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Psychiatric comorbidity does not only depend on diagnostic thresholds: an illustration with major depressive disorder and generalized anxiety disorder

Hanna M. van Loo, MD, PhD[1]

Robert A. Schoevers, MD, PhD[1]

Kenneth S. Kendler, MD[2,3,4]

Peter de Jonge, PhD[1]

Jan-Willem Romeijn, PhD[5]

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Author affiliations:

[1] University of Groningen, University Medical Center Groningen, Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion Regulation (ICPE), Groningen, The Netherlands.

[2] Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia, United States of America.

[3] Department of Psychiatry, Virginia Commonwealth University, Richmond, Virginia, United States of America.

[4] Department of Human and Molecular Genetics, Virginia Commonwealth University, Richmond, Virginia, United States of America.

[5] University of Groningen, Faculty of Philosophy, Groningen, The Netherlands.

Corresponding author:

Hanna M. van Loo, Interdisciplinary Center Psychopathology and Emotion Regulation (ICPE), Department of Psychiatry, University of Groningen, University Medical Center Groningen, Hanzeplein 1, PO Box 30.001, 9700 RB, Groningen, The Netherlands.

E-mail: h.van.loo@umcg.nl

Tel: +31 50 361 2008; Fax: +31 50 361 9722

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Conflict of interest

None.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Abstract

Background:

High rates of psychiatric comorbidity are subject of debate: to what extent do they depend on classification choices such as diagnostic thresholds? This paper investigates the influence of different thresholds on rates of comorbidity between major depressive disorder (MDD) and generalized anxiety disorder (GAD).

Methods:

Point prevalence of comorbidity between MDD and GAD was measured in 74,092 subjects from the general population (LifeLines) according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria. Comorbidity rates were compared for different thresholds by varying the number of necessary criteria from ≥1 to all 9 symptoms for MDD, and from ≥1 to all 7 symptoms for GAD.

Results:

According to DSM-thresholds, 0.86% had MDD only, 2.96% GAD only and 1.14% both MDD and GAD (odds ratio (OR) 42.6). Lower thresholds for MDD led to higher rates of comorbidity (1.44% for ≥4 of 9 MDD-symptoms, OR 34.4), whereas lower thresholds for GAD hardly influenced comorbidity (1.16% for ≥3 of 7 GAD-symptoms, OR 38.8). Specific patterns in the distribution of symptoms within the population explained this finding: 37.3% of subjects with core criteria of MDD and GAD reported subthreshold MDD symptoms, whereas only 7.6% reported subthreshold GAD symptoms.

Conclusions:

Lower thresholds for MDD increased comorbidity with GAD, but not vice versa, owing to specific symptom patterns in the population. Generally, comorbidity rates result from both empirical symptom distributions and classification choices and cannot be reduced to either of these exclusively. This insight invites further research into the formation of disease concepts that allow for reliable predictions and targeted therapeutic interventions.

Introduction

Comorbidity rates between mental disorders are high, with about 35-45% of patients having two or more disorders in the course of a year [1-3]. The high overlap between disorders has fueled the debate on the validity of the current classification of mental disorders: what do all the different disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM) [4] refer to if so many patients have at least two or three of them? [5, 6] The high level of comorbidity thus highlights wide-ranging conceptual problems in our understanding of mental disorders.

Previous comorbidity studies have mainly focused on two, largely opposing, types of explanations for these high rates of comorbidity. First, some studies have focused on causal links between psychiatric comorbidity as comorbidity may be a consequence of the fact that different mental disorders have common causes, such as precipitating factors (e.g. childhood trauma), genetic vulnerability, or neurobiological abnormalities [7, 8]. According to this 'realist' interpretation of comorbidity, its existence could be seen as a sign of a common etiology of the disorders that may be further investigated and elucidated in the future.

Other authors have focused on a second type of explanation, namely that comorbidity is the consequence of particular classification choices. The idea is that rates of comorbidity have increased by the expansion of the number of diagnoses, the reduction of exclusionary criteria, and the fact that different diagnoses may have overlapping symptoms [5, 9]. According to this view, a change in for instance diagnostic thresholds is supposed to have strong effects on the rates of comorbidity: reducing the number of necessary criteria and thus making a disorder more inclusive will increase comorbidity rates [9, 10]. If comorbidity depends heavily on classification choices, this suggests that comorbidity itself is not based on objective features of reality, but is an artifact of imposing definitions onto empirical reality. From this 'constructivist' interpretation it follows that comorbidity is not a reflection of different co-occurring disorders that are causally connected. Rather, high comorbidity would illustrate that the classifications themselves are inadequate, and do not establish a strict partition of mental disorders in the population [6].

Although several studies have hypothesized about the influence of classification choices on rates of comorbidity among DSM-disorders, no previous studies have systematically tested these hypotheses in empirical data. The aim

of this paper was to empirically explore different classifications of major depressive disorder (MDD) and generalized anxiety disorder (GAD), specifically in terms of diagnostic thresholds, in a large population sample of adults living in the Northern Netherlands. MDD and GAD are important to examine in this context because these are highly comorbid disorders: 28-55% of subjects are diagnosed with both disorders instead of MDD or GAD only (Zbozinek 2012, Moffitt 2007, Hunt 2004, Johansson 2013) [1, 11-13]. Moreover, the non-specificity of some of the diagnostic criteria and overlapping symptoms of MDD and GAD have led some to debate the usefulness of these entities as separate categories [8, 14]. For these reasons, rates of comorbidity among these two disorders would be expected to be particularly highly dependent on classification choices. However, based on findings of a previous study on comorbidity among a limited selection of psychiatric symptoms [15], we hypothesize that rates of comorbidity will not always fluctuate when diagnostic thresholds are adjusted. To investigate this, we studied whether different threshold levels of MDD or GAD affect rates of comorbidity in order to clarify the origins of comorbidity.

Method

Sample

Data were derived from LifeLines, a multi-disciplinary prospective population-based cohort study examining the health and health-related behaviours of 167,729 persons living in the North East region of The Netherlands [16, 17]. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the physical and psychological health and disease of the general population, with a special focus on multi-morbidity and complex genetics. For a further description of demographic, socioeconomic, and general health characteristics of the LifeLines cohort, we refer to a comprehensive study of these characteristics (Klijs et al. 2015). From this dataset, individuals were selected with complete data of current depression and anxiety symptoms measured with the Mini-International Neuropsychiatric Interview (MINI) [18].

Since the beginning of 2012, a unique adaptation of the MINI was implemented in LifeLines that made the current study possible: although the MINI originally skipped several items (i.e. not all depressive symptoms were measured if the core symptoms depressed mood or interest loss were absent), we implemented a version in which all symptoms were scored in all participants. A total of 74,092 individuals were evaluated with this version in the period between February 2012 and December 2013. All participants provided written informed consent; the medical ethical committee of the University Medical Center Groningen [17].

Different thresholds for MDD and GAD

Trained research assistants administered sections of the MINI concerning MDD, GAD and other internalizing disorders to all participants. The MINI is a short structured diagnostic interview designed to measure DSM-IV and ICD-10 disorders [18]. All nine symptoms representing criterion A for MDD in the DSM were rated as present if subjects had them almost daily during the past two weeks; the seven symptoms representing criteria A, B, and C of GAD in the DSM were rated as present if subjects experienced them on most days during the past six months, consistent with duration criteria in the DSM [4, 19].

We used dummy-coded variables for MDD- and GAD-classifications with both higher and lower threshold levels, i.e. with more and less necessary criteria. According to the DSM, MDD is present if a patient satisfies at least 5 out of 9 symptoms during the same two-week period, with at least one of the core symptoms depressed mood and loss of interest endorsed [4, 19]. For the present study we used 9 binary dummy-coded variables for MDD-classifications, where each variable was determined by a different numbers of necessary criteria, varying from a minimum of ≥1 of 9 to a maximum of all 9 symptoms, without changing the requirement of having one out of two core symptoms depressed mood and loss of interest. So, for example, dummy-coded variable D_3 (MDD with threshold of ≥3 symptoms) is set to 1 for all subjects who suffer from at least 3 depressive symptoms of which at least one is a core symptom of depression, and D_3 is set to 0 for all subjects who do not qualify as such. Dummy-coded variables D_i for other values of i are defined in similar fashion. Likewise, we constructed seven separate binary dummy-coded variables for GAD-classifications, each with a different diagnostic threshold level varying

from a minimum of ≥1 of 7 to a maximum of all 7 symptoms, without changing the requirement of the core criterion of excessive anxiety and worry. According to the DSM, GAD is present when a patient satisfies at least 4 of 7 symptoms, including at least the core criterion excessive anxiety and worry, which is difficult to control, for the majority of the time in six months [4, 19]. We did not account for the exclusionary rule that GAD should not be diagnosed if excessive anxiety is present exclusively in a period with MDD [4, 19], to increase our comparability to other epidemiological studies [20-22]. For the purpose of the current study – to clarify how classification choices and rates of comorbidity interact – we investigated also very weak disease definitions (e.g., with threshold levels of ≥2 of 9 MDD symptoms, or ≥2 of 7 GAD symptoms), which does not imply that we consider these definitions to be useful classifications or 'pathological' symptom patterns.

Assessment of comorbidity rates

Point prevalences of comorbid MDD and GAD, MDD only, and GAD only were assessed for all different threshold levels of MDD (i.e. for all 9 possible threshold levels from a minimum of ≥1 of 9 to a maximum of all 9 MDD symptoms present), while keeping the GAD threshold at DSM-level (≥4 of 7). Likewise, we assessed these prevalences for all different threshold levels of GAD (i.e. for all 7 possible threshold levels from a minimum of ≥1 of 7 to a maximum of all 7 symptoms present), while keeping the MDD threshold at DSM-level (≥5 of 9). We did not change the thresholds levels for MDD and GAD simultaneously in order to assess the eventual differential influence of changes in MDD and GAD threshold levels on rates of comorbidity. In the same way, we calculated odds ratios and confidence intervals as measures of association between MDD and GAD for all different threshold levels, using logistic regression (R package *stats*) [23]. In addition, we assessed the number of depressive and anxiety symptoms in a subsample of 1,395 subjects who reported core criteria of both MDD and GAD (anxiety, difficult to control and depressed mood/interest loss). All analyses were performed in R [23]; plots were made with R-package ggplot2 [24].

Results

Sample characteristics

The sample consisted of 41.7% men and 58.3% women, with a mean age of 45.0 years (standard deviation (SD) 13.5 years). 40.2% reported at least one symptom of MDD in the past two weeks or GAD in the past six months. Of the 9 MDD and 7 GAD symptoms, the GAD criteria fatigue and feeling tense were most common, with approximately 19.8% and 17.7% of subjects reporting these symptoms as frequently present during the past six months (Supplemental Table 1). Other symptoms were relatively rare, such as feelings of guilt or worthlessness and suicidal thoughts (2.4% and 0.7%, resp.). In general, subjects reported fewer depressive symptoms in the past two weeks than general anxiety symptoms in the past six months (mean number of 9 MDD symptoms 0.55 (SD 1.21), mean number of 7 GAD symptoms 0.96 (SD 1.70). Tetrachoric correlations between symptoms were high on average (mean rho 0.61, SD 0.12) (Supplemental Table 1 and Figure 1). Symptoms that were often co-occurring were depressed mood and interest loss (rho 0.87) and feeling nervous and tense (rho 0.93). Also the overlapping symptoms – the symptoms which are DSM-criteria of both MDD and GAD – were highly correlated: sleep difficulties, fatigue, and concentration problems (Supplemental Table 1). Correlations among GAD symptoms were in general higher (mean rho 0.72, SD 0.08) than among MDD symptoms (mean rho 0.61, SD 0.11).

< Figure 1 >

Comorbidity of MDD and GAD according to different threshold levels

Point prevalence for MDD and GAD according to DSM-criteria was 2.00% (n=1,479) and 4.10% (n=3,039) respectively. Most prevalent was GAD only (2.96%, n=2,195), then comorbidity between MDD and GAD (1.14%,

n=844), whereas least subjects reported MDD only (0.86%, n=635) (Table 1 and Table 2). This ordering in prevalence turned out to be robust under most variations in threshold values that we considered, except for low threshold levels of MDD and high threshold levels of GAD. Varying MDD thresholds affected comorbidity rates more than varying GAD thresholds. A higher threshold for MDD resulted in fewer subjects with comorbidity than a higher threshold for GAD. The number of subjects with comorbid MDD and GAD decreased considerably if the MDD-threshold increased from ≥1 of 9 to ≥7 of 9 symptoms (factor 3.8 decrease; from 1.74% to 0.46%), whereas the number of subjects with comorbidity remained relatively stable if the GAD-threshold increased from ≥1 of 7 to 7 of 7 symptoms (factor of 1.8 decrease; from 1.18% to 0.65%). Note that the factors provided here are descriptive statistics: they refer to the actual proportions among the subjects in the sample. Comorbidity rates remained remarkably stable for GAD-thresholds ranging from ≥1 up to ≥5 out of 7 symptoms (comorbidity rates decreased slightly from 1.18% to 1.09%). See Figures 2a and 2b.

In general, a higher threshold for MDD resulted in a larger drop in total number of MDD-patients than a higher threshold for GAD in total number of GAD-patients. The proportion of subjects satisfying MDD reduced with a factor of 7.7 with an increasing MDD-threshold of ≥1 of 9 to ≥7 of 9 symptoms present (from 5.20% to 0.67%), whereas the proportion of subjects satisfying GAD decreased with a factor of 3.5 with an increasing GAD-threshold of ≥1 of 7 to all 7 symptoms (from 4.95% to 1.42%). It follows that threshold levels influenced the number of subjects with MDD only and GAD only more than the number of comorbid MDD and GAD.

As a result, odds ratios increased with higher threshold levels, indicating a stronger association between MDD and GAD. The presence of MDD increased the likelihood of also having GAD, especially when high thresholds required that many symptoms had to be present of one of both disorders. This effect, again, was much more pronounced for higher thresholds of MDD than for higher thresholds of GAD. ORs were relatively stable for different threshold levels of GAD (ranging from 36.1-60.9), but varied considerably for different threshold levels of MDD (ranging from 19.7-94.9).

<Table 1; Table 2>

Changing thresholds for MDD and GAD had different effects on the proportion of comorbidity among all subjects with at least one diagnosis (Figures 2c and 2d). According to the DSM-thresholds for MDD and GAD, the proportion of subjects with comorbidity was 23.0%. The proportion of subjects with comorbidity changed considerably with a changing threshold for MDD. A higher threshold for MDD resulted in proportionally less comorbidity, with a minimum of 1.4% when all 9 symptoms were required for MDD, whereas a lower threshold for MDD led to more comorbidity with a maximum proportion of 25.8% for ≥3 or ≥4 of 9 symptoms. However, for very low MDD-thresholds, proportions of comorbidity between MDD and GAD showed a slight decrease, as these thresholds resulted in relatively more patients with MDD only than patients with both MDD and GAD.

The proportion of subjects with comorbidity was less sensitive to changing thresholds for GAD, and the relation between threshold level and comorbidity rates was inverted. The proportion of comorbidity remained relatively stable, ranging from 20.5% for a threshold of ≥1 of 7 symptoms to 26.5% for a threshold of ≥6 of 7 symptoms. In other words, the direction of the effect was different for the proportion of subjects with comorbidity: lower thresholds levels of GAD led to proportionally less comorbidity, whereas higher threshold levels led to proportionally more comorbidity.

<Figure 2>

Distribution of symptoms in subsample with core symptoms of MDD and GAD

In brief, we found a relative stability of comorbidity rates with changing GAD thresholds, but instability of comorbidity rates with changing MDD thresholds. These findings derived from the fact that most subjects who satisfy the core criteria of both MDD and GAD (a requirement for comorbidity) have many or all GAD symptoms, but fewer subjects have many or all MDD symptoms (Figure 3). Among 1,395 subjects who reported core criteria of MDD and GAD (anxiety and depressed mood/interest loss), 92.4% reported ≥4 GAD symptoms and most subjects reported 6 or all GAD symptoms (26.9% and 41.4%). A high number of depressive symptoms was less likely: 62.7% reported ≥5 MDD symptoms, and most reported exactly 5 or 6 symptoms (19.4% and 17.8%), whereas 8 or 9

symptoms were less frequently reported (8.4% and 3.3%). So, subthreshold GAD was rare, whereas subthreshold MDD was more common in this subsample. Hence, a shift in MDD-threshold had more consequences for comorbidity rates than a shift in GAD-threshold.

<Figure 3>

Discussion

To investigate the influence of classification choices on rates of comorbidity, we analyzed rates of comorbidity between MDD and GAD for classifications with different thresholds. Comorbidity rates increased considerably for lower thresholds of MDD, but remained stable and proportionally decreased for lower thresholds of GAD, as subjects with core criteria of both MDD and GAD mostly had all anxiety symptoms, but not all depressive symptoms. Hence, comorbidity rates do not necessarily increase when the thresholds of diagnostic criteria are lowered, as would be expected from a constructivist view. Naturally, the absolute number of (comorbid) patients will not decrease if a disease definition is made less restrictive. But in terms of proportions, fewer people might suffer from comorbidity if a lower threshold leads to the inclusion of symptom combinations which are rarely occurring in a population.

This study thus shows that comorbidity rates are the result of both (as opposed to only) symptom distributions and classification choices, as opposed to only the one or the other. Comorbidity patterns are not independent of classification systems, nor completely determined by or an artefact of these systems. On the one hand, rates of comorbidity depend on classification choices that determine the range of potential disordered symptom profiles: thresholds, overlapping symptoms, exclusionary criteria, etcetera. On the other hand, rates of comorbidity depend on the actual occurrence of these symptom combinations in the population. Thus, neither a constructivist nor a realist position fully explains rates of comorbidity. This finding corresponds to observations in other sciences, such as psychology and even physics. Measurements of latent psychological variables and physical quantities depend on

certain definitions or classification choices (e.g., personality traits, temperature), but they also depend on psychological or physical properties [26, 27],. Measurement results are relative to initial definitions of the concepts that are supposed to be measured, but not fully determined by these definitions [26, 28]. In line with similar studies on MDD [29, 30], our study illustrates that the same is true for comorbidity rates in psychiatry: comorbidity rates depend both on classification choices (which symptom profiles potentially satisfy both MDD and GAD?) and on population characteristics (which of these symptom profiles occur in the population?). Thus, comorbidity rates might be best understood from a position in-between a constructivist and realist stance [15].

The findings of this study should be interpreted in light of several strengths and limitations. First, the prevalence rates of MDD, GAD and comorbidity naturally depend on the time frame in which they were measured. In LifeLines, participants reported on MDD symptoms that were present in the majority of the days during the past two weeks and reported on GAD symptoms that were often present during the past six months, consistent with current duration criteria in the DSM. The strength of this design is that it enables the estimation of point prevalences of these disorders, and that the recall period is minimal. However, prevalence estimates of MDD would probably have been higher if MDD symptoms were measured in the same time period as GAD symptoms, as suggested by the differences in prevalence rates of the symptoms which occur in both MDD and GAD: sleep problems, fatigue, and concentration difficulties. These overlapping symptoms were less often reported during the past two weeks (MDD) than during the past six months (GAD). Nevertheless, we do not expect that a different time frame would have affected the general finding of this study - comorbidity rates increase for lower thresholds of MDD, but remain stable for lower thresholds of GAD - as it is unlikely that all subjects reporting core criteria of both MDD and GAD would have reported (almost) all depressive symptoms in the past six months (conform GAD symptoms), as some depressive symptoms are known to be very rare in the general population [31].

Second, in this study we did not take disability into account, which is a requirement in the DSM for diagnosing both disorders [4, 19]. This might have increased our point prevalence estimates of MDD, GAD and comorbidity, but if this is the case, the effect is probably limited. Previous studies have showed that MDD and GAD are highly associated with disability [13, 32], even for subthreshold levels of depression and generalized anxiety in population samples [33-

[35]. Indeed, our estimates of DSM-threshold GAD (4.10%) and MDD (2.00%) do not exceed estimates of previous community-based studies that incorporated disability: these reported current GAD prevalence rates ranging from 1.5% - 8.8% [22, 35] and current MDD prevalence rates ranging from 4.4 - 5.2% [22, 36]. The fact that our point prevalence of MDD (2.00%) was even lower than in previous community-based studies is likely due to the more restrictive criteria we used in our study (symptoms had to be present almost daily during the past two weeks, instead of only several days during the past two weeks [22] or during the past month [36]).

Third, this study demonstrated with one example (MDD and GAD) that comorbidity rates depend on both classification choices and population characteristics, but follow-up studies focusing on other psychiatric disorders are warranted to investigate the generalizability of our results. After all, MDD and GAD have particular characteristics: overlapping symptoms, high correlations between symptoms, and high comorbidity. Future studies with different disorders could investigate how stable comorbidity rates are with respect to threshold levels to test the generalizability of our findings.

Finally, we draw attention to a strength of our study. Admittedly we are not the first to consider that MDD and GAD are highly comorbid disorders. In fact, an anxiety specifier for MDD has recently been added in the DSM-5 [4], to account for the fact that anxiety often occurs in patients with MDD, and also predicts a more severe course of illness and less favorable treatment reaction [37-39]. Our main contribution is that it offers a more nuanced understanding of the comorbidity between MDD and GAD. Ours is the first to systematically investigate the effects of choosing different threshold levels of MDD and GAD in a large general population sample of whom reliable data were available of all MDD and GAD symptoms. Our study thereby significantly adds to the extant literature.

Our findings have several implications for the interpretation of comorbidity. First, since rates of comorbidity are partly determined by objective features of psychiatric diseases, they might hint at possible pathways underlying different psychiatric disorders. For instance, there are specific comorbidity patterns with somatic disorders, such as that depression predicts the development of diabetes [40]. Such patterns might inform us on the nature and causal background of different psychiatric and somatic diseases. Second, high comorbidity rates should not necessarily be

avoided in future disease classifications. Our findings show that comorbidity is to some extent inherent to how symptoms are distributed in the population. It would therefore be artificial to purge our classification system from all comorbidity, by imposing that disorders form a collection of mutually exclusive or hierarchical sets of symptom profiles. Such a restriction might well stand in the way of developing a classification that optimizes on research goals or clinical use. Also a redefinition of psychiatric disorders in terms of specific causes [6] will probably not rule out high rates of comorbidity [41]. As is frequently the case in medicine, there are many causal associations that are relevant to several disorders, also when these are defined in terms of causes (e.g., between human immunodeficiency virus and tuberculosis) [42].

Future studies could expand these analyses in order to be informative for the design of classification systems. In the foregoing we focused on symptom profiles only, without studying their associations with other clinically relevant criteria. For instance, we might ask which symptom profiles are most predictive for a certain treatment reaction or a severe course of illness? This could inform clinicians dealing with heterogeneous classes of patients, and it could eventually be useful for revisions of the DSM (at least as long as symptoms are the most important part of classifications of psychiatric disorders). A natural criterion for diagnostic systems is their ability to identify groups of patients that are similar in causal background, course of illness, and treatment reaction [43]. So the challenge would be to find definitions of disorders that capture a relatively homogeneous group of patients concerning these clinically relevant aspects. Whether or not alterations in the definitions will then lead to higher rates of comorbidity can justifiably be discarded as a secondary issue. Another direction in which we might improve the analyses exploits longitudinal studies. In the examples above we have used cross-sectional data. It would be interesting to investigate with prospective data how individuals move within the landscape of symptom profiles. For instance, we might ask which symptom profiles predict spontaneous recovery and which symptom profiles predict a move to a more severe combination of symptoms. Can we see general patterns, or are patterns highly individual? If certain symptoms combinations present specific risks, this might warrant the definition of a separate disorder or subtype.

Conclusions

Comorbidity patterns depend on both our classification scheme and on robust distributions of symptoms in the population, and cannot be traced back exclusively to either of these. Thus, rates of comorbidity are informative about psychiatric reality, and can be used to evaluate possible alterations in the definition of disorders in a systematic way. This insight invites further research into the formation of disease concepts that allow for reliable predictions and facilitate targeted therapeutic interventions. Next to continued empirical research in psychopathology, we propose that the field will benefit from the active reconsideration of the classification and conceptual structure of mental illness.

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Table 1. Prevalences of MDD, GAD and comorbidity for different thresholds of MDD

Threshold MDD	Population prevalence MDD only (%)	Population prevalence GAD only (%)	Population prevalence MDD & GAD (%)	Proportion comorbidity (%)	OR	95% CI
1	3.46	2.36	1.74	23.0	19.7	(18.1-21.3)
2	2.90	2.39	1.72	24.5	23.0	(21.2-25.0)
3	2.21	2.47	1.63	25.8	27.9	(25.6-30.5)
4	1.49	2.66	1.44	25.8	34.4	(31.2-37.8)
5	0.86	2.96	1.14	23.0	42.6	(38.1-47.7)
6	0.46	3.31	0.79	17.3	49.0	(42.6-56.3)
7	0.21	3.64	0.46	10.7	56.9	(46.9-69.0)
8	0.06	3.89	0.22	5.2	85.2	(61.3-118.6)
9	0.02	4.04	0.06	1.4	94.9	(49.0-183.9)

Abbreviations: GAD, generalized anxiety disorder; MDD, major depressive disorder; OR, odds ratio; 95% CI, 95% confidence interval.

Point prevalences of MDD only, GAD only and comorbidity between MDD and GAD for different thresholds of MDD and a fixed DSM-threshold for GAD (≥4 of 7 symptoms). We performed multinomial tests to compare the distributions of threshold *x* with threshold *x+1*. Distributions for all different threshold levels differed significantly at the p<0.0001 level (Monte Carlo approach, distance measure Pearson's chisquare) [44].

[a] Different thresholds for MDD, varying from ≥1 of 9 to all 9 necessary symptoms. The grey colored row indicates the current DSM-threshold (≥5 of 9 symptoms).

[b] Proportion of subjects with comorbidity among all subjects satisfying a diagnosis.

[c] Odds ratios and 95% confidence intervals representing the strength of association between MDD and GAD.

Table 2. Prevalences of MDD, GAD and comorbidity for different thresholds for GAD

Threshold GAD	Population prevalence MDD only (%)	Population prevalence GAD only (%)	Population prevalence MDD & GAD (%)	Proportion comorbidity (%)	OR	95% CI
1	0.82	3.77	1.18	20.5	36.1	(32.3-40.3)
2	0.83	3.58	1.17	20.9	36.9	(33.1-41.3)
3	0.84	3.36	1.16	21.6	38.8	(34.7-43.3)
4	0.86	2.96	1.14	23.0	42.6	(38.1-47.7)
5	0.91	2.40	1.09	24.7	47.4	(42.1-53.1)
6	1.03	1.65	0.97	26.5	54.8	(48.8-61.6)
7	1.35	0.77	0.65	23.5	60.9	(53.1-69.8)

Abbreviations: GAD, generalized anxiety disorder; MDD, major depressive disorder; OR, odds ratio; 95% CI, 95% confidence interval.

Point prevalences of MDD only, GAD only and comorbidity between MDD and GAD for different thresholds of GAD and a fixed DSM-threshold for MDD (≥5 of 9 symptoms). We performed multinomial tests to compare the distributions of threshold *x* with threshold *x+1*. Distributions for all different threshold levels differed significantly at the p<0.0001 level, except distributions of GAD threshold 1 and 2, *p*-value 0.051; and GAD threshold 2 and 3, *p*-value 0.016 (Monte Carlo approach, distance measure Pearson's chisquare) [44].

[a] Different thresholds for GAD, varying from ≥1 of 9 to all 9 necessary symptoms. The grey colored row indicates the current DSM-threshold (≥4 of 7 symptoms).

[b] Proportion of subjects with comorbidity among all subjects satisfying a diagnosis.

[c] Odds ratios and 95% confidence intervals representing the strength of association between MDD and GAD.

Supplemental Table 1. Distribution of and correlations among MDD and GAD symptoms

		MDD symptoms									GAD symptoms					
	%	dep	int	wgt	slp.m	mot	fat.m	glt	con.m	sui	anx	nerv	ten	fat.g	con.g	irr
MDD symptoms																
Dep	3.5	1														
int	3.7	0.87	1													
wgt	5.0	0.49	0.51	1												
slp.m	14.1	0.50	0.50	0.41	1											
mot	6.7	0.66	0.65	0.52	0.57	1										
fat.m	12.7	0.66	0.72	0.48	0.56	0.64	1									
glt	2.4	0.77	0.75	0.50	0.48	0.63	0.66	1								
con.m	6.3	0.70	0.71	0.49	0.52	0.68	0.70	0.75	1							
sui	0.7	0.68	0.67	0.47	0.43	0.56	0.56	0.75	0.64	1						
GAD symptoms																
anx	5.0	0.69	0.65	0.42	0.46	0.59	0.58	0.70	0.71	0.60	1					
nerv	12.6	0.64	0.61	0.40	0.45	0.67	0.56	0.66	0.66	0.55	0.76	1				
ten	17.7	0.64	0.62	0.41	0.45	0.63	0.58	0.67	0.66	0.57	0.78	0.93	1			
fat.g	19.8	0.57	0.63	0.43	0.48	0.58	0.84	0.60	0.65	0.51	0.67	0.72	0.75	1		
con.g	10.4	0.59	0.61	0.42	0.44	0.60	0.62	0.64	0.82	0.53	0.74	0.76	0.76	0.78	1	
irr	13.7	0.59	0.61	0.42	0.41	0.56	0.57	0.62	0.62	0.51	0.68	0.75	0.80	0.74	0.74	1
slp.g	17.2	0.48	0.47	0.37	0.91	0.55	0.55	0.50	0.53	0.43	0.57	0.62	0.64	0.64	0.61	0.60

Distribution of symptoms of major depressive disorder in the past two weeks and symptoms of generalized anxiety disorder in the past six months in a general population sample (column 2, n=74,092). Note that the common symptoms sleep problems, fatigue and concentration difficulties are more prevalent in GAD than MDD, which can be explained by the different criteria for GAD (often in six months) and MDD (almost daily in past 2 weeks). Columns 3 to 17 show the tetrachoric correlations among all MDD and GAD symptoms.

Abbreviations: dep, depressed mood; int, loss of interest; wgt, appetite/weight loss or appetite/weight gain; slp, sleep disturbance; mot, psychomotor disturbance; fat, fatigue; glt, feelings of guilt or worthlessness; con, concentration difficulties; sui, suicidal thoughts; anx, excessive, difficult to control, anxiety and worries; nerv, nervous; ten, feeling tense; irr, irritability. The additional “m” or “g” indicate that the symptom is measured as part of MDD (“m”) or GAD (“g”). Note that the MINI uses the general term ‘feeling tense’ instead of the more specific DSM-criterion ‘muscle tension’.

Figure legends

Figure 1. Highly correlated MDD and GAD symptoms

The highest tetrachoric correlations between all MDD and GAD symptoms, edges are displayed for rho correlation coefficients ≥ 0.5; the thicker edges indicate stronger correlations. The nodes on the left side of the network represent the GAD symptoms; the nodes on the right side of the plot represent the MDD symptoms. We used R-package qgraph for this plot [45].

Abbreviations: dep, depressed mood; int, loss of interest; wgt, appetite/weight loss or appetite/weight gain; slp, sleep disturbance; mot, psychomotor disturbance; fat, fatigue; glt, feelings of guilt or worthlessness; con, concentration difficulties; sui, suicidal thoughts; anx, excessive, difficult to control, anxiety and worries; nerv, nervous; ten, feeling tense; irr, irritability. The additional "m" or "g" indicates that the symptom is measured as part of MDD ("m") or GAD ("g"). Note that the MINI uses the general term 'feeling tense' instead of the more specific DSM-criterion 'muscle tension'.

Figure 2. Comorbidity prevalence for different MDD and GAD thresholds

Point prevalences of comorbid MDD and GAD, MDD only and GAD only for different thresholds for MDD (Figure 2a, using a DSM-threshold for GAD) and GAD (Figure 2b, using a DSM-threshold for MDD) in a general population sample of adults (n=74,092). Figures 2c and 2d show proportions of subjects with comorbidity among all subjects with MDD or GAD. Dashed vertical lines represent current DSM thresholds for MDD (≥5 of 9 symptoms) and GAD (≥4 of 7 symptoms).

Figure 3. Number of symptoms among subjects with core symptoms of MDD and GAD

Number of MDD and GAD symptoms of 1,395 subjects reporting core criteria of both MDD and GAD (i.e., anxiety and depressed mood or loss of interest). The horizontal blue line represents the current DSM-threshold for MDD (≥5 of 9 symptoms); the vertical green line represents the current DSM-threshold for GAD (≥4 of 7 symptoms). Column and row sums are given above and to the right of the scatter plot, respectively.