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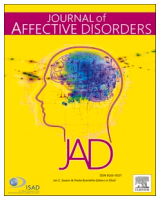

Review Article

Youth depression: An overview of genetic findings and the challenge of heterogeneity

Anita Thapar [a,b,*], Olakunle Oginni [a,b], Charlotte A. Dennison [a,b], Frances Rice [a,b]

[a] Wolfson Centre for Young People's Mental Health, Cardiff University, UK
[b] Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, UK

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ABSTRACT

Background: Depression in youth is common but a highly heterogenous disorder. In the last decade there have been much larger family and twin studies as well as molecular genetic advances. However, although considered as a unitary diagnostic concept, depression is extremely variable in terms of its definition, measurement, age-at-onset, clinical antecedents or comorbidities, and long-term outcomes.
Method: In this narrative review, we summarise findings on the genetics of youth depression, as well as consider the many challenges around heterogeneity.
Results: Youth depression is familial, modestly heritable, and inter-generational transmission appears to be explained by rearing as well as genetic contributions. Non-shared environmental factors are a major contributor and gene-environment correlation is especially important for youth depression. Although there is overlap between youth and adult depression in genetic liability, youth-onset depressive disorder may represent a distinct subtype in terms of its genetic profile. Familial loading and heritability are higher when youth-onset depressive disorder is recurrent, chronic and more severe than when depression is milder and defined more broadly. Polygenic scores and pharmacogenetic testing are not ready for clinical use. There are many inconsistencies in findings that may be explained by heterogeneity.
Limitations: There are no large genome-wide association studies of youth depression. The lack of diversity in ancestry is a problem.
Conclusion: We highlight that future genetic studies of youth depression need to consider more careful harmonisation of definitions, measures, take into account recurrence or chronicity and severity of depression as well as include more diverse populations.

1. Introduction

Depression is common, a leading cause of global disability, and rising rates in young people represent a growing concern (Thapar et al., 2022). It has a complex multi-factorial aetiology, and genetic factors are known to contribute to risk. In the last decade, there have been enormous advances in genomic methods and technologies that together with unprecedented, large-scale international collaborations have led to an explosion of psychiatric genetic discoveries (Andreassen et al., 2023). In this article, we provide an initial update of key genetic findings on youth depression and then consider the many challenges of depression heterogeneity that impact on the interpretation of genetic research findings. We recognise the importance of environmental and cultural factors, but it is beyond the scope of this review to review all measured aspects of environment that have been shown to be associated with depression (see reviews of environmental risks: Cairns et al., 2014; Gradisar et al., 2022; LeMoult et al., 2020; Stirling et al., 2015; Thapar et al., 2022)).

Our primary focus is on studies that use depression-specific measures rather than broader measures of emotional or internalising symptoms. Where data on youth are sparse, we draw on research literature involving adults. We define youth as age 10–24 years (Sawyer et al., 2012).

2. Familial aggregation

There is substantial evidence that depression clusters within families (Rasic et al., 2014; Rice et al., 2002a; Uher et al., 2023). Family studies

* Corresponding author at: Hadyn Ellis Building, Cardiff University, Maindy Road, Cardiff CF24 4HQ, UK.
E-mail address: thapar@cardiff.ac.uk (A. Thapar).

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use two main approaches, which are to investigate the rates of disorder in the biological offspring of parents with a diagnosis of depression ("top-down" studies), and to examine the rates of disorder in first degree relatives of young people with a diagnosis of depression ("bottom-up" studies).

Bottom-up family studies of children and adolescents with a diagnosis of depression report a relative risk of approximately 2 for first degree relatives compared to unaffected or psychiatric control groups (Klein et al., 2001; Rice et al., 2002a). Similarly, prospective high-risk and registry-based studies of the biological offspring of parents with depression indicate that the relative risk of depression in offspring is 2.3 (95 % CI 1.9, 2.6) compared to offspring of unaffected parents, and the absolute risk is 14 % (95 % CI 5, 36) (Uher et al., 2023). It is noteworthy that the confidence intervals for absolute risk are wide, and several factors appear to contribute to this variation including offspring age and parent depression severity. In terms of offspring age, prospective family high-risk studies show that the risk period for depression onset spans childhood to early adult life (Powell et al., 2023; Uher et al., 2023; Weissman et al., 2006). A meta-analysis of prospective "top-down" studies (Uher et al., 2023) showed that when followed to adult life, the absolute risk to offspring increases dramatically, from 14 % to 50 % (i.e. 1 in 2 develop depression by early adult life). This result not only highlights the importance of offspring age, consistent with evidence on the peak period of incidence for depressive disorder (Solmi et al., 2022), but also indicates that cross-sectional "snapshots" may dramatically underestimate risk to offspring if they do not span the full period of risk.

There is a relative dearth of top-down studies that investigate the role of *paternal* depression (Ramchandani and Psychogiou, 2009). Several studies highlight the role of parent sex in familial loading (Klein et al., 2005). While these differences do not appear substantial (Brophy et al., 2021) there is evidence from multiple types of family and adoption studies for a slightly stronger familial risk for offspring from maternal compared to paternal depression (Brophy et al., 2021; Kendler et al., 2018; Klein et al., 2005; Rice, 2022; Upadhyaya et al., 2025). There is also some evidence suggesting offspring sex effects, where familial risk for depression is greater for adolescent females. This sex difference levels out in early adult life suggesting that familial risk for depression may manifest later in males (Powell et al., 2023). This finding is consistent with the epidemiology of depression (Patton et al., 2014). Examining sex effects in both parent and offspring merits further investigation. Indeed, we are only aware of a small number of genetically informative studies that have examined the role of both parent and child sex. These studies examined the inter-generational transmission of emotional (depression/anxiety) symptoms (Lewis et al., 2011; Rice et al., 2013). Both of those studies used the in vitro fertilisation (IVF) design (see later) and reported greater similarity and environmental transmission between mother-daughter than mother-son pairs. However, those findings require replication in samples that specifically assess depression and in different study designs.

Finally, it is worth noting that the pattern of strengths and weaknesses may differ for different types of family study methodology. Help-seeking behavior for young people is correlated with a range of factors including parental functioning and mental health (Potter et al., 2012); so it is not clear if help-seeking biases will affect estimates from "bottom-up" studies in a particular direction. There do, however, appear to be subtle systematic differences in results of family studies based on clinical diagnostic research interview and those based on registry diagnoses (clinically recognised depression). Studies based on registries generate risk estimates that are significantly lower than those using clinical interview and this difference in methodology contributes to heterogeneity in estimates of absolute risk (Uher et al., 2023). Nonetheless, the strengths of registry studies often include large sample sizes and full population coverage (Uher et al., 2023), which cannot be achieved using clinical interview designs. Family studies also suggest that familial loading appears to be higher in depression that onsets early (i.e. adolescence), is recurrent or chronic, and has a more severe impairment (Kendler et al., 2023, 1999; Klein et al., 2004, 2002; Nierenberg et al., 2007; Upadhyaya et al., 2025; Weissman et al., 1997).

2.1. Twin research

Twin studies of youth depression have mainly focused on depression symptoms although one twin study and an extended family study have examined adolescent major depressive disorder (MDD)(Glowinski et al., 2003; Nguyen et al., 2023). Those studies of MDD find heritability estimates between 40 % and 45 % (95 % CI 23.9, 47.5) with evidence of higher heritability for the syndrome of MDD (40 %) than for a broader phenotype (24 %)(Glowinski et al., 2003) and for adolescent onset $\leq$ 21 years (55.1 %; 95 % CI = 51.2, 59.0) versus adult onset MDD $\geq$25 years (43.8 %, 95 % CI = 39.5, 48.2). Overall, the estimates of the heritability of depressive symptoms in adolescence vary widely, after excluding small samples and shared environment influences, ranging between 32 and 48 % (Eley, 1997; Happonen et al., 2002; Lau and Eley, 2008; Rice et al., 2003, 2002b; Silberg et al., 1999; Thapar and McGuffin, 1994; Waszczuk et al., 2014). This variability in heritability estimates may be explained by differences in development, sex, rater, measure, depression severity and sample type. Regardless, results of these studies show that environmental factors are important contributors to depression liability. In twin studies, phenotypic variance is partitioned into heritability, "shared environment", which is the component of non-heritable influences that contributes to greater twin similarity and "non-shared environment", that is the non-heritable variance which accounts for twin dissimilarities. Non-shared environmental variance would include environmental factors that are unique to each twin, measurement error and stochastic factors (Rutter et al., 2001). Overall, shared environment decreases and heritability increases from childhood to adolescence (Rice, 2010). This increase is thought to be explained by increased gene-environment correlation as adolescents are more able to select their environments (Franić et al., 2010) (Fig. 1).

Gene-environment correlation describes the observed correlations between genetic liability and environmental influences. These associations can occur because (i) parents provide both the genes and the risk environments which are 'passively' experienced by the children (passive rGE), (ii) a child's genetic propensity for depression could evoke negative reactions from people in their environment that increases their risk for depression (evocative rGE), and (iii) as children grow older and independent, their genetic liability for depression could lead to selection and creation of environments that increase their risk for depression (active rGE). Passive rGE is thought to be more likely when children are younger and more dependent on their families, while active and evocative rGE are thought to become more prominent in adolescence as children grow older.

Longitudinal twin studies also highlight that genetic factors contribute to the stability of youth depressive symptoms during adolescence, and that innovative genetic influences also arise during this time which we will discuss later (Hannigan et al., 2017).

Evidence for sex differences in heritability from twin studies is inconsistent. Some studies have reported sex differences that differ according to who rated the symptoms (parent or young person), sex differences in opposite directions, and others find no evidence for sex differences (Eaves et al., 1997; Glowinski et al., 2003; Happonen et al., 2002; Lau and Eley, 2006; Rice et al., 2002b; Scourfield et al., 2003). Overall, there is little robust evidence of sex differences in the aetiology of youth depression from twin studies.

An important consideration is rater effects. If parents rate twins as being more similar (parent-report) than when twins rate themselves (self-reports), this would decrease the heritability and increase the estimate of shared environmental influences. There are no consistent findings on the impact of rater on twin studies of youth depression symptoms, with studies reporting similar heritability between parent and self-ratings (Happonen et al., 2002; Sallis et al., 2017), higher heritability for peer-report (Happonen et al., 2002), and others

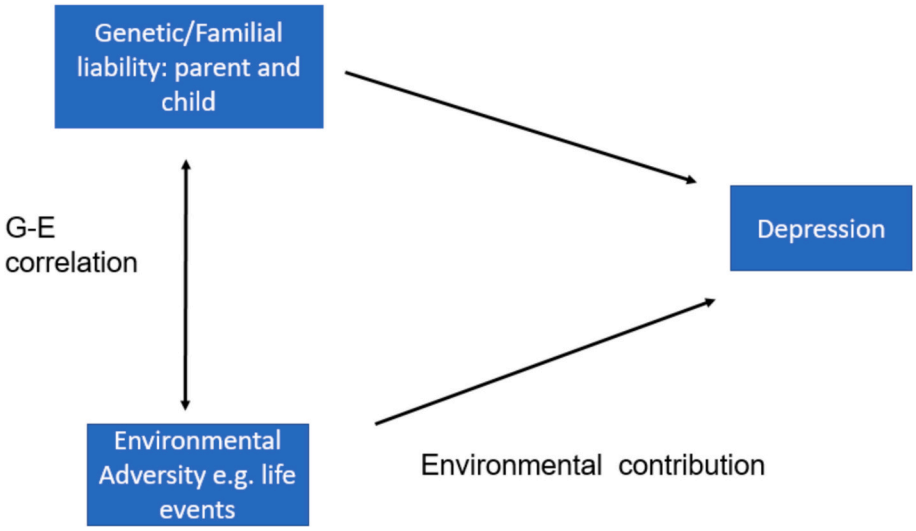

Fig. 1. Gene-environment correlation.

identifying higher heritability for self-reports compared to parent-reports (Rice et al., 2002b). One study, and that was of emotional problems (anxiety/depression), found higher heritability for parent-reports compared to self-report (Nivard et al., 2015). Nevertheless, correlations across informants are consistently weak, and rater effects remain an important source of heterogeneity in studies of youth depression.

One concern that has often been raised in epidemiological and genetics research is that depressive symptoms rated using questionnaires, high levels of depression symptoms and diagnoses of major depressive disorder can be regarded as the same. Twin studies suggest this may not be the case. There is consistent evidence from three independent twin studies of lower heritability and greater shared environment contribution for high depressive symptom scores in youth when this measure is compared to normal variation in depression scores (Eley, 1997; Rende et al., 1993; Rice et al., 2002b). There is also evidence that heritability of a broader depression phenotype is lower than that for the syndrome of MDD (Glowinski et al., 2003). Glowinski et al. found evidence of lower heritability and greater shared environment for a broad depressive phenotype (two weeks of low mood, irritability or anhedonia) compared to the narrower syndrome of MDD. Collectively, these results suggest that elevated depressive symptoms are more susceptible to shared environmental influences (including adverse family environments) than major depressive disorder (MDD) in young people, which appears to be more heritable and has a greater contribution from non-shared environmental rather than shared environmental risk factors.

2.2. Adoption, children-of-twins and in-vitro fertilisation studies

A range of genetically sensitive designs that involve comparing phenotypic resemblance in parent-child pairs that differ in their degree of genetic relatedness have been used to investigate the intergenerational transmission of depression or depressive symptoms. These include adoption, children of twins and in-vitro fertilisation (IVF), designs. Only one adoption study of depressive disorder has focused on adolescent depression (Tully et al., 2008). It examined the similarity between adoptive (unrelated) parents and adolescents for lifetime MDD as well as a control sample of non-adopted children and their biological parents. Adoptive adolescents whose unrelated parents had experienced lifetime MDD showed elevated rates of depression compared with adopted adolescents whose unrelated parents had not had MDD (odds ratio = 2.19), suggesting an important contribution of the rearing environment to the intergenerational transmission of depression. Inherited influences did make some contribution as the same comparison in the biologically related group resulted in a slightly, though not significantly, higher risk to offspring (odds ratio = 2.96). One large extended adoption study of adults (aged 26–58 years) based on Swedish registry data (Kendler et al., 2022), found evidence suggesting slightly stronger inter-generational correlations for the transmission of anxiety disorders and MDD in younger (aged 26–42) compared to older (aged 45–58) halves of the cohort suggesting possible developmental differences in intergenerational transmission (Rice, 2022).

The children of twins (CoT) design separates genetic from rearing (environmental) effects in cross-generational risk transmission by comparing parent-child similarity in identical and non-identical parents as twins and their offspring. There is one CoT each for depressive disorder (Singh et al., 2011) and depressive symptoms (Silberg et al., 2012), and both show evidence of rearing effects on the intergenerational risk transmission for depressive symptoms. Rearing effects for maternal depression and offspring emotional (anxiety/depression) symptoms were also demonstrated using the IVF design (Lewis et al., 2011). The IVF design compares parents and children who differ in their genetic relatedness due to assisted reproductive technologies, and can be used to disentangle prenatal environments from maternally provided genetic effects (Thapar and Rice, 2021).

3. Brief overview of molecular genetic approaches

Gene discovery capitalizes on different types of DNA variation. Genetic variants, can encompass differences in DNA sequence or microstructure of chromosomes, known as copy number variation (CNV). Genetic variants also vary in frequency in the general population; those present in >1 % of the population typically are termed common, and ones that are rare have a lower frequency. Millions of common DNA variants across the genome, single nucleotide polymorphisms (SNPs), can be genotyped at low cost using microarrays.

Genome-wide association studies (GWAS), involve comparing millions of SNPs in cases versus controls. The large multiple testing burden means sample sizes of tens or hundreds of thousands are needed. Studies using DNA sequencing require even larger sample sizes.

Hypothesis-free GWAS have supplanted candidate gene studies that involved presuming what gene/s might be involved based on knowledge of pathogenesis. Candidate gene approaches, for example those examining variants in serotonergic genes, are now considered an unreliable approach for a variety of reasons (Duncan et al., 2019). These were initially appealing because of hypotheses around the involvement of neurotransmitters in depression. Also, at the time, until genome-wide

genotyping arrays became affordable, it was only feasible to genotype a select number of gene variants. However, a history of non- replicated findings, false positives and concerns about the robustness of evidence have meant that such studies are no longer considered reliable (Border et al., 2019; Duncan et al., 2019). Thus, findings from candidate gene studies will not be reviewed further in this review.

3.1. Common gene variant contributions

To date, only one GWAS on depressive symptoms has been carried out among adolescents with the heritability attributed to SNPs estimated as 17 % (Sallis et al., 2017). Currently, much larger GWASs of youth depression symptoms and MDD are under way (Grimes et al., 2024a). The largest GWAS of depression to date included 685,808 adults with major depression from 29 countries and identified 636 genomic loci (Adams et al., 2025). The estimated SNP-based heritability was 8.4 %, and thus still explains only a proportion of twin heritability. This GWAS showed enrichment of genes involved in neuronal differentiation and receptor clustering; associated alleles were also enriched for gene targets of both antidepressants and antipsychotics, and for two serotonin partial agonists. However, the authors noted that the analytical method does not indicate whether drug effects are in the same or opposing direction as the genetic effects. As depression GWAS have only been conducted in adult populations, it is currently unknown whether findings extend to child- and adolescent-onset depression.

GWAS findings represent only a first step. The causal genes and the molecular mechanisms by which they confer risk to disorder still need to be identified. Other areas of interest include identifying potential mediators of genetic risk, such as imaging markers, Although there was initial enthusiasm about mediators or endophenotypes, robust evidence here has yet to emerge (Goldstein and Klein, 2014; Sanchez-Roige and Palmer, 2020).

There are two key sets of findings that have emerged from GWAS that are salient to youth depression. First, few loci identified in European samples were transferable to non-European ancestry populations (Meng et al., 2024), and PGS trained on European data do not predict depression in adolescents from non-European ancestries (Grimes et al., 2024b). This underpins the urgent need for genetic research in young people of diverse ancestries. Second, depression showed genetic correlations with all the other psychiatric and neurodevelopmental conditions as well as many physical health-related phenotypes including cardiometabolic disease (Adams et al., 2025; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). This highlights that genetic loci identified for depression have pleiotropic effects beyond depression and are not depression-specific. This observation has been made for all other psychiatric disorders (Lee et al., 2021).

3.1.1. Polygenic scores

In keeping with the links between youth and adult depression, a composite of common gene variants derived from adult depression GWAS, known as polygenic score (PGS), has been shown to predict elevated adolescent depression symptom scores (Halldorsdottir et al., 2019; Kwong et al., 2021) and age at onset of youth depression, where those with earlier onset depression have higher depression PGS scores (Halldorsdottir et al., 2019). One population-based study also observed that those with elevated depression symptoms that onset in early adolescence were associated with ADHD PGS(Rice et al., 2019b). Taken together with family and cross-generational studies these findings support the premise that adult and youth depression share genetic liability, but age effects will be discussed later. Depression polygenic scores also appear to predict first episode depression but so do schizophrenia and bipolar PGS (Musliner et al., 2019). Depression PGS also is associated with recurrence of clinically recognised depression (Musliner et al., 2021) but is a weak predictor and does not appear to robustly predict recurrence of adolescent emotional disorder (Dennison et al., 2023). Overall although PGS are commercially available, there is no evidence currently to support their use in predicting youth depression onset or recurrence.

3.1.2. Cross-generational transmission

Finally, several studies have investigated the association between parental genotype (transmitted and non-transmitted alleles) and child depressive (and anxiety) symptoms (Cheesman et al., 2020; Jami et al., 2020; Shakeshaft et al., 2024). These approaches assess the extent to which intergenerational genetic effects are direct (i.e. via inherited routes) or indirect (genetic nurture). Genetic nurture can be thought of as genetically influenced parental traits that impact on child outcome via the rearing environment (i.e. a form of passive gene-environment correlation). A range of techniques can be used that involve either the total common variant contribution to depressive symptoms or polygenic scores derived from GWAS. Overall, studies focusing on adolescence (rather than children) find little evidence of non-transmitted genetic effects suggesting that parental polygenic psychiatric liability does not impart risk to offspring via non-transmitted rearing effects (Jami et al., 2020; Shakeshaft et al., 2024). This finding may seem somewhat inconsistent with family and adoption studies of depression which imply that passive gene-environment correlation may be present. However, direct comparison with adoption and similar study designs (which suggest the importance of rearing effects for youth depression) are challenging due to different assumptions of the design (e.g. adoption studies assume passive gene-environment correlation is removed in adoptive families). One methodological issue worth considering is that genetic heterogeneity between generations (i.e. different genetic influences on the trait in adults and young people) could bias findings (Silberg et al., 2010).

3.2. Rare gene variants

There has only been one investigation of rare gene variants in youth depression that examined copy number variants in youth depression. That study assembled 4 population cohorts and did not find an increased burden of rare CNVs in those with early-onset depression or very early-onset depression (< 15 years) ((Dennison et al., 2025).

3.3. Gene-environment correlation

The role of gene-environment correlations in the aetiology of youth depression was initially indicated by early family and twin study findings that stressful life events, a known risk factor for depression, are subject to genetic influences (Dahoun et al., 2025; Kendler and Baker, 2007; Polderman et al., 2015). More recent studies observed similar associations between psychiatric polygenic risk scores and environmental adversities (Thapar et al., 2022). In relation to youth depression, gene-environment correlations have been demonstrated with a wide array of environmental risk exposures such as stressful life events (Feurer et al., 2022), adverse home environments (Hannigan et al., 2017), parent-child conflict (Samek et al., 2018), disruption of romantic relationships (Lau and Eley, 2008), and peer victimisation (Perret et al., 2023). These relatively robust findings suggest that the genetic liability of youth depression is likely to include gene-environment correlations.

3.4. Gene-environment interaction

Gene-environment interaction describes the differential impact of the environment depending on genetic liability. Although gene-environment interaction is intuitively important, unlike findings on gene-environment correlation, robust evidence on gene-environment in psychiatric genetics is scarce and findings have been subject to much criticism (Border et al., 2019; Duncan and Keller, 2011; Kendall et al., 2021; Peyrot et al., 2018).

Twin studies have fewer limitations than molecular genetic studies because they capture all genetic variance. Such studies suggest that

gene-environment interaction maybe a contributor to depression risk. Early twin studies suggested that genetic liability for youth depression increases the impact of stressful life events (Silberg et al., 2001), social isolation (Jacobson and Rowe, 1999) and suboptimal home environments (Wilkinson et al., 2013). However, the evidence is also mixed as this effect was not demonstrated for peer victimisation (Perret et al., 2023). Thus, family and twin study findings are potentially consistent with a diathesis-stress model of depression (Monroe and Simons, 1991) where the effects of stress on depression risk are dependent on underlying vulnerabilities including genetic liability. However, as highlighted earlier, there is much more robust evidence that stressors which are most relevant to depression are correlated with genetic liability.

There has been a huge literature on gene-environment interaction using molecular genetic approaches but notably nearly all have been based on candidate-gene studies (Dunn et al., 2011). This approach is now no longer considered as methodologically robust (Border et al., 2019; Duncan et al., 2019) and has largely been abandoned due to the risks of false positives and findings not replicating (Andreassen et al., 2023). More recent studies have tested for gene-environment interaction using polygenic scores (e.g., Nelemans et al. (2021)), but most have focused on adults, with results being mixed and with variable effect sizes (Grillo, 2025).

Epigenetic effects, whereby environmental exposures regulate gene expression without changes to the DNA sequence, have been proposed as a mechanism for gene-environment interactions (Penner-Goeke and Binder, 2019). Again, epigenetic findings have attracted much attention but robust evidence is lacking (Park et al., 2019). The challenges of psychiatric epigenetic studies are many (Cecil et al., 2023). First, epigenetic changes are tissue-, time- and age-specific, which poses difficulties for psychiatric studies that involve the brain but rely on peripheral (e.g. blood, saliva) epigenetic markers and post-mortem brain tissue. Second, unlike molecular genetic studies based on DNA sequence, epigenetic changes have the limitations of all environmental association studies in epidemiology including reverse causation and confounding which can lead to spurious causal claims. These challenges limit confidence in epigenetic findings on youth depression to date (see Cecil et al. (2023) for a detailed discussion).

In summary, currently whilst there has been much interest in gene-environment interaction and epigenetics in psychiatry including for youth depression, so far, the evidence for gene-environment interactions in relation to youth depression is not robust (Singh et al., 2024).

4. Pharmacogenetics and pharmacogenomics

Pharmacogenetic and genomics represent a specific type of gene-environment interaction whereby response to treatment, pharmacological or non-pharmacological (e.g. psychotherapy), varies depending on genetic liability (either based on a single genetic variant or genome-wide liability). The idea of differential susceptibility to different types of depression treatment, as is the case for all types of gene-environment interaction, is very appealing. However, so far there are no robust, replicated findings to guide practitioners (Pardiñas et al., 2021).

Genetic variants can impact on an individual's pharmacokinetic and pharmacodynamic processes (Wehry et al., 2018). The former indexes gene variants that affect the distribution, metabolism and excretion of drugs while pharmacodynamics refer to the mechanisms of action of the drugs e.g., via receptors, transporters and enzymes (Namerow et al., 2020).

With respect to drug metabolism, the enzymes of the hepatic cytochrome P450 (CYP450) system are potentially the most studied because they are responsible for the metabolism of many specific drugs. For example, Sertraline is substantially metabolized by CYP2C19 while fluvoxamine and duloxetine are metabolized by CYP1A2. Genetic variation may enhance or decrease the activity of the enzymes with the consequent phenotypes ranging from individuals who are 'ultrarapid' or 'poor' drug metabolisers at extremes of the high and low ends of the spectrum of drug metabolism respectively (Wehry et al., 2018). Thus, fluvoxamine will be expected to be less efficacious in young people who are ultra-rapid metabolisers for CYP1A2. However, other factors come into play such as faster drug clearance in younger children compared to adolescents and enzyme inducer effects of psychoactive substances like tobacco (Wehry et al., 2018). With respect to pharmacodynamic effects (i.e., the mechanism of action of drugs) and testing for genetic differences in response to psychological treatments for depression, most have focused on candidate genes and so far no robust findings have emerged using other approaches (Namerow et al., 2020).

Overall, while a few studies suggest potential benefits of pharmacogenetic testing (Dagar et al., 2022), the evidence remains inconsistent (Namerow et al., 2022, 2020; Vande Voort et al., 2022), which limits its real-world application at the present time. Other cautions include the risk of making clinicians depart from evidence-based guidelines for treatment (Namerow et al., 2022), the dearth of pharmacogenomic research among children and adolescents (Ramsey et al., 2019) and the need for clear guidance on implementing findings from pharmacogenomic research (Namerow et al., 2022). Current guidelines published by the Royal College of Psychiatrists in the UK (Royal College of Psychiatrists, 2023), the International Society for Psychiatric Genetics (International Society of Psychiatric Genetics, 2019) and the American Academy of Child and Adolescent Psychiatry (American Academy of Child and Adolescent Psychiatry, 2020) do not recommend routine pharmacogenetic testing for youth depression.

5. The challenge of heterogeneity

Whilst gene discovery necessitates the largest possible sample size, findings from these studies can be utilized to address different questions. However, depression heterogeneity represents a major challenge to interpreting and using genetic study findings (Cai et al., 2020) (Fig. 2). Here we focus on four different sources of heterogeneity that are salient to youth depression. These include i) the diversity of depression definitions and measures, ii) age-at-onset and development, iii) the different clinical antecedents or comorbidities of youth depression and iv) outcomes of depression.

5.1. Definition and measures

5.1.1. Definition

For clinical and many research purposes, depression is defined as a diagnostic category using DSM or ICD classification systems. Many clinicians are taught that the quality of low mood that commonly occurs after experiencing disappointment or loss is different to low mood that characterizes depressive disorder. Family studies suggest that phenotype definition matters for depression as using a more severe depression phenotype, yields higher familial loading (Klein et al., 2004, 2002).

An alternative approach to conceptualising depression as a diagnostic category is to view it as lying along a continuum i.e., a quantitative trait typically assessed by computing total depression symptom scores. A polygenic liability threshold model would suggest that genetic risk for clinically recognised depression would lie towards the extreme upper end of a continuum of genetic liability. The definition of depression for the purpose of genetic studies has been subject to significant dispute (Flint, 2023). Some would argue, that definition does not matter especially where large samples sizes are needed, as is the case for GWAS. Epidemiological studies highlight that youth and adult depression symptoms and sub-threshold depression are associated with increased risk of subsequent major depressive disorder (Bertha and Balázs, 2013; Noyes et al., 2022; Zhang et al., 2023). Genome-wide association studies also observe a high genetic correlation ($r_g = 0.76$) between trait and categorical measures of depression in adult samples, as well as between different definitions of depression (Adams et al., 2025; Flint, 2023). Similarly, categorically defined depression PGS predict population depression symptom scores in youth (Kwong et al., 2021). While these

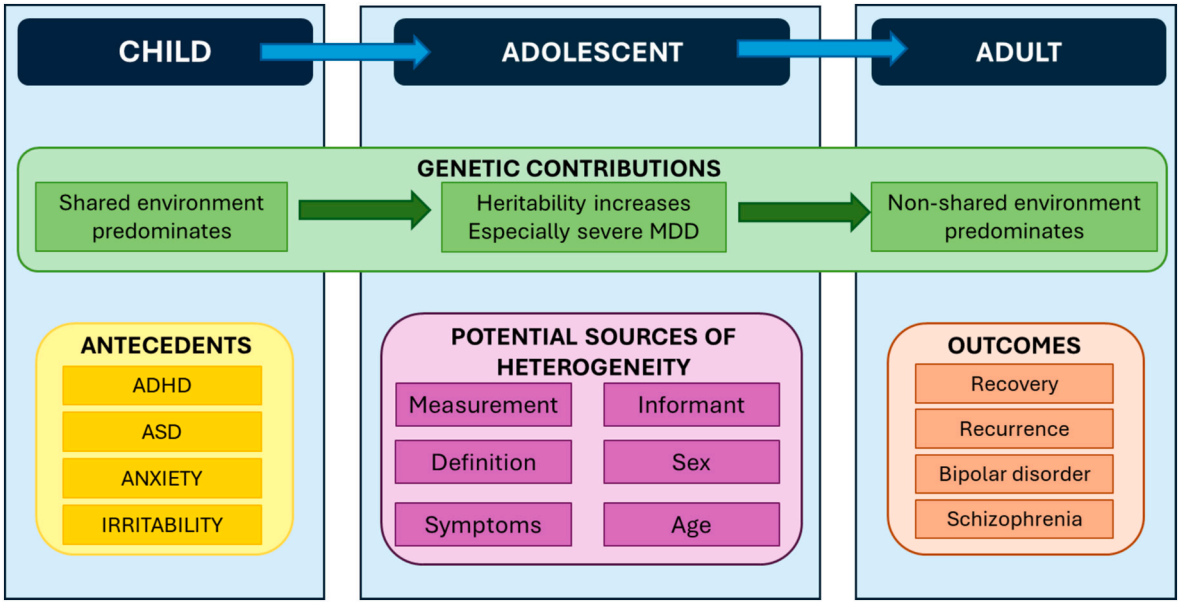

Fig. 2. A developmental view of youth depression genetics and heterogeneity.

results suggest that depression can be viewed as a quantitative dimension, it also has been strongly argued that depression symptoms and the categorically defined disorder cannot be viewed as the same phenotype.

Flint (2023) highlights that high genetic correlations cannot be assumed to show that two phenotypes are the same. For example, while depression shows high genetic correlations with personality traits such as neuroticism (Adams et al., 2020), few would argue that neuroticism is the same as depressive disorder. Also, Mendelian Randomisation designs, which are used to infer causal relationships, show differential effects when defining adolescent depression as a symptom score compared to a clinical diagnosis (Shakeshaft et al., 2025). As discussed earlier, twin studies of youth depression symptoms have suggested that the contribution of shared environment is higher for those with extreme depression symptom scores (Eley, 1997; Glowinski et al., 2003; Rende et al., 1993; Rice et al., 2002b) compared to both normal variation in low mood and the syndrome of MDD. In summary, although much epidemiological and genetic evidence favours viewing depression as a quantitative trait, it is not possible to dismiss the premise that how broadly depression is defined matters. The family and twin study findings, as discussed earlier, certainly vary depending on the severity and definition of youth depression.

5.1.2. *Measures*

DSM-5 criteria for Major Depressive Disorder include 9 types of symptoms, of which five are required to meet the symptom criteria for a diagnosis of MDD. The same criteria are used to define MDD in youth with the exception that irritability rather than low mood can be a core symptom. It has been estimated that this leads to 227 possible symptom constellations that constitute MDD (Zimmerman et al., 2015). When one considers the differing symptom directions for certain items (e.g. significant weight loss or gain; insomnia or hypersomnia), and symptoms that are not in diagnostic criteria but are of importance to people with lived experience (Viduani et al., 2024), the possible combinations increase to thousands. However, fewer symptoms are reported to be observed in clinical practice (Zimmerman et al., 2015) and some symptoms may only present at particular levels of severity (Cole et al., 2011). Depression questionnaire measures reflect this heterogeneity as the items assessed do not necessarily coincide with the ones included in DSM-5 or ICD-11 criteria and similarly can be rated in different directions (Fried, 2017). This applies to the commonly used youth depression questionnaires (e.g. Mood and Feelings Questionnaire MFQ (Angold et al., 1995), Patient Health Questionnaire PHQ-9 (Kroenke et al., 2001)). Different questionnaires will differentially capture symptoms and the underlying construct they are designed to measure. This results not only in heterogeneity in the literature, but serves to reify the diagnostic criteria for depression, which are intended only to be an indicator of the syndrome of depression, and resultantly restricts the field and its impact (Kendler, 2016).

The situation for depression contrasts with many other types of psychopathology, where, although there is heterogeneity in definitions and measures, items tend to be rated along one direction (e.g. hyperactivity for ADHD, worrying for generalised anxiety). Some symptoms, particularly somatic and vegetative symptoms, may be more common in adolescents than adults (Rice et al., 2019a), yet, to the best of our knowledge, the genetic architecture of different depression items has not been extensively examined in youth. In one study of the PHQ-9 in adults in the UK Biobank, genetic correlations between different items varied from 0.54 to 0.96 and reported SNP heritability for different items ranged from 6 to 9 % (Thorp et al., 2020). Similarly, other studies in adults report that genetic influences vary across symptoms (Kendler et al., 2013) and highlight the need to assess directionality, which may be particularly important for appetite changes (Adams et al., 2024).

In summary, symptom combinations for depressive disorder are highly variable. Even for trait measures, each symptom is weighted equally, yet the question of whether symptoms indicate a uniform or equivalent underlying genetic liability has not been well examined. Definitions of depression for youth depression are also very heterogenous owing to the wide number of questionnaires, some of which omit key depressive symptomatology, emphasise only certain symptoms, or combine depression with anxiety. Given this source of heterogeneity, future research should aim to look at and report results for individual depression items. This would help with harmonizing items across studies more carefully which may help resolve inconsistencies in research findings. Research that amalgamates findings across different studies (e.g. meta-analyses) also need to carefully consider and report the different definitions and measures used across studies.

A final concern, relates to cultural factors which is especially important given evidence that youth depression is more prevalent in non-Western settings (Shorey et al., 2022). However, nearly all psychiatric as well as genetic research has been conducted in high income, Western countries. There is therefore a need for much more youth depression research, including genetic studies, to be conducted in non-

Western or low- and middle- income contexts to examine the contribution of cultural differences.

5.2. Age-at-onset and development

The incidence of depression rises steadily from mid-adolescence onwards peaking in early adult life (Solmi et al., 2022). There is much to suggest that the liability to youth-onset depression is similar to adult depression (Thapar and Riglin, 2020). Importantly, there are strong continuities across the life span. As previously highlighted, youth who develop depression are much more likely to show recurrence in adult life (Thapar et al., 2022) and the offspring of adults with depression are at elevated risk of developing depression themselves. However, there are also age-related differences. The sex ratio for depression in children is equal and the female excess emerges from early to mid-adolescence onwards (Wade et al., 2002). Treatment response also differs in adolescent-onset compared to adult-onset depression (Cipriani et al., 2016). Whilst there are some similarities between youth and adult depression, the clinical outcomes, treatment response and genetic loading are not identical, so it is important to consider development in genetic studies. Also, in youth, many genetic studies of depression have focused on symptoms rather than MDD.

As previously discussed, early family studies consistently highlighted that early-onset depression (onset by the early 20s) is more highly familial and shows a worse prognosis than depression that onsets later in keeping with many other clinical conditions (Klein et al., 1999; Weissman et al., 1988). A recent nationwide study in Sweden reported that early-onset youth depression (<21 years) showed the highest heritability of the depression subgroups. However, whilst other depression subgroups were highly correlated ($r_g = 0.75–0.90$), youth vs. adult-onset depression had the lowest genetic correlation ($r_g = 0.33$) (Nguyen et al., 2023).

Defining age-at-onset retrospectively is fraught with problems for all psychopathology (Hardt and Rutter, 2004; Moffitt et al., 2010). However, evidence from initial GWAS suggested that earlier onset depression may be more genetically similar to schizophrenia and bipolar disorder than later later-onset MDD (Musliner et al., 2019; Power et al., 2017). In a UK population-based study that prospectively investigated depression symptom trajectories within adolescence, there was further evidence of age-at-onset variation (Rice et al., 2019b). Those with early adolescent-onset symptoms showed a higher rate of neurodevelopmental conditions and a more robust association with schizophrenia and ADHD PGS than later adolescent-onset depression with both showing associations with depression PGS (Rice et al., 2019b; Weavers et al., 2021). In summary, family and molecular genetic studies all suggest that youth-onset depression shows differences in heritability and genetic architecture to adult-onset depression.

A related issue to age-at-onset is that of developmental change. Here, longitudinal twin studies have been invaluable and again have consistently showed age-related differences. Meta-analyses and longitudinal twin designs suggest that the heritability of depression rises in adolescence and then declines through adult life when non-shared environmental contributions increase (Bergen et al., 2007; Nivard et al., 2015) (See Fig. 2). This decline is mainly explained by an increased contribution of non-shared environment through adulthood. Continuities in depression across age are mainly explained by genetic influences (Nivard et al., 2015). Twin studies further show dynamic changes notably during adolescence with new genetic influences coming into play (genetic innovation) and other genetic influences declining (genetic attenuation) (Kendler et al., 2008; Nivard et al., 2015). Overall, these developmental studies highlight that not only does heritability differ across ages and development and that there are genetic influences on depression persistence, but these genetic influences are dynamic especially across adolescence. Taken together findings suggest further investigations are needed into age effects and caution is needed in lumping depression across development in order to better understand depression heterogeneity.

5.3. Clinical antecedents and comorbidities

Depression typically onsets after mid-adolescence but is commonly preceded by a diverse range of psychiatric and neurodevelopmental disorders in childhood and early adolescence as well as later comorbidities. These antecedents may present as concurrent comorbidities of youth depression and include childhood anxiety, neurodevelopmental disorders including ADHD and autism spectrum disorder (ASD), conduct and oppositional defiant disorders among others (Pine and Fox, 2015; Thapar et al., 2022). These comorbidities further contribute to depression clinical heterogeneity. Some of this comorbidity is explained by shared genetic liability as shown by twin studies (Eley et al., 2008; Rice et al., 2004; Stringaris et al., 2012) and molecular genetic studies (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). However, certain antecedents appear to have potentially causal effects on depression, notably childhood anxiety (Uher et al., 2024), ADHD (Garcia-Argibay et al., 2024; Riglin et al., 2021) and irritability (Shakeshaft submitted) suggesting that they represent important targets for prevention and early intervention. Future genetic studies could help identify causal routes into depression as well as examine whether the different clinical precursors and clinical outcomes of depression index biologically meaningful heterogeneity.

5.4. Clinical outcomes

One major clinical challenge is that depression shows very variable outcomes and that seems especially important in adolescence. Whilst up to 70 % of adolescents show recurrence or persistence of major depression, for a subgroup, depression will represent the first presentation of bipolar disorder or subsequent psychosis. Other adolescents will show spontaneous remission. Several studies have shown that the persistence of youth depression is associated with a family history of depression and comorbidities (Thapar et al., 2022) and conversely, that one-off episodes are related to adolescent-specific stressors such as interpersonal stress and adolescent academic achievement/school examinations (Weavers et al., 2021). A large-scale health registry study in Denmark examined hospital treated depression in those aged 10 to 32 years and found that depression PGS but not the other neuropsychiatric PGS predicted recurrence (Musliner et al., 2021). Using the same Danish health-record cohort of those aged 10–35 years with major depression; schizophrenia and bipolar disorder PGS were associated with risk of progression to bipolar disorder or psychosis but the effect sizes were small, and family history was a stronger predictor of transition (Musliner et al., 2020). In summary, so far PGS do not appear to predict depression outcomes more strongly than family history and clinical variables (Agerbo et al., 2021; Dennison et al., 2023). Future research may yield different findings by including more powerful PGS, rare variants, and robustly defined measures of family history, clinical, and social variables. Prediction in psychiatry that includes genetic variants, could also involve machine learning but the risks of bias are many and these have been discussed elsewhere (Bracher-Smith et al., 2021).

6. Summary and future directions

There is consistent evidence that depression is familial and moderately heritable but not as heritable as some other psychiatric or neurodevelopmental conditions. Familial loading and heritability maybe higher for youth depressive disorder than adult depression, especially where there is recurrence, chronicity and greater severity. Unlike some types of psychopathology, intergenerational transmission of depression involves a strong shared environmental or rearing component. However non-shared environment effects and gene-environment correlations appear to be a major contributor to depression risk in young people. So far GWAS have identified several hundred risk loci in adults but no

adequately-powered studies, to date, have specifically focused on youth. However, future large-scale genomic discovery studies of youth depression are underway. One major finding from molecular genetic studies of depression is that ancestry is important and that diverse populations are needed not only to ensure equity but also because ancestral diversity can aid the identification of causal genes.

There have been many controversies and debates around how depression is best conceptualized but so far, many but not all genetic findings suggest that depression behaves as a quantitative trait with the disorder lying at one extreme. However, there are mixed findings and views about this and boundaries between wellness, distress, depression symptoms and MDD are unclear.

One of the main conclusions of this review is that there are many inconsistencies and complexities in the depression genetics literature that mean interpreting findings is challenging especially for youth depression. We highlight some of the potential sources of heterogeneity. Future research needs to consider how important these complexities are and whether they matter for a specific scientific question. Another issue that needs to be considered is to what extent cultural and geographical context are important when defining and conceptualising depression as nearly all youth depression research has been conducted in Western contexts. These may be as important as genetic differences due to ancestry.

Going forward, genetic designs and approaches can be used to address many of these questions and controversies around depression. Whilst much attention is focused on genomic discoveries, traditional genetic designs (e.g. twin studies) provide a very powerful method for capturing genetic liability and a strong design for addressing some of the questions we have raised. As highlighted repeatedly by others, scientists and clinicians need to address inequities in genetics (and other) research. Finally, a key ambition of genetic studies is to improve prevention and clinical management of depression and reduce adverse outcomes.

It will be important that those interpreting findings from genetic studies consider the clinical implications of genetic studies and take these forward into clinical research when possible.

CRediT authorship contribution statement

Anita Thapar: Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Olakunle Oginni:** Writing – review & editing, Writing – original draft. **Charlotte A. Dennison:** Writing – review & editing, Writing – original draft. **Frances Rice:** Writing – review & editing, Writing – original draft.

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