



Cumulative depressive burden, functional impairment, depressive symptomatology and treatment response in Major Depressive Disorder: results from the STAR*D and GSRD studies

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ABSTRACT

Background: Major Depressive Disorder (MDD) is a frequently recurrent condition that substantially impairs functioning; however, the contribution of illness course to functional impairment remains less well understood. This study investigated the association between Cumulative Depressive Burden-CDB (a composite measure incorporating lifetime disease duration, number of depressive episodes and duration of current episode) and functioning, depressive symptomatology and treatment response in MDD. Associations with the individual components of CDB were also examined.

Materials and methods: Data were collected in the context of the “Group for the Study of Resistant Depression” (GSRD) and “Sequenced Treatment Alternatives to Relieve Depression” (STAR*D) trials. Functioning was assessed using the Work and Social Adjustment Scale in STAR*D and the Sheehan Disability Scale in GSRD. Depressive symptoms were assessed real-time in the STAR*D (through the 30-item Inventory for Depressive Symptomatology) and retrospectively in the GSRD (through the retrospective Montgomery-Åsberg depression rating scale). Linear or logistic regression models were used to investigate the associations between CDB, depressive symptoms, functioning and treatment response.

Results: The individual CDB components showed different patterns of association across the two cohorts, while higher CDB was consistently associated with worse functioning. Associations with depressive symptom dimensions were less consistent between datasets. Higher CDB was strongly associated with poorer treatment response in the GSRD sample.

Conclusions: CDB may represent a clinically meaningful operational construct reflecting longitudinal illness load in MDD. Its association with functional impairment and treatment response supports a more comprehensive conceptualization of illness course in MDD.

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1. Introduction

Major Depressive Disorder (MDD) is a widespread and burdensome condition, predicted to become the leading cause of years lost to disability by 2030 (World Health Organization, 2011). Given the heterogeneity of MDD in terms of overall severity, symptomatology profile and disease course, with age-related clinical features also contributing to this variability (Olgiati et al., 2023), there is growing interest in identifying clinical features that may predict depression outcome. From this perspective, research has mainly focused on remission and treatment resistance (McIntyre et al., 2023; Sforzini et al., 2022). Baseline severity of depressive symptoms has consistently been indicated as a negative predictor of remission during antidepressant treatment, alongside psychosocial factors and comorbid psychiatric and organic conditions (Carter et al., 2012; Chen et al., 2024; Rossom et al., 2016; Serretti, 2024). Similarly, reports from the “Group for the Study of Resistant Depression” (GSRD) have identified depression severity as one of the key predictors of treatment-resistant depression (TRD), along with other clinical variables such as the duration of the current depressive episode, recurrence, anhedonic features, anxiety comorbidity, suicidality and the number of hospitalizations (Bartova et al., 2019; Luca et al., 2024, 2025; Souery et al., 2007). In the “Sequenced Treatment Alternatives to Relieve Depression” (STAR*D) study, recurrence and the presence of a chronic index episode (lasting more than 2 years) emerged as significant clinical predictors of depression relapse (Rush et al., 2012); in contrast, episode duration showed a limited impact on remission rates (Gilmer et al., 2008; Rush et al., 2006). Other studies did not confirm the relationship between a chronic or recurrent course of depressive disorders and remission outcome (Sung et al., 2012, 2013).

However, remitting from depressive symptoms may not be the only meaningful treatment goal. Defining remission merely as the resolution of symptoms has been criticized as overly reductive, as it overlooks functional outcomes and quality of life—key components of patients’ lived experience (Zimmerman et al., 2008). Thus, identifying clinical features that could predict social and personal functioning is of paramount importance for the management of MDD, since impaired functioning may continue to hinder patients’ full life realization even after symptomatic remission (Hirschfeld et al., 2000; Rhebergen et al., 2010; Schwarz et al., 2024; Rytälä et al., 2005). Concerning functional outcomes, a report from the STAR*D study identified sad mood and concentration problems as related to functioning (work, home management, social activities, private activities and close relationships) (Fried and Nesse, 2014). The majority of studies focused on recurrence, consistently reporting it as a predictor of poor functioning (Bromberger et al., 2005; de Jonge et al., 2018; Wilson et al., 2015). On the other hand, a cross-sectional study including nearly 300 individuals with MDD found that social, functional and work disability were negatively impacted by older age, recurrence of depression and severity, the latter variable confirmed as a predictor of poor functioning in a 2-years longitudinal research (Hammer-Helmich et al., 2018; Rytälä et al., 2005). These data suggest that severity, symptomatology profile and disease course may represent predictors of functional outcomes in MDD. Nevertheless, there remains a shortage of studies that investigate the clinical determinants of functioning from a comprehensive and integrative perspective. Indeed, studies often focus on single dimensions (e.g. number of previous depressive episodes) without capturing the illness load accumulated over time. Hence, it may be useful to consider variables related to the longitudinal disease trajectory (such as the number of depressive episodes, the duration of the current episode, and the total duration of illness) from an integrated perspective. In fact, taken together, these course-related factors may reflect an illness load which could progressively impair functioning over time.

Beyond functioning, little is known about whether the disease trajectory is associated with specific dimensions of depressive symptomatology. Identifying symptom profiles associated with greater illness load may contribute to a better clinical characterization of patients with

more chronic and recurrent form of MDD and may improve our understanding of illness heterogeneity. In light of these considerations, we hypothesized that illness load could be associated with functional outcomes, specific symptom profiles and treatment response in MDD.

Building upon this, our study analyzed samples from the STAR*D and GSRD studies to investigate cumulative depressive burden-CDB (a composite measure accounting for lifetime disease duration, number of depressive episodes and duration of current depressive episode) as a clinical correlate of functional outcomes (primary aim), specific symptom profiles (secondary aim) and treatment response (tertiary aim) in MDD.

2. Materials and methods

Participants were collected in the context of the GSRD and STAR*D (level 1) trials (Dold et al., 2016; Rush et al., 2006).

All the Ethical Committees of the participating centers approved the study protocol. The enrolled subjects signed a written informed consent prior inclusion.

2.1. STAR*D trial

The STAR*D study was a large multicenter effectiveness trial conducted in adult outpatients with non-psychotic Major Depressive Disorder (MDD) recruited from primary care and psychiatric settings (Rush et al., 2006). Eligibility required a DSM-IV diagnosis of non-psychotic MDD, age between 18 and 75 years, and the absence of bipolar disorder, psychotic disorders, or primary substance use disorders. In the present secondary analysis, we included level 1 participants with complete data for the variables required to operationalize CDB and investigate functional outcome and depressive symptomatology. Illness-course variables included the number of depressive episodes, current episode duration (days), and lifetime illness duration (years). Depression severity at baseline was assessed using the clinician-rated 30-item Inventory of Depressive Symptomatology, IDS-C₃₀ (Rush et al., 1996). Functioning was assessed through the Work and Social Adjustment Scale, WSAS (Mundt et al., 2002). Each item is rated on a scale from 0 to 8, with higher scores reflecting poor functioning (Mundt et al., 2002). This scale is generally interpreted in terms of total score and the areas of investigation (e.g. work, close relationships) are not to be interpreted as validated sub-scales. However, in order to provide a more comprehensive assessment of functional outcomes, we also examined such areas as domain-level indicators of impairment in work, home management, social leisure activities, private leisure activities and close relationships.

2.2. GSRD trial

The GSRD study was a multicenter study conducted in tertiary psychiatric centers and including patients with MDD, many of whom had treatment-resistant depression (Dold et al., 2016). Participants were adults diagnosed with MDD according to standardized diagnostic criteria and were recruited from specialized psychiatric services across several European countries. In the present secondary analysis, we included participants with complete data for the variables required to operationalize CDB and investigate functional outcome and depressive symptomatology. Illness-course variables included the number of depressive episodes, current episode duration (days), and lifetime illness duration (years). Depression severity at baseline was assessed retrospectively using the Montgomery-Åsberg Depression Rating Scale, rMADRS (Montgomery and Åsberg, 1979), while functioning was assessed through the Sheehan Disability Scale, SDS (Sheehan, 1983). The SDS consists of the following subscales: work/school; social life/leisure activities; family life/home responsibilities. Each subscale is rated on a 0 to 10 visual analog scale, with higher scores indicating greater functional impairment. A total SDS score can also be obtained (Sheehan, 1983).

2.3. Standardization of clinical and functional measures

Treatment response was defined as a $\geq 50\%$ improvement in depressive symptoms following antidepressant treatment, while remission was indicated by an end-of-study total score < 13 and ≤ 10 , respectively, for the IDS-C₃₀ (STAR*D) and the rMADRS (GSRD).

In this study, responders and remitters were grouped into the same category.

Standardized z-values were computed for both the total scores and subscales of the IDS-C₃₀, rMADRS, SDS and WSAS.

2.4. Cumulative depressive burden

For descriptive purposes, standardized variables were dichotomized at the median and combined into a categorical CDB measure (low vs high burden).

More specifically, the raw values concerning *lifetime disease duration*, *number of depressive episodes* and *duration of current depressive episode* were standardized (z-values) and categorized into a binary scale: 0 (equal to or below the median) and 1 (above the median). These values were then summed into an index ranging from 0 to 3, named “**Cumulative Depressive Burden**” (CDB), which was subsequently categorized as 0 (scores 0–1: low burden) and 1 (scores 2–3: high burden).

For inferential analyses, a continuous CDB measure was computed as the sum of the standardized values of lifetime disease duration, number of depressive episodes, and duration of current depressive episode.

2.5. Statistical analysis

Both datasets (STAR*D and GSRD) were analyzed separately with STATA v. 18 (Acock, 2008). For descriptive purposes, participants were categorized into low and high cumulative depressive burden (CDB) groups. Continuous variables were compared using t-tests, whereas categorical variables were compared using chi-square tests.

To investigate the association between illness load and clinical outcomes, CDB was analyzed as a continuous measure. More specifically, linear regression models were used to assess the relationship between CDB and continuous outcomes (e.g. depressive symptoms, functioning), while logistic regression models were used to examine the association between CDB and treatment response, which was coded as a binary outcome. The same analytical approach was also applied to the individual components of CDB, namely number of depressive episodes, current episode duration, and lifetime illness duration, in order to explore their separate associations with clinical and functional outcomes. A multivariate analysis was then performed in relation to all the significant associations detected at the univariate analysis. Age, sex, and family history of depression were included as potential confounders because these variables significantly differed between low- and high-CDB groups in both STAR*D and GSRD trials.

Statistical significance was set at $p < 0.05$. Given the exploratory nature of the item-level analyses, no formal correction for multiple comparisons was applied (Amrhein et al., 2019). Findings should therefore be interpreted with caution and considered hypothesis-generating.

3. Results

3.1. STAR*D sample

The STAR*D sample included 1676 individuals, of whom 764 with high CDB (greater depressive strain) and 912 with low CDB (mostly females, $p = 0.001$). Individuals with high CDB were older and more likely to report a family history of depression. Despite the two groups presenting similar response rates, those with high CDB showed greater depression severity and functional impairment (Table 1).

When the illness-course dimensions composing CDB were examined

separately, duration of current depressive episode and lifetime disease duration showed several associations with depressive symptomatology and functioning (most of them confirmed after adjustment for age, sex and family history of depression), whereas number of depressive episodes showed only limited associations (Tables 2 and 3).

The continuous CDB measure (integrating these illness-course dimensions) showed several association with depressive symptomatology and functional outcome. In particular, higher CDB was associated, also at the multivariate analysis, with: overall depression severity ($p = 0.007$) and symptom dimensions (future pessimism, suicidal thoughts, psychomotor agitation, panic/phobic symptoms), WSAS total

Table 1

Socio-demographic and clinical features by high and low cumulative depressive burden in the STAR*D sample.

STAR*D	Low CDB (n = 912)	High CDB (n = 764)	p-value
Age	40.7 $\pm$ 14.0	46.0 $\pm$ 12.4	<.001
Sex (F)	591 (64.8%)	436 (57.1%)	.001
Family history-Depression	463 (51.0%)	445 (58.7%)	.002
Family history-Bipolar	68 (7.5%)	76 (10.1%)	.064
IDS-C ₃₀ ,total (obs. 863,728)	34.7 $\pm$ 11.5	36.5 $\pm$ 11.1	.002
IDS-C ₃₀ ,initial insomnia	1.6 $\pm$ 1.2	1.6 $\pm$ 1.2	.529
IDS-C ₃₀ , middle insomnia (obs. 861,725)	1.9 $\pm$ 1.2	2.0 $\pm$ 1.1	.056
IDS-C ₃₀ ,early morning awakening (obs. 862,728)	1.1 $\pm$ 1.2	1.2 $\pm$ 1.2	.059
IDS-C ₃₀ ,sleeping too much (obs. 862,728)	.4 $\pm$.8	.4 $\pm$.9	.783
IDS-C ₃₀ ,feeling sad	2.0 $\pm$.7	2.0 $\pm$.8	.380
IDS-C ₃₀ ,feeling irritable	1.2 $\pm$.8	1.3 $\pm$.8	.376
IDS-C ₃₀ ,feeling anxious or tense	1.4 $\pm$.9	1.4 $\pm$.9	.238
IDS-C ₃₀ ,reactivity of mood (obs. 863,726)	1.3 $\pm$ 1.0	1.3 $\pm$ 1.0	.640
IDS-C ₃₀ ,diurnal variation of mood	.9 $\pm$ 1.1	1.0 $\pm$ 1.2	.096
IDS-C ₃₀ ,quality of mood	1.7 $\pm$ 1.2	1.6 $\pm$ 1.2	.807
IDS-C ₃₀ ,appetite disturbance	1.2 $\pm$ 1.1	1.2 $\pm$ 1.1	.975
IDS-C ₃₀ ,weight change (obs. 862,728)	1.1 $\pm$ 1.2	1.1 $\pm$ 1.2	.596
IDS-C ₃₀ ,concentration/decision making	1.9 $\pm$.9	2.0 $\pm$.9	.726
IDS-C ₃₀ ,self-criticism and blame (obs. 862,727)	1.8 $\pm$ 1.2	1.9 $\pm$ 1.2	.125
IDS-C ₃₀ ,future pessimism	1.3 $\pm$.9	1.4 $\pm$ 1.0	.012
IDS-C ₃₀ ,suicidal thoughts (obs. 862,728)	.6 $\pm$.7	.7 $\pm$.7	<.001
IDS-C ₃₀ ,interest in people/activities	1.7 $\pm$ 1.0	1.8 $\pm$ 1.0	.009
IDS-C ₃₀ ,energy/fatigability	1.7 $\pm$.9	1.8 $\pm$.9	.002
IDS-C ₃₀ ,pleasure/enjoyment	1.4 $\pm$ 1.1	1.4 $\pm$ 1.1	.959
IDS-C ₃₀ ,interest in sex	1.6 $\pm$ 1.3	1.6 $\pm$ 1.3	.333
IDS-C ₃₀ ,psychomotor retardation	.7 $\pm$.6	.7 $\pm$.6	.053
IDS-C ₃₀ ,psychomotor agitation	.8 $\pm$.7	.9 $\pm$.8	.043
IDS-C ₃₀ ,aches and pains	1.3 $\pm$ 1.0	1.4 $\pm$ 1.0	.059
IDS-C ₃₀ ,sympathetic arousal (obs. 862,728)	.9 $\pm$.8	1.0 $\pm$.8	.002
IDS-C ₃₀ ,panic/phobic symptoms	.6 $\pm$.9	.7 $\pm$.9	.060
IDS-C ₃₀ ,constipation/diarrhoea	.6 $\pm$.8	.7 $\pm$.9	.009
IDS-C ₃₀ ,interpersonal sensitivity	1.2 $\pm$ 1.2	1.3 $\pm$ 1.2	.403
IDS-C ₃₀ ,Leadon paralysis/physical energy	.8 $\pm$ 1.1	.9 $\pm$ 1.1	.095
WSAS-total (obs. 868,743)	22.4 $\pm$ 9.4	24.1 $\pm$ 8.8	<.001
WSAS-work	4.1 $\pm$ 2.4	4.3 $\pm$ 2.3	.034
WSAS-home management	4.3 $\pm$ 2.3	4.7 $\pm$ 2.1	<.001
WSAS-social leisure activities	5.1 $\pm$ 2.3	5.4 $\pm$ 2.1	.006
WSAS-private leisure activities	4.5 $\pm$ 2.4	4.8 $\pm$ 2.2	.010
WSAS-close relationships	4.4 $\pm$ 2.4	4.9 $\pm$ 2.3	<.001
Responders (obs. 703,637)	388 (55.2%)	319 (50.1%)	.061

Legend. The values are shown as mean $\pm$ standard deviation or number and percentage. Statistically significant results in bold.

CDB: Cumulative Depressive Burden. IDS-C₃₀: 30-item Inventory for Depressive Symptomatology, Clinician-rated.

WSAS: Work and Social Adjustment Scale.

score ($p = 0.002$) and specific functional impairment areas (social activities, private activities and close relationships). For more details, see [Tables 2 and 3](#)

3.2. GSRD sample

The GSRD sample included 1081 individuals, of whom 477 with high CDB and 604 with low CDB. Individuals with high CDB were older, more frequently female and likely to report a family history of depression. In addition, those with high CDB showed greater depressive severity and functional impairment along with significantly lower rates of treatment response ($p < 0.001$). For more details, see [Table 4](#).

Considering the illness-course dimensions, all of them showed some significant associations with depressive symptom dimensions both at the univariate and multivariate analyses. Concerning functioning, only number of depressive episodes showed statistically significant associations, confirmed at the multivariate analysis, with SDS total score and all functional impairment areas (work/school/social life/leisure activities, family life/home responsibilities). A higher number of depressive episodes, a longer duration of current depressive episode and a longer lifetime disease duration were consistently associated with lower rates of treatment response ([Tables 5 and 6](#)).

As related to the continuous composite measure, higher CDB was associated, also at the multivariate analysis, with: depressive symptom dimensions (reduced appetite, concentration difficulties, lassitude, inability to feel), SDS total score ($p < 0.001$) and all functional impairment areas (work/school, social life/leisure activities, family life/home responsibilities). In addition higher CDB was strongly associated with lower rates of treatment response ($p < 0.001$). For more details, see [Tables 5 and 6](#)

4. Discussion

The present study investigated the associations between CDB and its components (number of depressive episodes, duration of current depressive episode, lifetime disease duration) with functional impairment, depressive symptomatology, and treatment response in MDD. While the contribution of individual illness-course variables differed between datasets, CDB showed robust associations across both samples, supporting the usefulness of a composite measure addressing heterogeneous illness-course trajectories.

In addition, our findings suggest that CDB may represent a more robust clinical correlate of functional impairment than of a specific depressive symptom profile. Indeed, although several symptom dimensions were associated with CDB, these associations were more variable across datasets and did not always parallel overall depression severity. By contrast, although STAR*D and GSRD were analyzed separately and differed in clinical setting, assessment procedures, and patient characteristics, the composite CDB measure showed clinically meaningful associations across both cohorts in relation to functioning.

Moreover, the association between higher CDB and poorer treatment response in the GSRD sample further supports the potential clinical relevance of this construct, also considering that this trial included a substantial proportion of difficult-to-treat patients, making the observed relationship particularly meaningful from a clinical perspective.

Taking into account the phenomenology of the depressive experience (reduced energy, emotional and physical difficulties, pessimism) it is apparent how repeated illness episodes and prolonged disease duration may progressively interfere with educational attainment, occupational functioning, social participation and interpersonal relationships ([Kerr et al., 2023](#)). Over time, these difficulties may accumulate and contribute to persistent functional limitations that are not fully captured by symptom severity alone. This interpretation is consistent with growing evidence suggesting that remission of depressive symptoms does not necessarily translate into full functional recovery, and that functioning represents a clinically meaningful outcome in its own right

([Zimmerman et al., 2008](#)). Biological mechanisms may also explain the association between illness-course and functioning in MDD. Indeed, previous studies have linked recurrent or prolonged depression to neuroprogressive processes and alterations in white matter integrity, particularly in relation to illness duration, severity, and recurrence ([Moylan et al., 2013](#); [de Diego-Adeliño et al., 2014](#); [van Velzen et al., 2020](#)). Given the wide range of biological correlates of MDD (neuro-inflammation, altered neurogenesis, mitochondrial dysfunction, impaired signaling, etc.) it would not be unreasonable to conceptualize the disease course in terms of neuroprogression, with longer and more frequent depressive episodes accelerating functional decline ([Moylan et al., 2013](#)).

However, the present study did not include neuroimaging data, and these mechanisms should therefore be considered speculative.

The findings of our study is in line with previous research relating recurrence to worse functional outcomes ([Bromberger et al., 2005](#); [de Jonge et al., 2018](#); [Wilson et al., 2015](#)), while extending current knowledge on the topic. In fact, providing a more comprehensive account of long-term depressive strain, we propose a novel and clinically accessible metric (the CDB) incorporating the longitudinal course of MDD.

Indeed, while depression severity has consistently been associated with poorer functioning ([Hammer-Helmich et al., 2018](#); [Rytsälä et al., 2005](#)), our findings suggest that illness-course characteristics may also be clinically relevant when evaluating long-term outcomes in MDD.

Our findings should be interpreted with caution, since this study has some limitations that may be addressed in future research. First, the cross-sectional nature of the analyses precludes causal inferences regarding the relationship between CDB and clinical outcomes and the lack of correction for multiple comparisons raises the possibility of type I errors. Second, although the analyzed illness-course variables reflect the longitudinal history of depression, the present analyses focused on baseline clinical and functional measures and did not model time-dependent changes during follow-up. Third, we examined two different cohorts, whereby the inter-sample differences in terms of patients characteristics and data collection methods (real-time versus retrospective assessment, different measures of functioning) may influence the comparability of the findings. Fourth, CDB was operationalized as a composite measure derived from three illness-course dimensions. Although analyses of the individuals components were conducted and generally supported the relevance of the composite measure, CDB remains an operational rather than a formally validated construct. Lastly, since the CDB does not account for other variables potentially moderating the impact of depressive illness on functioning (e.g. coping, social support, financial issues related to workplace absenteeism), its predictive value may be suboptimal across different clinical profiles. Future studies should explore how these variables interact with our burden measure. However, there are some strengths enhancing the trustworthiness of our findings. First of all, the analysis of two among the largest and well-characterized independent clinical cohorts. Second, the reliance on standardized psychometric tools. Third, the use of a novel composite measure, namely the CDB, reflecting real-world trajectories of disease burden in MDD.

Overall, our findings suggest that CDB may represent a clinically meaningful operational construct for capturing the impact of illness-course trajectories in MDD, particularly in relation to functional impairment and treatment response. Future longitudinal studies are needed to validate CDB as a clinical marker, clarify its relevance for prognosis and treatment planning and test its potential use in biological studies.

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Table 2

Factors associated with outcome in the STAR*D sample. Univariate analysis.

STAR*D	number of depressive episodes			duration of current depressive episode			Lifetime disease duration			cumulative depressive burden (continuous)		
	coeff	95%CI	p	coeff	95%CI	p	coeff	95%CI	p	coeff	95%CI	p
IDS-C ₃₀ ,total	.001	-.003 to .006	.501	.000	-6.31e-06 to .000	.119	.004	.000 to .008	.017	.029	.004 to .055	.019
IDS-C ₃₀ ,initial insomnia	-.002	-.007 to .001	.215	2.16e-06	-.000 to .000	.891	-.003	-.007 to .000	.061	-.019	-.044 to .005	.128
IDS-C ₃₀ , middle insomnia	.001	-.003 to .005	.620	.000	1.29e-06 to .000	.041	.004	.001 to .008	.010	.033	.008 to .058	.010
IDS-C ₃₀ ,early morning awakening	.002	-.002 to .007	.286	.000	1.36e-06 to .000	.041	.005	.002 to .009	.002	.040	.015 to .066	.002
IDS-C ₃₀ ,sleeping too much	.001	-.002 to .006	.448	-5.92e-06	-.000 to .000	.709	.000	-.003 to .003	.904	.003	-.021 to .028	.789
IDS-C ₃₀ ,feeling sad	-.003	-.007 to .001	.170	.000	-8.11e-07 to .000	.056	.000	-.003 to .003	.864	.004	-.020 to .029	.741
IDS-C ₃₀ ,feeling irritable	.002	-.001 to .007	.242	.000	-6.00e-06 to .000	.114	.000	-.003 to .003	.960	.018	-.006 to .043	.155
IDS-C ₃₀ ,feeling anxious or tense	-.000	-.005 to .003	.724	.000	-5.73e-07 to .000	.054	.002	-.001 to .006	.175	.018	-.006 to .044	.142
IDS-C ₃₀ ,reactivity of mood	-.000	-.005 to .004	.838	.000	-.000 to .000	.242	-.000	-.004 to .003	.830	.004	-.020 to .030	.711
IDS-C ₃₀ ,diurnal variation of mood	.002	-.002 to .006	.383	-.000	-.000 to .000	.339	-.001	-.004 to .002	.534	-.004	-.029 to .020	.733
IDS-C ₃₀ ,quality of mood	.003	-.001 to .007	.152	-.000	-.000 to -.000	.002	-.001	-.004 to .002	.545	-.013	-.039 to .011	.277
IDS-C ₃₀ ,appetite disturbance	-.000	-.005 to .004	.852	-.000	-.000 to -8.67e-06	.012	.000	-.002 to .004	.668	-.014	-.039 to .010	.257
IDS-C ₃₀ ,weight change	-.001	-.006 to .003	.510	-.000	-.000 to .000	.246	-.000	-.004 to .003	.792	-.013	-.038 to .011	.291
IDS-C ₃₀ ,concentration/decision making	.000	-.004 to .004	.973	3.95e-06	-.000 to .000	.802	.002	-.001 to .005	.235	.009	-.015 to .034	.457
IDS-C ₃₀ ,self-criticism and blame	-.000	-.005 to .004	.861	-.000	-.000 to -8.05e-06	.014	-.000	-.003 to .003	.864	-.018	-.043 to .007	.158
IDS-C ₃₀ ,future pessimism	.001	-.003 to .005	.668	.000	2.53e-06 to .000	.034	.004	.001 to .008	.010	.033	.008 to .058	.010
IDS-C ₃₀ ,suicidal thoughts	.001	-.002 to .006	.443	.000	-.000 to .000	.393	.005	.002 to .009	.002	.031	.005 to .056	.016
IDS-C ₃₀ ,interest in people/activities	.001	-.003 to .005	.661	.000	-.000 to .000	.270	.002	-.000 to .006	.108	.020	-.004 to .045	.111
IDS-C ₃₀ ,energy/fatigability	-.000	-.005 to .004	.870	8.51e-06	-.000 to .000	.590	.007	.003 to .010	<.001	.026	.001 to .052	.037
IDS-C ₃₀ ,pleasure/enjoyment	-.002	-.007 to .001	.245	.000	.000 to .000	.002	.000	-.003 to .003	.971	.012	-.012 to .037	.328
IDS-C ₃₀ ,interest in sex	.000	-.003 to .005	.758	.000	-.000 to .000	.372	.002	-.001 to .005	.230	.015	-.009 to .040	.225
IDS-C ₃₀ ,psychomotor retardation	.001	-.002 to .006	.418	.000	-5.60e-06 to .000	.108	.003	-.000 to .007	.061	.028	.002 to .053	.030
IDS-C ₃₀ ,psychomotor agitation	.005	.00 to .010	.020	7.55e-06	-.000 to .000	.635	.002	-.000 to .006	.114	.029	.003 to .054	.025
IDS-C ₃₀ ,aches and pains	.004	.00 to .009	.048	.000	-.000 to .000	.412	-.000	-.004 to .003	.765	.016	-.008 to .041	.200
IDS-C ₃₀ ,sympathetic arousal	.002	-.002 to .006	.342	.000	-3.14e-06 to .000	.078	.004	.001 to .008	.010	.034	.009 to .059	.007
IDS-C ₃₀ ,panic/phobic symptoms	.002	-.002 to .007	.271	.000	-7.73e-06 to .000	.140	.002	-.001 to .006	.169	.029	.000 to .051	.045
IDS-C ₃₀ ,constipation/diarrhoea	-.000	-.004 to .004	.969	.000	-7.62e-06 to .000	.140	.003	-.000 to .007	.055	.021	-.003 to .046	.091
IDS-C ₃₀ ,interpersonal sensitivity	.000	-.004 to .005	.854	1.92e-06	-.000 to .000	.903	.001	-.002 to .004	.581	.005	-.019 to .030	.663
IDS-C ₃₀ ,Leadren paralysis/physical energy	-.001	-.006 to .002	.432	.000	.000 to .000	.001	.004	.001 to .008	.011	.032	.007 to .057	.011
WSAS-total	-.000	-.004 to .004	.900	.000	.000 to .000	.004	.004	.001 to .008	.006	.035	.010 to .060	.005
WSAS-work	-.000	-.005 to .003	.761	.000	7.34e-06 to .000	.015	.003	-.000 to .006	.065	.025	.000 to .050	.041
WSAS-home management	.000	-.003 to .005	.727	.000	-.000 to .000	.464	.005	.001 to .008	.006	.024	-.000 to .049	.051
WSAS-social leisure activities	-.000	-.005 to .003	.699	.000	.000 to .000	.005	.003	-.000 to .006	.079	.027	.002 to .051	.032
WSAS-private leisure activities	-.001	-.005 to .003	.600	.000	7.82e-06 to .000	.013	.004	.000 to .008	.014	.028	.003 to .053	.024
WSAS-close relationships	.000	-.003 to .005	.711	.000	.000 to .000	.003	.003	.000 to .007	.045	.034	.009 to .059	.007
Responders	.992	.982 to 1.002	.153	.999	.999 to .999	.042	.994	.986 to 1.001	.144	.930	.880 to .984	.012

The Table shows the relationship between cumulative depressive burden (and each one of its components) and: depressive symptoms, functioning, response to treatment. Statistically significant results in bold.

IDS-C₃₀: 30-item Inventory for Depressive Symptomatology, Clinician-rated. WSAS: Work and Social Adjustment Scale.

Table 3

Factors associated with outcome in the STAR*D sample. Multivariate analysis.

STAR*D adjusted for age, sex, family history of depression	number of depressive episodes			duration of current depressive episode			Lifetime disease duration			cumulative depressive burden (continuous)		
	coeff	95%CI	p	coeff	95%CI	p	coeff	95%CI	p	coeff	95%CI	p
IDS-C ₃₀ ,total							.005	.001 to .009	.008	.036	.009 to .063	.007
IDS-C ₃₀ ,initial insomnia												
IDS-C ₃₀ ,middle insomnia				.000	−.000 to .000	.248	−.000	−.004 to .003	.918	.008	−.017 to .035	.508
IDS-C ₃₀ ,early morning awakening				.000	−.000 to .000	.202	.001	−.002 to .005	.455	.017	−.008 to .044	.194
IDS-C ₃₀ ,sleeping too much												
IDS-C ₃₀ ,feeling sad												
IDS-C ₃₀ ,feeling irritable												
IDS-C ₃₀ ,feeling anxious or tense												
IDS-C ₃₀ ,reactivity of mood												
IDS-C ₃₀ ,diurnal variation of mood												
IDS-C ₃₀ ,quality of mood				−.000	−.000 to −.000	.003						
IDS-C ₃₀ ,appetite disturbance				−.000	−.000 to −5.52e-06	.021						
IDS-C ₃₀ ,weight change												
IDS-C ₃₀ ,concentration/decision making												
IDS-C ₃₀ ,self-criticism and blame				−.000	−.000 to 3.13e-06	.078						
IDS-C ₃₀ ,future pessimism				.000	9.78e-07 to .000	.043	.004	.000 to .008	.020	.032	.006 to .059	.016
IDS-C ₃₀ ,suicidal thoughts							.008	.004 to .012	<.001	.036	.009 to .063	.007
IDS-C ₃₀ ,interest in people/activities												
IDS-C ₃₀ ,energy/fatigability							.006	.002 to .010	.002	.022	−.003 to .049	.092
IDS-C ₃₀ ,pleasure/enjoyment				.000	.000 to .000	.002						
IDS-C ₃₀ ,interest in sex												
IDS-C ₃₀ ,psychomotor retardation										.024	−.002 to .051	.079
IDS-C ₃₀ ,psychomotor agitation	.004	.000 to .009	.044							.036	.009 to .062	.009
IDS-C ₃₀ ,aches and pains	.006	.001 to .010	.011									
IDS-C ₃₀ ,sympathetic arousal							.001	−.002 to .005	.345	.020	−.006 to .047	.134
IDS-C ₃₀ ,panic/phobic symptoms										.027	.000 to .054	.049
IDS-C ₃₀ ,constipation/diarrhoea												
IDS-C ₃₀ ,interpersonal sensitivity												
IDS-C ₃₀ ,Leadon paralysis/physical energy				.000	.000 to .000	.004	.003	−.001 to .007	.144	.023	−.003 to .050	.085
WSAS-total				.000	.000 to .000	.003	.006	.002 to .010	.002	.041	.015 to .068	.002
WSAS-work				.000	5.12e-06 to .000	.022				.020	−.005 to .047	.121
WSAS-home management							.005	.001 to .009	.011			
WSAS-social leisure activities				.000	.000 to .000	.002				.036	.010 to .063	.006
WSAS-private leisure activities				.000	6.20e-06 to .000	.018	.005	.001 to .008	.014	.031	.005 to .058	.018
WSAS-close relationships				.000	.000 to .000	.001	.007	.003 to .011	<.001	.051	.024 to −.077	<.001
Responders				.999	.999 to 1.000	.098				.953	.898 to 1.012	.117

The Table shows the relationship between cumulative depressive burden (and each one of its components) and: depressive symptoms, functioning, response to treatment after adjusting for possible confounders. Statistically significant results in bold.

IDS-C₃₀: 30-item Inventory for Depressive Symptomatology, Clinician-rated. WSAS: Work and Social Adjustment Scale.

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Maria Luca: Writing – original draft. **Paolo Olgiati:** Writing – review & editing. **Antonina Luca:** Writing – review & editing. **Siegfried**

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Table 4

Socio-demographic and clinical features by high and low cumulative depressive burden in the GSRD sample.

GSRD	Low CDB (n = 604)	High CDB (n = 477)	p- value
Age	49.4 ± 14.9	54.9 ± 12.8	<.001
Sex (F)	367 (60.8%)	327 (68.5%)	.008
Family history-Depression	187 (31.1%)	176 (36.9%)	.044
Family-Bipolar	26 (4.3%)	25 (4.2%)	.478
MADRS-total (obs. 601,472)	35.1 ± 7.6	36.2 ± 7.6	.011
MADRS-apparent sadness	4.2 ± 1.0	4.5 ± 1.0	<.001
MADRS-reported sadness	4.3 ± 1.0	4.5 ± 1.0	.006
MADRS-inner tension	3.7 ± 1.2	3.8 ± 1.2	.223
MADRS-reduced sleep	3.5 ± 1.4	3.6 ± 1.5	.409
MADRS-reduced appetite	2.5 ± 1.7	2.4 ± 1.6	.478
MADRS-concentration difficulties	3.7 ± 1.1	3.8 ± 1.1	.058
MADRS-lassitude	3.8 ± 1.2	4.1 ± 1.0	<.001
MADRS-inability to feel	3.6 ± 1.2	3.9 ± 1.0	<.001
MADRS-pessimistic thoughts	3.4 ± 1.3	3.5 ± 1.2	.054
MADRS-suicidal thoughts	2.2 ± 1.8	2.1 ± 1.7	.336
SDS-total	19.1 ± 7.6	20.3 ± 6.9	.010
SDS-work/school (obs. 556,453)	6.7 ± 2.9	7.0 ± 2.6	.220
SDS-social life/leisure activities (obs. 600,474)	6.7 ± 2.6	7.0 ± 2.3	.047
SDS-family life/home responsibilities (obs. 593,464)	6.4 ± 2.7	6.9 ± 2.4	.001
Responders	194 (32.1%)	80 (16.8%)	<.001

Legend. The values are shown as mean ± standard deviation or number and percentage. Statistically significant results in bold.

CDB: Cumulative Depressive Burden. MADRS: Montgomery and Åsberg, retrospectively assessed. SDS: Sheehan Disability Scale.

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editing. **Guillermo Perez Algorta:** Writing – review & editing. **Raffaele Ferri:** Writing – review & editing. **Julien Mendlewicz:** Writing – review & editing. **Alessandro Serretti:** Supervision.

Declaration of competing interest

Dr. Rujescu served as consultant for Janssen, received honoraria from Boehringer-Ingelheim, Gerot Lannacher, Janssen and Pharmagenetix, received research/travel support from Angelini, Boehringer-Ingelheim, Janssen and Schwabe, and served on advisory boards of AC Immune, Boehringer-Ingelheim, Roche and Rovi. Dr. Souery has received grant/research support from GlaxoSmithKline and Lundbeck; and he has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, and Lundbeck. Dr. Mendlewicz is a member of the board of the Lundbeck International Neuroscience Foundation and of the advisory board of Servier. Dr. Zohar has received grant/research support from Lundbeck, Servier, and Pfizer; he has served as a consultant or on the advisory boards for Servier, Pfizer, Solvay, and Actelion; and he has served on speakers' bureaus for Lundbeck, GlaxoSmithKline, Jazz, and Solvay. Dr. Montgomery has served as a consultant or on advisory boards for AstraZeneca, Bionevia, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Grunenthal, Intellect Pharma, Johnson & Johnson, Lilly, Lundbeck, Merck, Merz, M's Science, Neurim, Otsuka, Pierre Fabre, Pfizer, Pharmaneuroboost, Richter, Roche, Sanofi, Sepracor, Servier, Shire, Synosis, Takeda, Theracos, Targacept, Transcept, UBC, Xytis, and Wyeth. Dr. Serretti has served as a consultant or speaker for Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boehringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, and Servier and Taliaz. Dr. Kasper has received grant/

Table 5

Factors associated with outcome in the GSRD sample. Univariate analysis.

GSRD	number of depressive episodes			duration of current depressive episode			Lifetime disease duration			cumulative depressive burden (continuous)		
	coeff	95%CI	p	coeff	95%CI	p	coeff	95%CI	p	coeff	95%CI	p
MADRS-total	.046	.023 to .068	<.001	-.000	-.000 to -2.16e-06	.048	.002	-.002 to .006	.327	.025	-.006 to .056	.115
MADRS-apparent sadness	.042	.020 to .065	<.001	-.000	-.000 to .000	.753	.002	-.002 to .006	.339	.036	.004 to .067	.023
MADRS-reported sadness	.037	.015 to .060	.001	.000	-.000 to .000	.763	-.001	-.006 to .002	.488	.024	-.007 to .055	.130
MADRS-inner tension	.024	.002 to .047	.030	-.000	-.000 to .000	.149	.002	-.002 to .007	.278	.015	-.016 to .046	.348
MADRS-reduced sleep	.006	-.016 to .028	.0583	-.000	-.000 to .000	.284	-.001	-.006 to .002	.493	-.009	-.041 to .021	.531
MADRS-reduced appetite	-.023	-.065 to -.000	.046	-.000	-.000 to -.000	.005	.002	-.001 to .007	.259	-.030	-.061 to .000	.057
MADRS-concentration difficulties	.031	.009 to .053	.006	-.000	-.000 to .000	.258	.006	.001 to .010	.009	.034	.003 to .066	.028
MADRS-lassitude	.060	.038 to .082	<.001	-.000	-.000 to .000	.072	.006	.001 to .010	.007	.051	.019 to .082	.001
MADRS-inability to feel	.053	.030 to .075	<.001	.000	-.000 to .000	.679	.004	-.000 to .008	.063	.057	.026 to .088	<.001
MADRS-pessimistic thoughts	.047	.024 to .069	<.001	-.000	-.000 to -.000	.009	-.000	-.005 to .003	.685	.008	-.022 to .040	.573
MADRS-suicidal thoughts	.023	.001 to .046	.038	-.000	-.000 to .000	.589	-.003	-.007 to .001	.150	.000	-.030 to .032	.957
SDS-total	.037	.014 to .059	.001	.000	-.000 to .000	.459	.003	-.001 to .007	.148	.044	.014 to .075	.004
SDS-work/school	.029	.006 to .051	.013	.000	-.000 to .000	.814	.002	-.001 to .007	.231	.033	.001 to .065	.041
SDS-social life/leisure activities	.030	.007 to .052	.008	.000	-.000 to .000	.126	.004	-.000 to .008	.067	.049	.018 to .081	.002
SDS-family life/home responsibilities	.029	.007 to .052	.009	-.000	.000 to .000	.350	.004	-.000 to .008	.062	.045	.013 to .076	.005
Responders	.881	.830 to .935	<.001	.998	.997 to .999	<.001	.979	.968 to .990	<.001	.777	.716 to .844	<.001

Legend. The Table shows the relationship between cumulative depressive burden (and each one of its components) and: depressive symptoms, functioning, response to treatment. Statistically significant results in bold. MADRS: Montgomery and Åsberg, retrospectively assessed. SDS: Sheehan Disability Scale.

Table 6

Factors associated with outcome in the GSRD sample. Multivariate analysis.

GSRD	number of depressive episodes			duration of current depressive episode			Lifetime disease duration			cumulative depressive burden (continuous)		
	coeff	95%CI	p	coeff	95%CI	p	coeff	95%CI	p	coeff	95%CI	p
adjusted for age, sex, family history of depression												
MADRS-total	.045	.022 to .067	<.001	–.000	–.000 to 5.43e-06	.054						
MADRS-apparent sadness	.040	.017 to .063	<.001							.031	–.001 to .064	.059
MADRS-reported sadness	.036	.014 to .059	.002									
MADRS-inner tension	.025	.003 to .048	.026									
MADRS-reduced sleep												
MADRS-reduced appetite	–.027	–.050 to –.005	.016	–.000	–.000 to –.000	.007						
MADRS-concentration difficulties	.030	.008 to .053	.008				.006	.001 to .011	.015	.033	.001 to .066	.042
MADRS-lassitude	.055	.032 to .077	<.001				.003	–.001 to .008	.180	.037	.005 to .070	.023
MADRS-inability to feel	.053	.030 to .076	<.001							.060	.027 to .092	<.001
MADRS-pessimistic thoughts	.048	.026 to .071	<.001	–.000	–.000 to –.000	.008						
MADRS-suicidal thoughts	.028	.005 to .051	.014									
SDS-total	.043	.020 to .065	<.001							.065	.033 to .097	<.001
SDS-work/school	.035	.012 to .058	.003							.055	.021 to .088	.001
SDS-social life/leisure activities	.033	.011 to .056	.003							.063	.031 to .095	<.001
SDS-family life/home responsibilities	.031	.008 to .053	.008							.051	.018 to .083	.002
Responders	.888	.836 to .942	<.001	.998	.997 to .999	<.001	.982	.970 to .994	.004	.786	.722 to .855	<.001

Legend. The Table shows the relationship between cumulative depressive burden (and each one of its components) and: depressive symptoms, functioning, response to treatment after adjusting for possible confounders. Statistically significant results in bold.

MADRS: Montgomery and Åsberg, retrospectively assessed. SDS: Sheehan Disability Scale.

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Glossary

CDB	Cumulative Depressive Burden
GSRD	Group for the Study of Resistant Depression
IDS-C ₃₀	30-item Inventory for Depressive Symptomatology – Clinician-rated
MDD	Major Depressive Disorder
rMADRS	retrospective Montgomery-Åsberg Depression Rating Scale
SDS	Sheehan Disability Scale

STAR*D Sequenced Treatment Alternatives to Relieve Depression

TRD Treatment-Resistant Depression

WSAS Work and Social Adjustment Scale

Data availability

STAR*D data are available through the National Institute of Mental Health (NIMH) Data Archive/NIMH Repository and Genomics Resource (NDA/NGR) upon application and approval by the repository (<https://nda.nih.gov/>). GSRD data are not publicly available but may be made available by the corresponding authors upon reasonable request and subject to approval by the GSRD consortium and local ethical regulations.

References

- Acock, A.C., 2008. *A Gentle Introduction to Stata, second ed., second ed.* Stata Press, Philadelphia, PA.
- Amrhein, V., Greenland, S., McShane, B., 2019. Scientists rise up against statistical significance. *Nature* 567, 305–307.
- Bartova, L., Dold, M., Kautzky, A., Fabbri, C., Spies, M., Serretti, A., Souery, D., Mendlewicz, J., Zohar, J., Montgomery, S., Schosser, A., Kasper, S., 2019. Results of the European Group for the Study of Resistant Depression (GSRD) - basis for further research and clinical practice. *World J. Biol. Psychiatr.* 20, 427–448.
- Bromberger, J.T., Kravitz, H.M., Wei, H.-L., Brown, C., Youk, A.O., Cordal, A., Powell, L. H., Matthews, K.A., 2005. History of depression and women's current health and functioning during midlife. *Gen. Hosp. Psychiatry* 27, 200–208.
- Carter, G.C., Cantrell, R.A., Victoria, Zarotsky, Haynes, V.S., Phillips, G., Alatorre, C.I., Goetz, I., Paczkowski, R., Marangell, L.B., 2012. Comprehensive review of factors implicated in the heterogeneity of response in depression. *Depress. Anxiety* 29, 340–354.
- Chen, L.-C., Chen, M.-H., Bai, Y.-M., Chen, T.-J., Su, T.-P., 2024. Resistance to antidepressant treatment among patients with major depressive disorder: a nationwide study. *Int. Clin. Psychopharmacol.* <https://doi.org/10.1097/YIC.0000000000000574>.
- de Diego-Adelino, J., Pires, P., Gómez-Ansón, B., Serra-Blasco, M., Vives-Gilbert, Y., Puigdemont, D., Martín-Blanco, A., Alvarez, E., Pérez, V., Portella, M.J., 2014.

- Microstructural white-matter abnormalities associated with treatment resistance, severity and duration of illness in major depression. *Psychol. Med.* 44, 1171–1182.
- de Jonge, M., Bockting, C.L.H., van Oppen, P., Van, H.L., Peen, J., Kikkert, M.J., Dekker, J.J.M., 2018. The association between the number of previous episodes and modifiable vulnerability factors in remitted patients with recurrent depression. *PLoS One* 13, e0206495.
- Dold, M., Kautzky, A., Bartova, L., Rabl, U., Souery, D., Mendlewicz, J., Porcelli, S., Serretti, A., Zohar, J., Montgomery, S., Kasper, S., 2016. Pharmacological treatment strategies in unipolar depression in European tertiary psychiatric treatment centers - a pharmacoepidemiological cross-sectional multicenter study. *Eur. Neuropsychopharmacol.* 26, 1960–1971.
- Fried, E.I., Nesse, R.M., 2014. The impact of individual depressive symptoms on impairment of psychosocial functioning. *PLoS One* 9, e90311.
- Gilmer, W.S., Gollan, J.K., Wisniewski, S.R., Howland, R.H., Trivedi, M.H., Miyahara, S., Fleck, J., Thase, M.E., Alpert, J.E., Nierenberg, A.A., Warden, D., Fava, M., Rush, A. J., 2008. Does the duration of index episode affect the treatment outcome of major depressive disorder? A STAR*D report. *J. Clin. Psychiatry* 69, 1246–1256.
- Hammer-Helmich, L., Haro, J.M., Jönsson, B., Tanguy Melac, A., Di Nicola, S., Chollet, J., Milea, D., Rive, B., Saragoussi, D., 2018. Functional impairment in patients with major depressive disorder: the 2-year PERFORM study. *Neuropsychiatric Dis. Treat.* 14, 239–249.
- Hirschfeld, R.M., Montgomery, S.A., Keller, M.B., Kasper, S., Schatzberg, A.F., Möller, H. J., Healy, D., Baldwin, D., Humble, M., Versiani, M., Montenegro, R., Bourgeois, M., 2000. Social functioning in depression: a review. *J. Clin. Psychiatry* 61, 268–275.
- Kerr, C., Denece, T., Vincent, S.-A., Bailey, K.M., Young, A.H., Rathod, S., Desai, M., Baldock, L., Jacobsen, N., 2023. The lived experience of major and treatment-resistant depression in England: a mixed-methods study. *Acta Psychol.* 240, 104035.
- Luca, A., Luca, M., Kasper, S., Pecorino, B., Zohar, J., Souery, D., Montgomery, S., Ferentinos, P., Rujescu, D., Messina, A., Zanardi, R., Ferri, R., Tripodi, M., Baune, B. T., Fanelli, G., Fabbri, C., Mendlewicz, J., Serretti, A., 2024. Anhedonia is associated with a specific depression profile and poor antidepressant response. *Int. J. Neuropsychopharmacol.* 27. <https://doi.org/10.1093/ijnp/pyae055>.
- Luca, M., Luca, A., Messina, A., Bartova, L., Kasper, S., Zohar, J., Souery, D., Montgomery, S., Ferentinos, P., Rujescu, D., Mendlewicz, J., Zanardi, R., Ferri, R., Lanuzza, B., Benedetti, F., Pecorino, B., Baune, B.T., Fanelli, G., Fabbri, C., Serretti, A., 2025. Specific symptomatology profile associated with treatment resistant depression: a multicentric study from the Group for the Study of Resistant Depression with a focus on sex. *J. Affect. Disord.* 375, 249–255.
- McIntyre, R.S., Alsuwaidan, M., Baune, B.T., Berk, M., Demyttenaere, K., Goldberg, J.F., Gorwood, P., Ho, R., Kasper, S., Kennedy, S.H., Ly-Uson, J., Mansur, R.B., McAllister-Williams, R.H., Murrrough, J.W., Nemeroff, C.B., Nierenberg, A.A., Rosenblatt, J.D., Sanacora, G., Schatzberg, A.F., Shelton, R., Stahl, S.M., Trivedi, M.H., Vieta, E., Vinberg, M., Williams, N., Young, A.H., Maj, M., 2023. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry* 22, 394–412.
- Montgomery, S.A., Åsberg, M., 1979. A new depression scale designed to be sensitive to change. *Br. J. Psychiatry* 134, 382–389.
- Moylan, S., Maes, M., Wray, N.R., Berk, M., 2013. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. *Mol. Psychiatry* 18, 595–606.
- Mundt, J.C., Marks, I.M., Shear, M.K., Greist, J.H., 2002. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *Br. J. Psychiatry* 180, 461–464.
- Olgati, P., Fanelli, G., Serretti, A., 2023. Age or age of onset: which is the best criterion to classify late-life depression? *Int. Clin. Psychopharmacol.* 38, 223–230.
- Rhebergen, D., Beekman, A.T.F., de Graaf, R., Nolen, W.A., Spijker, J., Hoogendijk, W.J., Penninx, B.W.J.H., 2010. Trajectories of recovery of social and physical functioning in major depression, dysthymic disorder and double depression: a 3-year follow-up. *J. Affect. Disord.* 124, 148–156.
- Rossum, R.C., Solberg, L.I., Vazquez-Benitez, G., Whitebird, R.R., Crain, A.L., Beck, A., Unützer, J., 2016. Predictors of poor response to depression treatment in primary care. *Psychiatr. Serv.* 67, 1362–1367.
- Rush, A.J., Gullion, C.M., Basco, M.R., Jarrett, R.B., Trivedi, M.H., 1996. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol. Med.* 26, 477–486.
- Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., Niederehe, G., Thase, M.E., Lavori, P.W., Lebowitz, B.D., McGrath, P.J., Rosenbaum, J.F., Sackeim, H.A., Kupfer, D.J., Luther, J., Fava, M., 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am. J. Psychiatry* 163, 1905–1917.
- Rush, A.J., Wisniewski, S.R., Zisook, S., Fava, M., Sung, S.C., Haley, C.L., Chan, H.N., Gilmer, W.S., Warden, D., Nierenberg, A.A., Balasubramani, G.K., Gaynes, B.N., Trivedi, M.H., Hollon, S.D., 2012. Is prior course of illness relevant to acute or longer-term outcomes in depressed out-patients? A STAR*D report. *Psychol. Med.* 42, 1131–1149.
- Rytsälä, H.J., Melartin, T.K., Leskelä, U.S., Sokero, T.P., Lestelä-Mielonen, P.S., Isometsä, E.T., 2005. Functional and work disability in major depressive disorder. *J. Nerv. Ment. Dis.* 193, 189–195.
- Schwarz, R., Munkholm, K., Christensen, M.S., Kessing, L.V., Vinberg, M., 2024. Functioning in patients with major depressive disorder in remission: a systematic review and meta-analysis. *J. Affect. Disord.* 363, 112–123.
- Serretti, A., 2024. Modulating factors in mood disorders treatment. *Int. Clin. Psychopharmacol.* 39, 47–50.
- Sforzini, L., Worrell, C., Kose, M., Anderson, I.M., Aouizerate, B., Arolt, V., Bauer, M., Baune, B.T., Blier, P., Cleare, A.J., Cowen, P.J., Dinan, T.G., Fagioli, A., Ferrier, I. N., Hegerl, U., Krystal, A.D., Leboyer, M., McAllister-Williams, R.H., McIntyre, R.S., Meyer-Lindenberg, A., Miller, A.H., Nemeroff, C.B., Normann, C., Nutt, D., Pallanti, S., Pani, L., Penninx, B.W.J.H., Schatzberg, A.F., Shelton, R.C., Yatham, L. N., Young, A.H., Zahn, R., Aislaithner, G., Butlen-Ducuing, F., Fletcher, C., Haberkamp, M., Laughren, T., Mäntylä, F.-L., Schruers, K., Thomson, A., Arteaga-Henriquez, G., Benedetti, F., Cash-Gibson, L., Chae, W.R., De Smedt, H., Gold, S.M., Hoogendijk, W.J.G., Mondragón, V.J., Maron, E., Martynowicz, J., Melloni, E., Otte, C., Perez-Fuentes, G., Poletti, S., Schmidt, M.E., van de Ketterij, E., Woo, K., Flossbach, Y., Ramos-Quiroga, J.A., Savitz, A.J., Pariente, C.M., 2022. A delphi-method-based consensus guideline for definition of treatment-resistant depression for clinical trials. *Mol. Psychiatry* 27, 1286–1299.
- Sheehan, D.V., 1983. *The Anxiety Disease*. Scribner Book Company.
- Souery, D., Oswald, P., Massat, I., Bailer, U., Bollen, J., Demyttenaere, K., Kasper, S., Lecrubier, Y., Montgomery, S., Serretti, A., Zohar, J., Mendlewicz, J., Group for the Study of Resistant Depression, 2007. Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. *J. Clin. Psychiatry* 68, 1062–1070.
- Sung, S.C., Haley, C.L., Wisniewski, S.R., Fava, M., Nierenberg, A.A., Warden, D., Morris, D.W., Kurian, B.T., Trivedi, M.H., Rush, A.J., CO-MED Study Team, 2012. The impact of chronic depression on acute and long-term outcomes in a randomized trial comparing selective serotonin reuptake inhibitor monotherapy versus each of 2 different antidepressant medication combinations. *J. Clin. Psychiatry* 73, 967–976.
- Sung, S.C., Wisniewski, S.R., Balasubramani, G.K., Zisook, S., Kurian, B., Martin, N.G., Trivedi, M.H., Rush, A.J., CO-MED Study Team, 2013. Does early-onset chronic or recurrent major depression impact outcomes with antidepressant medications? A CO-MED trial report. *Psychol. Med.* 43, 945–960.
- van Velzen, L.S., Kelly, S., Isaev, D., Aleman, A., Aftanas, L.I., Bauer, J., Baune, B.T., Brak, I.V., Carballedo, A., Connolly, C.G., Couvy-Duchesne, B., Cullen, K.R., Danilenko, K.V., Dannlowski, U., Enneking, V., Filimonova, E., Förster, K., Frodl, T., Gotlib, I.H., Groenewold, N.A., Grotegerd, D., Harris, M.A., Hatton, S.N., Hawkins, E. L., Hickie, I.B., Ho, T.C., Jansen, A., Kircher, T., Klimes-Dougan, B., Kochunov, P., Krug, A., Lagopoulos, J., Lee, R., Lett, T.A., Li, M., MacMaster, F.P., Martin, N.G., McIntosh, A.M., McLellan, Q., Meinert, S., Nenadić, I., Osipov, E., Penninx, B.W.J.H., Portella, M.J., Repple, J., Roos, A., Sacchet, M.D., Sämann, P.G., Schnell, K., Shen, X., Sim, K., Stein, D.J., van Tol, M.-J., Tomyshev, A.S., Tozzi, L., Veer, I.M., Vermeiren, R., Vives-Gilabert, Y., Walter, H., Walter, M., van der Wee, N.J.A., van der Werf, S.J.A., Schreiner, M.W., Whalley, H.C., Wright, M.J., Yang, T.T., Zhu, A., Veltman, D.J., Thompson, P.M., Jahanshad, N., Schmaal, L., 2020. White matter disturbances in major depressive disorder: a coordinated analysis across 20 international cohorts in the ENIGMA MDD working group. *Mol. Psychiatry* 25, 1511–1525.
- Wilson, S., Hicks, B.M., Foster, K.T., McGue, M., Iacono, W.G., 2015. Age of onset and course of major depressive disorder: associations with psychosocial functioning outcomes in adulthood. *Psychol. Med.* 45, 505–514.
- World Health Organization, 2011. *Global Burden of Mental Disorders and the Need for a Comprehensive, Coordinated Response from Health and Social Sectors at the Country Level*.
- Zimmerman, M., McGlinchey, J.B., Posternak, M.A., Friedman, M., Boerescu, D., Attiullah, N., 2008. Remission in depressed outpatients: more than just symptom resolution? *J. Psychiatr. Res.* 42, 797–801.