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Epidemiological Aspects of Obsessive- Compulsive Disorder in Community Adolescents and Young Adults: Subsequent Psychopathology and Risk Factors

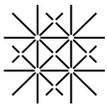
Inaugural Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy to the Department of Psychology of the University of Basel by

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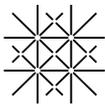
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Declaration of Authorship

I, Patrizia Hofer (born April 10, 1990), hereby declare that I have contributed independently and substantially to this dissertation without any assistance from third parties who are not indicated. I have used only the resources indicated and have cited all references. Published manuscripts or manuscripts submitted for publication were prepared in cooperation with coauthors and have not been submitted elsewhere for review or consideration, nor have they been published elsewhere. This dissertation includes the following three manuscripts:

- Hofer, P. D., Wahl, K., Meyer, A. H., Miché, M., Beesdo-Baum, K., Wong, S. F., Grisham, J. R., Wittchen, H.– U., Lieb, R. (2018). Obsessive-compulsive disorder and the risk of subsequent mental disorders: A community study of adolescents and young adults. *Depression and Anxiety*, 35, 339-345.
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Abbreviations

AF	Attributable fraction
BI	Behavioral inhibition
BIP	Bipolar disorder
DIA-X/M-CIDI	Computer-assisted Munich Composite International Diagnostic Interview
DSM-IV	<i>Diagnostic and Statistical Manual of Mental Disorders</i> , 4th ed.
EDSP	Early Developmental Stages of Psychopathology
GAD	Generalized anxiety disorder
OCD	Obsessive-compulsive disorder
PAF	Population attributable fraction
PTSD	Post-traumatic stress disorder
QRPRB	Questionnaire of Recalled Parental Rearing Behavior
RSRI	Retrospective Self-Report of Inhibition
T0	Baseline of the EDSP study
T1	First follow-up assessment of the EDSP study
T2	Second follow-up assessment of the EDSP study
T3	Third follow-up assessment of the EDSP study

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Abstract

Obsessive-compulsive disorder (OCD) is associated with severe interference in social and occupational functioning, quality of life, and substantial comorbidity. Improved knowledge of risk factors for OCD and pathways to subsequent mental disorders could set the stage for successfully preventing OCD and the progression of psychopathology. Thus, the aim of this thesis was to examine (1) whether OCD predicts the subsequent onset of various mental disorders and (2) whether certain risk factors, that is, behavioral inhibition (BI), parental rearing, and adverse life events and the interaction thereof, are associated with an increased risk of OCD. A representative community sample of 3,021 adolescents and young adults was prospectively followed for up to 10 years. *DSM-IV* OCD, other mental disorders, and adverse life events were assessed using the DIA-X/M-CIDI. Parental rearing and BI (social and nonsocial fear components) were assessed with self-report questionnaires. OCD was associated with the subsequent onset of social phobia, generalized anxiety disorder (GAD), bipolar disorder (BIP), dysthymia, and bulimia nervosa. Total BI, both its components, and paternal rejection were found to increase the risk of OCD. Components of BI moderated the effect of adverse life events and paternal rearing on OCD. Maternal and paternal emotional warmth moderated the association between adverse life events and OCD. The findings indicate that interventions for individuals with OCD are important to prevent the subsequent onset of internalizing disorders. Further research is required to fully understand the underlying mechanisms. Knowledge of the demonstrated risk factors and moderators might inform future prevention efforts for OCD. Results emphasize the need to investigate (1) whether early treatment of OCD reduces the risk of subsequent psychopathology and (2) the effectiveness of prevention programs that target individuals at high risk of OCD.

Introduction

The profound public health burden associated with OCD has repeatedly been demonstrated (Murray & Lopez, 1996; Wittchen et al., 2011). Individuals with OCD experience impaired functioning in social, family, and occupational domains (Fineberg, Hengartner, Bergbaum, Gale, Gamma, et al., 2013; Ruscio, Stein, Chiu, & Kessler, 2010), report higher comorbidity with physical diseases (Witthauer, Gloster, Meyer, & Lieb, 2014), and are at higher risk of suicide attempts than those without OCD (Miché et al., 2018). Findings from epidemiological studies suggest that approximately 1–3% of the general population meet criteria for OCD in their lifetime (Beesdo-Baum et al., 2015; Fineberg, Hengartner, Bergbaum, Gale, Gamma, et al., 2013; Fontenelle, Mendlowicz, & Versiani, 2006). The onset of OCD typically occurs in adolescence or young adulthood (Ruscio et al., 2010). High lifetime rates of comorbidity with a range of other mental disorders, such as affective disorders, anxiety disorders, and substance use disorders, have been demonstrated in population-based studies (e.g. De Graaf, Bijl, Spijker, Beekman, & Vollebergh, 2003; Ruscio et al., 2010). Comorbidity has serious implications as it has been linked with worse functioning in family and work relationships (Fineberg, Hengartner, Bergbaum, Gale, Rössler, et al., 2013), higher distress, and suicidality (Angst et al., 2005).

Recent evidence suggests that individuals with OCD are at an increased risk of developing various subsequent mental disorder such as depression (Goodwin, 2002; Meier, Petersen, et al., 2015), BIP (Cederlöf, Lichtenstein, et al., 2015; Kessler et al., 2011), or anorexia (Cederlöf, Thornton, et al., 2015; Meier, Bulik, et al., 2015). Knowledge about a heightened risk of secondary mental disorders could inform interventions aimed either at preventing secondary disorders from occurring or at detecting and treating these disorders when they do occur (Kessler & Price, 1993), potentially reducing the burden associated with OCD. It might also lead to insight into possible etiological patterns regarding the development of secondary mental disorders (Lieb, 2006). However, prior studies that addressed whether OCD is

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a risk factor for subsequent psychopathology were based on designs that limit the validity of their results: Studies using data from nationwide patient registers may have generated biased estimates of comorbidity, as comorbidity increases the likelihood of treatment seeking (Galbaud du Fort, Newman, & Bland, 1993). Furthermore, these studies used only a small set of outcome diagnoses or used cross-sectional data with retrospectively collected age-of-onset information, which is prone to recall bias. An evaluation of the potential impact of OCD on the development of secondary mental disorders is still lacking.

Another approach to reduce the burden associated with OCD is not to await its emergence and then attempt to treat the disorder and reduce disability (i.e., tertiary prevention) but to prevent future OCD and intervene before OCD occurs (i.e., primary preventions (Haggerty & Mrazek, 1994). One of the challenges in prevention research is the need for a sophisticated understanding of risk factors and vulnerability processes for the respective mental disorder (Kraemer et al., 1997; Zvolensky, Schmidt, Bernstein, & Keough, 2006). The evaluation of risk factors for OCD is therefore an important first step in the development of prevention programs. However, OCD is thought to be most comprehensively explained by the interplay of *numerous* factors. It is assumed that individuals vary in the degree to which they are affected by environmental stress depending on predisposing factors (i.e., the vulnerability-stress model; Williams, Reardon, Murray, & Cole, 2005) or exposure to modifying factors (e.g., protective factors; Rutter, 1995). A core task of OCD risk factor research is to identify not only main effects but also how such factors interact with one another in the pathogenesis of OCD, for example, among whom or under what conditions a specific factor increases the risk.

Over the last decades, numerous studies have investigated possible risk factors that might contribute to the development of OCD. BI (Coles, Schofield, & Pietrefesa, 2006), adverse life events, and parental rearing (Brander, Perez-Vigil, Larsson, & Mataix-Cols, 2016), which are thought to contribute to other internalizing disorders, may be of special interest from the perspective of primary prevention in the context of OCD. Although prior studies provided

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valuable knowledge concerning the association of BI and parental rearing with OCD, they were limited in a number of ways. They lacked either (a) representative population samples, (b) reliable OCD diagnoses, or (c) prospective longitudinal data, which allow conclusions about the direction of the effect. Furthermore, analysis of the interaction between various environmental factors (e.g., paternal rearing and adverse life events) and between temperament and environmental factors (e.g., BI and adverse life events or parental rearing) might have theoretical and practical implications for etiology and prevention. An early indication of an interaction between BI and parental rearing came from a cross-sectional study of college students, in which BI moderated the association between parental overprotection and symptoms of OCD. Other potential interactions between BI, parental rearing, and adverse life events that might be relevant for the development of OCD have not yet been examined.

This literature emphasizes the need to improve our knowledge about OCD and its trajectory to subsequent mental disorders and of risk factors for OCD. Large epidemiological studies that prospectively follow a representative community sample through the high-risk period for the onset of OCD and subsequent mental disorders (adolescence and early adulthood; Kessler et al., 2007) are essential. Thus, the objectives of this thesis were (1) to investigate whether OCD increases the risk of the subsequent onset of mental disorders and (2) to examine whether BI, adverse life events, and parental rearing and their interaction are associated with an increased risk of OCD in a longitudinal, community-based study of adolescents and young adults.

Theoretical Background

OCD

In the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-IV; American Psychiatric Association, 1994), OCD is characterized by repetitive, intrusive, and undesired thoughts, impulses, or images (obsessions) and repetitive actions or mental acts (compulsions) that are performed in response to obsessions to reduce distress or avoid feared

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outcomes. Disorder-related thoughts and behaviors are recognized as being unreasonable or excessive and cause major distress or impairment.

OCD and the Risk of Subsequent Mental Disorders

Around 84–90% of individuals with OCD meet criteria for at least one other mental disorder in 12-month (Adam, Meinschmidt, Gloster, & Lieb, 2012) and lifetime (Douglass, Moffitt, Dar, McGee, & Silva, 1995; Ruscio et al., 2010) comorbidity estimates. Evidence suggests that OCD is associated with the onset of subsequent mental disorders, such as depression (Goodwin, 2002; Kessler et al., 2011; Meier, Petersen, et al., 2015), BIP (Cederlöf, Lichtenstein, et al., 2015; Kessler et al., 2011), a range of anxiety disorders (Kessler et al., 2011), anorexia nervosa (Buckner, Silgado, & Lewinsohn, 2010; Cederlöf, Thornton, et al., 2015; Meier, Bulik, et al., 2015), and drug dependence (Kessler et al., 2001). In sum, studies have reported on OCD and the risk of subsequent mental disorders, but data are limited. Patterns found in nationwide patient registers may not reflect the natural patterns of comorbidity as comorbidity increases the likelihood of treatment seeking (Wittchen et al., 2014). Additionally, previous studies analyzed only a small set of outcome diagnoses or were reliant on cross-sectional data, which might introduce a recall bias (Moffitt et al., 2010). Information on the potential impact of OCD on secondary mental disorders is still missing.

Risk Factors for OCD

Risk factor definition. Risk factors play an important role in the prediction and prevention of mental disorders (Kazdin, Kraemer, Kessler, Kupfer, & Offord, 1997). Their identification is a crucial but complex domain in epidemiology. According to Kraemer et al.'s (1997) risk factor concept, for a variable to qualify as a risk factor, it must be associated with an increased probability of the outcome and precede the outcome. Accordingly, a causal risk factor can be changed and when manipulated, alter the risk of the outcome under consideration. Hence, for effective prevention efforts, only causal risk factors should be targeted.

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To identify fixed characteristics (e.g., gender or independently documented early factors such as prenatal complications) cross-sectional designs are appropriate. To demonstrate that a variable characteristic is a risk factor, prospective longitudinal study designs ensure temporal priority of the risk factors: the risk factor is assessed in individuals who do not meet criteria for the outcome, who are then followed up to the outcome. If the temporal precedence of the risk factor cannot be shown, the variable should be referred to as a “correlate” rather than a risk factor. Research has focused on possible risk factors that might be involved in the development of OCD. Given their role in other internalizing disorders, BI, adverse life events, and parental rearing (Brander et al., 2016; Coles et al., 2006) might be particularly significant for primary prevention.

BI. BI refers to the consistent tendency to react to novel social and nonsocial stimuli with high levels of restraint, fearfulness, or withdrawal (Kagan, Snidman, & Arcus, 1998). BI affects 10–15% of children (Hirshfeld-Becker, Biederman, & Rosenbaum, 2004) and appears to be moderately stable from childhood to early adulthood (Gest, 1997). It has been suggested that BI is to some extent heritable and has a genetic basis (Dilalla, Kagan, & Reznick, 1994). Several studies have revealed that BI is associated with anxiety disorders and possibly depressive disorders, too (for an overview, see Klein & Mumper, 2018). With regard to OCD, retrospective self-report of childhood BI was found to be cross-sectionally associated with obsessive-compulsive symptoms in adolescents (Coles et al., 2006; Muris, Meesters, & Spinder, 2003; Muris, Merckelbach, Schmidt, Gadet, & Bogie, 2001). This is in contrast to findings from longitudinal community studies in which childhood BI was not prospectively associated with OCD in adolescents (Rapee, 2014) or young adults (Caspi, Moffitt, Newman, & Silva, 1996). Another cross-sectional study of preschoolers also failed to find a link between laboratory-assessed BI and OCD (Hudson, Dodd, & Bovopoulos, 2011). In sum, findings regarding the association between BI and OCD are inconsistent, and data are limited: Two studies failing to find an association may not have been sufficiently powered with only four individuals with

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OCD, and one did not find BI at 3 years to be predictive for OCD or any anxiety disorder, including social phobia (Caspi et al., 1996), which has been repeatedly shown in other studies (Chronis-Tuscano et al., 2009; Rohrbacher et al., 2008). More community-based studies are required to shed light on the prospective relationship between BI and OCD.

There is evidence suggesting that BI is bidimensional, consisting of a social and a nonsocial fear component (Dyson, Klein, Olino, Dougherty, & Durbin, 2011). Inclusion of only one of the two components might have contributed to the aforementioned contradictory findings, as they have been shown to be relatively independent and to have distinct correlates (Dyson et al., 2011). Consequently, it has been recommended that future research should distinguish between these two constructs. In a student sample, obsessive and compulsive symptoms were linked to both the social and nonsocial fear component of BI (Coles et al., 2006). Whether these dimensions are both relevant in threshold OCD remains unclear but may have etiological implications and be relevant for prevention.

Adverse life events. Adverse life events have been defined as events with a clear onset and ending that may contribute to an increasing vulnerability for psychopathology (Goodyer, 2001). It is well-documented that adverse life events increase the risk of various unfavorable health outcomes and mental disorders (Kessler et al., 2010). Prospective population-based studies have revealed that adverse life events, that is, traumatic events (Asselmann, Wittchen, Lieb, Perkonig, & Beesdo-Baum, 2017), undesirable life events and sexual and physical abuse, number of residence changes, but not the loss of a parent (Grisham et al., 2011), are associated with an increased risk of OCD. In this thesis, particularly their interaction with other factors in predicting OCD is of interest.

Parental rearing. For children and adolescents, parental rearing is of profound importance for their psychosocial development (Rapee, 1997). Parental rearing can be characterized along three dimensions: rejection, emotional warmth, or overprotection (Winefield, Goldney, Tiggemann, & Winefield, 1989). Previous research has established direct,

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cross-sectional relationships between parental overprotection, paternal rejection, and OCD (For an overview, see Brander et al., 2016). Prospective associations between parental rearing and the subsequent onset of OCD, however, are lacking. Thus, no conclusions about the direction of the effect can be made.

Interaction Between Potential Risk Factors

It is generally accepted that mental disorders do not have a single cause but that multifactorial models for the development of mental disorders are most appropriate. Psychological models that integrate complex interactive effects between genetic, environmental, psychosocial, and biological variables form the basis for research on developmental pathways and are required for successfully developing prevention and early treatment interventions (Wittchen & Jacobi, 2011).

Vulnerability-stress model. Central to the vulnerability-stress model is that individuals vary in whether and how much they are adversely affected when exposed to an environmental stressor, due to relatively stable, enduring traits (vulnerability; Ingram & Luxton, 2005). Vulnerability factors may be of behavioral/temperamental, physiological, psychological or endophenotypic character, or of genetic origin.

Consistent with the vulnerability-stress model is the suggestion that the interaction between BI and environmental stressors (e.g., adverse life events or parental rearing) may contribute to the development of anxiety disorders (Craske, 1997; Degnan, Almas, & Fox, 2010; Lewis-Morrarty et al., 2012). Investigating its relevance for OCD, Coles et al. (2006) demonstrated in a cross-sectional study of college students that overprotective parenting moderated the impact of BI on symptoms of OCD. It remains unclear, however, if BI also interacts with parental rearing or other environmental factors such as adverse life events in predicting the subsequent onset of threshold OCD in a representative community sample.

Modifying factors. An individual's response to an environmental stressor may also be altered, changed, or ameliorated by modifying factors (Rutter, 1995). In contrast to vulnerability

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factors, modifying factors (e.g., an environmental stressor) do not necessarily reside within the person (Ingram & Luxton, 2005). Adverse life events and parental rearing (Brander et al., 2016) are examples of potentially important contextual factors in the development of OCD. Functional parental rearing may be beneficial for a child's sense of self-efficacy, mastery, and sense of control (Rapee, 1997; Wood, McLeod, Sigman, Hwang, & Chu, 2003) and therefore possibly help a child adequately react and successfully cope with an adverse life event. However, whether parental rearing as a modifying factor interacts with an adverse life event in predicting subsequent OCD remains unexamined.

Research Questions

Against this background, (1) to investigate whether OCD increases the risk of the subsequent onset of mental disorders and (2) to examine whether BI, adverse life events, parental rearing, and the interactions thereof increase the risk of the subsequent onset of OCD, the following specific research questions were addressed in three studies, reported in Manuscripts 1–3, which together constitute this thesis (see Appendices A–C).

Manuscript 1: OCD and the risk of subsequent mental disorders: A community study of adolescents and young adults

- Is OCD associated with an increased risk of the subsequent onset of mental disorders in the core incidence phase for first onset of mental disorders?
- If so, what proportion of new onsets could conceivably be prevented by effective prevention or early treatment of OCD, assuming a causal relationship?

Manuscript 2: The role BI, perceived parental rearing, and adverse life events in adolescents and young adults with incident OCD

- Are BI, its components, and maternal and paternal rearing associated with an increased risk of OCD?
- Does BI moderate the potential association between adverse life experiences/parental rearing and OCD?

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Manuscript 3: *Maternal and paternal emotional warmth interact with traumatic events in predicting the subsequent onset of OCD in a community sample of adolescents and young adults*

- Does parental rearing moderate the association between adverse life experiences and OCD?

Method

The Early Developmental Stages of Psychopathology (EDSP) Study

Design and sample. The three manuscripts presented in this thesis are based on data of the longitudinal EDSP study. In the German EDSP study, a representative sample of 3,021 adolescents and young adults aged 14 to 24 years was randomly drawn from population registries (Munich area) and followed for up to 10 years, from 1995 to 2005. The study included a baseline (T0) and three follow-up waves (T1, T2, T3). The response rate of the total baseline sample was 70.9%. At T1 (1.2–2.1 years after baseline), only the subsample of the T0 14- to 17-year-olds was reassessed ($N=1,228$, 88.0% of the T0 14- to 17-year-olds). At T2 (2.8–4.1 years after baseline), 2,548 participants of the total T0 sample (84.3% of the T0 14- to 24-year-olds) and at T3 (7.3–10.6 years after baseline), 2,210 participants of the T0 sample (73.2%) were reinterviewed. The focus of the study was on the early developmental stages of psychopathology, thus 14- to 15-year-olds were sampled at twice the probability of 16- to 21-year-olds, and 22- to 24-year-olds at half the probability of 16- to 21-year-olds. All analyses in this thesis take this scheme into account by using sample weights. We found no selective attrition between T0 and T3 based on age, sex, geographic distribution, or OCD diagnostic status (Beesdo-Baum et al., 2015). Details about the EDSP study methods, design, and sample can be found elsewhere (Beesdo-Baum et al., 2015; Lieb, Isensee, von Sydow, & Wittchen, 2000; Wittchen, Perkonigg, Lachner, & Nelson, 1998).

Measures

OCD. OCD was assessed with the computer-assisted version of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI; Wittchen & Pfister, 1997) at all waves. In

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the OCD module, obsessions and compulsions were assessed in two separate parts. In the obsession section, one stem question was assessed to identify a wide range of potential obsessive cognitions. In the compulsion section, three stem questions were assessed to identify a wide range of repetitive behaviors or mental acts. Individuals who confirmed at least one of the stem questions were asked about the remaining mandatory *DSM-IV* OCD criteria, the first onset, and last occurrence. At follow-up assessments, in addition to the stem questions, a list of potential obsessions and compulsions was presented to improve recall.

Other mental disorders. In all waves, diagnostic assessment of other mental disorders was made using the DIA-X/M-CIDI. It allows for the standardized assessment of symptoms, syndromes, and diagnoses along with information about age of onset. At T0, lifetime history of disorders was assessed. In the follow-up waves, disorders occurring during the interval since the previous wave were assessed. Mental disorders used in this thesis include anxiety disorders (panic disorder, agoraphobia, social phobia, specific phobia, GAD, post-traumatic stress disorder (PTSD)), affective disorders (major depression, BIP, dysthymia), substance use disorders (nicotine dependence, alcohol and illegal drug use disorder), and eating disorders (anorexia and bulimia nervosa). Test–retest reliability and validity for the DIA-X/M-CIDI have been presented elsewhere (Reed et al., 1998; Wittchen, Lachner, Wunderlich, & Pfister, 1998).

Risk factors for OCD.

BI. BI was assessed at baseline with a self-report questionnaire, the German version of the Retrospective Self-Report of Inhibition (RSRI; Lieb, 2003; Reznick, Hegeman, Kaufman, Woods, & Jacobs, 1992). The RSRI measures BI on a total scale and in two dimensions: social/school and fear/illness. These dimensions correspond to the social and nonsocial fear components of BI. Childhood behavior from age 5 to 16 years was assessed with 30 items and rated on a 5-point scale from 1 (*never*) to 5 (*very often*), with higher scores indicating higher BI. To diminish the effect of mood or current psychopathology, items refer to particular events/situations rather than subjective impressions. Evidence for internal consistency,

convergent, concurrent, and predictive validity for the German version of the RSRI including its two dimensional subscales has been reported elsewhere (Rohrbacher et al., 2008).

Adverse life events. In this thesis, the category adverse life events indicates lifetime exposure to any traumatic or any separation event and was assessed at baseline. Separation events were assessed as part of the family history section of the DIA-X/M-CIDI and covered death of a parent and parental separation or divorce. Traumatic events were assessed according to the *DSM-IV* PTSD criterion A1 and included eight specific events (war experience, physical attack, rape, sexual abuse as a child, natural disasters, serious accidents, imprisonment, and witnessing of traumatic events of others) and one open category (other traumatic events).

Parental rearing. Perceived parental rearing was assessed with the German version of the Questionnaire of Recalled Parental Rearing Behavior (QRPRB; Schumacher, Eisenmann, & Brahler, 1999). The QRPRB measures parental rearing on three subscales: emotional warmth, overprotection, and rejection. They are assessed separately for mothers and fathers on 24 items on a 4-point scale from 1 (*no, never*) to 4 (*yes, always*) at T1 for the younger and at T2 for the entire cohort. Analyses in this study refer to parental rearing assessed at T2.

Statistical Analyses

In all manuscripts analyses were performed using Stata Software Package 13.1 (StataCorp, 2013). Data were weighted by age, sex, and geographic location at T0 to account for different sampling probabilities and ensure community representativeness. In Manuscript 1 we analyzed in the total sample ($N = 3,021$) whether OCD was associated with an increased risk of the first onset of subsequent mental disorders with a Cox regression with time-dependent covariates (Therneau & Grambsch, 2000). Hazard ratios served as a measure of strength. We used the aggregated information from all four assessments and age-of-onset data to establish the temporal precedence of OCD. Models were adjusted for age, sex, and mental disorders that occurred prior to the onset of OCD. The latter variable was constructed as a time-varying covariate (Höfler, Brückl, Lieb, & Wittchen, 2005). To estimate the potential for prevention, the

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population attributable fraction (PAF) and the attributable fraction (AF) were calculated. The PAF and the AF are defined as the proportion of a disorder that can be attributed to a specific risk factor, under the assumption that that the risk factor causally leads to the disorder (Gordis, 2014). In Manuscripts 2 and 3 we used separate logistic regression models with risk ratios as a measure of strength to investigate (1) the longitudinal associations between potential risk factors and the subsequent onset of OCD and (2) whether potential risk factors interact in predicting the subsequent onset of OCD. For these analyses, we included the data of individuals who completed the T3 assessment ($N = 2,210$). Potential risk factors assessed at baseline (BI and adverse life events) or at T2 (parental rearing) were included as predictors and the incidence rate observed between baseline and T3 (for the analysis of a main effect of BI and adverse life events) or between T2 and T3 (for the analysis of a main effect of parental rearing or interaction effects) of OCD as outcome.

Results

OCD and the Risk of Subsequent Mental Disorders

Prior OCD was associated with an increased risk of the subsequent onset of social phobia, GAD, BIP, dysthymia, and bulimia nervosa but not of the other disorders. Hazard ratios ranged from 2.2 for social phobia to around 6.9 for bulimia nervosa and BIP. Of these disorders, between 66% (social phobia) and 85% (BIP) could be attributed to OCD in the exposed groups (AFs). Further, between 1.5% (social phobia) and 7.7% (bulimia nervosa) could be attributed to OCD in the total sample (PAFs). For detailed results, see Appendix A.

Risk Factors for OCD and Their Interactions

BI, adverse life events, and parental rearing. As can be seen in Figure 1, both the total score and the two components (social and nonsocial fear) of BI increased the risk of OCD. Any adverse life event, including traumatic and separation events, was not associated with an increased risk of OCD. As previously reported based on the EDSP data (Asselmann et al., 2017), individuals exposed to any traumatic event had an increased risk of OCD. In contrast,

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individuals exposed to any separation event did not have an elevated risk of OCD. Among parental rearing only paternal rejection was associated with an increased risk of OCD. None of the maternal or other paternal rearing styles increased the risk of the subsequent first onset of OCD.

BI as a moderator of the association between parental rearing/adverse life events and the subsequent onset of OCD. The total scale of BI did not interact with parental rearing or adverse life events. The component nonsocial fear BI, however, moderated the association between paternal emotional warmth and OCD. In addition, social BI moderated the association between paternal overprotection and OCD and also the association between adverse life events and OCD. All three interactions demonstrated the same pattern: Paternal overprotection, a lack of paternal emotional warmth, and adverse life events increased the risk of OCD more strongly for those with a high degree of the BI component compared to those with mean or low levels of the BI component (Appendix B). Interaction effects are summarized in Fig. 1.

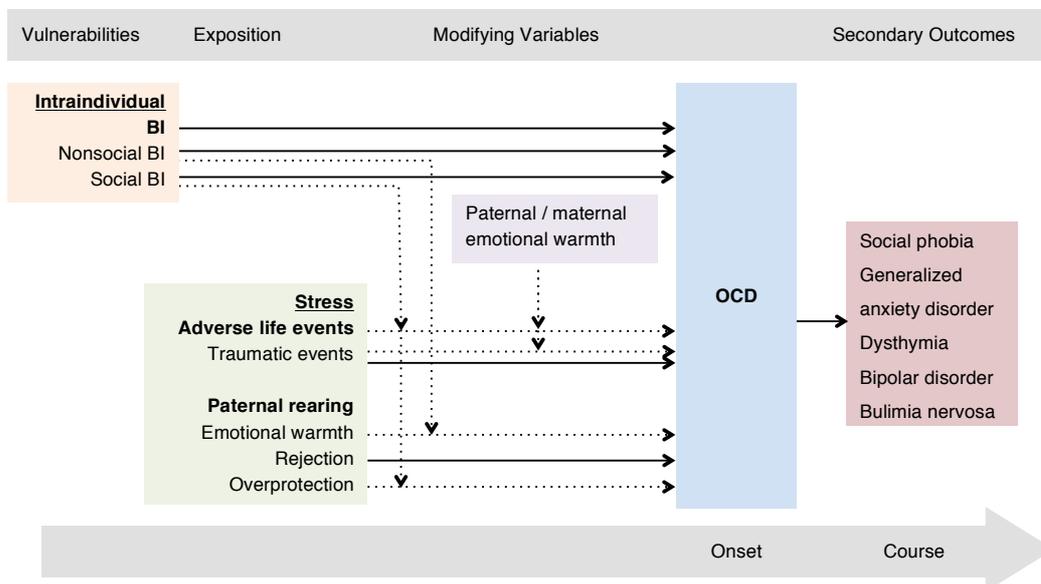


Figure 1. Vulnerability-stress model (Wittchen & Jacobi, 2011) modified to show the associations between potential risk factors and OCD / OCD and subsequent mental disorders identified in this thesis. Note that all associations were analyzed in separate models; they are included in the same figure only for illustration and summary purposes. Solid thick line: Predictor directly increases risk of outcome; dashed line: predictor increases risk of OCD in interaction with another factor. Only significant results are depicted. For detailed results, see Appendices A–C. BI = Behavioral inhibition.

Parental rearing as a moderator between adverse life events and the subsequent onset of OCD. As can be seen in Fig. 1, both maternal and paternal emotional warmth, but not overprotection or rejection, moderated the association between any adverse life event and the subsequent first onset of OCD. The association increased with decreasing parental emotional warmth. The same pattern was found only for any traumatic event and not for any separation event (Appendix C).

Discussion

To reduce the burden associated with OCD, effective and feasible interventions that prevent OCD and the progression to subsequent various forms of psychopathology are needed (Brakoulias, Perkes, & Tsalamaniotis, 2018). Therefore, the identification of risk factors for OCD and knowledge of the risk of subsequent mental disorders are indispensable for identifying high-risk individuals and developing a foundation for these interventions. This dissertation complements existing research by demonstrating that prior OCD is associated with an increased risk of a range of internalizing disorders. Analyses demonstrated for the first time that BI, both components thereof, and paternal rejection are associated with an increased risk of OCD. Consistent with a vulnerability–stress model, more dysfunctional paternal rearing and adverse life events were shown to increase the risk of OCD more strongly for those with higher (vs. lower) BI components who(temperamental vulnerability). Moreover, adverse life events, specifically traumatic events, were associated more strongly with the subsequent onset of OCD when maternal and paternal emotional warmth were low compared to high.

OCD and the Risk of Subsequent Mental Disorders

The findings that individuals with OCD are at an increased risk of subsequent onset of social phobia, GAD, BIP, dysthymia, and bulimia nervosa highlight that OCD might be an important marker regarding the developmental psychopathology of internalizing disorders. These results are in line with results from cross-sectional World Health Organization World Mental Health surveys, in which OCD, together with specific phobia, stood out as the most

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important internalizing predictor for the subsequent onset of internalizing disorders (Kessler et al., 2011). Together, these findings underline the importance of early interventions for OCD, before an individual's life is burdened by additional psychopathology. However, to derail progression to subsequent mental disorders, the mechanisms that account for these longitudinal associations need to be better understood.

Etiological considerations. Assuming a *causal relationship*, our findings about the substantial proportion of subsequent mental disorders (65–85%) that could potentially be prevented among individuals with OCD, if prior OCD was prevented or treated early, emphasize the role of a possible pathway for prevention of internalizing disorders through early treatment of OCD. For example, the demoralizing effect of OCD symptoms or symptom-related avoidance could lead to barriers to pleasurable social activities (Ruscio et al., 2010) and might place individuals with OCD at higher risk of dysthymia. In accordance with these speculations are findings that reductions in OCD symptoms during an exposure and response prevention therapy for individuals with OCD mediated subsequent reductions in depressive symptoms (Zandberg et al., 2015). An alternative to a causal association is well worth considering: The association between OCD and temporally secondary disorders might also be due to shared *common risk factors*, increasing the risk of both disorders. This model matches with observations that vice versa, social phobia, GAD, and BIP were also found to increase the risk for subsequent OCD (Ruscio et al., 2010). Thus, treatment approaches that also focus on risk factors underlying both OCD and the temporally secondary disorder, instead of only specific presented symptoms (Lahey, Zald, Hakes, Krueger, & Rathouz, 2014; Nolen-Hoeksema & Watkins, 2011), might prevent the subsequent onset of an internalizing disorder. One such potential risk factor that may play a role in the development of a broad range of internalizing disorders as a more proximal factor is experiential avoidance (Levin et al., 2014). One way to reduce experiential avoidance is through acceptance and commitment therapy (ACT; Hayes, Luoma, Bond, Masuda, & Lillis, 2006). Adding ACT to exposure and response prevention for OCD (Twohig et al., 2018) could

be an option for early treatment that might simultaneously be effective in preventing the subsequent onset of internalizing disorders.

Risk Factors for OCD and Their Interaction

Risk factors for OCD. The strong impact of BI on OCD supports the importance of temperament in the development of OCD (Coles et al., 2006). Studies of potential developmental mechanism linking BI to OCD are needed. BI as a distal factor has been linked to dysfunctional emotion regulation, such as rumination (Leen-Feldner, Zvolensky, Feldner, & Lejuez, 2004), which might be a more proximal risk factor for OCD. Ruminating over the meanings of common obsessive thoughts and compulsive behavior might contribute to the onset of OCD, by lessening the reduction of the urge to neutralize through compulsions (Wahl, van den Hout, & Lieb, in press) or maintaining distress associated with the obsessive thought (Mazanec et al., in preparation). Extending cross-sectional studies, we showed that paternal rejection increased the risk of OCD. Paternal rejection might be linked to OCD by contributing to a family environment that is perceived as threatening or dangerous (Hudson & Rapee, 2001) and increases children's vigilance for signs of threat. Overestimation of threat, in turn, has emerged as a prominent factor in the development of OCD (Salkovskis, 1985).

Risk factor interactions. Our findings yielded some support for a vulnerability–stress model, in which environmental factors, specifically paternal overprotection, a lack of paternal emotional warmth, and adverse life events, are more strongly associated with an increased risk of OCD for those with a higher (vs. lower) BI component. These results are broadly in line with a recent review that concluded that the interaction between parenting and child BI plays an essential role in internalizing symptoms (Ryan & Ollendick, 2018). Regarding the interaction between parental rearing and adverse life events, our findings indicate that maternal and paternal emotional warmth may buffer the association between adverse life events and the subsequent onset of OCD.

Implications. These findings provide important information for selective prevention efforts: Isolating moderating factors is an indispensable step in identifying at-risk individuals who might profit most from prevention (Cuijpers, 2003). They might also point toward processes (e.g., emotional warmth) that could be manipulated in preventive interventions to reduce the risk of an onset of OCD in those with an increased risk (e.g., exposure to a traumatic event). In terms of prevention, our findings raise the question of whether BI and parental rearing are malleable and if yes, whether their manipulation alters the risk of OCD. There is some support for interventions that have effectively reduced BI using approaches grounded in parent–child interaction therapy (Chronis-Tuscano et al., 2015) or cognitive behavior therapy (Anticich, Barrett, Silverman, Lacharez, & Gillies, 2013; Kennedy, Rapee, & Edwards, 2009), as well as emerging evidence that parental rearing such as emotional warmth (e.g., Breitenstein, Fogg, Ocampo, Acosta, & Gross, 2016; Landry, Smith, Swank, & Guttentag, 2008) or overprotection (Lau, Rapee, & Coplan, 2017) might be modifiable through interventions. In summary, evidence is beginning to accumulate suggesting that interventions directed at BI (Rapee & Bayer, 2018) and parental rearing (Yap et al., 2016) may be effective for preventing anxiety disorders in general. Whether changing BI or parental rearing alters the risk of OCD from a preventative standpoint remains to be addressed.

BI, parental rearing, and adverse life events have been considered as more distal, unspecific risk factors, which may be linked to multiple disorders (Green et al., 2010; Klein & Mumper, 2018; Yap & Jorm, 2015) through mediating proximal risk factors. These proximal risk factors (e.g., rumination) may in turn interact with moderators to determine what specific disorder individuals will experience (e.g., loss as a moderator for predicting depression, basal ganglia dysfunction for OCD; Nolen-Hoeksema & Watkins, 2011). Investigating the effect of preventive interventions targeting BI, parental rearing and adverse life events on a broader range of mental disorders might prove fruitful, as the efficacy and cost-effectiveness of these transdiagnostic interventions might be enhanced (Dozois, Seeds, & Collins, 2009).

Strengths and Limitations

This thesis has several strengths: (1) the 10-year, population-based longitudinal study design on which the manuscripts are based, which minimized both referral and recall bias; (2) the repeated assessment in the high-risk period for the onset of OCD and other mental disorders; (3) conclusions about the direction of the effect as a result of considering the temporal relationship of predictor and outcome; (4) the valid and reliable clinical interview (DIA-X/M-CIDI) that was used to assess OCD and other mental disorders; and (5) the easy-to-administer and cost-effective assessment of BI, adverse life events, and parental rearing, which could be used to identify at-risk individuals for selective prevention efforts. Several limitations, however, should be considered: Despite the large overall sample size, some estimations of the longitudinal associations were based on a relatively small number of OCD cases, given the combination with subsequent mental disorders (Manuscript 1) and interaction analyses (Manuscripts 2 and 3). Still, replication of the analyses for less severe forms of OCD to obtain bigger cell numbers yielded similar results, which is indicative of the robustness of the results. Furthermore, the results should be interpreted only within the context of *DSM-IV* diagnoses.

For Manuscript 1 we used retrospectively assessed age of onset of OCD and other mental disorders that may be subject to recall bias, although chances of this bias were minimized by the three follow-up assessments over a 5- to 10-year period, reducing the time frame for retrospective assessments.

Outlook

Investigation of possible mediators and moderators of the association between OCD and subsequent mental disorders and between the demonstrated risk factors and OCD is warranted. Whether early treatment of OCD can prevent the progression to subsequent psychopathology should be explored. Our sample size was too small to apply inferential statistics that might predict risk factors associated with the progression from OCD to subsequent mental disorders, so it might be fruitful to analyze combined data of different longitudinal studies sources.

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Studies investigating whether interventions that experientially manipulate BI and parental rearing result in a reduced risk for the onset of OCD are lacking. Randomized controlled studies should investigate their potential for the prevention of OCD and whether their change mediates the reduced risk of OCD. Delivery of brief, accessible preventive interventions through self-help books and Web- or mobile-based programs with minimal guidance might be studied, as they could overcome some of the barriers to broad dissemination. Given that subthreshold obsessions and compulsions are quite common and are associated with substantial impairment (Adam et al., 2012), investigating their potential as risk factors for psychopathology and whether they and OCD share similar risk factors might guide future prevention efforts.

Conclusion

Different approaches to reducing the burden associated with OCD are promising. Our findings that OCD may be a valuable marker of individuals at high risk for progression to internalizing disorders highlight the importance of the development of early interventions to prevent the onset of subsequent mental disorders. In terms of risk factors, BI and paternal rejection were shown to enhance the risk for the onset of OCD. Consistent with a vulnerability–stress model, adverse life events and dysfunctional paternal parenting were found to increase the risk of OCD more strongly when the individuals were characterized by temperamental vulnerability (BI). Parental emotional warmth may buffer the detrimental effect of adverse life events on OCD. Although the results of this thesis are only a starting point for a better understanding on how to reduce the burden associated with OCD, the findings could help identify individuals at higher risk of OCD who might particularly profit from preventive interventions and point to factors that could be modified in preventive interventions for OCD. Future studies should replicate and extend the current findings and investigate whether or which specific interventions prevent OCD or derail progression to other internalizing disorders in those with OCD.

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Appendix A (Manuscript 1)

**Obsessive–compulsive disorder and the risk of subsequent mental disorders: A
community study of adolescents and young adults**

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RESEARCH ARTICLE

Obsessive–compulsive disorder and the risk of subsequent mental disorders: A community study of adolescents and young adults

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Background: Comorbidity of obsessive–compulsive disorder (OCD) with other mental disorders has been demonstrated repeatedly. Few longitudinal studies, however, have evaluated the temporal association of prior OCD and subsequent mental disorders across the age period of highest risk for first onset of mental disorders. We examined associations between prior OCD and a broad range of subsequent mental disorders and simulated proportions of new onsets of mental disorders that could potentially be attributed to prior OCD, assuming a causal relationship.

Methods: Data from 3,021 14- to 24-year-old community subjects were prospectively collected for up to 10 years. DSM-IV OCD and other DSM-IV mental disorders were assessed with the Munich-Composite International Diagnostic Interview. We used adjusted time-dependent proportional hazard models to estimate the temporal associations of prior OCD with subsequent mental disorders.

Results: Prior OCD was associated with an increased risk of bipolar disorders (BIP; [hazard ratio, HR = 6.9, 95% confidence interval, CI, (2.8,17.3)], bulimia nervosa [HR = 6.8 (1.3,36.6)], dysthymia [HR = 4.4 (2.1,9.0)], generalized anxiety disorder (GAD; [HR = 3.4 (1.1,10.9)], and social phobia [HR = 2.9 (1.1,7.7)]). Of these outcome disorders, between 65 and 85% could be attributed to OCD in the exposed group, whereas between 1.5 and 7.7% could be attributed to OCD in the total sample.

Conclusions: This study provides strong evidence that prior OCD is associated with an increased risk of subsequent onset of BIP, bulimia nervosa, dysthymia, GAD, and social phobia among adolescents and young adults. Future studies should evaluate if early treatment of OCD can prevent the onset of these subsequent mental disorders.

KEYWORDS

anxiety/anxiety disorders, bipolar disorder, comorbidity, depression, eating disorders, epidemiology, GAD/generalized anxiety disorder, mood disorders, substance use disorders

1 | INTRODUCTION

The second and third decade of life constitute the core incidence period for the first manifestation of obsessive–compulsive disorder (OCD; Fineberg et al., 2013; Grabe et al., 2001; Karno, Golding, Sorenson, & Burnam, 1988; Weissman et al., 1994) and other mental disorders (Beesdo-Baum et al., 2015; Kessler et al., 2005, 2007; Kim-Cohen et al., 2003). In adults, cross-sectional associations between OCD

and other mental disorders have been found in several population-based studies (Adam, Meinschmidt, Gloster, & Lieb, 2012; Fineberg et al., 2013; Ruscio, Stein, Chiu, & Kessler, 2010; Weissman et al., 1994). In epidemiological studies with younger samples, comorbidity between OCD and other mental disorders has been observed across the core incidence period for first onset of psychopathology (Canals, Hernandez-Martinez, Cosi, & Voltas, 2012; Heyman et al., 2001; Valleni-Basile et al., 1994).

Few studies with community and patient-register samples have extended cross-sectional comorbidity analyses to focus on longitudinal comorbidity patterns and whether temporally prior OCD predicts the onset of temporally secondary mental disorders. We first give a short overview of those that have investigated associations between prior OCD and subsequent mental disorders in patients, adult community members, and younger community members.

Studies using data from nationwide patient registers found that compared to individuals without OCD, patients first diagnosed with OCD were at increased risk of later diagnosis of bipolar disorders (BIP), schizophrenia, schizoaffective disorder (Cederlöf et al., 2015), and anorexia nervosa (Cederlöf et al., 2015). Similarly, patients with hospital contact for prior OCD were at increased risk of subsequent anorexia nervosa (Meier et al., 2015), schizophrenia, schizophrenia spectrum disorder (Meier et al., 2014), and depression (Meier et al., 2015). These patient-based findings suggest that prior OCD may increase the risk of subsequent onset of BIP, schizophrenia, anorexia nervosa, or depressive disorder.

We identified three community-based studies relying on adult population-based samples (age ≥ 18 years), that directly addressed whether prior OCD increases the risk of secondary other mental disorders. With data from seven cross-sectional community surveys, Kessler et al. (2001) used retrospective age-of-onset information to investigate the temporal relationships across various forms of mental disorders and substance use disorders (SUDs) in adults. They showed that prior DSM-III-R/DSM-IV OCD was associated with the subsequent onset of drug dependence. Goodwin (2002) used prospective data from the Epidemiologic Catchment Area Program survey and found that DSM-III OCD elevated the risk of subsequent onset of major depression among adults in the community. Finally, Kessler et al. (2011) evaluated data from the World Health Organization World Mental Health (WHO-WMH) surveys using a cross-sectional approach and retrospective estimates of the temporal order of disorder onset. OCD predicted the subsequent onset of all other included anxiety disorders (generalized anxiety disorder [GAD], separation anxiety disorder, posttraumatic stress disorder, panic disorder, agoraphobia, specific phobia, social phobia) and affective disorders (BIP, unipolar depression) but not SUDs. Highest odds ratios were found for subsequent onset of BIP, GAD, agoraphobia, and social phobia. Additionally, Hofmeijer-Sevink et al. (2017) showed in a study based on the Netherlands Study of Anxiety and Depression cohort that obsessive compulsive symptomatology predicted the onset of DSM-IV anxiety and/or depressive disorder in healthy controls.

Since epidemiological studies have demonstrated that roughly 75% of all lifetime mental disorders have their onset by an individual's late 20s (Kessler et al., 2007), analyses that explore associations between prior OCD and subsequent psychopathology specifically in younger individuals would facilitate early identification and prevention of psychopathology development. We identified only two community-based studies that investigated OCD as a risk factor for onset of subsequent psychopathology before adulthood. Using a longitudinal design and a community sample aged 1–10 years at baseline and up to 28 years at follow-up, Peterson, Pine, Cohen, and Brook (2001) evaluated whether prior OCD symptoms predicted later onset of symptoms of depression

and other anxiety disorders (including specific phobia, social phobia, and GAD). Multivariate analyses revealed that OCD symptoms were associated with symptoms of depression, specific phobia, and GAD at follow-up. Buckner, Silgado, and Lewinsohn (2010) prospectively examined temporal associations between anxiety and eating disorders in adolescents aged 14–18 years at baseline using data from the Oregon Adolescent Depression Project. Adolescents with DSM-III-R OCD at baseline had a higher risk of subsequent onset of anorexia nervosa but not bulimia nervosa at age 30 than those without OCD. These two studies provided the first population-based evidence that by an early age, OCD is associated with an increased risk of the later development of mental disorders such as depression, anorexia nervosa, and certain anxiety disorders.

Although these studies provided valuable knowledge regarding the association between prior OCD and the subsequent onset of other mental disorders, we note the following limitations: these studies (a) used either a small set of outcome diagnoses, (b) used cross-sectional data with retrospectively collected age-of-onset information, which is prone to recall bias, or (c) compared referred-patient data with data from community subjects, which is prone to referral bias. Only two community-based studies included individuals during the high-risk phase for the development of psychopathology. Further, they did not address the potential effect of OCD prevention on new onsets of other mental disorders.

Our goal is to contribute to the understanding of the longitudinal association between prior OCD and the subsequent onset of a broad range of mental disorders. Using data from the 10-year prospective population-based Early Developmental Stages of Psychopathology (EDSP) study, we asked whether primary OCD is associated with an increased risk of secondary mental disorders in the core incidence phase for first onset of mental disorders and if so, what proportion of new onsets could conceivably be prevented by effective prevention or early treatment of OCD, assuming a causal relationship.

2 | METHODS

2.1 | Design and sample

Data came from the EDSP study, which was based on a community sample of originally $N = 3,021$ adolescents and young adults aged 14–24 years at baseline in 1995. The study included a baseline (T0) and three follow-up waves (T1, T2, T3). Individuals were randomly drawn from government registries of the greater Munich area in Germany. The study emphasized early developmental stages of psychopathology by sampling 14- to 15-year-olds at twice the probability of 16- to 21-year-olds, and 22- to 24-year-olds at half the probability of 16- to 21-year-olds. Subsequent analyses take this scheme into account by using sample weights.

The response rate at T0 was 70.9%. At T1 (1.2–2.1 years after T0) only the younger cohort (aged 14–17 years at T0) was approached and $N = 1,228$ (88.0% of the T0 14- to 17-year-olds) could be reinterviewed. At T2 and T3 the entire T0 sample was approached again. At T2 (2.8–4.1 years after T0), 2,548 participants (84.3% of the T0

sample) and at T3 (7.3–10.6 years after T0), 2,210 participants (73.2% of the T0 sample) were reinterviewed.

We found no selective attrition between T0 and T3 based on age, sex, geographic distribution, or OCD diagnostic status (Beesdo-Baum et al., 2015). Detailed descriptions of the EDSP study methods, design, and sample characteristics have been presented elsewhere (Beesdo-Baum et al., 2015; Lieb, Isensee, von Sydow, & Wittchen, 2000; Wittchen, Perkonig, Lachner, & Nelson, 1998). The study was approved by the Ethics Committee of the Medical Faculty of the Technische Universität Dresden, Germany (No: EK-13811). All participants provided informed consent.

2.2 | Assessment

Diagnostic assessments in all waves were based on the computer-assisted version of the Munich-Composite International-Diagnostic-Interview (DIA-X/M-CIDI; Wittchen & Pfister, 1997), which allows for the standardized assessment of symptoms, syndromes, and diagnoses of DSM-IV disorders and collects information about age of onset, duration, and severity. Trained clinical interviewers performed the 2–3 hr face-to-face interviews. At T0, the lifetime version of the DIA-X/M-CIDI was used. At each follow-up assessment, the DIA-X/M-CIDI interval version, which refers to the period between the last and current assessment, was applied. DIA-X/M-CIDI diagnoses showed substantial test–retest reliability (Wittchen, Lachner, Wunderlich, & Pfister, 1998). Good to excellent agreement was found between the clinicians and the DIA-X/M-CIDI diagnoses for the majority of diagnoses. Across all diagnoses, excellent sensitivity and specificity estimates were found (Reed et al., 1998). For OCD, 1-week test–retest reliability was $\kappa = 0.81$ (Wittchen et al., 1998); validity was $\kappa = 0.91$ (Reed et al., 1998). DSM-IV hierarchy rules were not applied in the current analyses.

The DIA-X/M-CIDI OCD module consisted of one part for the assessment of obsessions and one for the assessment of compulsions. Both parts begin with stem questions to identify a range of potential obsessive cognitions, repetitive behaviors, or mental acts. Individuals who confirmed any of the stem questions were assessed using the remaining mandatory DSM-IV OCD criteria before first onset, and last occurrence was assessed. At follow-up assessments, two symptom lists containing 14 items on potential obsessions and 10 items on compulsions were presented in addition to the stem questions to improve recall.

2.3 | Data analysis

Analyses were based on the total sample ($N = 3,021$). We used information from both dropouts and individuals who were assessed at follow-ups; that is, for every individual we used the information obtained before dropout, regardless of when it occurred. Data were weighted by age, sex, and geographic location at T0 to account for different sampling probabilities and ensure community representativeness. Analyses were performed using Stata Software Package 13.1 (StataCorp, 2013). Statistical significance was set at $P < .05$. We aggregated T0 and follow-up data and determined for all 55 lifetime OCD cases (until T3) comorbidity and temporal priority of OCD and comorbid disorders

using retrospectively assessed age-of-onset information. An examination of the reliability of the age-of-onset questions showed intraclass coefficients between 0.45 for specific phobia and 0.96 for GAD and 0.8 for obsessions and 0.6 for compulsions (Wittchen et al., 1998). To analyze whether having OCD increased the risk of subsequent mental disorders we performed Cox regressions with time-dependent covariates with hazard ratios (HRs) as a measure of effect (Therneau & Grambsch, 2000). Survival models were adjusted for age, sex, and mental disorders that occurred prior to OCD. We calculated the latter variable according to Höfler, Brückl, Lieb, and Wittchen (2005). Among individuals without OCD, the control variable was defined as any mental disorder that preceded the median age of onset of OCD in the respective age group (14–15, 16–17, 18–19, 20–21, and 22–24 years at T0).

To simulate the potential for prevention, we calculated the population attributable fraction (PAF) and the attributable fraction (AF). The PAF is the proportion of subsequent disorders in the total population that would not have occurred in the absence of OCD under the assumption that the HRs reflect causal effects of OCD. The AF denotes the proportion of subsequent disorders within the exposed group (individuals with OCD) that would not have occurred in the absence of OCD, again under the assumption that the HRs reflect causal effects of OCD. Although we cannot infer causality from an observational study, these two measures may offer an impression of potential effects of prevention of OCD on new onsets of other mental disorders. For the calculation of AFs and PAFs, we included significant predictors of the survival models and used the formula suggested by Porta (2014). The PAF was calculated as $Pd((HR - 1)/HR)$, where Pd is the exposure prevalence among cases with the respective mental disorder. The AF was calculated as $(HR - 1)/HR$.

3 | RESULTS

3.1 | Frequency of OCD

At T0, 0.7% ($N = 20$) of the total sample met lifetime DSM-IV criteria for OCD. At T3, 55 cases met criteria for DSM-IV OCD (cumulative lifetime incidence at T3: 1.8%). These 55 cases represent the OCD cases available for the risk analyses. Of them, 52 (94.3%) had at least one comorbid lifetime disorder.

3.2 | OCD and the risk of subsequent mental disorders

Proportional hazard analyses adjusted for sex, age, and any other disorder occurring prior to OCD (see Figure 1) revealed the strongest association between prior OCD and subsequent onset of BIP ($HR = 6.9$; 95% confidence interval [CI]: 2.8, 17.3). OCD was also associated with the onset of subsequent bulimia nervosa ($HR = 6.8$; 95% CI: 1.3, 36.6) and dysthymia ($HR = 4.4$; 95% CI: 2.1, 9.0). Among anxiety disorders, elevated risks were found for GAD ($HR = 3.4$; 95% CI: 1.1, 10.9) and social phobia ($HR = 2.9$; 95% CI: 1.1, 7.7). We observed no association between OCD and the subsequent onset of

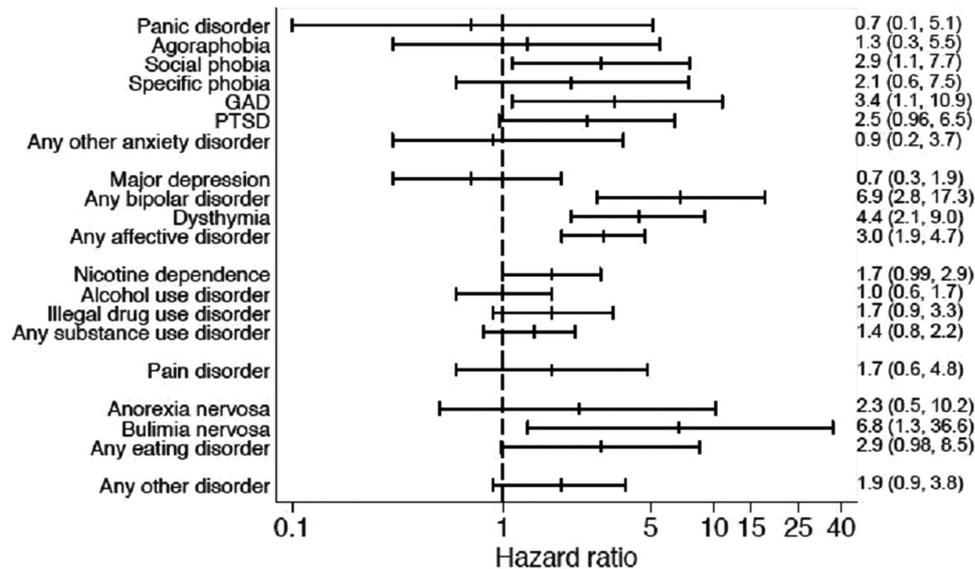


FIGURE 1 Temporal associations between prior DSM-IV obsessive-compulsive disorder (OCD) and subsequent onset of other mental disorders, adjusted for sex, age, and mental disorder other than the outcome disorder with an onset prior to OCD. Mean hazard ratios (HRs) from Cox regression models with time-dependent covariates are displayed with 95% confidence intervals. The dashed line represents a HR of 1. The risk is elevated whenever the lower bound of the 95% confidence interval is above 1. The horizontal axis is logarithmically transformed. GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder

TABLE 1 Attributable Fractions (AF) for the OCD Group and Population Attributable Fractions (PAF)

Outcome Disorder	AF	PAF
Other anxiety disorders		
Social phobia	65.6	1.5
GAD	71.0	3.1
Affective disorders		
Any bipolar disorder	85.5	4.2
Dysthymia	77.2	4.8
Any affective disorder	66.4	1.4
Eating disorders		
Bulimia nervosa	85.3	7.7

Note. OCD = obsessive compulsive disorder; GAD = generalized anxiety disorder. Estimation of AFs and PAFs were adjusted for age, sex, and mental disorders other than the outcome disorder with an onset prior to OCD.

major depression (HR = 0.7; 95% CI: 0.3,1.9) or SUDs (HR = 1.4; 95% CI: 0.8,2.2).

3.3 | Attributable fractions

For mental disorders with significant HRs, Table 1 displays the percentage of those disorders attributable to OCD in both the OCD group (AF) and the total population (PAF), assuming a causal relationship.

In line with the magnitude of the HRs for the associated outcome disorders, the highest AFs for the OCD group were found for BIP and bulimia nervosa (both > 80%). For all other significant outcome disorders, AF estimates were higher than 65%. At the population level, PAF estimates indicate that 3% of the incidence of GAD, 4–5% of BIP and dysthymia, and 8% of bulimia nervosa were attributable to prior OCD.

4 | DISCUSSION

Our results support the notion that OCD can be conceptualized as a significant risk factor for the onset of several other mental disorders (Kraemer et al., 1997). Our data suggest that OCD is associated with an increased risk of BIP (590%), bulimia nervosa (580%), dysthymia (340%), GAD (240%), and social phobia (190%) among adolescents and young adults. Extending earlier findings, we simulated the proportion of mental disorders that could be potentially prevented if prior OCD was prevented or treated early, assuming a causal relationship. Highest AFs of the OCD group (65–85%) were estimated for BIP and bulimia nervosa, followed by dysthymia, GAD, and social phobia. Estimated PAFs were remarkably lower. Nevertheless, our findings indicate that at the population level, up to 8% of the incidence of bulimia nervosa was attributable to prior OCD.

One of our major findings was that prior OCD was associated with the highest increase in risk for subsequent onset of BIP, confirming the risk association between prior OCD and BIP reported by Cederlöf et al. (2015). Likewise one of the strongest associations emerged between OCD and subsequent BIP in the analyses based on cross-sectional WHO-WMH survey data (Kessler et al., 2011). Cross-sectional associations between OCD and BIP have been found consistently in large-scale epidemiological samples (Adam et al., 2012; Angst et al., 2004; de Graaf, Bijl, Spijker, Beekman, & Vollebergh, 2003; Ruscio et al., 2010).

Another important finding was the association between prior OCD and risk of subsequent bulimia nervosa onset. Two population-based studies have reported cross-sectional associations between OCD and bulimia nervosa (Angst et al., 2004; Hudson, Hiripi, Pope, & Kessler, 2007) and only one (Buckner et al., 2010) included longitudinal associations with bulimia nervosa as outcome diagnosis. Since no incident bulimia nervosa cases could be observed in follow-up among OCD

cases, associations could not be estimated in this study. Our study provides the first quantitative evidence of the longitudinal association between OCD and bulimia nervosa in a large-scale community study. Therefore, our findings must be seen as preliminary and need replication. Turning to anorexia nervosa, we could not replicate results from previous longitudinal studies showing an association with prior OCD (Buckner et al., 2010; Cederlöf et al., 2015; Meier et al., 2015), although our point estimate was 2.3. We assume that we could not prove statistical significance because of the low number of incident cases.

Our elevated risks for subsequent onset of social phobia, GAD, and dysthymia were consistent with Kessler et al.'s (2011) results, but they used the combined group "major depression/dysthymia" as outcome, so our risk association between OCD and dysthymia can be only partially compared with this study and needs further exploration. In contrast to Meier, Petersen, et al.'s (2015) and Goodwin's (2002) results, OCD was not associated with an elevated risk of major depression onset in our analyses. However, these findings were consistent with results reported by Fineberg et al. (2013), who found no association between lifetime OCD and major depression in a Swiss sample followed for over 30 years. They raised concerns about the potential misclassification of BIP as major depression, resulting in false positive associations between OCD and major depression. Another explanation might be the older age of Goodwin's (2002) sample. With older age and thus possibly more chronic OCD, individuals may have had an increased risk for major depression due to the demoralizing effect of OCD symptoms (Ravizza, Maina, & Bogetto, 1997). In our study, OCD was not associated with an elevated risk of SUDs. Findings concerning this matter have been inconsistent (Kessler et al., 2001, 2011) and may be related to Cuzen, Stein, Lochner and Fineberg's (2014) heuristic, which argues that risk for SUDs in OCD increases with increasing severity of OCD but only to a certain threshold, beyond which compulsivity may decrease the risk of incidence of SUDs. Thus, it may be that the severity of OCD in participants varied between samples.

Several mechanisms might explain how prior OCD could lead to the development of subsequent mental disorders: (a) Because of the demoralizing effects of OCD, affective disorders may emerge as a consequence of obsessions and compulsions (Shear, Bjelland, Beesdo, Gloster, & Wittchen, 2007; Wittchen, Kessler, Pfister, & Lieb, 2000). OCD patients with BIP or unipolar disorders have reported greater OCD symptom severity than OCD patients without bipolar/unipolar disorders (Timpano, Rubenstein, & Murphy, 2012). (b) Anxiety symptoms already present in OCD (Fontenelle et al., 2010) may progress into a clinically relevant anxiety disorder, such as panic disorder or social phobia (Nestadt et al., 2001). (c) Structural brain alterations in OCD (Pujol et al., 2004) may render the brain more vulnerable to the development of subsequent other mental disorders. (d) Social discomfort around obsessions and compulsions might place individuals with OCD at higher risk for social phobia. In a clinical sample with childhood OCD, patients reported substantial impairment related to social settings (Valderhaug & Ivarsson, 2005).

Our estimations of AFs and PAFs provide a preliminary estimate of the proportions of mental disorders that could be prevented if OCD were prevented, assuming causality. Our PAFs were rather low since overall prevalence of OCD is also low in the population (Beesdo-Baum

et al., 2015). Among individuals with OCD, however, 65–80% of the incidence of subsequent dysthymia, BIP, social phobia, or GAD was attributable to prior OCD. This large AF illustrates the remarkable potential impact of OCD on subsequent psychopathology among OCD cases. However, considering the PAFs obtained for other factors, for example, specific phobia (Lieb et al., 2016), OCD seems to be a less likely target for reducing the incidence of specific disorders in universal prevention strategies but a suitable target for selective prevention strategies.

The present study has several methodological strengths. First, we studied a community sample of adolescents and young adults within an observation period that included the high-risk periods of both the first onset of OCD and the first onset of other mental disorders and used a prospective design. We thus minimized selection and recall bias, and collected data close to the first onset of OCD and other mental disorders. Second, our analyses were strengthened by a comprehensive set of outcome diagnoses, which allowed us to evaluate a range of mental disorders.

Nevertheless, several study limitations are noteworthy. Our findings should be interpreted only within the context of the DSM-IV definitions of mental disorders. Age of onset of OCD and other mental disorders was assessed with retrospective reports, which may introduce recall bias. This bias was lessened by our longitudinal study design of three follow-up assessments over a 5- to 10-year period, which decreased the time frame for retrospective assessments. Estimates of longitudinal associations were based on a small number of cases, resulting in large CIs in some analyses. The AFs and PAFs as a preliminary quantitative appraisal of the impact of OCD on the risk of subsequent mental disorders should be interpreted with caution since they assume causality and absence of bias. Disorders known to be associated with OCD were not examined in our study (e.g., schizophrenia, Cederlöf et al., 2015, and personality disorders, Torres et al., 2006). Finally, although we adjusted for possible confounding factors, we cannot exclude that observed associations may have been biased by hidden third variables or may be explained by unmeasured shared overlapping causal factors.

5 | CONCLUSION

Our study provides valuable new findings about OCD and the risk for the development of bulimia nervosa, BIP, dysthymia, social phobia, and GAD in the high-risk age period for the onset of psychopathology. Our findings highlight the need for early treatment efforts and the development of early prevention of secondary mental disorders. As the effectiveness of cognitive-behavioral treatment of OCD in children has been demonstrated (Öst, Riise, Wergeland, Hansen, & Kvale, 2016), adolescents may be a relevant target for early diagnosis and treatment that may reduce the risk for subsequent mental disorders. Our AFs provide a first appraisal of the impressive proportion of secondary mental disorders that could be prevented among young individuals with OCD. If prevention could be shown to reduce the risk for subsequent disorders, then OCD could be conceptualized as a causal

risk factor for psychopathology (Kraemer et al., 1997). Further studies are needed to explore the mechanisms behind the associations of OCD with specific subsequent mental disorders.

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Appendix B (Manuscript 2)

The role of behavioral inhibition, perceived parental rearing, and adverse life events in adolescents and young adults with incident obsessive-compulsive disorder

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The role of behavioral inhibition, perceived parental rearing, and adverse life events in adolescents and young adults with incident obsessive-compulsive disorder



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ABSTRACT

The role of behavioral inhibition (BI), parental rearing, and adverse life events in the development of obsessive-compulsive disorder (OCD) is unresolved. We prospectively examined whether BI and perceived parental rearing predicted the subsequent first onset of OCD and whether BI moderated the association between perceived parental rearing/adverse life events and the first onset of OCD. Data come from a prospective-longitudinal study among community adolescents and young adults (aged 14–24) who were followed up over 10 years ($N = 2210$). OCD and adverse life events were assessed with the DSM-IV/M-CIDI. BI and parental rearing were assessed by self-report. In adjusted logistic regressions, BI (risk ratio, $RR = 8.8, 95\%$ confidence interval, $CI, [3.3, 23.2]$), both the social ($RR = 2.6, 95\%CI[1.04, 6.3]$) and nonsocial fear ($RR = 4.5, 95\%CI[2.3, 8.6]$) components, and paternal rejection ($RR = 3.9, 95\%CI[1.6, 9.7]$) predicted OCD. Social BI moderated the association of adverse life event ($RR = 11.98, 95\%CI[1.8, 82.1]$) and paternal overprotection ($RR = 5.5, 95\%CI[2.1, 14.8]$) with OCD. Nonsocial fear BI moderated the association between paternal emotional warmth ($RR = 0.37, 95\%CI[0.1, 0.99]$) and OCD. BI and paternal rejection were associated with an increased risk of first onset of OCD. Individuals with high social BI who experienced paternal overprotection or any adverse life events may profit from early targeted prevention. Emotional warmth may buffer the association between nonsocial fear BI and OCD.

1. Introduction

Obsessive-compulsive disorder (OCD) is listed among the 10 most debilitating mental and physical disorders worldwide (Murray & Lopez, 1996) and is associated with substantial psychosocial impairment (Fineberg et al., 2013) and an increased risk of subsequent mental disorders (Hofer et al., 2018). Over the last few decades, a number of studies have focused on possible risk factors that might contribute to the development of OCD. Similar to other internalizing disorders, behavioral inhibition (BI), adverse life events, and parental rearing (Brander, Perez-Vigil, Larsson, & Mataix-Cols, 2016; Coles, Schofield, & Pietrefesa, 2006) are of special interest from the perspective of primary prevention. From a diathesis–stress perspective, BI might be viewed as placing individuals along a continuum of vulnerability to develop OCD

in the face of stress that comes with exposure to critical environmental factors such as adverse life events or dysfunctional parental rearing.

BI is a dispositional factor that is thought to be involved in the pathogenesis of OCD (Coles et al., 2006). BI has been described as a tendency to react to social and nonsocial novelty with behavior characterized by high levels of restraint, withdrawal, and avoidance (Kagan, Reznick, Clarke, Snidman, & Garcia-Coll, 1984). There is evidence for a genetic contribution to behavioral inhibition (Dilalla, Kagan, & Reznick, 1994).

Appreciating OCD as belonging to the wider spectrum of anxiety disorders (see Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013)) the etiological pathways to anxiety suggest that the avoidance of novel situations and stimuli may undermine an individual's ability to learn that anxiety-

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provoking situations are not threatening or unmanageable (Chorpita & Barlow, 1998; Foa & Kozak, 1986). Thus, BI may foster avoidance behavior and prevent opportunities in which disconfirming information about the threat value of these situations/stimuli can be obtained. Previous research has identified associations between BI and anxiety disorders in general (Beesdo, Pine, Lieb, & Wittchen, 2010; Knappe et al., 2011; Wittchen, Kessler, Pfister, & Lieb, 2000). Three population-based studies suggested that there is a relationship between a behaviorally inhibited temperament in childhood and obsessive-compulsive symptoms. Muris, Meesters, and Spinder (2003) and Muris, Merckelbach, Schmidt, Gadet, and Bogie (2001) found an association between self-reported BI and obsessive-compulsive symptoms in a cross-sectional study of two samples of adolescents. In another cross-sectional study of students, Coles et al. (2006) demonstrated that retrospective self-reports of childhood BI were associated with the frequency of current obsessive-compulsive symptoms. At odds with these studies are results from two prospective population-based studies of BI and threshold OCD (Caspi, Moffitt, Newman, & Silva, 1996; Rapee, 2014). In these studies, childhood BI did not predict OCD in adolescents (age 15; Rapee, 2014) or young adults (age 21; Caspi et al., 1996). Additionally, Hudson, Dodd, and Bovopoulos (2011) failed to find a link between laboratory-assessed BI and OCD in a cross-sectional study of preschoolers, age 3–4 years. However, Rapee (2014) and Hudson et al. (2011) identified only four children with OCD, and thus it is likely that their analyses were not sufficiently powered. Furthermore, Caspi et al. (1996) did not find behavioral styles at 3 years to be predictive for OCD or any anxiety disorder, including social phobia, at 21 years. To conclude, only three studies have examined whether BI increased the risk of subsequent OCD and findings were hampered by methodological limitations.

Research has provided evidence that BI is bidimensional, consisting of a social and a nonsocial fear component. It has been suggested that these components should be treated as different constructs as they have been shown to be relatively independent and to have distinct correlates (Dyson, Klein, Olino, Dougherty, & Durbin, 2011; Kochanska, 1991; Majdandzic & van den Boom, 2007; Mick & Telch, 1998; Neal, Edelmann, & Glachan, 2002; Poole, Jetha, & Schmidt, 2017; Rubin, Hastings, Stewart, Henderson, & Chen, 1997; Schofield, Coles, & Gibb, 2009). Using a student sample, Coles et al. (2006) showed associations between obsessive and compulsive symptoms and both the social and nonsocial fear components of BI. Whether these dimensions are both relevant in threshold OCD remains unclear.

Among environmental factors, parental rearing is thought to be related to anxiety disorders (e.g. Asselmann, Wittchen, Lieb, & Beesdo-Baum, 2016; Knappe et al., 2009b; Möller, Nikolic, Majdandzic, & Bögels, 2016). In a recent systematic review of environmental risk factors for OCD, Brander et al. (2016) concluded that self-reported parental overprotection and paternal rejection are associated with OCD. All of the reviewed studies, however, were flawed in that they (a) used cross-sectional data and did not consider temporal sequence of parental rearing and OCD, making it impossible to disentangle risk factors from concomitants or consequences, and (b) were based on clinical samples or students, limiting generalizability of the results.

Increasingly, experiencing adverse life events has been recognized as a possible important negative environmental factor in OCD (for a review, see Brander et al., 2016). In recent prospective analyses based on the Early Developmental Stages of Psychopathology (EDSP) Study (Asselmann, Wittchen, Lieb, Perkonig, & Beesdo-Baum, 2017), traumatic events at baseline were associated with an increased risk of OCD. Valleni-Basile et al. (1996) showed in a prospective study that undesirable life events increased the risk of OCD in adolescents. In the Dunedin Multidisciplinary Health and Development Study, retrospectively assessed childhood stressors, such as sexual and physical abuse, number of residence changes, but not the loss of a parent, were associated with increased odds of OCD, compared to healthy controls (Grisham et al., 2011).

Consistent with a diathesis–stress model is the suggestion that BI is one manifestation of a genetic vulnerability factor, which in interaction with an environmental stressor (e.g., adverse life events or parental rearing) may play a role in the development of an anxiety disorder (see Craske, 1997; Muris & Merckelbach, 2000; Ollendick & Hirshfeld-Becker, 2002; Turner & Beidel, 1996). Little is known concerning these interaction effects in predicting OCD. Some evidence has suggested that overprotective parenting might moderate the impact of BI on the obsessive-compulsive symptoms of OCD (Coles et al., 2006), but we have not identified any study reporting on interaction effects between BI and adverse life events or parental rearing in predicting threshold OCD.

Although the reported studies provide valuable knowledge regarding the association between BI and OCD and between perceived parental rearing and OCD, we note the following limitations: Studies (a) used convenience samples such as student samples, which were not representative of the general population, (b) assessed symptoms instead of reliable OCD diagnoses, (c) used cross-sectional data, which makes it difficult to disentangle risk factors from concomitants or consequences, or (d) were not sufficiently powered. Whether the interaction between temperament and other environmental factors that have been hypothesized to be relevant to OCD, such as adverse life experiences and perceived parental rearing, predicts incident OCD has not been investigated so far.

As such, the goal of this study was to contribute to the understanding of the longitudinal association between BI/parental rearing and OCD among adolescents and young adults. Using data from the 10-year prospective population-based EDSP Study, we addressed the following questions: Is BI associated with an increased risk of OCD? Furthermore, are both the social and nonsocial fear subscales of BI associated with an increased risk of OCD? Are maternal and paternal parenting styles associated with an increased risk of OCD? And finally, given the interest in the potential interaction between temperament and environmental factors, does BI moderate the potential association between adverse life experiences/parental rearing and OCD?

2. Methods

2.1. Sample

Data came from the 10-year prospective EDSP Study, which assessed *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-IV; American Psychiatric Association, 1994) mental disorders and associated risk factors in a representative sample of adolescents and young adults. The study included a baseline assessment (T0, 1995, $N = 3021$, response rate 70.8%) and three follow-up waves (T1, 1996/1997, only the subsample of the T0 14- to 17-year-olds was re-interviewed, $N = 1228$, response rate 88.0%; T2, 1998/1999, $N = 2548$, response rate 84.3% of the T0 sample; T3, 2003, $N = 2210$, response rate 73.2% of the T0 sample). Individuals were age 14–24 years at baseline and 21–34 years at last follow-up. They were randomly drawn from government registries of the Munich area. The study underscored the early developmental stages of psychopathology by sampling 14- to 15-year-old individuals at twice the probability of 16- to 21-year-old individuals and 22- to 24-year-old individuals at half the probability of 16- to 21-year-old individuals. Analyses took this scheme into account by using sample weights. No selective attrition between T0 and T3 based on age, sex, geographic distribution, or OCD diagnostic status was found (Beesdo-Baum et al., 2015). Detailed descriptions of the EDSP Study methods, design, and sample characteristics have been published elsewhere (Beesdo-Baum et al., 2015; Lieb, Isensee, von Sydow, & Wittchen, 2000; Wittchen, Perkonig, Lachner & Nelson, 1998). The study protocol was reviewed by the Ethics Committee of the Medical Faculty of the Technische Universität Dresden (No: EK-13811). All participants provided written informed consent.

Table 1
Illustration of time of assessment of risk factors and included outcome information.

	T0: 1995 age 14-24	T1: 1996/7 age 15-19	T2: 1998/9 age 17-28	T3: 2003/4/5 age 21-34
DSM-IV OCD	x	x	x	x
Behavioral inhibition	x	—————>		
Adverse life events	x	—————>		
Parental rearing			x	—————>
Risk factor interactions	x		x	—————>

Note. x refers to the timepoint at which the construct was assessed. The arrows refer to the outcome OCD and the timespan in which new onsets of OCD were included as incident cases. Individuals who met criteria for OCD at any point before the arrow were excluded from the analysis to ensure temporal priority of the risk factors.

2.2. Diagnostic assessment

At all waves, *DSM-IV* mental disorders were assessed using the computer-assisted version of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI Wittchen & Pfister, 1997), which allows for the standardized assessment of symptoms, syndromes, and diagnoses of *DSM-IV* disorders along with information about age of onset, duration, and severity. Trained clinical interviewers performed the 2- to 3-h face-to-face interviews. At T0, the lifetime version of the DIA-X/M-CIDI was applied. At each follow-up assessment, the DIA-X/M-CIDI interval version, which referred to the period between the last and current assessment, was used. Test–retest reliability and validity for the full DIA-X/M-CIDI have been reported elsewhere (Reed et al., 1998; Wittchen, 1994; Wittchen, Lachner, Wunderlich & Pfister, 1998).

The OCD module of the DIA-X/M-CIDI first assessed obsessions and then compulsions. The obsession part begins with one stem question and the compulsion part with three stem questions to identify a wide range of potential obsessive cognitions or repetitive behaviors or mental acts. Individuals who answered yes to any of the stem questions were assessed using the remaining mandatory *DSM-IV* OCD criteria before first onset and last occurrence was assessed. At follow-up assessments, two symptom lists containing 14 items on potential obsessions and 10 items on compulsions were presented in addition to the stem questions to improve recall. *DSM-IV* hierarchy rules were not applied in the analyses reported in this paper.

2.3. Assessment of BI

BI was retrospectively assessed at T0 using the German version of the Retrospective Self-Report of Inhibition (RSRI; Lieb, 2003; Reznick, Hegeman, Kaufman, Woods, & Jacobs, 1992). The RSRI is a self-report instrument that includes a total scale and two subscales: social/school and fear/illness. These subscales are consistent with the social and nonsocial fear components of BI. Thirty items that assess childhood behavior from age 5–16 years in different situations are rated on a 5-point scale ranging from 1 (*never*) to 5 (*very often*). Higher scores indicate higher BI. Items refer to specific events/situations rather than subjective impressions to reduce the influence of mood or current psychopathology (Reznick et al., 1992). Based on the EDSP data, evidence in support of internal consistency and convergent, concurrent, and predictive validity for the German version of the RSRI including its two dimensional subscales was provided (Rohrbacher et al., 2008).

2.4. Assessment of adverse life events

The category any adverse life event covers both separation events and traumatic life event. Separation events were assessed at baseline as part of the family history section of the DIA-X/M-CIDI and included death of a parent and parental separation or divorce. Traumatic events were assessed with the section for posttraumatic stress disorder (PTSD). Eight specific events (war experience, being physically attacked, rape, sexual abuse as a child, natural disasters, serious accidents, imprisonment, and witness of traumatic events of others) and one open category (other traumatic events) were assessed according to the *DSM-IV* PTSD criterion A1.

2.5. Assessment of parental rearing

Parental rearing was retrospectively assessed using the German version of the Questionnaire of Recalled Parental Rearing Behavior (QRPRB; Schumacher, Eisenmann, & Brahler, 1999). In the QRPRB, perceived maternal and paternal emotional warmth, overprotection, and rejection are assessed with 24 items on a 4-point scale ranging from 1 (*no, never*) to 4 (*yes, always*) at T1 for the younger cohort and at T2 for all participants. The German version of the QRPRB revealed a Cronbach's α of 0.85, 0.69, and 0.75, for emotional warmth, parental overprotection, and rejection, respectively, at T1 (Knappe et al., 2009a) and an at least moderate temporal stability in community adolescents (Asselmann, Knappe, Wittchen, Lieb, & Beesdo, 2015). The present analyses refer to recalled parental rearing assessed at T2 to obtain a larger sample size.

2.6. Statistical analyses

Statistical analyses were conducted with Stata 13.1 (StataCorp, 2013). Statistical significance was set at $p < .05$. Analyses for this report were restricted to individuals who completed the T3 assessment ($N = 2210$) and who provided data on BI and any adverse life event at T0 and OCD at any follow-up wave or who provided data on parenting at T2 and OCD at T3. An illustration of time of assessment of risk factors and included outcome information is presented in Table 1. Because not all individuals provided data on each parenting dimension, numbers differed for these analyses. Data were weighted by age, sex, and geographic location at baseline to account for different sampling probabilities and to ensure community representativeness.

In the first model, we used separate logistic regression analyses to estimate associations between the risk factors BI/adverse life events/perceived parental rearing and the subsequent first onset of OCD. We

analyzed (a) whether BI and adverse life events that were retrospectively assessed at T0 were associated with the subsequent first onset of DSM-IV OCD between T0 and T3. Furthermore, we investigated (b) whether retrospectively assessed perceived parental rearing at T2 was associated with the subsequent first onset of DSM-IV OCD between T2 and T3. Incident OCD was used as outcome to ensure the temporal priority of the risk factor. Thus, it was possible to disentangle risk factors from concomitant factors or consequences. Participants who met criteria for lifetime OCD at T0 were excluded from Analysis 1 and participants who met criteria for OCD at T0, T1, or T2 were excluded from Analysis 2.

In the second model, we used separate logistic regression analyses to test whether the association (a) between parental rearing and the subsequent first onset of OCD between T2 and T3 and (b) between adverse life events and the subsequent first onset of OCD between T2 and T3 was moderated by BI (interaction). Whenever the interaction effect reached significance, the association between the respective risk factor and the subsequent first onset of OCD between T2 and T3 was plotted for the mean of BI, high ($M + SD$) and low levels of BI ($M - SD$). We used risk ratios (RRs) as a measure of strength and adjusted all analyses for sex and age at last assessment.

3. Results

3.1. Cumulative lifetime incidence of OCD

The cumulative lifetime incidence of OCD at T3 was 2.1%. This result has previously been reported based on the EDSP data (Beesdo-Baum et al., 2015). Estimates were higher for females (2.9%) than for males (1.2%; RR = 2.5, 95% confidence interval, CI, [1.2, 5.1]).

3.2. Associations of BI, adverse life events, and perceived parental rearing with subsequent first onset of OCD

Table 2 presents associations between possible risk factors and subsequent first onset of OCD: BI increased the risk of subsequent onset of OCD between T0 and T3 (RR = 8.8, 95% CI [3.3, 23.2]). Both subscales, that is, the nonsocial fear (RR = 4.5, 95% CI [2.3, 8.6]) and the social (RR = 2.6, 95% CI [1.04, 6.3]) BI, were associated with subsequent onset of OCD. Having experienced traumatic events (RR = 3.0, 95% CI [1.3, 7.0]) predicted the subsequent first onset of OCD, a result

Table 2
Association of BI, adverse life events and parental rearing with incident OCD (N = 2210).

Factor	N	RR	95% CI	
BI total	2197	8.79	3.32	23.24
BI nonsocial fear	2197	4.47	2.33	8.56
BI social	2197	2.56	1.04	6.33
Any adverse life event	2197	2.34	0.97	5.63
Separation event	2197	1.28	0.56	2.94
Traumatic event	2197	2.99	1.28	7.01
Parental rearing				
Maternal				
Emotional warmth	1943	0.84	0.31	2.30
Overprotection	1954	2.01	0.61	6.58
Rejection	1899	2.27	0.80	6.46
Paternal				
Emotional warmth	1850	0.48	0.17	1.42
Overprotection	1864	0.99	0.25	3.87
Rejection	1822	3.89	1.56	9.66

Note. BI = Behavioral inhibition; CI = confidence interval; OCD = obsessive-compulsive disorder; RR = risk ratio. Models were adjusted for sex and age at last assessment. In the models with BI and adverse life events as predictors (T0), incident OCD refers to new onsets between T0 and T3. In the models with parental rearing as predictors (T2), incident OCD refers to new onsets between T2 and T3.

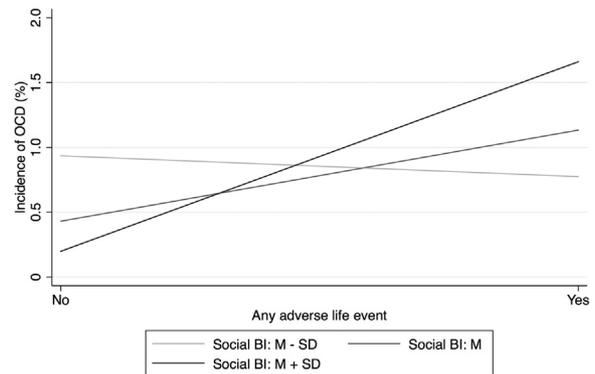


Fig. 1. Social behavioral inhibition (BI) moderation of the association between adverse life events and first onset of obsessive-compulsive disorder (OCD) from T2 to T3.

that was reported in a previous paper based on the EDSP study (Asselmann et al., 2017). Other adverse life events at baseline did not predict the subsequent first onset of OCD. Of the parental rearing styles, only paternal rejection was associated with first onset of OCD between T2 and T3 (RR = 3.9, 95% CI [1.6, 9.7]). None of the other maternal or paternal rearing styles were associated with subsequent first onset of OCD.

3.3. BI as moderator of the association between adverse life events and subsequent first onset of OCD

Social BI moderated the association between any adverse life event (RR = 11.98, 95% CI [1.7, 82.1]) and first onset of OCD from T2 to T3 (Fig. 1). An increase of social BI by one standard deviation ($SD = 0.47$) thereby increased the RR of the positive association between any adverse life event and first onset of OCD by a factor of 3.2. There were no other moderator effects for any of the other BI scales (see Table 3).

3.4. BI as moderator of the association between perceived parental rearing and subsequent onset of first OCD

When testing the moderating effects of BI on the association between parental rearing style and first onset of OCD from T2 to T3, we observed an interaction effect between nonsocial fear BI and paternal emotional warmth (RR = 0.4, 95% CI [0.1, 0.99]; see Fig. 2). An increase of nonsocial fear BI by one standard deviation ($SD = 0.50$) increased the RR of the negative association between paternal emotional warmth and first onset of OCD by a factor of 1.7.

In addition, social BI moderated the association between paternal overprotection and first onset of OCD from T2 to T3 (RR = 5.5, 95% CI [2.1, 14.8]; see Fig. 3). More specifically, an increase of social BI by one standard deviation ($SD = 0.47$) increased the RR of the association between paternal overprotection and first onset of OCD by a factor of 2.2. We observed no other moderator effects for BI on the association between perceived parental rearing and first onset of OCD from T2 to T3 (see Table 3).

4. Discussion

In this 10-year prospective-longitudinal study among adolescents and young adults, higher total BI, social BI, nonsocial fear BI, and paternal rejection were associated with an elevated risk of first onset of OCD. The total scale of BI did not interact with perceived parental rearing or adverse life events in predicting subsequent first onset of OCD. The nonsocial fear component of BI, however, moderated the association between paternal emotional warmth and OCD. Higher paternal emotional warmth was associated with a decreased risk of OCD in individuals with higher but not lower nonsocial fear BI. Furthermore,

Table 3
Interaction effects between BI and adverse life events or parental rearing on predicting incident OCD between T2 and T3, N = 2210.

Interaction	N	OCD									
		BI total				BI nonsocial fear			BI social		
		RR	95% CI			RR	95% CI		RR	95% CI	
Any adverse life event	2185	5.50	0.36	85.13	0.57	0.15	2.16	11.98	1.75	82.11	
Separation event	2185	3.70	0.46	29.60	0.66	0.18	2.41	7.06	0.98	50.83	
Traumatic event	2185	1.20	0.15	9.31	0.52	0.11	2.53	2.75	0.29	25.65	
Parental rearing at T2											
Maternal											
Emotional warmth	1943	0.71	0.20	2.53	0.62	0.28	1.38	1.46	0.14	14.75	
Overprotection	1954	0.31	0.02	5.34	0.42	0.08	2.16	0.48	0.01	24.35	
Rejection	1899	0.19	0.02	2.06	0.57	0.22	1.45	^a			
Paternal											
Emotional warmth	1850	0.21	0.03	1.63	0.37	0.14	0.99	0.47	0.11	2.02	
Overprotection	1864	4.53	0.64	32.16	0.40	0.09	1.75	5.54	2.08	14.75	
Rejection	1822	2.75	0.35	21.49	0.80	0.28	2.26	3.30	0.60	18.15	

Note. BI = Behavioral inhibition; CI = confidence interval; OCD = Obsessive-compulsive disorder. Models were adjusted for sex and age at last assessment. Incident OCD only refers to incident OCD between T2 and T3.

^a This model could not be estimated because of lack of convergence.

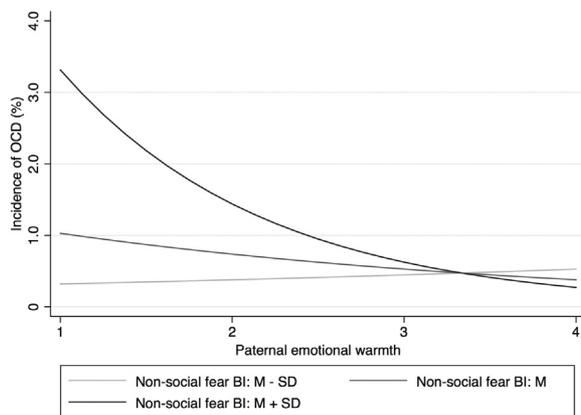


Fig. 2. Moderation of nonsocial fear behavioral inhibition (BI) on the association between paternal emotional warmth and first onset of obsessive-compulsive disorder (OCD) from T2 to T3.

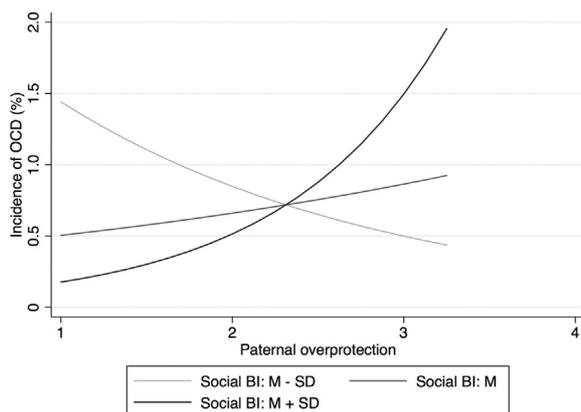


Fig. 3. Moderation of social behavioral inhibition (BI) on the association between paternal overprotection and first onset of obsessive-compulsive disorder (OCD) from T2 to T3.

we observed an interaction between the social component of BI and environmental factors. Any adverse life event and paternal overprotection were associated with an increased risk of subsequent first onset of OCD in those with higher levels but not in those with lower levels of social BI.

Our results substantially extend earlier reports, as our findings come from a community sample of adolescents and young adults who were followed up over a period of up to 10 years, and we (a) differentiated between the social and nonsocial fear component of BI, (b) considered strictly prospective associations between perceived parental rearing and subsequent first onset of OCD, and (c) considered the interactions between temperament and environmental factors such as parental rearing or adverse life events, which have not yet been investigated for threshold OCD.

To our knowledge, this study is the first to document that BI prospectively increased the risk of OCD. Furthermore, the impact of BI was found to be remarkably strong, as the risk of OCD was elevated by 780% per unit. Our results are consistent with cross-sectional studies that have demonstrated a relationship between self-reported BI and obsessive-compulsive symptoms in nonclinical samples of children and adolescents (Coles et al., 2006; Muris et al., 2003, 2001). However, they stand at odds with prior studies, which did not show that BI, assessed using observational methods, was prospectively (Caspi et al., 1996; Rapee, 2014) or cross-sectionally (Biederman et al., 2001; Hudson et al., 2011) related to OCD. This might be explained by the fact that we retrospectively assessed BI, which may represent a more proximal risk factor in contrast to BI observed at a very young age, or also by the method of assessment: In the literature, associations between BI and OCD or OCD symptoms were found in studies that assessed BI using self-report in older children or adolescents (age 11–18; Coles et al., 2006; Muris et al., 2003, 2001) but not in studies using observations in young children (age 2–6; Biederman et al., 2001; Caspi et al., 1996; Hudson et al., 2011; Rapee, 2014). Furthermore, we had a bigger sample than most studies (Biederman et al., 2001; Hudson et al., 2011; Rapee, 2014) and were thus more likely to detect an effect. Our findings support the theory underlying some of the etiological pathways to OCD; that is, BI might contribute to the avoidance of situations and stimuli that are associated with obsessions or compulsions and may prevent individuals from learning new associations with what they fear (Chorpita & Barlow, 1998; Foa & Kozak, 1986). However, our findings must be replicated in future studies and the underlying mechanisms that may lead to OCD must be examined more thoroughly before theoretical implications can be identified. If the strong relationship to subsequent OCD is replicated, BI may be an important marker for future OCD, and individuals with high BI could be targeted for testing the effects of selective prevention efforts. Furthermore, the assessment of BI using a self-report questionnaire, as was done in our study, may have several advantages in the context of prevention, as questionnaires offer a cost- and time-efficient option to identify at-risk individuals.

Our findings point out that both the social and the nonsocial fear component of BI are longitudinally associated with the subsequent onset of OCD. This result is consistent with other research in which similar cross-sectional associations between obsessive-compulsive symptoms and the two components of BI in a student sample were observed (Coles et al., 2006). Our results, while still preliminary until replicated, suggest that the two BI components might, however, interact differently with environmental factors, such as parental rearing and adverse life events, in the prediction of subsequent first onset of OCD. Therefore, our results further underscore the importance of distinguishing between the social and nonsocial fear components in future research on OCD.

One major finding of our study is that paternal rejection increased the risk of OCD. Our results therefore support and extend prior findings, that paternal rejection is cross-sectionally associated with OCD (Alonso et al., 2004; Ehiobuche, 1988; Ivarsson, Saavedra, Granqvist, & Brobert, 2015; Lennertz et al., 2009). We did not find that paternal or maternal overprotectiveness or lack of emotional warmth directly increased the risk of subsequent first onset of OCD. Prior findings of a relationship between overprotectiveness and OCD from cross-sectional studies (Brander et al., 2016) may be explained by the direction of the effect. That is, children with OCD may elicit overprotective rearing behavior, which may be more of a consequence of OCD than a risk factor for it. On the other hand, as demonstrated in our study, paternal parenting might increase the risk for only a subset of individuals with social BI. Inconsistent result might therefore stem from varying proportion of individuals with high social BI. Our findings on the role of paternal rearing style for OCD are in line with evidence suggesting that fathers have a relevant and unique role in the development of children (Bögels & Phares, 2008). However, most studies have neglected the role of fathers in investigations concerning the relationship between rearing and mental disorders in research and prevention programs (Bögels & Phares, 2008). Our findings further underscore the importance of including paternal rearing in research, treatment, and prevention of OCD. Our results do not show that maternal rearing styles directly increase the risk of the subsequent onset of OCD. There might be two explanations: One is that we might not have sufficient statistical power to detect such an effect due to a relatively small number of incident cases. The second is more substantive: According to theoretical assumptions paternal rearing is more strongly related to a child's anxiety than maternal rearing (Bögels & Perotti, 2011; Bögels & Phares, 2008). It has been suggested that from an evolutionary perspective a father's role is to open children to the outside world, strengthen the independence and encourage risk-taking, whereas mothers are more specialized in caring, nurturing and protective behavior. Thus, if fathers demonstrate overprotective or rejecting behaviors, instead of enhancing independence or stimulating risk-taking, this may contribute more strongly to child anxiety, than when mothers demonstrate similar parenting behaviors (Bögels & Perotti, 2011).

Other prospective community-based studies suggest, that BI (Caspi et al., 1996; Rapee, 2014; Rohrbacher et al., 2008; von Sydow, Lieb, Pfister, Höfler, & Wittchen, 2002), parental rearing (Oldehinkel, Hartman, Van Oort, & Nederhof, 2015; Overbeek, ten Have, Vollebergh, & de Graaf, 2007) and adverse life events (Asselmann et al., 2017; Goodwin, Fergusson, & Horwood, 2005; Grisham et al., 2011) are associated with an increased risk of a range of mental disorders. These observations suggest that these risk factors may play an important role not only in the etiology of OCD, but also of other mental disorders.

Our findings yielded some support for a diathesis–stress model, in which a stressor in the environment (perceived paternal rearing and adverse life events) more strongly increases the risk of the subsequent first onset of OCD among individuals with higher BI compared to individuals with lower BI. Any adverse life event more strongly increased the risk of subsequent onset of first OCD in individuals with higher social BI compared to individuals with lower social BI. To our knowledge, the interaction between adverse life events and BI has not yet

been investigated for OCD. Therefore, our findings need replication. For any adverse life event, separation event and traumatic life event were aggregated in our analyses. Therefore, our results may be partly comparable with a study in which high fearfulness, a temperamental construct conceptually similar to BI, moderated the impact of parental separation on internalizing problems (Sentse, Ormel, Veenstra, Verhulst, & Oldehinkel, 2011). Individuals with high social BI may be less able to compensate for the consequences of separation events and the stress associated with it compared to individuals with low social BI. Social withdrawal, lack of a feeling of belonging, and lack of social reinforcement may contribute to the development of OCD among socially inhibited individuals, as social isolation was reported to increase the risk of OCD (Grisham et al., 2011). In the context of anxiety symptoms in general, negative life events did not interact with BI in the prediction of anxiety symptoms in a longitudinal study among children (Muris, van Brakel, Arntz, & Schouten, 2011). Further studies need to investigate whether interaction effects between BI and adverse life events are specific to social BI, are stronger for separation events than for other adverse life events, and apply to OCD specifically.

Consistent with a diathesis–stress model, nonsocial fear BI and paternal emotional warmth interacted in predicting the subsequent onset of first OCD in our analyses. Paternal emotional warmth seemed to be associated with a decreased risk of subsequent OCD but only in individuals with high and not low nonsocial fear BI. Likewise, paternal overprotection interacted with social BI in that it increased the risk of subsequent first onset of OCD in individuals with high social BI but not in individuals with low social BI. A father's role may be especially important in the development of a behaviorally inhibited child's OCD. It may be essential for fathers to push and challenge their socially inhibited child while putting limits on their avoidant behavior to allow the child to develop skills and confidence in managing potential social challenges. Nevertheless our results also suggest that it may be beneficial for children with high nonsocial fear BI for their fathers to show emotional warmth, characterized by behaviors such as acceptance, comforting, and support of children. Our findings are consistent with a study that demonstrated that BI and an overprotective parenting style interacted in predicting obsessive-compulsive symptoms (Coles et al., 2006). As this study did not investigate the specific role of the father and assessed only obsessive and compulsive symptoms, our findings can only be partially compared and need replication in further studies. A similar interaction effect has also been found for symptoms of social anxiety disorder: Maternal overcontrol was positively associated with subsequent social anxiety symptoms only among adolescents with a history of high childhood BI across childhood, and not among those with lower or less consistent childhood BI (Lewis-Morrarty et al., 2012). Whether the interactions between BI and parental rearing act similar in other mental disorders needs to be addressed in future research.

Otherwise our results concerning interactions are only partly consistent with theoretical models (Degnan, Almas, & Fox, 2010; Rapee, Schniering, & Hudson, 2009) but are in keeping with a small number of previous studies that suggested BI and some environmental factors might instead have an additive effect on anxiety disorders/symptoms of anxiety disorder (Hudson et al., 2011; Hudson, Dodd, Lyneham & Bovopoulos, 2011; Muris et al., 2011; Van Brakel, Muris, Bögels, & Thomassen, 2006).

The present study has several methodological strengths. We studied a representative sample of adolescents and young adults during the high-risk period of the first onset of OCD. Therefore we reduced selection and recall bias and gathered data close to the first onset of OCD. Furthermore, we performed prospective analyses that allow conclusions about the direction of the effect. Nonetheless, results of this study must be interpreted with several limitations in mind. Our sample was larger than most previous comparable studies, but our number of incident OCD cases was still not large in terms of longitudinal prediction. Effects of childhood risk factors and their interaction are likely to be modest, and our study may not have been sufficiently powered to detect small

effects in some analyses. BI, parental rearing, and adverse life events were retrospectively assessed and might therefore have been biased through symptomatic obsessions and compulsions that may have occurred before the onset of threshold OCD. Furthermore BI, parental rearing, and the experience of adverse life events were assessed through self-report only and may therefore be subject to evaluation and recall bias.

5. Conclusion

Our study provides evidence that BI and paternal rejection are related to an increased risk of OCD. The association between any adverse life event/paternal overprotection and the subsequent first onset of OCD varied by level of social BI, whereas the association between paternal emotional warmth and the subsequent first onset of OCD varied by level of nonsocial fear BI. However, future studies need to replicate our findings and explore the mechanisms behind the associations between BI, traumatic life events, and paternal rejection and OCD. Knowledge about the dynamic interplay between different risk factors may help identify those individuals most at risk of developing OCD. Preventive interventions for OCD may be particularly effective in individuals with a temperamental vulnerability who were exposed to paternal overprotection, a lack of emotional warmth, or adverse life events. For prevention interventions to be based on solid evidence, however, only causal risk factors should be targeted. If the manipulation of BI, parental rearing, or prevention of traumatic life events showed a reduced incidence of OCD, these factors could be conceptualized as causal risk factors (Kraemer et al., 1997). Considering the dearth of evidence regarding causal risk factors for OCD, the lack of prevention interventions for OCD is not surprising. Therefore, further studies are needed to investigate causal risk factors and develop and test preventive interventions for OCD in specified high-risk populations.

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Declarations of interest

None.

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Appendix C (Manuscript 3)

Maternal and paternal emotional warmth interact with traumatic life events in predicting the subsequent onset of obsessive-compulsive disorder in a community sample of adolescents and young adults

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submitted to *Journal of Anxiety Disorders*

Maternal and Paternal Emotional Warmth Interact with Traumatic Life Events in Predicting
the Subsequent Onset of Obsessive-Compulsive Disorder in a Community
Sample of Adolescents and Young Adults

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Abstract

Adverse life events increase the risk of obsessive-compulsive disorder (OCD). Parental rearing may serve as a protective factor in the face of adversity. We investigated whether parental rearing moderates the association between adverse life events and the subsequent first onset of OCD. A representative sample of individuals aged 14 to 24 years was followed for over 10 years ($N=2,210$). OCD and any adverse life event, that is, any separation event or any traumatic life event, were assessed using the DIA-X/M-CIDI. Parental rearing was assessed by self-report, using the Questionnaire of Recalled Parental Rearing Behavior. In adjusted logistic regressions both maternal (risk ratio, $RR=0.08$, 95%confidence interval, CI [0.02,0.31]) and paternal ($RR=0.16$, 95%CI [0.03,0.89]) warmth moderated the association between any adverse life event and OCD. Maternal ($RR=0.16$, 95%CI [0.03,0.77]) and paternal ($RR=0.17$, 95%CI [0.04,0.78]) emotional warmth interacted specifically with any traumatic life event but not with any separation event in predicting OCD. We did not find any interactions with parental overprotection or rejection in predicting OCD. Parental emotional warmth may be a protective factor for OCD among individuals who experience traumatic life events. Future studies should evaluate whether interventions enhancing parental emotional warmth among those who experience traumatic life events can prevent the development of OCD.

Keywords: epidemiology, moderator, adverse life event, risk factor, parental rearing

1. Introduction

Obsessive-compulsive disorder (OCD) ranks among the 10 most debilitating mental and physical disorders worldwide (Murray & Lopez, 1996) and there have been efforts to identify risk factors that predispose to this disorder. As such, adverse life events have been suggested to play a role in the origins of OCD (Brander, Perez-Vigil, Larsson, & Mataix-Cols, 2016; Fontenelle et al., 2012). In prospective analyses based on longitudinal data, traumatic life events (Asselmann, Wittchen, Lieb, Perkonigg, & Beesdo-Baum, 2017), undesirable life events (Valleni-Basile et al., 1996), and childhood stressors including sexual and physical abuse and number of residence changes (Grisham et al., 2011) were associated with an increased risk of the subsequent onset of OCD. It is, however, not clear how adverse or traumatic life events would be etiologically related to OCD. Rachman (1997, 1998) developed a cognitive theory that suggests obsessions are more likely to be experienced when an individual is exposed to stressful situations and that external stimuli might provoke obsessional thoughts. He proposed that the level of stressfulness of the external stimuli is linked to the frequency of the obsessional thoughts and the distress associated with them. Furthermore, he suggested that compulsions are related to an individual's assumption that she or he holds a special responsibility to prevent an unwanted event, such as an adverse life event, from reoccurring (Rachman, 2002). As a consequence, an individual may respond with compulsions in an attempt to prevent the dreaded situation from happening.

Although the risk of OCD following an adverse life event is increased, in general, most people do not develop OCD. Additional variables may “modify, ameliorate, or alter a person's response to some environmental hazard that predisposes to a maladaptive outcome” (Rutter, 1995, p. 600). Thus, both maladaptive and protective factors may manifest their effects not directly, but in combination with a risk variable, such as the exposure to an adverse life event. One potentially important factor in the development of OCD is parental rearing (Brander et al., 2016). The association between parental rearing and OCD has been widely

examined in cross-sectional studies. Most found associations between perceived parental overprotection and paternal rejection and OCD (for a recent systematic review see Brander et al. (2016). Extending these cross-sectional studies, we showed in our own prospective analyses based on the longitudinal Early Developmental Stages of Psychopathology (EDSP) study (Hofer et al., 2018) that paternal rejection was associated with an increased risk of subsequent onset of OCD. Furthermore, we demonstrated that paternal emotional warmth and paternal overprotection interacted with components of behavioral inhibition in predicting the subsequent onset of OCD. Favorable parental rearing may be beneficial for a child's sense of self-efficacy, mastery, and autonomy and control (Rapee, 1997; Wood, McLeod, Sigman, Hwang, & Chu, 2003). Thus, it seems possible that these qualities could help a child adequately react to and successfully cope with stressful situations such as adverse life events. Based on data from the 10-year population-based EDSP study, this prospective-longitudinal study examined if parental rearing moderates the association between any adverse life event and OCD.

2. Material and Methods

2.1 Sample

Data came from the prospective EDSP study, which followed a representative community sample of adolescents and young adults for up to 10 years. The study included a baseline (T0, 1995, $N = 3,021$, response rate 70.8%) and three follow-up (T1, 1996/97, only T0 14- to 17-year-olds were reinterviewed, $N = 1,228$, response rate 88.0% of the T0 sample; T2, 1998/99, $N = 2,548$, response rate 84.3% of the T0 sample; T3, 2003, $N = 2,210$, response rate 73.2% of the T0 sample) investigations. Individuals were aged 14 to 24 years at baseline and 21 to 34 years at last follow-up and were randomly drawn from government registries of the Munich area in Germany. The early developmental stages of psychopathology were emphasized in the study by sampling 14- to 15-year-olds at twice the probability of 16- to 21-year-olds and 22- to 24-year-olds at half the probability of 16- to 21-year-olds. This scheme

was taken into account by using sample weights in the analyses. Detailed descriptions of the EDSP study methods, design, and sample characteristics have been published elsewhere (Beesdo-Baum et al., 2015; Lieb, Isensee, von Sydow, & Wittchen, 2000; Wittchen, Perkonig, Lachner, & Nelson, 1998). The study was approved by the Ethics Committee of the Medical Faculty of the Technische Universität Dresden (No. EK-13811). All individuals provided informed consent.

2.2 Assessment of OCD

Diagnostic information about OCD according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994) was assessed at all waves, using the computer-assisted lifetime (baseline) and interval (follow-up) version of the Munich-Composite International-Diagnostic-Interview (DIA-X/M-CIDI Wittchen & Pfister, 1997). Test–retest reliability and validity for the full DIA-X/M-CIDI have been reported elsewhere (Reed et al., 1998; Wittchen, 1994; Wittchen, Lachner, Wunderlich, & Pfister, 1998).

Within the DIA-X/M-CIDI OCD module, first obsessions and then compulsions were assessed. Potential obsessive cognitions or repetitive behaviors including mental acts were identified by asking one or three stem questions. Individuals who confirmed any of the stem questions were assessed for the remaining mandatory *DSM-IV* OCD criteria before first onset and last occurrence were assessed. To improve recall at follow-up assessments, two symptom lists containing 14 items on potential obsessions and 10 items on compulsions were presented in addition to the stem questions.

2.3 Assessment of any adverse any life event, separation event, and traumatic life event

Exposure to any adverse life event over the lifetime included both separation and traumatic life events and was assessed at baseline with the DIA-X/M-CIDI. Separation events included the death of a parent and parental separation or divorce. Traumatic life events covered eight specific life events (war experience, being physically attacked, rape, sexual

abuse as a child, natural disasters, serious accidents, imprisonment, and witnessing others' traumatic life events) and one open category (other traumatic life events) according to the *DSM-IV* posttraumatic stress disorder criterion A1.

2.4 Assessment of perceived parental rearing

Perceived parental rearing was measured with the German version of the Questionnaire of Recalled Parental Rearing Behavior (QRPRB; Schumacher, Eisenmann, & Brahler, 1999). Three subscales (emotional warmth, overprotection, and rejection) were separately assessed for mothers and fathers on 24 four-point items scaled from 0 to 3 (from “no, never” to “yes, always”) at T1 for the younger cohort and at T2 for all participants. The German version of the QRPRB yielded a Cronbach's α of .85, .69, and .75 for emotional warmth, parental overprotection, and rejection, respectively, at T1 (Knappe et al., 2009) and an at least moderate temporal stability in community adolescents (Asselmann, Knappe, Wittchen, Lieb, & Beesdo, 2015). Analyses in this study refer to recalled parental rearing for the entire sample assessed at T2.

2.5 Statistical analyses

Analyses were performed with Stata 13.1 (StataCorp, 2013). We included only individuals who completed the T3 assessment and who provided data on traumatic life events at T0, parental rearing at T2, and OCD at T3. Because not all individuals provided data on each parenting dimension, numbers differed for the analyses ($N = 1,822-1,954$). Data were weighted by age, sex, and geographic location at baseline to ensure community representativeness.

Statistical significance was set at $p < .05$. We used separate logistic regression models with an interaction term to test whether any adverse life event interacted with parental rearing in predicting incident OCD between T2 and T3. Individuals who reported OCD for the first time at T0 ($n = 13$), T1 ($n = 2$), or T2 ($n = 10$) were excluded from the incidence rate of OCD between T2 and T3. The timeframe of T2 to T3 for incident OCD was used as an outcome to

ensure the temporal priority of adverse life events and parental rearing. In the case of a significant interaction, margins of the incidence of OCD for those with and without any adverse life event were estimated from predictions of the respective model and plotted for low levels ($M - SD$), the mean, and high levels ($M + SD$) of the respective parental rearing style. As a measure of strength we used risk ratios (RRs) and adjusted all analyses for sex and age at last assessment.

3. Results

3.1 Cumulative lifetime incidence and incidence between T2 and T3

Over the entire study period, 45 individuals met criteria for *DSM-IV* OCD, resulting in a cumulative lifetime incidence of OCD at T3 of 2.1%. Between T2 and T3, 20 individuals (0.84%) met criteria for *DSM-IV* OCD for the first time.

3.2 Association of any adverse life event with the subsequent first onset of OCD

As already reported in a previous EDSP paper (Asselmann et al., 2017), any traumatic life event (RR = 2.99, 95% confidence interval, CI, [1.28, 7.01]) was associated with an increased risk of the subsequent first onset of OCD between baseline and T3. In contrast, any separation event (RR = 1.28, 95% CI [0.56, 2.94]) and the overall group any adverse life event (RR = 2.34, 95% CI [0.97, 5.63]) did not predict the subsequent first onset of OCD.

3.3 Interaction between parental rearing and any adverse life event

Both maternal (RR = 0.08, 95% CI [0.02, 0.31]) and paternal (RR = 0.16, 95% CI [0.03, 0.89]) emotional warmth moderated the association between any adverse life event and the subsequent first onset of OCD between T2 and T3, as shown in Figure 1. The association between any adverse life event and the subsequent first onset of OCD increased with decreasing parental emotional warmth. An increase of maternal or paternal emotional warmth by 1 *SD* (0.53, 0.63, respectively) decreased the RR of the positive association between any

adverse life event and the subsequent first onset of OCD by a factor of 3.7 and 3.1, respectively ($1/(RR^{SD})$). When examining the interaction for any separation and traumatic life event separately, only the interaction between emotional warmth and any traumatic life event and not any separation event reached significance (see Table 1 and Figure 2). We could not demonstrate any moderator effects for maternal or paternal rejection or overprotection.

4. Discussion

The aim of this prospective-longitudinal community study among adolescents and young adults was to examine whether parental rearing moderated the impact of any adverse life event on the subsequent first onset of OCD. Results suggest that parental emotional warmth interacts with any adverse life event and specifically traumatic life events in predicting the subsequent onset of OCD. Both maternal and paternal emotional warmth buffered the association between any adverse life event and the subsequent first onset of OCD. Therefore, in the face of adverse life events, emotional warmth may be an important protective factor. Any adverse life event consisted of the two categories any separation event and any traumatic life event. When investigating these categories separately, we could demonstrate an interaction only between maternal and paternal emotional warmth and any traumatic life event and not any separation event. We did not find that overprotection or rejection moderated the effect of any adverse life event on OCD. Our findings are in line with a study among adolescents in foster care in which a perceived warm relationship with a caregiver moderated the association between trauma and self-reported internalizing behavior (Wojciak, Thompson, & Cooley, 2017). Furthermore, findings from rat studies suggested a direct effect of maternal care on neural structures that are associated with stress responsiveness on a cognitive, emotional, and neuroendocrine level (Meaney, 2001), which may play a role in the vulnerability to OCD.

Contra-intuitively, in individuals without any adverse life events, maternal emotional warmth seemed to be associated with a higher risk of OCD. We have no clear explanation for

this unexpected result. There are, however, two possibilities: First, it might be a methodological issue as all individuals with new onsets of OCD and without adverse life events reported rather high perceived emotional warmth (range 2.13–2.88). Thus, this effect in the group without adverse life events might not be a real finding but rather a methodological artifact. Second, this result is comparable to the finding in a study based on community twins that maternal care may not always be helpful (Ibarra et al., 2014). This study showed that high levels of maternal care were positively associated with different psychiatric symptoms. Similarly, Oldehinkel, Hartman, Van Oort, and Nederhof (2015) suggested that those adolescents with a negative emotion recognition specialization may, in fact, be more likely to develop an anxiety or depressive disorder at high compared to low levels of emotional warmth. Using an animal model, Koehl, van der Veen, Gonzales, Piazza, and Abrous (2012) examined neurogenesis in the hippocampus, which is involved in cognitive and emotional processing. They found that high rates of maternal care were associated with low levels of neurogenesis and concluded that high maternal care might only be beneficial when necessary. This possible risk linked to maternal emotional warmth is counterintuitive and contradicts previous studies that have shown beneficial consequences for child mental health when the mother is affectionate and supportive (Lima, Mello, & Mari Jde, 2010; Overbeek, ten Have, Vollebergh, & de Graaf, 2007). Therefore, our findings need further research and replication.

It is interesting to note that the point estimation for the interaction between paternal rejection and any adverse life event was remarkably high but did not reach statistical significance, which might be due to the low incidence rate of OCD. Paternal rejection seemed to increase the risk of subsequent onset of OCD only for those with any adverse life event and not for those without any adverse life event. Given the low number of cases in our analyses, this interaction needs to be further studied before firm conclusions can be drawn.

There is emerging evidence that parental emotional warmth can be successfully promoted (Breitenstein, Fogg, Ocampo, Acosta, & Gross, 2016; Landry, Smith, Swank, & Guttentag, 2008; Puffer, Annan, Sim, Salhi, & Betancourt, 2017). Future studies should investigate whether fostering parental emotional warmth can be an effective intervention to prevent OCD among those who experience any traumatic life event. Further, it is unknown whether the interaction is specific to OCD or also applies to other mental disorders. The role of age of exposure to an adverse life event and also the number of adverse life events experienced may be important variables to consider in future studies.

Strengths of the current study include a representative sample of adolescents and young adults who were assessed several times during the high-risk period for first onset of OCD. Furthermore, we used prospective analyses that considered the temporal sequence of predictor and outcome variable. Importantly, the interaction effect between any adverse life event and parental rearing has not yet been examined for OCD. Finally, OCD was assessed with a valid and reliable standardized interview (DIA-X/M-CIDI).

Nonetheless, this study is limited in several ways: First, on the one hand the number of individuals with a subsequent first onset of OCD may not have been large enough to detect small effects in the interaction analyses. On the other hand there is a chance of overfitting. The small numbers in some cells of our analyses may therefore limit the conclusions that can be drawn. To test the robustness of our results, we replicated our analyses for analog outcomes such as OCD without the impairment criteria being met or including less severe forms such as the experience of obsessions and compulsions and obtained comparable results based on bigger cell numbers. Second, parental rearing and adverse life events were assessed retrospectively through self-report and may have been biased through subclinical obsessions and compulsions and recall bias. Third, we have included only new onsets of OCD between T2 and T3, during which individuals were 17 to 34 years old, to ensure the temporal precedence of risk factors. Therefore, our results may not be generalizable to OCD with an

earlier onset. Fourth, we did not take into account the information about the number of exposures or age of exposure to any adverse life events due to the small number of cases. These variables may further specify under what conditions any traumatic life events may increase the risk of OCD. Fifth, our results should be interpreted only within the context of *DSM-IV* OCD diagnoses. Probably the most significant change in the diagnostic criteria of OCD in the *DSM-5* (American Psychiatric Association, 2013) is that individuals are no longer required to recognize their obsessions or compulsions as excessive or unreasonable. As this criterion did not affect the diagnostic status of the OCD cases in our study, our results remain unchanged when taking into account this modification. Sixth, we cannot exclude that observed associations may have been biased by hidden third variables or may be explained by unmeasured shared overlapping causal factors. Finally, interaction effects between any adverse life event and parental rearing have not yet been examined for OCD and therefore our results need replication.

In conclusion, the present study adds to the literature by demonstrating that parental emotional warmth may mitigate the effect of any adverse life event, specifically of any traumatic life event, on the subsequent onset of OCD. Whether interventions that target low parental emotional warmth in high-risk groups for traumatic life events can prevent the development of OCD needs to be investigated in further studies.

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INTERACTION OF PARENTAL REARING AND ADVERSE LIFE EVENTS ON OCD

Table 1

Interaction Effects Between Adverse Life Events and Parental Rearing at T2 in Predicting Incident OCD Between T2 and T3

Interaction	Any adverse life event			Any separation event			Any traumatic life event		
	RR	95% CI		RR	95% CI		RR	95% CI	
		LL	UL		LL	UL		LL	UL
Maternal									
Emotional warmth	0.08	0.02	0.31	0.26	0.05	1.37	0.16	0.03	0.77
Overprotection	0.94	0.11	8.42	0.75	0.07	7.65	0.36	0.03	4.59
Rejection	0.99	0.11	8.84	0.54	0.06	5.02	0.81	0.11	6.17
Paternal									
Emotional warmth	0.16	0.03	0.89	0.37	0.07	2.02	0.16	0.04	0.70
Overprotection	0.86	0.07	11.13	0.40	0.02	7.59	0.87	0.04	17.33
Rejection	13.89	0.68	282.93	0.51	0.05	4.95	1.83	0.15	22.76

Note. OCD = obsessive-compulsive disorder; CI = confidence interval; LL = lower limit; UL

= upper limit; RR = risk ratio. Models were adjusted for sex and age at last assessment.

Results in bold indicate significant interactions.

INTERACTION OF PARENTAL REARING AND ADVERSE LIFE EVENTS ON OCD

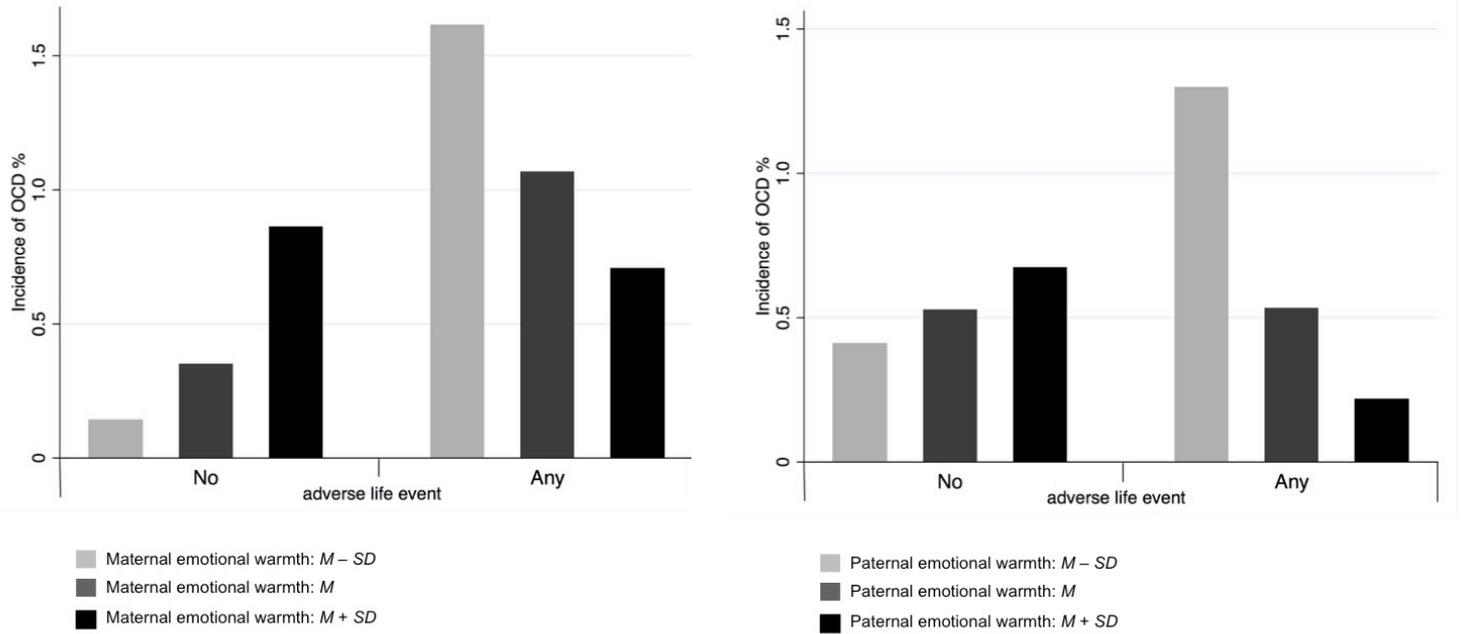


Figure 1. Parental emotional warmth moderates the association between any adverse life event and first onset of obsessive-compulsive disorder (OCD) from T2 to T3.

INTERACTION OF PARENTAL REARING AND ADVERSE LIFE EVENTS ON OCD

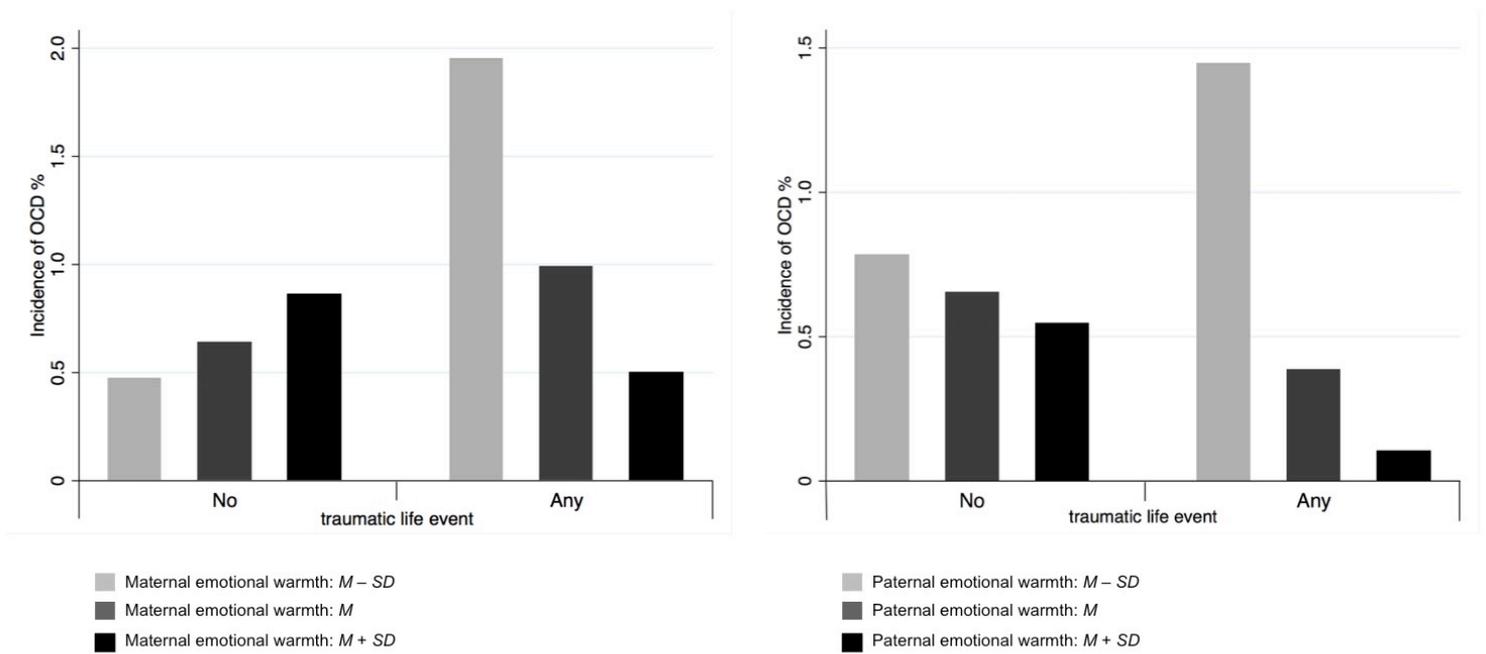


Figure 2. Parental emotional warmth moderates the association between any traumatic life event and first onset of obsessive-compulsive disorder (OCD) from T2 to T3.