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Introduction.

Major depressive disorder (MDD) is a common, debilitating psychiatric problem and is a leading contributor to global disability (WHO, 2017). The course of MDD varies substantially, with approximately half of individuals experiencing recurrent episodes following initial onset (Eaton et al., 2008; Musliner et al., 2016) and approximately 80% of those with a history of two or more episodes experiencing another recurrence (Burcusa & Iacono, 2007). Longitudinal studies of major depressive episodes (MDEs) (Hoertel et al., 2017; Patten et al., 2010) and persistently elevated depressive symptoms (Mars et al., 2015; Musliner et al., 2016; Rhebergen et al., 2012), and family/genetic studies (Als et al., 2023; Kendler et al., 1999; Nguyen et al., 2023) have identified putative risk factors for recurrent depression. These risk factors include clinical characteristics of depression, such as a younger age-of-onset and severe previous MDEs (defined as prior suicidality, hospitalisation or severe impairment) (Hoertel et al., 2017; Mars et al., 2015; Musliner et al., 2016; Patten et al., 2010; Rhebergen et al., 2012). Greater familial loading for depression (defined as the number of first-degree relatives with a depressive disorder) (Patten et al., 2010; Rhebergen et al., 2012), higher heritability (Kendler et al., 1999; Nguyen et al., 2023) and increased polygenic load for MDD, anxiety and bipolar disorder, have also been associated with increased risk of recurrent MDEs (Als et al., 2023; Musliner et al., 2016).

Several theoretical explanations have been proposed as to why risk factors may be somewhat different for persistent versus single episodes of depression (Burcusa & Iacono, 2007; Kendler et al., 1999; National Research Council (US) and Institute of Medicine (US) Committee on Depression et al., 2009; Post, 1992). These can be broadly

summarised as being driven by aetiological differences, differences in stress exposure, or a combination of the two. Thus, one possible explanation is that persistent depression is somewhat aetiologically distinct from less persistent depression, for example showing different associated clinical comorbidities (National Research Council (US) and Institute of Medicine (US) Committee on Depression et al., 2009). Studies have estimated that 60-70% of adults with lifetime MDD have at least one comorbid psychiatric disorder (Kessler, 1997; Rush et al., 2005; Steffen et al., 2020) and approximately 50% show lifetime suicidal behaviours (Dong et al., 2018; Weintraub et al., 2017). Depression with additional clinical comorbidities, including ADHD, manic/hypomanic symptoms, anxiety and self-harm, is more complicated to treat, often showing poorer treatment response (Davey & McGorry, 2019; Kaiser et al., 2023; McAllister-Williams et al., 2020; Powell et al., 2021; Vöhringer et al., 2021). Persistent depression might therefore show a distinct pattern of clinical features compared to less persistent depression, as a reflection of it being somewhat aetiologically distinct.

An alternative explanation is that a persistent course is largely explained by ongoing environmental stressors. It is well-reported that stressful life events (SLEs) are more frequently reported in depressed compared to non-depressed adults (Hammen, 2005; Kessler, 1997). Depressed adults report increased interpersonal, job and financial stress. (Goodman & Gotlib, 1999). In particular, relationship difficulties and marital discord are frequently reported (Goodman & Gotlib, 1999). It is important to recognise the role of person-environment correlation in stress generation (Rutter et al., 1997), as well as processes such as kindling (Kendler et al., 1999; Post, 1992) whereby exposure to prior episodes of depression may reduce the threshold for stress to elicit depression (Hammen, 2006; Monroe & Harkness, 2005; Rutter et al., 2006). Also important is how

individuals appraise SLEs as stressful, which has been implicated in the onset and persistence of depressive symptoms (Bergdahl & Bergdahl, 2002; Cristóbal-Narváez et al., 2020; Lazarus & Folkman, 1984). Individuals with high levels of perceived stress report greater emotional reactivity to SLEs and more daily stressors (van Eck et al., 1998). Maladaptive emotional regulation strategies may worsen emotional reactivity to stress and are more common in individuals with MDD (Visted et al., 2018) and associated with increased perceived stress (Zahniser & Conley, 2018). This might begin a cycle of increased perceived stress, increased depression and increased stressors. (Zahniser & Conley, 2018) Many of the social determinants of depression, such as poverty, lower educational attainment and being a single parent are also associated with an increased risk for SLEs (Daryanani et al., 2017; Feizi et al., 2012; Goodman, 2020). These socio-economic factors may perpetuate the chronicity of depression and stressors.

A final possibility is that both hypotheses are partially correct. Individuals with pre-existing vulnerabilities, such as increased genetic vulnerability to MDD, may be particularly affected by stressors in the development and persistence of depression (Tafet & Nemeroff, 2016). Models such as the diathesis-stress model, stress sensitisation and kindling highlight the relationship between stressors and vulnerabilities. The diathesis-stress model of depression states that the effects of stress on depression risk are dependent on underlying vulnerabilities (Monroe & Simons, 1991; Robins & Block, 1989), such that increased genetic liability to MDD may predispose underlying vulnerability to depression, which is triggered by stress into psychopathology. In addition, genetic predispositions can increase the likelihood that an individual is exposed to environments that increase depression risk (i.e. gene-

environment correlation) (Rutter et al., 2006). Consistent with this, research has indicated that the relationship between stress and depression is bidirectional (Hammen, 2015). Depression contributes to the occurrence of stressors and the characteristics of individuals with depression also predict the occurrence of stressors, which in turn increase depression risk (Hammen, 2015). Thus, both pre-existing vulnerabilities and environmental stressors may contribute to the depression persistence.

This study aimed to better understand heterogeneity in the longitudinal course of depression, using four repeated measures of a DSM-IV (American Psychiatric Association, 1994) MDD symptom count across a 13-year period. Depression trajectories were characterised in adults with a history of recurrent depression. We tested for associations between risk factors for persistent MDD, clinical comorbidities, and ongoing stressors, and depression trajectory classes. We expected that these factors would be associated with a persistent depressive symptom trajectory (symptoms that remained high across the study period) compared to less persistent trajectories. The pattern of results was evaluated according to two hypotheses: a) persistent depression is aetiologically distinct from less persistent depression, and/or b) persistent depression is largely explained by ongoing exposure to environmental stressors. It was expected that if persistent depression is aetiologically distinct, the pattern of risk factors and clinical comorbidities associated with persistent depression would be distinct from all other trajectory classes. In contrast, if persistent depression is explained by ongoing environmental stressors, then it was expected that stressors would be more strongly associated with classes showing persistent depressive symptoms.

Methods.

Participants and design.

Data came from the Early Prediction of Adolescent Depression (EPAD) study, a prospective longitudinal study of recurrently depressed adults and their biological adolescent offspring (Mars et al., 2012). This study included data from 337 adults with a history of recurrent depression (defined as two or more lifetime episodes of DSM-IV MDD (American Psychiatric Association, 1994)). Participants completed four assessments between April 2007 and October 2020 including interviews and questionnaires. On average there was a 16-month period between waves 1 and 2, a 13-month period between waves 2 and 3 and an 8-year period between waves 3 and 4. More detailed information on recruitment, assessment and sample characteristics can be found elsewhere (Mars et al., 2012, 2015; Powell et al., 2021). Baseline participants were 93.5% female with a mean age of 41.6 years (range 26–55 years). At baseline, 337 individuals took part; at wave 2, data (interview and/or questionnaire) were available on 319 (94.7%) individuals, at wave 3 data were available on 309 individuals (91.7%) and at wave 4 data were available on 194 individuals (58.5%).

Assessment procedure.

Families were recruited to the study if parents had a history of recurrent depression and if they lived with the biological child who also enrolled into the study. Participants were not required to be in a current depressive episode. Participants were excluded if they either had a history of or met criteria for psychosis, schizoaffective disorder or bipolar disorder at baseline. Ethical approval was granted by the Multi-

Centre Research Ethics Committee for Wales and from the School of Medicine Ethics Committee, Cardiff University.

Measures.

DSM-IV MDD symptom count.

A DSM-IV MDD symptom count was derived at each wave based on information from the Schedules for Clinical Neuropsychiatry (SCAN) (Wing et al., 1990). This was used to derive trajectories. The SCAN is a semi-structured clinical interview assessing psychiatric disorders over the preceding month. We coded depressive symptoms as present if they were present at a level sufficient for diagnostic criteria (i.e. at a moderate/severe intensity for at least half of the time) (Wing et al., 1990). The nine SCAN items relating to DSM-IV MDD (American Psychiatric Association, 1994) were recoded as binary variables (not present/present) and summed to create a depressive symptom score (range 0–9). Participants were screened for core MDD (American Psychiatric Association, 1994) symptoms, meaning that depressive symptom scores above zero included at least one core MDD symptom and therefore scores of five or more were indicative of meeting diagnostic criteria for a DSM-IV defined MDE (American Psychiatric Association, 1994).

Unless otherwise stated, all variables tested for association with trajectory class were assessed at baseline.

Demographics.

Demographic information was collected from self-reported questionnaires. We used age, biological sex, current partner status (no/yes), low educational attainment (no/yes) (defined as achieving no GCSEs (General Certificate of Secondary Education) or equivalent (Department for Education, 2022)) and low income (no/yes) (defined as an annual gross family income of less than £20,000 (Stephens et al., 2023)).

Risk factors for recurrent MDD.

We used measures of prior clinical severity of depression: history of a severely impairing MDE (defined as a Global Assessment of Functioning (GAF) score < 50) (American Psychiatric Association, 1994) in line with previous research (Rice et al., 2017)), history of hospitalisation for depression (no/yes) and depression age-of-onset. These were measured using the SCAN interview (see Supplementary Text).

We assessed family history of depression (no/yes), defined as whether the participant self-reported having a parent with depression. We derived polygenic scores (PGS) to index genetic liability for MDD, anxiety, bipolar disorder, schizophrenia and ADHD. DNA samples were collected during assessments via saliva samples. Details of genotyping, imputation, quality control and ancestry can be found in the Supplementary Text. PGS were calculated using the Polygenic Risk Score Continuous Shrinkage (PRS-CS) approach (Ge et al., 2019). To adjust for population stratification, we included population covariates in the analysis. Discovery summary statistics from the largest published genome-wide association studies (GWAS) at the time were used for MDD (Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, 2025), anxiety (Purves et al., 2019), bipolar disorder (Mullins et al., 2021),

schizophrenia (Trubetsky et al., 2022) and ADHD (Demontis et al., 2023). For further details, see Supplementary Text.

Additional clinical comorbidities.

Anxiety symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). This is a 7-item, well-validated self-report questionnaire assessing anxiety symptoms over the past week (Bjelland et al., 2002). Items were scored on a 0–3 scale and summed (range 0–21).

Cyclothymia symptoms were derived using 12 cyclothymia items of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego-auto-questionnaire short-version (TEMPS-A) (Akiskal et al., 2005). This is a self-reported questionnaire measuring temperament. The cyclothymia items were rated as false=0 or true=1 and summed (range 0–12).

Self-harm or suicide attempt in the previous month (no/yes) was measured using one item from the SCAN depression section (Wing et al., 1990)..

ADHD symptoms were assessed at wave 4 using the self-reported Adults ADHD Investigator Symptom Rating Scale (AISRS) (Spencer et al., 2009). The 18 items were rated on a 0–3 scale and summed (range 0–54).

Ongoing environmental stressors.

Stressors were assessed at all four waves and associations with trajectory class were tested at each wave to assess the persistence of stressors over time.

Threatening life events were measured using the List of Threatening Experiences Questionnaire (LTEQ) (Brugha & Cragg, 1990). This is a 12-item self-reported

questionnaire assessing SLEs occurring in the previous 6-months. Life events included death of a partner or close relative/friend, major financial crisis and having problems with the police. Two items were combined (separation due to marital difficulties and broke-off a steady relationship) giving 11 items overall. Each item was scored as absent/present and summed (range 0–11).

Relationship satisfaction was measured using the Locke-Wallace Short Marital Adjustment Test (LWSMAT) (Locke & Wallace, 1959) asking: “rate the degree of happiness, everything considered, in your relationship”. This was scored on a 7-point scale where 1=very unhappy and 7=perfectly happy. Only adults who had a current partner completed this.

Perceived stress was measured using the Perceived Stress Scale (PSS) (Cohen et al., 1983). This 10-item self-reported questionnaire measures how much an individual perceives their life as uncontrollable, unpredictable or overwhelming. Items were rated 0–4 and summed (range 0-40).

Depression medication.

Baseline antidepressant medication was assessed using participant self-report of current medication(s). First-line medication was defined as SSRIs (Selective Serotonin Reuptake Inhibitors), and non-first-line medication was defined as non-SSRIs, two or more antidepressants, or an antidepressant augmented with lithium or an antipsychotic, consistent with previous research (Powell et al., 2021). Further details can be found in the Supplementary Text. We tested medication use (first-line and non-first-line) for association with trajectory classes. We considered medication use as a sensitivity check because evidence suggests this can be confounded with indicators of

depression severity, complexity and tolerability (McAllister-Williams et al., 2020; National Institute for Health and Care Excellence, 2022; Wickramaratne et al., 2011). This means that it is not possible to draw strong conclusions about the direction of influence.

Statistical analysis.

We used growth mixture modelling (GMM) in Mplus version 8.8 (Muthén & Muthén, 2017) to describe depression trajectories. GMM is a probability-based technique that groups individuals into more homogenous groups based on initial levels of depression symptoms and change over time (Jung & Wickrama, 2008). It identifies unobserved sub-populations (classes) within a population and describes longitudinal changes (Ram & Grimm, 2009). First, we compared linear and quadratic models of change to assess which pattern of change best described the data. Next, we assessed the optimum number of classes. Model selection was informed by theory and overall model fit indices, including sample size-adjusted Bayesian information criteria (SABIC), log-likelihood (LL), Vuong-Lo-Mendell-Rubin likelihood test (VLMR-LT) and the Bootstrap Log-likelihood ratio test (BLRT). Further details of model selection are in the Supplementary Text.

The four assessments were defined based on the average completion date of the sample in months (wave 1=0 months, wave 2=16 months, wave 3=29 months and wave 4=125 months). We tested associations of key study variables (risk factors, additional clinical comorbidities, and stressors) with trajectory class using a bias-adjusted 3-step approach (BCH) (Asparouhov & Muthén, 2019), implemented in Mplus. Full information

maximum likelihood (FIML) estimation was used in MPlus and included all individuals with at least one depression assessment in the analysis (N=337; Supplementary Text). For tests of association with trajectory class, MPlus utilises cases with complete data on the variable of interest. For that reason, we reran analyses using inverse probability weighting (IPW) (Seaman & White, 2013) to address any potential bias caused by participant attrition. IPW involves weighting the analysis sample by the inverse probability of being missing (Seaman & White, 2013). Variables relating to attrition included age, sociodemographic variables, impaired functioning and depressive symptoms. Details of the IPW analysis can be found in the Supplementary Text and Supplementary Table S3. The results with the IPW weights were similar to the unweighted results and the interpretation was the same (Supplementary Table S4 and S5). Therefore, the unweighted results were presented in the main text.

Results.

Baseline characteristics.

Table 1 shows the sample's baseline characteristics and mean depressive symptoms for each wave. The majority of the sample were female and had a partner. Mean depressive symptoms were similar across assessments but slightly higher at wave 1 and wave 4.

****TABLE 1****

Depression trajectories.

A 3-class solution optimally characterised depressive symptoms over time (see Supplementary Text and Supplementary Table S1 and S2). Figure 1 shows the three trajectory classes: low (63.7%, N≈215), intermediate (17.3%, N≈58) and severe persistent (18.9%, N≈64). Ns are approximate due to the probabilistic nature of GMM. The low class showed a mean depressive symptom score below the DSM-IV MDD diagnostic threshold (five symptoms) throughout the study period. The intermediate class showed a mean symptom score that began above the DSM-IV threshold and declined to below threshold at subsequent waves. The severe persistent class showed a mean symptom score above the DSM-IV symptom threshold throughout the study period. The proportion of individuals who met MDD criteria at wave 1 through wave 4 for each trajectory class were: low: 0%, 6%, 7% and 22%; intermediate: 50%, 16%, 2% and 36%; and severe persistent: 85%, 74%, 77% and 60%.

****FIGURE 1****

Association between risk factors and trajectory classes.

This study aimed to test two hypotheses regarding persistent depression, therefore it was most appropriate to compare the severe persistent class to the other two classes. In all tests of association, the severe persistent class was used as the reference to test whether it differed from the other classes.

Table 2 shows the association between risk factors and trajectory classes. A greater proportion of the severe persistent class had a history of a severely impairing episode (over 80%) compared to the other two classes (53% intermediate class; 57% low class). A younger age-of-onset for depression was apparent in the severe persistent class compared to the low class, but this did not differ between the severe persistent and intermediate classes. There was limited evidence that family history of depression or history of hospitalisation for depression distinguished the severe persistent class from the low or intermediate classes. There was no strong evidence that genetic liability to MDD, anxiety, bipolar, schizophrenia and ADHD differed between trajectory classes.

****TABLE 2****

Association of clinical comorbidities and trajectory classes.

Table 3 shows the associations between clinical comorbidities and trajectory classes. Mean anxiety, cyclothymia and ADHD symptom scores were higher in the severe persistent compared to the low class, but there was no strong evidence of differences between the severe persistent and the intermediate class. A greater proportion of the severe persistent class showed self-harm or suicide attempt (15%) compared to the low and the intermediate class (both estimated as 0%).

****TABLE 3****

Association of ongoing stressors and trajectory classes.

Table 4 shows the tests of association between ongoing stressors and trajectory class. The severe persistent class showed more threatening life events and lower relationship satisfaction at waves 1 to 3 compared to the low class. The severe persistent class showed higher perceived stress than the low class at wave 1, and higher perceived stress than both the low and the intermediate classes at all other waves.

****TABLE 4****

Sensitivity analysis.

Table 5 shows the tests of association between first-line and non-first-line medication and trajectory class. Approximately a third in each class were using first-line depression medication at baseline. The severe persistent class showed higher non-first-line medication use compared to the low and intermediate classes.

****TABLE 5****

Discussion.

This study aimed to better understand heterogeneity in the longitudinal course of depressive symptoms in adults with a history of recurrent MDD over 13 years. We evaluated two potential explanations for the persistence of depressive symptoms: a)

persistent depression is aetiologically distinct from a less persistent course, and/or b) depression persists due to ongoing exposure to environmental stressors, by testing associations between trajectory class and risk factors for persistent MDD, clinical comorbidities and ongoing stressors. We considered evidence for both hypotheses and the possibility that both hypotheses may be somewhat correct.

As expected, we found significant heterogeneity in the longitudinal course of depression among adults with a history of recurrent depression. Three trajectory classes were identified: a low class (64%) showing minimal depressive symptoms throughout the study period; an intermediate class (17%) where mean symptom scores were above the DSM-IV MDD symptom threshold at baseline only; and a severe persistent class (19%) where mean symptoms were above the threshold throughout the study period. As expected, these results contrasted with findings based on general population samples where typically less than 10% of individuals report persistent symptoms (Musliner et al., 2016). It is notable that the largest class was a low group given that the sample had prior recurrent MDD. However, due to the skip rule in the SCAN interview used to assess depression, where all depression symptom questions were asked only when individuals screened positive for at least one core symptom (i.e. low mood and loss of interest or pleasure), it is possible that the number of depressive symptoms in the low class were underestimated.

We identified three variables which distinguished the severe persistent trajectory from both other trajectory classes. First, the persistent trajectory included a higher proportion of participants with a history of a severely impairing episode, with over 80% having experienced an episode with major impairment in social or occupational

functioning , prior to the study period. This is somewhat consistent with previous studies, as several (but not all) have found that markers of depression severity, such as number or duration of previous MDEs, predict persistent depression (Hoertel et al., 2017; Mars et al., 2015). However, some studies have failed to identify predictors of persistence (Eaton et al., 2008; Wang et al., 2012). Second, self-harm or suicide attempt was higher in the persistent trajectory, where 15% reported baseline self-harm or suicide attempt compared to 0% in the other trajectory groups - in line with previous research. (Parker et al., 2005). Self-harm or suicide attempt in individuals with depression is associated with a less favourable course of depression (e.g. poor treatment response), compared to those with depression and no self-harm or suicide attempt (Costa et al., 2022; Kautzky et al., 2017; Kraus et al., 2019). Finally, perceived stress was found to be highest for the persistent trajectory compared to other trajectories across all waves. Psychological theories of depression such as the appraisal theory and the stress generation theory (Hammen, 1991; Lazarus & Folkman, 1984) have highlighted the relevance of how an individual interprets SLEs and its association with depression onset. These theories pose that individuals with cognitive vulnerabilities are more susceptible to either appraising experiences as stressful (appraisal theory) or experiencing more stress through creating stressful contexts (stress generation theory), thereby increasing the likelihood of persistent depressive symptoms. This is also consistent with genetic studies showing that individual characteristics (including genetic effects) can influence exposure to environmental stressors (Rutter et al., 1997).

Other risk factors for MDD (history of hospitalisation, depression age-of-onset, family history of depression and genetic liability for psychiatric/neurodevelopmental

disorders), additional comorbidities (anxiety, cyclothymia and ADHD) and environmental stressors (threatening life events and lower relationship satisfaction) showed some evidence of being higher in the persistent trajectory compared to the low trajectory. However, they did not clearly differentiate the severe persistent class from the intermediate trajectory. Our results are consistent with systematic reviews of different subtypes of depression, which show quantitative rather than qualitative differences between depression subtypes (Baumeister & Parker, 2012). Nonetheless, caution should be taken interpreting the genetic analyses due to small sample size and the low predictive power of PGS (Martin et al., 2019).

Although the severe persistent and intermediate classes showed similar associations with the tested variables, their differing trajectories might be in some part explained by how adequately their depression was treated. Our results suggested that individuals in the severe persistent class may have been more likely to experience a more complex presentation of depression or low tolerability to first-line medication, as indicated by having increased rates of non-first-line treatment use. Markers of prior severe depression and clinical comorbidities are risk factors for poor treatment response (McAllister-Williams et al., 2020), which might explain in part why the severe persistent class showed a non-remitting course. However, indices of depression severity and treatment are inter-correlated (Wickramaratne et al., 2011) which precludes strong conclusions about the direction of influence particularly in the absence of a randomised design. Nevertheless, we did not investigate longitudinal treatment changes which could be associated with depressive course.

Regarding the first hypothesis, if a persistent course of depression characterised a somewhat distinct form of depression, we expected to observe differential associations for the persistent class versus other trajectory classes with the risk factors and clinical comorbidities examined. We found somewhat inconsistent results for this. Although the persistent trajectory was more likely to show a severely impairing previous episode and self-harm or suicide attempt, there were many similarities between the severe persistent and intermediate classes in relation to risk factors and clinical comorbidities. This is not consistent with the hypothesis that persistent depression is aetiologically distinct compared to depression with a less persistent course for those with a history of recurrent depression.

Regarding the second hypothesis, that persistent depression is at least partially explained by ongoing environmental stressors, we also found inconsistent results, suggesting that persistent depression is likely a combination of aetiological differences and ongoing stressors. While the severe persistent and intermediate trajectory classes showed similar levels of threatening life events (slightly higher in the severe persistent class), those in the severe persistent class tended to report higher perceived stress. Therefore, it could be that the severe persistent class appraised the stress as greater compared to the intermediate class (Lazarus & Folkman, 1984). Alternatively, perceived stress could be a more sensitive measure of stress than objective checklists as it taps into the cognitive experience of the events. Given that the relationship between stress and depression is potentially influenced by individual vulnerabilities, as detailed in the diathesis-stress model (Monroe & Simons, 1991), the subjective experience of stress may be a helpful consideration when examining stress and depression. Further elucidation of the mechanisms involved in how perceived stress is associated with

depression seems warranted. These processes likely involve complex chains of events involving chronic and acute stressors, social determinants that compound the impact of stress on a person (e.g. poverty, housing, financial security), internal biological processes and the cognitive appraisals of stress. One possible bio-psycho-social mechanism could include maladaptive emotional regulation which has been associated with perceived stress, depression and genetic vulnerabilities (Visted et al., 2018; Zahniser & Conley, 2018). The genetic effects underlying perceived stress are largely shared with those that influence depression (Rietschel et al., 2014), highlighting the intricacies of this relationship.

This work gives several practical intervention insights for reducing depression persistence. We identified factors associated with depression persistence, namely prior functional impairment and self-harm suggesting that screening for these variables might help inform treatment decisions in primary care settings, where the majority of depressed adults are treated. Perceived stress was also associated with persistent depression, which may be a helpful target for interventions such as cognitive behavioural therapy or stress inoculation in reducing depression persistence.

Strengths of this study include comprehensive assessments of adults with a history of recurrent depression allowing the analysis of depressive symptoms spanning 13 years. Limitations of this study were the relatively small sample size, meaning that power was likely to be low when testing associations, especially for measures of genetic liability (Martin et al., 2019). We used symptoms included in the current DSM MDD criteria to derive depressive trajectories, however there is growing interest in defining depression differently (e.g. network analysis) . The sample primarily included females

and therefore may not generalise to depressed males. Research has indicated some differences in the pathways to depression for males and females (Kendler et al., 2002, 2006) and also differences in stress response (Verma et al., 2011). The analysis was based on data at four assessments, where the gap between the third and fourth was 8 years on average. There was little information about symptoms between assessments so episodes may have been missed, which may have influenced trajectory class classification. Nevertheless, entropy for the derived classes (a standardised measure of uncertainty) was good suggesting that this did not substantially impact the pattern of results (Asparouhov & Muthén, 2019). Whilst we examined baseline comorbidities as predictors, it is possible we missed emerging comorbidities, including anxiety disorders and bipolar disorder. Although baseline medication was used in the sensitivity analysis, we were unable to investigate treatment changes over time, which could influence trajectories. However, conversely, depression trajectories may also influence treatment changes (Wickramaratne et al., 2011). Evidence suggests possible aetiological differences in depression that are indicated by age-of-onset (Kessler et al., 2005; Thapar et al., 2022). It is possible that the results might differ according to the age of the population studied. As is common in longitudinal studies, non-random attrition occurred in this sample over time. We used two approaches to deal with partially missing data. First, we implemented FIML when deriving the depression trajectories, which allowed for partially missing depression data to be included. Second, we identified factors associated with attrition across the study (detailed in Supplementary Table 3) and derived IPW weights based on factors that predicted missingness and included these in tests of association with trajectory class. Results of tests of association between variables and trajectory class remained similar when IPW weights

were applied, suggesting bias due to missingness was minimal for these associations (Seaman & White, 2013).

To conclude, the longitudinal course of depression in adults with a history of depression is heterogenous. We found that prior severely impairing episodes, self-harm or suicide attempts, and ongoing perceived stress distinguished depression that persisted from a less persistent course. This research highlights the potential long-term association between prior impairment and self-harm and depressive course.

Perceptions of stress may be a more sensitive measure of stress compared to objective measures and therefore may be a better indicator of depressive course persistence. Our findings also suggested that a proportion of those with persistent depression require more intensive treatment and suggest careful monitoring of treatment response and symptom chronicity may be indicated.

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