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The Long-Term Outcomes of Prepubertal Depression and Internalizing Problems: A Scoping Review

Adam Sands, MD, MPH,
Department of Psychiatry, Vagelos College of Physicians and Surgeons, Columbia University

New York-Presbyterian Hospital/Columbia University Medical Center, New York, NY

Milenna T. van Dijk, PhD,
Department of Psychiatry, Vagelos College of Physicians and Surgeons, Columbia University

Division of Translational Epidemiology, New York State Psychiatric Institute, New York, NY

Eyal Abraham, PhD,
Department of Psychiatry, Vagelos College of Physicians and Surgeons, Columbia University

Division of Translational Epidemiology, New York State Psychiatric Institute, New York, NY

Tenzin Yangchen, MA,
Division of Translational Epidemiology, New York State Psychiatric Institute, New York, NY

Ardesheer Talati, PhD,
Department of Psychiatry, Vagelos College of Physicians and Surgeons, Columbia University

Division of Translational Epidemiology, New York State Psychiatric Institute, New York, NY

Myrna M. Weissman, PhD
Department of Psychiatry, Vagelos College of Physicians and Surgeons, Columbia University

Division of Translational Epidemiology, New York State Psychiatric Institute, New York, NY

Abstract

Learning objectives: After participating in this activity, learners should be better able to:

• Discuss whether prepubertal depression shows longitudinal continuity with depression in adulthood.

• Summarize existing literature on adult emotional and functional outcomes of prepubertal depression and internalizing problems.

Correspondence: Myrna M. Weissman, PhD, Columbia University Vagelos College of Physicians and Surgeons, Mailman School of Public Health, Division of Translational Epidemiology, New York State Psychiatric Institute, 1051 Riverside Dr. Unit 24, New York, NY 10032. myrna.weissman@nyspi.columbia.edu.

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Background: Adolescent- and young adult–onset depression are common, recurrent, and can cause significant distress and psychosocial impairment across the life span, but recognition of prepubertal internalizing problems and depression, along with their prevalence, clinical course, and long-term outcomes, remains elusive.

Objective: To examine whether prepubertal depression, which can manifest differently from adult depression, shows longitudinal continuity with depression in adulthood, and to summarize existing literature on adult emotional and functional outcomes of prepubertal depression and internalizing problems.

Methods: A scoping review was conducted for peer-reviewed cohort articles published between 2000 and 2020 using PubMed and PsycINFO. From 4309 identified references, 17 articles were included.

Results: Prepubertal depression confers increased risk of recurrence of depression in adulthood, with similar findings for prepubertal internalizing problems. No studies found prepubertal depression or internalizing problems predicting adult substance abuse, and no studies asked about adult bipolar diagnoses. More research is needed to draw clear conclusions regarding their implications for other psychiatric, medical, or psychosocial outcomes.

Conclusion: The reviewed studies provide limited evidence that prepubertal depression onset predicts adult depression. The small evidence base and heterogeneous methodological assessments may limit, however, the ability to draw meaningful conclusions about the long-term course of prepubertal-onset depression. Well-designed studies with longer follow-up and multiple assessments in adulthood are needed to clarify and assess the potential effects of prepubertal depression on adult health and functioning. This information will eventually become available as the samples in recently initiated longitudinal cohort studies of children mature further.

Keywords

adult outcomes; childhood-onset; depression; internalizing problems; prepubertal children

INTRODUCTION

For many years there was doubt among researchers and clinicians as to whether prepubertal depression constituted a true clinical syndrome,[1] but it is now understood that depression can manifest even in children as young as three years old.[2] While pediatric depression may present with the typical symptoms listed in the *Diagnostic and Statistical Manual for Mental Disorders* (DSM) criteria, frequently it can be characterized by other symptoms, including irritable mood, impulsivity, crying or shouting outbursts, low self-esteem, difficulty verbalizing feelings, changes in play behaviors, and somatic complaints.[3] Mood reactivity may also be more common in children.[4] It is therefore not surprising that prepubertal depression may be clinically underdiagnosed[3] and undertreated.[3,5] Even so, when DSM criteria are used in population surveys, the prevalence is as high as 2%–5% in children aged 6 to 12 years.[6]

In addition to these diagnostic limitations, when studying prepubertal depression it is common to use dimensional measures of childhood psychopathology, such as

internalizing problems (i.e., symptoms of depression, anxiety, social withdrawal, and somatic complaints), given that relying solely on dichotomous categorical classifications may obscure important “sub-threshold” childhood behavioral patterns that nevertheless predict later outcomes.[7,8] It is therefore not surprising that the frequency of clinically significant depressive symptoms before puberty and their long-term course are not entirely understood, although studies have shown that if major depressive disorder (MDD) emerges with prepubertal onset, it is predominantly in the offspring of depressed parents.[9] However, the question remains, is prepubertal depression the early onset of a chronic disorder that continues into adulthood, or does it have a distinct course and set of outcomes? It is useful to understand the long-term outcomes of prepubertal depressive symptoms in order to plan early interventions to mitigate their repercussions on morbidity and mortality across the lifespan.

This scoping review was conducted to learn whether prepubertal depression predicts adult depression or other psychiatric disorders, or if it tends to occur without substantial impact on adult health and functioning. Prospective, longitudinal studies that follow depressed prepubertal children into adulthood have the potential to answer this question. A number of reviews have examined prospective data on the adult outcomes of adolescent depression,[10–12] but the same cannot be said for prepubertal depression. A review by Birmaher and colleagues (2002)[13] found evidence that depression in childhood can predict a (statistically) significant increase in morbidity and mortality, including an increased risk for adolescent depression, suicide, substance use, and psychosocial impairment. This review found few studies, however, that followed children into adulthood, with mixed evidence for a direct association between childhood-onset and adulthood depressive disorders.[13] A 2013 review that reported on childhood and adolescent risk factors for adult psychiatric disorders found that childhood/adolescent depression and internalizing symptoms did increase risk of later psychiatric illness, including adult depression, but it included little discussion of whether prepubertal depression has a long-term course distinct from adolescent depression.[14] Also, the authors did not investigate psychosocial or medical outcomes, and other reviews of psychiatric and psychosocial outcomes have almost exclusively focused on studies of adolescent depression.[14] Meanwhile, no reviews were found that specifically examine the impact of prepubertal depression on adult medical or psychosocial outcomes. The current review seeks to fill this gap in the literature by providing an overview and assessment of recent prospective investigations into the adult outcomes of prepubertal depression and internalizing problems.

Therefore, this scoping review describes recent prospective research on the extent to which prepubertal depression occurring before age 13 may predict adulthood (18 years or older) psychopathology, including the following: depression, anxiety disorders, and substance use; psychosocial functioning; and the development of non-psychiatric medical conditions. For practical purposes, age 13 was used as the cutoff to distinguish prepubescence from adolescence, as few studies in this area report on whether participants have entered biological puberty. Pubertal timing varies significantly by sex and ethnicity. Still, it has been estimated that among North American children, 95% of girls enter the earliest stage of puberty by age 12–13, and boys by age 13–14.[15] Additionally, given that studies of prepubertal depression frequently use dimensional measures of childhood

psychopathology, studies that examined childhood internalizing problems or that utilized continuous depression symptom scales were included alongside those that made formal diagnoses of MDD. It was also important to include studies that investigated internalizing problems because many earlier models of childhood psychopathology often did not make specific diagnostic distinctions between childhood mood and anxiety symptoms.

METHODS

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Review Guideline (PRISMA-ScR).[16] Supplemental Figure 1, http://links.lww.com/HRP/A197, presents the process of searching and selecting the studies.

Selection Criteria

To be eligible for inclusion, articles had to report findings from prospective observational studies that investigated the association of prepubertal depression or internalizing problems with adulthood depressive disorders, suicidality, substance use, non-psychiatric medical illness, or psychosocial functioning. Bipolar disorder and anxiety disorder outcomes were also recorded if they were investigated alongside the aforementioned outcomes. Studies had to include at least one assessment of psychopathology at <13 years of age and at least one repeat assessment of a relevant outcome at ≥18 years of age. Depression was defined according to the diagnostic criteria of DSM-III or later, or *International Statistical Classification of Diseases and Related Health Problems* (ICD) ninth edition or later. Studies had to employ validated, age-appropriate measures of depression, depressive symptoms, or internalizing symptoms, including diagnostic interviews or self/informant-report scales. The comparator was defined as children who did not meet the criteria for depression or did not display notable internalizing problems. Articles were excluded if (1) assessments conducted in childhood and adolescence were grouped together in the analyses; (2) assessments of adulthood depression could include adolescent-onset illness, such as with instruments that measure “lifetime” diagnoses; (3) the study was a follow-up of an intervention study in which the intervention effect was a primary outcome or membership in the intervention group was not controlled for in the relevant analyses. Additionally, when multiple eligible studies used data from the same cohort to examine similar outcomes, only the most recent study was included. Among the outcomes of interest were the following: adult internalizing psychopathology, including depressive and anxiety disorders; substance use; psychosocial outcomes; and non-psychiatric medical outcomes. If articles that examined the aforementioned outcomes also investigated other adult psychiatric illnesses, these findings were also recorded.

Only articles published in peer-reviewed journals, in English, published in 2000 or thereafter, were included. This time range was chosen because the first longitudinal, epidemiologic studies using clinical criteria for psychiatric diagnoses were published in 1984.[17,18] Consequently, many of the participants in these studies only reached adulthood around the year 2000 or later, and it was decided to limit the literature search to this time frame.

Search Strategy and Study Selection

A systematic literature search was conducted for studies published between 1 January 2000 and 1 November 2019 in two electronic databases: PubMed and PsycINFO. With the assistance of a research librarian, a search strategy was formulated first for PubMed using a combination of MeSH terms and keywords (see Supplemental Appendix, http://links.lww.com/HRP/A198), which was then adapted for PsycINFO. Reference lists of selected studies were then searched to identify potentially relevant articles.

The initial search yielded a total of 4309 articles (see Supplemental Figure 1, http://links.lww.com/HRP/A197). After deduplication, the abstracts of all studies were screened based on study type, population, defining variables, and outcomes. For the 456 articles not excluded in the abstract-screening phase, the full text was retrieved and reviewed for eligibility against the inclusion criteria. After narrowing the inclusion criteria as described previously, 17 articles were selected for inclusion. Abstract and full-text screening was conducted using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia).

Data Extraction and Study Quality

Data extraction and quality assessment of studies eligible for inclusion were conducted using DistillerSR (Evidence Partners, Ottawa, Canada). A data extraction template was used for all studies that included the following: authors, title, year of publication, study setting, cohort type, cohort name (if applicable), country, eligible and analysis sample sizes, percentage of female participants, age at childhood assessments, age at adult assessments, defining variable and method of assessment, outcome and method of assessment, prevalence of depression or notable internalizing problems at baseline, prevalence of depression at adult follow-up, measures of association, and covariates. The quality of included studies was assessed using the Newcastle-Ottawa Scale,[19] a tool that uses a star rating system to indicate the risk of bias of nonrandomized studies in three categories: selection of the exposed and unexposed samples, comparability of the groups, and assessment of outcome. A total of nine stars can be assigned indicating low risk of bias, with a maximum of four, two, and three stars assigned for selection, comparability, and outcome, respectively. Newcastle-Ottawa Scale scores of 1–3, 4–6, and 7–9 were defined as corresponding to low, moderate, and high methodological quality.

RESULTS

Cohort Characteristics

The 17 articles reviewed were drawn from studies of 12 unique cohorts, including 5 articles from the same birth cohort in Finland (From a Boy to a Man cohort), and 2 from the same birth cohort in the United Kingdom (1958 British Birth Cohort); the remaining 10 articles each examined a different cohort (see Supplemental Table 1, http://links.lww.com/HRP/A200). The 12 cohorts (overall) were drawn from eight different countries: Australia (1), Canada (1), Finland (1), Germany (1), New Zealand (1), Spain (1), United Kingdom (1), and United States (5). Four (33%) were birth cohorts, 3 (25%) were school-based cohorts, 2 (17%) were community cohorts, 2 (17%) were family cohorts, and one (8%) was a high-risk

birth cohort. Sample sizes ranged from 168 to 8289, with a mean of 2524 (median = 1642; SD = 2815). Among the distinct cohorts, age at entry ranged from 4.5 to 12 years, and age at follow-up ranged from 18 to 45 years, although in most studies participants were under 25 years old, with only 5 studies assessing participants at later ages.[20,23,24,32,33]

Defining and Outcome Variables

The articles varied considerably in how similar defining and outcome variables were measured (see Table 1), but overall, 12 (70%) measured depression diagnoses or symptoms as a defining variable, 9 (57%) assessed internalizing problems, and 4 derived from the From a Boy to a Man cohort measured both internalizing and depressive symptoms.[17,25–27] Regarding outcomes, 5 assessed for depressive disorders, 2 others measured depressive symptoms without assigning a DSM- or ICD-based diagnosis, 3 assessed for anxiety disorders, 3 assessed for substance use disorder, and one assessed for insomnia. For non-psychiatric medical outcomes, 2 studies assessed tobacco use, 2 measured body mass index, and one examined a range of chronic medical conditions. For psychosocial outcomes, one study examined job characteristics, and another examined release from mandatory military service (see Supplemental Table 1, http://links.lww.com/HRP/A200).

Clinical Findings

The measures and selected findings from the reviewed studies can be found in Table 1.

Prepubertal Depression or Depressive Symptoms

Two studies conducted semistructured interviews for childhood depressive disorders based on DSM criteria,[20,28] and another used a structured interview, the Short Depression Interview, which is not diagnostic but identifies participants as having depression with medium or high certainty.[32] Four studies used self-report,[21,22,29,31] and one used teacher-report,[30] measures. Three studies used the Children's Depression Inventory,[21,22,31] one of which used a cutoff score to distinguish children with "significant" depressive symptoms.[22] The other two studies used the Child Behavior Checklist[30] and the Dimensions of Depression Profile for Children and Adolescents.[29]

Of the two studies that conducted diagnostic interviews in childhood, one study found that childhood MDD significantly predicted adult MDD when participants were assessed at ages >25 years but not from ages 20–25.[20] The other study, which was substantially larger (although with a higher attrition rate), did not find a significant association between childhood depressive disorders, including MDD, dysthymia, and depressive disorder not otherwise specified, and adulthood depressive disorders; likewise, there were no associations with adulthood agoraphobia or substance use disorders.[28] However, there was a significant association with adulthood generalized anxiety disorder and panic disorder.

Among the studies that used self- or teacher-report measures of childhood depressive symptoms, four out of five found significant positive associations with adulthood depressive symptoms.[17,21,22,29,30] Canals and colleagues (2002),[21] however, found a significant association between girls' depressive symptoms and any ICD-10 depressive disorder only at age 11 but not for girls' symptoms measured at age 12 or when the outcome included only

major depressive episodes and dysthymia, and analyses were not adjusted for covariates. Only one of five studies examined other psychiatric outcomes, but associations with ICD-10 anxiety disorders and substance use disorders did not remain significant after covariate adjustment, including the Children's Depression Inventory score.[17]

In the two studies that assessed adult body mass index as the primary outcome, only one found a significant, positive association with prepubertal depression in the adjusted analysis.[31,32] Of note, the study which found a positive association was much larger, although it also had a higher rate of attrition. One study found an association between adult asthma diagnosis and prepubertal depressive symptoms,[27] while another found an association with both "moderate" and "heavy smoking" in adulthood.[26]

Childhood Internalizing Problems

A total of nine studies assessed internalizing problems in childhood. Several different self- or parent/teacher-report measures were used across cohorts, including the Rutter parent and teacher scales,[17,25,26,33] a modified Child Behavior Checklist,[35] and the Bristol Social Adjustment Guide,[23,24] a survey that draws on self, parent, and teacher reports. One study used a structured interview, the Mannheim Parent Interview.[34] Two studies using the Rutter scales[25,27] and the two studies using the Bristol Social Adjustment Guide[23,24] used a cutoff score for identifying children with substantial internalizing problems.

One of two studies found significant associations between childhood internalizing problems and adult depressive disorder diagnosed based on ICD-10 criteria in adjusted analyses.[17,23] In Clark and colleagues (2007),[23] having internalizing problems at either age 7 or age 11 was associated with higher risk of adult depression after covariate adjustment. Additionally, Clark and colleagues found that significant internalizing at age 7 predicted generalized anxiety disorder (GAD), while Sourander and colleagues (2005)[17] found that, after controlling for covariates, parent-rated internalizing problems predicted having any anxiety disorder but that teacher-rated scores did not. Of note, Clark and colleagues[23] examined a much larger sample than Sourander and colleagues,[17] and included both girls and boys in the analysis, as opposed to the all-male sample used by Sourander and colleagues.

Neither of the two studies assessing illicit substance use in adulthood found significant associations in adjusted analyses.[17,34] Two studies assessed adult tobacco use, with mixed findings.[26,35] Niemela and colleagues (2009)[26] found significant associations between teacher-reported internalizing problems and smoking frequency, whereas Fischer and colleagues (2012)[35] did not find such an association with either self-reported or interviewer-assessed tobacco use.

DISCUSSION

This review summarizes the findings of 17 prospective studies (12 unique cohorts) that investigated the association of prepubertal depression and internalizing problems with adult psychiatric, medical, or psychosocial outcomes. Overall, the reviewed studies provide limited evidence that prepubertal depression confers an increased risk of recurrence of depression in adulthood. There was more scarce and mixed evidence for internalizing

problems as a predictor of depression, although it should be noted that the study that identified a significant association utilized a much larger sample size and included participants of both sexes, in contrast to the study with nonsignificant findings.[17,23] Certain other findings are also notable. For instance, Wickramaratne and colleagues (2000)[20] found that a parental history of MDD was associated with continuity of prepubertal-onset MDD into adulthood, and in this group the risk of MDD recurrence was greater for females than for males.[20] Likewise, Canals and colleagues[21] found that only females with prepubertal depression had a significantly increased risk of adult recurrence.[21] Unfortunately, no studies examined adult psychiatric outcomes of subjects with depressive symptoms under the age of 7, and subjects in early-middle childhood (age 6–8) and late-middle childhood (ages 9–12) were grouped together. Therefore, no conclusions can be drawn regarding whether depression occurring at different developmental stages confers varying degrees of risk. Regarding prepubertal internalizing problems, there was stronger evidence that internalizing predicted adult GAD, which is unsurprising given that internalizing problems encompass depressive, anxious, and somatic symptoms. In contrast to the literature on adolescent depression,[12] no studies found evidence that either depression or internalizing problems in prepubescence predict adult substance use disorders, although few studies actually examined this outcome.

Regarding medical outcomes, only two pairs of studies can be directly compared to each other based on similar defining and outcome variables, although again, the high degree of variability in how these were measured and the inconsistent results prevent drawing conclusions.[26,31,32,35] Two studies found weak evidence for an association between prepubertal depression and higher adult body mass index,[31,32] while two others found mixed evidence for childhood depressive symptoms as a predictor of adult nicotine use.[26,35] As for psychosocial outcomes, only two studies were found, each examining very different outcomes. Thus, considerably more research is needed before any patterns can emerge.[24,25]

The available data suggest that prepubertal depression and internalizing problems may indeed be predictors of depression in adulthood. The evidence is limited, however, and stands in contrast to the larger body of literature on adolescent-onset depression, which consistently shows increased risk of adult depression as well as adult anxiety disorders, psychosocial outcomes such as unemployment and failure to complete secondary school, and higher rates of substance use.[10–12] At this time, it is unclear whether prepubertal depression/internalizing problems have weaker or more circumscribed effects on later outcomes relative to adolescent-onset depression. If so, it would suggest that adolescent-onset and prepubertal depression are different constructs or at least that the time of onset plays a critical role in the overall course of the illness. Further research is needed to clarify the possible associations, suggested by the above findings, between prepubertal depression/internalizing problems and later outcomes.

This review found certain limitations in the existing body of literature that complicate the task of identifying clear associations, including (1) few studies investigated each particular outcome of interest, (2) substantial differences in how variables were measured, (3) not controlling for important covariates, such as childhood comorbidities, and (4) a short duration of follow-up and lack of assessments at multiple time points in adulthood.

The heterogeneity of the methods used in these studies hinders the ability to draw conclusions from the findings. As an example, among the seven studies that examined the association between prepubertal depression and adult psychiatric outcomes, five different measures of childhood symptoms and seven different measures of the outcomes were used. Additionally, some studies used rating-scale cutoff scores to identify participants with notable childhood symptoms, whereas others did not. No clear patterns emerged when comparing the minority of studies that used cutoffs versus those that did not, although the value of using rating-scale cutoffs to identify individuals with clinically significant symptoms is in question.[36–38] An additional limitation of the data is that only two studies of prepubertal depression used semistructured diagnostic interviews,[20,28] and only one of them was blinded.[20] While these studies had sample sizes in the hundreds, as opposed to thousands of participants in many of the studies that employed rating scales, semistructured interview instruments allow formal diagnoses to be made, which rating scales typically do not, and they generally have greater discriminant validity than rating scales.[39] It should be noted, however, that, as previously mentioned, many of the studies that used rating scales conducted analyses using continuous scores, which generally have greater reliability and validity than when scores are interpreted using cutoffs.[38] Some of the available evidence suggests, moreover, that depression may be more accurately viewed as a dimensional construct[40,41] and that this conceptualization may better predict outcomes,[37,42] possibly because it can identify associations with “subthreshold” yet clinically significant prepubertal depressive symptoms that may be missed by a categorical approach to measurement.[4,9] In this context it is interesting to note that while only one of the two studies that used diagnostic interviews in childhood found a significant association with adult depression, three of the four studies that measured prepubertal depressive symptoms on a continuous scale found a significant association; additionally, the study that did not find a significant association used teacher-reported ratings of depressive symptoms, as opposed to the others, which used self-report. These results lend support to the idea that using dimensional measures of pathology can reveal meaningful associations that may be obscured by a more restrictive, categorical approach. Overall, more studies of both types are needed: ones that employ semistructured interviews, which may be necessarily smaller but utilize the current “gold standard” assessment tools, and studies that use rating scales as continuous measures, which can be conducted on a larger scale and can provide valuable insight into how depression may predict later outcomes when considered as a dimensional construct.

Most of the reviewed studies did not control for other psychiatric diagnoses in prepubescence, and it is unclear whether the results were influenced by the presence of undetected comorbidities in childhood that independently affected the risk of specific outcomes later in life. For instance, in the studies of prepubertal depression reviewed here, only two controlled for other childhood psychiatric disorders, and one of these showed that co-occurring anxiety disorders in childhood accounted for the increased risk of adult depression observed in children with prepubertal depression.[28,31] This uncertainty, a potentially significant obstacle in the interpretation of results, is a factor that should be examined in future studies whenever possible. On a related note, it may be helpful for future studies to clarify whether specific depressive or internalizing symptoms have particular predictive value for later outcomes, especially in studies of internalizing problems, in which

measures of anxiety and depressive symptoms are typically combined into a single anxiety/depression domain.

Finally, since most of the reviewed studies followed participants only until relatively early in adulthood, it is unclear how distally the effects of prepubertal depression or internalizing problems may be felt. Regarding psychiatric outcomes, the small number of studies examining older adults that were identified may be a consequence of the methodology of this review, which excluded studies that assessed for "lifetime" psychiatric diagnoses; the studies that were included assessed only for current or recent—for example, past year's depression—and all did so at only a single time point in adulthood. It is therefore possible, and even likely, that episodes of psychiatric illness at other points in participants' lives were missed. More studies that assess participants at multiple points across the lifespan are needed to better elucidate how prepubertal depression may affect health and functioning in adulthood.

In addition to these methodological limitations, it is also important to acknowledge the challenges associated with diagnosing affective disorders in prepubertal children.[3,4,9] It is necessary to further identify the clinical features and course of prepubertal depression, and to develop more accurate diagnostic tools. Symptoms of prepubertal depression vary across time, and they may be dismissed as normal or expected emotional and psychological changes. Similarly, due to phenotypic differences in depression among young children compared to adults, standard DSM diagnostic criteria may fail to identify children experiencing clinically significant symptoms. This was demonstrated in Luby and colleagues (2003),[9] which used modified DSM criteria to identify preschool children who were experiencing notable depressive symptoms but did not fully meet standard diagnostic criteria.[9] Additionally, certain symptoms such as hopelessness and sadness can commonly manifest as irritability, acting out, or poor school performance. Consequently, many prepubertal children with depression can also meet criteria for other psychiatric disorders such as ADHD, disruptive behavior disorders, or anxiety disorders.

The findings of this review indicate that more research is needed to both accurately identify clinically significant depressive symptoms in childhood and to understand their long-term course. As the evidence suggests a relationship between prepubertal depression and outcomes later in life, it is important to conduct long-term prospective studies to better understand what domains are most likely to be affected by prepubertal depression, as well as what factors in childhood may modify these associations. Future research should especially focus on depression in early childhood, as a dearth of studies examine the course of depressive symptoms during this sensitive developmental period. Better understanding of the course and modifying factors of prepubertal depression in different developmental periods will enable more individually tailored interventions to be delivered as early as possible in order to mitigate the risk of later psychopathology and functional impairment.

A number of large, prospective data sets such as the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Environmental Influences on Child Health Outcomes (ECHO) program present opportunities to address many of the concerns raised in this review, as they have been able to assess children on a wide range of factors and are currently following

them into adulthood. For example, a subset of the ALSPAC cohort (www.bris.ac.uk/alspac) numbering in the thousands was assessed using the Moods and Feelings Questionnaire for depressive symptoms and also using various other measures of mental health and psychosocial functioning beginning at age 7. This group has thus far been followed up to age 25, and data collection is ongoing. Meanwhile, the ECHO program seeks to join together approximately 70 existing pediatric cohorts to standardize new data collection and to follow the participants into adulthood, with the aim of enrolling greater than 50,000 participants in observational studies (www.echochildren.org). It is recommended that these cohorts use one of several comparable measures of depressive symptoms and emotional problems, as well as other measures of physical health and neurodevelopment, from early childhood through the age of 21 and potentially beyond. Initiatives such as the ECHO program may help alleviate the issue of measurement heterogeneity found in the current review.

CONCLUSION

The results of this review suggest that prepubertal depression may predict adult depression and that prepubertal internalizing problems may predict adult anxiety disorders; however, no clear conclusions can be drawn regarding their implications for other psychiatric, medical, or psychosocial outcomes. The reviewed findings do not mirror the strong associations observed between adolescent depression and adult outcomes, but available evidence points to associations with various domains of adult life. Therefore, further studies are warranted to investigate and clarify these relationships. This is particularly true for psychosocial outcomes, given that few studies examined how prepubertal depression may affect adult functioning. Additionally, none of the studies reviewed reported on bipolar disorder outcomes.

More prospective research is needed, and the field would benefit from a greater consensus regarding the preferred tools for measuring psychopathology in childhood and adulthood, as the wide variety of instruments used in the reviewed studies posed an obstacle to making meaningful comparisons. Additionally, longer durations of follow-up and multiple assessments in adulthood are necessary, and it would be beneficial to use instruments that assess for more than a single disorder or group of disorders, as psychiatric comorbidity in childhood may be an important factor in interpreting associations with later outcomes. Finally, the field would benefit from a deeper understanding of the unique features and course of prepubertal depression.

Large research initiatives such as the ALSPAC cohort and the ECHO program will allow a great deal of information to be gathered about the outcomes of these prepubertal children across the life span in a standardized fashion while enabling identification of important subgroup differences and moderating factors. Comparing such trends found in larger studies with the findings of smaller studies using interview-based measures will help clarify the long-term implications of prepubertal depression. In turn, understanding the associations between prepubertal depression and later outcomes may improve the current understanding of prepubertal depression and allow identification of modifiable risk factors for depression and other adverse health and functional outcomes later in life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Study Measures and Significant Results

Study	Defining variables (measures)	Outcome variables			Prepubertal depression prevalence	Adult depression prevalence	Measures of association between prepubertal depression/internalizing symptoms and adult outcomes	Covariates
		Depression	Other psychiatric	Medical & others				
Wickramaratne et al. (2000)[20]	MDD (K-SADS, DSM-III-R)	MDD (SADS-LA, DSM-III-R)			MDD: 10.7%	MDD childhood-onset group: 38.9% MDD total sample: 29.8%	MDD after age 20: adjusted RR = NS MDD after age 25: adjusted RR = 4.01; 95% CI, 1.07–15.1; p < .05	Sex, age at last interview
Canals et al. (2002)[21]	Depressive symptoms (CDI, CDRS-R, DSM-III-R)	MDD, dysthymia, depressive disorders (SCAN, ICD-10)	Adjustment disorders (SCAN, ICD-10)		NR	MDE: 3.4% Dysthymia: 6.5 % NOS depressive disorder: 0.7%	MDE and dysthymia: all associations NS MDE, dysthymia, depressive disorder NOS, and adjustment disorder with depressive reaction: Females age 11: OR = 1.21; p = .01	NR
Haavisto et al. (2004)[22]	Depressive symptoms (CDI)	Depressive symptoms (BDI)			Depressive symptoms: 15.7%	NR	Unadjusted: Cumulative OR: 3.0; 95% CI, 2.2–4.1; p < .001 Adjusted: Cumulative OR model 1: 2.6; 95% CI, 1.8–3.6; p < .00 Cumulative OR model 2: 2.4; 95% CI, 1.6–3.7; p < .001	Model 1, age 8 variables: family structure, biological parent vs. others, somatic complaints, Rutter A2 parent and B2 teacher scales total scores, parents' and teachers' consideration of child psychiatric treatment Model 2, age 18: variables significant in prior analyses except CDI score, adaptive functioning, number of friends, somatic problems, alcohol use, and illicit substance use frequency
Sourander et al. (2005)[17]	Internalizing problems (Rutter A2 parent and B2 teacher scales) Depressive symptoms (CDI)	Depressive disorder (ICD-10 diagnosis at military call-up health examination)	SUDs, anxiety disorder (ICD-10 diagnosis at military call-up health examination)		NR	Depressive disorder: 1.7%	Unadjusted OR: Depression Parent-rated emotional problems: OR = 1.4; 95% CI, 1.1–1.8; p < .05 Teacher-rated emotional problems: OR = 1.3; 95% CI, 1.1–1.7; p < .05 CDI score: OR = 1.5; 95% CI, 1.2–1.9; p < .01 Anxiety Parent-rated emotional problems: OR = 1.7; 95% CI, 1.4–2.0; p < .001	Family background nonintact family; parent-rated conduct and emotional problems; teacher-rated psychological problems, poor school performance, conduct problems, and emotional problems; CDI score; self-report

Study	Defining variables (measures)	Outcome variables			Prepubertal depression prevalence	Adult depression prevalence	Measures of association between prepubertal depression/internalizing symptoms and adult outcomes	Covariates
		Depression	Other psychiatric	Medical & others				
							Teacher-rated emotional problems: OR = 1.4; 95% CI, 1.1–1.7; p < .01; CDI score: OR = 1.4; 95% CI, 1.2–1.8, p < .001 Substance use Parent-rated emotional problems: OR = 1.6; 95% CI, 1.3–2.1; p < .001 Teacher-rated emotional problems: OR = 1.7; 95% CI, 1.4–2.1; p < .001; CDI score: OR = 1.4; 95% CI, 1.1–1.7; p < .01 Adjusted OR: Depression CDI score: OR = 1.4; 95% CI, 1.2–1.8; p < .001 Anxiety Parent-rated emotional problems: OR = 1.3; 95% CI, 1.04–1.7; p < .05	psychosomatic problems score
Clark et al. (2007)[23]	Internalizing problems (BSAG)	Depressive episode (CIS-R, ICD-10)	GAD, any GAD (CIS-R, ICD-10)		Internalizing problems Age 7: 11.3% Age 11: 10.2%	Depression: 2.2% (1.6% male; 2.8% female)	Adjusted model 1: Depressive episode case, age 7: OR = 2.12; 95% CI, 1.34–3.36; p < .001 Borderline, age 11: OR = 1.65; 95% CI, 1.13–2.42; p < .01; case, age 11: OR = 2.53; 95% CI, 1.58–4.05; p < .001 GAD case, age 7: OR = 2.08; 95% CI, 1.43–3.04; p < .001 Any GAD + comorbid disorder Borderline, age 7: OR = 1.40; 95% CI, 1.07–1.83; p < .05; case, age 7: OR = 2.07; 95% CI, 1.47–2.93; p < .001; case, age 11: OR = 1.68; 95% CI, 1.16–2.45; p < .01 Adjusted model 2: Depressive episode case, age 7: OR = 1.91; 95% CI, 1.20–3.04; p < .01; borderline, age 11: OR = 1.49; 95% CI, 1.01–2.19; p < .05; case, age 11: OR = 2.24; 95% CI, 1.40–3.60; p < .001 GAD case, age 7: OR = 1.91; 95% CI, 1.31–2.79; p < .001 Any GAD + comorbid disorder Borderline, age 7: OR = 1.31; 95% CI, 1.01–1.73; p < .05; case, age 7: OR = 1.90; 95% CI, 1.34–2.68; p < .001; case, age 11: OR = 1.51; 95% CI, 1.03–2.20; p < .05	Model 1: Household tenure at age 7 years and sex Model 2: Household tenure at age 7 years, sex, and malaise at age 23 years
Stansfeld et al. (2008)[24]	Internalizing problems (BSAG)			Job demands, job decision latitude, job	NR	Depressive disorder: 3.7%	High job demands: RR = 0.80; 95% CI, 0.71–0.91; p < .001 Low decision latitude: RR = 1.51; 95% CI, 1.31–1.74; p < .001 Mid decision latitude: RR = 1.26; 95%	Sex, marital status at 45 years, housing tenure at 45 years, long-standing illness at 42 years, qualifications at 33 years,

Study	Defining variables (measures)	Outcome variables			Prepubertal depression prevalence	Adult depression prevalence	Measures of association between prepubertal depression/internalizing symptoms and adult outcomes	Covariates
		Depression	Other psychiatric	Medical & others				
				insecurity, job strain, job social support (SRQ derived from Whitehall II study)			CI, 1.09–1.46; p < .001 Low social support: RR = 1.20; 95% CI, 1.05–1.38; p < .01 Job Demands Scale: β = −0.048; p < .001 Job Latitude Scale: β = −0.301; p < .001 Job Insecurity Scale: β = −0.008; p < .001	and any RCIS diagnosis at 45 years
Multimaki et al. (2008)[25]	Internalizing problems (Rutter A2 parent and B2 teacher scales) Depressive symptoms (CDI)			Permanent or temporary release from military service (military register)	Parent-rated emotional problems: 10.3% Teacher-rated emotional problems: 6.5%	NR	Unadjusted: Permanent release from military service Teacher-rated emotional problems: OR = 3.8; 95% CI, 2.3–6.4 Temporary release from military service Teacher-rated emotional problems: OR = 2.3; 95% CI, 1.3–3.8 Depressive symptoms: OR = 2.6; 95% CI, 1.7–3.9 Adjusted: Permanent release from military service Teacher-rated emotional problems: OR = 2.3; 95% CI, 1.1–4.5; p < .05 Temporary release from military service Depressive symptoms: OR = 2.1; 95% CI, 1.2–3.7; p < .05	Family background, family structure nonintact family, parent report of child somatic health problems, parent and teacher reports of having considered psychological evaluation treatment for child, Rutter A2 conduct and hyperkinetic problems, Rutter B2 conduct, hyperkinetic, and emotional problems, teacher-reported psychological problems, school performance, CDI score, psychosomatic problems scale score
Niemela et al. (2009)[26]	Internalizing problems (Rutter A2 parent and B2 teacher scales) Depressive symptoms (CDI)			Smoking frequency in past 6 months (self-report)	NR	NR	Adjusted model 1: Occasional smoking Teacher-reported emotional problems: OR = 0.9; 95% CI, 0.8–0.98; p = .028 Moderate smoking Teacher-reported emotional problems: OR = 0.9; 95% CI, 0.8–0.97; p = .028 Depressive symptoms: OR = 1.2; 95% CI, 1.1–1.4; p < .001 Heavy smoking Depressive symptoms: OR = 1.4; 95% CI, 1.2–1.6; p < .001 Adjusted Model 2: Occasional smoking Teacher-reported emotional problems: OR = 0.8; 95% CI, 0.7–0.9; p = .026 Moderate smoking Teacher-reported emotional problems: OR = 0.8; 95% CI, 0.7–0.9; p = .026 Depressive symptoms: OR = 1.2; 95% CI, 1.02–1.3; p = .005 Heavy smoking Teacher-reported emotional problems:	Model 1 adjusted for family structure, and mother's and father's education levels Model 2 adjusted for maternal and paternal education levels, family structure, school performance, parent and teacher reports of conduct, hyperactive and emotional symptoms, child self-reported depressive symptoms

Study	Defining variables (measures)	Outcome variables			Prepubertal depression prevalence	Adult depression prevalence	Measures of association between prepubertal depression/internalizing symptoms and adult outcomes	Covariates
		Depression	Other psychiatric	Medical & others				
							OR = 0.8; 95% CI, 0.6–0.9; p = .026 Depressive symptoms: OR = 1.2; 95% CI, 1.14–1.4; p = .005 Unadjusted Variables: Moderate smoking High parent-reported emotional problems: OR = 0.5; 95% CI, 0.3–0.9; p = .007 High depressive symptoms among offspring of fathers with low education level: OR = 7.1; 95% CI, 1.5–34.5; p = .027 Heavy smoking High parent-reported emotional problems: OR = 0.5; 95% CI, 0.3–0.8; p = .007 High depressive symptoms among offspring of fathers with low education level: OR = 12.4; 95% CI, 1.5–102.0; p = .027	
Copeland et al. (2009)[28]	MDD, dysthymia, depressive disorder not otherwise specified (CAPA, DSM-IV)	MDD, dysthymia (YAPA, DSM-IV)	GAD, panic disorder without agoraphobia, agoraphobia without panic, SUD (YAPA, DSM-IV)		NR	NR	Unadjusted: GAD: OR = 3.7; 95% CI, 1.0–13.7; p < .05 Adjusted: GAD: OR = 2.7; 95% CI, 1.0–7.5; p < .05 Panic disorder: OR = 4.3; 95% CI, 1.2–15.5; p < .05	Other childhood psychiatric disorders, including overanxious disorder, separation anxiety disorder, GAD, ADHD, conduct disorder, and ODD
Bureau et al. (2009)[29]	Depressive symptoms (DDPCA)	Depressive symptoms (CES-D)			NR	NR	Model 1: Unstandardized beta = 9.28; SE = 3.35; p = .01 Model 2: Unstandardized beta = 8.27; SE = 3.41; p = .02	Model 1: gender and clinical risk status Model 2: gender, maternal depressive symptoms in infancy and at age 19
Kosterman et al. (2009)[30]	Depressive symptoms (CBCL teacher report)	Depressive episode (DIS, DSM-III-R)			NR	Depressive episode: 20%	OR = NS	Gender, ethnicity, and childhood poverty
McClure et al. (2012)[31]	Depressive symptoms (CDI)			BMI (self-reported height and weight)	Tested positive on the CDI for depression: 5.1%	NR	Pearson's correlation: r = 0.11; p < .05 Adjusted OR: NS	Assignment to LIFT intervention group, overweight at age 10 and 14, family household income in 5th grade, parental smoking, family communication age 14, CDI score at age 14, conduct disorder symptoms at ages 10 and 14, CBCL and

Study	Defining variables (measures)	Outcome variables			Prepubertal depression prevalence	Adult depression prevalence	Measures of association between prepubertal depression/internalizing symptoms and adult outcomes	Covariates
		Depression	Other psychiatric	Medical & others				
								Over/Covert Antisocial Questionnaire, ADHD symptoms at ages 10 and 14, CBCL and Over/Covert Antisocial Questionnaire, number of biological children
Fischer et al. (2012)[35]	Internalizing problems (modified short-form CBCL)		Nicotine dependence, self-reported tobacco smoking frequency (YASR, CIDI-Auto, DSM-IV)		Notable internalizing psychopathology: 11%	NR	All associations: NS	Model 1 : aggression and attention problems at age 5 Model 2: aggression and attention problems at age 5, family poverty, maternal smoking, depression and anxiety, marital changes by age 14
Korczak et al. (2014)[32]	MDE (SDI, DSM-III-R)			BMI (self-reported weight and height)	MDD: 2.9%	NR	Unadjusted: Mean adult BMI with vs. without childhood MDD: 27.3 kg/m2 (SD = 6.4) vs. 25 kg/m2 (SD 4.8); p = .02 Adjusted: Boys only: β coefficient = 0.10; p = .022 Adult BMI of boys with vs. without childhood MDD: 28.6 kg/m2 vs. 25.5 kg/m2; p < .05	Age, sex, SES, parental psychiatric illness, and adult depression
Goldman-Mellor et al. (2014)[33]	Internalizing problems (Rutter A2 parent and B2 teacher scales)		Insomnia diagnosis (interview)		NR	16.3%	Unadjusted: RR = 1.21; 95% CI, 1.08–1.36; p = .001 Adjusted: RR = 1.14; 95% CI, 1.01–1.28; p = .031	Sex, family social class, depression, GAD, PTSD, any fear or phobia, alcohol dependence, cannabis dependence, or hard drug dependence at age 38
Zohsel et al. (2016)[34]	Internalizing problems (MEI, DSM-IV)		Problematic cannabis use, cannabis abuse or dependence (SCID-I, DSM-IV SDS)		NR	NR	All associations: OR = NS	Model 1: sex, psychosocial adversity Model 2: Sex, psychosocial adversity, comorbid CD/ODD symptoms, attention problems, hyperactivity/ impulsivity

ADHD, attention-deficif/hyperactivity disorder; BDI, Beck Depression Inventory; BSAG, Bristol Social Adjustment Guide; CAPA, Child and Adolescent Psychiatric Assessment; CBCL, Child Behavior Checklist; CDI, Children's Depression Inventory; CDRS-R, Children's Depression Rating Scale–Revised; CES-D, Center for Epidemiological Studies Depression Scale; CI, confidence interval; CIDI-Auto, Composite International Diagnostic Interview; CIS-R, Clinical Interview Schedule–Revised; DDPCA, Dimensions of Depression Profile for Children and Adolescents; DE, depressive episode; DIS, Diagnostic Interview Schedule; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; GAD, generalized anxiety disorder; ICD, *International Statistical Classification of Diseases and Related Health Problems*; K-SADS, Schedule for Affective Disorders and Schizophrenia in School-Age Children; MDD, major depressive disorder; MDE, major depressive episode; MEI, Mannheim Parent Interview; NR, not reported; NS, not significant; ODD, oppositional defiant disorder; OR, odds ratio; RCIS, Revised Clinical Interview Schedule; RR, risk ratio; SADS-LA, Schedule for Affective Disorders and

Schizophrenia—Lifetime Version modified for the study of anxiety disorders; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; SCID-I, Structured Clinical Interview for DSM-IV; SD, standard deviation; SDI, Survey Diagnostic Instrument; SDS, Severity of Dependence Scale; SE, standard error; SES, socioeconomic status; SUD, substance use disorder; YAPA, Young Adult Psychiatric Assessment; YASR, Young Adult Self Report.