Association between generalized anxiety levels and pain in a community sample: Evidence for diagnostic specificity

Katja Beesdo ^{a,*}, Jürgen Hoyer ^a, Frank Jacobi ^a, Nancy C.P. Low ^b, Michael Höfler ^a, Hans-Ulrich Wittchen ^a

^a Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Chemnitzer Str. 46, 01187 Dresden, Germany

^b Department of Psychiatry, McGill University, Montreal, Canada

Abstract

Background: It is unclear whether generalized anxiety disorder (GAD) has a specific relationship to pain syndromes, going beyond the established association of pain with anxiety syndromes in general. **Methods:** Mental disorders were assessed in a community sample (N = 4181; 18–65 years) using the DSM-IV/M-CIDI. Several threshold definitions were used to define GAD and medically unexplained pain.

Results: The association between pain and GAD (odds ratio, OR = 5.8 pain symptoms; OR = 16.0 pain disorder) is stronger than the association between pain and other anxiety disorders (OR = 2.4 pain symptoms; OR = 4.0 pain disorder). This association extends to subthreshold level definitions of GAD with some indication for a non-linear dose–response relationship. The GAD-pain link cannot sufficiently be explained by demographic factors, comorbid mental or physical disorders.

Conclusions: The association of pain and generalized anxiety is not artifactual. Compared to other anxiety syndromes, it appears to be stronger and more specific suggesting the need to explore clinical and public health implications.

Keywords: Generalized anxiety disorder, Pain, Epidemiology, Population-based sample

1. Introduction

Generalized anxiety disorder (GAD) is a common condition in the general population (lifetime prevalence 5–6%) associated with significant individual and societal burden as well as tremendous health care costs (Olfson & Gameroff, 2007; Ormel et al., 2008; Ruscio et al., 2007; Wittchen, Beesdo, & Kessler, 2002). The occurrence of GAD with other mental disorders, particularly depression, has been studied extensively (Judd et al., 1998; Kessler, Walters, & Wittchen, 2004; Moffitt et al., 2007; Wittchen, Kessler, et al., 2002), but the relationship between GAD and pain conditions has only recently received some research attention. Primary care patients with GAD frequently present to their general practitioner with pain as initial reason for help-seeking (Wittchen, Kessler, et al., 2002). In addition, GAD patients suffer greater overall pain interference, compared to unaffected patients, and also have disproportionally high medical health care costs (Olfson & Gameroff, 2007).

Recent epidemiologic data provide evidence for strong associations between GAD and pain conditions (Demyttenaere et al., 2007; Gureje et al., 2008; McWilliams, Cox, & Enns, 2003; McWilliams, Goodwin, & Cox, 2004; Von Korff, Crane, et al., 2005). For example, in the National Comorbidity Survey—Replication (NCS-R), GAD appeared among several anxiety disorders to be particularly strongly related to chronic back pain (Von Korff, Crane, et al.,

2005). A similar finding was reported from the World Mental Health surveys across 18 developing and western countries (Demyttenaere et al., 2007) where GAD was found to have a higher pooled odds ratio than the other anxiety disorders, major depression and alcohol abuse/dependence. Furthermore, there was an association between number of painful body sites and GAD (Gureje et al., 2008). McWilliams et al. (2004) also found stronger associations for GAD compared to panic attacks and major depression in two out of three pain conditions (arthritis and migraine) in the Midlife Development in the United States Survey (MIDUS), even after adjustment for sociodemographic variables and other pain and medical conditions. Moreover, GAD in this study was the mental condition that had the strongest association with multiple pain conditions. In the German Health Survey (GHS), from among a wide range of specific depressive and anxiety disorders, GAD was most strongly associated with clinically significant pain symptoms (Beesdo et al., 2007). Interestingly, all GAD sufferers reported pain and the association seemed to be particularly pronounced with medically unexplained pain symptoms and pain disorder.

In summary, recent findings indicate a strong relationship between GAD and pain syndromes. However, to date, there has been no comprehensive investigation examining the nature and the specificity of this finding. Yet, it is noteworthy that there are a number of observations and a priori assumptions that make the specificity of the association between GAD and pain highly probable.

First, GAD differs from other anxiety disorders in several aspects. GAD has a different incidence pattern characterized by a later high risk period for first onset (mid-teens until later adulthood) (Beesdo, 2006; Bijl, de Graaf, Ravelli, Smit, & Vollebergh, 2002; Kessler et al., 2005; Ruscio et al., 2005). GAD has been described as the most frequent anxiety disorder in the elderly (Beekman et al., 1998). This incidence pattern corresponds with that of chronic pain syndromes which are also notable for onsets until older age (Bellach, Ellert, & Radoschewski, 2000; Elliott, Smith, Penny, Smith, & Chambers, 1999; Eriksen, Jensen, Sjogren, Ekholm, & Rasmussen, 2003; McBeth & Jones, 2007; Torrance, Smith, Bennett, & Lee, 2006). Further, in contrast to some other anxiety disorders with a more variable symptom course, GAD-symptoms – by definition – have to occur almost daily over a time period of at least 6 months, and episodes persist with some waxing and waning of symptoms for many years (Wittchen & Hoyer, 2001). Similar patterns of course have been described for most chronic pain syndromes (Smith, Elliott, Hannaford, Chambers, & Smith, 2004). Therefore, one might expect a closer relationship between pain and GAD than other anxiety disorders.

Second, despite no overlap between pain disorder and GAD in DSM-IV diagnostic criteria, both conditions share some features which would suggest a strong association between both conditions. Among such common features are core cognitive symptoms (such as anxious expectation), some physiological symptoms (such as muscle tension), hypervigilance symptoms (such as sleeping problems, irritability, and restlessness), and behavioral symptoms (such as avoidance). It should be noted that autonomic symptoms were deleted as mandatory diagnostic criteria for GAD in DSM-IV in favour of a list of symptoms that can broadly be characterized as a chronic hypervigilance syndrome. In this respect, GAD differs from the other anxiety disorders which again would suggest a particular relationship to pain.

Third, there are some recent speculations on common psychological and (neuro-)biological mechanisms and pathways in fear/anxiety and pain conditions (Price, 2002), which indicate strong associations between them. Consistent with this, similar pharmacological (Grothe, Scheckner, & Albano, 2004; Gutierrez, Stimmel, & Aiso, 2003) as well as non-

pharmacological therapeutic interventions (Borkovec & Ruscio, 2001; Hoyer et al., 2009; Turner- Stokes et al., 2003) seem to work in both GAD and pain patients.

Based on these considerations one would not only expect a significant relationship between pain syndromes and DSM-IV GAD, but also between pain syndromes and generalized anxiety syndromes below the full diagnostic threshold. To our knowledge, such relationships have not been studied. The aim of this current investigation is to use a large, nationally representative population sample to examine: (1) whether medically unexplained pain is more strongly associated with GAD than with other anxiety disorders, (2) whether medically unexplained pain is associated with generalized anxiety below the full diagnostic threshold, and (3) how pain and generalized anxiety occurring together are related to negative outcomes in terms of disability, quality of life, and service utilization. We focus on clinically significant, medically unexplained (somatoform) pain because of indications that particularly unexplained pain may be important in GAD (Beesdo et al., 2007). It should be noted, however, that there is an ongoing controversy surrounding this type of pain classification (Hiller, 2006; Kroenke, 2006; Mayou, Kirmayer, Simon, Kroenke, & Sharpe, 2005; Sharpe, Mayou, & Walker, 2006; Sullivan, 2000; Sykes, 2006). Some (Kroenke, 2006; Mayou et al., 2005; Sharpe et al., 2006) point out the theoretical and practical difficulties in categorizing symptoms to be „medically unexplained (somatoform)“ suggesting a simplified categorization and „etiologically neutral“ terminology for physical symptoms including pain. Others (Hiller, 2006), in contrast, emphasize the progress that has been made with research on somatoform diagnoses as mental disorders integrating biological, psychological, and social aspects.

2. Method

The data presented in this paper come from the German National Health Interview and examination survey, mental health supplement (GHS-MHS) conducted in 1998–1999. The survey was approved by the Institutional Review Board of the Robert Koch Institute (Berlin, Germany). All participants provided written informed consent. Aims, design, and methods of the survey have been described in detail elsewhere (Jacobi et al., 2002).

2.1. Sample

The GHS (core survey) covered a range of medical and social assessments in a multistage, stratified, cross-sectional, random sample of the general German population aged 18–79 years, drawn from population registries (N = 7124; response rate: 61.5%). The MHS (one of several supplements) included a subsample of the core survey (N = 4181; conditional response rate: 87.6%). This subsample can be regarded as representative for the German noninstitutionalized adult population in the age-range of 18–65 years (Jacobi et al., 2002). Older individuals were excluded from the MHS due to unsatisfactory psychometric properties of the used diagnostic assessment instrument (the Munich Composite International Diagnostic Interview (DIA-X/M-CIDI)) in these populations (Knäuper & Wittchen, 1994).

2.2. Measures

2.2.1. Assessment of disorders

Assessment of mental disorders was based on the Computer- Assisted Version (CAPI) of the Munich Composite International Diagnostic Interview (DIA-X/M-CIDI) (Wittchen & Pfister, 1997; Wittchen, Lachner, Wunderlich, & Pfister, 1998), a modified version of the World Health Organization (WHO) CIDI, version 1.2, supplemented by questions to cover DSM-IV

(APA, 1994) and ICD-10 criteria (WHO, 1993). The DIA-X/M-CIDI was administered by clinically trained interviewers (psychologists and MDs). Psychometric properties of the DIA-X/M-CIDI were found to range between acceptable to very good (retest-reliability: kappa = 0.45 for GAD to 1.00 for panic disorder; kappa = 0.62 for any somatoform disorder; validity: kappa = 0.50 for somatoform disorder to 0.96 for major depressive episode; kappa = 0.79 for any anxiety disorder (Lachner et al., 1998; Reed et al., 1998; Wittchen, 1994; Wittchen et al., 1998). All analyses in this paper are based on 12-month prevalence criteria.

2.2.1.1. Pain symptoms and pain disorder. Diagnosis of (somatoform) pain disorder was generated by using the standard DSM-IV/ M-CIDI algorithms (Wittchen & Pfister, 1997). In the somatoform disorders section of the DIA-X/M-CIDI, presence of the following painful conditions is initially assessed from the respondents on a lifetime basis: abdominal pain, back pain, joint pain, limb pain, chest pain, headache, excessively painful menstruation, rectal and genital pain, and other pain. For common experienced pain types (abdominal pain, back pain, headache, and painful menstruation) the threshold for positive endorsement was increased by asking whether the respondent has ever had „a lot of trouble“ with this pain. Whenever the respondent acknowledged having experienced at least one of these pain types, the interviewer enters a standardized complex set of probe questions to evaluate the nature of the complaint (Rubio-Stipec et al., 1993; Wittchen, Essau, Rief, & Fichter, 1993).

There are several levels of probing before a pain symptom ultimately is considered to be „clinically significant“ and „medically unexplained.“ The probe questions start with establishing clinical severity/significance. A symptom is considered „clinically significant“ if: such symptom prompts seeking help from a medical doctor or other health professional; medication was used more than once for it; or the symptom interfered a lot with life or activities (criterion A). For headaches and painful menstruation, positive endorsement of medication use more than once was not considered as sufficient for establishing clinical significance. Here, respondents must have additionally reported medication prescription by a doctor (pertaining to headaches and painful menstruation), or the use of prescription-free medication at least three times a week (pertaining to headaches) (Wittchen & Pfister, 1997). Next, further complex probe questions were used to establish whether there are any physical or substance related factors that explain the occurrence of the pain symptom („medically explained“ pain). Only if the symptom was not (or not always) explained by a medical diagnosis (e.g., doctor's diagnosis of migraine for headaches), an injury, or the use of medication, drugs or alcohol, it was rated as „medically unexplained.“ This was counted towards the DSM-IV criterion C (note that the controversial 'psychological factors' criterion (Hiller, 2006; Kroenke, 2006; Mayou et al., 2005; Sharpe et al., 2006; Sullivan, 2000; Sykes, 2006) is particularly difficult to assess with a standardized instrument in an epidemiological study).

If at least one painful condition was found to be present as clinically relevant and medically unexplained, further questions were asked regarding the recency of pain symptoms (12-month status) and regarding the diagnosis of pain disorder (criterion B). (1) Did the pain keep you from working or seeing friends or relatives for 6 months or more? (2) How much did the pain interfere with your life and daily activities? If the respondent acknowledged impairment for 6 months or at least a lot interference with life, the diagnosis of pain disorder was made.

DSM criterion D (the symptom is not intentionally produced or feigned) was not assessed by the DIA-X/M-CIDI. The exclusion criterion E (the pain is not better accounted for by a mood, anxiety, or psychotic disorder) is considered in the present analysis by providing the

proportion of respondents who reported that their physician attributed their pain to „anxiety, panic attacks, or depression“.

Keeping the controversy about somatoform pain and pain disorder in mind, we consider in the current paper and if not otherwise stated, three hierarchical, mutually exclusive pain groups as based on respondents' self-reports: (1) no unexplained pain (no UP), representing individuals with either no clinically significant pain symptoms or with medically explained pain symptoms, (2) at least one medically unexplained pain symptom (UPS), and (3) pain disorder (PD) as per DIA-X/M-CIDI algorithms. Individuals with explained pain symptoms were combined with the no pain group for two reasons. First, recent findings of our group using the same sample showed that virtually all GAD patients reported some significant pain at some point during their life indicating an important role of unexplained pain in GAD (Beesdo et al., 2007). Second, medically explained pain symptoms were assessed on a lifetime basis without assessing 12-month prevalence. Our group definition can be regarded as conservative because the inclusion of individuals with exclusively medically explained pain symptoms in the no UP group creates a stricter reference group than if these individuals were excluded from the analyses.

2.2.1.2. GAD and generalized anxiety below the diagnostic threshold. The GAD section of the DIA-X/M-CIDI began with a screening question: „In the last 12 months, have you had a period of a month or more when most of the time you felt worried, tense, or anxious about everyday problems?“ The entire section was skipped if the respondent did not endorse this question. Respondents who reported at least 1 month of anxious worrying were asked to report the longest period (in the past 12 months) that they had felt worried. If this period was less than 3 months, the rest of the section was skipped. Those with at least 3 months of anxious worrying were asked the complete series of CIDI questions in this section to assess the DSM-IV GAD criteria (APA, 1994). Exclusionary criteria were not applied for the present diagnostic analyses to facilitate comparisons with the majority of other research on GAD that also does not apply these criteria. Previous work done by Carter, Wittchen, Pfister, and Kessler (2001) found that application of these criteria decreases the prevalence rate of GAD very little.

Since most of the GAD section of the DIA-X/M-CIDI was skipped if the respondent reported less than 3 months of persistent anxious worrying, information about fulfilment of the other DSM-IV criteria for GAD was available only for those respondents with episode duration of at least 3 months. Three diagnostic threshold levels for GAD were defined for the purposes of examining the association with pain: (1) GAD symptoms—anxious worrying for at least 1 month, (2) subthreshold GAD—anxious worrying for at least 3 months with at least two of the other DSM-IV criteria for GAD (B: uncontrollable worry, C: at least 3 out of 6 physical symptoms, or E: distress/impairment), and (3) threshold GAD—anxious worrying for at least 6 months (DSM-IV criterion A) and all other DSM-IV criteria for GAD (B, C, and E). If not otherwise stated in the text, these groups are considered mutually exclusive. It is noteworthy that all DSM-IV criteria must be met during the last year for the application of a 12-month diagnosis of threshold GAD. This can be considered as very strict, especially regarding the A-criterion which requires a 6-month period of persistent anxious worrying.

2.2.1.3. Other mental disorders. Depressive disorders (major depression and dysthymia), anxiety disorders (specific phobia, social phobia, agoraphobia without panic disorder, phobia not otherwise specified (NOS), panic disorder with or without agoraphobia, and obsessive compulsive disorder (OCD)), and substance use disorders (alcohol abuse and dependence, nicotine dependence, illegal drug/medication abuse and dependence) were assessed using the

DSM-IV/M-CIDI (Wittchen & Pfister, 1997) and considered for analyses as control variables if 12-month DSM-IV criteria were met.

2.2.1.4. Physical disorders. A self-report questionnaire was used to assess presence of 44 physical diagnoses from 16 disease groups (e.g., cardiac diseases, diabetes, cancer, allergies (Jacobi et al., 2002)). Considering this self-report, study doctors used a computer-assisted standardized interview to establish lifetime, 12-month and point prevalences of physical disorders. In this paper, we use a variable containing the number of physical disorders during the past 12 months (range 0–9) as control variable.

2.2.2. Other measures

2.2.2.1. Assessment of health related quality of life. The German version (Bullinger & Kirchberger, 1998; Ware & Sherbourne, 1992) of the well-validated self-report Medical Outcome Study 36-item short form (SF-36) (Bullinger et al., 1998; Butterworth & Crosier, 2004; Ellert & Bellach, 1999; Hopman et al., 2000; McHorney, Ware, & Raczek, 1993; Sullivan & Karlsson, 1998) was used to assess eight health concepts (e.g., general health, physical function, emotional role) within the past 30 days. Principal components analysis has identified 2 dimensions of the SF-36: a physical component score and a mental component score (Ware et al., 1998). These scores were standardized to $M = 50$ and $S.D. = 10$.

2.2.2.2. Assessment of disability. Similar to previous surveys (e.g., Sareen et al., 2006) past 4-week disability was examined by the self-reported number of days individuals were unable to carry out usual daily activities (school, study, work, and household) due to: (1) mental (emotional, psychosomatic, or psychiatric) problems, (2) alcohol, drug or medication use, or (3) physical problems and illnesses. Number of overall disability days was generated by counting a full day for each day the respondent was totally unable to carry out usual activities and adding a half-day for each day the respondent was partly disabled to carry out usual activities. This summary variable reflects the number of disability days in the past month ranging from 0 to 28 days (if higher summary scores occurred they were coded to 28 days).

2.2.2.3. Assessment of health care utilization. Assessment of health care utilization included self-reported data on the number of (1) general practice visits, (2) consultations with specialists (including neurologists, psychiatrists, and psychologists), and (3) days spent in hospital within the past 12 months. The total number of health care visits reflects the sum of the three domains.

2.3. Statistical analyses

Statistical analyses were carried out with the STATA software package, release 10.0 (StataCorp, 2007). Data (percentages, %; means, M ; standard deviations, $S.D.$; ratio's from regressions, R) were weighted for age, gender, region and screening status in order to address different sampling probabilities and systematic nonresponse (Jacobi et al., 2002). The number of cases (N , n) is reported unweighted.

In order to examine whether association between medically unexplained pain (UPS, PD) and GAD was greater than that of other anxiety disorders, three mutually exclusive diagnostic groups were created: no anxiety disorder, any anxiety disorder but no GAD, and DSM-IV GAD irrespective of comorbidity. Multinomial logistic regression models (odds ratios, OR with 95% confidence intervals, CIs) were used to quantify associations. Further, multinomial logistic regression models were also used to quantify associations between medically

unexplained pain (UPS, PD) and the different levels of generalized anxiety (GAD symptoms, subthreshold GAD, and DSM-IV GAD). All associations were tested to see whether they persisted after adjustment for sociodemographic variables (age, gender) as well as comorbid mental and physical disorders. Statistical significance was evaluated at the 0.05 level using twotailed tests.

Additionally, models were fit to examine correlates (e.g., quality of life, role impairment) for three mutually exclusive groups: generalized anxiety alone, medically unexplained pain alone, and comorbid generalized anxiety and medically unexplained pain. Here, generalized anxiety is composed of symptomatic, subthreshold and threshold GAD and medically unexplained pain is composed of UPS and PD. Associations with count variables (i.e., number of impairment days, number of health care visits) were assessed using mean ratios (MRs) from negative binomial regressions (Lawless, 1987). These regressions are useful for positively skewed distributions of infrequent events and the associated mean ratios reflect the change in the expected count of a particular event per unit increase in the covariate. Mean ratios from gamma regressions were used for gamma-distributed SF-36 outcomes. A significant ratio of <1 indicates a decrease of health related quality of life. We further assessed whether the combination of generalized anxiety and medically unexplained pain revealed superadditive associations (on the ln-outcome scale) fitting models with the main effect terms of generalized anxiety (yes/no) and pain (yes/no) and their interaction term.

3. Results

3.1. 12-Month prevalence of generalized anxiety and pain in the general population

In the prior 12 months, 8.1% of the general population met criteria for PD; an additional 15.4% experienced at least one UPS. The 12-month prevalence rates for threshold GAD, subthreshold GAD, and symptomatic GAD were 1.5%, 2.1%, and 4.2%, respectively. Women were significantly more frequently affected by generalized anxiety and pain at all diagnostic levels (OR range: 1.7–2.7, all p-values < 0.01). Higher rates with older age (age as dimensional variable) were found for DSM-IV threshold GAD only (OR = 1.03; 95% CI: 1.01–1.05, $p = 0.011$).

3.2. Is there a specific association between pain and DSM-IV GAD?

Relative to individuals with no anxiety disorder, the proportion of both UPS and PD was increased among individuals with anxiety disorders, and particularly among those with GAD (Table 1, column percentages). And vice versa, among individuals with UPS and PD, increased proportions of any anxiety disorder and GAD were found as compared to individuals without unexplained pain (row percentages).

As shown in Table 2, medically unexplained pain was associated with anxiety disorders other than GAD (column 1: OR = 2.4, 95% CI: 1.9–3.0, $p < 0.001$ for UPS; OR = 4.0, 95% CI: 3.0–5.3, $p < 0.001$ for PD) but particularly with GAD (column 2: OR = 5.8, 95% CI: 3.0–11.1, $p < 0.001$ for UPS; OR = 16.0, 95% CI: 8.6–29.8, $p < 0.001$ for PD). The pain-GAD association appeared to be strong and specific over and above the association of pain with other anxiety disorders (column 3: OR = 2.4, 95% CI: 1.2–4.7, $p = 0.010$ for UPS; OR = 4.0, 95% CI: 2.1–7.6, $p < 0.001$ for PD). All associations persisted (all p-value < 0.05) even following adjustment for age, sex, comorbid depressive disorders, comorbid substance use disorders, and number of comorbid physical illnesses.

3.3. Pain and generalized anxiety on different diagnostic levels

Proportions for UPS or PD were not only increased among individuals with DSM-IV GAD, but also among individuals with generalized anxiety below the diagnostic threshold as compared to individuals without any GAD symptoms (Table 3, column percentages). Vice versa, all diagnostic levels of GAD occurred more frequently among individuals with UPS and particularly with PD as compared to individuals with no medically unexplained pain (Table 3, row percentages).

Although more than 80% of individuals with UPS or PD reported no GAD symptoms, strong associations were found between pain and generalized anxiety on all diagnostic levels (crude OR range: 2.4–13.4, all p -values < 0.001 ; Table 4) with the exception of UPS and symptomatic GAD. There is some evidence for a non-linear dose–response relationship as indicated by increasing ORs towards stricter definitions of both disorders with a particularly pronounced association for PD and DSM-IV GAD (OR = 13.4, 95% CI: 7.2–24.8, $p < 0.001$).

While adjusting for demographic variables decreased the associations only slightly, there was a major drop in the magnitude of the ORs when depressive disorders were added to the multiple model. However, only the association between PD and subthreshold GAD was attenuated. The model additionally adjusting for other anxiety disorders revealed a further modest decrease in OR size with OR attenuation for PD and symptomatic GAD. No further change in associations was found when substance use disorders and number of physical illnesses were added to the model. Therefore, the associations to DSM-IV GAD endured independent of effects of demographic variables and a number of comorbid conditions for UPS (OR = 3.6, 95% CI: 1.9–7.1, $p < 0.001$) and particularly PD (OR = 4.7, 95% CI: 2.3–9.5, $p < 0.001$), as was the association between UPS and subthreshold GAD (OR = 1.8, 95% CI: 1.1–1.3, $p = 0.020$).

To further rule out artifactual comorbidity between unexplained pain and generalized anxiety, we first examined the temporal order of onset of these conditions. One would expect misclassifications to be reflected in frequent onsets within the same year. However, only few cases with comorbid UPS/PD and subthreshold/threshold GAD ($n = 101$; note: no age of onset available for most respondents with symptomatic GAD) reported a same year onset ($n = 10$, 9.4%). Pain began at least 1 year prior to GAD in the majority of cases ($n = 71$, 72.3%); a secondary onset of pain was found in one-fifth of the subjects ($n = 20$, 18.4%). We also examined among respondents who were classified with unexplained pain and who consulted their medical doctor for at least one of their pain symptoms ($n = 842$ of the UPS/PD cases without comorbid generalized anxiety, $n = 151$ of the UPS/PD cases with comorbid symptomatic, subthreshold or threshold GAD) how frequently physicians – as per respondents' report – directly attributed the pain to anxiety, panic attacks, or depression. Also providing evidence against misclassification, very few of the respondents with UPS/PD ($n = 2/842$, 0.2% of the respondents without comorbid generalized anxiety, $n = 4/151$, 2.6% of the respondents with comorbid generalized anxiety) stated that their physician explained their pain by anxiety, panic or depression. In contrast, 16.8% ($n = 145$) of the respondents with UPS/PD alone and 27.7% ($n = 42$) of the respondents with comorbid UPS/PD and generalized anxiety reported that their pain was specifically attributed to nerves or stress by their physician.

3.4. Correlates of generalized anxiety and pain

Table 5 shows measures of quality of life, disability, and health care utilization for four mutually exclusive groups: individuals with: (1) no unexplained pain symptoms and no generalized anxiety, (2) unexplained pain (UPS or PD) alone, (3) generalized anxiety (symptomatic GAD, subthreshold GAD, or threshold GAD) alone, and (4) both unexplained pain and generalized anxiety.

Compared to individuals without unexplained pain and generalized anxiety, all three syndrome groups – unexplained pain alone, generalized anxiety alone, and co-occurring unexplained pain and generalized anxiety – were associated with decreased quality of life, disability and health care utilization (all p -values < 0.05) with the exception that individuals with generalized anxiety alone, as expected, did not report reduced physical health related quality of life or disability due to physical problems. However, these individuals had a significantly more decreased mental health related quality of life (OR = 0.90, 95% CI: 0.86–0.93, $p < 0.001$) and increased disability days due to mental health problems (OR = 2.6, 95% CI: 1.5–4.5, $p = 0.001$) as compared to individuals with unexplained pain alone. As expected, the group with both unexplained pain and generalized anxiety reported the lowest quality of life and greatest disability and health care utilization.

In comparison to individuals with unexplained pain alone, the co-occurrence of generalized anxiety in unexplained pain was associated with decreased mental health related quality of life (OR = 0.78, 95% CI: 0.74–0.82, $p < 0.001$), a greater number of disability days due to mental problems (OR = 5.4, 95% CI: 3.3–8.8, $p < 0.001$), and a higher number of health care visits (OR = 1.5, 95% CI: 1.2–1.9, $p = 0.001$). Compared to the generalized anxiety alone group, individuals with co-occurring unexplained pain and generalized anxiety reported significantly lower mental (OR = 0.87, 95% CI: 0.82–0.93, $p < 0.001$) and physical (OR = 0.93, 95% CI: 0.89–0.97, $p = 0.001$) health related quality of life, as well as more disability days due to mental problems (OR = 2.1, 95% CI: 1.2–3.7, $p = 0.009$), and a greater number of health care visits (OR = 1.4, 95% CI: 1.1–1.9, $p = 0.012$). In the model with generalized anxiety (yes/no), pain (yes/no) and the interaction anxiety $\times$ pain we only found one significant interaction: the main effects of pain (ratio main effect estimated as 0.95 in this model) and generalized anxiety (ratio main effect estimated as 0.85 in this model) on mental health related quality of life (SF36) were significantly enhanced when both conditions were present (interaction: R = 0.92, 95% CI: 0.86–0.98, $p = 0.009$).

Adjusting all analyses for comorbid anxiety and depressive disorders, as the both groups of diagnoses having the most influence on the pain-generalized anxiety association, we found that most associations with negative correlates remained significant (Table available upon request).

4. Discussion

Using 12-month data from a large general population sample we examined the association between medically unexplained pain and GAD as assessed by a standardized diagnostic interview. The major findings emerging from our analyses are: (1) GAD was specifically and more strongly than other anxiety disorders associated with medically unexplained pain, (2) this specific association also applied to subthreshold levels of GAD with some indication of a non-linear dose–response relationship, (3) associations were not attributable to demographic factors or comorbid mental and physical disorders, and (4) the co-occurrence of medically unexplained pain and generalized anxiety was associated with poorer negative outcomes in terms of quality of life, disability, and health care utilization.

The conceptualization and classification of both GAD (Beesdo, 2006; Hettema, 2008; Hoyer, Beesdo, Becker, & Wittchen, 2003; Kessler, 2002; Mennin, Heimberg, Fresco, & Ritter, 2008; Moffitt et al., 2007; Watson, O'Hara, & Scott, 2008) and unexplained, somatoform conditions (Hiller, 2006; Kroenke, 2006; Mayou et al., 2005; Sharpe et al., 2006; Sullivan, 2000; Sykes, 2006) has been surrounded by controversy. Acknowledging this controversy, the current study provides epidemiological evidence that the association between generalized anxiety and medically unexplained pain is strong, not due to diagnostic artifact, and has clinical and public health implications.

Some limitations of our study must be carefully considered for interpretation of our findings. We assessed and categorized clinically significant, medically unexplained pain symptoms and pain disorder based on participants' response to DIA-X/M-CIDI questions. In our population-based sample, we were unable to confirm clinical significance or the unexplained nature of pain symptoms through medical records or routine diagnostic work-up. Thus, our diagnostic categories rely on respondents' self-report. The DIA-X/M-CIDI diagnoses of pain disorder therefore have imperfect validity. However, diagnostic categorizations were based on a series of sophisticated DIA-X/M-CIDI probe questions. For example, several probe questions explicitly asked for doctor's diagnoses or test results in relation to the pain. Only if physical and substance related factors were ruled out was the pain then classified as „medically unexplained“. Moreover, in order to rule out misclassification and thus artifactual comorbidity between unexplained pain and generalized anxiety, we investigated whether physicians attributed the pain explicitly to anxiety (or depression), or whether pain and generalized anxiety symptoms emerged at the same time. None of these explanations sufficiently accounted for our findings. It is also important to note that artifactual comorbidity is not created by the DSM-IV given the fact that GAD and pain disorder do not share any symptom criteria. Thus, there is evidence for these two distinct entities that appear to be strongly associated.

Consistent with the few available recent epidemiological findings (Demyttenaere et al., 2007; Gureje et al., 2008; McWilliams et al., 2004; Von Korff, Crane, et al., 2005), we also found associations between pain and other anxiety disorders (GAD excluded from the combined group). The association between GAD and pain, however, was particularly pronounced. As some anxiety disorders known to have strong associations to pain (such as posttraumatic-stress disorder) were not assessed in our study, it remains to be delineated to what degree the specificity in the association between GAD and pain over and above the other anxiety disorders would persist if these conditions were included in the combined anxiety group. Unfortunately, lack of power prevented us to examine the specificity of the GAD-pain association in regard to each of the individual anxiety disorders. However, we controlled the GAD-pain association for comorbid mental disorders as well as physical disorders and demographic factors and the association remained, supporting the robustness of our finding. Among control variables, depressive disorders had the largest, though not attenuating effect on the GAD-pain association. Given the well-known high rates of comorbidity between GAD and depression (Kessler et al., 2004), our findings suggest that the GAD-pain association is independent and not confounded by comorbid depression. This also is indirect support for the view that GAD is a discrete disorder and not only a manifestation of other psychopathology such as depressive disorders (Kessler, 2002).

A closer investigation of symptomatic and subthreshold definitions of GAD also revealed associations with medically unexplained pain, albeit these were lower, less consistent and less stable when confounding factors were controlled. These findings, however, suggest that generalized anxiety and medically unexplained pain, in addition to being associated on a

DSM-IV disorder level, are also related on a continuum of symptom levels. There is indication of a non-linear dose–response relationship as the association was observed to increase from the symptom to the disorder levels of the conditions with an especially pronounced association between DSM-IV defined GAD and pain disorder.

Reasons for the strong association between GAD and pain are currently unclear. Several theoretical explanations are possible. Three of them are the most viable for future investigation of the mechanisms and pathways of this association. First, there may be a direct link between GAD and pain. Experience of pain symptoms may trigger anxious worrying and therefore may contribute to the development of GAD, and vice versa, the muscular tension associated with GAD may lead to pain symptoms. Given our finding of a non-linear dose–response relationship between generalized anxiety and pain, it may be assumed that these processes are more likely to occur if worrying and pain reach a certain level of severity or chronicity to trigger the onset of the other condition. Our exploration of temporal order of onset would support the bi-directional causal hypothesis with some indication that pain is more likely to trigger GAD than the reverse. This, however, needs further investigation, optimally in prospective longitudinal observational studies.

The potential second explanation for comorbidity between pain and GAD is the perpetuating or exacerbating role of anxious worrying and pain after the initial onset of the other condition. That is, unexplained pain may be a source for more anxious expectation and worrying among individuals with generalized anxiety and therefore a mediator for the development of threshold GAD. Vice versa, anxious worrying occurring among individuals with pain symptoms may exaggerate awareness and attention to pain and therefore contribute to pain persistence and chronicity.

Third, other variables such as biological, psychological and/or social factors may contribute to both GAD and pain by acting either as mediators or vulnerability factors in a common pathogenetic pathway. For example, cognitive distortions (e.g., catastrophizing, fear of pain, and pain/anxiety sensitivity) (Asmundson, Norton, & Vlaeyen, 2004; Cohen & Rodriguez, 1995; Norton & Asmundson, 2004; Rief & Broadbent, 2007), dysfunctional behaviors (e.g., avoidance, reassurance seeking) (Asmundson et al., 2004; Cohen & Rodriguez, 1995; Norton & Asmundson, 2004; Rief & Broadbent, 2007) or neuro-chemical processes (e.g., dysfunction in serotonergic and noradrenergic neurotransmitter systems) (Cohen & Rodriguez, 1995; Rief & Broadbent, 2007; Smith, Macfarlane, & Torrance, 2007) arising from experiencing pain or GAD may be associated with the onset of the other condition (mediator-hypothesis) or may be the vulnerability for the independent development of both conditions (common pathogenetic vulnerability hypothesis). Further research is necessary to investigate the role of these possible explanations for the GAD-pain association and, in particular, to identify the mechanisms contributing to the specificity of this association for GAD in contrast to other anxiety disorders.

Identification of the contributors and causes of the high comorbidity between pain and GAD is important, particularly in light of our finding that the GAD-pain co-occurrence is linked to more adverse negative correlates such as higher disability, decreased quality of life, and increased service utilization relative to individuals with only one of these two conditions. Clinicians should be aware of the strong relationship between pain and GAD, and assess anxious worrying and more severe GAD-levels in patients presenting with (unexplained) pain and vice versa. Diagnosis of GAD frequently presents a greater challenge than asking and following up on pain symptoms. As shown in a primary care study, GAD is frequently not recognized, correctly diagnosed and treated by physicians (Wittchen, Kessler, et al., 2002).

This may be the case because patients with GAD present with pain as their primary presenting complaint rather than with anxiety or worry. Yet, there are feasible screening instruments (GAD-Q-IV, Newman et al., 2002; ASQ-15, Wittchen & Boyer, 1998) available to assist clinicians' evaluations.

If both conditions are present, the clinical implication for improved treatment is to consider intervention methods known to be effective in both GAD and pain. Such treatment options include both pharmacologic (Allgulander et al., 2007; Briley, 2004; Crofford et al., 2005; Grothe et al., 2004; Meoni, Hackett, & Lader, 2004; Mitte, 2005; Montgomery, Tobias, Zornberg, Kasper, & Pande, 2006) and psychological interventions (Borkovec & Ruscio, 2001; Hoyer et al., 2009; Turner-Stokes et al., 2003). An optimized treatment would improve patient care. For example, prescribing a medication known to be effective for both conditions reduces the number of medications, drug–drug interactions, and side effects. For non-pharmacologic treatment, cognitive-behavioral psychotherapeutic (CBT) approaches are the most promising (Borkovec & Ruscio, 2001; Hoyer et al., 2009; Turner-Stokes et al., 2003). Several CBT interventions target similar mechanisms of change related to both conditions. For example, a common element in pain and GAD treatment is relaxation training to decrease muscle tenderness and symptoms of hypervigilance. The fear of pain and also the fear of experiencing anxiety may be challenged with cognitive restructuring or exposure therapy. Confrontation interventions also target decreasing avoidance and increasing physical activity and goal-directed behaviour.

Given high prevalence of GAD and pain-conditions in the community, it appears also important to test the efficacy of prevention and early intervention programs in order to reduce the risk for the development of the full-blown condition and secondary complications. Goodwin and Gorman (2002) showed in a US-population sample (NCS) that treatment of GAD with psychotropic medications significantly decreased the risk for subsequent onset of major depression. It remains to be investigated whether GAD treatment also reduces the onset of pain conditions and whether early intervention among individuals with pain decreases the risk for the development of GAD. Two recent primary care studies assessing the efficacy of brief CBT programs for enhancing chronic back pain are promising in regard to the latter question, as they showed reductions in back-related worries and fear-avoidance beliefs (Moore, VonKorff, Cherkov, Saunders, & Lorig, 2000; Von Korff, Balderson, et al., 2005).

In conclusion, this study based on a large epidemiological sample provides evidence for: (a) a strong association between medically unexplained pain and GAD on a disorder and syndromal level, (b) diagnostic specificity for the pain association with GAD versus other anxiety syndromes, and (c) high magnitude of this association persisting even when adjusting for comorbid conditions. Co-occurrence of unexplained pain with both subthreshold and threshold levels of GAD represents a substantial health problem given their high prevalence, impairment/disability, and health care utilization rates. Greater recognition of these comorbid conditions and understanding the pathways and mechanisms of co-occurrence may lead to better treatment strategies as well as prevention of secondary long-term complications.

Table 1
The 12-month co-occurrence of medically unexplained pain and anxiety disorders (N = 4181).

Pain ^a	Anxiety disorders ^b									Total		
	No anxiety disorder			Any anxiety disorder ^c but no GAD			DSM-IV GAD ^d					
	n ^e	% row ^f	% col ^g	n ^e	% row ^f	% col ^g	n ^e	% row ^f	% col ^g			
No UP	2704	89.6	80.1	371	9.8	58.0	23	0.6	30.9	3098	100.0	76.5
UPS	520	76.6	13.8	168	20.3	24.2	23	3.1	31.0	711	100.0	15.4
PD	230	64.6	6.1	115	28.3	17.8	27	7.1	38.0	372	100.0	8.1
Total	3454	85.6	100.0	654	12.9	100.0	73	1.5	100.0	4181	100.0	100.0

^a Diagnostic groups mutually exclusive; no UP: no unexplained pain, UPS: unexplained pain symptoms, PD: pain disorder.

^b Diagnostic groups mutually exclusive.

^c Includes specific phobia, social phobia, agoraphobia without panic disorder, phobia NOS, panic disorder with or without agoraphobia, and obsessive compulsive disorder.

^d Generalized anxiety disorder irrespective of comorbidity.

^e n: unweighted number.

^f % row: weighted row percentages.

^g % col: weighted column percentages.

Table 2
Associations between medically unexplained pain and anxiety disorders versus generalized anxiety disorder (N = 4181).

Pain ^a	Any anxiety disorder ^b but no GAD ^c vs. no anxiety disorder		GAD ^c vs. no anxiety disorder		GAD ^c vs. any other anxiety disorder ^b	
	OR ^d	(95% CI)	OR ^d	(95% CI)	OR ^d	(95% CI)
<i>Crude model (unadjusted)</i>						
UPS	2.4 [*]	(1.9–3.0)	5.8 [*]	(3.0–11.1)	2.4 [*]	(1.2–4.7)
PD	4.0 [*]	(3.0–5.3)	16.0 [*]	(8.6–29.8)	4.0 [*]	(2.1–7.6)
<i>Models adjusted for:</i>						
<i>Age and gender</i>						
UPS	2.2 [*]	(1.8–2.8)	5.6 [*]	(3.0–10.6)	2.5 [*]	(1.3–4.9)
PD	3.5 [*]	(2.6–4.6)	14.3 [*]	(7.6–26.8)	4.1 [*]	(2.2–7.9)
<i>Age, gender, and depressive disorders</i>						
UPS	2.1 [*]	(1.6–2.6)	4.6 [*]	(2.4–8.9)	2.2 [*]	(1.1–4.3)
PD	2.8 [*]	(2.1–3.8)	7.9 [*]	(4.2–14.9)	2.8 [*]	(1.5–5.4)
<i>Age, gender, depressive and substance use disorders</i>						
UPS	2.1 [*]	(1.6–2.6)	4.6 [*]	(2.4–8.8)	2.2 [*]	(1.1–4.3)
PD	2.7 [*]	(2.0–3.6)	7.6 [*]	(4.0–14.4)	2.9 [*]	(1.5–5.4)
<i>Age, gender, depressive and substance use disorders and number of physical disorders</i>						
UPS	2.0 [*]	(1.5–2.5)	4.5 [*]	(2.3–8.6)	2.3 [*]	(1.2–4.4)
PD	2.3 [*]	(1.7–3.2)	6.9 [*]	(3.6–13.4)	3.0 [*]	(1.5–5.8)

^a UPS: unexplained pain symptoms (n = 711), PD: pain disorder (n = 372).

^b Includes specific phobia, social phobia, agoraphobia without panic disorder, phobia NOS, panic disorder with or without agoraphobia, and obsessive compulsive disorder (n = 654).

^c GAD: generalized anxiety disorder (n = 73).

^d Odds ratio (95% confidence interval) from multinomial logistic regressions, reference: no unexplained pain.

^{*} OR significant at the .05 level, 2-sided test.

Table 3
The 12-month co-occurrence of medically unexplained pain and different diagnostic thresholds of generalized anxiety (N = 4181).

Pain ^a	Generalized anxiety ^b												Total		
	No GAD symptoms			Symptomatic GAD			Subthreshold GAD			DSM-IV GAD					
	n	%row	%col	n	%row	%col	n	%row	%col	n	%row	%col	n	%row	%col
No UP	2891	94.1	78.0	129	3.7	67.8	55	1.6	56.8	23	0.6	30.9	3088	100.0	76.5
UPS	621	88.5	14.8	36	4.7	17.4	31	3.8	27.4	23	3.1	31.0	711	100.0	15.4
PD	296	81.2	7.2	29	7.6	14.8	20	4.1	15.7	27	7.1	38.0	372	100.0	8.1
Total	3808	92.2	100.0	194	4.2	100.0	106	2.1	100.0	73	1.5	100.0	4181	100.0	100.0

n: unweighted number; % col: weighted column percentages; % row: weighted row percentages.

^a Mutually exclusive diagnostic groups; no UP: no unexplained pain; UPS: unexplained pain symptoms; PD: pain disorder.

^b Mutually exclusive diagnostic groups; GAD: generalized anxiety disorder.

Table 4Associations between diagnostic levels of medically unexplained pain and generalized anxiety (crude and adjusted models; *N* = 4181)

Pain ^a	Generalized anxiety ^b					
	Symptomatic GAD (<i>n</i> = 194)		Subthreshold GAD (<i>n</i> = 106)		DSM-IV GAD (<i>n</i> = 73)	
	OR ^c	(95% CI)	OR ^c	(95% CI)	OR ^c	(95% CI)
UPS (<i>n</i> = 711)						
Crude model	1.4	(0.9–2.1)	2.5*	(1.6–4.1)	5.3*	(2.8–10.1)
Models adjusted for:						
Age and gender	1.3	(0.8–2.0)	2.4*	(1.5–3.9)	5.1*	(2.7–9.7)
Age, gender and depressive disorders	1.2	(0.7–1.8)	2.0*	(1.2–3.4)	4.0*	(2.1–7.8)
Age, gender, depressive disorders and other anxiety disorders	1.0	(0.7–1.6)	1.8*	(1.1–3.0)	3.6*	(1.9–7.1)
Age, gender, depressive disorders, other anxiety disorders and substance use disorders	1.0	(0.7–1.6)	1.8*	(1.1–3.0)	3.6*	(1.9–7.1)
Age, gender, depressive disorders, other anxiety disorders, substance use disorders and number of somatic disorders	1.0	(0.6–1.6)	1.8*	(1.1–3.0)	3.6*	(1.9–7.1)
PD (<i>n</i> = 372)						
Crude model (unadjusted)	2.4*	(1.5–3.7)	3.4*	(1.7–5.3)	13.4*	(7.2–24.8)
Models adjusted for:						
Age and gender	2.2*	(1.4–3.4)	2.7*	(1.5–4.7)	12.2*	(6.5–22.8)
Age, gender and depressive disorders	1.6*	(1.0–2.5)	1.7	(1.0–3.1)	6.2*	(3.3–11.7)
Age, gender, depressive disorders and other anxiety disorders	1.3	(0.8–2.1)	1.4	(0.8–2.6)	4.7*	(2.4–9.3)
Age, gender, depressive disorders, other anxiety disorders and substance use disorders	1.3	(0.8–2.1)	1.4	(0.8–2.6)	4.7*	(2.4–9.3)
Age, gender, depressive disorders, other anxiety disorders, substance use disorders and number of somatic disorders	1.3	(0.8–2.0)	1.4	(0.8–2.5)	4.7*	(2.3–9.5)

^a Mutually exclusive diagnostic groups; UPS: unexplained pain symptoms; PD: pain disorder.^b Mutually exclusive diagnostic groups; GAD: generalized anxiety disorder.^c Odds ratio (95% confidence interval) from multinomial logistic regression; reference: no unexplained pain respectively no generalized anxiety.

* OR significant at the .05 level, 2-sided test.

Table 5Impairment/disability measures and health care utilization in individuals with medically unexplained pain^a and/or generalized anxiety^b (*N* = 4181).

	No unexplained pain and no generalized anxiety (<i>n</i> = 2891)		Unexplained pain alone (no generalized anxiety) (<i>n</i> = 917)			Generalized anxiety alone (no unexplained pain) (<i>n</i> = 207)			Co-occurring unexplained pain and generalized anxiety (<i>n</i> = 166)		
	M ^c	(SD)	M ^c	(SD)	R ^d (95% CI)	M ^c	(SD)	R ^d (95% CI)	M ^c	(SD)	R ^d (95% CI)
Mental health related quality of life (SF-36) ^e	51.8	(7.8)	49.1	(9.2)	0.95* (0.94–0.97)	44.2	(11.6)	0.85* (0.82–0.89)	38.3	(11.1)	0.75* (0.71–0.78)
Physical health related quality of life (SF-36) ^e	50.1	(8.4)	46.6	(9.2)	0.93* (0.92–0.95)	49.4	(9.7)	0.99 (0.96–1.03)	45.8	(8.9)	0.92* (0.89–0.96)
Mean number of partial or total disability days ^f during past 4 weeks due to mental problems	0.2	(1.7)	0.6	(2.7)	2.5* (1.6–3.8)	1.6	(4.2)	6.3* (3.7–10.7)	3.6	(6.9)	13.3* (8.5–20.8)
Mean number of total disability days ^f during past 4 weeks due to physical problems or illness	0.8	(3.5)	1.5	(4.8)	1.8* (1.4–2.4)	1.2	(4.5)	1.3 (0.7–2.5)	1.6	(4.9)	1.9* (1.1–3.1)
Mean number of health care visits ^g during past 12 months	8.6	(12.7)	12.2	(17.9)	1.4* (1.2–1.6)	13.2	(17.3)	1.5* (1.2–1.8)	19.8	(25.2)	2.1* (1.7–2.6)

^a Unexplained pain contains unexplained pain symptoms and pain disorder.^b Generalized anxiety includes symptomatic GAD, subthreshold GAD and DSM-IV GAD.^c Mean (Standard Deviation).^d Ratios (95% Confidence Interval): Mean ratios from negative binomial regressions for count variables; Ratio from gamma regression for SF-36-Mean Scores (interpretation: a significant ratio of <1 indicates a decrease of health related quality of life); reference group: no unexplained pain and no generalized anxiety; all ratios adjusted for age and gender.^e SF-36 sum scores mental and physical health (*M* = 50, *SD* = 10).^f Reported number of days being unable to carry out usual activities.^g Includes general practice visits, specialist visits, and days in hospital.

* OR significant at the .05 level, 2-sided test.

Conflict of interest

Dr. Beesdo has received speaking honoraria from Pfizer and travel support from Eli Lilly. Dr. Wittchen has received research support from Eli Lilly, and speaking honoraria from Novartis, and Pfizer. He has been a consult for Eli Lilly, GlaxoSmithKline Pharmaceuticals, Novartis, and Pfizer. Dr. Hoyer, Dr. Jacobi, Dr. Low, and Dr. Höfler have nothing to declare.

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Germany. Principal investigator was Dr. Hans-Ulrich Wittchen. Reported somatic health status variables come from the GHS-Core Survey, conducted by the Robert Koch-Institute, Berlin, Germany. Principal investigators of the GHS-Core Survey were Dr. Bärbel-Maria Kurth and Dr. Wolfgang Thefeld.

Note: Data from this study are available as a Public Use File from: Dr. Frank Jacobi, Institute of Clinical Psychology and Psychotherapy, Chemnitzer Str. 46, 01187 Dresden, Germany; EMail: jacobi@psychologie.tu-dresden.de. For further information about the Core Survey and its Public Use File, contact the Robert Koch-Institute, Dr. Heribert Stolzenberg, Nordufer 20, 13353 Berlin, Germany; E-Mail: stolzenbergh@rki.de.

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