From Mental-Physical Comorbidity to Somatic Symptoms –

Insights Gained from Research on Symptoms of Mental Disorders

Inaugural Dissertation

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by

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Declaration of Authorship

I hereby declare that I have written the submitted doctoral thesis “From Mental-Physical Comorbidity to Somatic Symptoms – Insights Gained from Research on Symptoms of Mental Disorders” without any assistance from third parties not indicated. Furthermore, I confirm that no other sources have been used in the preparation and writing of this thesis other than those indicated.

Place and date: Binningen, 18.05.2015

Donja Rodic: ______________________________

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Abbreviations

SD	Somatoform Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th edition
WHO	World Health Organization
SHS	Swiss Health Survey

Abstract in English

Background: Mental health and physical health are substantially associated with each other. The early recognition of co-occurring mental-physical conditions, as well as the early recognition of pathophysiological mechanisms underlying somatic symptoms, might be of special relevance for a better understanding of early phases of disorder development and hence prevention.

Aim: To examine associations between symptoms of mental disorders (depressive symptoms and gambling behavior) and physical diseases, as well as associations between somatic symptoms and sensory responsiveness.

Methods: We estimated (1) the association between depressive symptoms and physical diseases (N = 14,348), (2) the association between gambling and physical diseases (N = 11,385), and (3) the association of sensory responsiveness with somatic symptoms and illness anxiety (N = 205). Logistic regression analyses were conducted to estimate the associations in studies (1) and (2). To estimate the associations in study (3) we conducted a linear multiple regression model. We controlled for potential confounders in all three studies.

Results: (1) Depressive symptoms were associated with Arthrosis and Arthritis and any physical disease. (2) Gambling in the past 12 months was associated with Diabetes, Arthrosis and Arthritis, High blood pressure, allergies like Hay Fever, and any physical disease. (3) Increased sensory responsiveness was associated with increased scores of the overall illness anxiety scale and its constituent subscale disease conviction.

Discussion: Symptoms of mental disorders were associated with physical diseases and increased sensory responsiveness was associated with illness anxiety. Scrutinizing these associations might contribute to a better understanding of mental-physical comorbidity and might therefore have implications for early recognition, treatment and health care policy.

Abstract in German

Hintergrund: Psychische und körperliche Gesundheit sind stark miteinander verbunden. Die Früherkennung von gemeinsam auftretenden psychisch-körperlichen Erkrankungen, sowie somatischen Symptomen zugrundeliegenden pathophysiologischen Mechanismen, könnte zu einem besseren Verständnis der frühen Krankheitsentwicklung und somit der Prävention beitragen.

Ziel: Untersuchung der Zusammenhänge zwischen Symptomen psychischer Störungen (depressive Symptome und Glücksspielverhalten) und körperlichen Erkrankungen, sowie der Zusammenhänge zwischen somatischen Symptomen und sensorischer Empfindlichkeit.

Methode: Untersucht wurden die Assoziation zwischen (1) depressiven Symptomen und körperlichen Erkrankungen (N = 14,348), (2) Glücksspielverhalten und körperlichen Erkrankungen (N = 11,385), und (3) sensorischer Empfindlichkeit und somatischen Symptomen oder Krankheitsangst (N = 205). Assoziationen in Studie (1) und (2) wurden anhand logistischer Regressionen geschätzt. In Studie (3) wurde ein lineares multiples Regressionsmodells verwendet. Potenzielle Störvariablen wurden in allen drei Studien kontrolliert.

Resultate: (1) Depressive Symptome waren mit Arthrose und Arthritis und irgendeiner körperlichen Erkrankung assoziiert. (2) Glücksspiele spielen in den letzten 12 Monaten war mit Diabetes, Arthrose und Arthritis, hohem Blutdruck, Allergien wie Heuschnupfen und irgendeiner körperlichen Erkrankung assoziiert. (3) Erhöhte sensorische Empfindlichkeit war mit höheren Werten auf der allgemeinen Krankheitsangstskala und der Unterskala Krankheitsüberzeugung assoziiert.

Diskussion: Symptome psychischer Störungen waren assoziiert mit körperlichen Erkrankungen und erhöhte sensorische Empfindlichkeit war assoziiert mit Krankheitsangst. Die eingehende Untersuchung dieser Zusammenhänge könnte zu einem besseren Verständnis psychisch-körperlicher Komorbiditäten beitragen und somit Implikationen für die Früherkennung, Behandlung und Gesundheitspolitik haben.

„The greatest mistake in the treatment of diseases is that there are physicians for the body and physicians for the soul, although the two cannot be separated."

Plato (427–347 BC)

Introduction

Why do people consult a doctor? One of the most common reasons for consultations in primary care is the presence of physical symptoms (Schappert, 1998). According to a study of primary care patients, 15% of the physical symptoms have purely somatic causes (Kroenke & Mangelsdorff, 1989). 10% to 15% of primary care patients report physical symptoms without clear somatic causes (Kroenke, 2003), and up to 20% of patients in primary care studies fulfill the diagnostic criteria for the mental disorder category of Somatoform Disorders (SD) according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) (Körber, Frieser, Steinbrecher, & Hiller, 2011). Mental disorders are syndromes incorporating clinically relevant emotional, cognitive or behavioral dysfunction in individuals (American Psychiatric Association, 2013). Thereby, mental disorders lead to disability in different areas of life, such as social or professional functioning (American Psychiatric Association, 2013). Mental Disorders often remain undetected and untreated in primary care as individuals suffering from symptoms of mental disorders may report multiple bodily symptoms (Cassano & Fava, 2002). Although, not all individuals suffering from symptoms of mental disorders develop full blown clinical mental conditions, symptoms of mental disorders can lead to disability comparable with that seen in fully diagnosed mental disorders (Ayuso-Mateos, Nuevo, Verdes, Naidoo, & Chatterji, 2010; Haller, Cramer, Lauche, Gass, & Dobos, 2014; Lieb, Pfister, Mastaler, & Wittchen, 2000).

In this context, it is hardly surprising that population-based studies around the world revealed a frequent co-occurrence of mental disorders and non-communicable physical diseases (Scott et al., 2009; Von Korff, Scott, & Gureje, 2009). Physical diseases are also accompanied by behavioral, emotional and cognitive changes (World Health Organization, 2011, 2013). In general, patients suffering from physical diseases and comorbid mental disorders experience increased burden, impairment and decreased quality of life as compared to patients with physical diseases without comorbid mental disorders (Baumeister & Härter, 2005; Sareen, Cox, Clara, & Asmundson, 2005; Sareen et al., 2006; Sartorius, Holt, & Maj, 2015; Scott et al., 2009). Moreover, mental disorders co-occurring with physical diseases are more difficult to detect than mental disorders occurring alone (Goldberg, 2010; Kapfhammer, 2015; Stark & House, 2000). Lack of an exact diagnosis makes it difficult to choose the right therapy for patients, which might lead to a worse outcome of either of the comorbid conditions (Baumeister & Härter, 2005; Naylor et al., 2012).

Depression has frequently been associated with physical diseases (Patten et al., 2009; Patten et al., 2008). Moreover, it has been shown that even subthreshold depressive conditions can cause impairment comparable with that seen in full blown depressive conditions (Ayuso-Mateos et al., 2010; Kessing, 2007; Klein, Shankman, Lewinsohn, & Seeley, 2009). In addition, physical diseases have also been associated with other mental disorders, such as Anxiety Disorders (Kariuki-Nyuthe & Stein, 2015; Roy-Byrne et al., 2008) and Gambling Disorder (American Psychiatric Association, 2013; Black, Shaw, McCormick, & Allen, 2013; Morasco, Pietrzak, et al., 2006), formerly referred to as Pathological Gambling and assigned to the category of Impulse Control Disorders Not Elsewhere Classified (American Psychiatric Association, 1994). Notably, Pathological Gambling deserves special attention because of the strong growth rate of the gambling industry, especially in the online sector (European Commission, 2012). Recent research has already shown that there is an association between Pathological Gambling and physical diseases (Black et al., 2013; Desai, Desai, & Potenza, 2007; Morasco, Pietrzak, et al., 2006; Pietrzak, Morasco, Blanco, Grant, & Petry, 2007). However, is not yet clear whether gambling behavior itself, as an important dimension of Gambling Disorder, is associated with physical diseases.

For the reasons mentioned above, it is essential to scrutinize mental-physical comorbidity patterns. An improved early assessment of unfavourable behavior and an early recognition of dimensions and symptoms of mental disorders could improve therapy for subjects with comorbid conditions. Findings on comorbidity might also reveal potential mechanisms in the etiopathogenesis of respective conditions.

As previously mentioned, apart from mental-physical comorbidity, there are disorders comprising mental and physical symptoms referred to as SD in the DSM-IV (American Psychiatric Association, 1994). This disorder category has been criticised over years (Kroenke, Sharpe, & Sykes, 2007; Mayou, Kirmayer, Simon, Kroenke, & Sharpe, 2005; Rief & Isaac, 2007; Voigt et al., 2010), as it comprises subcategories with different key aspects, including the two main subcategories Somatization Disorder (key aspect: quantity of somatic symptoms) and Hypochondriasis (key aspect:

anxiety of having a serious disease). Despite the reconceptualised diagnostic criteria for SD within the new Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) category Somatic Symptom and Related Disorders (American Psychiatric Association, 2013), the etiology of SD is not yet fully established (Brown, 2004; Deary, Chalder, & Sharpe, 2007; Witthoft & Hiller, 2010).

Although the co-occurrence of mental disorders and physical diseases has been repeatedly demonstrated (Iacovides & Siamouli, 2008; Kolappa, Henderson, & Kishore, 2013; Leentjens, 2010; Olaya et al., 2012; Prince et al., 2007; Von Korff et al., 2009), factors underlying the mental-physical comorbidity are not clearly understood yet (Valderas, Starfield, Sibbald, Salisbury, & Roland, 2009; Von Korff et al., 2009).

Taken together, these highlights the importance of studying mental-physical comorbidity patterns, as respective findings may inform about the early recognition and underlying factors and of related clinical conditions. Moreover, this highlights the importance of conducting population-based studies and studies with non-clinical samples as these studies have the advantage of allowing to capture subclinical symptoms of mental disorders, which may be of special relevance for a better understanding of the early phases of disorder development and hence prevention.

Scope of the Thesis

As a part of the superior research field on associations between mental and physical health, the findings presented here address some of the above mentioned issues. The general scope of this thesis is to contribute to a better understanding of the comorbidity of symptoms of mental disorders and physical diseases, as well as a better understanding of the pathophysiology underlying Somatic Symptom and Related Disorders. In the present thesis a symptom of a mental disorder is referred to as a single criterion or component of a mental disorder.

Objectives

The presented thesis is based on three papers. The first two investigated the association between symptoms of mental disorders and physical diseases, including (1) depressive symptoms and physical diseases (*depressive symptoms*) and (2) gambling and physical diseases (*gambling*). The third study investigated the association between (3) illness anxiety, somatic symptoms and sensory responsiveness (*somatic symptoms*). Scrutinizing these associations could contribute to a better understanding of the early phases of disorder development and hence prevention.

Research Questions

Based on previous research and the papers presented here this thesis addresses the following specific questions:

(1) *Depressive symptoms*: Can previous findings on the associations between depressive symptoms and physical diseases be replicated?

(2) *Gambling*: Is gambling behavior itself associated with physical diseases?

(3) *Somatic symptoms:* Could sensory responsiveness as a biological correlate contribute to a better understanding of the pathophysiology underlying Somatic Symptom and Related Disorders?

(4) *Overall research question 1* (based on paper one *depressive symptoms* and paper two *gambling):* Are there similarities between mental-physical associations, with regard to physical diseases, in paper one and two?

(5) *Overall research question 2*: Are different symptoms of mental disorders associated with physical diseases and physiological reactions?

Approach

To answer the questions above the following approaches were used:

(1) *Depressive symptoms*: The association between depressive symptoms and a wide range of physical diseases was estimated using data from a population-based survey.

(2) *Gambling*: Data from the same population-based survey was used to evaluate the association between gambling and a wide range of physical diseases.

(3) *Somatic symptoms:* In a different non-clinical sample, the association between sensory responsiveness (measured via vibrotactile perception thresholds) and somatic symptoms, illness anxiety and trait anxiety was explored.

(4) *Overall research question 1*: The findings from the *depressive symptoms* and *gambling* paper were summarized and compared.

(5) *Overall research question 2*: General integration of the findings derived from the three papers.

Outline of the Thesis

The structure of this thesis is as follows: The "Introduction" gave an overview of the relevance and scope of the research presented in this thesis. In the section "Theoretical Background" the theoretical background and current state of research with regard to mental disorders and symptoms of mental disorders, physical diseases and the comorbidity of mental disorders and physical diseases will be covered. The "Methods" briefly describe the methodology used for the designs, the collection of data and statistical analyses. The section "Results and Main Conclusions" summarizes the results of this thesis and condenses them into a main conclusion. Finally, the "General Discussion" will show implications derived from the here presented papers, including strengths and limitations of the three papers, and present an outlook for future research. A detailed description of the three presented scientific papers can be found in Appendix A to C.

Theoretical Background

Overview of Selected Mental Disorders and Symptoms of Mental Disorders

Mental disorders can lead to disability in different areas of life, such as social or professional functioning (American Psychiatric Association, 2013). They are syndromes incorporating clinically relevant emotional, cognitive or behavioral dysfunction in individuals (American Psychiatric Association, 2013). Mental disorders have a profound impact on the social and economic burden worldwide (Alonso et al., 2011; R. C. Kessler & Ustun, 2008). In Europe, an estimated 38.2% of the population suffers from a diagnosed mental disorder per year (Wittchen et al., 2011). Although, not all individuals suffering from symptoms of mental disorders develop full blown clinical mental conditions, individual symptoms of mental disorders, such as depressive symptoms not qualifying for a diagnosis, can lead to disability comparable with that seen in fully diagnosed Depressive Disorders (Ayuso-Mateos et al., 2010). Epidemiological studies revealed that mental disorders – including anxiety, mood and behavior disorders – manifest themselves mostly in the second and third decades of life (Merikangas et al., 2010; Wittchen, Nelson, & Lachner, 1998), whereby Anxiety Disorders show the earliest onset (Andrade et al., 2000).

Current models of the etiology of mental disorders assume that an interplay of neurobiological, psychological and social factors (diathesis/vulnerability) together with stressors (such as critical life events) and modifying factors (such as natural resilience) accounts for the development of mental disorders (Wittchen & Hoyer, 2011). Further evidence suggests that modifiable unfavourable behaviour (also referred to as lifestyle factors), such as smoking, and physical inactivity, might as well play a crucial role in the development of mental disorders (Oldenburg, O`Neil, & Cocker, 2015).

The presence of subthreshold mental conditions (Ayuso-Mateos et al., 2010; Judd, Rapaport, Paulus, & Brown, 1994), as well as individual symptoms of mental disorders is widespread in the general population (Ayuso-Mateos et al., 2010; Wittchen, Lieb, Pfister, & Schuster, 2000). Therefore scrutinizing research on symptoms of mental disorders might improve our understanding of the pathogenesis and etiopathology of respective clinical conditions.

Depressive Disorders

Depressive Disorders are characterized by the feeling of sadness, emptiness or irritable mood and involve somatic and cognitive changes (American Psychiatric Association, 2013). According to the World Health Organization (WHO), around 350 million people suffer from depression worldwide (World Health Organization, 2012). Depressive Disorders cause substantial impairment, decrease quality of life and increase mortality (Culpepper, 2011), which makes them one of the greatest contributors to the global disease burden (Ferrari et al., 2013; Wittchen et al., 2011). Additionally, Depressive Disorders are highly comorbid with other mental disorders, somatic symptoms and pain (Lieb, Mastaler, & Wittchen, 1999). Moreover, subthreshold depressive conditions can cause impairment comparable with that seen in full blown Depressive Disorders (Ayuso-Mateos et al., 2010; Kessing, 2007; Klein et al., 2009). Thus, even individual depressive symptoms can cause substantial distress and lead to significant impairment in everyday functioning (Ayuso-Mateos et al., 2010). Moreover, primary care studies revealed that individuals with depressive conditions more frequently report physical health problems than mentally healthy individuals (Smith et al., 2014). Although depressive symptoms are common in primary care patients (Pieper, Schulz, Klotsche, Eichler, & Wittchen, 2008), they often remain unrecognized and untreated (Cassano & Fava, 2002). In this context, especially the co-occurrence of depressive symptoms and physical diseases poses great challenges for health care and prevention (Sartorious, 2013; Sartorius et al., 2015; Smith et al., 2014).

Gambling Disorder

Gambling Disorder, the only non-substance-related addictive disorder included in the DSM-5, formerly known as Pathological Gambling, is characterized by constant and recurring problematic gambling behavior (American Psychiatric Association, 2013). This leads to clinically significant impairment or distress, such as the need to gamble for increasing stakes in order to experience the desired excitement, or restlessness or irritability when trying to reduce the time spent gambling (American Psychiatric Association, 2013). More specifically, pathological gambling has been associated with lower social functioning (Bergh & Kuhlhorn, 1994), lower physical activity and obesity (Black et al., 2013), and affective and substance use disorders (Dowling et al., 2015; El-

Guebaly et al., 2006; Lorains, Cowlishaw, & Thomas, 2011) resulting in poorer psychosocial well-being (Bergh & Kuhlhorn, 1994) and poorer general physical health due to the excessive amounts of time spent pursuing this activity (Erickson, Molina, Ladd, Pietrzak, & Petry, 2005; Morasco, Eigen, & Petry, 2006). Evidence suggests associations between pathological gambling and a variety of physical diseases (Black et al., 2013; Desai et al., 2007; Morasco, Pietrzak, et al., 2006; Pietrzak et al., 2007). However, findings on the associations between pathological gambling and physical diseases are largely based on data from the U.S. National Epidemiologic Survey on Alcohol and Related Conditions and therefore studies replicating these results are highly warranted. Moreover, and if compared to other smaller studies, the findings remain heterogeneous due to the different criteria and thresholds for pathological gambling, as well as assessment instruments used to assess gambling behavior. It is not yet known whether gambling behavior itself, as an important dimension of Gambling Disorder, is associated with physical diseases. However, further research, especially regarding possible correlates of gambling behavior, is highly warranted.

Somatic Symptom and Related Disorders

In the course of the DSM-5 development, SD (DSM-IV) have been reconceptualized as Somatic Symptom and Related Disorders, with a stronger emphasis on a subjects thoughts and feelings (American Psychiatric Association, 2013). Up to 20% of patients in primary care studies fulfill the diagnostic criteria for SD according to DSM-IV (Körber et al., 2011). Annually, an estimated 4.9% of the European population suffers from SD (Wittchen et al., 2011). These disorders include somatic symptoms in association with high distress and impairment (American Psychiatric Association, 1994) comparable with that seen in Depressive and Anxiety Disorders (De Waal, Arnold, Eekhof, & Van Hemert, 2004; Kroenke et al., 1997). Even somatic symptoms not qualifying for a diagnosis of SD cause substantial impairment and may pave the way for the development of other mental disorders (Lieb et al., 2000). Moreover, SD often co-occur with Anxiety and Depressive disorders, but the underlying factors of this comorbidity remain elusive (Lieb, Meinlschmidt, & Araya, 2007).

The DSM-IV diagnostic category of SD is an accumulation of disorders with different symptom clusters, mainly defined by somatic symptoms (American Psychiatric Association, 1994). The two main DSM-IV categories of SD comprise Somatization Disorder (key aspect: quantity of somatic symptoms) and Hypochondriasis (key aspect: anxiety of having a serious disease) (American Psychiatric Association, 1994). The latter diagnosis, Hypochondriasis, has been discussed repeatedly (Noyes, Stuart, Watson, & Langbehn, 2006), as its key aspect “anxiety of having a serious disease” suggests an overlap with other Anxiety Disorders. Therefore, it could be argued that Hypochondriasis belongs to the group of Anxiety Disorders (Noyes, 1999; Olatunji, Deacon, & Abramowitz, 2009).

In this context, evidence suggests that Somatosensory Amplification (Barsky, Wyshak, & Klerman, 1990) might play a crucial role in the etiology of all DSM-IV SD (Brown, 2004; Deary et al., 2007; Witthoft & Hiller, 2010). Somatosensory Amplification is the exaggerated perception of bodily sensations and their attribution to disease (Barsky et al., 1990). However, despite the DSM-5 reconceptualization of SD it remains unclear, whether the etiology of these disorders includes truly altered physiological sensitivity to sensory input and not merely subjective exaggerated perception of bodily sensations (Brown, 2004; Deary et al., 2007; Witthoft & Hiller, 2010).

Physical Diseases

Non-communicable physical diseases are chronic medical conditions which are non-transmissible between individuals (World Health Organization, 2013). The most common non-communicable physical diseases are Cardiovascular Diseases, Cancer, Chronic Respiratory Disease and Diabetes (World Health Organization, 2011, 2013). The WHO reports that non-communicable diseases, such as Diabetes and Cardiovascular Diseases, account for the highest proportion of burden and disability worldwide, leading to more than 36 million people dying from these diseases annually (World Health Organization, 2013). Physical diseases share common traits, including a long etiopathology and slow progression of symptoms (World Health Organization, 2013). Moreover, they also have multiple common behavioral risk factors, including unhealthy lifestyle, excessive tobacco use or physical inactivity and are accompanied by behavioral, emotional and cognitive changes (World Health Organization, 2011, 2013). Summarized, the above highlights the importance of scrutinizing mental correlates of physical diseases.

Comorbidity of Mental Disorders and Physical Diseases

Comorbidity is defined as the co-occurrence of more than one distinct mental or physical disorder in one person in a defined time interval (Feinstein, 1970; Lieb, Schreier, & Müller, 2003; Valderas et al., 2009; Wittchen & Hoyer, 2011). Evidence shows that comorbidity is common between all types of disease, whether mental or physical (mental-mental, physical-physical, mental-physical) (Von Korff et al., 2009; Wittchen & Hoyer, 2011). Especially the comorbidity of mental disorders with physical diseases poses great demands on health care, as comorbid conditions decrease the quality of life, prolong illness duration and lead to worse health outcomes (Kolappa et al., 2013; Sartorious, 2013; Sartorius et al., 2015). These circumstances increase the economic burden to society due to increased health care use and a loss of productivity (Sartorius et al., 2015).

Notably, mental disorders are more common in patients with physical diseases than in the general population (Clarke & Currie, 2009). Comorbidity has a huge impact on role disability (Merikangas et al., 2007) and patients suffering from physical diseases and comorbid mental disorders show increased mortality rates and decreased quality of life as compared to patients with physical diseases without comorbid mental disorders (Baumeister, Balke, & Harter, 2005). According to a cross-sectional population-based study, individuals with Depressive Disorders and comorbid physical disease report greater disability and increased healthcare-utilization than individuals without comorbid Depressive Disorders (Stein, Cox, Afifi, Belik, & Sareen, 2006). Population-based studies found similar patterns for people suffering from individual symptoms of mental disorders, such as depressive symptoms: increased rates of a wide range of physical diseases and impairment comparable to that seen in fully diagnosed patients (Von Korff et al., 2009). Moreover, the comorbidity of mental disorders and physical diseases is regarded as an important factor within the estimation of health care costs (Gustavsson et al., 2011), since individuals with comorbid conditions generate much higher health care costs than individuals with single mental disorders or physical diseases (Hochlehnert et al., 2011; Hutter, Schnurr, & Baumeister, 2010; Mc Daid & Park, 2015; Unutzer et al., 2009).

Until now, the etiology of mental-physical comorbidity is not yet fully understood (Von Korff et al., 2009). Härter, Baumeister, and Bengel (2007) propose five different simplified models for the association between mental disorders and physical diseases. Figure 1 illustrates the proposed models.

The first model assumes that on a bio-physiological level a physical disease (or corresponding medical treatment) might cause a mental disorder. For example it has been shown that the hypofunction of the thyroid can trigger depressive symptoms (Chakrabarti, 2011). The second model proposes that within genetically vulnerable individuals the onset of a physical disease might precede the onset of a mental disorder. Cushing`s disease, a disease of the pituitary gland, for example, might precede Major Depression episodes (Sonino & Fava, 1998). Within the third model a mental disorder might emerge as a reaction to a physical disease (or corresponding medical treatment). Thus, Cancer patients frequently suffer from mood disorders (Mitchell et al., 2011). Model four assumes that a mental disorder precedes the onset of a physical disease (or symptom) or may have an adverse impact on the respective disease. For example, an untreated Depressive Disorder together with acute back pain might lead to chronic back pain (Larson, Clark, & Eaton, 2004). In this context, different studies even suggest that Depressive Disorders might be a risk factor for mortality in patients with Coronary Heart Disease (Barth, Schumacher, & Herrmann-Lingen, 2004; Vieweg et al., 2006). In the fifth model, Härter et al. (2007) suggest that the comorbidity of mental and physical diseases is coincidental: Posttraumatic Stress Disorder, for example, together with Rheumatoid Arthritis. Additionally, there is growing evidence that unfavourable behaviour, including smoking, physical inactivity and unhealthy diet, might represent risk factors for both non-communicable physical diseases and mental disorders (Oldenburg et al., 2015).

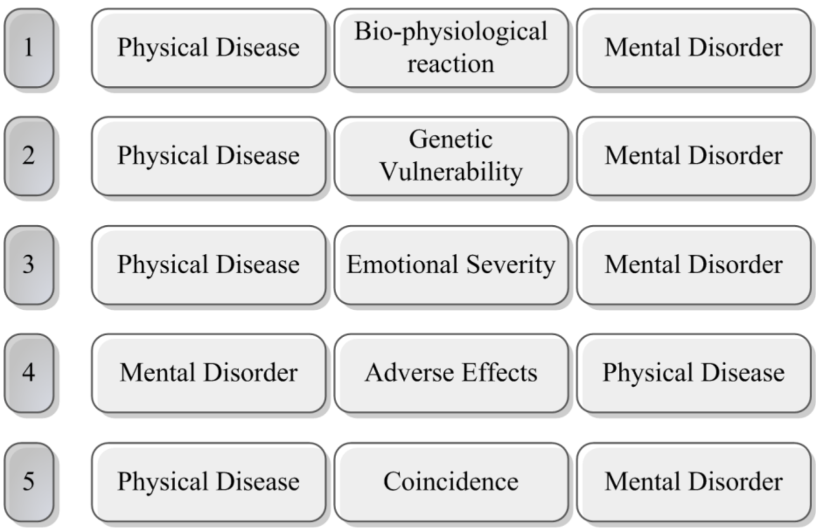

Figure 1. Simplified models for the association between mental disorders and physical diseases.

Previous studies showed strong associations between Depressive Disorders and Cardiovascular Diseases (Hesslinger et al., 2002), Diabetes (Anderson, Freedland, Clouse, & Lustman, 2001; Härter & Berger, 2000), Chronic Obstructive Pulmonary Disease (Mikkelsen, Middelboe, Pisinger, & Stage, 2004), and Chronic Musculoskeletal Disorders (Dickens, McGowan, Clark-Carter, & Creed, 2002; Rosemann et al., 2007). However, findings on the direction of the respective associations remain heterogeneous (Härter et al., 2007; Katon, 2011; Mezuk, Eaton, Albrecht, & Golden, 2008; Wagner, Icks, Albers, & Abholz, 2012). Until now, the factors underlying mental and physical comorbidity are still not fully understood (Härter et al., 2007).

Taken together, findings on mental-physical comorbidity patterns might inform about potential mechanisms underlying the etiology of respective disorders.

Methods

This section gives an overview on study design, sample and methods applied in the three papers. A detailed description for each study is given in the respective paper, which can be found in Appendices A to C. All studies applied a cross-sectional study design. All tests were two-tailed with a significance level of 0.05.

Depressive Symptoms

The sample (*N* = 14,348) of the depressive symptoms paper consisted of participants of the Swiss Health Survey (SHS) conducted in Switzerland in 2007. This periodic population-based survey includes, amongst others, data on depressive symptoms and a wide range of physical diseases. Depressive symptoms were assessed with the screening scale for depression from the World Health Organization Composite International Diagnostic Interview Short Form (R. C. Kessler, Andrews, G., Mroczek, D., Ustun, B., & Wittchen, H. U., 1998) and physical diseases were assessed with a self-report checklist based on the European Health Interview Survey (Eurostat Working Group on Public Health Statistics, 2006). To estimate the associations between depressive symptoms and different physical diseases we applied logistic regression models and controlled for multiple testing using the Holm-Bonferroni method (Holm, 1979). We adjusted the same models for age, sex, education, occupation and equivalised household income.

Gambling

Participants of the Swiss Health Survey 2007, a periodic and population-based survey conducted in Switzerland, make up the sample of the gambling paper (*N* = 11,385). Amongst others, this Swiss Health Survey includes data on gambling and a wide range of physical diseases. In the SHS; gambling was assessed with self-report questions on gambling behavior with the following two questions: “Have you ever played games of chance in your lifetime?” and “Have you played games of chance in the past 12 months?”. Physical diseases were assessed with a self-report checklist based on the European Health Interview Survey (Eurostat Working Group on Public Health Statistics, 2006). We examined the associations between gambling and the presence/absence of physical diseases in the past 12 months applying separate logistic regression models. Gambling versus not gambling in the past 12 months was used as predictor. Adjustment was made for age, sex, education, occupation and equivalised household income.

Somatic Symptoms

The non-clinical sample (*N* = 205) of the somatic symptoms study consisted of participants recruited by advertisements on the web page of the University of Basel and the study database of the Department of Psychology in Basel, Switzerland. All participants underwent a single individual session including standardized questionnaires and different physiological measurements. Sensory responsiveness was assessed on the fingertip via vibrotactile perception thresholds using the HVLab Vibrotactile Perception Meter (Institute of Sound and Vibration Research, University of Southampton, United Kingdom). Somatic symptoms were assessed with a Screening for Somatoform Symptoms (Rief, Hiller, & Heuser, 1997). Illness anxiety was assessed with a self-rating questionnaire (overall sum score for illness anxiety and the scores for the three subscales disease phobia, bodily preoccupation and disease conviction (Hiller & Rief, 2004) and trait anxiety were assessed with a self-rating scale (Laux, Glanzmann, Schaffner, & Spielberger, 1981). We examined the association between sensory responsiveness and somatic symptoms, illness anxiety and trait anxiety using a linear multiple regression model and nonparametric unconditional bootstrapping (Canty & Ripley, 2011; Davison & Hinkley, 1997; Harrell, 2001). We adjusted the same model for age, sex and socioeconomic status.

Results and Main Conclusions

This section provides a brief summary of the results and the main conclusions drawn in the three research papers. For more detailed information on the results, see Appendices A to C.

Depressive Symptoms

The presence of depressive symptoms was associated with any physical disease. More specifically, depressive symptoms were related to an increased risk for Arthrosis and Arthritis. Thus, we were able to replicate previous findings on the associations between depressive symptoms and physical diseases in general (Chapman, Perry, & Strine, 2005; Clarke & Currie, 2009; Evans et al., 2005; Klesse, Baumeister, Bengel, & Härter, 2008) and associations between depression and Arthrosis and Arthritis in specific (Dickens et al., 2002; Dobkin, Filipski, Looper, Schieir, & Baron, 2008; Looper et al., 2011). The finding that depressive symptoms were related to Arthrosis and Arthritis might have implications for clinical practice, such as screening subjects with Arthrosis and Arthritis for depressive symptoms and vice versa. Early recognition of the co-occurrence of depressive symptoms with Arthrosis or Arthritis might allow for an improved coordination of interdisciplinary treatment. This may positively influence the course of both conditions. Moreover, our results might have implications for more precise future estimates of costs related to depression and, by accounting for co-occurrence of comorbid conditions, might contribute to more precise future estimates for costs of co-occurring depressive symptoms and physical diseases.

Gambling

In this paper, we estimated an association between gambling behavior in the past 12 months and an increased risk of Diabetes, Arthrosis and Arthritis, High Blood Pressure, allergies like Hay Fever, and any physical disease in the past 12 months. Our findings might point to the importance of the early assessment of gambling behavior in general and might have implications for the prevention of physical diseases in gamblers through the assessment of gambling behavior and associated risk-factors.

Moreover, early recognition of pathological gambling and associated risk-factors as well as physical conditions, might assist in the reduction of the costs to the health care system.

Somatic Symptoms

We estimated an association between increased illness anxiety and higher sensory responsiveness in general and an association between disease conviction and higher sensory responsiveness in particular. Somatic symptoms and trait anxiety were not associated with sensory responsiveness. These findings suggest that the pathophysiological mechanisms underlying illness anxiety might be different from those underlying other somatic symptoms. Our results may have the potential to contribute to a better understanding of pathophysiological mechanisms in Illness Anxiety Disorder and might therefore improve the classification and treatment of Somatic Symptom and Related Disorders.

Overall Research Question 1

The overall research question 1 was whether there were similarities between mental-physical associations, with regard to physical diseases, in the papers one (*depressive symptoms*) and two (*gambling*). In the *gambling* paper some of the disease categories were excluded from the analyses (too small number of subjects reporting respective conditions), thus Table 1 only summarizes the associations of the included disease categories in the *gambling* paper. Although the methods of the two papers are not completely comparable, especially regarding the different mental components *depressive symptoms* and *gambling*, and the control for multiple testing in the *depressive symptoms* paper, the results show comparable associations (Table 1). The associations estimated in both papers might point to a shared etiology of mental and physical conditions. Moreover, the estimated associations might suggest common risk factors for mental and physical conditions.

However, these conclusions are purely speculative and should be scrutinized in future studies.

TABLE 1. Summary of the associations.

	Depressive symptoms		Gambling	
Physical diseases	Crude[a]	Adjusted[b]	Crude	Adjusted
Any physical disease	✓	✓	✗	✓
Asthma	✗	✗	✗	✗
Diabetes	✗	(✓)	✗	✓
Arthrosis, Arthritis	(✓)	✓	✗	✓
High Blood Pressure	✗	✗	✓	✓
Allergies, Hay Fever	(✓)	(✓)	✓	✓

[a]Unadjusted for covariates.
[b]Adjusted for age, sex, education, occupation, and household income.
✓ = significant association, (✓) = association not significant after controlling for multiple testing, ✗ = not significant association.

Overall Research Question 2

The overall research question 2 was whether different symptoms of mental disorders were associated with physical diseases and physiological reactions. In general, we clearly showed that there is a substantial association between symptoms of mental disorders and physical diseases in the *depressive symptoms* and *gambling* paper. Additionally, in the *somatic symptoms* paper we were able to show that illness anxiety, as a symptom of a mental disorder, is associated with increased sensory responsiveness, a physiological reaction. If the estimated associations in all papers prove to be causal, one may speculate that the detection of mere symptoms, in contrast to full blown clinical conditions, might allow for the prevention of related clinical disorders.

General Discussion

The aim of the three research papers presented within this thesis was to investigate different aspects of the association between symptoms of mental disorders and physical diseases, as well as the association between illness anxiety, somatic symptoms and sensory responsiveness. Two papers (*depressive symptoms* and *gambling*) investigated the association between symptoms of mental disorders and physical diseases. First, depressive symptoms were associated with an increased risk for any physical disease; specifically depressive symptoms were related to an increased risk for Arthrosis and Arthritis. Second, gambling in the past 12 months was associated with an increased risk of Diabetes, Arthrosis and Arthritis, High Blood Pressure, allergies like Hay Fever, and any physical disease. The third paper (*somatic symptoms*) explored, whether sensory responsiveness could contribute to a better understanding of pathophysiological mechanisms underlying somatic symptoms and illness anxiety: whereas increased illness anxiety in general and disease conviction in particular were associated with higher sensory responsiveness, neither somatic symptoms nor trait anxiety were associated with sensory responsiveness.

General Implications

The here presented findings have the potential to contribute to a better understanding of associations between mental and physical conditions. Moreover, findings on comorbidity patterns could provide a basis for hypotheses about the etiology of the comorbid conditions. As the implications of the specific findings have been discussed in the respective papers in the Appendices A to C, this chapter will provide possible comprehensive implications for early recognition, treatment and health care policy.

Implications for Early Recognition

The findings presented here confirm the importance of properly identifying comorbid conditions, since many mental disorders and physical diseases share comparable symptoms (Goldberg, 2010; Kapfhammer, 2015). This makes the recognition of comorbid conditions extremely difficult (Goldberg, 2010; Kapfhammer, 2015; Stark & House, 2000). As symptoms of mental disorders are common in the general population and strongly associated with physical diseases (Von Korff et al., 2009), the detection of symptoms of mental disorders and associated risk-factors as well as physical conditions should be improved in general. Subjects with physical disorders should be screened for symptoms of mental disorders and vice versa. Additionally, the assessment of vibrotactile perception thresholds could be used as a new technique to differentiate between subtle somatic symptoms at an early stage of disorder development, especially with regard to illness anxiety. Not only do our results imply that it is important to screen subjects for common symptoms of mental disorders, such as depressive symptoms, but also they point to the need for recognising unfavourable behavioral patterns, such as excessive gambling. The latter has also been shown to have a negative impact on physical health (Erickson et al., 2005; Morasco, Eigen, et al., 2006). The early recognition of symptoms of mental disorders or physical diseases could improve the course of the emerging condition, as well as the comorbid disorder.

Implications for Treatment

Early recognition of the co-occurrence of mental and physical conditions might allow for an improved coordination of interdisciplinary treatment, which may in turn positively influence the course of both mental and physical conditions. Previous studies showed that if there is an association between mental and physical conditions, failing to treat one condition correctly negatively impacts the other (Hochlehnert et al., 2011; Kolappa et al., 2013). This point to the importance of an early and correct detection of comorbid conditions, allowing for optimized treatment. It could be argued that another aspect of optimizing treatment for comorbid conditions is the detection of risk factors: for example, physical inactivity is a well-known risk factor for physical diseases (World Health Organization, 2011). Physical inactivity is however also a symptom of Depressive and other mental disorders (American Psychiatric Association, 2013). Therefore, taking physical activity into account for the comprehensive treatment of comorbid conditions might positively influence the course and outcome of either one or both conditions.

Implications for Health Care Policy

An increase in the prevalence of comorbid mental-physical conditions is expected due to the worldwide demographic development (Sartorious, 2013; Sartorius et al., 2015). Unrecognized comorbid conditions already pose a substantial financial burden on health care systems (Mc Daid & Park, 2015). Moreover, it has been shown that symptoms of mental disorders cause substantial distress and impairment comparable with that seen in full blown mental conditions (Ayuso-Mateos et al., 2010; Haller et al., 2014; Lieb et al., 2000). The presence of symptoms of mental disorders in subjects with a physical disease increases treatment costs for this disease, as compared to subjects without symptoms of mental disorders suffering from the same physical disease (Hochlehnert et al., 2011; Hutter et al., 2010; Iacovides & Siamouli, 2008; Unutzer et al., 2009). Thus, the costs to the health care system could be reduced through early recognition of comorbid conditions (Mc Daid & Park, 2015). Therefore, changes to the health care system reflecting the reality of comorbid conditions are highly warranted. However, it is not yet clear how these changes will affect the financial aspect of future health care policies.

General Strengths and Limitations

The presented studies have several general strengths and limitations. Details on the strengths and limitations of the individual studies can be found in Appendices A to C.

General Strengths

- *Sample:* All three studies included non-clinical samples, two included large representative population-based samples, one included young adults (mainly university students). Findings on an early stage of disorder development, in terms of symptoms and not fully blown clinical conditions, may have implications for the early recognition and treatment of respective clinical conditions.
- *Mental-physical comorbidity patterns:* In the *depressive symptoms* paper previous findings were replicated in a large representative nation-wide sample in the context of a small high-income country. The *gambling* study has the potential to contribute to a better understanding

of correlates of gambling behavior itself. In general, findings on comorbidity patterns could provide a basis for hypotheses about the etiology of the comorbid conditions.

- *Vibrotactile perception thresholds:* The assessment of sensory responsiveness via vibrotactile perception thresholds in the context of the *somatic symptoms* study is highly innovative and may contribute to an optimized classification and treatment of Somatic Symptom and Related Disorders.
- *Statistical analyses:* In all three studies potential socio-demographic confounders, which have previously been linked to the respective predictors and outcomes, were controlled.

General Limitations

- *Sample:* The number of subjects suffering from some physical diseases, especially with regard to the two population-based studies, was relatively small. Moreover, all three studies contained non-clinical samples (two samples were population-based and one mainly contained university students), which might have led to an underestimation of present symptoms. Thus, small effects might not have been statistically detected due to a lack of statistical power. However, it can be assumed that there was enough variance in the respective samples, but the results should be replicated in sufficiently large clinical samples.
- *Response rate:* The two population-based studies had a high non-response rate, which might have caused a selection bias (Volken, 2013). Therefore studies aiming to achieve a higher response rate are needed.
- *Study design:* The cross-sectional study design of all three studies does not allow for conclusions about the causality of the estimated associations. Therefore we can only speculate about the possible explanations for the estimated associations and their direction.
- *Assessment of symptoms of mental disorders:* Some symptoms may not have entered the studies because of the used screenings and the above mentioned sample composition. The *somatic symptoms* study included one screening which required confirmation of medical consultations for positive screening outcome. As the sample included mainly university

students, this screening most likely led to underestimation of respective symptoms, as the participants reported not to seek medical help due to financial reasons and/or a lack of time.

- *Generalizability:* With regard to generalizability of the findings, caution is warranted. First, data from the *depressive symptoms* paper derived from a population with high-income, above average standard of living and a high preforming health care system. Thus, it is questionable whether the findings apply to other countries. Second, in the *gambling* paper gambling behavior itself and not pathological gambling was assessed. Therefore, caution is warranted with regard to generalizability of the findings to pathological gambling. Third, the *somatic symptom* study included a high functioning sample of volunteers (mainly university students) and the results are therefore not generalizable to other samples.

Outlook

There is a need for prospective, longitudinal studies with representative samples in the field of comorbidity research. Previous studies have demonstrated an association between mental disorders and physical diseases repeatedly (Von Korff et al., 2009). Current theoretical models on the etiology of mental-physical comorbidity are based on the assumptions that the link between mental disorders and physical disease is unidirectional, bidirectional, or results from underlying risk factors common to both conditions (Oldenburg et al., 2015; Von Korff et al., 2009). Thus, future research should focus on the strength, direction and underlying risk factors of mental-physical comorbidity. Moreover, in order to identify underlying mechanisms in the pathogenesis of comorbid conditions, changes of comorbidity patterns over time need to be assessed in future studies. In this context, special attention should be paid to unfavourable behavioral patterns (such as physical inactivity) as the characteristics of these patterns coincide with symptoms of common mental disorders and represent risk factors for physical diseases.

With regard to the *somatic symptoms* study future studies should focus on the pathophysiological mechanisms underlying illness anxiety. In this context, it would be interesting to replicate our findings in clinical samples and to evaluate if the measurement of vibrotactile perception thresholds represents a valid screening method for Illness Anxiety Disorder.

Overall Conclusion

The papers investigating depressive symptoms and physical diseases (*depressive symptoms*), and gambling and physical diseases (*gambling*) showed that different psychological components – the affective component in the *depressive symptoms* paper and the behavioral in the *gambling* paper – are associated with physical diseases. This not only confirms previous findings on general mental-physical associations, but also expands findings by a behavioral component. In the light of social and economic changes, unhealthy lifestyles choices have reached epidemic proportions (World Health Organization, 2009). This fact together with current evidence on behavioral risk factors common to mental disorders and physical diseases (Oldenburg et al., 2015; Von Korff et al., 2009), calls for integrative prevention strategies for mental and physical health (Hosman, 2015; Kolappa et al., 2013; Prince et al., 2007). Additionally, the results from the investigations on *somatic symptoms* highlight that the measurement of vibrotactile perception thresholds, if confirmed in other studies and in association with other symptoms of mental disorders, might contribute to the development of new physiological screening methods for mental disorders.

Taken together, a better understanding of the associations between mental and physical conditions, as well as a better understanding of factors underlying these associations, allows for the conception of new strategies for early recognition, treatment and health care policy. The insights gained from this research might help us to overcome the traditional gap between medicine of the body and medicine of the mind.

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Appendices A to C

Appendix A

Rodic, D., Meyer, A. H., Meinlschmidt, G. (2015). The association between depressive symptoms and physical diseases in Switzerland: a cross-sectional general population study. *Frontiers in Public Health* **3**:47. doi: 10.3389/fpubh.2015.00047

Appendix B

Rodic, D., Meyer, A. H., Meinlschmidt, G. (submitted). The Association between Gambling and Physical Diseases: a Cross-Sectional Population-Based Study.

Appendix C

Rodic, D., Meyer, A. H., Lieb, R., Meinlschmidt, G. (2015). The Association of Sensory Responsiveness with Somatic Symptoms and Illness Anxiety. *International Journal of Behavioral Medicine.* doi: 10.1007/s12529-015-9483-1

Appendix A

The association between depressive symptoms and physical diseases in Switzerland: a cross-sectional general population study

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The association between depressive symptoms and physical diseases in Switzerland: a cross-sectional general population study

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Objective: To estimate the association between depressive symptoms and physical diseases in Switzerland, as respective findings might inform about future estimates of mental and physical health care costs.

Methods: A population-based study, using data from the Swiss Health Survey collected by computer-assisted telephone interviews and additional written questionnaires during the year 2007 ($n = 18{,}760$) in Switzerland. The multistage stratified random sample included subjects aged 15 years and older, living in a private Swiss household with a telephone connection. Complete data were available for 14,348 subjects (51% of all subjects reached by telephone). Logistic regression analyses were used to estimate the associations between depressive symptoms and any physical disease, or a specific physical disease out of 13 non-communicable physical diseases assessed with a self-report checklist on common physical diseases. Analyses were adjusted for sex, age, education, occupation, and household income.

Results: In the adjusted models, depressive symptoms were associated with arthrosis and arthritis [Odds Ratio (OR) = 1.79, 95% confidence interval (CI) = 1.28-2.50] and any physical disease (OR = 1.67, 95% CI = 1.33-2.10) after controlling for multiple testing.

Conclusion: Our findings contribute to a better understanding of the comorbidity of depressive symptoms and arthrosis and arthritis in Switzerland and might have implications for more precise future estimates of mental and physical health care costs.

Keywords: comorbidity, co-occurrence, depressive symptoms, major depression, mental–physical, mental–somatic, physical disease

INTRODUCTION

Depression is a global leading cause of disability (1–3), affecting 350 million people worldwide (4). According to the World Health Organization, annually more than 36 million people die of non-communicable physical diseases worldwide (5). Population-based studies around the world revealed that the presence of depressive symptoms is strongly associated with the presence of a wide range of physical diseases (6). This association has especially been reported in subjects with migraine (7, 8), asthma (7), diabetes (9, 10), chronic musculoskeletal disorders (11, 12), such as rheumatoid arthritis (13), stomach and duodenal ulcer (14), osteoporosis (15), chronic obstructive pulmonary disease (COPD) (16, 17), cardiovascular diseases (18), high blood pressure (19), myocardial infarction (20), apoplexy (21), renal disease and calculi (22), cancer (23), and allergies (24). Previous research showed that depression is associated with a wide range of physical diseases with the strongest association being reported with cardiovascular diseases (18), diabetes (9, 10), COPD (16), and chronic musculoskeletal disorders (11, 12). However, findings on the direction of the respective associations remain heterogeneous (25–28).

While there are a couple of studies, which assessed the patterns of depressive symptoms and physical diseases in large (>10,000 participants) samples (6, 7, 29–31), the majority of studies comprised much smaller samples (e.g., in the field of depression and arthrosis and arthritis 13). Therefore, high quality replication studies, assessing depression in large representative nation-wide samples are highly warranted.

While these findings cover the situation in a broad number of low-, middle-, and large high-income countries (6), less focus has been spent on small high-income countries, such as Switzerland (32). Switzerland ranks among the top three countries in overall prosperity (33) and has one of the best and most expensive health care systems worldwide (34). Therefore, it might be interesting to examine whether previous findings on the association between depression and physical diseases extend to Switzerland.

Furthermore, increased life expectancy together with an overall increased average age, not only in Switzerland (34) but also in most other regions of the world (5), is expected to result in higher

Abbreviations: CI, confidence interval; CIDI-SF, Composite International Diagnostic Interview Short Form; COPD, chronic obstructive pulmonary disease; OR, odds ratio; SHS, Swiss health survey.

prevalence of physical diseases (5, 35). At the same time, the prevalence of mental disorders within the working population is rising in Switzerland (36). Unfortunately, we are not yet in a position to estimate whether the comorbidity of chronic physical diseases and depression is about to increase as well, as the pattern of comorbidity has, to the best of our knowledge, not yet been determined in Switzerland. Our study might lay the foundation for further studies assessing the changes of mental–physical comorbidity patterns over time, as the present data derive from a nation-wide health survey conducted every 5 years in Switzerland.

Evidence suggests that patients suffering from physical diseases and comorbid mental disorders show increased mortality rates, decreased quality of life, and poorer health care outcomes as compared to patients with physical diseases without comorbid mental disorders (37, 38). Thus, scrutinizing the associations between mental disorders and physical diseases could provide implications for improved health care for patients with comorbid mental and physical conditions.

The presence of depressive symptoms in subjects with a physical disease increases treatment costs for this disease, as compared to subjects without depressive symptoms suffering from the same disease (39–41). To date, a potential effect of depression on treatment costs for related physical diseases was not taken into account for precise estimates of the economic burden caused by depression in Switzerland (42). Thus, it is essential to estimate the prevalence of conditions comorbid with depression, and this article might therefore contribute to more precise future estimates of costs related to depression in Switzerland and comparable countries.

Additionally, to estimate the costs for co-occurring depressive symptoms and physical diseases, it is important to not simply add the separate costs related to depressive symptoms (costs related to depression per person, multiplied by number of subjects with depression) to the separate costs related to physical diseases (costs related to physical disease, multiplied by number of subjects with physical disease), which is referred to as double counting (1). Thus, by accounting for co-occurrence of these conditions, double counting can be avoided. Thereby, the estimation of the prevalence of comorbid conditions might contribute to more precise future estimates of costs of co-occurring depressive symptoms and physical diseases.

The aim of this article was to estimate the association between depressive symptoms and physical disease in Switzerland.

MATERIALS AND METHODS

DESIGN AND SAMPLE

Data were drawn from the Swiss Health Survey (SHS) conducted by the Swiss Federal Statistical Office and carried out by the M.I.S.-Trend S.A Institute in Lausanne and Gümligen in 2007 (43). The data collection and storage for the SHS do not require formal approval by an ethical committee, as this data collection, preparation, and storage are specifically permitted under Swiss law and participants could decline to participate or withdraw at any time (SR 431.012.1; SR 431.112.1). The authors of this manuscript were not involved in data collection. Anonymized data for further analysis were obtained upon signing a data confidentiality and privacy contract from the Swiss Federal Statistical Office upon request.

The SHS is a periodic, nation-wide, and cross-sectional survey consisting of a computer assisted telephone interview followed by a written questionnaire. The multistage stratified random sample included subjects aged 15 years and older, living in a private Swiss household with a telephone connection in 2007. Out of the 30,179 randomly selected private households a total of 18,760 subjects completed the telephone interview, corresponding to a response rate of 66% (**Figure 1**). The additional written questionnaire was completed by 77% ($n = 14{,}348$) of the interview participants (**Figure 1**).

The SHS, among others, provides representative data on mental and physical health and healthcare utilization (43). A detailed description of the SHS methodology and sampling has been described elsewhere (44) and descriptive results of the SHS have been reported in the Swiss Health Observatory of 2013 (45).

ASSESSMENT OF DEPRESSIVE SYMPTOMS

Depressive symptoms were assessed with the screening scale for depression (46) from the World Health Organization Composite International Diagnostic Interview Short Form (CIDI-SF) in the SHS. Participants were asked whether they felt sad, blue, or depressed for two or more weeks during the past 12 months, followed by a series of questions on symptoms related to depression, such as weight gain or loss. A summary score was calculated based on the positive responses to these symptom-related questions (range 0–7). Subjects scoring above a cut-off of three symptoms were screened positive for major depression. A detailed description of the CIDI-SF scoring has been reported elsewhere (47). The CIDI-SF has demonstrated good performance for depression in large community samples (48–50). Moreover, the CIDI-SF screening scale for depression demonstrated good reliability and validity in the SHS sample (51).

ASSESSMENT OF PHYSICAL DISEASES

In the SHS, common non-communicable physical diseases were assessed with a self-report checklist, based on the European Health Interview Survey (52). Participants were asked whether they received recent (more than 12 months ago) or current (during the past 12 months) treatment by a medical doctor for each physical disease out of a list of 13 conditions. These conditions included migraine, asthma, diabetes, arthrosis and arthritis, stomach ulcer and duodenal ulcer, osteoporosis, COPD and emphysema, high blood pressure, myocardial infarction, apoplexy, renal disease and renal calculi, cancer and blastoma, and allergies like hay fever. Comparable checklists have shown high accord with medical records (53, 54) and better accuracy than consultation rates in national studies (55).

ASSESSMENT OF SOCIO-DEMOGRAPHIC MEASURES

We considered sex, age, education, occupation, and equivalized household income as covariates as these characteristics have previously been linked to depression (56–58) and physical diseases (59). Age was treated as categorical variable grouped into six categories: 15–30, 31–40, 41–50, 51–60, 61–70, and 71 years and above. The educational level comprised three categories: mandatory school, secondary school, and university (60). Occupation was categorized into the four categories middle/higher senior management,

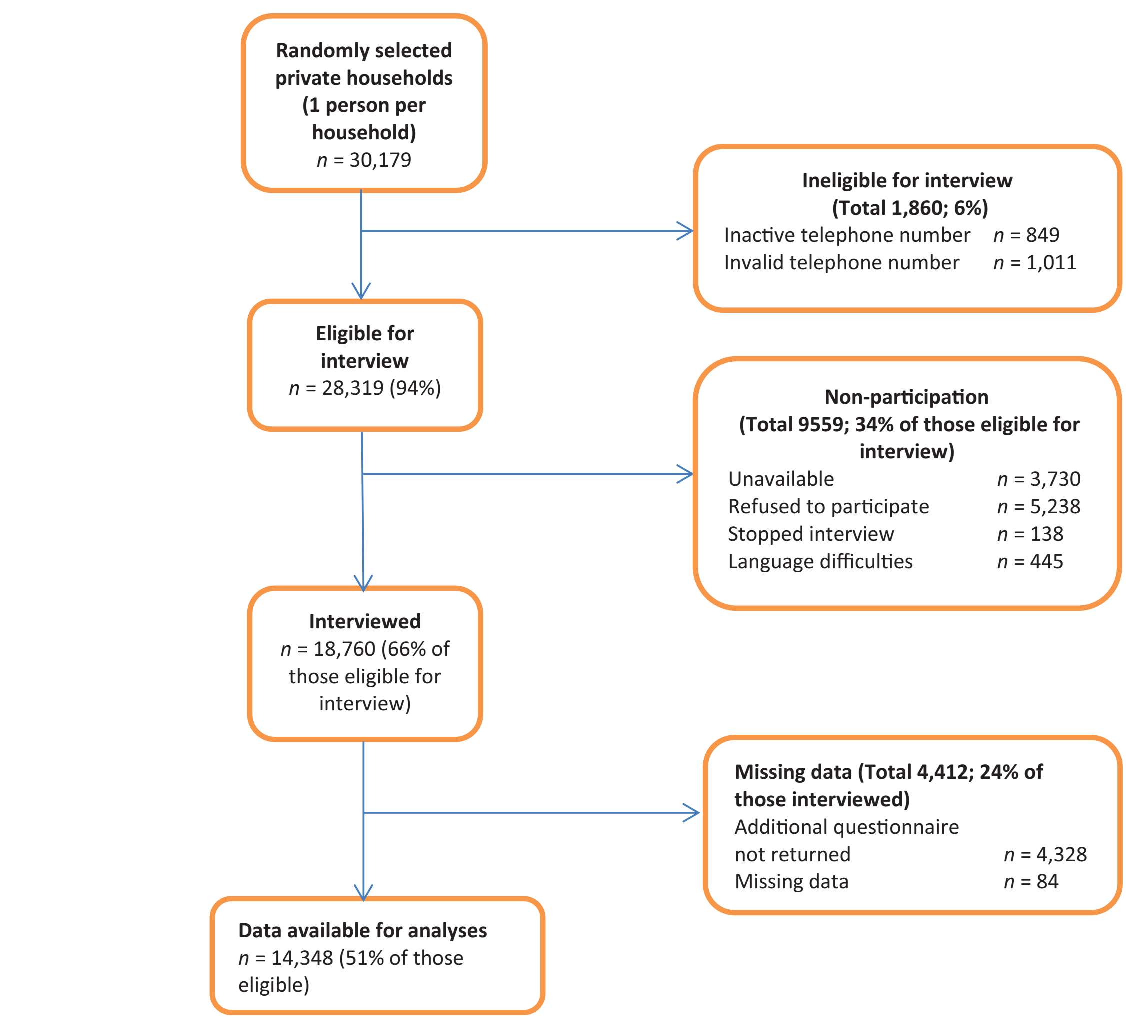

FIGURE 1 | Flowchart of study participants.

office employees/other non-manual professions, small business owners/independent craftspeople, and workpeople, based on the Erikson–Goldthrope–Portocarero classification of occupation (60, 61). The equivalized household income, a continuous index representing a gradient between low and high income, was calculated by dividing the monthly household income by the weighted number of person in the household, where a weight of 1.0 was set for the first person over 15 years, 0.5 for each additional person, and 0.3 for each child under 15 years (60, 62).

STATISTICAL ANALYSES

The goal was to assess the relationship between depressive symptoms and various types of physical disease. We run 14 separate logistic regression models (unadjusted models) with depressive symptoms (yes/no) as predictor, and each of the 13 physical diseases (yes/no) or all combined diseases ("any physical disease"; yes/no) as outcomes. We additionally ran the same 14 models, controlling for the following covariates: sex, age, education, occupation, and equivalized household income (adjusted models). Results reported in the main test derived from the adjusted models. Results from the unadjusted models can be found in the online Supplementary Material (Table S1). A significance test for the predictor depressive symptoms was obtained by comparing the full model with the same model while excluding the predictor depressive symptoms, using a likelihood ratio test.

All analyses were carried out with the recommended standardized sampling weights for the SHS sample (44). Descriptive analyses were performed using the IBM Statistical Package for Social Sciences 21 (IBM Corp. Released 2012, IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.). Regression analyses were performed using R, version 2.14.2 (63), including the R package survey (64). All tests were two-tailed with a significance level of 0.05. We controlled for multiple testing using the Holm–Bonferroni method (65).

RESULTS

Complete data were available for 14,348 subjects (51% of all subjects reached by telephone). **Table 1** presents the characteristics of this subsample. Of the 14,348 subjects, 740 (weighted percentage = 5.2) were screened positive for depressive

Table 1 | Sample characteristics ($n = 14{,}348$).

Socio-demographics	N	% (%[w])
Sex		
Female	8,057	56.2 (51.1)
Male	6,291	43.8 (48.9)
Age in years		
15–30	2,221	15.5 (24.0)
31–40	2,589	18.0 (17.5)
41–50	2,714	18.9 (19.5)
51–60	2,354	16.4 (15.1)
61–70	2,382	16.6 (12.5)
71+	2,088	14.6 (11.3)
Educational level		
Mandatory school	1,725	12.0 (11.7)
Secondary level	8,660	60.4 (61.7)
University	3,963	27.6 (26.7)
Occupation		
Workpeople	3,428	23.9 (25.4)
Small business owners/ independent craftspeople	1,164	8.1 (7.6)
Office employee/other non-manual professions	3,497	24.4 (22.9)
Middle/higher senior management	5,628	39.2 (38.3)
Unknown	631	4.4 (5.8)

	Median (25th–75th percentile)
Equivalized household income in CHF[a]	3,700 (2,500–5,333)

	n (%[w])	
Physical diseases	**With depressive symptoms $n = 740$**	**Without depressive symptoms $n = 13{,}608$**
Any physical disease	270 (35.8)	4,127 (30.4)
Migraine	46 (6.1)	315 (2.3)
Asthma	28 (3.7)	354 (2.6)
Diabetes	23 (3.1)	398 (2.9)
Arthrosis, arthritis	82 (10.9)	1,104 (8.1)
Stomach ulcer, duodenal ulcer	16 (2.1)	124 (0.9)
Osteoporosis	30 (4.0)	327 (2.4)
COPD, emphysema	23 (3.1)	249 (1.8)
High blood pressure	80 (10.6)	1,841 (13.5)
Myocardial infarction	8 (1.1)	173 (1.3)
Apoplexy	4 (0.5)	73 (0.5)
Renal disease, renal calculi	17 (2.3)	125 (0.9)
Cancer, blastoma	28 (3.7)	216 (1.6)
Allergies, hay fever	67 (8.9)	806 (5.9)

n, unweighted number of subjects; %[w], weighted percentage; CHF, Swiss Franc, COPD, chronic obstructive pulmonary disease.
[a]Gradient between low and high income.

symptoms. The number of subjects with specific physical diseases, stratified by the presence/absence of depressive symptoms, is presented in **Table 1**.

Table 2 | Adjusted logistic regression models[a] of physical diseases predicted by depressive symptoms ($n = 14{,}348$).

Physical disease	n of subjects with condition	OR (95% CI)	$p_{uncontrolled}$/$p_{controlled}$[b]
Any physical disease	4,397	1.67 (1.33, 2.10)	<0.001*/–
Migraine	361	2.07 (1.27, 3.39)	0.008*/0.087
Asthma	382	1.49 (0.91, 2.44)	0.137/0.694
Diabetes	421	2.05 (1.17, 3.61)	0.023*/0.182
Arthrosis, arthritis	1,186	1.79 (1.28, 2.50)	0.002*/0.021*
Stomach ulcer, duodenal ulcer	140	1.44 (0.71, 2.94)	0.340/1.000
Osteoporosis	357	1.86 (0.91, 3.81)	0.116/0.694
COPD, emphysema	272	2.33 (1.29, 4.21)	0.012*/0.123
High blood pressure	1,921	1.29 (0.92, 1.81)	0.159/0.694
Myocardial infarction	181	0.90 (0.33, 2.45)	0.828/1.000
Apoplexy	77	1.37 (0.33, 5.83)	0.680/1.000
Renal disease, renal calculi	142	2.63 (1.31, 5.29)	0.017*/0.149
Cancer, blastoma	244	2.45 (1.40, 4.30)	0.005*/0.064
Allergies, hay fever	873	1.59 (1.05, 2.41)	0.042*/0.297

OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.
$^*p < 0.05$.
[a]Results are adjusted for age, sex, education, occupation, and household income.
[b]Controlled for multiple testing using Holm–Bonferroni method.

The results of the logistic regression models are presented in **Table 2**. Depressive symptoms were associated with an increased risk for migraine, diabetes, arthrosis and arthritis, COPD and emphysema, renal disease and renal calculi, cancer and blastoma, allergies like hay fever, and the risk for any physical disease. However, after Holm–Bonferroni correction, only the association of depressive symptoms with arthrosis and arthritis remained (OR = 1.79, 95% CI = 1.28-2.50).

DISCUSSION

The aim of the present analyses was to estimate the association between depressive symptoms and physical diseases in a representative population sample in Switzerland. The presence of depressive symptoms was associated with an increased risk for any physical disease and after correcting for multiple testing with an increased risk for arthrosis and arthritis.

To the best of our knowledge, this is the first study to determine the pattern of comorbidity of depressive symptoms and physical diseases in Switzerland. Our results are in line with previous studies reporting associations between depression and physical diseases in general (66–70) and associations between depression and arthrosis and arthritis (6, 11, 71, 72) in particular. Moreover, our findings are in line with findings on the high prevalence of depression in patients with different physical diseases (26), as well as in patients with musculoskeletal disorders, such as osteoarthritis and rheumatoid arthritis (11, 12). In addition, a recent meta-analysis confirmed the high prevalence of depression in patients with rheumatoid arthritis (13). However, our findings are not in line with previous studies reporting comorbid depressive symptoms in patients with cardiovascular disease (18, 73), diabetes (9, 10), or COPD (16, 17).

However, this might be due to a relatively lower statistical power and related less precise estimation of comorbidity for those physical diseases under study with lower prevalence (including, stomach and duodenal ulcer, COPD and emphysema, myocardial infarction, apoplexy, renal disease and calculi, cancer, and blastoma).

Due to the cross-sectional nature of this study, we are not able to draw conclusions about the causality of the estimated associations. We consider three different models to explain the estimated associations: (A) depressive symptoms may lead to physical diseases, more specifically to arthrosis and arthritis; (B) physical diseases, among other arthrosis and arthritis, may lead to depressive symptoms; (C) there may be common factors leading to both depressive symptoms and physical diseases, especially arthrosis and arthritis.

With regard to (A), it has been shown that depressive symptoms cause disability (1) and are related to a loss of interest in everyday activities (74). Moreover, depressive symptoms have been associated with unfavorable health behavior, such as smoking (75, 76). Therefore, one may speculate that depressive symptoms may, via unfavorable health behavior, pave the way for chronic physical disease. More specifically, depression is related to reduced physical activity (77) and that has been associated with musculoskeletal disorders, such as osteoarthritis (12).

With regard to (B), one may speculate that having a chronic physical disease decreases quality of life (78, 79), which might affect the mental health status of a person with a physical disease (23, 80, 81) resulting in reduced subjective well-being and ability to cope with everyday life in individuals with poor mental health (82). The perception of being unable to cope with everyday requirements has been associated with depression (83, 84) and this might lead to a loss of interest in daily activities, resulting in decreased positive reinforcement to participate in everyday life, which has been associated with depression (85, 86). More specifically, arthrosis and arthritis have been associated with reduced physical activity (87) and it has been shown that physical activity has a beneficial effect on depressive symptoms (88–90). Thus, arthrosis and arthritis might therefore favor the development of depressive symptoms.

With regard to (C), we can only speculate about potential further factors. Interestingly, different immune parameters, such as cytokines, have been associated with both depressive symptoms (91) and physical diseases (68, 92). Whether these parameters represent mediators of the observed associations or common risk factors for depression and physical diseases is largely unknown. Thus, further research is needed to scrutinize the mechanisms underlying the association between depression and physical diseases.

Our analysis has several strengths: first, we included a representative population sample totaling 14,348 subjects. Second, the presence of physical diseases was verified by receiving treatment from a medical doctor. Third, we controlled for potential confounders that have been previously linked to depression (56–58) and physical diseases (59). Finally, we corrected for multiple testing, as recommended (93–95).

This study also has limitations and our findings need replication in an independent dataset. First, the non-response rate within the SHS might have caused a selection bias (96). Therefore future studies aiming to a higher response rate are needed in Switzerland. Second, we were not able to determine the severity of depressive symptoms and any of the physical diseases, as this information was not available from the SHS data. This might have led to underestimation of conditions present in the general population. Therefore, studies precisely aiming to investigate the prevalence and severity of depressive symptoms and depressive disorders, as well as physical diseases, in the general population are urgently needed in Switzerland. Future studies should allow for the detection of subtle variations of depressive symptoms in the general population, and estimate how these variations relate to comorbidity with physical diseases. Third, physical diseases were assessed with a self-report checklist. However, comparable checklists highly accorded with medical records (53, 54) and showed better accuracy than consultation rates in national studies (55). Furthermore, all data on physical diseases and corresponding disease categories were predefined in the SHS. Thus, we were not able to analyze the conditions arthrosis and arthritis as separate diagnoses, as this information was not available from the SHS data. However, both conditions are diseases of the musculoskeletal system and connective tissue and involve similar symptoms, such as pain and inflammation (97).

With regard to generalizability of the findings, caution is warranted. It is questionable whether our findings on the association between depressive symptoms and physical diseases in Switzerland are applicable to other high-income countries because of Switzerland's high performing health care system (34). However, our results on the association between depressive symptoms and arthrosis and arthritis in Switzerland do not substantially differ from representative community-based results in Canada (7), which is also a high-income country (32).

Due to the cross-sectional nature of our study, we abstained from expressing a clear preference for one of the possible explanations given for the associations between depressive symptoms and any physical diseases, respectively, arthrosis and arthritis. In this study, depressive symptoms were associated with any physical disease and depressive symptoms were related to an increased risk for arthrosis and arthritis. Our findings may contribute to a better understanding of the comorbidity of depressive symptoms and physical diseases, as well as provide the basis for a better understanding of the changes of mental–physical comorbidity over time in Switzerland. We found that depressive symptoms were related to arthrosis and arthritis, which might have implications for clinical practice. They suggest considering to encourage the screening of subjects with arthrosis and arthritis for depressive symptoms and vice versa. Early recognition of the co-occurrence of depressive symptoms with arthrosis or arthritis might allow for an improved coordination of interdisciplinary treatment (specialized therapies depending on the outcome of the screening) and this may positively influence the course of both conditions. Treatment costs of physical diseases are higher for subjects with co-occurring depressive symptoms than for subjects without depressive symptoms suffering from the same disease (39–41). Thus, knowledge about the comorbidity of depression and physical diseases may allow a more comprehensive estimate of the overall costs related to depression. Therefore, our results might have implications for more precise future estimates of costs related to depression, including secondary costs, related to increased expenditures for co-occurring physical conditions in Switzerland. Additionally, by accounting for co-occurrence of comorbid conditions, double counting can be avoided (1), which might contribute to more precise future estimates for costs of co-occurring depressive symptoms and physical diseases.

Future studies should focus on the mechanisms underlying the association between depressive symptoms and the increased risk for physical disease in general and arthrosis and arthritis in particular.

AUTHOR CONTRIBUTIONS

DR drafted the manuscript. DR and GM conceived and designed the research question and analyses. AM performed the statistical analyses. DR and GM interpreted the results. GM supervised the study and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/Journal/10.3389/fpubh.2015.00047/abstract

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Appendix B

The Association between Gambling and Physical Diseases: a Cross-Sectional Population-Based Study

Submitted to Psychological Medicine

Title

The Association between Gambling and Physical Diseases: a Cross-Sectional Population-Based Study

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ABSTRACT

Background: With the growth and online expansion of the gambling industry, games of chance have become more accessible. Pathological gambling has been associated with physical diseases. Whether gambling behavior itself is associated with physical diseases is still to be determined.

Objective: To estimate if gambling is associated with a wide range of non-communicable physical diseases in a population-based survey.

Methods: Population-based study, using data from the Swiss Health Survey collected during the year 2007 (n=18,760, age>15 years) in Switzerland**.** Complete data was available for 11,385 subjects (61% of interviewed subjects). We conducted separate logistic regression models with each out of five non-communicable physical diseases or any physical disease in the past 12 months as outcomes. We used gambling versus not gambling in the past 12 months as predictor, controlling for sex, age, education, occupation, and household income.

Results: Subjects who reported to have gambled in the past 12 months had an increased risk of diabetes (Odds Ratio [OR]=1.34, 95%Confidence Interval [CI]=1.02−1.75), arthrosis and arthritis (OR=1.29, 95%CI=1.07−1.56), high blood pressure (OR=1.20, 95%CI=1.03−1.40), allergies like hay fever (OR=1.36, 95%CI=1.10−1.68), and any physical disease (OR=1.25, 95%CI=1.10−1.41).

Conclusions: Our findings contribute to a better understanding of the co-occurrence of gambling and physical diseases and might have implications for the prevention of physical diseases associated with gambling. Understanding the association between gambling and physical conditions might assist in the reduction of the costs to the health care system.

Keywords: gambling, comorbidity, co-occurrence, correlates, physical diseases

Introduction

Gambling, in terms of participating in games of chance with an opportunity to profit, is a widespread behavior (Bundeszentrale für gesundheitliche Aufklärung, 2014, Hodgins *et al.*, 2011, Wardle *et al.*, 2011, Welte *et al.*, 2002), with up to 82% of the general adult population in the US engaging in gambling within 12 months (Welte *et al.*, 2002). In Germany, 39% to 55% of the general adult population reported having participated in some sort of gambling in the past 12 months (Bundeszentrale für gesundheitliche Aufklärung, 2014). In 2011 the overall European gambling market showed a projected annual growth rate of approximately 3%, with online gambling showing the highest annual growth rate of around 15% (European Commission, 2012). Persistent problematic gambling behavior leading to clinically significant impairment, defined as Gambling Disorder in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) (American Psychiatric Association, 2013), formerly referred to as "Pathological Gambling" in the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) (American Psychiatric Association, 1994), has been associated with several mental disorders, such as affective and substance use disorders (Dowling *et al.*, 2015, El-Guebaly *et al.*, 2006, Lorains *et al.*, 2011, Petry *et al.*, 2005, Yip *et al.*, 2011). Moreover, pathological gambling has been associated with lower social functioning and psychosocial wellbeing (Bergh and Kuhlhorn, 1994), poorer general physical health (Erickson *et al.*, 2005, Morasco *et al.*, 2006b), and lower physical activity and obesity (Black, Shaw, McCormick, & Allen, 2013).

Notably, physical inactivity, obesity, tobacco use and alcohol abuse are among the leading risk factors for mortality, as they raise the risk for chronic non-communicable physical diseases (World Health Organization, 2009). According to the World Health Organization, more than 36 million people die of non-communicable physical diseases worldwide, with the main causes of death being cardiovascular diseases, cancer, diabetes and chronic lung diseases (World Health Organization, 2011). However, and to the best of our knowledge, there are only three publications based on large (> 10,000 participants) nationally representative samples estimating the association between pathological gambling and selected physical diseases (Black *et al.*, 2013).

Notably, all three publications were based on data from the National Epidemiologic Survey on Alcohol and Related Conditions, including a representative sample of 43,093 noninstitutionalized adults in the U.S. Pathological gamblers (subjects who had gambled five or more times in a single year and fulfilled at least five out of ten DSM-IV criteria for pathological gambling) more frequently reported to be diagnosed (self-reported medical diagnoses) with tachycardia, angina, cirrhosis, and other liver diseases in the past year than individuals who were identified as at low-risk for gambling (subjects who had never gambled and those who may have gambled in their lifetime, but not more than five times in a single year) (Morasco *et al.*, 2006a). Moreover, participants identified as problem gamblers (gambled five or more times in a single year and met three or four DSM-IV pathological gambling symptoms) and at-risk gamblers (gambled five or more times in a single year and met zero to two DSM-IV symptoms) more likely reported to be diagnosed with hypertension in the past year than low-risk individuals, whereas problem gamblers more frequently reported to be diagnosed with angina and cirrhosis in the past year than low-risk individuals (Morasco *et al.*, 2006a). Older subjects (60 years and older) with a lifetime history of disordered gambling (category includes problem and pathological gamblers, who gambled five or more times in a single year and met at least three, respectively five, DSM-IV symptoms for pathological gambling in the past year and/or at some previous point in lifetime) more likely had a past-year diagnosis of angina and arthritis than older non-gamblers (subjects who had never gambled five or more times in a single year in their lifetime) (Pietrzak *et al.*, 2007). Problem gamblers between 40 to 64 years (gambled five or more times in a single year and met at least three DSM-IV symptoms) more frequently reported to be diagnosed with obesity, heart disease, cirrhosis and other liver diseases, stomach diseases, arthritis, and any chronic medical condition in the past year than recreational gamblers (gambled more than five times in a single year in their lifetime and met zero to two DSM-IV symptoms) and non-gamblers (never gambled more than five times in a single year in their lifetime) (Desai *et al.*, 2007). Another study, comparing pathological gamblers (lifetime South Oaks Gambling Score and DSM-IV Screen for Gambling Problems over five, and met DSM-IV criteria for pathological gambling) (*n* = 95) to matched subjects not engaging in gambling (lifetime South Oaks Gambling Score below two and DSM-IV Screen for Gambling Problems score of zero) (*n* = 91), reported higher prevalence of any chronic physical health condition (self-reported), obesity, heartburn/stomach condition, headache, and sleep disorders (Black *et al.*, 2013) in pathological gamblers as compared to non-gamblers. A recent study assessing self-reported gambling addiction (comparable with pathological gambling) in participants from the general population in Japan (*n* = 5,003) did not find any associations between lifetime gambling addiction and a wide range of current self-reported chronic physical diseases, except for the association between gambling addiction and hay fever (Shiue, 2015). Taken together, these studies provided evidence for associations between pathological gambling and a variety of physical diseases. More specifically, pathological gambling (past 12 months and lifetime) was linked to an increased risk for certain physical diseases in the past 12 months. However, these findings remain heterogeneous due to the different criteria and thresholds for pathological gambling, as well as assessment instruments used to assess gambling behavior. It is not yet known whether gambling behavior per se, as an important dimension of Gambling Disorder, is associated with physical diseases.

To the best of our knowledge, this is the first study assessing the association between gambling behavior and non-communicable physical diseases in a large-scale, nation-wide, representative population-based survey.

The purpose of this study was to estimate whether gambling is associated with a wide range of physical diseases. More specifically, we wanted to estimate whether subjects who had gambled in the past 12 months compared with subjects who had not gambled in the past 12 months had an increased risk for any or a specific physical disease in the past 12 months.

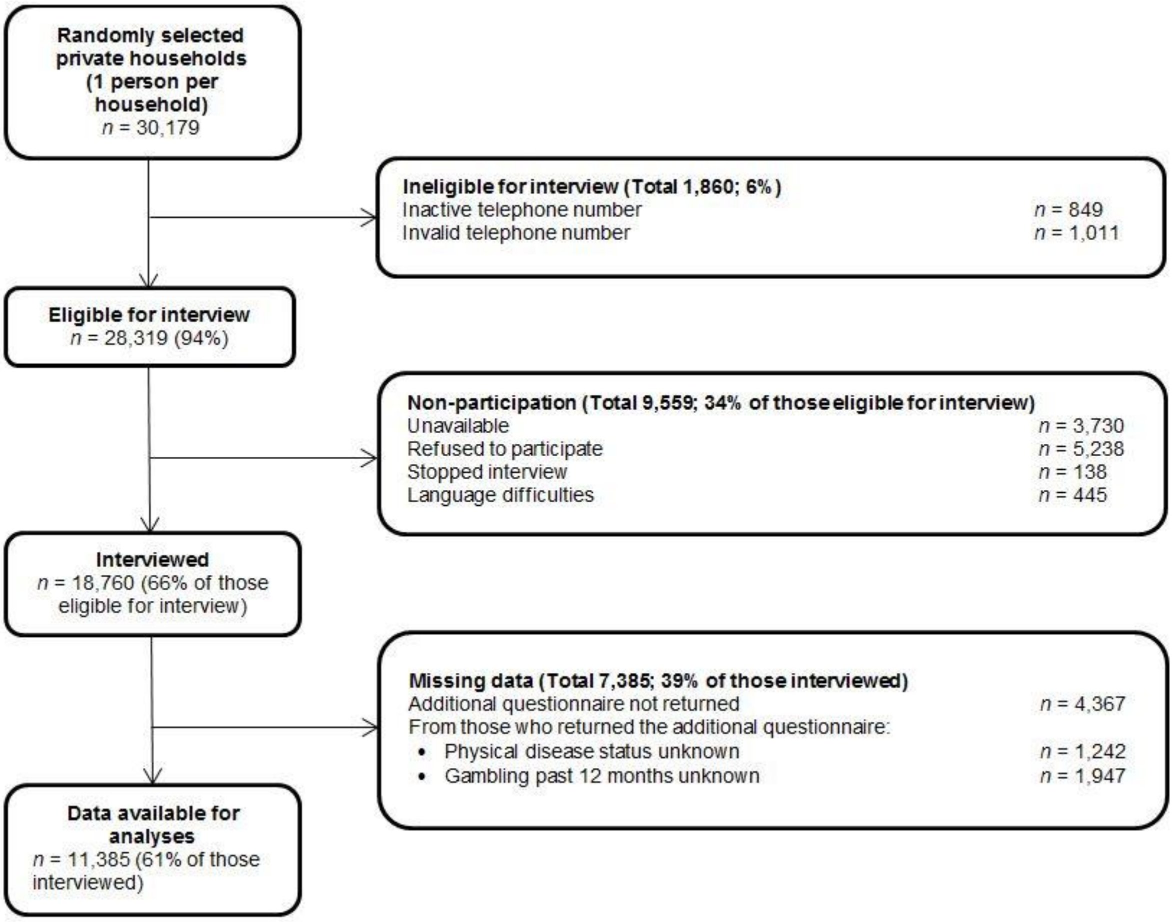
Methods

Design and sample

This study is based on data from the Swiss Health Survey (SHS), carried out by the M.I.S.-Trend S.A Institute in Lausanne and Gümligen in 2007 and conducted by the Swiss Federal Statistical Office (Bundesamt für Statistik, 2008). The data collection and storage for the Swiss Health Survey does not require formal approval by an ethical committee, as this data collection, preparation and storage are specifically permitted under Swiss law and participants could decline to participate or withdraw at any time (SR 431.012.1; SR 431.112.1). The authors of this manuscript were not involved in data collection. Anonymized data for further analyses was obtained upon signing a data confidentiality and privacy contract from the Swiss Federal Statistical Office.

The SHS is a cross-sectional, periodic survey, including a computer assisted telephone interview and an additional written questionnaire. Subjects aged 15 and older, living in private Swiss households with a telephone connection in 2007, were part of the multistage stratified random sample. Out of 30,179 randomly selected private households, 18,760 completed the telephone interview, corresponding to a response rate of 66% (Bundesamt für Statistik, 2008) (Figure 1). The SHS methodology and sampling have been described elsewhere (Graf, 2010).

FIGURE 1. Flowchart of study participants



Assessment of Gambling

Gambling was assessed with self-report questions in the SHS survey. Subjects first answered the question *Have you ever played games of chance in your lifetime?* with the reply categories *Yes, at least once in lifetime* and *No, I have never played*. Subjects who replied *Yes, at least once in lifetime* or did not reply (did not give an answer) to this question were further asked *Have you played games of chance in the past 12 months?* with the reply categories *Yes*, *No* and a category containing subjects who did not give an answer. Out of the replies to these two questions we build the following two gambling categories: 1) *Gambled in the past 12 months* (replied *Yes, at least once in lifetime* to the first question and *Yes* to the second question, or did not reply to the first question and replied *Yes* to the second question) and 2) *Not gambled in the past 12 months* (replied *Yes, at least once in lifetime* to the first question and *No* to the second question; or replied *No, I have never played* to the first question; or did not reply to the first question and replied *No* to the second question). All participants, who replied *Yes, at least once in lifetime* to the first question and did not reply to the second question; or did not reply to the first and the second question, were treated as ambiguous or missing information and were therefore not included in the statistical analyses. Thus, the gambling variable consisted of the two categories *Gambled in the past 12 months* and *Not gambled in the past 12 months.*

Assessment of physical diseases

In the SHS, common non-communicable physical diseases were assessed with a self-report checklist, based on the European Health Interview Survey (Eurostat Working Group on Public Health Statistics, 2006). Participants were asked whether they received recent (more than 12 months ago) or current (during the past 12 months) treatment by a medical doctor for each physical disease out of a list of 13 conditions. We used the presence/absence of each physical disease in the past 12 months or any out of the 13 physical diseases combined as outcome. The diseases included migraine, asthma, diabetes, arthrosis and arthritis, stomach ulcer and duodenal ulcer, osteoporosis, chronic obstructive pulmonary disease (COPD) and emphysema, high blood pressure, myocardial infarction, apoplexy, renal disease and renal calculi, cancer and blastoma, and allergies like hay fever. Comparable checklists have shown high agreement with medical records (Baker *et al.*, 2004, National Center for Health Statistics, 1994) and better accuracy than consultation rates in national studies (Knight *et al.*, 2001).

Assessment of socio-demographic measures

We considered sex, age, education, occupation, and equivalised household income as covariates, as these characteristics have previously been linked to gambling (Johansson *et al.*,

2009) and physical diseases (Dalstra *et al.*, 2005). We grouped age into six categories: *15–30 years*, *31–40 years*, *41–50 years*, *51–60 years*, *61–70 years* and *71 years and above*. In the SHS, the educational level comprised three categories: *mandatory school*, *secondary school* and *university (Bundesamt für Statistik, 2007)*. Occupation was categorized into the five categories *middle/higher senior management*, *office employees/other non-manual professions*, *small business owners*/*independent craftspeople*, *workpeople*, and *unknown* based on the Erikson-Goldthrope-Portocarero classification of occupation (Bundesamt für Statistik, 2007, Erikson *et al.*, 1979). In the SHS, the equivalised household income, a continuous index representing a gradient between low and high income, was calculated by dividing the monthly household income by the weighted number of persons in the household, where a weight of 1.0 was set for the first person over 15 years, 0.5 for each additional person and 0.3 for each child under 15 years (Bundesamt für Statistik, 2007, Statistical Commission and Economic Commission for Europe, 1994).

Statistical analyses

Our goal was to examine the associations between gambling and the presence/absence of physical diseases in the past 12 months. Some of the disease categories comprised a small number of cases with the respective condition. Although it has been shown that a minimum of 5 events per predictor variable is sufficient for logistic regression models (Vittinghoff and McCulloch, 2007), we wanted to be conservative and only included disease categories with a minimum of 10 events per predictor in the analyses (Peduzzi, Concato, Kemper, Holford, & Feinstein, 1996). Thus, the following eight disease categories were excluded from further analyses: migraine, stomach and duodenal ulcer, osteoporosis, COPD and emphysema, myocardial infarction, apoplexy, renal diseases and renal calculi, as well as cancer and blastoma. The five remaining physical disease categories asthma, diabetes, arthrosis and arthritis, high blood pressure, and allergies like hay fever, as well as the presence of any of all 13 diseases (*any physical disease*) were used in the analyses.

We conducted separate logistic regression models with each of the five physical diseases (yes/no) or all 13 combined diseases (*any physical disease*; yes/no) as outcomes. We used gambling as predictor with the two categories 1) *Gambled in the past 12 months* and 2) *Not gambled in the past 12 months.* All models were adjusted for the following covariates: sex, age, education, occupation, and equivalised household income outlined in Table 1. As the equivalised household income comprised missing values, we created an additional predictor indicating whether a value for equivalised household income was present or not. If a value for the equivalised income was present then the income category was added to the analyses. For the sake of transparency, we provided additional crude results based on logistic models unadjusted for covariates, in the online supplement (Table 3).

All analyses were carried out with the recommended standardized sampling weights for the SHS sample (Graf, 2010). Analyses were performed using R, version 2.14.2 (R Development Core Team, 2012), including the R package survey (Lumley, 2012). All tests were two-tailed with a significance level of 0.05.

Results

Complete data was available for 11,385 subjects. Table 1 presents the characteristics of this sample stratified according to gambling behavior (*Gambled in the past 12 months* or *Not gambled in the past 12 months*).

TABLE 1. Sample Characteristics (*n* = 11,385)

	Gambled in the past 12 months (*n* = 5,624)	Not gambled in the past 12 months (*n* = 5,761)	Total sample (*n* = 11,385)
Socio-demographics			
Sex (n, % [w])			
Female	2,755 (43.1)	3,625 (58.9)	6,380 (51.0)
Male	2,869 (56.9)	2,136 (41.1)	5,005 (49.0)
*Age in years (n, % [w])**			
15-30	967 (26.7)	918 (24.8)	1,885 (25.7)
31-40	1,180 (19.9)	904 (15.1)	2,084 (17.5)
41-50	1,167 (20.5)	990 (18.0)	2,157 (19.3)
51-60	1,023 (15.9)	888 (14.7)	1,911 (15.3)
61-70	822 (10.8)	1,012 (13.2)	1,834 (12.0)
71+	465 (6.1)	1,049 (14.1)	1,514 (10.1)
Educational Level (n, % [w])			
Mandatory School	580 (10.2)	726 (12.5)	1,306 (11.4)
Secondary Level	3,604 (65.0)	3,389 (60.2)	6,993 (62.6)
University	1,440 (24.8)	1,646 (27.3)	3,086 (26.0)
*Occupation (n, % [w])**			
Workpeople	1,417 (27.0)	1,297 (23.9)	2,714 (25.4)
Small business owners[a]	431 (7.2)	493 (7.9)	924 (7.5)
Office employee (and other non-manual)	1,473 (25.1)	1,355 (21.5)	2,828 (23.3)
Senior management (middle and higher)	2,150 (36.3)	2,275 (39.1)	4,425 (37.7)
Unknown	153 (4.3)	341 (7.6)	494 (6.0)
Equivalised household income in CHF [b] (Median, 25th−75th percentile)	3,733 (2,581−5,333)	3,600 (2,400−5,100)	3,696 (2,500−5,250)
Physical diseases			
Any physical disease[c] (*n*, %[w])	1,835 (29.3)	2,008 (30.9)	3,843 (30.1)
Migraine[c] (*n*, %[w])	146 (2.8)	170 (3.2)	316 (3.0)
Asthma[c] (*n*, %[w])	175 (3.0)	173 (3.1)	348 (3.0)
Diabetes[c] (*n*, %[w])	181 (2.6)	183 (2.6)	364 (2.6)
Arthrosis, Arthritis[c] (*n*, %[w])	466 (6.8)	560 (7.6)	1,026 (7.2)
Stomach Ulcer, Duodenal Ulcer[c] (*n*, %[w])	64 (1.0)	63 (1.0)	127 (1.0)
Osteoporosis[c] (*n*, %[w])	99 (1.3)	221 (2.9)	320 (2.1)
COPD, Emphysema[c] (*n*, %[w])	126 (2.1)	124 (1.9)	250 (2.0)
High Blood Pressure[c] (*n*, %[w])	765 (11.5)	917 (13.3)	1,682 (12.4)
Myocardial Infarction[c] (*n*, %[w])	74 (1.0)	86 (1.5)	160 (1.2)
Apoplexy[c] (*n*, %[w])	33 (0.5)	38 (0.4)	71 (0.4)
Renal Disease, Renal Calculi[c] (*n*, %[w])	77 (1.2)	52 (0.8)	129 (1.0)
Cancer, Blastoma[c] (*n*, %[w])	105 (1.8)	109 (1.8)	214 (1.8)
Allergies, Hay Fever[c] (*n*, %[w])	434 (8.4)	347 (6.7)	781 (7.5)

n = unweighted number of subjects; %[w] = weighted percentage; CHF = Swiss Franc, COPD = chronic obstructive pulmonary disease.
* % may not sum up to 100% due to rounding.
[a] Including independent craftspeople.
[b] Gradient between low and high income. Missing information on equivalised household income: number of missings = 535.
[c] Analyses are based on completer samples due to missing information on physical diseases (migraine: *n* = 10,855; asthma: *n* = 10,881; diabetes: *n* = 10,792; arthrosis, arthritis: *n* = 10,954; stomach ulcer, duodenal ulcer: *n* = 10,852; osteoporosis: *n* = 10,884; COPD,

emphysema: *n* = 10,866; high blood pressure: *n* = 11,087; myocardial infarction: *n* = 10,874; apoplexy: *n* = 10,851; renal disease, renal calculi: *n* = 10,870; cancer, blastoma: *n* = 10,885; allergies, hay fever: *n* = 10,886; any physical disease: *n* = 10,451).

The results of the adjusted logistic regression models are presented in Table 2. Subjects who gambled in the past 12 months had an increased risk of diabetes (OR = 1.34, 95% CI = 1.02−1.75), arthrosis and arthritis (OR = 1.29, 95% CI = 1.07−1.56), high blood pressure (OR = 1.20, 95% CI = 1.03−1.40), allergies like hay fever (OR = 1.36, 95% CI = 1.10−1.68), and any physical disease (OR = 1.25, 95% CI = 1.10−1.41) as compared to subjects who did not gamble in the past 12 months.

TABLE 2. Association between gambling and physical diseases. Results based on adjusted[a] logistic regression models (*n* = 11,385).

		Gambled vs. not gambled in the past 12 months	
Physical Disease	Total *n* of subjects with physical disease	OR (95% CI)	*p*
Any Physical Disease[b]	3,837	1.25 (1.10, 1.41)	<0.001*
Asthma[b]	348	1.12 (0.83, 1.52)	0.447
Diabetes[b]	363	1.34 (1.02, 1.75)	0.034*
Arthrosis, Arthritis[b]	1,025	1.29 (1.07, 1.56)	0.008*
High Blood Pressure[b]	1,677	1.20 (1.03, 1.40)	0.023*
Allergies, Hay Fever[b]	781	1.36 (1.10, 1.68)	0.004*

n = unweighted number of subjects, OR = Odds Ratio, CI = Confidence Interval
* $p < 0.05$
[a] Results are adjusted for age, sex, education, occupation, and household income.
[b] Due to missing information on physical diseases, analyses are based on completer samples (asthma: n = 10,881; diabetes: n = 10,792; arthrosis, arthritis: n = 10,954; high blood pressure: n = 11,087; allergies, hay fever: n = 10,886; any physical disease: n = 10,451).

Discussion

The aim of the current study was to estimate the association between gambling and physical diseases in a representative population sample. Subjects who gambled in the past 12 months compared to subjects who did not gamble in the past 12 months showed an increased risk for diabetes, arthrosis and arthritis, high blood pressure, allergies like hay fever, and any physical disease in the past 12 months.

Our finding that gambling in the past 12 months was associated with an increased risk for any physical disease is in line with previous research on the association between pathological gambling and physical diseases (Black *et al.*, 2013, Morasco *et al.*, 2006a, Pasternak and Fleming, 1999). Our finding that gambling in the past 12 months was associated with an increased risk for diabetes is not in line with one other study reporting no associations between pathological gambling and diabetes (Black *et al.*, 2013). However, the sample of the study by Black and colleagues (2013) comprised only a small number of individuals reporting diabetes, thus, the confidence interval of the estimates may have been too large to provide precise results. Our finding that gambling in the past 12 months was associated with an increased risk for arthrosis and arthritis is in line with two publications reporting association between pathological gambling and arthrosis and arthritis (Desai *et al.*, 2007, Pietrzak *et al.*, 2007). Our finding that gambling in the past 12 months was associated with an increased risk for high blood pressure is in line with one study reporting associations between problematic gambling and high blood pressure (Morasco *et al.*, 2006a), whereas another study did not find any associations between pathological gambling and high blood pressure (Black *et al.*, 2013). A possible explanation for these discrepant findings might be the large difference in sample size between the study by Morasco *et al.* (2006a) and the study by Black *et al.* (2013). Another possible explanation is that we assessed gambling behavior as an activity without explicitly focusing on pathological gambling. However, gambling is an important dimension of Gambling Disorder (American Psychiatric Association, 2013) and research on gambling behavior itself, including recreational as well as pathological gambling, might therefore reveal the associations between gambling and physical diseases more clearly. Our finding that gambling in the past 12 months was associated with allergies like hay fever is in line with one study reporting associations between gambling addiction and hay fever (Shiue, 2015). Due to the cross-sectional nature of this study, we were not able to draw conclusions about the causality of the estimated associations. However, we considered three different models to explain the estimated associations. First, gambling has been associated with unfavorable health behavior, such as alcohol abuse and nicotine dependence (Dowling *et al.*, 2015), lower physical activity, and obesity (Black *et al.*, 2013). As it has been shown that alcohol abuse, tobacco addiction, lower physical activity, and obesity are risk factors for a wide range of physical diseases, such as diabetes, arthrosis and arthritis, and high blood pressure (World Health Organization, 2011), one may speculate that gambling, via unfavorable health behavior, might pave the way for physical diseases. With regard to allergies like hay fever, one may speculate that in vulnerable individuals (family history of allergies) (Kaiser, 2004) unfavourable behavior associated with gambling, such as smoking cigarettes (Dowling *et al.*, 2015), might pave the way for the allergic condition. Second, one may speculate that the disability caused by physical diseases (World Health Organization, 2011) limits a subjects ability to perform daily routines and tasks, which might result in long periods of inactivity in which the subject may resort to gambling. Third, there may be common factors leading to both, gambling and physical diseases, although we can only speculate about potential underlying factors. For example, physical inactivity and obesity have been associated with both gambling (Black *et al.*, 2013) and physical diseases (World Health Organization, 2009). Notably, whether these factors represent mediators of the observed associations or common risk factors for gambling and physical diseases is largely unknown. Thus, further research is needed to scrutinize the mechanisms underlying the association between gambling and physical diseases.

Our analyses have several strengths: First, we included a representative population sample totaling 11,385 subjects. Second the presence of physical diseases was verified by receiving treatment from a medical doctor. Third, we controlled for potential confounders that have been previously linked to gambling and physical diseases.

This study also has limitations and our findings need replication in an independent dataset. First, the non-response rate within the SHS might have caused a selection bias (Volken, 2013). Therefore future studies aiming at a higher response rate are needed. Second, we were not able to determine the severity of any of the physical diseases, as this information was not available from the SHS data. Third, physical diseases were assessed with a self-report checklist. However, comparable checklists highly accorded with medical records (Baker *et al.*, 2004, National Center for Health Statistics, 1994) and showed better accuracy than consultation rates in national studies (Knight *et al.*, 2001).

We refrained from applying the Bonferroni method to adjust for multiple testing, as the approach is critically discussed as too conservative, leading to lower power and increasing publication bias (Nakagawa, 2004, Perneger, 1998).

As we assessed gambling behavior itself and not pathological gambling, caution is warranted with regard to generalizability of the findings to pathological gamblers. However, we believe that our findings can be generalized to other community-based samples, as our results on the association between gambling and physical diseases do not substantially differ from other studies (Black *et al.*, 2013, Morasco *et al.*, 2006a, Pasternak and Fleming, 1999).

If the causality between gambling and physical diseases is confirmed in future studies, our results might point to the importance of the early assessment of gambling behavior in general, not only pathological gambling. Our findings might have implications for the prevention of physical diseases in gamblers through the assessment of gambling behavior and associated risk-factors. The treatment of non-communicable physical diseases is highly cost intensive (World Health Organization, 2011), thus an argument can be made that through early recognition of pathological gambling and associated risk-factors as well as physical conditions, the costs to the health care system could be reduced. Moreover, pathological gambling is strongly associated with financial problems (Holdsworth *et al.*, 2013, Ladouceur *et al.*, 1994, Mathews and Volberg, 2013) and might therefore increase societal costs (inability to pay for health insurance, debts). Physical health problems arising from pathological gambling further add to that burden.

In this study gambling in the past 12 months was associated with an increased risk for diabetes, arthrosis and arthritis, high blood pressure, allergies like hay fever, and any physical disease. Our findings may contribute to a better understanding of correlates of gambling in the general population. Moreover, if confirmed in independent samples, our findings may point to the potential effect of gambling on the development of physical diseases. Thus, our findings may have implications for the prevention of physical diseases. Future studies should focus on the mechanisms underlying the association of gambling and physical diseases in general and diabetes, arthrosis and arthritis, high blood pressure, and allergies like hay fever in particular.

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Conflicts of interest

None.

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Other Supplementary Material

TABLE 3. Association between gambling and physical diseases. Results based on unadjusted logistic regression models (*n* = 11,385).

		Gambled vs. not gambled in the past 12 months	
Physical Disease	Total *n* of subjects with physical disease	OR (95% CI)	*p*
Any Physical Disease[a]	3,837	0.93 (0.83, 1.03)	0.157
Asthma[a]	348	0.98 (0.73, 1.31)	0.863
Diabetes[a]	363	1.02 (0.78, 1.34)	0.886
Arthrosis, Arthritis[a]	1,025	0.88 (0.74, 1.04)	0.145
High Blood Pressure[a]	1,677	0.85 (0.74, 0.97)	0.017*
Allergies, Hay Fever[a]	781	1.27 (1.04, 1.56)	0.021*

n = unweighted number of subjects, OR = Odds Ratio, CI = Confidence Interval

* $p < 0.05$

[a] Due to missing information on physical diseases, analyses are based on completer samples (asthma: n = 10,881; diabetes: n = 10,792; arthrosis, arthritis: n = 10,954; high blood pressure: n = 11,087; allergies, hay fever: n = 10,886; any physical disease: n = 10,451).

Appendix C

The Association of Sensory Responsiveness with Somatic Symptoms and Illness Anxiety

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Title

The Association of Sensory Responsiveness with Somatic Symptoms and Illness Anxiety

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Abstract

Background: Somatoform Disorders or Somatic Symptom and Related Disorders are a major public health problem. The pathophysiology underlying these disorders is not yet understood.

Purpose: The aim of this study was to explore if sensory responsiveness could contribute to a better understanding of pathophysiological mechanisms underlying two key symptoms of Somatoform Disorders, namely somatic symptoms and illness anxiety.

Methods: We measured vibrotactile perception thresholds with the HVLab Perception Meter and examined their association with somatic symptoms, illness anxiety and trait anxiety. A sample of 205 volunteers participated in the study.

Results: Sensory responsiveness was neither associated with somatic symptoms (β=−0.01; 95 % confidence interval (CI), −0.37, 0.39) nor trait anxiety (β=−0.07; 95 % CI, −0.30, 0.07). However, lower vibrotactile perception thresholds were associated with increased scores of the overall illness anxiety scale (β=−0.65; 95 % CI, −1.21, −0.14) and its constituent subscale disease conviction (β=−2.07; 95%CI, −3.94, −0.43).

Conclusions: Our results suggest that increased sensory responsiveness is associated with illness anxiety and hence should be examined further as potential target within the etiopathology of somatoform disorders.

Keywords illness anxiety, medically unexplained somatic symptoms, sensory responsiveness, vibrotactile perception threshold

Abbreviations

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders IV

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders 5

VPT = Vibrotactile perception threshold

EKBB = Ethics Committee Basel

SOMS = Screening for Somatoform Symptoms

WI = Whiteley-Index

STAI = State-Trait Anxiety Inventory

SES = Socio-Economic Status

dB = Decibel

Hz = Hertz

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Introduction

Ten to fifteen percent of primary care patients report persistent bodily complaints for which no clear organic reason can be found (medically unexplained symptoms) [1–3], while up to 20 % of patients in primary care studies fulfill the diagnostic criteria for Somatoform Disorders according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSMIV) [4].

Within the diagnostic category of Somatoform Disorders, all disorders share the following common aspects: the presence of bodily complaints that are not fully explainable by a medical condition, other mental disorder or by the effect of any substance, the affected subject does not meet the criteria for malingering or factitious disorder, and the complaints cause substantial impairment in at least one area of life [5]. The functional impairment associated with these conditions is comparable with that seen in Anxiety and Depressive Disorders [6, 7]. This DSM-IV category of mental disorders includes Somatization Disorder, Undifferentiated Somatoform Disorder, Conversion Disorder, Pain Disorder, Hypochondriasis, Body Dysmorphic Disorder and Somatoform Disorder Not Otherwise Specified [5]. Clinically relevant somatization, in terms of psychological needs being expressed as physical symptoms are major public health problem affecting 20.4 million persons annually in Europe [8]. Moreover, it leads to excessive health care use, costing the US health care system an estimated $100 billion annually [9].

In recent years, different models on the etiology of Somatoform Disorders have been proposed [10–13]. Among them is an innovative conceptual model, restructuring and extending existing theories on dissociation (attentional dysfunction due to traumatic memories triggers somatic sensations), conversion (traumatic affect transformed into somatic

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symptoms) and somatization (biopsychosocial factors leading to psychological distress and misinterpretation of symptoms) by integrating well-established cognitive psychological principles (attention, consciousness, control) [14]. Thus, the model explains how dissociation, conversion and somatization together with normal cognitive psychological mechanisms can bias the perception of bodily sensations and therefore lead to symptom-focused attention and misinterpretation of bodily sensations [14, 15].

However, the classification and the underlying diagnostic criteria of Somatoform Disorders have been criticized over years: while some authors suggested regrouping and abolition of the existing categories [16–18], others proposed collapsing [19, 20]. Especially the two DSM-IV diagnoses Somatization Disorder (key aspect: quantity of somatic symptoms) and Hypochondriasis (key aspect: anxiety of having a serious disease) have been discussed repeatedly [21, 22]. Thus, some authors favoured the movement of Hypochondriasis out of the group of Somatoform Disorders into the group of Anxiety Disorders [23, 24], while others emphasized the overlap between Hypochondriasis and Somatization Disorder and proposed that they might be dimensions of Somatoform Disorders, as somatic symptoms are a predominant aspect of both disorders [25, 26]. Notably, in the new Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) Somatoform Disorders are reconceptualised as Somatic Symptom and Related Disorders, including Somatic Symptom Disorder (former Somatization Disorder though less restrictive with regard to number of symptoms that must be present; key aspect: somatic symptom burden) and Illness Anxiety Disorder (key aspect: preoccupation with being ill, while no or only mild somatic symptoms are present). The former diagnosis Hypochondriasis has been removed from the DSM-5. With this diagnostic reconceptualization, only 25 % of the patients with the former diagnosis of Hypochondriasis will qualify for the diagnosis of Illness Anxiety Disorder, while the remaining 75 % [27] will

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be subsumed under the diagnosis of Somatic Symptom Disorder [27], which includes subjects with concomitant somatic symptoms and illness anxiety. Despite this reconceptualization the etiology of Somatoform Disorders is not yet established [10, 13, 14].

There is increasing accordance that selective, exaggerated perception of bodily sensations and their attribution to disease, referred to as Somatosensory Amplification [28] may play an important role in the etiology of all Somatoform Disorders, since all current models emphasize the importance of symptom-focused attention [10, 13, 14]. Indeed, the most widespread concept for describing Hypochondriasis is Somatosensory Amplification [28]. Thus, patients with illness anxiety report Somatosensory Amplification when questioned about their sensitivity to normal bodily sensations [28–30]. Interestingly, patients with predominant illness anxiety do not perform better in detecting their resting heartbeat [31] and are not more sensitive to painful heat stimuli [32], nor to non-painful stimuli [29]. In contrast, subjects diagnosed with predominant somatic symptoms show increased sensitivity to auditory tones [33–35], innocuous heat [36, 37] and electrical stimulation [38]. Although, Somatosensory Amplification has been researched thoroughly, to date it remains unclear whether Somatosensory Amplification involves a truly altered physiological sensitivity to sensory input (referred to as altered sensory responsiveness in this article) or subjective exaggerated perception of bodily sensations in subjects with Somatoform Disorders. There may be several reasons for the inconsistent findings. Firstly, different, incomparable stimuli were used in earlier studies, such as auditory tones [33] and innocuous heat [37]. Secondly, earlier studies focused on different sensory aspects, such as heartbeat detection [31] and pain perception [32]. As a biological correlate, altered sensory responsiveness might contribute to a better understanding of the pathophysiology underlying Somatic Symptom and Related Disorders. If sensory responsiveness turned out to represent a correlate of somatic symptoms

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or illness anxiety, this may point to sensory responsiveness as an important new target for prevention and intervention.

Our primary objective was to evaluate if altered sensory responsiveness is associated with somatic symptoms and illness anxiety in a non-clinical sample, as respective findings may inform about the early recognition of related clinical conditions. We aimed to apply a non-invasive, comparable and symptom independent method that may inform about altered physiological sensitivity in healthy subjects with somatic symptoms and illness anxiety. We hypothesize that if altered sensory responsiveness is related to both somatic symptoms as well as illness anxiety, psychophysiological similarity will provide an argument for common underlying pathophysiological mechanisms in the related clinical conditions. If sensory responsiveness is associated only with one of them, this might point to differences in the underlying pathophysiology. If sensory responsiveness is associated with illness anxiety, but not with somatic symptoms, the question will arise whether sensory responsiveness is associated with different forms of anxiety, beyond illness related content, such as trait anxiety, that is anxiety in form of a personal characteristic, showing up in a range of typical situations.

Methods

Ethics Statement

All participants gave written informed consent before participating. The local ethics committee Basel (EKBB) approved the study.

Participants

We conducted the present study at the University of Basel, Department of Psychology.Atotal of 205 persons (103women, aged 18 to 40 years) participated in the study (Fig. 1). Inclusion

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criteria were assessed by questionnaires and included right-handedness, fluent German language, no severe physical disability and no regular medication intake. Due to the large effort required to rearrange the measurement set-up, only right handed participants were included. Subjects were recruited by advertisements on the web page of the University of Basel and the study database of the department of psychology. All participants received either financial compensation (40 CHF) or signatures required for course of studies (students of psychology) for participation.

Procedure and Materials

The study consisted of a single individual session including a questionnaire part, followed by the measurement of vibrotactile perception thresholds (VPT) and a second questionnaire part. We used the Screening for Somatoform Symptoms (SOMS) to assess medically unexplained somatic symptoms. The SOMS is a standardized self-rating symptom checklist covering DSM-IV and ICD-10 criteria for Somatoform Disorders [39]. Symptoms are rated as present or absent during the last two years. We calculated the complaint index (sum of all mentioned symptoms) for further analysis. The SOMS demonstrates good reliability and validity [40]. We used the German version of the Whitely Index (WI) to assess illness anxiety [41]. The WI is a standardized 14-item self-rating questionnaire with dichotomous answer categories (true/false).We calculated the WI overall sum score and the scores for the three subscales disease phobia (fear of developing a serious disease), bodily preoccupation (subjective perception to suffer from multiple bodily symptoms) and disease conviction (strength of the belief of suffering from a serious disease) for further analyses [41]. The overall WI score and the subscales demonstrate good reliability and validity [41, 42]. We used the trait scale of the State-Trait Anxiety Inventory (STAI) to assess trait anxiety [43]. The 20 items are rated on 4-point scales from almost never to almost always.

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We calculated the sum score for further analysis. The STAI demonstrates good reliability and validity [43]. Participants completed additional questionnaires to assess socio-demographic data and socio-economic status (SES).

Sensory responsiveness was assessed via VPT using the HVLab Vibrotactile Perception Meter and corresponding diagnostic software (Institute of Sound and Vibration Research, University of Southampton, United Kingdom) on the fingertip of digit two (middle finger) of the right hand. We instructed the participant to place the fingertip over a vibrating probe while resting the arm on a support. Push force on the surround was set to 2 Newton Meter and the probe diameter was 6 mm, concentric to a 10 mm diameter hole in the surround. To reduce the possibility that the participants see the stimulated finger during VPT measurement, as this might affect tactile processing [44], they were instructed to monitor the pressure they exerted on the probe by tracking a force meter located distant to the probe on the control box of the Vibrotactile Perception Meter (10 cm distance from table surface) 60 cm in front of them and to keep pressure constant. The vibrating probe was placed out of direct sight on the right side of the participant. To reduce the possibility that the participants could hear the vibration of the vibrating probe, the probe was placed on a firm surface and a computer controlled background acceleration check was done before each measurement. We did not perform measurements above 125 Hz for which the manufacturer recommended that participants use ear plugs. VPT were measured by the up-and-down method of limits, also called “von Békésy method” [45, 46], with a stimulus change rate of 3 decibel (dB) per second: vibration increased until the participants pushed a response button with their left hand and then decreased until the participants released the response button. Each participant completed 10 measurement trials (5 for the lower frequency, 5 for the higher) including at least 6 cycles for 30 s per measurement. Vibration magnitude was automatically varied as a function of pressing and releasing the response button. Vibrating probe magnitude, participant’s push force and the

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vibration value at the participant's response were recorded by the HVLab diagnostic software on a computer connected to the Vibrotactile Perception Meter control box. We determined VPT at the frequencies of 31.5 hertz (Hz) (low-frequency) and 125 Hz (high-frequency), which provides information about the functionality of fast adapting type I and II mechanoreceptors [45]. Type I, or Meissner corpuscles, are responsible for the detection and discrimination of low frequency vibration, whereas type II, or Pacinian corpuscles, are responsible for the perception of high frequency stimuli [47]. In a short training session, we introduced the method to the participant. Thresholds with peaks/troughs deviating more than 10 dB and a variation of more than 6 dB between the means of each pair of peaks and troughs were treated as irregular measures and excluded from analyses. We calculated the thresholds as defined by the HVLab software: geometric mean of the vibration magnitude at the peaks and troughs for all reversals excluding the first peak and first trough. To establish the reliability of the vibrotactile measurements, we calculated intraclass correlation coefficients (ICC) for the five low- and the five high-frequency measurement trials. ICC values were high for both low- and high-frequency measurements (0.83 and 0.94, respectively), thus demonstrating good reliability for VPT measurements. Further method details are described in studies on normative vibrotactile thresholds [48–50].

Statistical Analyses

We performed descriptive analyses of the VPT and questionnaire data by inspecting residual plots of all available variables to verify normality, linearity, and heteroscedasticity. For normally distributed variables, we calculated means and standard deviations, for non-normally distributed data medians and ranges (Table 1). Data on low- and high-frequency VPT fulfilled the assumptions. However, questionnaires data (SOMS, WI, STAI) were non-

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normally distributed. For age, gender and socioeconomic status we calculated frequencies and percentages (Table 1).

We performed Pearson’s correlations between the VPT and questionnaire variables to see how the variables are related to each other (Table 2). Low- and high frequency threshold were highly correlated with each other, we therefore computed a mean score VPT combining low- and high-frequency VPT (Table 2).

To assess socioeconomic status (SES) we adapted social class categories on the basis of the Winkler Index [51]. Categories were built using the comparative price levels of 2010 for Switzerland [52], including a 50 % price increase during the last 15 years. Resulting categories which came closest to the predefined ones within education, occupation and household-income were kept. Since only three participants qualified for the category high SES, we dichotomized the variable SES by summarizing the categories high and medium SES into middle SES. Table 1 gives details on descriptive data parameters and sample composition.

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TABLE 1. Sample characteristics

Descriptive data	n	Mean (SD)
Vibrotactile Perception Thresholds *(dB)*		
VPT low-frequency	182	102.36 (6.54)
VPT high-frequency	185	102.74 (9.68)
VPT mean	179	102.51 (7.70)
Questionnaires (score ranges)	n	Median (25 percentile; 75 percentile)
SOMS[a] *(from 0 to 18)*	202	0 (0;1)
WI[b] *(from 0 to 10)*	203	1 (0;2)
WI disease phobia	203	0 (0;1)
WI bodily preoccupation	203	0 (0;0)
WI disease conviction	203	0 (0;0)
STAI *(from 22 to 69)*	203	36 (31;42)
Demographics	n (%)	-
Age *(years)*		
<20	28 (13.7)	-
21 -23	82 (40.0)	-
24 -26	43 (21.0)	-
27 -29	19 (9.3)	-
>29	30 (14.6)	-
Unknown	3 (1.4)	-
Gender		
Male	102 (49.8)	-
Female	103 (50.2)	-
SES		
Middle	97 (47.3)	
High	3 (1.4)	-
Medium	94 (45.9)	-
Low	104 (50.7)	-
Unknown	4 (2.0)	-

dB = Decibel; SD = Standard deviation; VPT = Vibrotactile perception threshold, VPT mean = Mean of low- and high-frequency perception threshold, SOMS = Screening for Somatoform Symptoms; WI = Whiteley-Index; STAI = State-Trait Anxiety Inventory; SES = Socio-Economic Status

[a]45 participants (25% of 179 participants) reported to suffer from at least 1 somatic symptom

[b]129 participants (72% of 179 participants) reported overall illness anxiety, 68 (40% of 179 participants) reported disease phobia, 15 (8% of 179 participants) reported bodily preoccupation, 30 (17% of 179 participants) reported disease conviction

To estimate the association between somatic symptoms, illness anxiety and trait anxiety and VPT, we conducted a linear multiple regression model with VPT as outcome and the respective predictor somatic symptoms, illness anxiety or trait anxiety (unadjusted model). We then repeated the analysis, by including age, gender and socioeconomic status as

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covariates (adjusted model). Since the theoretical distribution for some predictors was unknown, we used nonparametric unconditional bootstrapping [53–55] to calculate standardized regression coefficients (β), 95 % confidence intervals and p values for all variables. A posteriori, we analysed whether gender might have a moderating effect on the association between somatic symptoms, illness anxiety and trait anxiety and VPT, as gender has been shown to be associated with increased symptom reporting in patients [56]. We repeated the adjusted regression analyses by including gender (n=179) as moderator. All tests were two-tailed and we set the level of significance at 0.05. For statistical analyses, we used the Statistical Package for Social Sciences (SPSS 20.0 Inc., USA) and R, version 2.14.2 [57].

Results

Sample Characteristics

Of the 456 persons interested in the study, we considered 237 (85 %) eligible for participation. Out of these, 205 (86 %) participated in the study. The only reason for non-participation when eligible was failure to appear at the appointment (14 %). The final sample consisted of students (university and college students) and employees. Missing data was caused by technical difficulties during VPT measurement, computation of VPT mean, missing questionnaires and two participants turning out ineligible at a later inspection (Fig. 1).

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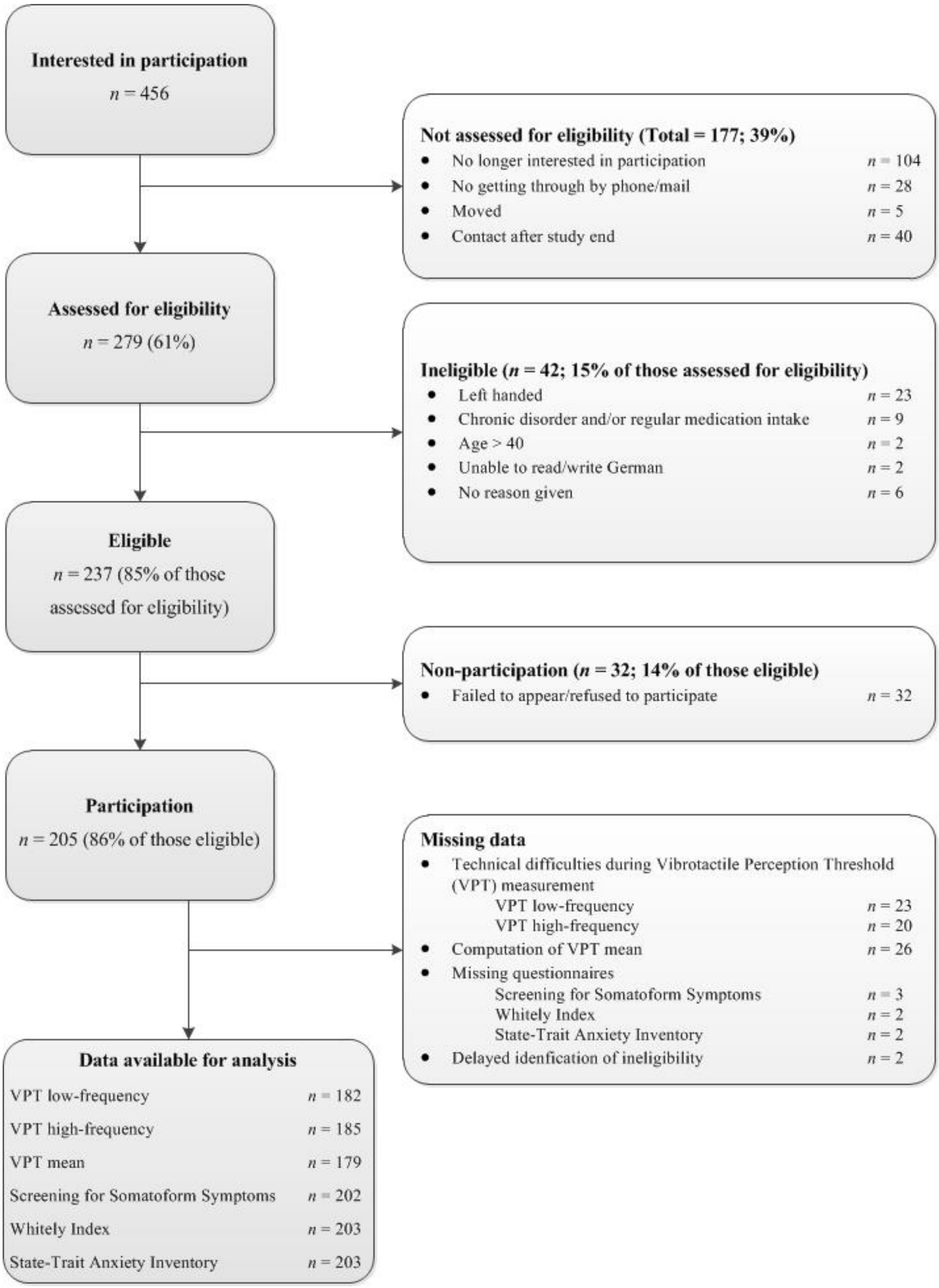
Figure 1. Flowchart of study participants



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Zero-Order Correlations

Pearson's correlations between the VPT and questionnaire variables are provided in Table 2. Data on low and high frequency VPTwere substantially correlated with each other (r=0.79, p<0.001). For further analyses we computed a mean score combining low- and high-frequency VPT into one mean score VPT. The new VPT mean score remained negatively correlated with the WI overall score (r=−0.15, p=0.05) and disease conviction subscale (r=−0.15, p=0.04). The association between the VPT mean score and the SOMS score was non-significant (r=−0.01, p=0.91) The WI overall score was positively correlated with all WI subscales and the WI subscales were positively correlated with each other (Table 2). Trait anxiety was positively correlated with all other questionnaire scores (Table 2).

TABLE 2. Correlations between vibrotactile perception thresholds and questionnaires

	VPT LF	VPT HF	VPT mean	SOMS	WI_GE	WI_KA	WI_SB	WI_KU	STAI
VPT LF	−								
VPT HF	0.79**	−							
VPT mean	0.92**	0.97**	−						
SOMS	−0.04	0.01	−0.01	−					
WI_GE	−0.20*	−0.11	−0.15*	0.22**	−				
WI_KA	−0.12	−0.05	−0.08	0.10	0.87**	−			
WI_SB	−0.10	−0.02	−0.06	0.36**	0.44**	0.20*	−		
WI_KU	−0.17*	−0.13	−0.15*	0.24**	0.60**	0.29**	0.28**	−	
STAI	−0.11	−0.04	−0.07	0.28**	0.42**	0.36**	0.27**	0.33**	−

VPT LF = Low-frequency vibrotactile perception threshold; VPT HF = High-frequency vibrotactile perception threshold; VPT mean = Mean of low- and high-frequency perception threshold;
SOMS = Screening for Somatoform Symptoms; WI_GE = Whiteley-Index overall score; WI_KA = Whiteley-Index disease phobia subscale; WI_SB = Whiteley-Index bodily preoccupation subscale; WI_KU = Whiteley-Index disease conviction subscale; STAI = State-Trait Anxiety Inventory
*p<0.05; **p<0.001

Bootstrapping Analysis

When using bootstrapping analysis, decreased VPT remained associated with increased scores on the overall Whitely-Index of illness anxiety (β=−0.65; 95%CI, −1.21, −0.14) and on its

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constituent subscale disease conviction (β=−2.07; 95 % CI, −3.94, −0.43), whether adjusting for age, gender and socioeconomic status or not (Table 3).

TABLE 3. Results of regression model with bootstrapping[a]

Unadjusted Model	Outcome VPT (n = 179)		
	β [95% Cl]	p	R^2
Predictor			
SOMS	−0.00 [−0.32, 0.36]	0.868	<.001
WI_GE	−0.62 [−1.14, −0.05]	0.021	0.022
WI_KA	−0.48 [−1.36, 0.26]	0.239	0.007
WI_SB	−1.17 [−2.90, 0.56]	0.158	0.003
WI_KU	−1.91 [−3.83, −0.26]	0.027	0.023
STAI	−0.06 [−0.28, 0.08]	0.499	0.005
Adjusted Model	Outcome VPT (n = 179)		
	β [95% Cl]	p	R^2
Predictor			
SOMS	−0.01 [−0.37, 0.39]	0.894	0.035
WI_GE	−0.65 [−1.21, −0.14]	0.017	0.057
WI_KA	−0.49 [−1.42, 0.23]	0.237	0.040
WI_SB	−1.09 [−3.30, 1.16]	0.261	0.038
WI_KU	−2.07 [−3.94, −0.43]	0.016	0.061
STAI	−0.07 [−0.30, 0.07]	0.483	0.045

β = Standardized Regression Coefficients

Cl = Confidence Interval for Bootstrapping

R^2 = Explained variance of outcome by respective predictor and all covariates

SOMS = Screening for Somatoform Symptoms

STAI = State-Trait Anxiety Inventory

WI_GE = Whiteley-Index overall score; WI_KA = Whiteley-Index subscale disease phobia; WI_SB = Whiteley-Index subscale bodily preoccupation; WI_KU = Whiteley-Index subscale disease conviction

[a]Results are presented without and with covariates (age, gender, socioeconomic status). Bootstrap is based on 5000 replicates.

Thus, increased sensory responsiveness was associated with increased illness anxiety and increased disease conviction. All other associations were not significant, whether adjusting for

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age, gender and socioeconomic status or not (Table 3). Exploring whether the above associations varied by gender, we did not find any significant interaction with gender regarding any association: VPT with Whitely-Index overall score (β=0.30; 95 % CI, −1.12, 1.39; p=0.76), VPT with disease conviction subscale (β=0.91; 95 % CI, −3.24, 5.28; p=0.61), VPT with disease phobia subscale (β=−0.49; 95 % CI, −2.78, 0.98; p=0.55), VPT with bodily preoccupation subscale (analysis could not be performed; 5 male participants), VPT with somatic symptoms (β=0.67; 95 % CI, −0.22, 1.53; p=0.18), VPT with trait anxiety (β=−0.06; 95 % CI, −0.50, 0.23; p=0.64).

Discussion

The aim of the current study was to evaluate if altered sensory responsiveness is associated with somatic symptoms, illness anxiety and trait anxiety in a non-clinical sample. We hypothesize that if somatic symptoms and illness anxiety share common pathophysiological mechanisms both should be associated with altered sensory responsiveness. If altered sensory responsiveness is associated only with somatic symptoms or illness anxiety, differences between the underlying pathophysiological mechanisms may account for these conditions. Moreover, if altered sensory responsiveness is associated with illness anxiety, but not with somatic symptoms, the question will arise whether altered sensory responsiveness is associated with different forms of anxiety, beyond illness related content.

While increased illness anxiety in general and disease conviction in particular were associated with higher sensory responsiveness, measured via VPT, this was not the case for somatic symptoms or trait anxiety. Our findings suggest that the pathophysiological mechanisms underlying illness anxiety might be different from those underlying other somatic symptoms. If present and confirmed in clinical samples, these relations could contribute to the

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understanding of pathophysiological mechanisms involved in the development of symptoms related to Somatic Symptom and Related Disorders (DSM-5).

Our findings may have the potential to contribute to the understanding of pathophysiological mechanisms in Illness Anxiety Disorder. Nevertheless, the integration of our findings in the existing literature is challenging. First, we did not find an association between altered sensory responsiveness and predominant somatic symptoms whereas most previous studies did [33–38]. Contradictory, other studies with subjects diagnosed with somatic symptoms reported that their symptoms were less related to physiological perception than those of controls in rebreathing tasks [58], and patients with severe somatoform symptoms were not more accurate in heartbeat discrimination and mental tracking tasks than controls [59, 60]. Our results seem more in line with two studies with university students, one study reporting that high somatic symptom reporters were less accurate than low reporters in a symptom related rebreathing test [61] and the second study reporting no associations between accurate heartbeat detection and somatization tendencies in university students [62].

One explanation for these inconsistent findings might be related to the composition of the study sample: while we examined a non-clinical sample, most other studies assessed subjects with full-blown somatic conditions [34, 37, 38, 58]. An alternative explanation for the different results might be the use of different methods to assess sensory responsiveness. While we assessed nonpainful VPT, most other studies used pain thresholds [34, 37, 38, 58]. In general, the comparability between respective findings is exacerbated due to the use of different methods to assess sensory responsiveness.

Second, our finding that altered sensory responsiveness is not associated with trait anxiety is in line with one study investigating different bodily sensations and their relation to trait anxiety in a non-clinical sample of volunteers [63], but there is one other study reporting a

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positive association between high cardiovascular response, trait anxiety and accuracy to heartbeat detection in non-clinical participants [64].

One potential explanation for the lack of associations between trait anxiety and altered sensory responsiveness might be the low trait anxiety-scores in our sample, thus leading to reduced statistical power due to deflated correlation. However, it remains unclear whether the findings are indeed comparable due to the use of different methods to assess sensory responsiveness, such as cardiovascular response and heartbeat detection [64] and high pulse, shortness of breath and sweaty hands [63].

Third, our finding of the association between altered sensory responsiveness and illness anxiety, especially disease conviction, is not in line with clinical studies reporting no changes in sensory responsiveness among patients with illness anxiety [31, 32]. However, two other studies among subjects with diagnosed illness anxiety reported associations between accurate heartbeat detection and illness anxiety [65], as well as associations between increased pain perception and illness anxiety [66]. Other studies with student samples reported that participants with illness anxiety tendencies performed less accurately in a heartbeat detection task [67] and were even less precise in heartbeat and skin fluctuation detection tasks [68]. Again, possible explanations for these discrepant findings might be different sample characteristics and measurement methods, such as the use of pain thresholds.

One explanation for the association between illness anxiety and sensory responsiveness may be that the anxiety of having a serious disorder, especially in terms of disease conviction, activates the limbic system in a way comparable to other anxiety disorders which has shown to be connected to neuronal pathways involved in tactile sensation, respectively, emotional touch [69]. Indeed, evidence suggests that cognitive processes underlying illness anxiety might be comparable with cognitive processes involved in anxiety disorders [16, 24].

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Furthermore, research has indicated that anxiety in general is associated with increased amygdala activity [70]; thus, illness anxiety might be associated with an increased amygdala activity as well. As illness anxiety is defined as a multidimensional construct including affective, behavioral, perceptual and cognitive components it could be argued that the conviction of having a serious disease, together with biased attention to bodily symptoms results in lower vibrotactile perception thresholds. However, molecular transduction mechanisms of mechanoreceptors in mammals are not clearly understood yet [71, 72]. Therefore, we can only speculate about underlying processes.

This study has important strengths. First, most of our participants were young adults from a non-clinical sample, aged 21 to 24. Somatization tendencies are reported very early and the onset time for the development of Somatic Symptom and Related Disorders is located in young adulthood [73]. The inclusion of somatoform complaints on an early stage of development might have implications for the prevention and therapy of Somatic Symptom and Related Disorders. Second, the applied instrument (HVLab Vibrotactile Perception Meter) measures VPT according to ISO 13091-1:2001 on a physiological basis. Finally, we adjusted our analyses for potential confounders, including gender, age and socioeconomic status. Biological mechanisms accounting for the association between vibrotactile thresholds and illness anxiety remain to be determined.

There are also limitations to this study. First, to detect somatic symptoms, participants filled out the SOMS checklist, requiring the reporting of all symptoms experienced over the last 2 years for whom a doctor was consulted and no medical explanation was found. Because the majority of our participants were students, they reported not to seek medical help because of financial reasons and a lack of time due to examination. Thus, some symptoms may have not entered the study. However, this will most likely only lead to underestimation of somatic

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symptoms. Second, we studied a non-clinical sample what may have limited the generalizability of our findings to subjects with full-blown conditions. However, we assume that there was enough variance in our sample, but our results should be scrutinized in a clinical sample in future studies. Moreover, this approach has the advantage of allowing to capture psychobiological correlates of subclinical somatic symptoms and illness anxiety, which may be of special relevance for a better understanding of early phases of disorder development and hence prevention. Third, results including the bodily preoccupation subscale should be interpreted with caution due to the insufficient amount of male participants reporting bodily preoccupation. However, our results should be scrutinized in a sufficiently large clinical sample. We refrained from applying the Bonferroni method to adjust for multiple testing, as the approach is critically discussed as too conservative, leading to lower power and increasing publication bias [74, 75].

Conclusion

In this study, illness anxiety was related to altered sensory responsiveness, whereas somatic symptoms and trait anxiety were not. Our findings may contribute to a better understanding of pathophysiological mechanisms underlying illness anxiety. Given that the association between VPT and illness anxiety was rather small, involved mechanisms should be investigated more closely in the future. In the long run, the better understanding of pathophysiological mechanisms underlying somatic symptoms and illness anxiety may contribute to an optimized treatment and classification of Somatic Symptom and Related Disorders [76].

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Conflict of Interest

The authors, DR, AHM, RL and GM declare that they have no conflict of interest. The authors alone are responsible for the content and writing of the paper. This work was supported by Forschungsfonds of the University of Basel (to GM) and the Swiss National Science Foundation (SNSF number 100014_135328; to GM and RL). Additionally, GM receives funding from the Korea Research Foundation within the Global Research Network Program under project no. 2013S1A2A2035364 and from the Swiss National Science Foundation under project no. 100014_135328. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Ethical Standards

"All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants for being included in the study."

Authors' Contributions

DR carried out participant testing and drafted the manuscript. AHM performed statistical analysis. GM designed the study and obtained funding. GM and RL supervised the study and revised the manuscript. All authors read and approved the final manuscript.

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