The role of gender and anxiety in the association between somatic diseases and depression: findings from three combined epidemiological studies in primary care

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Aims. Although associations between various somatic diseases and depression are well established, findings concerning the role of gender and anxiety disorders for these associations remain fragmented and partly inconsistent. Combining data from three large-scaled epidemiological studies in primary care, we aim to investigate interactions of somatic diseases with gender and anxiety disorders in the association with depression.

Methods. Self-reported depression according to the International Classification of Diseases, Tenth Edition (ICD-10) was assessed in $n=83\,737$ patients from three independent studies [DETECT (Diabetes Cardiovascular Risk Evaluation: Targets and Essential Data for Commitment of Treatment), Depression-2000 and Generalized Anxiety and Depression in Primary Care (GAD-P)] using the Depression Screening Questionnaire (DSQ). Diagnoses of depression, anxiety disorders and somatic diseases were obtained from treating physicians via standardised clinical appraisal forms.

Results. In logistic regressions, adjusted for gender, age group and study, each somatic disease except for arterial hypertension and endocrine diseases was associated with self-reported depression (odds ratio, OR 1.3–2.6) and each somatic disease was associated with physician-diagnosed depression (OR 1.1–2.4). Most of these associations remained significant after additional adjustment for anxiety disorders and other somatic diseases. The associations with depression increased with a higher number of somatic diseases. Cardiovascular diseases (OR 0.8), diabetes mellitus (OR 0.8) and neurological diseases (OR 0.8) interacted with gender in the association with self-reported depression, while endocrine diseases (OR 0.8) interacted with gender in the association with physician-diagnosed depression. That is, the associations between respective somatic diseases and depression were less pronounced in females *v.* males. Moreover, cardiovascular diseases (OR 0.7), arterial hypertension (OR 0.8), gastrointestinal diseases (OR 0.7) and neurological diseases (OR 0.6) interacted with anxiety disorders in the association with self-reported depression, and each somatic disease interacted with anxiety disorders in the association with physician-diagnosed depression (OR 0.6–0.8). That is, the associations between respective somatic diseases and depression were less pronounced in patients with *v.* without anxiety disorders; arterial hypertension was negatively associated with self-reported depression only in patients with anxiety disorders, but not in patients without anxiety disorders.

Conclusions. A range of somatic diseases as well as anxiety disorders are linked to depression – and especially patients with co-/multi-morbidity are affected. However, interactions with gender and anxiety disorders are noteworthy and of relevance to potentially improve recognition and treatment of depression by physicians. Somatic diseases are associated more strongly with depression in males *v.* females as well as in patients without *v.* with anxiety disorders, primarily because women and patients with anxiety disorders per se are characterised by considerably increased depression prevalence that only marginally changes in the presence of somatic comorbidity.

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Introduction

There is consistent evidence from epidemiological (Egede, 2007; Moussavi *et al.* 2007; Scott *et al.* 2007; Stegmann *et al.* 2010; Teesson *et al.* 2011; Patten *et al.*

2016) and primary care studies (Kroenke *et al.* 1994; Kroenke *et al.* 1997; Lyness *et al.* 2006; Pieper *et al.* 2008; Gili *et al.* 2010; Østergaard & Foldager, 2011) that somatic diseases are associated with depression and that these associations increase with higher severity, chronicity and comorbidity of somatic diseases (Østergaard & Foldager, 2011; Merikangas *et al.* 2015). However, depression in primary care patients is often not accurately recognised, diagnosed and adequately treated so far (Wittchen & Pittrow, 2002; Mitchell *et al.* 2009). Additional research efforts are thus necessary to further specify patients at increased risk for depression as well as to improve an early recognition and treatment.

To date, it remains unresolved whether the associations between different somatic diseases and depression vary by gender: Respective findings were inconclusive ranging from evidence for no significant gender differences (Patten, 2001; Patten *et al.* 2005; Engum, 2007; Frasure-Smith & Lesperance, 2008; Gerrits *et al.* 2014) to evidence for more pronounced associations between somatic symptoms/diseases and depression in males (Patten *et al.* 2005) or females (Carnethon *et al.* 2003; Beesdo *et al.* 2010). For instance, while diabetes and unexplained pain symptomatology were associated more strongly with depression in females (Carnethon *et al.* 2003; Beesdo *et al.* 2010), food allergies and chemical sensitivities were associated more strongly with depression in males (Patten *et al.* 2005). Additional studies are therefore needed to examine gender-specific differences in associations between a variety of somatic diseases and depression. Because females *per se* are at considerably increased risk for depression (Kessler *et al.* 2003; Kessler *et al.* 2005; Jacobi *et al.* 2014), the probability of depression might increase less strongly with somatic diseases in females *v.* males.

Moreover, only a minority of studies in the field considered the role of comorbid anxiety. Depression and anxiety frequently co-occur, with comorbidity being associated with higher severity and impairment (Kessler *et al.* 2003; Kessler *et al.* 2005; Jacobi *et al.* 2014); also, both conditions are associated with somatic diseases (Scott *et al.* 2007; Gili *et al.* 2010; Bhattacharya *et al.* 2014; Bekhuis *et al.* 2015). A consideration of comorbid anxiety is thus particularly important. Previous research demonstrated that most of the associations between somatic symptoms/diseases and depression remained similar when accounting for anxiety disorders; some associations, however, were attenuated to non-significance (Strik *et al.* 2003; Beesdo *et al.* 2010; Chou *et al.* 2013; Bekhuis *et al.* 2015; Kahl *et al.* 2015; Niles *et al.* 2015). Further studies distinguished between pure depression, pure anxiety and their comorbidity and evidenced that somatic diseases

were particularly associated with comorbid depressive and anxiety disorders (Scott *et al.* 2007; Bhattacharya *et al.* 2014). Additional research, however, is necessary to resolve whether the associations between various somatic diseases and depression (a) remain stable after taking into account anxiety disorders and/or (b) differ in patients with and without anxiety disorders. The fact that anxiety disorders substantially increase the risk for depression (Kessler *et al.* 2003; Kessler *et al.* 2005; Jacobi *et al.* 2014) suggests that somatic comorbidities in those with anxiety disorders might add little in risk. In other words, the probability of depression might increase less strongly with somatic diseases in patients with *v.* without anxiety disorders.

Using combined data from three epidemiological studies in primary care ($n=83\,737$ patients), we aim to examine associations between various somatic diseases (cardiovascular diseases, arterial hypertension, endocrine diseases, diabetes mellitus, gastrointestinal diseases and neurological diseases) and depression, taking into account the role of gender, anxiety disorders and somatic comorbidity. Because previous research revealed that self-reported depression (assessed via interview/questionnaire) and depression as diagnosed by primary care physicians (clinical appraisal) often disagree (Wittchen *et al.* 2001; Wittchen *et al.* 2002), both self-reported and physician-diagnosed depression will be considered as outcomes. The following hypotheses will be investigated:

1. Each somatic disease is associated with depression, even after taking into account not only gender, age and study, but also the presence of anxiety disorders and somatic comorbidity. The associations with depression increase with a higher number of somatic diseases.
2. Anxiety disorders are associated with depression, even after taking into account not only gender, age and study, but also the presence of somatic comorbidity.
3. Somatic diseases interact with gender and anxiety disorders in the association with depression. That is, because females and patients with anxiety disorders *per se* are at considerably increased risk for depression, the associations between somatic diseases and depression are less pronounced in females *v.* males as well as in patients with *v.* without anxiety disorders.

Method

Design

Data from three independent large-scaled epidemiological studies in primary care settings in Germany were combined (total $n=83\,737$ patients). Detailed

information on these studies, namely DETECT (Diabetes Cardiovascular Risk Evaluation: Targets and Essential Data for Commitment of Treatment) (Wittchen *et al.* 2005), Depression 2000 (Wittchen & Pittrow, 2002) and Generalized Anxiety and Depression in Primary Care (GAD-P) (Wittchen *et al.* 2002) has been previously presented and is summarised briefly here.

DETECT was conducted in Germany from 09/2003 until 12/2004. The study sample was drawn randomly from a nationwide database of primary care physicians. The cross-sectional main study (data used herein) was conducted among $n=3188$ primary care physicians and their primary care attendees on two specific target days in September 2003.

In Depression 2000, $n=510$ physicians were selected out of an approximate total of $n=56\,000$ primary care physicians in Germany. $n=412$ physicians (81%) were willing to participate. Physicians and their primary care attendees were assessed on a specific target day in April 2000.

In GAD-P, $n=628$ physicians were selected out of an approximate total of $n=56\,000$ primary care physicians in Germany. A total of $n=558$ (89%) physicians were willing to participate. Physicians and their primary care attendees were assessed on a specific target day in September 2000.

In all three studies, information on physical and mental health was assessed from patients and their treating physicians using standardised self-report questionnaires and clinical appraisal forms. Complete information on gender, age, self-reported depression and physician-diagnosed depression, anxiety disorders and somatic diseases was available for $n=51\,206$ patients in DETECT, for $n=14\,664$ patients in Depression 2000 and for $n=17\,867$ patients in GAD-P.

Diagnostic assessment of depression and anxiety disorders

Depressive symptoms during the past 2 weeks were assessed via self-report in patients using the Depression Screening Questionnaire (DSQ) (Wittchen & Perkonig, 1997). The DSQ assessed ten symptoms of depression with three-point scaled items labelled 0 = never, 1 = on some days and 2 = on the majority of days; in GAD-P, however, a slightly modified response format was used (0 = seldom/never, 1 = often and 2 = on the majority of days). The DSQ is well established and has been used in epidemiological studies in primary care in various countries (Munk-Jorgenson *et al.* 2006). Test-retest reliability and convergent validity [diagnosis of major depression based on the DSQ as compared with the Composite International Diagnostic Interview (Wittchen & Pfister, 1997)] have been shown to be high (Wittchen & Perkonig, 1997).

Due to the diverging response format in GAD-P, depression according to the International Classification of Diseases, Tenth Edition (ICD-10) herein is defined slightly more stringent than in previous studies (Winter *et al.* 2000; Pieper *et al.* 2008; Pieper *et al.* 2011), namely as present when at least four items were answered with 2 = on the majority of days.

Moreover, physician diagnoses of depression and anxiety disorders were assessed with standardised clinical appraisal forms. In each study, physicians were asked to indicate the presence of depression and anxiety disorders out of a list with different mental disorders (and somatic diseases in DETECT). In GAD-P, panic disorder, generalised anxiety disorder and other anxiety disorders were assessed separately. In Depression 2000 and GAD-P, physicians were additionally asked to rate whether individual diagnoses were certain, subthreshold or questionable. Only diagnoses of depression judged as certainly present are included herein.

Diagnostic assessment of somatic diseases

Information on somatic diseases was assessed from physicians using standardised clinical appraisal forms. In Depression 2000 and GAD-P, physicians were asked to indicate the presence of different somatic diseases out of a list with 11 or ten response categories, respectively. In DETECT, somatic diseases including additional laboratory parameters were assessed in further detail. Cardiovascular diseases, arterial hypertension, endocrine diseases, diabetes mellitus, gastrointestinal diseases and neurological diseases or (acute) diseases of the nervous system were assessed in each study; thus, these somatic diseases are considered herein. It has to be noted that in DETECT, cardiovascular, endocrine and neurological diseases were not assessed as general categories. Instead, the following diseases were separately assessed: (1) left ventricular hypertrophy, atrial fibrillation and cardiac insufficiency (cardiovascular diseases); (2) neuropathy, cerebral insult, transient ischaemic attack and carotid stenosis (neurological diseases); and (3) thyroid diseases (endocrine diseases). Other somatic diseases were inconsistently assessed across studies and therefore are not considered in this paper (e.g. respiratory diseases were only assessed in Depression 2000 and GAD-P, but not in DETECT).

Statistical analyses

Combined data from DETECT, Depression 2000 and GAD-P were used. Only cases with complete data on gender, age and self-reported depression as well as diagnostic information from physicians on depression,

anxiety disorders and somatic diseases were included, resulting in a total of $n=83\,737$ patients. Additional information respecting the sample composition by study, gender and age group is presented in online Supplementary Table S1. Statistical analyses were conducted using Stata 14.1 (StataCorp, 2015).

First, logistic regressions adjusted for age group and study (DETECT, Depression 2000 and GAD-P) were used to estimate associations (odds ratio, OR) of gender with depression, anxiety disorders and somatic diseases. Multinomial logistic regressions adjusted for gender, age group and study were applied to calculate associations between sample/clinical characteristics and depression status (no depression, self-reported depression only, physician-diagnosed depression only, self-reported and physician-diagnosed depression). Outcome groups were pairwise compared, i.e. no depression, self-reported depression only or physician-diagnosed depression only were used as reference group.

Second, we examined main effects of somatic diseases in predicting self-reported as well as physician-diagnosed depression. That is, logistic regressions adjusted for gender, age group and study (model 1) were used to estimate associations of individual somatic diseases with self-reported and physician-diagnosed depression. These analyses were repeated and adjusted for (a) anxiety disorders (model 2) or (b) anxiety disorders and other somatic diseases (model 3).

Third, logistic regressions were used to test whether the associations between somatic diseases and depression increased with a higher number of somatic diseases (model 1: adjusted for gender, age group and study; model 2: adjusted for gender, age group, study and anxiety disorders). Because only few patients were affected by more than three disease categories, a dummy variable was generated to compare (a) cases with one, two or more than two disease(s), respectively, to cases without disease as well as (b) cases with two or more than two diseases, respectively, to cases with one disease in terms of depression risk.

Fourth, associations between anxiety disorders and depression were estimated using logistic regressions (model 1: adjusted for gender, age group and study; model 2: adjusted for gender, age group, study and somatic diseases).

Fifth, logistic regressions with interaction terms were applied to test whether somatic diseases interacted with gender in the association with depression (model 1: adjusted for age group and study; model 2: adjusted for age group, study and anxiety disorders; model 3: adjusted for age group, study, anxiety disorders and other somatic diseases). Moreover, we

assessed separate associations between somatic diseases and depression in males and females.

Sixth, logistic regressions with interaction terms were applied to test whether somatic diseases interacted with anxiety disorders in the association with depression (model 1: adjusted for gender, age group and study; model 2: adjusted for gender, age group, study and other somatic diseases). Besides, we tested separate associations between somatic diseases and depression in patients with anxiety disorders and patients without anxiety disorders.

We note that the ORs from interaction terms must be seen on a multiplicative scale: an OR <1 means that the combined effect of the respective somatic disease and gender/anxiety disorder is less than the product of the ORs for both individual (simple) effects. For instance, obtaining an OR <1 for the interaction term *cardiovascular disease* $\times$ *gender* would mean that the association between cardiovascular diseases and depression is less pronounced in females (coded as 1) *v.* males (coded as 0).

Each significant interaction was decomposed and visualised in an interaction graph. Absolute risk differences for depression (a) in males and females with and without respective somatic disease as well as (b) in patients with and without anxiety disorders with and without respective somatic disease can be visually assessed from these graphs (Fig. 1).

Results

Prevalence of depression, anxiety disorders and somatic diseases

Prevalences for depression, anxiety disorders and somatic diseases in the total sample as well as by gender are shown in Table 1. Depression, anxiety and endocrine diseases were more prevalent among women (OR 1.4–3.3), while cardiovascular diseases, arterial hypertension, diabetes mellitus and neurological diseases were more prevalent among men (OR 0.6–0.9). There were $n=2528$ (3.0%) patients with self-reported depression only, $n=6902$ (8.2%) with physician-diagnosed depression only and $n=1708$ (2.0%) with both self-reported and physician-diagnosed depression. Sensitivity of physician-diagnosed *v.* self-reported depression was higher in woman than in men (43.3% *v.* 34.5%); however, specificity was lower in woman than in men (89.3% *v.* 94.2%). Sample and clinical characteristics (age, gender, number of somatic diseases, number of visits during the past 12 months and physician-diagnosed anxiety disorders) partially differed by depression status. Respective findings are presented in online Supplementary Table S2.

Fig. 1. (a) Interactions of cardiovascular diseases, diabetes mellitus and neurological diseases with gender in the association with self-reported depression; (b) interactions of endocrine diseases with gender in the association with physician-diagnosed depression; (c) interactions of cardiovascular diseases, arterial hypertension, gastrointestinal diseases and neurological diseases with anxiety disorders in the association with self-reported depression; (d) interactions of cardiovascular diseases, arterial hypertension, endocrine diseases, diabetes mellitus, gastrointestinal diseases and neurological diseases with anxiety disorders in the association with physician-diagnosed depression. Note: OR: odds ratios; dx: disorder; statistically significant associations (with p -values <0.05) are presented in bold.

Table 1. Prevalences of depression, anxiety disorders and somatic diseases in the total sample, males and females (n = 83 737)

Depression/anxiety/somatic disease	Total (n = 83 737)		Males (n = 34 239)		Females (n = 49 498)		Association			
	N	%	N	%	N	%	OR	95% CI	p	
Self-reported depression	4236	5.1	1436	4.2	2800	5.7	1.4	1.3	1.5	<0.001
Physician-diagnosed depression	8610	10.3	2387	7.0	6223	12.6	2.0	1.9	2.1	<0.001
Physician-diagnosed anxiety	5045	6.0	1471	4.3	3574	7.2	1.8	1.6	1.9	<0.001
Cardiovascular disease	17 351	20.7	8551	25.0	8800	17.8	0.6	0.6	0.6	<0.001
Arterial hypertension	28 189	33.7	12 227	35.7	15 962	32.3	0.9	0.9	0.9	<0.001
Endocrine disease	8478	10.1	1643	4.8	6835	13.8	3.3	3.1	3.5	<0.001
Diabetes mellitus	10 437	12.5	4974	14.5	5463	11.0	0.7	0.7	0.8	<0.001
Gastrointestinal disease	8979	10.7	3769	11.0	5210	10.5	1.0	0.9	1.0	0.066
Neurological disease	4693	5.6	2289	6.7	2404	4.9	0.7	0.7	0.8	<0.001

OR, odds ratios from logistic regressions with gender (0 = male, 1 = female) as predictor and depression, anxiety or somatic disease as outcome, adjusted for study and age group; CI, confidence interval.

Associations between somatic diseases and depression

Prevalences of depression in patients with *v.* without somatic diseases are presented in Table 2 (upper part). Associations between somatic diseases and depression are shown in Table 3. Except for arterial hypertension and endocrine diseases, all somatic diseases were positively associated with self-reported depression in model 1 (adjusted for gender, age group and study; OR 1.3–2.6), model 2 (adjusted for gender, age group, study and anxiety disorders; OR 1.3–2.3) and model 3 (adjusted for gender, age group, study, anxiety disorders and other somatic diseases; OR 1.2–2.1). Arterial hypertension was negatively associated with self-reported depression in model 3 (OR 0.8).

Moreover, all somatic diseases were positively associated with physician-diagnosed depression in model 1

(OR 1.1–2.4), model 2 (OR 1.1–2.1) and model 3 (OR 1.2–2.0), except for arterial hypertension and diabetes mellitus not being associated with physician-diagnosed depression in model 3.

Associations with depression increased with a higher number of somatic diseases (online Supplementary Table S3). More specifically, increasing ORs were obtained for (a) one (self-report: OR 1.1; physician diagnosis: OR 1.2), two (self-report: OR 1.3; physician diagnosis: OR 1.5) and more than two disease(s) (self-report: OR 2.1; physician diagnosis: OR 2.2) *v.* no disease as well as for (b) two (self-report: OR 1.2; physician diagnosis: OR 1.3) and more than two (self-report: OR 1.9; physician diagnosis: OR 1.9) diseases *v.* one disease (model 1). Findings remained similar after additionally adjusting for anxiety disorders

Table 2. Prevalences of depression in patients with and without somatic disease or anxiety disorder (n = 83 737)

Somatic disease/anxiety disorder	Self-reported depression (n = 4236)				Physician-diagnosed depression (n = 8610)			
	No respective disease		Respective disease		No respective disease		Respective disease	
	N	%	N	%	N	%	N	%
Cardiovascular disease (n = 17 351)	3170	4.8	1066	6.1	6192	9.3	2418	13.9
Arterial hypertension (n = 28 189)	2846	5.1	1390	4.9	5143	9.3	3467	12.3
Endocrine disease (n = 8478)	3766	5.0	470	5.5	7389	9.8	1221	14.4
Diabetes mellitus (n = 10 437)	3620	4.9	616	5.9	7350	10.0	1260	12.1
Gastrointestinal disease (n = 8979)	3634	4.9	602	6.7	7221	9.7	1389	15.5
Neurological disease (n = 4693)	3734	4.7	502	10.7	7633	9.7	977	20.8
Anxiety disorder (n = 5045)	3324	4.2	912	18.1	6080	7.7	2530	50.1

Table 3. Associations between somatic diseases and depression (n = 83 737)

	Self-reported depression											
	Model 1 ^a				Model 2 ^b				Model 3 ^c			
	OR	95% CI		<i>p</i>	OR	95% CI		<i>p</i>	OR	95% CI		<i>p</i>
Cardiovascular disease	1.5	1.4	1.7	<0.001	1.4	1.3	1.6	<0.001	1.4	1.3	1.5	<0.001
Arterial hypertension	1.0	0.9	1.1	0.920	1.0	0.9	1.0	0.323	0.8	0.8	0.9	<0.001
Endocrine disease	1.0	1.0	1.2	0.390	1.0	0.9	1.1	0.714	1.0	0.9	1.1	0.505
Diabetes mellitus	1.3	1.2	1.5	<0.001	1.3	1.2	1.5	<0.001	1.2	1.1	1.3	0.001
Gastrointestinal disease	1.4	1.3	1.5	<0.001	1.3	1.2	1.4	<0.001	1.3	1.2	1.4	<0.001
Neurological disease	2.6	2.4	2.9	<0.001	2.3	2.0	2.5	<0.001	2.1	1.9	2.4	<0.001

Somatic disease	Physician-diagnosed depression											
	Model 1 ^a				Model 2 ^b				Model 3 ^c			
	OR	95% CI		<i>p</i>	OR	95% CI		<i>p</i>	OR	95% CI		<i>p</i>
Cardiovascular disease	1.5	1.4	1.6	<0.001	1.4	1.3	1.5	<0.001	1.3	1.2	1.4	<0.001
Arterial hypertension	1.1	1.1	1.2	<0.001	1.1	1.0	1.1	0.008	1.0	0.9	1.1	0.831
Endocrine disease	1.3	1.2	1.4	<0.001	1.2	1.1	1.3	<0.001	1.2	1.1	1.2	<0.001
Diabetes mellitus	1.1	1.0	1.2	0.029	1.1	1.0	1.2	0.012	1.0	0.9	1.0	0.228
Gastrointestinal disease	1.7	1.6	1.8	<0.001	1.6	1.4	1.7	<0.001	1.5	1.4	1.7	<0.001
Neurological disease	2.4	2.2	2.6	<0.001	2.1	1.9	2.3	<0.001	2.0	1.8	2.2	<0.001

OR, odds ratios from logistic regressions with respective somatic disease as predictor and depression as outcome; CI, confidence interval.

^aAdjusted for gender, age group and study.

^bAdjusted for gender, age group, study and anxiety disorders.

^cAdjusted for gender, age group, study, anxiety disorders and other somatic diseases.

(model 2), except that one *v.* no disease no longer predicted self-reported depression.

Associations between anxiety disorders and depression

Prevalences of depression in patients with *v.* without anxiety disorders are presented in Table 2 (lower part). Anxiety disorders were associated with self-reported depression (OR 5.0, CI 4.6–5.4; $p < 0.001$) and physician-diagnosed depression (OR 11.5, CI 10.6–12.6; $p < 0.001$) (model 1). These associations remained similar when additionally adjusting for somatic diseases (self-report: OR 4.6, CI 4.3–5.1; $p < 0.001$; physician diagnosis: OR 10.9, CI 10.0–11.8; $p < 0.001$) (model 2).

Interactions between somatic diseases and gender in the association with depression

Interactions between somatic diseases and gender (reference group: males) in the association with

depression are presented in online Supplementary Table S4a: cardiovascular diseases (OR 0.8), diabetes mellitus (OR 0.8) and neurological diseases (OR 0.8) interacted with gender in the association with self-reported depression, while endocrine diseases (OR 0.8) interacted with gender in the association with physician-diagnosed depression (model 1). That is, the associations between respective somatic diseases and depression were less pronounced in females *v.* males (Fig. 1a and 1b).

Similar findings were obtained in models 2 and 3, except that in model 3, diabetes mellitus no longer interacted with gender in the association with self-reported depression, while arterial hypertension interacted with gender in the association with physician-diagnosed depression (OR 1.2). That is, in model 3, the association between hypertension and physician-diagnosed depression was more pronounced in females *v.* males.

Separate associations between somatic diseases and depression in males and females are presented in online Supplementary Tables S4b and S4c.

Interactions between somatic diseases and anxiety disorders in the association with depression

Interactions between somatic diseases and anxiety in the association with depression are presented in online Supplementary Table S5a: cardiovascular diseases (OR 0.7), arterial hypertension (OR 0.8), gastrointestinal diseases (OR 0.7) and neurological diseases (OR 0.6) interacted with anxiety disorders in the association with self-reported depression, and each somatic disease interacted with anxiety disorders in the association with physician-diagnosed depression (OR 0.6–0.8) (model 1). That is, the associations between respective somatic diseases and depression were less pronounced in patients with *v.* without anxiety disorders; arterial hypertension was negatively associated with self-reported depression only in patients with anxiety disorders, but not in patients without anxiety disorders (Fig. 1c and 1d).

Interactions remained similar when additionally adjusting for other somatic diseases (model 2), except that cardiovascular diseases no longer interacted with anxiety disorders in the association with physician-diagnosed depression.

Separate associations between somatic diseases and depression in patients without anxiety disorders and patients with anxiety disorders are presented in online Supplementary Tables S5b and S5c.

Discussion

Main findings from this large combined epidemiological study among $n=83\,737$ patients are that (1) most somatic diseases were associated with both self-reported and physician-diagnosed depression, even after taking into account not only the role of gender, age and study, but also the role of anxiety disorders and somatic comorbidity. The associations with depression increased with higher co-/multimorbidity of somatic diseases. (2) Anxiety disorders were associated with both depression outcomes, over and above the effects of gender, age and study as well as somatic comorbidity. (3) Some somatic diseases interacted with gender and nearly all somatic diseases interacted with anxiety disorders in the association with self-reported and/or physician-diagnosed depression: the associations between respective somatic diseases and depression were less pronounced in females *v.* males as well as in patients with *v.* without anxiety disorders.

First, in line with previous research (Kroenke *et al.* 1994; Kroenke *et al.* 1997; Lyness *et al.* 2006; Egede, 2007; Moussavi *et al.* 2007; Scott *et al.* 2007; Pieper *et al.* 2008; Gili *et al.* 2010; Stegmann *et al.* 2010; Østergaard & Foldager, 2011; Teesson *et al.* 2011;

Merikangas *et al.* 2015), we could demonstrate that nearly all somatic diseases were associated with depression and that the associations with depression increased with higher co-/multimorbidity of somatic diseases. However, consistent with earlier findings (Lyness *et al.* 2006; Pieper *et al.* 2008; Pfaff *et al.* 2009) we also found that in some models arterial hypertension and endocrine diseases were not significantly or even negatively associated with depression. Associations between these somatic diseases and depression have been found to be particularly complex and affected by a variety of variables such as age, comorbidity and specific medication, which may explain our findings (Roberts *et al.* 2006; Licht *et al.* 2009). However, additional research is needed to further examine the role of arterial hypertension and endocrine diseases for depression onset and course.

Second, anxiety disorders were strongly associated with both depression outcomes, which is consistent with previous evidence that anxiety and depression often co-occur (Kessler *et al.* 2003; Kessler *et al.* 2005; Jacobi *et al.* 2014).

Third, investigating interactive effects between somatic diseases and gender revealed that the associations between individual somatic diseases and self-reported and/or physician-diagnosed depression were less pronounced in females *v.* males. Interaction graphs indicated that this was because females *per se* were at increased risk for depression that changed less in the presence of somatic diseases. One might speculate whether males with somatic diseases experienced higher role impairment and disability as compared with females – for instance, because physical illness specifically conflicts with male gender stereotypes such as masculinity, power and strength. Males with somatic diseases might have also engaged less often in health-promoting behaviours, thus fostering subjective feelings of illness and associated secondary complications such as depression (Courtenay, 2000). Our findings are particularly noteworthy as previous research on gender-specific association between somatic diseases and depression was often restricted to individual symptoms/diseases and characterised by inconsistent findings (Patten, 2001; Carnethon *et al.* 2003; Patten *et al.* 2005; Engum, 2007; Frasure-Smith & Lesperance, 2008; Beesdo *et al.* 2010; Gerrits *et al.* 2014).

Investigating interactive effects between somatic diseases and anxiety disorders showed that the associations between nearly all of the examined somatic diseases and self-reported as well as physician-diagnosed depression were less pronounced in patients with *v.* without anxiety disorders. As visualised in Fig. 1, this was because patients with anxiety disorders *per se* were at considerably increased risk

for depression that was nearly unaffected by somatic comorbidity (ceiling effect). Therefore, it has to be noted that – although somatic diseases were less strongly associated with depression in patients with anxiety disorders – depression prevalences in those with anxiety disorders (with and without somatic diseases) were considerably higher as compared with those without anxiety disorders. Our findings might be explained by the possibility that anxiety disorders were associated with significant burden and impairment (Wittchen *et al.* 2000; Bittner *et al.* 2004), thus leading to an increased risk for depression irrespective of whether additional somatic diseases were present or not. Our findings are remarkable given that no prior epidemiological primary care study examined differences in associations between a wide variety of somatic diseases and depression in patients with *v.* without anxiety disorders.

Strengths and limitations

We investigated associations between a wide variety of somatic diseases and depression. We considered both self-reported and physician-diagnosed depression as outcome and investigated the role of gender, anxiety disorders and somatic comorbidity. Data from three large-scaled epidemiological studies among primary care patients were combined.

However, our study is not without limitations:

First, self-reported depression was assessed using an established screening questionnaire [DSQ (Wittchen & Perkonig, 1997)], but full diagnostic information on depressive disorders, e.g. by standardised interview, was not assessed.

Second, no self-reported anxiety symptoms were assessed in DETECT and Depression 2000. Therefore, only physician-diagnosed anxiety disorders were considered herein.

Third, our study was based on combined data of three large-scaled epidemiological studies that, however, slightly differed respecting the assessment of individual somatic diseases.

Fourth, our cross-sectional findings do not allow any temporal or causal conclusions. Previous (prospective) evidence suggests that complex bidirectional associations exist between psychological distress and somatic morbidity. That is, somatic diseases might lead to depression (e.g. due to functional impairment and burden, leading to increasing demoralisation), but also depression might lead to physical health impairments (e.g. due to altered functioning of the hypothalamic-pituitary-adrenal axis and inflammatory processes) (Pan *et al.* 2011; Nemeroff & Goldschmidt-Clermont, 2012; Russ *et al.* 2012; Ferro *et al.* 2016; Shen *et al.* 2016). It is also possible that individual

somatic diseases in our cross-sectional study were associated particularly with more unfavourable course characteristics (rather than first onset) of depression.

Fifth, our epidemiological study among primary care patients might be affected by selection biases (e.g. especially individuals with depressive symptoms might have tended to seek help from a physician due to somatic complaints), limiting the generalisability of our findings to the general population.

Conclusions

Primary care physicians should be aware that not only females and patients with anxiety disorders, but also males and patients without anxiety disorders (*per se* rather considered low-risk groups for depression) affected by somatic diseases are at increased risk for depression. Because comorbid depression might lead to further complications and negatively affect treatment of somatic diseases (DiMatteo *et al.* 2000; Moussavi *et al.* 2007), an early recognition and treatment of depression is crucial. Furthermore, patients with somatic diseases might profit from targeted early interventions supporting them to successfully cope with disease-associated burden and impairment to potentially prevent depression.

However, prospective-longitudinal studies among primary care and general population samples are needed to replicate our findings as well as to disentangle temporal and potentially causal relationships. The role of additional factors such as age should also be examined. Age was shown to alter the link between somatic diseases and depression in a complex way and might thus be particularly important (Patten *et al.* 2016). Moreover, the role of somatic diseases as a risk factor for first onset *v.* more unfavourable course characteristics (e.g. persistence, risk of recurrence) of depression requires further investigation.

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Conflict of Interest

Dr Hans-Ulrich Wittchen reports the following items that might be perceived as a potential conflict of interest: Dr Hans-Ulrich Wittchen is on the advisory board and has received grant support to his institution by Lundbeck. All other authors declare that they have no financial relationships that might be perceived as a potential conflict of interest.

Ethical Standards

All three studies were carried out in accordance with the Helsinki Declaration of 1975 (as revised in 2013) and were approved by the Ethics Committee of the Medical Faculty of the Technische Universität Dresden.

Availability of data and materials

Data are available at the Center for Clinical Epidemiology and Longitudinal Studies (CELOS) for re- or further analyses. Access can be granted by the senior author (KBB).

Supplementary material

The supplementary material for this article can be found at <https://doi.org/10.1017/S2045796017000567>.

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