Data-driven subtypes of major depressive disorder
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Psychiatric comorbidity does not only depend on diagnostic thresholds: an illustration with major depressive disorder and generalized anxiety disorder

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Submitted
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 symptom distributions 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 distributions 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.
Background

Comorbidity rates between mental disorders are high with about 50% of patients having two or more disorders in the course of a year, and ‘pure’ disorders often having lower prevalence rates than combined disorders [1]. For example, most patients with major depressive disorder (MDD) also have generalized anxiety disorder (GAD) instead of MDD only [1]. The high overlap between disorders fuels the debate on the validity of the current classification of mental disorders [2]: what is the use of distinguishing a few hundred different disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM) [3] if the majority of patients have at least two or three of them? Although it is the intention to improve the quality of the classification of mental disorders in each subsequent version of DSM, rates of comorbidity have not decreased. Moreover, the clinical and construct validity of the disorders have not been improved, as the nature and etiology of these disorders remains by and large elusive [4]. The high level of comorbidity highlights broader ranging conceptual problems in our understanding of mental disorders: if there is so much comorbidity, does this reflect an artificial consequence of DSM classification rules, or is this a factual representation of psychiatric morbidity patterns?

When looking at the high levels of comorbidity found in current classification systems, two largely opposing interpretations can be given. On the one extreme, comorbidity may be a representation of the fact that different mental disorders have common causes, such as precipitating factors (e.g. childhood trauma), genetic vulnerability, or neurobiological abnormalities. As an example, obesity may lead to diabetes and to hypertension [5], so it is not surprising that these disorders are often comorbid. Similar patterns have been suggested to explain the high rates of comorbidity in psychiatry [6, 7]. 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.

On the other end of the spectrum, comorbidity can be interpreted as a 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 [8, 9]. According to this view, a change in the 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 illustrate that the classifications themselves are inadequate, and do not establish a strict partition of mental disorders in the population [2].

In this paper we will illuminate this issue by empirically exploring different classifications of major depressive disorder (MDD) and generalized anxiety disorder (GAD) in a large population sample of adults living in the Northern Netherlands. Our aim is to investigate whether changes in classification rules, specifically in terms of diagnostic thresholds, affect rates of comorbidity of MDD and GAD in order to clarify the origins of comorbidity.
Methods

Sample
Data were derived from LifeLines, a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in the North East region of The Netherlands [11, 12]. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. From this dataset, individuals were selected with complete data of current depression and anxiety symptoms measured with the Mini-International Neuropsychiatric Interview (MINI) [13].

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 [12].

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 [13]. 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, conform the duration criteria in the DSM [14].

We constructed dummy 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, with at least one of the core symptoms depressed mood and loss of interest [14]. For the present study we constructed 9 dummy variables for MDD-classifications with different diagnostic thresholds. For each dummy we used a different number 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.

Likewise, we constructed dummy variables for GAD-classifications with different diagnostic thresholds. 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 [14]. For the present study we constructed 7 dummy variables for GAD-classifications with different diagnostic thresholds. For each dummy we used a different number of necessary criteria varying from a minimum of ≥1 of 7 to a maximum of all 7, without changing the requirement of the core criterion of excessive anxiety and worry. 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 [14], to increase our comparability to other epidemiological studies [15-17].
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, while keeping the GAD threshold at DSM-level (≥4 of 7). Likewise, we assessed these prevalences for all different threshold levels of GAD, while keeping the MDD threshold at DSM-level (≥5 of 9). 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) [18]. 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).

Assessment of symptom combinations
Since diagnoses of MDD and GAD are defined in terms of specific symptom combinations, we mapped the prevalence of combinations of six MDD and GAD symptoms (depressed mood/interest loss; guilt; suicidality; anxiety; feeling tense; concentration difficulties) to illustrate how prevalent versus rare symptom distributions influence comorbidity rates. For the purpose of illustration, the number of symptoms in the analysis was limited to six, leading to a total number of 64 (2^6) possible symptom combinations. All possible combinations were plotted in heat maps; the basic structure of these plots was derived from Karnaugh maps [19]. All analyses were performed in R [18]; plots were made with R-package ggplot2 [20].

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); feeling nervous and tense (rho 0.93); and the overlapping symptoms sleep difficulties (rho 0.91), fatigue (rho 0.84), and concentration problems (rho 0.82) (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).
Psychiatric comorbidity does not only depend on diagnostic thresholds. We used R-package *qgraph* for this plot [33]. 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").

**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.

Comorbidity of MDD and GAD according to different threshold levels

Point prevalence for MDD and GAD according to DSM-criteria was 2.00% and 4.10% 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%) (Figures 2a and 2b). 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%).

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 total number 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 total number of subjects satisfying GAD decreased with a factor of 3.5 with an increasing GAD-threshold of ≥1 of 7 to
Psychiatric comorbidity does not only depend on diagnostic thresholds. 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 outspoken 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).

**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).

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% (1.14% of a total of 4.96% subjects with at least one diagnosis). 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. This is in accordance with the idea that making a disease definition more inclusive enlarges the overlap with other diseases and hence increases comorbidity.
However, for very low MDD-thresholds, proportions of comorbidity between MDD and GAD showed a slight decrease (24.5% for ≥2 or 23.0% for ≥1 of 9 symptoms), as these thresholds resulted in relatively more patients with MDD only than patients with both MDD and GAD.

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

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

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).

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.

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

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

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

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 (≥5 of 9 symptoms).

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.

Abbreviations: GAD, generalized anxiety disorder; MDD, major depressive disorder; OR, odds ratio; 95% CI, 95% confidence interval.
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 \( \geq 1 \) of 7 symptoms to 26.5% for a threshold of \( \geq 6 \) of 7 symptoms. In other words, the direction of the effect was different for the proportion of subjects with comorbidity: lower thresholds levels led to proportionally less comorbidity, whereas higher threshold levels led to proportionally more comorbidity. The reason is that, while higher thresholds obviously lead to the inclusion of more subjects into a disease profile, the number of newly included subjects with comorbidity does not increase in proportion to the total number of newly included subjects by the change in threshold.

**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 \( \geq 4 \) 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 \( \geq 5 \) 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.** 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 line represents the current DSM-threshold for MDD (\( \geq 5 \) of 9 symptoms); the vertical line represents the current DSM-threshold for GAD (\( \geq 4 \) of 7 symptoms). Column and row sums are given above and to the right of the scatter plot, respectively.
Prevalence of specific symptom combinations

To gain further insight in such effects, we studied the prevalence of 64 symptom combinations of six depressive and anxiety symptoms. Some combinations were reported frequently, but others seldom or not at all (Figure 4). In total, 22.8% (n=16,900) of the sample reported one or more out of the six selected symptoms. 60.5% of these subjects reported three specific symptom combinations: feeling tense without any other symptoms, concentration difficulties only, and a combination of these two symptoms. Four other frequently observed symptom patterns concerned anxiety, combined with feeling tense with and without concentration difficulties, and depressed mood or feeling tense only. These four combinations were reported by approximately one sixth of the group of subjects having one or more symptoms (17.6%). Another one sixth of subjects (16.7%) had 13 relatively frequent symptom combinations, which were reported >100-500 times, including the combination of all six symptoms. Then there were 25 less common symptom combinations (reported by >10-100 subjects) and 17 uncommon symptom combinations (reported by ≥1-10 subjects). In total, 5.2% of subjects with symptoms were spread over these 42 uncommon combinations. Combinations that were reported infrequently for included combinations of guilt and suicidality, especially in absence of feeling tense. If suicidality was present, it was most likely in addition to all other symptoms. One symptom combination was not reported at all, which was the combination of anxiety, feelings of guilt and suicidality, without depressed mood, concentration difficulties and feeling tense.

Figure 4. Symptom combinations of six depression and anxiety symptoms
Heatmap of observed symptom combinations of six depression and anxiety symptoms in the general population of LifeLines (n=74,092). Every cell represents an unique symptom combination; the numbers in each cell are the raw frequencies in the Lifelines sample (n=74,092), with lighter colors indicating higher frequencies and darker colors indicating lower frequencies. Column and row sums are given above and to the right of the heatmap, respectively. The six selected symptoms include three criteria of MDD, two criteria of GAD and one overlapping symptom, i.e. a criterion of both MDD and GAD.

Abbreviations: anx: excessive rumination and worry about a number of activities in daily life, present during the majority of the days and difficult to control in the past 6 months, representing core criterion of GAD (criterion A and B for GAD) [14]; con: concentration difficulties in the past 6 months; additional symptom of both GAD and MDD; dep: persisting depressed mood and/or loss of interest in the past 2 weeks combined into one binary variable representing the core symptoms of MDD (conform criterion A for MDD) [14]; glt: feelings of guilt or worthlessness in the past 2 weeks, additional MDD criterion; sui: death wishes or thoughts and plans of suicide in the past 2 weeks, additional MDD Criterion; ten: feeling tense in the past 6 months, additional GAD criterion.

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 mostly had all anxiety symptoms, but not all depressive symptoms. GAD symptoms were more highly correlated than MDD symptoms, and rates of GAD were thus less sensitive to changes in thresholds. 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 that 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. 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 realistic position fully explains rates of comorbidity. This finding corresponds to observations in other sciences, such as physics. Measurements in space and time depend on certain definitions or classification choices (e.g., straight lines, temperature, color), and on properties of actual space. Measurement results in physics are relative to these first definitions, but not fully determined by these definitions [21, 22]. 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 seen from a position in-between a constructivist and realist stance [23].

The findings of this study should be interpreted in light of several strengths and limitations. First, like in other studies, the prevalence rates of MDD, GAD and comorbidity naturally
Psychiatric comorbidity does not only depend on diagnostic thresholds, but also 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, conform 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). Thus, prevalence estimates of MDD could have been higher if depressive symptoms were assessed in the past six months instead of in the past two weeks. 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 [24].

Second, in this study we did not take disability into account, which is a requirement for diagnosing both disorders [14]. This might have increased our rates of MDD, GAD and comorbidity. Indeed, our estimates of GAD are higher than compared to other population studies in which year prevalences were found of 1.5% - 3.2% [1, 15, 25]. However, it is likely that reported prevalences are not much overestimated as they are lower than recently reported point prevalences in the Swedish population (MDD 5.2%; GAD 8.8%; MDD-GAD comorbidity 28.2%) [17].

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.

Fourth, this study is not the first to show that MDD and GAD are highly comorbid disorders. In fact, an anxiety specifier for MDD has recently been added in the DSM-5 [3], 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 [26-28].

Despite these limitations, this is the first study that systematically investigated 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, and contributes to the literature on comorbidity. 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 [29]. 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
Psychiatric comorbidity does not only depend on diagnostic thresholds 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 [2] will probably not rule out high rates of comorbidity [30]. 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) [31].

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 [32]. 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.
References


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

<table>
<thead>
<tr>
<th>MDD symptoms</th>
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<tr>
<td>%</td>
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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”).
Psychiatric comorbidity does not only depend on diagnostic thresholds.