Journal of Affective Disorders 273 (2020) 41–47

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Symptoms of depersonalization/derealization are independent risk factors for the development or persistence of psychological distress in the general population: Results from the Gutenberg health study

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ARTICLE INFO

Keywords:
Depersonalization
Derealization
Depression
Anxiety

ABSTRACT

Background: Symptoms of depersonalization (DP) and derealization (DR) have a high prevalence in patient and community samples. Previous studies suggested that DP/DR symptoms might represent a marker of disease severity and poor prognosis. However, population-based studies investigating the impact of DP/DR symptoms on the course of depression and anxiety are sparse. Therefore, we aimed to analyze whether symptoms of DP/DR are longitudinally associated with the persistence or incidence of elevated symptoms of depression/anxiety.
Methods: We analyzed observational data from a sample of 13.182 participants of the Gutenberg Health Study. The outcomes were elevated symptoms of depression/anxiety at the 2.5 years follow-up as determined by the 2-item depression scale (PHQ-2), the 2-item anxiety scale (GAD-2), and the compound measure PHQ-4 respectively. The predictor was the 2-item Cambridge Depersonalization Scale (CDS-2).
Results: 8.7% of the sample were bothered by symptoms of DP/DR at baseline. They had an increased risk for elevated symptoms of depression/anxiety at the 2.5-year follow-up beyond baseline depression/anxiety and other factors. Each point increment in the CDS-2 scale, ranging from 0-6, was associated with a 21% increase of risk for PHQ-4 ≥ 3 at the follow-up (odds ratio 1.21, 95% confidence interval 1.11-1.32).
Limitations: The study was mostly questionnaire-based.
Conclusion: Symptoms of DP/DR are independent risk factors for the persistence or incidence of elevated symptoms of depression/anxiety. Symptoms of DP/DR represent an easily assessable risk factor for the course of mental disorders. Treatment and prevention of mental disorders might benefit from the broader recognition of these phenomena.

1. Introduction

Symptoms of depersonalization (DP) and derealization (DR) refer to a “subjective state of feeling estranged, detached or disconnected from their own being” or “a sense of unfamiliarity or detachment from one`s surroundings as, e.g., people or objects” (Simeon, 2004). Symptoms of DP/DR occur on a continuum from normal to pathological states, e.g., in healthy persons due to fatigue or in patients with mental disorders. In some persons, these symptoms are not experienced as distressing or dysfunctional, and even can be elicited purposefully (Cardeña et al., 2014). Symptoms of DP/DR can be transiently triggered by substances such as cannabis, and rarely result from medical diseases such as temporal lobe epilepsy, migraine, vestibular disorder or specific visual disturbances (Cahill and Murphy, 2004; Medford, 2014; Michal et al., 2006; Tschan et al., 2013). Symptoms of DP/DR occur with a high prevalence of 30–80% in various mental disorders such as anxiety disorders, posttraumatic stress disorder, depression, or, less often, as the main complaint in patients with depersonalization-derealization

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https://doi.org/10.1016/j.jad.2020.04.018
Received 11 November 2016; Received in revised form 15 April 2020; Accepted 20 April 2020
Available online 07 May 2020
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disorder (Baker et al., 2003; Hunter et al., 2004; Lambert et al., 2002; Mula et al., 2007). The life-time prevalence of DP/DR-symptoms in the general population is 26-70% (Hunter et al., 2004). Several population-based surveys found the prevalence of DP/DR-symptoms varied, mainly depending on age characteristics: Based on the same criteria, the prevalence rate for clinically significant symptoms of DP/DR was 11.9% in a large student sample with a mean age around 16 years (Michal et al., 2015a), and 0.8% in a large community sample with a mean age of 55 ± 10 years (Michal et al., 2011).

Although symptoms of DP/DR are common and rank among the most frequent symptoms in psychiatric patients, they remain mostly undetected (Hunter et al., 2017; Simeon, 2014; Stewart, 1964). Regarding their clinical importance, DP/DR symptoms have been independently associated with the impairment of mental and physical health (Aderibigbe et al., 2001; Baker et al., 2003; Michal et al., 2011; Segui et al., 2000; Simeon et al., 2003). They constitute a marker of disease severity, a risk factor for a chronic course, and poor treatment response in depression and anxiety disorders (Katerndahl, 2000; Mula et al., 2007).

Despite their clinical importance, longitudinal studies investigating symptoms of DP/DR as a prognostic factor are rare. To our best knowledge, there is no population-based study on the longitudinal association between DP/DR-symptoms and the course of depression and anxiety. Therefore, we sought to examine the following research questions in a large representative population-based sample: 1) Are symptoms of DP/DR associated with the persistence or new incidence of elevated symptoms of depression and anxiety, and 2) is this effect independent from baseline depression and anxiety? Results will help to determine whether symptoms of DP/DR represent an independent risk factor for depression and anxiety.

2. Methods

2.1. Study sample

We investigated participants of the Gutenberg Health Study (GHS) at baseline and the 2.5-year follow-up. From n = 15,010 participants at baseline, n = 698 were excluded due to missing baseline data of depression, anxiety and/or DP/DR, and n = 1,130 due to missing 2.5-year follow-up data of depression and anxiety measurement thus leaving 13,182 participants to be analyzed. Participants were enrolled from April 2007 to April 2012. The characteristics of the sample are displayed in *Table 1*.

The GHS is a population-based, prospective, observational single-center cohort study. The study is settled in the Rhine-Main-region in western Mid-Germany (Wild et al., 2012). The sample was stratified 1:1 for sex and residence and in equal strata for decades of age. Inclusion criteria were age range from 35 to 74 years and written informed consent. Exclusion criteria were insufficient knowledge of the German language and physical and mental disability to participate. The study was approved by the local ethics committee of the Medical Chamber of Rhineland-Palatinate, Germany (reference no. 837.020.07; original vote: 22nd March 2007, latest update: 20th October 2015) and by the local and federal data safety commissioners.

2.2. Assessment

The baseline examination at the study center took 5 hours per participant. It included the evaluation of classical cardiovascular risk factors and clinical variables, questionnaires, a computer-assisted personal interview, laboratory, and further medical examinations.

2.2.1 Outcome

The outcome variables at the 2.5-years follow-up were symptoms of depression and anxiety as defined by the PHQ-2, the GAD-2, or the PHQ-4 (as the combined measure of the PHQ-2 and GAD-2). The two-item questionnaire PHQ-2 measures impairment by anhedonia ("Little interest or pleasure in doing things") and depressed mood ("Feeling down, depressed or hopeless") over the past two weeks (Kroenke et al., 2003). The PHQ-2 score has a range from 0 to 6. A cut-off score of 3 or more provides a sensitivity of 79 % and a specificity of 86 % for any depressive disorder (Löwe et al., 2005). The PHQ-2 shows high reliability of $\alpha = 0.83$ (Löwe et al., 2005). In this study, PHQ-2 ≥ 3 defined the outcome "elevated depressive symptoms". Symptoms of anxiety were measured with the two-item questionnaire GAD-2 (Kroenke et al., 2007), asking about being bothered over the last 2 weeks by "feeling nervous, anxious, or on edge" and "not being able to stop or control worrying". The total GAD-2 score has a range from 0 to 6. The reliability of the GAD-2 is acceptable ($\alpha = 0.75$, Löwe et al. 2010). With a cut-off score of 3 or more, the GAD-2 identifies any anxiety disorder (e.g., generalized anxiety disorder, social phobia, or panic disorder) with a sensitivity of 65 % and specificity of 88 %. GAD-2 ≥ 3 was used to determine the endpoint "elevated anxiety symptoms". The PHQ-4 represents a combination of PHQ-2 and GAD-2 (Kroenke et al., 2009; Löwe et al., 2010). The total score ranges from 0 to 12. The cut-off PHQ-4 ≥ 3 determines the occurrence of mild to severe symptoms of depression/anxiety and PHQ-4 ≥ 6 the occurrence of clinically relevant symptoms (Löwe et al., 2010). Both criteria were used as endpoints.

2.2.2 Predictor variable

Symptoms of DP/DR were assessed with the CDS-2 (Michal et al., 2010b), the 2-item version of the Cambridge Depersonalization Scale (CDS) (Sierra and Berrios, 2000). It measures symptoms of DP/DR by asking for information about the frequency of derealization ("My surroundings feel detached or unreal as if there was a veil between me and the outside world") and depersonalization ("Out of the blue, I feel strange, as if I were not real or as if I were cut off from the world") over the last two weeks ("Over the past 2 weeks, how often have you been bothered by…"). The cut-off CDS-2 ≥ 3 determines clinically significant DP/DR with a sensitivity of 78.9 % and a specificity of 85.7 %. The CDS-2 has a high reliability (Cronbach's $\alpha = 0.92$). The CDS-2 correlated strongly ($r = 0.77$) with a structured interview measuring the severity of DP/DR (Michal et al., 2010b).

2.2.3 Covariates

The following covariates were included: Baseline depression (PHQ-2) and anxiety (GAD-2); a medical history of any depressive or anxiety disorder, age, sex, partnership, and socioeconomic status. Medical history (MH) of any depressive or of any anxiety disorder was identified at baseline during the computer-assisted personal interview by the following questions: "Have you ever received the definite diagnosis of any depressive disorder/anxiety disorder by a physician?". The socioeconomic status (SES) was defined according to Lampert and Kroll (2009). The SES comprises the dimensions of education, occupational position, and household income. The SES has a range from 3 to 21, with 3 indicating the lowest and 21 the highest SES (Lampert and Kroll, 2009). Further, we included the following common medical conditions as covariates: Medical history of cardiovascular disease (CVD, comprising coronary heart disease, heart failure, stroke, myocardial infarction, and peripheral arterial disease), history of chronic lung disease (chronic obstructive pulmonary disease or asthma), migraine headache, cancer, cataract, glaucoma, and age-related macular degeneration. These covariates were included because medical diseases can impact depressive symptoms (Moussavi et al., 2007). Common eye diseases were supposed to be taken in because DR symptoms might be related to eye diseases (e.g., cataract).

2.3. Statistical analysis

Data were presented as means ± standard deviations or numbers (n) and percentages. In order to describe the study sample, we displayed the scores for the total sample and stratified by "CDS-2 = 0"

Table 1
Characteristics of the sample stratified by "being bothered by symptoms of depersonalization/derealization" (CDS-2 ≥ 1).

	Total sample (n = 13,182)	Comparison		p
		CDS-2 = 0 (n = 12,032)	CDS-2 ≥ 1 (n = 1,150)	
Age, years	54.8 ± 10.9	54.8 ± 11.0	53.5 ± 10.6	<0.0001
Female	49.5 % (6,526/13,182)	49.0 % (5,896/12,032)	54.8 % (630/1,150)	<0.0001
Partnership (living in a partnership)	75.2 % (9,917/13,180)	76.6 % (9,215/12,030)	61.0 % (702/1,150)	<0.0001
Socioeconomic status (SES, 3-21)	13.2 ± 4.4	13.2 ± 4.4	12.2 ± 4.3	<0.0001
Depression at T0, PHQ-2 ≥ 3	5.8 % (758/13,182)	3.6 % (436/12,032)	28.0 % (322/1,150)	<0.0001
Anxiety at T0, GAD-2 ≥ 3	6.3 % (833/13,182)	4.1 % (496/12,032)	29.3 % (337/1,150)	<0.0001
Depressive and/or anxiety symptoms at T0, PHQ-4 ≥ 3	27.3 % (3,600/13,182)	22.4 % (2,694/12,032)	78.8 % (906/1,150)	<0.0001
Medical history of any depressive disorder	11.6 % (1,534/13,179)	9.1 % (1,100/12,029)	37.7 % (434/1,150)	<0.0001
Medical history of any anxiety disorder	7.0 % (919/13,179)	5.6 % (678/12,029)	21.0 % (241/1,150)	<0.0001
Endpoints at 2.5-year follow-up (T1)				
Depression at T1, PHQ-2 ≥ 3	8.3 % (1,098/13,182)	6.6 % (790/12,032)	26.8 % (308/1,150)	<0.0001
Anxiety at T1, GAD-2 ≥ 3	7.8 % (1,032/13,182)	6.2 % (740/12,032)	25.4% (292/1,150)	<0.0001
Depressive and/or anxiety symptoms at T1, PHQ-4 ≥ 3	24.2 % (3,194/13,182)	21.1 % (2,537/12,032)	57.1 % (657/1,150)	<0.0001
Depressive and/or anxiety symptoms at T1, PHQ-4 ≥ 6	6.1 % (809/13,182)	4.6 % (549/12,032)	22.6% (260/1,150)	<0.0001
Medical Histories of somatic conditions				
Cardiovascular Disease (CVD)	9.6% (1,259/13,180)	9.3% (1,120/12,030)	12.1% (139/1,150)	0.003
Chronic lung disease (COPD/asthma)	4.7% (616/13,175)	4.5% (546/12,026)	6.1% (70/1,149)	0.021
Diabetes	8.5% (1,119/13,182)	8.3% (1,002/12,032)	10.2% (117/1,150)	0.033
Cancer	8.8% (1,160/13,171)	8.7% (1,049/12,022)	9.7% (111/1,149)	0.276
Migraine headache	25.2% (3,285/13,054)	24.4% (2,904/11,920)	33.6% (381/1,134)	<0.0001
Cataract	4.7% (611/12,912)	4.8% (564/11,785)	4.2% (47/1,127)	0.377
Glaucoma	4.2% (557/13,182)	4.3% (517/12,032)	3.5% (40/1,150)	0.221
Age related macular-degeneration	2.5% (330/13,182)	2.5% (301/12,032)	2.5% (29/1,150)	0.932

Note. **T0**, baseline; **T1**, 2.5-year follow-up; data are described as mean ± standard deviation or percentage with proportional numbers in brackets (n/n); **CVD** includes coronary heart disease, myocardial infarction, heart failure, peripheral artery disease, and stroke.

versus "CDS ≥ 1 at baseline. Continuous and binomial variables of both groups were compared by student's t-test and Chi-square tests, respectively. The longitudinal associations between symptoms of DP/DR with depression and anxiety at the 2.5-year follow-up were examined by logistic regression analyses. The dependent variables were depressive and anxiety symptoms at the 2.5-year-follow-up as determined by PHQ-2 ≥ 3, GAD-2 ≥ 3, PHQ-4 ≥ 3, and PHQ-4 ≥ 6.

The predictor variable was symptoms of DP/DR at baseline, as measured by CDS-2. Two models of adjustment were applied. Model 1 included the independent variables CDS-2, age, sex, partnership, SES. The fully adjusted model 2 comprised CDS-2, PHQ-2, GAD-2, MH depression, MH anxiety, age, sex, partnership, SES, history of any cardiovascular disease, chronic lung disease, migraine headache, cancer, cataract, glaucoma, and age-related macular degeneration. We calculated the regression models for the complete sample and exploratively in the subgroup of participants with elevated depressive and anxiety symptoms (PHQ-4 ≥ 3) at baseline. Statistical analyses were performed using SPSS Statistics 23 (IBM-Corp., 2015).

3. Results

3.1. Characteristics of the sample

From 13,182 participants, a proportion of 8.7% indicated they were bothered by symptoms of DP/DR (CDS-2 ≥ 1) at least at several days over the past two weeks. Persons scoring above 0 in the CDS-2 were less likely to live in a current partnership, more likely to suffer from clinically significant depressive or anxiety symptoms, and more frequently had a medical history of any depressive or anxiety disorder. Concerning sociodemographic characteristics, they were younger, more likely to be female, and had a lower socioeconomic status (Table 1). Concerning medical conditions, they were more likely to report a medical history of CVD, chronic lung disease, diabetes, and migraine headache.

3.2. Longitudinal association of CDS-2 with depressive/anxiety symptoms at the 2.5-year follow-up

The regression analysis demonstrated that each 1-point increment in the CDS-2 doubled the risk of elevated depressive and anxiety symptoms at 2.5-year follow-up in regression model 1. Additional adjustment for baseline depression, anxiety, and medical conditions decreased the odds ratios for the association of CDS-2 with depression/anxiety at the 2.5-year follow-up to 15-19% (Table 2). A very similar picture emerged in the subsample of persons with elevated symptoms of depression/anxiety at baseline (Table 3, see supplement). The medical histories of any anxiety disorder or any depressive disorder were only marginally related to elevated symptoms of depression/anxiety at the 2.5-year follow-up.

Fig. 1 shows the increasing rates of elevated symptoms of depression/anxiety (PHQ-4 ≥ 3) by increasing CDS-2 scores (test of trend: $p < 0.0001$). The same pattern has been found for increasing PHQ-2 and GAD-2 scores (tests of trend: $p < 0.0001$, see Fig. 2 and 3).

4. Discussion

In summary, symptoms of DP/DR were strongly associated with the prevalence of depression and anxiety symptoms at the 2.5-year follow-up. DP/DR symptoms predicted elevated depression and anxiety symptoms at the 2.5-year follow-up even after adjustment for baseline depression and anxiety symptoms, medical history of depression/anxiety, sociodemographic factors, and medical conditions. Important to note, persons with clinically significant symptoms of DP/DR at baseline had a very high prevalence – i.e., 72% - of elevated distress as determined by PHQ-4 ≥ 3 2.5 years later.

This study demonstrated that symptoms of DP/DR are associated with the severity of mental distress and that they indicate a higher risk for an unfavorable prognosis. In line with previous studies, we assume that symptoms of DP/DR represent a marker of disease severity (Michal et al., 2009; Mula et al., 2007). Symptoms of DP/DR are particularly common in persons with complex and severe mental disorders (Leichsenring and Rabung, 2011; Michal et al., 2016). Clinical surveys

Table 2
Prediction of depressive and anxiety symptoms by symptoms of DP/DR and covariates at the 2.5-year follow-up (T1) in the complete sample (n = 13,182).

	Endpoints at the 2.5-year follow-up (T1)							
	PHQ-2 ≥ 3 (n = 1,089/13,124, 8.29 %)		GAD-2 ≥ 3 (n = 1,020/13,124, 7.77 %)		PHQ-4 ≥ 3 (n = 3,173/13,124, 24.17 %)		PHQ-4 ≥ 6 (n = 799/13,124, 6.09 %)	
	Adj. OR (95 % CI)	p	Adj. OR (95 % CI)	p	Adj. OR (95 % CI)	p	Adj. OR (95 % CI)	p
Model 1								
CDS-2	**2.07 (1.91 – 2.24)**	**< 0.0001**	**2.04 (1.89 – 2.21)**	**< 0.0001**	**2.29 (2.12 – 2.48)**	**< 0.0001**	**2.14 (1.97 – 2.32)**	**< 0.0001**
Model 2								
CDS-2	**1.19 (1.09 – 1.30)**	**< 0.0001**	**1.18 (1.07 – 1.29)**	**0.001**	**1.21 (1.11 – 1.32)**	**< 0.0001**	**1.15 (1.04 – 1.27)**	**0.007**
PHQ-2	**1.74 (1.63 – 1.86)**	**< 0.0001**	**1.36 (1.27 – 1.46)**	**< 0.0001**	**1.66 (1.57 – 1.74)**	**< 0.0001**	**1.63 (1.51 – 1.75)**	**< 0.0001**
GAD-2	**1.29 (1.22 – 1.38)**	**< 0.0001**	**1.61 (1.52 – 1.72)**	**< 0.0001**	**1.65 (1.57 – 1.73)**	**< 0.0001**	**1.53 (1.43 – 1.64)**	**< 0.0001**
MH depression	0.99 (0.97 – 1.01)	0.349	0.99 (0.97 – 1.01)	0.299	0.99 (0.98 – 1.01)	0.358	0.98 (0.95 – 1.01)	0.125
MH anxiety	**1.03 (1.01 – 1.04)**	**0.004**	**1.02 (1.01 – 1.04)**	**0.013**	1.01 (0.99 – 1.03)	0.267	**1.03 (1.02 – 1.05)**	**< 0.0001**
sex (m = 1, f = 2)	0.87 (0.75 – 1.01)	0.073	**1.23 (1.06 – 1.43)**	**0.008**	**1.22 (1.10 – 1.34)**	**< 0.0001**	1.08 (0.91 – 1.28)	0.381
SES (range 3-21)	**0.94 (0.92 – 0.96)**	**< 0.0001**	**0.96 (0.94 – 0.98)**	**< 0.0001**	**0.97 (0.96 – 0.98)**	**< 0.0001**	**0.95 (0.93 – 0.97)**	**< 0.0001**
Age (per year)	**0.99 (0.98 – 0.99)**	**0.001**	**0.98 (0.98 – 0.99)**	**< 0.0001**	**0.98 (0.98 – 0.99)**	**< 0.0001**	**0.99 (0.98 – 0.99)**	**0.001**
Partnership	0.86 (0.74 – 0.99)	0.041	0.89 (0.76 – 1.04)	0.149	0.92 (0.82 – 1.01)	0.090	0.92 (0.77 – 1.09)	0.327

Note. Logistic regression analyses with the dependent variables PHQ-2 ≥ 3, GAD-2 ≥ 3, PHQ-4 ≥ 3, and PHQ-4 ≥ 6 at T1; **Model 1:** CDS-2, age, sex, partnership, SES; **Model 2**: CDS-2, age, sex, partnership, SES, PHQ-2, GAD-2, MH depression, MH anxiety, CVD, diabetes, chronic lung disease, cancer, migraine headache, cataract, glaucoma, age-related macular degeneration; **SES**, socioeconomic status; **MH**, medical history.

found that patients with symptoms of DP/DR have more comorbid mental disorders and are more severely impaired than patients without co-occurring DP/DR (Michal et al., 2016; Michal et al., 2009). Persons with severe or complex mental disorders are at an increased risk of poor prognosis (Grilo et al., 2010; Gunderson et al., 2008; Leichsenring and Rabung, 2011). Accordingly, symptoms of DP/DR might warn the clinician about the need for more intense treatment for the individual patient. Symptoms of DP/DR indicate a specific impairment of the capacity to regulate emotions, thus increasing the risk of a chronic course and poor treatment response (Ebner-Priemer et al., 2009; Kleindienst et al., 2011). Finally, symptoms of DP/DR remain largely unrecognized by health care professionals, despite the high distress usually associated with them. This lack of therapeutic awareness also might increase the risk of an unfavorable outcome (Hunter et al., 2017; Michal et al., 2016; Michal et al., 2010a).

Surprisingly, the medical histories of any anxiety or depressive disorder were only marginally or even not associated with the occurrence of psychological distress at the 2.5-year follow-up. Only the questionnaire-based symptoms predicted the outcome. This finding is not easy to understand, because the history of a previous mental disorder represents a strong risk factor for the persistence or recurrence of mental disorders (Biaggi et al., 2016; Keller et al., 1984). Several reasons might have contributed to this finding: Firstly, the history of a mental illness implies that the individual had previously received at least some kind of mental health treatment. Once a person had access to mental health care, the person might have a better chance to receive mental health care again. Thus, the associations might be confounded with undetected treatment effects. Secondly, the lack of a significant association of the predictor “history of mental disorder” with the outcome might be due to a sizeable diagnostic gap. Many participants might have had a previous episode of major depression or an anxiety disorder that remained undetected by health care professionals. This interpretation is supported by a recent longitudinal study, demonstrating that a medical history of depression was not associated with excess mortality, whereas depressive symptoms, as measured by the PHQ-2, showed a strong and robust association (Michal et al., 2015b).

The following limitations of the present study must be kept in mind. First, there was no clinical interview for identifying mental disorders, thus making conclusions about clinical endpoints difficult. However, the applied questionnaires have proved their validity. They have shown that they are strongly related to important clinical endpoints, such as psychosocial functioning and mortality (Batty et al., 2016; Löwe et al., 2010). Secondly, the use of questionnaires precludes any conclusion about the underlying pathogenesis. For example, symptoms of DP/DR might be attributable to the physiological effects of drugs or medical conditions such as seizures or rare visual disorders (Medford, 2014; Michal et al., 2006). However, we believe that this shortcoming is counterbalanced by the comprehensive model of adjustment and the size and representativeness of the sample.

We conclude that symptoms of DP/DR represent an independent risk factor for the course of symptoms of depression/anxiety and psychological distress, respectively. Patients who are bothered by symptoms of DP/DR seem to be more likely to become or remain impaired by depressive and anxiety symptoms over 2.5-years. Therefore, we recommend that symptoms of DP/DR should be assessed thoroughly in patients and should be explicitly addressed in the treatment of individuals with mental disorders (Eckhardt-Henn, 2004; Hunter et al., 2004; Michal et al., 2005). Future research should examine the long-term impact of DP/DR symptoms on health and search for predictors for the persistence of DP/DR symptoms.

Funding

The Gutenberg Health Study is funded through the government of Rhineland-Palatinate ("Stiftung Rheinland-Pfalz für Innovation", contract AZ 961-386261/733), the research programs "Wissen schafft

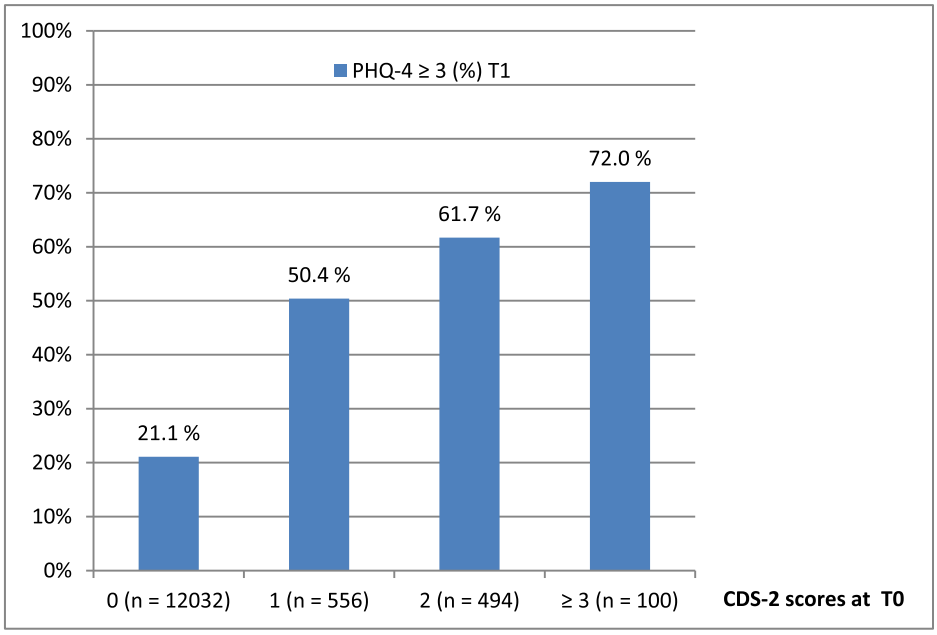

Fig. 1. Increasing prevalence of elevated symptoms of depression/anxiety by CDS-2 scores at the 2.5-year follow-up *Note.* Test of trend $p < 0.0001$; increasing prevalence of PHQ-4 ≥ 3 at the 2.5-year follow-up (T1) by CDS-2 scores at baseline (T0).

Zukunft" and "Center for Translational Vascular Biology (CTVB)" of the Johannes Gutenberg-University of Mainz, and its contract with Boehringer Ingelheim and PHILIPS Medical Systems, including an unrestricted grant for the Gutenberg Health Study. Philipp S. Wild is funded by the Federal Ministry of Education and Research (BMBF 01EO1503) and he is PI of the German Center for Cardiovascular Research (DZHK). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CRediT authorship contribution statement

Jasmin Schlax: Formal analysis, Methodology, Writing - original draft. **Jörg Wiltink:** Writing - review & editing. **Manfred E. Beutel:** Conceptualization, Funding acquisition, Project administration. **Thomas Münzel:** Conceptualization, Funding acquisition, Project administration, Writing - review & editing. **Norbert Pfeiffer:** Conceptualization, Funding acquisition, Project administration, Writing - review & editing. **Philipp Wild:** Conceptualization, Funding acquisition, Project administration, Writing - review & editing. **Maria Blettner:** Writing - review & editing. **Jasmin Ghaemi Kerahrodi:** Writing - review & editing. **Matthias Michal:** Formal analysis, Methodology, Writing - original draft.

Declaration of Competing Interest

The authors declare that they have no competing interests.

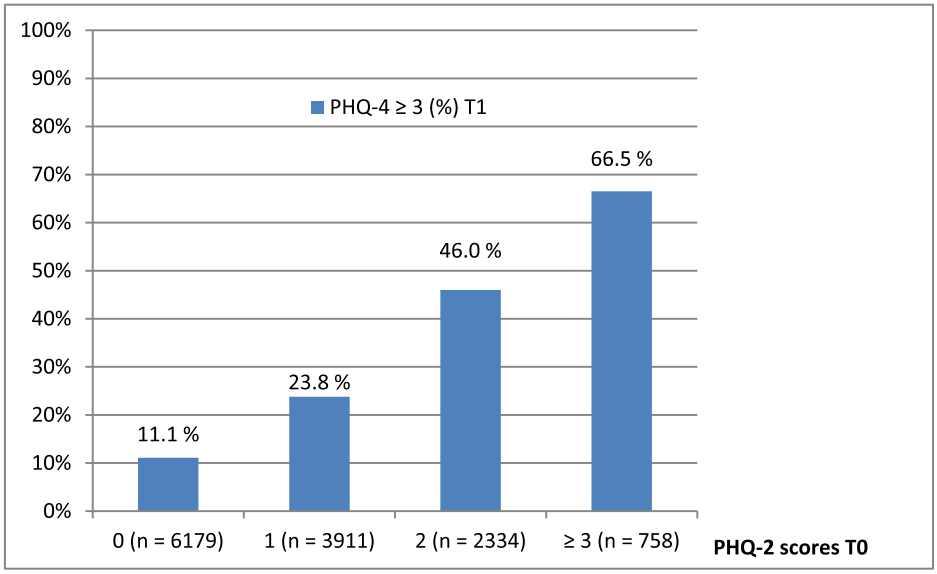

Fig. 2. Increasing prevalence of elevated symptoms of depression/anxiety by PHQ-2 scores at the 2.5-year follow-up *Note.* Test of trend $p < 0.0001$; increasing prevalence of PHQ-4 ≥ 3 at the 2.5-year follow-up (T1) by PHQ-2 scores at baseline (T0).

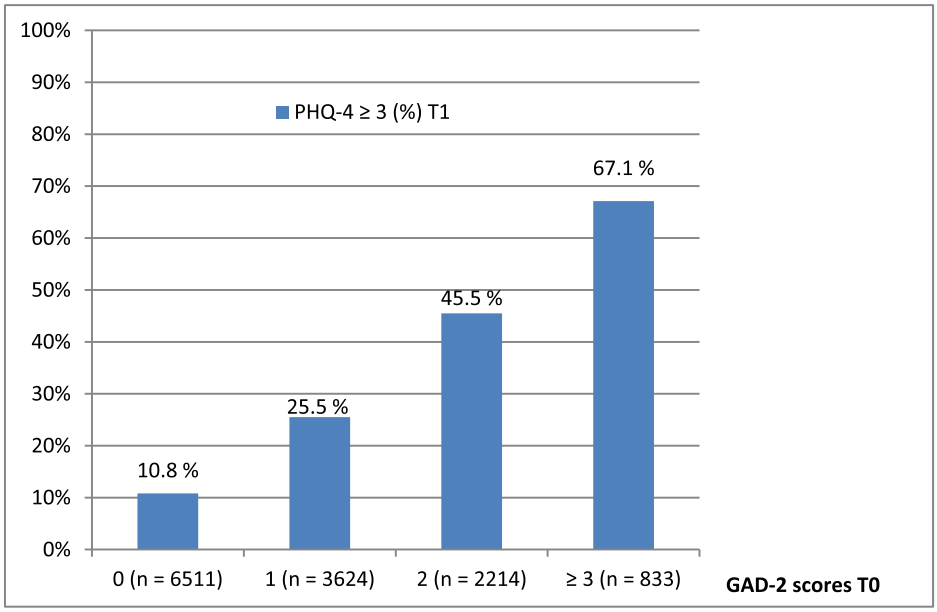

Fig. 3. Increasing prevalence of elevated symptoms of depression/anxiety by GAD-2 scores at the 2.5-year follow-up *Note.* Test of trend $p < 0.0001$; increasing prevalence of PHQ-4 ≥ 3 at the 2.5-year follow-up (T1) by GAD-2 scores at baseline (T0).

Acknowledgements

The Gutenberg Health Study is funded through the government of Rhineland-Palatinate ("Stiftung Rheinland-Pfalz für Innovation", contract AZ 961-386261/733), the research programs "Wissen schafft Zukunft" and "Center for Translational Vascular Biology (CTVB)" of the Johannes Gutenberg-University of Mainz, and its contract with Boehringer Ingelheim and PHILIPS Medical Systems, including an unrestricted grant for the Gutenberg Health Study. We thank all study participants for their willingness to provide data for this research project and we are indebted to all coworkers for their enthusiastic commitment.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.04.018.

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