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Review article

Is subthreshold depression in adolescence clinically relevant?

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ABSTRACT

Background: Subthreshold depression is highly prevalent in adolescence, but compared to major depressive disorder, the clinical impact is under-researched. The aim of this review was to compare subthreshold depression and major depressive disorder in adolescents by reviewing available literature on epidemiology, risk factors, illness trajectories, brain anatomy and function, genetics, and treatment response.

Methods: We conducted a scoping review of papers on subthreshold depression and major depressive disorder in adolescence published in English. Studies in adults were included when research in adolescence was not available.

Results: We found that individuals with subthreshold depression were similar to individuals with major depressive disorder in several regards, including female/male ratio, onset, functional impairment, comorbidity, health care utilization, suicidal ideation, genetic predisposition, brain alterations, and treatment response. Further, subthreshold depression was about two times more common than major depressive disorder.

Limitations: The definition of subthreshold depression is highly variable across studies. Adolescent-specific data are limited in the areas of neurobiology and treatment.

Conclusions: The findings of the current review support the idea that subthreshold depression is of clinical importance and provide evidence for a spectrum, versus categorical model, for depressive symptomatology. Given the frequency of subthreshold depression escalating to major depressive disorder, a greater recognition and awareness of the significance of subthreshold depression in research, clinical practice and policy-making may facilitate the development and application of early prevention and intervention.

1. Introduction

Subthreshold depression (also referred to as subsyndromal depression, subclinical depression, or mild depression) is an umbrella term that encompasses several conditions that do not meet criteria for a depressive disorder outlined by the past and current versions of nosological manuals such as the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013). Whereas an increasing number of studies focus on subthreshold depression, its definitions differ substantially across them, requiring the presence of various number, frequency, and duration of symptoms (Carrellas et al., 2017; Bertha and Balázs, 2013; Rodríguez et al., 2012). However, most studies define subthreshold depression as two to four symptoms of depression lasting for two weeks or more, and all definitions require that individuals with subthreshold depression have a decrease in quality of life or overall health (Rodríguez et al., 2012). In this review, we refer to subthreshold depression as depression not fulfilling the requirements for any specified depressive disorder diagnosis in the DSM-5, but that negatively impacts quality of life, and is not due to another condition.

A growing body of research has called for psychiatric disorders, including depressive disorders, to be viewed on a spectrum rather than categorically (see Fig. 1; Bakker, 2019; Krueger et al., 2018; Carragher

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et al., 2015; Wright et al., 2013). Those in favour of a spectrum model argue that the current cut-offs between a healthy individual and an individual with a certain diagnosis are arbitrary (Bakker, 2019). Additionally, since the DSM has a polythetic system (a certain number of symptoms must be present out of a larger number of symptoms – e.g., for major depressive disorder (MDD), youone must meet five out of nine symptoms), a categorical approach could lead to hundreds of possible clinical profiles for the same diagnosis (Buch and Liston, 2021; Mullins and Lewis, 2017). A spectrum or symptom-based model of depression would allow clinical heterogeneity to be addressed and would recognize subthreshold depression; however, this is yet to be common practice.

Though understudied, subthreshold depression may have significant functional consequences, comparable to depression above the diagnostic threshold (Bertha and Balázs, 2013; Wesselhoeft et al., 2013). Understanding how subthreshold depression manifests in adolescence is crucial for early prevention and intervention. Prior reviews on adolescent depression have focused primarily on MDD (Mullen, 2018; Pataki and Carlson, 2016; Thapar et al., 2012) or subthreshold depression (Rodríguez et al., 2012). However, the literature is lacking recent comprehensive reviews that compare MDD and subthreshold depression in adolescents. The last two reviews the authors are aware of were published in 2013 (Bertha and Balázs, 2013; Wesselhoeft et al., 2013). Additionally, the preceding reviews did not include neural anatomy, neural networks, or molecular studies. Thus, the aim of the current paper is to review new research, highlight the spectrum of severity of depressive disorders in adolescents, and to consider the severity of subthreshold depression by comparing it directly to MDD. We will discuss epidemiology, illness trajectories and risk factors, neural anatomy and networks, genetics, and treatment options for adolescents with subthreshold depression versus MDD. Our overarching hypothesis is that adolescents with subthreshold depression are more similar to those with MDD than healthy adolescents and should be treated as such.

2. Method

We conducted a scoping literature review to investigate similarities between adolescents with subthreshold depression and MDD in terms of epidemiology, risk factors, illness trajectories, brain anatomy and function, genetics, and treatment response. We searched literature from 2000 to 2021 in Google Scholar, PubMed and PsycInfo using combinations of the following search terms: depression, MDD, subthreshold, subclinical, symptoms, adolescence, demographics, epidemiology, risk factors, trajectory, genetics, epigenetics, neuroimaging, and treatment. Reference lists were also searched for relevant articles. We included papers in the English language that were primarily focused on adolescent populations (12–19 years). If there was no or limited availability of adolescent data in an area of research, studies conducted in adult samples were included.

3. Results

3.1. Epidemiology

There is no doubt that MDD is a significant problem for public health, as the leading cause of disability worldwide (World Health Organization, 2017). Though prevalence estimates for MDD based on DSM-5 criteria are limited, estimates based on the DSM-IV range from 5 to 19.4% (Méndez et al., 2021). Estimated prevalences of subthreshold depression are higher than the ones observed for MDD, with evidence that up to 29.2% of adolescents are affected by subthreshold depression (Carrellas et al., 2017; Wesselhoeft et al., 2013; Bertha and Balázs, 2013).

Prevalence of MDD increases as adolescents age, peaking in the mid-late teenage years (Avenevoli et al., 2015). There is also a fundamental gender difference, with MDD affecting approximately twice as many females than males across adolescence (Hyde and Mezulis, 2020; Salk et al., 2017). This gender difference peaks around age 13–15, with a ratio as high as 3:1 females to males diagnosed with MDD (Salk et al., 2017). Females also have depressive episodes that are longer in duration and are more likely to be on a trajectory of increasing symptoms (Lewis et al., 2020; Essau et al., 2010). As in adults, depressive disorders in adolescents are often accompanied by comorbid mental disorders, which are most frequently anxiety disorders (Dold et al., 2017; Petersen et al., 2009; Zimmerman et al., 2000). Other common comorbidities include externalizing disorders (oppositional defiant disorder, conduct disorder, attention deficit hyperactivity disorder) and substance use disorders (Avenevoli et al., 2015), though many combinations of one or more different disorders are possible and prevalent.

Like MDD, females have elevated rates of subthreshold depression in comparison to males (Crockett et al., 2020; Balázs et al., 2013; Shankman et al., 2008). Age has a similar effect in subthreshold depression, with prevalence increasing with age and peaking in mid-adolescence (Bertha and Balázs, 2013; Wesselhoeft et al., 2013). The rate of comorbidity of specific disorders varies across studies; however, the rate of adolescents with subthreshold depression who have any comorbid psychiatric disorder is reported to be between 30.6 and 53.3%, compared to between 53.5 and 62.2% for adolescents with MDD in the same studies (Wesselhoeft et al., 2013). One longitudinal study followed a large birth cohort sample of late adolescents with MDD, subthreshold depression, and controls for seven years into their mid-20s (Fergusson et al., 2005). Notably, at the end of the study, adolescents with subthreshold depression did not differ significantly from adolescents with MDD in rates of treatment-seeking (requesting help from a general practitioner, psychiatrist, psychologist, or counsellor) or suicidal ideation and had higher rates of treatment-seeking and suicidal ideation than controls (Fergusson et al., 2005). This relationship between subthreshold depression, treatment-seeking, and suicidality has also been shown in

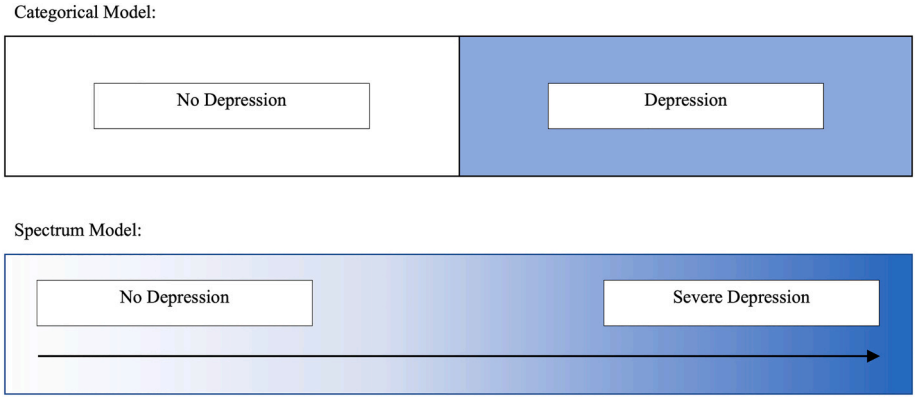

Fig. 1. Two opposing models of depression.

several other studies (Wesselhoeft et al., 2013), with one study reporting adolescents with subthreshold depression utilizing mental health services more than adolescents with MDD (González-Tejera et al., 2005). Overall, subthreshold depression is associated with higher functional impairment and lower quality of life than controls (Balázs et al., 2013; Rodríguez et al., 2012).

In sum, data suggest that subthreshold depression has similar gender and age distributions to MDD but affects a larger number of adolescents. Though lower in number of symptoms, subthreshold depression is significantly impactful on quality of life and the health care system, and an important risk factor for later MDD and suicidality.

3.2. Trajectories and risk factors

Homotypic continuity describes how disorders predict presence of that same disorder at a later age, whereas heterotypic continuity describes how disorders predict presence of other disorders at a later age (Shevlin et al., 2017; Wichstrøm et al., 2017; Lahey et al., 2014). Between the ages of 7.5 and 14 years, homotypic continuity is not unusual for MDD; however, heterotypic continuity is also common during this age range, especially for other disorders such as generalized anxiety disorder (GAD) or post-traumatic stress disorder (PTSD; Shevlin et al., 2017). Similar results have been found in adults, where homotypic continuity was significant for MDD after three years, and heterotypic continuity was strong for internalizing disorders, especially dysthymia (now called persistent depressive disorder) and GAD (Lahey et al., 2014). Homotypic and heterotypic continuity has been investigated in adolescents with subthreshold depression to a lesser extent. One study found that subthreshold depression in adolescence predicted development of mood disorders, disruptive disorders, personality disorders, and generalized anxiety disorder in adulthood (Johnson et al., 2009). However, another found that subthreshold depression in adolescence predicted development of depressive disorders but did not predict development of other disorders examined by age 30 (anxiety, bipolar disorder, alcohol use disorder, substance use disorder, conduct disorder/antisocial personality disorder, attention deficit hyperactivity disorder) (Shankman et al., 2009). As depressive symptoms could be an early clinical manifestation of various types of mental disorders, additional large-scale longitudinal studies in young individuals with subthreshold depression are needed to better understand the developmental trajectories of people with subthreshold depression throughout the lifespan.

Of particular interest is the development of subthreshold depression into MDD. A longitudinal study that examined adolescents with subthreshold depression until age 30 found that over half developed a full depressive disorder, with the average age of full disorder development being 22.2 years (Klein et al., 2009). A number of other studies have found that risk for people with subthreshold depression of developing MDD is higher than in healthy individuals without subthreshold depression (Jinnin et al., 2016; Johnson et al., 2009; Fergusson et al., 2005). Most of the symptoms of MDD in the DSM have been found to contribute to MDD risk, with sad mood contributing unique variance (Georgiades et al., 2006). Additionally, severity of psychiatric symptoms, physical symptoms, suicidal ideation, comorbid anxiety, and family history of depressive disorders have been identified as predictors for developing MDD (Klein et al., 2009). However, one 15-year longitudinal study found that found that adolescents with and without subthreshold depression did not differ in likelihood of developing MDD and did not differ in overall adult mental health (Jonsson et al., 2011).

Many longitudinal studies have identified similar groups of depressive symptom trajectories: consistently low, consistently high, moderate, decreasing, and increasing (Ellis et al., 2017; Mezulis et al., 2014; Chaiton et al., 2013; Wickrama and Wickrama, 2010). A year-long longitudinal study of depressive symptoms in adolescents found that the number of depressive symptoms were stable in healthy adolescents, but unstable in those with subthreshold depression, with most experiencing a decrease or increase in symptoms (Jinnin et al., 2016). The most common predictors of 'high' and 'increasing' symptom trajectories are being female, having lower socioeconomic status, and experiencing stressful life events, conduct issues, and/or substance abuse (Shore et al., 2018). Several other biological, psychological, and social factors predicting trajectory group membership have been identified in the literature (see Table 1) (Shore et al., 2018; Schubert et al., 2017; Musliner et al., 2016). Longitudinal research has shown that adolescents in these trajectories are also more likely to engage in risky lifestyle behaviors including crime, having multiple sexual partners, excessive drinking, and smoking in young adulthood (Wickrama and Wickrama, 2010).

A few studies have found that peer and parental support have a positive impact on depressive symptoms in adolescence over time (Shore et al., 2018). One study found that friend social support was the strongest predictor of whether or not an adolescent with subthreshold depression would develop MDD (Hill et al., 2014). Another study found that following stressful life events, adolescents with stronger social support had a lower increase in depressive symptoms than those with less social support (Yang et al., 2010). In adolescent offspring of parents with depression, those who had co-parent support, high quality social relationships, high self-efficacy, and who exercised regularly had lower mood symptoms than peers who did not at a four-year follow up (Collishaw et al., 2016). Thus, identifying reliable support is beneficial in both subthreshold depression and MDD, and is crucial to improving prognosis.

3.3. Brain structure and networks

Structural magnetic resonance imaging studies have found alterations in white matter integrity in people with MDD (Shen et al., 2017; Schmaal et al., 2020) as well as structural differences in the lobes and subcortical regions of the brain (Schmaal et al., 2020; Zhang et al., 2018). In a large-scale meta-analysis combining neuroimaging data from 14 countries, the ENIGMA group identified differential associations in brain structures depending on age, with adolescents with MDD having lower global cortical surface area than healthy adolescents (Schmaal et al., 2020). Further, adults who had MDD onset in adolescence had smaller hippocampal volume as well as reduced thickness and surface area in the hippocampus and amygdala (Schmaal et al., 2020), consistent with prior literature (Castanheira et al., 2019). A recent review on brain structure and subthreshold depression found that a higher number of symptoms was associated with lower grey matter volume in the hippocampus and the anterior cingulate cortex (ACC; Besteher et al., 2020). However, the correlation in the ACC was only present for females, and the authors noted various methodological limitations of the reviewed studies (Besteher et al., 2020).

Functional MRI studies have found several differences in connectivity between individuals with MDD and controls. The default mode

Table 1
Commonly identified biological, psychological, and social risk factors for being in a 'high' or 'increasing' depression symptom trajectory (Shore et al., 2018; Schubert et al., 2017; Musliner et al., 2016).

Biological Risk Factors	Female sex/gender[a], dopamine receptor DRD2 and DRD4 variants, monoamine oxidase A (MAOA) genotype, chronic health conditions, parental depression/history of psychopathology
Psychological Risk Factors	Low self-esteem[b], negative cognitive style[b], low agency[b], poor adaptive coping, impulsivity in early adolescence, higher stress reactivity, history of psychopathology, high impulsivity in early adolescence, psychosocial adversity
Social Risk Factors	Low socioeconomic status/family income, stressful life events, conduct issues, substance use, low academic achievement, minority ethnic group membership, sexual minority orientation, problems in peer and parental relationships

[a] The distinction between sex and gender in many studies is unclear.
[b] Risk factor found for females only.

network (DMN) is a network known to be activated during rest and deactivated during tasks, and resting-state connectivity within the anterior DMN, and between the DMN and other areas is associated with MDD (Mulders et al., 2015). Altered resting-state connectivity has also been found in individuals with subthreshold depression relative to controls, with decreases between the dorsolateral prefrontal cortex (DLPFC) and other areas involved in cognitive control (Hwang et al., 2015). Task-based fMRI studies have found hyperactivity in the amygdala and regions of the anterior cingulate cortex in adults and adolescents with MDD (Arnone, 2019; Kerestes et al., 2013). Similarly, individuals with subthreshold depression have also been found to have greater activity in the amygdala and anterior cingulate cortex than controls when viewing negative stimuli (Li et al., 2017). Activation in the ventral striatum, part of the reward network, is reduced in both subthreshold depression and MDD compared to healthy individuals (Stringaris et al., 2015).

Another way to investigate the integrity of neural networks is through eye-tracking research. There is a wealth of knowledge regarding the control of eye movements, which can be used as an atlas to probe brain function based upon eye-tracking behavior (Coe and Munoz, 2017; Munoz and Everling, 2004). A review on eye-tracking in unipolar and bipolar depression found that individuals with MDD have an increased saccadic reaction time compared to controls (Carvalho et al., 2015), and reaction time is longer for those high in rumination (De Lissnyder et al., 2011). As well, individuals with MDD have higher saccade error rates during cognitive tasks than controls (Carvalho et al., 2015). Individuals with MDD tend to fixate longer on negative stimuli when given the chance to explore a scene (Suslow et al., 2020; Carvalho et al., 2015; Armstrong and Olatunji, 2012) and have reduced attention to positive stimuli (Suslow et al., 2020). This attention bias is also present in subthreshold depression (Li et al., 2017).

Though more imaging and investigation of neural networks is warranted in adolescents with subthreshold depression, preliminary data point to an anatomical and functional continuum between subthreshold depression and MDD.

3.4. Genetics

Risk of depression in adolescence is significantly higher than that in the general population when parents, and even grandparents, have a history of depression (Weissman et al., 2016; Weissman et al., 2005). Twin studies estimate the heritability of MDD to be between 30 and 40% (Flint and Kendler, 2014). An estimate of 37% heritability has been reported for subthreshold depression (Corfield et al., 2017), and relatives of someone with subthreshold depression have a higher risk of developing MDD (24.3% of relatives) than those with no family history of mood disorders (20.2% of relatives; Lewinsohn et al., 2003).

Candidate gene studies have found some associations between genotypes and depression risk, such as genotypes of dopamine receptor D4 (*DRD4*), monoamine oxidase A (*MAOA*), tryptophane hydroxylase 2 (*TPH2*), among others (Gatt et al., 2015). The most studied genotype is in the functional polymorphism *5-HTTLPR* on the serotonin transporter gene (*SLC6A4*). The short allele on *5-HTTLPR* has been linked to higher depression levels in clinical samples (Shadrina et al., 2018) and in subthreshold samples (Gonda et al., 2005). This is especially the case in the context of early adversity. Notably, individuals who experience a stressful life event are more likely to get an MDD diagnosis if they have the short allele on *5-HTTLPR* than those with the long allele (Karg et al., 2011; Caspi et al., 2003); a classic example of gene-environment interaction. Other genes of interest in depression shown to interact with environmental influences include brain-derived neurotropic factor (*BDNF*) and *FKBP5* (Lopizzo et al., 2015). However, critics of candidate gene studies assert that they are often inconsistent and underpowered (Tubbs et al., 2020; Lopizzo et al., 2015; Flint and Kendler, 2014).

Over the years, there has been a shift from candidate gene studies toward genome-wide approaches. However, these analyses have struggled to identify significant loci for MDD. One possible explanation is that many loci with small effects may contribute, rendering them less detectable in genome-wide analyses (Shadrina et al., 2018; Lopizzo et al., 2015; Flint and Kendler, 2014). However, by pooling three large samples together – which included those with self-reported symptoms and those identified through clinical interviews - the Psychiatric Genomics Consortium was able to identify 269 genes associated with depression (Howard et al., 2019). Several of these genes have roles in neurotransmitter functioning, the stress response, and immune functioning (Tubbs et al., 2020). Utilizing 15 loci previously identified in a genome-wide approach (Hyde et al., 2016) and a large sample of over 2,500 twin pairs split between two cohorts, Corfield et al. (2017) showed that subthreshold depression and MDD have similar genetic liability. The strength of association between identified loci and depression was increased when the authors added subthreshold cases to the MDD group (Corfield et al., 2017).

In addition to studying genotypes, epigenetic processes such as DNA methylation have been studied in relation to depression (Talarowska, 2020). It has been proposed that epigenetic processes are physiological mechanisms for how gene and environmental factors interact and underlie risk for depression (Booij et al., 2013). One of the most investigated genes in such studies is *SLC6A4* (Chmielewska et al., 2019; Kader et al., 2018). Depressive symptoms and family history of depression have been found to correlate with *SLC6A4* methylation in some studies (Bakusic et al., 2017; Palma-Gudiel and Fañanás, 2017). *SLC6A4* methylation has also been found to be associated with resting state functional connectivity and grey matter volume in the inferior orbitofrontal gyrus in adolescents with depression (Chiarella et al., 2020) as well as hippocampal volume and altered responses to negative stimuli in adults with depression (Booij et al., 2015; Frodl et al., 2015). Several studies have also found increased methylation on *NR3C1* (a glucocorticoid receptor involved in the HPA axis) or *BDNF* in individuals with MDD compared to controls (Chen et al., 2017; Bakusic et al., 2017). Associations between depressive symptom scores and DNA methylation have also been found in community samples (Klinger-König et al., 2019; Khulan et al., 2014). For a comprehensive review of DNA methylation in depression, including epigenome-wide association studies, see Bakusic et al. (2017).

3.5. Treatment

The most common treatment methods for adolescent MDD are psychotherapy, pharmacotherapy, or a combination of the two (Young et al., 2010). Recent reviews of psychotherapy in adolescents with MDD indicated that individual Cognitive Behavioral Therapy (CBT) and individual Interpersonal Psychotherapy (IPT) are the most effective treatment options (Méndez et al., 2021; Weersing et al., 2017). CBT and IPT have also been mildly to moderately effective in children and adolescents with subthreshold depression, lowering depressive symptoms – though fewer studies have been conducted on this age group (Cuijpers et al., 2021; Wesselhoeft et al., 2013). Programs focused on behavioral activation have been effective at reducing Beck Depression Inventory (BDI) scores in older adolescents with subthreshold depression (Takagaki et al., 2018; Takagaki et al., 2016). Internet-based psychotherapy has shown potential benefits for adolescents with MDD and heightened depressive symptoms compared to controls receiving no treatment, but more research is required to determine if it is as efficacious as in-person psychotherapy (Christ et al., 2020). Further, mindfulness-based intervention training has been effective at lowering BDI scores in older adolescents with MDD and subthreshold depression (Gómez-Odriozola and Calvete, 2021; Zhang et al., 2019).

Pharmaceutical treatment is recommended for more severe cases of MDD, and selective serotonin reuptake inhibitors (SSRIs) are the first line of treatment with a 60% response rate (Pataki and Carlson, 2016). For those adolescents that do not respond to the initial SSRI, switching to a second SSRI is recommended, and then an alternative antidepressant

(DeFilippis and Wagner, 2014). There is a lack of research on the efficacy of pharmaceutical treatment in adolescents with subthreshold depression; however, research in adults with subthreshold depression indicates that antidepressants are superior to placebos in several randomized studies (Naber and Bullinger, 2018; De Lima and Hotopf, 2003). Another review found weaker evidence for antidepressants in subthreshold depression and suggested they should be used after psychotherapy – though the authors acknowledged several methodological limitations in the studies reviewed (Barbui et al., 2011). Further, the combination of psychotherapy and pharmacotherapy is recommended if the adolescent with depression has also experienced trauma or maltreatment (De Bellis et al., 2019).

The short duration of a depressive episode is a predictor of better treatment response – the less time an episode goes untreated, the better (Kraus et al., 2019). Since subthreshold depression in adolescence is a risk factor for later development of MDD (Klein et al., 2009), this group should be targeted for early intervention. Additionally, as suicide is the second leading cause of death of adolescents aged 15–19 worldwide (World Health Organization, 2017), it is important to consider the relationship between level of depressive symptoms and suicidal ideation. Alarmingly, suicidal ideation in adolescence does not differ significantly between individuals with subthreshold and major depression in western countries (Wesselhoeft et al., 2013; Sihvola et al., 2007; Fergusson et al., 2005; Stewart et al., 2002). Thus, it is critical to treat subthreshold depression in adolescents early to address barriers to treatment response and remission. However, since subthreshold depression is not a formal diagnostic classification, access to actual clinical services may be limited (Hickie et al., 2019). Overall, the efficacy of treatment in adolescents with subthreshold depression is understudied.

4. Discussion

The key findings from this scoping review are summarized in Table 2. MDD and subthreshold depression affect more females than males, and prevalence peaks in mid-adolescence in both groups, though subthreshold depression affects more individuals overall. Both subthreshold depression and MDD significantly impair functioning. Adolescents with MDD and subthreshold depression share similar rates of comorbid disorders, and the same rates of health care usage and suicidal ideation. Heritability estimates are similar for both conditions. Neural anatomy and network research is limited in adolescents, but research in adults has indicated several structural and functional similarities in the brains of individuals with subthreshold depression and MDD. Finally, well-established psychotherapeutic treatments (CBT, IPT) for MDD have been promising for treating symptoms of subthreshold depression, however, limited research is available on the efficacy of pharmacotherapy (SSRIs) in this group. Given these results, it is evident that subthreshold depression in adolescence is clinically relevant.

Table 2
Summary of results on similarities and differences between subthreshold depression and major depressive disorder in adolescents. * Indicates that there is a limited number of studies. For further detail and specific references, see main text.

	Major Depressive Disorder	Subthreshold Depression
Prevalence	5–19.4%	Up to 29.2%
More Prevalent in Females	Yes	Yes
Prevalence Peaks in Mid-Adolescence	Yes	Yes
Functional Impairment	Yes	Yes
Healthcare Usage	Equal levels	
Suicidal Ideation	Equal levels	
Rate of Any Psychiatric Disorders	Equal levels	
Heritability	30–40%	37%
Altered Grey Matter Volume	Yes	Yes*
Altered Resting State Connectivity and Task-Based Activation	Yes	Yes*
Benefit from Psychotherapy (CBT/IPT)	Yes	Yes*
Benefit from Pharmacotherapy (SSRIs)	Yes	Unknown*

As subthreshold depression is not considered a formal diagnostic category, the way subthreshold depression is defined is highly variable. Two recently developed classification systems challenge the traditional categorical method of classifying psychiatric disorders: the Research Domain Criteria (RDoC) and the Hierarchical Taxonomy of Psychopathology (HiTOP; Michelini et al., 2021; Hengartner and Lehmann, 2017). The RDoC is comprised of domains of functioning (e.g., negative valence systems, cognitive systems), units of analysis (e.g., genes, self-reports), environment, and development (Insel et al., 2010). The HiTOP system starts at Homogenous Components (symptoms) and then works its way up to Maladaptive Traits, Syndromes, Spectra (e.g., internalizing or externalizing) and finally Superspectra (such as 'p'; Kotov et al., 2017). Although both the RDoC and HiTOP have yet to be widely integrated in clinical research and practice (Ruggero et al., 2019; Cuthbert, 2014), both models provide an informative research framework for conceptualizing and investigating the dimensionality of depression in ongoing and future work.

Regarding the study of psychopathology, eye-tracking has emerged as a useful tool in understanding the neurobiology of disorders, specifically through deficits in attention, cognitive control, autonomic, and sensory-motor processing. In contrast to neural imaging, eye-tracking techniques would provide a less invasive and more cost-effective means to further investigate the integrity of neural networks in adolescent subthreshold depression. While much eye-tracking has been performed on those with MDD and other categorized disorders, eye-movement research in adolescents with subthreshold depression is limited. Investigating how those with subthreshold depression perform compared to controls and MDD patients could provide more evidence for the dimensionality of depression and could be a non-invasive way to identify biomarkers for later development of MDD.

Further, many large effect sizes in psychiatric research can be attributed to researchers comparing "picture-perfect controls" (i.e., no lifetime psychiatric diagnosis) to "prototypical patients" (i.e., with only one DSM-based diagnosis). Additionally, comorbid disorders or people with subthreshold diagnoses of multiple disorders are often excluded from research to control for confounds in order to have a heterogenous study sample. Albeit such studies may provide important insight into a specific disorder, results may be more difficult to generalize to the majority of individuals seen in clinical settings (Kirkpatrick et al., 2020; Kapur et al., 2012). On the other hand, increasing heterogeneity also reduces statistical power. Therefore, studies with large sample sizes, that allow precise and reliable modelling of clinical heterogeneity (e.g., using normative modelling; Khundrakpam et al., 2021), are highly needed.

4.1. Limitations

This review is not without limitations. Firstly, our decision to perform a scoping versus a systematic review means we may not have included all relevant research. Ultimately, we decided to perform an exploratory scoping review as we wanted to keep this paper as a concise though comprehensive narrative overview. Another factor was that definitions of subthreshold depression vary significantly across studies and make it difficult to compare results. This limitation was outlined previously by Rodríguez et al. (2012), and the present review found that the lack of consistency in definitions of subthreshold depression continues to be a challenge.

Additionally, the number of empirical studies focused on adolescents are limited, with many studies on subthreshold depression including youth up to age 25 or focusing on older adults. This is especially true for neuroimaging and treatment studies. Including data from young adults allowed us to give more insight into subthreshold depression in this paper; however, many biological changes occur between adolescence and young adulthood. As such, any results in these areas should be

cautioned until more adolescent-specific data are available. Further, even within a certain domain (e.g., neuroimaging, epidemiology), studies highly differ in specific research methodology. There is also a lack of research that integrates symptoms, genotypes, and brain structure to form a predictive model for subthreshold depression.

5. Conclusion

Adolescent depressive disorders are highly heterogenous, manifesting in a range of severities and travelling on different trajectories. Many risk factors contribute to the development of MDD, including the presence of subthreshold depression. As it stands, the categorical system of classifying psychiatric disorders does not capture the early stages of illness and the psychopathology of subthreshold depression, especially in young people. This review summarized available research confirming that adolescents with subthreshold depression experience significant impairment and have staggering similarities to adolescents with MDD. Psychosocial and pharmaceutical treatments have shown to be promising in subthreshold depression; however, more research is required. Additionally, the many similarities between subthreshold depression and MDD in adolescence suggest that depression is better viewed on a spectrum. Moving forward, a greater recognition and awareness of the significance of subthreshold conditions among researchers, clinicians, and health policy-makers may facilitate the development and application of early intervention.

CRediT authorship contribution statement

BKN and LB planned the article. BKN completed the literature review and drafted the manuscript. DPM, SKK, EB, and LB provided edits. LB supervised the work.

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Conflict of Interest

None.

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References

American Psychiatric Association, 2013. Diagnostic And Statistical Manual of Mental Disorders, fifth ed. American Psychiatric Association, Washington, DC. https://doi.org/10.1176/appi.books.9780890425596.

Armstrong, T., Olatunji, B.O., 2012. Eye tracking of attention in the affective disorders: a meta-analytic review and synthesis. Clin. Psychol. Rev. 32, 704–723. https://doi.org/10.1016/j.cpr.2012.09.004.

Arnone, D., 2019. Functional MRI findings, pharmacological treatment in major depression and clinical response. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 91, 28–37. https://doi.org/10.1016/j.pnpbp.2018.08.004.

Avenevoli, S., Swendsen, J., He, J.P., Burstein, M., Merikangas, K.R., 2015. Major depression in the national comorbidity survey-adolescent supplement: prevalence, correlates, and treatment. J. Am. Acad. Child Adolesc. Psychiatry 54, 37–44.e2. https://doi.org/10.1016/j.jaac.2014.10.010.

Bakker, G.M., 2019. A new conception and subsequent taxonomy of clinical psychological problems. BMC Psychology 7, 46. https://doi.org/10.1186/s40359-019-0318-8.

Bakusic, J., Schaufeli, W., Claes, S., Godderis, L., 2017. Stress, burnout and depression: a systematic review on DNA methylation mechanisms. J. Psychosom. Res. 92, 34–44. https://doi.org/10.1016/j.jpsychores.2016.11.005.

Balázs, J., Miklósi, M., Keresztény, A., Hoven, C.W., Carli, V., Wasserman, C., Apter, A., Bobes, J., Brunner, R., Cosman, D., et al., 2013. Adolescent subthreshold-depression and anxiety: psychopathology, functional impairment and increased suicide risk. J. Child. Psychol. Psychiatry 54, 670–677. https://doi.org/10.1111/jcpp.12016.

Barbui, C., Cipriani, A., Patel, V., Ayuso-Mateos, J.L., van Ommeren, M., 2011. Efficacy of antidepressants and benzodiazepines in minor depression: Systematic review and meta-analysis. Br. J. Psychiatry 198. https://doi.org/10.1192/bjp.bp.109.076448, 11-1.

Bertha, E.A., Balázs, J., 2013. Subthreshold depression in adolescence: a systematic review. Eur.ChildAdolesc.Psychiatry 22, 589–603. https://doi.org/10.1007/s00787-013-0411-0.

Besteher, B., Gaser, C., Nenadić, I., 2020. Brain structure and subclinical symptoms: a dimensional perspective of psychopathology in the depression and anxiety spectrum. Neuropsychobiology 79, 270–283. https://doi.org/10.1159/000501024.

Booij, L., Wang, D., Levesque, M.L., Tremblay, R.E., Szyf, M., 2013. Looking beyond the DNA sequence: the relevance of DNA methylation processes for the stress-diathesis model of depression. <sb:contribution><sb:title>Philos. Trans. R. Soc. Lond.</sb:title> </sb:contribution><sb:host><sb:issue><sb:series><sb:title>Ser. B Biol. Sci.</sb:title></sb:series></sb:issue></sb:host> 368, 1–16.

Booij, L., Szyf, M., Carballedo, A., Frey, E.-M., Morris, D., Dymov, S., Vaisheva, F., Ly, V., Fahey, C., Meaney, J., Gill, M., Frodl, T., 2015. DNA methylation of the serotonin transporter gene in peripheral cells and stress-related changes in hippocampal volume: a study in depressed patients and healthy controls. PLoS ONE 10, 1–14. https://doi.org/10.1371/journal.pone.0119061.

Buch, A.M., Liston, C., 2021. Dissecting diagnostic heterogeneity in depression by integrating neuroimaging and genetics. Neuropsychopharmacology 46, 156–175. https://doi.org/10.1038/s41386-020-00789-3.

Carragher, N., Krueger, R.F., Eaton, N.R., Slade, T., 2015. Disorders without borders: current and future directions in the meta-structure of mental disorders. Soc. Psychiatry Psychiatr. Epidemiol. 50, 339–350. https://doi.org/10.1007/s00127-014-1004-z.

Carrellas, N.W., Biederman, J., Uchida, M., 2017. How prevalent and morbid are subthreshold manifestations of major depression in adolescents? A literature review. J. Affect. Disord. 210, 166–173. https://doi.org/10.1016/j.jad.2016.12.037.

Carvalho, N., Laurent, E., Noiret, N., Chopard, G., Haffen, E., Bennabi, D., Vandel, P., 2015. Eye movement in unipolar and bipolar depression: A systematic review of the literature. Front. Psychol. 6, 1809. https://doi.org/10.3389/fpsyg.2015.01809.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., Poulton, R., 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301, 386–389. https://doi.org/10.1126/science.1083968.

Castanheira, L., Silva, C., Cheniaux, E., Telles-Correia, D., 2019. Neuroimaging correlates of depression-implications to clinical practice. Front.Psychiatry 10, 703. https://doi.org/10.3389/fpsyt.2019.00703.

Chaiton, M., Contreras, G., Brunet, J., Sabiston, C.M., O'Loughlin, E., Low, N.C., Karp, I., Barnett, T.A., O'Loughlin, J., 2013. Heterogeneity of depressive symptom trajectories through adolescence: Predicting outcomes in young adulthood. J. Can. Acad. Child Adolesc. Psychiatry 22, 96–105.

Chen, D., Meng, L., Pei, F., Zheng, Y., Leng, J., 2017. A review of DNA methylation in depression. J.Clin.Neurosci. 43, 39–46. https://doi.org/10.1016/j.jocn.2017.05.022.

Chiarella, J., Schumann, L., Pomares, F.B., Frodl, T., Tozzi, L., Nemoda, Z., Yu, P., Szyf, M., Khalid-Khan, S., Booij, L., 2020. DNA methylation differences in stress-related genes, functional connectivity and gray matter volume in depressed and healthy adolescents. J. Affect. Disord. 271, 160–168. https://doi.org/10.1016/j.jad.2020.03.062.

Chmielewska, N., Szyndler, J., Maciejak, P., Płaźnik, A., 2019. Epigenetic mechanisms of stress and depression. Psychiatr. Pol. 53, 1413–1428. https://doi.org/10.12740/PP/94375.

Christ, C., Schouten, M.J., Blankers, M., van Schaik, D.J., Beekman, A.T., Wisman, M.A., Stikkelbroek, Y.A., Dekker, J.J., 2020. Internet and computer-based cognitive behavioral therapy for anxiety and depression in adolescents and young adults: Systematic review and meta-analysis. J. Med. Internet Res. 22, e17831 https://doi.org/10.2196/17831.

Coe, B.C., Munoz, D.P., 2017. Mechanisms of saccade suppression revealed in the anti-saccade task. <sb:contribution><sb:title>Philos. Trans. R. Soc. Lond.</sb:title> </sb:contribution><sb:host><sb:issue><sb:series><sb:title>Ser. B Biol. Sci.</sb:title></sb:series></sb:issue></sb:host> 372, 20160192. https://doi.org/10.1098/rstb.2016.0192.

Collishaw, S., Hammerton, G., Mahedy, L., Sellers, R., Owen, M.J., Craddock, N., Thapar, A.K., Harold, G.T., Rice, F., Thapar, A., 2016. Mental health resilience in the adolescent offspring of parents with depression: a prospective longitudinal study. Lancet Psychiatry 3, 49–57. https://doi.org/10.1016/S2215-0366(15)00358-2.

Corfield, E.C., Yang, Y., Martin, N.G., Nyholt, D.R., 2017. A continuum of genetic liability for minor and major depression. Transl. Psychiatry 7, e1131. https://doi.org/10.1038/tp.2017.99.

Crockett, M.A., Martínez, V., Jiménez-Molina, Á., 2020. Subthreshold depression in adolescence: Gender differences in prevalence, clinical features, and associated factors. J. Affect. Disord. 272, 269–276. https://doi.org/10.1016/j.jad.2020.03.111.

Cuijpers, P., Pineda, B.S., Ng, M.Y., Weisz, J.R., Muñoz, R.F., Gentili, C., Quero, S., Karyotaki, E., 2021. A meta-analytic review: Psychological treatment of subthreshold depression in children and adolescents. J. Am. Acad. Child Adolesc. Psychiatry 60, 1072–1084. https://doi.org/10.1016/j.jaac.2020.11.024.

Cuthbert, B.N., 2014. Research domain criteria: toward future psychiatric nosology. Asian J. Psychiatr. 7, 4–5. https://doi.org/10.1016/j.ajp.2013.12.007.

De Bellis, M.D., Nooner, K.B., Scheid, J.M., Cohen, J.A., 2019. Depression in maltreated children and adolescents. Child Adolesc. Psychiatr. Clin. N. Am. 28, 289–302. https://doi.org/10.1016/j.chc.2019.02.002.

De Lima, M.S., Hotopf, M., 2003. Benefits and risks of pharmacotherapy for dysthymia: a systematic appraisal of the evidence. Drug Saf. 26, 55–64. https://doi.org/10.2165/00002018-200326010-00006.

De Lissnyder, E., Derakshan, N., De Raedt, R., Koster, E.H.W., 2011. Depressive symptoms and cognitive control in a mixed antisaccade task: specific effects of depressive rumination. Cogn. Emot. 25, 886–897. https://doi.org/10.1080/02699931.2010.514711.

DeFilippis, M., Wagner, K.D., 2014. Management of treatment-resistant depression in children and adolescents. Paediatr. Drugs 16, 353–361. https://doi.org/10.1007/s40272-014-0088-y.

Dold, M., Bartova, L., Souery, D., Mendlewicz, J., Serretti, A., Porcelli, S., Zohar, J., Montgomery, S., Kasper, S., 2017. Clinical characteristics and treatment outcomes of patients with major depressive disorder and comorbid anxiety disorders - results from a European multicenter study. J. Psychiatr. Res. 91, 1–13. https://doi.org/10.1016/j.jpsychires.2017.02.020.

Ellis, R., Seal, M.L., Simmons, J.G., Whittle, S., Schwartz, O.S., Byrne, M.L., Allen, N.B., 2017. Longitudinal trajectories of depression symptoms in adolescence: psychosocial risk factors and outcomes. Child Psychiatry Hum. Dev. 48, 554–571. https://doi.org/10.1007/s10578-016-0682-z.

Essau, C.A., Lewinsohn, P.M., Seeley, J.R., Sasagawa, S., 2010. Gender differences in the developmental course of depression. J. Affect. Disord. 127, 185–190. https://doi.org/10.1016/j.jad.2010.05.016.

Fergusson, D.M., Horwood, L.J., Ridder, E.M., Beautrais, A.L., 2005. Subthreshold depression in adolescence and mental health outcomes in adulthood. Arch. Gen. Psychiatry 62, 66–72. https://doi.org/10.1001/archpsyc.62.1.66.

Flint, J., Kendler, K.S., 2014. The genetics of major depression. Neuron 81, 484–503. https://doi.org/10.1016/j.neuron.2014.01.027.

Frodl, T., Szyf, M., Carballedo, A., Ly, V., Dymov, S., Vaisheva, F., Morris, D., Fahey, C., Meaney, J., Gill, M., Booij, L., 2015. DNA methylation of the serotonin transporter gene (SLC6A4) is associated with brain function involved in processing emotional stimuli. J.PsychiatryNeurosci. 40, 296–305. https://doi.org/10.1503/jpn.140180.

Gatt, J.M., Burton, K.L.O., Williams, L.M., Schofield, P.R., 2015. Specific and common genes implicated across major mental disorders: A review of meta-analysis studies. J. Psychiatr. Res. 60, 1–13. https://doi.org/10.1016/j.jpsychires.2014.09.014.

Georgiades, K., Lewinsohn, P.M., Monroe, S.M., Seeley, J.R., 2006. Major depressive disorder in adolescence: the role of subthreshold symptoms. J. Am. Acad. Child Adolesc. Psychiatry 45, 936–944. https://doi.org/10.1097/01.chi.0000223313.25536.47.

Gómez-Odriozola, J., Calvete, E., 2021. Effects of a mindfulness-based intervention on adolescents' depression and self-concept: the moderating role of age. J. Child. Fam. Stud. 30, 1501–1515. https://doi.org/10.1007/s10826-021-01953-z.

Gonda, X., Juhasz, G., Laszik, A., Rihmer, Z., Bagdy, G., 2005. Subthreshold depression is linked to the functional polymorphism of the 5HT transporter gene. J. Affect. Disord. 87, 291–297. https://doi.org/10.1016/j.jad.2005.05.007.

González-Tejera, G., Canino, G., Ramírez, R., Chávez, L., Shrout, P., Bird, H., Bravo, M., Martínez-Taboas, A., Ribera, J., Bauermeister, J., 2005. Examining minor and major depression in adolescents. J. Child. Psychol. Psychiatry 46, 888–899. https://doi.org/10.1111/j.1469-7610.2005.00370.x.

Hengartner, M.P., Lehmann, S.N., 2017. Why psychiatric research must abandon traditional diagnostic classification and adopt a fully dimensional scope: two solutions to a persistent problem. Front. Psychiatry 8, 101. https://doi.org/10.3389/fpsyt.2017.00101.

Hickie, I.B., Scott, E.M., Cross, S.P., Iorfino, F., Davenport, T.A., Guastella, A.J., Naismith, S.L., Carpenter, J.S., Rohleder, C., Crouse, J.J., 2019. Right care, first time: a highly personalised and measurement-based care model to manage youth mental health. Med. J. Aust. 211 (Suppl. 9), S3–S46. https://doi.org/10.5694/mja2.50383.

Hill, R.M., Pettit, J.W., Lewinsohn, P.M., Seeley, J.R., Klein, D.N., 2014. Escalation to major depressive disorder among adolescents with subthreshold depressive symptoms: Evidence of distinct subgroups at risk. J. Affect. Disord. 158, 133–138. https://doi.org/10.1016/j.jad.2014.02.011.

Howard, D.M., Adams, M.J., Clarke, T.K., Hafferty, J.D., Gibson, J., Shirali, M., Coleman, J., Hagenaars, S.P., Ward, J., Wigmore, E.M., et al., 2019. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat. Neurosci. 22, 343–352. https://doi.org/10.1038/s41593-018-0326-7.

Hwang, J.W., Egorova, N., Yang, X.Q., Zhang, W.Y., Chen, J., Yang, X.Y., Hu, L.J., Sun, S., Tu, Y., Kong, J., 2015. Subthreshold depression is associated with impaired resting-state functional connectivity of the cognitive control network. Transl. Psychiatry 5, e683. https://doi.org/10.1038/tp.2015.174.

Hyde, J.S., Mezulis, A.H., 2020. Gender differences in depression: Biological, affective, cognitive, and sociocultural factors. Harv. Rev. Psychiatry 28, 4–13. https://doi.org/10.1097/HRP.0000000000000230.

Hyde, C.L., Nagle, M.W., Tian, C., Chen, X., Paciga, S.A., Wendland, J.R., Tung, J.Y., Hinds, D.A., Perlis, R.H., Winslow, A.R., 2016. Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. Nat. Genet. 48, 1031–1036. https://doi.org/10.1038/ng.3623.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., Wang, P., 2010. Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. Am. J. Psychiatry 167, 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379.

Jinnin, R., Okamoto, Y., Takagaki, K., Nishiyama, Y., Yamamura, T., Okamoto, Y., Miyake, Y., Takebayashi, Y., Tanaka, K., Sugiura, Y., 2016. Detailed course of depressive symptoms and risk for developing depression in late adolescents with subthreshold depression: A cohort study. Neuropsychiatr. Dis. Treat. 13, 25–33. https://doi.org/10.2147/NDT.S117846.

Johnson, J.G., Cohen, P., Kasen, S., 2009. Minor depression during adolescence and mental health outcomes during adulthood. Br. J. Psychiatry J. Ment. Sci. 195, 264–265. https://doi.org/10.1192/bjp.bp.108.054239.

Jonsson, U., Bohman, H., von Knorring, L., Olsson, G., Paaren, A., von Knorring, A.L., 2011. Mental health outcome of long-term and episodic adolescent depression: 15-year follow-up of a community sample. J. Affect. Disord. 130, 395–404. https://doi.org/10.1016/j.jad.2010.10.046.

Kader, F., Ghai, M., Maharaj, L., 2018. The effects of DNA methylation on human psychology. Behav. Brain Res. 346, 47–65. https://doi.org/10.1016/j.bbr.2017.12.004.

Kapur, S., Phillips, A.G., Insel, T.R., 2012. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? Mol. Psychiatry 17, 1174–1179. https://doi.org/10.1038/mp.2012.105.

Karg, K., Burmeister, M., Shedden, K., Sen, S., 2011. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: Evidence of genetic moderation. Arch. Gen. Psychiatry 68, 444–454. https://doi.org/10.1001/archgenpsychiatry.2010.189.

Kerestes, R., Davey, C.G., Stephanou, K., Whittle, S., Harrison, B.J., 2013. Functional brain imaging studies of youth depression: A systematic review. NeuroImage Clin. 4, 209–231. https://doi.org/10.1016/j.nicl.2013.11.009.

Khulan, B., Manning, J.R., Dunbar, D.R., Seckl, J.R., Raikkonen, K., Eriksson, J.G., Drake, A.J., 2014. Epigenomic profiling of men exposed to early-life stress reveals DNA methylation differences in association with current mental state. Transl. Psychiatry. 4, e448 https://doi.org/10.1038/tp.2014.94.

Khundrakpam, B., Tuerk, C., Booij, L., 2021. Understanding heterogeneity in autism spectrum disorder: A methodological shift in neuroimaging research from investigating group differences to individual differences. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 6, 762–764. https://doi.org/10.1016/j.bpsc.2021.04.004.

Kirkpatrick, R.H., Munoz, D.P., Khalid-Khan, S., Booij, L., 2020. Methodological and clinical challenges associated with biomarkers for psychiatric disease: a scoping review. J. Psychiatric Res. 143, 572–579. https://doi.org/10.1016/j.jpsychires.2020.11.023.

Klein, D.N., Shankman, S.A., Lewinsohn, P.M., Seeley, J.R., 2009. Subthreshold depressive disorder in adolescents: predictors of escalation to full-syndrome depressive disorders. J. Am. Acad. Child Adolesc. Psychiatry 48, 703–710. https://doi.org/10.1097/CHI.0b013e3181a56606.

Klinger-König, J., Hertel, J., Van der Auwera, S., Frenzel, S., Pfeiffer, L., Waldenberger, M., Golchert, J., Teumer, A., Nauck, M., Homuth, G., Volzke, H, Grabe, H.J., 2019. Methylation of the FKBP5 gene in association with FKBP5 genotypes, childhood maltreatment and depression. Neuropsychopharmacology 44, 930–938. https://doi.org/10.1038/s41386-019-0319-6.

Kotov, R., Krueger, R.F., Watson, D., Achenbach, T.M., Althoff, R.R., Bagby, R.M., Brown, T.A., Carpenter, W.T., Caspi, A., Clark, L.A., 2017. The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. J. Abnorm. Psychol. 126, 454–477. https://doi.org/10.1037/abn0000258.

Kraus, C., Kadriu, B., Lanzenberger, R., Zarate Jr., C.A., Kasper, S., 2019. Prognosis and improved outcomes in major depression: a review. Transl. Psychiatry 9, 127. https://doi.org/10.1038/s41398-019-0460-3.

Krueger, R.F., Kotov, R., Watson, D., Forbes, M.K., Eaton, N.R., Ruggero, C.J., Simms, L. J., Widiger, T.A., Achenbach, T.M., Bach, B., et al., 2018. Progress in achieving quantitative classification of psychopathology. World Psychiatry 17, 282–293. https://doi.org/10.1002/wps.20566.

Lahey, B.B., Zald, D.H., Hakes, J.K., Krueger, R.F., Rathouz, P.J., 2014. Patterns of heterotypic continuity associated with the cross-sectional correlational structure of prevalent mental disorders in adults. JAMA Psychiatry 71, 989–996. https://doi.org/10.1001/jamapsychiatry.2014.359.

Lewinsohn, P.M., Klein, D.N., Durbin, E.C., Seeley, J.R., Rohde, P., 2003. Family study of subthreshold depressive symptoms: Risk factor for MDD? J. Affect. Disord. 77, 149–157. https://doi.org/10.1016/s0165-0327(02)00106-4.

Lewis, A.J., Sae-Koew, J.H., Toumbourou, J.W., Rowland, B., 2020. Gender differences in trajectories of depressive symptoms across childhood and adolescence: A multi-group growth mixture model. J. Affect. Disord. 260, 463–472. https://doi.org/10.1016/j.jad.2019.09.027.

Li, H., Wei, D., Sun, J., Zhang, Q., Qiu, J., 2017. Fronto-limbic alterations in negatively biased attention in young adults with subthreshold depression. Front. Psychol. 8, 1–10. https://doi.org/10.3389/fpsyg.2017.01354.

Lopizzo, N., Bocchio Chiavetto, L., Cattane, N., Plazzotta, G., Tarazi, F.I., Pariante, C.M., Riva, M.A., Cattaneo, A., 2015. Gene-environment interaction in major depression: Focus on experience-dependent biological systems. Front.Psychiatry 6, 68. https://doi.org/10.3389/fpsyt.2015.00068.

Méndez, J., Sánchez-Hernández, Ó., Garber, J., Espada, J.P., Orgilés, M., 2021. Psychological treatments for depression in adolescents: More than three decades later. Int. J. Environ. Res. Public Health 18, 4600. https://doi.org/10.3390/ijerph18094600.

Mezulis, A., Salk, R.H., Hyde, J.S., Priess-Groben, H.A., Simonson, J.L., 2014. Affective, biological, and cognitive predictors of depressive symptom trajectories in adolescence. J. Abnorm. Child Psychol. 42, 539–550. https://doi.org/10.1007/s10802-013-9812-2.

Michelini, G., Palumbo, I.M., DeYoung, C.G., Latzman, R.D., Kotov, R., 2021. Linking RDoC and HiTOP: A new interface for advancing psychiatric nosology and neuroscience. Clin. Psychol. Rev. 86, 102025 https://doi.org/10.1016/j.cpr.2021.102025.

Mulders, P.C., van Eijndhoven, P.F., Schene, A.H., Beckmann, C.F., Tendolkar, I., 2015. Resting-state functional connectivity in major depressive disorder: A review.

Neurosci. Biobehav. Rev. 56, 330–344. https://doi.org/10.1016/j.neubiorev.2015.07.014.
Mullen, S., 2018. Major depressive disorder in children and adolescents. Ment Health Clin. 8, 275–283. https://doi.org/10.9740/mhc.2018.11.275.
Mullins, N., Lewis, C.M., 2017. Genetics of depression: progress at last. Curr. Psychiatry Rep. 19, 43. https://doi.org/10.1007/s11920-017-0803-9.
Munoz, D.P., Everling, S., 2004. Look away: The anti-saccade task and the voluntary control of eye movement. Nat. Rev. Neurosci. 5, 218–228. https://doi.org/10.1038/nrn1345.
Musliner, K.L., Munk-Olsen, T., Eaton, W.W., Zandi, P.P., 2016. Heterogeneity in long-term trajectories of depressive symptoms: Patterns, predictors and outcomes. J. Affect. Disord. 192, 199–211. https://doi.org/10.1016/j.jad.2015.12.030.
Naber, D., Bullinger, M., 2018. Should antidepressants be used in minor depression? Dialogues Clin. Neurosci. 20, 223–228. https://doi.org/10.31887/DCNS.2018.20.3/dnaber.
Palma-Gudiel, H., Fañanás, L., 2017. An integrative review of methylation at the serotonin transporter gene and its dialogue with environmental risk factors, psychopathology and 5-HTTLPR. Neurosci. Biobehav. Rev. 72, 190–209. https://doi.org/10.1016/j.neubiorev.2016.11.011.
Pataki, C., Carlson, G.A., 2016. Major depressive disorder among children and adolescents. In: Focus, 14. American Psychiatric Publishing, pp. 10–14. https://doi.org/10.1176/appi.focus.20150037.
Petersen, T., Andreotti, C.F., Chelminski, I., Young, D., Zimmerman, M., 2009. Do comorbid anxiety disorders impact treatment planning for outpatients with major depressive disorder? Psychiatry Res. 169, 7–11. https://doi.org/10.1016/j.psychres.2008.10.036.
Rodríguez, M.R., Nuevo, R., Chatterji, S., Ayuso-Mateos, J.L., 2012. Definitions and factors associated with subthreshold depressive conditions: A systematic review. BMC Psychiatry 12, 181. https://doi.org/10.1186/1471-244X-12-181.
Ruggero, C.J., Kotov, R., Hopwood, C.J., First, M., Clark, L.A., Skodol, A.E., Mullins-Sweatt, S.N., Patrick, C.J., Bach, B., Cicero, D.C., 2019. Integrating the Hierarchical Taxonomy of Psychopathology (HiTOP) into clinical practice. J. Consult. Clin. Psychol. 87, 1069–1084. https://doi.org/10.1037/ccp0000452.
Salk, R.H., Hyde, J.S., Abramson, L.Y., 2017. Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. Psychol. Bull. 143, 783–822. https://doi.org/10.1037/bul0000102.
Schmaal, L., Pozzi, E., Ho, T.C., van Velzen, L.S., Veer, I.M., Opel, N., Van Someren, E., Han, L., Aftanas, L., Aleman, A., et al., 2020. ENIGMA MDD: seven years of global neuroimaging studies of major depression through worldwide data sharing. Transl. Psychiatry 10, 172. https://doi.org/10.1038/s41398-020-0842-6.
Schubert, K.O., Clark, S.R., Van, L.K., Collinson, J.L., Baune, B.T., 2017. Depressive symptom trajectories in late adolescence and early adulthood: A systematic review. Aust.N.Z.J.Psychiatry 51, 477–499. https://doi.org/10.1177/0004867417700274.
Shadrina, M., Bondarenko, E.A., Slominsky, P.A., 2018. Genetics factors in major depression disease. Front.Psychiatry 9, 334. https://doi.org/10.3389/fpsyt.2018.00334.
Shankman, S.A., Klein, D.N., Lewinsohn, P.M., Seeley, J.R., Small, J.W., 2008. Family study of subthreshold psychopathology in a community sample. Psychol. Med. 38, 187–198. https://doi.org/10.1017/S0033291707001857.
Shankman, S.A., Lewinsohn, P.M., Klein, D.N., Small, J.W., Seeley, J.R., Altman, S.E., 2009. Subthreshold conditions as precursors for full syndrome disorders: a 15-year longitudinal study of multiple diagnostic classes. J. Child. Psychol. Psychiatry 50, 1485–1494. https://doi.org/10.1111/j.1469-7610.2009.02117.x.
Shen, X., Reus, L.M., Cox, S.R., Adams, M.J., Liewald, D.C., Bastin, M.E., Smith, D.J., Deary, I.J., Whalley, H.C., McIntosh, A.M., 2017. Subcortical volume and white matter integrity abnormalities in major depressive disorder: Findings from UK Biobank imaging data. Sci. Rep. 7, 5547. https://doi.org/10.1038/s41598-017-05507-6.
Shevlin, M., McElroy, E., Murphy, J., 2017. Homotypic and heterotypic psychopathological continuity: A child cohort study. Soc. Psychiatry Psychiatr. Epidemiol. 52, 1135–1145. https://doi.org/10.1007/s00127-017-1396-7.
Shore, L., Toumbourou, J.W., Lewis, A.J., Kremer, P., 2018. Longitudinal trajectories of child and adolescent depressive symptoms and their predictors - a systematic review and meta-analysis. Child Adolesc. Mental Health 23, 107–120. https://doi.org/10.1111/camh.12220.
Sihvola, E., Keski-Rahkonen, A., Dick, D.M., Pulkkinen, L., Rose, R.J., Marttunen, M., Kaprio, J., 2007. Minor depression in adolescence: Phenomenology and clinical correlates. J. Affect. Disord. 97, 211–218. https://doi.org/10.1016/j.jad.2006.06.019.
Stewart, S.M., Lewinsohn, P.M., Lee, P.W., Ho, L.M., Kennard, B., Hughes, C.W., Emslie, G.J., 2002. Symptom patterns in depression and "subthreshold" depression among adolescents in Hong Kong and the United States. J. Cross-Cult. Psychol. 33, 559–576. https://doi.org/10.1177/022022102238269.
Stringaris, A., Vidal-Ribas Belil, P., Artiges, E., Lemaitre, H., Gollier-Briant, F., Wolke, S., Vulser, H., Miranda, R., Penttilä, J., Struve, M., et al., 2015. The brain's response to reward anticipation and depression in adolescence: Dimensionality, specificity, and longitudinal predictions in a community-based sample. Am. J. Psychiatry 172, 1215–1223. https://doi.org/10.1176/appi.ajp.2015.14101298.
Suslow, T., Hußlack, A., Kersting, A., Bodenschatz, C.M., 2020. Attentional biases to emotional information in clinical depression: A systematic and meta-analytic review of eye tracking findings. J. Affect. Disord. 274, 632–642. https://doi.org/10.1016/j.jad.2020.05.140.
Takagaki, K., Okamoto, Y., Jinnin, R., Mori, A., Nishiyama, Y., Yamamura, T., Yokoyama, S., Shiota, S., Okamoto, Y., Miyake, Y., et al., 2016. Behavioral activation for late adolescents with subthreshold depression: A randomized controlled trial. Eur. Child. Adolesc. Psychiatry 25, 1171–1182. https://doi.org/10.1007/s00787-016-0842-5.
Takagaki, K., Okamoto, Y., Jinnin, R., Mori, A., Nishiyama, Y., Yamamura, T., Yokoyama, S., Shiota, S., Okamoto, Y., Miyake, Y., 2018. Enduring effects of a 5-week behavioral activation program for subthreshold depression among late adolescents: An exploratory randomized controlled trial. Neuropsychiatr. Dis. Treat. 14, 2633–2641. https://doi.org/10.2147/NDT.S172385.
Talarowska, M., 2020. Epigenetic mechanisms in the neurodevelopmental theory of depression. Depress. Res. Treat. 2020, 6357873. https://doi.org/10.1155/2020/6357873.
Thapar, A., Collishaw, S., Pine, D.S., Thapar, A.K., 2012. Depression in adolescence. Lancet 379, 1056–1067. https://doi.org/10.1016/S0140-6736(11)60871-4.
Tubbs, J.D., Ding, J., Baum, L., Sham, P.C., 2020. Systemic neuro-dysregulation in depression: Evidence from genome-wide association. Eur. Neuropsychopharmacol. 39, 1–18. https://doi.org/10.1016/j.euroneuro.2020.08.007.
Weersing, V.R., Jeffreys, M., Do, M.T., Schwartz, K.T., Bolano, C., 2017. Evidence base update of psychosocial treatments for child and adolescent depression. J. Clin. Child. Adolesc. Psychol. 46, 11–43. https://doi.org/10.1080/15374416.2016.1220310.
Weissman, M.M., Wickramaratne, P., Nomura, Y., Warner, V., Verdeli, H., Pilowsky, D.J., Grillon, C., Bruder, G., 2005. Families at high and low risk for depression: a 3-generation study. Arch. Gen. Psychiatry 62, 29–36. https://doi.org/10.1001/archpsyc.62.1.29.
Weissman, M.M., Wickramaratne, P., Gameroff, M.J., Warner, V., Pilowsky, D., Kohad, R. G., Verdeli, H., Skipper, J., Talati, A., 2016. Offspring of depressed parents: 30 years later. Am. J. Psychiatry 173, 1024–1032. https://doi.org/10.1176/appi.ajp.2016.15101327.
Wesselhoeft, R., Sørensen, M.J., Heiervang, E.R., Bilenberg, N., 2013. Subthreshold depression in children and adolescents - a systematic review. J. Affect. Disord. 151, 7–22. https://doi.org/10.1016/j.jad.2013.06.010.
Wichstrøm, L., Belsky, J., Steinsbekk, S., 2017. Homotypic and heterotypic continuity of symptoms of psychiatric disorders from age 4 to 10 years: A dynamic panel model. J. Child. Psychol. Psychiatry 58, 1239–1247. https://doi.org/10.1111/jcpp.12754.
Wickrama, T., Wickrama, K.A., 2010. Heterogeneity in adolescent depressive symptom trajectories: Implications for young adults' risky lifestyle. J. Adolesc. Health 47, 407–413. https://doi.org/10.1016/j.jadohealth.2010.02.013.
World Health Organization, 2017. Depression and other common mental disorders: global health estimates. https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf accessed 26 July 2021.
Wright, A.G., Krueger, R.F., Hobbs, M.J., Markon, K.E., Eaton, N.R., Slade, T., 2013. The structure of psychopathology: toward an expanded quantitative empirical model. J. Abnorm. Psychol. 122, 281–294. https://doi.org/10.1037/a0030133.
Yang, J., Yao, S., Zhu, X., Zhang, C., Ling, Y., Abela, J.R., Esseling, P.G., McWhinnie, C., 2010. The impact of stress on depressive symptoms is moderated by social support in Chinese adolescents with subthreshold depression: a multi-wave longitudinal study. J. Affect. Disord. 127, 113–121. https://doi.org/10.1016/j.jad.2010.04.023.
Young, J.F., Miller, M.R., Khan, N., 2010. Screening and managing depression in adolescents. Adolesc. Health Med. Ther. 1, 87–95. https://doi.org/10.2147/AHMT.S7539.
Zhang, F.F., Peng, W., Sweeney, J.A., Jia, Z.Y., Gong, Q.Y., 2018. Brain structure alterations in depression: Psychoradiological evidence. CNS Neurosci. Ther. 24, 994–1003. https://doi.org/10.1111/cns.12835.
Zhang, J.Y., Ji, X.Z., Meng, L.N., Cai, Y.J., 2019. Effects of modified mindfulness-based stress reduction (MBSR) on the psychological health of adolescents with subthreshold depression: A randomized controlled trial. Neuropsychiatr. Dis. Treat. 15, 2695–2704. https://doi.org/10.2147/NDT.S216401.
Zimmerman, M., McDermut, W., Mattia, J.I., 2000. Frequency of anxiety disorders in psychiatric outpatients with major depressive disorder. Am. J. Psychiatry 157, 1337–1340. https://doi.org/10.1176/appi.ajp.157.8.1337.