



Research paper

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

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### ABSTRACT

**Background:** Recent systematic reviews highlight great variability in defining and assessing treatment-resistant depression (TRD). A key problem is that definitions are consensus rather than data-led. This study seeks to offer a comprehensive socio-demographic and clinical description of a relevant sample.

**Methods:** As part of a pragmatic randomized controlled trial, patients ( $N = 129$ ) were managed in primary care for persistent depression and diagnosed with TRD. Data included previous treatment attempts, characteristics of the depressive illness, functioning, quality of life, co-occurring problems including suicidality, psychiatric and personality disorders, physical health conditions, and adverse events.

**Results:** Findings show a severe and chronic course of depression with a duration of illness of 25+ years. Overall, 82.9 % had at least one other psychiatric diagnosis and 82.2 % at least one personality disorder; 69.8 % had significant musculoskeletal, gastrointestinal, genitourinary, or cardiovascular and respiratory physical health problems. All but 14 had severe difficulties in social and occupational functioning and reported severely impaired quality of life. Suicidal ideation was high: 44.9 % had made at least one serious suicide attempt and several reported multiple attempts with 17.8 % reporting a suicide attempt during childhood or adolescence. Of the patients, 79.8 % reported at least one adverse childhood experience.

**Limitations:** Potential for recall bias, not examining possible interactions, and absence of a control group.

**Conclusions:** Our findings reveal a complex and multifaceted condition and call for an urgent reconceptualization of TRD, which encompasses many interdependent variables and experiences. Individuals with TRD may be at a serious disadvantage in terms of receiving adequate treatment.

### 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 and 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

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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 and 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 and 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 and 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 and 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

#### 2.3.1. Socio-demographic and treatment history

Data on socio-demographics, prior treatment failures and suicidality were sourced from the Client Service Receipt Inventory (CSRI, Beecham and 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.

#### 2.3.2. Depression severity

2.3.2.1. *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 0.89.

2.3.2.2. *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 0.92 for outpatient samples) and diagnostic efficacy (Nezu et al., 2000).

2.3.2.3. *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.

#### 2.3.3. Functional assessment

2.3.3.1. *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,

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

| Description  | Count (%) or mean (SD) |
|--|------------------------|
| <b>Demographic details</b>                         |                        |
| Age (years, mean ± SD (range))                     | 44.35 ± 10.27 (22–66)  |
| Sex (female)                                       | 85 (65.9 %)            |
| <b>Ethnicity</b>                                   |                        |
| 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 %)            |
| <b>Previous treatment attempts</b>                 |                        |
| 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 %)             |
| <b>Depression severity</b>                         |                        |
| 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 %)            |
| <b>Functioning</b>                                 |                        |
| 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 %)              |
| <b>CORE-OM (N = 122)</b>                           |                        |
| 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 %)            |
| <b>Q-les-Q (mean ± SD)</b>                         |                        |
| Physical health (n = 123)                          | 28.50 (15.77)          |
| Mood (n = 123)                                     | 34.40 (16.08)          |

**Table 1 (continued)**

| Description                                | Count (%) or mean (SD) |
|--|------------------------|
| 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)          |
| <b>Suicidality</b>                         |                        |
| 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 %)              |
| <b>Thoughts of death/suicide at intake</b> |                        |
| 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.

resulting in an ICC of 0.91.

**2.3.3.2. 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 0.75–0.95), convergent validity, and change sensitivity (Evans et al., 2000).

**2.3.3.3. 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 (0.60–0.89) and its subscales show high internal consistency (0.82–0.93) (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.

**2.3.4. Comorbidity**

**2.3.4.1. 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).

**2.3.4.2. Personality disorders.** The Shedler–Westen Assessment Procedure Q-sort (SWAP-II) (Shedler and 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 and Muderrisoglu, 2003; Westen and 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.

**2.3.4.3. 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.

**2.3.4.4. 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 ( $\leq 11$  years), adolescence (12–18 years), and adulthood ( $\geq 19$  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.

### 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 ( $SD = 0.61$ ), 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. Fig. 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.

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. Fig. 2 shows the

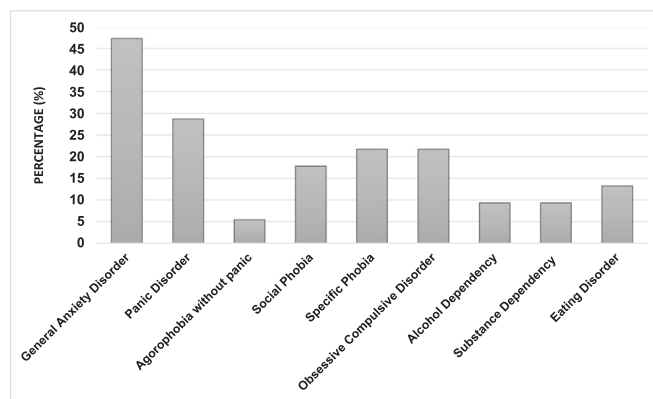


Fig. 1. Percentage of patients with comorbid DSM IV psychiatric disorders ( $n = 129$ ).

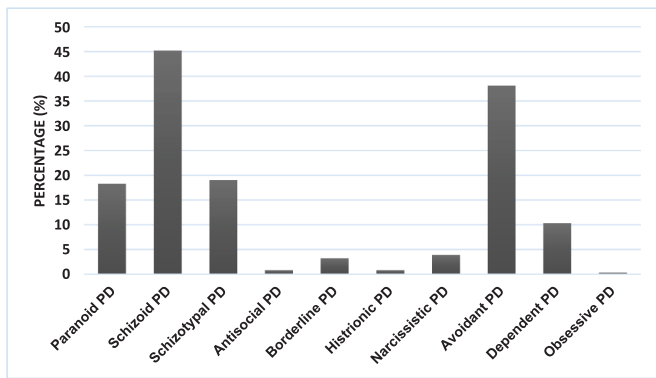


Fig. 2. Percentages of patients (n = 126) with comorbid SWAP-II DSM personality disorders.

prevalence of specific PDs, of which schizoid PD (n = 58; 44.9 %) and avoidant PD (n = 49; 37.9 %) were the most common.

### 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. Fig. 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.

### 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; 85.5 %) 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 =

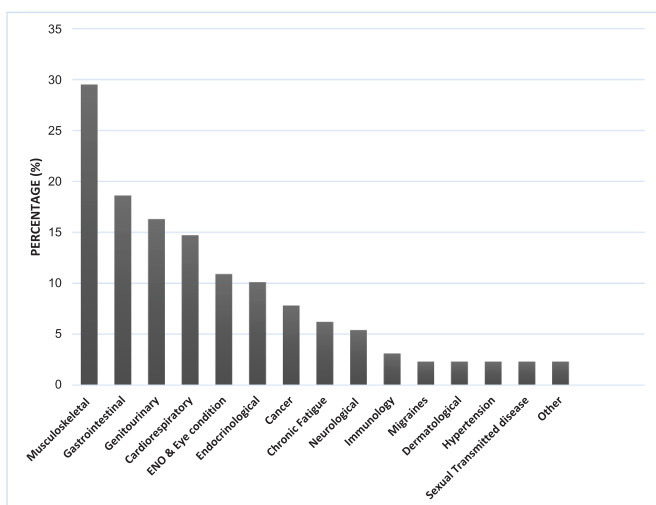


Fig. 3. Percentages of patients (n = 129) with comorbid physical health problems.

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.

Experience of significant early losses and neglect was notable: 13 (10.1 %) of participants had lost a significant other by death before age

Table 2

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

| Description                   | Count (%)   |
|-------------------------------|-------------|
| <b>During childhood</b>       |             |
| 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 %)   |
| <b>During Adolescence</b>     |             |
| 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 %)   |
| <b>During Adulthood</b>       |             |
| 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 %) |

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 et al., 2001) and the Hospital Anxiety and Depression Scale (HADS, Zigmond and 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; Dôme 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 and Klinetob, 2000; Nelson et al., 2017; Tunnard et al., 2014; Yroni 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 and 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., Berlin and 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., Dôme 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 and 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 contribute 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 and Fonagy, 2019). The bifactor model consistently excels in elucidating psychopathology data covariation (Caspi et al., 2014; Gluschkoff et al., 2019; Kim and Eaton, 2015; Lahey et al., 2012, 2018; Pettersson et al., 2016). The p factor potentially encapsulates a general predisposition toward any psychopathology (Caspi and 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 expectation that our sample includes a slightly higher percentage of people identifying as Black and a smaller percentage identifying 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.

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### CRediT authorship contribution statement

**Felicitas Rost:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Thomas Booker:** Writing – review & editing, Validation, Project administration, Data curation, Investigation. **Aneliya Gonsard:** Writing – review & editing, Data curation. **Giulio de Felice:** Writing – review & editing, Investigation, Data curation. **Lorena Asseburg:** Writing – review & editing, Investigation, Data curation. **Javier Malda-Castillo:** Writing – review & editing, Investigation, Data curation. **Iakovina Koutoufa:** Validation, Investigation, Data curation, Writing – review & editing. **Hannah Ridsdale:** Data curation, Investigation, Project administration, Writing – review & editing. **Rebecca Johnson:** Data curation, Investigation, Validation, Writing – review & editing. **David Taylor:** Conceptualization, Funding acquisition, Writing – review & editing. **Peter Fonagy:** Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

### Declaration of competing interest

There are no financial conflicts of interest.

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