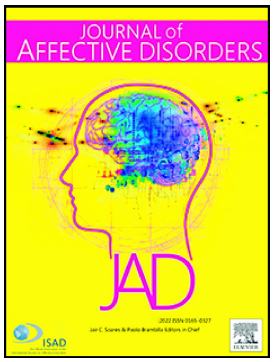

The complexity of treatment-resistant depression: A data-driven approach

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The Complexity of Treatment-Resistant Depression: A Data-driven Approach

Felicitas Rost[a,b]*; Thomas Booker[a,c], Aneliya Gonsard[a]; Giulio de Felice[a]; Lorena Asseburg[a], Javier Malda-Castillo[a]; Iakovina Koutoufa[a]; Hannah Ridsdale[a], Rebecca Johnson[a], David Taylor[a]; and Peter Fonagy[c]

a Tavistock and Portman NHS Foundation Trust, London, UK

b The Open University, School of Psychology and Psychotherapy, Faculty of Arts and Social Sciences, Milton Keynes, UK.

c Research Department of Clinical, Educational and Health Psychology, University College London, UK

*Corresponding author at: Dr Felicitas Rost. The Open University, School of Psychology and Psychotherapy, Faculty of Arts and Social Sciences, Milton Keynes, UK.

E-mail: felicitas.rost@open.ac.uk

1. Introduction

The global prevalence of depression has risen by 25% since the start of the Covid-19 pandemic (WHO, 2022). This surge is particularly concerning given that the incidence of depression was already escalating before the pandemic began. Approximately 175 million individuals globally are afflicted with major depressive disorder (MDD) (Global Health Data Exchange, 2023). Although treatment availability has advanced in high-income countries, it remains suboptimal, leaving many underserved (Jorm et al., 2017). Those with severe

manifestations of depression who fail to benefit from primary treatment modalities are particularly vulnerable.

The notion of treatment-resistant depression (TRD) was introduced to elucidate the considerable proportion of MDD patients who are unresponsive to at least two antidepressant regimens, spurring extensive research into its underpinnings and potential interventions (Thase & Rush, 1997). The prevalence of TRD, contingent on whether one employs the response (<25% symptom diminution) or remission (<50% symptom diminution) criteria, ranges from 21.7% to 44% in clinical investigations (Li, 2023). A salient characteristic of TRD-afflicted individuals is their elevated contribution to the overall disease burden of depression. They incur not only higher direct treatment costs but also greater indirect expenses such as family care, hospitalization, and lost wages, exceeding those with non-treatment-resistant depression (Fabbri et al., 2021; Gibson et al., 2010; Ivanova et al., 2010). Economic ramifications further extend to increased productivity losses due to unemployment and higher dependency on state benefits (Mrazek et al., 2014). Critically, the risk of suicide for TRD patients is increased (Pérez-Sola et al., 2021; Reutfors et al., 2018), and in certain European countries, such as Belgium and the Netherlands, TRD constitutes approximately half of requests for assisted dying (Kim et al., 2016). Clearly, the economic toll mirrors a profound human cost, marked by intense distress, diminished quality of life and, at times, fatal outcomes.

Despite the clinical significance of TRD, our understanding of its clinical manifestation and characteristics remains limited, occasionally leading to detrimental stigmatization and restricted access to treatment (Bennabi et al., 2015; Demyttenaere & Van Duppen, 2019). Hence, there is an imperative to not only revisit our mental health services but also refine our research pursuits to better understand this subtype of depression. Numerous scholars have identified significant challenges regarding TRD's definition and

evaluation (e.g., Brown et al., 2019; Demyttenaere & Van Duppen, 2019; Gaynes et al., 2020; Li, 2023; Murphy et al., 2017; Nemeroff, 2007). The prevailing definition presupposes a consensus on what constitutes an appropriate dose of antidepressant medication (ADM) and its desired outcome, an agreement that remains elusive. Moreover, most definitions overlook psychological interventions, despite numerous treatment guidelines advocating for the integration of short-term psychotherapy with ADM (Bauer et al., 2007; Cleare et al., 2015; Kennedy et al., 2016; Malhi & Mann, 2018; NICE, 2022). Most critically, these definitions often neglect observed intricacies such as comorbid diagnoses, functional challenges, interpersonal issues, and other potential sustaining factors.

Two recent systematic reviews underscored a significant inconsistency in how studies define and assess TRD, with methodologies markedly deviating from clinical applications (Brown et al., 2019; Gaynes et al., 2020). These findings accentuate an immediate demand to re-evaluate the TRD framework. Addressing this, Sforzini et al. (2022) introduced a Delphi-method-derived consensus guideline for defining TRD in research contexts. Although they acknowledge coexisting personality disorders (PDs) and other mental health conditions, their framework remains tethered to the existing definition of TRD. Meanwhile, some critics, challenging the underlying biomedical perspective, have advocated for a paradigmatic shift to enhance both research and treatment outcomes (Johnstone et al., 2018; Murphy et al., 2017).

Consistent with several authors (e.g., Cepeda et al., 2018; Pérez-Sola et al., 2021), we suggest that an effective reconceptualization of TRD should be data-driven rather than consensus-driven, promoting a more robust empirical model of TRD. The recent accessibility of expansive insurance and healthcare databases offers a promising avenue for these data-driven methodologies. However, although these databases facilitate statistically significant comparisons between populations of depressed individuals with and without TRD, the results

are constrained by challenges related to the accurate identification of MDD and TRD, and the nature of the data gathered.

The objective of this study is to provide a detailed socio-demographic and clinical profile of a cohort diagnosed with TRD. The data are sourced from a pragmatic randomized controlled trial, the Tavistock Adult Depression Study (TADS) (Fonagy et al., 2015), carried out in the UK, where the majority of patients with chronic and severe depression are treated in primary care settings. To the best of our knowledge, this is the first study to offer such an extensive dataset, collated from diverse sources such as primary care records, self-reports, and clinical evaluations.

2. Method

2.1. Data and Study Design

We analyzed data from the Tavistock Adult Depression Study (TADS, Fonagy et al., 2015), a randomized controlled trial comparing the efficacy of long-term psychoanalytic psychotherapy (LTPP) with treatment as usual (TAU). This trial was conducted at the Tavistock and Portman NHS Foundation Trust in London. An important aim of the RCT was to increase the generalization of experimental findings to real-world settings (ecological validity), and as such, inclusion and exclusion criteria were kept to a minimum. A comprehensive overview of TADS's design and primary outcomes can be found in previous publications (Fonagy et al., 2015; Rost et al., 2019; Taylor et al., 2012). LTPP entailed weekly sessions facilitated by experienced psychotherapists. TAU encompassed an array of short-term therapies endorsed by the National Institute for Health and Care Excellence (NICE, 2009), such as cognitive-behavioral therapy, counselling, and other brief psychotherapies. The study secured approval from the NHS West Midlands Research Ethics Committee (MREC02/07/035), and participants gave informed consent before randomization.

2.2. Participants

The cohort comprised 44 (35%) male and 85 (65%) female participants. Following the TADS guidelines, a patient was classified with TRD if they had a current diagnosis of MDD determined by the Structured Clinical Interview for DSM-IV (SCID-I, First & Gibbon, 2004) coupled with a minimum history of depression of 2 years' duration and at least two unsuccessful prior treatments, one with an ADM and another with either an additional ADM or psychotherapeutic intervention. This information was confirmed through interviews and medical record reviews. Exclusion criteria for patients included bipolar disorder, psychosis, or a documented diagnosis of substance abuse or dependence. A high proportion (82%) of participants identified as white, and participants' ages ranged from 22 to 66 years (M = 44, SD = 10.27). See Table 1 for a full participant description.

2.3. Assessments and Measures

Socio-demographic and Treatment History: Data on socio-demographics, prior treatment failures and suicidality were sourced from the Client Service Receipt Inventory (CSRI, Beecham & Knapp, 1992), a self-report tool capturing demographic and healthcare utilization details, and the baseline SCID-I assessment. This information was cross-referenced with participants' primary care (general practice; GP) medical records.

Depression Severity:

Hamilton Rating Scale of Depression (HRSD) (Hamilton, 1967): A widely recognized interview-based instrument for assessing depression severity with known psychometric reliability (Bagby et al., 2004). This 17-item scale has scores ranging from 0 to 53. Dual blind

assessors conducted ratings, achieving an excellent intra-class correlation coefficient (ICC) of .89.

Beck Depression Inventory-II (BDI-II) (Beck et al., 1996): A commonly used self-report tool for depression measurement, comprising 21 items with scores ranging from 0 to 63. It demonstrates high reliability (coefficient alpha of .92 for outpatient samples) and diagnostic efficacy (Nezu et al., 2000).

Illness Duration and History of Suicidal Ideation: These details were ascertained via patient self-report (using the CSRI and SCID-I) and subsequently validated against patients' GP medical records.

Functional Assessment:

Global Assessment of Functioning Scale (GAF) (Hilsenroth et al., 2000): An observer-rated tool gauging overall mental functioning across a theoretical 0–100 spectrum. GAF ratings were embedded within the SCID-I interview and counterchecked by an independent evaluator, resulting in an ICC of .91.

Clinical Outcomes in Routine Evaluation questionnaire (CORE-OM) (Evans et al., 2000): A 34-item self-report tool measuring subjective wellbeing, common problems, social functioning, and suicide risk, scaled from 0 (not at all) to 4 (almost always). The aggregate score signifies overall psychological distress. Standardized scores, indicating clinical thresholds and distress intensities for the total and all sub-scores, were adopted as described in the official guidelines (Evans et al., 2002). All dimensions exhibit strong internal consistency (ranging .75–.95), convergent validity, and change sensitivity (Evans et al., 2000).

Quality of Life: The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-les-Q) (Endicott et al., 1993) was employed to assess quality of life. This 93-item self-report tool

covers eight life domains: general activities, physical health, subjective feelings, social relationships, leisure activities, work, household duties, and school (last three when relevant). Items are rated on a five-point scale reflecting satisfaction in the past week. Scores are expressed as percentages of the maximum, with higher percentages denoting greater satisfaction. The Q-les-Q exhibits satisfactory test–retest reliability (.60–.89) and its subscales show high internal consistency (.82–.93) (Schechter et al., 2007). Severity criteria from Rapaport et al. (2005) were adopted, defining severe impairment as scores two or more standard deviations below community norms.

Comorbidity:

Psychiatric Disorders: Diagnosis relied on the SCID-I interview for DSM-IV, a standard tool with suitable inter-rater reliability (0.60–0.82; Lobbestael et al., 2011).

Personality Disorders: The Shedler–Westen Assessment Procedure Q-sort (SWAP-II) (Shedler & Westen, 2007) was utilized. This tool comprises 200 statements describing personality or psychological features, rated on a scale from 0 to 7. It offers clinical threshold guidelines aligned with DSM categorization. The reliability, validity, and inter-rater consistency of the SWAP-II are well established (Westen & Muderrisoglu, 2003; Westen & Shedler, 1999). Trained assistants who reviewed comprehensive baseline interviews performed SWAP-II ratings. Owing to missing data for three participants, PD ratings were made for 126 participants, of which 50.8% were double rated. The ICC indicated robust inter-rater consistency.

Physical Health: Information was sourced from the self-report CSRI and corroborated by patients' medical records. Individual illnesses were categorized in accordance with the area of health they captured. For example, musculoskeletal problems included arthritis, back pain, knee and joint pain, osteoporosis, and muscle spasms; gastrointestinal problems included

irritable bowel syndrome, bowel problems, and stomach pain and upset; genitourinary problems included chronic bladder symptoms, incontinence, fibroids, and kidney problems.

Adverse Events: Information on adverse events (AEs) was sourced from retrospective accounts provided during SCID-I interviews, the CSRI, and corroborated by medical records. Adopting criteria from Bremner et al. (2000), researchers coded AEs occurring in childhood (≤ 11 years), adolescence (12-18 years), and adulthood (≥19 years), encompassing experiences such as abuse, parental loss, and suicide of family members. In line with established methodologies for assessing adverse childhood experience (ACEs) (Bellis et al., 2014), event counts served as a surrogate for the severity of AEs.

2.4. Procedure and Data Analysis

Following the TADS protocol, participants underwent comprehensive research and clinical diagnostic evaluations prior to randomization. Data extraction and categorization were managed by two independent research assistants. Any discrepancies between raters were arbitrated by a third party, the first author. Descriptive statistics and composite scores were generated using SPSS Statistics 23 (IBM).

3. Results

3.1. Socio-demographic Profile

Table 1 shows the socio-demographic and clinical characteristics of the cohort.

Insert Table 1 here.

3.2. History of Treatment

Only 24% of participants had had only two previous unsuccessful treatments; the remainder had pursued more extensive interventions. Every participant had trialed multiple courses of ADM over their lifetime, with some maintaining continuous use of ADM for extensive periods. Table 1 details the diversity of psychological treatments reported, with numbers of treatments varying between two and nine and a mean of 3.7 (*SD* = 1.57).

3.3. Depression Metrics and Disease Chronology

The entire cohort was diagnosed with MDD, of which 86% (*n* = 111) manifested melancholic features and 76.7% (*n* = 99) were co-diagnosed with dysthymic disorder. The mean duration of depression spanned 25.3 years (*SD* = 12.28), and the current MDD episode had lasted, on average, 3.7 years (*SD* = 2.95). The age at onset of depression ranged from 4 to 51 years, with a mean of 18.69 (*SD* = 10.79). Thirty-six (27.9%) had commenced their depressive episodes in childhood, and 33.3% (*n* = 43) began in adolescence. Table 1 delineates the depression severity metrics: the mean BDI score was 36.6 (*SD* = 9.8), and 75.9% (*n* = 98) of participants' scores indicated severe symptoms. The mean HRSD score was 20.1 (SD = 5.0), and 56.6% (*n* = 73) of scores were within the severe spectrum.

3.4. Functional Competence and Life Quality

As shown in Table 1, the mean GAF score was 48.8 (*SD* = 6.6), indicating pronounced global functional challenges with 54.2% (*n* = 70) facing severe restrictions in global functioning. With respect to the CORE-OM, the mean score was 2.24 (*SD* = .61), with 89.2% (*n* = 115) of participants surpassing the clinical threshold. Data on all subscales (see Table 1) underscore pronounced functional difficulties, with 62% (*n* = 80) of participants exceeding the clinical threshold for suicidal tendencies. Participants' quality of life was significantly compromised as evidenced by the Q-les-Q mean score of 34.2 (*SD* = 15.13).

Across all subscales, satisfaction metrics was low, confirming widespread life-domain deficits.

3.5. Suicidality

Of the participants, 44.9% (*n* = 58) had attempted suicide at least once, and many reported multiple attempts (see Table 1). Overdosing was the method in 62% (*n* = 36) of these attempts. A number of participants had made suicide attempts in early life: 10.9% (*n* = 14) made their first attempt during childhood and 6.9% (*n* = 9) during adolescence. Among the participants, 9.3% (*n* = 12) reported a parent's suicide during their childhood. Initial assessments revealed significant suicidal thoughts and ideation in just over half of the participants. During the study, 19 participants (14.7%) attempted suicide, with one fatality in the TAU group. Post-study data indicated an additional four suicides of three from the TAU group and one from the LTPP group; the latter participant , who had withdrawn from the study prematurely.

3.6. Comorbid Psychiatric Disorders

A minority, 17.1% (*n* = 22), of participants had no additional psychiatric diagnoses. Of the remaining participants, 30.2% (*n* = 39) were diagnosed with one comorbidity, 33.3% (*n* = 43) with two, and 20.9% (*n* = 27) with three or more than three. Figure 1 shows the prevalence of individual disorders, of which generalized anxiety disorder was the most common (*n* = 61; 47%). Notably, although those who were receiving active psychiatric treatment for addiction were excluded from the study, 9.3% (*n* = 12) met criteria for alcohol dependency and another 9.3% (*n* = 12) for substance dependency.

Insert Figure 1 here.

Regarding PDs, 82.2% (*n* = 106) met diagnostic criteria for at least one PD: 38.8% (*n* = 50) had one, 27.1% (*n* = 35) had two, 13.9% (*n* = 18) had three, and 3.1% (*n* = 4) had four PD diagnoses. Figure 2 shows the prevalence of specific PDs, of which schizoid PD (*n* = 58; 44.9%) and avoidant PD (*n* = 49; 37.9%) were the most common.

Insert Figure 2 here.

3.7. Comorbid Physical Health Problems

Most participants (*n* = 90; 69.8%) reported having one or more physical ailments; 25.6% (*n* = 33) had one ailment, 13.9% (*n* = 18) had two, 10.9% (*n* = 14) had three, and 19.4% (*n* = 25) had four or more. Figure 3 provides details of the percentages of participants with specific physical health problems. Musculoskeletal problems were the most common (*n* = 39; 30.2%), followed by gastrointestinal (n = 25; 19.4%) and genitourinary (*n* = 21; 16.3%) problems. Additionally, 14.7% (*n* = 19) indicated cardiorespiratory problems, primarily asthma, and 7.8% (*n* = 10) had a cancer diagnosis.

Insert Figure 3 here.

3.8. Adverse Events

In general, participants had a pattern of multiple and accumulative AEs across life stages, and a high proportion of the sample (*n* = 109; 8.5%) reporting at least one during adulthood and 79.8% (*n* = 103) reported at least one during childhood. ACEs ranged between one and six events, with a total of 260 s across all participants (*M* = 2.02, *SD* = 1.66); 27.9% (*n* = 36) reported one ACE, 14.7% (*n* = 19) two, 17.1% (*n* = 22) three, and 20.2% (*n* = 26)

four or more. Although the total number of ACEs decreased to 201 during adolescence (range 1–6; *M* = 1.56, *SD* = 1.41), 76.7% (*n* = 99) still reported at least one event, and 19.4% (*n* = 25) reported three or more. In adulthood, there were 245 AEs reported (range 1–6; *M* = 1.90, *SD* = 1.49), with 83.7% (*n* = 108) of participants experiencing at least one event and 31.0% (*n* = 40) reporting three or more. Specific frequencies of AEs during each life stage are detailed in Table 2, with emotional abuse being the most prevalent, followed by intrafamilial physical abuse, sexual abuse, peer bullying and exposure to domestic violence.

Insert Table 2 here.

Experience of significant early losses and neglect was notable: 13 (10.1%) of participants had lost a significant other by death before age 11, and a further 16 (12.4%) by age 18. Whilst parental separation was reported (13.2% during childhood and 18.6% during adolescence), of note was the absence of one parent in 13% (*n* = 17) during childhood, and in 19.4 (*n* = 25) during adolescence. Neglect was reported by 14.7% (*n* =19) during childhood and 17.1% (*n* = 22) during adolescence. Peer bullying was reported by 25.6% (*n* =33) during childhood and 13.9% (*n* =18) in adolescence. In adulthood, the most reported AEs were physical abuse (*n* = 28; 21.7%), sexual abuse *n* = 23; 17,8%), and emotional abuse (*n* = 15; 11.6%). Specific traumatic experiences included rape (*n* = 9 ; 6.9%) and the death of a significant other, including their young child (*n* = 6; 4.7%) and partner (*n* = 7; 5.4%)

4. Discussion

We sought to offer an in-depth socio-demographic and clinical characterization of a cohort of patients diagnosed with TRD to advance the crucial endeavor of refining our understanding of this condition (Brown et al., 2019; Gaynes et al., 2020). To the best of our

understanding, this represents the first study to use such a thorough evaluation, incorporating both robust self-report and hetero-assessment methods. The data underscore the insufficiency of exclusively examining symptoms of depression, their intensity, and trends of persistence or remission post-treatment. Instead, they suggest the necessity to consider broader aspects that appear central to both comprehending and defining TRD. Our observations elucidate TRD as a multifaceted syndrome marked by various severity indicators and indicate that TRD patients are a distinct group contending with extensive challenges across diverse life areas, sometimes with lethal outcomes.

Our findings confirm results of other studies that reported associations between TRD and depression intensity and persistence (e.g., Cepeda et al., 2018) and early onset (Dudek et al., 2010; Souery et al., 2007). The mean lifetime period of depression reported was 25 years and 76% of individuals met criteria for double depression, that is, the coexistence of MDD and persistent dysthymic disorder. According to both the observer-rated HRSD and self-rated BDI, the vast majority of participants scored within the severe range of depression symptomatology. Compared with 45 studies reported in a recent meta-analysis of the transdiagnostic treatment of depression and anxiety (Cuijpers et al., 2023), our sample seems to be much more severely affected in terms of both depression severity and other clinical indicators. For example, of the 13 studies using the BDI, two reported severity of mild depression and 11 of moderate depression. In the two studies using the HRSD, participants fell within mild and moderate ranges, respectively. Only in five studies did participants fall within severe ranges on their respective self-report measures, which included the Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer & Williams, 2001) and the Hospital Anxiety and Depression Scale (HADS, Zigmond & Snaith, 1983).

Moreover, aligned with extant literature on risk factors, our results corroborate findings from studies that observed a co-existence of TRD with other psychiatric conditions

(Crawford et al., 2007; Souery et al., 2007), PDs (Johnson et al., 2005; Souery et al., 2007; Stevenson et al., 2016), severe physical ailments (Cepeda et al., 2018; Döme et al., 2021; Hung et al., 2019), deteriorated quality of life and relational challenges (DiBernardo et al., 2018; Murphy et al., 2017), elevated instances of suicide attempts and completions (Pérez-Sola et al., 2021; Reutfors et al., 2018; Souery et al., 2007), and reported ACEs (e.g., Kaplan & Klinetob, 2000; Nelson et al., 2017; Tunnard et al., 2014; Yrondi et al., 2020). Although some studies have also found a higher prevalence among women (Hung et al., 2019; Lähteenvuo et al., 2022), it remains to be established whether female sex is a risk factor for TRD. Given that women are twice as likely as men to be diagnosed with major depression (Hyde and Mezulis, 2020), and are more likely to be prescribed ADM (McIntyre et al., 2023), the ratio found in the present study might align with established sex differences. Overall, our findings propose potential criteria for a more encompassing definition of TRD, suggesting a broader reconceptualization than the recent consensus-based definition presented by Sforzini et al. (2022).

The relationship between MDD and PD has been established, with an approximate 50% prevalence of comorbidity (Voytenko & Huprich, 2022). Systematic reviews (Newton-Howes et al., 2006, 2014; Young, 2020) concur that this co-occurrence yields poorer treatment outcomes. Evidence indicates that patients with dual diagnoses of MDD and PD often have earlier onset of illness, coupled with a more severe and prolonged trajectory of depression (e.g., Grilo et al., 2010; Skodol et al., 2011). Yet, there has been little research examining the direct TRD–PD relationship, and few studies have elucidated associations with specific PDs. Stevenson et al. (2016) identified 41% of their TRD cohort exhibiting at least one PD, predominantly borderline PD (BPD) at 62%. In contrast, our findings show that a very high proportion (89%) of participants have at least one PD, with many meeting multiple

PD criteria, chiefly for schizoid PD (45%) and paranoid PD (38%). As Voytenko and Huprich (2022) posited, the oversight in diagnosing and addressing underlying personality issues may contribute to treatment inefficacy in TRD.

Our cohort also demonstrated significant comorbidities with other psychiatric and physical ailments. Links between TRD and disorders such as anxiety, obsessive–compulsive disorder, substance abuse, and insomnia are established (e.g., Berlim & Turecki, 2007; Brown et al., 2019; Cepeda et al., 2018; Fabbri et al., 2021; Huang et al., 2020; Souery et al., 2007). However, few studies have probed the TRD–physical health nexus, and those that exist have yielded inconclusive results. Some reported no tangible physical health distinctions between TRD and non-TRD MDD (e.g., Amital et al., 2013), whereas others emphasized an increased prevalence of specific ailments in TRD cohorts (e.g., Döme et al., 2021; Huang et al., 2020). Notably, Amital et al. (2013) solely identified marginal significance for cancer, a finding echoed in our sample. The need for research to rigorously investigate the spectrum of physical health conditions in TRD is evident.

Although the connection between ACEs and MDD is recognized (e.g., Heim & Nemeroff, 2001; Hovens et al., 2012), few studies have focused on the history of ACE occurrence in individuals with TRD. The ACE frequencies in our study substantially exceed those reported in community, general psychiatric, and specific TRD samples (e.g., Anda et al., 2002; Bellis et al., 2014; Laporte et al., 2011; Lu et al., 2008; Negele et al., 2015; Stevenson et al., 2016). Tunnard et al. (2014) reported that 62% of their TRD group had at least one ACE. Predominant ACEs in our study included emotional, physical, and sexual abuse, and parental loss. Although all these adversities have been correlated with severe depression (Negele et al., 2015; Peng et al., 2022), their role in TRD requires further exploration. The recurring nature of the AEs faced by the individuals in this sample is clearly

discernable. Hence, unique person–environment interactions might not only underpin the onset of psychopathology but also perpetuate it into adulthood (Luyten et al., 2006).

What is clear, though, is that such AEs can profoundly impact on individuals' social and occupational functioning. Consistent with prior research (e.g., DiBernardo et al., 2018), our cohort exhibited significant impairments in these areas. Of grave concern are our findings highlighting the depth of the participants' struggles. Elevated levels of suicidal ideation and a history of serious suicide attempts were prevalent, with 17.8% of participants reporting their first attempt during childhood or adolescence. Tragically, 3.8% of our participants died by suicide. This finding aligns with studies that reported a higher suicide rate among TRD patients than among those with non-TRD depression (e.g., Pérez-Sola et al., 2021; Reutfors et al., 2018), emphasizing the dire need for effective clinical interventions. Although our study sheds light on a spectrum of ACEs that might contributing to the onset of TRD, the cross-sectional design limits our ability to discern whether these factors are outcomes or contributors to TRD. It is plausible that a dynamic interaction exists between these factors, cumulatively exacerbating disability and hampering recovery.

Contextually, our findings might touch upon broader concerns regarding diagnostic taxonomies. The validity of these classifications often hinges on significant co-occurrence with other presumed distinct disorders (Kessler et al., 2005; Merikangas et al., 2010). It is conceivable that this pattern arises from the inherent limitations of our diagnostic system failing to capture the true essence of nature (Kessler et al., 2005). Comorbidity extends beyond diagnoses; symptom overlap is commonplace among recognized indicators of mental disorder (e.g., Budde et al., 2019; Merikangas et al., 2010). If we reframe TRD as a marker of a latent transdiagnostic continuum, its concurrence with other diagnoses might be seen as shared phenotypic and genotypic traits (Goldberg, 2015). Recent research employing the bifactor model posits that a single factor, known as the p factor (Caspi et al., 2014), accounts

for the common variance in all symptom-level variables, separate from covariance explained by symptom clusters (Markon, 2019). Accordingly, TRD may be indicative of elevated p factor scores, which predominantly capture what is gauged during assessments (Constantinou & Fonagy, 2019). The bifactor model consistently excels in elucidating psychopathology data covariation (Caspi et al., 2014; Gluschkoff et al., 2019; Kim & Eaton, 2015; Lahey et al., 2012, 2018; Pettersson et al., 2016). The p factor potentially encapsulates a general predisposition toward any psychopathology (Caspi & Moffitt, 2018) or an aggregate severity index (Smith et al., 2020). Elevated p factor scores correlate with early adverse experiences and familial psychopathology history (Caspi et al., 2014; Deutz et al., 2020; Hyland et al., 2021; Lahey et al., 2012; Martel et al., 2017; Schaefer et al., 2018). Pertinently, the p factor is linked with socioeconomic disadvantage markers (Blanco et al., 2021; McElroy et al., 2018; Snyder et al., 2016, 2019). Future investigations should further demystify this overarching psychopathology construct, ultimately guiding more effective therapeutic strategies.

4.1. Limitations and Future Research

Our study has inherent limitations. The potential for recall bias, particularly in retrospective data such as prior treatments, ACEs, and suicide attempts, cannot be ignored. Additionally, we did not probe the complex interrelationships or potential interactions among the diverse variables. Analyzing such multifaceted data requires robust computational capabilities (Behn, 2019). For meaningful interpretation of relationships, longitudinal methodologies are essential. The intricate, bidirectional, and potentially synergistic relationships between variables might challenge clear elucidation (Johnstone et al., 2018). Notably, our data indicate that individuals had frequently experienced ACEs. The persistence of some ACEs into adulthood further complicates discernment of their distinct impacts. The absence of a control group limits our ability to make relative comparisons. Hence, we cannot

determine whether TRD patients exhibit differing patterns of suicide attempts, health concerns, or functional impairments compared with individuals with untreated or remitted depression. Although our trial's pragmatic design facilitated broader inclusion, promoting a more representative clinical sample, the broader generalizability and relevance of the findings is uncertain due to the relatively small sample size and predominantly White female sample. While we can expect women to represent the majority of participants in a TRD study (McIntyre et al., 2023), our study did not include an option of non-binary gender. It is also notably limited in that it does not include a broader range of people from different ethnic backgrounds to allow generalizability across different cultures, although our cohort appears to be representative of the distribution of ethnicity in England and Wales, with the expetion that our sample includes a slightly higher percentage of people identifying as Black and a smaller percentage identfying as Asian (Office for National Statistics, 2021). Moreover, our study is anchored to the prevailing diagnostic framework for depression. As highlighted by some authors (e.g., Murphy et al., 2017), the ambiguity surrounding the transition to "treatment resistance" might be rooted in our understanding of depression. It is conceivable that current classifications might be outdated. Subsequent research should align with the clinical nuances of TRD and treatment modalities. Although we anticipate our findings to steer this discourse, we concede that more transformative shifts may be essential. As advocated by Johnstone et al. (2018), an approach that interprets distress as a meaningful response to life events, molded by cultural and psychosocial factors and past experiences, might be more pertinent. Formulation-driven or trauma-aware perspectives might offer a more effective alternative to the dominant symptom-focused model.

5. Conclusion

Our study highlights a population grappling with a debilitating condition that is critically underserved in terms of therapeutic provision. An emerging consensus suggests that without a unified definition of TRD, research progression may stall. Definitional endeavors should be data-informed, veering away from potentially biased consensus-based delineations influenced by healthcare structures and clinical notions. Our socio-demographic and clinical characterization portrays a multifaceted profile, indicative of a unique patient cluster with myriad challenges contributing to their perceived "resistance" to suboptimal care. We urge researchers and clinicians to present comprehensive profiles of their cohorts, spanning both trial settings and real-world contexts. This can foster a richer understanding of TRD, propelling research aimed at identifying enhanced treatment strategies.

Tables

Table 1: Demographic and clinical description of the sample (*N* = 129)

Description	Count (%) or mean (*SD*)
Demographic details	
Age (years, mean ± *SD* (range))	44.35 ± 10.27 (22–66)
Sex (female)	85 (65.9%)
Ethnicity	
White British	76 (58.9%)
White Other	28 (21.7%)
Asian	9 (6.9%)
Black	8 (6.2%)
Mixed	2 (1.6%)
Other	4 (3.1%)
Not disclosed	2 (1.6%)
Educational status (tertiary)	61 (47.3%)
Employment	53 (41.1%)
Receipt of benefits	68 (52.7%)
Marital status (single)	67 (51.9%)
Relationship status (in romantic relationship)	42 (32.6%)
Living alone	67 (51.9%)
Living with children	18 (13.9%)
Children (at least one)	50 (38.8%)
Child under the age of 18	24 (18.6%)
Previous treatment attempts	
Two	31 (24.0%)
Three	38 (29.5%)
Four	26 (20.2%)
Five	19 (14.7%)
Six or more	15 (11.6%)
Counselling (at least one course)	126 (97.7%)
Two courses	26 (20.2%)
Cognitive-behavioral therapy (at least one course)	43 (33.3%)
Two courses	5 (3.9%)

Psychodynamic therapy (at least one course)	12 (9.3%)
Two courses	1 (0.8%)
Psychotherapy, unspecified (at least one course)	66 (51.2%)
One course	48 (37.2%)
Two or more courses	18 (13.9%)
Group psychotherapy (at least one course)	24 (18.6%)
Two courses	6 (4.7%)
Clinical psychologist	47 (36.4%)
Crisis team and community mental health service	66 (51.2%)
Inpatient psychiatric stay (at least one)	40 (31.0%)
One hospitalization	19 (14.7%)
Two hospitalizations	11 (8.5%)
Three or more hospitalizations	10 (7.8%)
Depression severity	
BDI (mean ± *SD*)	36.6 (9.8)
Mild (14–19)	5 (3.9%)
Moderate (20–28)	26 (20.2%)
Severe (29–63)	98 (75.9%)
HRSD (mean ± *SD*)	20.1 (5.0)
Mild (8–13)	12 (9.3%)
Moderate (14–18)	44 (34.1%)
Severe (19–22)	31 (24.0%)
Very severe (>23)	42 (32.6%)
Functioning	
GAF (mean ± *SD*)	48.8 (6.6)
Mild difficulties (61–70)	1 (0.8%)
Moderate difficulties (51–60)	58 (44.9%)
Serious impairment (41–50)	52 (40.3%)
Some impairment in reality testing (31–40)	15 (11.6%)
Serious impairment (<40)	3 (2.3%)
CORE-OM (*N* = 122)	
Total score (mean ± *SD*)	2.24 (0.61)
Above clinical threshold	115 (89.2%)
Wellbeing (mean ± *SD*)	2.79 (0.76)

Above clinical threshold	112 (86.8%)
Social functioning (mean ± *SD*)	2.30 (0.68)
Above clinical threshold	112 (86.8%)
Problems and symptoms (mean ± *SD*)	2.72 (0.73)
Above clinical threshold	113 (87.6%)
Suicide risk (mean ± *SD*)	0.81 (0.77)
Above clinical threshold	80 (62.0%)
Q-les-Q (mean ± *SD*)	
Physical health (*n* = 123)	28.50 (15.77)
Mood (*n* = 123)	34.40 (16.08)
Leisure activities (*n* = 123)	42.65 (21.89)
Social relationships (*n* = 122)	42.12 (18.21)
Household duties (*n* = 119)	41.0 (22.09)
Work activities (*n* = 111)	24.56 (27.28)
School/course work (*n* = 39)	16.17 (5.37)
General activities (*n* = 122)	29.03 (14.84)
Mean Q-les-Q score	34.23 (15.13)
Suicidality	
Previous suicide attempt	58 (44.9%)
One attempt	26 (20.2%)
Two attempts	12 (9.3%)
Three attempts	9 (6.9%)
Four or more attempts	11 (8.5%)
Suicide attempt during childhood	14 (10.9%)
Suicide attempt during adolescence	9 (6.9%)
Thoughts of death/suicide at intake	
No thoughts of death	39 (30.2%)
Recurrent suicidal thoughts	57 (44.2%)
Recurrent suicidal ideation	28 (21.7%)
Made specific suicide plan	4 (3.1%)
Made a serious attempt over the past month	1 (0.8%)
Suicide history in the family	23 (17.8%)
Father	4 (3.1%)
Mother	8 (6.2%)

Sibling	5 (3.9%)
Extended family member	6 (4.7%)
Suicide by partner or close friend	9 (6.9%)
Suicide by a child	2 (1.6%)

Note: BDI = Beck Depression Inventory, CORE = Clinical Outcomes in Routine Evaluation; GAF= Global Assessment of Functioning Scale; HRSD = Hamilton Rating Scale for Depression.

Table 2: Count and percentages of specific adverse events during childhood, adolescence, and adulthood (N = 129)

Description	**Count (%)**
During Childhood	
Physical abuse in family	35 (27.1%)
Sexual abuse	30 (23.3%)
Sexual abuse by family member	16 (12.4%)
Sexual abuse by non-family	14 (10.9%)
Emotional abuse	52 (40.3%)
Neglect	19 (14.7%)
Witness of violence in family	26 (20.2%)
Peer bullying	33 (25.6%)
Life-threatening accidents	2 (1.6%)
Death in family	13 (10.1%)
Father	2 (1.6%)
Mother	5 (3.9%)
Both parents	2 (1.6%)
Sibling	4 (3.1%)
Parental separation	17 (13.2%)
Absent mother	9 (6.9%)
Absent father	8 (6.2%)
Care/adoption	7 (5.4%)
During Adolescence	
Physical abuse	23 (17.8%)
Sexual abuse	11 (8.5%)
Sexual abuse by family member	8 (6.2%)
Sexual abuse by non-family	3 (2.3%)

Emotional abuse	52 (40.3%)
Neglect	22 (17.1%)
Witness of violence in family	18 (13.9%)
Peer bullying	18 (13.9%)
Death in family	16 (12.4%)
Father	2 (1.6%)
Mother	4 (3.1%)
Both parents	1 (0.8%)
Sibling	4 (3.1%)
Significant other	5 (3.9%)
Parental separation	24 (18.6%)
Parental absence	25 (19.4%)
Foster care/adoption	6 (4.7%)
Parental mental illness	31 (24.0%)
Father depression	12 (9.3%)
Mother depression	17 (13.2%)
Both parents depression	2 (1.6%)
Parental trauma	43 (33.3%)
Suicide in family	18 (13.9%)
Father	1 (0.8%)
Mother	6 (4.7%)
Sibling	4 (3.1%)
Extended family member	7 (5.4%)
During Adulthood	
Physical abuse	28 (21.7%)
Sexual abuse	23 (17.8%)
Rape	9 (6.9%)
Emotional abuse	15 (11.6%)
Physical neglect	7 (5.4%)
Witnessing of violence	6 (4.7%)
Bullying/mobbing	7 (5.4%)
Life-threatening accidents	7 (5.4%)
Death	
Sibling	4 (3.1%)

Child	6 (4.7%)
Partner	7 (5.4%)
Close friend	17 (13.2%)

References

Amital, D., Fostick, L., Silberman, A., Calati, R., Spindelegger, C., Serretti, A., Juven-Wetzler, A., Souery, D., Mendlewicz, J., Montgomery, S., Kasper, S., & Zohar, J. (2013). Physical co-morbidity among treatment resistant vs. treatment responsive patients with major depressive disorder. *European Neuropsychopharmacology*, *23*(8), 895-901. https://doi.org/https://doi.org/10.1016/j.euroneuro.2012.09.002

Anda, R. F., Chapman, D. P., Felitti, V. J., Edwards, V., Williamson, D. F., Croft, J. B., & Giles, W. H. (2002). Adverse childhood experiences and risk of paternity in teen pregnancy. *Psychiatric Services*, *53*(8), 1001-1009. https://doi.org/10.1016/s0029-7844(02)02063-x

Bagby, R. M., Ryder, A. G., Schuller, D. R., & Marshall, M. B. (2004). The Hamilton Depression Rating Scale: has the gold standard become a lead weight? *The American Journal of Psychiatry*, *161*(12), 2163-2177. https://doi.org/10.1176/appi.ajp.161.12.2163

Bauer, M., Bschor, T., Pfennig, A., Whybrow, P. C., Angst, J., Versiani, M., & Möller, H. J. (2007). World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders in Primary Care. *The World Journal of Biological Psychiatry*, *8*(2), 67-104. https://doi.org/10.1080/15622970701227829

Beck, A. T., Steer, R. A., & Brown, G. (1996). *Manual for the Beck Depression Inventory-II*. Psychological Corporation.

Beecham, J., & Knapp, M. (1992). *Costing psychiatric intervention*. Gaskell.

Behn, A. (2019). Working with clients at the intersection of depression and personality dysfunction: Scientific and clinical findings regarding complex depression. *Journal of Clinical Psychology*, *75*(5), 819-823. https://doi.org/10.1002/jclp.22758

Bellis, M. A., Hughes, K., Leckenby, N., Hardcastle, K. A., Perkins, C., & Lowey, H. (2014). Measuring mortality and the burden of adult disease associated with adverse childhood experiences in England: a national survey. *Journal of Public Health 37*(3), 445-454. https://doi.org/DOI:10.1093/pubmed/fdu065

Bennabi, D., Aouizerate, B., El-Hage, W., Doumy, O., Moliere, F., Courtet, P., Nieto, I., Bellivier, F., Bubrovsky, M., Vaiva, G., Holztmann, J., Bougerol, T., Richieri, R., Lancon, C., Camus, V., Saba, G., Haesbaert, F., d'Amato, T., Charpeaud, T., . . . Haffen, E. (2015). Risk factors for treatment resistance in unipolar depression: a systematic review. *Journal of Affective Disorders*, *171*, 137-141. https://doi.org/10.1016/j.jad.2014.09.020

Berlim, M. T., & Turecki, G. (2007). Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. *Canadian Journal of Psychiatry*, *52*(1), 46-54. https://doi.org/10.1177/070674370705200108

Blanco, C., Wall, M. M., Hoertel, N., Krueger, R. F., Liu, S.-M., Grant, B. F., & Olfson, M. (2021). Psychiatric disorders and risk for multiple adverse outcomes: a national prospective study. *Molecular Psychiatry*, *26*(3), 907-916. https://doi.org/10.1038/s41380-019-0459-4

Bremner, J. D., Vermetten, E., & Mazure, C. M. (2000). Development and preliminary psychometric properties of an instrument for the measurement of childhood trauma:

the early trauma inventory. *Depression and Anxiety*, *12*(1), 1-12 https://doi.org/10.1002/1520-6394(2000)12:1<1::AID-DA1>3.0.CO;2-W

Brown, S., Rittenbach, K., Cheung, S., McKean, G., MacMaster, F. P., & Clement, F. (2019). Current and Common Definitions of Treatment-Resistant Depression: Findings from a Systematic Review and Qualitative Interviews. *The Canadian Journal of Psychiatry*, *64*(6), 380-387. https://doi.org/10.1177/0706743719828965

Budde, M., Anderson-Schmidt, H., Gade, K., Reich-Erkelenz, D., Adorjan, K., Kalman, J. L., Senner, F., Papiol, S., Andlauer, T. F. M., Comes, A. L., Schulte, E. C., Klöhn-Saghatolislam, F., Gryaznova, A., Hake, M., Bartholdi, K., Flatau, L., Reitt, M., Quast, S., Stegmaier, S., . . . Heilbronner, U. (2019). A longitudinal approach to biological psychiatric research: The PsyCourse study. *American Journal of Medical Genetics B Neuropsychiatric Genetetics*, *180*(2), 89-102. https://doi.org/10.1002/ajmg.b.32639

Caspi, A., Houts, R. M., Belsky, D. W., Goldman-Mellor, S. J., Harrington, H., Israel, S., Meier, M. H., Ramrakha, S., Shalev, I., Poulton, R., & Moffitt, T. E. (2014). The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders? *Clinical Psychology Science*, *2*(2), 119-137. https://doi.org/10.1177/2167702613497473

Caspi, A., & Moffitt, T. E. (2018). All for One and One for All: Mental Disorders in One Dimension. *American Journal of Psychiatry*, *175*(9), 831-844. https://doi.org/10.1176/appi.ajp.2018.17121383

Cepeda, M. S., Reps, J., Fife, D., Blacketer, C., Stang, P., & Ryan, P. (2018). Finding treatment-resistant depression in real-world data: How a data-driven approach compares with expert-based heuristics. *Depression and Anxiety*, *35*(3), 220-228. https://doi.org/10.1002/da.22705

Cleare, A., Pariante, C. M., Young, A. H., Anderson, I. M., Christmas, D., Cowen, P. J., Dickens, C., Ferrier, I. N., Geddes, J., Gilbody, S., Haddad, P. M., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R. H., Ramchandani, P., Scott, J., Taylor, D., & Uher, R. (2015). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology, 29*(5), 459-525. https://doi.org/10.1177/0269881115581093

Constantinou, M., & Fonagy, P. (2019). Evaluating Bifactor Models of Psychopathology Using Model-Based Reliability Indices. https://doi.org/10.31234/osf.io/6tf7j (accessed 10.11.2023)

Crawford, J. G., Parker, G. B., Malhi, G. S., Mitchell, P. B., Wilhelm, K., & Proudfoot, J. (2007). Social inhibition and treatment-resistant depression *Personality and Mental Health*, *1*(1), 62-73. https://doi.org/10.1002/pmh.5

Cuijpers, P., Miguel, C., Ciharova, M., Ebert, D., Harrer, M., & Karyotaki, E. (2023). Transdiagnostic treatment of depression and anxiety: a meta-analysis. Psychological Medicine, 53(14), 1-12. https://doi.org/10.1017/s0033291722003841

Demyttenaere, K., & Van Duppen, Z. (2019). The Impact of (the Concept of) Treatment-Resistant Depression: An Opinion Review. *International Journal of Neuropsychopharmacology*, *22*(2), 85-92. https://doi.org/10.1093/ijnp/pyy052

Deutz, M. H. F., Geeraerts, S. B., Belsky, J., Deković, M., van Baar, A. L., Prinzie, P., & Patalay, P. (2020). General Psychopathology and Dysregulation Profile in a Longitudinal Community Sample: Stability, Antecedents and Outcomes. *Child Psychiatry and Human Development*, *51*(1), 114-126. https://doi.org/10.1007/s10578-019-00916-2

DiBernardo, A., Lin, X., Zhang, Q., Xiang, J., Lu, L., Jamieson, C., Benson, C., Lee, K., Bodén, R., Brandt, L., Brenner, P., Reutfors, J., & Li, G. (2018). Humanistic outcomes in treatment resistant depression: a secondary analysis of the STAR*D study. *BMC Psychiatry*, *18*(1), 352. https://doi.org/10.1186/s12888-018-1920-7

Döme, P., Kunovszki, P., Takács, P., Fehér, L., Balázs, T., Dede, K., Mulhern-Haughey, S., Barbreau, S., & Rihmer, Z. (2021). Clinical characteristics of treatment-resistant depression in adults in Hungary: Real-world evidence from a 7-year-long retrospective data analysis. *PLoS One*, *16*(1), e0245510. https://doi.org/10.1371/journal.pone.0245510

Dudek, D., Rybakowski, J. K., Siwek, M., Pawłowski, T., Lojko, D., Roczeń, R., & Kiejna, A. (2010). Risk factors of treatment resistance in major depression: association with bipolarity. *Journal of Affective Disorders*, *126*(1-2), 268-271. https://doi.org/10.1016/j.jad.2010.03.001

Endicott, J., Nee, J., Harrison, W., & Blumenthal, R. (1993). Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacol Bull*, *29*(2), 321-326.

Evans, C., Connell, J., Barkham, M., Margison, F., McGrath, G., Mellor-Clark, J., & Audin, K. (2002). Towards a standardised brief outcome measure: psychometric properties and utility of the CORE—OM. *The British Journal of Psychiatry*, *180*, 51- 60. https://doi.org/https://doi.org/10.1192/bjp.180.1.51

Evans, C., Mellor-Clark, J., Margison, F., Barkham, M., Audin, K., Connell, J., & McGrath, G. (2000). CORE: Clinical outcomes in routine evaluation. *Journal of Mental Health*, *9*(3), 247-255. https://doi.org/https://doi.org/10.1080/jmh.9.3.247.255

Fabbri, C., Hagenaars, S. P., John, C., Williams, A. T., Shrine, N., Moles, L., Hanscombe, K. B., Serretti, A., Shepherd, D. J., Free, R. C., Wain, L. V., Tobin, M. D., & Lewis, C. M. (2021). Genetic and clinical characteristics of treatment-resistant depression using

primary care records in two UK cohorts. *Molecular Psychiatry*, *26*(7), 3363-3373. https://doi.org/10.1038/s41380-021-01062-9

First, M. B., & Gibbon, M. (2004). The structured clinical interview for DSM-IV Axis I disorders (SCID-I) and the structured clinical interview for DSM-IV Axis II disorders (SCID-II). In M. J. Hilsenroth & D. L. Segal (Eds.), *Comprehensive handbook of psychological assessment, Vol. 2: Personality assessment* (pp. 134-143). John Wiley & Sons Inc.

Fonagy, P., Rost, F., Carlyle, J., McPherson, S., Thomas, R., Fearon, R. M. P., Goldberg, D., & Taylor, D. (2015). Pragmatic randomized controlled trial of long-term psychoanalytic psychotherapy for treatment-resistant depression: the Tavistock Adult Depression Study (TADS). *World Psychiatry*, *14*(3), 312-321. https://doi.org/10.1002/wps.20267

Gaynes, B. N., Lux, L., Gartlehner, G., Asher, G., Forman-Hoffman, V., Green, J., Boland, E., Weber, R. P., Randolph, C., Bann, C., Coker-Schwimmer, E., Viswanathan, M., & Lohr, K. N. (2020). Defining treatment-resistant depression. *Depression and Anxiety*, *37*(2), 134-145. https://doi.org/10.1002/da.22968

Gibson, T. B., Jing, Y., Smith Carls, G., Kim, E., Bagalman, J. E., Burton, W. N., Tran, Q. V., Pikalov, A., & Goetzel, R. Z. (2010). Cost burden of treatment resistance in patients with depression. *The American Journal of Managed Care*, *16*(5), 370-377.

Global Health Data Exchange (2023). Retrieved 23.08.2023 from http://ghdx.healthdata.org/gbd-results-tool.

Gluschkoff, K., Jokela, M., & Rosenström, T. (2019). The General Psychopathology Factor: Structural Stability and Generalizability to Within-Individual Changes. *Frontiers in Psychiatry*, *10*, 594. https://doi.org/10.3389/fpsyt.2019.00594

Goldberg, D. (2015). Psychopathology and classification in psychiatry. *Social Psychiatry and Psychiatric Epidemiology*, *50*(1), 1-5. https://doi.org/10.1007/s00127-014-0924-y

Grilo, C. M., Stout, R. L., Markowitz, J. C., Sanislow, C. A., Ansell, E. B., Skodol, A. E., Bender, D. S., Pinto, A., Shea, M. T., Yen, S., Gunderson, J. G., Morey, L. C., Hopwood, C. J., & McGlashan, T. H. (2010). Personality disorders predict relapse after remission from an episode of major depressive disorder: a 6-year prospective study. *Journal of Clinical Psychiatry*, *71*(12), 1629-1635. https://doi.org/10.4088/JCP.08m04200gre

Hamilton, M. (1967). Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology*, *6*(4), 278-296. https://doi.org/10.1111/j.2044-8260.1967.tb00530.x

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biological Psychiatry*, *49*(12), 1023-1039. https://doi.org/10.1016/s0006-3223(01)01157-x

Hilsenroth, M. J., Ackerman, S. J., Blagys, M. D., Baumann, B. D., Baity, M. R., Smith, S. R., Price, J. L., Smith, C. L., Heindselman, T. L., Mount, M. K., & Holdwick, D. J. (2000). Reliability and validity of DSM-IV axis V. *The American Journal of Psychiatry*, *157*(11), 1858-1863. https://ajp.psychiatryonline.org/doi/full/10.1176/appi.ajp.157.11.1858

Hovens, J. G., Giltay, E. J., Wiersma, J. E., Spinhoven, P., Penninx, B. W., & Zitman, F. G. (2012). Impact of childhood life events and trauma on the course of depressive and anxiety disorders. *Acta Psychiatrica Scandinavica*, *126*(3), 198-207. https://doi.org/10.1111/j.1600-0447.2011.01828.x

Huang, S.-S., Chen, H.-H., Wang, J., Chen, W. J., Chen, H.-C., & Kuo, P.-H. (2020). Investigation of early and lifetime clinical features and comorbidities for the risk of

developing treatment-resistant depression in a 13-year nationwide cohort study. *BMC Psychiatry*, *20*(1), 541. https://doi.org/10.1186/s12888-020-02935-z

Hung, C. I., Liu, C. Y., & Yang, C. H. (2019). Persistent depressive disorder has long-term negative impacts on depression, anxiety, and somatic symptoms at 10-year follow-up among patients with major depressive disorder. *Journal of Affective Disorders*, *243*, 255-261. https://doi.org/10.1016/j.jad.2018.09.068

Hyde, J. S. and Mezulis, A. H. (2020) 'Gender Differences in Depression: Biological, Affective, Cognitive, and Sociocultural Factors', *Harvard Review of Psychiatry*, 28(1). https://doi.org/10.1097/hrp.0000000000000230

Hyland, P., Murphy, J., Shevlin, M., Bentall, R. P., Karatzias, T., Ho, G. W. K., Boduszek, D., & McElroy, E. (2021). On top or underneath: where does the general factor of psychopathology fit within a dimensional model of psychopathology? *Psychological Medicine*, *51*(14), 2422-2432. https://doi.org/10.1017/s003329172000104x

Ivanova, J. I., Birnbaum, H. G., Kidolezi, Y., Subramanian, G., Khan, S. A., & Stensland, M. D. (2010). Direct and indirect costs of employees with treatment-resistant and non-treatment-resistant major depressive disorder. *Current Medical Research and Opinion*, *26*(10), 2475-2484. https://doi.org/10.1185/03007995.2010.517716

Johnson, J. G., Cohen, P., Kasen, S., & Brook, J. S. (2005). Personality disorder traits associated with risk for unipolar depression during middle adulthood. *Psychiatry Research*, *136*(2), 113-121. https://doi.org/https://doi.org/10.1016/j.psychres.2005.02.007

Johnstone, L., Boyle, M. w., Cromby, J., Dillon, J., Harper, D., Kinderman, P., Longden, E., Pilgrim, D., & Read, J. (2018). *The Power Threat Meaning Framework: Towards the identification of patterns in emotional distress, unusual experiences and troubled or troubling behaviour, as an alternative to functional psychiatric diagnosis.* British

Psychological Society. https://www.bps.org.uk/member-networks/division-clinical-psychology/power-threat-meaning-framework (accessed: 25.03.2024)

Jorm, A. F., Patten, S. B., Brugha, T. S., & Mojtabai, R. (2017). Has increased provision of treatment reduced the prevalence of common mental disorders? Review of the evidence from four countries. *World Psychiatry*, *16*(1), 90-99. https://doi.org/10.1002/wps.20388

Kaplan, M. J., & Klinetob, N. A. (2000). Childhood emotional trauma and chronic posttraumatic stress disorder in adult outpatients with treatment-resistant depression. *The Journal of Nervous and Menteal Disease*, *188*(9), 596-601. https://doi.org/10.1097/00005053-200009000-00006

Kennedy, S. H., Lam, R. W., McIntyre, R. S., Tourjman, S. V., Bhat, V., Blier, P., Hasnain, M., Jollant, F., Levitt, A. J., MacQueen, G. M., McInerney, S. J., McIntosh, D., Milev, R. V., Müller, D. J., Parikh, S. V., Pearson, N. L., Ravindran, A. V., & Uher, R. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. *Canadian Journal of Psychiatry*, *61*(9), 540-560. https://doi.org/10.1177/0706743716659417

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*, *62*(6), 593-602. https://doi.org/10.1001/archpsyc.62.6.593

Kim, H., & Eaton, N. R. (2015). The hierarchical structure of common mental disorders: Connecting multiple levels of comorbidity, bifactor models, and predictive validity. *Journal of Abnormal Psychology*, *124*(4), 1064-1078. https://doi.org/10.1037/abn0000113

Kim, S. Y., De Vries, R. G., & Peteet, J. R. (2016). Euthanasia and Assisted Suicide of Patients With Psychiatric Disorders in the Netherlands 2011 to 2014. *JAMA Psychiatry, 73*(4), 362-368. https://doi.org/10.1001/jamapsychiatry.2015.2887

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *Journal of General Internal Medicine,* 16(9), 606-613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x

Lähteenvuo, M., Taipale, H., Tanskanen, A., Rannanpää, S. and Tiihonen, J. (2022) 'Courses of treatment and risk factors for treatment-resistant depression in Finnish primary and special healthcare: A nationwide cohort study', *Journal of Affective Disorders*, 308, pp. 236-242. https://doi.org/10.1016/j.jad.2022.04.010

Lahey, B. B., Applegate, B., Hakes, J. K., Zald, D. H., Hariri, A. R., & Rathouz, P. J. (2012). Is there a general factor of prevalent psychopathology during adulthood? *Journal of Abnormal Psychol, 121*(4), 971-977. https://doi.org/10.1037/a0028355

Lahey, B. B., Zald, D. H., Perkins, S. F., Villalta-Gil, V., Werts, K. B., Van Hulle, C. A., Rathouz, P. J., Applegate, B., Class, Q. A., Poore, H. E., Watts, A. L., & Waldman, I. D. (2018). Measuring the hierarchical general factor model of psychopathology in young adults. *International Journal of Methods in Psychiatric Research, 27*(1). https://doi.org/10.1002/mpr.1593

Laporte, L., Paris, J., Guttman, H., & Russell, J. (2011). Psychopathology, childhood trauma, and personality traits in patients with borderline personality disorder and their sisters. *Journal of Personality Disorder, 25*(4), 448-462. https://doi.org/10.1521/pedi.2011.25.4.448

Li, C. T. (2023). Overview of treatment-resistant depression. *Progress in Brain Research, 278*, 1-23. https://doi.org/10.1016/bs.pbr.2023.03.007

Lobbestael, J., Leurgans, M., & Arntz, A. (2011). Inter–rater reliability of the structured clinical interview for DSM Axis I disorders (SCID I) and Axis II disorders (SCID II). *Clinical Psychology & Psychotherapy*, *18*(1), 75-79. https://doi.org/10.1002/cpp.693

Lu, W., Mueser, K. T., Rosenberg, S. D., & Jankowski, M. K. (2008). Correlates of adverse childhood experiences among adults with severe mood disorders. *Psychiatric Services*, *59*(9), 1018-1026. https://doi.org/10.1176/ps.2008.59.9.1018

Luyten, P., Blatt, S. J., Van Houdenhove, B., & Corveleyn, J. (2006). Depression research and treatment: are we skating to where the puck is going to be? *Clinical Psychology Review*, *26*(8), 985-999. https://doi.org/10.1016/j.cpr.2005.12.003

Malhi, G. S., & Mann, J. J. (2018). Depression. *Lancet*, *392*(10161), 2299-2312. https://doi.org/10.1016/s0140-6736(18)31948-2

Markon, K. E. (2019). Bifactor and Hierarchical Models: Specification, Inference, and Interpretation. *Annual Review of Clinical Psychology*, *15*(1), 51-69. https://doi.org/10.1146/annurev-clinpsy-050718-095522

Martel, M. M., Pan, P. M., Hoffmann, M. S., Gadelha, A., do Rosário, M. C., Mari, J. J., Manfro, G. G., Miguel, E. C., Paus, T., Bressan, R. A., Rohde, L. A., & Salum, G. A. (2017). A general psychopathology factor (P factor) in children: Structural model analysis and external validation through familial risk and child global executive function. *Journal of Abnormal Psychology*, *126*(1), 137-148. https://doi.org/10.1037/abn0000205

McIntyre, R. S., Alsuwaidan, M., Baune, B. T., Berk, M., Demyttenaere, K., Goldberg, J. F., . . . Maj, M. (2023). Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry*, *22*(3), 394-412. https://doi.org/10.1002/wps.21120

McElroy, E., Fearon, P., Belsky, J., Fonagy, P., & Patalay, P. (2018). Networks of Depression and Anxiety Symptoms Across Development. *Journal of the American Academy of Child & Adolescence Psychiatry*, *57*(12), 964-973. https://doi.org/10.1016/j.jaac.2018.05.027

Merikangas, K. R., He, J. P., Burstein, M., Swanson, S. A., Avenevoli, S., Cui, L., Benjet, C., Georgiades, K., & Swendsen, J. (2010). Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication--Adolescent Supplement (NCS-A). *Journal of the American Academic of Child and Adolescent Psychiatry*, *49*(10), 980-989. https://doi.org/10.1016/j.jaac.2010.05.017

Mrazek, D. A., Hornberger, J. C., Altar, C. A., & Degtiar, I. (2014). A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatric Services*, *65*(8), 977-987. https://doi.org/10.1176/appi.ps.201300059

Murphy, J. A., Sarris, J., & Byrne, G. J. (2017). A Review of the Conceptualisation and Risk Factors Associated with Treatment-Resistant Depression. *Depression Research and Treatment*, *2017*, 4176825. https://doi.org/10.1155/2017/4176825

Negele, A., Kaufhold, J., Kallenbach, L., & Leuzinger-Bohleber, M. (2015). Childhood Trauma and Its Relation to Chronic Depression in Adulthood. *Depression Research and Treatment*, *2015*, 650804. https://doi.org/https://doi.org/10.1155/2015/650804

Nelson, J., Klumparendt, A., Doebler, P., & Ehring, T. (2017). Childhood maltreatment and characteristics of adult depression: meta-analysis. *The Bristish Journal of Psychiatry*, *210*(2), 96-104. https://doi.org/10.1192/bjp.bp.115.180752

Nemeroff, C. B. (2007). Prevalence and management of treatment-resistant depression. *The Journal of Clinical Psychiatry*, *68 Suppl 8*, 17-25.

Newton-Howes, G., Tyrer, P., & Johnson, T. (2006). Personality disorder and the outcome of depression: Meta-analysis of published studies. *The British Journal of Psychiatry, 188*(1), 13-20. https://doi.org/10.1192/bjp.188.1.13

Newton-Howes, G., Tyrer, P., Johnson, T., Mulder, R., Kool, S., Dekker, J., & Schoevers, R. (2014). Influence of personality on the outcome of treatment in depression: systematic review and meta-analysis. *Journal of Personality Disorders, 28*(4), 577-593. https://doi.org/10.1521/pedi_2013_27_070

Nezu, A. M., Ronan, G. F., Meadows, E. A., & McClure, K. S. (2000). *Practitioner's guide to empirically based measures of depression* (A. M. Nezu, G. F. Ronan, E. A. Meadows, & K. S. McClure, Eds.). Kluwer Academic Publishers.

NICE (2009). *Depression in adults: Recognition and management. Clinical Guideline CG90.* London, UK: National Institute for Health and Clinical Excellence Retrieved from https://www.nice.org.uk/guidance/cg90 (accessed:25.03.2024)

NICE (2022). *Depression in adults: treatment and management. Guideline NG222.* London, UK: National Institute for Health and Care Excellence. Retrieved from https://www.nice.org.uk/guidance/ng222 (accessed: 25.03.2024)

Office for Natinal Statistics (2021) Rreleased 29 November 2022, ONS website, statistical bulletin, Ethnic group, England and Wales: Census 2021. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/bulletins/ethnicgroupenglandandwales/census2021 (accessed: 25.03.2024)

Peng, A., Qiu, X., Ji, S., Hu, D., Dong, B., Song, T., Huang, C., & Chen, L. (2022). The impact of childhood parental loss on risk for depression and anxiety in adulthood: A community-based study in Southwest China. *Journal of Affective Disorders, 298*(Pt A), 104-109. https://doi.org/10.1016/j.jad.2021.10.093

Pérez-Sola, V., Roca, M., Alonso, J., Gabilondo, A., Hernando, T., Sicras-Mainar, A., Sicras-Navarro, A., Herrera, B., & Vieta, E. (2021). Economic impact of treatment-resistant depression: A retrospective observational study. *Journal of Affective Disorders*, *295*, 578-586. https://doi.org/https://doi.org/10.1016/j.jad.2021.08.036

Pettersson, E., Larsson, H., & Lichtenstein, P. (2016). Common psychiatric disorders share the same genetic origin: a multivariate sibling study of the Swedish population. *Molecular Psychiatry*, *21*(5), 717-721. https://doi.org/10.1038/mp.2015.116

Rapaport, M. H., Clary, C., Fayyad, R., & Endicott, J. (2005). Quality-of-Life Impairment in Depressive and Anxiety Disorders. *American Journal of Psychiatry*, *162*(6), 1171-1178. https://doi.org/10.1176/appi.ajp.162.6.1171

Reutfors, J., Andersson, T. M. L., Brenner, P., Brandt, L., DiBernardo, A., Li, G., Hägg, D., Wingård, L., & Bodén, R. (2018). Mortality in treatment-resistant unipolar depression: A register-based cohort study in Sweden. *Journal of Affective Disorders*, *238*, 674-679. https://doi.org/https://doi.org/10.1016/j.jad.2018.06.030

Rost, F., Luyten, P., Fearon, P., & Fonagy, P. (2019). Personality and Outcome in Individuals With Treatment-Resistant Depression—Exploring Differential Treatment Effects in the Tavistock Adult Depression Study (TADS). *Journal of Consulting and Clinical Psychology*, *87*(5), 433-445. https://doi.org/DOI:10.1037/ccp0000391

Schaefer, J. D., Moffitt, T. E., Arseneault, L., Danese, A., Fisher, H. L., Houts, R., Sheridan, M. A., Wertz, J., & Caspi, A. (2018). Adolescent Victimization and Early-Adult Psychopathology: Approaching Causal Inference Using a Longitudinal Twin Study to Rule Out Noncausal Explanations. *Clinical Psychological Science*, *6*(3), 352-371. https://doi.org/10.1177/2167702617741381

Schechter, D., Endicott, J., & Nee, J. (2007). Quality of life of 'normal' controls: association with lifetime history of mental illness. *Psychiatry Research*, *152*(1), 45 - 54. https://doi.org/DOI:10.1016/j.psychres.2006.09.008

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., Fagiolini, A., Ferrier, I. N., Hegerl, U., Krystal, A. D., Leboyer, M., McAllister-Williams, R. H., McIntyre, R. S., . . . Pariante, C. M. (2022). A Delphi-method-based consensus guideline for definition of treatment-resistant depression for clinical trials. *Molecular Psychiatry*, *27*(3), 1286-1299. https://doi.org/10.1038/s41380-021-01381-x

Shedler, J., & Westen, D. (2007). The Shedler-Westen Assessment Procedure (SWAP): making personality diagnosis clinically meaningful. *Journal of Personality Assessment*, *89*(1), 41-55. https://doi.org/10.1080/00223890701357092

Skodol, A. E., Grilo, C. M., Keyes, K. M., Geier, T., Grant, B. F., & Hasin, D. S. (2011). Relationship of personality disorders to the course of major depressive disorder in a nationally representative sample. *American Journal of Psychiatry*, *168*(3), 257-264. https://doi.org/10.1176/appi.ajp.2010.10050695

Smith, G. T., Atkinson, E. A., Davis, H. A., Riley, E. N., & Oltmanns, J. R. (2020). The General Factor of Psychopathology. *Annual Review of Clinical Psychology*, *16*, 75-98. https://doi.org/10.1146/annurev-clinpsy-071119-115848

Snyder, H. R., Young, J. F., & Hankin, B. L. (2016). Strong Homotypic Continuity in Common Psychopathology-, Internalizing-, and Externalizing-Specific Factors Over Time in Adolescents. *Clinical Psychological Science*, *5*(1), 98-110. https://doi.org/10.1177/2167702616651076

Snyder, H. R., Young, J. F., & Hankin, B. L. (2019). Chronic Stress Exposure and Generation Are Related to the P-Factor and Externalizing Specific Psychopathology in Youth.

Journal of Clinical Child & Adolescent Psychology, *48*(2), 306-315. https://doi.org/10.1080/15374416.2017.1321002

Souery, D., Oswald, P., Massat, I., Bailer, U., Bollen, J., Demyttenaere, K., Kasper, S., Lecrubier, Y., Montgomery, S., Serretti, A., Zohar, J., & Mendlewicz, J. (2007). Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. *Journal of Clinical Psychiatry*, *68*(7), 1062-1070. https://doi.org/10.4088/jcp.v68n0713

Stevenson, J., Haliburn, J., & Halovic, S. (2016). Trauma, personality disorders and chronic depression – the role of the conversational model of psychodynamic psychotherapy in treatment resistant depression. *Psychoanalytic Psychotherapy*, *30*(1), 23-41. https://doi.org/10.1080/02668734.2015.1107122

Taylor, D., Carlyle, J., McPherson, S., Rost, F., Thomas, R., & Fonagy, P. (2012). Tavistock Adult Depression Study (TADS): A randomised controlled trial of psychoanalytic psychotherapy for treatment-resistant/treatment-refractory forms of depression. *BMC Psychiatry*, *12*, 60. https://doi.org/10.1186/1471-244X-12-60

Thase, M. E., & Rush, A. J. (1997). When at first you don't succeed: sequential strategies for antidepressant nonresponders. *The Jounral of Clinical Psychiatry*, *58 Suppl 13*, 23-29.

Tunnard, C., Rane, L. J., Wooderson, S. C., Markopoulou, K., Poon, L., Fekadu, A., Juruena, M., & Cleare, A. J. (2014). The impact of childhood adversity on suicidality and clinical course in treatment-resistant depression. *Journal of Affective Disorders*, *152-154*, 122-130. https://doi.org/10.1016/j.jad.2013.06.037

Voytenko, V. L., & Huprich, S. K. (2022). Chapter 30 - Managing treatment-resistant depression with comorbid personality disorders. In J. Quevedo, P. Riva-Posse, & W. V. Bobo (Eds.), *Managing Treatment-Resistant Depression* (pp. 441-459). Academic Press.

Westen, D., & Muderrisoglu, S. (2003). Reliability and validity of personality disorder assessment using a systematic clinical interview: evaluating an alternative to structured interviews. *Journal of Personality Disorder*, *17*, 350-368. https://doi.org/10.1176/appi.ajp.163.7.1285

Westen, D., & Shedler, J. (1999). Revising and assessing axis II, Part II: toward an empirically based and clinically useful classification of personality disorders. *The American Journal of Psychiatry*, *156*(2), 273-285. https://doi.org/10.1176/ajp.156.2.273

WHO (2022). *COVID-19 pandemic triggers 25% increase in prevalence of anxiety and depression worldwide*. https://www.who.int/news/item/02-03-2022-covid-19-pandemic-triggers-25-increase-in-prevalence-of-anxiety-and-depression-worldwide. (accessed: 25.03.2024

Young, M. (2020). Prognostic Significance of Personality Disorders in Patients with Major Depressive Disorder. *Current Treatment Options in Psychiatry*, *7*(4), 559-569. https://doi.org/10.1007/s40501-020-00227-7

Yrondi, A., Aouizerate, B., Bennabi, D., Richieri, R., D'Amato, T., Bellivier, F., Bougerol, T., Horn, M., Camus, V., Courtet, P., Doumy, O., Genty, J. B., Holtzmann, J., Lancon, C., Leboyer, M., Llorca, P. M., Maruani, J., Moirand, R., Molière, F., . . . El-Hage, W. (2020). Childhood maltreatment and clinical severity of treatment-resistant depression in a French cohort of outpatients (FACE-DR): One-year follow-up. Depresion and Anxiety, 37(4), 365-374. https://doi.org/10.1002/da.22997

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. Acta Psychiatrica Scandinavia, 67(6), 361-370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x *Depression and Anxiety*, *37*(4), 365-374. https://doi.org/10.1002/da.22997

Highlights

- First study to offer extensive data-driven socio-demographic and clinical profile of a cohort diagnosed with TRD.
- Findings underscore the insufficiency of exclusively examining depression symptoms, their intensity, and trends of persistence or remission post-treatment.
- TRD is a multifarious syndrome marked by various severity indicators.
- These include high prevalence of several comorbid psychiatric and physical diagnoses, severe difficulties in social and occupational functioning, previous suicide attempts, and substantial number of childhood adverse events.

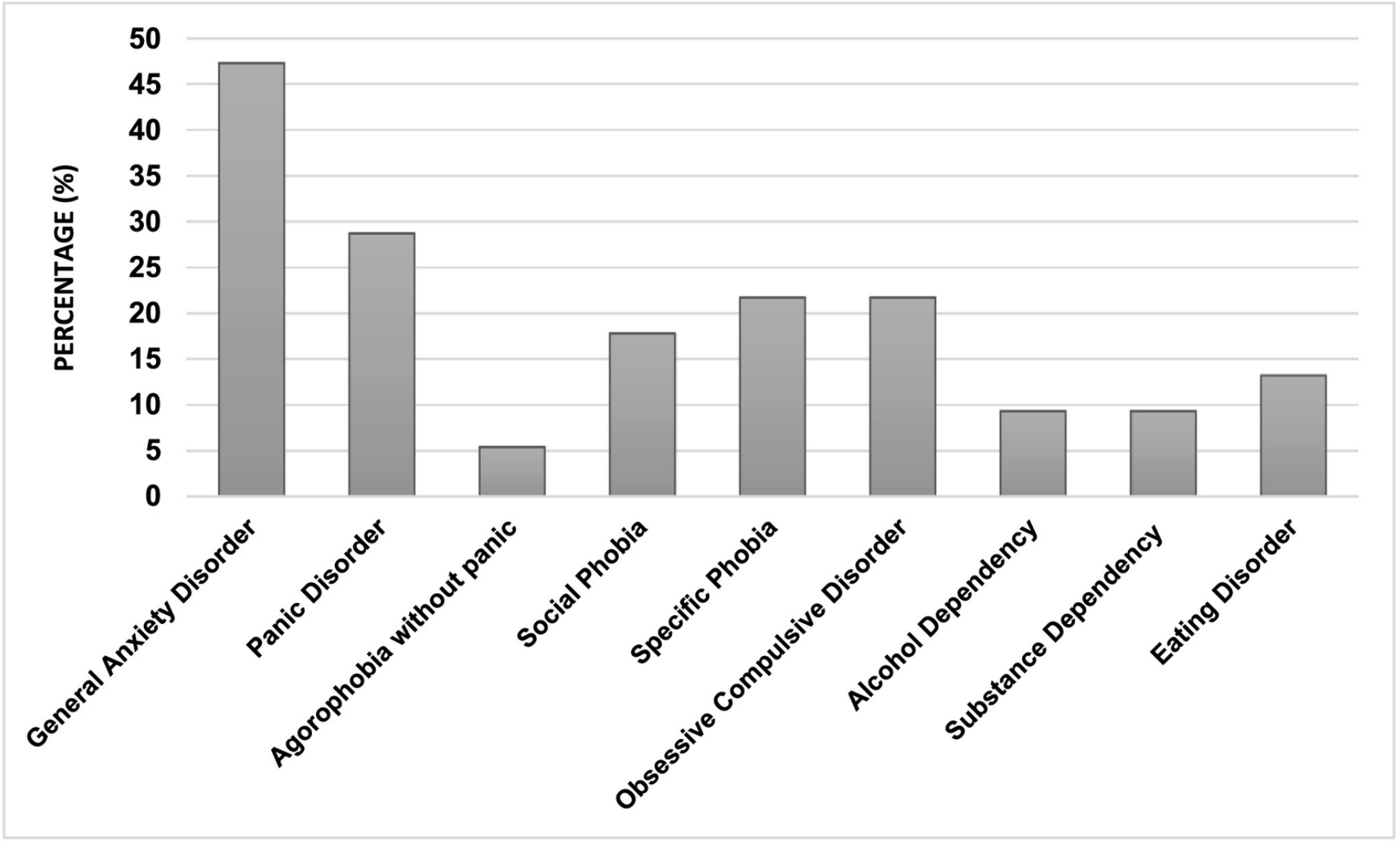
PERCENTAGE (%)
50
45
40
35
30
25
20
15
10
5
0
General Anxiety Disorder
Panic Disorder
Agorophobia without panic
Social Phobia
Specific Phobia
Obsessive Compulsive Disorder
Alcohol Dependency
Substance Dependency
Eating Disorder

Figure 1

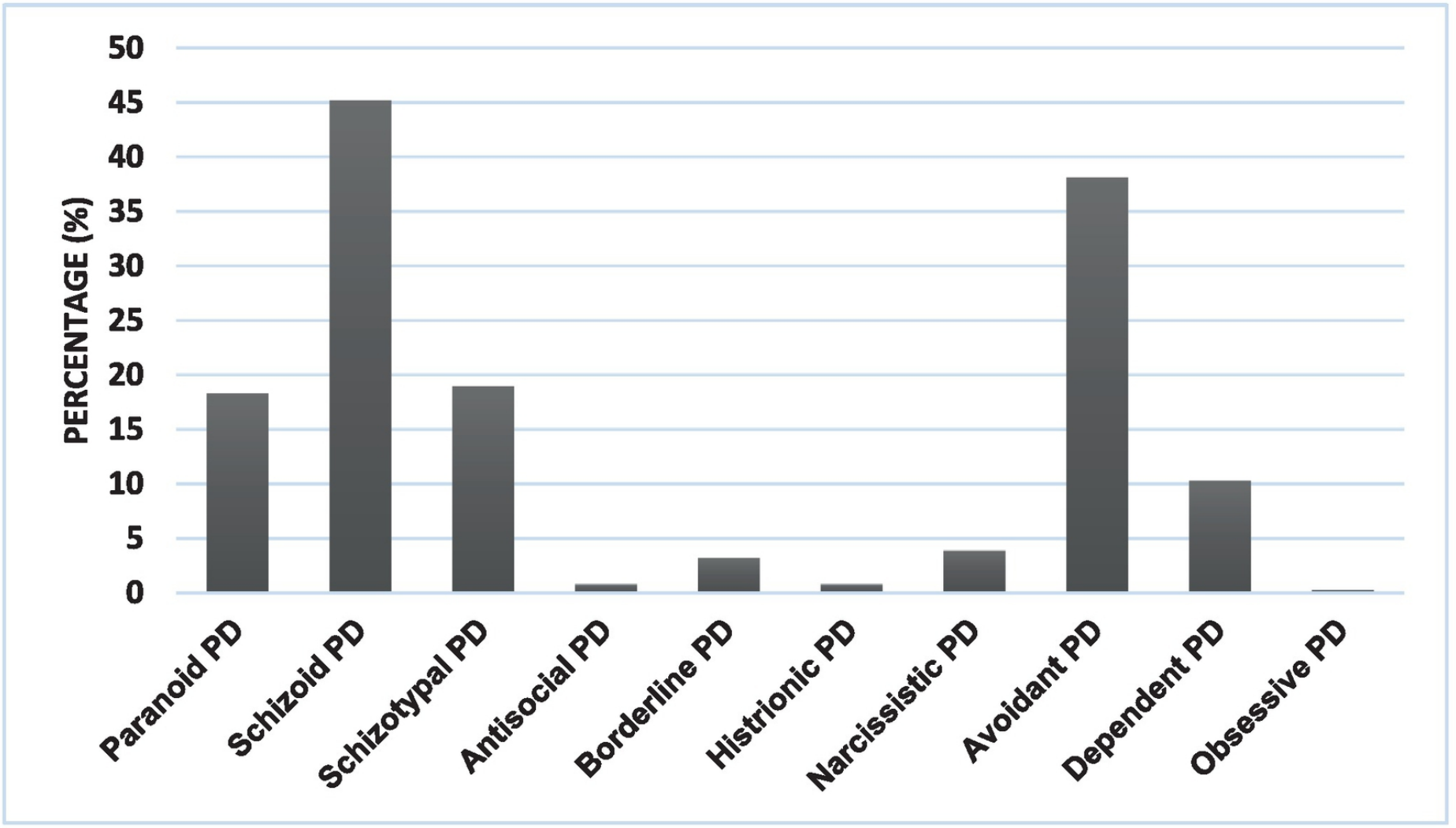
PERCENTAGE (%)
50
45
40
35
30
25
20
15
10
5
0
Paranoid PD
Schizoid PD
Schizotypal PD
Antisocial PD
Borderline PD
Histrionic PD
Narcissistic PD
Avoidant PD
Dependent PD
Obsessive PD

Figure 2

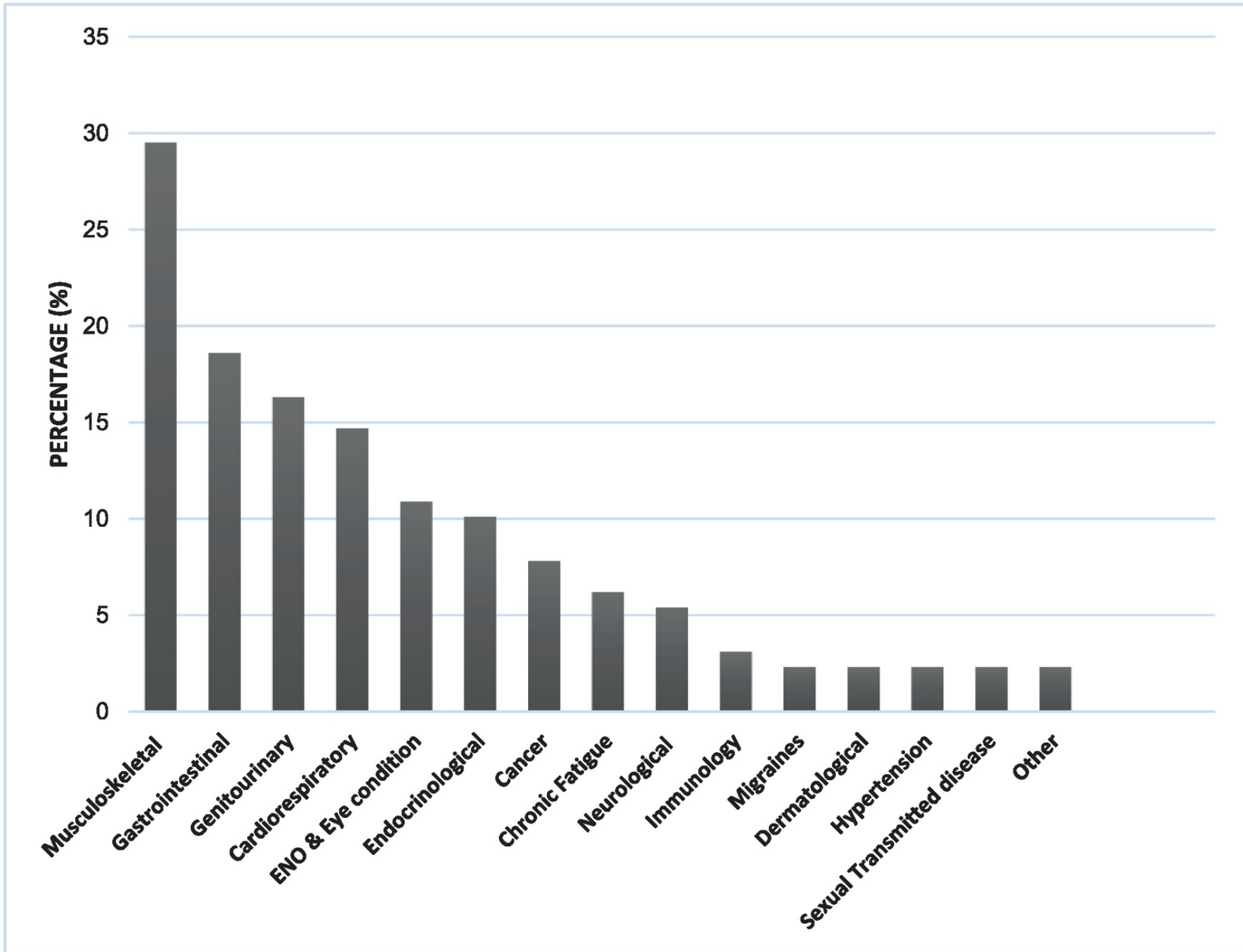
35
30
25
20
15
10
5
0
PERCENTAGE (%)
Musculoskeletal
Gastrointestinal
Genitourinary
Cardiorespiratory
ENO & Eye condition
Endocrinological
Cancer
Chronic Fatigue
Neurological
Immunology
Migraines
Dermatological
Hypertension
Sexual Transmitted disease
Other

Figure 3