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Longitudinal Associations Between Depression and Functioning In Midlife Women

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Abstract

Associations between depression and impaired functioning are well known and have been documented in numerous clinical, primary care and epidemiological studies. Reviews of this research have focused on the elderly. Recent studies suggest that women become increasingly vulnerable during the menopausal transition to declines in physical and role function and increases in depressive symptoms. The purpose of the current research is to review the literature since 1966 for studies examining the association between depression and physical and psychosocial impairment in midlife women. We selected only longitudinal studies that had the potential to elucidate the nature of the complex relationship between depression and functioning. Results of the review indicate evidence for bi-directional associations between depression and functioning in middle-aged women. However, the studies are only broadly informative. Most adjusted for only a limited group of factors that could be associated with both depression and functioning. None of them directly examined potential moderators or mediators of the relationship between depression and impaired functioning.

Keywords

Depression; functioning; females; middle-aged; longitudinal

1. Introduction

Associations between depression and impaired functioning are well known and have been documented in numerous clinical, primary care and epidemiological studies [1,2,3,4,5,6]. Seminal work conducted in the Medical Outcomes Study (MOS) of 11,242 outpatients demonstrated that patients with either current depressive disorder or depressive symptoms only

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Dr. Lanza di Scalea conducted the computerized literature searches, reviewed the first group of abstracts, contributed to the content of the tables and reviewed the first drafts.

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had similar or worse physical, social, and role functioning than patients with eight major chronic medical conditions including hypertension, diabetes, coronary artery disease, and arthritis [2]. Subsequent cross-sectional studies of primary care and community populations of varying ages and longitudinal studies of the elderly have replicated the findings of the MOS [7,8,9].

The relationship between depression and functioning is complex for several reasons, including the reciprocal nature of and the extent of confounding in the association between the two. Major depression is defined in part by reduction in functioning (e.g. changes in psychomotor activity, decreased enjoyment in and ability to concentrate on interpersonal and work activities). Compromised functioning before or after a depression diagnosis may represent, respectively, prodromal or residual effects of depression. Further, depressed individuals often engage in unhealthy lifestyle behaviours associated with poorer health (e.g. smoking, lack of exercise), and report somatic symptoms (e.g. sleep disturbances and fatigue) which may exacerbate symptoms of some medical conditions and ultimately lead to compromised functioning.

On the other hand, longitudinal studies of the elderly have found that physical disability or limitations is associated with subsequent depression [10,11]. This finding is not surprising given that alterations in functioning, (e.g., carrying out daily activities and responsibilities), is a significant stressor and a well-established risk factor for depression. Furthermore, disability is often the consequence of a medical condition, such as arthritis or cardiovascular disease, which may be associated with depression independent of functional effects. Finally, some studies of the elderly suggest that depression may have a synergistic effect with initial impairment that accelerates the disability process as described above [12], reflecting the interrelatedness and reciprocal nature of the association between depression and functioning.

Depression in its many forms (i.e., symptoms, syndromes and disorders) is highly prevalent in women [3] and thus, the relationship between depression and functioning is particularly relevant for them. Although a number of reviews examined studies of depression and impaired functioning [13,14,15] among the elderly (≥ 65 y.o.), none have addressed the middle-aged (40 - 65 y.o). Because of the qualitative and quantitative differences in the functioning and physical health of elderly and middle-aged women, it is likely that the relationship among depression, functioning and medical conditions may also vary. Furthermore, recent studies suggest that women become increasingly vulnerable to declines in physical and role function and increases in depressive symptoms during the menopausal transition and after [16,17,18,19,20].

Because of the complexity of the bi-directional and confounding relationship of depression with functioning, we include only longitudinal studies in the current review as they are the best way available to try to disentangle the relationship. The specific objectives of this review are to evaluate (1) the evidence for a prospective association between depression and subsequent impaired functioning, (2) the evidence that impaired functioning is a risk factor for later depression, and (3) what type of functioning is most consistently associated with depression among midlife women.

2. Method

2.1. Domains of disability

In this review, we include studies that used self-reported physical and psychosocial functioning. These include restrictions or limitations in performing activities of daily living (i.e. self-care or tasks related to independence) as well as impairments in role function. Because prevalence of chronic medical conditions and disability are lower in middle-aged populations than in the elderly, in addition to physical disability, this review covers functional endpoints in multiple psychosocial domains and role limitations in work, spousal/partner relationships, interpersonal

relationships, housekeeping, and caregiving. Role function may be more important for middle-aged than for older women because the middle-aged are more likely to be employed and to have family and caretaking responsibilities.

2.2. Definitions of depression

We include only studies that assess depression with a standard measure as a medically defined syndrome known as clinical depression (major depressive disorder or minor depression (subthreshold depression)) or as a group of symptoms that cluster together to indicate levels of depressive symptoms or a syndrome of depression.

The methods we used to identify and review published studies are described below. Three issues are noteworthy. First, although we focus on midlife (i.e., 40-65 years), many studies included wider age ranges [21,22]. Second, some studies followed participants for many years (e.g., 8 years [23]; 25 years [24]) which meant that some participants could have been middle-aged at the start of the study and some at the end. Third, very few studies either included only women or presented results separately for men and women. Because of the limited number of longitudinal studies, we decided to include those studies in which at least 40%-50% of the sample was 40-65 at some point during the study, and in which at least 50% of the sample was female.

2.3. Data sources and search terms

PubMed, Medline, and PsychINFO were searched for articles published between January 1966 and April 2009. The initial search was based on the identification of titles and abstracts containing an appropriate combination of the following search terms: functioning/impairment/disability (physical, psychological, psychosocial, role), depression, longitudinal/cohort/prospective, epidemiological/community sample/population based/general population, primary care/general health care, female/women, middle-aged. Keyword truncation (i.e. depress*) was used to account for possible variations (e.g. depressive symptoms, major depression). Additional articles were identified from reference lists of reviewed articles.

2.3.1. Inclusion criteria—The inclusion criteria for this review were : 1) peer-reviewed English-language articles, 2) longitudinal design, 3) community based or primary care setting (studies conducted in psychiatric settings have been excluded), 4) sample size of 200 or more with at least 50% females; 5) age range 40-65 or mean age 40-65 years or approximately 50% or more of the sample were in this range and analysis adjusted for age; 6) standardized measures of depression.

2.3.2. Procedure—Two thousand five hundred ten titles were generated in the initial search based on functional and depression search terms, Follow-up steps were conducted as described in Figure 1. In brief, 1182 abstracts were identified and reviewed to determine whether study design criteria were met. Seventy eight abstracts were read and papers excluded if the studies did not meet sample size, age, and gender criteria. Of the 78 abstracts, 37 papers were read in full and 14 studies were found to meet all the inclusion criteria.

3. Results

A total of 14 articles representing 11 cohorts met criteria and were reviewed. Duration of follow-ups ranged from 12 months to 25 years. We organized studies into three groups: 1) depression as the predictor of later functioning (Table 2), 2) functional status as the predictor of subsequent depression (Table 3), and 3) both depression and functioning as predictor and outcome (Table 4). Table 1 describes measures of functioning and depression used in the reviewed studies.

3.1. Depression predicting functional status

Eight studies, seven conducted in community populations [23,24,25,26,27,28,29] and one in general health care [30], examined the association of baseline depression with subsequent functioning. Two community studies assessed major depressive episode (MDE) [25,26] and five assessed depressive symptoms [23,24,27,28,29]. The general health care study assessed clinical depressive disorders [30]. Numbers and timing of follow-up assessments varied from 1-4 follow-ups and ranged from 2 years to 25 years between them.

All 8 studies reported that baseline depression was significantly associated with some aspect of impaired functioning at follow-up. However, not all functioning and disability outcomes were significant. Additionally, the covariates and confounders included in analyses varied among the studies as did the timing of their collection.

3.1.1. Studies of activities of daily living (ADL)/physical functioning—Dunlop [26] evaluated more than 6,000 men and women, aged 54-65 years, in a population-based national sample from the Health and Retirement Study (HRS) free of ADL disability at baseline of which 7% met criteria for MDE according to the Composite International Depression Interview-Short Form (CIDI-SF). After two years of follow-up, adjusted analyses indicated that the prevalence of incident ADL disability was twice as high among the initially depressed as the non-depressed. The effect of depression on ADL disability did not differ by gender or race/ethnicity (African American or Hispanic) in the fully adjusted model. Importantly, the study did not control for depression status at follow-up.

In the Beijing Longitudinal Study of Aging (BLSA) cohort of residents, ≥ 50 years, those without ADLs or Instrumental Activities of Daily Living (IADLs) at baseline in 1992 were followed for 8 years and assessed every two years [23]. At baseline, 16.6% had a CES-D score ≥ 16 . Multivariable analyses, adjusted for baseline covariates, showed that at the end of 8 years of follow-up baseline depression was associated with relative risks of 2.20 for ADL disability and 4.29 for IADL disability. Among the incident ADLs, only difficulty bathing varied significantly between the depressed and non-depressed. In contrast, all the IADL items were significantly more prevalent among the depressed than the non-depressed. Depression at the 3-follow-ups was not included in the analyses and thus, it is possible that depression concurrent with functioning confounded the observed relationship between baseline depression and follow-up functioning.

A third study conducted among an HRS sample of nearly 8,000 participants, aged 50-61 years, included three follow-ups two years apart after the 1994 assessment, and was primarily interested in the effect of depressive symptoms and comorbid pain assessed at baseline on multiple functional outcomes [27]. The sample included only those without ADL limitations at baseline. Results of adjusted analyses showed that depression without pain was only significantly associated with limitations in ADLs in 1996, OR=1.51, compared to those with no depression or pain. Severe pain alone and depression plus mild, moderate, or severe pain were associated with greater risks of ADL limitations, ORs = 5.15, 4.89, 6.37, respectively. The study did not control for depression status at follow-ups.

The Upper Bavarian Study (UBS) conducted a 25 year follow-up of 465 women, mean age at baseline, 34 -41 years, who were originally part of a representative community sample [24]. Of these, 106 had depressive syndrome, 246 had depressive symptoms that did not meet criteria of MDE in the last seven days, and 251 reported no depressive symptoms. Disability at 25-year follow-up was assessed with the WHODAS II. Results showed that compared to controls, those with depressive syndrome at baseline had significantly higher scores on a scale that measured ability to get around but not one measuring self-care. Findings for men were non-

significant. A major limitation in this study is the absence of adjustments for functioning at baseline, depression at follow-up, and chronic medical conditions at baseline and follow-up.

The Whitehall II Study [28] examined the association between depressive symptoms and subsequent changes in domains of functioning measured by the SF-36 in 2,489 British women, aged 39-64 years, over an eight to ten year period. Women were recruited as part of a larger prospective study of employed persons from 20 London-based civil service departments. The analyses adjusted for earlier age and employment grade (an indicator of socioeconomic status). Results showed declines in all scales of the SF-36 for both perimenopausal and postmenopausal women. Declines on the physical functioning scale were small, however, 1.5 -3.4 points among those with a lot of depressive symptoms compared to those with none. No adjustments were made for medical conditions and depression at follow-up.

The Medical Outcome Study (MOS) of patients in a General Medical practice used the MOS SF-36 at baseline and two year follow-up to assess multiple domains of functioning within four groups of depressive disorders and among those with chronic medical conditions [30]. Of the 1556 patients, 428 had some type of depressive disorder at baseline: subthreshold, major, dysthymia, and double depression (i.e. major depressive episode superimposed on dysthymia). Baseline and two year physical functioning scores adjusted for age, gender, ethnicity, system of care, and comorbid medical conditions were similar and did not differ significantly among the different depressive disorders. Thus, the association of different depressive disorders with subsequent physical functioning remained fairly stable over two years, but whether this was due to the persistence of depression during this time or its presence at two years post baseline cannot be determined as the study did not control for depression status at follow-up.

3.1.2. Psychosocial/Role functioning—Six studies in community populations examined perceived functioning in employment and regular activities roles. In the UBS, role functioning as assessed by the Life Activities scale of the WHODAS II (i.e. domestic responsibilities, leisure, and work), was significantly worse at follow-up among the depressed women compared to controls [24]. However, only age at study entry was controlled in the analysis.

The MOS [30], the Whitehall II [28], and the Study of Women's Health Across the Nation [25] assessed role functioning with scales from the SF-36. The aims of the studies were different and yielded different results. The MOS aimed to evaluate and compare the persistence of and change in functional limitations associated with depression or chronic medical conditions among general health care patients over two years. Role limitations due to physical health (SF-36 role physical) were significantly worse for dysthymia than the other depressive disorders at both assessments, but did not change for each of the disorders over the two years of follow-up. Role limitations due to emotional problems (SF-36 role emotional) were significantly greater in the dysthymic and those with double depression than those with subthreshold depression and over two years, decreased in those with major depression and double depression but increased in those with dysthymia [30]. As noted above, whether the patterns of role functioning at baseline and follow-up were due to earlier depression, its persistence or its recurrence at follow-up cannot be determined because depression at follow-up was not included in the analyses. The Whitehall II study evaluated the association of initial depressive symptoms with changes in role functioning in middle-aged women over 8-10 years [28]. Results of this study showed significant increases in role physical and emotional limitations among depressed individuals compared to non-depressed over the follow-up period. Analyses did not control for medical conditions.

The SWAN study [25] sought to determine whether past depression was associated with subsequent functioning in the absence of concurrent depression in a community based sample of 780 midlife pre- and early perimenopausal women, aged 42-52. Data on role limitations were

collected at baseline and the assessment of lifetime psychiatric disorders was also conducted at baseline with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). The authors found no significant associations between past subthreshold or major depression with either baseline role physical or role emotional in analyses adjusted for race/ethnicity, hot flashes, history of panic disorder or alcohol abuse/dependence. Number of chronic medical conditions was relatively low and not significantly related to role functioning. SWAN could only compare functioning among women with different past exposures to depression because it did not have data on past functioning measures. While there could be some misclassification of diagnoses, it is unlikely that perceived functioning would influence reporting of past disorders.

Two studies, the Health Study of Nord-Trondelag County (HUNT-2) [29] and the Health and Retirement Study (HRS) [27], specifically evaluated the relationship between depressive symptoms and work-related functioning using disability pension award [29] and onset of work disability and loss of employment [27] as outcomes. The Hunt study consisted of more than 37,000 Norwegians, half of whom were women, with a mean age of about 42 years, and employed. Its primary aim was to determine the relative effect of depressive syndrome and insomnia on the awarding of a medically certified disability pension 18-48 months later. Results of analyses comparing four groups with and without insomnia and/or depression adjusted for gender, age, somatic disease, pain, education and SES, and health behaviors showed that the depression only, the insomnia only and the depression and insomnia groups were all at significantly greater risk of receiving a disability pension than the group without either disturbance [29]. Neither study controlled for depression status at follow-up.

The HRS study of 4,850 employed individuals, 50 to 61 years, aimed to determine the odds of depressive symptoms and pain, separately and jointly, predicting employment problems or unemployment at three follow-up assessments, (i.e. 1996, 1998, and 2000) [27]. Results adjusted for multiple covariates showed that only in 1998 was depression alone a significant predictor of work-limiting health problems whereas depression plus pain was consistently significantly associated with these problems at all follow-ups. Depression alone did not predict subsequent loss of employment, but depression plus severe pain did so at all three follow-ups.

Four studies evaluated the relationship of depression and social functioning [24,25,28,30]. In the MOS, the only significant change in social functioning over time was in those with double depression, whose scores improved from 56 (out of 100) at baseline to 72 at follow-up. There were no changes within the other depressive disorders in social functioning [30]. In the Whitehall II those with depression compared to those without depression, showed a significant decline in social functioning as they did in other role functioning, (9.9-13.9 points) [28]. In SWAN, women with past recurrent major depression had a significantly greater odds of poor social functioning (bottom quartile of the scores), (OR=2.1), than those with no type of past depression [25]. The UBS study reported no significant differences in interpersonal interactions (i.e. WHODAS domain “getting along with people”) for both women and men [24].

3.2. Functional status predicting depression

Three studies evaluated domains of functioning at baseline as predictors of depressive symptoms or disorder (two primary care [21,31], and one community study [32]). Zeiss and colleagues assessed functional impairment across several domains including vision, hearing and walking mobility, using a measure developed specifically for this community study of 680 persons ≥ 50 years without MDE at baseline who were reassessed two to four years later [32]. Results showed that those with high functional impairment were more likely to develop depression subsequently than were those with low or medium functional impairment, independent of age and gender. There were no significant gender effects. In contrast, number of physical diseases was not related to depression risk. Follow-up analyses comparing

combinations of number of diseases and impairment indicated that the two groups who were highly impaired (with or without any disease) were more likely to develop depression than the non-impaired well or diseased groups.

Two studies conducted with samples from the World Health Organization (WHO) collaborative study on 'Psychological Problems in General Health Care', examined social disabilities with the GSDS [21,31]. This WHO project is a prospective study of mental disorders in primary care centers in 15 cities/countries. In the first [21], 2,445 non-depressed persons (no current MDE), aged 15-65 years, were assessed for MDE depression 12 months later. Of these, 4.4% met ICD-10 criteria for a depressive episode at follow-up. In univariate analyses, some, moderate, or severe social disability compared to no disability at baseline was significantly associated with the odds of subsequent depression (OR, ranged from 2.25 -11.54). In the stepwise logistic regression, social disability was no longer significant. However, there were multiple psychiatric and somatic factors at baseline, such as pain disorder, previous episodes of depression, an ICD-10 current disorder, high psychological distress before baseline, suicidal thoughts as well as at least two chronic diseases that were significantly associated with later MDE that may have confounded or overcontrolled for the association between social disability and risk for depression.

The second study using the WHO sample focused on 725 persons with ICD-10 depression and evaluated multiple factors as prospective predictors of a depressive episode 12 months later (persistent depression) [31]. Similar to the results for the predictors of onset depression, this study found a significant univariate association between baseline moderate or severe social disability and depression at follow-up, but not in the multivariable analyses. In this case, severe baseline depression was significantly associated with depression at follow-up (OR=3.27) and this along with suicidal thoughts of depression may have reduced the direct association between social disability and later depression.

3.3. Both depression and functioning as predictor and outcome

Three studies evaluated the reciprocal associations between depression and functioning (two community studies [22,33] and one primary care study [34]). The latter assessed among nearly 200 patients, the extent to which changes in severity of depression, anxiety, and mixed anxiety/depression were associated with changes in role disability at two follow-ups over 3.5 years. Results showed that decreases in severity of depression among those with clinical or subclinical disorder were significantly associated with improvements in role functioning, independent of physical illness, across the 3.5 years [34]. However, other potential confounders, such as age, gender, or education were not included in analyses.

The two community studies employed the NEMESIS data, a psychiatric epidemiology population-based survey of 4,796 individuals, aged 18-64 years, from the Dutch general population [22,33]. Assessments of MDE/symptoms and functioning were conducted at baseline (1996) and two follow-ups (1997 and 1999). Spijker [33] examined the relationship between duration and recovery from incident MDE between 1997 and 1999 with role and social functioning and number of weeks of sickness absence in 273 individuals. In analyses adjusted for significant covariates, compared to the total NEMESIS sample, those who developed depression between 1997 and 1999, had lower functioning prior to depression onset in 1997. These differences remained at follow up irrespective of whether the individuals recovered or were still depressed. Compared to the recovered, impairment was significantly greater among the still depressed as was number of sickness days. In those recovered from depression in 1999, shorter duration of recovery was significantly inversely associated with role emotional limitations, but the association was not linear. Social functioning and number of sickness absence days remained fairly constant over the duration of recovery.

Ormel [22] extended these findings by comparing psychosocial disability (GSDR) according to length of premorbid and postmorbid periods among those who developed a MDE between 1997 and 1999. Results showed that disability scores did not differ in 1996 and 1999, 1 year before depression onset and 1 year post remission in 1999. However, when shorter premorbid periods were compared to longer remission periods, disability was significantly greater for the former which showed the largest, though small, effect size difference of .37. The opposite results were found for the reverse, longer premorbid compared to shorter postmorbid. This suggests that impaired functioning precedes the onset of major depression in this cohort and that variation in functioning during pre- and postmorbid periods may be due to prodromal or residual depressive symptoms. An additional analysis found greater disability after than before episode onset in those with severe recurrent MDEs which might reflect the more deleterious effect of this type of depression on functioning. It appears that all analyses were unadjusted for any covariates.

4. Discussion

Despite the large literature demonstrating cross-sectional and longitudinal associations between depression and impaired functioning in the elderly, few prospective studies have followed younger individuals through midlife to old age or the middle-aged into old age to examine this association. Even fewer addressed this association separately or specifically among women who are at the greatest risk for depression and for whom midlife is marked by multiple physical, biological and psychosocial changes. To our knowledge, this is the first paper to try to review systematically and comprehensively studies of midlife depression and functioning in any gender. The majority of the selected studies focused on depression as the predictor and functional status as the outcome. In three studies both depression and functional limitations were examined as predictors and outcomes. None of the studies included objective measures of physical performance. Functional measures were all self-report. Although informative, the methodology (e.g. sample composition, measures, covariates, duration/frequency of follow-ups) varied considerably across studies.

4.1. What is the evidence for a prospective association between depression and subsequent impaired functioning?

In the eight studies that assessed depression as a predictor of later functioning, the frequencies and lengths of follow-ups ranged from one to three conducted over two to 25 years. All reported a long-term association between initial depression and subsequent functioning. Four out of six studies reported a significant association between baseline major depression or depressive symptoms and subsequent limitations in personal care activities or physical activities such as pushing a vacuum cleaner, or carrying groceries [23,24,26,28]. A fifth study found an association at only one of three follow-ups [27]. The six studies that evaluated depression as a predictor of functioning in different roles (i.e. work, household, social) [24,25,27,28,29,30] reported at least one significant result for depression as a predictor of impaired role functioning.

Several points are worth noting. Three of studies followed a sample without functional impairments at baseline which likely means that the initial depression was less severe and raises a question about the role of intervening depressive episodes or symptom levels and other unmeasured variables [23,26,27]. The one time observation of significant associations in the Emptage [27] study may reflect this dynamic as it was the groups with depression comorbid with pain or pain alone that had significantly increased risk for ADLs across all follow-ups. The UBS [24] was the weakest of all the studies, since it did not control for baseline physical disability or medical conditions, lost substantial numbers of participants to follow-up, and did not account for differential survival. The two studies that assessed change in functioning had very different cohorts. Unlike the British study that followed up a cohort of employed women

who presumably remained employed [28], the primary care patients had clinical depressive disorders with initial low functioning scores [30]. Thus, the severity of depression at baseline was much greater in the latter cohort among whom 25% of the baseline subthreshold group and more than 50% of the dysthymic group had a major depressive episode during the follow-up [30].

An important limitation in all of these studies is the absence of control for depression status at follow-ups. Because of the high concurrent relationship between depression and functioning, the absence of follow-up depression in the analyses obfuscates the interpretation of the temporal relationship between the two. Without adjusting for concurrent depression it is difficult to know whether the disability at follow-up is due to earlier or concurrent depression or to both. Similarly, not taking into account the course of depression and disability over the follow-up period limits the interpretation of results.

4.2. What is the evidence that impaired functioning is a risk factor for later depression?

Three studies that addressed impaired functioning as predictors of later depression reported mixed results. Zeiss [32] found strong and consistent associations between high functional impairment in a large community sample of middle-aged persons without MDE at baseline and depression two to four years later whether or not they had had physical diseases. The two studies from the WHO General Health Care project found significant associations in unadjusted analyses between social disability in a sample without MDE at baseline and incident MDE 12-months later [21] and between social disability in a sample with MDE at baseline and subsequent (“persistent”) MDE [31]. However, in analyses adjusted for multiple confounders, such as high psychological distress before baseline and baseline suicidal thoughts, the associations were no longer significant. These data suggest that while impaired functioning may be a risk factor for subsequent onset of depression or depression two years later (either persistent or recurrent), other factors, such as educational attainment, medical morbidity, psychiatric morbidity, history of MDE and depression severity (among the initially depressed), and education may mediate or moderate the functioning-depression relationship.

4.3. Bi-directional prospective associations?

Three studies examined bi-directional relationships between depression and functioning. One primary care study showed that over 3.5 years, decreases in severity of depression among those with clinical or subclinical depressive disorder were concurrent with improvements in role functioning independent of physical illness [34]. Both studies of the NEMESIS [22,33] sample suggest that individuals who develop depression may have lower functioning prior to and after the onset of depression whether or not they remain depressed and that premorbid and/or postmorbid functioning of less than 1 year before or after the depressive episode may reflect prodromal and residual depression, respectively. The data also suggest that a severe long lasting depression was associated with greater subsequent impaired functioning for more than one year.

4.4. What type of functioning is most consistently associated with depression among midlife women?

Two broad domains of functioning were assessed in the reviewed papers: activities of daily living/physical functioning and psychosocial/role functioning. Neither domain was more consistently associated with depression. Within domains there was inconsistency in associations between specific measures of functioning and depression whether measured as disorder or symptoms. This may be due to the absence of true differences in these associations, the variation in study designs and methods, or the differences in items or domains in measures that purported to measure the same phenomena (see Table 1).

4.5 Future research

The available literature provides evidence for longitudinal and bi-directional associations between depression and functioning in middle-aged women. However, the studies are only broadly informative. Most studies adjusted for only a limited group of factors that could be associated with both depression and functioning. None included potential confounders, such as low social support or stressful events. None of the longitudinal studies directly examined potential moderators or mediators of the relationship between depression and impaired functioning. For example, although some studies adjusted for the effects of medical comorbidity as a confounder, none assessed the potential for prior or current comorbid medical conditions to increase the effect of impaired functioning on subsequent depression or depression on later functioning. Other moderators could be race/ethnicity, socioeconomic status, or poor health behaviors, such as smoking or being sedentary. No study had significant numbers of minority participants to assess potential race/ethnic differences in the depression-functioning relationship.

For a better understanding of the reciprocal nature of the depression-functioning relationship we conclude that future research should 1) take into account potential biases in perceptions of self-rated functioning among depressed individuals by including objective measure of performance; 2) include factors that may be mediators of the depression-functioning relationship, such as biological changes (e.g., immune markers, blood pressure), treatment, stressors, poor health behaviors, especially in those studies with more than one follow-up. Increased knowledge about such factors along with more frequent follow-ups can inform understanding of how depression and impaired functioning are connected and guide clinical interventions early in the course and cycle of depression and compromised functioning.

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Figure n. 1.
Sequential process of the articles selection

Table 1

Table 1A. Measures of Depression and functioning

Measure	Description	Characteristics	Studies reviewed
Composite International Diagnostic Interview, CIDI (World Health organization, 1990) 35	Fully structured diagnostic interview to enable trained lay interviewers to make current and lifetime diagnoses of psychiatric disorders according to DSM-IV and ICD-10 criteria.	Widely used in international and national (U.S.) epidemiological studies including the National Comorbidity Surveys (NCS and NCS-R) and in primary care settings. Good reliability and validity.	21,22,24,26,33
Diagnostic Interview Schedule, DIS (Robins et al., 1981) 36	Fully structured diagnostic interview to enable trained lay interviewers to make current and lifetime diagnoses of psychiatric disorders according to DSM-III criteria. It has been adapted to assess DSM-IV criteria.	Used in many epidemiological studies throughout the world. The current version is used as a diagnostic instrument in community and clinical settings.	30
Present State Examination, PSE (Wing et al., 1974) 37	Semi-structured diagnostic interview conducted by trained clinicians, designed to assess the individual's present mental state (past month) according to DSM-IV criteria.	Used in large-scale international studies and in smaller studies. Good reliability.	34
Structured Clinical Interview for the Diagnosis of DSM-IV Axis I Disorders ,SCID (Spitzer et al., 1992) 38	Semi-structured diagnostic interview designed to enable trained clinicians to make current and lifetime DSM-IV Axis I psychiatric diagnoses	Used in many different ethnic groups. Extensive field testing has demonstrated the SCID's suitability for research purposes; adequate reliability has been demonstrated in numerous studies	25
Schedule for Affective Disorders and Schizophrenia, SADS (Endicott and Spitzer, 1978) 39	Semi-structured diagnostic interview designed to enable trained clinicians to make current and lifetime diagnoses of affective disorders and schizophrenia according to DSM-III criteria.	Used in clinical research and epidemiologic/ screening surveys; it was adapted for use in community-based longitudinal studies. Adequate reliability, validity	32
Longitudinal Interval Follow-up Evaluation, LIFE (Shapiro and Keller, 1979) 40	Semi-structured interview which obtains data on the longitudinal course of psychiatric disorders and the nature and quantity of all treatments received over time.	Used in major longitudinal studies of eating disorders and Axis I psychiatric disorders. Adequate validity, reliability.	32
Life Chart Interview, LCI (Lyketos et al., 1994) 41	Semi-structured interview conducted by trained clinicians which utilizes autobiographical memory cues, age, and life changes as anchors to obtain retrospective information about the course of a disorder.	Used in community based studies to determine the course of psychopathology. Test-retest and interrater reliability of a similar life chart instrument were satisfactory.	22,33
General Health Questionnaire, GHQ (Goldberg, 1972) 42	Self-report questionnaire available in a variety of versions using 12, 28, 30 or 60 items that identify psychological symptoms in the past few weeks. Each item is scored from 0-3, typically being 'not at all', 'no more than usual', 'rather more than usual' and 'much more than usual'. Scores are totaled and a cut-off of 4 identifies 'psychiatric caseness'.	Designed as a screening tool to detect psychiatric disorders in community settings and non-psychiatric clinical settings, such as primary care or general practice. Adequate validity, reliability.	28
Center for Epidemiologic Studies Depression Scale, CES-D (Radloff, 1977) 43	A 20-item self-report questionnaire that asks about the frequency with which each depressive symptom was experienced during the week prior to the interview. Response categories indicate the frequency of occurrence of each item, and are scored on a 4-point scale ranging from 0 (rarely or none of the time) to 3 (most or all of the time). Total scores range from 0-60. A score of ≥ 16 is often used as the cut-off for potentially significant depressive symptoms	It was designed to measure severity of depressive symptoms in community samples and has been used extensively for research purposes in non-psychiatric populations. Good reliability and validity across a wide variety of demographic characteristics in the general population .	23,27,32
Hospital Anxiety and Depression Scale Depression items, HADS-D (Zigmond et al., 1983) 44	Self-report questionnaire comprising 14 four-point likert-scaled items, of which 7 measure depression. It assesses how the respondent has felt in the week prior to the interview. A cut-off score of 8 on the depression subscale defines caseness	Originally intended for use in screening patients in a general hospital setting, it was found to assess well severity and caseness of depression in primary care, and general hospital patients, and in the general population.	29

Table 1B. Instruments used to measure Functioning/Disability.

Measure	Description	Characteristics	Studies reviewed
World Health Organization Disability Assessment Schedule II, WHODAS II (World Health Organization, 1992) 45	36 -item fully structured interview to enable lay interviewers to assess functioning. It asks about difficulties in <u>six domains</u> of life during the last 30 days including: moving and getting around (mobility), self care (attending to one's hygiene, dressing, eating and staying alone), getting along with people (interpersonal	All questions have good sensitivity, specificity, reliability, validity and cross-population comparability and sensitivity to change. The authors provided no information on which version of the WHODAS II was used, i.e., self-administered versus interviewer	24

	interactions), life activities (domestic responsibilities, leisure, and work), participation in society (joining in community activities). For all domains the WHODAS gives profiles and a single summary score.	administered and 12- or 36-item version, although, only the latter provides scores on domain.	
Activities of daily living (ADL) Scale (Katz Index of ADL: Katz, 1970) 46 and Instrumental Activities of Daily Living (IADL) (Spector et al, 1987) 47	The items assess difficulty in at least one of the following 6 basic activities of daily living (ADL): feeding, grooming, dressing, transferring, bathing, moving about inside home. Individuals are scored yes/no for independence in each of the six functions. A score of 6 indicates full function, 4 moderate impairment, and 2 or less severe functional impairment. IADL: items vary but include functional limitations in performance of physical tasks e.g. walking several blocks, climbing several flights of stairs without resting, shopping, cooking, lifting heavy objects, managing money.	Used among older adults in a variety of care settings. Although no formal reliability and validity reports could be found in the literature, it has demonstrated its utility in evaluating functional status in the elderly populations. An additional scale for instrumental activities of daily living (IADL) was included with the ADL in some versions.	23,26,27
Short Form-36 (SF-36) (Rose et al., 1999, Ware, 1992) 48, 50	Self-report questionnaire that yields subscales describing physical health and mental health: <u>physical functioning</u> , <u>role limitations</u> due to physical health, <u>role limitations</u> due to emotional problems, <u>bodily pain</u> , <u>general health</u> , <u>vitality</u> , <u>social functioning</u> , and <u>mental health</u> . The SF-36 subscales are frequently dichotomized using the 25 th % of the sample as the cut point between good and poor functioning ↑ scores = ↑ functioning.	Used throughout the world in surveys of general and specific populations to evaluate health benefits of different treatments and to compare the relative burden of chronic diseases). The subscales have good reliability and construct validity.	28,30
Groninger Social Disability Schedule, GSDS (Wiersma et al., 1988) 49	Semi-structured interview conducted by trained clinicians focusing on disability in 8 roles for the month preceding the interview (self-care role, family role, kinship role, partner role, parental role, citizen role, social role, work role). The interviewer rates each role as: no disability (0), a slight disability with only minimal negative consequences for the patient or others (1), a clear disability with negative consequences for the patient or others (2), a severe disability requiring professional help (3).	Used in primary care general populations and psychiatric settings. It has good reliability and validity	21,22,31,34
Global assessment of Functioning Scale, GAF (DSM-IV, APA, 2000)	Numeric scale (0 through 100) used by mental health professionals to subjectively rate the social, occupational and psychological functioning of adults. It is included in the DSM-IV	Used extensively in clinical practice and research. Adequate reliability, validity	24
Physical Functioning	Composite measure using the following self-report variables: vision, hearing, disabilities other than hearing or vision, impact of health problems, ability to walk.	Developed by investigators	32
Disability pension awards	Disability pension awards (Disability pension award in Norway 18 to 48 months after the survey) as a measure of role disability.		29
Work role disability	Investigators used their own measures of role disability: Onset of work disability (do health problems currently limit them in the type or amount of paid work that they can do); Changes in employment status from "working" to "not working".		27

Table 2

Depression as Predictor of Later Functioning

Study	Design	Sample	Depression Measure(s)	Functioning/Disability Measure(s)	Covariates	Outcome	Results
Hays et al., 1995 30 Medical Outcome Study (MOS)	General medical sector, 2 assessments: baseline (T1) and 2-year follow-up (T2)	N=428 with depression, mean age (SD)=55.5 (16.3), 60.5% F, (16.5% with subthreshold depression, 5.6% with major depression, 3.7% with dysthymia, 4.1% with double depression).	DIS at T1	SF-36 at T2 subscales: role limitation due to emotional problems or to physical problems, social functioning, physical functioning	Baseline age, education, income, gender, ethnicity, site, medical comorbidity	SF-36 subscales at T2	Over two years, mean (SD) scores of physical functioning were similar for all depression groups ($p>.05$), role limitations due to emotional problems increased in dysthymia, mean (SD) scores, $T1=64$ (9); $T2=42$ (10) and decreased in MDE [$T1=41$ (6); $T2=62$ (7)] and double depression [$T1=32$ (6); $T2=46$ (7)]. Mean (SD) score in social functioning ↑ over time only in double depression [$T1=56$ (4); $T2=72$ (5)] ($p<.05$)
Jiang et al., 2004 23 Beijing Longitudinal Study of Aging (BLSA)	Population-based, 8-year follow-up, 4 assessments: baseline (T1), and 2 (T2), 5 (T3), 8 (T4) -yr follow-ups	N=1828, N= 687 in the age range group 55-64, 49.7% F. All individuals were free from ADL and IADL disabilities at baseline	CES-D at T1, ADL at T2, T3, T4	ADL at T2, T3, T4	Baseline age, gender, marital status, education, region of residence, economic status, depression, chronic diseases (hypertension, heart disease, arthritis, cerebrovascular disease, diabetes, cancers), having intimate friends, quality of family relationships	Onset of ADL disability during 8-years of follow-up	Depression was associated with ↑ risk of ADL and IADL disability onset: Adj. Relative Risk (95% CI) of ADL disability onset at 8-year follow-up was 2.2 (1.33, 3.62) and of IADL was 4.29 (2.08, 8.86). All differences in IADL items were sig. ($p<.0001$). Only "difficulty in bathing" was sig. different between depressed and non-depressed (4.5% for non-depressed, 17.3% for depressed) ($p<.0001$)
Dunlop et al., 2005 26 Health and Retirement Study (HRS)	Population-based, 2 assessments: baseline (T1) and 2-year follow-up (T2)	N=6871, age range=54-65 years, 52.2% F, All individuals were free from ADL disability at baseline.	CIDI-SF at T1	ADL at T2	Baseline gender, race, age, marital status, lived alone, education, wealth, family income, number of chronic diseases, functional limitations (difficulty in walking several blocks, climbing, pulling/pushing heavy objects, lifting/carrying heavy objects (IADL disability)	Onset of ADL disability at T2	↑ risk of ADL disability onset in depressed compared to non-depressed at baseline: Adj OR (95% CI), 2.04 (1.34, 3.09)
Emptage et al., 2005 27 Health and Retirement Study (HRS)	Population-based, 6-year follow-up, 4 assessments: baseline (1994=T1), 2 yr (1996=T2), 4 yr (1998=T3), and 6 yr follow-up (2000=T4)	N=8,280, mean age = 57 yrs, 54.5% F. For outcome ADL, no ADL disability at baseline, for outcome work limitations, no work disability at baseline. 5 groups (Ns vary): depress. only, mild/moderate pain only, severe pain only, depress. + mild/moderate pain, depress. + severe pain	CES-D at T1, work disability, changes in employment status, before each interview at T2, T3, T4	ADL, onset of work disability, changes in employment status, before each interview at T2, T3, T4	Baseline age, race, gender, yrs of education, marital status, employment status, household income. Follow-ups - number of chronic health condition during the previous 2 years.	Onset of ADL disability, work disability, change in employment status, at T2, T3, T4	Compared to no depression group: (1) depression only was associated with ADL disability (OR=1.51, $p=.03$) at T2 and with work disability at T3 (OR=1.39, $p=.03$) (2) depression with pain and pain alone were associated with ADL disability at T2, T3, and T4 (ORs ranged from 1.90-6.37, $ps=.01$) and with work disability at T2, T3, and T4 (ORs ranged from 2.09 – 5.37, $ps=.01$) (3) among those employed at baseline, odds of employment at follow-ups were sig. less only in depression with pain group at T2 and T3 (OR=.42 and .45, $ps\leq.02$)
Kumari et al., 2005 28 Whitehall II Study	Population-based, 8 to 10-yr. follow-up, 4 assessments:	N=2489 F, age range =39-64, mean = 51.4 yrs.	PHQ at T1	SF-36 at T1, T2, T3, T4 subscales: role	Baseline age and employment grade (administrative, professional/executive,	Change in SF-36 subscales scores from	Compared to non depressed, depressed women reporting "a lot" of depression had a sig. greater decrease in mean scores (SD) of physical functioning [-15 (1.1), $p\leq.05$], role

Study	Design	Sample	Depression Measure(s)	Functioning/ Disability Measure(s)	Covariates	Outcome	Results
	baseline (1991-1993=T1) and every 2 yrs (1995=T2; 1997-1999=T3; 2001=T4)			limitations due to emotional problems or physical problems, social funct, physical funct	clerical/support, missing)	T1-T4	limitation due to emotional problems [-18.4 (2.3), p<.001], role limitation due to physical problems [-4.9 (2.4) p<.01], social functioning [-13.9(0.9) p<.001]
Bromberger et al., 2005 Study of Women Across the Nations (SWAN)	Population based, 2 assessments: baseline (T1) and 2-9 months later (T2)	N=922, age range=42-52 years, 100% F	SCID 2-9 months after the data on health and functioning	SF-36 at T1 subscales: social functioning, pain	Baseline race/ethnicity, hot flashes, history of panic disorder or alcohol abuse/dependence	Social and Role functioning (SF-36) at T1	Past recurrent MDE was associated with ↑ odds of low social function. at baseline: OR (95% CI) from adj. analysis for low social funct among women with past recurrent MDE compared to those with no past depression was 2.1 (1.20-3.80) (p=.05)
Fitcher et al., 2008 24 Upper Bavarian Study (UBS)	Population-based, 25-year follow up, 3 assessments: baseline (T1), and at 5 (T2), and 25-year follow up (T3)	N= 465 F, age range 34-41 yrs. (n=106 with depressive syndrome, n=246 with depressive symptoms, n=251 with no depression)	SPI at T1, T2, T3, and CIDI at T3	GAF at T3 and WHODAS II at T3 domains: getting around, self-care, getting along with people, life activities, participation in society	Age at baseline	WHODAS II and GAF at T3	At T3 women with depressive syndrome had a ↑ mean (sd) score (more impairment) in "getting around" [1.55 (0.89)] and in "life activities" (role functioning) [1.46 (0.87)] compared to controls [1.21(0.43)] and [1.25 (0.66), respectively. Differences in "self-care" score were not sig. (p>.05)
Overland et al., 2008 29 Nord-Trøndelag County in Norway (HUNT-2)	Population-based, 18-48 month follow-up	N=37,302, age range=20-66 yrs, 53.4% F; 4 groups: 1) Insomnia only (N=2999); 2) depression only (N=2137); 3) depression + insomnia (N=800); 4) neither insomnia nor depression (N=31,336)	HADS at baseline	The National Insurance Administration Disability Pension Award was obtained 18-48 months after the survey.	Baseline age, gender, current job, yrs of education, smoking, alcohol, physical activity, pain for 3 months during the last year, self-report somatic disorders, blood pressure	Disability Pension Award	Depression only, depression + insomnia, insomnia only associated with ↑ risk for disability pension award. Adj. OR (95% CI) were 1.56(1.24-1.96), 2.76(2.11-3.61), and 1.66 (1.37-2.01), respectively.

Abbreviations. DIS= Diagnostic Interview Schedule, CES-D= Center for Epidemiologic Studies Depression Scale, ADL= Activities of Daily Living Scale, CIDI-SF= Composite International Diagnostic Interview-short form; GHQ= General Health Questionnaire; SCID= Structured Clinical Interview for the Diagnosis of DSM-IV Axis I Disorders; SPI= Standardized Psychiatric Interview; WHODAS II = WHO Disability Assessment Schedule II; GAF= Global Assessment Functioning Scale; HADS= Hospital Anxiety and Depression Scale Depression items; OR=Odds Ratio; Adj=Adjusted; Sig=Significant.

Table 3

Functional status predicting depression

Study	Design	Sample	Depression Measure(s)	Functioning/Disability Measure(s)	Covariates	Outcome	Results
Zeiss et al., 1996 32	Population-based, 2 assessments: baseline (T1), and after 2-4 year follow-up (T2)	N=680, ≥ 50 yrs, means = 62-65 yrs, >50 % F, without MDE at baseline. 3 groups by impairment: Low (n=327); Medium (n=177); High (n=176)	SADS at T1 and T2, LIFE at T2.	Developed by investigators. Self-reported physical disability measures at baseline: vision, hearing other disabilities, impact of health problems, ability to walk	Baseline age, gender	Depression onset at T2	functional impairment was associated with ↑ risk of depression onset at T2 [sig difference between "low" and "high" (p<.001), and between "medium" and "high" (p<.05)]. Mean survival time (months) to onset of depression for the 3 groups was 43 (low impair), 41.9 (medium impair), 38 (high impair), respectively, (p<.01). Physical illness was not associated with onset of depression (p>.05)
Barkow et al., 2002 21 WHO collaborative study on "Psychological Problems in General health Care"	Primary-care, 2 assessments: baseline(T1) and 12-month follow-up (T2)	N=2,445; 15-65 yrs, mean (SD)= 40.64(13.45), 63.5% F. Participants did not meet ICD-10 criteria for current MDE at baseline.	CIDI at T1 and T2	Social disability (GSDS) at T1	Gender, age at follow-up, site	MDE at T2 (ICD-10 criteria)	MDE at T2. OR (95% CI) of MDE from univariate analysis at T2 for patients with some, moderate, and severe social disability were 2.15 (1.46-3.18), 3.32 (2.2-5.01), 4.8 (2.50-8.82), respectively (P<.001) at baseline. In stepwise logistic regression social disability was no longer sig.
Barkow et al., 2003 31 WHO collaborative study on "Psychological Problems in General health Care"	Primary-care, 2 assessments: baseline (T1) and 12-month follow-up (T2)	N=725 with ICD-10 MDE, age range=15-65 years, 73.7% F	CIDI at T1 and T2	Social disability (GSDS) at T1	Gender, age at follow-up, site	MDE at T2 (ICD-10 criteria)	In univariate analyses moderate and severe disability at T1 were associated with ↑ risk of MDE at T2 [OR (95% CI) =1.79 (1.06-3.02) and 3.13 (1.73-5.66) (p<.001), respectively]. In stepwise logistic regression only severe disability at T1 was associated with ↑ risk of MDE at T2 [OR (95% CI) =3.27 (1.90-5.61) (p<.001)]

Abbreviations. SADS=Schedule for Affective Disorders and Schizophrenia; LIFE= Longitudinal Interval Follow-up Evaluation; CES-D= Center for Epidemiologic Studies Depression Scale; MDE= major depressive episode; CIDI= Composite International Diagnostic Interview; SDS= Social Disability Schedule; Sig= Significant.

Table 4

Depression and functioning as predictor and outcome

Study	Design	Sample	Depression Measure(s)	Functioning/Disability Measure(s)	Covariates	Outcome(s)	Results
Ormel et al., 1993 34	Primary care study, 3 assessments: baseline(T1), 1 year (T2), and 3.5-year follow-up(T3)	N=285, age range=16-65 yrs, >50% F. 194 recent and remote onset depressed cases (PSE ≥3) and 91 non-cases. Non-cases were excluded at T2 and T3	PSE at T1, T2, T3	Social disability (GSDS) at T1, T2, T3	Severity of physical illness (assessed at T1, T2, T3)	Association between changes in depression (improvement=50% or more decrease in mean of follow-ups from baseline) and disability level at T2 and T3	At baseline, mean disability scores were sig. ↑ in cases (1.23-1.57) than non-cases (.43). Longitudinal analysis showed sig. interaction between time and improvement status (F=50.1, p<.001). Patients whose symptoms improved had ↓disability scores at follow-up than unimproved patients.
Spijker et al., 2004 33	Population-based study, 2 assessments: baseline (1997=T1) and 2-year follow-up (1999=T2)	Total N=4796, Depressed N=273, mean age (sd)=41.7 (10.7), 66.8% F. Onset of MDE between T1 and T2 and no 1-month prevalence of MDE at T1. At T2, 69 still depressed, 181 recovered.	CIDI at T1 and T2, LCI at T2 to determine persistence or relapse between T1 and T2	SF-36 (social functioning, role limitation due to emotional problems) higher scores = better functioning, and absence days from work at follow-up	Gender, age at one year before baseline	Social and role functioning at T2, absence days from work between T1 and T2.	Compared to total sample; those who developed MDE between T1 and T2 had ↓ functioning at T1 whether or not they had recovered at T2; mean scores (SD) of role limitations due to emotional problems at T1: depressed = 80.9 (34.2); recovered = 76 (38.1); NEMESIS=92.7 (22.5) p<.001. Shorter duration of recovery from MDE was associated with ↑ role limitations due to emotional problems: mean score (SD) of role limitation due to emotional problems by recovery duration (months) at T2: ≤3 =62.1 (42.4); 3-6 = 83.3 (36.8); 6-12= 95.7 (17.4); 12-24= 81.4 (35.9), p<.001. Change in social functioning and number of absence days from work was not sig. associated with duration of recovery.
Ormel et al., 2004 22 (NEMESIS)	Population-based study, 3 assessments: baseline (1996=T1), 1-year (1997=T2) and 3-yr follow-up (1999=T3)	N=4,796, age range=18-64 yrs. In MDE groups, mean age= 41 yrs, 53.5% females. 3,736 never depressed, 409 onset MDE between T2 and T3, 334 remitted at T3.	CIDI at T1, T2, T3; LCI at T3	GSDS at T1, T2, T3 domains: spouse/partner, employment, housekeeping, leisure time	No covariates	Depression and disability levels at T2 and T3	T1 mean disability scores were sig ↑ in the remitted first MDE group than in the never MDE group. Total disability score was ↓ before the MDE onset than during episode. Mean (SD) scores before episode were 12.03 (3.06) and during 13.42(3.38) (p=.01) in first MDEs. All domains except housekeeping also ↑ during MDE (ps<.05). Overall, pre- and postmorbidity disability scores did not differ, but differences in length of premorbid and postmorbidity periods were associated with differences in disability scores. Long (>1yr) premorbid (T1) compared to short (<1yr) postmorbidity (T3) had ↓disability score T1 (11.22) ; T3 (11.91) (p=.049). Short premorbid compared to long postmorbidity had ↑ disability scores, T1 (11.80), T3 (10.74) (p<.001). Severe depression had long term effect on disability: Before-after disability comparison for severe depression (total disability score=11.41 vs 12.38; ES= 0.37; 95% CI: 0.09-0.65)

Study	Design	Sample	Depression Measure(s)	Functioning/Disability Measure(s)	Covariates	Outcome(s)	Results
Abbreviations. PSE= Present State Examination, GSDS= Groninger Social Disability Schedule, CIDI= Composite International Diagnostic Interview, LCI = Life Chart Interview, MDE= major depressive episode; Sig=Significant.							