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## Depression in young people

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**Contribution of authors:**

AT led the organisation, drafted introduction, conclusion, epidemiology, risk factors and antecedents, assessment and figures and conducted the final editing.

OE drafted outcomes, screening and measures, table of measures and oversaw literature search.

VP drafted prevention and oversaw sections on LMIC

DB drafted pathophysiology and interventions.

All authors conducted additional literature reviews and contributed to editing all sections.

## **Abstract**

Depression rates in young people have risen sharply in recent years, especially among females; a concern given this is a period of rapid social, emotional and cognitive development and key life transitions. Adverse outcomes, include depression recurrence, other psychiatric disorders and wider, protracted impairments in interpersonal, social, educational and occupational functioning. Thus, prevention and early intervention are priorities. These typically target predisposing factors, antecedents and symptoms of depression. Those with a family history of depression, exposed to social stressors and who belong to certain subgroups (e.g. chronic physical health problem, sexual minority) are at especially high risk. Clinical antecedents include depressive symptoms, anxiety and irritability. Evidence currently favours indicated and targeted over universal prevention. Emerging school-/community-level social interventions show some promise. Depression is highly heterogeneous. A step-wise treatment approach is recommended starting with brief psychosocial interventions, then a specific psychological therapy and finally including antidepressant medication.

**Search strategy and selection criteria:**

We searched MEDLINE via Ovid using the search term “depression” combined with “child”, “adolescent” or “teenager”. These terms were combined with search terms covering epidemiology, aetiology, pathophysiology, assessment, diagnosis, treatment, outcomes, prevention and intervention. We limited the search to review papers in the English language published since 2011, and primary research papers in the English language published since 2018. We focused on meta-analyses and systematic reviews where available and included primary research papers for relevant recent findings. A full list of search terms used can be found in supplementary materials.

## Introduction

Depression is a leading contributor to the global burden of disease and is associated with enormous personal, societal and economic burden<sup>1</sup>. Depression in young people is a growing concern; not only because it occurs during a period of rapid social, emotional, and cognitive development and key life transitions<sup>2</sup> but also because its prevalence in this age group has risen sharply in recent years, especially among females<sup>3</sup>.

Depression describes a variety of mood-related concepts and a spectrum of difficulties (Figure 1). At one end of this spectrum, it can refer to a mood state in the context of normative mood fluctuations. An elevated level of depressive symptoms that does not meet full diagnostic criteria for major depressive disorder (MDD) is commonly termed “subthreshold depression”<sup>4</sup> which itself has negative impacts on quality of life and is a risk indicator of a later depressive disorder. Depressive or mood disorders lie at the other extreme. A diagnosis of MDD is characterised by depressed mood that is present nearly every day, for most of the day, for at least two weeks or loss of interest or enjoyment (anhedonia), and accompanied by a constellation of other symptoms (see Figure 2) including irritability in children and young people. These symptoms need to interfere with daily life functioning and represent a change from how the person functioned before. However, even with this definition, MDD is highly heterogeneous. There is variability in the different depressive symptom combinations; its clinical severity, captured by the descriptors “mild”, “moderate” or “severe” depression; age at first onset; comorbidities; and outcomes. Depression can spontaneously remit, recur or persist (persistent depressive disorder) but also herald the onset of later bipolar disorder or schizophrenia. MDD and persistent depressive disorder are grouped with other depression-related diagnoses as depressive disorders in DSM-5<sup>5</sup> and as mood disorders in ICD-11<sup>6</sup>. Most of this review will focus on MDD, although in some instances where relevant (e.g. for public health, low and middle income countries LMIC) we include research using broader definitions of depressive disorder and depression symptoms. Despite the fact that over 80% of the world’s young people live in LMIC, most of the research we identified was conducted in high-income

countries; thus, we have purposively identified studies from LMIC to supplement this evidence, especially in relation to interventions.

Our primary focus is on adolescence that traditionally spans age 10 to 19 years (see Figure 3 for age-groups). However, in some instances we also consider childhood because of its relevance to later adolescence and also, transitions to young adult life. That is because of growing calls to define adolescence more broadly between ages 10 and 24 years<sup>2</sup>.

### **Epidemiology**

The prevalence of MDD is low in childhood (0.6%<sup>7</sup>- 1.1%<sup>8</sup>), and increases sharply across adolescence and early adult life, especially among females<sup>9,10</sup>. The rise in incidence across adolescence and young adulthood may be due to increased social demands and stressors, hormonal changes and brain development<sup>11</sup>. Exact prevalence rates of depression vary depending on the age sampled and how broadly depression has been defined.

A meta-analysis of 41 population-based studies of children and adolescents conducted across 27 countries from every world region<sup>12</sup> suggested a world-wide one-year prevalence rate of 1.3% (CI 95% 0.7–2.3) for MDD. However significant heterogeneity was observed due to sample representativeness, sampling frame and diagnostic instrument. A more recent systematic review and meta-analysis of children and adolescents yielded a similar prevalence of 1.3% in high-income countries<sup>13</sup>.

Although one-year MDD prevalence rates look fairly low, these studies cover a wide age range and depression typically first arises during adolescence and early adulthood. For example, a 2017 mental health survey conducted in England showed that rates of emotional disorder were 9% among 11-16 year olds and 14.9% in 17-19 year olds; in the older age group, 1 in 4 females (22.4%) had an emotional disorder. For narrowly defined MDD, this survey observed an overall prevalence of 2.1% among 5- 19 year olds; in the oldest 17-19 year old group, the rate was 4.8%.



A current concern is that the prevalence rates of MDD, broader definitions of depression, and emotional disorders, which include anxiety and depression, have risen sharply among young people over the last decade (Figure 4), especially in females. This 1.5 to 2-fold rise in prevalence was observed, even before the Covid-19 pandemic and rates appear to have risen even further subsequently<sup>14</sup>.

For broadly-defined depression (Figure 4), the annual cross-sectional US National Survey on Drug Use and Health also reported that the 1-year prevalence increased from 8.3% to 12.9% in 12-17 year olds between 2011 and 2016<sup>10</sup>. This trend was paralleled by increased adolescent mental health service use between 2005 to 2018 with greater demands on specialist mental health services for emotional problems (anxiety, depressive symptoms and suicidal behaviour)<sup>15</sup>. England's Mental Health of Children and Young People Survey showed a similar increased rate of probable emotional disorders from 3.9% in 2004 to 5.8% in 5 to 15-year olds in 2017 (Figure 4). Finally, using broader indicators of mental health in young adults, the UK Office of National Statistics<sup>16</sup> found that 31% of women aged 16 to 24 years reported some evidence of depression or anxiety, representing an increase from the previous year (26%) and five years earlier (26%).

These and other recent surveys all suggest that depression, no matter how defined, has become more common in later adolescence and early adulthood, especially among females. Rates are higher in those with special educational needs, a chronic health problem and who come from socio-economically disadvantaged households<sup>8</sup>.

Depression is approximately twice as common in females than males; this gender gap is observed across the life span but first arises after puberty<sup>17</sup> and appears to be mediated by increases in oestradiol and, in some studies, testosterone<sup>18</sup>. A recent meta-regression of studies published between 1980 and 2019 showed that despite substantial societal changes, while the gender gap in depression across the lifespan for the US has stayed the same, it

has increased for depression (disorder and symptoms) in 10-19 year olds<sup>17</sup>. It has been hypothesised that social changes, such as greater loneliness, academic strain, widening socio-economic inequality, or a greater willingness to disclose mental health difficulties may account for the rise in depression rates<sup>3</sup> and increased gender gap, but what these factors are remains unknown.

## **Outcomes**

Depression in adolescence and early adult life is associated with recurrence in later life.

Approximately 50% of adolescents will experience a further episode<sup>19,20</sup>, with a nearly 3-fold increased risk of depression in adulthood<sup>21-22</sup>. Factors increasing recurrence risk include female gender, multiple depressive episodes in adolescence, poor parental mental health, family history of depression recurrence, chronic interpersonal stress, poor peer-relationships and comorbid anxiety disorder<sup>23-25</sup>.

There also is elevated risk of other psychopathology including later anxiety disorders<sup>21,26</sup>, and increased rates of conversion from depression to bipolar affective disorder<sup>27</sup>. Furthermore depressive symptoms have been found to be associated with eating disorders<sup>28</sup> and functional somatic symptoms<sup>29</sup>. High risk behaviours associated with depression in young people, include increase in suicide attempts<sup>21</sup>, alcohol, nicotine and substance use<sup>30</sup>, and risky sexual behaviours<sup>31,32</sup>. Physical health outcomes include increased risk of cardiovascular disease<sup>33</sup> and obesity<sup>34</sup>.

In addition to adverse mental and physical health outcomes, depression in young people has widespread negative impacts on psychosocial functioning including lower educational attainment, higher welfare dependence and unemployment in adulthood<sup>22,35,36</sup>. There is also evidence to suggest impacts on future interpersonal difficulties, including marital functioning<sup>37</sup>, increased loneliness<sup>38</sup> and a greater need for social support<sup>39</sup>. Conversely, preventing the onset or recurrence of depression, at least in adolescence, predicts better adult functioning<sup>40</sup>.

To date, longitudinal research has focused on outcomes into early adulthood (up to age 35 years), with little information on mid-life and beyond. However, persistent depressive disorder in adolescence has been shown to predict use of health care resources in mid adulthood up to age 40, suggesting the impact of adolescent depression continues beyond early adulthood<sup>41</sup>.

Although depression in young people is associated with a broad range of adverse outcomes, long-term outcomes vary across individuals<sup>42</sup>. Outcomes may differ depending on the number and severity of depressive episodes<sup>42</sup>. Studies examining trajectories of depression across adolescence and early adulthood have found those with more persistent depression over time have particularly poor adult outcomes in terms of mental health difficulties, self-harm, substance misuse, physical health and increased likelihood of not being in education, employment and training at age 25 years<sup>43-45</sup>. The presence of comorbid disorders also impacts on outcomes. For example, comorbid neurodevelopmental disorders (Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD)) are associated with an earlier onset and more persistent course of depression<sup>46</sup>. The presence of comorbid conduct disorder increases the risk for later drug misuse, alcoholism and antisocial personality disorder<sup>47</sup> and comorbid alcohol and substance misuse increases future risk of suicidality and suicide<sup>48</sup>. There are also factors that are associated with improved outcomes, for example, positive attributional style and good parent-child relationships are associated with more optimal outcomes<sup>20</sup>.

Treatment trials often use the absence of diagnosis or reduction in depressive symptoms as evidence of good outcomes, typically relying on clinician report<sup>49</sup>. However, service users have described a need to measure outcomes beyond symptoms, including interpersonal relationships and coping with problems<sup>49</sup>. These factors are considered infrequently in existing studies<sup>49</sup>. Measuring what matters most to young people and their families and what leads to optimal interpersonal, educational, and occupational outcomes are important

considerations in deciding which interventions provide the most benefit for patients, families, and society.

### **Risk factors, antecedents and pathophysiology**

Depression is explained by multiple different risk factors that have probabilistic risk effects; no single risk factor is necessary or sufficient to explain its aetiology. Recognising common risk factors and clinical antecedents of depression can be helpful in guiding prevention and surveillance efforts (Figure 5).

#### *Individual-level risk factors*

Pooled twin studies suggest that approximately 40% of the variance in depression is explained by genetic factors with genetic risk higher for more severe, recurrent and early-onset depression<sup>50,51</sup>. Notably, genetic liability for depression is correlated with exposure to social stressors. This gene-environment correlation means that those with higher genetic loading are also more likely to be exposed to stressors, thereby creating a “double whammy” risk effect<sup>52</sup>.

Genetic studies of adult depression have identified more than a hundred common genetic risk variants, each of small effect size<sup>53</sup>. Rare, larger effect size copy number variants (CNVs; chromosomal deletions and duplications) also contribute risk<sup>54</sup>. Depression genetic risk variants are highly pleiotropic and also are associated with schizophrenia, bipolar disorder, ADHD and ASD among other disorders<sup>55</sup>. A composite of common genetic risk variants (polygenic risk scores [PRS]) predicts adolescent<sup>56</sup> as well as adult depression although prediction is too weak to have current clinical utility. Depression PRS also are associated with exposure to maltreatment<sup>57</sup> and bullying<sup>58</sup>, further demonstrating gene-environment correlation, although gene-environment interactions have failed to withstand meta-analyses or replications<sup>e.g.59</sup>.

Other individual risk factors include temperament (e.g. negative and positive emotionality)<sup>60</sup>, personality (e.g. neuroticism<sup>61</sup>) and certain styles of thinking and behaving (e.g. cognitive rumination<sup>62</sup>). More proximal cognitive-behavioural mechanisms (see pathogenesis) have long been considered important mediators of risk and are the target of many psychological interventions for depression.

Depression typically onsets from adolescence onwards. However, for many, the first episode is preceded by clinical antecedents including extended periods of subthreshold depressive symptoms or a different mental or neurodevelopmental disorder. Anxiety in childhood and early adolescence is the most common antecedent<sup>63</sup>. Another consistent finding is that childhood irritability also predicts future depression in adolescence<sup>64</sup>. DSM-5 disruptive mood dysregulation disorder (DMDD), defined by early onset, severe irritability characterised by recurrent temper outbursts, is grouped with Depressive Disorders but in ICD-11, irritability remains a feature of oppositional defiant disorder, a behavioural problem. Another group at elevated risk for adolescent depression includes those with a neurodevelopmental disorder<sup>65,66</sup>, specifically ADHD and ASD. It is not clear whether these antecedents represent a prodrome to illness, have causal risk effects on later depression or whether they simply reflect overlapping aetiology. If causal, then early treatment of antecedents where possible should reduce risks for adolescent depression. There is some evidence to suggest that effective treatment of anxiety<sup>67</sup> and ADHD<sup>68</sup> may reduce risks for depression but no definitive evidence yet that treatment of other antecedents prevents later depression<sup>69</sup>.

Another important risk group are those with a history of chronic physical illness, particularly those that affect the central nervous system (e.g., migraine, epilepsy)<sup>70</sup>. Given undetected depression can lead to non-adherence with treatment, risky behaviours and decreased engagement with health services, the possibility of depression in those with a physical health condition needs to be considered by those working in both primary and secondary care.

There is some evidence to suggest small effect size associations between sleep disruption and adolescent depression<sup>71</sup> with similar findings for obesity and depression. However, the relationships between both sleep and obesity with depression may be bidirectional, and association explained by confounders<sup>72</sup>. Links between sedentary behaviour and adolescent depression also have been found. This behaviour is closely related to Body Mass Index (BMI) and screen time and prospective studies suggest sedentary behaviour is a risk factor while exercise is protective<sup>73</sup>.

#### *Family-, school- and peer-level risk factors*

One especially common risk factor is having a parent with depression. Approximately 40% of those with an affected parent develop depression<sup>74</sup> with risks highest for offspring of parents who have a history of multi-generational, recurrent, severe and early-onset depression. Inter-generational transmission appears to be explained by both inherited and social mechanisms including offspring exposure to current parent depression<sup>75–77</sup>. Some adolescents are resilient to the impact of parental depression, protected by high-quality relationships with the other parent and friends, connection to school, participation in sports, and exercise<sup>78</sup>.

Social stressors associated with subsequent adolescent depression include exposure to maltreatment<sup>79</sup>, early life trauma and adversities including disrupted caregiving<sup>80</sup>, bullying<sup>81</sup>, social isolation<sup>82</sup>, discordant relationships as well as stressful life events such as death of a loved one, loss of a romantic relationship<sup>80</sup>. Current evidence, which is far from definitive, suggests there are some benefits of digital technology as well as risks such as cyber-bullying, interference with sleep, unfavourable social comparison, and addiction<sup>83</sup>.

#### *Group- and population-level risk factors*

The most widely studied community-level stressors<sup>84</sup> associated with an increased prevalence of depression across age groups include living in poverty, violent

neighbourhoods, homelessness, being a refugee or displaced, exposure to war or terrorism and the near universal exposure of the Covid-19 pandemic which has had a disproportionate impact on young people<sup>85</sup>. These stressors and traumas disproportionately impact on some racial or ethnic minority groups thereby increasing risk for depression. However, illustrative of wide variability in the effect of ethnicity and culture on depression, UK studies have observed *lower* rates of adolescent depression in some minority ethnic groups (those of South Asian origin) than among white UK children and adolescents, suggesting either differences in reporting or protective, cultural effects<sup>8</sup>. Young people who are members of sexual or gender minority groups show especially increased rates of depression, in part attributable to peer victimization, family conflict and rejection<sup>86</sup>.

### **Pathophysiology**

While there are multiple studies on the processes by which environmental stressors are translated to depressive symptoms via hormonal, autonomic, and epigenetic processes, the most coherent findings informing depression pathophysiology come from studies that probe neurocircuitry and cognitive-behavioural processes. Neuroimaging studies of depressed adolescents have documented a neural basis for long-standing observations about the roles that impairments in reward response, impaired top-down cognitive control of emotions, selective over-attention to negative emotional stimuli, and negative, ruminative self-scrutiny have played in the aetiology of depression<sup>87,88</sup>.

Blunted response to rewarding stimuli predicts the onset of depression, and is associated with anhedonia and depressive severity. Depressed adolescents show hypoactivation of the ventral striatum when anticipating reward, and diminished response in orbital prefrontal cortex (OPC) and other prefrontal structures with reward receipt. The reward response network consisting of frontal and striatal structures, may show increased connectivity within the network early in depression, and diminished connectivity in children and adolescents, especially those who have experienced multiple depressive episodes<sup>87,89,90</sup>. This reward

network has been reported to be highly heritable, although reward function is also disrupted by early life trauma, particularly related to deprivation<sup>91</sup>.

Depressed adolescents show difficulty with top-down cognitive control of emotion (i.e., emotion regulation), and so are less effective at attenuating a negative emotional response to a distressing situation or probe. In response to such negatively-valenced probes, depressed children and adolescents show altered activation of fronto-cingulate, parietal, and subgenual and dorsal anterior cingulate cortical (ACC) regions<sup>87,92</sup>. The cognitive control network, comprised of these regions, most commonly shows increased connectivity. Early life stress, particularly involving impaired caregiving also is associated with these psychological and attendant neural alterations<sup>93</sup>. Conversely, the development of medial prefrontal cortex (PFC)-amygdala connectivity in adolescents exposed to adverse caregiver experiences may render them more resilient to depression, connectivity that may be facilitated by later positive interactions with caregivers<sup>94</sup>. PFC- amygdala connectivity appears to be primarily accounted for by environmental effects<sup>95</sup>.

Depressed individuals selectively attend to negatively-valenced stimuli that further reinforce depressive symptoms<sup>88</sup>. Accordingly, in response to negative emotional stimuli (e.g., social rejection), depressed adolescents demonstrate increased activation in the amygdala, supragenual ACC, and the orbitofrontal cortex (OFC). Greater connectivity within this affective circuitry, as well as in the broader salience network, which includes the above structures as well as the ventrolateral PFC is observed in young people with depression. Exposure to threat increase the likelihood of developing these cognitive biases<sup>91</sup>.

Depressed individuals show a tendency for self-referential thinking, manifested by rumination, frequent use of first-person pronouns, and alterations in autobiographical memory<sup>87</sup>. The circuitry that supports introspection and self-reflection, commonly referred to



as the default mode network, consists of the precuneus, posterior cingulate cortex, medial PFC, and the inferior parietal cortex.

These different circuits described above also show altered interrelationships in depressed adolescents. For example consistent with the view that depression is related to impaired top-down cognitive control of emotion, depressed adolescents show decreased connectivity between the cognitive control and affective networks<sup>87</sup>.

## **Prevention**

Preventive interventions can include the entire population (universal) or target sub-groups at high risk (selective) or individuals with sub-threshold depression (indicated). When considering the strength of evidence on prevention, it is important to acknowledge that this is heavily biased towards proximal targets, typically those which can be modified at the individual level, for example using cognitive behavioural principles, as it is more feasible to randomize these interventions.

*Individual level:* A number of universal interventions targeting social-emotional competencies and based on cognitive-behavioural principles have been delivered via the school system, such as the Penn Resilience Program in the USA<sup>96</sup>. Other interventions have been based on psychoeducation, mindfulness, interpersonal therapy (IPT)<sup>97</sup> and psychosocial support among others. A recent systematic review of all school-based universal interventions focused solely on preventing depression concluded little evidence that any are effective<sup>98</sup> including in low and middle income countries<sup>99</sup> and recommended multi-level, systems-based interventions in the future.

Indicated interventions also have typically comprised CBT principles or, in a few instances, IPT. Systematic reviews report small to moderate effects of such interventions in reducing subthreshold depression, corresponding to a number-needed-to-treat (NNT) of 8.4<sup>100</sup>. Meta-

analyses of school-delivered programmes find that effects are only observed in the short-term<sup>101,102</sup> and may not prevent future MDD. However one indicated CBT prevention programme delivered in health-care settings resulted in better adult functioning six years later suggesting delaying depression onset may have benefits<sup>40</sup>. Digitally delivered interventions potentially are more scalable but require better quality evaluation<sup>103</sup>; the rates of non-completion are high although engagement is greatly enhanced by coaching support. These interventions seem to be more effective in adolescents who exhibit lower substance use and whose parents do not have depression<sup>104</sup>.

Selective prevention targets individuals in high-risk groups, exposed to recognised depression risk factors<sup>105</sup>. Prevention programmes for offspring of depressed parents have been found to be effective although less so if the parent is currently depressed<sup>106</sup>. Evidence on the longer term benefits of these interventions is mixed<sup>105,107</sup>.

*Schools and community-level:* An alternative approach to preventing depression is to target systems, for example school climate, rather than the individual. Systematic reviews have shown that school based interventions have relatively small effects, but the evidence from low and middle-income countries is very limited<sup>98,99</sup>. One successful example is SEHER (Strengthening Evidence base on sChool-based intErventions for pRomoting adolescent health), a school based intervention with universal, group and targeted strategies; a trial in rural India demonstrated large reductions in depressive symptoms where the intervention was delivered by lay counsellors<sup>108,109</sup>. However, the same intervention when delivered by school staff was ineffective, a finding also observed in other trials<sup>110</sup>, suggesting the moderating role of the delivery agent. Another school-based intervention in the UK that targeted the social environment showed improvements in some outcomes but not depression<sup>111</sup>.

At the population level, interventions that target messaging which encourages skewed body image preferences, gender inequality and discrimination against certain groups (e.g. sexual minority adolescents), through appropriate legislation, public campaigns and peer support programs, may all contribute to reduced risk for depression. Similarly programmes that target early parenting and known risk factors such as bullying and income support, through cash transfers, to families and young people, may also contribute to reducing suicide and improving mental health<sup>112</sup>.

### **Screening, diagnostic assessment and measures**

**Screening:** Depression in adolescents is under-recognised<sup>113</sup>. Although routine screening has potential to improve identification, international guidelines differ, with American guidelines supporting universal screening for adolescent depression<sup>114</sup>, while both Canadian<sup>115</sup> and UK guidelines<sup>116</sup> view the extant data as not supportive of universal screening.

While specific screening instruments will be reviewed below, broadly, there is moderate sensitivity and specificity across measures but positive predictive values are poor, so a high proportion of those screening positive do not meet criteria for depression diagnosis. In resource scarce contexts, where clinical assessment of screen positives may not be possible, the threshold should be increased. In primary care, as depression is often missed, screening maybe useful if follow-up assessment is possible. Within specialist child and adolescent mental health services (CAMHS), depression screening tools perform similarly<sup>117</sup>, but false positives may be less problematic, as systems are in place to assess the young person further. In fact, NICE guidelines recommend screening young people  $\geq 11$  years referred to CAMHS without a diagnosis of depression<sup>116</sup>. Currently there is little evidence to support universal adolescent depression screening programs and it should only be implemented if there are systems in place for further assessment, diagnosis, and treatment.

Young people with depressive symptoms should be screened for current and recent suicidal ideation, suicide intent, and a history of previous suicidal behaviour; a safety plan for coping with suicidal thoughts should be developed with the patient and family. NICE guidance recommends that children and young people with suspected severe depression and at high risk of suicide are assessed by a CAMHS professional within a maximum of 24 hours of referral<sup>116</sup>.

**Diagnostic assessment:** The first key step is to establish a warm, trusting relationship with the young person that can require time and effort, especially if the young person has been reluctant to seek help. Dysphoria, sadness and short-lived depression (Figure 1) are common in adolescence,<sup>118,119</sup> and the majority of adolescents with these symptoms do not require referral to a mental health specialist. Current UK guidelines<sup>116</sup> suggest that healthcare professionals in primary care, schools and other community settings should be trained to detect symptoms of depression and assess those at risk. Referral from primary to secondary care CAMHS is indicated if the young person presents with severe depressive symptoms, complex symptomatology or comorbidity (e.g., mania, substance abuse, high suicidal risk), if symptoms or distress persist despite appropriate support, continued interference with functioning, or if the patient has indicators that make the likelihood of depressive onset high (e.g., personal or family history of depression)<sup>116,120</sup>.

It is helpful to gather information not just about specific depression symptoms (Figure 2), but also to ask for descriptions and contexts in which these symptoms impact daily functioning. Identifying the functional consequences of depression can aid in collaboration with the young person to identify what outcomes matter most to them and what they seek to change<sup>121</sup>. Caregiver report is vital to complement information gleaned from young people, especially younger adolescents, and liaison with schools is important when depression impacts school function.

Depression in adolescence and early adult life may increase the normative tendency for risk-taking to result in increased risk-taking behaviours and this further highlights the importance of assessing suicidal and other risks<sup>122</sup>. Irritability may be a more prominent feature of depression in adolescents than in adults. Recognising comorbidity among those with MDD (e.g., anxiety, ADHD) also is important as this is associated with worse depression outcomes and may require adjustments to the support or intervention package. Anxiety is the most common comorbidity, but disordered eating is increasingly common<sup>9</sup> and neurodevelopmental disorders (ADHD, ASD) are easily missed in females.

Differential diagnosis needs to include the consideration of whether depression is the initial presenting feature of another condition e.g., bipolar disorder or schizophrenia. While most young people with depression do not progress to these major mental disorders, careful assessment should be undertaken so that they are not missed; obtaining a family history can indicate risks of transition to these disorders and suggest a more cautious approach to treatment, monitoring and follow-up. Complex post-traumatic stress disorder (PTSD) also needs to be considered as a differential diagnosis due to overlapping symptoms and comorbidity with depression.

Finally, assessment and treatment require clinicians to characterise the social, family (including romantic partner), education or work contexts of the young person. Some guidelines also recommend profiling risk in community settings as well as in specialist settings<sup>116</sup>. Assessing quality of interpersonal relationships and support networks is especially important as is identifying risk exposures such as bullying, maltreatment, life events, a history of trauma and lifestyle factors and whether the young person belongs to a high-risk group (e.g. special educational needs, sexual or gender minority group, chronic physical illness). Identifying a young person's strengths and protective factors (e.g. family support) and investigating how the young person manages mood and suicidal urges

currently are also important for shaping the different components of a collaborative intervention package.

***Depression measures:*** Questionnaires can be used for screening, assessment of depression symptoms, and monitoring response to treatment. Some general questionnaires incorporate depression items, others specifically measure depression symptoms. When selecting a questionnaire to use, there are a number of considerations, including its psychometric properties, recommended age range, and practical issues such as the time taken to complete or cost. The most commonly used depression questionnaires for children and adolescents are summarised in table 1. Due to the large number of these measures, there have been recent efforts to streamline their use. The Revised Child Anxiety and Depression Scale (RCADS) has been recommended by the international consortium for health outcomes measurement (ICHOM)<sup>121</sup> for assessing depression symptom response to clinical care. The Mood and Feelings Questionnaire (MFQ) is another commonly used questionnaire with good psychometric properties and recommended for assessment and treatment monitoring of adolescent depression<sup>123</sup>. With regards to screening, the Patient Health Questionnaire-Adolescent (PHQ-A) and Beck's Depression Inventory (BDI) have been suggested as appropriate measures<sup>124</sup>. Although structured and semi-structured diagnostic interviews (e.g. Schedule for Affective Disorders and Schizophrenia for School-Aged Children, K-SADS Kiddie-S; Development and Wellbeing Assessment<sup>125</sup>, DAWBA<sup>126</sup>) are important research tools and can be helpful in some secondary care clinics (e.g. for diagnostic dilemmas), a flexible approach to history taking and mental state assessment (as described above) whilst including the rigour and detail of these instruments is generally preferred in routine practice.

## **Treatment**

**General approach:** Guidelines in many countries cover depression in children and adolescents up to age 18, and suggest a step-wise approach to treating depression and to avoid prescribing antidepressants alone<sup>116</sup>. As recommended by UK NICE<sup>116</sup>, for mild depression, support and psychoeducation include attending to lifestyle (e.g. sleep, diet, substance use) and may be sufficient, along with ongoing monitoring. Recognising and assessing the contribution of risk and traumatic exposures (e.g. dating violence) to distress also is an important first step. UK NICE<sup>116</sup> recommends watchful waiting of up to 4 weeks for those with mild depression. For those who do not spontaneously remit, referral for supportive and psychological interventions (see later) in the community (e.g. schools, tier 2 CAMHS) is indicated. The addition of exercise and behaviour activation to a person's daily routine may be helpful at all stages. More recently, single-session interventions for adolescents that focus on self-efficacy and a growth mindset have been shown to result in significant reductions in depressive symptoms<sup>127,128</sup> and could represent an important first step for treatment of mild depression in the community. Meta-analyses and individual trials from LMIC find that adaptations of extant and culturally adapted psychological and psychosocial interventions that focus on problem-solving<sup>129</sup> or positive human attributes (e.g. growth mindset, gratitude) including single session and lay-led group sessions<sup>130,131</sup> can effectively reduce depressive symptoms. For example, a recent RCT found that a lay-person delivered group intervention focused on teaching growth mindset, gratitude, and value affirmation for sixty minutes per week for four weeks reduced anxiety and depression in Kenyan adolescents for up to 7 months<sup>131</sup>. These studies highlight the potential effectiveness of low-cost interventions in LMIC where resources are scarce and also could be relevant to many HIC settings where resources are constrained.

Specialist care may be indicated for moderate- severe depression, those with comorbidity, or with suicidality. For moderate depression, treatment with an evidence-based psychotherapy is first indicated or combined treatment with medication. UK NICE guidance<sup>116</sup> suggests

there is little clear evidence to favour one psychotherapy over another. For chronic and/or severe depression a combination of medication and psychotherapy is indicated, after ruling out presence of bipolar disorder in the patient or first-degree relatives. If the young person does not improve within 4-6 weeks, one should first reassess to make sure that there are no other factors that could be contributing to the patient's clinical picture, such as peer victimization, poor sleep, problems from a comorbid condition like anxiety or ADHD, family conflict, same-sex attraction, and past or current trauma. If no psychosocial contributor to non-response is identified, for those receiving psychotherapy alone, combined treatment should be provided and for those receiving medication, it is reasonable to try an alternative psychotherapy and/or increase the dose of the antidepressant. If a young person does not respond to an adequate dose of medication and psychotherapy, it is reasonable to switch to another antidepressant. When faced with a partial response to an antidepressant plus psychotherapy, augmentation with another agent is a reasonable next step. The evidence on these interventions is considered next.

***Specific psychological therapies for depression:***

While head-to-head comparisons of CBT and IPT are few and equivocal, meta-analyses suggest that IPT has stronger effects than CBT relative to control interventions<sup>132,133</sup>. CBT that includes behaviour activation, and caregiver involvement as well as challenging cognitive distortions, has been found to be more effective than CBT that exclusively focuses on cognitive distortions. Greater severity of depression, history of maltreatment and the presence of non-suicidal self-injury decreases the likelihood of CBT response<sup>134,135</sup>. An initial "dose" of either IPT or CBT is 8-16 sessions delivered over 3-4 months. A recent meta-analysis<sup>136</sup> showed that online-delivered CBT effects on depressive symptoms with higher therapist involvement was more effective than in those with low involvement (Cohen's  $d=0.52$  vs.  $0.16$ ).

In a large, UK-based, pragmatic trial for adolescent depression, CBT was compared to a brief problem-solving intervention (BPI), and to short-term psychodynamic therapy. BPI



targeted behaviour activation, problem-solving, and interpersonal effectiveness. All three interventions resulted in a 50% decline in depressive symptoms, with no group differences; therefore, the brief problem-solving intervention was viewed as the most cost-effective<sup>137</sup>. Other promising interventions that have shown efficacy in single trials include a modification of Parent-Child Interaction Therapy, with an additional module on emotion regulation for depressed 3-7 year olds and Family-Focused Therapy for depressed pre-adolescents<sup>138,139</sup>.

***Modular and transdiagnostic approaches:*** A modular approach to treatment involves prioritizing and sequencing interventions to address what the parent and young person view as the most challenging mental health issues and has been shown to be effective in improving mental health. A trial using a modular approach to treatment conducted in schools showed improvements in functioning, anxiety, depression and behaviour problems compared to usual care, although attempts at replication have been equivocal<sup>140</sup>.

***Medication:*** Most treatment trials either span ages 18 to 65 or focus on those under age 18. Thus, there is much less known about the 18 to 24-year-old group specifically. For adolescents under the age of 18, recently-conducted network meta-analyses of clinical trials find that fluoxetine, either alone, or in combination with CBT is superior to pill placebo, and CBT; fluoxetine in combination with CBT was not superior to fluoxetine<sup>132</sup>. Venlafaxine showed the highest risk for suicidal events relative to pill placebo, whereas fluoxetine did not show a statistically significant elevation in suicidal events relative to pill placebo. There is modest evidence for efficacy in adolescent depression for escitalopram, sertraline, and duloxetine<sup>141</sup>. NICE guidelines<sup>116</sup> recommend against the use of paroxetine and venlafaxine.

While a higher dose of an antidepressant is not associated with a greater likelihood response in adults, this may not be the case in adolescents with treatment-resistant depression<sup>142</sup>. Maternal depression, greater symptom severity and sleep difficulties, are

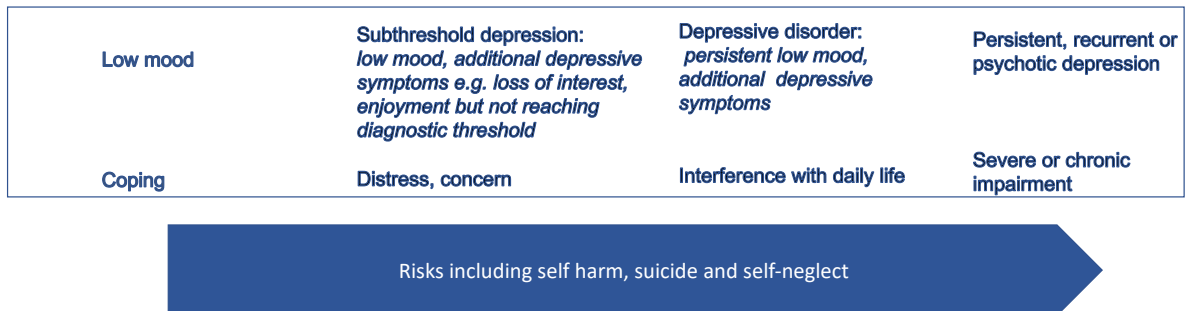
associated with a poorer response to antidepressant<sup>134,143</sup>. Continued treatment with antidepressant medication after recovery from depression for an additional 6 months results in a much lower rate of relapse and recurrence than treatment with placebo<sup>144</sup>. Addition of CBT to antidepressant has been observed to result in even more complete protection against relapse over the year<sup>145</sup>. Studies of treatment-resistant depression have shown that in adolescents who have not responded to an initial trial with a selective serotonin reuptake inhibitor (SSRI), a switch to another SSRI, with the addition of CBT results in the highest response rate, relative to a medication switch alone<sup>146</sup>. UK NICE guidance<sup>116</sup> suggests intensive psychological therapy with or without fluoxetine, sertraline, citalopram and augmentation with an antipsychotic. Ketamine shows promise in treatment-resistant depressed adolescents, but there are no large trials or long-term follow-up to document efficacy or longer term benefits or risks<sup>147</sup>. Although safe and well-tolerated, rapid trans-magnetic stimulation compared to a sham treatment is not superior for the relief of treatment resistant depression<sup>148</sup>. Although there are no clinical trials of electroconvulsive therapy (ECT) for adolescent depression, open data and clinical experience suggest that ECT is indicated for adolescents who have not responded to at least 3 antidepressant trials, especially in the face of psychotic depression, a history of mania, and/or psychomotor retardation.

## **Conclusion**

More than a decade has elapsed since the last Lancet seminar on adolescent depression and during this time, its prevalence has sharply increased, especially in females during late adolescence and early adult life. There is greater appreciation that research and clinical services are immensely hampered by rigid, aged 18 boundaries. This gap needs to be further addressed going forward and we welcome the growing interest in youth psychiatry<sup>149</sup>. Although there are multiple meta-analyses of risk factors, it is unknown why depression rates in young people have risen or what needs to be done to reduce population levels. That is a priority for the next generation of research. Prevention and early intervention are

important and appear more effective when targeted at the highest risk groups. How these interventions are best delivered remains a topic that requires more research and innovation. Moreover, more distal public health strategies also require evaluation even if RCTs are not possible. Although treatment recommendations are not radically different to a decade ago, a broader set of psychological and behavioural interventions now are available to the clinician. However, there are remarkably few new treatment trials to guide clinicians managing more severe forms of depression. Finally, depression is highly heterogeneous, more so in young people, and spans a spectrum of severity. Going forward, neuroscience and genetics discoveries coupled with social and clinical data could be utilised to personalize treatment and improve outcomes.

**Figure 1 The spectrum of depression**



**Figure 2**

**Core clinical symptoms of major depressive disorder<sup>150</sup>**

- Depressed mood or for children and adolescents- irritable mood
- Diminished interest or pleasure
- Significant weight loss/gain or decrease/increase in appetite\*
- Insomnia or hypersomnia\*
- Psychomotor agitation or retardation
- Loss of energy or fatigue\*
- Feelings of excessive/inappropriate guilt or worthlessness
- Loss of concentration, reduced ability to think or indecisiveness
- Recurrent thoughts of death, suicidal ideas or suicide attempt

\*symptoms that were found to be more common in adolescents than adults with depression in a two generation study



### Figure/Panel 3

#### Defining age groups<sup>2</sup>

Childhood: <10 years

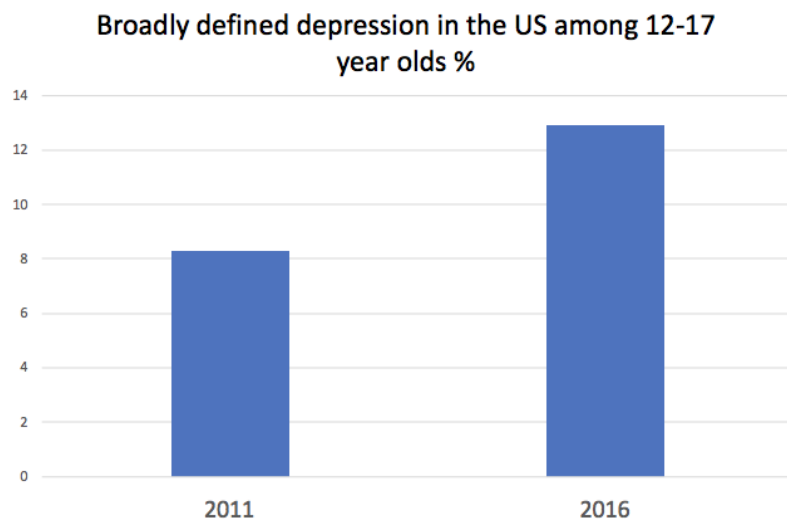
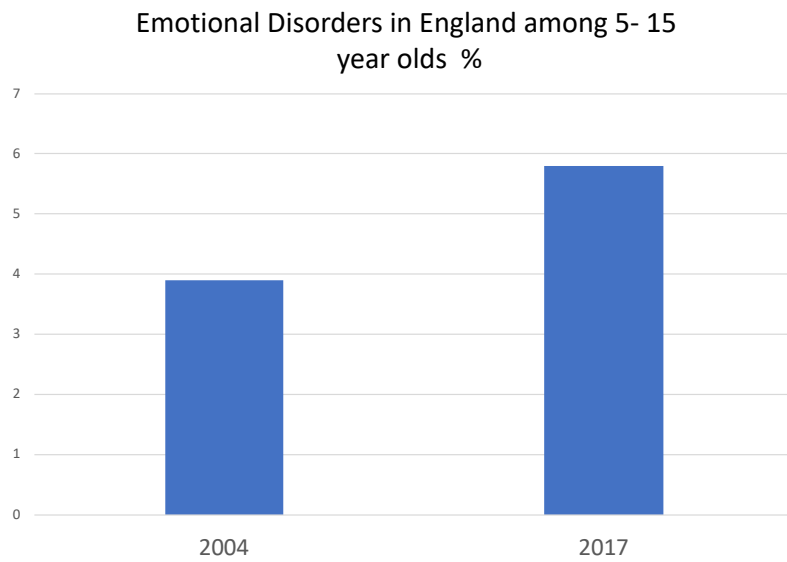
Adolescence: 10- 19 years

Youth: 15–24 years

“Young people” or “adolescents and young adults”: 10–24 years

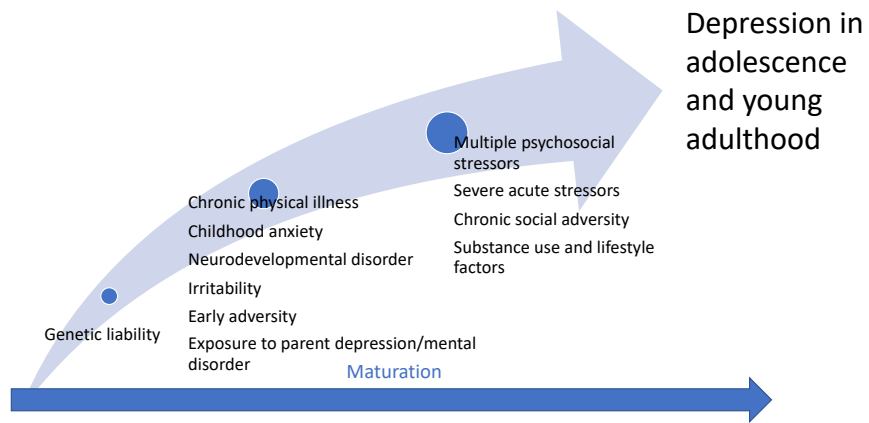
Age 18: the legal age of adulthood in many countries and a common age boundary for inclusion and exclusion from services and research for children and adolescents vs. adults  
e.g. treatment trials

**Figure 4 Increased rates of emotional disorders and depression over time in two countries<sup>8,151</sup>**





**Figure 5. Aetiology and Development**



**Table 1 Questionnaires commonly used to measure depression symptoms in young people**

Questionnaire measure	Summary: age, rater, scale, time taken, related scales, recommended?	Reliability and Validity	Cut off, Sensitivity, Specificity, PPV, NPV, AUC	Free?
<b>Beck's Depression Inventory (BDI)</b>	Developed as a depression symptom rating scale for adults, now widely used in adolescents <sup>117</sup> . <b>Age:</b> 13-80 <b>Rater:</b> Self report <b>Scale:</b> 21 items, scoring 0-3, range 0-63 <b>Time:</b> 10 minutes to complete <b>Related scales:</b> BDI-Y (part of Beck Youth Inventory), BDI-PC (for primary care) <b>Recommended</b> for adolescent depression screening by US Task Force <sup>124</sup> .	<b>Reliability:</b> Internal consistency: Clinical samples: $\alpha=0.79-0.94$ ; non-clinical samples: $\alpha=0.82-0.90$ ; Pooled: $\alpha=0.86$ <sup>117</sup>	<b>Cut off:</b> Optimal cut offs vary across samples. Range from $\geq 11$ to 24 <sup>117,152</sup> <b>Sensitivity:</b> 84-100; <b>Specificity:</b> 81-97; <b>PPV:</b> 10-86; <b>NPV:</b> 98-100 <sup>152</sup> <i>Sensitivity and specificity similar across clinical and non-clinical samples, but PPV higher overall in clinical samples</i> <sup>117</sup> <b>AUC:</b> 0.92 <sup>117</sup> .	No
<b>Center for Epidemiological Studies Depression Scale (CES-D)</b> <sup>153</sup>	Designed to detect depression in adults in the general population, but suitable for use in adolescents. <b>Rater:</b> Self report <b>Scale:</b> 20 items, scoring 0-3, range 0-60 <b>Related scales:</b> CES-DC (child version)	<b>Reliability:</b> Internal consistency: $\alpha=0.88$ . Clinical samples: $\alpha=0.83-0.84$ ; Non-clinical samples: $\alpha=0.81-0.93$ <sup>117</sup>	<b>Cut off:</b> Optimal cut offs vary across samples. Range from 12 to 24 <sup>117,152</sup> . Cut off 16 suggested for moderate depression <sup>123</sup> <b>Sensitivity:</b> 70-84; <b>Specificity:</b> 45-75, <b>PPV:</b> 8-21 <b>NPV:</b> 88-99 <sup>152</sup> <b>AUC:</b> 0.83 <sup>117</sup>	Yes
<b>Children's Depression Inventory (CDI)</b> <sup>117,154,155</sup>	Originated from Beck Depression Inventory (BDI), for use in children. <b>Age:</b> 7-18 <b>Rater:</b> self, parent, teacher <b>Scale:</b> 27 items, scoring 0-2, range 0-54 <b>Time:</b> 15 minutes to complete <b>Related scales:</b> CDI-2	<b>Reliability:</b> Internal consistency: $\alpha=0.86$ <b>Validity:</b> High predictive, convergent and construct validity	<b>Cut off:</b> Optimal cut offs vary across samples. Range from 11-19. Suggested cut off $>20$ . <b>Sensitivity:</b> 83; <b>Specificity:</b> 84; <b>PPV:</b> 21-90; <b>NPV:</b> 63-100). <b>AUC:</b> 0.83	No

<b>Mood and Feelings Questionnaire (MFQ)</b> <sup>156</sup>	Designed to assess depression symptoms in children and adolescents. <b>Age:</b> 8-18 <b>Rater:</b> self and parent <b>Scale:</b> 33 items (parent report- 34 items), scoring 0-2, range= 0-66. <b>Time:</b> 10 minutes <b>Related scales:</b> short Mood and Feelings Questionnaire (sMFQ) <b>Recommended</b> to monitor clinical progress NICE guidance on Depression in Children and Young People <sup>116</sup>	<b>Reliability (self-report):</b> Internal consistency: $\alpha = 0.94$ <sup>157</sup> ; Test-retest reliability: high <b>Validity (self-report):</b> Good content and criterion validity <sup>158</sup>	<b>Cut off:</b> Optimal cut points vary across samples: $\geq 28$ <sup>159</sup> to $\geq 29$ <sup>160</sup> for self-report and $\geq 27$ for parent report. <b>Sensitivity:</b> 68-84; <b>Specificity:</b> 70-85; <b>PPV:</b> 75.9; <b>NPV:</b> 84.4 <sup>157,159,160</sup> <b>AUC:</b> 0.82 (self), 0.69 (parent) <sup>157</sup>	Yes
<b>Patient Health Questionnaire-9 (PHQ-9)</b> <sup>161</sup>	Developed as a screening questionnaire for adults in primary care but also shown to be a good screening tool in adolescents <sup>162</sup> <b>Rater:</b> self <b>Scale:</b> 9 items, scoring 0-3, range 0-27. <b>Related scales:</b> PHQ-2, PHQ-A <sup>161</sup> (PHQ-A recommended by US Preventative Services Task Force to screen depression in adolescents aged 12-18	<b>Reliability (In adults):</b> Internal consistency: $\alpha = 0.86-0.89$ . Test re-test reliability: excellent <sup>161</sup>  <b>Validity (in adults):</b> good criterion and construct validity <sup>161</sup>	<b>Cut off:</b> Optimal cut points vary across samples. Range from $\geq 5$ to $\geq 15$ <sup>152</sup> Cut off of 10 often used in adults, Recommended cut off of 11 in adolescents <sup>152</sup> . <b>Sensitivity:</b> 72-89; <b>Specificity:</b> 78-95; <b>PPV:</b> 15-65; <b>NPV:</b> 97-99 <sup>152</sup>  <b>AUC:</b> 0.88 <sup>152</sup>	Yes
<b>Reynolds Adolescent Depression Scale (RADS)</b> <sup>163</sup>	Developed to assess depression symptom severity in adolescents. <b>Age:</b> 13-18 years <b>Scale:</b> 30 items, scoring 1-4, range 30-120 <b>Rater:</b> Self report <b>Time:</b> 10 minutes <b>Related Scales:</b> RADS-2	<b>Reliability:</b> Internal consistency: $\alpha = 0.93$ <sup>117</sup>	<b>Cut off:</b> A cut off of 77 suggested <sup>123</sup>	No
<b>Revised Child Anxiety and Depression Scale (RCADS)</b> <sup>164</sup>	For measurement of anxiety and depression symptoms in young people. <b>Age:</b> 8-18	<b>Reliability:</b> Internal consistency of depression subscale: $\alpha = 0.82$ <sup>165</sup>	<b>Cut off:</b> A t-score for the appropriate grade level is calculated from a raw score.	Yes

	<p><b>Scale:</b> 47 items, grouped into 6 subscales. 1 subscale measures depression symptom (10 items), each item rated 0-4.</p> <p><b>Rater:</b> Self and parent</p> <p><b>Time:</b> 5-10 minutes</p> <p><b>Related scales:</b> RCADS-25 and RCADS-25-P</p> <p><b>Recommended</b> for use in research relating to young people with depression and anxiety (Wellcome and NIMH) and for assessing depression symptoms in response to clinical care (international consortium for health outcomes measurement)<sup>49</sup></p>	<p><b>Validity:</b> Good convergent and concurrent validity<sup>164</sup>.</p>	<p>Clinical threshold is top 2% of scores (t-score of <math>\geq 70</math>).</p>	
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PPV= Positive Predictive Value; NPV=Negative Predictive Value; AUC= Area Under Curve.

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