The Comorbidity of Anxiety Disorders and Physical Diseases:

An Epidemiological Approach

Inaugural Dissertation

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by

Cornelia Witthauer

from Basel (BS), Switzerland

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Approved by the Department of Psychology

At the request of

Prof. Dr. Roselind Lieb (Referee)

and

Prof. Dr. Gunther Meinlschmidt (Co-Referee)

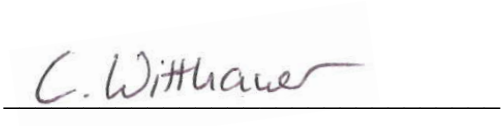
Basel, 01.06.15

Prof. Dr. Roselind Lieb (Dean)

Declaration of Authorship

I, Cornelia Witthauer (born January 7, 1988), hereby declare that I have written this dissertation titled "The Comorbidity of Anxiety Disorders and Physical Diseases: An Epidemiological Approach" without any assistance from third parties who are not indicated. I have not used any other sources in the preparation and writing of this dissertation other than those indicated and I marked all citations.

Basel, April 7, 2015



Cornelia Witthauer

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Abbreviations

APA	American Psychiatric Association
CRH	Corticotropin-Releasing Hormone
DIA-X/M-CIDI	Munich-Composite International Diagnostic Interview
DSM-III	*Diagnostic and Statistical Manual of Mental Disorders*, Third Edition
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition
GHS	German Health Interview and Examination Survey
GHS-MHS	German Health Interview and Examination Survey - Mental Health Supplement
HPA	Hypothalamic-Pituitary-Adrenal
ICD-10	*International Classification of Diseases*, Tenth Revision
OCD	Obsessive-Compulsive Disorder
OCS	Obsessive-Compulsive Symptoms
OR	Odds Ratio
SF-36	36-Item Short Form Health Survey
WHO	World Health Organization

Abstract in English

Background: Anxiety disorders are highly comorbid with other mental disorders. This has important implications for individuals' burden, etiology of the comorbid diseases and treatment. Knowledge about the comorbidity with physical diseases in the community, however, is limited, especially for specific anxiety disorders. This dissertation evaluates the comorbidity of specific anxiety disorders and noncommunicable and communicable physical diseases in the general population. Further, it investigates the association of comorbidity with measures of burden, namely, quality of life and disability.

Method: Data of the German Health Interview and Examination Survey (GHS), a representative general population survey from Germany with 4,181 subjects aged 18-65 years, were used. Anxiety disorders were diagnosed using the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI), noncommunicable physical diseases were assessed through a self-report questionnaire and a standardized medical interview, and communicable physical diseases through a self-report questionnaire.

Results: Both obsessive-compulsive disorder (OCD) and specific phobia were associated with migraine and respiratory diseases. Additionally, subthreshold forms of OCD were associated with specific noncommunicable physical diseases. Agoraphobia, specific phobia, and generalized anxiety disorder were all associated with whooping cough. The documented comorbidity was associated with increased disability and decreased quality of life.

Discussion: The detected comorbidity patterns may contribute to a better understanding of the psychobiological pathways of comorbidity. Further, increased burden of individuals affected underlines the need for studies evaluating the effect of treatment in comorbid cases.

Abstract in German

Hintergrund: Angststörungen weisen eine hohe Komorbidität mit anderen psychischen Störungen auf. Dies hat wichtige Implikationen für die Belastung der Betroffenen, sowie für die Ätiologie und Therapie der komorbiden Störungen. Die Datenlage zur Komorbidität mit körperlichen Erkrankungen in der Bevölkerung ist jedoch für spezifische Angststörungen eingeschränkt. Die vorliegende Dissertation untersucht den Zusammenhang zwischen spezifischen Angststörungen und nichtübertragbaren und übertragbaren körperlichen Erkrankungen in der Bevölkerung. Weiter wird die Assoziation der Komorbidität mit Lebensqualität und Beeinträchtigung untersucht.

Methode: Analysiert wurden die Daten des Bundesgesundheitssurvey, einer repräsentativen Bevölkerungsstichprobe Deutschlands mit 4'181 Probanden im Alter von 18-65 Jahren. Angststörungen wurden mit dem DIA-X/M-CIDI Interview erhoben, nichtübertragbare körperliche Erkrankungen mit einem ärztlichen Interview, sowie mit einem Fragebogen und übertragbare körperliche Erkrankungen mit einem Fragebogen.

Resultate: Sowohl die Zwangsstörung als auch die Spezifische Phobie traten gehäuft mit Migräne und Atemwegserkrankungen auf. Auch subklinische Formen der Zwangsstörung waren mit spezifischen, nichtübertragbaren körperlichen Erkrankungen assoziiert. Agoraphobie, Spezifische Phobie und Generalisierte Angststörung gingen mit erhöhten Prävalenzraten von Keuchhusten einher. Komorbidität war mit erhöhter Beeinträchtigung und niedrigerer Lebensqualität assoziiert.

Diskussion: Die Komorbidiätsmuster können zu einem besseren Verständnis der zugrundeliegenden Mechanismen beitragen. Die assoziierte Belastung unterstreicht die Bedeutung weiterer Forschung zur Wirksamkeit der Therapie bei komorbiden Erkrankungen.

> We must . . . make efforts to convince decision makers, educators, clinicians, and community members that comorbidity is one of the most urgent challenges to the quality of health care in the early decades of the twenty first century that must be recognized and dealt with without delay.
>
> —Norman Sartorius, 2013
>
> Former director of the World Health Organization's Division of Mental Health

Introduction

Mental disorders are associated with high social and financial burden worldwide (Kessler et al., 2009; Wittchen et al., 2011). Among the most prevalent mental disorders are anxiety disorders (Jacobi et al., 2014) with a 12-month prevalence rate about 14% and 61.5 million individuals affected in Europe (Wittchen et al., 2011).

The majority of individuals with anxiety disorders have at least one additional mental disorder at the same time (Jacobi et al., 2004; Kessler, Chiu, Demler, & Walters, 2005). This so-called comorbidity (Jacobi, Vossen, & Wittchen, 2009; Wittchen, 1996b) has been impressively documented in clinical (Sartorius, Uestuen, Lecrubier, & Wittchen, 1996) and community studies (Kessler et al., 2005) and has several important implications.

In terms of implications for health care costs, studies have shown that comorbidity is associated with an increased use of the health system (Souetre et al., 1994). Further, it may have implications for the burden of individuals affected as studies have shown that having two conditions at the same time is associated with increased impairment in comparison to having one condition (Kessler, DuPont, Berglund, & Wittchen, 1999). It may additionally have clinical implications as treatment strategies for individuals with several disorders may differ from treatment strategies for individuals affected by a single diagnosis (Lieb, Meinlschmidt, & Araya, 2007). In addition, the investigation of patterns of comorbidity can have etiological implications as it may contribute to a better understanding of the etiological pathways of the comorbid diseases (Lieb, 2006; Merikangas & Swanson, 2010).

A recent line of evidence suggests that in addition to being comorbid with other mental disorders, anxiety disorders are also associated with physical diseases. Clinical and community studies have revealed that the group of anxiety disorders is associated with a wide range of noncommunicable physical diseases, also known as chronic diseases (Haerter, Conway, & Merikangas, 2003; Roy-Byrne et al., 2008). Further, the comorbidity of anxiety disorders and noncommunicable physical diseases seems

to affect individuals' burden, too: Researchers have found that having a noncommunicable physical disease in addition to any anxiety disorder is associated with increased disability and poor quality of life in comparison to having one condition (Sareen, Cox, Clara, & Asmundson, 2005; Sareen et al., 2006). Some studies have additionally suggested that anxiety can complicate the treatment of physical diseases and may be associated with worse treatment outcome (Dahlen & Janson, 2002; DiMatteo, Lepper, & Croghan, 2000). Therefore, knowledge of the pathways of comorbidity is important as this may inform treatment and prevention and hence contribute to the reduction of burden.

Yet before the pathways behind comorbidity can be unraveled, a careful evaluation of the nature of comorbidity is important (Degenhardt, Hall, & Lynskey, 2003). More community studies investigating especially the association of specific anxiety disorders and a wide range of physical diseases are necessary to gain more consolidated knowledge and to enable the derivation of hypotheses concerning etiology of comorbidity. Many studies have employed study designs that limit the validity of the findings: On the one hand, studies involving clinical samples may not reflect the natural patterns of comorbidity, as comorbidity is associated with treatment seeking behavior (selection bias) (Lieb et al., 2007). On the other, community studies so far have concentrated mainly on the comorbidity of the whole group of anxiety disorders (Sareen et al., 2006). Further, those studies that addressed the comorbidity of specific anxiety disorders and noncommunicable physical diseases, focused more on some anxiety disorders (e.g., panic disorder; Zaubler & Katon, 1995) than others (e.g., OCD or specific phobia). Also, the data of some studies were limited due to methodological issues, such as a lack of standardized diagnostic interviews for the assessment of mental disorders (Weisskopf, Chen, Schwarzschild, Kawachi, & Ascherio, 2003).

In addition, the comorbidity of symptoms of anxiety disorders below the diagnostic threshold – so called subthreshold forms – and physical diseases should be investigated as research has suggested that comorbidity of these subthreshold forms and other mental disorders may be substantial (Adam,

Meinlschmidt, Gloster, & Lieb, 2012). Further, comorbidity analyses should also address subtypes of specific anxiety disorders, such as those of specific phobia (Sareen, Cox, Clara, & Asmundson, 2005), because research has shown that these subtypes may differ in their comorbidity patterns (Becker et al., 2007). This may have etiological implications for the subtypes. Finally, to further supplement the existing knowledge, it is necessary to include communicable physical diseases in the comorbidity analyses, as a few recent studies have suggested an association of anxiety disorders and communicable diseases (Goodwin, 2011; Leonard & Swedo, 2001; Vogelzangs, Beekman, de Jonge, & Penninx, 2013) such as the common cold (Adam, Meinlschmidt, & Lieb, 2012).

To summarize, it is important to gather more differentiated knowledge on the comorbidity of specific anxiety disorders and noncommunicable and communicable physical diseases in the general population. This may provide a basis for the better understanding of their etiological pathways and therefore may influence prevention and treatment of the comorbid conditions.

The objective of this dissertation is therefore to examine the comorbidity between specific anxiety disorders and noncommunicable and communicable physical diseases in the general population and the association of comorbidity with measures of burden, namely, quality of life and disability. This dissertation comprises three manuscripts (see Appendices A–C). Two manuscripts analyzed the association of two specific anxiety disorders and noncommunicable physical diseases: the first manuscript addressed the comorbidity of OCD and subthreshold forms with noncommunicable physical diseases, the second focused on the association of specific phobia and its subtypes with noncommunicable physical diseases. The third manuscript examined the association of different specific anxiety disorders and communicable physical diseases in the community.

The rest of this dissertation is structured as follows: In the Theoretical Background section I describe the major theoretical concepts and the research background on which the three manuscripts are based. I present the derived specific research questions of the three manuscripts and the overall research

questions in the section Research Questions. The Methods section describes the methodology and the Results section the major results of the three manuscripts. Finally, in the Discussion I discuss the implications, strengths, and limitations.

Theoretical Background

Anxiety Disorders

Anxiety is a fundamental human feeling that is adaptive in threatening situations. However, if the extent and/or the duration of the response of fear are experienced as disproportionately strong, or subjectively unfounded, or if the anxiety-producing situation is being consistently avoided, anxiety is pathological (Lieb & Wittchen, 2011). Pathological anxiety is the core symptom of anxiety disorders, a group of mental disorders that are associated with psychological strain and impairment (Lieb & Wittchen, 2011). Anxiety disorders are highly prevalent mental disorders in Europe: Studies have shown a 12-month prevalence of about 14% in the community (Jacobi et al., 2014; Wittchen et al., 2011).

Anxiety disorders are currently classified in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5;* American Psychiatric Association [APA], 2013) and the *International Classification of Diseases* (10th rev.; *ICD-10;* World Health Organization [WHO], 1993). However, the DIA-X/M-CIDI that was used in the present studies covers *DSM-IV* (4th ed., *DSM-IV*; APA, 1994) and *ICD-10* criteria. The following short description of the anxiety disorders is therefore based on the classification of the *DSM-IV*. Because of limited space, only the main characteristics of specific anxiety disorders are presented here. Further, posttraumatic stress disorder is not described, as it was not assessed in the study sample used for the analyses.

Agoraphobia. Agoraphobia is characterized by anxiety about or avoidance of places or situations from which escape might be difficult in situations where panic-like symptoms might occur. Such situations include public transport, crowds, or stores (APA, 1994).

Specific phobia. Individuals with specific phobia experience significant anxiety when they are exposed to a specific feared object or situation usually leading to avoiding behavior. Different subtypes can be specified: The animal subtype refers to fear related to a specific animal such as a spider or a dog, the natural subtype refers to fear related to height, storm, water, the blood-injection subtype refers to fear

related to seeing blood, injection, or going to the dentist or hospital, the situational subtype refers to fear of flying in a plane or of being in a small closed room, in a cellar, tunnel, or elevator and the other subtype refers to any other specific fear not matching any other subtype (APA, 1994).

Social phobia. Social phobia is characterized by significant anxiety that is experienced in social and performance situations such as public eating or speaking. Individuals fear that they will act in an embarrassing way or show symptoms that may be humiliating. Individuals with specific phobia either avoid the situations or experience distress in the situations (APA, 1994).

Panic disorder. Panic disorder is characterized by recurrent unexpected panic attacks, which are episodes of intensive fear with a sudden onset. During a panic attack, individuals experience symptoms such as shortness of breath, palpitations, discomfort, or fear of losing control. Individuals with panic disorder avoid situations in which panic attacks may occur. The *DSM-IV* differentiates between panic disorder with and without agoraphobia (APA, 1994).

Generalized anxiety disorder. Individuals with generalized anxiety disorder have worried for at least 6 months about a number of events or activities such as work or school performance. Anticipation of diseases, accidents, or blows of fate that is associated with several physiological and cognitive symptoms such as palpitations or rumination is also characteristic (APA, 1994).

Obsessive-Compulsive Disorder. Note: In the new *DSM-5* classification (APA, 2013), OCD is classified in the new chapter on obsessive-compulsive and related disorders. As the study reported here was based on *DSM-IV* criteria, I focus on *DSM-IV* criteria in the following.

OCD is characterized by obsessions and/or compulsions. Obsessions are recurrent and persistent thoughts, impulses, or images that cause significant anxiety. Compulsions are repetitive behavior that individuals feel driven to perform in response to the obsessions. The aim of the compulsions is to prevent or reduce distress or some dreaded situation or event (APA, 1994).

Noncommunicable and Communicable Physical Diseases

The WHO distinguishes between noncommunicable and communicable physical diseases. Noncommunicable physical diseases, also known as chronic diseases, are not passed from one person to another. Generally, they progress slow and have a long duration (WHO, 2015b). Communicable physical diseases, also known as infectious diseases, are caused by a pathogenic microorganism such as a virus, bacterium, or a parasite. They can be passed from one person to another (WHO, 2015a).

Comorbidity

The term comorbidity was coined by Feinstein (1970), who introduced the term in the literature of physical diseases. From the late 1980s on (Brieger & Marneros, 2000; Krueger & Markon, 2006), the term has been used in the psychological literature. This may be attributable to the introduction of the *DSM-III* (3rd ed; APA, 1980) and therefore to the introduction of explicit operational criteria for mental disorders. The comorbidity related to epidemiological and clinical research I discuss in this dissertation was defined as "the presence of more than one disorder in a person in a defined period of time" (Wittchen, 1996b, p.7). Various time intervals such as 6 months, a year, or even lifetime can be used[1]. Mental disorders can occur at the same time as well as at different times during this time interval (Lieb, Schreier, & Mueller, 2003). Besides the time interval, the design of the study (cross-section vs. longitudinal), the characteristics of the sample (clinical sample vs. general population sample) and methods of the assessment (case definition and case identification) are also important to consider for the interpretation of comorbidity (Jacobi et al., 2009). Comorbidity can be observed among mental disorders, but also among mental disorders and physical diseases. In the following section, I explore the association of anxiety disorders and physical diseases.

Comorbidity of anxiety disorders and noncommunicable physical diseases. Clinical and community studies have established associations between the group of anxiety disorders and

[1] In our data, we used 12 months and lifetime as time intervals, for details see the Methods section.

noncommunicable physical diseases. Clinical studies with patients have revealed associations between anxiety disorders and thyroid diseases (Lindemann, Zitrin, & Klein, 1984), heart diseases (Haerter et al., 2003; Kawachi et al., 1994), cardiovascular diseases (Batelaan, ten Have, van Balkom, Tuithof, & de Graaf, 2014; Roy-Byrne et al., 2008), hypertension (Haerter et al., 2003), gastrointestinal diseases (Haerter et al., 2003), migraine (Haerter et al., 2003; Smitherman, Penzien, & Maizels, 2008), arthritis (El-Miedany & Rasheed, 2002; Isik, Koca, Ozturk, & Mermi, 2007), and respiratory diseases (Goodwin et al., 2003; Katon, Richardson, Lozano, & McCauley, 2004; Nascimento et al., 2002; Roy-Byrne et al., 2008; Willgoss & Yohannes, 2013). Community studies have established associations between anxiety disorders and thyroid diseases (Patten, Williams, Esposito, & Beck, 2006), respiratory diseases (Scott et al., 2007), gastrointestinal diseases (Goodwin, Cowles, Galea, & Jacobi, 2013), arthritis, allergies (Sareen et al., 2006), migraine (Merikangas, Angst, & Isler, 1990; Sareen et al., 2006), heart diseases (Ormel et al., 2007), and vascular diseases (Goodwin, Davidson, & Keyes, 2009).

In sum, studies have reported comorbidity of anxiety disorders and noncommunicable physical diseases, but the data are limited: The patterns found in clinical samples may not reflect the natural patterns of comorbidity because they may be associated with a selection bias (Lieb et al., 2007). Additionally, the studies focused mainly on one specific physical disease, whereas for the detection of patterns a wide range of physical diseases should be analyzed. Further, much less is known about the comorbidity of specific anxiety disorders – as opposed to the whole group – and physical diseases. For some specific anxiety disorders, especially OCD and specific phobia, there is a need for further community-based studies, as shown in the following.

Comorbidity of obsessive-compulsive disorder, subthreshold forms, and noncommunicable physical diseases. Especially for OCD, the data concerning comorbidity with physical diseases are limited. In one study, subjects with OCD reported a decreased physical wellbeing (Stengler-Wenzke, Kroll, Riedel-Heller, Matschinger, & Angermeyer, 2007). Another study showed that the presence of

any chronic physical condition is associated with an increased prevalence of obsessive-compulsive symptoms (OCS; Fullana et al., 2010). It has been established that OCS below the diagnostic threshold for full-blown OCD seems to be more prevalent in the general population than the full diagnosis (Angst et al., 2004; de Bruijn, Beun, de Graaf, ten Have, & Denys, 2010; Grabe et al., 2001). Subjects with such subthreshold forms of OCD showed higher disability and increased health care utilization in comparison to subjects without these symptoms (Adam et al., 2012). However, no community study has analyzed the association of OCD and its subthreshold forms with physical diseases yet, even though this information may be highly relevant for the health care system or may have etiological implications.

Comorbidity of specific phobia, its subtypes, and noncommunicable physical diseases. Community studies have established associations between specific phobia and different noncommunicable physical diseases, namely, migraine (Merikangas et al., 1990), respiratory diseases (Sareen et al., 2006), ulcer, arthritis (Kessler, Ormel, Demler, & Stang, 2003), vascular diseases (Goodwin et al., 2009), and heart diseases (Scott et al., 2013). However, the data are limited as they mainly focused on one specific physical disease or they were mainly based on self-report of noncommunicable physical diseases (e.g., Kessler et al., 2003). In addition, the comorbidity among subtypes of specific phobia and physical diseases has not been evaluated so far, even though the subtypes differ in their comorbidity patterns with other mental disorders (Becker et al., 2007; LeBeau et al., 2010; Park et al., 2011). It has also been observed that subjects with different subtypes of specific phobia differ in their physiological fear response: Blood-injection phobia is associated with vasovagal fainting, whereas other phobias are not (LeBeau et al., 2010). The natural subtype of specific phobia was further associated with more somatic symptoms than the animal subtype (Ollendick, Raishevich, Davis, Sirbu, & Oest, 2010), suggesting that comorbidity among the subtypes and physical diseases might also differ and should be analyzed. The gained knowledge might influence research on etiology.

Comorbidity of anxiety disorders and communicable physical diseases. The association of childhood streptococcal infections and OCD has been widely discussed and may be the most prominent example of an association of an anxiety disorder and a communicable physical disease (Leonard & Swedo, 2001). Further, community studies have established associations of anxiety disorders and communicable physical diseases: Two cross-sectional community studies have revealed that an infection in the first year of life (Goodwin, 2011) and having experienced a common cold in the last 12 months is associated with anxiety disorders (Adam et al., 2012). Studies targeting biomarkers have shown that anxiety disorders are associated with inflammatory markers such as C-reactive protein (Vogelzangs et al., 2013) and subjects with higher cytomegalovirus antibodies are more likely to be anxious (Phillips, Carroll, Khan, & Moss, 2008). Additionally, in anxious women an impairment of several immune functions was found (Arranz, Guayerbas, & de la Fuente, 2007). However, studies addressing the comorbidity of specific anxiety disorders and a wide range of communicable physical diseases are still lacking.

Burden of comorbidity. Community studies have revealed that the comorbidity of any mental disorder and any physical disease is associated with higher disability (Scott et al., 2009) and more impairment (Kessler et al., 2003) compared to only one condition. Regarding the group of anxiety disorders, the comorbidity with any noncommunicable physical disease is associated with lower quality of life and higher disability (Sareen et al., 2006). However, there is a need for further information regarding potential implications of comorbidity for the burden of subjects affected on the level of specific anxiety disorders and noncommunicable and communicable physical diseases.

Research Questions

The specific research questions addressed in the three manuscripts arose from the background presented above:

Manuscript 1: *Physical diseases among persons with obsessive-compulsive symptoms and disorder: A general population study* (published in *Social Psychiatry and Psychiatric Epidemiology*)

- Which noncommunicable physical diseases are associated with OCD and subthreshold forms?
- Is this comorbidity associated with decreased quality of life?

Manuscript 2: *Associations of specific phobia and its subtypes with physical diseases: An adult community study* (submitted to *PLOS ONE*)

- Which noncommunicable physical diseases are associated with specific phobia and its subtypes?
- Can the associations established be replicated in a second community-based sample?

Manuscript 3: *Comorbidity of infectious diseases and anxiety disorders in adults and its association with quality of life: A community study* (published in *Frontiers in Public Health*)

- Which communicable physical diseases are associated with specific anxiety disorders?
- Is this comorbidity associated with increased impairment?

Based on these specific research questions, the overall research questions of the dissertation are the following:

- Over the three manuscripts, what patterns of comorbidity can be detected among specific anxiety disorders?
- What implications for subjects' burden are associated with the comorbidity?

Methods

Epidemiological Approach

Epidemiology can be generally defined as "the study of the occurrence and distribution of health-related events, states, and processes in specified populations, including the study of the determinants influencing such processes, and the application of this knowledge to control relevant health problems" (Porta, Greenland, Hernan, Dos Santos Silva, & Last, 2014, p.95). Further, epidemiology can be separated into two main subdisciplines, descriptive epidemiology and analytical epidemiology. Descriptive epidemiology assesses the distribution and course of health-related states or events such as a mental disorder in certain populations (Lieb, 2013). Analytical epidemiology concerns factors that can contribute to the etiology of mental disorders and how these factors can be implemented in prevention (Lieb, 2013). However, the two disciplines can supplement each other, as descriptive analyses may lead directly to questions of etiology (Lieb, 2006) as shown later in this dissertation. For both analytical and descriptive epidemiology different study designs can be applied that strongly affect the validity of the conclusions derived from the studies (Lieb, 2006): clinical trials versus general population surveys, experimental versus observational studies, and cross-sectional versus longitudinal studies. Due to the limited space in this dissertation, I focus on the characteristics of the design used in the reported manuscripts.

The three manuscripts presented in this dissertation are based on the data of the GHS, which is a cross-sectional general population survey. In a cross-sectional survey a defined population is examined at one time point regarding a phenomenon of interest (Lieb, 2013; Wittchen & Jacobi, 2011). In a general population survey the targeted disorder can be examined independently of a treatment institution avoiding a possible selection effect in clinical samples (Lieb, 2013; Wittchen & Jacobi, 2011). Such an observational study has the further advantage of being conducted in a naturalistic setting (Lieb, 2013).

The German Health Interview and Examination Survey

Design and sample. The GHS is the first representative survey in Germany to examine the prevalence and comorbidity of physical diseases and mental disorders in the adult population (Jacobi et al., 2004; Jacobi et al., 2002). It additionally aimed at providing data about quality of life as well as impairment and disability, and estimating the met and unmet needs and service utilization patterns of the adult population (Jacobi et al., 2002). The GHS consisted of a core-survey and several linked supplementary surveys, including the Mental Health Supplement (GHS-MHS) (Jacobi et al., 2004). The GHS-MHS was administered to 4,181 subjects aged 18–65 years. Further information concerning the structure of the GHS-MHS can be found elsewhere (Jacobi et al., 2002).

Measures.

Anxiety disorders. Anxiety Disorders were assessed with the DIA-X/M-CIDI which is a modified version of the WHO's Composite International Diagnostic Interview, version 1.2 (Wittchen & Pfister, 1997) as part of the GHS-MHS. Trained psychologists and physicians conducted the interviews in the homes of the respondents. The test-retest reliability and the validity of the diagnoses were good (for further details see, Jacobi et al., 2002, and Wittchen, Lachner, Wunderlich & Pfister, 1998). As this dissertation focuses on anxiety disorders, the following list presents the anxiety disorders that were assessed in the GHS-MHS (for all anxiety disorders 12-month prevalence was assessed, for panic disorder lifetime prevalence was additionally assessed).

- Panic disorder with and without agoraphobia
- Agoraphobia without the history of panic disorder
- Specific phobia (animal type, natural type, blood-injection type, situational type, other type)
- Social phobia
- Generalized anxiety disorder
- OCD

- Anxiety disorder not otherwise specified

For our analyses 12-month prevalence of all anxiety disorders was used.

Subthreshold forms of obsessive-compulsive disorder. OCD symptoms were classified into three groups according to the affirmation of the stem questions[2] of the DIA-X/M-CIDI and the number of *DSM-IV* criteria fulfilled. The groups were: (a) subthreshold OCD and OCD (subthreshold OCD: one stem question, at least one diagnostic criterion, but not all; OCD: full *DSM-IV* diagnostic criteria), (b) OCS (at least one stem question but no *DSM-IV* diagnostic criteria), and (c) the reference group no OCS (no stem question was affirmed).

Noncommunicable physical diseases. Noncommunicable physical diseases were assessed during the core survey using three methods. First, subjects completed a self-report questionnaire, which assessed the lifetime prevalence of 44 noncommunicable physical diseases. Second, on the basis of subjects' answers, physicians collected detailed information on lifetime prevalence, 12-month prevalence, and point prevalence (4 weeks) of noncommunicable physical diseases. Third, blood pressure and anthropometric measurements were conducted and blood and urine samples were collected (Jacobi et al., 2002). The final diagnoses were then supplemented and revised based on these laboratory analyses. Table 1 shows the groups of noncommunicable physical diseases used for our analyses. These analyses are based on 12-month prevalence.

[2] In the obsession section of the DIA-X/M-CIDI the stem question refers to a wide range of potential thoughts and cognitions. In the compulsion section three stem questions are asked to assess repetitive behaviors. If subjects approve at least one of the stem questions they are asked about the mandatory *DSM-IV* criteria (criteria A: diagnostic details of obsessions and compulsions, B: recognition that obsessions or compulsions are excessive or unreasonable, and C: evaluation if disorder causes distress or dysfunction).

Table 1

Noncommunicable Physical Diseases Covered in the German Health Interview and Examination Survey (12-Month Prevalence)

Group of physical diseases	Included physical diseases
Hypertension	Hypertension
Cardiac diseases	Heart circulation disturbances, narrowing of the coronary vessels, angina pectoris, cardiac infarct, heart weakness, heart insufficiency
Respiratory diseases	Asthma, chronic bronchitis
Gastrointestinal diseases	Ulcer, gastritis
Diabetes	Diabetes with or without insulin treatment
Arthritic conditions	Wear-and-tear type, inflammatory diseases of the joints
Allergies	Hay fever, allergic eczema, allergic hives, neurodermatitis, food allergy, allergic conjunctivitis
Migraine headaches	Migraine
Neurological diseases	Epilepsy, Parkinson's disease, multiple sclerosis
Thyroid diseases	Thyroid diseases
Vascular diseases	Stroke, brain circulation disturbance, leg circulation disturbances, artery occlusion, varicose veins, vein thrombosis

Note. To facilitate comparisons with prior work, the groups were built according to Sareen et al., 2006.

Communicable physical diseases. Communicable physical diseases were assessed in a paper-and-pencil questionnaire in the core survey. The subjects had to indicate which of the following

infectious diseases they had had during their lifetime (lifetime prevalence): diphtheria, whooping cough, measles, mumps, rubella, chicken pox, scarlet fever, tuberculosis, dysentery, or typhus. As only lifetime prevalence was available, we used this information for our analyses.

Burden: Disability and quality of life. In this dissertation, disability and quality of life are considered as measures of burden. Disability was assessed in the self-report questionnaire of the core survey. The subjects were asked whether they were completely or partially unable to carry out daily activities (i.e., function in work, school, or family) because of psychological problems or in a second question because of physical problems in the 4 weeks before the interview took place.

Quality of life was assessed in the core survey with a self-report questionnaire, the German version of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36; Bullinger et al., 1998). The SF-36 measures health-related quality of life in eight dimensions in the past 30 days (physical functioning, social functioning, role limitations due to physical problems, bodily pain, mental health, role limitations due to emotional problems, vitality, and general health) and is a well-validated instrument (Hopman et al., 2000). Two summary component scales can be derived, the mental and physical quality of life (Ware et al., 1998).

Statistical Analyses

In all manuscripts, logistic regression analyses were conducted and odds ratios (ORs) were calculated. An OR is a measure of association that entails the odd that a certain outcome (e.g. physical disease) will occur given a particular exposure (e.g. anxiety disorder) in comparison to the odd of the outcome occurring in the absence of that exposure (Hoefler, 2004; Lieb, 2013). For this, no incidence rates have to be available. Therefore the OR is an appropriate measure to be used in a cross-sectional study (Hoefler, 2004; Lieb, 2013) such as the GHS-MHS. The ORs of the specific associations can be found in the respective manuscripts in Appendices A–C.

Results

Noncommunicable Physical Diseases

Obsessive-compulsive disorder. Subthreshold OCD and OCD were associated with migraine and respiratory diseases. Further, OCS were associated with allergies, migraine, and thyroid diseases. Regarding disability, we showed that the comorbidity of OCS (combining OCS and subthreshold OCD and OCD) and any noncommunicable physical disease was associated with the highest number of days of disability due to physical or psychological problems during the past 30 days compared to subjects with only OCS, only physical disease or neither of them. We further checked whether the combined effect of both OCS and physical disease on disability is larger than the sum of the individual effects (called biological interaction, see Rothman, 2002). We did not find such an interaction suggesting independence of OCS and physical diseases as risk factors for disability (see Appendix A).

Specific phobia. Specific phobia was associated with cardiac diseases, gastrointestinal diseases, migraine, respiratory diseases, arthritic conditions, and thyroid diseases. Among subtypes, different patterns were detected. The situational subtype was associated with the most physical diseases. The results are summarized in Table 2.

Table 2

Associations Between Obsessive-Compulsive Disorder and Its Subthreshold Forms, and Specific Phobia and Its Subtypes, with Noncommunicable Physical Diseases from Manuscripts 1 and 2

Anxiety disorder (12-month prevalence)	Associated noncommunicable disease (12-month prevalence)
Subthreshold OCD and OCD	Migraine, respiratory diseases
OCS	Allergies, migraine, thyroid diseases
Specific phobia	Migraine, respiratory diseases, cardiac diseases, gastrointestinal diseases, arthritic conditions, thyroid diseases
Specific phobia subtype:	
Animal	Gastrointestinal diseases, respiratory diseases, allergies
Natural	Migraine
Blood-Injection	Respiratory diseases
Situational	Gastrointestinal diseases, arthritic conditions, migraine, thyroid diseases
Other	Thyroid diseases

Note. OCD = obsessive-compulsive disorder; OCS = obsessive-compulsive symptoms.

We replicated the associations of specific phobia with respiratory diseases and migraine in a second population-based sample from Lausanne, Switzerland (Preisig et al., 2009). Among subtypes, the animal and natural subtypes were associated with respiratory diseases and migraine (see Appendix B).

Communicable Physical Diseases

Regarding communicable diseases, we established associations of three anxiety disorders (agoraphobia, specific phobia, and generalized anxiety disorder) and whooping cough as can be seen in Table 3. Panic disorder was associated only with diphtheria, whereas agoraphobia was associated with four communicable diseases: whooping cough, mumps, scarlet fever, and tuberculosis. We further established that having one or more anxiety disorders was associated with an increased number of infectious diseases compared to having no anxiety disorder. However, analyses revealed that having more than one anxiety disorder did not further increase the number of infectious diseases relative to having one anxiety disorder. Concerning quality of life, the comorbidity of any anxiety disorder with a communicable physical disease was associated with lower both mental and physical quality of life compared to only one or neither condition (see Appendix C).

Table 3

Associations Between Anxiety Disorders and Communicable Physical Diseases in the German Health Interview and Examination Survey – Mental Health Supplement from Manuscript 3

Anxiety disorders (12-month prevalence)	Associated communicable diseases (lifetime prevalence)
Panic disorder	Diphtheria
Agoraphobia without panic disorder	Whooping cough, mumps, scarlet fever, tuberculosis
Specific phobia	Whooping cough
Generalized anxiety disorder	Whooping cough

Note. No associations were found between social phobia, OCD, and anxiety disorder not otherwise specified with communicable physical diseases.

Patterns

Over the three manuscripts, the following patterns were detected (only including the group subthreshold OCD/OCD [in the following called OCD in combination with patterns] and specific phobia not separated by the subtypes): First, OCD and specific phobia were both associated with migraine and respiratory diseases. Second, three anxiety disorders, namely, agoraphobia, specific phobia, and generalized anxiety disorder were associated with whooping cough.

Burden

Over the two manuscripts assessing measures for subjects burden (manuscripts 1 and 3), comorbidity was associated with increased burden in terms of a loss of quality of life and increased disability, as seen in Table 4.

Table 4

Associations of Comorbidity With Measures of Burden From Manuscripts 1 and 3

Assessed comorbidity	Associated measure of burden
OCS and any noncommunicable physical disease	Increased disability
Any anxiety disorder and any communicable physical disease	Decreased mental and physical quality of life

Note. OCS includes OCS, subthreshold OCD, and OCD.

Discussion

This dissertation complements the existing research on the comorbidity of specific anxiety disorders and physical diseases in that it analyzed the comorbidity of specific phobia and OCD with a wide range of noncommunicable physical diseases in the community based on a consolidated methodological approach. Further, the manuscripts demonstrate that even subthreshold forms of OCD show increased prevalence rates with specific noncommunicable physical diseases and that the subtypes of specific phobia differ in their comorbidity patterns. Additionally, the analyses demonstrate that specific anxiety disorders are associated not only with noncommunicable physical diseases, but also with specific communicable physical diseases. Last, the findings indicate that comorbidity is associated with increased burden.

General Implications of the Manuscripts

Subthreshold forms. The comorbidity analyses on subthreshold forms of OCD highlight that even symptoms of an anxiety disorder presently not captured by the *DSM-IV* diagnostic criteria are associated with increased prevalence of specific noncommunicable physical diseases. This shows that not only a full-blown diagnosis but also subthreshold symptoms are clinically meaningful and therefore should be recognized and treated in clinical care. Because some noncommunicable physical diseases were only associated with OCS and not subthreshold OCD or OCD or vice versa, it may be that different etiological factors are related to OCS, subthreshold OCD and OCD. Future studies evaluating the etiology of comorbidity should also include subthreshold forms of OCD to examine this hypothesis.

Subtypes. Different patterns of comorbidity with noncommunicable physical diseases among the subtypes of specific phobia were established. This matches with previous research showing different patterns of comorbidity with mental disorders among subtypes (Becker et al., 2007). The different patterns might point towards different etiological mechanisms such as different biological processes that may play a role in the different subtypes.

Communicable diseases. The analyses revealed that specific anxiety disorders are comorbid not only with noncommunicable physical diseases, but also with specific communicable physical diseases. Therefore research should target immunological processes that may play a role in the emergence of comorbidity.

Because the single associations of specific anxiety disorders and specific physical diseases have been discussed in the respective manuscripts (Appendices A–C), in the following discussion I focus on the implications of the patterns over the three manuscripts.

Major Implications of the Patterns

As our data encompassed a broad range of physical diseases, it was possible to detect patterns of comorbidity with a sound methodology that included physician-diagnosed noncommunicable physical diseases. The analyses therefore constitute a major contribution to the existing research. Two patterns among noncommunicable physical diseases, namely, the association of specific phobia and OCD with both migraine and respiratory diseases were revealed. It is noticeable that these two patterns match with previous research establishing associations of anxiety disorders with migraine (Breslau, Davis, & Andreski, 1991; Ratcliffe, Enns, Jacobi, Belik, & Sareen, 2009) and respiratory diseases (Goodwin, Fergusson, & Horwood, 2004; Hasler et al., 2005) in studies focusing on the particular physical disease. Our analyses therefore underline the importance of these patterns and further indicate that the associations with migraine and respiratory diseases seem not to be specific to a particular anxiety disorder. This may lead to crucial hypotheses regarding etiology of comorbidity that will be discussed in the following section.

We also examined the comorbidity of specific anxiety disorders and communicable physical diseases, which provides a further complement to the comorbidity research. From this, we established a third pattern, namely, associations of whooping cough with agoraphobia, specific phobia, and generalized anxiety disorder that may also have etiological implications.

Etiological considerations of the patterns. Several models have been proposed for the etiology of the comorbidity that can be basically characterized by the following scenarios (excluding explanations due to methodological shortcomings, Lieb, 2015; Wittchen, 1996a): Two models assume that anxiety disorders and physical diseases are causally linked. Either an anxiety disorder causes a temporally secondary physical disease or the physical disease causes a temporally secondary anxiety disorder (Lieb, 2015; Sareen et al., 2006). The third model assumes that anxiety disorders and physical diseases share common genetic, environmental, or personality factors that contribute to the co-occurrence (Lieb, 2015; Sareen et al., 2006). To further clarify the interplay of the comorbid conditions, once an association has been established, the next step is to evaluate the temporal sequence (Lieb, 2015). Addressing the predictive association of two disorders makes it possible to deduce if one disorder might be a risk factor for another disorder (Kraemer et al., 1997). However, being a risk factor for another disorder does not imply causality. In addition to a risk association, other criteria need to be examined to determine whether an association of two disorders is causal (see also Rothman & Greenland, 2005).

As some temporal sequences are more probable than others for the comorbidity patterns, I discuss these in the next section to provide hypotheses for future studies trying to unravel the psychobiological underpinnings of the comorbidity.

Migraine. Reviewing studies that have evaluated the temporal sequence of any anxiety disorder and migraine in retrospective assessments in cross-sectional or even in longitudinal studies suggests that the group of anxiety disorders generally precedes migraine (Breslau et al., 1991; Merikangas et al., 1990; Merikangas, Merikangas, & Angst, 1993; Waldie & Poulton, 2002). However, much less is known concerning the temporal sequence of specific anxiety disorders and migraine. A population survey revealed a median age at onset of migraine of 24 years for men and 25 years for women (Stewart, Wood, Reed, Roy, & Lipton, 2008). Studies on the age at onset of specific phobia and OCD have revealed that specific phobia emerges during childhood or youth (Lieb et al., 2003) whereas OCD emerges during

early adulthood (Reinecker, 2011). This suggests that specific phobia might precede migraine, whereas OCD might emerge during the same time period as migraine. Regarding data about the temporal sequence of specific phobia and OCD with migraine, one study established that specific phobia was predictive of migraine, whereas for OCD this association was not established (Swartz, Pratt, Armenian, Lee, & Eaton, 2000) matching with the age at onset findings reported above. Based on our analyses with a broad range of physical diseases and complemented by the existing research, I suggest that specific phobia might be a risk factor (according to Kraemer et al., 1997) for migraine.

However, the same cannot be assumed for OCD, because OCD seems not to precede migraine but to emerge during the same time period as migraine, as shown by the age at onset reports. On the basis of these temporal considerations and the fact that the associations seem not to be specific to a particular anxiety disorder, I propose that the group of anxiety disorders and migraine might share certain common etiological factors that may increase the risk of both disorders. Therefore in my opinion the model including shared factors seems more plausible than a causality model for a specific anxiety disorder. This is supported by some psychobiological considerations: As both OCD (Micallef & Blin, 2001) and specific phobia (Zohar & Westenberg, 2000) are associated with serotonin abnormalities and migraine has been associated with serotonin abnormalities (Hamel, 2007), too, this might be a common psychobiological factor. Further, it has been reported that some anxiety disorders are associated with a corticotropin-releasing hormone (CRH) dysfunction (Risbrough & Stein, 2006). CRH is a peptide that is thought to be a key signal within the hypothalamic-pituitary-adrenal (HPA) axis in the stress response of an organism and leads to the release of cortisol (Sauro & Becker, 2009). Sauro and Becker (2009) further proposed that stress can trigger migraine through an increased activation of the CRH release. It may therefore be that individuals with specific phobia or OCD show an altered CRH release which is also associated with migraine.

***Respiratory diseases*.** The patterns also show that the associations with respiratory diseases seem to be unspecific to a particular anxiety disorder, too. Regarding the temporal sequence, studies have shown that a bidirectional association, namely, anxiety disorders generally preceding respiratory diseases and respiratory diseases preceding anxiety disorders, is possible (Hasler et al., 2005; Katon et al., 2004; Roy-Byrne et al., 2008). Psychobiological explanations such as hyperventilation associated with anxiety or anxiogenic properties of asthma medications have been discussed for both directions (Roy-Byrne et al., 2008).

Regarding especially OCD and specific phobia, the high-risk periods for the first manifestations of OCD (early adulthood) and specific phobia (childhood or youth) seem to overlap with those of respiratory diseases (childhood and adolescence; see Katon et al., 2004). Promising research has suggested that shared etiological factors (either environmental or genetic) of some anxiety disorders and respiratory diseases may account for the comorbidity (Goodwin et al., 2004; Roy-Byrne et al., 2008). For such factors, a genetic vulnerability to both asthma and anxiety disorders has been discussed. In addition, a longitudinal study revealed that childhood adversities are associated with both asthma and anxiety disorders (Goodwin et al., 2004). Therefore I suggest that the model including shared etiological factors of both respiratory diseases and anxiety disorders is the most plausible yet.

Whooping cough. We established associations of agoraphobia, specific phobia, and generalized anxiety disorders with whooping cough. Regarding their temporal sequence, I would postulate the following: The age at onset of whooping cough is thought to be mainly in early childhood, namely, the first years of life (Wendelboe, Van Rie, Salmaso, & Englund, 2005), whereas specific phobia emerges for the first time during childhood or youth (Lieb et al., 2003). Agoraphobia and generalized anxiety disorder have their age at onset later in adolescence or in adulthood (Lieb et al., 2003). Additionally, a cross-sectional study reported that infections in the first year of life (assessed retrospectively) are associated with an increased risk of anxiety disorders in childhood (Goodwin, 2011). Taking all this

information into account, I suggest that whooping cough might precede the three anxiety disorders and therefore could be a risk factor for some anxiety disorders, namely, specific phobia, agoraphobia, and generalized anxiety disorder.

With the combined results of manuscripts 2 and 3, we showed that specific phobia was associated not only with whooping cough but also with respiratory diseases. Other studies have stated that early life infections may increase the probability of asthma in childhood (Busse, Lemanske, & Gern, 2010; Mackenzie, Anderton, & Schwarze, 2014). Taking into account this information and the already described association of infections in the first year of life (assessed retrospectively) and an increased risk of anxiety disorders in childhood (Goodwin, 2011), I postulate that whooping cough as an infectious disease might be a common risk factor of both asthma and specific phobia. Whooping cough may act as an early life stressor that might be associated with an increased expression of pro-inflammatory cytokines (Hou, Tang, & Baldwin, 2012; Leonard & Myint, 2009; Tonon et al., 2002). It has been shown that these cytokines can change the metabolism of serotonin and the function of the HPA axis via the release of CRH and cortisol (Hou et al., 2012). As specific phobia is associated with an altered serotonin function (Zohar & Westenberg, 2000), this matches with the postulated pathway. This example shows that combining information from the associations of specific anxiety disorders and both noncommunicable and communicable physical diseases might contribute to new hypotheses regarding the etiology of comorbidity.

Considerations of the patterns for the new *DSM-5* classification. As previously stated in the Theoretical Background section, in the new *DSM-5*, OCD is now classified in the group of obsessive-compulsive and related disorders. This is due to emerging evidence that OCD has several features such as an obsessive preoccupation or repetitive behaviors in common with body dysmorphic disorder, trichotillomania, hoarding disorder, and excoriation disorder (APA, 2013) and research showing similarities in courses of illness and comorbidity patterns with other mental disorders (Phillips et al.,

2010). Mental disorders are classified by a descriptive, atheoretical approach, independent of possible etiological considerations (Wittchen, 2011). From this descriptive point of view, besides comorbidity with mental disorders, comorbidity with physical diseases may provide further information on what physical disorders occur more frequently among individuals with a specific mental disorder. Two disorders classified in the same group of disorders might therefore show similar comorbidity patterns among mental disorders (Phillips et al., 2010) but also among physical diseases. The patterns in our manuscripts suggest that OCD and specific phobia show associations with the same noncommunicable physical diseases, namely, migraine and respiratory diseases. The data also show that specific phobia was in addition associated with other noncommunicable physical diseases with which OCD was not associated. Further, OCD was not associated with any communicable physical disease, whereas other anxiety disorders were associated with specific communicable diseases. Therefore comparing comorbidity patterns of OCD and anxiety disorders in our manuscripts, it is not evident whether they differ in their comorbidity patterns, which one might expect given the new classification. Future manuscripts could examine comorbidity of other obsessive-compulsive spectrum disorders with physical diseases and evaluate if the comorbidity patterns of OCD are more similar to those of other obsessive-compulsive spectrum disorders or to those of anxiety disorders. For this, more comparable data on the comorbidity of the other obsessive-compulsive spectrum disorders and a broad range of physical diseases are needed. These considerations show that our analyses of comorbidity with physical disease might also provide a basis for future considerations of classification.

Major Implications of the Burden of Comorbidity

The comorbidity of OCD even under the diagnostic threshold and a noncommunicable physical disease was associated with increased disability. In manuscript 1, we suggest that the increased disability associated with comorbidity of OCD and a physical disease is an additive effect as no indication of interaction was found. To reduce disability in an additive model as suggested by our data, it is important

to treat both conditions to reduce their joint disability (Scott et al., 2009). Therefore the manuscripts presented underline the need for the recognition and treatment of both anxiety disorders and physical diseases and may thereby also provide crucial knowledge for health care policy. The importance of recognition of comorbid conditions is supported by studies showing that anxiety disorders may be associated with noncompliance (DiMatteo et al., 2000) or worse treatment outcomes of the physical disease (Dahlen & Janson, 2002). For treatment, studies indicate that cognitive-behavioral therapy is effective in reducing anxiety symptoms in subjects with specific noncommunicable physical diseases (Kariuki-Nyuthe & Stein, 2015). However, more randomized controlled trials are needed to evaluate therapy in individuals with specific anxiety disorders and comorbid physical diseases. This might also guide treatment choices in individuals with both conditions.

Further, the comorbidity of an anxiety disorder and a communicable physical disease was associated with decreased quality of life. This shows that communicable diseases that are generally more time limited than noncommunicable physical diseases may additionally play an important role in the quality of life of individuals affected. Moreover, as infectious diseases such as whooping cough may be a risk factor for specific anxiety disorders, this additionally supports the need for preventive strategies of infectious diseases, such as vaccination.

Strengths of the Manuscripts

- *Representative sample:* A clear strength of the manuscripts presented here is the use of a representative community sample of subjects aged 18–65 years in Germany. Therefore the analyses are not limited by sampling biases found in treatment-seeking samples.
- *Case identification:* Anxiety disorders were assessed with a valid and reliable clinical interview (DIA-X/M-CIDI). As noncommunicable physical diseases were assessed by physicians and supplemented by laboratory measures, the results are less limited by recall biases than community surveys using self-report measures.

- *Case definition:* As the DIA-X/M-CIDI is based on *DSM-IV* criteria, this constitutes an improvement to some earlier studies that did not use diagnostic criteria of specific anxiety disorders.
- *Different anxiety disorders:* As many different anxiety disorders were assessed in the GHS-MHS, analyses including different specific anxiety disorders were possible.
- *A broad range of physical diseases:* A broad range of physical diseases was assessed, which enabled the detection of comorbidity patterns among many different physical diseases.
- *Noncommunicable and communicable physical diseases:* The integration of communicable physical diseases in the comorbidity analyses provides a new perspective on mental-physical comorbidity and therefore for possible etiological implications.
- *Assessment of quality of life:* The measure used for quality of life (SF-36) is a reliable and valid measure.
- *Replication:* In manuscript 2, we partially replicated our findings of the associations of specific phobia and noncommunicable physical diseases. More studies are needed to replicate the findings of the other manuscripts.

Limitations of the Manuscripts

- *Generalizability:* As the targeted population was subjects living in Germany aged 18-65 years with sufficient German language skills, the results cannot be generalized to subjects aged younger than 18 or older than 65 years. Further, no conclusions can be drawn for subjects who are nonregistered in Germany, subjects living in community institutions such as a hospital, or have insufficient language skills.
- *Sample size:* In some anxiety disorders the sample size was rather small. When combined with physical diseases the sample size became even smaller. Therefore it is possible that some associations could not be established even though they might exist.

- *Causality:* Due to the cross-sectional design used, no causal inferences can be drawn. No models concerning the etiology of comorbidity can therefore be excluded.
- *Communicable physical diseases:* As the prevalence rates of communicable physical diseases were based on self-reports, it may be that some diseases were misunderstood (e.g. whooping cough could be a generic cough or a symptom of asthma). Even though there are studies showing that the validity of self-report of some communicable physical diseases is high (Macintyre & Pritchard, 1989) future studies should assess infectious diseases with a medical interview or by laboratory blood tests. Further, we had lifetime information only for the communicable diseases, whereas for anxiety disorders, 12-month prevalence was available. Future studies should use the same time frame to increase comparability.

Outlook

There is a need for longitudinal studies of the comorbidity of specific anxiety disorders and a wide range of noncommunicable and communicable physical diseases in the community that address the temporal sequence of the diseases. These studies should also include neurobiological (e.g., CRH) and immunological parameters to further evaluate possible shared mechanisms relevant for comorbidity. Further, future studies could also evaluate possible mediators or moderators of the association of anxiety disorders and physical diseases that might modify the associations (e.g., physical activity). Additionally, more research is needed to establish the associations of subthreshold forms of specific anxiety disorders and physical diseases in the community and to test whether different etiological mechanisms are involved in specific phobia subtypes. Future studies should also evaluate the influence of comorbidity on treatment outcome of comorbid conditions, especially for specific anxiety disorders such as OCD and examine the effect of treatment of an anxiety disorder on the physical disease and vice versa.

Overall Conclusions

This dissertation shows that specific anxiety disorders are highly comorbid with specific noncommunicable and communicable physical diseases in the general population and that even subthreshold forms may show substantial comorbidity. The manuscripts reported in this dissertation established patterns of associations of both specific phobia and OCD with migraine and respiratory diseases. Further, agoraphobia, specific phobia, and generalized anxiety disorders were all associated with whooping cough. These patterns – supplemented by the already existing research on other specific anxiety disorders – suggest that the migraine-anxiety association and the respiratory diseases-anxiety associations are not specific to a particular anxiety disorder. Considerations of the temporal sequence and psychobiological processes further suggest that the comorbidity of both specific anxiety disorders and the two noncommunicable physical diseases might be better explained by shared etiological factors than by a causality model. The associations of anxiety disorders and communicable physical diseases highlight that immunological processes should also be considered as possible mechanisms in the etiology of comorbidity. Further, comorbidity was associated with increased burden even in subthreshold forms of specific anxiety disorders or with communicable physical diseases. This might have unique implications for treatment and prevention.

In sum, this dissertation contributes to a better understanding of the comorbidity of anxiety disorders and physical diseases in the community as it may influence future research evaluating the etiology of comorbidity and provide a first step to optimize treatment strategies for comorbid conditions that aim to reduce burden of individuals affected.

> Scientific knowledge is knowledge, not fact—a gallery of pictures painted by scientists to portray in some simplified, comprehensive way the (seemingly) infinite complexity of nature. The pictures are put up and taken down, cleaned, replaced, and destroyed. Any account of scientific knowledge is therefore . . . an account of unfinished business.
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> —Holden, 1980

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Appendix A

Physical diseases among persons with obsessive compulsive symptoms and disorder: a general population study

Cornelia Witthauer, Andrew T. Gloster, Andrea H. Meyer, Roselind Lieb

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ORIGINAL PAPER

Physical diseases among persons with obsessive compulsive symptoms and disorder: a general population study

Cornelia Witthauer · Andrew T. Gloster · Andrea Hans Meyer · Roselind Lieb

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Abstract

Purpose This study aimed at evaluating the comorbidity between DSM-IV obsessive compulsive disorder (OCD) and subthreshold forms and physical diseases in the general population as well as disability associated with comorbidity.

Methods We used data from the 1998 German Mental Health Survey, a representative survey of the German population. Mental disorders and physical diseases of 4181 subjects (aged 18–65) were cross-sectionally assessed. Mental disorders were diagnosed using the M-CIDI/DIA-X interview. Physical diseases were assessed through a self-report questionnaire and a standardized medical interview. We created three groups of obsessive–compulsive symptoms: (1) no obsessive compulsive symptoms (n = 3,571); (2) obsessive compulsive symptoms (OCS, n = 371; endorsement of OCS (either obsession or compulsion) without fulfilling any core DSM-IV criteria); (3) subthreshold OCD/OCD (n = 239; fulfilling either some or all of the core DSM-IV criteria).

Results In comparison to subjects without OCS, subjects with subthreshold OCD/OCD showed higher prevalence rates of migraine headaches (OR 1.7; 95 % CI 1.1–2.5) and respiratory diseases (OR 1.7; 95 % CI 1.03–2.7); subjects with OCS showed higher prevalence rates of allergies (OR 1.6; 95 % CI 1.1–2.8), migraine headaches (OR 1.9; 95 % CI 1.4–2.7) and thyroid disorders (OR 1.4; 95 % CI 1.01–2.0). Subjects with both OCS and physical disease reported the highest number of days of disability due to physical or psychological problems during the past 30 days compared to subjects with only OCS, only physical disease or neither of them.

Conclusions OCD and subthreshold forms are associated with higher comorbidity rates with specific physical diseases and higher disability than subjects without OCS. Possible etiological pathways should be evaluated in future studies and clinicians in primary care should be aware of these associations.

Keywords OCD · Subthreshold types · Physical disease · Epidemiology · Obsessive compulsive symptoms · Disability

Abbreviations

OCD	Obsessive compulsive disorder
OCS	Obsessive compulsive symptoms
GHS-MHS	German health interview and examination survey and its mental health supplement
DIA-X/M-CIDI	The Munich composite international diagnostic interview
DSM-IV	Diagnostic and statistical manual of mental disorders, Fourth Edition
ICD-10	International classification of diseases, Tenth Edition
CI	Confidence interval
OR	Odds ratio
IRR	Incidence risk ratio
RERI	Relative excess risk due to interaction
AP	The attributable proportion due to interaction
S	Synergy index

Introduction

There is increasing evidence that mental disorders frequently co-occur with physical diseases [1–4]. Such

C. Witthauer · A. T. Gloster · A. H. Meyer · R. Lieb
Department of Psychology, Division of Clinical Psychology and Epidemiology, University of Basel, Missionsstrasse 62a, 4055 Basel, Switzerland
e-mail: roselind.lieb@unibas.ch

comorbidity between mental and physical diseases has been found in patients diagnosed with schizophrenia, bipolar disorder, schizoaffective disorder and major depressive disorder [5]. Among these patients, nutritional and metabolic diseases, cardiovascular diseases, viral diseases, respiratory tract diseases, musculoskeletal diseases, pregnancy complications and stomatognathic diseases were found to be more prevalent than in the general population [1, 6, 7]. Due to their higher risk of cardiovascular diseases, patients with affective disorders are even known to be at high risk for premature death [4, 8].

There is evidence from patients and community-based studies that physical health problems are also associated with anxiety disorders [2, 3, 9, 10]. Significant associations between anxiety disorders and cardiac disorders, hypertension, gastrointestinal problems, genitourinary disorders and migraine have been found in patients recruited from treatment and community sources [2]. Additionally, increased rates of arthritis, asthma and ulcers were detected in patients with anxiety disorders [10]. Likewise, population surveys showed that depressive and anxiety disorders without comorbidity were associated in equal degree with physical conditions [3]. In addition, analyses revealed that the presence of an anxiety disorder was significantly associated with thyroid disease, respiratory disease, gastrointestinal disease, arthritis, migraine headaches and allergic conditions in the general population [9]. Even community samples across different countries showed that anxiety disorders occurred at higher rates in persons with heart diseases compared to those without heart disease [11]. Moreover, community analyses revealed that specific anxiety disorders are also significantly associated with medically explained pain symptoms, unexplained pain symptoms and pain disorder [12].

This mental-physical comorbidity has negative consequences for subjects' disability in daily life. Subjects with comorbid physical and anxiety disorders are more likely to be severely disabled than subjects with either condition alone [9, 13, 14]. This may suggest that it should be ensured that subjects with mental-physical comorbidity receive enough clinical care in order to recognize and treat both disorders.

Additionally, cross-sectional analyses of the association of specific physical diseases with certain mental disorders can lead to hypotheses concerning etiological mechanisms at least in subgroups of affected subjects. For example, asthma has been found to be associated with panic disorder in many cross-sectional community-based studies [15]. These findings stimulated longitudinal studies to evaluate the role of smoking as an etiological factor in asthma and panic disorder [15]. This illustrates how hypotheses of certain etiological factors can be derived from cross-sectional associations of mental-physical comorbidity.

Based on the fact that several studies showed associations between many mental disorders and specific physical diseases, we will report for the first time the association of specific physical diseases and OCD and disability related to this comorbidity. This is important because epidemiological studies showed that across anxiety disorders obsessive compulsive disorder (OCD) was found to be the disorder with the highest estimate of the number of life years lost due to the disease in men and second highest in women behind panic disorder [16]. Increased health care utilization among individuals with OCD [17] and decreased physical wellbeing (referring to physical health, sleep and pain) in patients with OCD [18] were found. Additionally, one study revealed that the presence of any chronic physical condition increases the prevalence of obsessive–compulsive symptoms [19]. Furthermore, it is known that subthreshold types of OCD that do not fulfill all DSM-IV diagnostic criteria are more prevalent in the general population compared to OCD [20–22]. Adam et al. [17] could show that subjects with such "subthreshold" OCD (i.e. fulfilling some but not all core DSM-IV criteria) and obsessive compulsive symptoms (i.e. endorsement of stem questions without fulfilling any core DSM-IV criteria) report higher disability and increased health care utilization in the community than subjects without these symptoms.

To our knowledge no community study about the physical health problems of individuals with OCD and subthreshold forms has been published, even though subthreshold forms of OCD are known to be associated with comparable disability as full diagnostic OCD. As shown above, these analyses are relevant for implications of the health care system and to generate etiological hypotheses of OCD.

In this report we, therefore, evaluate the association between physical diseases and individuals with OCD and subthreshold forms in the general population and the disability associated with comorbidity. For this purpose we use representative community data from the German Health Interview and Examination Survey and its Mental Health Supplement.

Method

Design and sample

We used Data from the German Health Interview and Examination Survey and its Mental Health Supplement (GHS-MHS) conducted in 1997. The GHS was the first nationwide cross-sectional study for medical and social assessments in Germany and was commissioned by the German Ministry of Science, Research and Education and the Robert Koch Institute and authorized by the relevant

institutional review board and ethics committee. The aim of the core study was the assessment of sociodemographic characteristics, physical diseases, impairments and health-care utilization in a representative community sample of 7,124 subjects aged 18–79 (overall response rate 61.5 %). It was a stratified, randomized sample from 113 communities throughout Germany with 130 sampling units (sampling steps: (1) selection of communities, (2) selection of sampling units, (3) selection of inhabitants) [23, 24]. To handle the stratified sampling design the data were weighted and confidence intervals were calculated by the Huber-White sandwich method to account for the weighting scheme as well as the stratified sampling design [24].

For the assessment of mental disorders in the GHS-MHS, a two-stage design was used: The first stage entailed the administration of a 12-item screening questionnaire for mental disorders at the end of the medical examination of the core survey (CID-S) [25]. The second stage involved the administration of a structured psychopathological interview, the Munich Composite International Diagnostic Interview (DIA-X/M-CIDI), to all core survey subjects who had screened positive for a mental disorder and to a random sample of 50 % who screened negative [25]. This subsample of the GHS built the sample of the Mental Health Supplement and included 4,181 subjects aged 18–65 years. The conditional response rate (i.e., subjects who completed the M-CIDI interview) was 87.6 %. All subjects gave their informed consent. Further description of aims, design and methods as well as sociodemographic characteristics of the whole GHS-MHS sample can be found elsewhere [23].

Assessment of OCD

For the diagnostic assessments, a modified version of the fully structured interview DIA-X/M-CIDI was used [26]. The questions covered DSM-IV and ICD-10 criteria. The DIA-X interview enables the assessments of symptoms, syndromes and onset, duration and severity. The interview was conducted by trained psychologists and physicians [27]. The test–retest reliability for OCD was found to be excellent ($k = 0.81$) with an average time interval of 38 days between interviews in a sample of 60 subjects in the community. The validity of the DIA-X/M-CIDI OCD diagnoses compared to diagnoses from independent treating physicians in a sample of 68 randomly chosen patients was also excellent ($k = 0.91$). The sensitivity was 100 %, while the specificity was 98.4 % [17, 28].

The DIA-X/M-CIDI module for OCD includes two parts: one for the assessment of obsessions and one for the assessment of compulsions. In each part, stem questions are asked at the beginning. In the obsession section the stem question refers to a wide range of potential thoughts and cognitions presented in the form of a symptom list: "During the last 12 month, have you been bothered by having certain unpleasant thoughts or images like recurrent arbitrary thoughts, such as the idea that your hands are dirty or have germs on them?" (yes or no). In the compulsion section three stem questions are asked to assess repetitive behaviors ("doing something like washing hands over and over again (yes or no) or "checking several times whether the door is locked" (yes or no) or mental acts ("counting something like tiles in a floor" (yes or no)). If the subject approves one of these stem questions, they are subsequently asked for the mandatory DSM-IV criteria. The DSM-IV mandatory criteria include criteria A for the diagnostic details of obsessions and compulsions, criteria B for the recognition that the obsessions or compulsions are excessive or unreasonable and C for the evaluation if the disorder causes distress or dysfunction. Diagnostic criteria refer to the past 12 months.

To facilitate comparisons with prior work [17], this paper splits the sample into the following three mutually exclusive groups:

1. Subthreshold OCD/OCD (either (a) subthreshold OCD: the subject affirmed at least one of the stem questions for obsessive or compulsive symptoms and fulfilled at least one of the DSM-IV diagnostic criteria A, B or C, but not the full DSM-IV criteria, or (b) OCD: the subject met full DSM-IV criteria A, B and C for OCD)
2. OCS (the subject affirmed at least one of the stem questions for obsessive or compulsive symptoms, but did not fulfill any of the DSM-IV criteria A, B or C)
3. No OCS (the subject did not affirm any of the stem questions for obsessions or compulsions)

Due to the small group size of full diagnostic OCD (see Table 1) and the small cell sizes when combined with physical diseases, we merged the groups OCD and subthreshold OCD (group 1) in contrast to Adam et al. [17].

Assessment of physical conditions

In the GHS, physical conditions were assessed by a self-report questionnaire and a standardized computer-assisted medical interview by a general practice physician.

Based on the information on physical diseases in the self-report questionnaire, the physicians conducted information about lifetime prevalences, 12-month prevalences and point prevalences (4 weeks) of 44 physical diseases [23].

Additionally anthropometric and blood pressure measurements were conducted as well as blood and urine samples. Based on these laboratory analyses diagnoses were then supplemented and revised [23]. The following

Table 1 12-month prevalences of no OCS, OCS and subthreshold OCD/OCD and physical diseases in the total sample (n = 4,181)

	No. (%)
no OCS	3,571 (86.5)
OCS	371 (8.3)
Subthreshold OCD/OCD	239 (5.2)
Subthreshold OCD	201 (4.5)
OCD	38 (0.7)
Hypertension	581 (13.1)
Cardiac diseases (heart circulation disturbances, Narrowing of the coronary vessels, angina, pectoris, cardiac infarct, heart weakness, heart, insufficiency)	100 (2.2)
Respiratory diseases (asthma, chronic bronchitis)	284 (7.0)
Gastrointestinal diseases (ulcer, gastritis)	268 (6.3)
Diabetes (with or without insulin treatment)	115 (2.7)
Arthritic conditions (wear and tear type, inflammatory diseases of the joints)	1,107 (25.9)
Allergies (hay fever, allergic eczema, allergic hives, neurodermatitis, food allergy, allergic conjunctivitis)	747 (18.1)
Migraine headaches	491 (10.3)
Neurological diseases (epilepsy, parkinson disease, multiple sclerosis)	27 (0.5)
Thyroid diseases	445 (10.0)
Vascular diseases (stroke, brain circulation disturbance, leg circulation disturbances, artery occlusion, varicose veins, vein thrombosis)	536 (12.4)

OCS obsessive–compulsive symptoms, OCD obsessive–compulsive disorder, No. unweighted number of subjects, % weighted percentage

analyses are based on the physicians' diagnoses during the medical interview. We, therefore, grouped the disorders into eleven groups of disorders (see Table 1).

Assessment of disability

Disability was assessed by asking the subjects whether he or she was completely or partially unable to carry out daily activities (i.e., function in work, in school or in family), because of psychological problems in the 4 weeks before the interview took place (yes or no) and whether he or she was completely or partially unable to carry out daily activities (function in work, in school or in family), because of physical problems in the 4 weeks before the interview took place (yes or no).

Sociodemographic correlates

For the present sample, earlier analyses revealed no associations between OCS, subthreshold OCD, OCD and gender, employment status and social class [17]. Significant associations between age and subthreshold OCD and OCS were found: the 12-month prevalence was lower in the older age group. Additionally, the 12-month prevalence of OCS was higher in the separated, divorced or widowed subjects group. More details can be seen elsewhere [17].

Statistical analyses

Comorbidity between OCS and physical diseases

We used logistic regression [odds ratio (OR) with 95 % confidence intervals (CI)] to examine associations between the groups OCS and subthreshold OCD/OCD and physical diseases. We considered a p value <0.05 as statistically significant. For the logistic regression analyses we used the STATA software package, version 11.0 [29].

Disability

To analyze the association between OCS and physical disease on the risk of physical or psychological disability we used the two factors OCS (combining both OCS groups) and physical disease (which includes any of the physical diseases), both having two levels (yes or no). To determine whether comorbidity of OCS and physical disease were associated with an increased likelihood of past 30-day disability due to physical or psychological problems, we considered the zero inflated negative binomial model and the Hurdle model as these models account for excessive zeros (85.8 % of subjects reported 0 days of disability due to physical problems and 98.7 % of subjects reported 0 days of disability due to psychological problems). These two models led to almost identical results and fitted the data equally well (based on the Akaike information criterion, AIC). We chose the Hurdle model because we think that its underlying process is somewhat more comprehensible compared with the zero inflated negative binomial model. The hurdle model (OR with 95 % CI and incidence risk ratio (IRR) with 95 % CI) assumes negative binomial (physical disability) or Poisson (psychological disability) distributed outcomes. This model accounts not only for the excessive number of zeros observed, but also for overdispersion (i.e. the fact that the observed variability in the outcome was higher than its mean, see e.g. [30]). Hurdle models consist of two parts. In the first part, a binomial model is used to model the probability of zeros versus non-zeros. In the second part that deals with the non-zero counts and which is hence often called the "count model", a Poisson or a negative binomial model is used (depending on whether the counts are over dispersed or not). As only non-zero values are considered in this second part, this model is zero-truncated [31].

Our model contained the two factors OCS and physical disease plus the interaction between the two. For both factors we were thus able to test (1) whether they had an

impact on the probability of physical or psychological disability and (2) whether they affected the number of days of disability among those subjects who have reported at least 1 day of disability. The interaction thereby tested whether subjects having both OCS and physical disease were (1) at a particularly high risk of physical or psychological impairment and (2) if so, how strongly. For calculating the hurdle model we used the software MPlus (version 6) [32].

To check for biological interaction as described by Rothman [33], i.e. whether the combined effect of both factors OCS and physical disease is larger than the sum of the individual effects of these two factors, denoting deviation from additivity in disease risks, we additionally calculated the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP) and the synergy index (S) [34], using the software R (version 2.14) [35]. Absence of biological interaction thereby suggests independence of OCS and physical disease as risk factors of disability.

Results

12-month prevalence

The 12-month prevalence rate was 8.3 % for OCS, and 5.2 % for the combined OCD and subthreshold OCD (Table 1). Among physical diseases, the highest 12-month prevalence rate was detected for arthritic conditions (25.9 %), the lowest for neurological diseases (0.5 %).

Associations of physical diseases and OCS, subthreshold OCD/OCD

Significantly higher prevalence rates in subjects with OCS were found for allergies (OR 1.6; 95 % CI 1.1–2.8), migraine (OR 1.9; 95 % CI 1.4–2.7) and thyroid diseases (OR 1.4; 95 % CI 1.01–2.0) compared to the no OCS group (see Table 2).

The subthreshold OCD/OCD group was associated with elevated odds for respiratory diseases (OR 1.7; 95 % CI 1.03–2.7) and migraine (OR 1.7; 95 % CI 1.1–2.5).

Disability

Disability due to physical problems

We used the two factors OCS (combining both OCS groups) and physical disease (which includes any of the physical diseases) to analyze the association with disability. As there was no indication of statistical interaction between the two factors for both the binomial ($p = 0.40$) and the count model parts ($p = 0.77$), we reran the model without interaction. The binomial part of the model revealed that both OCS and physical disease significantly increased the probability of disability (OCS: OR 1.9; 95 % CI 1.4–2.5, $p < 0.001$; physical disease: OR 1.7; 95 % CI 1.2–2.2, $p < 0.001$). The count model part of the model showed that physical disease significantly increased the number of days of disability (IRR 1.6; 95 % CI 1.1–2.2, $p = 0.008$), whereas OCS did not (IRR 1.3; 95 % CI 0.9–1.8, $p = 0.064$).

As shown in Fig. 1, the highest number of days of disability due to physical diseases was reported by subjects with both OCS and physical disease ($n = 95$ (2.74 %), M 2.33; 95 % CI 1.61–3.05), followed by subjects with OCS only (M 1.10; 95 % CI 0.64–1.55) and by subjects with physical disease only (M 1.09; 95 % CI 0.86–1.34). Subjects with neither OCS nor physical disease indicated the lowest number of days of disability (M 0.50; 95 % CI 0.3–0.7). There was no indication for the presence of biological interaction for any of the three measures (SI, RERI, AP; $p > 0.05$ in each case).

Disability due to psychological problems

As there was no indication of statistical interaction between the two factors for both the binomial ($p = 0.24$) and the count model parts ($p = 0.74$) in the disability due to psychological problems, we again reran the model without the interaction. The binomial part of the model revealed that both OCS and physical disease significantly increased the probability of disability (OCS: OR 3.8; 95 % CI 2.1–6.9, $p < 0.01$; physical disease: OR 3.7; 95 % CI 1.4–9.8, $p < 0.01$). Contrary to the disability due to physical problems, the count model part of the model revealed that there was no significant effect of both factors on the number of days of disability due to psychological problems ($p > 0.55$ for both model parts).

As for disability due to physical problems, the highest number of days of disability due to psychological problems was reported by subjects with both OCS and physical disease ($n = 19$ (0.55 %), M 0.47; 95 % CI 0.17–0.76), followed by subjects with OCS only (M 0.14; 95 % CI 0.03–0.31) and by subjects with physical disease only (M 0.10; 95 % CI 0.05–0.16). Subjects with neither OCS nor physical disease indicated the lowest number of disability days (M 0.03; 95 % CI 0.00–0.06; Fig. 1). Again, no indication for biological interaction was found for any of the three measures (SI, RERI, AP; $p > 0.05$ in each case).

Discussion

To the best of our knowledge, this is the first study that analyses the association between OCD and subthreshold

Table 2 Associations between 12 months physical diseases and 12-months obsessive–compulsive symptoms and disorder

Physical diseases[a]	no OCS (n = 3,571)	OCS (n = 371)		Subthreshold OCD/OCD (n = 239)	
	No. %	No. (%)	OR (CI)	No. (%)	OR (CI)
Hypertension					
No hypertension (n = 3,372)	2,868 (81.6)	303 (83.5)	1.0	201 (87.4)	1.0
Hypertension (n = 581)	513 (13.7)	43 (9.7)	0.7 (0.4–1.0)	25 (8.7)	0.6 (0.3–1.0)
Cardiac diseases					
No cardiac diseases (n = 3,982)	3,394 (95.6)	358 (97.5)	1.0	230 (95.6)	1.0
Cardiac diseases (n = 100)	89 (2.3)	6 (1.3)	0.6 (0.2–1.4)	5 (2.8)	1.2 (0.4–3.5)
Respiratory diseases					
No respiratory diseases (n = 3,728)	3,201 (89.6)	321 (87.6)	1.0	206 (85.6)	1.0
Respiratory diseases (n = 284)	234 (6.8)	26 (6.7)	1.0 (0.6–1.6)	24 (10.8)	1.7 (1.03–2.7)*
Gastrointestinal diseases					
No gastrointestinal diseases (n = 3,090)	2,264 (75.5)	263 (71.3)	1.0	163 (68.3)	1.0
Gastrointestinal diseases (n = 268)	215 (6.1)	29 (7.2)	1.3 (0.8–2.0)	24 (8.7)	1.6 (0.9–2.7)
Diabetes					
No diabetes (n = 4,022)	3,430 (96.5)	360 (97.2)	1.0	232 (97.2)	1.0
Diabetes (n = 115)	102 (2.8)	7 (2.2)	0.8 (0.3–1.8)	6 (2.4)	0.9 (0.3–2.5)
Arthritic conditions					
No arthritic conditions (n = 2,907)	2,495 (70.7)	248 (69.0)	1.0	164 (70.6)	1.0
Arthritic conditions (n = 1,107)	938 (25.8)	107 (27.9)	1.1 (0.8–1.5)	62 (25.1)	1.0 (0.7–1.4)
Allergies					
No allergies (n = 2,682)	2,334 (65.6)	207 (54.3)	1.0	141 (58.3)	1.0
Allergies (n = 747)	614 (17.3)	81 (23.5)	1.6 (1.1–2.8)*	52 (21.9)	1.4 (0.9–2.1)
Migraine					
No migraine (n = 3,497)	3,016 (86.5)	292 (80.8)	1.0	189 (80.9)	1.0
Migraine (n = 491)	384 (9.5)	68 (17.0)	1.9 (1.4–2.7)*	39 (14.6)	1.7 (1.1–2.5)*
Neurological diseases					
No neurological diseases (n = 4,114)	3,517 (99.0)	362 (98.3)	1.0	235 (98.2)	1.0
Neurological diseases (n = 27)	21 (0.5)	4 (0.9)	1.9 (0.6–5.8)	2 (0.9)	2.0 (0.4–9.7)
Thyroid diseases					
No thyroid diseases (n = 3,451)	2,973 (84.8)	284 (77.6)	1.0	194 (82.1)	1.0
Thyroid diseases (n = 445)	367 (9.7)	49 (12.6)	1.4 (1.01–2.0)*	29 (11.0)	1.2 (0.7–1.9)
Vascular diseases					
No vascular diseases (n = 3,351)	2,859 (81.1)	302 (82.8)	1.0	190 (80.8)	1.0
Vascular diseases (n = 536)	459 (12.5)	42 (11.2)	0.9 (0.5–1.4)	35 (13.7)	1.1 (0.7–1.7)

OR odds ratios from logistic regression, CI confidence intervals, OCS obsessive–compulsive symptoms, OCD obsessive–compulsive disorder, No. unweighted number of subjects, % weighted percentage

* $p < 0.05$

[a] Subjects reporting physical diseases during their lifetime but not within the past 12 months were excluded from the analyses

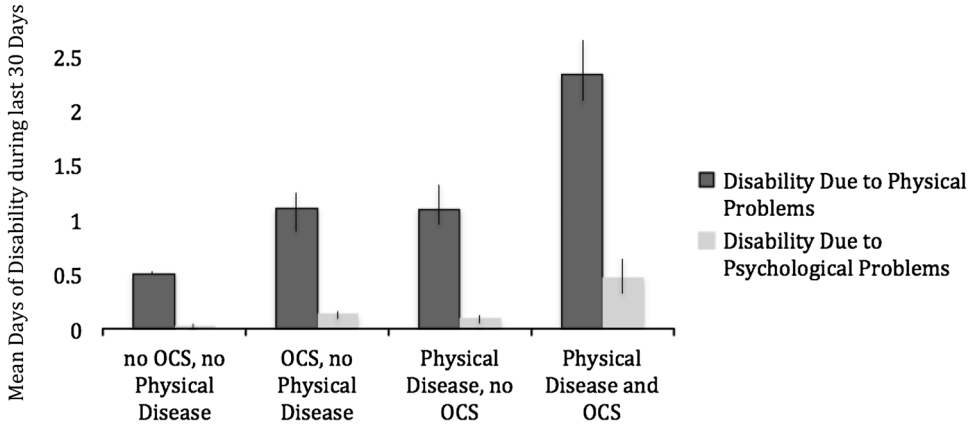

Fig. 1 Mean days of disability during past 30 days. OCS obsessive compulsive symptoms; Error bars indicate standard errors

OCS obsessive compulsive symptoms;. Error bars indicate standard errors

forms and physical diseases in a representative community sample.

Our results show that obsessive compulsive symptoms are associated with higher prevalence rates of specific physical diseases in the general population. These results add to the body of literature on the comorbidity of physical diseases and other anxiety disorders. In comparison to findings from other anxiety disorders, we found associations with migraine headaches, allergies and thyroid diseases in OCS and significant associations with respiratory diseases and migraine headaches in subthreshold OCD/OCD [2, 9, 10]. Further, our analyses revealed that subjects with both OCS and physical disease report the highest number of days of disability compared to subjects having only OCS (without physical disease), only a physical disease or neither of them.

Different models exist to explain the cooccurrence of anxiety disorders and physical diseases: anxiety as consequent or antecedent factor of a physical disease, third variables that lead to the comorbidity or, common genetic, environmental or personality factors that contribute to the cooccurrence [9]. Even though only few specific hints for the explanations of associations between OCS and physical diseases exist, these hints can point towards important etiological pathways in subgroups of OCD patients and, therefore, will be discussed in the following.

First, defects in serotonin metabolism as possible neurochemical basis of both migraine and OCD have been proposed [36]. An abnormal serotonin function in subjects with OCD is one of the most consistent pathophysiologic findings [37]. Similarly, serotonin abnormalities have been implicated in the pathogenesis of migraine [36, 38]. Alternatively it has been proposed that anxiety disorders may be involved in peripheral and central mechanisms of pain sensitization which contributes to the evolution of chronic headaches [39]. Against this background, our results can support a suggested role of serotonin in an etiological pathway of OCD.

Second, an increased rate of immune-related symptoms among OCD patients has been reported [40]. As a possible explanation, one theory suggests that postinfectious autoimmune responses might be associated with the development of pediatric OCD, which leads to an increased rate of immune-related diseases in adults with OCD [40]. Our cross-sectional results match with this theory, as we found increased rates of allergies in subjects with OCS. Studies showed that especially immune responses to streptococcal infections may be relevant for the etiology of OCD [41]. Our analyses support a suggested involvement of immune responses that may be relevant in the etiology of a subgroup of OCD.

Third, the association between asthma and anxiety disorders, especially in panic disorder, is well established [42, 43]. Explanations range from hyperventilation that is commonly associated with anxiety disorders, subjective psychological disturbance which could lead to enhanced bronchoconstriction to biological effects of anxiety on immunological or biological factors [44]. Specific explanations of the association between OCD and respiratory diseases lack, however. Therefore, we can only speculate that comparable to other anxiety disorders, subjects with OCD could have an altered symptom perception leading to enhanced awareness of breathlessness and bronchoconstriction and therefore to asthma-like symptoms. Despite that no specific explanation for this association exists, our results nevertheless show that an involvement of the respiratory tract may be important in OCD.

Fourth, pervasive evidence documents the relationship between thyroid diseases and mental symptoms such as impairment of cognitive functions or behavioral and mood disturbances [45, 46]. Concerning OCD, some observations of increased rates of obsessive–compulsive symptoms in subjects with thyroid disease have been found [46]. As an explanation, common biochemical abnormalities that play a role for both thyroid diseases and OCD may exist [46]. A

diminished thyrotropin releasing hormone (TRH) response to a TRH stimulation was detected in subjects with OCD, also [47] suggesting an alteration in the serotonergic system, as a decreased central serotonergic activity is associated with blunted TSH response [47]. The increased rates of thyroid diseases in our analyses support the hypothesis of an alteration of the hypothalamic-pituitary-thyroid axis in the pathophysiology of OCD, too.

Fifth, it could be suggested that certain behaviors that occur in OCD increase the vulnerability to develop a physical disease. As a lack of exercise has been associated with anxiety disorders [48] and physical inactivity is associated with many chronic physical diseases such as cardiovascular diseases or diabetes [49], it could be suggested that subjects with OCD are at increased risk to develop physical illnesses through physical inactivity. Further, it has been shown that cleaning activities related to exposure to certain cleaning products in the household are associated with asthma [50]. Extensive hand washing or cleaning can be a symptom of OCD. Through exposure to poisonous cleaning agents this could lead to higher prevalence of respiratory diseases in subjects with OCD. Additionally, subjects with OCD avoid uncertainty [51]. This might in addition be related to an increased prevalence of physical diseases in these subjects, as isolation and, therefore, a lack of exercise may be the consequences.

Given these etiological considerations, our results may be useful to deduce hypotheses concerning the involvement of certain physiological factors in the etiology of OCD in subgroups of subjects. Future studies are clearly needed to replicate these findings.

As some physical diseases were only associated with OCS and not OCD (higher prevalence of allergies and thyroid diseases only in OCS) or vice versa, it is possible that different etiological factors are related to OCS, subthreshold OCD and OCD. Future studies should, therefore, not only include OCD but also subthreshold forms to test these hypotheses.

Besides the documentation of the associations between physical diseases and OCS and the deduction of potential etiological hypotheses, our analyses show that both subjects with OCS or physical diseases have an increased probability of disability due to psychological or physical problems during the past 30 days. Comparable to previous studies on anxiety disorders [9] or mental disorders in general [13] and physical diseases, the highest number of days of disability was reported in the group with both OCS and physical diseases. This is supported by previous findings that subjects with both mental and physical conditions are more likely to be severely disabled than those with either condition alone [13].

Due to the fact that no indication for biological interaction was found between OCS and physical disease, the increased disability of subjects affected by both OCS and physical disease may be seen as an additive rather than a synergistic effect of both disorders.

The mechanisms leading to this specific increased disability are unknown. Research on other anxiety disorders, however, suggest that anxiety is associated with poor adherence to self-care regimen and increased medical complications in patients with chronic medical illness [52]. This could lead to decreased active behavioral self-management strategies and, therefore, to an increased burden of the physical disease in anxiety in general [53] and specifically in OCD.

The increased disability in subjects with both OCS and physical disease may reflect an increased need of recognition and treatment of both physical disorder and OCS in primary health care. Future studies could additionally investigate whether this comorbidity is associated with a loss in quality of life.

The current study has a number of limitations. First, the survey is limited to subjects aged 18–65 years, which does not enable generalization of the results to younger or older subjects. Second, as already mentioned by Sareen et al. [9], even though physicians' diagnoses were used, certain diagnoses are more reliant on self-report data (e.g. arthritis) than others (e.g. diabetes). That may have led to over reporting of physical symptoms in anxious patients. Third, due to the cross-sectional nature of the study, it is not possible to draw conclusions about the causal nature of the associations between OCD or OCS and physical diseases. Fourth, although we used a large representative sample with 4,181 subjects, the sample size of full diagnostic OCD is rather small ($n = 38$). In addition, the combinations between OCD symptoms and physical diseases led to small cell sizes (especially in cardiac diseases, diabetes and neurological diseases). Fifth, it has to be considered that comorbidity between OCD and subthreshold forms and other mental disorders has been reported [17]. Thus, further investigation is needed to examine specificity of the results.

With these limitations in mind, our community study shows that subjects affected by DSM-IV obsessive compulsive disorder either on the full/subthreshold or even on the symptomatic level report higher rates of certain physical diseases than subjects without these symptoms. This comorbidity is associated with higher impairment than either condition alone.

These findings can be helpful to detect new etiological pathways underlying OCD in subgroups of affected subjects or support the ones suggested in earlier studies. In addition, clinicians and doctors in primary care need to be sensibilized for these associations to recognize and treat both physical disease and OCS to reduce disability in affected subjects.

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Appendix B

Associations of specific phobia and its subtypes with physical diseases: an adult community study

Cornelia Witthauer, Vladeta Ajdacic-Gross, Andrea Hans Meyer, Peter Vollenweider, Gerard Waeber, Martin Preisig, Roselind Lieb

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Associations of Specific Phobia and Its Subtypes with Physical Diseases: An Adult Community Study

Cornelia Witthauer[1], Vladeta Ajdacic-Gross[2,3], Andrea Hans Meyer[1], Peter Vollenweider[4], Gerard Waeber[4], Martin Preisig[5], Roselind Lieb[1]*

Short title: Specific Phobia and Physical Diseases

[1]Department of Psychology, Division of Clinical Psychology and Epidemiology, University of Basel, Basel, Switzerland

[2]Department of Psychiatry, Psychotherapy, and Psychosomatics, University Hospital of Psychiatry, University of Zurich, Zurich, Switzerland

[3]ZInEP, The Zurich Program for Sustainable Development of Mental Health Services, University of Zurich, Zurich, Switzerland

[4]Department of Medicine, Internal Medicine, University Hospital of Lausanne, Switzerland

[5]Department of Psychiatry, University Hospital of Lausanne, Lausanne, Switzerland

*Corresponding author

roselind.lieb@unibas.ch (RL)

Abstract

Objective: Specific phobia is the most prevalent anxiety disorder in the community and is associated with substantial impairment. Comorbidity with physical diseases is assumed and may provide information about possible etiological mechanisms. However, data are limited due to methodological issues, and subtypes have not been investigated yet. We examined the association of specific phobia and its subtypes with physical diseases in a representative community sample with physician-diagnosed physical diseases and diagnostic criteria of specific phobia.

Method: We used data of the German Mental Health Survey from 4,181 subjects aged 18–65 years. Specific phobia was diagnosed using M-CIDI/DIA-X interview; physical diseases were assessed through a self-report questionnaire and a medical interview. Logistic regression analyses adjusted for sex were calculated.

Results: Specific phobia was associated with cardiac diseases, gastrointestinal diseases, respiratory diseases, arthritic conditions, migraine, and thyroid diseases (odds ratios between 1.49 and 2.53). Among the subtypes, different patterns of associations with physical diseases were found. The findings were partially replicated in the Swiss PsyCoLaus Study.

Conclusions: From our findings etiological mechanisms of specific phobia and physical disease can be deduced. As subtypes differed in their patterns of associations with physical diseases, different etiological mechanisms may play a role.

Key words: specific phobia, comorbidity, physical diseases, representative survey

Introduction

Specific phobia is the most prevalent anxiety disorder in the community [1,2]. It is associated with significant impairment and distress [3] and with a loss of work days [4]. Further, specific phobia is a predictor for increased suicidal tendency [5] and it is thought to be a risk factor for the later development of other mental disorders such as major depression [6,7] or anxiety disorders [8]. Additionally, specific phobia is highly comorbid with other mental disorders, especially with anxiety disorders and mood disorders [9,10].

Research has suggested that besides being comorbid with other mental disorders, specific phobia may be highly comorbid with physical diseases, too. Having any anxiety disorder during the last year has been associated with neurological, vascular, respiratory, gastrointestinal, metabolic, bone, and infectious diseases [11-14]. Further, a longitudinal analysis showed that self-reported gastrointestinal disease predicted the onset of specific phobia in older adults during the next three years [15]. Subjects with coronary heart disease reported elevated levels of phobic anxiety [16] and phobic anxiety is associated with cardiac mortality [17]. Among men with high levels of phobic anxiety, an increased prevalence rate of Parkinson's disease was found compared to men with low levels of phobic anxiety [18]. Further, a review revealed that subjects with chronic obstructive pulmonary disease reported a prevalence of 10–17% of specific phobia [19]. Community studies in addition found an association between specific phobia and migraine [20], respiratory diseases [11], ulcer [21], vascular diseases [22] and heart diseases [23].

Most research has suggested a link between specific phobia and physical diseases. However, there are methodological issues that limit the generalizability of the findings. First, not all studies used *Diagnostic and Statistical Manual of Mental Disorders (DSM)* [24] or *International Classification of Diseases* (*ICD*) [25] diagnostic criteria of specific phobia. Second, the physical diseases were mainly assessed by self-report rather than diagnosed by a

physician. Third, most studies focused on one specific physical disease and therefore provide limited information on the association with different physical diseases.

Knowledge of the comorbidity of specific phobia and physical diseases could influence research on the etiology of both physical diseases and specific phobia through the detection of possible etiological mechanisms. It is also relevant because some studies have suggested that anxiety can complicate the treatment of chronic medical diseases and may therefore be associated with worse treatment outcomes [26,27].

To the best of our knowledge, no study has evaluated the association between subtypes of specific phobia and physical diseases. This comorbidity might differ, given that the different subtypes of specific phobia show different comorbidity patterns with other mental disorders [28-30]: Youths with natural phobias reported more depressive symptoms and showed higher prevalence rates of other anxiety disorders than youths with animal phobias [31]; situational phobia was associated with more panic attacks than other specific phobia subtypes [30]; and individuals with blood-injection phobia had a higher prevalence of marijuana abuse, depression, panic disorder, obsessive-compulsive disorder, or social phobia compared to individuals without blood-injection phobia [30,32,33]. Further, some evidence suggests physical discrepancies among subtypes of specific phobia. Subjects with different subtypes differ in their physiological fear response [30]: Blood-injection phobia is associated with vasovagal fainting, whereas other phobias are not [32]. Differences in the neural response patterns between blood-injection phobia and animal phobia have been suggested, too [34,35]. Additionally, subjects with natural environment phobia reported more somatic symptoms than subjects with animal phobia [31]. The comorbidity pattern of subtypes of specific phobia and physical diseases could be similarly different. Analyses addressing similarities and differences among specific phobia subtypes are important to elucidate potential etiological pathways. However, no study to date has analyzed the association between subtypes of specific phobia and physical diseases.

Aims of the Study

The aim of our study therefore was to analyze the association of *DSM-IV* specific phobia and its subtypes and a broad range of physical diseases in the German Health Interview and Examination Survey, Mental Health Supplement (GHS-MHS). We addressed the methodological limitations reported above by using a wide range of physician-diagnosed physical diseases and specific phobia assessed by a well-validated structured interview. Further, we aim to replicate the findings in a separate data set, the baseline investigation of the PsyCoLaus Study.

Materials and Methods

Design and Sample of the GHS-MHS

The GHS-MHS, conducted in 1997, was the first nationwide cross-sectional study for medical and social assessments in Germany. The GHS-MHS was commissioned by the German Ministry of Science, Research and Education and approved by the relevant institutional review board of the Robert Koch Institute (Berlin, Germany). The aim of the core study was the assessment of sociodemographic characteristics, physical diseases, impairments, and health-care utilization in a representative community sample of 7,124 subjects ages 18–79 years (overall response rate 61.5%). The sample was stratified and randomized from 113 communities throughout Germany with 130 sampling units (step 1: selection of communities, step 2: selection of sampling units, step 3: selection of inhabitants) [2,36]. The data were weighted and confidence intervals were calculated by the Huber–White sandwich method to account for the weighting scheme as well as the stratified sampling design [36].

Mental disorders were assessed in a two-stage design: The first stage entailed the administration of a 12-item screening questionnaire for mental disorders at the end of the

medical examination of the core survey (the Composite International Diagnostic Screener) [37]. The second stage involved the administration of a structured psychopathological interview, the Munich Composite International Diagnostic Interview (DIA-X/M-CIDI) to all core survey respondents who had been screened positive for a mental disorder and to a random sample of 50% who screened negative [37]. This subsample of the GHS is the sample of the Mental Health Supplement and included 4,181 subjects aged 18–65 years. The M-CIDI interview was completed by 87.6% of the subjects (conditional response rate). All subjects gave their written informed consent. Further descriptions of aims, design, and methods as well as sociodemographic characteristics of the whole GHS-MHS sample can be found elsewhere [36].

Specific Phobia in the GHS-MHS

The fully structured DIA-X/M-CIDI interview was used for the diagnostic assessments in the GHS-MHS [38] covering both *DSM-IV* and *ICD-10* criteria. Through the structured interview symptoms, syndromes, onset, duration and severity were assessed. Trained psychologists and physicians conducted the interview [36]. The DIA-X/M-CIDI diagnostic algorithms were used to obtain the diagnostic findings reported in this paper [39]. There was substantial test–retest reliability (kappa values between 0.56 and 0.81) [40]; the sensitivity of the DIA-X/M-CIDI diagnoses ranges from 87.5% to 100%, their specificity from 71.2% to 100% [41]. The validity of the full diagnoses ranges from moderate to excellent when compared to diagnoses made by independent treating physicians in a sample of randomly chosen patients [41].

We used the 12-month *DSM-IV* diagnosis of specific phobia. Additionally, the 12-month diagnoses of the following subtypes of specific phobia were used: the animal subtype (referring to fear related to insects, snakes, birds, or other animals), the natural subtype (referring to fear related to height, storm, water), the blood-injection subtype (referring to fear related to seeing blood, injection, going to the dentist or hospital), the situational subtype

(referring to flying in a plane, being in a small closed room, in a cellar, tunnel, or elevator), and the other subtype (referring to any other specific fear not matching any other subtype).

Physical Diseases in the GHS-MHS

Physical diseases were assessed by a self-report questionnaire and a standardized computer-assisted medical interview by a general practice physician. Using the information on physical diseases in the self-report questionnaire, the physician collected data on lifetime prevalence, 12-month prevalence, and point prevalence (4 weeks) of 44 physical diseases [36]. Blood pressure and anthropometric measurements were conducted and blood and urine samples were collected. Diagnoses were then supplemented and revised based on these laboratory analyses [36]. The present analyses are based on the physicians' diagnoses during the medical interview.

Replication Study

Design and Sample of the PsyCoLaus Study

As a replication study, we used the baseline investigation of the CoLaus/PsyCoLaus cohort study [42,43]. CoLaus/PsyCoLaus conducted in Lausanne, Switzerland, was designed to study mental disorders and cardiovascular risk factors in the general population. The subjects aged 35-75 years were randomly selected through the population register of the city of Lausanne. All participants of the somatic investigation (CoLaus) aged between 35 and 66 years were asked to also undergo a comprehensive psychiatric evaluation (PsyCoLaus), resulting in a subsample of 3720 subjects (response rate: 67%) [43]. The psychiatric assessment took place between 2004 and 2008.

Specific Phobia in the PsyCoLaus Study

The psychiatric evaluation in PsyCoLaus was based on the French version of the semi-structured Diagnostic Interview for Genetic Studies (DIGS; [44,45]), which elicits DSM-IV axis I criteria and suicidal behavior and extensive information on the course and chronology

of comorbid conditions. As the phobia section of the original DIGS interview was brief [45] it was replaced by the chapter from the semi-structured Schedule for Affective Disorders and Schizophrenia – Lifetime Version (SADS-LA) [46,47]. The semi-structured interview revealed excellent inter-rater and fair to good test-retest reliability for major mood and psychotic disorders [48,49]. Regarding anxiety disorders, applying the French translation of the SADS-LA, Leboyer et al. [45] found satisfactory test-retest reliability (mean interval 3.2 months) for panic disorder/agoraphobia (Yule's Y = 0.43), GAD (Yule's Y = 0.61) and phobic disorders (Yule's Y = 0.66). The Yule coefficient for the overall category of anxiety disorders was 0.49. Our own reliability study [49], based on a sample of 136 patients who also completed the combined DIGS – SADS-LA section for specific anxiety disorders, revealed perfect inter-rater agreement for all specific anxiety disorders except for agoraphobia (Yule's Y = 0.96). The Yule's Y coefficients for the 6-week test-retest reliability were 0.58 for panic disorder, 0.55 for agoraphobia, 0.44 for social phobia, 0.77 for specific phobia and 0.64 for OCD. Regarding GAD, no test-retest agreement was obtained.

During the interview, the subjects were asked if they had experienced symptoms of anxiety during certain situations related to the *DSM-IV* subtypes of specific phobia during their lifetime (e.g. “Did you feel anxious when you were flying in a plane?” or “Did you feel anxious when you were facing a certain animal?”). Subtypes were then derived from the information collected during the interview. For our analyses, the following subtypes were created based on *DSM-IV* criteria (comparable to those of the GHS-MHS): animal, natural, situational, blood-injection and the other subtype. As the ages of onset and offset of each disorder were assessed, 12 month prevalence of specific phobia and its subtypes could be established.

Physical Diseases in the PsyCoLaus Study

Cardiovascular and metabolic diseases were assessed during the physical CoLaus evaluation through a medical interview, physical examinations and blood and urine tests. Moreover, in the medical part of the DIGS interview during the psychiatric evaluation information was collected on additional physical lifetime diseases.

For the present analyses, we used data from the CoLaus and PsyCoLaus Studies. Cardiac diseases and vascular diseases were diagnosed during the CoLaus Study by an adjudication committee according to the latest diagnostic criteria, and diagnoses of hypertension and diabetes were based on measurements of blood pressure and fasting glucose [42]. For the other groups of diseases data stemmed from the medical part of the psychiatric interview. To enable comparison with the GHS-MHS, the same groups of physical diseases were built. However, in the groups of cardiac diseases, arthritic conditions and vascular diseases not all or different physical diseases were assessed among these groups in both studies (as indicated in table 1). The Ethics Committee of the University of Lausanne approved both the physical (CoLaus) and psychiatric (PsyCoLaus Study) evaluation. All subjects gave their written informed consent [43].

Statistical Analyses

Logistic regression analyses were used to evaluate the association of specific phobia and physical diseases in both the GHS-MHS and the PsyCoLaus Study (specific phobia as predictor, physical diseases as outcome). As specific phobia and physical diseases were both associated with sex, the associations were controlled for sex. We considered a p value <0.05 as statistically significant. The analyses in the GHS-MHS study were carried out using STATA 11.0 [50]. The analyses in the PsyCoLaus Study were carried out using SPSS version 20 [51].

Results

The 12-Month Prevalence of Specific Phobia and Physical Diseases in the GHS-MHS

In the GHS-MHS, the 12-month prevalence of specific phobia was 7.6%, as shown in Table 1. The most prevalent subtype of specific phobia was the situational subtype (1.8%), and the other subtype was the least prevalent (0.08%). The most prevalent physical diseases were arthritic conditions with a 12-month prevalence of 25.9%, followed by allergies (18.1%). The least prevalent physical diseases were neurological diseases (0.5%).

Association Between Specific Phobia and Physical Diseases in the GHS-MHS

As shown in Table 2, having any specific phobia was associated with cardiac diseases, gastrointestinal diseases, respiratory diseases, arthritic conditions, migraine, and thyroid diseases (odds ratios [ORs] ranging between 1.49, 95% CI [1.15–1.92], for arthritic conditions and 2.53, CI [1.73–3.69], for gastrointestinal diseases). Additionally, having any specific phobia was associated with any physical disease (OR=1.87, [1.30–2.68]).

Among subtypes, the situational subtype was associated with the most (4 of 10) physical diseases, whereas only one association was found between the natural subtype (migraine, OR=2.40, 95% CI [1.29–4.45]) and the blood-injection subtype (respiratory diseases, OR=2.14, 95% CI [1.05–4.36]) and physical diseases. Gastrointestinal diseases, respiratory diseases, migraine, and thyroid diseases were all associated with two subtypes.

Replication Analysis

In the CoLaus/PsyCoLaus Study, any specific phobia was associated with gastrointestinal, respiratory, arthritic conditions, allergic diseases and migraine (ORs ranging between 1.30, 95% CI [1.04–1.63], for arthritic conditions and 1.68, 95% CI [1.33–2.13], for

migraine). Further, having any specific phobia was associated with having any physical disease (OR=1.34, 95% CI [1.07–1.68]).

Among subtypes, the animal and natural subtype were associated with respiratory diseases (animal: OR=1.62, 95%CI [1.02–2.55]; natural: OR=2.36, 95%CI [1.16–4.82]) and migraine (animal: OR=1.71, 95% CI [1.09–2.69]; natural: OR=2.38, 95%CI [1.16–4.85]). Additionally, the natural subtype was associated with having any physical disease (OR=3.03, 95% CI [1.06–8.57]; No other associations were found between subtypes of specific phobia and physical diseases in the PsyCoLaus Study. Results of the PsyCoLaus data are available on request.

Discussion

The aim of our study was to determine the association between specific phobia and its subtypes and physical diseases in a general population sample to extend information from earlier studies by using improved methods (physician-diagnosed physical diseases, standardized diagnostics of specific phobia, a wide range of physical diseases assessed within one sample). Our study suggests an association of specific phobia and several physical diseases in the community. In line with earlier studies, we found an association between specific phobia and respiratory diseases [11,52], heart diseases [16,17], vascular diseases [22] and cardiac diseases [23]. An association with gastrointestinal diseases has also been found, but in comparison to our study the association did not remain significant after adjusting for sex [15]. Additionally, we found an association between specific phobia and arthritic conditions, migraine, and thyroid diseases. We could replicate the associations between any specific phobia and gastrointestinal diseases, respiratory diseases, arthritic conditions and migraine in the PsyCoLaus Study. Associations with these physical diseases have already been documented within the GHS-MHS for the group of anxiety disorders [11].

As this is cross-sectional data, the temporal sequence of specific phobia and physical diseases cannot be determined and different models can be considered for the explanation of the comorbidity (specific phobia may be an antecedent or a consequent factor of a specific physical disease; there may be common biological or social factors that increase the risk of having both specific phobia and physical diseases; or a third variable may contribute to the comorbidity through an indirect mechanism). Even though the temporal sequence cannot be determined, these analyses can contribute to the deduction of possible etiological pathways of both specific phobia and physical diseases.

It has been suggested that certain pathophysiological mechanisms related to affective and anxiety disorders, such as sympathoadrenal hyperactivity, reduced heart-rate variability, heightened platelet activity, and endothelial dysfunction, may be of interest in the etiology of heart diseases, too [23]. Additionally, ventricular arrhythmia and hyperventilation causing coronary spasm have been named as possible mechanisms by which phobic anxiety and therefore specific phobia cause coronary heart disease [16,53].

As a plausible explanation for the comorbidity of gastrointestinal and anxiety disorders it has been suggested that the pain or functional limitation of gastrointestinal disease could lead to increased feelings of anxiety [54] or that anxiety could lead to an irritation of the gastrointestinal system, leading to a gastrointestinal disease [54]. It has also been shown that the neurotransmitter serotonin, which is implicated in anxiety disorders in general and specifically in specific phobia [55], is also known to affect the gastrointestinal system [56].

Asthma may, on the one hand, increase the level of anxiety because asthma can be a life-threatening condition [52]. Presuming a vulnerability-stress model [57], the probability for the development of an anxiety disorder such as specific phobia may increase through such a stressful condition. On the other hand, it has been shown that asthma medications have some anxiogenic properties [52,58] and it could be that subjects with high levels of anxiety

overuse these medications and this may lead to exacerbation of the anxiety symptoms and therefore to a full diagnosis of specific phobia.

Arthritic conditions have mainly been associated with depression, but anxiety disorders seem to be rather common in subjects with arthritis, too [59]. It has been reported that subjects with arthritic conditions may restrict their physical activity and therefore increase their risk for a mental disorder such as specific phobia [60]. Further, certain cytokines that increase during the treatment of arthritic conditions may be associated with mental disorders [60], and a decrease in immunoglobulins may be associated with anxiety [60].

Several studies have discussed the association of migraine and psychopathology [20,61,62]. Psychosocial factors related to stress and therefore specific phobia can act as a trigger for migraine [20]. Additionally, a diminished serotonin level, which is also associated with anxiety disorders, has been detected in subjects with migraine [61]. Further, psychosocial factors such as avoidance of certain situations that trigger migraine may increase the anxiety sensitivity [61].

An increased rate of subjects with specific phobia has been documented in thyroid disease compared to subjects in the general population [63,64]. However, studies on possible common pathways are lacking. Common neurochemical abnormalities have been identified as a possible link between anxiety and thyroid disease [63].

Beside the association between specific phobia and physical diseases, different patterns of associations between the subtypes of specific phobia and physical diseases have been detected. Most associations were found between the situational subtype and physical diseases. This is in line with a finding from an earlier study that situational phobia has higher rates of comorbid psychopathology than animal and natural phobias [65]. Another study found more somatic symptoms in subjects with natural phobia compared to subjects with

animal phobia [31], which might suggest a somatic vulnerability of the natural subtype. In our study, however, the natural subtype was only associated with one physical disease.

The different patterns of associations between the subtypes and physical diseases may point toward different etiological mechanisms that need to be addressed in future studies. As blood-injection phobia is—alone of the subtypes—associated with vasovagal fainting [30], it could be, for instance, that people with this phobia profit from their rather low blood pressure, leading to a reduction of their risk for certain physical ailments, such as cardiovascular diseases or hypertension.

The current study has a number of limitations. First, the subjects assessed were between 18 and 65 years of age. Therefore the results cannot be generalized to younger or older subjects. Second, some diagnoses may rely more on self-report data (e.g. arthritis) than other (e.g. diabetes) [11]. This could lead to over-reporting of certain symptoms in subjects with specific phobia. Third, no conclusions concerning the causal nature of the associations between specific phobia and physical diseases can be drawn. Fourth, although the sample size is 4,181 subjects, the combination of physical diseases and specific phobia led to relatively small cell sizes, especially in the subtype analyses in the GHS-MHS. Fifth, the comparability of the GHS-MHS and PsyCoLaus study was limited with respect to methodology used and data collected, as different timeframes (12 months vs. lifetime diagnosis of physical diseases) and different age ranges of subjects (18–65 vs. 35–66 years) were used. Further, not all physical diseases were assessed in both studies. Accordingly, it was not surprising that the results from the GHS-MHS study could be partially replicated. Several associations were only observed in the GHS-MHS study, which could be attributable to the younger age of the sample. Indeed, in the older CoLaus/PsyCoLaus sample the prevalence of almost all physical diseases was considerably higher than in the GHS-MHS study and it is therefore possible that an increased number of age related factors predisposing to these diseases could have blurred their association with specific phobia in CoLaus/PsyCoLaus.

Despite these limitations, our study shows that specific phobia is highly comorbid with different physical diseases. Moreover, the different subtypes show different patterns of comorbidity with physical diseases in a community sample.

The comorbidity of specific phobia and physical diseases has been rarely evaluated until now. However, the findings in our community sample support the importance of further research within this field, as the comorbidity may influence the burden of subjects affected and treatment outcome.

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Tables

Table 1. Frequency of Specific Phobia and Its Subtypes and Physical Diseases in the GHS-MHS (12 Months) and the PsyCoLaus Study (12 Months for Specific Phobia and Lifetime for Physical Diseases).

Phobia/Disease	GHS-MHS		PsyCoLaus	
	No.	%	No.	%
Any specific phobia[a]	388	7.6	518	13.9
Subtypes[b]				
Animal subtype	68	1.5	112	3.0
Natural subtype	75	1.4	37	1.0
Blood-injection subtype	64	1.5	18	0.5
Situational subtype	89	1.8	48	1.3
Other subtype	3	0.08	10	0.3
Hypertension	581	13.1	1,110	29.8
Cardiac diseases (heart circulation disturbances, narrowing of the coronary vessels, angina pectoris, cardiac infarct, heart weakness, heart insufficiency)[c]	100	2.2	199	5.3
Respiratory diseases (asthma, chronic bronchitis)	284	7.0	572	15.3
Gastrointestinal diseases (ulcer, gastritis)	268	6.3	252	6.7
Diabetes (with or without insulin treatment)	115	2.7	194	5.2
Arthritic conditions (wear and tear type, inflammatory diseases of the joints)[d]	1,107	25.9	773	20.8
Allergies (hay fever, allergic eczema, allergic hives, neurodermatitis, food allergy, allergic conjunctivitis)	747	18.1	1,018	27.3
Migraine headaches	491	10.3	562	15.2
Neurological diseases (epilepsy, Parkinson's disease, multiple sclerosis)	27	0.5	94	2.5
Thyroid diseases	445	10.0	164	4.4
Vascular diseases (stroke, brain circulation disturbance, leg circulation disturbance, artery occlusion, varicose veins, vein thrombosis)[e]	536	12.4	303	8.2

Note. No.: Unweighted number of subjects; %: Percentage (in the GHS-MHS: weighted percentage); GHS-MHS: German Health Survey, Mental Health Supplement [a]Including animal, natural, blood-injection, situational, or any other subtype. [b]subjects did not fulfill the criteria of any other subtype. [c]In the PsyCoLaus Study: coronary artery disease, angina, myocardial infarct, percutaneous coronary intervention, coronary artery bypass graft, pacing, heart failure, valvular heart disease, cardiomyopathy. [d]In the PsyCoLaus Study: rheumatoid arthritis, osteoarthritis, arthritis. [e]In the PsyCoLaus Study: arrhythmia, stroke, peripheral artery diseas

Table 2. Odds Ratios and Confidence Intervals of Physical Diseases (12 Months) for Specific Phobia and Its Subtypes (12 Months) Compared to a Reference Group That Had no Specific Phobia During the past 12 Months in the German Health Survey – Mental Health Supplement (N=4,181).

Phobia	**Physical disease**											
	Hypertension (*n*=581)	**Cardiac diseases** (*n*=100)	**Gastro-intestinal diseases** (*n*=268)	**Respiratory diseases** (*n*=284)	**Diabetes** (*n*=115)	**Arthritic conditions** (*n*=1,107)	**Allergies** (*n*=747)	**Migraine** (*n*=491)	**Neurological diseases** (*n*=27)	**Thyroid diseases** (*n*=445)	**Vascular diseases** (*n*=536)	**Any physical disease** (*n*=2,602)
Any specific phobia (*n*=388)	1.22 (0.88–1.67) (*n*=69)	1.94 (1.05–3.57)* (*n*=16)	2.53 (1.73–3.69)* (*n*=47)	2.20 (1.52–3.16)* (*n*=49)	1.26 (0.63–2.51) (*n*=12)	1.49 (1.15–1.92)* (*n*=131)	1.29 (0.94–1.76) (*n*=80)	1.99 (1.47–2.69)* (*n*=78)	0.68 (0.09–4.95) (*n*=1)	1.72 (1.24–2.37)* (*n*=69)	1.17 (0.83–1.65) (*n*=62)	1.87 (1.30–2.68)* (*n*=289)
Animal subtype[a] (*n*=68)	0.88 (0.39–1.97) (*n*=8)	2.76 (0.82–9.17) (*n*=3)	3.53 (1.73–7.19)* (*n*=14)	2.52 (1.10–5.76)* (*n*=8)	1.92 (0.45–8.15) (*n*=2)	0.93 (0.48–1.78) (*n*=15)	2.02 (1.008–4.05)* (*n*=18)	1.54 (0.79–2.99) (*n*=13)	4.07 (0.52–31.37) (*n*=1)	1.44 (0.73–2.86) (*n*=13)	1.04 (0.49–2.20) (*n*=10)	1.24 (0.53-2.87) (*n*=48)
Natural subtype[a] (*n*=75)	1.45 (0.75–2.80) (*n*=15)	2.28 (0.76–6.87) (*n*=4)	2.53 (0.99–6.41) (*n*=6)	1.66 (0.62–4.38) (*n*=6)	0.86 (0.19-3.81) (*n*=2)	1.55 (0.90–2.65) (*n*=26)	1.28 (0.61–2.65) (*n*=13)	2.40 (1.29–4.45)* (*n*=17)	-[1]	1.41 (0.70–2.80) (*n*=13)	1.74 (0.89–3.40) (*n*=16)	2.02 (0.99–4.09) (*n*=58)
Blood-injection subtype[a] (*n*=63)	0.89 (0.38–2.06) (*n*=8)	2.05 (0.47–8.80) (*n*=2)	2.20 (0.89–5.39) (*n*=6)	2.14 (1.05-4.36)* (*n*=10)	1.03 (0.14–7.49) (*n*=1)	1.25 (0.68–2.25) (*n*=19)	0.84 (0.40–1.73) (*n*=9)	1.60 (0.71–3.55) (*n*=8)	-[1]	1.56 (0.64–3.73) (*n*=7)	0.75 (0.30–1.85) (*n*=6)	0.99 (0.50–1.95) (*n*=35)
Situational subtype[a] (*n*=88)	1.49 (0.86–2.56) (*n*=22)	1.81 (0.64–5.14) (*n*=5)	2.35 (1.14–4.85)* (*n*=10)	1.63 (0.77–3.44) (*n*=9)	1.17 (0.40–3.44) (*n*=4)	1.82 (1.12–2.93)* (*n*=34)	0.84 (0.46-1.52) (n=17)	2.08 (1.16–3.70)* (*n*=18)	-[1]	2.55 (1.42–4.57)* (*n*=21)	0.71 (0.36–1.37) (*n*=13)	1.70 (0.76-3.80) (*n*=69)
Other[a] (*n*=3)	-[1]	-[1]	-[1]	-[1]	-[1]	-[1]	-[1]	-[1]	-[1]	29.91 (2.36-378.42)* (*n*=2)	-[1]	1.55 (0.12–19.62) (*n*=2)

Note. CI confidence interval, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; *NOS* not other specified, *OR* Odds Ratio, *n* unweighted number of subjects, *%* weighted percentage, adjusted for sex.

* $p<0.05$, [1]empty cell size, [a] Subjects did not fulfill the criteria of any other subtype

Appendix C

Comorbidity of infectious diseases and anxiety disorder in adults and its association with quality of life: a community study

Cornelia Witthauer, Andrew T. Gloster, Andrea Hans Meyer, Renee D. Goodwin, and Roselind Lieb

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Comorbidity of infectious diseases and anxiety disorders in adults and its association with quality of life: a community study

Cornelia Witthauer[1], *Andrew T. Gloster*[1], *Andrea Hans Meyer*[1], *Renee D. Goodwin*[2,3] *and Roselind Lieb*[1]*

[1] *Department of Psychology, Division of Clinical Psychology and Epidemiology, University of Basel, Basel, Switzerland*
[2] *Department of Psychology, Queens College and The Graduate Center, City University of New York, New York, NY, USA*
[3] *Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA*

Edited by:
Alexandre Andrade Loch, University of São Paulo, Brazil

Reviewed by:
Erica Toledo Piza Peluso, Universidade Bandeirante Anhanguera, Brazil
Ivan Aprahamian, University of São Paulo, Brazil

***Correspondence:**
Roselind Lieb, Department of Psychology, Division of Clinical Psychology and Epidemiology, University of Basel, Missionsstrasse 62a, 4055 Basel, Switzerland
e-mail: roselind.lieb@unibas.ch

Objective: Infectious diseases and anxiety disorders are common and both are associated with substantial burden to individual, families, and society. A better understanding of their association may be helpful in explicating possible etiological mechanisms related to both. The goal of the current study was to investigate the relationship between specific infectious diseases and anxiety disorders among adults in the community, and to examine whether the co-occurrence of the two is associated with poorer quality of life compared to subjects with one or neither condition.

Methods: We used data from the 1998 German Mental Health survey with 4181 subjects aged 18–65. Various infectious diseases (lifetime) and health-related quality of life were assessed via self-report questionnaires and anxiety disorders (past 12-months) were diagnosed using M-CIDI interviews. Logistic regression analyses were used to evaluate the association between infectious diseases and anxiety disorders; a linear model adjusted for sex was used to examine whether comorbidity of infectious diseases and anxiety disorders was associated with quality of life.

Results: Whooping cough [odds ratio (OR) = 1.69, 95% confidence intervals (CI) = 1.36–2.09], scarlet fever (OR = 1.31, 95% CI = 1.02–1.68), and diphtheria (OR = 1.79, 95% CI = 1.21–2.64) were associated with increased prevalence of any anxiety disorder. Subjects with both infectious diseases and anxiety disorders reported lower levels of both mental and physical quality of life, compared with subjects with only one or neither condition.

Conclusion: Extending prior research, this study suggests a relationship between specific infectious diseases and anxiety disorders in an adult community sample. Research targeting etiological mechanisms related to the interplay between infectious diseases and anxiety disorders is warranted.

Keywords: representative survey, anxiety disorder, comorbidity, infectious diseases, quality of life

INTRODUCTION

Approximately 26% of the total global burden of disease is attributable to infectious diseases (1). Studies have also revealed that mental disorders are a leading contributor to the total all cause burden of disease worldwide (2, 3). Such rates render the refined understanding, treatment, and prevention of both infectious disease and mental disorders as important public health goals. Toward this end, it is crucial to understand etiological pathways involved in disease and associated burden. Importantly, increasing evidence points to associations between some infectious diseases and mental disorders that may hint at overlapping etiologic pathways.

Major depressive disorder is associated with streptococcal infections (4). Further, severe infections such as hepatitis infections or sepsis infections are associated with subsequent mood disorder diagnosis in a longitudinal study (5). In addition, studies have shown that pre-natal exposure to viruses increases the offsprings risk of unipolar affective disorder (6). Due to the association of infectious diseases and affective disorders, there have been efforts to detect potential etiological mechanisms related to both infectious diseases and affective disorders (7, 8).

While much is known about infectious disease and mood disorders, relatively little has been done to investigating the possibly link between infectious disease and anxiety disorders. Some research findings suggest that infectious diseases could be related to the development of specific anxiety disorders. Among infectious diseases, childhood group A streptococcal infections appear to be associated with obsessive–compulsive disorder and/or tic disorders (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection or PANDAS) (9) based on the results of several studies. Other studies have found increased prevalence rates of posttraumatic stress disorder in HIV positive subjects across different demographic, cultural, and socioeconomic

backgrounds (10). Additionally, anxiety disorders are associated with inflammatory markers such as C-reactive protein in men (11) and were found to be associated with having experienced a common cold during the last 12 months compared to subjects without (12). Furthermore, it was found that in older subjects with cytomegalovirus (CMV) antibodies, individuals with higher CMV specific antibody titers were more likely to be anxious than subject with lower CMV antibodies (13). A cross-sectional study looking at the association of infections in the first year of life (reported by the parents) and anxiety disorders found that there is an association between having any infection during the first year of life and anxiety disorders (14). However, no differentiation was made between different types of infections in this study. Additionally, very small cell sizes prohibited more informative analyses (14). No prior study has examined the relationship between anxiety disorders and specific infectious disease among adults in the community.

Additionally, research has shown that the comorbidity of anxiety disorders and physical health problems such as chronic physical diseases is related to a decrease in health-related quality of life (15). To date, no study has investigated whether the comorbidity between infectious diseases and anxiety disorders is associated with an excess loss of health-related quality of life.

The goal of the current study was to investigate the relationship between infectious diseases and anxiety disorders in a larger cross-sectional sample of adults in the community. We also investigated whether comorbidity of anxiety disorders and infectious disease is associated with an excess loss of health-related quality of life.

MATERIALS AND METHODS

DESIGN AND SAMPLE

Data were drawn from the German Health Interview and Examination Survey and its Mental Health Supplement (GHS-MHS) conducted in 1997. The German Health Survey (GHS) was the first nationwide cross-sectional study for medical and social assessments in Germany, commissioned by the German Ministry of Science, Research and Education, and the Robert Koch Institute and authorized by the relevant institutional review board and ethics committee. The aim of the core study was the assessment of sociodemographic characteristics, physical diseases, impairments, and healthcare utilization in a representative community sample of 7124 subjects aged 18–79 (Overall Response Rate: 61.5%). It was a stratified, randomized sample from 113 communities throughout Germany with 130 sampling units (sampling steps: 1: selection of communities, 2: selection of sampling units, 3: selection of inhabitants) (16, 17). To handle the stratified sampling design the data were weighted and confidence intervals (CI) were calculated by the Huber–White sandwich method to account for the weighting scheme as well as the stratified sampling design (16).

For the assessment of mental disorders in the GHS-MHS a two-stage design was used: The first stage entailed the administration of a 12-item screening questionnaire for mental disorders at the end of the medical examination of the core survey (CID-S) (18). The second stage involved the administration of a structured psychopathological interview, the Munich Composite International Diagnostic Interview (DIA-X/M-CIDI) to all core survey respondents who had been screened positive for a mental disorder and to a random sample of 50% who screened negative (18). This subsample of the GHS built the sample of the Mental Health Supplement and included 4181 subjects aged 18–65 years. The conditional response rate (i.e., subjects who completed the M-CIDI interview) was 87.6%. All participants gave their informed consent. Further description of aims, design, and methods as well as sociodemographic characteristics of the whole GHS-MHS sample can be found elsewhere (16).

MEASURES

Mental disorders

For the diagnostic assessments, a modified version of the fully structured interview DIA-X/M-CIDI was used (19). The questions cover DSM-IV and ICD-10 criteria. The DIA-X interview enables the assessments of symptoms, syndromes and onset, duration, and severity. The interview was conducted by trained psychologists and physicians (20). The DIA-X/M-CIDI diagnostic algorithms were used to obtain diagnostic findings reported in this paper (21). The test–retest reliability of the DIA-X/M-CIDI was substantial (kappa values ranging between 0.56 and 0.81) (20) and the sensitivity of the DIA-X/M-CIDI diagnoses ranges from 87.5 to 100%; and their specificity from 71.2 to 100% (22). Analyses revealed that the validity of the full diagnoses ranges from moderate to excellent when compared to diagnoses administered from independent treating physicians in a sample of randomly chosen patients (22).

The present study used the following 12-months DSM-IV mental disorders: agoraphobia, social phobia, specific phobia (animal, natural environment, blood–injection–injury, situational type), panic disorder, generalized anxiety disorder, and obsessive–compulsive disorder. We also included panic attacks during the last 12 months.

Infectious diseases

Subjects were queried via a paper–pencil questionnaire: "which of the following infectious diseases did you have during your lifetime: diphtheria, whooping cough, measles, mumps, rubella, chicken pox, scarlet fever, tuberculosis, dysentery, or typhus?"

Quality of life

We used the German version (23) of the well-validated (24–26) SF-36 quality of life questionnaire. The SF-36 assesses health-related quality in eight dimensions during the past 30 days (physical functioning, social functioning, role limitations due to physical problems, bodily pain, mental health, role limitations due to emotional problems, vitality, and general health). Principal component analysis revealed two robust factor dimensions of physical and mental health: the Physical Component Score (PCS) and the Mental Component Score (MCS) (27).

STATISTICAL ANALYSES

Association between infectious diseases and anxiety disorders

We used logistic regression analyses [odds ratio (OR) with 95% CI] to examine associations between infectious diseases (yes/no, the predictors in the model) and anxiety disorders (yes/no, the outcome in the model). We considered a p value <0.05 as statistically significant. As the analyses revealed that there was an association between both anxiety disorders and infectious diseases and sex

the models were controlled for sex. We additionally built a variable called any anxiety disorder, which includes any of the anxiety disorders. As we had additional lifetime information for panic disorder and panic attacks, we checked for an association of these variables with infectious diseases.

We further tested whether subjects with one or more than one anxiety disorder report more infectious diseases than subjects without any anxiety disorder. As the assumptions (homoscedasticity and normality) were fulfilled, we set up a linear model with the number of anxiety disorders (three categories: none, one, and more than one disorder) as independent variable and the mean number of infectious diseases (ranging from zero to nine) as dependent variable. In all analyses, sex was included as covariate. For all analyses, we used the STATA software package, version 11.0 (28).

Association between comorbidity and quality of life

To analyze the association between anxiety disorders and infectious diseases and quality of life we used the two variables anxiety disorder (including any of the anxiety disorder) and infections (including any of the infectious diseases), both having two levels (yes/no). We combined these two variables and built a factor with four levels: one level with subjects with no infection and no anxiety disorder, one with only infection and no anxiety disorder, one with no infection but with anxiety disorder, and one level with both anxiety disorder and infection. To examine the association between this factor and the dependent variable, the PCS and MCS of the SF-36, we used a linear model with sex as covariate. For all analyses, we used the STATA software package, version 11.0 (28).

RESULTS

ASSOCIATION OF INFECTIOUS DISEASES AND ANXIETY DISORDERS

As shown in **Table 1**, most associations (five out of nine) were found between whooping cough and 12-month anxiety disorders [ORs ranging from 1.52 (95% CI = 1.15–2.00) for simple phobia to 2.15 (95% CI = 1.36–3.40) for agoraphobia without panic disorder]. The associations between measles, rubella, chicken pox, and anxiety disorders were not significant. Additionally, most infectious diseases (4 out of 10) were associated with agoraphobia without panic disorder (ORs ranging from 1.79 (95% CI = 1.06–3.00) for mumps and 2.61 (95% CI = 1.001–6.82) for tuberculosis), whereas no associations between infectious diseases and phobic disorder not other specified, social phobia and obsessive–compulsive disorder were found.

Whooping cough (OR = 1.69, 95% CI = 1.36–2.09), scarlet fever (OR = 1.31, 95% CI = 1.02–1.68), and diphtheria (OR = 1.79, 95% CI = 1.21–2.64) were associated with having any 12-month anxiety disorder.

Additional analyses with lifetime diagnoses of panic disorder and panic attacks and infectious diseases revealed that whooping cough (OR = 1.46, 95% CI = 1.02–2.07), typhus (OR = 4.24, 95% CI = 1.80–9.97), and diphtheria (OR = 2.39, 95% CI = 1.36–4.21) were associated with panic disorder, whereas whooping cough (OR = 1.42, 95% CI = 1.09–1.85), scarlet fever (OR = 1.37, 95% CI = 1.01–1.86), dysentery (OR = 2.41, 95% CI = 1.04–5.56), typhus (OR = 2.62, 95% CI 1.21–5.66), and diphtheria (OR = 2.25, 95% CI = 1.42–3.55) were associated with panic attacks during lifetime.

As shown in **Figure 1**, having one or more anxiety disorders was associated with an increased number of infectious diseases compared to no anxiety disorder (mean number of infectious diseases with no anxiety disorder: 2.42, 95% CI = 2.36–2.48; one anxiety disorder: 2.76; 95% CI = 2.60–2.91; two or more: 2.75; 95% CI = 2.51–2.99, $z = 2.76$, $p < 0.006$). Contrast analysis in addition showed that having more than one anxiety disorder did not further increase the number of infectious diseases relative to having one anxiety disorder ($z = 0.26$, $p < 0.798$).

ASSOCIATION OF COMORBIDITY AND QUALITY OF LIFE

As shown in **Figure 2**, subjects with both infectious disease and anxiety disorders report a lower level in the MCS ($M = 43.6$, 95% CI = 42.5–44.7) than subjects with only infectious disease (51.6, 95% CI = 51.3–52.0, $z = -14.23$, $p < 0.000$) or neither of them ($M = 50.5$, 95% CI = 49.1–52.0, $z = -7.32$, $p < 0.000$). In the PCS subjects with only anxiety disorder ($M = 42.3$, 95% CI = 35.5–48.0, $z = -2.09$, $p < 0.037$) and with both infectious disease and anxiety disorder ($M = 46.2$, 95% CI = 45.2–47.1, $z = -2.35$, $p < 0.019$) report a lower level when compared to subjects with neither condition ($M = 48.9$, 95% CI = 47.2–50.7).

Additionally, subjects with only anxiety disorder ($M = 42.3$, 95% CI = 35.5–48.0) report a lower quality of life in the PCS compared to subjects with only infectious disease ($M = 49.6$, 95% CI = 49.2–50.0, $z = -2.48$, $p < 0.013$). Further, subjects with both anxiety disorder and infectious diseases ($M = 46.2$, 95% CI = 45.2–47.1) report a lower quality of life in the PCS when compared to subjects with only infectious disease ($M = 49.6$, 95% CI = **49.2–50.0**, $z = -6.61$, $p < 0.000$). All other comparisons were not significant.

DISCUSSION

This study investigated the associations between infectious diseases and anxiety disorders in a representative adult community sample. The results of this study suggest that specific infectious diseases are associated with significantly increased prevalence of anxiety disorders, compared with those without infectious diseases, and that the co-occurrence of the two is associated with substantial loss in quality of life. Specifically, our findings revealed associations between whooping cough, scarlet fever, and diphtheria and increased likelihood of having anxiety disorder. Additionally, associations between whooping cough, mumps, scarlet fever, tuberculosis, dysentery, typhus, diphtheria, and specific anxiety disorders were found. Our findings are partly in line with an earlier study suggesting an association between an infection in the first year of life and panic disorder, social phobia, and overanxious disorder (14). As in that study, we found associations of infectious diseases and anxiety disorders in general. In contrast, we did not find an association between any of the investigated infectious diseases and social phobia.

The findings are based on data from a representative community sample and therefore the results are not limited by the same biases as in clinical samples. However, due to the cross-sectional nature of this study, no conclusions concerning the temporal sequence of infectious diseases and anxiety disorders can be made. Therefore to explain the observed associations, three different models will be considered.

Table 1 | Odds Ratios of infectious diseases (lifetime) for anxiety disorders (12 months) compared to the reference group that had no indexed anxiety disorder during the past 12 months ($N = 4181$).

DSM-IV mental disorder	Whooping cough ($n = 977$, 23.6%)	Measles ($n = 2591$, 63.2%)	Mumps ($n = 2066$, 48.7%)	Rubella ($n = 1467$, 35.1%)	Chicken pox ($n = 2390$, 58.1%)	Scarlet fever ($n = 632$, 14.9%)	Tuberculosis ($n = 91$, 2.2%)	Dysentery ($n = 52$, 0.9%)	Typhus ($n = 48$, 1.1%)	Diphtheria ($n = 181$, 4.1%)
Any anxiety disorder[a] ($n = 727$, 14.5%)	1.69 (1.36–2.09)* ($n = 220$)	1.00 (0.78–1.28) ($n = 458$)	1.13 (0.92–1.40) ($n = 377$)	0.96 (0.78–1.20) ($n = 265$)	1.07 (0.84–1.36) ($n = 430$)	1.31 (1.02–1.68)* ($n = 128$)	1.51 (0.83–2.73) ($n = 18$)	1.90 (0.86–4.18) ($n = 12$)	1.17 (0.54–2.53) ($n = 11$)	1.79 (1.21–2.64)* ($n = 49$)
Panic disorder with/without agoraphobia ($n = 121$, 2.3%)	1.52 (0.97–2.34) ($n = 41$)	0.68 (0.41–1.13) ($n = 73$)	0.97 (0.62–1.52) ($n = 65$)	0.91 (0.58–1.44) ($n = 46$)	0.89 (0.54–1.45) ($n = 72$)	1.08 (0.65–1.80) ($n = 25$)	0.52 (0.07–3.87) ($n = 1$)	0.82 (0.19–3.48) ($n = 2$)	0.57 (0.07–4.31) ($n = 1$)	2.82 (1.48–5.39)* ($n = 14$)
Panic attack ($n = 241$, 4.7%)	1.49 (1.07–2.06)* ($n = 76$)	0.91 (0.62–1.34) ($n = 149$)	1.19 (0.85–1.66) ($n = 130$)	0.97 (0.69–1.35) ($n = 89$)	1.17 (0.79–1.72) ($n = 149$)	1.29 (0.88–1.89) ($n = 47$)	1.31 (0.52–3.34) ($n = 6$)	1.21 (0.33–4.35) ($n = 4$)	0.55 (0.13–2.36) ($n = 2$)	2.46 (1.46–4.14)* ($n = 22$)
Agoraphobia without panic disorder ($n = 105$, 2.0%)	2.15 (1.36–3.40)* ($n = 42$)	1.81 (0.91–3.60) ($n = 81$)	1.79 (1.06–3.00)* ($n = 67$)	1.12 (0.68–1.83) ($n = 42$)	0.78 (0.45–1.33) ($n = 64$)	1.97 (1.17–3.33)* ($n = 25$)	2.61 (1.001–6.82)* ($n = 5$)	2.71 (0.69–10.58) ($n = 4$)	2.12 (0.55–8.13) ($n = 3$)	1.93 (0.83–4.47) ($n = 8$)
Simple phobia ($n = 388$, 7.6%)	1.52 (1.15–2.00)* ($n = 111$)	0.80 (0.59–1.09) ($n = 244$)	1.00 (0.76–1.30) ($n = 196$)	1.03 (0.78–1.37) ($n = 146$)	1.18 (0.86–1.67) ($n = 234$)	1.18 (0.85–1.63) ($n = 65$)	1.54 (0.70–3.39) ($n = 9$)	1.15 (0.37–3.56) ($n = 4$)	0.96 (0.31–2.96) ($n = 4$)	1.50 (0.92–2.45) ($n = 26$)
Phobic disorder NOS ($n = 173$, 3.4%)	1.49 (0.99–2.24) ($n = 48$)	1.01 (0.63–1.61) ($n = 110$)	1.08 (0.73–1.60) ($n = 88$)	0.86 (0.58–1.28) ($n = 61$)	0.84 (0.55–1.28) ($n = 102$)	1.08 (0.66–1.76) ($n = 26$)	1.81 (0.57–5.73) ($n = 5$)	2.88 (0.76–10.82) ($n = 3$)	0.77 (0.17–3.38) ($n = 2$)	1.56 (0.76–3.17) ($n = 10$)
Social phobia ($n = 94$, 1.9%)	1.35 (0.80–2.27) ($n = 26$)	1.71 (0.85–3.45) ($n = 55$)	0.71 (0.43–1.18) ($n = 45$)	0.82 (0.49–1.38) ($n = 33$)	1.08 (0.56–2.10) ($n = 55$)	0.64 (0.31–1.34) ($n = 10$)	0.95 (0.21–4.17) ($n = 2$)	–[b]	0.24 (0.03–1.77) ($n = 1$)	1.36 (0.54–3.37) ($n = 6$)
Generalized anxiety disorder ($n = 73$, 1.5%)	1.94 (1.12 –3.35)* ($n = 28$)	1.28 (0.64–2.54) ($n = 50$)	1.28 (0.71–2.30) ($n = 37$)	0.80 (0.44–1.45) ($n = 26$)	1.40 (0.68–2.85) ($n = 45$)	1.32 (0.67–2.60) ($n = 14$)	1.41 (0.33–5.93) ($n = 2$)	1.62 (0.21–11.97) ($n = 1$)	–[b]	1.39 (0.31–6.53) ($n = 2$)
Obsessive–compulsive disorder ($n = 38$, 0.7%)	1.15 (0.53–2.49) ($n = 11$)	0.82 (0.35–1.94) ($n = 25$)	0.78 (0.34–1.76) ($n = 16$)	0.95 (0.41–2.20) ($n = 13$)	1.32 (0.51–3.38) ($n = 23$)	1.10 (0.36–3.27) ($n = 5$)	1.50 (0.32–6.80) ($n = 2$)	–[b]	–[b]	2.16 (0.62–7.54) ($n = 3$)

*CI, confidence interval; DSM-IV, diagnostic and statistical manual of mental disorders, fourth edition; NOS, not other specified; OR, odds ratio; n, unweighted number of subjects, % weighted percentage, *$p < 0.05$, adjusted for sex.*

[a] *including any anxiety disorder during the past 12 months.*

[b] *empty cell size.*

First, infectious diseases may precede anxiety disorders. Through biochemical processes, infections may increase the risk of having an anxiety disorder. Some infectious diseases such as scarlet fever mainly have their first onset in early childhood (29), whereas most anxiety disorders emerge for the first time during puberty (17, 30). We might therefore suggest that some infectious diseases do emerge before anxiety disorders do. This interpretation may be supported by the findings of the above mentioned cross-sectional study addressing the relationship of infectious diseases and anxiety disorders, showing that severe infections during the first year of life (reported by the parents) are associated with increased anxiety disorders among 9–17-year olds, therefore suggesting that infections occur before anxiety disorders emerge (14). Research suggests that increased concentration of proinflammatory cytokines could contribute to feeling of depression, and also anxiety (13). Additionally, it is known that some viral infections, such as tuberculosis, can directly affect the brain (31). These processes may damage the brain and therefore cognitive impairments and behavioral changes can occur (31). Cognitive impairment in different domains such as executive functioning or visual memory has been found to be common among people with anxiety disorders (32) and is thought to reduce coping abilities and impact social and occupational functioning (32), which could lead to an intensification of anxiety symptoms.

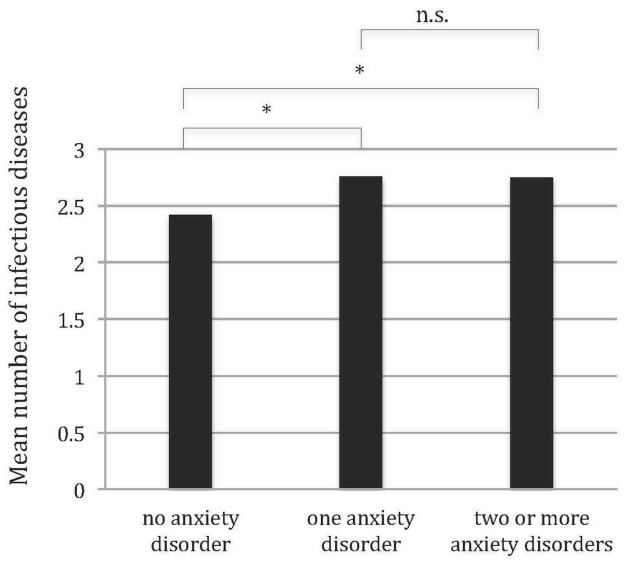

FIGURE 1 | Mean number of infectious diseases (lifetime) for subjects with no anxiety disorder, with one anxiety disorder, and with two or more anxiety disorders (12 months). Mean scores adjusted for sex; *n.s.* not significant, $*p < 0.05$, weighted data.

Second, it may be that anxiety disorders precede infectious diseases. One explanation for this path would be that anxiety disorders are related to psychological disturbance and stress. Stress is associated with an increased cortisol secretion and may contribute to an immune function decline. An immune function decline in anxious subjects had been shown on a physiological level, namely in a reduction of chemotaxis, phagocytosis, and lymphoproliferation (33). Alternatively, studies have shown that the extent and quality of general medical health care among those with mental disorders might be poor (31). Even though the association has mainly been shown in psychotic and substance use disorders (31), it may be that people with anxiety disorders receive less medical information and therefore the frequency of vaccination could be lower among these subjects leading to increased rates of some infectious diseases.

Third, it may be that there is a common factor related to an increased risk of having both infectious diseases and anxiety disorders at the same time. Both genetic and environmental common factors could be considered. In our analyses, we found increased rates of whooping cough, scarlet fever, dysentery, typhus, and

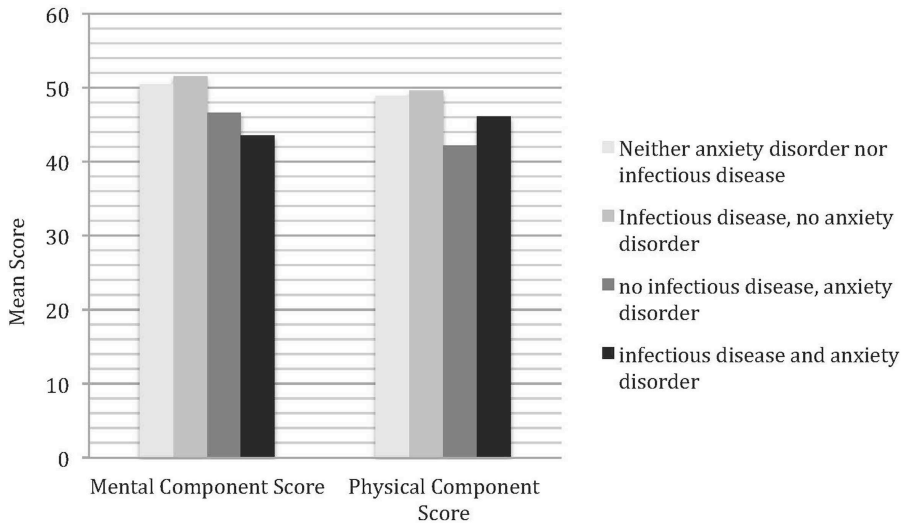

FIGURE 2 | The association of anxiety disorders and infectious diseases and health-related quality of life. Mean scores adjusted for sex.

diphtheria in subjects with panic attacks. In prospective analyses, prior regular smoking was found to increase the risk of panic attacks (34). Smoking on the other hand increases the risk of bacterial or viral infections (35). One might therefore speculate that smoking could act as a common environmental risk factor for both infectious diseases and mental disorders.

Our results also show that individuals with both conditions have a loss in health-related quality of life. This is in line with earlier findings of those with anxiety disorders and chronic physical diseases reporting decreased health-related quality of life (15). Our analyses additionally show that infectious diseases are not associated with a significantly lower quality of life if they appear alone when compared to people with neither condition. In combination with anxiety disorders, however, they are. Our results therefore extend previous findings and show that not only chronic physical diseases, but – at least partly – well treatable and time-limited infections are related to lower quality of life in subjects with anxiety disorders.

The current study has a number of limitations. First, the prevalence rates of the infectious diseases are based on self-report. Therefore, it may be that some infectious diseases are misunderstood (e.g., whooping cough may be confused to cough in general or may be overreported). Even though there is evidence suggesting that the validity of self-assessment of certain infectious diseases such as a common cold is high (36), it is additionally known that negative emotional style can be associated with an over-reporting of unverified symptoms (reporting bias) (37). This needs to be addressed in future studies by assessing infectious diseases with medical interview or by laboratory blood tests. Second, the combination of infectious diseases and anxiety disorder led to some small cell sizes, especially in tuberculosis, dysentery, typhus, and diphtheria. Third, due to the cross-sectional nature of the study, no conclusions can be drawn concerning the causal relationship of the observed associations. Fourth, the results cannot be generalized to subjects younger than 18 and older than 65 years. Fifth, we only had 12-month diagnoses for anxiety disorders (except for panic disorder), whereas infectious diseases were assessed over lifetime. Future studies should address this issue by comparing both infectious diseases and anxiety disorders during the same time frame. Sixth, potential other confounders may play a role in the associations.

With these limitations in mind, our study extends prior findings (14) about the association between infectious diseases and anxiety disorders. Our study suggests that adults with infectious diseases report higher prevalence rates of anxiety disorders and that this comorbidity is associated with a health-related loss in quality of life. Future longitudinal studies should clarify the temporal relationship of these disorders and evaluate the pathways contributing to this comorbidity with targeted psychological and immunological parameters. The health-related loss in quality of life could underline the importance of disease prevention (e.g., vaccination) in people with anxiety disorders as especially subjects with both infectious disease and anxiety disorder reported an impairment in quality of life. The associations additionally show that infectious diseases and anxiety disorders might increase the risk of having one another, and/or they might have common shared risk factors at least in subtypes. This research could initiate future research on the linkage of infectious diseases and anxiety disorders.

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