Systematic Review and Meta-Analysis: Predictors of Relapsing, Recurrent, and Chronic Depression in Young People

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Objective: Youth depression disrupts the social and vocational transition into adulthood. Most depression burden is caused by recurring or chronic episodes. Identifying young people at risk for relapsing, recurring, or chronic depression is critical. We systematically reviewed and meta-analyzed the literature on prognostic factors for relapsing, recurrent, and chronic depression in young people.

Method: We searched the literature up (MEDLINE, PsycINFO, CINAHL, Embase, CENTRAL, WHO ICTRP, ClinicalTrials.gov, bioRxiv, MedRxiv) to March 6, 2024, and included cohort studies and randomized trials that assessed any prognostic factor for relapse, recurrence, or chronicity of depression in young people (aged 10-25 years at baseline) with a minimum of a 3-month follow-up. We assessed individual study risk of bias using the QUIPS tool and the certainty of evidence via the GRADE approach. We conducted random-effects meta-analyses with Hartung–Knapp–Sidik–Jonkman adjustment when 3 or more estimates on the same prognostic factor were available. Qualitative synthesis was conducted to identify promising prognostic factors that could not be meta-analyzed.

Results: A total of 76 reports of 46 studies (unique cohorts or trials) were included that tested 388 unique prognostic factors in 7,488 young people experiencing depression. The majority of the reports were at high risk of bias (87%). We conducted 22 meta-analyses on unadjusted, and 7 on adjusted, prognostic factors of a poor course trajectory (ie, combined relapse, recurrence, and chronicity). Female sex (adjusted; odds ratio [95% CI = 1.49 [1.15, 1.93], $p = .003$), higher severity of depressive symptoms (unadjusted; standardized mean difference [95% CI] = 0.53 [0.33, 0.73], $p < .001$), lower global functioning (unadjusted; standardized mean difference [95% CI] = −0.35 [−0.60, −0.10], $p = .005$), more suicidal thoughts and behaviors (unadjusted; standardized mean difference [95% CI] = 0.52 [0.03, 1.01], $p = .045$), and longer sleep-onset latency (unadjusted; mean difference [95% CI] = 6.96 [1.48, 12.44] minutes, $p = .013$) at baseline predicted a poor course trajectory of depression. The certainty of the evidence was overall very low to moderate. Promising prognostic factors that could not be meta-analyzed included relational/interpersonal factors (friend relationships and family relationships/structure).

Conclusion: Our findings demonstrate the prognostic value of demographic and clinical factors for poor course trajectories of depression in young people. More research is needed to confirm the potential value of relational/interpersonal factors in predicting poor depression course. Limitations of the literature include the high risk of bias of included studies, which indicates that future studies should include large sample sizes and wider diversity of prognostic markers (eg, genetic and neurobiological) in multivariable models. The critical next step is to combine the identified prognostic factors and to evaluate their clinical value in identifying individuals at risk for a poor course trajectory of depression during youth, a life stage in which most of the disability and burden attributable to depression can be averted.

Plain language summary: This systematic review and meta-analysis summarized the evidence for factors that can be used to identify relapsing, recurrent, and chronic depression in young people. Data from 76 reports of 46 unique cohorts, including a total of 7,488 young people experiencing depression, found that female sex, more severe depressive symptoms, suicidal thoughts and behaviors, lower global functioning, and longer sleep-onset latency were predictive of a poor course trajectory of depression. This information has the potential to identify youth at risk for a poor course of depression, a life stage in which most of the disability and burden attributable to depression can be averted.

Study preregistration information: Prognostic factors for relapsing, recurrent or chronic depression in youth: a systematic review with meta-analysis; https://www.crd.york.ac.uk/PROSPERO/view/CRD42023458646.

Key words: adolescence; young adult; prediction; mental health; psychiatry

D epression in young people represents a global crisis.[1] Depression onset peaks during adolescence and young adulthood.[2-5] For example, 1 in 5 young people will experience depression by age 25 years,[6] making it the leading cause of disability in this age group worldwide.[7] Because of its high prevalence and association

with suicide, depression causes enormous human suffering and costs society billions of dollars each year.[8] The burden and costs in young people are driven largely by recurrent/chronic depression due to its association with increased risks for physical ill health (particularly chronic diseases), treatment resistance, lower educational attainment, productivity loss, long-term unemployment, and suicide.[9]

Diagnostic criteria that are used to define major depressive disorder in children and adolescents are similar to those used in adults, with the exception that the criteria allow irritable rather than depressed mood as a core diagnostic mood symptom for children and adolescents.[10] In addition, compared to adults, specific (subclinical) comorbid disorders or those such as attention-deficit/hyperactivity disorder[11] and psychotic symptoms[12] appear to be more common in children and adolescents. Although many experience transient depressive symptoms, for some young people, depression becomes a chronic mental disorder with either lifetime recurring episodes or persistent symptomatology. After recovery from a first occurrence of a depressive episode, up to 72% of young people will have a subsequent episode.[13-15] Importantly, recurrent depression increases the risk of treatment resistance, leading to chronic depression.[16] Recurrent or chronic depression in young people is particularly detrimental because it interferes with normal developmental milestones and successful transition to adulthood.[17,18] Therefore, preventing recurrence or chronicity during the early stage of depression in young people could avert treatment resistance and limit early-onset disability, which could have major economic implications worldwide.

Clinical prediction models aimed at identifying people at greater risk for developing recurrent or chronic depression can help to prioritize follow-up care, as well as to identify potentially modifiable risk and protective factors to target for further treatment.[19] Well-developed clinical prediction models can improve health care in terms of care costs, treatment efficacy, and overall resource allocation.[20] Yet, to date, models developed in prior research have focused primarily on predicting either recurrence or chronicity in adults with depression,[21] or the first onset of depressive disorders in young people.[22-24] Recent (umbrella) reviews and meta-analyses of studies in adults have implicated several risk factors for relapse, recurrence, and chronicity of depression, including younger age, earlier first onset of depression, symptom severity at onset, number of previous episodes, residual symptoms after treatment, time to remission or response, comorbid psychiatric symptoms or disorders (especially anxiety), presence of psychiatric family history, lower functioning, negative life events, and childhood trauma.[25,26] Yet, there is no systematic review and meta-analysis summarizing the available evidence on prognostic factors for relapsing, recurrent, and chronic depression in young people, evidence that is critical to guide prediction modeling. We aimed to fill this gap by conducting a systematic review and meta-analysis of prognostic factors for a poor course trajectory of depression (relapse, recurrence, and chronicity) in young people. We define young people as those 10 to 24 years of age, in line with World Health Organization definitions.[27]

METHOD

This review was prospectively registered with PROSPERO (CRD42023458646) and the Open Science Framework.[28] Extracted data and statistical code are also available on the Open Science Framework. This systematic review is reported in accordance with 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Tables S1 and S2).[29] Any review deviations from our initial registration, with justification, are reported in Table S3, available online.

Search Strategy

We conducted an electronic database search of MEDLINE, PsycINFO, CINAHL, Embase, CENTRAL using combined terms for depressive disorders, young people, prognosis and prediction, and chronicity, recurrence, and relapse on March 1, 2023, and updated this search on March 6, 2024. We also searched trials (WHO ICTRP, ClinicalTrials.gov) and preprint registries (bioRxiv, MedRxiv) for potential articles. Full search strings and results of these searches across both dates are available in Tables S4 and S5. In addition, we screened the references of 8 prior systematic reviews on risk factors for youth depression (not focused specifically on relapse, recurrence, or chronicity), identified via the Cochrane Database of Systematic Reviews and Google Scholar.[30-37] We also completed forward and backward citation tracking of all included reports. For backward citation tracking, the reference lists of included reports were screened. Forward citation tracking was completed through Web of Science.

Inclusion and Exclusion Criteria

Two independent assessors (SDT and LKMH or MK or JN) screened reports at both title/abstract and full-text phases of the review. From here we define reports as the published articles emanating from each unique cohort study or randomized trial (termed studies). Inclusion criteria followed the Population, Index Prognostic Factors, Comparator Prognostic Factors, Outcome, Timing, Setting (PICOTS) framework.[38] Reports were required to be published in a peer-reviewed journal article or as a preprint in English.

TABLE 1 Definitions for Depressive States Used in Our Systematic Review[10]

Label	Definitions for depression criteria
Review populations	
Episode	A current symptomatic episode of 2 weeks or longer in duration in which the symptoms exist most of the day almost every day and that meet other *DSM*[10] or *ICD*[41] criteria
Remission	A period of no or reduced symptoms and/or no longer in a depressive episode but not meeting criteria for recovery (ie, for a period of less than 2 months)[40]
Recovered	A period of no or reduced symptoms and/or no longer in a depressive episode for a period of 2 months or more. Given that both *DSM-5*[10] and *ICD-11*[41] both consider a recurrent episode to occur after 2 months without symptoms, we used this time threshold to separate remission and recovery
Review outcomes	
Relapse/recurrence[a]	A relapse or recurrence is an episode that has occurred following a period of remission or recovery
Chronicity/persistence	An episode of depression that has persisted or lasted to the follow-up (eg, minimum 3 months in this review) and in which there have been no periods of remission or recovery

Note: As noted in the Method section, we included all studies on these concepts regardless of definition and aimed to conducted subgroup analysis on standard vs nonstandard definitions where possible.

[a]Given that the concept of "relapse" coined by Frank et al.[39] does not exist in the current DSM-5[10] and ICD-11,[41] we combined relapse/recurrence as an outcome in our primary meta-analysis, and completed a separate sensitivity analysis where appropriate, to account for the discrepancies in older and newer definitions of relapse/recurrence.

Population. We included samples with a lower age limit of 10 years and an upper age limit of 25 years at baseline.[32] If the age range crossed the lower age boundary (eg, 8-18 years), we included this sample if the mean or median age fell within our target range (10-25 years) to capture the transition through our period of interest. The sample had to be either in recovery or remission from a primary depressive disorder, in a current depressive episode at baseline, or experiencing an episode during the follow-up period that allowed for assessment of the outcomes.[39] Given heterogeneity around the definitions of episode, remission, and recovery,[40] we extracted all studies; however, we operationalized our standard definitions in Table 1.[10,39,41] Studies that reported on depression as secondary to a primary condition (such as cancer, diabetes, autoimmune disorders, primary bipolar and psychotic disorders, and other medical conditions) were excluded. We did not exclude participants experiencing a depressive disorder with psychotic features, or a substance-induced depressive disorder, if these participants did not meet criteria for a primary bipolar, psychotic, or substance use disorder.

Prognostic Factors. We included any prognostic factor for the relapse, recurrence, or chronicity of youth depression to capture all research on the topic.

Comparator Prognostic Factors. There were no comparator prognostic factors.

Outcome. Outcomes were the relapse/recurrence and chronicity of depression (categorical diagnostic outcome of yes/no) (Table 1).[10,39,41] We extracted and meta-analyzed all outcomes of relapse/recurrence and chronicity as defined by each individual study; however, we operationalized our standard definitions in Table 1, and completed moderation analysis on standard vs nonstandard definitions where possible.[10,39,41] For our primary analysis, we combined relapse/recurrence and chronicity as a "poor course trajectory" outcome.

Timing. We included prognostic factors measured at baseline (as defined by the report). Reports were required to have a minimum follow-up period of 3 months. This follow-up duration was chosen to capture appropriate timeframes for the relapse, recurrence, or chronicity of depressive episodes.[10,39,41]

Setting. Any setting (eg, primary, secondary, or community).

Data Extraction

Two independent assessors (SDT and LKMH or MK) extracted data from the included reports. Report information extraction and risk of bias assessment were completed using a custom sheet in Covidence (Melbourne, Victoria, Australia), whereas effect estimates were extracted using a custom Microsoft Excel sheet.

Data extraction was completed using guidance from the Checklist for Critical Appraisal and Data Extraction of Prognostic Factor Studies (CHARMS-PF),[38] and included the following: relevant publication information (ie, author, title, year, journal), source of data, participant and study information (eg, follow-up timepoints), outcomes, prognostic factors, sample size, missing data, analysis, results, interpretation, and if the report was

associated with a larger cohort study or other reports included in our review.

We extracted both unadjusted (from univariable models) and adjusted (from multivariable models) prognostic factors. The effect estimates of interest included odds ratios, risk ratios, hazard ratios, beta coefficients, and relevant 95% confidence intervals. We also extracted the means and standard deviations for baseline differences in the prognostic factors relative to the follow-up outcome, if reported. We extracted the total number of prognostic factors (and covariates) from multivariable models. Standard formulas were used to calculate the effect sizes and/or confidence intervals where required (Table S6, available online).[42-45]

When it was not possible to extract the required data, information was requested from the report authors a minimum of 3 times over a 4-week period. Any discrepancies were discussed by the 2 independent assessors, with further disagreement addressed via an adjudicator.

Study Risk of Bias and Reporting Bias Assessment
The Quality in Prognostic Factor Studies (QUIPS) tool was used to evaluate the overall risk of bias of individual studies across 6 domains (participation, attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis and reporting).[46] We generated risk of bias figures using the "robvis" shiny app.[47] Reporting biases via the QUIPS tool considered the proportion of studies suspected of reporting on statistically significant results.[46]

Synthesis Methods
All preprocessing steps and statistical analyses were completed in R Version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) using the "meta v6.5-0" package.[48] Statistical significance was set at an alpha of <0.05. Details on our preprocessing steps and handling of multiple outcomes/reports per study are available in Table S7, available online. We progressed to meta-analysis if 3 or more estimates were available for a prognostic factor following these steps.

Meta-Analytic Approach for Ratios Measures. Random-effects generic inverse variance meta-analysis with a Paule–Mandel estimator was used when ratio estimates were available ("metagen"). Ratio data was transformed to a natural log scale and back transformed during the analysis for ease of interpretation.

Meta-Analytic Approach for Means and Standard Deviations. Random effects meta-analysis with a restricted maximum likelihood estimator was used to estimate differences in baseline prognostic factors for which means and SDs were available ("metacont"). If all included data were collected using the same measure, we analyzed these as mean differences, or, if scales were different, as standardized mean differences (SMD; Hedges *g*).

Estimation of 95% Confidence Intervals. Given the expected heterogeneity, we applied the Hartung–Knapp–Sidik–Jonkman method with ad hoc variance correction (95% CI method) for a maximally conservative estimate of the 95% CIs.[49-51] In the presence of heterogeneity, the Hartung–Knapp–Sidik–Jonkman method outperforms standard random effects estimators for more conversative error rates.[50]

Assessment of Heterogeneity. Heterogeneity was also assessed as the between-study variance (Tau^2), proportion of variance from between-study inconsistency (I^2), and heterogeneity of the observed effects via the prediction interval.

Meta-Regression and Subgroup Analysis. When 10 or more studies were available for meta-analysis, we used meta-regression to explore the moderating effects of study design (cohort study or randomized trial), age group (adolescent [age 10-17 years] or young adult [age 18-25 years]), outcome type (relapse/recurrence or chronicity), and outcome definition (yes vs no/unclear for meeting our operating definitions in Table 1) on the prognostic factor for a poor course trajectory of depression.[42] When there were fewer than 10 studies, we performed subgroup analysis on these moderators if 2 or more studies in each subgroup were available.

Sensitivity Analysis
We conducted 3 different sensitivity analyses: (1) outlier and influential study analysis using the "dmetar" package in R[52]; (2) meta-analysis with the standard random effects estimator of the 95% CIs, rather than the Hartung–Knapp–Sidik–Jonkman method[49-51]; and (3) meta-analysis swapping prognostic factors/outcomes for studies with multiple available in a single analysis where appropriate. We also calculated the effect size for each meta-analysis that could be detected at a power of 80% and an alpha of 0.05 via sensitivity power analysis using the "power.analysis" function of the "dmetar" package.[52]

Small-Study Effects. Small-study effects were assessed using contour enhanced funnel plots when 10 or more studies were available in the meta-analysis.[53]

Certainty Assessment
The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach was used to assess the certainty of the effect estimates from meta-

analysis.[54] We followed guidance for the use of GRADE in assessing evidence regarding prognostic factors.[55] Our operating criterion for GRADE is available in Table S8, availabe online.

RESULTS

Study Selection

Overall, 10,700 reports were screened at the title/abstract phase and 698 full-text reports were assessed (Figure 1). The reasons for exclusion of individual reports are available in Table S9, available online. Subsequently, 76 reports[13-15,56-128] (from 46 unique studies) were included in qualitative synthesis and were available to be considered in quantitative synthesis.

We contacted the authors of 22 reports for effect estimates or additional clarification around the data.[15,59,62,63,65-68,70,74,76,84,91,94,95,97-99,116,124,125,127] Further details on author contacts are available in Table S10, available online. Five reports were not included in quantitative synthesis because of a lack of relevent quantitative data.[62,67,94,124,127]

Study Characteristics

Of the 46 unique studies, there were 37 cohort studies and 9 randomized trials, with a total of 7,488 participants (sample sizes ranging from n = 26 to n = 831). Overall, 49% of reports had a sample size of less than 100, whereas 75% had a sample size of less than 200. For age groups, 40 studies were considered adolescent (87%), 4 young adult (9%), and 2 mixed (4%). For funding, 44 studies were publicly funded (96%), whereas 2 studies did not explicitly state the source of funding (4%). In all, 28 (61%) of the unique studies were conducted in the United States, 5 (11%) in the United Kingdom, 3 (7%) in Germany, 2 (4%) in Finland, 2 (4%) in Canada, 2 (4%) in Australia, 1 (2%) in Sweden, 1 (2%) in Spain, 1 (2%) in Mexico, and 1 (2%) in Hungary. In terms of sex assigned at birth in the 41 unique studies reporting this, 67% of participants (4,061 of 6,090) were female. In terms of diversity and inclusion, of the 28 unique studies reporting on race/ethnicity, 87% of the included participants (4,964 of 5,736) were White. No studies reported on the LGBTQI+ status of included participants. Five unique studies (11%) mentioned including major depression with psychotic features,[70,71,85,103,111] whereas none reported on substance-induced depression. Less than 1% of the participants in these 5 studies relative to the total included in the review (37 of 7,488) were reported to meet the criteria for major depression with psychotic features. Further details are reported in Table 2.

There were 60 reports on cohort studies,[13,14,56,58,60,62,64-66,68-71,76-83,85-91,93-104,106-113,115-124,127,128] 14 on randomized trials,[15,59,61,63,67,72,73,75,84,92,105,114,125,126] and 2

that used mixed data from a cohort study and randomized trial.[57,73] All were peer-reviewed journal articles. Of the cohort reports, 38 assessed relapse/recurrence (61%), 14 chronicity (23%), 4 both separately (6%), and 6 had a mixed outcome (10%). Of these, 38 met our outcome definition (61%), whereas 5 did not (8%), and 19 were unclear (eg, diagnostic timeframe not specified) (31%). Of the randomized trials, 8 assessed relapse/recurrence (57%), 1 chronicity (7%), 3 reported on both outcomes (21%), and 2 had a mixed outcome (14%). Of these, 10 met our outcome definition (71%), 1 report did not (7%), and 3 reports were unspecified beyond relapse, recurrence, or chronicity (21%). Finally, 39 reports (51%) noted that a parent was included in the assessment of participant depressive status at baseline. Further details on the characteristics of individual study reports are available in Table 2.

Risk of Bias and Reporting Biases

The risk of bias assessment for each report is available in Figure 2 and the overall summary is provided in Figure S1, available online. For overall bias, of the 76 reports, none were at low risk of bias, 10 (13%) were at moderate risk of bias,[14,61,63,71,91,105-108,121] and 66 (87%) were considered at high risk of bias.[13,15,56-60,62,64-70,72-90,92-104,109-120,122-129] The main areas of bias were attrition and statistical analysis and reporting. For attrition bias, 2 reports were considered low risk of bias (3%), 18 moderate risk of bias (24%), and 56 high risk of bias (74%). For statistical analysis and reporting, 21 reports were considered low risk of bias (28%), 20 moderate risk of bias (26%), and 35 high risk of bias (46%). In terms of statistical reporting, 46 reports (61%) were suspected of statistical reporting biases.
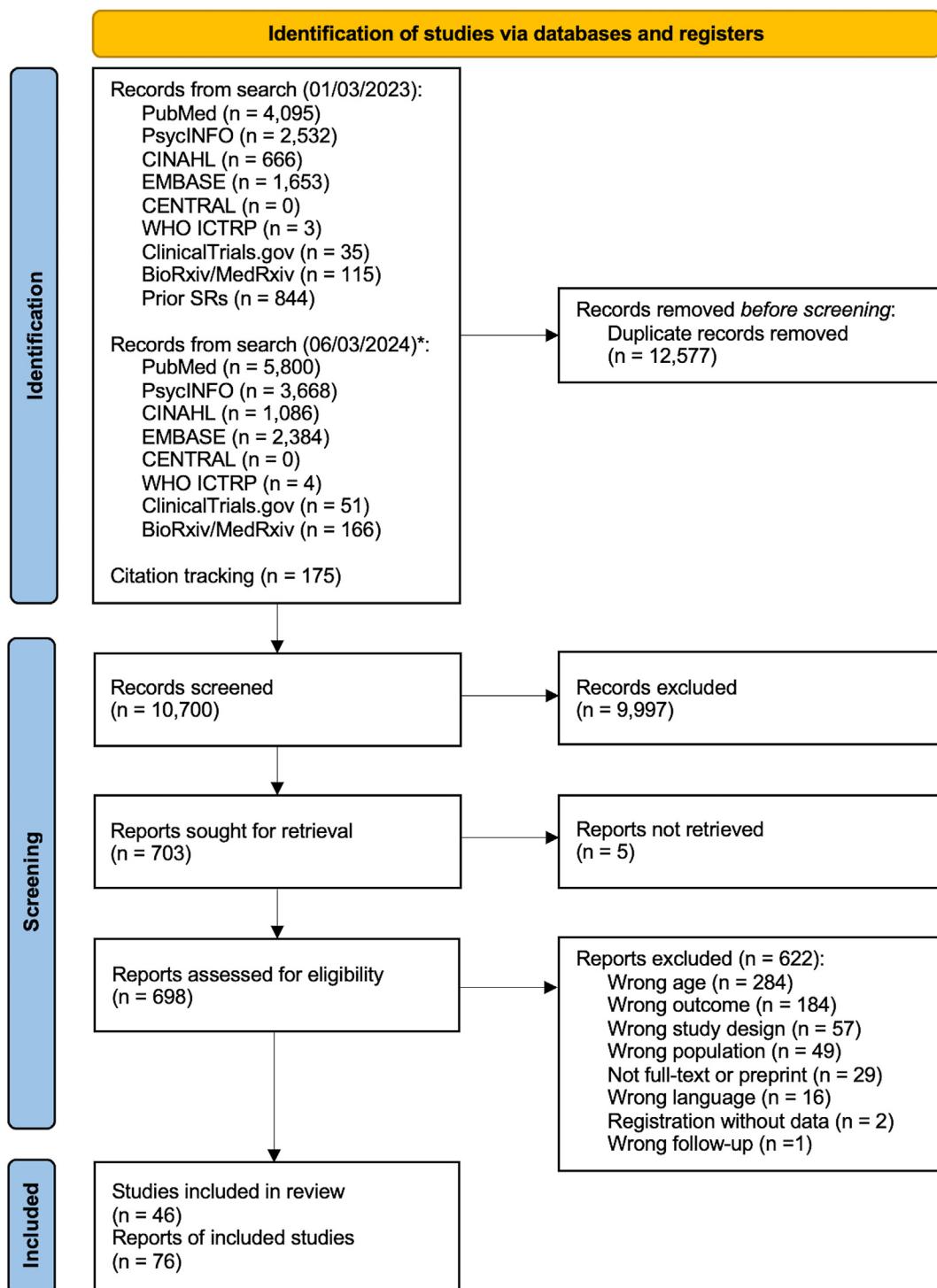
Quantitative Synthesis

A summary on how we handled data during extraction is available in Table S11, available online. Information on how we extracted each prognostic factor is reported in Tables S12 and S13, availabe online. Decisions to progress to meta-analysis across our steps are available in Table S14, available online. We report the following meta-analysis estimates as odds ratios (ORs), mean differences (MDs), and standard mean differences (SMDs) where appropriate. Of the 875 extracted estimates, 613 (70%) were unadjusted, 246 were adjusted (26%), and 16 (2%) were unclear as to whether they were adjusted or unadjusted. Details on the studies included in each meta-analysis are available in Figure 3.

Unadjusted Prognostic Factors

We were able to conduct 22 meta-analyses on 21 unadjusted prognostic factors from univariable/univariate models (11 ORs, 5 MDs, and 5 SMDs; suicidal thoughts and behaviors could be

FIGURE 1 PRISMA Flow Diagram

Note: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses. *Updated search included the additional term "persis*" as explained in the protocol deviations section (Table S3, available online). Studies indicate the unique samples included in this review, whereas reports are the identified manuscripts emanating from these studies.

TABLE 2 Characteristics of Reports of Studies Included in This Review

First author, year, reference	Country	Setting	Follow-up	Age group	Population	Outcome	N baseline[a]	N females	Race/ethnicity[b]	N dropouts	N outcome	Predictors	Model	Links
Alaie 2020[56]	Sweden	Community	180	Adolescent	Current episode	Mixed	227	180	NR	3	NR	Sociodemographic, clinical, psychological,	Logistic regression	Uppsala Longitudinal Adolescent Depression Study
Asarnow 1993[58]	US	Secondary care	12	Adolescent	Current episode	Chronicity	26	9	1 Black; 1 Hispanic; 24 White	NR	18	Expressed emotion, sociodemographic, clinical	Fisher exact, logistic regression	No link to other included reports
Benjet 2020[60]	Mexico	Community	96	Adolescent	Current episode	Relapse/recurrence	107	75	NR	NR	49	Sex, living with parents, parental education, presence of psychiatric disorders, traumatic events	Logistic regression	Mexican Adolescent Mental Health Survey
Birmaher 2004[62]	US	Mixed	55	Adolescent	Current episode	Relapse/recurrence	68	29	53 White	0	27	Demographic, clinical, familial, environmental, biological	Cox proportional hazards model	No link to other included reports
Blazquez 2016[64]	Spain	Secondary care	12	Adolescent	Current episode	Chronicity	46	36	NR	0	20	Psychological, genetic	t Test, χ^2 test, Fisher exact	No link to other included reports
Bohman 2012[65]	Sweden	Community	180	Adolescent	Current episode	Mixed	217	NR	NR	NR	NR	Somatic symptoms	Logistic regression	Uppsala Longitudinal Adolescent Depression Study
Bohman 2017[66]	Sweden	Community	180	Adolescent	Current episode	Mixed	227	180	NR	NR	NR	Familial	Logistic regression	Uppsala Longitudinal Adolescent Depression Study
Cohen 2019[68]	US	Community	36	Adolescent	No depression, but tracked at follow-up to allow assessment of the outcome	Relapse/recurrence	473	270	43 Asian; 57 Black; 33 Hispanic; 52 Other; 288 White;	NA	84	Depressive symptoms, rumination, cognition, dysfunctional attitudes	Hierarchical logistic regression	No link to other included reports
Craighead 2011[69]	US	Community	16	Young adult	Remitted/recovered	Relapse/recurrence	130	104	10 Asian; 1 Black; 14 Latino; 1 Native American; 12 Other; 92 White	27	36	Demographics, comorbid diagnoses, personality disorders, depressive symptoms, dysfunctional attitudes	Cox proportional hazards model	Sheets, 2014a; Sheets, 2014b; Craighead, 2011
Dunn 2006[70]	United Kingdom	Community; Primary care	94	Adolescent	Current episode	Both, separately	113	73	NR	NR	Recurrence: 36, Chronicity: 15	Demographics, comorbid diagnoses, depressive symptoms, pubertal stage	Cox proportional hazards model	Goodyer, 1997a; Goodyer, 1997b; Goodyer, 1998; Goodyer 2001; Dunn, 2006

(continued)

TABLE 2 Continued

First author, year, reference	Country	Setting	Follow-up	Age group	Population	Outcome	N baseline[a]	N females	Race/ ethnicity[b]	N dropouts	N outcome	Predictors	Model	Links
Emslie 1997[71]	US	Secondary care	43	Adolescent	Current episode	Relapse/ recurrence	59	27	54 White	NR	36	Demographic, comorbidities, psychological, familial	Cox proportional hazards model	Armitage, 2002; Emslie, 1997; Emslie, 2001
Essau 2007[76]	Germany	Community	15	Adolescent	Current episode	Chronicity	90	NR	NR	NR	22	Demographic, comorbid, familial, psychological, social	Logistic regression	No link to other included reports
Ford 2017[77]	United Kingdom	Community	36	Adolescent	Current episode	Chronicity	93	54	70 White	NR	21	Child, family, psychological	Logistic regression	British Child and Adolescent Mental Health Surveys
Goetz 2001[78]	US	Secondary care	119	Adolescent	Mixed	Relapse/ recurrence	53	23	NR	NR	28	Age, sleep	Analysis of covariance	No link to other included reports
Goodyer 1997[79]	United Kingdom	Secondary care	8	Adolescent	Current episode	Chronicity	78	40	NR	NR	34	Demographics, clinical features, comorbidities	Logistic regression	Goodyer, 1997a; Goodyer, 1997b; Goodyer, 1998; Goodyer, 2001; Dunn, 2006
Goodyer 1997[80]	United Kingdom	Secondary care	8	Adolescent	Current episode	Chronicity	68	NR	NR	NR	34	Life events, difficulties	Logistic regression	Goodyer, 1997a; Goodyer, 1997b; Goodyer, 1998; Goodyer, 2001; Dunn, 2006
Goodyer 1998[81]	United Kingdom	Secondary care	8	Adolescent	Current episode	Chronicity	55	33	NR	NR	28	Cortisol, DHEA, life events	Backward stepwise logistic regression	Goodyer, 1997a; Goodyer, 1997b; Goodyer, 1998; Goodyer, 2001; Dunn, 2006
Goodyer 2001[82]	United Kingdom	Other: Unclear	17	Adolescent	Current episode	Chronicity	53	33	NR	Unclear	20	Psychological, cortisol, DHEA	Backward stepwise logistic regression	Goodyer, 1997a; Goodyer, 1997b; Goodyer, 1998; Goodyer, 2001; Dunn, 2006
Goodyer 2003[83]	United Kingdom	Community	24	Adolescent	Current episode	Chronicity	30	22	NR	NR	11	Demographics, psychological, hormone	Backward stepwise logistic regression	No link to other included reports
Halonen 2022[85]	Finland	Secondary care	150	Adolescent	Current episode	Relapse/ recurrence	237	165	232 White	NR	84	Familial, comorbidities	Stepwise logistic regression	No link to other included reports

(continued)

TABLE 2 Continued

First author, year, reference	Country	Setting	Follow-up	Age group	Population	Outcome	N baseline[a]	N females	Race/ ethnicity[b]	N dropouts	N outcome	Predictors	Model	Links
Hamlat 2020[86]	US	Community	36	Adolescent	Mixed	Relapse/ recurrence	603	338	Race: 5 American Indian or Native Alaskan; 55 Asian or Pacific Islander; 63 Black; 64 Other; 416 White Ethnicity: 77 Hispanic	NR	61	Past depression, pubertal timing	Cox proportional hazards model	Gene, Environment, and Mood Study
Hammen 2008[87]	Australia	Community	60	Adolescent	Other: Lifetime diagnosis	Relapse/ recurrence	99	70	NR	NR	50	Cognitive, interpersonal	Multivariate analyses of variance	MaterUniversity Study of Pregnancy (MUSP)
Hammen 2008[88]	Australia	Community	60	Adolescent	Other: Lifetime/ current at baseline	Relapse/ recurrence	99	70	NR	NR	50	Sex, maternal depression, interpersonal dysfunction	Logistic regression	MaterUniversity Study of Pregnancy (MUSP)
Hart 2001[89]	US	Community	18	Young adult	Remitted/ recovered	Relapse/ recurrence	65	50	7 Other; 58 White	11	27	Demographic, clinical, psychological	Cox proportional hazards model	No link to other included reports
Jonsson 2011[90]	Sweden	Community	180	Adolescent	Current episode	Mixed	229	191	NR	75	84	Demographics, comorbidities, psychological, familial	Logistic regression	Uppsala Longitudinal Adolescent Depression Study
Karlsson 2008[91]	Finland	Community; Secondary care	12	Adolescent	Current episode	Both, separately	174	141	NR	29	Recurrence: 22, Chronicity: 86	Sociodemographic, clinical, comorbidities	Logistic regression, Cox proportional hazards model	Adolescent Depression Study
Kiviruusu 2020[14]	Finland	Secondary care	96	Adolescent	Current episode	Relapse/ recurrence	148	122	NR	70 (of 218)	99	Sociodemographic, clinical, comorbidities, treatment	Logistic regression	Adolescent Depression Study
Klein 2023[93]	US	Community	72	Adolescent	No depression, but tracked at follow-up to allow assessment of the outcome	Chronicity	150	150	Race: 20 Non-White; 130 White Ethnicity: 19 Hispanic	NR	60	Clinical, psychological, social, familial	Correlations, Phi-coefficients	Adolescent Development of Emotions and Personality Traits
Kovacs 1984[94]	US	Secondary care	78	Adolescent	Current episode	Relapse/ recurrence	65	33	27 Black; 4 Other; 34 White	NR	Unclear	Demographic, clinical	Cox proportional hazards model	Kovacs, 2016a; Kovacs, 1984; Kovacs, 2001

TABLE 2 Continued

First author, year, reference	Country	Setting	Follow-up	Age group	Population	Outcome	N baseline[a]	N females	Race/ ethnicity[b]	N dropouts	N outcome	Predictors	Model	Links
Kovacs 2001[95]	US	Secondary care	76	Adolescent	Current episode	Relapse/ recurrence	92	51	59 White	NR	32	Demographic	Cox proportional hazards model	Kovacs, 2016a; Kovacs, 1984; Kovacs, 2001
Kovacs 2016[96]	Hungary	Secondary care	24	Adolescent	Remitted/ recovered	Relapse/ recurrence	178	NR	171 White	NR	30	Mood repair	Structural equation model	No link to other included reports
Kovacs 2016[13]	US	Primary care	180	Adolescent	Current episode	Relapse/ recurrence	102	52	33 Black; 2 Mixed Origin; 67 White	NR	54	Demographic, clinical, familial, treatment	Cox proportional hazards model	Kovacs, 2016a; Kovacs, 1984; Kovacs, 2001
Langenecker 2018[97]	US	Community	17	Young adult	Remitted/ recovered	Relapse/ recurrence	55	36	NR	NR	21	Sociodemographic, comorbidities, brain function	Seed-based cross-correlation analysis	No link to other included reports
Lara 2000[98]	US	Community	6	Young adult	Current episode	Relapse/ recurrence	84	72	43 White	Unclear	12	Sociodemographic, clinical, psychological, familial	Cox proportional hazards model	No link to other included reports
Lewinsohn 1994[99]	US	Community	14	Adolescent	Remitted/ recovered	Relapse/ recurrence	336	NR	30 Other; 306 White	NR	84	Demographic, familial, clinical, comorbidities	Cox proportional hazards model	Oregon Adolescent Depression Project
Lewinsohn 1999[100]	US	Community	14	Adolescent	Other: Lifetime depression	Relapse/ recurrence	286	NR	26 Other; 260 White	NR	43	Life events, depressive symptoms, dysfunctional attitudes	Logistic regression	Oregon Adolescent Depression Project
Lewinsohn 2000[101]	US	Community	91	Adolescent	Remitted/ recovered	Relapse/ recurrence	274	192	244 White	NR	125	Sociodemographic, clinical, psychological, comorbidities, familial	Logistic regression	Oregon Adolescent Depression Project
Mathew 2003[102]	US	Secondary care	119	Adolescent	Current episode	Relapse/ recurrence	56	NR	NR	NR	NR	Cortisol	Analysis of covariance	No link to other included reports
McCauley 1993[103]	US	Secondary care	36	Adolescent	Current episode	Relapse/ recurrence	65	28	6 African American; 2 Other; 57 White	Unclear	35	Sociodemographic, clinical, psychological, social, familial	Cox proportional hazards model	No link to other included reports
McCleary 2002[104]	Canada	Secondary care	12	Adolescent	Current episode	Chronicity	57	39	NR	6	22	Expressed emotion	Logistic regression	No link to other included reports
Michelini 2021[106]	US	Community	36	Adolescent	No depression, but tracked at follow-up to allow assessment of the outcome	Mixed	550	550	50 Hispanic; 424 White	71	52	Clinical, familial, personality, interpersonal, biological	Logistic regression, multinomial logistic regression	Adolescent Development of Emotions and Personality Traits

(continued)

TABLE 2 Continued

First author, year, reference	Country	Setting	Follow-up	Age group	Population	Outcome	N baseline[a]	N females	Race/ ethnicity[b]	N dropouts	N outcome	Predictors	Model	Links
Monroe 1999[107]	US	Community	14	Adolescent	Other: Lifetime Depression Diagnosis	Relapse/ recurrence	248	181	218 White	NR	43	Sociodemographic, psychological, life events	Logistic regression	Oregon Adolescent Depression Project
Park 2005[108]	United Kingdom	Secondary care	12	Adolescent	Current episode	Chronicity	94	66	NR	NR	64	Sociodemographic, psychological	Backward stepwise logistic regression	No link to other included reports
Pettit 2006[109]	US	Community	96	Adolescent	Other: Lifetime Depression Diagnosis	Relapse/ recurrence	564	371	513 White	77	224	Sociodemographic, clinical, psychological symptoms	Cox proportional hazards model	Oregon Adolescent Depression Project
Pettit 2013[110]	US	Community	150	Adolescent	No depression, but tracked at follow-up to allow assessment of the outcome	Relapse/ recurrence	59	40	NR	NR	43	Sociodemographic, comorbidities, psychological, social, familial	Logistic regression	Oregon Adolescent Depression Project
Rao 1995[111]	US	Secondary care	84	Adolescent	Current episode	Relapse/ recurrence	28	18	6 Black; 1 Other; 21 White	2	20	Sociodemographic	Analysis of variance	Rao, 1996; Rao, 1995
Rao 1996[112]	US	Unclear	84	Adolescent	Current episode	Relapse/ recurrence	28	18	6 Black; 1 Other; 21 White	2	15	Sleep, cortisol	Analysis of variance	Rao, 1996; Rao, 1995
Rao 2010[113]	US	Community; Primary care	42	Adolescent	Current episode	Relapse/ recurrence	55	32	26 Other; 29 White	4	20	Sociodemographic, clinical, biological	Cox proportional hazards model	No link to other included reports
Rohde 2005[115]	US	Community	82	Adolescent	Mixed	Relapse/ recurrence	244	171	222 White	NR	Unclear	Familial	Logistic regression	Oregon Adolescent Depression Project
Rohde 2009[116]	US	Community	84	Adolescent	No depression, but tracked at follow-up to allow assessment of the outcome	Relapse/ recurrence	88	88	15 Asian or Pacific Islander; 25 Black; Latina; 25 Other; 342 White	NR	26	Socio-demographic	Unclear	No link to other included reports
Rohde 2013[117]	US	Community	60	Adolescent	Other: Lifetime diagnosis	Relapse/ recurrence	816	480	24 American Indian; 24 Asian; 8 Black; 24 Hispanic; 10 Other; 726 White	NR	109	Sex assigned at birth	Logistic regression	Oregon Adolescent Depression Project
Sanford 1995[118]	Canada	Primary care; Secondary care	12	Adolescent	Current episode	Chronicity	67	45	NR	6	20	Sociodemographic, clinical, psychological, social	χ^2, t test	No link to other included reports

(continued)

TABLE 2 Continued

First author, year, reference	Country	Setting	Follow-up	Age group	Population	Outcome	N baseline[a]	N females	Race/ ethnicity[b]	N dropouts	N outcome	Predictors	Model	Links
Schmidt-Gies 2014[119]	Germany	Mixed	6	Adolescent	Current episode	Chronicity	71	71	NR	NR	37	Demographic, comorbidities, psychological, physical	Logistic regression	No link to other included reports
Sheets 2014[120]	US	Community	17	Young adult	Remitted/ recovered	Relapse/ recurrence	119	94	85 White	27	34	Depressive symptoms, dysfunctional attitudes, personality disorders, stress	Cox proportional hazards model	Sheets, 2014a; Sheets, 2014b; Craighead, 2011
Sheets 2014[121]	US	Community	16	Young adult	Remitted/ recovered	Relapse/ recurrence	130	104	10 Asian; 1 Black; 14 Latino; 1 Native American; 12 Other; 92 White	27	37	Depressive symptoms, personality disorders	Cox proportional hazards model	Sheets, 2014a; Sheets, 2014b; Craighead, 2011
Stein 2001[122]	Germany	Community	42	Mixed	Other: Lifetime/12-Month Diagnosis	Mixed	358	NR	NR	NR	102	Social anxiety	Logistic regression	Early Developmental Stages of Psychopathology
Sumner 2011[123]	US	Community	16	Adolescent	Remitted/ recovered	Relapse/ recurrence	55	41	NR	NR	10	Memories, chronic stress, depressive symptoms	Logistic regression	Youth Emotion Project
Urrila 2014[124]	Finland	Mixed	12	Adolescent	Current episode	Both, separately	166	137	NR	24	Recurrence: 14; Chronicity: 79	Sleep	Linear regression	Adolescent Depression Study
Warner 1992[127]	US	Community; Research Unit	24	Mixed	Current episode	Relapse/ recurrence	31	Unclear	31 White	NR	5	Demographic, clinical, comorbidities, social, family risk	Logistic regression	No link to other included reports
Wilson 2014[128]	US	Community	216	Adolescent	Other: Unclear	Relapse/ recurrence	831	Unclear	814 White	Unclear	428	Parental psychiatric disorders, personality, psychopathology, physical development, childhood maltreatment	Logistic regression	Minnesota Twin Family Study
Randomized Trials														
Barbe 2004[59]	US	Mixed	24	Adolescent	Current episode	Mixed	72	54	58 White	4	32	Sexual abuse, treatment, maternal depression, race	Logistic regression	Barbe, 2004; Birmaher, 2000; Brent, 2001; Renaud, 1998
Bessette 2020[61]	US	Community; Primary care	24	Adolescent	Remitted/ recovered	Relapse/ recurrence	29	15	1 Asian; 4 Black; 5 Hispanic; 4 Other; 15 White	6	20	Treatment, DMN+, SV-SM	Mixed effects model	No link to other included reports

(continued)

TABLE 2 Continued

| First author, year, reference	Country	Setting	Follow-up	Age group	Population	Outcome	N baseline[a]	N females	Race/ethnicity[b]	N dropouts	N outcome	Predictors	Model	Links
Birmaher 2000[63]	US	Secondary care	24	Adolescent	Current episode	Both, separately	107	81	89 White	3	Recurrence: 26, Chronicity: 22	Demographic, clinical, treatment, environmental	Logistic regression, Cox proportional hazards model	Barbe, 2004; Birmaher, 2000; Brent, 2001; Renaud, 1998
Brent 2001[67]	US	Secondary care	24	Adolescent	Current episode	Relapse/recurrence	107	74	81 White	8	20	Psychological, functional, familial	Logistic regression, random effects regression, Cox proportional hazards model	Barbe, 2004; Birmaher, 2000; Brent, 2001; Renaud, 1998
Curry 2011[15]	US	Mixed	63	Adolescent	Current episode	Relapse/recurrence	196	110	16 Black; 18 Hispanic; 8 Other; 154 White	NR	88	Demographic, comorbidities, psychological, familial	Logistic regression	Treatment for Adolescents with Depression Study
Emslie 1998[72]	US	Secondary care	12	Adolescent	Current episode	Both, separately	87	41	NR	NR	Recurrence: 17, Chronicity: 13	Demographics, clinical, functioning, comorbidities	Cox proportional hazards model	Armitage, 2002; Emslie, 1998; Emslie, 2001
Emslie 2010[74]	US	Unclear	6	Adolescent	Current episode	Relapse/recurrence	334	233	277 White	59	30	Treatment, psychological, comorbidities	Logistic regression	Treatment of Resistant Depression in Adolescents
Emslie 2015[75]	US	Secondary care	18	Adolescent	Current episode	Relapse/recurrence	144	77	Race: 1 Asian; 15 Black; 9 Multiracial; 1 Native American; 118 White Ethnicity: 43 Hispanic; 101 Non-Hispanic	47	49	Demographic, comorbidities, psychological, treatment	Cox proportional hazards model	No link to other included reports
Gordon 2011[84]	Australia	Community; Primary care	7	Adolescent	Current episode	Chronicity	130	85	NR	34	26	Demographic, clinical	Logistic regression	Berriga House, Time for a Future Trial
Kennard 2018[92]	US	Community; Primary care	6	Adolescent	Current episode	Relapse/recurrence	102	37	9 Black; 15 Hispanic; 6 Other; 72 White	NR	36	Demographic, clinical, comorbidities	Logistic regression	No link to other included reports
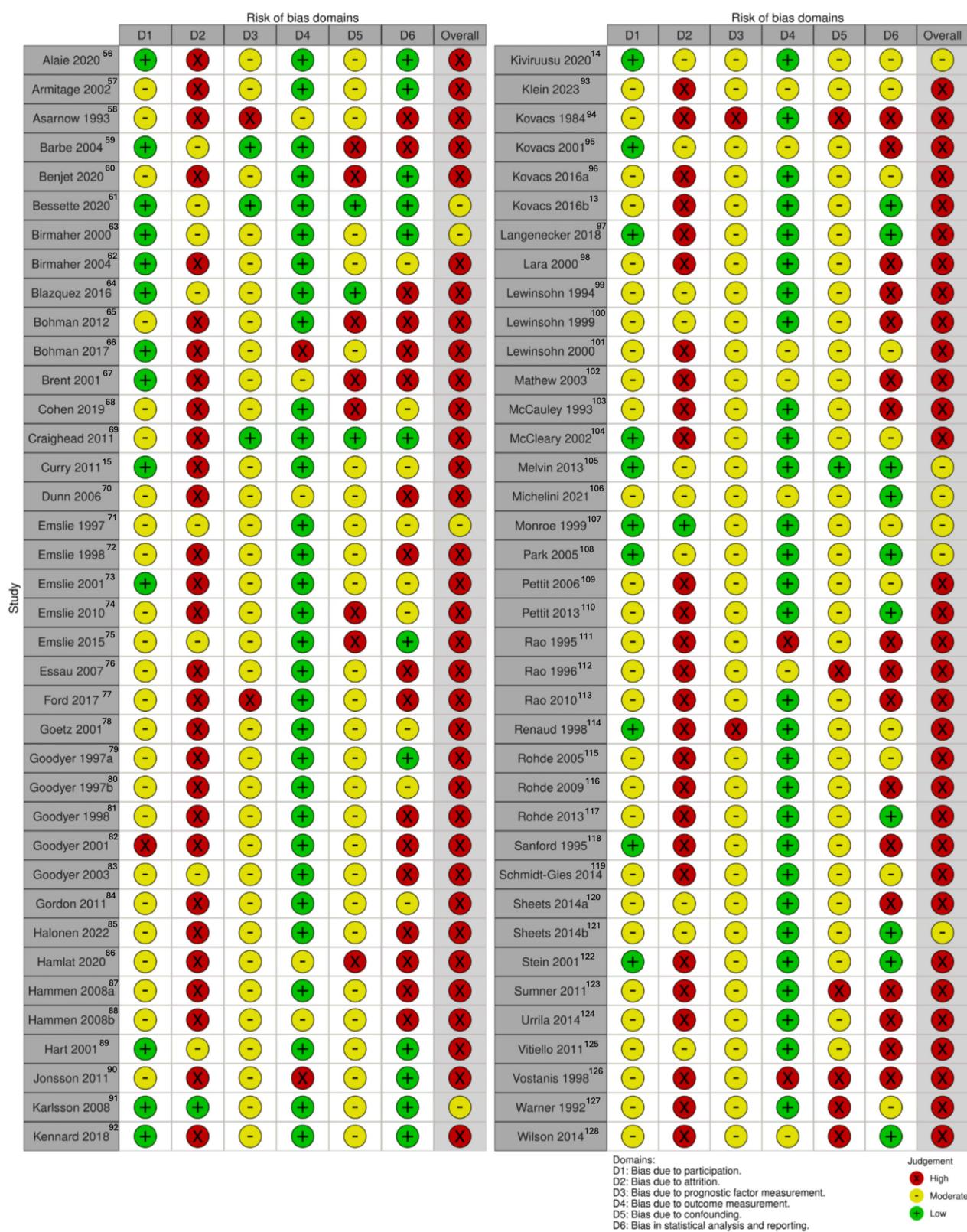
(continued)

TABLE 2 Continued

First author, year, reference	Country	Setting	Follow-up	Age group	Population	Outcome	N baseline[a]	N females	Race/ ethnicity[b]	N dropouts	N outcome	Predictors	Model	Links
Melvin 2013[105]	Australia	Community; Primary care	68	Adolescent	Current episode	Both, separately	140	93	3 Asian; 137 White	29	Recurrence: 55, Chronicity: 8	Sociodemographic, psychological, clinical, familial	Logistic regression	Berriga House, Time for a Future Trial
Renaud 1998[114]	US	Secondary care	24	Adolescent	Current episode	Relapse/ recurrence	100	75	85 White	NR	Unclear	Treatment response	Cox proportional hazards model	Barbe, 2004; Birmaher, 2000; Brent, 2001; Renaud, 1998
Vitiello 2011[125]	US	Secondary care	17	Adolescent	Current episode	Relapse/ recurrence	334	234	2 American/ Alaskan Native; 6 Asian or Pacific Islander; 16 Biracial; 11 Black; 18 Hispanic; 4 Other; 277 White	170	33	Demographic, clinical	Cox proportional hazards model	Treatment of Resistant Depression in Adolescents
Vostanis 1998[126]	NA	Secondary care	24	Adolescent	Current episode	Mixed	57	32	NR	3	11	Sociodemographic, comorbidities, treatment, psychological	Stepwise forward logistic regression	No link to other included reports
Mixed cohorts/trials														
Armitage 2002[57]	US	Unclear	12	Adolescent	Current episode	Both, separately	47	22	NR	NR	Recurrence: 14, Chronicity: 11	Sociodemographic, psychological, comorbidities, sleep	Multiple regression analysis	Armitage, 2002; Emslie, 1997; Emslie, 1998; Emslie, 2001
Emslie 2001[73]	US	Mixed	12	Adolescent	Current episode	Relapse/ recurrence	102	47	90 White	NR	36	Demographic, comorbid diagnoses, psychological, sleep	Analysis of variance	Armitage, 2002; Emslie, 1997; Emslie, 1998; Emslie, 2001
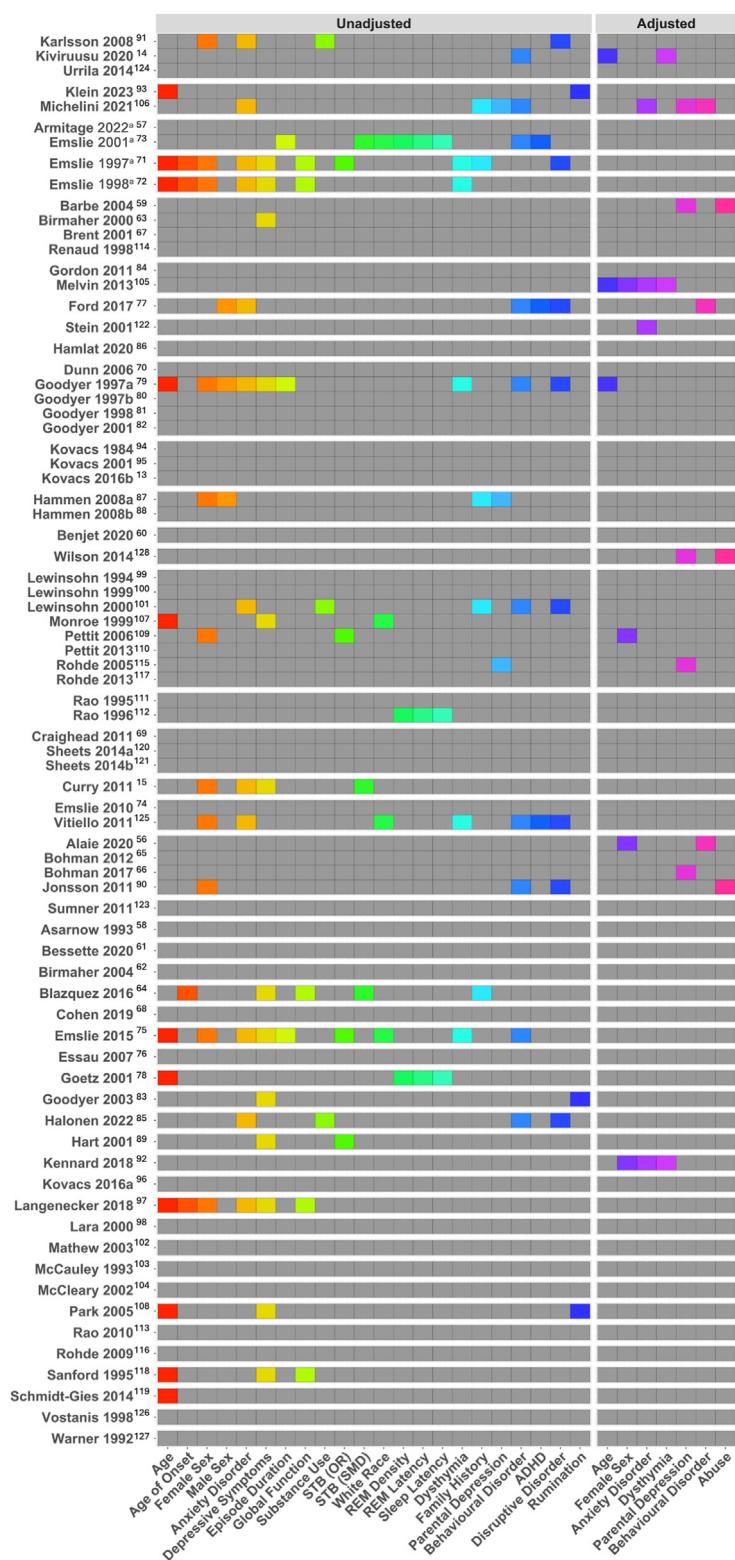
Note: DHEA = dehydroepiandrosterone; DMN+ = default mode network plus brain regions; NR = not reported; SV-SM = salience-emotion, visual, and sensorimotor brain regions.
[a]This number reflects individuals with or developing a depressive disorder in the study (as some studies had larger samples with and without a depressive disorder).
[b]The numbers for race/ethnicity may reflect the full sample in some studies (including those without a depressive disorder), because of the availability of reporting on race/ethnicity.

FIGURE 2 Individual Risk of Bias Assessment Across Included Reports

Note: Figure generated using the "robvis" shinyapp tool.[47] Please note color figures are available online.

FIGURE 3 Summary of Reports

Note: Summary of reports, split by each unique study, contributing to each primary meta-analysis on each prognostic factor after the pre-processing steps for this study and handling of multiple outcomes/reports (Table S14 for further details, available online). Colored squares indicate that a study contributed to the meta-analysis; gray squares indicate that no estimate was available. Please note color figures are available online.
[a]Emslie 1997 and 1998 are unique studies, whereas Emslie 2001 and Armitage 2002 included a combination of these samples.

meta-analyzed as both an OR and SMD). Female sex (OR [95% CI] = 1.41 [1.14, 1.76], *p* = .005, n studies=11, n participants = 1,601) was associated with a poorer course trajectory (relapse, recurrence, or chronicity) of depression in young people. Compared to individuals without the event at follow-up, those with a poor course trajectory of depression had higher depressive symptoms (SMD [95% CI] = 0.53 [0.33, 0.73], *p* < .001, n studies = 13, n participants = 1,155), lower global functioning (SMD [95% CI] = −0.35 [−0.60, −0.10], *p* = .005, n studies = 5, n participants = 308), more suicidal thoughts and behaviors (SMD [95% CI] = 0.52 [0.03, 1.01], *p* = .045, n studies = 3, n participants = 337), and a longer sleep-onset latency (MD [95% CI] = 6.96 [1.48, 12.44], *p* = .013, n studies = 3, n participants = 174) at baseline. Male sex, anxiety disorders, substance use disorders, White race, dysthymia, any family history of depression, parental depression, any behavioral disorder, attention-deficit/hyperactivity disorder, disruptive disorders, age, age of onset, episode duration, sleep rapid eye movement (REM) latency and density, and rumination were not significantly associated with a poor course trajectory of depression in young people. Further details on these estimates are available in Figure 4, Table S15, available online (with sensitivity power estimates), and Figures S2 through S23, available online.

Meta-Regression/Subgroup Analysis. Meta regression on age, female sex, anxiety disorders, depressive symptoms, and any behavioral disorders revealed no significant influence of study design, age group, and outcome type and definition (Table S16, available online). In subgroup analysis (Table S17, available online), poorer global functioning was significantly different at baseline only for chronicity (SMD [95% CI] = −0.35 [−0.68, −0.02]) compared to that in the nonevent group, but not for relapse/recurrence (SMD [95% CI] = −0.23 [−0.86, 0.42]).

Sensitivity Analysis. There was a change to significance for parental depression predicting a poorer course trajectory when excluding an influential study (OR [95% CI] = 1.33 [1.04, 1.70]) (Table S18, available online). No other significant changes were observed in outlier and influential study analyses. In sensitivity analysis using a standard random effects estimator (Table S19, available online), rumination was significantly higher at baseline between individuals with a poor course trajectory of depression compared to those without (SMD [95% CI] = 0.29 [0.04, 0.54], *p* = .023, n studies = 3, n participants = 271). Sensitivity analysis exchanging chronicity for relapse/recurrence outcomes when a report examined both outcomes showed no significant differences from the original results (Table S20, available online).

Adjusted Prognostic Factors
We were able to meta-analyze 7 adjusted prognostic factors from multivariable models. Only female sex (OR [95% CI] = 1.49 [1.15, 1.93], *p* = .003, n studies = 4, n participants = 906) was significantly associated with a poorer course trajectory of depression in young people. Anxiety disorders, dysthymia, parental depression, any behavioral disorder, and physical/sexual abuse were not significantly associated with a poorer course trajectory of depression in young people. Further details on these estimates are available in Figure 4, Table S21, available online (with sensitivity power estimates), and Figures S24 through S30, available online.

Meta-Regression/Subgroup Analysis. We were unable to perform meta-regression on any adjusted factors. Results of subgroup analyses are reported in Table S22, available online, with no significant differences observed.
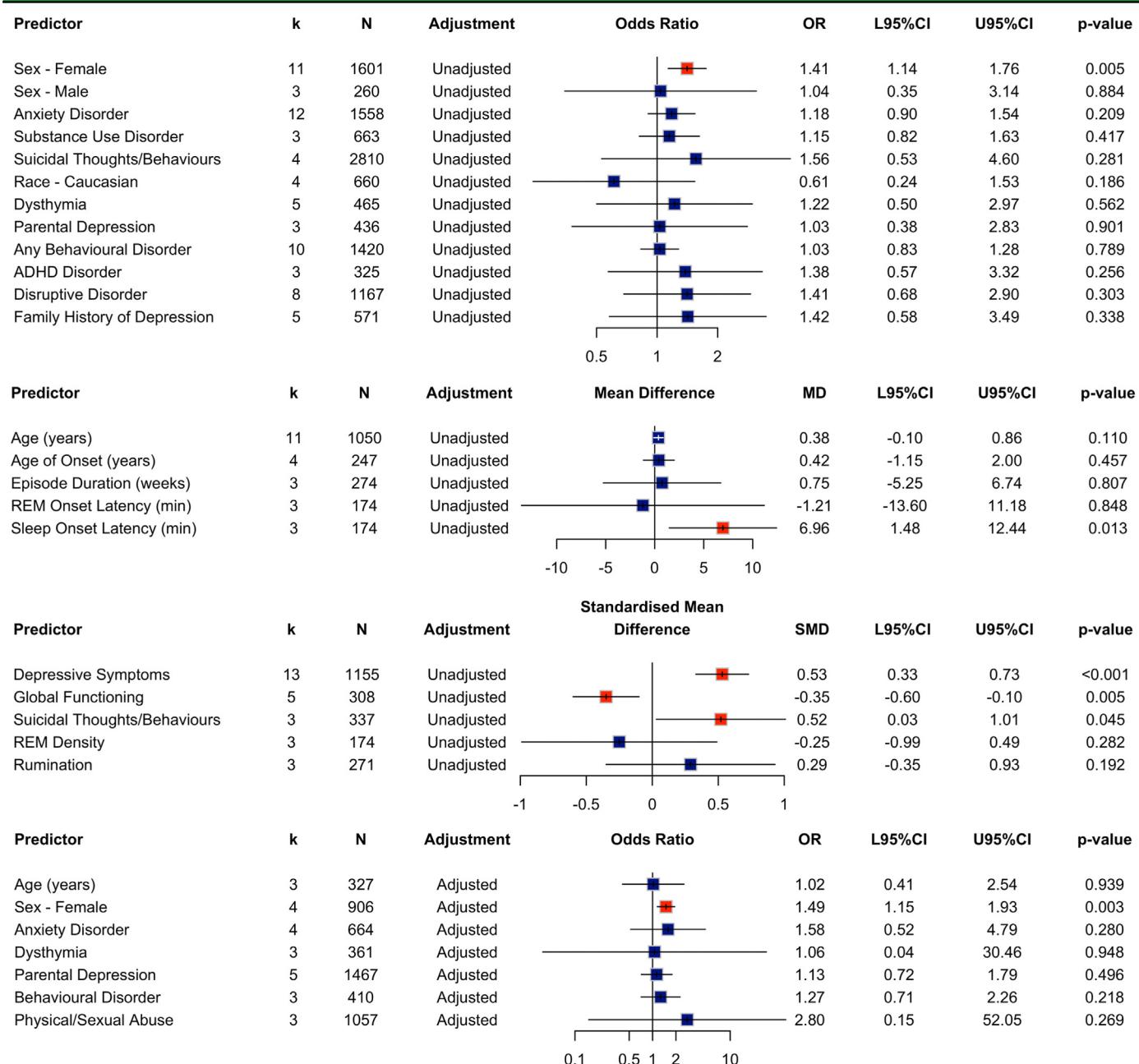
Sensitivity Analysis. No significant changes to our primary estimates on adjusted prognostic factors were observed across sensitivity analyses (Tables S23-S25).

Certainty of evidence
The overall GRADE certainty of meta-analytic evidence ranged from very low to moderate. Most of the estimates were of low to very low certainty, with only adjusted female sex demonstrating moderate certainty. Further details on the individual assessments of certainty are available in Table S26, available online. Contour-enhanced funnel plots for the 5 meta-analyses with more than 10 estimates are reported in Figures S31 through S35, available online.

Qualitative Summary of Prognostic Markers That Could Not Be Meta-Analyzed
Most prognostic factors that could be included in the meta-analyses were demographic and clinical factors. Outside of this, interpersonal factors may be promising for predicting a poor course trajectory of youth depression (Table S12 and S13, available online). For example, 5 estimates from 3 reports showed that the lack of friendship relationships were likely important predictors of a poorer course trajectory of depression,[87,93,106] whereas 1 estimate from 1 report did not support this finding.[110] Furthermore, 15 estimates related to family relationships or structure (eg, parent conflict, care, discipline, separation, and involvement, and family functioning, support and structure) from 8 reports were significant predictors of a poorer course trajectory of youth depression,[56,63,72,90,93,98,106,118] whereas 11 estimates from 5 reports were not.[56,66,101,110,118] Given the heterogeneity in definitions and scaling, these interpersonal

FIGURE 4 Forest Plots of the Overall Summary Effect for Individual Prognostic Factors on the Relapse, Recurrence, or Chronicity of Depression in Young People

Predictor	k	N	Adjustment	Odds Ratio	OR	L95%CI	U95%CI	p-value
Sex - Female	11	1601	Unadjusted		1.41	1.14	1.76	0.005
Sex - Male	3	260	Unadjusted		1.04	0.35	3.14	0.884
Anxiety Disorder	12	1558	Unadjusted		1.18	0.90	1.54	0.209
Substance Use Disorder	3	663	Unadjusted		1.15	0.82	1.63	0.417
Suicidal Thoughts/Behaviours	4	2810	Unadjusted		1.56	0.53	4.60	0.281
Race - Caucasian	4	660	Unadjusted		0.61	0.24	1.53	0.186
Dysthymia	5	465	Unadjusted		1.22	0.50	2.97	0.562
Parental Depression	3	436	Unadjusted		1.03	0.38	2.83	0.901
Any Behavioural Disorder	10	1420	Unadjusted		1.03	0.83	1.28	0.789
ADHD Disorder	3	325	Unadjusted		1.38	0.57	3.32	0.256
Disruptive Disorder	8	1167	Unadjusted		1.41	0.68	2.90	0.303
Family History of Depression	5	571	Unadjusted		1.42	0.58	3.49	0.338

Predictor	k	N	Adjustment	Mean Difference	MD	L95%CI	U95%CI	p-value
Age (years)	11	1050	Unadjusted		0.38	-0.10	0.86	0.110
Age of Onset (years)	4	247	Unadjusted		0.42	-1.15	2.00	0.457
Episode Duration (weeks)	3	274	Unadjusted		0.75	-5.25	6.74	0.807
REM Onset Latency (min)	3	174	Unadjusted		-1.21	-13.60	11.18	0.848
Sleep Onset Latency (min)	3	174	Unadjusted		6.96	1.48	12.44	0.013

Predictor	k	N	Adjustment	Standardised Mean Difference	SMD	L95%CI	U95%CI	p-value
Depressive Symptoms	13	1155	Unadjusted		0.53	0.33	0.73	<0.001
Global Functioning	5	308	Unadjusted		-0.35	-0.60	-0.10	0.005
Suicidal Thoughts/Behaviours	3	337	Unadjusted		0.52	0.03	1.01	0.045
REM Density	3	174	Unadjusted		-0.25	-0.99	0.49	0.282
Rumination	3	271	Unadjusted		0.29	-0.35	0.93	0.192

Predictor	k	N	Adjustment	Odds Ratio	OR	L95%CI	U95%CI	p-value
Age (years)	3	327	Adjusted		1.02	0.41	2.54	0.939
Sex - Female	4	906	Adjusted		1.49	1.15	1.93	0.003
Anxiety Disorder	4	664	Adjusted		1.58	0.52	4.79	0.280
Dysthymia	3	361	Adjusted		1.06	0.04	30.46	0.948
Parental Depression	5	1467	Adjusted		1.13	0.72	1.79	0.496
Behavioural Disorder	3	410	Adjusted		1.27	0.71	2.26	0.218
Physical/Sexual Abuse	3	1057	Adjusted		2.80	0.15	52.05	0.269

Note: The top panel shows the estimates analyzed as unadjusted odds ratios, the second as mean differences, and the third as standardized mean differences (Hedges g), each from univariable/univariate models. The bottom panel shows adjusted odds ratios from multivariable models. Red squares indicate statistically significant prognostic factors. k = Number of studies included in the meta-analysis; N = number of participants included in the meta-analysis. Please note color figures are available online.

factors could not be pooled in meta-analysis. Neuro-cognitive, neurobiological (eg, neuroimaging, cortisol, inflammation), psychological (eg, self-criticism, self-efficacy, attentional and cognitive biases, coping style) and molecular genetic factors were considered by too few studies, thus precluding any conclusions regarding their role in predicting a poor course trajectory of youth depression.

DISCUSSION

This was the first systematic review and meta-analysis to summarize the available evidence on prognostic factors for relapsing, recurrent, and chronic depression in young people. Identifying young people most at risk for relapsing, recurring, or chronic depression is critical to reducing the long-term burden and costs associated with youth

depression. Our results showed that female sex, higher depressive symptoms, poorer global functioning, more suicidal thoughts and behaviors, and longer sleep-onset latency at baseline are predictive of a poorer course trajectory of depression in young people. Based on subgroup analysis, the result for global functioning may be specific to chronicity and not relapse/recurrence, whereas sensitivity analysis showed that parental depression and greater rumination may be associated with an overall poorer course trajectory. Our findings demonstrate the prognostic value of easily measured demographic, clinical, and psychosocial factors for poor course trajectories of depression in young people. The critical next step is to combine the identified prognostic factors and to evaluate their clinical value in identifying individuals at risk for a poor course trajectory of depression during youth. Further work should consider how this information could be used to streamline health care systems to better prioritize follow-up care and to target modifiable risk and protective factors in young people with depression. The importance of such efforts cannot be overstated, given that most of the disability and burden attributable to depression can still potentially be averted with effective early intervention in youth.

The findings from our review show similarities to but also differences from previous reviews of prognostic factors in adults. Reviews in adults have shown younger age, younger age of first onset, symptom severity at onset, number of previous episodes, residual symptoms after treatment, time to remission or response, comorbid psychiatric symptoms or disorders (especially anxiety), presence of psychiatric family history, lower functioning, negative life events, and childhood trauma to be associated with a poor course trajectory.[25,26] Similar to the adult findings, we also found that greater baseline depression symptoms, presence of any suicidal behaviors, lower functioning, and potentially parental depression were associated with a poor course trajectory of depression in young people, whereas age, age of onset, physical or sexual abuse, and other comorbidities were not. Importantly, the latter nonsignificant results (eg, physical or sexual abuse and other comorbidities) should be considered in the context of the low number of studies and statistical power (eg, high imprecision) in some of our meta-analyses that could become significant with the addition of new evidence. Furthermore, given that all participants included in our review were young and that the age range was limited, it may not be surprising that age and age of onset were not significantly associated with outcome in our review, whereas these factors were found to predict depression course in adult studies.

We extend previous findings in adults with the presence of delayed sleep-onset latency, any suicidal behaviors, and

greater levels of rumination as significant predictors in youth. Sleep-onset latency is the length of time that it takes to accomplish the transition from full wakefulness to sleep. Adolescence is a period in which the sleep schedule often becomes delayed.[129] Prior evidence suggests that sleep problems, particularly excessive wakefulness in bed (eg, delayed sleep onset latency), precede the development of depression in adolescence,[130] and here we show that delayed sleep-onset latency is also a significant prognostic factor for depression relapse, recurrence, and chronicity in youth. This is in line with findings of associations between depression-related sleep disturbances and a lack of antidepressant treatment response[131,132] and higher risk for suicide.[133] Given that clinicians and general practitioners tend to give less weight to depression-related sleep disturbances than to affective and cognitive symptoms in their severity judgment,[134] our results call for routine screening for sleep problems and sleep disorders and implementation of sleep interventions in clinical practice to prevent poor depression course trajectories in youth.

Rumination (defined as repetitive and passive focus on the causes or consequences of distress) has been shown to be an important prognostic factor for first-onset depression in young people.[135] In our sensitivity analyses, we showed rumination to also be an important prognostic factor for poor depression course trajectories. In line with research on depression onset, this indicates that rumination should be examined in future research to confirm its relationship with relapsing, recurrent, and chronic depression in young people.

Furthermore, based on our qualitative review, relational factors pertaining to impaired family and friend relationships may be unique predictors for poor depression course trajectories in youth relative to adults, as these were found to be significant in various (larger-scale) studies included in the present review. Adolescents often live with their parents, and relationships with parents continue to change throughout adolescence.[136] Adolescence is also a key developmental period during which friendships become increasingly close and supportive[136,137] and poor relationships with or limited support from parents/families and/or peers may have a profound influence on longer-term outcomes in young people with depression. However, as these relational factors could not be meta-analyzed because of differences in measurement and definitions, more studies with harmonized definitions and measurements are required to confirm the potentially important role of these relational factors.

Importantly, many of the significant factors in our review are potentially modifiable in young people. For example, depressive symptoms, suicidal ideation, sleep-onset

latency, rumination, and functioning could be targeted with various behavioral, psychological, and physical interventions,[138–142] whereas family therapy and social skills therapy could be used to improve family and other interpersonal relationships.[143] Together, these prognostic factors could be considered in clinical practice to reduce the likelihood of a poor course trajectory of youth depression.

Strengths of our systematic review include robust search strings without restrictions based on a single prognostic factor, which allowed us to identify wide research on this topic. Second, we applied the Hartung–Knapp–Sidik–Jonkman adjustment in our meta-analyses,[49-51] which reduces the risk of false-positive results in the presence of heterogeneity,[50] and we mitigated the risk of false-negative results by conducting sensitivity analysis with a standard random effects estimator. From these sensitivity analyses, we observed differences in the results for only rumination. However, even with this strength, given the low number of available studies and participants in some of our analyses, further consideration of false-positive and false-negative results as well as low statistical power is required for interpretation. Third, we conducted a wide range of other meta-regression, subgroup, and sensitivity analyses to confirm the robustness of our results. Fourth, we cross-checked duplicate reports from the same study (cohort/trial), the prognostic factors, and their definitions to include these in meta-analyses as appropriate. Finally, we reported all data included in the review, as well as any protocol deviations and differences, and we uploaded the statistical code and data on the Open Science Framework for full transparency and reproducibility of our analyses.[28] Finally, we conducted sensitivity power analysis to determine the critical effect sizes that each of our meta-analysis could detect at a power of 80% and an alpha of 0.05. However, for various predictors, such as substance use disorders, attention-deficit/hyperactivity disorder, and parental and family history of depression, because of the low number of studies and/or high heterogeneity, we were powered to detect only large effect sizes, and these should be validated in future research.

We also identified limitations, including attrition, statistical reporting, and publication biases in included reports. Most of the located evidence was at high risk of overall bias, and the certainty of evidence was mostly low to very low (only 1 moderate certainty estimate). In addition, many included studies had small samples sizes, with 75% having a sample size of less than 200. Compared to adults,[25,26] there is limited research in young people, which is a critical issue given that adolescence and young adulthood are the peak periods of onset of depression and of depression recurrence,[117] and preventing recurrence in youth can significantly increase "human capital" (educational and vocational attainment) and alter the life trajectory of young people.[144] The majority of the included participants were of White race/ethnicity, and no studies reported on LBGTQI+ status. This indicates that future research needs to evaluate these minority identities, both as prognostic markers and as of the population of interest, for relapsing, recurrent, and chronic depression in young people. Approximately half of the included reports indicated that both the young person and their parent or guardian were interviewed for the diagnosis of depression. Further attention to the use of additional informants should be considered, particularly in the transition to adulthood, when the parent or guardian may become less involved. Most studies included only demographic and clinical prognostic factors, and few studies included psychological, social, cognitive, neurobiological, and genetic risk factors. For example, a recent large cohort study (n = 16,180) showed promising evidence that a higher polygenic risk score for major depression was associated with increased risk of depression recurrence in younger individuals (aged 10-32 years) diagnosed with depression in hospital-based settings; this study was not included in the current review because the upper age limit fell outside of our prespecified age range and, regardless, would not have been able to be meta-analyzed because of the lack of other studies exploring polygenic risks scores as prognostic factors.[145] Most studies focused on a single or a few predictors, with many of our meta-analyses limited by the available number of studies and participants. For example, we could conduct only 7 analyses of adjusted prognostic factors, 6 of which were included in the unadjusted analyses. Even though we observed no differences in results across these analyses, future work should consider and explore the role of confounding on these estimates with additional evidence. Furthermore, differences in the scaling of prognostic factors (eg, difference scaling in continuous measures or cut-offs in categorical measures) limited our ability to conduct some analyses on ratio measures (eg, beta coefficients, odds ratios). However, we followed best practice and pooled equivalent measures to ensure comparability in analysis.[38] Because the etiology of depression recurrence is complex and multifaceted, robust individualized multivariable models will be required for more successful prediction of recurrence or chronicity.[22,146] Despite these limitations, our systematic review and meta-analysis included 76 reports of 46 studies, comprising 7,488 young people, and 388 unique prognostic variables, making it the most comprehensive review on relapsing, recurrent, and chronic depression in young people to date.

Results from this review provide clear directions for future research. Specifically, future research should: (1) consider cohort study retention strategies to reduce attrition levels and

report on these strategies[147-151]; (2) adhere to reporting guidelines, particularly around statistical significance[152]; (3) follow established methods of *a priori* calculating sample sizes required in prognostic modeling[19]; (4) identify earlier markers of relapsing, recurrent, and chronic depression by conducting more studies in young people; (4) include a wider range of demographic, clinical, psychological, social, cognitive, genetic, and neurobiological markers using standard clinical measures and definitions[22,146]; and (5) analyze these data in multivariable models (both statistical and machine learning) that can address the complexity of relapse, recurrence, and chronicity of youth depression and further subgroup these individuals.[21] Furthermore, future research should investigate the vulnerability of female individuals to poorer course trajectories of youth depression. Together, these steps would continue to build on the important findings of our review, and to use this information to generate early and targeted assessments and interventions to reduce the global burden of (youth) depression.

Future research should determine whether combining the factors identified in this review, including baseline depressive symptoms, suicidal thoughts and behaviors, functioning, sleep latency, parental depression, and rumination, as well as factors potentially related to family and friend relationships, in a multivariable clinical prediction model (eg, using machine learning methods) that could predict poor depression course trajectories in young people at the individual level, as opposed to merely considering group-level differences. If done, such studies should consider and plan for clinical translation and implementation of recognized prognostic factors that could be used in predictive modeling. Decision curves aim to determine thresholds where there is likely benefit or harm (eg, such as reduced risk of relapse, recurrence, and chronicity of depression), otherwise known as net benefit, and streamline treatment decisions in clinical practice.[153] For example, a decision curve analysis can label individuals as low or high risk, such that high-risk individuals progress to additional treatments, enabling determination of whether there is a likely benefit from classification.[153] Yet, there has been limited use of net-benefit analyses to assess clinical utility in youth depression research to date.[21] Conducting such analysis has the potential to improve the utility of recognized prognostic factors in predictive modeling. Finally, our review focused on the relapse, recurrence, and chronicity of unipolar depressive disorders. Given that it is known that many people transition through psychiatric disorders, future research could define risk factors for migration from unipolar depression to other psychiatric disorders in young people.[5] This is particularly true for bipolar and anxiety disorders, given the high rates and co-occurrence of anxiety,[5] and the risk of transition from unipolar to bipolar depression.[154]

Our results showed that female sex, higher depressive symptoms, lower functioning, more suicidal thoughts and behaviors, and longer sleep-onset latency are significant predictors associated with subsequent relapse, recurrence, or chronicity of depression in young people. Sensitivity analysis showed that parental depression and greater rumination may also be associated with relapse, recurrence, or chronicity of youth depression. Our findings point to the key prognostic value of these easily measured demographic, clinical, and psychosocial factors for poor course trajectories of depression in young people, which can guide future research and intervention strategies. With the goal of averting the subsequent major disability and burden attributable to youth depression, combining and evaluating the significance of identified prognostic factors and determining their clinical value in improving course trajectories of youth depression is a critical next step.

CRediT authorship contribution statement

Scott D. Tagliaferri: Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Laura K.M. Han:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Muskan Khetan:** Writing – review & editing, Investigation. **Joshua Nguyen:** Writing – review & editing, Investigation. **Connie Markulev:** Writing – review & editing, Methodology. **Simon Rice:** Writing – review & editing, Methodology. **Susan M. Cotton:** Writing – review & editing, Methodology. **Michael Berk:** Writing – review & editing, Methodology. **Enda M. Byrne:** Writing – review & editing, Methodology. **Debra Rickwood:** Writing – review & editing, Methodology. **Christopher G. Davey:** Writing – review & editing, Methodology. **Peter Koval:** Writing – review & editing, Methodology. **Aswin Ratheesh:** Writing – review & editing, Methodology. **Patrick D. McGorry:** Writing – review & editing, Methodology. **Mario Alvarez-Jimenez:** Writing – review & editing, Methodology. **Lianne Schmaal:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

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