

<i>Author(s)</i>	<i>Title</i>	<i>Study Objective</i>	<i>Salient findings</i>
<i>Studies Addressing Prevalence</i>			
<i>Cross-sectional (Level IV)</i>			
Brotman et al., 2006	Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children	Examine prevalence, concurrent Axis I diagnoses, and longitudinal outcome of childhood irritability	Lifetime prevalence of SMD was 3.3%. Most (67.7%) SMD youth had an Axis I diagnosis, most commonly attentiondeficit/hyperactivity disorder (26.9%), CD (25.9%), and/or ODD (24.5%). Youth who met criteria for SMD (mean age 10.6 +/- 1.4 years) were more likely to be diagnosed with a depressive disorder (OR 7.2, CI 1.3-38.8, p = .02)
Copeland et al., 2013	Prevalence, comorbidity, and correlates of DSM-5 proposed disruptive mood dysregulation disorder	Estimate prevalence, comorbidity, and correlates of Childhood Irritability	Three-month prevalence rates for DMDD was 0.8% to 3.3%, with highest rate in preschool age. DMDD co-occurred with common psychiatric disorders. Highest levels of co-occurrence were depressive disorders and ODD. It co-occurred with both an emotional and a behavioral disorder 30%70% of the time. Children displayed elevated rates of social impairments, school suspension, service use, and poverty.
Copeland et al., 2015	Normative Irritability in Youth: Developmental Findings From the Great Smoky Mountain Study	Examine the developmental epidemiology of normative irritability and its tonic and phasic components	Low levels of either tonic or phasic irritability increased risk for disrupted functioning concurrently and at 1-year follow-up.
Althoff et al., 2016	Disruptive Mood Dysregulation Disorder at Ages 13-18: Results from the National Comorbidity SurveyAdolescent Supplement	Determine the utility of DMDD and the clinical correlates in participants/subjects	Rates of comorbidity and functional impairment were similar for adolescents with DMDD. A steep decline in prevalence rate suggests that DMDD construct may not be similar in youths <18 years of age, though the DSM-5 criteria suggests so across this age range.

Bielas et al., 2016	The associations of cumulative adverse childhood experiences and irritability with mental disorders in detained male adolescent offenders	Examine if accumulation of ACEs, irritability, or both predicted mental disorders in incarcerated adolescents with and without controlling for one another and for sociodemographic factors.	The ACE total score was positively related to irritability and predicted depressive disorders, suicidality, post-traumatic stress disorder (PTSD), and anxiety disorders.
Moore et al., 2019	Heritability, stability, and prevalence of tonic and phasic irritability as	Examine prevalence, stability, and heritability of tonic irritability, phasic irritability, and a DMDD proxy	Lifetime prevalence of pDMDD was 7.46%. The heritability of tonic irritability (54%)
	indicators of disruptive mood dysregulation disorder	(pDMDD)	was slightly lower than that of phasic irritability (approximately 60%)
<i>Case Control (Level III)</i>			
Harima et al, 2022	Associations Between Chronic Irritability and Sensory Processing Difficulties in Children and Adolescents	Determine prevalence of chronic irritability and its association with SPD	The irritability group was more likely to have ODD, externalizing problems, and attention issues. SPD were reported in 36% of patients in the irritability group ($p = 0.029$).
<i>Studies Linking Prenatal Stress and Childhood Irritability</i>			
<i>Prospective (Level II)</i>			
Luoma et al., 2001	Longitudinal study of maternal depressive symptoms and child wellbeing	Investigate association between perinatal maternal depressive symptoms and level of psychosocial functioning or emotional/behavioral problems in schoolage children.	Low social competence and adaptive functioning were associated with maternal depressive symptoms. Postnatal depressive symptoms predicted low social competence. Maternal depressive symptoms was a strong predictor of high level of externalizing problem. The timing and the recurrence of perinatal depressive symptoms affect the childhood outcomes
Luoma et al., 2004	A longitudinal study of maternal depressive symptoms, negative expectations, and perceptions of child problems	Examine the associations between maternal depressive symptoms and perceptions of children's problems. Maternal prenatal depressive symptoms, the continuity of negative expectations to postnatal problem perceptions, and high problem level in preschool age predicted high problem level in school age	Maternal prenatal depressive symptoms, continuous negative expectations, postnatal problem perceptions, and high problem level in preschool age predicted high problem level in older school age children

McGrath et al., 2008	Maternal depression and infant temperament characteristics.	Determine the differences in infant temperament ratings or childcare stress of women depressed during the third trimester or 2 and 6 postpartum	Depressed mothers report more difficult infant temperament at both measurement points even after controlling for history of maternal abuse or prenatal anxiety in depressed mothers
Sandman and Glynn., 2009	Corticotropin-Releasing Hormone (CRH) Programs the Fetal and Maternal Brain	Determine fetal origins of disease and the impact of maternal programming	Both mother and fetus are vulnerable to adverse outcomes due to exposure to elevated levels of pCRH. Therefore, midgestation pCRH could be a diagnostic tool to identify women who are at risk for PPD
Fraser et al., 2013	The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort.	Understand how genetic and environmental characteristics influence health and development in parents and children	Positive associations of prenatal anxiety with offspring diurnal salivary cortisol patterns, childhood behavior
<i>Cross sectional (Level IV)</i>			
Dieter et al., 2001	Maternal depression and increased fetal activity	Determine if maternal depression correlates with increased fetal activity in fetuses in second and or third trimester of	A third of variance fetal activity may be due to both depression and trait anxiety scores in
		pregnancy	mothers. Maternal depression correlates with increased fetal activity suggesting potential effects of stress hormones on fetal activity
Davis et al., 2007	Prenatal exposure to maternal depression and cortisol influences infant temperament	Examine the consequences of prenatal exposure to stress and stress hormones	Increased cortisol level between 30-32 weeks of pregnancy, was associated with greater infant negative reactivity
Deave et al., 2008	The impact of maternal depression in pregnancy on early child development	Examine the associations between maternal stress and child development at 18 months of age.	14% of women were depressed antenatally but not postnatally. 9% of children were developmentally delayed at 18 months of age. Persistent depression is associated with developmental delay
Diego et al., 2009	Prenatal depression restricts fetal growth	Identify prenatal depression as a risk factor for restriction in fetal growth.	Prenatal maternal cortisol levels play a role in facilitating premature delivery and slower fetal growth rates.

Koutra et al., 2013	Antenatal and postnatal maternal mental health as determinants of infant neurodevelopment at 18 months of age in a mother-child cohort (Rhea Study) in Crete, Greece	Examine the effect of maternal mental health on infant neurodevelopment in 18-month-old children	Maternal mental health and well-being have significant impact on early child neurodevelopment.
Wiggins et al., 2014	Developmental trajectories of irritability and bidirectional associations with maternal depression	Identify classes of irritability trajectories from toddlerhood to middle childhood; characterize maternal depression and other variables within each irritability trajectory class; examine bidirectional associations between maternal depression and child irritability	Children with more severe irritability trajectories are more likely to have mothers with recurrent depression. Maternal depression at ages 1 and 3 is associated with increased childhood irritability at ages 3 and 5 which is in turn associated with increased maternal depression at ages 5 and 9, respectively.
Whelan et al., 2015	Pathways from maternal depressive symptoms to adolescent depressive symptoms: the unique contribution of irritability symptoms	Determine three possible pathways linking prenatal maternal depressive symptoms to adolescent depressive symptoms	The pathways went through childhood Irritability Symptoms, Anxiety/Depressive Symptoms or Conduct Problems
Dahlerup et al., 2018	Maternal stress and placental function, a study using questionnaires and biomarkers at birth	Investigate the effect of prenatal maternal stress on the ratio of cortisol and cortisone in maternal and fetal blood at birth	Significant associations were observed between fetal cortisol exposure, AFCE and plasma concentrations of maternal cortisol and fetal cortisone with exposure to Pregnancy Related Anxiety (PRA). Reduced associations observed with adjustments for birth related variables
Huang et al., 2019	Correlation study between increased fetal movement during the third	Analyze the correlation between increased fetal movements in the third trimester and neonatal outcomes	Increased fetal movements exhibited at 31 and 39 weeks of gestation were associated
	trimester and neonatal outcome		with number of previous deliveries, gestational age (less than 34 weeks and more than 37 weeks) and vaginal birth rate.
Review (Level V)			

Van den Bergh et al., 2020	Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy	Identify harmful stressors, vulnerable periods during pregnancy, specificities in the outcome and biological correlates of the relationship between maternal stress and offspring outcome	Male and female offspring are susceptible to prenatal stress, though effects differ. Non identifiable specific vulnerable period of gestation. Prenatal stress effects vary for gestational ages depending on the developmental stage of brain areas and circuits, stress and immune system
<i>Systematic review and Meta-analysis (Level I)</i>			
Finlay–Jones et al., 2023	Systematic Review and MetaAnalysis: Early Irritability as a Transdiagnostic Neurodevelopmental Vulnerability to Later Mental Health Problems	Determine strength of association between irritability at 0-5 years and future externalizing and internalizing symptoms	Small to moderate pooled associations between irritability, externalizing and internalizing symptoms
<i>Pathogenesis, Pathophysiology, Mechanism, and Components of Childhood irritability</i>			
<i>Prospective (Level II)</i>			
Chess et al., 1963	Interaction of temperament and environment in the production of behavioral disturbances in children	Determine the nature of variables that contribute to formation of personality and the characteristic of the process among these variables	Behavioral disturbance is accounted for by temperament-environment interactions that follow a pattern
Stringaris et al., 2010	Pediatric Bipolar Disorder Versus Severe Mood Dysregulation: Risk for Manic Episodes on Follow-Up	Determine if youth with severe mood dysregulation are less likely to develop (hypo-)manic or mixed episodes than youth with bipolar disorder.	Youths with SMD are unlikely to develop (hypo-)manic or mixed episodes over a 2 year follow up period
Orri et al., 2018	Association of Childhood Irritability and Depressive/Anxious Mood Profiles With Adolescent Suicidal Ideation and Attempts	Identify developmental patterns of childhood irritability and direct association between childhood irritability and with suicidality or indirect association with intermediate mental health symptoms	Children following a rising or persistent irritability trajectory were at risk for higher suicidality. Indirect association with depressive symptoms but anxiety, disruptiveness, and hyperactivityimpulsivity
Eyre et al., 2019	Irritability in ADHD: association with later depression symptoms	Examine the association between childhood irritability and depression symptoms, and the association of persistence irritability	Persistent irritability was associated with depression symptoms at follow-up, especially after controlling comorbid psychiatric confounders like ADHD

Silver et al., 2021	Differential outcomes of tonic and phasic irritability in adolescent girls	Examine tonic and phasic irritability as empirically separable constructs and predict forms of psychopathology	Tonic irritability predicted the development of depressive and generalized anxiety disorders. Phasic irritability an increased probability of ODD, CD, substance use disorder, and relational aggression
<i>Systematic review/Meta analysis (Level I)</i>			
Vidal- Ribas et al., 2016	The Status of Irritability in Psychiatry: A Conceptual and Quantitative Review	Review the evidence on reliably measuring irritability and its validity	Irritability forms a distinct dimension with considerable stability across time, and that it is specifically associated with depression and anxiety longitudinally
<i>Cross sectional (Level IV)</i>			
Leibenluft et al., 2006	Chronic versus episodic irritability in youth: a community-based, longitudinal study of clinical and diagnostic associations	Examine the validity of the distinction between chronic and episodic irritability	Episodic and chronic irritability in adolescents are distinct stable constructs that require elucidation of longitudinal associations
Stringaris et al., 2013	Irritable mood as a symptom of depression in youth: prevalence, developmental, and clinical correlates in the Great Smoky Mountains Study	Determine the genetic factors that account for the association between irritability and depression	Irritability was significantly higher in girls than in boys and headstrong/hurtful behaviors were more common in boys than girls
Malhi et al., 2017	Irritability and internalizing symptoms: Modeling the mediating role of emotion regulation	Examine how emotion regulation mediates the relationship between irritability and internalizing symptoms	Indirect effect that suggests the relationship between irritability and internalizing symptoms is mediated by emotion dysregulation.
Deveney et al., 2019	On Defining Irritability and its Relationship to Affective Traits and Social Interpretations	Examine how emotion regulation mediates the relationship between irritability and internalizing symptoms	Indirect effect that suggests the relationship between irritability and internalizing symptoms is mediated by emotion dysregulation.
Liu et al., 2021	Differential associations of phasic and tonic irritability to suicidality among U.S. adults	Examine the role of tonic and phasic irritability in suicidal ideation, planning, and attempt	Both tonic and phasic irritability were associated with increased odds of suicidal ideation, age at first suicidal ideation and suicide attempt

Edmunds et al., 2023	Irritability as a Transdiagnostic Risk Factor for Functional Impairment in Autistic and Non-Autistic Toddlers and Preschoolers.	Determine the genetic factors that account for the association between irritability and depression	Irritability was significantly higher in girls than in boys and headstrong/hurtful behaviors were more common in boys than girls
Review (Level V)			
Safer et al., 2009	Irritable mood and the Diagnostic and Statistical Manual of Mental Disorders	Review of DSM categories described by irritability, anger, and aggression	Irritability is a non-specific term used in the DSM with an adverse effect on diagnostic specificity and treatment
Leibenluft E and Stoddard J., 2013	The developmental psychopathology of irritability	Review the construct of irritability, describe two broad neurocognitive systems differentiating irritable from nonirritable youths, suggest behavioral, neurocognitive, and physiologic measures to study irritability and argue for therapeutic trials targeting irritability and its associated	Significant progression has been made to clarify the irritability construct, create measures to enable research, establish the importance of irritability in developmental affective psychopathology, and suggest
		disruptive behavior.	neurocognitive and affective mechanisms.
Hameed et al., 2016	Irritability in Pediatric Patients: Normal or Not?	Describe the concept of irritability in neurobehavioral, organic, and nonorganic disorders	Distinguishing normal from abnormal irritability has significant clinical implications for establishing a diagnosis and implementing a treatment plan in primary care
Brotman et al., 2017	Irritability in Children and Adolescents	Clarify the definition of irritability, incorporate clinical and translational animal work; review historical context of irritability; review prevalence, clinical correlates, and longitudinal course of irritability; present behavioral and neurobiological findings associated with irritability; explore treatment options and propose future research directions	Aberrant reward learning and sensitivity, greater vulnerability to frustration, misinterpretation of facial emotions and perception of vague and neutral facial expressions as threatening, with corresponding neural dysfunction in the amygdala and prefrontal cortex during face emotion processing
Leibenluft E., 2017	A Systems Neuroscience Approach	To examine the clinical presentation, longitudinal course, clinical phenotypes, and genetic epidemiology of childhood irritability	Hyperreactivity to threat was found in irritable youth. This is mediated by dysfunction in amygdala, medial prefrontal cortex, ACC, insula, striatum, and association cortex

Riglin et al., 2017	Investigating the genetic underpinnings of early-life irritability	Examine the genetic underpinnings of irritability using a molecular genetic approach. To test the hypothesis that early irritability is associated with genetic risk for ADHD, and to investigate associations between irritability and polygenic risk scores (PRS) for major depressive disorder (MDD).	Early irritability traits share genetic risk with ADHD and indicate a marker of higher genetic loading in individuals with a ADHD.
Stringaris et al., 2018	Practitioner review: definition, recognition, and treatment challenges of irritability in young people	Discuss the presence of severe irritability in the context of other disorders, and recommend treatment algorithm	Irritability is a mood problem common to young people and associated with substantial impairment. exposure-based cognitive behavioral therapy techniques and interpretation bias training (IBT) are promising approaches that rely on pathophysiological findings
<i>Temperament- Irritability Axis</i>			
<i>Prospective (Level II)</i>			
Wiggins 2018	Identifying Clinically Significant Irritability in Early Childhood	Investigate the predictive validity of the cutoff for impairment and irritability trajectories and DSM disorders	The use of brief, developmentally optimized indicators can enhance the identification of early-onset irritability
<i>Cross-Sectional (Level IV)</i>			
Zentner M., 2020	Identifying child temperament risk	Develop a scale of child temperament characteristics that	Childhood temperament characteristics at
	factors from 2 to 8 years of age: validation of a brief temperament screening tool in the US, Europe, and China	predict behavior problems, are represented across models of temperament, and exhibit measurement invariance over childhood periods in different countries	risk for developing future behavior problems can be easily and effectively, assessed across age group given the balance between brevity and screening accuracy
Silver et al., 2023	Irritability and Temperament: Concurrent and Prospective Relationships in Childhood and Adolescence	Investigate cross-sectional and longitudinal associations between symptoms of irritability and temperament traits	Irritability symptoms are strongly associated with both temperamental negative affectivity and dysregulation of attention and behavior
<i>Review (Level V)</i>			
Rettew DC and MKee L., 2005	Temperament and its role in developmental psychopathology	Review core concepts relating to temperament, its origins and development.	Early identification of both external and internal temperamental risk factors in

			children allow for early interventions that truncate pathological trajectories
Gartstein and Skinner, 2018	Prenatal influences on temperament development: The role of environmental epigenetics	Summarize knowledge and future in relation to environmental epigenetics and development of temperament	Epigenetics plays a role in the molecular mechanism within environmental factors that impact early brain and temperament development.
<i>Genetics</i>			
<i>Cross-Sectional (Level IV)</i>			
Stringaris et al., 2012	Adolescent irritability: phenotypic associations and genetic links with depressed mood	Test the association between irritability and depression as mediated by “generalist genes that underlie phenotypic overlap between disorders.	Genes of general effects mediate the association between irritability and depression
<i>Systematic Review (Level I)</i>			
Akingbuwa et al., 2021	Systematic Review: Molecular Studies of Common Genetic Variation in Child and Adolescent Psychiatric Disorders	Review of studies utilizing molecular genetics and statistical approaches to investigate genetic variation in the development, persistence, and comorbidity of childhood psychiatric attributes	Genetic variation plays a considerable role in childhood psychiatric traits
<i>Early Life or Childhood Stress/Programming/Epigenetics/Biomarker</i>			
<i>Cross-Sectional (Level IV)</i>			
Brujin et al., 2009	Prenatal maternal emotional complaints are associated with cortisol responses in toddler and preschool aged girls	Examine differences in cortisol responses of prenatally exposed and nonexposed male and female children	Prenatally exposed girls showed higher cortisol levels across three episodes compared to nonexposed girls. No differences were identified in boys.
<i>Review (Level V)</i>			
Faravelli et al., 2012	Childhood stressful events, HPA axis and anxiety disorders.	Review data on function of HPA axis in anxiety disorders and the relationship between stressful life events in childhood and neuroendocrine dysfunction	Stressful childhood life events and HPA abnormalities may be related to all anxiety disorders, and more broadly, to all psychiatric disorders.
Duthie L and Reynolds RM., 2013	Changes in the maternal	To examine changing linkage in the maternal HPA axis	Excess glucocorticoid exposure is associated

	hypothalamic-pituitary-adrenal axis in pregnancy and postpartum: influences on maternal and fetal outcomes	intra and postpartum with the role of 11 β -hydroxysteroid dehydrogenase type 2 (HSD11B2) in maternal and fetal outcomes	with lower birth weight, shorter gestation at birth and re-setting of the HPA axis and vulnerability to neurodevelopmental problems on the long term. Changes in the maternal HPA axis, especially during the postpartum period, may increase susceptibility to mood disturbances.
Salponsky RM., 2015	Stress and the brain: individual variability and the inverted-U		
Bergh et al., 2020	Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy	To identify harmful stressors, vulnerable periods during pregnancy, specificities in the outcome and biological correlates of the relation between maternal stress and offspring outcome	Vulnerable period of gestation are nonspecific and prenatal stress effects differ for gestational ages depending on developmental stages of the growing brain, stress, and immune system
Dziurkowska E and Wesolowski M., 2021	Cortisol as a Biomarker of Mental Disorder Severity	Review reports on cortisol levels in healthy participants and highlights the current state of knowledge on changes in cortisol levels in people at risk for mood disorders, and psychosis.	Long-term exposure to high levels of cortisol in sensitive brain structures, could result in neurodegenerative changes and poor or failed response to treatment.