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CLINICAL CHARACTERISTICS AND TREATMENT OUTCOMES IN BODY DYSMORPHIC DISORDER

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Clinical Characteristics and Treatment Outcomes in Body Dysmorphic Disorder

Thesis for Doctoral Degree (Ph.D.)

By

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To mom and dad

Popular science summary of the thesis

Body dysmorphic disorder (BDD) is a mental disorder that has its onset in early adolescence. A person with BDD is preoccupied with one or several flaws in physical appearance that are not visible or appear slight to others. This preoccupation typically leads to time-consuming behaviors (such as mirror-checking and excessive use of make-up), severe anxiety and avoidance of social situations (such as being with friends or in school). Research on this disorder is limited, especially on young people with BDD. Furthermore, most people with BDD do not get access to the recommended treatment, cognitive-behavior therapy (CBT). The overall aim of this thesis was to describe BDD in more detail, and to help more young people with BDD get access to CBT.

In Study 1, 600 individuals with a diagnosis (according to the diagnostic system ICD-10) of hypochondriasis or dysmorphophobia (i.e., BDD) (300 each) were randomly selected from the Swedish National Patient Register. Eighty-four medical files of people with hypochondriasis and 122 files of people with BDD were received and used for analyses. Two independent raters (physicians or psychologists working with these disorders) read all medical files and decided independently if the diagnoses in the files were correct. Both raters agreed to a high extent in their judgements regarding the presence or absence of a diagnosis (95.2% for hypochondriasis and 92.6% for BDD). They considered the diagnosis to be correct in 80% of the hypochondriasis files and in 91% of the BDD files. These results confirmed that clinicians are good at assigning these diagnostic labels and, therefore, the Swedish ICD-10 codes for hypochondriasis and BDD are of sufficiently good quality to be used in register-based studies.

Following up on Study 1, Study 2 was a population-based study using the Swedish registers and included 2,833 individuals with BDD from all over Sweden diagnosed from 1997 to 2020. We matched each person with BDD with 10 individuals without BDD from the general population in order to compare them. During the study period, 466 (16.5%) individuals with BDD and 1,071 (3.8%) individuals without BDD had at least one record of intentional self-harm in the National Patient Register, translating into a risk of self-harm more than three times higher in individuals with BDD, compared to the matched controls. Furthermore, a total of 17 (0.6%) individuals with BDD and 27 (0.1%) without BDD died by suicide during the study period, with a risk of death by suicide three times higher in individuals with BDD, compared with the matched controls. In sum, this study showed that individuals with BDD have an increased risk of both self-harming and of dying by suicide, compared to individuals without BDD.

In Studies 3 and 4 the aims were to explore the characteristics of a large group of adolescents with BDD, to evaluate how well this group responded to treatment, and to examine factors that may predict treatment response. We saw that most adolescents (71.5%) with BDD had other mental health diagnoses. Other common features in this group were the presence of self-harm (52.1%), suicide attempts (11.0%), desire for cosmetic procedures (53.7%), and school dropout (32.4%). After receiving treatment consisting of CBT and medication when deemed necessary,

79% of the participants were classified as treatment responders and 59% as full or partial remitters (meaning that they did no longer meet the formal criteria for BDD). Encouragingly, BDD symptoms continued to improve one year after the end of the treatment. We could not find any specific characteristics of the participants that predicted who was going to respond to treatment. The conclusion of these studies was that, while BDD in young people can be a serious and disabling disorder accompanied with risky behaviors and problems in everyday functioning, the evaluated treatment is effective in both the short- and long-term when provided flexibly within a specialist clinic.

Finally, in Study 5, we transferred the treatment protocol evaluated in Study 4 to an online format. The treatment was considered both credible and satisfactory and the participants had a large reduction in BDD symptoms after treatment. Three months after treatment, 74% of the participants were classified as responders and 63% as full or partial remitters, and the results were maintained over the following year. The therapist supporting the participants through the online treatment online spent, on average, 8 minutes per participant and week. We also confirmed that risky behaviors typical of this patient group, such as self-harm and suicide attempts, must be carefully monitored during treatment. The conclusion of this study was that CBT treatment delivered over the Internet with minimal therapist support is feasible for adolescents with BDD and shows promising effects in reducing BDD symptoms, both in the short- and the long-term.

To summarize, this thesis concludes that BDD can be a severe and impairing mental disorder with several risks, including an elevated risk of self-harm and death by suicide. It further suggests that CBT for young people with BDD can be successfully implemented in specialist clinics. Online delivery of this treatment is a promising strategy to make it available to a larger number of young people with the disorder.

Abstract

Body dysmorphic disorder (BDD) is an early onset mental disorder characterized by a preoccupation with perceived flaws in physical appearance. Research on the presentation of the disorder is sparse, especially on young people with BDD. Furthermore, the availability of cognitive-behavior therapy (CBT) for the disorder is generally low, despite being recommended in treatment guidelines. The overall aim of this thesis was to further describe the clinical characteristics of BDD and to promote the dissemination of CBT among youth with BDD.

In Study 1, 600 individuals with an ICD-10 diagnosis of hypochondriasis or dysmorphophobia (i.e., BDD) (300 each) were randomly selected from the Swedish National Patient Register. Eighty-four medical files of individuals with hypochondriasis and 122 files of individuals with dysmorphophobia were received and used for analyses. Two independent raters assessed the validity and reliability of the diagnosis by performing an evaluation of the clinical charts. The inter-rater agreement regarding the presence or absence of a diagnosis was high for both disorders (95.2% for hypochondriasis and 92.6% for dysmorphophobia), and 80% of the hypochondriasis files and 91% of the dysmorphophobia files were considered 'true positive' cases. These results confirmed that the Swedish ICD-10 codes for hypochondriasis and dysmorphophobia are sufficiently valid and reliable to be used in register-based studies.

Following up on Study 1, Study 2 was a Swedish nationwide matched-cohort study of 2,833 individuals with an ICD-10 diagnosis of BDD, each matched with 10 unaffected individuals from the general population. During the study period, 466 (16.45%) individuals with BDD and 1,071 (3.78%) unexposed controls from the general population had at least one record of intentional self-harm. In adjusted models, an elevated risk of intentional self-harm was observed among individuals with BDD (IRR=3.37 [95% CI, 3.02-3.76]). Additionally, a total of 17 (0.60%) individuals with BDD and 27 (0.10%) individuals from the general population died by suicide (HR=3.47 [95% CI, 1.76-6.85]). In sum, individuals with BDD showed an increased risk of self-harm and death by suicide, compared to individuals without BDD.

In Studies 3 and 4 the aims were to explore the characteristics of a large cohort of adolescents with BDD, to evaluate the multimodal treatment outcomes of this cohort, and to examine potential predictors of treatment response. In our sample, we observed high rates of psychiatric comorbidity (71.5%), self-harm (52.1%), suicide attempts (11.0%), desire for cosmetic procedures (53.7%), and school dropout (32.4%). After receiving multimodal treatment consisting of CBT and medication when deemed necessary, 79% of the participants were classified as treatment responders and 59% as full or partial remitters. Encouragingly, BDD symptoms continued to improve up to one year after the end of the treatment. BDD symptom severity was identified as a predictor of treatment outcomes at post-treatment, but no consistent predictors were found at the one-year follow-up. The conclusion of these studies was that, while BDD in young people can be a serious and disabling disorder, often accompanied with

substantial functional impairment and risky behaviors, multimodal treatment is effective in both the short- and the long-term when provided flexibly within a specialist setting.

Finally, in Study 5, we transferred the treatment protocol evaluated in Study 4 to an online version. The treatment was considered both credible and satisfactory and was associated with a large reduction in BDD symptoms. At the a priori primary endpoint (3-months follow-up), 74% of the participants were classified as responders and 63% as full or partial remitters, and the results continued to improve up to the 12-month follow-up. Furthermore, the average therapist support time was 8 minutes per participant and week. Nonetheless, risky behaviors typical of this patient group should be carefully monitored during treatment. CBT delivered in an online format with minimal therapist support is a feasible, potentially efficacious, and durable treatment for adolescents with BDD.

To summarize, this thesis concludes that BDD can be a severe and impairing mental disorder with several risks, including an elevated risk of intentional self-harm and death by suicide. It further suggests that face-to-face CBT for young people with BDD can be successfully implemented in specialist outpatient settings. To further increase treatment availability, CBT may also be delivered remotely, which has the potential to improve access to evidence-based treatment for youth with BDD.

List of scientific papers

I. **Rautio, D.**, Vilaplana-Pérez, A., Gumpert, M., Ivanov, V. Z., Linde J, Österman, S., Flygare, O., Isung, J., Isomura, K., Krig, S., Serlachius, E., Högström, J., Rück, C., Mataix-Cols, D., & Fernández de la Cruz, L. (2021). Validity and reliability of the diagnostic codes for hypochondriasis and dysmorphophobia in the Swedish National Patient Register: A retrospective chart review. *BMJ Open, 11*(12), e051853.

II. **Rautio, D.**, Isomura, K., Bjureberg, J., Rück, C., Lichtenstein, P., Larsson, H., Kuja-Halkola, R., Chang, Z., D'Onofrio, B. M., Brikell, I., Sidorchuk, A., Mataix-Cols, D., & Fernández de la Cruz, L. Intentional self-harm and deaths by suicide in body dysmorphic disorder: A population-based study in Sweden. *Submitted manuscript.*

III. **Rautio, D.**, Jassi, A., Krebs, G., Andrén, P., Monzani, B., Gumpert, M., Lewis, A., Peile, L., Sevilla-Cermeño, L., Jansson-Fröjmark, M., Lundgren, T., Hillborg, M., Silverberg-Mörse, M., Clark, B., Fernández de la Cruz, L., & Mataix-Cols, D. (2022). Clinical characteristics of 172 children and adolescents with body dysmorphic disorder. *European Child and Adolescent Psychiatry*, *31*(1), 133–144.

IV. **Rautio, D.***, Gumpert, M.*, Jassi, A., Krebs, G., Flygare, O., Andrén, P., Monzani, B., Peile, L., Jansson-Fröjmark, M., Lundgren, T., Hillborg, M., Silverberg-Mörse, M., Clark, B., Fernández de la Cruz, L., & Mataix-Cols, D. (2022). Effectiveness of multimodal treatment for young people with body dysmorphic disorder in two specialist clinics. *Behavior Therapy*, *53*(5), 1037–1049. [* joint first authors]

V. **Rautio, D.**, Andrén, P., Gumpert, M., Jolstedt, M., Jassi, A., Krebs, G., Jansson-Fröjmark, M., Lundgren, T., Serlachius, E., Mataix-Cols, D., & Fernández de la Cruz, L. (2023). Therapist-guided, Internet-delivered cognitive-behaviour therapy for adolescents with body dysmorphic disorder: A feasibility trial with long-term follow-up. *Internet Interventions*, *34*, 100688.

Scientific papers not included in this thesis

I. Gumpert, M., **Rautio, D**., Monzani, B., Jassi, A., Krebs, G., Fernández de la Cruz, L., Mataix-Cols, D., & Jansson-Fröjmark, M. (2024) Psychometric evaluation of the Appearance Anxiety Inventory in adolescents with body dysmorphic disorder. *Cognitive Behaviour Therapy.* Jan 4:1-13. Online ahead of print.

II. Mataix-Cols, D., Isomura, K., Sidorchuk, A., **Rautio, D.**, Ivanov, V. Z., Rück, C., Österman, S., Lichtenstein, P., Larsson, H., Kuja-Halkola, R., Chang, Z., Brickell, I., Hedman-Lagerlöf, E., & Fernández de la Cruz, L. (2023). All-cause and cause-specific mortality in hypochondriasis. *JAMA Psychiatry*. Advanced online publication, December 13.

III. **Rautio, D**., Andrén, P., Bjureberg, L., Silverberg-Mörse, M., Mataix-Cols, D., & Fernández de la Cruz, L. (2023). Body-Focused Repetitive Behavior Disorders in Children and Adolescents: Clinical Characteristics and Treatment Outcomes in a Naturalistic Setting. *Behavior Therapy.* Advanced online publication July 27.

IV. Monzani, B., Fallah, D., **Rautio, D**., Gumpert, M., Jassi, A., Fernández de la Cruz, L., Mataix-Cols, D., & Krebs, G. (2022). Psychometric Evaluation of the Yale-Brown Obsessive-Compulsive Scale Modified for Body Dysmorphic Disorder for Adolescents (BDD-YBOCS-A). *Child Psychiatry and Human Development, 54*(6), 1799–1806.

V. Krebs, G., Fernández de la Cruz, L., Rijsdijk, F. V., **Rautio, D**., Enander, J., Rück, C., Lichtenstein, P., Lundström, S., Larsson, H., Eley, T. C., & Mataix-Cols, D. (2022). The association between body dysmorphic symptoms and suicidality among adolescents and young adults: a genetically informative study. *Psychological Medicine*, *52*(7), 1268–1276.

VI. De Visscher, C., Hesselmark, E., **Rautio, D**., Djupedal, I. G., Silverberg, M., Nordström, S. I., Serlachius, E., & Mataix-Cols, D. (2021). Measuring clinical outcomes in children with pediatric acute-onset neuropsychiatric syndrome: data from a 2-5 year follow-up study. *BMC Psychiatry*, *21*(1), 484.

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VIII. Vilaplana-Pérez, A., Isung, J., Krig, S., Vigerland, S., Jolstedt, M., Bjureberg, J., Högström, J., Isomura, K., **Rautio, D**., Serlachius, E., Rück, C., Mataix-Cols, D., & Fernández de la Cruz, L. (2020). Validity and reliability of social anxiety disorder diagnoses in the Swedish National Patient Register. *BMC Psychiatry*, *20*(1), 242.

IX. Sevilla-Cermeño, L., **Rautio, D**., Andrén, P., Hillborg, M., Silverberg-Morse, M., Lahera, G., Mataix-Cols, D., & Fernández de la Cruz, L. (2020). Prevalence and impact of insomnia in children and adolescents with body dysmorphic disorder undergoing multimodal specialist treatment. *European Child & Adolescent Psychiatry*, *29*(9), 1289–1299.

X. Choque Olsson, N., **Rautio, D**., Asztalos, J., Stoetzer, U., & Bölte, S. Social skills group training in high-functioning autism: A qualitative responder study. (2016). *Autism*, *20*(8), 2016, 995–1010.

Contents

List of abbreviations

BDD	Body Dysmorphic Disorder
BDD-YBOCS-A	Yale-Brown Obsessive-Compulsive Scale Modified for BDD, Adolescent Version
CBT	Cognitive-Behavior Therapy
CI	Confidence Interval
CGI-S	Clinical Global Assessment Scale - Severity
DSM	Diagnostic and Statistical Manual of Mental Disorders
ERP	Exposure with Response Prevention
FU	Follow-up
GAF	Global Assessment of Functioning
GDPR	General Data Protection Regulation
GWAS	Genome-wide association studies
HR	Hazard Ratio
ICC	Intraclass Correlation Coefficient
ICD	International Statistical Classification of Diseases and Related Health Problems
IRR	Incidence Rate Ratio
NPR	National Patient Register
OCD	Obsessive-Compulsive Disorder
PPV	Positive Predictive Value
RCT	Randomized Controlled Trial
SSRI	Selective Serotonin Reuptake Inhibitors

1 Introduction

Body dysmorphic disorder (BDD) is a mental health condition that has been known for over a century. It was first described in 1891 by the Italian psychiatrist, Enrico Morselli. He named the disorder "dysmorphophobia," from the Greek word 'dismorfia', where 'dis' means abnormal and 'morpho' means shape. Over the decades that followed, several case studies of individuals with dysmorphophobia were presented by Pierre Janet and Sigmund Freud, among others (França et al., 2017). These historical case studies have a striking resemblance to the cases we meet at our clinics today, illustrating the fact that this is a disorder that has been around for a long time.

Despite having been known for more than a century, it was not until the eighties that the disorder made its way into the official diagnostic manuals. It was first described in the third edition of the American Diagnostic and Statistical Manual (DSM-III) (American Psychiatric Association, 1980) as an "atypical somatoform disorder". In the revised version of this edition (DSM-III-R), published in 1987 (American Psychiatric Association, 1987), the term *body dysmorphic disorder* was used for the first time and it has since been since then the "official" name for the disorder, even if the term dysmorphophobia is still used in some parts of the world, for example in Sweden (as *dysmorfofobi*).

Over the years, individuals with BDD have had a hard time earning a proper understanding of their problems and having their suffering correctly diagnosed. Knowledge of BDD among professionals has been and continues to be limited. Also, criteria have changed over time and the disorder has been classified and/or described as somatoform, hypochondriacal, delusional, and/or obsessive-compulsive (Phillips et al., 2010). Gaps in knowledge and lack of diagnostic accuracy are probably important reasons why this patient group has been severely underdetected and underresearched for a long time. It is, for obvious reasons, difficult to receive the right treatment if you do not get the right diagnosis.

However, even if you, as a sufferer, manage to make your way to a clinic where professionals are familiar with BDD, are thoroughly assessed, and receive the correct diagnosis, there is no guarantee that you will receive evidence-based treatment for BDD. Compared to other psychiatric disorders, there are not many treatment evaluations in adult patients with BDD and, when it comes to children and adolescents, the empirical base is close to non-existent (Harrison, Fernández de la Cruz, Enander, Radua, & Mataix-Cols, 2016). Thus, expertise on how to treat BDD and access to evidence-based treatments are still generally low.

In an attempt to fill these gaps, this thesis aimed to broaden the knowledge about BDD and to promote dissemination of effective treatments. The first part of the thesis aims first paves the way to conduct a register-based study on clinically diagnosed individuals with this disorder, which to our knowledge has never been done before, to later perform such study focusing on two relevant outcomes: self-harm and suicide. The second part focuses specifically on children and adolescents with BDD, a group that has so far received very little attention. The combined ambition of these two parts is to spread knowledge about the disorder and to investigate ways to provide effective treatment to as many young sufferers as possible.

2 Literature review

2.1 Diagnostic features

2.1.1 Description

Body dysmorphic disorder (BDD), also known as dysmorphophobia, is an often severe and disabling mental health condition (American Psychiatric Association, 2013). The disorder is characterized by a preoccupation with perceived defects or flaws in physical appearance that are not visible or appear slight to others. Normally, individuals with BDD are preoccupied with multiple areas of their appearance, mainly skin, hair, nose, and face, but any part of the body may be seen as defective or flawed (Albertini & Phillips, 1999; Phillips et al., 2006). Because of the perceived flaw, the sufferer engages in a range of time-consuming repetitive behaviors, like camouflaging, excessive use of make-up or mirror checking (American Psychiatric Association, 2013). The disorder is associated with high levels of distress and global functional impairment (Albertini & Phillips, 1999; Mataix-Cols et al., 2015; Phillips et al., 2006).

The clinical presentation of BDD in adolescents is thought to be as severe as the adult presentation, but so far only a few case series and case reports (Horowitz, Gorfinkle, Lewis, & Phillips, 2002; Krebs, Turner, Heyman, & Mataix-Cols, 2012; Phillips, Atala, & Albertini, 1995; Sobanski & Schmidt, 2000) and three modestly sized clinical studies (n range=30-36) have reported on the clinical characteristics of young people with BDD (Albertini & Phillips, 1999; Mataix-Cols et al., 2015; Phillips et al., 2006). Thus, more research specifically targeting young people with BDD is needed.

Individuals suffering from BDD are often unwilling to seek mental health care, in large part due to poor or delusional insight into the condition, which is common in this patient group (Phillips et al., 2006). People with BDD are often convinced that they have a genuine physical flaw, and therefore may not perceive a need for any psychiatric or psychological treatment, but rather have a desire for cosmetic procedures or other interventions that can modify their external appearance (Bowyer, Krebs, Mataix-Cols, Veale, & Monzani, 2016; Phillips et al., 2006). This leads to lower help-seeking rates than in other, generally egodystonic, disorders such as obsessive-compulsive disorder (OCD). Another reason why BDD is often under detected in mental health settings is that individuals with BDD are often reluctant to disclose their body image concerns due to shame or embarrassment. A third reason why BDD may be overlooked, especially among adolescents with BDD, is that the excessive worries about appearance may be seen as normal teenage concerns (Krebs, Fernández de la Cruz, & Mataix-Cols, 2017; Veale, Gledhill, Christodoulou, & Hodsoll, 2016).

2.1.2 Diagnostic criteria

The formal definition and classification of BDD has changed several times over the years. In the DSM-III, BDD was described for the first time in the diagnostic system, but with no specific associated diagnostic criteria. The disorder was referred to as “dysmorphophobia” and was an example of an atypical somatoform disorder (American Psychiatric Association, 1980). In the

revised version of the same manual (DSM-III-R), BDD was for the first time classified as a separate disorder with distinct diagnostic criteria within the somatoform section. These first formal criteria were: A) preoccupation with an imagined defect in appearance; B) this preoccupation is non-delusional; and C) the preoccupation does not exclusively occur during the course of anorexia or transsexualism (American Psychiatric Association, 1987).

The disorder was further revised in the DSM-IV. The most significant change, compared to the previous DSM version, was the addition of a criterion B (i.e., clinically significant impairment) to differentiate BDD from normal appearance concerns. Moreover, in the DSM-IV, the distinction between delusional and non-delusional BDD was removed because there was preliminary evidence suggesting that both delusional and non-delusional BDD may be variants of the same disorder (American Psychiatric Association, 1994). The diagnostic criteria for the disorder did not change in the DSM-IV-TR (American Psychiatric Association, 2000).

The current version of the DSM (DSM-5), published in 2013, introduced a major change, which was the classification of BDD under the newly created obsessive-compulsive and related disorders chapter. Additionally, a new diagnostic criterion was included, together with the preoccupations with the appearance (criterion A), consisting in the presence of repetitive behaviors (e.g., mirror checking, excessive grooming) (criterion B), assimilating BDD to the diagnostic criteria for OCD (i.e., including obsessions and compulsions) (American Psychiatric Association, 2013).

In the more recently published ICD-11, in which the mental disorders chapter largely mimics the classification presented in the DSM-5, BDD is also classified under a new obsessive-compulsive or related disorders chapter and presented as an independent condition within this group (6B21) (World Health Organization, 2018). However, in the previous ICD-10, dysmorphophobia appeared only as an inclusion term under hypochondriasis, coded F45.2, and was classified as a somatoform disorder (F45) under the neurotic, stress-related, and somatoform disorders section (F40-F45) in chapter V, mental and behavioral disorders (World Health Organization, 1992). Thus, in the ICD-10, BDD and hypochondriasis shared the same diagnostic code, which administratively makes it impossible to differentiate them from one another. However, interestingly, in the Swedish version of the ICD-10 there is a possibility to code hypochondriasis as F45.2 and dysmorphophobia as F45.2A, which provides an opportunity to differentiate these conditions. To pave the way for future epidemiological research on these disorders, the codes have now been validated by our research group as part of this thesis.

2.2 Epidemiology

2.2.1 Prevalence

BDD has an estimated prevalence of around 2% in community samples of both adolescents and adults (Buhlmann et al., 2010; Krebs, Clark, Ford, & Stringaris, 2023; Veale et al., 2016). The prevalence has shown to be higher in clinical settings, with a suggested rate of 7.4% in adult psychiatric inpatients and 5.8% in adult outpatients, and between 6.7%-14.3% in adolescent psychiatric inpatient settings (Veale et al., 2016). The prevalence is even higher in

dermatology and cosmetic surgery settings, with estimated rates around 15%-20% (McGrath, Oey, McDonald, Berle, & Wootton, 2023; Ribeiro, 2017; Veale et al., 2016).

In adult community samples, the disorder is only slightly more common in women, compared to men (Buhlmann et al., 2010; Koran, Abujaoude, Large, & Serpe, 2008; Veale et al., 2016), while BDD has shown to be much more common among women in adolescents and young adults (Enander et al., 2018; Krebs et al., 2023). In clinical settings, as well as in dermatology and cosmetic surgery settings, studies also show an overrepresentation of women (Ribeiro, 2017; Veale et al., 2016).

The difference in prevalence rates between men and women tends to decrease with age (Enander et al., 2018), as confirmed by recent findings suggesting that men, on average, have a later age of BDD onset (Krebs et al., 2023). However, it may be that the disorder is more difficult to detect among boys, and it is possible that socio-cultural factors play a role on this, whereby it might be less socially acceptable for boys to disclose appearance-related problems. An underrepresentation of men in clinical samples may also indicate a reluctance among men to seek proper care. All in all, this highlights the need to screen for the disorder extra carefully among boys and men.

2.2.2 Course

The onset of BDD often occurs during adolescence, with a reported mean age of onset around 16 years (Bjornsson et al., 2013; Phillips et al., 2006). Additionally, adults who self-report an early onset of their BDD (i.e., at age 17 or younger), compared to a later onset, have described to have greater symptom severity, higher risk of attempted suicide, and more psychiatric comorbidities (Bjornsson et al., 2013).

Long-term follow-up studies on adults with the disorder suggest that BDD tends to have a chronic and unremitting course if left untreated (Phillips, Menard, Quinn, Didie, & Stout, 2013), which further highlights the need for early detection and treatment.

2.2.3 Comorbidities

Studies on the adult BDD population suggest that psychiatric comorbidity is the norm (Gunstad & Phillips, 2003), with high rates of mood and anxiety disorders, but also OCD, both in clinical and community samples (Phillips et al., 2006; Veale et al., 2016).

Previous studies on adolescent BDD have also reported very high rates of psychiatric comorbidity. In community samples, most adolescents with BDD have at least one comorbid psychiatric condition (Enander et al., 2018; Schneider, Turner, Mond, & Hudson, 2017). This is more pronounced in clinical samples, where more than two thirds of the participants have shown to have psychiatric comorbidities, most commonly mood and anxiety disorders (Albertini & Phillips, 1999; Mataix-Cols et al., 2015; Phillips et al., 2006).

2.3 Etiology and neurobiological correlates

2.3.1 Etiological factors

BDD has shown to be familial. One family study (Bienvenu et al., 2000) found that individuals with a first-degree relative with BDD were 4 to 8 times more likely to meet criteria for BDD themselves, compared to other individuals that had no relatives with BDD. To the best of my knowledge, four twin studies have examined to which extent genetic factors account for the variance of BDD symptoms (Enander et al., 2018; López-Solà et al., 2014; Monzani et al., 2012; Monzani, Rijsdijk, Harris, & Mataix-Cols, 2014). The results suggest that genetic factors explain about 39%-49% of the variance and that the impact of the shared environment in the etiology of BDD is negligible; hence, the remaining variance is thought to be explained by non-shared environmental factors.

Only one small candidate gene study (Phillips et al., 2015) with inconclusive results has been published on BDD, but no genome-wide association studies (GWAS) have yet been conducted in this field. Thus, no specific risk genes have yet been identified. Regarding non-shared environmental risk factors, few factors have been studied. Bullying and appearance-related teasing have been suggested to be common among young people with BDD (Buhlmann, Cook, Fama, & Wilhelm, 2007; Weingarden, Curley, Renshaw, & Wilhelm, 2017). Also, adults with BDD have reported elevated levels of abuse, compared to healthy controls (Buhlmann, Marques, & Wilhelm, 2012). A recent meta-analysis found a moderate association between BDD symptoms and experiences of teasing (r=0.42) and smaller associations with experiences of bullying (r=0.28) and childhood abuse (r=0.22) (Longobardi, Badenes-Ribera, & Fabris, 2022). However, it is unknown whether these associations are causal. Also, the existing literature has a number of methodological limitations, including small sample sizes (Krebs, Fernández de la Cruz, & Mataix-Cols, 2017).

In sum, results from twin and family studies suggest that BDD has a genetic basis and that non-shared environmental factors are at least as important in the etiology of the disorder. However, the literature is very scarce and further studies focusing on what specific genes and environmental factors increase the risk for developing BDD are needed.

2.3.2 Neurobiological correlates and neuropsychological performance

Other studies have tried to find brain abnormalities associated with BDD. A recent review of brain structure and function identified the temporal gyrus, limbic system, and prefrontal cortex as important regions in understanding BDD (Grace, Labuschagne, Kaplan, & Rossell, 2017). However, sample sizes for most studies in this area are still small (n<20) and no specific abnormalities in certain parts of the brain have been reliably linked to BDD. Hence, the understanding of the pathophysiology of BDD remains unknown.

Another important field of research in BDD, aiming at better understanding how symptoms of BDD are initiated and maintained, focuses on the differences in neuropsychological performance associated with the disorder, compared to those of individuals without the disorder. A systematic review on visual processing in BDD (Beilharz, Castle, Grace, & Rossell,

2017) found several deficits in visual processing in individuals with the disorder, including face recognition, emotion identification, aesthetics, object recognition, and gestalt processing. In line with these results, a meta-analysis on visual processing in BDD and anorexia nervosa (Lang et al., 2021) found that individuals with BDD showed poorer global processing and an over-focus on details, compared to healthy controls. It is suggested that this visual processing style may be associated with a distorted body image, due to selective attention towards the perceived appearance flaws (Fang & Wilhelm, 2015; Lang et al., 2021).

Another meta-analysis on cognitive processing deficits associated with BDD (Johnson, Williamson, & Wade, 2018) found that certain cognitive processing abnormalities, such as interpretive biases, selective attention, and memory deficits may be associated with how BDD symptoms are initiated and maintained.

These neuropsychological findings provide a better picture of the BDD brain. However, more research is needed to design interventions that target and potentially remediate specific differences in neuropsychological performance in individuals with BDD. This research may help improving psychological interventions targeting BDD symptoms.

2.4 Impact

In the literature, BDD is described as a severe and disabling disorder associated with several risky behaviors. Of these, probably the most worrying consequence of BDD are the associated suicidal thoughts and suicide attempts, which have been well documented in adult BDD (Angelakis, Gooding, & Panagioti, 2016; Pellegrini et al., 2021). High rates of suicidal ideation, self-harm, and suicide attempts have also been described in clinical samples of adolescents with BDD (Albertini & Phillips, 1999; Mataix-Cols et al., 2015; Phillips et al., 2006). Moreover, in a large cross-sectional survey, 46.3% (95% CI, 33.3%-59.8%) of young people with BDD reported a lifetime history of self-harm or suicide attempts, compared to 8% (95% CI, 7.2%-9.0%) of those without BDD (Krebs et al., 2023). Similarly, in a register-based study using the Swedish twin register, young adults with probable BDD were more likely to self-report suicidal ideation and suicidal behaviors than those without these symptoms. One in four of those with probable BDD self-reported lifetime suicide attempts, compared to 5% of those without probable BDD (Krebs et al., 2020).

Adolescents with BDD also have shown high rates of school dropout (Albertini & Phillips, 1999; Mataix-Cols et al., 2015; Phillips et al., 2006). Missing school days may affect educational attainment and limit the chances of going into higher education, which could affect future employment opportunities, further increasing the functional impairment caused by the disorder. This risk of educational underachievement has been described using objectively collected data in OCD and social anxiety disorder, two disorders that share many characteristics with BDD (Pérez-Vigil et al., 2018; Vilaplana-Pérez et al., 2021). However, it has not been systematically studied in BDD.

Another BDD-related risky behavior perceived as particularly worrying in those of young age is the pursuit of unneeded cosmetic procedures and surgeries. These behaviors might be more prominent in those with low insight, given that individuals with BDD tend to believe that one's

physical appearance is objectively flawed, and therefore may be fixed through these procedures (Albertini & Phillips, 1999; Phillips et al., 2006; Phillips et al., 2012). Existing evidence, although scarce, suggests that undergoing such cosmetic procedures is probably associated with poor outcomes in individuals with BDD (Bowyer et al., 2016). Therefore, cosmetic surgery can be considered a contraindication in those with BDD, and cosmetic and surgical interventions among individuals with BDD should generally be discouraged (Bowyer et al., 2016; Castle et al., 2021).

2.5 Evidence-based treatments for BDD

2.5.1 Cognitive-behavior therapy

The existing treatment guidelines recommend cognitive-behavior therapy (CBT) as the first line treatment for both adolescents and adults with BDD (National Institute for Health and Care Excellence, 2005). CBT has shown to be efficacious in a meta-analysis of seven randomized controlled trials (RCT) of CBT for BDD (Harrison et al., 2016). Three additional RCTs published after this meta-analysis support the efficacy of CBT for BDD (Ritter, Schüller, Berkmann, von Soosten-Höllings-Lilge, & Stangier, 2023; Wilhelm et al., 2019; Wilhelm et al., 2022). However, only one of the 10 above-mentioned RCTs tested CBT for BDD in the pediatric population (Mataix-Cols et al., 2015).

This single pilot RCT on adolescents (Mataix-Cols et al., 2015) showed that participants in the CBT condition (n=15) had a significantly larger reduction on BDD symptoms than those participants in the control condition (n=15), both at post-treatment and two months after the intervention. Additionally, 40% of the participants in the CBT group, compared to 6.7% in the control group, were classified as responders at both time-points (Mataix-Cols et al., 2015). The results were maintained up to 12 months after treatment in a naturalistic follow-up. At that time point, half of the participants receiving CBT were classified as responders and 23% as remitters (Krebs, Fernández de la Cruz, Monzani, et al., 2017).

Besides this RCT, there are only a small number of uncontrolled studies evaluating treatment outcomes in adolescent BDD, including one small case series with six participants (Krebs et al., 2012) and one open trial with 13 participants (Greenberg, Mothi, & Wilhelm, 2016). In the case series, four out of six participants were classified as responders at the end of the treatment and results were maintained up to six months after treatment (Krebs et al., 2012). In the open pilot, nine out of 12 participants with available data were classified as responders at post-treatment and gains were maintained six months after treatment completion (Greenberg et al., 2016).

2.5.2 Exposure and response prevention

As in OCD, the CBT treatment of choice for BDD is exposure with response prevention (ERP), often supported by differing amounts of additional cognitive techniques, such as cognitive restructuring (Harrison et al., 2016; Phillips, 1986). The main goal of the exposure is to stop

avoiding anxiety-provoking situations. For a person with BDD, that may be going to school or work, or participating in social situations. The purpose of the response prevention is to stop all the unhelpful repetitive rituals and behaviors (i.e., excessive mirror checking, camouflaging, excessive use of make-up). The ERP tasks are based on the individual's goals and are performed both during and between sessions (i.e., homework tasks).

In most cases, the parents or primary caretakers, partners or other family members of the individual with BDD are involved in the rituals and avoidant behaviors, which is referred to as family accommodation (Jassi, Baloch, Thomas-Smith, & Lewis, 2020). It is therefore important to engage these relatives in treatment. Involving persons that are close to the person with BDD often improves the chances to change the unhelpful patterns caused by BDD. In treatment, relatives receive psychoeducation and learn strategies to assist the person with BDD in the ERP tasks.

2.5.3 Internet-based cognitive-behavior therapy

Even though CBT has shown to be efficacious for adults (Harrison et al., 2016; Wilhelm et al., 2019) and, based on limited literature, adolescents with BDD (Mataix-Cols et al., 2015) and is recommended in treatment guidelines (National Institute for Health and Care Excellence, 2005), this treatment in unfortunately not accessible for all sufferers due to lack of available resources. Barriers to receive treatment include few clinics that can offer this specialized treatment and lack of trained therapists that can deliver such interventions (Comer & Barlow, 2014). One alternative way of delivering evidence-based treatment is therapist-supported Internet-delivered CBT (ICBT) (Andersson, Titov, Dear, Rozental, & Carlbring, 2019; Comer & Barlow, 2014).

ICBT includes the same content as traditional face-to-face CBT but, in the online version, participants follow an interactive program, often with regular support via online text messages from a trained professional. Compared to traditional psychotherapy, online psychological interventions have numerous advantages. As a patient, you can get access to the treatment whenever and from wherever you want. Thus, participants do not need to consider travel distances and appointments do not interfere with the school day (for the young person) or workday (for the adult/parent). Also, ICBT has shown to be cost-effective, needing less therapist time per patient, and efficacious for several somatic and mental health disorders in adults as well as young people (Andersson, Cuijpers, Carlbring, Riper, & Hedman, 2014; Hedman, Ljótsson, & Lindefors, 2012; Vigerland et al., 2016).

Another important aspect of ICBT is that it can be used as part of a stepped care model in the health system (Jolstedt et al., 2021). The idea behind this approach is not to replace all face-to-face CBT appointments, but to offer ICBT as a first step, and then traditional face-to-face CBT only those patients who fail to benefit enough from ICBT, resulting in a better use of resources and reduced costs for the health system.

ICBT has been successfully evaluated in adult BDD. A Swedish program called BDD-NET showed response rates in line with traditional face-to-face CBT. BDD-NET was first evaluated in a feasibility trial (n=23) (Enander et al., 2014) and then in a larger RCT (n=94) (Enander et

al., 2016). The results were maintained up to two years after the end of treatment (Enander et al., 2019). The program is now implemented and has been evaluated in the regular health care system in Sweden (Lundström et al., 2023), making BDD-NET available to adult BDD patients from all over the country. Additionally, a smartphone-delivered CBT intervention has been successfully evaluated in an open pilot trial (n=10) (Wilhelm et al., 2020) and then in a large-scale RCT (n=80) (Wilhelm et al., 2022) in the US. Finally, the feasibility of a short guided ICBT intervention for adults with BDD (Schoenenberg et al., 2023) has also been examined in Germany. Another German ICBT program targeting both adolescents and young adults (ages 15-21) called ImaginYouth is currently being evaluated in an RCT (n=40) (Hartmann et al., 2021), as is a short guided smartphone app for early intervention on BDD also targeting young people (age 14-21) (Kuck, Dietel, Nohr, Vahrenhold, & Buhlmann, 2022).

2.5.4 Medication

In case that the person with BDD cannot access CBT, does not improve with CBT alone or it is not possible to motivate them to participate in psychological treatment, treatment guidelines also recommend the use of selective serotonin reuptake inhibitors (SSRIs) (National Institute for Health and Care Excellence, 2005). In a handful of controlled studies on the adult BDD population, SSRIs have shown to be effective (Hollander et al., 1999; Phillips, Albertini, & Rasmussen, 2002). However, there are no studies yet that have evaluated the effect of medication for children and adolescents with BDD. Another possibility to further improve treatment outcomes is to combine CBT with SSRIs, but controlled studies evaluating the efficacy of this combined treatment versus either treatment alone are yet not available, neither in adults nor in adolescents.

In naturalistic 'real life' clinical settings, different treatment modalities (i.e., CBT and SSRIs) are more likely to be used in combination, compared to the strict conditions of an RCT. However, data on pediatric BDD from such naturalistic settings have also been lacking. In order to assess the generalizability of the results from clinical trials, it is important to conduct naturalistic evaluations, where multimodal treatment tends to be the norm (Weisz et al., 2013).

2.6 Conclusions

BDD often appears early in adolescence and is associated with high levels of occupational and social disability and reduced quality of life. Importantly, BDD has also been associated with high rates of suicidality. However, the methodological quality of the studies exploring the clinical correlates of BDD is generally low and large-scale studies relying on prospectively collected data are unfortunately non-existent.

The available evidence on treatment outcomes, although sparse, suggests that CBT is feasible and probably efficacious to treat both adolescents and adults with the disorder. However, very few studies have focused on young individuals with BDD and there is also a lack of data from clinical settings. A further challenge is that treatments are often not available due to lack of trained therapists and large geographical distances to specialist centers.

There is therefore a real need to further study the characteristics of BDD, particularly in the adolescent years. It is important to evaluate treatment effectiveness in clinical settings, and help implementing and disseminating the limited evidence-based treatments for BDD across the health system. Remote delivery of CBT could be a way to reach more individuals in need of treatment. ICBT has been evaluated in adult BDD with promising results, but it has not yet been evaluated in adolescents with BDD.

3 Research aims

The overall objective of this doctoral project was to further explore the clinical characteristics of BDD and to develop ways to increase treatment availability in the adolescent population. The specific aims of each of the five included studies are presented below.

3.1 Study 1: To validate BDD diagnostic codes

The aim of the first study was to validate the ICD-10 codes for BDD and hypochondriasis in the Swedish National Patient Register (NPR) to ensure that future population-based studies on these disorders are of good quality.

3.2 Study 2: To explore intentional self-harm and death by suicide

The aim of this population-based matched-cohort study was to quantify the risk of intentional self-harm and death by suicide in individuals with BDD at the population level using the Swedish national registers.

3.3 Study 3: To explore clinical characteristics

The aim of Study 3 was to describe the demographic and clinical characteristics of a large cohort of youth with BDD at two different specialist clinics in Europe.

3.4 Study 4: To evaluate treatment outcomes

The aim of the fourth study was to explore the multimodal treatment outcomes of the cohort in Study 3, both in the short and the long term, and to examine potential predictors of treatment response.

3.5 Study 5: To transfer face-to-face treatment to an online version

The aim of Study 5 was to adapt a face-to-face CBT intervention for children and adolescents with BDD into an Internet-based intervention with therapist support, involving both young people and their parents, and assess its feasibility, acceptability, safety, and preliminary efficacy in a feasibility study.

4 Materials and methods

4.1 Methods of Study 1

For the first study, 600 hundred individuals with a diagnosis of hypochondriasis or dysmorphophobia (300 each) were randomly selected from the NPR. We then requested their medical files from the corresponding clinics around Sweden. A total of 117 files for hypochondriasis and 136 for dysmorphophobia were received and used for analyses. Two independent raters assessed each file according to ICD-10 definitions and DSM-IV-TR and DSM-5 criteria. Raters also completed the Clinical Global Impression–Severity (CGI-S) and the Global Assessment of Functioning (GAF). The percent agreement between the two evaluators for each file was calculated. Additionally, for each diagnosis, we calculated the positive predictive value (PPV) and intraclass correlation coefficients (ICC) to assess the inter-rater agreement for the CGI-S and the GAF scales.

4.2 Methods of Study 2

In Study 2, we used a matched-cohort design including data from nationwide Swedish administrative and health registers. We identified all individuals with a validated ICD-10 diagnosis of BDD (or dysmorphophobia, in the ICD-10 nomenclature) diagnosed between January 1, 1997 and December 31, 2020, and matched each of them on sex, birth year, and county of residence with 10 unaffected individuals from the general population. Conditional Poisson regression models estimated incidence rate ratios (IRRs) and 95% confidence intervals (95% CI) for intentional self-harm, and stratified Cox proportional hazards models estimated hazard ratios (HRs) and 95% CI for death by suicide. Socioeconomic factors and psychiatric comorbidities were controlled for in the models.

4.3 Methods of Study 3

Study 3 was a naturalistic evaluation of 172 young people consecutively referred to two specialist pediatric obsessive-compulsive and related disorders outpatient clinics in Stockholm, Sweden (n=100) and in London, England (n=72). A series of clinician-, self-, and parent-reported measures were administered, and descriptive statistics were used to describe the demographic and clinical characteristics of the combined sample. Stratified analyses by gender and age group were also reported.

4.4 Methods of Study 4

Study 4 was an open longitudinal study using the cohort in Study 3. We included all BDD patients who had received evidence-based treatment at the specialist clinics and had at least one follow-up measure. In total, we included 140 individuals (age range 10-18); 96 from

Stockholm and 44 from London, who had been seen between January 2015 and April 2021. Participants received CBT and, in 72% of the cases, also medication, primarily SSRIs. The CBT protocol used at both clinics builds upon the manual developed for the Mataix-Cols et al. (2015) RCT. The main focus of the protocol is ERP techniques and emphasizes parental/carer involvement.

We collected data at baseline, post-treatment, and 3, 6, and 12 months after treatment. The primary outcome measure was the Yale-Brown Obsessive-Compulsive Scale Modified for BDD, Adolescent version (BDD-YBOCS-A). Secondary outcomes included measures of self-reported BDD symptoms, depressive symptoms, and global functioning. All available data were also used to explore potential predictors of treatment outcome. Mixed-effects regression models for repeated measures with maximum likelihood estimation of parameters were used to evaluate treatment outcomes, and linear regression models were used to identify significant baseline predictors of BDD-YBOCS-A scores at post-treatment and at the 12-month follow-up.

4.5 Methods of Study 5

Study 5 was an open feasibility trial with the aim to investigate whether a therapist-guided ICBT program is feasible and preliminary efficacious for adolescents with BDD. In this open trial, 19 participants were offered 12 modules of therapist guided ICBT for BDD and were followed up to 12 months after the end of treatment. The treatment was an adaptation of the protocol used in Study 4.

Preliminary efficacy was measured at the a priori primary endpoint (3-month follow-up), as well as at the, 1-, 2-, 6-, and 12-month follow-up with the clinician-rated BDD-YBOCS-A. We implemented mixed-effects regression models similar to those employed to evaluate treatment outcomes in Study 4.

4.6 Ethical considerations

The studies received ethical approval by the Swedish Ethical Review Authority (Studies 1 and 5) and the Regional Ethical Review Board in Stockholm (Studies 2 to 4). Details on ethical considerations are described below.

4.6.1 Studies 1 and 2

Informed consent is most times fundamental in research with human participants. However, in accordance with the protocol approved by the ethical review board for Study 1, the individuals whose charts were reviewed were not asked for consent. The rationale for this is that this would introduce selection biases. Nonetheless, all medical files were reviewed by clinical psychologists and/or medical doctors working in the health care system, where laws and

regulations regarding patient secrecy are applied. The medical files were stored in locked cabinets accessible only to the research study personnel. All data were pseudonymized before analyses. After publication of the manuscript, and in accordance with the ethics protocol, all medical files were destroyed.

In this type of validation studies, the participant is never contacted. There is no direct benefit for the study participants, but they may benefit indirectly through the potential progress in the research field. The cost for a limited number of patients to have one's medical file examined is thought to be outweighed by the benefit of this important type of studies (which is conducted in many different research fields involving human participants).

Study 2 was a register-based study. The requirement for informed consent in this type of studies is waived because the included individuals are not identifiable at any time. Still, this kind of sensitive data are always stored and handled in a secure way, and prior to receiving the data, the personal identification numbers are removed and replaced by unique ID numbers and the code key is kept at the National Board of Health and Welfare. Additionally, all results are presented in an aggregated form which makes identification of individual participants impossible. Similar to the validation study, there is no direct benefit for patients in participating. However, trying to quantify the risks of intentional self-harm and death by suicide in BDD is highly important for the research field, the sufferers themselves, and society at large. Hence, it is reasonable to assume that this new knowledge can benefit all participants, at least indirectly.

4.6.2 Studies 3 to 5

In both Study 3 and Study 4, all participating children, adolescents, and parents/primary caregivers recruited from the OCD and related disorders clinic in Stockholm provided written informed consent. The same applied for participants in Study 5. In that process, they received written information that participation was voluntary and that they could withdraw their consent without explanation. The families also had the possibility to ask questions, and age-adapted information about the participation in the study was provided to the participants. In the London site (which provided participants for Studies 3 and 4), informed consent was not required because the study was part of an audit of routinely collected clinical data.

In both naturalistic studies, participants were routine patients referred to active clinics. All data were gathered for clinical purposes and participation in the study did not add any additional measures or assessments. All patients received the same specialist treatment regardless of whether they consented to provide data for research purposes. Therefore, the above-mentioned studies can be considered low-risk studies from the ethical point of view. There are, however, always risks involved in the process of handling sensitive data. The database used, named BASS, where all data for Studies 3, 4 and 5 are stored, requires double authentication to login, and is GDPR compliant.

In Study 5, some minor and temporary adverse events were anticipated, based on previous similar ICBT studies. However, since there are no documented long-term health risks of ICBT and, based on previous studies, it was reasonable to believe that serious adverse events would be rare. Still, as previously described, BDD is a disorder associated with relatively high rates

of intentional self-harm and suicide attempts, so adverse events may occur. Participants were thus closely monitored by the study team, and there were procedures described in the study protocol regarding how to handle potential serious adverse events.

All participants in Study 5 were also enrolled as patients at the OCD and related disorders clinic in Stockholm and, as patients, they were followed according to the ordinary clinical routines. In the study protocol, we outlined specific procedures to handle potential acute situations (e.g., suicidal ideation, self-harm or suicide attempts), and there was always the possibility to contact the participants via telephone and refer them to their local mental health services or emergency services during their participation, if needed. Furthermore, all study participants received treatment above and beyond ordinary care and, if a participant did not respond to ICBT, they were offered traditional face-to-face CBT.

To summarize, the potential risks of participating in Study 5 were most likely outweighed by the benefits the individual may have and the scientific value of the study.

5 Results

5.1 Results of Study 1

Of the requested clinical files, we were able to retrieve 117 for the diagnosis of hypochondriasis and 136 for dysmorphophobia, of which 84 and 122, respectively, were finally analyzed. The raters agreed on the presence or absence of a diagnosis in 95.2% of the hypochondriasis files and 92.6% of the dysmorphophobia files. A total of 67 hypochondriasis files (79.8%) and 111 dysmorphophobia files (91.0%) were defined as 'true positive' cases (PPV=0.80 and PPV=0.91, respectively). According to the raters' CGI-S scores, the levels of symptom severity for both disorders ranged from moderate to marked, while their GAF scores indicated moderate impairment for hypochondriasis and moderate to serious impairment for dysmorphophobia. Finally, the inter-rater agreement for the CGI-S and the GAF was good for hypochondriasis and moderate for dysmorphophobia.

5.2 Results of Study 2

We identified a total of 3,342 cases diagnosed with BDD in the NPR during the period from 1997 to 2020. After applying the predetermined exclusion criteria, we reached a final cohort of 2,833 individuals with BDD. They were then each matched with 10 individuals that had never been diagnosed with BDD under the study period.

A total of 466 (16.45%) individuals with BDD and 1,071 (3.78%) matched individuals had at least one record of intentional self-harm. Among individuals with BDD with one or more records of intentional self-harm, 314 (67.38%) had their first record of intentional self-harm prior to being diagnosed with BDD for the first time (Figure 1). In models adjusted for all sociodemographic factors, a significantly higher risk of intentional self-harm was observed among individuals with BDD, compared with unexposed individuals (HR=3.37 [95% CI, 3.02-3.76]). The results slightly attenuated but were largely similar after additional adjustment for lifetime psychiatric comorbidities.

A total of 17 (0.60%) individuals with BDD and 27 (0.10%) controls died by suicide, corresponding to a crude mortality rate of 1.02 and 0.16 per 1,000 person-years, respectively (HR=3.47 [95% CI, 1.76-6.85]). Adjustment for psychiatric comorbidities reduced the associations (HRs ranging from 1.06 to 3.51), and the risks were no longer significant when adjusting for anxiety-related and depressive disorders. It was significantly more common among individuals with BDD who died by suicide to have at least one previous lifetime record of intentional self-harm, compared to unexposed individuals who died by suicide (52.94% vs. 22.22%; Chi-square=4.38, p=0.036).

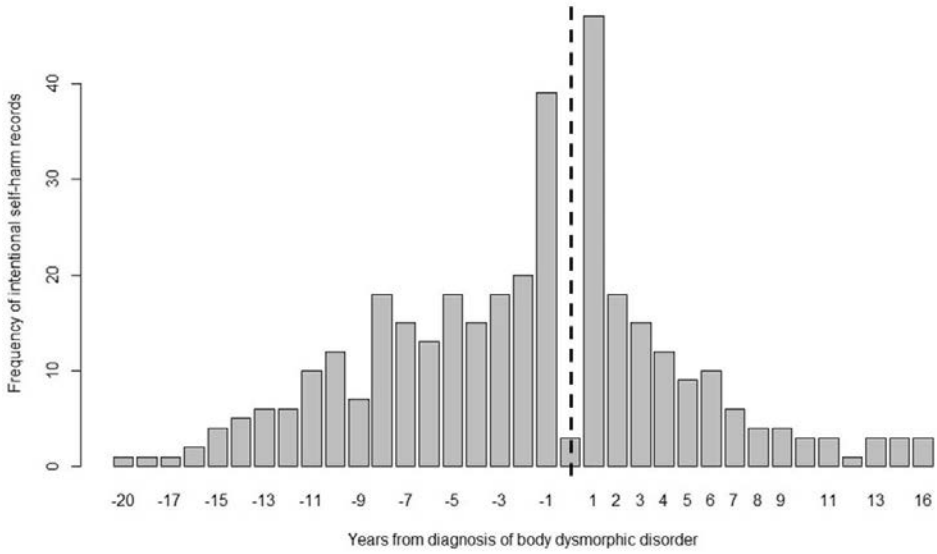

Figure 1. Histogram depicting the frequency of the first recorded intentional self-harm event in relation to the time of the first diagnosis of body dysmorphic disorder.

Note: The vertical, dotted line represents the date of the first BDD diagnosis

5.3 Results of Study 3

In this study, we included a total of 172 children and adolescents with BDD: 136 girls, 32 boys, and four transgender individuals (age range 10-19 years). They were assessed at an average age of 16 years, and they self-reported a mean age of onset of the symptoms at around 13 years. They had moderate to severe BDD symptoms. More than half of the sample reported poor insight into the symptoms. The rates of psychiatric comorbidity were high (71.5%), as were the rates of self-harm (52.1%), suicide attempts (11.0%), desire for cosmetic procedures (53.7%), and school dropout (32.4%). Most individuals described multiple body areas of concern, most commonly preoccupation with the skin, nose, hair, face, and stomach. Finally, we observed few differences in the clinical presentation between boys and girls (**Figure 2**), as well as between younger (up to 14 years old) and older participants.

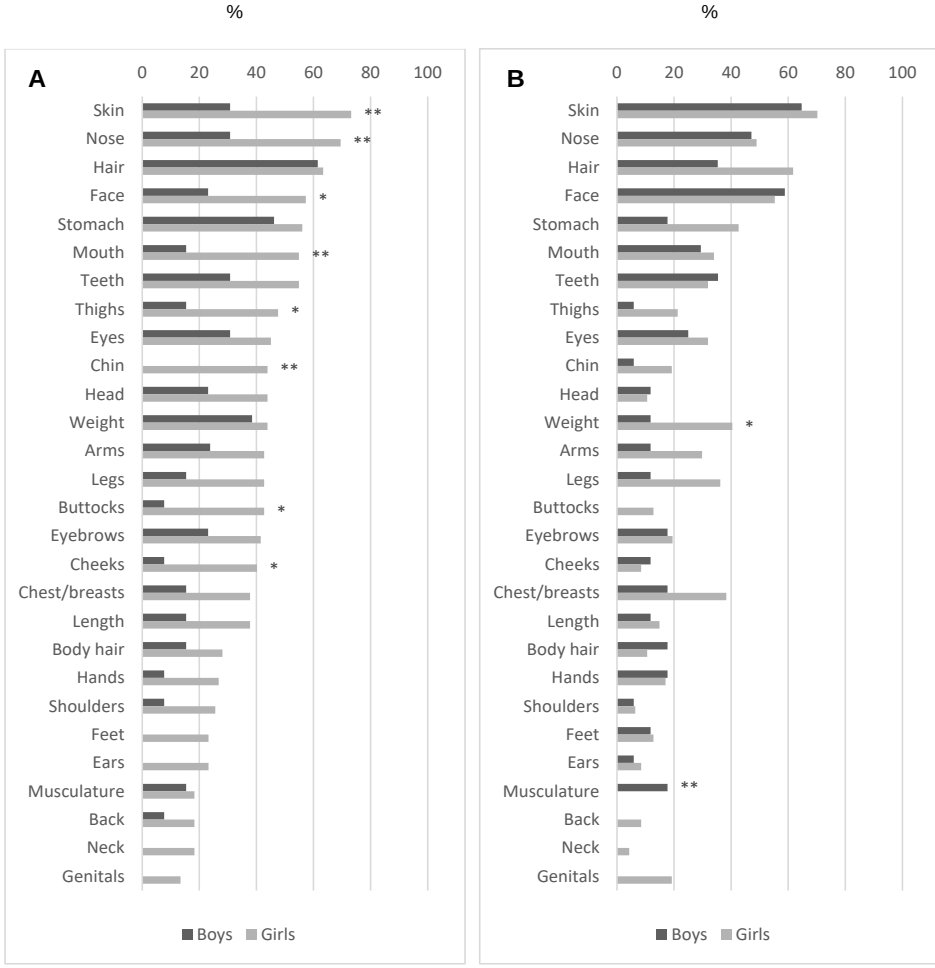

Figure 2. Areas of preoccupation in a sample of adolescents with body dysmorphic disorder, by sex, in the two different sites; Panel A: Stockholm (n=99) and Panel B: London (n=64).

* Significant at 0.05; ** significant at 0.01.

5.4 Results of Study 4

A total of 140 of the 172 participants in Study 3 were also included in Study 4 as they were treated at the clinic and had follow-up data. Their clinical presentation was very similar to that of the cohort described above.

The median number of CBT sessions received by the participants was 15 (mean=17.2, SD=10.4, range 2-80). Missing sessions (i.e., planned sessions that were not attended) were only registered at the Stockholm site. Only 15 (15.6%) of the participants attended all scheduled sessions, 22 (22.9%) missed between 1 and 2 sessions, and 59 (61.5%) missed 3 or more

sessions. The median number of missed session (of the participants who missed at least one session) was 5 (mean=5.5, SD=4.6, range 1-28). A total of 37 participants (26.4%) received some kind of enhanced treatment at some point during the active treatment phase, consisting of sessions longer than one hour (n=12), home visits (n=14) or extra sessions (n=14). During the one-year follow-up, a third of the participants received one or more booster sessions. Ninety-seven participants (72.4%) received medication for their BDD at some point during treatment, mostly SSRIs. Furthermore, most participants (n=86/114; 75.4%), received medication for their BDD at some point during the follow-up year. At the 12-month follow-up, 59.6% (n=56/94) of participants were on medication for their BDD.

Mixed-effects regression models showed that BDD-YBOCS-A scores decreased significantly from baseline to post-treatment (Figure 3), resulting in a large within-group effect size (d=2.08). At the end of treatment, 79% of the participants were classified as responders and 59% as full or partial remitters. Symptoms of BDD continued to improve throughout the follow-up, and improvement was also seen on all secondary outcome measures.

BDD symptom severity at the initial assessment was found to be a predictor of treatment outcome at the end of treatment, but we were not able to find any consistent predictors of treatment outcome at the 12-month follow-up.

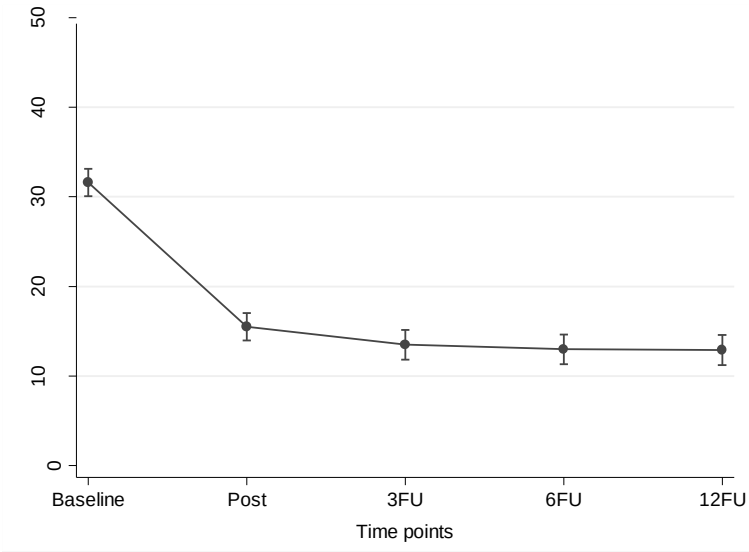

Figure 3. Estimated means on the BDD-YBOCS-A from a mixed-effects regression model including all five time points.

Note: Error bars indicate 95% confidence intervals. Abbreviations: BDD-YBOCS-A, Yale-Brown Obsessive-Compulsive Scale, modified for BDD – Adolescent version; 3FU, 3-month follow-up; 6FU, 6-month follow-up; 12FU, 12-month follow-up.

5.5 Results of Study 5

A total of 20 participants (12-17-year-olds) meeting criteria for BDD were recruited from all over Sweden to a specialist outpatient clinic in Stockholm, Sweden. One participant withdrew consent, and their data could not be analyzed, resulting in a sample of 19 individuals. The sample included 11 self-referred participants and 8 clinical referrals. Most of the participants were girls (n=17, 89.5%), with a mean age of 15.6 years (SD=1.3, range 12-17). Ten (52.6%) adolescents met diagnostic criteria for at least one additional mental disorder, most commonly attention-deficit/hyperactivity disorder or an anxiety disorder. At the start of treatment, seven participants (36.8%) were on pharmacological treatment, mostly SSRIs.

The ICBT treatment was rated as credible and satisfactory, and therapist support time (8 minutes per participant and week) was markedly lower than in traditional CBT. Furthermore, at the primary endpoint (3 months after end of the treatment), ICBT was associated with a significant reduction of BDD symptoms (**Figure 4**), with a large within-group effect size (*d*=2.94). At this timepoint, 73.7% of the adolescents were classified as responders, and 63.2% as full or partial remitters. These numbers increased to 78.9% and 73.7%, respectively, at the one-year follow-up. During the study period (i.e., from baseline to the 12-month follow-up), two of the participants attempted suicide and another two reported non-suicidal self-injuries.

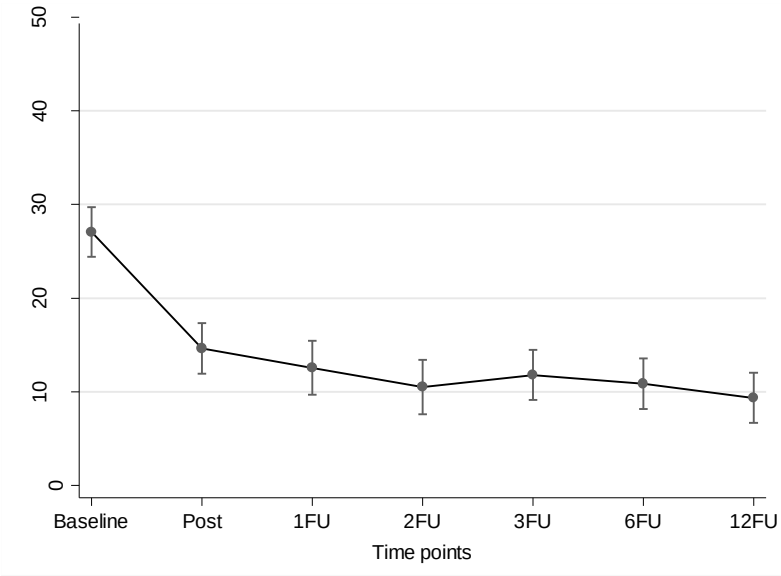

Figure 4. Estimated means on the BDD-YBOCS-A from a mixed-effects regression model including all seven time points.

Note: Error bars indicate 95% confidence intervals. Abbreviations: 1FU, 1-month follow-up; 2FU, 2-month follow-up; 3FU, 3-month follow-up; 6FU, 6-month follow-up; 12FU, 12-month follow-up; BDD-YBOCS-A, Yale-Brown Obsessive-Compulsive Scale, modified for BDD – Adolescent version; Post, Post-treatment.

6 Discussion

The overall objective of this doctoral project was to further explore the clinical characteristics of BDD and to develop ways to increase treatment availability in the adolescent population.

6.1 Clinical characteristics

In the first study, we took advantage of a unique circumstance in the Swedish version of the ICD-10. In this classification of disorders, hypochondriasis and dysmorphophobia (i.e., BDD) are registered under the same diagnostic code (F45.2). However, the Swedish ICD-10 allows for these disorders to be coded separately (F45.2 and F45.2A, respectively), potentially offering unique opportunities for register-based research on these conditions. We therefore conducted Study 1, where we assessed the validity and reliability of these ICD-10 codes in the NPR. We concluded that the Swedish ICD-10 codes for hypochondriasis and dysmorphophobia are sufficiently valid and reliable for register-based studies.

Following up on Study 1, in Study 2 we were for the first time able to quantify the risk of intentional self-harm and death by suicide in individuals with clinically diagnosed BDD at the population level. After controlling for several relevant socioeconomic variables, we found that individuals with BDD had a 3.4-fold risk of intentional self-harm, compared to matched individuals from the general population. This risk estimate remained largely unchanged after adjusting for lifetime psychiatric comorbidities and was in line with the results of a previous meta-analysis including smaller studies (Angelakis et al., 2016). Another meta-analysis (Pellegrini et al., 2021) found that 35.2% of individuals with BDD had a lifetime suicide attempt, which is higher than the 16.5% of intentional self-harm in our cohort. However, records of suicide attempts in previous studies have generally been self-reported, unlike the outcomes in our study, which were recorded by doctors in specialist services. This may have contributed to higher prevalence rates in previous samples.

Additionally, we saw that two thirds of individuals with BDD had one or more records of intentional self-harm which had been registered before their first BDD diagnosis. A similar pattern was found in our naturalistic sample (Studies 3 and 4), where a majority of the participants reported a history of self-harm *prior* to their initial assessment at our clinic. This points to a worrying gap between the onset of symptoms and the first BDD diagnosis. Furthermore, this stresses the importance to screen for BDD among individuals that seek health care due to intentional self-harm.

In line with these results, we also saw, in Study 2, that a majority of the suicide deaths amongst individuals with BDD were preceded by at least one record of intentional self-harm, compared to around 20% amongst individuals without BDD. Additionally, we observed several instances of intentional self-harm in the sample of our feasibility trial (Study 5) where, among 19 participants, two reported intentional self-harm and two attempted suicide during the study period. In sum, the recommendation following these studies is to always monitor suicide risk when assessing or treating individuals with BDD. Additionally, this patient group may benefit from further suicide prevention efforts.

The risk of death by suicide reported in Study 2 was more than three times higher in individuals with BDD, compared to matched unexposed individuals, a risk that dropped in models adjusting for lifetime psychiatric comorbidities. Moreover, when adjusting for anxiety-related and depressive disorders, the estimates lost significance. However, these results should be interpreted cautiously given that power was limited due to the low number of deaths by suicide and that about two thirds of the individuals with BDD also had been diagnosed with either an anxiety-related or a depressive disorder. It is also possible that some of these comorbidities are previous misdiagnoses rather than true comorbidities, as BDD has been reported to be a diagnosis that is often missed and/or misdiagnosed (Veale et al., 2016).

This reported risk of death by suicide is comparable to the risk reported for other psychiatric disorders in the same spectrum, such as OCD (Fernández de la Cruz et al., 2023), hypochondriasis (Mataix-Cols et al., 2023) or Tourette syndrome (Fernández de la Cruz et al., 2017). However, the risk was substantially lower than previously suggested (Phillips & Menard, 2006). As mentioned in the introduction of this thesis, BDD has been considered a disorder with strikingly high risk of suicide but, in light of our findings, it is possible that previous estimations have been exaggerated, since most data on suicidality in BDD come from a few highly specialist centers, including the most severe cases of BDD. Still, the methodological differences between studies call for cautious comparisons.

Besides the elevated frequency of self-harm in our naturalistic sample of children and adolescents with BDD (Study 3 and 4), these participants also presented with high rates of psychiatric comorbidity, desire for cosmetic procedures, and school dropouts. We observed a similar presentation between boys and girls and between younger and older participants. Overall, our results mirrored those of previous studies with considerably smaller sample sizes (Albertini & Phillips, 1999; Mataix-Cols et al., 2015; Phillips et al., 2006), confirming that BDD in young people is indeed a severe and disabling disorder associated with substantial functional impairment and several risky behaviors.

Another important risk that we could confirm in our naturalistic evaluation was the generally poor insight related to this disorder. This lack of insight is often accompanied with a preference and a desire for cosmetic procedures and an unwillingness to seek mental health care. The reluctance to seek mental health help contributes to low detection rates in the population. This and the fact that BDD is still unknown to many clinicians are relevant contributors to the disorder being underdiagnosed at the population level. This was reflected in Study 2 where, over a period of 24 years, we identified less than 3,000 cases of BDD in the Swedish registers. Hence, detection of BDD should be a priority. Training of mental health clinicians and other personnel in settings other than mental health who may be in contact with these group is required. There is a need to work closely with dermatologists, beauty clinics, and plastic surgeons to identify individuals with BDD and to minimize unnecessary procedures.

6.2 Treatment outcomes

In Study 4, we evaluated the short- and long-term outcomes of a large cohort of children and adolescents with BDD receiving specialist multimodal treatment. Our findings showed that,

when provided flexibly within a specialist setting, this treatment has both acute and durable effects for young individuals with BDD. It was encouraging to see that improvements were also seen on other comorbid symptoms and global functioning.

Overall, the results were better than those from the only RCT on pediatric BDD (Mataix-Cols et al., 2015). However, it is important to note that the participants treated in this naturalistic setting were on average slightly less severe and received a rather flexible treatment, compared to those in the trial. Most individuals received medication in addition to CBT and, for about a third of the participants, the treatment protocol was adapted (i.e., providing home-visits, additional sessions, or longer sessions) both during the active phase of the treatment and the follow-up. Taken together, the results from the naturalistic study suggest that individuals with BDD may benefit from a structured but flexible treatment approach.

In Study 4, we also used all available data to explore potential predictors of treatment outcome, an aim that we regarded as exploratory based on the limited literature. In line with two previous studies on adult BDD (Flygare et al., 2020; Phillips et al., 2013), we found that higher BDD severity at baseline predicted poorer outcomes at post-treatment. However, this result did not extend to the one-year follow-up. Other predictors reported in the literature, including duration of the BDD symptoms, insight, depressive symptoms, and serotonin reuptake inhibitors use (Flygare et al., 2020; Greenberg, Phillips, Steketee, Hoeppner, & Wilhelm, 2019; Phillips et al., 2021; Phillips et al., 2013) could not be replicated, indicating the difficulty to accurately predict who will benefit from treatment. Thus, our recommendation is that CBT (and SSRI medication, if required) should continue to be offered to all young people with BDD, regardless of their characteristics at initial assessment. Future prediction models will need much larger samples and probably include other kinds of data (e.g., genetic markers) (Flygare et al., 2020).

In Study 5, we transferred our face-to-face CBT protocol to an online version with the eventual aim to increase treatment availability for young people with BDD. The treatment was rated by both patients and caretakers as credible and satisfactory and was associated with a large reduction in BDD symptom severity. A large proportion of participants were classified as treatment responders, in line with the results from the naturalistic evaluation (Study 4). Similar to the individuals treated face-to-face at the two specialist clinics in Study 4, the treatment gains after ICBT also continued to improve up to the 12-month follow-up. However, those who received face-to-face sessions required sessions lasting 45 to 60 minutes each week, while the average therapist support for those participating in the online treatment time was only 8 minutes per participant per week. Thus, ICBT for BDD has the potential to save resources and have beneficial health economic effects.

6.3 Strengths and limitations of the studies

The main strength of the validation study (Study 1) was the nationwide random selection of cases and the thorough review of the medical files by multiple independent expert raters, showing good inter-rater agreement. However, the study has limitations important to consider. These mainly include that the study had no control diagnostic group, which may have led to an over confirmation of the target diagnosis, and a potential risk of selection bias, since only about

a third of the requested files could be analyzed. Nonetheless, we saw no signs of a systematic bias. Rather, the reasons behind the exclusion of most files were eminently practical (e.g., some clinics had closed, had concerns about confidentiality or had no personnel available to send the requested files).

The main strength of Study 2 was the nationwide cohort design, with a long follow-up time, and the adjustment for sociodemographic variables and psychiatric comorbidities. Furthermore, this study was, to the best of my knowledge, the largest cohort of formally diagnosed individuals with BDD ever studied. Some limitations are also worth noting. First, because BDD is an underdiagnosed disorder, most BDD cases do not appear in the registers. That means that there are probably individuals with undiagnosed BDD in the unexposed cohort. If that is the case, the risks reported in this study may be an underestimation. Second, both outcomes (i.e., intentional self-harm and death by suicide) are also probably underreported and may be misclassified as accidents or other causes of death. To account for this, we also included events recorded as undetermined intents, in line with previous studies in the field (Chen et al., 2014; Runeson, Tidemalm, Dahlin, Lichtenstein, & Långström, 2010; Sahlin et al., 2017). Finally, due to the low number of deaths by suicide, the results referring to this outcome should be interpretated cautiously.

The main strength of the naturalistic studies (Studies 3 and 4) was the large and well-characterized sample. Another strength was the use of validated measures with good psychometric properties. However, these studies also had some limitations. Because of the naturalistic design of Study 4, it is not possible to be certain that the abovementioned improvements were exclusively due to the evaluated treatment, a limitation that also applies to the open feasibility trial (Study 5). However, we have little reason to expect spontaneous improvements in individuals with BDD without proper treatment (Harrison et al., 2016). Furthermore, the data used in both Studies 3 and 4 were collected over a period of more than six years, which inevitably resulted in some minor but expected data loss. Additionally, the exploratory nature of the predictor analysis and the relatively small sample size in Study 4 limited its statistical power and may have been a reason for the inconclusive results. Finally, the results from Studies 3 and 4 may not generalize to non-specialist clinics.

Finally, the main strength of the feasibility trial (Study 5) was the use of a novel approach to deliver treatment for individuals with BDD under the age of 18. This sample was milder than the one is the naturalistic evaluation. Thus, a limitation was that we cannot be certain that ICBT works equally well for individuals with more severe and complex BDD. Further, all participants were assessed and treated by one single clinical psychologist highly trained and experienced in the treatment of BDD (i.e., me).

7 Future directions

Much has happened in the field of BDD over the last decades. However, compared to other research fields in psychiatry, high-quality studies on BDD in general and in young individuals with BDD in particular are still very sparse. The following sections expand on potential future studies that may help strengthening the research field of BDD, as well as the clinical practice.

7.1 Epidemiology and etiology

Two groups that have received very little empirical attention in BDD are boys and pre-pubertal children. Prevalence numbers in both these groups seem to be low. For example, a recent study using a representative sample of young people drawn from the general population (Krebs et al., 2023) estimated that BDD was strikingly more common among girls than among boys (1.8% vs. 0.3%), and much more common among adolescents than among children (1.9% vs. 0.1%). Still, future studies with a particular focus on these groups are needed. Other population groups that deserve further investigation are transgender individuals with BDD, as well as individuals with BDD from non-Western countries and ethnic minorities.

Until this thesis, no register-based studies on clinically diagnosed BDD had been conducted. With the validation study, we have now shown that the Swedish diagnostic code for BDD is valid and reliable to be used in epidemiological research, and hopefully, future studies using the Swedish population registers will broaden our knowledge about this disorder. Important topics for such future studies include the long-term impacts of BDD, including school failure, unemployment, somatic health problems, and mortality due to causes other than suicide (e.g., natural causes).

The genetic and environmental risk factors underlying BDD are also still largely unknown. To date, no GWAS have been conducted on this disorder. The few existing twin studies on BDD have found that shared environment has a negligible role in the etiology of BDD (Enander et al., 2018; López-Solà et al., 2014; Monzani et al., 2012; Monzani et al., 2014). However, more longitudinal studies with genetically informative designs are needed to identify non-shared environmental risk factors. Once identified, these factors could lead to strategies for the early detection of BDD, and even prevention of the disorder.

7.2 Treatment

Treatment studies in the field of BDD that can help guiding health care interventions are sorely needed. For example, the field would benefit from a head-to-head comparison of treatment with CBT and SSRIs for individuals with BDD, both adults and children and adolescents. Such studies would provide important information on the potential differences in treatment effects, including side effects (both short- and long-term), and the effect of monotherapy vs. combined treatment.

Additionally, a better understanding of the mechanisms of change involved in CBT for BDD could also lead to improved treatment effects. To study potential mechanisms, large samples are needed. Mechanisms can be investigated in the context of clinical trials designed to examine them. For example, participants may be randomized to two (or more) interventions differing on the hypothesized mechanism (Kazdin, 2007). Another way to evaluate potential mechanisms is through experimental laboratory studies, where one manipulates the hypothesized mechanism of change (e.g., habituation or inhibitory learning) and evaluates if the effect is moderated by certain behaviors (e.g., BDD rituals or self-focused attention). Both these approaches make it possible to establish a timeline where the proposed mechanism precedes the outcome (Kazdin, 2007).

Some cognitions and behaviours (e.g., maladaptive appearance beliefs, checking and grooming behaviors) (Fang et al., 2020), as well as some neurocognitive processes (e.g., detail processing, maladaptive beliefs, emotion recognition) (Greenberg et al., 2023), have been suggested as potential mechanisms underlying improvement with CBT for BDD – the hypothesis being that improvements in these constructs occur *prior* to reduction of BDD symptoms and therefore partially or fully *cause* the improvement. However, these studies were not able to confirm the hypothesized mechanisms and, so far, we have very little knowledge of why or how effective treatments for BDD work. More studies are clearly needed to understand what components are associated with symptom improvement.

7.3 Implementation of treatment

For me, as a clinician with many years of experience in child and adolescent psychiatry in Sweden, my main priority is to deliver evidence-based treatment to as many individuals with BDD as possible. However, to be able to treat these individuals, we need to find them, and they need to find us. Thus, we need to continue to work together with professionals in different health care settings, as well as with interest organizations, to spread awareness about BDD. There is already a broad consensus in the field of BDD that more needs to be done to reduce stigma, improve detection of the disorder, and find individuals with BDD as early as possible to prevent chronicity and lifelong suffering and disability in this group.

Once an individual with BDD is detected, they need to be offered the recommended treatment. We know that, even after a correct diagnosis, it can still be difficult to access evidence-based treatment, especially CBT (Buhlmann, 2011; Marques, Weingarden, Leblanc, & Wilhelm, 2011). To a large extent, this is due to a general shortage of clinicians trained in CBT for BDD. Thus, there is a clear need to find more effective ways to train professionals working in different health care settings for patients to be detected, correctly diagnosed, and delivered appropriate treatment. An ongoing research project in our research group is now evaluating the feasibility of an online program to train clinicians in the assessment and treatment of BDD (preregistered at Open Science Framework; osf.io/7a4pz). If this project turns out to be successful, large amounts of professionals could be trained in a practical and cost-effective way, which would increase the chance for patients to receive CBT.

Another way of getting individuals with BDD the treatment that they need is making the traditional face-to-face CBT more accessible. Hence, one of the most important aims of this doctoral project was to explore the feasibility of developing a lower intensity treatment alternative for young people with BDD, similar to digital interventions that already exist for adults with BDD (Enander et al., 2016; Lundström et al., 2023; Wilhelm et al., 2022). The idea behind this stepped-care model is to reserve higher-intensity treatments for individuals for whom ICBT is not sufficient. The hope is that this can save healthcare costs by reducing the number of patients who need traditional face-to-face treatment at specialist clinics and, at the same time, reduce waiting times, as well as absenteeism from school (for adolescents) and work (for parents), which would also translate into societal savings.

Study 5 was the first step in a process to show that this approach can be implemented for the younger population with BDD. Following up on this study, we are now conducting a large scale RCT to evaluate the efficacy and cost-effectiveness of ICBT for adolescent BDD, compared with a credible control condition. Our hope is to lay a solid ground for the dissemination of CBT for young people with BDD. In the first instance, we will aim to make this intervention available in regular healthcare, initially in Sweden. In the long run, this can hopefully be disseminated far beyond the Swedish borders.

Finally, and to end this thesis on a positive note – while the scarcity of high-quality research in the field of BDD is still a concern, I think we have good reasons to be hopeful about the future. In the last couple of decades, this topic has moved from almost complete darkness to becoming a dynamic and promising research field. We still have, of course, much to learn, but just as we know so much more about this disorder now than we did in Morselli's time, there will come a time in the future (hopefully soon) when we will have a richer and more complete understanding of BDD, its etiology and, most importantly, how to best help as many individuals as possible who suffer from this often very painful disorder. My hope is that this thesis has helped the field to take yet another step on this important journey.

8 Conclusions

Study 1 concluded that the Swedish ICD-10 codes for both hypochondriasis and dysmorphophobia (BDD) in the Swedish NPR are sufficiently valid and reliable for their use in register-based studies.

Study 2 showed that individuals with BDD have an increased risk of both intentional self-harm and dying by suicide. This elevated risk was robust to adjustment for socioeconomic variables and lifetime psychiatric comorbidities.

Study 3 confirmed previous studies including smaller sample sizes and showed that child and adolescent BDD can be a severe and disabling condition associated with several important risks, including suicide risk, self-harm behaviors, desire for unhelpful cosmetic procedures, and school refusal.

Study 4 concluded that multimodal treatment for adolescent BDD is effective and has durable effects when provided flexibly within a specialist setting. BDD symptom severity was identified as a predictor of treatment outcomes at post-treatment, but no consistent predictors were found at the one-year follow-up.

Study 5 showed that ICBT with minimal therapist support is a feasible, preliminary efficacious, and durable treatment alternative for adolescents with BDD.

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