an eating disorder (1). The definition of BDD in DSM-5 has two specifiers: the presence or absence of muscle dysmorphia and the degree of insight (ranging from good or fair to absent or delusional) (1). This range of insight is consistent with the evidence showing that a broad range of insight can characterize BDD beliefs (30). Overall, individuals with BDD show poorer insight than individuals with OCD (31). The definition of BDD in the ICD-11 is similar to the above-mentioned diagnostic criteria in the DSM-5, stressing that the symptoms should result in significant impairment in important areas of functioning (2, 4).

The weighted prevalence of BDD in the community has been estimated to be 1.9% in adults and 2.2% in adolescents (32). Interestingly, the weighted prevalence of BDD in

cosmetic surgery settings has been found to be significantly higher (12.2%) (32). Regarding sex differences on its distribution, the prevalence of BDD has been found to be higher in females than in males (32, 33).

The mean age of onset of BDD has been reported to be around 16 years and it tends to follow a chronic course (34). More severe symptomatology, longer duration of the disease, and being an adult have been shown to be predictors of a lower probability of remission in BDD (35). Individuals with BDD tend to also have other psychiatric disorders during their lifetime, including social anxiety disorder, specific phobia, generalized anxiety disorder, major depressive disorder, dysthymia, and OCD (29).

The available studies assessing the aetiology of BDD have claimed that the disorder may be a result of an interaction between predisposing genetic factors and environmental stressors. Specifically, twin studies have shown that genetic factors account for approximately 42-44% of the variance in BDD symptomatology, with non-genetic, non-shared environmental factors accounting for the remaining variance (36, 37). With regard to the possible environmental factors implicated in BDD, the available evidence is scarce and limited, but peer victimisation in school has been prospectively associated with the onset of BDD (38).

1.2.2. Impairment

BDD is linked to considerable impairment across numerous domains. Among adults, BDD is associated with poor social functioning, high rates of unemployment, and low quality of life (39). During adolescence, BDD results into poor psychosocial functioning and low academic performance, with high rates of school abandonment (40,

41). Importantly, individuals with BDD also present increased odds of both suicidal ideation and suicide attempts (42).

A high proportion of individuals with BDD, around 76% of adults and over 40% of young patients, seek and receive cosmetic treatments, both surgical and less invasive treatments, in an attempt to repair the perceived defects in their appearance (43). Although the literature on this topic is limited, these procedures are generally associated with negative outcomes in this patient group, including worsening of BDD symptoms and self-reported dissatisfaction with the result of the cosmetic treatment (43).

Despite the impact of BDD, current evidence suggests that the disorder is often underrecognized and underdiagnosed (32). This could be influenced by the shame of patients in disclosing their BDD symptoms and their reluctance to seek specialist psychiatric help. In adolescence, it is also speculated that BDD symptoms may be undetected since they overlap with a period in the development when individuals tend to be naturally more focused on their physical appearance. Hence, there is a need to improve the low level of awareness and knowledge about BDD amongst the public and health professionals (32).

1.2.3. Current evidence-based treatment

As for OCD, the evidence-based treatment for BDD includes both CBT and pharmacotherapy (in particular, SSRIs) (22). There is evidence to recommend CBT as the first-line treatment for BDD (22). CBT, also based on ERP, has shown efficacy in the treatment of the main symptoms of BDD and some of its comorbid clinical features (depressive symptoms and low insight) with gains that are likely to persist, at least, around

2-4 months after treatment (44). Concernedly, 46% to 60% of patients do not respond sufficiently to CBT and remission is rare (44).

Regarding pharmacological treatment, SSRIs may be considered in patients with BDD (22). Clinical experience indicates that medication may be necessary in more severe cases and those with suicidal ideation. The available evidence supports the use of SSRIs, which have shown to be effective in the treatment of BDD in the short term (45) and in relapse prevention (46). Only two studies to date have assessed possible augmentation strategies for patients with BDD who do not respond or respond partially to SSRIs, one small open trial (47) and one randomised controlled trial (RCT) (48), which evaluated olanzapine and pimozide augmentation of fluoxetine, respectively. No beneficial effects of those augmentation strategies were found.

1.3.Insomnia

1.3.1. Insomnia and psychiatric disorders

Insomnia is a medical condition that affects approximately 10% of the general population (49). It represents a public health issue, having been associated with an increased risk of work disability, car accidents, cardiovascular disease, and an increased risk of mortality (50-53).

Previous research has suggested a link between sleep and psychopathology, which is complex and likely to be bidirectional. In contrast with the traditional view of insomnia as a consequence of psychiatric conditions (54), some recent research has provided evidence that insomnia and sleep onset problems can precede the onset of psychiatric diseases such as autism spectrum disorder (55) and bipolar disorder (56), which could suggest a potential causal role.

As a matter of fact, the association of insomnia with some psychiatric disorders has already been well documented. In depression, for example, insomnia is frequent and independently associated to the disorder, with greater functional impairment and depressive symptom severity in individuals suffering from it (57). Regarding anxiety disorders, generalized anxiety disorder has the most consistent association with insomnia, with approximately 60-70% rate of comorbid occasional symptoms of insomnia (58). However, sleep problems in general, and insomnia in particular, have been documented in almost all anxiety disorders. Surprisingly, little is known about sleep disturbances in OCD and related disorders.

1.3.2. Insomnia in obsessive-compulsive and related disorders

The scarce literature available has suggested a link between sleep disturbances and OCD both in paediatric and in adult samples. Both objective (59-61) and subjective measures (59) of sleep difficulties have been studied in OCD. Objective assessment of sleep is provided by the EEG study of sleep (e.g., polysomnography) or actigraphy, and subjective measures of sleep broadly include clinical interviews, questionnaires, and sleep diaries.

In adult OCD samples, abnormalities in *objective* sleep parameters have been found. For example, decreased sleep efficiency and sleep duration and increased rapid eye movement (REM) density (representing the total duration of REM during a REM period) have been significant findings in this population (62). An association between OCD and delayed sleep-wake phase disorder has also been suggested (63).

Regarding *subjective* sleep problems in adults, the available literature is also limited. Two studies have compared subjective measures of sleep disturbances in patients

with OCD *vs.* healthy controls (64, 65). The study by Bobdey et al. (64) compared a sample of 24 patients with OCD with and without comorbid depression (n=12 in each group) to a group of 57 healthy subjects in self-reports of sleep, as measured by the Pittsburgh Sleep Quality Index, and did not find differences in sleep patterns between patients with OCD and healthy controls. By contrast, they did find that patients with OCD and comorbid depression showed abnormalities in sleep when compared to controls, suggesting that the altered patterns in sleep in OCD may be due to the presence of comorbid depression (64). In the other referenced study, Donse et al. (65) measured sleep disturbances in 25 patients with OCD by actigraphy and sleep questionnaires and compared them to 26 healthy controls, showing that those with OCD exhibited objective and subjective sleep disturbances when compared to controls (65). In this work, the role of psychiatric comorbidities was not considered in the analyses (65). Other studies have assessed subjective sleep and OCD symptoms in adult community samples (66, 67). Ramsawh et al. (66) analysed data from a national survey in Germany, including 4181 individuals with self-reported measures of sleep quality and the computerized Munich Composite International Diagnostic Interview to asses DSM-IV psychiatric diagnoses. The findings suggested an increased likelihood of sleep disturbance in those with OCD. However, this association was no longer significant when controlling for comorbid depression and comorbid substance use disorders (66). Cox et al. (67) analysed data of 2,071 individuals from the general population who responded to a national survey including items regarding psychiatric symptomatology, with OCD symptoms among them, and sleep disturbance. Their results suggested that individuals with sleep disturbance reported increased obsessive-compulsive symptomatology, compared to individuals without sleep disturbance, and that this link was not accounted for by the presence of comorbid conditions (67). Interestingly, a small body of literature has

suggested a specific link between insomnia and obsessive-compulsive symptoms in non-clinical samples (68, 69). In a study including 352 young adults recruited from a university in the US, insomnia, as measured by a number of self-reported measures including the Insomnia Severity Index (ISI), was found to be specifically and significantly linked to obsessions, independently of comorbid depressive symptoms (68). In another study including 526 individuals from the community, insomnia, also as measured by the ISI, was associated with OCD symptoms and, specifically, with the unacceptable thoughts OCD dimension, as measured by the Dimensional Obsessive-Compulsive Scale (69).

In paediatric OCD samples, *objective* measures of sleep have also been found to be affected. In particular, children with OCD have shown to present reduced total sleep time, reduced non-REM sleep time, and longer sleep onset latencies when compared to healthy controls (70).

A small body of research has assessed *subjective* sleep in children with OCD (71-73), with the limitation of mainly using parent-reported measures of sleep, often derived from broad scales that assess a large number of heterogenous domains such as sleep problems (as described by the parents), talks or walks in sleep or the presence of nightmares. In general, sleep difficulties have frequently been found in paediatric OCD with inconclusive results regarding the possible correlation between sleep difficulties and OCD severity (71-73). A study comparing 185 children and adolescents with OCD, 177 non-OCD patients from a paediatric psychiatric outpatient clinic, and a group of 1,369 healthy controls showed significantly higher rates of sleep problems – reported by parents and measured by items from the Child Behaviour Checklist (CBCL) – in the OCD and in the psychiatric outpatient groups, compared to healthy controls (71). This study found

that, in the OCD group, other comorbid symptoms (e.g., somatic symptoms, anxiety/depression or aggressive behaviour), predicted sleep problems to a greater extent than OCD itself (71). In another study including 66 children with OCD, the number of sleep-related problems (measured by a composite of items extracted from the CBCL, the Multidimensional Anxiety Scale for Children, and the Children's Depression Inventory), was positively related to OCD severity, measured by the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) (72). By contrast, another case-control study including 30 patients with OCD and 30 matched controls did not find a correlation between the sleep disturbances measured by the parent-reported Sleep Disturbances Scale for Children and OCD severity (73).

To the best of our knowledge, only two studies to date have explored whether sleep difficulties interfere with treatment outcomes in paediatric OCD, yielding mixed results (74, 75). The study by Ivarsson et al. (74) included 269 children and adolescents with OCD, showing that more than two-thirds of the sample had at least one mild sleep problem, as measured by a sleep composite score based on the CBCL (74). This study reported that sleep problems at baseline predicted worse outcomes of CBT in this patient group (74). The work by Nabinger de Diaz et al. (75) included 105 children and adolescents with OCD and found that 84.4% of participants reported at least one sleep-related problem, as measured by a composite of items extracted from the CBCL, the Multidimensional Anxiety Scale for Children, and the Children's Depression Inventory (75). Conversely to Ivarsson et al. (74), this study found that baseline sleep-related problems did not predict a poorer treatment response at post-treatment and at 3-month follow-up (75).

Despite the fact that all these previous studies, both in adult and paediatric samples, are of value, they include a number of methodological limitations, namely small sample sizes (64, 65, 73), the use of mainly parent-reported measures which are not specifically designed to assess sleep (71-75), and the study of non-clinical samples (66, 67). Notably, before the studies included in this thesis were undertaken, the prevalence of insomnia in OCD remained unknown.

Moreover, sleep problems have seldom been studied in other OCRDs besides OCD. To our knowledge, to date, there have been no studies addressing sleep disorders in general, and insomnia in particular, in individuals with BDD. Therefore, it is urgent to address this evident gap in the literature. Only a couple of studies have focused on other OCDRDs. In a study comparing 259 adults with trichotillomania and 182 adults with excoriation disorder to 148 healthy controls, both clinical samples presented significantly greater sleep disturbance, as measured by a self-reported measure of sleep quality and disturbance during the past month, than the control group (76). Interestingly, those differences were no longer significant when controlling for internalizing (anxiety and depression) symptoms (76). Further, a recent study revealed that, in a sample of 24 individuals with hoarding disorder, insomnia was a predictor of increased hoarding severity, independently of internalizing symptoms (77).

Given the limited literature in the topic and the above-mentioned methodological limitations of these studies, this doctoral thesis focused on further studying subjective measures of sleep in two OCRDs. Specifically, the included studies were centred on insomnia in samples of children, adolescents, and adults with OCD, and in a sample of children and adolescents with BDD.

2. AIMS AND HYPOTHESES

2.1. Aims

The global aim of this doctoral thesis was to explore the prevalence of insomnia in OCD and BDD, both classified under the larger category of OCRDs, as well as its impact in treatment outcomes in these disorders. Specific aims for each of the three studies included in the thesis are listed below.

Study 1:

- To investigate the prevalence of insomnia in individuals with OCD, compared to unaffected individuals, at a nationwide population level.
- To investigate the association between OCD and insomnia while controlling for familial confounders shared by full siblings, including shared environmental factors such as socioeconomic status or parental education and part of the genetic variance.
- To explore the extent to which the association of OCD with insomnia can be explained by comorbid psychiatric conditions.

Study 2:

- To explore the prevalence of insomnia in paediatric patients with OCD referred to a specialist clinic.
- To compare the sociodemographic characteristics and clinical features of paediatric patients with OCD with and without insomnia.
- To explore whether insomnia is associated with worse multimodal treatment outcomes in paediatric patients with OCD.

Study 3:

- To explore the prevalence of insomnia in paediatric patients with BDD referred to a specialist clinic.
- To compare the sociodemographic characteristics and clinical features of paediatric patients with BDD with and without insomnia.
- To explore whether insomnia has a negative effect on the response to multimodal treatment for paediatric patients with BDD.

2.2. Hypotheses

Specific hypotheses for each of the three studies included in this doctoral thesis are enumerated below.

Study 1:

- The prevalence of insomnia in individuals with OCD will be higher than that in the general population.
- OCD will remain associated with insomnia when controlling for familiar confounders shared by full siblings.
- Comorbid psychiatric disorders, and specifically depression, will have an impact on the magnitude of the association between insomnia and OCD.

Study 2:

- Insomnia will be common in a sample of paediatric patients with OCD referred to a specialist clinic.

- Paediatric OCD patients with insomnia will be more severely affected by their psychiatric condition than those without insomnia.
- Insomnia will be associated with poorer multimodal treatment outcomes in this patient group.

Study 3:

- Insomnia will be common in paediatric patients with BDD referred to a specialist clinic.
- Children and adolescents with BDD and insomnia will be more severely affected by their psychiatric condition than those without insomnia.
- Insomnia will have a negative effect on the response to multimodal treatment in paediatric patients with BDD.

3. SCIENTIFIC PUBLICATIONS

STUDY 1: Insomnia in obsessive-compulsive disorder: A Swedish population-based cohort study

Reference: Sevilla-Cermeño L, Isomura K, Larsson H, Akerstedt T, Vilaplana-Pérez A, Lahera G, et al. Insomnia in obsessive-compulsive disorder: A Swedish population-based cohort study. J Affect Disord. 2020;266: 413-6.

Background: Insomnia is a public health issue associated with adverse outcomes. The association between specific psychiatric disorders and insomnia is well established, but the prevalence of insomnia in OCD is unknown. This population-based study aimed to examine the prevalence of insomnia in patients with OCD compared to unaffected individuals from the general population, taking into account a number of measured covariates. We used a sibling control design to control for familiar confounders shared by full siblings and evaluated the contribution of psychiatric comorbidities to the association between OCD and insomnia.

Methods: Using the personal identification numbers assigned to Swedish citizens as key, the following Swedish national population-based registers were linked and data from individuals in our cohort were obtained: (1) the Swedish Total Population Register, which contains demographic information on all Swedish inhabitants since 1968; (2) the Migration Register, including a record on every immigration into and emigration from Sweden; (3) the Cause of Death Register, containing a record of all deaths in Sweden since 1952; (4) the Multi-Generation Register, which links every person born in Sweden since 1933 and those who ever registered ad living in Sweden from 1960 to their parents, enabling researchers to obtain a family genealogy for each participant; (5) the Swedish National Patient Register (NPR), which comprises information on inpatient care (since

1969) and outpatient specialist services (since 2001) in Sweden, with the diagnoses based on ICD codes; (6) the Prescribed Drug Register (PDR), which includes a record of all medications prescribed and dispended in Sweden since 2005; (7) the Stockholm Primary Care Register (VAL), holding primary care diagnoses in the county of Stockholm since 2003.

Individuals diagnosed with OCD (ICD-10: F42; n=31,856) were identified in the NPR from a cohort of 13,017,902 individuals living in Sweden anytime between January 1, 1973 (when the NPR had complete nationwide coverage) and December 31, 2013. The outcome was defined as a lifetime diagnosis of insomnia (ICD-10: F51.0 or G47.0), also as registered in the NPR. Additionally, in order to improve coverage of the insomnia diagnosis, those individuals from the cohort who had been prescribed or dispended a drug with specific indication for insomnia (including Zopiclone, Zolpidem, Zaleplon, Melatonin, Nitrazepam and Triazolam) were also selected as having the outcome. As insomnia is often diagnosed in primary care settings rather than in specialist care, we additionally identified individuals diagnosed with OCD in primary care (ICD-10: F42; n=5,379) in the subset of individuals living in the Stockholm county during the study period (n=1,406,772). As above, the outcome was defined as a lifetime diagnosis of insomnia (ICD-10: F51.0 or G47.0) as registered in the Stockholm Primary Care Register and, individuals from the cohort who had been prescribed or dispended a drug with specific indication for insomnia, were also selected as having the outcome

Logistic regression analyses, expressed as OR with 95% confidence intervals (CIs), were used to investigate the odds of insomnia in individuals with OCD, compared to the general population and their unaffected full siblings. Models were adjusted by a number of covariates including sex, birth year, and somatic disorders with a known

association with insomnia. Sensitivity analyses were performed in subgroups from which all individuals with the following groups of comorbid psychiatric conditions were excluded: (1) schizophrenia, schizotypal and delusional disorders (ICD-10 codes F20-F29); (2) manic episode and bipolar disorder (ICD-10 codes F30-F31); (3) major depressive disorder (ICD-10 codes F32-F33); (4) persistent mood disorders and unspecified mood disorder (ICD-10 codes F34-F39); (5) phobic, anxiety, and reaction to severe stress and adjustment disorders (ICD-10 codes F40-F41 and F43); (6) attention-deficit/hyperactivity disorder (ICD-10 code F90); (7) pervasive developmental disorders and learning disabilities (ICD-10 codes F84, F81); (8) substance use disorders (ICD-10 codes F10-F19); and (9) personality disorders (ICD-10 codes F60-69).

Results: The main finding was that 42.2% of individuals with OCD and 11.0% of the unaffected individuals from the general population had an insomnia diagnosis or had been dispensed a medication with the specific indication for insomnia. Individuals with OCD showed almost 7-fold increased odds of insomnia, compared to unaffected individuals from the general population (OR=6.92 [95% CI, 6.76-7.08]). Similar results were obtained in the primary care setting (OR=6.43 [95% CI, 6.08-6.80]). The sibling analyses included 21,664 clusters of full siblings discordant for OCD and, although the magnitude of the estimates significantly decreased (OR=5.19 [95% CI, 4.94-5.46]), the odds remained substantial. Comorbid conditions did not fully explain the link between OCD and insomnia, but exclusion of individuals with comorbid depression and anxiety disorders significantly attenuated the odds (OR=4.97 [95% CI, 4.81-5.14] and OR=4.51 [95% CI, 4.33-4.69], respectively).

Conclusions: The odds of insomnia in individuals with OCD were significantly higher than in unaffected individuals. This association was independent from familial

factors shared with siblings. Comorbid psychiatric conditions did not account for the full association between OCD and insomnia, although exclusion of depression and anxiety disorders had an impact on the associations by attenuating the risk. Insomnia should be systematically evaluated and managed in individuals with OCD, particularly in those with comorbid depression and anxiety disorders.

Journal of Affective Disorders 266 (2020) 413–416

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Short communication

Insomnia in obsessive-compulsive disorder: A Swedish population-based cohort study

Laura Sevilla-Cermeño[a,b,c,*], Kayoko Isomura[a,b], Henrik Larsson[d,e], Torbjörn Åkerstedt[f], Alba Vilaplana-Pérez[a,b,g], Guillermo Lahera[c], David Mataix-Cols[a,b], Lorena Fernández de la Cruz[a,b]

[a] Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[b] Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden
[c] Departamento de Medicina y Especialidades Médicas, Universidad de Alcalá, Madrid, Spain
[d] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[e] School of Medical Sciences, Örebro University, Örebro, Sweden
[f] Psychology Division, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[g] Departament de Personalitat, Avaluació i Tractaments Psicològics, Universitat de València, Spain

A B S T R A C T

Background: The association between specific psychiatric disorders and insomnia is well established, but the prevalence of insomnia in obsessive-compulsive disorder (OCD) is unknown. This population-based study examined the prevalence of insomnia in patients with OCD compared to unaffected individuals from the general population and to their unaffected full siblings, and evaluated the contribution of psychiatric comorbidities to this association.

Methods: Individuals diagnosed with OCD (31,856) were identified from a cohort of 13,017,902 individuals living in Sweden anytime during 1973 and 2013. Logistic regression analyses were used to investigate the odds of insomnia in individuals with OCD, compared to the general population and their unaffected full siblings. Sensitivity analyses were performed in subgroups from which all individuals with comorbid psychiatric conditions were excluded, one at a time.

Results: Individuals with OCD had almost 7-fold increased odds of receiving an insomnia diagnosis or being dispensed a drug with specific indication for insomnia, compared to unaffected individuals from the general population (42.2% vs. 11.0%, respectively; OR = 6.92 [95% CI, 6.76-7.08]). Familiar factors shared with siblings and comorbid conditions did not fully explain this association, but when individuals with comorbid depression and anxiety disorders were excluded, the odds of insomnia were significantly reduced (OR = 4.97 [95% CI, 4.81-5.14] and OR = 4.51 [95% CI, 4.33-4.69], respectively).

Limitations: Due to the intrinsic coverage issues of the registers, results may not be generalizable to milder forms of the disorder and to individuals who do not seek help.

Conclusions: Insomnia should be systematically evaluated and managed in individuals with OCD, particularly in those with comorbid anxiety and depression.

1. Introduction

Insomnia is common in the general population (9-15%) (Ohayon, 2002) and associated with multiple adverse outcomes, including increased risk of cardiovascular disease (Javaheri and Redline, 2017), accidents (Leger et al., 2014), and work disability (Sivertsen et al., 2009). The co-occurrence of insomnia and specific psychiatric disorders (e.g., depression) is well established, but the prevalence of insomnia in obsessive-compulsive disorder (OCD) is unknown. Exploring a potential association between OCD and insomnia is important as it may help guide clinical practice. This population-based cohort study investigated the prevalence of insomnia in individuals with OCD, compared to unaffected individuals from the general population, and evaluated the contribution of psychiatric comorbidities to this association. Additionally, we employed a quasi-experimental family design to explore the role of unmeasured familial factors shared by full siblings and shed light on possible mechanisms that could account for the association between OCD and insomnia.

2. Methods

The Regional Ethical Review Board in Stockholm approved the study (reference number 2013/862-31/5). The requirement for informed consent was waived because the study was register-based and used de-identified data.

* Corresponding author at: Department of Clinical Neuroscience, Karolinska Institutet, Centre for Psychiatry Research, Gävlegatan 22B, 8th floor, 11330 Stockholm, Sweden.
E-mail address: laura.sevilla.cermeno@ki.se (L. Sevilla-Cermeño).

https://doi.org/10.1016/j.jad.2020.01.122
Received 3 October 2019; Received in revised form 15 December 2019; Accepted 20 January 2020
Available online 22 January 2020
0165-0327/

2.1. Study cohort and variables

The cohort consisted of all individuals living in Sweden anytime during 1973 and 2013. Individuals with a record of organic brain disorder (ICD-10 codes: F00-09) and/or epilepsy (ICD-10 code: G40) were excluded from the cohort. Using the personal identification numbers assigned to Swedish citizens as key (Ludvigsson et al., 2009), nationwide population-based registers were linked and data from the individuals in our cohort were obtained. The exposure was defined as receiving a lifetime diagnosis of OCD, according to the definition by the International Classification of Diseases, 10th edition (ICD-10), as recorded in the National Patient Register (NPR). The OCD code (F42) has been previously evaluated in the NPR, showing high validity and inter-rater reliability (Ruck et al., 2015). The NPR holds diagnostic information for each individual on inpatient care (available since 1969) and on specialist outpatient care (available since 2001) in Sweden. Individuals without a lifetime diagnosis of OCD were considered unexposed. Both cohorts of OCD exposed and unexposed individuals could have any other psychiatric disorders. The outcome was defined as a lifetime diagnosis of insomnia according to ICD-10 criteria (codes F51.0 or G47.0), as recorded in the NPR. Because insomnia is often diagnosed and managed in primary rather than specialist care, we also collected insomnia diagnoses from the primary care database at the Stockholm County Council (only for the subset of individuals living in Stockholm County during the study period). Further, to improve the coverage of insomnia cases, individuals who had been dispensed drugs with specific indication for insomnia (i.e., ATC codes N05CF01 [Zopiclone], N05CF02 [Zolpidem], N05CF03 [Zaleplon], N05CH01 [Melatonin], N05CD02 [Nitrazepam], and N05CD05 [Triazolam]), as registered in the Prescribed Drug Register, were also identified as having the outcome.

2.2. Statistical analyses

Logistic regression analyses were used to compare individuals with and without a diagnosis of OCD on the outcome (i.e., insomnia) expressed as odds ratios (OR) with 95% confidence intervals (CI). Models were adjusted by a number of covariates, including sex, birth year, and somatic disorders with a known association with insomnia (Mallon et al., 2014), including asthma (ICD-10 code J45), arthropaties (ICD-10 codes M00-M25), inflammatory bowel disease (ICD-10 codes K50-51), diseases of the liver (ICD-10 codes K70-K77), and ischemic heart diseases (ICD-10 codes I20-I25). As insomnia diagnoses may be primarily given by general practitioners, and therefore may not be covered by the NPR, analyses were conducted both in specialist care (NPR) and also in primary care (only for those residing in the Stockholm county).

A fixed-effects model was implemented in the subsample of clusters of all full siblings (those sharing the same mother and father) for comparison between individuals with OCD and their unaffected siblings (NPR only). By design, these models control for familiar confounders shared by siblings, in particular for unmeasured shared confounders (such as socioeconomic status or parental education) and partially for genetic factors, since full siblings share about 50% of the genetic liability (Allison, 2009).

Finally, sensitivity analyses were performed in subgroups from which all individuals with comorbid psychiatric conditions were excluded, one at a time, in order to investigate the impact of each group of comorbidities on the association between OCD and insomnia. Comorbidities were divided into nine groups: (1) schizophrenia, schizotypal and delusional disorders (ICD-10 codes F20-F29); (2) manic episode and bipolar disorder (ICD-10 codes F30-F31); (3) major depressive disorder (ICD-10 codes F32-F33); (4) persistent mood disorders and unspecified mood disorder (ICD-10 codes F34-F39); (5) phobic, anxiety, and reaction to severe stress and adjustment disorders (ICD-10 codes F40-F41 and F43); (6) attention-deficit/hyperactivity disorder (ICD-10 code F90); (7) pervasive developmental disorders and learning disabilities (ICD-10 codes F84, F81); (8) substance use disorders (ICD-10 codes F10-F19); and (9) personality disorders (ICD-10 codes F60-69). All analyses were conducted using SAS software, version 9.4 (SAS Institute Inc.).

3. Results

The study cohort consisted of 13,017,902 individuals (6,430,927 women; 49.4%), of which 31,856 had a diagnosis of OCD (18,107

Table 1
Odds ratios and corresponding 95% confidence intervals for insomnia among individuals with lifetime obsessive-compulsive disorder, compared to unaffected individuals from the general population and their unaffected siblings.

	Individuals with OCD (n = 31,856) n (%)	Individuals without OCD (n = 12,986,046) n (%)	OR (95% CI) Model 1[a]	OR (95% CI) Model 2[b]
General population comparison Specialist care (Sweden) and PDR	13,437 (42.2)	1,427,152 (11.0)	6.44 (6.29-6.58)	6.92 (6.76-7.08)
	Individuals with OCD (n =5,379) n (%)	Individuals without OCD (n = 1,401,393) n (%)	OR (95% CI) Model 1[a]	OR (95% CI) Model 2[b]
General population comparison Primary care (Stockholm) and PDR	2,444 (45.4)	237,016 (16.9)	6.43 (6.08-6.80)	6.43 (6.08-6.80)
	Individuals with OCD with unaffected full siblings (n = 21,908) n (%)	Unaffected full siblings of individuals with OCD (n = 35,457) n (%)	OR (95% CI) Model 1[a]	OR (95% CI) Model 2[b]
Full sibling comparison Specialist care (Sweden) and PDR	8,951 (40.9)	5,235 (14.8)	5.20 (4.94-5.47)	5.19 (4.94-5.46)

Abbreviations: CI confidence interval; OCD obsessive-compulsive disorder; OR odds ratio, PDR prescribed drug register.
[a] Model 1: Adjusted by sex and year of birth.
[b] Model 2: Adjusted by sex, year of birth, and somatic comorbidities, including asthma, arthropaties, inflammatory bowel disease, diseases of the liver, and ischemic heart diseases.

Table 2
Fully adjusted odds ratios and corresponding 95% confidence intervals for insomnia among individuals with lifetime obsessive-compulsive disorder, compared with unaffected individuals from the general population, excluding different groups of psychiatric comorbidities.

Excluded group of comorbidities	Individuals with OCD (n = 31,856) n (%)	Individuals without OCD (n = 12,986,046) n (%)	OR (95% CI)[a]
Schizophrenia, schizotypal and delusional disorders	3,139 (9.9)	82,666 (0.64)	6.46 (6.30-6.62)
Manic episode or bipolar disorder	2,799 (8.8)	57,515 (0.4)	6.35 (6.19-6.50)
Major depressive disorder	13,958 (43.8)	392,663 (3.0)	4.97 (4.81-5.14)
Persistent mood disorder and unspecified mood disorder	2,096 (6.6)	42,974 (0.3)	6.67 (6.51-6.83)
Phobic, anxiety and reaction to severe stress and adjustment disorders	18,119 (56.9)	454,421 (3.5)	4.51 (4.33-4.69)
Attention-deficit/hyperactivity disorder	4,407 (13.8)	103,596 (0.8)	6.54 (6.38-6.71)
Pervasive developmental disorders and learning disabilities	3,804 (11.9)	50,181 (0.4)	6.61 (6.45-6.78)
Substance use disorders	5,114 (16.1)	328,292 (2.5)	6.32 (6.16-6.49)
Personality disorders	5,229 (16.4)	65,090 (0.5)	6.01 (5.86-6.17)

Abbreviations: CI confidence interval; OCD obsessive-compulsive disorder; OR odds ratio.
[a] Adjusted by sex, year of birth, and somatic comorbidities, including asthma, arthropaties, inflammatory bowel disease, diseases of the liver, and ischemic heart diseases.

women; 56.8%). The results showed that 13,437 (42.2%) individuals with OCD and 1,427,152 (11.0%) unaffected individuals from the general population had an insomnia diagnosis or had been dispensed a drug to treat insomnia at some point during the study period (Table 1). In fully adjusted models, individuals with OCD had almost 7-fold increased odds of receiving an insomnia diagnosis or being dispensed a drug with specific indication for insomnia during the study period (OR = 6.92 [95% CI, 6.76-7.08]). Similar results were obtained in the primary care setting (OR = 6.43 [95% CI, 6.08-6.80]).

The sibling cohort consisted of all families (n = 2,589,677) with at least two singleton children, 21,664 of which included clusters of full siblings discordant for OCD. The magnitude of the estimates significantly decreased in the sibling comparison models, but the odds remained substantial (OR = 5.19 [95% CI, 4.94-5.46]) (Table 1).

An 81.6% of the individuals with OCD and an 8.4% of the individuals without OCD had a diagnosis of other psychiatric disorders. When different groups of these psychiatric comorbidities were systematically excluded from the analyses, each one of the nine groups at a time, results remained largely unchanged. However, the exclusion of depression and anxiety disorders resulted in significantly smaller odds (OR = 4.97 [95% CI, 4.81-5.14] and OR = 4.51 [95% CI, 4.33-4.69], respectively) (Table 2).

4. Discussion

This is the first study to estimate the prevalence of insomnia in OCD at the population level. Approximately 42% of individuals with OCD had a recorded insomnia diagnosis or had collected a drug prescription with specific indication for insomnia, compared to 11% in the general population. These figures correspond to a 7-fold increased odds of insomnia for individuals with OCD. Our lifetime prevalence figures for the unexposed cohort match previously reported insomnia rates in the general population (Ohayon, 2002), while the prevalence of insomnia in the OCD cohort was very similar to the estimated prevalence of self-reported insomnia in a sample of pediatric patients with OCD treated in a specialist outpatient clinic in Sweden (Sevilla-Cermeño et al., 2019), indicating that our combined outcome definition resulted in adequate coverage of the insomnia cases.

The discordant sibling analyses showed that individuals with OCD still had substantially higher odds of insomnia compared with their unaffected siblings, but the magnitude of the estimates was significantly reduced. Thus, while insomnia could be partly conceptualized as a functional consequence of OCD, which is likely to improve alongside OCD symptoms after successful treatment (Sevilla-Cermeño et al., 2019), shared familial factors, such as genetics and early environmental factors, may also play an important role in the observed association between OCD and insomnia. Further studies employing genetically informative designs are needed.

Our sensitivity analyses systematically excluding major groups of psychiatric conditions showed that OCD is associated with insomnia in its own right, since exclusion of different groups of psychiatric disorders did not substantially alter the magnitude of the association. The exceptions were comorbid depressive or anxiety disorders, which did contribute significantly to the observed associations (their exclusion reduced but did not eliminate the associations). From a clinical perspective, our results highlight the need to systematically evaluate and manage insomnia in patients with OCD, particularly if they present with comorbid depression and/or anxiety.

Limitations of the study include the intrinsic coverage issues of population registers. Patients included in the NPR may not be representative of all patients (e.g., diagnoses were only made by specialist doctors, outpatient care was only introduced in 2001). Additionally, not all patients seek help and therefore our cohort is restricted to those that are service users. These limitations can potentially compromise the generalizability of the results. Furthermore, we used two different methods to ascertain cases, one based on individuals being diagnosed with insomnia and another one based on individuals using specific medications for insomnia as a proxy for the diagnosis. However, it was reassuring that the combined use of these methods led to similar prevalence rates of insomnia than those reported in previous studies.

In conclusion, insomnia should be systematically evaluated in patients with OCD and managed according to the available evidence in order to minimize its potential negative impact in individuals with OCD. This is particularly important for those patients with comorbid anxiety and depression.

Funding

Ms. Sevilla-Cermeño and Ms.Vilaplana-Pérez were supported by grants from the Alicia Koplowitz Foundation. Dr. Fernández de la Cruz was supported by a grant from the Swedish Research Council for Health, Working Life and Welfare (FORTE grant number 2015-00569). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decisions to submit the manuscript for publication. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Laura Sevilla-Cermeño: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Writing - original draft, Writing - review & editing. **Kayoko Isomura:** Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Writing - review & editing. **Henrik Larsson:** Investigation,

Methodology, Resources, Software, Writing - review & editing. **Torbjörn Åkerstedt:** Investigation, Methodology, Resources, Writing - review & editing. **Alba Vilaplana-Pérez:** Investigation, Methodology, Resources, Writing - review & editing. **Guillermo Lahera:** Investigation, Methodology, Resources, Writing - review & editing. **David Mataix-Cols:** Conceptualization, Investigation, Methodology, Resources, Software, Supervision, Writing - original draft, Writing - review & editing. **Lorena Fernández de la Cruz:** Conceptualization, Investigation, Methodology, Resources, Software, Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

Prof. Larsson has served as a speaker for Evolan Pharma and Shire and has received research grants from Shire; all outside the submitted work. Dr. Lahera has been a consultant to or has received honoraria or grants from Janssen-Cilag, Otsuka-Lundbeck, Lilly, Astra-Zeneca, CIBERSAM, and Instituto de Salud Carlos III; all outside the submitted work. Prof. Mataix-Cols receives royalties for contributing articles to UpToDate, Wolters Kluwer Health and for editorial work from Elsevier. Dr. Fernández de la Cruz receives royalties for contributing articles to UpToDate, Wolters Kluwer Health.

Acknowledgements

None

References

Allison, P.D., 2009. Fixed Effects Regression Models. Sage Publications, Thousand Oaks, CA.

Javaheri, S., Redline, S., 2017. Insomnia and Risk of Cardiovascular Disease. Chest 152, 435–444.

Leger, D., Bayon, V., Ohayon, M.M., Philip, P., Ement, P., Metlaine, A., Chennaoui, M., Faraut, B., 2014. Insomnia and accidents: cross-sectional study (EQUINOX) on sleep-related home, work and car accidents in 5293 subjects with insomnia from 10 countries. J. Sleep Res. 23, 143–152.

Ludvigsson, J.F., Otterblad-Olausson, P., Pettersson, B.U., Ekbom, A., 2009. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur. J. Epidemiol. 24, 659–667.

Mallon, L., Broman, J.E., Akerstedt, T., Hetta, J., 2014. Insomnia in Sweden: a population-based survey. Sleep Disord. 2014, 843126.

Ohayon, M.M., 2002. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med. Rev. 6, 97–111.

Rück, C., Larsson, K.J., Lind, K., Perez-Vigil, A., Isomura, K., Sariaslan, A., Lichtenstein, P., Mataix-Cols, D., 2015. Validity and reliability of chronic tic disorder and obsessive-compulsive disorder diagnoses in the Swedish National Patient Register. BMJ Open 5, e007520.

Sevilla-Cermeño, L., Andren, P., Hillborg, M., Silverberg-Morse, M., Mataix-Cols, D., Fernández de la Cruz, L., 2019. Insomnia in pediatric obsessive-compulsive disorder: prevalence and association with multimodal treatment outcomes in a naturalistic clinical setting. Sleep Med. 56, 104–110.

Sivertsen, B., Overland, S., Pallesen, S., Bjorvatn, B., Nordhus, I.H., Maeland, J.G., Mykletun, A., 2009. Insomnia and long sleep duration are risk factors for later work disability, the Hordaland health study. J. Sleep Res. 18, 122–128.

3.2 STUDY 2: Insomnia in pediatric obsessive-compulsive disorder: prevalence and association with multimodal treatment outcomes in a naturalistic clinical setting

Reference: Sevilla-Cermeño L, Andrén P, Hillborg M, Silverberg-Morse M, Mataix-Cols D, Fernández de la Cruz L. Insomnia in pediatric obsessive-compulsive disorder: Prevalence and association with multimodal treatment outcomes in a naturalistic clinical setting. Sleep Med. 2019;56:104-10.

Background: Subjective sleep has been scarcely studied in the field of paediatric OCD and, specifically, little is known about the prevalence and impact of insomnia on the clinical outcomes of youth with OCD.

Methods: A total of 193 young patients meeting ICD-10 and DSM-5 criteria for OCD, consecutively referred to a specialist paediatric OCD clinic, completed a range of diagnostic and clinical measures, including the self-reported Insomnia Severity Index (ISI). The ISI is a well-validated self-reported instrument which specifically measures insomnia. Patients scoring above a previously validated cut-off on the ISI for insomnia (scores≥9) were compared to the rest of the sample on socio-demographic and clinical characteristics. Chi-squared and Fisher tests were used for comparisons of categorical variables and Student's t-tests for continuous variables. In a subsample of 143 patients (from the initial 193) who received multimodal OCD treatment at the clinic (CBT and, in 31.5% of cases, also medication), a mixed-model ANOVA was used to compare the treatment outcomes in the insomnia (n=60) *vs.* no insomnia (n=83) groups, as defined by the ISI cut-off. The primary outcome measure was the clinician-administered Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), applied at baseline, at post-treatment, and at 3-month follow-up. The mixed-model ANOVA adjusted for a number

of measures: baseline depression severity, number of CBT sessions received, and medication prescribed for insomnia. Sensitivity analyses were performed in which patients with comorbid autism spectrum disorder were excluded.

Results: The psychometric properties of the ISI in our sample were excellent. At baseline, 42% (81/193) of the sample scored above the ISI cut-off for clinical insomnia and the mean ISI score for the sample was 7.6 (SD=5.9). These participants were more frequently on pharmacological treatment, had higher rates of comorbid psychiatric disorders (specifically depression), scored significantly higher on all measures of OCD severity and depressive symptoms, and showed poorer general functioning than OCD patients scoring below the ISI cut-off for clinical insomnia. In the treated subsample, while the insomnia group showed more severe OCD symptomatology through the three time-points, both groups improved similarly on the CY-BOCS both at post-treatment and at 3-month follow-up.

Conclusions: Insomnia is common in paediatric OCD and is associated with more severe obsessive-compulsive and depressive symptomatology and with worse general functioning. However, with adequate multimodal, evidence-based treatment, these patients can improve as much as those without insomnia.

Sleep Medicine 56 (2019) 104–110

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Insomnia in pediatric obsessive–compulsive disorder: prevalence and association with multimodal treatment outcomes in a naturalistic clinical setting

Laura Sevilla-Cermeño [a, b, c, *], Per Andrén [a, b], Maria Hillborg [b], Maria Silverberg-Morse [b], David Mataix-Cols [a, b], Lorena Fernández de la Cruz [a, b]

[a] Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden
[b] Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden
[c] Departamento de Medicina y Especialidades Médicas, Universidad de Alcalá, Madrid, Spain

ARTICLE INFO

Article history:
Received 19 September 2018
Received in revised form
28 November 2018
Accepted 8 December 2018
Available online 30 January 2019

Keywords:
Obsessive-compulsive disorder
Insomnia
Cognitive-behavior therapy
Children
Adolescents

ABSTRACT

Objective: Little is known about the prevalence and impact of insomnia on clinical outcomes in youth with obsessive–compulsive disorder (OCD). This study aimed to investigate this subject.
Patients/methods: A total of 193 patients from a specialist pediatric OCD clinic completed a range of diagnostic and clinical measures, including the Insomnia Severity Index (ISI). Patients scoring above a previously validated cut-off on the ISI (score ≥9) were compared to the rest of the sample on socio-demographic and clinical characteristics. In a subsample of 143 (from the initial 193) patients who were treated at the clinic, a mixed-model analysis of variance (ANOVA) was used to compare the outcomes of multimodal OCD treatment in the insomnia ($N = 60$) vs no insomnia ($N = 83$) groups. The primary outcome measure was the clinician-administered Children's Yale–Brown Obsessive–Compulsive Scale (CY-BOCS) at post-treatment and at three-month follow-up.
Results: The psychometric properties of the ISI in our sample were excellent. At baseline, 42% (81/193) of the sample scored above the ISI cut-off for clinical insomnia. These participants had significantly higher OCD severity, higher rates of psychiatric comorbidities, more severe depressive symptoms, poorer general functioning, and were more likely to take sleep medications, compared to those who scored below the ISI cut-off. In the treated subsample, while the insomnia group remained more severely affected through the three time-points, both groups improved similarly on the CY-BOCS at post-treatment and at three-month follow-up.
Conclusion: Insomnia is relatively common in pediatric OCD and is associated with more severe psychopathology. However, with adequate multimodal, evidence-based treatment, these patients can improve as much as those without insomnia.

1. Introduction

Sleep is a biological process necessary for the maintenance of both physical and mental health. Reduced sleep in healthy children has been linked to impairment in cognitive and emotional functioning [1]. Shortened sleep duration has been associated with low performance on intelligence quotient measures [2] and with impairment in verbal and nonverbal cognitive abilities [3] in healthy school-age children. An interaction between sleep and psychopathology also seems to exist, and disrupted sleep has been shown to affect the course, severity, and prognosis of different psychiatric disorders in children [4]. For example, pediatric patients diagnosed with a major depressive episode who also experienced sleep disturbances were found to be more severely depressed than those without sleep disturbances [5], and poor sleep in children with autism was associated with higher parent ratings of hyperactive-impulsive behaviors, as well as oppositional behaviors [6]. Insomnia is also common in youth with anxiety disorders, and may be associated with more severe anxiety symptoms and more

* Corresponding author. Department of Clinical Neuroscience, Child and Adolescent Psychiatry Research Center, Gävlegatan 22 (Entré B), floor 8, SE-113 30 Stockholm.
E-mail address: laura.sevilla.cermeno@ki.se (L. Sevilla-Cermeño).

https://doi.org/10.1016/j.sleep.2018.12.024
1389-9457/

interference in family functioning [7]. Greater amounts of rapid eye movement sleep have been related to more somatic complaints in children with generalized anxiety disorder, when compared to healthy controls [8].

Notably, little is known about sleep difficulties in general, and insomnia in particular, in young people with obsessive–compulsive disorder (OCD), a relatively frequent and debilitating psychiatric condition that tends to start at a young age [9]. The scarce literature available suggests that adults with OCD show alterations in some objective sleep patterns. Specifically, adults with OCD have shown shorter sleep duration, increased wake after sleep onset, and late sleep onset and offset, compared to healthy controls [10,11]. Regarding the latter, a high prevalence of delayed sleep phase disorder has been found in OCD samples [11]. Furthermore, delayed bedtimes have been associated with a higher prevalence of obsessive-compulsive symptoms in non-clinical samples [12].

In pediatric OCD samples, children have shown reduced total sleep time (TST) and longer awake periods after sleep onset [13], and adolescents with OCD have been reported to present reduced TST, reduced non-REM sleep time, and longer sleep onset latencies when compared to healthy controls [14]. The small number of studies assessing subjective sleep disturbances in children with OCD have yielded mixed and inconclusive results. An observational study comparing 185 children and adolescents with OCD, 177 non-OCD patients from a child psychiatric outpatient clinic, and a group of 1369 healthy controls of the same age found significantly higher rates of sleep problems – reported by parents and measured by selected items from the Child Behavior Checklist (CBCL) – in the OCD and in the psychiatric outpatient groups, compared with healthy controls [15]. The same study also showed that, in the OCD group, other comorbid symptoms measured by the CBCL (eg, thought problems, somatic symptoms, anxious/depressed, and aggressive behavior), predicted sleep problems to a greater extent than OCD itself [15]. In another cohort study including 66 children with OCD, the number of sleep-related problems measured by a composite of items extracted from the CBCL, the Multidimensional Anxiety Scale for Children, and the Children's Depression Inventory was positively related to OCD severity, measured by the Children's Yale–Brown Obsessive–Compulsive Scale (CY-BOCS) [16]. By contrast, another case–control study including 30 patients with OCD and 30 matched controls did not find a correlation between the sleep disturbances measured by the parent-reported Sleep Disturbances Scale for Children and OCD severity [17]. A larger study including 269 children and adolescents with OCD showed that more than two-thirds of the sample had at least one mild sleep problem, using a sleep composite score based on the CBCL [18]. This is also the only observational study to date to explore whether sleep difficulties are associated with clinical outcomes in pediatric OCD. Specifically, the authors reported that sleep problems at baseline predicted worse outcomes of cognitive-behavior therapy (CBT) for OCD [18]. This is a potentially important finding that requires replication because it may indicate that patients with sleep difficulties may require additional interventions to fully benefit from CBT, the mainstream treatment for pediatric OCD.

One important limitation of previous studies in pediatric OCD is that they have primarily employed parent-reported measures, which were often derived from other scales, rather than specifically developed and validated sleep scales. In an attempt to overcome some of the limitations of the existing literature and extend our understanding of the prevalence and impact of sleep difficulties in this group, this study aimed to: (1) explore the extent to which pediatric patients with OCD referred to a specialized clinic suffer from clinical insomnia, according to a self-reported, sleep-specific measure; (2), compare the demographic and clinical characteristics of pediatric OCD patients with and without insomnia; and (3) explore whether insomnia is associated with poorer multimodal treatment outcomes in this patient group.

2. Methods

2.1. Clinical setting

All study participants were recruited from a specialist pediatric OCD and related disorders outpatient clinic in Stockholm, Sweden. The clinic receives referrals from Child and Adolescent Mental Health Services (CAMHS) and pediatric services primarily across the entire Stockholm region, and occasionally from other Swedish regions and Nordic countries. All patients and their parents/legal guardians routinely fill in questionnaires before their first appointment with the multidisciplinary clinical team, comprised of child psychiatrists, clinical psychologists, and nurses. This information is then used to conduct a more focused and efficient face-to-face diagnostic assessment. In the first 3-h appointment, detailed sociodemographic and clinical information is gathered from the patients and their parents, and clinical diagnoses are made according to ICD-10 and DSM-5 criteria [19,20] using semi-structured instruments, including the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) [21]. After the assessment, patients are either offered treatment at the clinic or referred to more appropriate services. For all patients undertaking treatment at the clinic, all clinical measurements are repeated at post-treatment and at several fixed follow-up times, set at 3, 6, and 12 months after the end of the treatment. All patients assessed at the clinic are routinely asked for consent to participate in research studies.

2.2. Participants

Participants were 193 children and adolescents consecutively referred to our specialist OCD and related disorders clinic between January 2015 and March 2018, meeting ICD-10 and DSM-5 criteria for OCD, and who consented to using their routinely collected clinical data for research purposes. Table 1 shows the sample characteristics at baseline for all the study participants. The sample (107 girls, 55.4%) had a mean age of 13.6 years (standard deviation (SD) = 2.4; range 6–17). The self-reported mean age of onset of their OCD was 10.8 years (SD = 2.8; range 3–17). The mean CY-BOCS score was 22.6 (SD = 4.4; range 11–33), indicating moderately severe OCD. Almost half of the sample (N = 93, 48.2%) had additional psychiatric diagnoses. One hundred and forty-three participants (74.1%) received treatment for their OCD at the clinic, while the remaining patients were referred elsewhere.

All young people and their parents gave written consent to participate in the current study, which was approved by the Regional Ethical Review Board in Stockholm (reference number 2015/1977–31/4).

2.3. Measures

All measures listed below were completed at baseline by all study participants (N = 193). Additionally, for the sample of patients treated at the clinic (N = 143), assessments were also performed at post-treatment and at three-month follow-up. Data from the 6- and 12-month follow-ups were not used in the current study as many patients are still in follow-up.

The Insomnia Severity Index (ISI) is a self-report instrument developed for the measurement of insomnia. It targets not only the symptoms but also the consequences of insomnia, as well as the degree of disturbance caused by the sleep impairment. It comprises seven Likert-type items ranging from 0 to 4, with a maximum total

Table 1
Baseline demographic and clinical characteristics of pediatric obsessive–compulsive disorder patients with and without clinical insomnia ($N = 193$).

Demographics	All participants ($N = 193$)		Clinical insomnia ($N = 81$)		No clinical insomnia (N = 112)		Statistic	p
	N	%	*N*	%	*N*	%	Chi-squared	
Girls	107	55.4	51	63.0	56	50.0	3.70	0.157
Family history of OCD	73	37.8	31	38.3	42	37.5	0.01	0.913
Any comorbid mental disorder	93	48.2	49	60.5	44	39.3	8.47[b]	0.004
ADHD	45	23.3	21	25.9	24	21.4	0.53	0.466
ASD	38	19.7	17	21.0	21	18.8	0.15	0.700
Depression	25	13.0	19	23.5	6	5.4	13.66[c]	0.000
Bipolar disorder	1	0.5	1	1.2	0	0	–	0.420[a]
Anxiety disorders	14	7.3	7	8.6	7	6.3	0.40	0.527
Tic disorders	12	6.2	4	4.9	8	7.1	0.39	0.531
Previous CBT treatment	88	45.6	31	38.3	57	50.9	3.02	0.082
On pharmacological treatment	84	43.5	42	51.9	42	37.5	3.94[b]	0.047
SRIs	53	27.5	23	28.4	30	26.8	0.06	0.805
Other antidepressants	1	0.5	1	1.2	0	0	–	0.420[a]
Antipsychotics	11	5.7	6	3.1	5	2.6	–	0.531[a]
Melatonin	26	13.5	21	25.9	5	4.5	18.57[c]	0.000
Antihistamines ($N = 192$)	18	9.4	9	11.1	9	8.0	0.53	0.468
Zolpidem	1	0.5	1	1.2	0	0	–	0.420[a]
Benzodiazepines ($N = 192$)	1	0.5	1	1.2	0	0	–	0.420[a]
ADHD medication	24	12.4	11	13.6	13	11.6	0.17	0.682
Others	1	0.5	1	1.2	0	0	–	0.420[a]
	Mean	SD	Mean	SD	Mean	SD	Student's *t*	*p*
Age at assessment	13.6	2.4	13.9	2.4	13.3	2.4	−1.86	0.064
Age of OCD onset ($n = 180$)	10.8	2.8	11.1	2.7	10.6	2.8	−1.09	0.279
Insomnia measure	Mean	SD	Mean	SD	Mean	SD	Student's *t*	*p*
ISI total	7.6	5.9	13.4	4.0	3.5	2.7	−19.63[c]	0.000
OCD measures	Mean	SD	Mean	SD	Mean	SD	Student's *t*	*p*
CY-BOCS								
CY-BOCS obsessions	11.2	2.3	11.6	2.1	10.9	2.3	−2.25[b]	0.026
CY-BOCS compulsions	11.3	2.4	11.9	2.1	10.9	2.5	−2.90[c]	0.004
CY-BOCS total	22.6	4.4	23.6	4.0	21.8	4.5	−2.72[c]	0.007
OCI-CV								
OCI-CV total	18.7	7.7	21.6	7.7	16.7	7.1	−4.56[c]	0.000
Other clinical measures	Mean	SD	Mean	SD	Mean	SD	Student's *t*	*p*
CDI-S ($N = 186$)	6.1	4.3	8.5	4.1	4.3	3.5	−7.48[c]	0.000
CGI-S ($N = 192$)	4.3	0.7	4.4	0.7	4.2	0.7	−2.02[b]	0.045
CGAS	50.7	5.9	49.4	5.7	51.6	5.8	2.57[b]	0.011

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorders; CBT, cognitive behavioral therapy; CDI-S, Children's Depression Inventory – Short Version; CGAS, Children's Global Assessment Scale; CGI-S, Clinical Global Impression – Severity; CY-BOCS, Children's Yale-Brown Obsessive–Compulsive Scale; ISI, Insomnia Severity Index; OCD, obsessive–compulsive disorder; OCI-CV, Obsessive–Compulsive Inventory – Child Version; SD, standard deviation; SRIs, serotonin reuptake inhibitors.
[a] Fisher test.
[b] Significant at 0.05.
[c] Significant at 0.01.

score of 28. The ISI is considered suitable for screening purposes and for measuring change over time [22]. The optimal cut-off score for clinically significant insomnia in adolescents has been established to be 9 [23]. In this study, we used the Swedish translation of the ISI, which has been adapted for use amongst young patients [24]. This version has shown adequate internal consistency and good correspondence with other measures of insomnia [24]. Using the previously established cut-off in young people [23], the OCD sample was divided into a clinical insomnia group (ISI scores $\geq$9) and a no clinical insomnia group (ISI scores <9).

The CY-BOCS is a clinician-rated, semi-structured interview used to assess the severity of the OCD symptoms [25]. It consists of five severity items for both obsessions and compulsions, with a total OCD severity score ranging from 0 to 40. The CY-BOCS has shown good reliability as well as good convergent and discriminant validity [26] and is the gold standard outcome measure in clinical trials of OCD.

The Obsessive–Compulsive Inventory – Child version (OCI-CV) is a self-reported measure of OCD symptom severity in children and adolescents. In addition to a total score, this multidimensional measure includes the following subscales: doubting/checking, obsessing, hoarding, washing, ordering, and neutralizing. Both the total score and the subscales of the OCI-CV have good internal consistency and test–retest reliability, as well as good convergent and discriminant validity [27].

The Children's Depression Inventory – Short Version (CDI–S) is a 10-item short version of the CDI assessing the presence and severity of depressive symptoms in children and adolescents [28].

The Clinical Global Impression-Severity (CGI-S) is a one-item clinician rating of symptom severity. It is rated on a seven-point scale ranging from 1 (no symptoms) to 7 (extremely severe symptoms) [29]. The Clinical Global Impression-Improvement (CGI-I) is a one-item clinician rating of symptom severity change from the baseline assessment. This scale ranges from 1 (very much improved) to 7 (very much worse) [30].

The Children's Global Assessment Scale (CGAS) is an adaptation of the Global Assessment Scale (GAS) designed to reflect the lowest level of functioning of a child or adolescent during a certain period of time. It ranges from 1 (more impaired) to 100 (best functioning) [31].

Additionally, following a consensus statement of international experts [32], 'treatment response' was defined as a 35% or greater drop on the CY-BOCS and a CGI-I score of 1 or 2, and 'remission' as a score of ≤12 on the C-YBOCS and a CGI-S rating of 1 or 2 [32].

2.4. Treatment

All patients treated at the clinic were offered a course of CBT and a subset of cases were additionally treated with medication, when deemed clinically relevant. The CBT was protocol-driven and focused on exposure with response prevention (ERP), with parental involvement [33,34]. Treatment was delivered by clinical psychologists with extensive experience in treating pediatric OCD. The treatment protocol included the following key components which, in most cases, were delivered in 12–14 sessions: psychoeducation about OCD and anxiety (two sessions), development of an ERP hierarchy and graded ERP (10 sessions), and relapse prevention (two sessions) [33,34]. However, the number of sessions could be adapted depending on the patient's severity and response to the intervention. Usually sessions lasted 1 h and were conducted weekly. Alternately, complex cases could be offered intensive (eg, several hours per day) clinic-based or home-based sessions (for homebound patients). Parental involvement in the treatment was encouraged in all cases, and the reduction of parental accommodation was often a specific treatment target. Homework tasks were assigned between sessions, which mainly consisted of encouraging daily practice of ERP tasks.

Patients with comorbid autism spectrum disorders (ASD) followed a modified protocol including additional parental education, a longer psychoeducation phase, use of concrete visual materials, use of examples and metaphors linked to the young persons' special interests, a higher number of therapy sessions and the involvement of additional therapists, when required [35]. No specific protocol-driven interventions were directed towards insomnia, although the clinic's treatment protocol for OCD cases with comorbid ASD includes an ancillary sleep hygiene module which is incorporated in the psychoeducation sessions. This module includes general sleep hygiene recommendations, such as encouraging patients to be outdoors and active during the day, not using smartphones or other electronic gadgets before bedtime, dimming the light about 1 h before bedtime, going to bed at the same time every day, or avoiding drinking coffee, tea, or energetic drinks before going to bed.

2.5. Statistical analyses

Data were analyzed using SPSS version 25.0 for Windows. Chi-squared and Fisher tests were used for between-group comparisons of categorical variables and Student's *t*-tests for continuous variables.

The psychometric properties of the ISI were examined in the current sample. Internal consistency was evaluated using Cronbach's alpha. The construct validity was assessed in two ways. First, the factor structure of the ISI was examined using principal component analysis (PCA). Second, Pearson's correlations were used to explore the convergence/divergence of the ISI with the above-described instruments. Following Cohen's classification, large correlations were defined as greater or equal to 0.50, medium correlations between 0.30 and 0.49, and small correlations from 0.10 to 0.29 [36].

A mixed-model analyses of variance (ANOVA) was used to test for a differential effect of group (clinical insomnia/no clinical insomnia) on OCD symptom improvement. The significance level was set at $p < 0.05$ (two-tailed). Different sample sizes may have been used in the analyses due to missing data.

3. Results

3.1. Psychometric properties of the ISI

The mean ISI score at baseline was 7.6 (SD = 5.9). The ISI showed good internal consistency, with a Cronbach's alpha value of 0.85. The PCA revealed a single factor solution. This factor had an eigenvalue of 3.74, accounting for 53.4% of the variance (Supplementary Table S1; Supplementary Fig. S1). Table 2 shows the pattern of correlations between the ISI and other measures of OCD severity, depression, and general functioning, all in the small to medium range.

3.2. Comparison of patients with and without clinical insomnia at baseline

According to previously established cut-offs in young people [23], a total of 81 out of 193 participants (42%) were considered to meet criteria for clinical insomnia at baseline. Demographic and clinical characteristics of the groups with and without insomnia are shown in Table 1. There were no significant between-group differences in terms of sex, age, age at onset of OCD, family history of

Table 2
Correlational analyses between the Insomnia Severity Index and other study measures.

		ISI	CY-BOCS	OCI-CV	CDI-S	CGAS
CY-BOCS	Pearson correlation	0.20[b]	1			
	p	0.005				
	N	193	193			
OCI-CV	Pearson correlation	0.34[b]	0.21[b]	1		
	p	0.000	0.003			
	N	191	191	191		
CDI-S	Pearson correlation	0.45[b]	0.31[b]	0.36[b]	1	
	p	0.000	0.000	0.000		
	N	186	186	184	186	
CGAS	Pearson correlation	−0.19[b]	−0.59[b]	−0.18[a]	−0.39[b]	1
	p	0.010	0.000	0.013	0.000	
	N	193	193	191	186	193
CGI-S	Pearson correlation	0.13	0.74[b]	0.21[b]	0.28[b]	−0.50[b]
	p	0.066	0.000	0.004	0.000	0.000
	N	192	192	190	185	192

CDI-S, Children's Depression Inventory – Short Version; CGAS, Children's Global Assessment Scale; CGI-S, Clinical Global Impression – Severity; CY-BOCS, Children's Yale–Brown Obsessive–Compulsive Scale; ISI, Insomnia Severity Index; OCI-CV, Obsessive Compulsive Inventory – Child Version.
[a] Significant at 0.05.
[b] Significant at 0.01.

OCD, or receipt of previous CBT. However, the presence of any comorbid mental disorder was more frequent in the insomnia group ($p = 0.004$), specifically depression ($p = 0.000$).

Participants with clinical insomnia scored significantly higher on all measures of OCD severity (CY-BOCS, OCI-CV, and CGI-S) and depressive symptoms (CDI-S). They also had lower scores on the CGAS, indicating worse general functioning (Table 1). A higher proportion of patients with insomnia were on pharmacological treatment ($p = 0.047$); this finding was driven by the higher rate of melatonin prescriptions in the insomnia group, compared to the no insomnia group (25.9% vs 4.5%, respectively).

3.3. Treatment characteristics and outcomes of OCD patients with and without insomnia

A total of 143 patients had treatment at the clinic and provided outcome data. Sixty of the 143 treated patients (42%) scored above the ISI cut-off, corresponding to clinical insomnia. All received CBT, and those with insomnia ($N = 60$) received more CBT sessions than those without insomnia ($N = 83$; 14.7 vs 12.0 sessions, respectively; Student's $t = -2.16$, $p = 0.033$).

Forty-five (31.5%) of the participants treated with CBT were also receiving medication for their OCD (mainly serotonin reuptake inhibitors). Of those, eight patients also received treatment with antipsychotics (mainly risperidone and aripiprazole) as an augmentation strategy. There were no significant differences in baseline OCD severity between those who received OCD medication, compared to those who did not (22.96 vs 22.13 on the CY-BOCS, respectively; Student's $t = -1.00$, $p = 0.321$). Those who received medication for their OCD scored similarly on the ISI at baseline to those that did not receive it (7.93 vs 7.53, respectively; Student's $t = -0.35$, $p = 0.730$).

Additionally, 24 of the 143 treated participants (16.8%) received medication for insomnia. Of these, 17 (11.9%) were on melatonin, 11 (7.7%) on antihistamines as sedatives, and one (0.7%) patient was on zolpidem. There were no significant differences in OCD severity at baseline between those who received sedative medication compared to the ones who did not (22.63 *vs* 22.34 on the CY-BOCS, respectively; Student's $t = -0.27$, $p = 0.786$). As expected, patients who received sedative medication scored significantly higher on the ISI (11.79 *vs* 6.82, respectively; Student's $t = -3.91$, $p = 0.000$).

The ISI, CY-BOCS, and OCI-CV mean scores for the groups with and without clinical insomnia at all time-points (baseline, post-treatment, and three-month follow-up) are shown in Table 3.

The mean percentage reduction in the total CY-BOCS score from baseline to post-treatment was 55.4% for the insomnia group and 62.5% in the non-insomnia group; corresponding reductions from baseline to the three-month follow-up were 62.8% and 71.8%, respectively. There was no significant correlation between the ISI score at baseline and the percentage reduction on the CY-BOCS from baseline to post-treatment ($r = -0.09$, $p = 0.294$) or from baseline to the three-month follow-up ($r = -0.15$, $p = 0.136$).

A total of 101 children and adolescents with available data in the three time points were used in a mixed-model ANOVA with time (baseline vs post-treatment vs three-month follow-up) as the within-subjects factor and group (with vs without clinical insomnia) as the between-subjects factor. The model revealed a main effect of time ($F(1.77, 174.88) = 345.61$, $p < 0.001$), indicating a significant reduction in the CY-BOCS total score over time. A significant main group effect ($F(1, 99) = 15.18$, $p < 0.001$) indicated that the insomnia group had more severe OCD symptoms, compared to the non-insomnia group. However, there was no significant time by group interaction effect ($F(1.77, 174.88) = 0.024$, $p = 0.966$), indicating that the two groups improved similarly with treatment (Fig. 1).

In order to investigate potential effects of the medication for insomnia, we next introduced medication for insomnia status as an additional factor in the mixed-model ANOVA. The results indicated significant main effects of time ($F(1.76, 170.43) = 176.76$, $p < 0.001$) and group ($F(1, 97) = 11.51$, $p = 0.001$), but no significant main effect of medication ($F(1, 97) = 0.785$, p=0.378), and no significant time by group ($F(1.76, 170.43) = 0.006$, $p = 0.989$), time by

Table 3
Mean Insomnia Severity Index (ISI), Children's Yale–Brown Obsessive–Compulsive Scale (CY-BOCS), and Obsessive–Compulsive Inventory – Child Version (OCI-CV) scores in treated study patients ($N = 143$) with and without clinical insomnia at baseline, post-treatment, and three-month follow-up.

	Clinical insomnia ($N = 60$)		No clinical insomnia ($N = 83$)		Statistic *t*-test	*p*
	Mean	SD	Mean	SD		
ISI total						
Baseline	13.4	4.0	3.5	2.9	−16.45[b]	0.000
Post-treatment	7.1	5.3	3.2	3.8	−3.97[b]	0.000
3-month follow-up	7.4	4.5	2.1	2.8	−6.56[b]	0.000
CY-BOCS total						
Baseline	23.9	4.1	21.3	4.6	−3.52[b]	0.001
Post-treatment	10.4	5.4	7.8	5.6	−2.85[b]	0.005
3-month follow-up	8.7	5.9	5.9	6.3	−2.27[a]	0.026
CY-BOCS obsessions						
Baseline	11.8	2.2	10.6	2.4	−3.11[b]	0.002
Post-treatment	5.4	2.8	3.9	2.9	−3.16[b]	0.002
3-month follow-up	4.4	3.0	3.0	3.2	−2.33[a]	0.022
CY-BOCS compulsions						
Baseline	12.1	2.1	10.7	2.5	−3.59[b]	0.000
Post-treatment	5.0	2.8	3.9	2.8	−2.36[a]	0.020
3-month follow-up	4.3	3.0	2.9	3.3	−2.09[a]	0.039
OCI-CV						
Baseline	21.5	8.2	16.3	6.9	−4.16[b]	0.000
Post-treatment	11.5	6.4	8.6	7.6	−2.07[a]	0.041
3-month follow-up	11.9	7.9	7.2	6.4	−3.20[b]	0.002

SD, standard deviation.
[a] Significant at 0.05.
[b] Significant at 0.01.

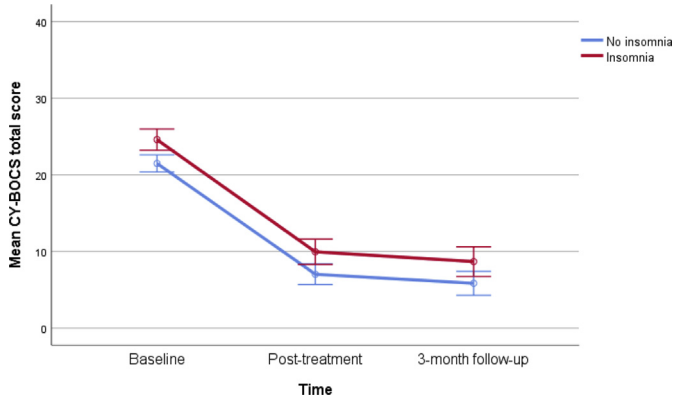

Fig. 1. Mean Children's Yale–Brown Obsessive–Compulsive Scale (CY-BOCS) total scores at each time point (baseline, post-treatment, and three-month follow-up), by insomnia status. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

medication ($F(1.76, 170.43) = 0.892$, $p = 0.400$), or time by group by medication ($F(1.76, 170.43) = 0.077$, $p = 0.904$) interactions.

Because we found significant differences between groups in depressive symptoms at baseline and in the number of sessions received, we ran a second model adjusting for these two variables. When adding these two covariates, the time by group interaction effect remained non-significant ($F(1.76, 170.99) = 0.233$, $p = 0.765$), but the main group effect disappeared ($F(1, 97) = 2.36$, $p = 0.128$).

In addition, we ran a sensitivity analysis excluding all those patients with comorbid ASD who undertook treatment at the clinic ($N = 23$; 16.1%). Results remained unchanged overall (time by group interaction effect: $F(1.71, 137.04) = 0.045$, p=0.936).

The proportion of treatment responders at post-treatment was 78.3% in the insomnia group and 79.3% in the non-insomnia group (Chi-squared = 0.02, $p = 0.893$). Similarly, the proportion of patients classed as being in remission at post-treatment was 56.7% in the insomnia group and 66.3% in the non-insomnia group (Chi-squared = 1.37, $p = 0.243$).

Of note, symptoms of insomnia, as measured by the ISI, improved during the course of the treatment in the whole group (effect of time: $F(1.68, 130.62) = 19.13$, $p < 0.001$). This improvement was more notable in the insomnia group than in the non-insomnia group (time by group interaction effect: $F(1.85, 142.23) = 22.89$, $p < 0.001$) (Table 3). When patients with comorbid ASD were removed, results remained overall unchanged (effect of time: $F(1.64, 110.16) = 15.86$, $p < 0.001$ and time by group interaction effect: $F(1.81, 119.51) = 21.56$, $p < 0.001$).

4. Discussion

This is, to our knowledge, the first study examining the prevalence of insomnia in a large sample of pediatric OCD patients using a self-reported, sleep-specific scale. We found that 42% of children and adolescents with OCD reached the cut-off for clinical insomnia on the ISI. Insomnia was not only common in our sample, but it was also associated with more severe psychopathology and lower general functioning. However, despite having higher OCD symptom severity throughout the study, patients with insomnia improved to a similar degree than patients without insomnia, and similar proportions were classed as treatment responders and remitters by the end of the treatment.

The prevalence of insomnia in children and adolescents with OCD had been examined in a handful of previous studies but their results were difficult to reconcile due to marked methodological differences and the use of a heterogeneous range of composite measures to measure sleep difficulties. For example, Jaspers-Fayer et al., [17] reported that 72% of their OCD participants scored above the cut-off for clinically disturbed sleep on the Sleep Disturbances Scale for Children, but this instrument is a broad sleep measure which captures a range of sleep-related problems, including insomnia. Similarly, Ivarsson et al., [18] found that the prevalence of mild sleep problems was 68.3% in a pediatric OCD sample, although this percentage included symptoms as heterogeneous as nightmares, talking in sleep, or 'sleeping more'. When looking at those sleep problems separately, the percentage of patients experiencing 'trouble sleeping' and 'sleeping less' was 40% and 29.5%, respectively; figures which are closer to those found in our study using a well-validated insomnia instrument. The psychometric properties of the ISI in our sample were excellent, with high internal consistency, a single factor structure, and construct validity.

Young patients with insomnia in our sample were more frequently on pharmacological treatment and had higher rates of comorbid mental disorders (specifically depression). They were more severely affected by obsessive–compulsive symptoms, depressive symptoms, and showed a lower level of global functioning when compared with patients without insomnia. We found a significant positive association between sleep impairment and the severity of obsessive-compulsive symptoms, although the correlation between the ISI and the CY-BOCS was modest. These results are in the same line as previous findings in young [13] and adult patients [37,38] that found positive associations between an objectively measured decrease in total sleep time [13,37] and a subjectively measured disturbance in sleep [38] with OCD severity. As it could be expected, the ISI's strongest correlation was with depressive symptoms, as measured by the CDI-S, despite the fact that this measure does not include any sleep-specific items.

Unlike Ivarsson et al. [18], who concluded that sleep problems might have a negative impact on CBT efficacy, we found that patients with insomnia were just as likely to respond to developmentally appropriate CBT as were patients without insomnia. The results remained unaltered after adjusting for baseline depression severity, number of CBT sessions, prescription of drugs for insomnia, and in a sensitivity analysis excluding patients with comorbid ASD who had received a specific sleep hygiene module as part of their treatment package.

There are some important differences between our study and that of Ivarsson et al., [18] that are worth considering when interpreting the results of both studies. First, Ivarsson et al., [18] reanalyzed data from a clinical trial evaluating CBT intervention for OCD using a strict protocol. Conversely, our study was conducted in a naturalistic setting where the multidisciplinary team had more flexibility to offer additional interventions, such as brief sleep hygiene advice or medication (including sedatives), or to deliver a larger number of CBT sessions (as was the case for the group with clinical insomnia), as required by the individual patient care plan. Thus, it may still be the case that insomnia interferes with the efficacy of pure CBT, but its detrimental effects on learning can be minimized if the treatment is delivered by a specialist multidisciplinary team in a naturalistic setting.

In our study, insomnia symptoms also improved significantly after treatment, although we cannot be sure whether this was due to the improvement in the OCD symptoms, additional interventions such as sleep hygiene advice or sleep medication, or a combination of these approaches. However, it is important to note that only a small proportion of cases in our sample (16.8%) received medication for their sleep problems.

This study addresses an important gap in the literature but it is not without limitations. First, the diagnosis of insomnia was made using the validated cut-off of a self-reported insomnia measure

[22,23], but structured diagnostic interviews for insomnia were not performed. Future studies would benefit from more structured assessment of diagnostic criteria for insomnia. Nonetheless, the clearly higher rate of sleep medication use in the insomnia group provided some concurrent validity to our grouping. Second, this study was conducted in a specialist clinic receiving referrals for relatively severe and/or treatment-refractory cases and, hence, the findings may not be generalizable to other samples and settings. However, many similarities were noted between the sample characteristics described here and in the previous literature. Third, results regarding the improvement in sleep symptoms should be interpreted cautiously due to the lack of control over potential sleep hygiene recommendations (not explicitly included in the OCD protocol) that the therapists could have provided during the treatment.

5. Conclusions

Insomnia is common among youth with OCD and its presence is associated with more severe obsessive–compulsive and depressive symptomatology. Yet, in our sample, insomnia did not seem to interfere with response to multimodal treatment for OCD, it should still be routinely evaluated and managed alongside the treatment of OCD.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2018.12.024.

Conflict of interest

D. Mataix-Cols and L. Fernández de la Cruz receive royalties for contributing articles to UpToDate, Wolters Kluwer Health. L. Sevilla-Cermeño was supported by a Fellowship from the Alicia Koplowitz Foundation. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decisions to submit the manuscript for publication.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.12.024.

References

[1] Vriend J, Davidson F, Rusak B, et al. Emotional and cognitive impact of sleep restriction in children. Sleep Med Clin 2015;10(2):107–15.
[2] Gruber R, Laviolette R, Deluca P, et al. Short sleep duration is associated with poor performance on IQ measures in healthy school-age children. Sleep Med 2010;11(3):289–94.
[3] Touchette E, Petit D, Seguin JR, et al. Associations between sleep duration patterns and behavioral/cognitive functioning at school entry. Sleep 2007;30(9):1213–9.
[4] Ramtekkar U, Ivanenko A. Sleep in children with psychiatric disorders. Semin Pediatr Neurol 2015;22(2):148–55.
[5] Liu X, Buysse DJ, Gentzler AL, et al. Insomnia and hypersomnia associated with depressive phenomenology and comorbidity in childhood depression. Sleep 2007;30(1):83–90.
[6] DeVincent CJ, Gadow KD, Delosh D, et al. Sleep disturbance and its relation to DSM-IV psychiatric symptoms in preschool-age children with pervasive developmental disorder and community controls. J Child Neurol 2007;22(2):161–9.
[7] Alfano CA, Ginsburg GS, Kingery JN. Sleep-related problems among children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry 2007;46(2):224–32.
[8] Palmer CA, Alfano CA. Sleep architecture relates to daytime affect and somatic complaints in clinically anxious but not healthy children. J Clin Child Adolesc Psychol 2017;46(2):175–87.
[9] Taylor S. Early versus late onset obsessive-compulsive disorder: evidence for distinct subtypes. Clin Psychol Rev 2011;31(7):1083–100.
[10] Nota JA, Sharkey KM, Coles ME. Sleep, arousal, and circadian rhythms in adults with obsessive-compulsive disorder: a meta-analysis. Neurosci Biobehav Rev 2015;51:100–7.
[11] Paterson JL, Reynolds AC, Ferguson SA, et al. Sleep and obsessive-compulsive disorder (OCD). Sleep Med Rev 2013;17(6):465–74.
[12] Coles ME, Schubert JR, Sharkey KM. Delayed bedtimes and obsessive-compulsive symptoms. Behav Sleep Med 2012;10(4):258–65.
[13] Alfano CA, Kim KL. Objective sleep patterns and severity of symptoms in pediatric obsessive compulsive disorder: a pilot investigation. J Anxiety Disord 2011;25(6):835–9.
[14] Rapoport J, Elkins R, Langer DH, et al. Childhood obsessive-compulsive disorder. Am J Psychiatry 1981;138(12):1545–54.
[15] Ivarsson T, Larsson B. Sleep problems as reported by parents in Swedish children and adolescents with obsessive-compulsive disorder (OCD), child psychiatric outpatients and school children. Nord J Psychiatr 2009;63(6):480–4.
[16] Storch EA, Murphy TK, Lack CW, et al. Sleep-related problems in pediatric obsessive-compulsive disorder. J Anxiety Disord 2008;22(5):877–85.
[17] Jaspers-Fayer F, Lin SY, Belschner L, et al. A case-control study of sleep disturbances in pediatric obsessive-compulsive disorder. J Anxiety Disord 2018;55:1–7.
[18] Ivarsson T, Skarphedinsson G. Sleep problems and cognitive behavior therapy in pediatric obsessive-compulsive disorder have bidirectional effects. J Anxiety Disord 2015;30:28–33.
[19] World Health Organization. International statistical classification of diseases, 10th revision (ICD-10). Geneva, Switzerland: World Health Organization; 1992.
[20] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington,VA: American Psychiatric Publishing; 2013.
[21] Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatr 1998;59(Suppl 20):22–33. quiz 4-57.
[22] Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2(4):297–307.
[23] Chung KF, Kan KK, Yeung WF. Assessing insomnia in adolescents: comparison of insomnia severity Index, Athens insomnia scale and sleep quality Index. Sleep Med 2011;12(5):463–70.
[24] Kanstrup M, Holmstrom L, Ringstrom R, et al. Insomnia in paediatric chronic pain and its impact on depression and functional disability. Eur J Pain 2014;18(8):1094–102.
[25] Scahill L, Riddle MA, McSwiggin-Hardin M, et al. Children's Yale–Brown obsessive compulsive scale: reliability and validity. J Am Acad Child Adolesc Psychiatry 1997;36(6):844–52.
[26] Gallant J, Storch EA, Merlo LJ, et al. Convergent and discriminant validity of the children's Yale-Brown obsessive compulsive scale-symptom checklist. J Anxiety Disord 2008;22(8):1369–76.
[27] Foa EB, Coles M, Huppert JD, et al. Development and validation of a child version of the obsessive compulsive inventory. Behav Ther 2010;41(1):121–32.
[28] Allgaier AK, Fruhe B, Pietsch K, et al. Is the Children's Depression Inventory Short version a valid screening tool in pediatric care? A comparison to its full-length version. J Psychosom Res 2012;73(5):369–74.
[29] Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont) 2007;4(7):28–37.
[30] Guy W. Assessment manual for psychopharmacology, revised. Washington DC: US Government Printing Office; 1976.
[31] Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). Arch Gen Psychiatr 1983;40(11):1228–31.
[32] Mataix-Cols D, Fernandez de la Cruz L, Nordsletten AE, et al. Towards an international expert consensus for defining treatment response, remission, recovery and relapse in obsessive-compulsive disorder. World Psychiatr 2016;15(1):80–1.
[33] Turner CM, Mataix-Cols D, Lovell K, et al. Telephone cognitive-behavioral therapy for adolescents with obsessive-compulsive disorder: a randomized controlled non-inferiority trial. J Am Acad Child Adolesc Psychiatry 2014;53(12):1298–12307 e2.
[34] Mataix-Cols D, Turner C, Monzani B, et al. Cognitive-behavioural therapy with post-session D-cycloserine augmentation for paediatric obsessive-compulsive disorder: pilot randomised controlled trial. Br J Psychiatry 2014;204(1):77–8.
[35] Russell AJ, Jassi A, Fullana MA, et al. Cognitive behavior therapy for comorbid obsessive-compulsive disorder in high-functioning autism spectrum disorders: a randomized controlled trial. Depress Anxiety 2013;30(8):697–708.
[36] Cohen J. Statistical power analyses for the behavioral sciences. (revised edition. New York: Academis Press; 1977.
[37] Robinson D, Walsleben J, Pollack S, et al. Nocturnal polysomnography in obsessive-compulsive disorder. Psychiatr Res 1998;80(3):257–63.
[38] Cox RC, Olatunji BO. Sleep disturbance and obsessive-compulsive symptoms: results from the national comorbidity survey replication. J Psychiatr Res 2016;75:41–5.

3.2 STUDY 3: Prevalence and impact of insomnia in children and adolescents with body dysmorphic disorder undergoing multimodal specialist treatment

Reference: Sevilla-Cermeño L, Rautio D, Andrén P, Hillborg M, Siveberg-Morse M, Lahera G, et al. Prevalence and impact of insomnia in children and adolescents with body dysmorphic disorder undergoing multimodal specialist treatment. Eur Child Adolesc Psychiatry. 2020;29(9):1289-1299.

Background: Paediatric BDD is a disabling psychiatric disorder which is challenging to treat. This study aimed to establish the prevalence of insomnia in paediatric patients with BDD and explore its impact on the clinical presentation and treatment outcomes in this patient group.

Methods: Sixty-six children and adolescents with BDD meeting ICD-10 and DSM-5 criteria for BDD, consecutively referred to a specialist clinic, completed a range of clinical measures, including the Yale-Brown Obsessive-Compulsive Scale Modified for BDD–Adolescent Version (BDD-YBOCS-A) and the Insomnia Severity Index (ISI). Patients with clinical insomnia (ISI score ≥9) were compared to the rest of the sample on socio-demographic and clinical features. Chi-square tests were used for comparison of categorical variables and Student's t-tests for continuous variables. Fifty-six patients who received multimodal treatment (CBT and, in 57.1% cases, also medication) were re-assessed at post-treatment. A mixed-model ANOVA was performed to compare treatment outcomes between the insomnia *vs.* no insomnia groups, adjusting for comorbid depression at baseline and age at assessment as covariates. Finally, chi-square tests were

used to compare response and remission rates between the insomnia and the non-insomnia group.

Results: According to the ISI, 48.5% (32/66) of the sample qualified as having insomnia at baseline and the mean ISI score for the sample was 9.2 (SD=6.2). These participants showed significantly higher self-reported BDD symptom severity, specifically avoidance behaviour, more depressive symptoms, and more functional impairment in daily activities, when compared to patients without insomnia. In the subsample of treated patients, individuals with insomnia improved less on the BDD-YBOCS-A than those without insomnia, although the difference did not reach statistical significance. The rates of responders and remitters were lower in the insomnia group, compared to the non-insomnia group.

Conclusions: Insomnia is common in paediatric BDD and is associated with higher scores on self-reported measures of BDD symptom severity, higher rates of comorbid depression, and worse functioning in daily activities. Furthermore, youth experiencing BDD and insomnia may benefit from multimodal treatment to a lesser extent than those without insomnia. If these results are replicated in larger samples, treatment refinements for paediatric BDD could include specific modules to directly target insomnia.

European Child & Adolescent Psychiatry
https://doi.org/10.1007/s00787-019-01442-1

ORIGINAL CONTRIBUTION

Prevalence and impact of insomnia in children and adolescents with body dysmorphic disorder undergoing multimodal specialist treatment

Laura Sevilla-Cermeño[1,2,3] · Daniel Rautio[1,2] · Per Andrén[1,2] · Maria Hillborg[2] · Maria Silverberg-Morse[2] · Guillermo Lahera[3] · David Mataix-Cols[1,2] · Lorena Fernández de la Cruz[1,2]

Received: 19 April 2019 / Accepted: 12 November 2019

Abstract

Pediatric body dysmorphic disorder (BDD) is challenging to treat. This study aimed to establish the prevalence of insomnia in youth with BDD and explore its impact on clinical outcomes. Sixty-six children and adolescents with BDD consecutively referred to a specialist clinic completed a range of clinical measures, including the Yale-Brown Obsessive–Compulsive Scale Modified for BDD-Adolescent Version (BDD-YBOCS-A), and the Insomnia Severity Index (ISI). Patients with clinical insomnia (ISI score ≥ 9) were compared to the rest of the sample on socio-demographic and clinical features. Fifty-six patients who received multimodal treatment were re-assessed post-treatment. A mixed-model ANOVA was performed to compare treatment outcomes between the insomnia vs. no insomnia groups, and Chi-squared tests were used to compare response and remission rates. According to the ISI, 48% of the sample qualified as having insomnia at baseline. These participants showed significantly higher self-reported BDD symptom severity, more depressive symptoms, and more functional impairment in daily activities. Patients with insomnia improved less on the BDD-YBOCS-A than those without insomnia, although the difference did not reach statistical significance. The rates of responders and remitters were lower in the insomnia group, compared to the non-insomnia group. Insomnia is prevalent in pediatric BDD, and is associated with more severe psychopathology and worse functioning in daily activities. Furthermore, youth experiencing BDD and insomnia may benefit from multimodal treatment to a lesser extent than those without insomnia. If these results are replicated in larger samples, treatment refinements for pediatric BDD could include specific modules to directly target insomnia.

Keywords Body dysmorphic disorder · Insomnia · Cognitive-behavior therapy · Children · Adolescents

Introduction

Body Dysmorphic Disorder (BDD) is a psychiatric disorder characterized by a recurrent preoccupation with perceived defects in physical appearance that are not observable or appear minimal to others. Excessive repetitive behaviors (e.g., mirror checking) or mental acts (e.g., comparing own appearance with that of others) are often performed in response to the appearance concerns [1]. The estimated prevalence of BDD in both adult and adolescent community samples is approximately 2% [2, 3]. The onset of BDD is usually during adolescence [4, 5]. BDD in young people is associated with poor psychosocial functioning and low academic performance, with high rates of school abandonment [6, 7]. Furthermore, adolescents with BDD have been reported to have high levels of suicidality [4].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00787-019-01442-1) contains supplementary material, which is available to authorized users.

✉ Laura Sevilla-Cermeño
laura.sevilla.cermeno@ki.se

[1] Karolinska Institutet, Department of Clinical Neuroscience, Child and Adolescent Psychiatry Research Center, Gävlegatan 22 (Entré B), Floor 8, 113 30 Stockholm, Sweden

[2] Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden

[3] Departamento de Medicina y Especialidades Médicas, Universidad de Alcalá, Madrid, Spain

Published online: 23 November 2019

Cognitive-behavior therapy (CBT) is a moderately effective treatment for pediatric BDD. In one wait-list controlled trial, the between-group effect size was large (Cohen's $d = 1.13$) at post-treatment and the response rate was 40% [8]. In the same trial, the effects of CBT were also durable over time (effect size = 1.70 at 12-month follow-up; response rate = 50%) [9]. CBT is recommended by clinical guidelines as the first-line treatment in children and adolescents with BDD [10]. If CBT is declined, not available, or the patient does not engage in it, a selective serotonin reuptake inhibitor (SSRI) may be considered [10]. However, while SSRIs are effective in adults with BDD, medication studies on pediatric patients are lacking. Importantly, although CBT is effective at the group level, a significant percentage of patients (46–60%) do not respond sufficiently to treatment [8, 11]. Hence, it is paramount to identify factors that could be hampering treatment adherence or response to CBT in patients with BDD to further improve outcomes in this vulnerable group.

Insomnia is a prevalent condition amongst youth [12, 13] and correlates with negative developmental outcomes, such as impaired emotional and behavioral regulation [14, 15]. The presence of insomnia has been linked to more severe psychopathology and worse general functioning in a variety of mental disorders in youth [16–18]. Additionally, reduced sleep has also been associated with impaired cognitive functioning, which may lead to impaired learning [19, 20]. As learning is a key aspect of CBT, poor sleep could potentially interfere with this treatment, reducing its overall efficacy. In other childhood psychiatric disorders, such as depression or bipolar disorder, there is solid evidence to indicate that sleep disturbances are associated with poorer treatment response and/or higher probabilities of relapse after remission [21, 22]. Conversely, interventions targeted at improving sleep have documented positive effects on various forms of psychopathology [23] and might even enhance the effects of CBT [24].

To our knowledge, to date, there have been no studies focusing on the prevalence of sleep problems in pediatric BDD and on whether these may interfere with evidence-based treatment. In an attempt to fill this gap in the literature, we report on one of the largest clinical samples of well-characterized youth with BDD, treated at a specialist obsessive–compulsive disorder (OCD) and related disorders clinic in Stockholm, Sweden. The aims of the study were threefold. First, we aimed to establish the prevalence of self-reported clinical insomnia in youth with BDD. Second, we aimed to compare the demographic and clinical characteristics of BDD patients with and without clinical insomnia. Finally, we aimed to explore whether insomnia had a negative effect on the response to multimodal treatment, including protocol-driven CBT and concurrent medication (when indicated), in this patient group.

Methods

Setting and participants

Participants were 66 children and adolescents meeting DSM-5 criteria for BDD [1] consecutively referred to a specialist pediatric OCD and related disorders outpatient clinic in Stockholm, Sweden, between January 2015 and March 2019. For a detailed description of the clinical setting, see Sevilla-Cermeño et al. [17]. The diagnoses were confirmed following a 3-h first assessment by a multidisciplinary clinical team, which included a full anamnesis and developmental history, full psychopathological screening with the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) [25], supplemented with additional modules for OCD and related disorders, and the Yale-Brown Obsessive–Compulsive Scale Modified for BDD-Adolescent Version (BDD-YBOCS-A) [26]. Socio-demographic information from the patients and their parents/caregivers was also gathered at this point. A series of self-reported measures covering a range of psychiatric conditions, including insomnia, were collected via an online platform (see "Measures" section below).

After the initial assessment, patients were offered treatment at our clinic, referred back to their local teams, or referred to more appropriate services elsewhere. Fifty-six (84.8%) of the sixty-six BDD patients received treatment for BDD at the clinic during the above-mentioned period.

All patients and their parents/legal guardians provided written consent to participate in the current study, which received ethical approval from the Regional Ethical Review Board in Stockholm (reference number 2015/1977-31/4).

Measures

The Swedish language versions of the following measures were administered to all participants ($N = 66$) at baseline and, to the patients who received treatment at the clinic ($n = 56$), also at post-treatment.

Clinician-administered measures

The *BDD-YBOCS-A* is a clinician-administered semi-structured interview which is considered the gold-standard measure to rate the severity of BDD symptoms [26]. It comprises 12 Likert-type items ranging from 0 to 4: five severity items for both obsessions and compulsions and two further items to measure degree of insight and avoidant behavior. The total BDD severity score ranges from 0 to 48 [26]. The BDD-YBOCS-A has good psychometric properties, including strong internal consistency, good reliability, good convergent

and discriminant validity, and sensitivity to change [27]. In our sample, the BDD-YBOCS-A had high internal consistency (Cronbach's alpha = 0.84). As is standard in the field, *treatment response* was defined as a 30% or greater drop on the BDD-YBOCS-A from baseline to post-treatment, and *full or partial remission* as a total score ≤ 16 on the BDD-YBOCS-A at post-treatment [27, 28].

The *Clinical Global Impression-Severity* (CGI-S) is a single-item clinician-rated measure of symptom severity [29]. The item is rated on a seven-point scale. The CGI-S has demonstrated good concurrent validity and sensitivity to change [30].

The *Children´s Global Assessment Scale* (CGAS) is a single-item clinician-rated measure of the global functioning of a child or an adolescent during a specific period of time. Scores range from 1 (more disabled) to 100 (best functioning) and it has shown good psychometric properties with high reliability and both discriminant and concurrent validity [31].

All the above-mentioned clinician ratings were based on both the children and the parents report on the day of the assessment.

Self- or parent-administered measures

The *Insomnia Severity Index* (ISI) is a self-reported instrument measuring insomnia. It is composed of seven Likert-type items with a total score that ranges from 0 to 28 [32]. The Swedish translation of the ISI, which has been modified for use amongst youth, was used in this study [33]. This version has shown excellent psychometric properties with high internal consistency, construct validity, and a single factor structure in a clinical sample of pediatric patients with OCD [17]. The optimal cut-off score for detecting clinical insomnia in youths has been established to be 9 [34]. Using this established cut-off, our BDD sample was categorized into a clinical insomnia group (ISI scores ≥ 9) and a non-clinical insomnia group (ISI scores < 9).

The *Appearance Anxiety Inventory* (AAI) is a self-reported measure that focuses on the cognitive and behavioral processes that are characteristic to BDD [35]. It comprises ten items, with a total score ranging from 0 to 40, and includes two subscales: one measuring avoidance and the other measuring threat monitoring [35].

Depressive symptoms were assessed by the *Children's Depression Inventory-Short Version* (CDI-S), a 10-item self-reported instrument examining the presence and severity of depressive symptoms in pediatric patients [36] and by the parent-reported version of the *Short Mood and Feeling Questionnaire (SMFQ-P),* a 13-item measure that evaluates mood in youths [37]. Both instruments have excellent psychometric properties.

The *Work, and Social Adjustment Scale-Youth Version* (WSAS-Y) is a short, self-reported instrument consisting of five items rated on a nine-point Likert scale. It assesses the degree of functional impairment in five areas, namely school, daily situations, social activities, leisure activities, and relationships [38]. The WSAS-Y is based on the original WSAS for adults [39] and has excellent psychometric properties [38]. The WSAS-Y also has a parent-rated version (WSAS-P) [38].

Treatment

All patients treated at the specialist clinic ($n = 56$) received individual CBT delivered by clinical psychologists with extensive experience in the treatment of BDD cases. Of these, 32 were additionally prescribed medication for their BDD when deemed clinically appropriate (see Results section below). The CBT was protocol-driven, based on the manual developed by Mataix-Cols et al. for their trial [8]. Based on the experience in this adolescent BDD trial [8], the manual has undergone continued development by our team, in collaboration with the BDD team at the Maudsley Hospital, London. The updated version of the manual used in this study involves more therapy sessions than the original (typically up to 20 rather than 14 sessions). The developmentally tailored protocol is heavily based on exposure with response prevention (ERP) strategies. Since insight in this patient group tends to be low, the therapists try to promote motivation and engagement with ERP, often including motivational interviewing approaches to address the patients' ambivalence. The treatment includes varying degrees of parental involvement, depending on the individual case formulation. In brief, the protocol consists of the following core elements: sessions 1 to 2–3 focus on psychoeducation about BDD and anxiety, perception, self-focused attention, and on the development of an ERP hierarchy; sessions 3–4 to 18 primarily focus on graded ERP (both therapist-assisted in vivo ERP and as homework assignments between sessions); and sessions 19 and 20 include strategies for relapse prevention and maintenance of the treatment gains. The protocol also includes optional modules, which are only used when required: these include mirror re-training, cognitive work, and attention re-training, amongst others (see Ref. [8]). Sessions last approximately 1 h and are usually conducted weekly, although complex patients are often offered more intensive approaches (e.g., several hours per day/week and home visits).

Statistical analyses

SPSS version 25.0 for Windows software was used to analyze the data. Student's *t* tests were used for between-group comparisons of continuous variables and Chi-squared tests

for categorical variables. A mixed-model analysis of variance (ANOVA) was carried out to test for a differential effect of clinical insomnia on responsiveness to treatment. Response and remission rates for the two groups were compared using Chi-squared tests. All statistical tests were two-tailed. Statistical significance was set at $p < 0.05$.

Results

Participant characteristics at baseline

The sample ($N = 66$) consisted predominantly of girls ($n = 56$; 84.8%), with a mean age of 15.4 years (SD = 1.5; range 10–17) at baseline. The self-reported mean age of onset of their BDD was 12.9 years (SD = 1.7; range 8–17). The mean BDD-YBOCS-A score was 30.2 (SD = 5.0), reflecting moderate BDD symptom severity. A high proportion of the sample ($n = 51$; 77.3%) had a comorbid psychiatric disorder. The most common comorbid disorder was depression ($n = 31$; 47.0%).

Prevalence of insomnia and characteristics of BDD patients with and without clinical insomnia at baseline

The mean ISI score for the sample was 9.2 (SD = 6.2). A total of 32 out of 66 participants with BDD (48.5%) scored above the established cut-off for clinical insomnia [34] at baseline. Table 1 shows the demographic and clinical characteristics of the groups with and without insomnia. Participants with clinical insomnia were slightly older at

Table 1 Comparison of demographic and clinical characteristics of patients with and without clinical insomnia at baseline ($N = 66$)

	Clinical insomnia ($n = 32$)		No clinical insomnia ($n = 34$)		Statistics	
	Mean	SD	Mean	SD	Student's *t*	*p*
Age at assessment	15.8	1.2	15.0	1.7	− 2.16	0.034*
Age of BDD onset ($n = 59$)	13.2	1.5	12.6	1.9	− 1.27	0.211
	N	%	*N*	%	Chi-square	*p*
Gender						
Girls	30	93.8	26	76.5	4.01	0.135
Boys	2	6.3	7	20.6	4.01	0.135
Other	0	0.0	1	2.9	4.01	0.135
Family history of BDD	1	3.1	6	17.6	–	0.106[a]
Any comorbid mental disorder	26	81.3	25	73.5	0.56	0.454
Depression	20	62.5	11	32.4	6.02	0.014*
Anxiety disorders	6	18.8	12	35.3	2.28	0.131
OCD	8	25.0	4	11.8	1.94	0.164
ADHD	4	12.5	5	14.7	–	1.000[a]
ASD	4	12.5	4	11.8	–	1.000[a]
Eating disorders	1	3.1	2	5.9	–	1.000[a]
Tourette syndrome	1	3.1	0	0	–	0.485[a]
Hypochondriasis	0	0.0	1	2.9	–	1.000[a]
Previous CBT treatment	11	34.4	15	44.1	0.66	0.418
On pharmacological treatment	14	43.8	15	44.1	0.00	0.976
SSRI	10	31.3	11	32.4	0.01	0.923
Other Antidepressants	1	3.1	3	8.8	–	0.614[a]
Antipsychotics	1	3.1	2	5.9	–	1.000[a]
Antihistamines	6	18.8	4	11.8	–	0.505[a]
Melatonin	3	9.4	4	11.8	–	1.000[a]
ADHD medication	3	9.4	2	5.9	–	0.668[a]
Buspirone	0	0.0	3	8.8	–	0.239[a]

ADHD attention-deficit/hyperactivity disorder, *ASD* autism spectrum disorders, *OCD* obsessive–compulsive disorder, *SD* standard deviation, *SSRI* selective serotonin reuptake inhibitors

*Significant at 0.05; **significant at 0.01

[a]Fisher's test

assessment than the participants without clinical insomnia (15.8 vs. 15.0 years, respectively; $p = 0.034$). Both groups were comparable in terms of gender, age at onset of BDD, family history of BDD, receipt of previous CBT, or prescription of any pharmacological treatment. The presence of comorbid depression was more frequent in the insomnia group, compared to those without insomnia (62.5% vs. 32.4%, respectively; $p = 0.014$), while the proportions of other comorbidities were not statistically different between groups.

There were no between-group differences on the BDD-YBOCS-A or on other clinical measures, with the exception of the AAI, the WSAS-Y, and the WSAS-P (Table 2). Participants with clinical insomnia scored significantly higher on the AAI total score and the AAI avoidance subscale at baseline, indicating more severe self-reported BDD symptomatology. They also had higher scores on both WSAS scales, indicating worse self-reported and parent-reported functioning in daily activities. Specifically, BDD participants with insomnia scored significantly higher on the WSAS-Y item regarding family and other relationships, and on the WSAS-P item regarding everyday situations (Table 2).

Treatment characteristics of BDD patients with and without insomnia

A total of 56 patients underwent CBT treatment at the clinic. There were no significant differences on any baseline clinical measures between those participants who were treated at the clinic and those who were not (Supplementary Table 1). The mean number of sessions received was 17.3

Table 2 Comparison of clinical measures of patients with and without clinical insomnia at baseline ($N = 66$)

	Clinical insomnia ($n = 32$)		No clinical insomnia ($n = 34$)		Statistics	
	Mean	SD	Mean	SD	Student's *t*	*p*
Insomnia measure						
ISI total	14.3	4.6	4.4	2.3	− 10.98	0.000**
BDD measures						
BDD-YBOCS-A total	30.3	5.0	30.2	5.1	− 0.06	0.953
BDD-YBOCS-A obsessions	13.0	2.4	12.8	2.3	− 0.41	0.687
BDD-YBOCS-A compulsions	12.6	2.5	12.9	2.3	− 0.54	0.593
AAI total ($n = 63$)	29.9	6.5	25.7	7.6	− 2.35	0.026*
AAI avoidance	19.7	4.1	16.1	5.4	− 3.02	0.004**
AAI threat monitoring	10.2	3.3	9.7	3.3	− 0.69	0.494
Other clinical measures						
CDI-S ($n = 44$)	11.9	4.3	10.6	4.7	− 0.95	0.351
SMFQ-P	15.6	6.3	15.1	5.9	− 0.38	0.708
CGI-S	4.8	0.6	4.7	0.6	− 1.04	0.302
CGAS	45.3	7.7	47.3	4.6	1.30	0.199
WSAS-Y total	23.2	6.9	18.9	4.9	− 2.94	0.005**
WSAS-Y school	6.3	1.5	5.7	1.8	− 1.50	0.138
WSAS-Y everyday situations	3.4	2.6	2.3	1.9	− 1.87	0.066
WSAS-Y social activities	5.8	2.0	5.4	1.8	− 0.86	0.396
WSAS-Y leisure time	2.5	2.4	1.6	1.9	− 1.66	0.102
WSAS-Y family and relationships	5.2	2.0	3.9	2.1	− 2.69	0.009**
WSAS-P total	23.8	7.0	20.3	6.4	− 2.10	0.040*
WSAS-P school	6.6	1.6	6.1	2.2	− 1.19	0.237
WSAS-P everyday situations	4.1	2.1	3.0	2.2	− 2.05	0.045*
WSAS-P social activities	5.6	2.1	5.6	2.2	− 0.01	0.994
WSAS-P leisure time	2.6	2.2	1.6	2.2	− 1.73	0.088
WSAS-P family and relationships	5.0	2.3	4.1	2.3	− 1.50	0.131

AAI Appearance Anxiety Inventory, *BDD-YBOCS* Yale-Brown Obsessive–Compulsive Scale Modified for BDD-Adolescent version, *CDI-S* Children's Depression Inventory-Short Version, *CGAS* Children's Global Assessment Scale, *CGI-S* Clinical Global Impression-Severity, *ISI* Insomnia Severity Index, *SMFQ-P* Short Mood and Feeling Questionnaire, *WSAS-Y* Work, Social and Adjustment Scale-Youth Version, *WSAS-P* Work, Social and Adjustment Scale-Parent Version

*Significant at 0.05; **significant at 0.01

(SD = 12.4; range 4–80). Twenty-four of the treated patients (42.9%) scored above the ISI cut-off for clinical insomnia. There were no significant differences between the insomnia ($n = 24$) and the non-insomnia ($n = 32$) groups in terms of the total number of CBT sessions received (16.5 vs. 17.9 sessions, respectively; Student's $t = 0.41$, $p = 0.687$).

Thirty-two (57.1%) of the participants received medication for their BDD alongside the CBT treatment. Of those, 26 patients received treatment with an SSRI, one patient with an antipsychotic (aripiprazole), and five patients received an SSRI in combination with an antipsychotic (aripiprazole in all five cases). There were no differences in BDD symptom severity between those receiving vs. those not receiving medication (30.7 vs. 30.3 on the BDD-YBOCS-A, respectively; Student's $t = –0.31$, $p = 0.762$). Similarly, the comparison between the percentage of patients on medication in the insomnia group (54.2%) and in the non-insomnia group (59.4%) did not reveal significant differences (Chi-square = 0.15, $p = 0.697$).

Additionally, 15 of the 56 treated participants (26.8%) received medication for insomnia. Of those, nine were prescribed melatonin, four received antihistamines as hypnotics, and two patients took melatonin in combination with an antihistamine. Patients receiving hypnotic medication showed equally severe BDD symptoms at baseline when compared to the ones who did not (31.7 vs 30.1 on the BDD-YBOCS-A, respectively; Student's $t = –1.01$, $p = 0.296$). Of note, the percentage of patients who received any hypnotic drugs in the insomnia group (29.2%) and in the non-insomnia group (25%) was not significantly different (Chi-square = 0.12, $p = 0.728$).

Treatment outcomes in BDD patients with and without clinical insomnia

Scores for the ISI, the BDD-YBOCS-A, the AAI, and other clinical measures in the groups with and without clinical insomnia at baseline and post-treatment are shown in Tables 3 and 4.

A mixed-model ANOVA with a within-subjects factor of time (baseline vs. post-treatment) and a between-subjects factor of group (with vs. without clinical insomnia) was performed. Because the groups differed at baseline regarding the presence of comorbid depression and the mean age at the time of assessment, we added comorbid depression (coded as present/absent) and age at assessment as covariates in

Table 3 Insomnia- and body dysmorphic disorder-specific severity scores at baseline and post-treatment, by insomnia status ($N = 56$)

	Clinical insomnia ($n = 24$)		No clinical insomnia ($n = 32$)		Statistic *t* test	*p*
	Mean	SD	Mean	SD		
ISI total						
Baseline	14.5	4.8	4.4	2.4	– 9.52	0.000**
Post-treatment	11.2	6.6	3.5	4.5	– 4.24	0.000**
BDD-YBOCS total						
Baseline	31.2	5.0	30.1	5.3	– 0.79	0.432
Post-treatment	15.5	9.6	11.3	6.9	– 1.91	0.062
BDD-YBOCS obsessions						
Baseline	13.3	2.3	12.8	2.3	– 0.87	0.390
Post-treatment	6.9	4.0	5.3	3.0	– 1.75	0.086
BDD-YBOCS compulsions						
Baseline	13.0	2.7	12.8	2.4	– 0.23	0.820
Post-treatment	6.4	4.6	4.6	3.3	– 1.64	0.110
AAI Total						
Baseline	30.5	6.7	25.5	7.6	– 2.46	0.017*
Post-treatment	17.4	12.2	12.0	8.7	– 1.71	0.095
AAI avoidance						
Baseline	19.9	3.9	15.9	5.4	– 3.12	0.003**
Post-treatment	10.8	7.8	8.0	5.7	– 1.39	0.172
AAI threat monitoring						
Baseline	10.6	3.5	9.7	3.4	– 1.00	0.324
Post-treatment	6.6	4.6	4.0	3.6	– 2.06	0.046*

AAI Appearance Anxiety Inventory, *BDD-YBOCS-A* Yale-Brown Obsessive–Compulsive Scale Modified for BDD-Adolescent version, *ISI* Insomnia Severity Index, *SD* standard deviation

*Significant at 0.05; **significant at 0.01

Table 4 Depression and general functioning scores at baseline and post-treatment, by insomnia status ($N=56$)

	Clinical insomnia ($n=24$)		No clinical insomnia ($n=32$)		Statistic *t* test	*p*
	Mean	SD	Mean	SD		
CDI-S						
Baseline	11.9	4.5	10.6	4.7	− 0.89	0.377
Post-treatment	8.6	5.3	6.0	4.3	− 1.75	0.087
SMFQ-P						
Baseline	15.7	6.2	15.5	5.8	− 0.13	0.898
Post-treatment	10.7	7.7	8.4	5.9	− 1.16	0.254
CGI-S						
Baseline	4.8	0.7	4.6	0.6	− 1.36	0.180
Post-treatment	3.0	1.4	2.0	1.1	− 2.86	0.006**
CGAS						
Baseline	43.8	7.7	47.2	4.7	2.02	0.048*
Post-treatment	52.9	7.4	59.6	9.7	2.40	0.020*
WSAS-Y						
Baseline	24.1	6.2	19.0	5.0	− 3.41	0.001**
Post-treatment	13.6	7.4	8.8	6.2	− 2.32	0.025*
WSAS-P						
Baseline	23.7	7.1	20.4	6.5	− 1.81	0.075
Post-treatment	16.8	8.0	11.9	7.4	− 2.13	0.038*

CDI-S Children's Depression Inventory-Short Version, *CGAS* Children's Global Assessment Scale, *CGI-S* Clinical Global Impression-Severity, *SMFQ-P* Short Mood and Feeling Questionnaire, *WSAS-Y* Work, Social and Adjustment Scale-Youth Version, *WSAS-P* Work, Social and Adjustment Scale-Parent Version

*Significant at 0.05; **significant at 0.01

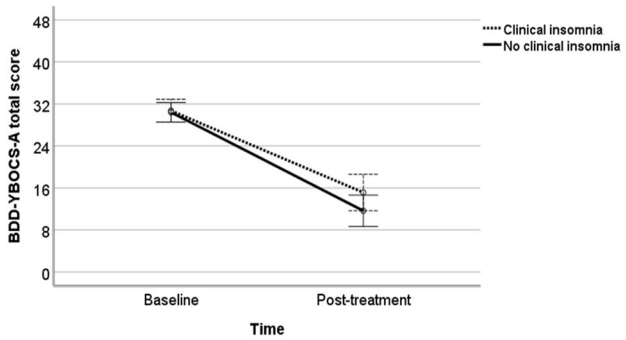

Fig. 1 Mean Yale-Brown Obsessive–Compulsive Scale Modified for BDD-Adolescent version (BDD-YBOCS) total scores at baseline and post-treatment, by insomnia status (baseline depression status—coded as present/absent—and age at assessment are included as covariates in the model)

the model. The model revealed a main effect of time (F [1, 52] = 328.77, $p < 0.001$), indicating a significant reduction in the BDD-YBOCS-A total score over the course of the treatment. There was no significant main effect of group (F [1, 52] = 0.59, $p = 0.446$) or time-by-group interaction (F [1, 52] = 2. 38, $p = 0.129$) (Fig. 1).

Given that we found differences in baseline self-reported BDD severity scores between groups, we repeated the same model using the AAI total score as the outcome variable. Results revealed a significant effect of time (F [1, 39] = 68.50, $p < 0.001$), as well as a significant group effect (F [1, 39] = 4.60, $p = 0.038$), indicating that the insomnia group had more severe self-reported BDD symptoms through treatment, but, mirroring the results of the analysis using the BDD-YBOCS-A, no significant time-by-group interaction effects were found (F [1, 39] = 0.12, $p = 0.733$).

A final model revealed that symptoms of clinical insomnia, as measured by the ISI, also improved during the course of the treatment in the whole, treated sample (F [1, 42] = 6.72, $p = 0.013$) (Table 3).

The mean percentage decrease in BDD symptom severity from baseline to post-treatment, measured by the BDD-YBOCS-A, was 51.6% in the clinical insomnia group and 62.8% in the non-clinical insomnia group (Student's $t = 1.82$, $p = 0.074$). The proportion of treatment responders in the insomnia group was lower (19/24, 79.2%) than the proportion of treatment responders in the non-insomnia group (30/32, 93.8%), but this difference did not reach statistical significance (Chi-square = 2.67, $p = 0.102$). However, the proportion of patients classed as being in full or partial remission at post-treatment was significantly lower in the insomnia group when compared

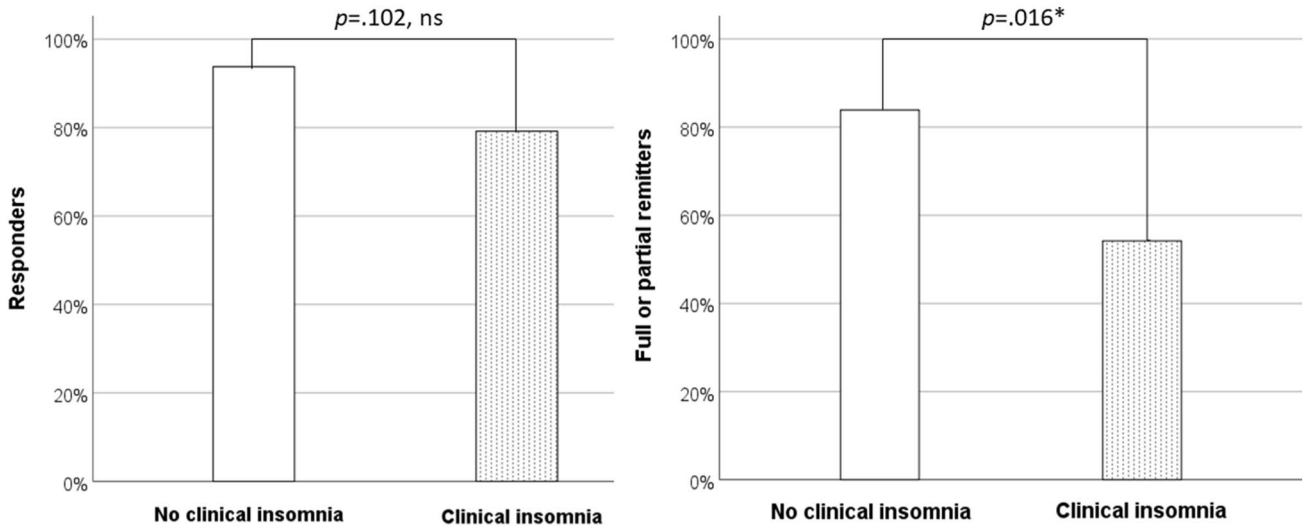

Fig. 2 Rates of responders and full or partial remitters, by insomnia status

to the non-insomnia group (13/24, 54.2% vs. 26/31, 83.9%, respectively; Chi-square = 5.79, $p = 0.016$) (Fig. 2).

Discussion

To our knowledge, the present study is the first to explore the prevalence of clinical insomnia in a large sample of well-characterized youth with BDD. We also examined the influence of insomnia on the clinical features and response to multimodal treatment in a subsample of treated patients. The study had three main findings.

Our first and main finding was that, in our sample, about half of the participants experienced significant insomnia according to the ISI, a well-validated insomnia measure. Furthermore, the ISI mean score for the whole group was slightly above the established cut-off for clinical insomnia [34]. The observed prevalence (48.5%) and overall severity of insomnia in this sample (a mean ISI score of 9.2) were both higher than those reported in a pediatric OCD sample of patients recruited from the same clinic (prevalence of 42% and mean ISI score of 7.6) [17], which is worth noting given the described similarities between the two disorders. These results suggest that insomnia is common and should be assessed and managed in young people with BDD.

Second, young people who experienced clinical insomnia scored higher on self-reported measures of BDD symptom severity, particularly avoidance behavior, had higher rates of comorbid depression, and also worse functioning in daily activities, when compared to patients without insomnia. Regarding BDD symptom severity at baseline, it is worth noting that no between-group differences were found on the clinician-rated BDD-YBOCS-A. The AAI and the BDD-YBOCS-A measure related constructs, but their content is only partially overlapping. In the original validation study, the correlation between these instruments was in the region of 0.5 [35]. In our study, the inter-correlation between these scales was 0.3. Notably, while the AAI has a separate avoidance scale, the BDD-YBOCS-A incorporates avoidance it its total score. Thus, our results might indicate that insomnia is most likely associated with the severity of avoidance in BDD.

Pediatric BDD patients with insomnia also had higher rates of comorbid depression than those without insomnia. This is somewhat expected given the known association between depression and sleep disorders [16], and the fact that insomnia and/or hypersomnia are listed as diagnostic criteria for depression [1]. Interestingly, however, no between-group differences were found in the self-reported or parent-reported measures of depressive symptoms. The fact that none of these instruments include sleep items could explain the lack of differences between groups. Thus, it is possible that individuals with insomnia in our sample may not be more depressed than those without, but be more likely to be diagnosed with depression, simply because insomnia is one of the diagnostic criteria for the disorder.

The BDD and insomnia group also had worse functioning in daily activities like family relationships, social, and everyday situations. The link between insomnia and worse functioning has also been previously reported in a variety of other psychiatric conditions in children and adolescents like OCD [17], anxiety disorders [40], autism spectrum disorders [41], and attention-deficit/hyperactivity disorder [42].

Third, we found suggestive evidence that insomnia may have a negative impact on treatment outcomes, although the results should be taken as preliminary until replicated

in larger samples. Our statistical model including insomnia status as a between-group factor and adjusting for comorbid depression and age at assessment did not show significant time-by-group interactions, implying that both groups, with and without insomnia, improved similarly. However, the proportion of responders and remitters after completing treatment was substantially lower in the insomnia group, when compared to the non-insomnia group. If confirmed, this may have important clinical implications as not reaching remission status after treatment has been associated with higher odds of relapse in related disorders like OCD [43]. It is worth noting that our study was conducted in a naturalistic setting where patients with self-reported insomnia problems may have received additional support during the course of the multimodal treatment (e.g., sleep hygiene instructions and hypnotic medication). Those additional interventions may have partially masked the impairment caused by the sleep problems on the patients' functioning and their treatment outcomes. Future studies using larger samples of BDD cases are warranted to elucidate the potential impact of insomnia on treatment response. If confirmed, the association between insomnia and worse clinical outcomes may suggest that current treatment protocols could be refined further to include specific insomnia modules.

Another intriguing implication for future research is that insomnia-specific interventions may, by themselves, have a beneficial effect on BDD symptoms without necessarily directly targeting the appearance concerns [23]. Interestingly, in our sample, insomnia symptoms also improved significantly after treatment. This finding is in line with the previous research in pediatric depression [44] and in pediatric OCD [17], showing that treatments targeting psychiatric symptoms also tend to improve sleep.

This study has some limitations. First, our sample size was modest and our analysis of the outcome data may have been underpowered to detect significant differences. The results will require replication and extension in larger patient cohorts. Second, we used a self-reported measure of insomnia rather than a structured diagnostic interview. However, the ISI cut-off employed in this study has been well validated against diagnosed insomnia cases [32]. Nevertheless, further studies including parent-reported and objective measures of insomnia are warranted. Third, this study was conducted in a specialist setting which receives referrals for relatively severe and/or complex cases, and hence, the findings may not be generalizable to other, milder populations of BDD cases. However, the clinical characteristics of our sample resemble those of other clinical BDD samples from around the world. Finally, follow-up data beyond the end of the treatment were not available for this study. It will be relevant for future studies to examine the possible influence of insomnia over the maintenance of treatment gains in the long run.

Conclusions

Insomnia is prevalent in pediatric BDD, and is associated with higher scores on self-reported measures of BDD symptom severity, higher rates of comorbid depression, and worse functioning in daily activities. Young BDD patients experiencing insomnia improved with multimodal treatment, but to a lesser extent than BDD patients without insomnia. If these results are replicated in larger samples, treatment refinements for pediatric BDD could include specific modules to directly target insomnia.

Acknowledgements Open access funding provided by Karolinska Institutet. This work used services from the eHealth Core Facility at Karolinska Institutet, which is supported by the Strategic Research Area Healthcare Science (SFO-V).

Funding Ms. Laura Sevilla-Cermeño was supported by a Fellowship from the Alicia Koplowitz Foundation. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decisions to submit the manuscript for publication. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest Dr. Lahera has been a consultant to or has received honoraria or grants from Janssen-Cilag, Otsuka-Lundbeck, Lilly, Astra-Zeneca, CIBERSAM, and Instituto de Salud Carlos III. David Mataix-Cols receives royalties for contributing articles to UpToDate, Wolters Kluwer Health, and for editorial work from Elsevier. Lorena Fernández de la Cruz receives royalties for contributing articles to UpToDate, Wolters Kluwer Health.

References

1. American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders, 5th edn. American Psychiatric Publishing, Arlington
2. Veale D, Gledhill LJ, Christodoulou P, Hodsoll J (2016) Body dysmorphic disorder in different settings: a systematic review and estimated weighted prevalence. Body Image 18:168–186. https://doi.org/10.1016/j.bodyim.2016.07.003
3. Enander J, Ivanov VZ, Mataix-Cols D, Kuja-Halkola R, Ljotsson B, Lundstrom S, Perez-Vigil A, Monzani B, Lichtenstein P, Ruck C (2018) Prevalence and heritability of body dysmorphic symptoms in adolescents and young adults: a population-based nationwide twin study. Psychol Med 48(16):2740–2747. https://doi.org/10.1017/S0033291718000375

4. Phillips KA, Didie ER, Menard W, Pagano ME, Fay C, Weisberg RB (2006) Clinical features of body dysmorphic disorder in adolescents and adults. Psychiatry Res 141(3):305–314. https://doi.org/10.1016/j.psychres.2005.09.014
5. Bjornsson AS, Didie ER, Grant JE, Menard W, Stalker E, Phillips KA (2013) Age at onset and clinical correlates in body dysmorphic disorder. Compr Psychiatry 54(7):893–903. https://doi.org/10.1016/j.comppsych.2013.03.019
6. Albertini RS, Phillips KA (1999) Thirty-three cases of body dysmorphic disorder in children and adolescents. J Am Acad Child Adolesc Psychiatry 38(4):453–459. https://doi.org/10.1097/00004583-199904000-00019
7. Schneider SC, Turner CM, Mond J, Hudson JL (2017) Prevalence and correlates of body dysmorphic disorder in a community sample of adolescents. Aust N Z J Psychiatry 51(6):595–603. https://doi.org/10.1177/0004867416665483
8. Mataix-Cols D, Fernandez de la Cruz L, Isomura K, Anson M, Turner C, Monzani B, Cadman J, Bowyer L, Heyman I, Veale D, Krebs G (2015) A pilot randomized controlled trial of cognitive-behavioral therapy for adolescents with body dysmorphic disorder. J Am Acad Child Adolesc Psychiatry 54(11):895–904. https://doi.org/10.1016/j.jaac.2015.08.011
9. Krebs G, Fernández de la Cruz L, Monzani B, Bowyer L, Anson M, Cadman J, Heyman I, Turner C, Veale D, Mataix-Cols D (2017) Long-term outcomes of cognitive-behavioral therapy for adolescent body dysmorphic disorder. Behav Ther 48(4):462–473. https://doi.org/10.1016/j.beth.2017.01.001
10. National Institute for Health and Clinical Excellence (2005) Obsessive-compulsive disorder: core interventions in the treatment of obsessive-compulsive disorder and body dysmorphic disorder. NICE, London
11. Harrison A, Fernández de la Cruz L, Enander J, Radua J, Mataix-Cols D (2016) Cognitive-behavioral therapy for body dysmorphic disorder: a systematic review and meta-analysis of randomized controlled trials. Clin Psychol Rev 48:43–51. https://doi.org/10.1016/j.cpr.2016.05.007
12. Badin E, Haddad C, Shatkin JP (2016) Insomnia: the sleeping giant of pediatric public health. Curr Psychiatry Rep 18(5):47. https://doi.org/10.1007/s11920-016-0687-0
13. Honaker SM, Meltzer LJ (2016) Sleep in pediatric primary care: a review of the literature. Sleep Med Rev 25:31–39. https://doi.org/10.1016/j.smrv.2015.01.004
14. Gregory AM, Van der Ende J, Willis TA, Verhulst FC (2008) Parent-reported sleep problems during development and self-reported anxiety/depression, attention problems, and aggressive behavior later in life. Arch Pediatr Adolesc Med 162(4):330–335. https://doi.org/10.1001/archpedi.162.4.330
15. Baum KT, Desai A, Field J, Miller LE, Rausch J, Beebe DW (2014) Sleep restriction worsens mood and emotion regulation in adolescents. J Child Psychol Psychiatry 55(2):180–190. https://doi.org/10.1111/jcpp.12125
16. Ramtekkar U, Ivanenko A (2015) Sleep in children with psychiatric disorders. Semin Pediatr Neurol 22(2):148–155. https://doi.org/10.1016/j.spen.2015.04.004
17. Sevilla-Cermeño L, Andren P, Hillborg M, Silverberg-Morse M, Mataix-Cols D, Fernández de la Cruz L (2019) Insomnia in pediatric obsessive-compulsive disorder: prevalence and association with multimodal treatment outcomes in a naturalistic clinical setting. Sleep Med. https://doi.org/10.1016/j.sleep.2018.12.024
18. Veatch OJ, Sutcliffe JS, Warren ZE, Keenan BT, Potter MH, Malow BA (2017) Shorter sleep duration is associated with social impairment and comorbidities in ASD. Autism Res 10(7):1221–1238. https://doi.org/10.1002/aur.1765
19. Steenari MR, Vuontela V, Paavonen EJ, Carlson S, Fjallberg M, Aronen E (2003) Working memory and sleep in 6- to 13-year-old schoolchildren. J Am Acad Child Adolesc Psychiatry 42(1):85–92
20. Astill RG, Van der Heijden KB, Van Ijzendoorn MH, Van Someren EJ (2012) Sleep, cognition, and behavioral problems in school-age children: a century of research meta-analyzed. Psychol Bull 138(6):1109–1138. https://doi.org/10.1037/a0028204
21. Manglick M, Rajaratnam SM, Taffe J, Tonge B, Melvin G (2013) Persistent sleep disturbance is associated with treatment response in adolescents with depression. Aust N Z J Psychiatry 47(6):556–563. https://doi.org/10.1177/0004867413481630
22. Harvey AG (2009) The adverse consequences of sleep disturbance in pediatric bipolar disorder: implications for intervention. Child Adolesc Psychiatr Clin N Am 18(2):321–338. https://doi.org/10.1016/j.chc.2008.11.006
23. Freeman D, Sheaves B, Goodwin GM, Yu LM, Nickless A, Harrison PJ, Emsley R, Luik AI, Foster RG, Wadekar V, Hinds C, Gumley A, Jones R, Lightman S, Jones S, Bentall R, Kinderman P, Rowse G, Brugha T, Blagrove M, Gregory AM, Fleming L, Walklet E, Glazebrook C, Davies EB, Hollis C, Haddock G, John B, Coulson M, Fowler D, Pugh K, Cape J, Moseley P, Brown G, Hughes C, Obonsawin M, Coker S, Watkins E, Schwannauer M, MacMahon K, Siriwardena AN, Espie CA (2017) The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis. Lancet Psychiatry 4(10):749–758. https://doi.org/10.1016/S2215-0366(17)30328-0
24. Kleim B, Wilhelm FH, Temp L, Margraf J, Wiederhold BK, Rasch B (2014) Sleep enhances exposure therapy. Psychol Med 44(7):1511–1519. https://doi.org/10.1017/S0033291713001748
25. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59(Suppl 20):22–33 **(quiz 34–57)**
26. Phillips KA, Hollander E, Rasmussen SA, Aronowitz BR, DeCaria C, Goodman WK (1997) A severity rating scale for body dysmorphic disorder: development, reliability, and validity of a modified version of the yale-brown obsessive compulsive scale. Psychopharmacol Bull 33(1):17–22
27. Phillips KA, Hart AS, Menard W (2014) Psychometric evaluation of the yale-brown obsessive-compulsive scale modified for body dysmorphic disorder (BDD-YBOCS). J Obsess Compuls Relat Disord 3:205–208
28. Fernández de la Cruz L, Enander J, Rück C, Wilhelm S, Phillips KA, Steketee G, Sarvode Mothi S, Krebs G, Bowyer L, Monzani B, Veale D, Mataix-Cols D Empirically defining treatment response and remission in body dysmorphic disorder. Psychol Med. https://doi.org/10.1017/S0033291719003003
29. Busner J, Targum SD (2007) The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont) 4(7):28–37
30. Leon AC, Shear MK, Klerman GL, Portera L, Rosenbaum JF, Goldenberg I (1993) A comparison of symptom determinants of patient and clinician global ratings in patients with panic disorder and depression. J Clin Psychopharmacol 13(5):327–331
31. Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S (1983) A children's global assessment scale (CGAS). Arch Gen Psychiatry 40(11):1228–1231
32. Bastien CH, Vallieres A, Morin CM (2001) Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2(4):297–307
33. Kanstrup M, Holmstrom L, Ringstrom R, Wicksell RK (2014) Insomnia in paediatric chronic pain and its impact on depression and functional disability. Eur J Pain 18(8):1094–1102. https://doi.org/10.1002/j.1532-2149.2013.00450.x
34. Chung KF, Kan KK, Yeung WF (2011) Assessing insomnia in adolescents: comparison of insomnia severity index, athens

insomnia scale and sleep quality index. Sleep Med 12(5):463–470. https://doi.org/10.1016/j.sleep.2010.09.019
35. Veale D, Eshkevari E, Kanakam N, Ellison N, Costa A, Werner T (2014) The Appearance Anxiety Inventory: validation of a process measure in the treatment of body dysmorphic disorder. Behav Cogn Psychother 42(5):605–616. https://doi.org/10.1017/S1352465813000556
36. Allgaier AK, Fruhe B, Pietsch K, Saravo B, Baethmann M, Schulte-Korne G (2012) Is the Children's Depression inventory short version a valid screening tool in pediatric care? A comparison to its full-length version. J Psychosom Res 73(5):369–374. https://doi.org/10.1016/j.jpsychores.2012.08.016
37. Rhew IC, Simpson K, Tracy M, Lymp J, McCauley E, Tsuang D, Stoep AV (2010) Criterion validity of the short mood and feelings questionnaire and one- and two-item depression screens in young adolescents. Child Adolesc Psychiatry Ment Health 4(1):8. https://doi.org/10.1186/1753-2000-4-8
38. Jassi A, Lenhard F, Krebs G, Gumpert M, Jolstedt M, Andrén P, Nord M, Aspvall K, Wahlund T, Volz C, Mataix-Cols D (2019) The work and social adjustment scale, youth and parent versions: psychometric evaluation of a brief measure of functional impairment in young people. PsyArXiv. https://doi.org/10.31234/osf.io/f8zev
39. Mundt JC, Marks IM, Shear MK, Greist JH (2002) The work and social adjustment scale: a simple measure of impairment in functioning. Br J Psychiatry 180:461–464
40. Alfano CA, Ginsburg GS, Kingery JN (2007) Sleep-related problems among children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry 46(2):224–232. https://doi.org/10.1097/01.chi.0000242233.06011.8e
41. Richdale AL, Baker E, Short M, Gradisar M (2014) The role of insomnia, pre-sleep arousal and psychopathology symptoms in daytime impairment in adolescents with high-functioning autism spectrum disorder. Sleep Med 15(9):1082–1088. https://doi.org/10.1016/j.sleep.2014.05.005
42. Craig SG, Weiss MD, Hudec KL, Gibbons C (2017) The functional impact of sleep disorders in children with ADHD. J Atten Disord. https://doi.org/10.1177/1087054716685840
43. Eisen JL, Sibrava NJ, Boisseau CL, Mancebo MC, Stout RL, Pinto A, Rasmussen SA (2013) Five-year course of obsessive-compulsive disorder: predictors of remission and relapse. J Clin Psychiatry 74(3):233–239. https://doi.org/10.4088/JCP.12m07657
44. Emslie G, Kratochvil C, Vitiello B, Silva S, Mayes T, McNulty S, Weller E, Waslick B, Casat C, Walkup J, Pathak S, Rohde P, Posner K, March J, Columbia Suicidality Classification G, Team T (2006) Treatment for Adolescents with Depression Study (TADS): safety results. J Am Acad Child Adolesc Psychiatry 45(12):1440–1455. https://doi.org/10.1097/01.chi.0000240840.63737.1d

4. DISCUSSION

4.1. General discussion of the main findings

The present doctoral thesis notably enhances the current knowledge on the association between insomnia and the two main OCDRs, namely OCD and BDD.

The first study provides objective data on the prevalence of insomnia in OCD at the population level in a register-based study in Sweden. Specifically, the prevalence of insomnia was set at 42% of those individuals with OCD diagnosed in specialist settings, compared to a prevalence of insomnia of 11% in those individuals from the general population without the disorder. This translated into almost 7-fold increased odds of insomnia in OCD, compared to the unaffected individuals. Of note, the prevalence rate of insomnia in the unaffected sample (i.e., 11%) matches previously reported figures for insomnia in the general population in other samples (78), providing validity to our combined outcome definition for insomnia, which ascertained cases not only by using ICD-10 diagnoses but also the use of medications with specific indication for insomnia in order to improve coverage.

The study is the first to date to estimate the prevalence rate of insomnia in OCD. To do so, we used a large cohort of more than 31,000 individuals with OCD, with this diagnosis having shown to be valid and reliable in the context of the epidemiological studies in Sweden (79), and with the diagnosis of insomnia having been assigned by a specialist doctor (or with a medical doctor having stablished the need to issue a prescription for this specific sleep disorder). By contrast, previous studies in the field have used very small OCD samples (64, 65), have been conducted in community samples (66, 67) or have used general surveys including a number of scales for the assessment of OCD symptoms (67) or self-reported measures of sleep disturbance (64, 66, 67).

A main strength of the first study included in the thesis was the inclusion of a discordant sibling analysis. This type of quasi-experimental designs comparing the exposed cohort with their full siblings (those sharing the same mother and father) allow to control for a large number of measured and unmeasured confounders, including 50% of the genetic liability, as well as great part of the shared environment (including for example parental history of both psychiatric and somatic disorders, parental education or socioeconomic level). Our results showed that individuals with OCD still had substantially higher odds of insomnia, compared to their unaffected siblings. However, compared to the general population analysis, the magnitude of the association was significantly reduced, suggesting that at least part of the association between OCD and insomnia could be attributed to early shared environmental and genetic factors. Those results are in line with a previous study assessing the association between insomnia and depressive symptoms in young adults, which used a sibling comparison plus a twin comparison design, and proposed that genetic factors may play a central role in the association between both disorders (80). However, the fact that the odds were still higher in the OCD siblings, compared to the unaffected siblings, still suggests a conceptualization of insomnia as a potential consequence of OCD.

When exploring whether the presence of other psychiatric conditions affected the association between OCD and insomnia, results showed that the exclusion of the individuals with several clusters of comorbid psychiatric disorders did not substantially affect the magnitude of the association. The only exception were comorbid depression and anxiety disorders. The exclusion of individuals with either of these disorders from the cohort attenuated the magnitude of the association, although it did not eliminate it, suggesting that OCD is associated with insomnia independently from these disorders. Previous research had yielded inconclusive results in this matter, with some studies

claiming that the association between sleep problems and OCD was driven by the presence of comorbid depression (64, 66) or substance use disorder (66), and some proposing that OCD was linked to sleep disturbance independently of the psychiatric comorbidities (67). The sensitivity analyses included in our study were better suited to conclude that OCD is associated with insomnia in its own right.

The second study included in this thesis also focused on insomnia in OCD, in this case in a consecutive sample of 193 children and adolescents seen in a specialist OCD clinic in Stockholm, Sweden. The results showed that 42% of children and adolescents with OCD referred to the clinic reached the cut-off score for clinical insomnia in a well-validated self-reported scale which was specific for insomnia. Relevantly, this prevalence figure matched that in the first study conducted at the population level using a different study design, which contributes to increase the validity of the method to assess insomnia with the insomnia-specific questionnaire. Previous studies in the field were limited by the use of mainly parent-reported sleep measures comprising items from other scales or a mixture of several sleep-related symptoms, including talking or walking while sleeping or the presence of nightmares, instead of a specific, well-validated measures for insomnia. Furthermore, some of the previous studies in the field were also limited by the use of small samples sizes (72, 73). In general, higher prevalence rates of heterogenous sleep problems had been reported in children and adolescents with OCD (73, 74) but, when looking at specific sleep problems closer to insomnia symptoms, the figures approached our reported prevalence of insomnia. For example, in the study by Ivarsson et al. (74), ‘troubled sleep’ was found in 40% of the sample of children and adolescents, while shorter sleep duration was reported by 29,5% of them.

When exploring whether the clinical characteristics of children and adolescents with OCD differed by insomnia status, we found that young patients with OCD and insomnia were more severely affected by obsessive-compulsive and depressive symptoms and showed a lower level of global functioning, compared to patients with OCD without insomnia. These findings are consistent with previous literature reporting a positive association between sleep disturbance and OCD severity (72, 73), internalizing symptomatology (71, 72), and functional impairment (75) in children and adolescents with OCD.

About 74% of the patients in our paediatric specialist sample undertook multimodal treatment for their OCD at the clinic. This treatment consisted of a course of protocol-driven CBT focused on ERP, with parental involvement. Furthermore, when deemed clinically indicated, some patients were additionally treated with medication. Despite the differences between those with and without insomnia, with the former tending to be more severe, in this sample, insomnia did not seem to interfere with response to the multimodal treatment. Those results remained unchanged when our model was adjusted for baseline depression severity, the number of CBT sessions received, and prescription of medication for insomnia, and in a sensitivity analysis excluding patients with comorbid autism spectrum disorders who had received a sleep hygiene module as a part of their treatment package. Conversely to our findings, Ivarsson et al. (74) reported that sleep problems at baseline in a sample of 269 paediatric patients with OCD predicted worse CBT outcomes at post-treatment (74). It is worth noting an important difference between this and our study. Ivarsson et al. (74) reanalysed data from an RCT evaluating a highly protocolized CBT intervention for OCD, while our study was conducted in a naturalistic setting where the clinicians had more flexibility to offer additional interventions, including brief sleep hygiene advice or

medication (including sedatives), or to deliver a larger number of CBT sessions as required by the individual patient care plan. Thus, it may still be the case that insomnia hampers the efficacy of CBT, but itds possible negative effects could potentially be minimized if the treatment is adapted in a naturalistic setting to accommodate the sleep-related symptoms. Our findings were however in line with the results in the study by Nabinger de Diaz et al. (75), who showed that sleep problems at baseline in a sample of 103 children and adolescents with OCD that were part of an RCT did not predict treatment response to another modality of treatment, specifically to intensive exposure therapy, at post-treatment and at 3-month follow-up.

The third study included in this thesis is, to our knowledge, the first to date to explore the prevalence and impact of insomnia in BDD. We used a sample of 66 children and adolescents with BDD who were seen in a specialist paediatric OCD and related disorders in Stockholm, Sweden. Our first and main finding was that approximately half of the patients (48,5%) experienced insomnia according to a well-validated specific insomnia measure. The prevalence, as well as the overall severity of insomnia (with an ISI mean score slightly above the cut-off for insomnia for the whole sample), were both higher than those reported in our previous study of insomnia in paediatric patients with OCD recruited from the same clinic (81) which used similar methods. This is relevant from the clinical point of view, given the similarities between both disorders.

When exploring the impact of insomnia on the clinical features of paediatric patients with BDD, we found that young patients with BDD and insomnia scored higher on self-reported measures of BDD symptom severity, particularly avoidance behaviour, had higher rates of comorbid depression, and showed worse functioning in daily activities, when compared to those without insomnia. Our findings are consistent with

previous studies on paediatric OCD showing a link between comorbid depression and the presence of sleep disturbance (71, 72, 81) and with a number of studies finding an association between insomnia and worse functioning in a variety of psychiatric conditions in children and adolescents like OCD (81), anxiety disorders (82), autism spectrum disorders (83), and attention-deficit/hyperactivity disorder (84).

About 85% of the patients in our paediatric specialist sample undertook multimodal treatment for their BDD at the clinic. This treatment consisted of individual protocol-driven CBT heavily based on ERP. Medication (mainly SSRIs) was also prescribed when deemed clinically appropriate. Our results showed that both groups, with and without insomnia, improved similarly during treatment. However, the proportion of responders and remitters after completing treatment was substantially lower in the insomnia group, when compared to the non-insomnia group. As mentioned for our second study, it is relevant to note that this study was conducted in a naturalistic setting where patients with sleep problems may have received additional interventions during the course of the treatment (e.g., brief sleep hygiene instructions, medication for sleep problems). Those additional interventions may have partially compensated for the reported impairment caused by the insomnia on the patients' treatment outcomes. Future studies using larger samples of BDD cases are warranted to elucidate the potential impact of insomnia on evidence-based treatment response for paediatric BDD.

4.2. Limitations

Limitations of the studies included in this thesis are detailed in the respective scientific publications. However, the main ones are also summarised here.

Common to all studies, it is important to note that individuals with OCD and BDD may not be completely representative of all people with these disorders in the general population. This may be due to several reasons. First, only treatment-seeking cases are

included. Second, the included OCD and BDD cases had been diagnosed in specialist care settings, leaving behind cases diagnosed/managed in primary care by their general practitioners. Thus, although the characteristics of our cohorts (e.g., severity, pattern of psychiatric comorbidities) generally resemble those from other OCD and BDD cohorts previously reported, it is possible that our results may not extrapolate to less severe patient samples. Specific to study 1 is the fact that, prior to 2001, the NPR includes inpatient admissions, with outpatient cases only being incorporated to the register from 2001.

Regarding specific limitations for study 1, we used a combined approach to improve the coverage of the insomnia cases. This was because individuals are generally diagnosed with insomnia in primary care, rather than in specialist services, which are the only diagnoses available in the NPR. Hence, in order to improve case coverage, we ascertained cases of insomnia not only by using the ICD-10 codes for this diagnosis, but also by identifying those individuals that had been dispensed medications specifically indicated for insomnia, as a proxy for the diagnosis. Of note, all dispensed medications are included in the registers, regardless of whether they have been prescribed in specialist services or not. Additionally, we also collected insomnia diagnoses from the primary care database in the Stockholm county, only for individuals living in this area during the study period (primary care data for other Swedish counties was not available to us). Reassuringly, the results obtained in this Stockholm cohort, which included primary care diagnoses, mirrored those from the whole population cohort. Furthermore, the prevalence rates of insomnia in the general population in our study resemble those from previous studies.

In studies 2 and 3, the diagnosis of insomnia was made according to the cut-off on a self-reported scale specific for insomnia (the ISI) and clinical diagnoses obtained via structured diagnostic interviews for insomnia were not performed. However, the cut-off

for insomnia used in these studies had been previously validated against insomnia cases diagnosed according to DSM-5 (85). In both studies, the sample sizes were modest, and the treatment outcome analyses may be underpowered to detect significant differences between groups. Further replication of these studies using larger cohorts of patients is warranted. As our studies were conducted in naturalistic settings, results regarding treatment outcomes should be interpreted cautiously due to the lack of control over potential interventions not necessarily included in the treatment protocols. Follow-up data beyond 3 months after treatment in the OCD study, and right after treatment in the BDD study, were not available. It would be relevant to address the possible impact of insomnia over the treatment gains in the long run for both patient groups.

4.3. Clinical implications

We have established that the prevalence of insomnia in OCD is 42%, based on two independent studies using different methods, and the prevalence of insomnia in adolescent BDD is 48%. These figures are relevant from a clinical perspective and clinicians, specifically psychiatrists and clinical psychologists, but also general practitioners or other health workers in contact with patients with OCD and BDD, should be made aware of the high rates of prevalence reported in these studies. In light of these results, the presence of insomnia, which has been associated with negative outcomes as relevant as increased risk of cardiovascular disease (51) or increased risk of car accidents (50) in previous studies, should be systematically assessed in patients with OCD and BDD. If present, insomnia in these disorders should be managed according to the available evidence in order to minimize its potential impact on health and quality of life. According to our findings, this is particularly relevant in OCD patients with comorbid depression or a comorbid anxiety disorder. Regarding paediatric patients with OCD or

BDD, the study of the impact of insomnia on their clinical outcomes is crucial, particularly because interventions made at this point in the lifespan may have a significant influence on the prognosis of the disease in the longer run. Our studies highlighted that the presence of insomnia in paediatric patients with OCD and BDD is associated with more severe psychopathology and with worse general functioning. We showed that, in paediatric patients with BDD, insomnia may have a negative impact on multimodal treatment gains, a finding that, if replicated in larger samples, could have implications for the treatment of paediatric BDD. Updated treatment protocols could include specific modules to target insomnia in order to improve treatment outcomes, a strategy that has proved beneficial in other forms of psychopathology by directly improving psychiatric symptoms (86) or enhancing CBT (87).

4.4. Research implications

The first study included in this thesis addressed many of the previous methodological limitations in previously published studies on the topic. The use of the longitudinal nationwide Swedish population registers, including one of the largest cohorts of individuals diagnosed with OCD (around 32,000 diagnosed individuals), provided unparalleled statistical power. The use of a quasi-experimental family design and the possibility of running sensitivity analyses are unique characteristics of this study, allowing us to control for relevant confounders like no previous study had done in this topic. With our family design, we showed that characteristics shared by full siblings, including genetic liability and early environmental shared factors, may play an important role in the association between insomnia and OCD. Previous research using twin designs has shown a significant genetic overlap between insomnia and other internalizing disorders such as major depressive disorder and generalised anxiety disorder (88), but

twin studies on the possible common aetiology between insomnia and OCD are lacking. Future genetically-informative studies investigating genetic and environmental overlap between insomnia and OCD are warranted. On the other hand, we concluded that OCD is associated with insomnia in its own right, independent from a number of comorbid psychiatric conditions, with the exception of depression and anxiety disorders, which did contribute significantly to the observed association. This last finding helps clarifying the association between OCD, depression, and insomnia, building on previous research which could not disentangle if the presence of sleep problems in general, and insomnia in particular, was attributable to other comorbid psychiatric conditions or OCD itself.

Our second and third studies addressed the association between insomnia and paediatric OCD and BDD by using a specific and well-validated insomnia measure, overcoming the limitations of previous research which tried to address this issue by the use of mainly parent-reported measures usually comprising sleep-related items of several non-specific scales. Furthermore, our study on insomnia in paediatric BDD is the first to date to address sleep in BDD, adding new knowledge to the available literature and representing the first step for future research in the field. In both studies, we provided treatment outcome data improving the previous scarce knowledge on the possible impact of insomnia on the treatment outcomes for both disorders in young people. Building on our preliminary findings, future controlled protocolized treatment studies on the impact of insomnia on the treatment outcomes for both paediatric OCD and BDD are warranted. Considering our novel results regarding the probable negative impact of insomnia on the treatment gains in children and adolescents with BDD, another interesting line of future research on this topic would be addressing if interventions targeted at improving insomnia would enhance the effects of the available evidence-based treatments for children and adolescents with BDD.

The results of the three studies included in this doctoral thesis suggest an association between insomnia and the main OCRDs, OCD and BDD. Given these findings and the scarce literature available, the field would benefit from further studies exploring the link between sleep disorders in general, and insomnia in particular, and other OCRDs such as hoarding disorder, trichotillomania or skin picking.

5. CONCLUSIONS

The main conclusions of the thesis, derived from Study 1, Study 2, and Study 3, can be summarized as follows:

- The prevalence of insomnia in OCD at the population-level is approximately 42% and individuals with OCD have 7-fold increased odds of insomnia than unaffected individuals from the general population.
- Familial factors shared by siblings and the presence of comorbid psychiatric conditions did not fully explain the association between insomnia and OCD, but the exclusion of individuals with comorbid depression and anxiety disorders significantly attenuated the odds of insomnia.
- The prevalence of insomnia in children and adolescents with OCD in a specialist setting matches that of patients seen in specialist care in the population (42%).
- Insomnia in children and adolescents with OCD is associated with more severe obsessive-compulsive and depressive symptomatology and with worse general functioning.
- In our specialist care sample of paediatric patients with OCD, insomnia did not seem to interfere with response to multimodal treatment for OCD.
- Insomnia is highly prevalent amongst children and adolescents with BDD attending a specialist outpatient clinic (48,5%).
- Insomnia in children and adolescents with BDD is associated with more severe self-reported BDD symptomatology, higher rates of comorbid depression, and worse functioning.

- Young patients with BDD and insomnia improve with multimodal treatment for BDD, but to a lesser extent than patients without insomnia.

6. SUMMARY IN SPANISH

6.1 Introducción

El insomnio es un problema de salud pública que tiene importantes consecuencias negativas para los individuos que lo padecen (50-52). Un número creciente de estudios científicos propone una relación bidireccional entre el insomnio y las enfermedades psiquiátricas, con evidencia firme de la coexistencia de insomnio y patologías psiquiátricas como la depresión (57) o el trastorno por ansiedad generalizada (58). Sin embargo, la evidencia científica disponible respecto a la prevalencia de insomnio en el trastorno obsesivo-compulsivo (TOC) y en el trastorno dismórfico corporal (TDC), tanto en pacientes adultos como en población infanto-juvenil, era escasa hasta la elaboración de esta tesis doctoral. Por lo tanto, los objetivos de este trabajo fueron: 1) establecer la prevalencia de insomnio en el TOC a nivel poblacional, usando para ello la mayor muestra de pacientes con diagnóstico de TOC utilizada hasta el momento para el estudio de insomnio en este trastorno; 2) estudiar la prevalencia de insomnio en una muestra pediátrica de pacientes con TOC derivados a una clínica especializada en el tratamiento de dicha patología en Estocolmo (Suecia), así como el impacto del insomnio en las características clínicas y en la respuesta al tratamiento multimodal de estos pacientes; y 3) estudiar la prevalencia de insomnio en una muestra pediátrica de pacientes con TDC derivados a una clínica especializada en el tratamiento de dicha patología en Estocolmo (Suecia), así como el impacto del insomnio en las características clínicas y en la respuesta al tratamiento multimodal de estos pacientes.

6.2. Métodos y Resultados

6.2.1 Estudio 1: El estudio identificó a los individuos diagnosticados de TOC en servicios de salud especializados (n= 31,856) en una cohorte que incluía a los individuos residentes en Suecia en el período de 1973 a 2013 (n=13,017,902). Se

utilizaron análisis de regresión lineal para investigar las probabilidades de sufrir insomnio en los pacientes con TOC, en comparación a los individuos sanos de la población general. Los modelos de regresión lineal se ajustaron por una serie de covariables tales como el sexo, año de nacimiento y enfermedades somáticas con una asociación demostrada con el insomnio. Se implementó un modelo de efectos fijos en una sub-cohorte que incluía aquellas parejas de hermanos de padre y madre discordantes para el diagnóstico de TOC, con el objetivo de comparar las probabilidades de sufrir insomnio de los pacientes con TOC y sus hermanos. Con este modelo se controló por factores de confusión familiares (ej. el nivel socioeconómico de los padres o factores genéticos). Por ultimo, se realizaron análisis de sensibilidad, excluyendo sucesivamente grupos de pacientes con patologías psiquiátricas comórbidas, con el objetivo de evaluar el posible impacto de dichas comorbilidades en la asociación entre insomnio y TOC.

Los individuos con TOC presentaron casi 7 veces más probabilidades de recibir un diagnóstico de insomnio, o de recibir una prescripción de un fármaco con la indicación única de tratamiento del insomnio, en comparación a los individuos de la población general (42.2% *vs.* 11.0%, respectivamente; OR=6.92 [95% CI, 6.76-7.08]). Los factores familiares compartidos por los hermanos, así como la presencia de otras patologías psiquiátricas comórbidas, no explicaron por completo la asociación entre insomnio y TOC. Aún así, la presencia de depresión o trastorno de ansiedad comórbidos en pacientes con TOC se asoció a una mayor probabilidad de sufrir insomnio.

6.2.2 Estudio 2: Los participantes del estudio fueron un total de 193 niños y adolescentes con un diagnóstico de TOC de acuerdo a las clasificaciones internacionales DSM-5 y CIE-10, derivados consecutivamente a una clínica pediátrica especializada en

el tratamiento del TOC y trastornos relacionados en niños y adolescentes en Estocolmo, Suecia. A estos pacientes se les realizaron una serie de entrevistas diagnósticas semiestructuradas y escalas clínicas y sociodemográficas, incluyendo una escala de autoevaluación específica para medir los síntomas de insomnio (*Insomnia Severity Index;* ISI). Los pacientes que puntuaron por encima del punto de corte validado para el diagnóstico de insomnio en el ISI fueron comparados con el resto de la muestra en las medidas sociodemográficas y clínicas previamente recogidas. De la muestra total, 143 pacientes recibieron tratamiento multimodal para el TOC en la clínica, que incluía terapia cognitivo-conductual y medicación en los casos necesarios. Un modelo estadístico mixto de análisis de varianza se utilizó para comparar los resultados de dicho tratamiento entre los pacientes con TOC e insomnio (N=60) y los pacientes con TOC sin insomnio (N=83) al finalizar el tratamiento y a los 3 meses de seguimiento después de su finalización.

Aproximadamente un 42% de la muestra puntúo por encima del punto de corte validado para el diagnostico de insomnio de acuerdo con la ISI. Un mayor porcentaje de participantes con TOC e insomnio estaba en tratamiento farmacológico, presentaron mayor gravedad de sintomatología TOC, mayor porcentaje de comorbilidad psiquiátrica (específicamente depresión) con mayor gravedad de sintomatología depresiva y un peor funcionamiento general, en comparación a los pacientes con TOC sin insomnio. En la muestra, los pacientes con insomnio y sin insomnio mejoraron con el tratamiento de forma equivalente tanto al final del tratamiento como en el seguimiento 3 meses después de su finalización.

6.2.3 Estudio 3: Los participantes de este estudio fueron un total de 66 niños y adolescentes con un diagnóstico de TDC de acuerdo a las clasificaciones internacionales DSM-5 y CIE-10, derivados consecutivamente a una clínica pediátrica especializada en

el tratamiento del TOC y trastornos relacionados, como el TDC, en niños y adolescentes en Estocolmo, Suecia. Estos participantes completaron una serie de medidas diagnósticas y clínicas entre las que se encontraba el ISI, también empleado en el Estudio 2. Los pacientes que puntuaron por encima del punto de corte validado para el diagnóstico de insomnio en el ISI fueron comparados con el resto de la muestra en una serie de medidas sociodemográficas y clínicas. De los 66 pacientes incluidos, 56 pacientes recibieron tratamiento multimodal para el TDC que consistió principalmente en terapia cognitivo-conductual y tratamiento farmacológico en los casos en los que se consideró clínicamente indicado. Un modelo mixto de análisis de varianza se utilizó para comparar los resultados tras el tratamiento en pacientes con TDC e insomnio y los pacientes con TDC sin insomnio. Además, se realizaron tests de Chi cuadrado para comparar las tasas de respuesta y de remisión tras el tratamiento de pacientes con TDC e insomnio con las de aquellos sin insomnio.

Aproximadamente un 48% de nuestra muestra puntúo por encima del punto de corte validado para el diagnóstico de insomnio de acuerdo con el ISI. Los participantes con TDC e insomnio mostraron mayor gravedad de sintomatología TDC auto-reportada, mayor frecuencia de depresión comórbida y peor funcionamiento general en actividades diarias. Los pacientes con insomnio mejoraron con el tratamiento multimodal pero en menor medida que aquellos sin insomnio, aunque la diferencia no alcanzó significación estadística. Las tasas de respuesta y remisión fueron menores en los pacientes con TDC e insomnio en comparación a los pacientes con TDC sin insomnio. Si estos resultados fueran replicados en muestras más grandes, el tratamiento del insomnio debería ser incluido dentro de los paquetes de tratamiento para el TDC pediátrico.

6.3. Conclusiones

Las conclusiones de esta tesis doctoral se resumen en las siguientes:

- La prevalencia de insomnio en el TOC a nivel poblacional es de aproximadamente 42% y las personas con TOC presentan 7 veces más probabilidades de sufrir insomnio que aquellas personas sin TOC en la población general.
- Los factores familiares compartidos con los hermanos y la presencia de comorbilidad psiquiátrica no explican por completo la asociación entre insomnio y TOC, aunque la exclusión de individuos con una depresión o un trastorno de ansiedad comórbidos atenuó significativamente las probabilidades de padecer insomnio.
- La prevalencia de insomnio en niños y adolescentes con TOC atendidos en una clínica especializada, coincide con la prevalencia de insomnio de los pacientes con TOC vistos en servicios especializados en la población general (42%).
- El insomnio en niños y adolescentes con TOC se asocia con una mayor gravedad de la sintomatología obsesiva-compulsiva y depresiva, así como con un peor nivel general de funcionamiento.
- En nuestra muestra de pacientes pediátricos con TOC atendidos en una clínica especializada, el insomnio pareció no interferir en la respuesta al tratamiento multimodal para el TOC.
- El insomnio es muy prevalente en niños y adolescentes con TDC que acuden a una clínica especializada en el tratamiento de dicho trastorno (48,5%).

- El insomnio en niños y adolescentes con TDC se asocia a mayor gravedad de sintomatología TDC auto-reportada, mayores porcentajes de depresión comórbida y peor nivel de funcionamiento.
- Los pacientes pediátricos con TDC e insomnio mejoran con el tratamiento multimodal para TDC, pero en menor medida que los pacientes con TDC sin insomnio.

7. REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

2. World Health Organization. International statistical classification of diseases, 11th revisión (ICD-11). Geneva, Switzerland: World Health Organization.

3. Phillips KA, Stein DJ, Rauch SL, Hollander E, Fallon BA, Barsky A, et al. Should an obsessive-compulsive spectrum grouping of disorders be included in DSM-V? Depress Anxiety. 2010;27(6):528-55.

4. Stein DJ, Kogan CS, Atmaca M, Fineberg NA, Fontenelle LF, Grant JE, et al. The classification of Obsessive-Compulsive and Related Disorders in the ICD-11. J Affect Disord. 2016;190:663-74.

5. Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry. 2010;15(1):53-63.

6. Fawcett EJ, Power H, Fawcett JM. Women Are at Greater Risk of OCD Than Men: A Meta-Analytic Review of OCD Prevalence Worldwide. J Clin Psychiatry. 2020;81(4).

7. Geller DA. Obsessive-compulsive and spectrum disorders in children and adolescents. Psychiatr Clin North Am. 2006;29(2):353-70.

8. Taylor S. Early versus late onset obsessive-compulsive disorder: evidence for distinct subtypes. Clin Psychol Rev. 2011;31(7):1083-100.

9. Mataix-Cols D, Rauch SL, Baer L, Eisen JL, Shera DM, Goodman WK, et al. Symptom stability in adult obsessive-compulsive disorder: data from a naturalistic two-year follow-up study. Am J Psychiatry. 2002;159(2):263-8.

10. Lochner C, Fineberg NA, Zohar J, van Ameringen M, Juven-Wetzler A, Altamura AC, et al. Comorbidity in obsessive-compulsive disorder (OCD): a report from the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS). Compr Psychiatry. 2014;55(7):1513-9.

11. Pauls DL, Abramovitch A, Rauch SL, Geller DA. Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. Nat Rev Neurosci. 2014;15(6):410-24.

12. Mataix-Cols D, Boman M, Monzani B, Ruck C, Serlachius E, Langstrom N, et al. Population-based, multigenerational family clustering study of obsessive-compulsive disorder. JAMA Psychiatry. 2013;70(7):709-17.

13. Brander G, Rydell M, Kuja-Halkola R, Fernandez de la Cruz L, Lichtenstein P, Serlachius E, et al. Association of Perinatal Risk Factors With Obsessive-Compulsive Disorder: A Population-Based Birth Cohort, Sibling Control Study. JAMA Psychiatry. 2016;73(11):1135-44.

14. Brander G, Perez-Vigil A, Larsson H, Mataix-Cols D. Systematic review of environmental risk factors for Obsessive-Compulsive Disorder: A proposed roadmap from association to causation. Neurosci Biobehav Rev. 2016;65:36-62.

15. Hollander E, Stein DJ, Fineberg NA, Marteau F, Legault M. Quality of life outcomes in patients with obsessive-compulsive disorder: relationship to treatment response and symptom relapse. J Clin Psychiatry. 2010;71(6):784-92.

16. Perez-Vigil A, Fernandez de la Cruz L, Brander G, Isomura K, Jangmo A, Feldman I, et al. Association of Obsessive-Compulsive Disorder With Objective Indicators of Educational Attainment: A Nationwide Register-Based Sibling Control Study. JAMA Psychiatry. 2018;75(1):47-55.

17. Perez-Vigil A, Mittendorfer-Rutz E, Helgesson M, Fernandez de la Cruz L, Mataix-Cols D. Labour market marginalisation in obsessive-compulsive disorder: a nationwide register-based sibling control study. Psychol Med. 2019;49(6):1015-24.

18. Isomura K, Brander G, Chang Z, Kuja-Halkola R, Ruck C, Hellner C, et al. Metabolic and Cardiovascular Complications in Obsessive-Compulsive Disorder: A Total Population, Sibling Comparison Study With Long-Term Follow-up. Biol Psychiatry. 2018;84(5):324-31.

19. Mataix-Cols D, Frans E, Perez-Vigil A, Kuja-Halkola R, Gromark C, Isomura K, et al. A total-population multigenerational family clustering study of autoimmune diseases in obsessive-compulsive disorder and Tourette's/chronic tic disorders. Mol Psychiatry. 2018;23(7):1652-8.

20. Meier SM, Mattheisen M, Mors O, Schendel DE, Mortensen PB, Plessen KJ. Mortality Among Persons With Obsessive-Compulsive Disorder in Denmark. JAMA Psychiatry. 2016;73(3):268-74.

21. Fernández de la Cruz L, Rydell M, Runeson B, D'Onofrio BM, Brander G, Ruck C, et al. Suicide in obsessive-compulsive disorder: a population-based study of 36 788 Swedish patients. Mol Psychiatry. 2017;22(11):1626-32.

22. National Institute for Health and Clinical Excellence (2005). Obsessive-compulsive disorder: core interventions in the tratment of obsessive-compulsive disorder and body dysmorphic disorder. NICE, London. 2005.

23. Ivarsson T, Skarphedinsson G, Kornor H, Axelsdottir B, Biedilae S, Heyman I, et al. The place of and evidence for serotonin reuptake inhibitors (SRIs) for obsessive compulsive disorder (OCD) in children and adolescents: Views based on a systematic review and meta-analysis. Psychiatry Res. 2015;227(1):93-103.

24. Andersson E, Enander J, Andren P, Hedman E, Ljotsson B, Hursti T, et al. Internet-based cognitive behaviour therapy for obsessive-compulsive disorder: a randomized controlled trial. Psychol Med. 2012;42(10):2193-203.

25. Lenhard F, Andersson E, Mataix-Cols D, Rück C, Vigerland S, Hogstrom J, et al. Therapist-Guided, Internet-Delivered Cognitive-Behavioral Therapy for Adolescents With Obsessive-Compulsive Disorder: A Randomized Controlled Trial. J Am Acad Child Adolesc Psychiatry. 2017;56(1):10-9 e2.

26. Aspvall K, Andren P, Lenhard F, Andersson E, Mataix-Cols D, Serlachius E. Internet-delivered cognitive behavioural therapy for young children with obsessive-compulsive disorder: development and initial evaluation of the BIP OCD Junior programme. BJPsych Open. 2018;4(3):106-12.

27. Skapinakis P, Caldwell DM, Hollingworth W, Bryden P, Fineberg NA, Salkovskis P, et al. Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2016;3(8):730-9.

28. Greenberg BD, Rauch SL, Haber SN. Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD. Neuropsychopharmacology. 2010;35(1):317-36.

29. Phillips KA, Didie ER, Menard W, Pagano ME, Fay C, Weisberg RB. Clinical features of body dysmorphic disorder in adolescents and adults. Psychiatry Res. 2006;141(3):305-14.

30. Phillips KA, Hart AS, Simpson HB, Stein DJ. Delusional versus nondelusional body dysmorphic disorder: recommendations for DSM-5. CNS Spectr. 2014;19(1):10-20.

31. Phillips KA, Pinto A, Hart AS, Coles ME, Eisen JL, Menard W, et al. A comparison of insight in body dysmorphic disorder and obsessive-compulsive disorder. J Psychiatr Res. 2012;46(10):1293-9.

32. Veale D, Gledhill LJ, Christodoulou P, Hodsoll J. Body dysmorphic disorder in different settings: A systematic review and estimated weighted prevalence. Body Image. 2016;18:168-86.

33. Enander J, Ivanov VZ, Mataix-Cols D, Kuja-Halkola R, Ljotsson B, Lundstrom S, et al. Prevalence and heritability of body dysmorphic symptoms in adolescents and young adults: a population-based nationwide twin study. Psychol Med. 2018;48(16):2740-7.

34. Bjornsson AS, Didie ER, Grant JE, Menard W, Stalker E, Phillips KA. Age at onset and clinical correlates in body dysmorphic disorder. Compr Psychiatry. 2013;54(7):893-903.

35. Phillips KA, Menard W, Quinn E, Didie ER, Stout RL. A 4-year prospective observational follow-up study of course and predictors of course in body dysmorphic disorder. Psychol Med. 2013;43(5):1109-17.

36. Monzani B, Rijsdijk F, Anson M, Iervolino AC, Cherkas L, Spector T, et al. A twin study of body dysmorphic concerns. Psychol Med. 2012;42(9):1949-55.

37. Lopez-Sola C, Fontenelle LF, Alonso P, Cuadras D, Foley DL, Pantelis C, et al. Prevalence and heritability of obsessive-compulsive spectrum and anxiety disorder symptoms: A survey of the Australian Twin Registry. Am J Med Genet B Neuropsychiatr Genet. 2014;165B(4):314-25.

38. Webb HJ, Zimmer-Gembeck MJ, Mastro S. Stress exposure and generation: A conjoint longitudinal model of body dysmorphic symptoms, peer acceptance, popularity, and victimization. Body Image. 2016;18:14-8.

39. Didie ER, Walters MM, Pinto A, Menard W, Eisen JL, Mancebo M, et al. A comparison of quality of life and psychosocial functioning in obsessive-compulsive disorder and body dysmorphic disorder. Ann Clin Psychiatry. 2007;19(3):181-6.

40. Albertini RS, Phillips KA. Thirty-three cases of body dysmorphic disorder in children and adolescents. J Am Acad Child Adolesc Psychiatry. 1999;38(4):453-9.

41. Mataix-Cols D, Fernández de la Cruz L, Isomura K, Anson M, Turner C, Monzani B, et al. A Pilot Randomized Controlled Trial of Cognitive-Behavioral Therapy for Adolescents With Body Dysmorphic Disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2015;54(11):895-904.

42. Angelakis I, Gooding PA, Panagioti M. Suicidality in body dysmorphic disorder (BDD): A systematic review with meta-analysis. Clin Psychol Rev. 2016;49:55-66.

43. Bowyer L, Krebs G, Mataix-Cols D, Veale D, Monzani B. A critical review of cosmetic treatment outcomes in body dysmorphic disorder. Body Image. 2016;19:1-8.

44. Harrison A, Fernández de la Cruz L, Enander J, Radua J, Mataix-Cols D. Cognitive-behavioral therapy for body dysmorphic disorder: A systematic review and meta-analysis of randomized controlled trials. Clin Psychol Rev. 2016;48:43-51.

45. Phillips KA, Albertini RS, Rasmussen SA. A randomized placebo-controlled trial of fluoxetine in body dysmorphic disorder. Arch Gen Psychiatry. 2002;59(4):381-8.

46. Phillips KA, Keshaviah A, Dougherty DD, Stout RL, Menard W, Wilhelm S. Pharmacotherapy Relapse Prevention in Body Dysmorphic Disorder: A Double-Blind, Placebo-Controlled Trial. Am J Psychiatry. 2016;173(9):887-95.

47. Phillips KA. Olanzapine augmentation of fluoxetine in body dysmorphic disorder. Am J Psychiatry. 2005;162(5):1022-3.

48. Phillips KA. Placebo-controlled study of pimozide augmentation of fluoxetine in body dysmorphic disorder. Am J Psychiatry. 2005;162(2):377-9.

49. Kay-Stacey M, Attarian H. Advances in the management of chronic insomnia. BMJ. 2016;354:i2123.

50. Leger D, Bayon V, Ohayon MM, Philip P, Ement P, Metlaine A, et al. Insomnia and accidents: cross-sectional study (EQUINOX) on sleep-related home, work and car accidents in 5293 subjects with insomnia from 10 countries. J Sleep Res. 2014;23(2):143-52.

51. Javaheri S, Redline S. Insomnia and Risk of Cardiovascular Disease. Chest. 2017;152(2):435-44.

52. Sivertsen B, Overland S, Pallesen S, Bjorvatn B, Nordhus IH, Maeland JG, et al. Insomnia and long sleep duration are risk factors for later work disability. The Hordaland Health Study. J Sleep Res. 2009;18(1):122-8.

53. Parthasarathy S, Vasquez MM, Halonen M, Bootzin R, Quan SF, Martinez FD, et al. Persistent insomnia is associated with mortality risk. Am J Med. 2015;128(3):268-75 e2.

54. McCall WV. A psychiatric perspective on insomnia. J Clin Psychiatry. 2001;62 Suppl 10:27-32.

55. MacDuffie KE, Shen MD, Dager SR, Styner MA, Kim SH, Paterson S, et al. Sleep Onset Problems and Subcortical Development in Infants Later Diagnosed With Autism Spectrum Disorder. Am J Psychiatry. 2020;177(6):518-25.

56. Gao X, Meng LX, Ma KL, Liang J, Wang H, Gao Q, et al. The bidirectional causal relationships of insomnia with five major psychiatric disorders: A Mendelian randomization study. Eur Psychiatry. 2019;60:79-85.

57. Asarnow LD, Manber R. Cognitive Behavioral Therapy for Insomnia in Depression. Sleep Med Clin. 2019;14(2):177-84.

58. Monti JM, Monti D. Sleep disturbance in generalized anxiety disorder and its treatment. Sleep Med Rev. 2000;4(3):263-76.

59. Cox RC, Olatunji BO. A systematic review of sleep disturbance in anxiety and related disorders. J Anxiety Disord. 2016;37:104-29.

60. Diaz-Roman A, Perestelo-Perez L, Buela-Casal G. Sleep in obsessive-compulsive disorder: a systematic review and meta-analysis. Sleep Med. 2015;16(9):1049-55.

61. Nota JA, Sharkey KM, Coles ME. Sleep, arousal, and circadian rhythms in adults with obsessive-compulsive disorder: a meta-analysis. Neurosci Biobehav Rev. 2015;51:100-7.

62. Perera MPN, Bailey NW, Herring SE, Fitzgerald PB. Electrophysiology of obsessive compulsive disorder: A systematic review of the electroencephalographic literature. J Anxiety Disord. 2019;62:1-14.

63. Coles ME, Schubert J, Stewart E, Sharkey KM, Deak M. Sleep duration and timing in obsessive-compulsive disorder (OCD): evidence for circadian phase delay. Sleep Med. 2020;72:111-7.

64. Bobdey M, Fineberg N, Gale TM, Patel A, Davies HA. Reported sleep patterns in obsessive compulsive disorder (OCD). Int J Psychiatry Clin Pract. 2002;6(1):15-21.

65. Donse L, Sack AT, Fitzgerald PB, Arns M. Sleep disturbances in obsessive-compulsive disorder: Association with non-response to repetitive transcranial magnetic stimulation (rTMS). J Anxiety Disord. 2017;49:31-9.

66. Ramsawh HJ, Stein MB, Belik SL, Jacobi F, Sareen J. Relationship of anxiety disorders, sleep quality, and functional impairment in a community sample. J Psychiatr Res. 2009;43(10):926-33.

67. Cox RC, Olatunji BO. Sleep disturbance and obsessive-compulsive symptoms: Results from the national comorbidity survey replication. J Psychiatr Res. 2016;75:41-5.

68. Timpano KR, Carbonella JY, Bernert RA, Schmidt NB. Obsessive compulsive symptoms and sleep difficulties: exploring the unique relationship between insomnia and obsessions. J Psychiatr Res. 2014;57:101-7.

69. Raines AM, Short NA, Sutton CA, Oglesby ME, Allan NP, Schmidt NB. Obsessive-compulsive symptom dimensions and insomnia: The mediating role of anxiety sensitivity cognitive concerns. Psychiatry Res. 2015;228(3):368-72.

70. Rapoport J, Elkins R, Langer DH, Sceery W, Buchsbaum MS, Gillin JC, et al. Childhood obsessive-compulsive disorder. Am J Psychiatry. 1981;138(12):1545-54.

71. Ivarsson T, Larsson B. Sleep problems as reported by parents in Swedish children and adolescents with obsessive-compulsive disorder (OCD), child psychiatric outpatients and school children. Nord J Psychiatry. 2009;63(6):480-4.

72. Storch EA, Murphy TK, Lack CW, Geffken GR, Jacob ML, Goodman WK. Sleep-related problems in pediatric obsessive-compulsive disorder. Journal of anxiety disorders. 2008;22(5):877-85.

73. Jaspers-Fayer F, Lin SY, Belschner L, Mah J, Chan E, Bleakley C, et al. A case-control study of sleep disturbances in pediatric obsessive-compulsive disorder. J Anxiety Disord. 2018;55:1-7.

74. Ivarsson T, Skarphedinsson G. Sleep problems and cognitive behavior therapy in pediatric obsessive-compulsive disorder have bidirectional effects. J Anxiety Disord. 2015;30:28-33.

75. Nabinger de Diaz NA, Farrell LJ, Waters AM, Donovan C, McConnell HW. Sleep-Related Problems in Pediatric Obsessive-Compulsive Disorder and Intensive Exposure Therapy. Behav Ther. 2019;50(3):608-20.

76. Ricketts EJ, Snorrason I, Rozenman M, Colwell CS, McCracken JT, Piacentini J. Sleep functioning in adults with trichotillomania (hair-pulling disorder), excoriation

(skin-picking) disorder, and a non-affected comparison sample. J Obsessive Compuls Relat Disord. 2017;13:49-57.

77. Raines AM, Portero AK, Unruh AS, Short NA, Schmidt NB. An Initial Investigation of the Relationship Between Insomnia and Hoarding. J Clin Psychol. 2015;71(7):707-14.

78. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev. 2002;6(2):97-111.

79. Rück C, Larsson KJ, Lind K, Perez-Vigil A, Isomura K, Sariaslan A, et al. Validity and reliability of chronic tic disorder and obsessive-compulsive disorder diagnoses in the Swedish National Patient Register. BMJ Open. 2015;5(6):e007520.

80. Gregory AM, Rijsdijk FV, Eley TC, Buysse DJ, Schneider MN, Parsons M, et al. A Longitudinal Twin and Sibling Study of Associations between Insomnia and Depression Symptoms in Young Adults. Sleep. 2016;39(11):1985-92.

81. Sevilla-Cermeño L, Andren P, Hillborg M, Silverberg-Morse M, Mataix-Cols D, Fernández de la Cruz L. Insomnia in pediatric obsessive-compulsive disorder: prevalence and association with multimodal treatment outcomes in a naturalistic clinical setting. Sleep Med. 2019.

82. Alfano CA, Ginsburg GS, Kingery JN. Sleep-related problems among children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2007;46(2):224-32.

83. Richdale AL, Baker E, Short M, Gradisar M. The role of insomnia, pre-sleep arousal and psychopathology symptoms in daytime impairment in adolescents with high-functioning autism spectrum disorder. Sleep Med. 2014;15(9):1082-8.

84. Craig SG, Weiss MD, Hudec KL, Gibbons C. The Functional Impact of Sleep Disorders in Children With ADHD. J Atten Disord. 2017:1087054716685840.

85. Chung KF, Kan KK, Yeung WF. Assessing insomnia in adolescents: comparison of Insomnia Severity Index, Athens Insomnia Scale and Sleep Quality Index. Sleep Med. 2011;12(5):463-70.

86. Freeman D, Sheaves B, Goodwin GM, Yu LM, Nickless A, Harrison PJ, et al. The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis. Lancet Psychiatry. 2017;4(10):749-58.

87. Kleim B, Wilhelm FH, Temp L, Margraf J, Wiederhold BK, Rasch B. Sleep enhances exposure therapy. Psychol Med. 2014;44(7):1511-9.

88. Lind MJ, Hawn SE, Sheerin CM, Aggen SH, Kirkpatrick RM, Kendler KS, et al. An examination of the etiologic overlap between the genetic and environmental influences on insomnia and common psychopathology. Depress Anxiety. 2017;34(5):453-62.