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Explaining heterogeneity in disability associated with current major depressive disorder: Effects of illness characteristics and comorbid mental disorders

Abstract

Background: Although major depressive disorder (MDD) is associated with disability, some persons do function well despite their illness. Aim of the present study was to examine the effect of illness characteristics and comorbid mental disorders on various aspects of disability among persons with a current MDD episode.

Methods: Data were derived from 607 participants with a current MDD based on the Composite International Diagnostic Interview (CIDI). Severity was assessed via the Inventory of Depressive Symptoms self-report (IDS-SR). For disability three outcome measures were used: World Health Organization Disability Assessment Schedule II (WHODAS) disability and its 7 dimensions, days out of role, and work absence. Using multiple regression analysis the effects of MDD characteristics and comorbid mental disorders were estimated.

Results: The IDS-SR core was the best predictor of all disability outcomes. Of the comorbid mental disorders, agoraphobia was significantly associated with overall disability. Collectively, all illness characteristics accounted for 43% of variance in WHODAS disability, 13% in days out of role and 10% in work absence, suggesting substantial unexplained variance.

Limitations: Only self-report measures of disability were used. There were no assessments of other diagnoses than depressive, anxiety and alcohol use disorders.

Conclusions: Although heterogeneity in disability of persons with current MDD is partially explained by illness characteristics of MDD (especially symptom severity) and comorbid mental disorders, most of the variance is not accounted for.
Introduction

In general, major depressive disorder (MDD) is associated with disability.\textsuperscript{1-5} Disability can be defined as any restriction or lack of capacity to perform an activity in a manner or within a range considered normal for a human being.\textsuperscript{6} Severity of depression and disability show synchrony of change during the course of the illness.\textsuperscript{7} Nevertheless, there are still individuals who function surprisingly well despite the presence of depressive symptomatology.

Although no previous studies have recognised normal functioning among persons with MDD, there are persons with high depressive symptom scores who report low disability scores. As an example, Zimmerman et al.\textsuperscript{8} observed discordance between severity of depression and the disability of individuals. This discordance was for the greater part represented by persons with significant depressive symptoms with normal levels of functioning. Furthermore, Geerlings et al.\textsuperscript{9} found that, at baseline, 46% of their subjects with high depressive symptom scores had no disability at all. The findings suggest that there is substantial variation in disability of people with MDD.

Explaining heterogeneity in disability amongst persons with a current episode of MDD is an important step forward in disentangling the complex relationship between MDD and disability. A starting point for understanding this heterogeneity is provided by The International Classification of Functioning, Disability and Health (ICF).\textsuperscript{10} The ICF views disability as the outcome of an interaction between health conditions and contextual factors. Among the health conditions are diseases, disorders and injuries. Among contextual factors are personal and environmental factors. Studying the effect of health conditions, among which characteristics of MDD and comorbid mental disorders, may therefore provide valuable information for the explanation of heterogeneity in disability with MDD (Figure 1).

![Figure 1. The International Classification of Functioning model, which views functioning as the outcome of interaction between health conditions and contextual factors (World Health Organization, 2002)](image-url)
Since persons suffering from MDD differ greatly in symptom characteristics, such as severity of depression,\textsuperscript{11,12} recurrence,\textsuperscript{13} and age of onset of depression,\textsuperscript{14} it is possible that individual characteristics of MDD and comorbid mental disorders account for the heterogeneity in disability. If this is the case, it is important to learn to what extent they do this, independently of the other characteristics. If these characteristics of psychopathology do not explain most of the variation in disability, this would suggest that other non-psychopathology related factors play a role.

Furthermore, possible predictors for disability with MDD are the specific symptom profile of MDD and the comorbidity pattern. Several symptom profiles of MDD have been specified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).\textsuperscript{15} Most important are MDD with melancholic features and MDD with atypical features. The identities of these profiles are supported in literature and they are found to differ from each other and from MDD with neither melancholic, nor atypical features.\textsuperscript{16,17} Nevertheless, there is very little known about the differences of these symptom profiles in relation to disability.

Another distinction, based on symptom profiles, is between unipolar MDD and bipolar disorder. In some studies a higher level of role disability has been reported for bipolar disorder,\textsuperscript{3} though not in all studies.\textsuperscript{18} These findings suggest that in persons with MDD the presence of bipolar (i.e. manic) features may be associated with more disability, but to our knowledge this has not been studied yet. Finally, it is likely that the presence of comorbid disorders does account for variation in disability, since comorbid conditions (e.g. dysthymia, anxiety disorders, or alcohol use disorders) are common in persons with MDD and have been found to have a substantial impact on disability\textsuperscript{19,20} and work presence\textsuperscript{21} even when non-comorbid.

The available evidence does not provide a clear view of factors that explain the disability associated with current MDD. Most studies include only one or a few characteristics out of the described range of potentially relevant illness characteristics. The present study, in contrast, examines the effect of several important characteristics of MDD, as well as major comorbid disorders simultaneously in a large cohort of patients with current MDD.

To assess disability, multiple measures can be used. These measures vary in specificity and subjectivity, and hence in possible association with depression characteristics. Therefore three measures were used, based on the World Health Organization Disability Assessment Schedule (WHODAS)\textsuperscript{22}: (i) “WHODAS disability”, a broad measure of perceived disability in many aspects of functioning; and (ii) days out of role, and (iii) absence from paid work, two more specific and objective measures.

In sum, this study investigates to what extent measures of MDD severity, other illness characteristics of MDD, and comorbid mental disorders can account for the heterogeneity in disability measures that differ in specificity and subjectivity.
Method

Sample
To study heterogeneity in disability with MDD, we used data from the Netherlands Study of Depression and Anxiety (NESDA). The design, recruitment, and instruments of NESDA have been described extensively by Penninx et al.\textsuperscript{23} In short, NESDA is a longitudinal cohort study that consists of a baseline interview and follow-up assessments to be completed in the future. Most participants were recruited in general practice and specialty mental health services. Participants with a diagnosis of schizophrenia or bipolar disorder, and those not speaking Dutch, were excluded. Data were collected using a face-to-face interview, self-report questionnaires (filled in before and after the interview), computer assignments, and a medical exam. In total, 2981 participants, aged 18 through 65, were included in the baseline NESDA sample. In the present study, we focus on the 607 participants with current MDD at baseline.

Current MDD was defined as a major depressive diagnosis in the last month before the interview. This diagnosis was based on the Composite International Diagnostic Interview (CIDI) version 2.1,\textsuperscript{24} according to DSM-IV criteria. The CIDI is a structured interview that is applicable for use by trained non-clinicians and has shown good reliability and validity.\textsuperscript{25}

Disability measures
For disability as an outcome in this study, we used three different measures. The first measure is WHODAS disability: the total score of the World Health Organization Disability Assessment Schedule (WHODAS).\textsuperscript{22} The WHODAS consists of seven domains with four to eight items, measuring functional impairments in the past thirty days. The domains are on communication, getting around (i.e. mobility), self-care, getting along (i.e. personal activities), life activities, and participation. The life activities domain has been divided into two separate domains: household activities and work activities. The latter part was only applicable if the participant had a paid job. The self-report questionnaire was sent to the participants and filled in before the interview. WHODAS disability ranges from 0 to 100 and has shown to be valid.\textsuperscript{26} Furthermore it has a very strong inter-item reliability ($\alpha=.95$). The reliability of the WHODAS domain scores range from $\alpha=.77$ to $\alpha=.93$.

WHODAS disability is a general measure and some domain items overlap with symptoms of depression. An example of overlap is the item “Concentrating on doing something for ten minutes”. Concentration problems can be a symptom of depression, but it can also be an indicator of disability. To also examine determinants of outcome measures that are more
distant from MDD symptoms, and to measure disability more specifically and objective, we included two measures on work and daily living. These outcome measures are role disability, and work absence.

The variable that described the number of days out of role was constructed using three items on the duration of role disability in the last month, as done before by Buist-Bouwman et al. Questions were: ‘How many days of the past 30 were you totally unable to work or carry out normal activities?’, ‘... were you able to work and do normal activities but had to cut down or did not do as much as usual?’, and ‘... did you have to cut back on the quality or carefulness of your work?’. These items showed good inter-item reliability (α=.75). The total score was calculated by adding the scores, weighing the first item as 1 for each day out of role and the latter two items by .5. Finally, the scores were recoded to create a scale with scores ranging from 0 to 100.

The third outcome we included was the period of time (number of workweeks) the participant was absent from work in the last six months. This information was gathered using the short form of the Health and Labour Questionnaire (SF-HLQ). This questionnaire examines, among other things, the duration of absence from work due to mental health problems in the last six months. Work absence was computed by dividing the number of days absent in the last six months by the number of days per week a person was supposed to work, as done by Plaisier et al. The range of this score was 0-26.

**Predictor variables**

Current severity of depressive symptoms was assessed with the self-report version of the Inventory of Depressive Symptoms (IDS-SR). The CIDI was used to assess the diagnosis of mental disorders and to establish the number of previous major depressive episodes (MDEs). This variable was dichotomised to single and recurrent MDD. Information on the age of first onset of MDD was also available from the CIDI. For information on the duration of recent MDEs, we used information from the Life Chart Interview which uses a calendar method to assess the number of months the participant had been feeling depressed in the last four years. The percentage of months in last four years with depressive symptoms was used as indicator.

To indicate different symptom profiles of MDD, we assessed melancholic, atypical, and manic features. For the diagnosis of the first two profiles, criteria were available from DSM-IV. To approximate the criteria for melancholic and atypical MDD we used items from the IDS-SR, as done before by Van Reedt-Dorland et al. The IDS-SR includes all items that inquire after the criteria needed for the diagnosis of both symptom profiles. For the assessment of manic features, the Mood Disorder Questionnaire (MDQ) was used. The MDQ is a well-established instrument to assess the lifetime presence of (subthreshold) manic symptoms, indicating the possible presence of undiagnosed bipolar disorder.
The diagnoses of comorbid dysthymia, anxiety disorders, and alcohol dependence disorder were made using the past month CIDI sections on dysthymia, generalised anxiety disorder (GAD), panic disorder, social phobia, agoraphobia, and alcohol dependence.

Statistical analysis

Univariate regression models were used to estimate univariate associations between variables. Multiple regressions were then conducted to test the effects of all predictor variables simultaneously. In this way, the most important predictors of disability can be isolated, adjusted for other depression characteristics. High multicollinearity between predictor variables may, however, influence the robustness of the results. Therefore we checked our analyses for harmful multicollinearity using the variance inflation factor. The distributions of all used outcome measures were near-normally distributed with all skewness and kurtosis values between -1 and 1. A p-value smaller than .05 was considered significant.

Missing values (N=72) on WHODAS disability and WHODAS domains were replaced by the mean of the participant’s other answers within the same domain, except when information on more than one question per domain was missing. Only participants with a paid job of more than eight hours a week were considered to be working (N=332). The analyses with work absenteeism were restricted to these 332 subjects. For days out of role and work absence no missing value imputations were made. Therefore persons with missing values on these outcomes were case wise deleted from the analyses in which they serve as outcome, resulting in different sample sizes per disability measure (WHODAS disability: N=562-576; days out of role: N= 589-604; work absence: N= 326-332).

Results

Sample characteristics

The majority of participants in our sample were women (66.9%) and the participants’ mean age was 42 years (Table 1). Comorbid mental disorders were considerably present, as 427 participants (70.3%) had one or more additional CIDI diagnoses. While a clinically recognised bipolar disorder was an exclusion criterion for the NESDA study, fifty-three participants (8.7%) had a positive screen for manic features.

Since a large part of the sample did not work at the time of the interview, we compared them to the working part of the sample. Participants without a paid job were comparable to participants with a paid job on gender (t=.18, p=.85), age (t=1.92, p=.06), age of onset (t=-1.29, p=.20), the lifetime number of episodes (t=-.81, p=.54), and WHODAS total score (t=1.83, p=.07). They, however, were significantly longer depressed in the past five years (t=4.44, p=<.001), and had higher IDS-SR symptom severity (t=2.4, p=.02).
Correlations between the outcome measures vary from .37 (p<.001) between WHODAS disability and work absence, and .45 (p<.001) between WHODAS disability and days out of role, to .50 (p<.001) between work absence and days out of role. The correlations between the domains of the WHODAS ranged from .16 between self-care and getting along to .52 between household activities and work activities (all significant with p<.001).

Regression analyses of the WHODAS disability, days out of role and work absence

In Table 2, the univariate and multivariate associations of the MDD characteristics with disability are reported in standardised beta values. The best fitting multivariate model was for the WHODAS disability, with a $R^2$ of .43. The explained variance in days out of role ($R^2$=.13) and work absence ($R^2$=.10) was considerably lower. There was no sign of multicollinearity in the models (VIF <2). Analysis of the residuals showed no proof of a non-linear relationship or heteroscedasticity, indicating that the results are robust.

MDD symptom severity as measured with the IDS-SR was clearly the strongest predictor of all three outcome measures, both univariate and multivariate. Although the different symptom profiles of MDD were associated with disability in the univariate models, in multivariate models the effects of all three symptom profiles on the disability measures did not reach statistical significance. The time a participant was depressed during the last five years was univariately associated with a higher disability level for all three disability measures. In contrast, recurrent MDD was univariately associated with lower disability. Both effects did, however, not remain significant in the multivariate analysis. In both the univariate and the multivariate model, an older age of onset predicted higher work absence. It was, however, unrelated to the other outcomes.

In the univariate models, WHODAS disability was associated with all comorbid mental disorders. Furthermore comorbid dysthymia, social phobia, GAD, and alcohol dependence were predictors for more days out of role. The estimate for absence from work increased when a participant suffered from panic disorder and/or agoraphobia. In the multivariate model almost all these effects fell below the statistical significance level of .05, except for two effects. First, a diagnosis of alcohol dependence predicted more days out of role. Second, agoraphobia was strongly associated with WHODAS disability.
Regression analyses of the WHODAS domains

The model fit of the regressions of the WHODAS domains was moderate. The explained variance ranged from $R^2=.14$ for household activities and work activities to $R^2=.29$ for participation. None of the multivariate models showed signs of malignant multicollinearity or non-linear relationships. Thus, the models seem appropriate and the results therefore robust.

Similar to the findings for the general outcomes, the MDD symptom severity was the best predictor of disability for all domains. It was significantly associated with all WHODAS domains, in both the univariate and multivariate models. Melancholic features were significantly univariately associated with higher disability in all WHODAS domains, but only the association between melancholic features and self-care remained in the multivariate model. Atypical and manic features had no consistent associations with the different domains and in the multivariate models, only having atypical features is significantly associated with higher work absence after adjustment for other predictors.
Higher duration of depression was associated with higher disability in all domains, except for work activities. In the multivariate model, however, only the association with the self-care domain remained statistically significant. Recurrent depression showed some contradictory effects on the domains. Univariately, recurrent depression was negatively related to the domains communication, self-care and getting along, but positively with getting around and participation. In the multivariate models all parameter estimates fell below the statistical significance level. For the age of onset the effects on getting around and self-care were positive in the multivariate models, but on getting along it was negative. Dysthymia was positively associated with most of the domains of the WHODAS, but none of these remained significant after controlling for the other characteristics. Of the anxiety disorders only agoraphobia had multiple strong positive associations in the multivariate model, though markedly smaller than the univariate ones. Panic disorder was associated with more limitations in communication, self-care, and participation but in the multivariate analysis it was associated with fewer limitations in communication, household activities and work activities. Social phobia was only associated with getting along in the multivariate model. For alcohol dependence disorder, there was only a small multivariate effect on self-care.
<table>
<thead>
<tr>
<th>Work absence</th>
<th>Days out of role</th>
<th>WHODAS</th>
<th>Communication</th>
<th>Getting around</th>
<th>Self-care</th>
<th>Getting along</th>
<th>Household activities</th>
<th>Work activities</th>
<th>Participation</th>
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<td>UV</td>
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</table>

**Illness characteristics**

<table>
<thead>
<tr>
<th>MDD symptom severity</th>
<th>WHODAS</th>
<th>Communication</th>
<th>Getting around</th>
<th>Self-care</th>
<th>Getting along</th>
<th>Household activities</th>
<th>Work activities</th>
<th>Participation</th>
</tr>
</thead>
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<td>0.30†</td>
<td>0.37†</td>
<td>0.36†</td>
<td>0.65†</td>
<td>0.58†</td>
<td>0.50†</td>
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<td>-0.01</td>
<td>-0.04</td>
<td>0.03</td>
<td>0.06</td>
<td>0.05</td>
<td>-0.05</td>
<td>-0.04</td>
</tr>
<tr>
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<td>0.06</td>
<td>-0.03</td>
<td>0.11**</td>
<td>-0.02</td>
<td>0.09</td>
<td>0.10</td>
<td>0.11**</td>
</tr>
<tr>
<td>Time depressed last 5 yrs</td>
<td>0.12*</td>
<td>0.03</td>
<td>0.13**</td>
<td>0.00</td>
<td>0.19†</td>
<td>-0.12**</td>
<td>-0.13**</td>
<td>0.03</td>
</tr>
<tr>
<td>Recurrence</td>
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<td>0.06</td>
<td>-0.09</td>
<td>0.00</td>
<td>-0.15</td>
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<td>Depression age of onset</td>
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<td>0.18*</td>
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<td>0.16†</td>
<td>0.09</td>
<td>0.15†</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Comorbid mental dis.**

| Panic disorder     | 0.12*  | 0.01          | -0.06         | 0.04      | 0.22†         | 0.07                | 0.10†           | 0.10†         |
| Social phobia      | 0.00   | -0.04         | 0.10*         | 0.01      | 0.25          | 0.04                | 0.18†           | 0.14**        |
| GAD                 | 0.04   | -0.04         | 0.13**        | 0.05      | 0.21†         | 0.02                | 0.18†           | 0.14**        |
| Agoraphobia         | 0.13*  | 0.07          | 0.08          | 0.02      | 0.24†         | 0.19†               | 0.19†           | 0.12**        |
| Alcohol dependence | -0.02  | -0.01         | 0.09          | 0.06      | 0.12**        | 0.09                | 0.05           | 0.10†         |

| R²                   | 0.10   | 0.13          | 0.43           | 0.25      | 0.28          | 0.15                | 0.22           | 0.14          |
| N                    | 326    | 314           | 589            | 566       | 566           | 573                 | 573            | 588          |

*Includes only people who were employed at the time of the assessment.

* p<.05, ** p<.01, † p<.001
Discussion

We investigated several characteristics of MDD and comorbid mental disorders (anxiety disorders, and alcohol dependence disorder) simultaneously to gather new insights into the relationship between MDD and various aspects of disability. For some part, the disability associated with a current episode of MDD is accounted for by characteristics of MDD and comorbid mental disorders, in particular symptom severity, but the amount is limited, in particular for role disability and absence from work. Thus, a considerable part of the variation in disability is unexplained, even when assuming 30% measurement error variance.

How much variation in disability is accounted for by characteristics of current psychopathology depends strongly on the subjectivity and specificity of the disability measure used. The measure for days out of role is more objective and specific than WHODAS disability and focuses on problems with performing daily activities, whereas the WHODAS disability also includes cognitive, physical, and interpersonal functioning. Using the well-defined measure of work absence is also far less subjective and more specific than the WHODAS disability as it provides a narrow indicator for impairments in the capacity to work.

We also included the domains of the WHODAS to determine the influence of characteristics of MDD and comorbidity on different domains of disability. These analyses revealed that characteristics of MDD are differently associated with the WHODAS domains of disability, which is consistent with Buist-Bouwman et al. A potential problem of the WHODAS is that some dimensions are conceptually less distinct from depressive symptomatology than role disability and work absence (e.g. communication, getting along).

Analysing illness characteristics revealed that the MDD symptom severity is the most important characteristic in explaining disability with a current MDD, confirming the findings of Spijker et al. and Rytsälä et al. There were no effects found for the duration of episodes in the last four years or for recurrence of MDD, supporting the findings of Kruijshaar et al. For the age of onset of depression, significant associations in both directions were found.

An onset of MDD at an older age was associated with more work absence, as well as with getting around and self-care WHODAS domains. Possibly, this can be due to adaptation in coping of persons that have the onset of MDD early in their lives and therefore experience less impairment. In contrast, a younger age at onset of MDD was associated with more disability on getting along WHODAS sub domain, suggesting that an early onset impairs the social skills somehow. In sum, these results suggest that age of onset of MDD has opposite effects on specific aspects of disability.

Although the illness characteristics of melancholic, atypical and manic features were associated with disability, in particular the WHODAS domains, nearly all associations disappeared in the multivariate analysis. Thus, the univariate associations are largely explained by the MDD symptom severity. This indicates that these symptom profiles do not
have an independent effect on disability over and above MDD symptom severity, with two exceptions. Patients with the melancholic symptom profile had more limitations in self-care and those with atypical features more limitations in work activities. Replication is needed because both could be chance findings.

Of the assessed comorbid mental disorders, only agoraphobia was significantly associated with more WHODAS disability, when controlling for MDD symptom severity and other characteristics. Surprisingly, MDD patients with comorbid panic disorder had fewer limitations in communication, household and work activities then MDD patients without panic disorder. Because we adjusted for MDD severity, this cannot be due to less severe depression in the context of comorbid panic disorder. Perhaps depressed panic disorder patients are more reluctant to give up their household and work activities, but this a post hoc speculation.

With the exceptions mentioned above, the univariate associations of comorbid anxiety disorders are largely explained by the severity of MDD, giving support to the idea that anxiety and depression are often intertwined illnesses. Having dysthymia (‘double depression’) showed no multivariate association with any of the disability measures. This contradicts several previous studies that found double depression to be more disabling than MDD alone.19,34,35 is probably due to the fact that we included a sensitive depression severity measure, which may also reflect dysthymia if present, and other time-related characteristics of MDD, which are associated with the diagnosis of dysthymia.

This study has some advantages over previous research performed on this topic. First of all, we used diverse measures of disability. The purpose of this was to make distinctions between the effects of features of MDD on measures of disability that differ in conceptual and operational distance from MDE symptoms. This issue is often neglected in similar studies. Secondly, we included multiple characteristics of MDD in combination with the most prevalent comorbid mental disorders in one model. Including multiple factors simultaneously reduces the chance of spurious findings and it thus provides more valid results. However, it may be possible that some effects are underestimated due to correlations among the predictors, though no signs of harmful multicollinearity were encountered in the analysis. Thirdly, we have a large sample of participants with a current diagnosis of MDD, allowing including multiple factors in one model, without over fitting it.

Besides, the study has some limitations. The disability measures are all based on self-report, where peer-reported disability might have provided additional information. Another limitation is that the self-report questionnaires were filled in prior - in some cases up to some weeks - to the actual interview. Since the WHODAS and IDS-SR were assessed in these questionnaires, the results may be distorted due to differences in mood status between the moment of filling in the self-report questionnaire and the time of the face-to-face interview. Another limitation of the NESDA study is the omission of CIDI section for other diagnoses than depressive, anxiety and alcohol use disorders, such as for psychosis, bipolar disorder.
(section on mania), and somatoform disorders.

In conclusion, characteristics of the MDD episode and comorbid dysthymia, anxiety disorders and alcohol dependence account for a substantial proportion of the variance in disability. Of the illness characteristics, severity of the depression was the most important factor in explaining disability. Measures of disability that are global and subjective have more conceptual overlap with depression and are better explained by symptom severity than more specific and objective disability measures. However, most variance, in particular in days out of role and work absence, is not accounted for. This supports the ICF model which proposes that in addition to illness characteristics, contextual factors (personal and environmental factors) play an important role in the disablement process.
References


