The Inherited Scars: How Ancestral Trauma Echoes in the Mental Health of Descendants: A Narrative Review.

Abstract

Background: Clinical and epidemiological observation over the past five decades indicates that severe adverse experience, depression, and anxiety in one generation are associated with elevated psychiatric morbidity in children and, in some populations, grandchildren, a phenomenon variously described as intergenerational, transgenerational, or historical trauma.

Objective: To synthesize evidence on how parental adverse experience, depression, and anxiety affect the mental health of children and grandchildren; to characterize the molecular pathology of the proposed epigenetic mechanisms; to examine prenatal and fetal programming pathways in depth; and to evaluate which treatments have been attempted and which have demonstrated success in interrupting this transmission.

Methods: A narrative review of peer-reviewed literature indexed in PubMed/MEDLINE, PsycINFO, Scopus, and Web of Science, following the SANRA quality criteria for narrative reviews, was conducted using structured keyword searches with defined inclusion and exclusion criteria.

Key Findings: Children of parents with trauma, depression, or anxiety show elevated risk of psychopathology through overlapping biological and psychosocial pathways, including glucocorticoid receptor and FKBP5 gene methylation transmitted through both maternal and paternal germlines, prenatal HPA-axis and placental programming, allostatic load and toxic-stress biological embedding, and disrupted attachment and modeled cognitive-affective style. Evidence for grandchild-level effects is strongest in famine and nutritional cohorts (Dutch Hunger Winter, Överkalix) and more limited and heterogeneous in psychiatric outcomes among third-generation Holocaust descendants; discrimination-related biological weathering extends this evidence to African American populations. Several interventions have been formally tested and shown measurable success: prenatal and infancy nurse home visitation, dyadic child-parent psychotherapy, attachment-based infant intervention, task-shared cognitive behavioral treatment of maternal depression, and narrative exposure therapy for the affected parent generation; a rodent model has further demonstrated that induced epigenetic marks are pharmacologically reversible, offering proof-of-principle rather than a current human treatment.

Conclusion: Ancestral trauma, depression, and anxiety act on descendants through modifiable, multifactorial pathways rather than fixed biological inheritance. The prenatal period constitutes a particularly high-yield and currently under-utilized window for prevention, and combined

biological-psychosocial models, together with evidence-based dyadic and home-visiting interventions, offer realistic means of breaking the cycle.

Introduction

Trauma has long been understood as an individual psychological injury, confined to the person who experienced it. Yet a growing body of clinical observation and empirical research indicates that the psychological sequelae of severe adversity, and of the depression and anxiety that so often follow it, can echo forward into the lives of children and, in some populations, grandchildren who never directly witnessed the precipitating event (1). This phenomenon, variously termed intergenerational trauma, transgenerational trauma, or historical trauma, was first described systematically among the children of Holocaust survivors, who were observed to present with anxiety, hypervigilance, and mood disturbance despite having no personal exposure to genocide (1). Subsequent decades of research extended this observation to the descendants of Indigenous peoples subjected to colonization and cultural genocide (2), to the children of refugees fleeing war and political violence (23,24), and to families marked by generations of childhood abuse, neglect, and parental mental illness as captured in the Adverse Childhood Experiences (ACEs) framework (3,4).

Much of the earlier literature in this area centered on parental post-traumatic stress disorder (PTSD) as the index exposure. Yet the majority of adults with significant trauma histories present clinically not with full PTSD but with depression and anxiety, and a substantial developmental literature independent of the trauma field has long documented that maternal and paternal depression and anxiety carry their own, partially distinct, risk to offspring through heritability, neuroregulatory, cognitive-behavioral, and contextual-stress pathways (5). Understanding how ancestral adversity affects descendants therefore requires attention not only to diagnosed PTSD but to the broader and more common presentations of depression and anxiety in affected parents (3,4,5).

The mechanisms proposed to explain this transmission are heterogeneous. Psychosocial theories emphasize disrupted attachment, parental affect dysregulation, altered communication, and modeled cognitive and emotional style (5,25). Biological theories, propelled by advances in molecular epigenetics, propose a genuine pathology of gene regulation: trauma and chronic distress alter DNA methylation, histone modification, and non-coding RNA content in genes governing the hypothalamic-pituitary-adrenal (HPA) axis, and some of these marks may be transmitted through gametic or gestational pathways to subsequent generations (6,7,8,9). Landmark rodent studies demonstrating that fear conditioning alters germline DNA methylation in unexposed offspring have lent biological plausibility to a phenomenon long observed only clinically (6,10). In humans, alterations in cortisol regulation and in glucocorticoid receptor gene (NR3C1) and FKBP5 methylation have been documented in the offspring of trauma survivors, offering a partial molecular correlate for clinically observed vulnerability (8,12,13,18).

This narrative review addresses six questions directly: how parental adverse experience, depression, and anxiety affect the mental health of children; what evidence exists for effects extending to grandchildren; what the underlying molecular pathology of epigenetic transmission actually consists of; what research shows about the prenatal period and fetal programming specifically; what treatments have been formally attempted and whether any have succeeded; and what additional steps might break the cycle and prevent these changes from taking hold. It further considers diagnostic implications under contemporary nosology (30,31,32) and examines resilience and post-traumatic growth as a counterweight to purely deficit-based models (33,34).

Methodology

This narrative review followed the Scale for the Assessment of Narrative Review Articles (SANRA) quality criteria, which emphasize transparent description of search strategy and balanced presentation of evidence, in place of the formal systematic review or meta-analytic protocols governed by PRISMA, which are not well suited to the conceptually heterogeneous, cross-disciplinary literature addressed here.

Databases searched: PubMed/MEDLINE, PsycINFO, Scopus, Web of Science, and Google Scholar were searched for literature published between January 1966 and June 2026, with particular emphasis on 2014 through 2026.

Search terms: Terms included, singly and in Boolean combination: “intergenerational trauma,” “transgenerational trauma,” “historical trauma,” “epigenetic inheritance,” “maternal depression offspring,” “prenatal anxiety fetal programming,” “adverse childhood experiences,” “Holocaust survivor offspring grandchildren,” “glucocorticoid receptor methylation,” “FKBP5,” “prenatal famine epigenetics,” “complex PTSD,” “child-parent psychotherapy,” and “nurse home visiting child abuse prevention.”

Inclusion criteria: Peer-reviewed, English-language original human cohort or case-control studies, translational animal studies with direct relevance to human trauma or depression transmission, randomized controlled trials of preventive or therapeutic interventions, systematic reviews and meta-analyses, and authoritative diagnostic guidance (DSM-5-TR, ICD-11) were included.

Exclusion criteria: Non-peer-reviewed sources, unindexed opinion pieces lacking empirical support, case reports without systematic data collection, and non-English publications without an available translation were excluded.

Reference lists of key retrieved articles were hand-searched to identify additional sources (snowball sampling). Given the breadth of disciplines involved, molecular epigenetics, developmental psychology, clinical psychiatry, and intervention science, a narrative rather than systematic synthesis was judged most appropriate.

Discussion

Historical and Conceptual Foundations of Intergenerational Trauma

The conceptual origins of intergenerational trauma theory trace to clinical observations made by psychoanalysts working with children of Holocaust survivors in the 1960s, who noted anxiety, guilt, and identity disturbance in offspring who had never themselves been persecuted (1). Rachel Yehuda and colleagues subsequently formalized this observation, establishing that offspring of Holocaust survivors with PTSD showed measurable alterations in cortisol regulation and increased vulnerability to PTSD themselves, despite growing up in relative safety (1,14,15).

Indigenous scholars in North America developed the parallel construct of historical trauma to describe the cumulative, multigenerational psychological wounding experienced by American Indian and Alaska Native communities following colonization, forced relocation, and boarding-school policies (2). Maria Yellow Horse Brave Heart explicitly drew on the Holocaust-offspring literature in articulating historical trauma as unresolved collective grief, transmitted through disrupted parenting and cultural discontinuity, manifesting as elevated depression, substance use disorder, and suicide (2).

A separate but complementary tradition emerged from the Adverse Childhood Experiences (ACEs) literature. The original CDC-Kaiser Permanente ACE study demonstrated a strong, graded relationship between childhood abuse, neglect, and household dysfunction (including parental mental illness) and adult depression, substance misuse, and suicidality (3). Subsequent meta-analytic work confirmed that this burden operates cumulatively, with four or more ACE categories conferring markedly elevated risk (4). Because parents with high ACE burden are themselves more likely to experience depression, anxiety, and impaired parenting capacity, the ACEs framework offers a psychosocial account of transmission operating independently of, but potentially alongside, biological mechanisms (3,4).

Taken together, Holocaust-offspring research, Indigenous historical trauma theory, and the ACEs framework converge on a shared observation: severe or chronic adversity in one generation is statistically associated with elevated psychiatric morbidity, most commonly depression and anxiety rather than full PTSD, in the next generation, even absent direct exposure (1,2,3,4).

The Pathology of Epigenetic Transmission: What Actually Changes at the Molecular Level

Understanding what is meant by an epigenetic “pathology” requires distinguishing it from a mutation: no letter of the DNA sequence is altered. Instead, chemical tags, principally methyl groups added to cytosine bases, along with histone modifications and changes in non-coding RNA content, alter how tightly DNA is packaged and how accessible a gene is to the transcriptional machinery that reads it (6,7,8). These marks are normally laid down during development to calibrate gene expression to the environment; the pathology arises when severe

or chronic adversity produces marks that persistently blunt or exaggerate expression of genes central to stress regulation, in a manner that outlives the original exposure and is passed to daughter cells, and in some documented cases to offspring (7,8).

The best-characterized target of this pathology is the glucocorticoid receptor gene, NR3C1, which governs how effectively cortisol shuts off the body's own stress response once a threat has passed. Foundational rodent work demonstrated that low maternal licking and grooming behavior produces increased methylation at a specific regulatory site (the NGFI-A binding site) in the NR3C1 promoter in offspring hippocampus, reducing glucocorticoid receptor expression and impairing negative feedback on the HPA axis; high maternal care produces the opposite, protective pattern, and the effect is reversible through cross-fostering, confirming it is epigenetic rather than genetic (7). The human translational counterpart came from postmortem hippocampal tissue: suicide victims with documented childhood abuse showed increased NR3C1 promoter methylation and reduced glucocorticoid receptor expression compared with suicide victims without abuse histories or non-suicide controls, directly demonstrating that early adversity leaves a measurable molecular scar on the human stress-regulation system (8).

A second, mechanistically distinct target is FKBP5, a co-chaperone protein that regulates how readily the glucocorticoid receptor translocates into the cell nucleus once cortisol binds it. Yehuda and colleagues found that Holocaust survivors and their offspring shared alterations at the same FKBP5 intron 7 site, and that maternal and paternal PTSD were associated with distinct patterns of both NR3C1 and FKBP5 methylation in adult offspring, with lower basal cortisol and enhanced dexamethasone suppression paralleling the pattern seen in the trauma-exposed parent (9,12,13,16,17). This produces a counterintuitive pathology: rather than the hypercortisolism one might expect from chronic stress, many trauma-exposed individuals and their offspring show hypocortisolism with heightened receptor sensitivity, a distinct risk phenotype rather than a simple exaggeration of normal stress physiology (14,16).

The most mechanistically direct evidence of true germline pathology comes from Dias and Ressler's demonstration that male mice conditioned to fear a specific odor transmitted heightened sensitivity to that odor, along with corresponding neuroanatomical change, to F1 and F2 offspring through hypomethylation of the relevant odorant receptor gene in sperm DNA, an effect preserved even with in vitro fertilization (6). Critically, this same research program demonstrated that the pathology is not fixed: targeted intervention could reverse the behavioral, neuroanatomical, and germline changes in subsequent generations, and separate rodent work showed that supplementing adult offspring's diet with methyl donors could reverse the maternal-care-induced NR3C1 methylation pattern and normalize stress behavior even after the critical developmental window had closed (10,11). These reversibility findings are conceptually important: they establish that epigenetic pathology, unlike a genetic mutation, is in principle modifiable rather than permanent, though translating methyl-donor or similar pharmacological reversal from rodents into a human treatment remains unestablished (10,11).

A caveat is essential to accurate interpretation. Klengel, Dias, and Ressler distinguish intergenerational transmission, in which the germ cells or fetus of the F1 generation are directly exposed to the ancestral stressor, from true transgenerational transmission, in which effects persist into the F3 generation without any direct exposure (9). Nearly all human data on Holocaust or refugee offspring examine the F1 generation, meaning current human evidence, while highly suggestive of a genuine molecular pathology, does not yet establish transgenerational germline inheritance in humans with the same certainty demonstrated in rodents (9,10).

This pathology is not limited to the maternal line. Rodgers and colleagues found that male mice exposed to chronic stress before mating produced offspring with altered HPA-axis regulation despite having no contact with those offspring after conception, and traced this paternal effect to changes in sperm microRNA content rather than DNA methylation alone, demonstrating that the father's stress history can be encoded epigenetically and transmitted independently of maternal caregiving or in-utero exposure (40). This finding is clinically relevant because much of the human literature, out of methodological necessity, has focused on maternal PTSD, potentially underestimating the paternal contribution to offspring risk (12,40).

Finally, it is important to distinguish this epigenetic pathology from ordinary genetic heritability. A classic twin study estimated that roughly thirty percent of the variance in liability to post-traumatic stress symptoms is attributable to genetic factors shared between twins, meaning that a substantial portion of intergenerational risk for PTSD reflects conventional inherited genetic vulnerability rather than any epigenetic mechanism (46). A subsequent review of the epigenetics-of-PTSD literature concluded that while several candidate genes, including NR3C1 and FKBP5, show replicated methylation differences associated with trauma exposure, most studies remain correlational, are drawn from peripheral blood rather than brain tissue, and cannot yet fully separate cause from consequence, underscoring that epigenetic pathology should be understood as one contributing layer within a broader genetic, epigenetic, and psychosocial risk architecture rather than the primary explanation on its own (41).

Allostatic Load and Toxic Stress: A Unifying Biological Framework

A useful way to integrate the molecular findings above with everyday clinical observation is the concept of allostatic load, introduced by McEwen to describe the cumulative physiological wear produced when stress-response systems, the HPA axis, the autonomic nervous system, and the immune and metabolic systems, are repeatedly activated or inadequately shut off over time (37). Unlike a single biomarker, allostatic load captures the combined toll of chronically elevated or dysregulated cortisol, inflammatory markers, and cardiometabolic stress mediators, and provides a physiological bridge between an individual's chronic stress history and later disease risk, including psychiatric illness (37,38).

Danese and McEwen extended this framework specifically to childhood adversity, proposing that ACEs become biologically embedded through allostatic overload during sensitive developmental periods, producing durable changes in stress physiology, immune function, and epigenetic regulation that persist into adulthood and, plausibly, into the next generation through the same prenatal and germline pathways discussed above (38). The American Academy of Pediatrics has since formalized a related three-tier model distinguishing positive stress (brief, buffered activation that builds healthy coping), tolerable stress (serious but time-limited activation buffered by a supportive adult relationship), and toxic stress (strong, frequent, or prolonged activation occurring without adequate adult buffering), with only the last category associated with the kind of lasting biological disruption relevant to intergenerational transmission (39).

This framework has direct clinical utility because it identifies the buffering relationship, most often a parent or consistent caregiver, as the single most important moderator determining whether a given adverse exposure produces toxic biological embedding or remains merely tolerable (38,39). It therefore reframes much of the evidence reviewed in this article: the pathology described in NR3C1 and FKBP5 methylation, in prenatal cortisol programming, and in disrupted attachment can all be understood as converging expressions of a single underlying process, allostatic overload occurring in the absence of adequate buffering, rather than as entirely separate mechanisms (7,8,16,18,37,38,39). This reframing also clarifies why interventions that restore a buffering relationship, discussed later in this review, have proven more effective than interventions directed at the child's symptoms in isolation (26,27,39).

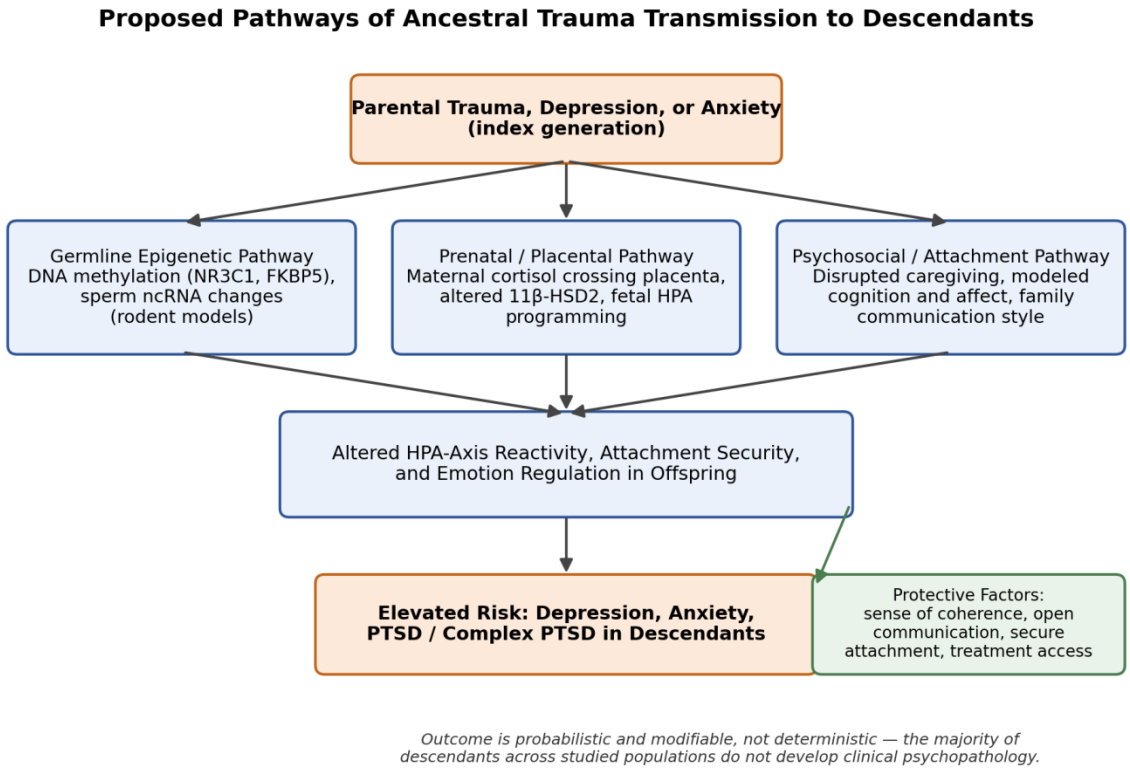

Figure 1. Three overlapping pathways — germline epigenetic, prenatal/placental, and psychosocial/attachment — by which parental trauma, depression, or anxiety may elevate descendant risk. Outcomes remain probabilistic and are moderated by protective factors (6–10,18–20,25,33,34).

Table 1. Key molecular targets implicated in epigenetic transmission of trauma

Gene / Target	Molecular Change	Functional Consequence	Population / Model	Ref.
NR3C1 (glucocorticoid receptor)	Increased promoter methylation at NGFI-A binding site	Reduced GR expression; impaired HPA-axis negative feedback	Rodent maternal-care model; human postmortem abuse/suicide tissue; Holocaust offspring	7,8,13
FKBP5	Altered methylation at intron 7	Reduced GR nuclear translocation; altered cortisol sensitivity	Holocaust survivors and offspring	9,12
Sperm microRNA (paternal)	Altered miRNA content following chronic stress	Reprogrammed offspring HPA-axis regulation independent of maternal care	Mouse, paternal-line transmission	40
Odorant receptor gene (Olfr151)	Sperm DNA hypomethylation	Transmitted odor-fear sensitivity; altered olfactory neuroanatomy	Mouse, F1/F2 generations	6,10
IGF2	Loss of imprinting / altered methylation	Dysregulated growth-gene expression	Dutch Hunger Winter famine cohort	19
Oxytocin-related signaling	Preliminary methylation differences (exploratory)	Proposed adaptive / protective phenotype	Third-generation Holocaust descendants	34

Children of Parents Who Experienced Adverse Events, Depression, or Anxiety

Independent of formal PTSD, the far more common parental presentation following adversity is depression and anxiety, and a substantial developmental literature has characterized how these conditions specifically affect children. Goodman and Gotlib's influential integrative model identifies four overlapping mechanisms of transmission from a depressed parent to a child: heritable biological vulnerability; innate dysfunctional neuroregulatory mechanisms present from infancy; the child's direct exposure to a parent's negative cognitions, withdrawn or irritable behavior, and blunted or dysregulated affect; and the broader stressful context, including marital conflict and socioeconomic strain, that so often co-occurs with parental depression (5). This model is useful precisely because it does not require any epigenetic mechanism to explain elevated offspring risk, while remaining fully compatible with the biological pathways described in the preceding sections operating in parallel (5,8,38).

Children of parents with high ACE burden, encompassing not only abuse and neglect but growing up with a parent who had depression, anxiety, or substance use disorder, show elevated rates of the same categories of adversity and psychiatric morbidity in the next generation, with the association strengthening as the number of parental ACE categories increases (3,4). Paternal depression and anxiety, historically understudied relative to maternal mental illness, has more recently been recognized as an independent risk factor and as a moderator that can either compound or partially buffer maternal-associated risk depending on the quality of the father-child relationship (5).

Much of this psychosocial transmission operates through attachment. Bowlby's original formulation proposed that infants form an internal working model of relationships based on the consistency and sensitivity of early caregiving, and Ainsworth's subsequent laboratory studies demonstrated that caregivers who are frightened, frightening, or unpredictable, patterns common among parents with unresolved trauma, depression, or anxiety, tend to produce insecure or disorganized attachment in their infants, itself a well-established predictor of later childhood and adult psychopathology (35,36). This attachment-based account provides the clearest mechanistic link between parental mental illness and offspring risk that does not depend on any biological or genetic pathway (35,36,5).

A large literature specific to antenatal (as opposed to postnatal) maternal anxiety and stress has found associations with altered fetal neurobehavioral development, including differences in fetal heart-rate variability and, postnatally, in infant temperament and attentional regulation, effects that appear at least partly independent of postnatal caregiving quality (42). A major Lancet review of perinatal mental disorders concluded that maternal depression, anxiety, and psychosis occurring specifically during pregnancy and the first postnatal year carry measurable and partly independent risks for offspring cognitive, behavioral, and emotional development, and explicitly

called for perinatal mental health treatment to be treated as a child-health intervention, not solely a maternal-health one (48). Glover's review reached a similar conclusion, arguing that the evidence base is now sufficient to justify the routine treatment of antenatal depression and anxiety as a means of primary prevention for offspring mental health problems, rather than waiting until postnatal symptoms or child difficulties emerge (49).

The clinical presentation in children of anxious or depressed parents commonly includes early behavioral inhibition, insecure attachment, elevated internalizing symptoms, and, by adolescence, their own depressive or anxiety disorders, a pattern that emerges gradually across development rather than as a discrete post-traumatic syndrome (5,25,35,36). This developmental, cumulative quality distinguishes the presentation of children of depressed or anxious parents from the more circumscribed, event-linked presentation associated with parental PTSD, even though the two frequently co-occur in the same families (5,14).

Effects on Grandchildren: What the Evidence Shows

Evidence bearing directly on grandchildren, as opposed to children, is more limited and derives from two distinct literatures: nutritional/famine cohorts and Holocaust-descendant cohorts. The Dutch Hunger Winter Families Study examined individuals conceived during the 1944-1945 famine in the Netherlands and found persistent DNA methylation differences, relative to same-sex unexposed siblings, at growth-regulatory loci measured six decades later, providing among the strongest human evidence that a discrete environmental exposure can leave a lifelong epigenetic signature (19). Because famine exposure during early gestation affects the developing germ cells of the exposed fetus as well as the fetus itself, this design permits inference about effects extending into the following (grandchild) generation, and associated cardiovascular and metabolic effects have been documented in that generation (19).

The Överkalix cohort in northern Sweden similarly found that grandparents' food availability during their own slow-growth period predicted their grandchildren's cardiovascular and all-cause mortality, with effects following a specific, sex-linked line of transmission (paternal grandfather to grandson, paternal grandmother to granddaughter), a pattern more consistent with a sex-specific germline mechanism than with shared family environment or genetics alone (20). While these two cohorts concern physical rather than psychiatric outcomes, they establish the biological plausibility of true multigenerational, non-genetic inheritance in humans, a plausibility that the psychiatric literature on Holocaust descendants has drawn upon by analogy (9,19,20).

For psychiatric outcomes specifically, evidence in third-generation Holocaust descendants is emerging but more heterogeneous than the first-generation offspring literature. Recent work has identified a “resilient-vulnerability” pattern in third-generation descendants, alongside preliminary biobehavioral findings suggesting that some inherited epigenetic profiles, for example those involving oxytocin signaling, may confer adaptive rather than purely pathological phenotypes (34). Second-generation offspring studies continue to find distinctive patterns of

psychological distress and altered sense of coherence relative to comparison groups, though findings are not uniform across cohorts and countries (33,34). Given the F1-versus-F3 distinction discussed above, current grandchild-level psychiatric findings should be regarded as suggestive rather than conclusive, and considerably more caution is warranted here than in the more mechanistically direct nutritional cohorts (9,19,20,34).

Pregnancy and the Fetal Environment: How Research Says This Happens Before Birth

Because most human intergenerational data reflect F1 (child) rather than F3 (grandchild) exposure, the prenatal period is the single best-characterized and most direct window through which parental adversity, depression, and anxiety are known to shape offspring biology, and it is also the window most amenable to intervention. Third-trimester maternal depressed or anxious mood is associated with increased methylation at a specific regulatory site within the NR3C1 promoter in neonatal cord blood, and this methylation pattern predicts elevated infant cortisol reactivity to stress at three months of age, independent of postnatal maternal mood, demonstrating that biological embedding of maternal psychological state can occur in utero, before any postnatal caregiving interaction (18).

Direct evidence on fetal and child brain development reinforces this picture. In a prospective cohort following maternal cortisol across the entirety of pregnancy, higher maternal cortisol, particularly earlier in gestation, predicted larger amygdala volume and more affective problems in the child years later, with effects differing by fetal sex and by the trimester of exposure, indicating that timing during gestation, not simply the presence of maternal distress, determines the specific developmental consequence (20). This timing-dependence is thought to reflect the placenta's own regulatory role: the enzyme 11β-hydroxysteroid dehydrogenase type 2 ordinarily degrades much of the cortisol that would otherwise cross from mother to fetus, but this placental barrier is itself sensitive to maternal stress and depression, and its natural decline nearer to term normally permits a late-gestation cortisol signal that supports organ maturation; disruption of this finely timed system by chronic maternal distress is one proposed route by which maternal mental illness becomes fetal biology (20).

Population-level natural experiments corroborate the plausibility of this pathway outside the psychiatric literature specifically. Women who were pregnant during the Dutch famine transmitted measurable epigenetic and metabolic consequences to their children that were detectable six decades later, establishing firmly that maternal physiological state during a discrete gestational window can leave a durable biological mark independent of any postnatal parenting effect (19). Applied to maternal mental illness specifically, this body of work indicates that treating depression, anxiety, and traumatic stress during pregnancy, not only after birth, may be biologically necessary rather than merely convenient, since the relevant programming can occur before any postnatal intervention is possible (18,19,20).

Population-Specific Evidence: Holocaust, Indigenous, and Refugee Descendants

Among Holocaust-survivor descendants, the evidence base is unusually mature, spanning more than three decades of biological, psychological, and epidemiological research (1,14,15). Offspring of survivors with PTSD have consistently shown alterations in cortisol regulation and elevated, though not universal, rates of PTSD and mood disorder, more pronounced when the mother, rather than the father, carried a PTSD diagnosis, suggesting an in-utero or early-postnatal contribution alongside genetic and psychosocial pathways (14,15,16,17).

Among Indigenous populations in North America, historical trauma theory has generated a substantial clinical and community-based literature linking the cumulative trauma of colonization and residential schooling to contemporary disparities in depression, substance use disorder, and suicide risk, generated predominantly through qualitative and community-based participatory methods rather than biological cohort studies (2).

Refugee populations, particularly Cambodian and Vietnamese refugees, provide a third well-studied population. Sack and colleagues found that parental PTSD symptoms following the Khmer Rouge genocide were significantly associated with PTSD and depressive symptoms in children with no direct exposure to the genocide itself (23). Field and colleagues identified emotionally overinvolved and restrictive parenting styles as key mediators of this transmission (24), while research on Southeast Asian refugee families in the United States found that maternal traumatic distress predicted poorer family functioning, which in turn predicted worse child mental health outcomes (25). Across these populations, parental trauma exposure is consistently associated with elevated offspring morbidity, more strongly when the affected parent is the mother, though the effect is never universal (1,2,23,24,25).

A fourth relevant body of evidence concerns African American populations, for whom the historical legacy of slavery, segregation, and ongoing structural discrimination has been studied primarily through the lens of biological “weathering” rather than the germline epigenetic paradigms applied to Holocaust or famine cohorts. Brody and colleagues found that rural African American adolescents who displayed high competence and self-control despite considerable socioeconomic adversity nonetheless showed elevated allostatic load by age nineteen, coining the term “skin-deep resilience” to describe apparently successful psychological adaptation purchased at a measurable biological cost (44). Simons and colleagues subsequently found that cumulative economic hardship and associated discrimination-related stress were associated with accelerated epigenetic aging in a sample of Black American women, providing molecular evidence that chronic social adversity, independent of any single discrete traumatic event, can produce the same category of biological embedding described throughout this review (45). While this literature has not yet been extended to direct intergenerational or germline transmission with the same rigor as the Holocaust or famine cohorts, it broadens the ancestral-trauma framework to

encompass chronic, structurally embedded adversity rather than only discrete historical catastrophe (38,44,45).

Diagnostic Considerations: Complex PTSD and Clinical Presentation in Descendants

The clinical presentation of trauma-affected descendants poses diagnostic challenges. DSM-5-TR retains a single PTSD diagnosis requiring a qualifying traumatic event, a framework that maps imperfectly onto descendants who present with trauma-related symptomatology inherited from a parent rather than personally experienced (31). ICD-11 addresses part of this gap through complex post-traumatic stress disorder (CPTSD), which adds disturbances in self-organization, affect dysregulation, negative self-concept, and relational difficulty, to the core PTSD clusters, a formulation designed for prolonged or developmentally early trauma exposure (30,32). A comprehensive review of the evidence found the ICD-11 PTSD/CPTSD two-factor structure empirically supported across most studies examined, with CPTSD associated with greater functional impairment than standard PTSD (30).

Because descendants frequently present with pervasive emotional dysregulation and relational instability rather than a discrete index trauma, the CPTSD construct may offer improved, though still incomplete, clinical utility for this population; neither DSM-5-TR nor ICD-11 contains a formal category for inherited or ancestral trauma exposure, and clinicians must rely on careful family and historical history-taking that standard interviews do not automatically elicit (30,31,32).

Interventions and Treatment Outcomes: What Has Been Tried, and What Has Worked

Several distinct interventions, targeting different points in the transmission pathway, have been formally tested in randomized controlled trials, and the evidence indicates that meaningful success is achievable, though no single intervention eliminates risk entirely.

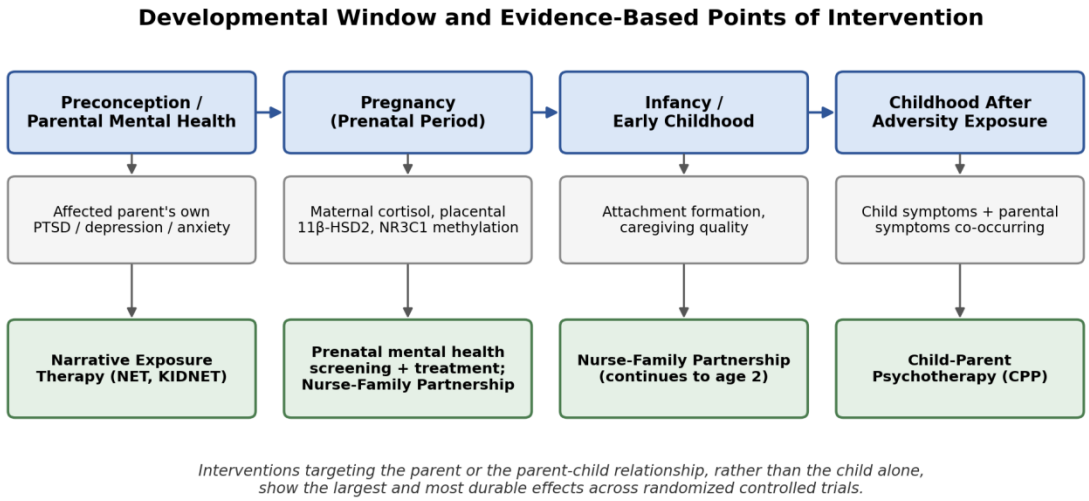

Figure 2. Developmental window and evidence-based points of intervention, from preconception treatment of the affected parent through childhood dyadic therapy (26–29,43,47,50).

Table 2. Interventions tested along the transmission pathway

Intervention	Target / Timing	Study Design	Key Outcome	Ref.
Nurse-Family Partnership	Prenatal through age 2; parent-focused	3 RCTs (Elmira, Memphis, Denver) + international replications	48% reduction in verified child abuse/neglect at 15-yr follow-up	26
Attachment and Biobehavioral Catch-up (ABC)	Infancy/toddlerhood; caregiver coaching	RCT, foster infants and toddlers	More normative diurnal cortisol production vs. control	50
Child-Parent Psychotherapy (CPP)	Parent-child dyad after trauma exposure	RCT, preschoolers exposed to marital violence	Reduced child PTSD/behavior problems and maternal PTSD/avoidance	27
Thinking Healthy Programme	Maternal depression (antenatal/postnatal)	Cluster-RCT, rural Pakistan	Improved maternal depression and infant growth/health outcomes	47
Narrative Exposure Therapy (NET/KIDNET)	Individual, affected parent or child	RCTs, refugee adults and children	Significant reduction in PTSD/depressive symptoms	28,29
Trauma-focused psychotherapy (CBT, EMDR, general)	Individual, affected parent generation	Cochrane systematic review of RCTs	Moderate-to-large reduction in chronic PTSD severity	43
Methyl-donor dietary supplementation	Germline/epigenetic reversal (preclinical)	Rodent model	Reversal of NR3C1 methylation and stress phenotype in adulthood	10,11

The earliest and most upstream approach is prenatal and infancy nurse home visitation. The Nurse-Family Partnership, tested across three independent randomized controlled trials in

different American cities, begins during pregnancy and continues through the child's second birthday; at fifteen-year follow-up, nurse-visited families showed a 48% reduction in state-verified child abuse and neglect relative to controls, alongside improvements in maternal life course and child developmental outcomes, and the program has since been replicated internationally with comparable effects on child maltreatment (26). Because this intervention begins in pregnancy, before the prenatal programming pathways described above can fully operate, it represents the most upstream evidence-based option currently available for interrupting transmission at its origin (18,19,20,26).

A second, more targeted approach is dyadic, relationship-based treatment for parent-child pairs already affected by trauma. Child-Parent Psychotherapy (CPP), tested in a randomized controlled trial of preschool-age children exposed to marital violence and their mothers, produced significant reductions in children's traumatic stress symptoms and behavior problems, together with reductions in mothers' avoidance symptoms and overall PTSD severity, with benefits durable at six-month follow-up (27). This finding is notable because it demonstrates that treating the parent and child together, rather than the child alone, can simultaneously reduce the parent's own symptom burden and the child's inherited risk, directly targeting the psychosocial transmission pathway described earlier in this review (5,25,27,35,36).

A closely related, explicitly attachment-focused approach is Attachment and Biobehavioral Catch-up (ABC), a short, coached parenting intervention designed for infants and toddlers at high risk for disrupted caregiving. In a randomized controlled trial with foster infants and toddlers, children who received ABC showed more normative diurnal cortisol production patterns than children who received a control intervention, providing rare human evidence that a brief, targeted attachment intervention can measurably shift the same HPA-axis biology implicated throughout this review's discussion of epigenetic pathology (50). Together with CPP, this supports the view that relationally focused interventions can act on the biological, and not only behavioral, level of transmission (27,50).

A fourth approach targets maternal depression specifically, rather than PTSD, and has been tested at scale in a low-resource setting. The Thinking Healthy Programme, a cognitive behavioral therapy-based intervention delivered by trained, non-specialist community health workers to depressed mothers in rural Pakistan, was evaluated in a cluster-randomized controlled trial and produced significant improvements in maternal depression along with improved infant growth and health outcomes at both six and twelve months, later adopted by the World Health Organization as a model for task-shared perinatal mental health care in low- and middle-income settings (47). This trial is particularly relevant to the question of whether treating parental depression, as opposed to trauma or PTSD specifically, can benefit offspring: because the intervention targeted the mother's depression directly and measured child outcomes as a secondary endpoint, it offers among the clearest experimental evidence that treating parental mental illness produces benefit for the child, and that such treatment can be delivered without requiring specialist mental health infrastructure (5,47,48).

A fifth approach targets the affected parent generation directly. Narrative Exposure Therapy (NET), a short-term, manualized treatment originally developed for survivors of war, torture, and organized violence, has demonstrated significant reductions in PTSD and depressive symptoms in randomized controlled trials among refugee adults, and a child-adapted version (KIDNET) has shown comparable efficacy in traumatized refugee children as young as seven (28,29). A broader Cochrane systematic review of psychological therapies for chronic PTSD in adults, encompassing trauma-focused cognitive behavioral therapy, eye movement desensitization and reprocessing, and related approaches, found consistent, moderate-to-large reductions in PTSD symptom severity relative to waitlist or usual care, confirming that effective, generalizable treatment exists for the parent generation's own trauma symptoms, independent of the refugee-specific NET literature (43). Because parental symptom severity is one of the more consistent predictors of offspring outcome across the Holocaust, refugee, and ACEs literatures, successfully treating the parent's own PTSD, depression, or anxiety is itself a plausible, evidence-supported route to reducing transmission risk, even though this has rarely been tested as a primary outcome in intergenerational-transmission trials specifically (9,14,23,24,28,29,43).

Finally, at the molecular level, rodent research offers proof-of-principle that the epigenetic pathology itself is reversible: supplementing the diet of adult offspring with methyl donors normalized both NR3C1 methylation and the associated stress-behavior phenotype that had been established by early maternal care, even after the sensitive developmental period had closed, and separate work reversed germline-transmitted changes in subsequent generations through targeted intervention (10,11). These findings are conceptually important and encouraging, but they remain preclinical; no human pharmacological intervention has yet been shown to reverse trauma-associated epigenetic marks, and this should not be overstated as an available treatment (10,11).

Taken together, the intervention evidence indicates that success has been demonstrated at several distinct points: prenatal and infancy support for the parent (26), attachment-focused coaching of caregivers of high-risk infants with measurable biological effect (50), dyadic treatment of the parent-child relationship after adversity has occurred (27), task-shared treatment of maternal depression with documented benefit to the child (47), and individual, generalizable treatment of the affected parent's own PTSD or depressive symptoms (28,29,43), with the common thread that interventions addressing the parent, or the parent-child relationship, rather than the child in isolation, consistently show the largest and most durable effects (5,26,27,47,50).

Resilience, Post-Traumatic Growth, and Protective Factors

A purely deficit-focused account risks obscuring an equally important finding: most descendants of severely affected populations do not develop clinically significant psychopathology, and many demonstrate resilience and post-traumatic growth (33,34). Fogelman's analysis of resilience among Holocaust-survivor descendants challenges narratives suggesting trauma is inevitably and deterministically “passed down” through biology, arguing that family communication style,

community support, and individual coping resources substantially moderate outcomes (33). Recent work on second-generation offspring has identified a “resilient-vulnerability” construct, and sense of coherence, an individual's capacity to perceive their world as comprehensible and manageable, has emerged as a protective factor distinguishing those who develop distress from those who do not (34).

Protective factors identified across populations include open, developmentally appropriate family communication about ancestral adversity; strong cultural or community connectedness; secure attachment within the family; and access to the evidence-based interventions described above (2,27,28,29,33,34). These findings collectively support conceptualizing intergenerational trauma as a modifiable risk state rather than a fixed inheritance.

Future Directions and Recommendations: Breaking the Cycle

- Treat maternal depression, anxiety, and PTSD during pregnancy, not only after birth, since fetal programming through cortisol and placental pathways can occur before any postnatal intervention is possible; prenatal mental health screening should be integrated into routine obstetric care with the same rigor as physical screening.
- Prioritize scale-up of prenatal and infancy nurse home visiting (e.g., Nurse-Family Partnership) for at-risk pregnant people, given its demonstrated, replicated reduction in child maltreatment and its position as the most upstream evidence-based intervention available.
- Expand access to attachment-focused caregiver coaching (e.g., Attachment and Biobehavioral Catch-up) and dyadic relationship-based treatment such as Child-Parent Psychotherapy for parent-child pairs after trauma exposure, since treating the relationship rather than the child alone reduces both parties' symptom burden and, in the case of ABC, has shown measurable biological effect.
- Invest in task-shared, low-resource models such as the Thinking Healthy Programme to treat maternal depression at scale, since specialist-delivered care alone will not reach the majority of affected parents globally, and this model has demonstrated benefit to both mother and infant.
- Ensure affected parents themselves receive evidence-based trauma treatment (e.g., Narrative Exposure Therapy, trauma-focused CBT, or EMDR), since parental symptom severity is among the most consistent predictors of offspring risk across populations studied, and meta-analytic evidence supports meaningful symptom reduction with these approaches.
- Adopt the allostatic-load and toxic-stress framework as a unifying clinical model, since it identifies the presence or absence of a buffering adult relationship, rather than the adverse exposure itself, as the key determinant of whether biological embedding occurs, directing intervention toward strengthening that relationship.
- Pursue prospective, multigenerational cohort designs that collect biological, prenatal, and psychosocial data concurrently in the same families, including paternal as well as maternal

exposure, to determine the relative contribution of each pathway rather than attributing outcomes to any single mechanism.

- Extend epigenetic and biological-weathering research on grandchildren and on discrimination-affected populations beyond famine, nutritional, and Holocaust-descendant cohorts into psychiatric outcomes specifically, using designs capable of distinguishing true transgenerational (F3) inheritance from intergenerational (F1) exposure.
- Develop a clinical framework, potentially an ICD-11 or DSM specifier, for trauma-related symptomatology in descendants who have not personally experienced a qualifying traumatic event.
- Communicate epigenetic findings to the public and to affected families with caution, since overstated claims of deterministic biological inheritance risk increasing stigma and fatalism without corresponding clinical benefit, when the evidence instead supports a modifiable risk model.

Conclusion

The evidence reviewed here indicates that parental adverse experience, depression, and anxiety measurably affect the mental health of children through overlapping biological and psychosocial pathways, including germline mechanisms transmitted through both the maternal and paternal line, prenatal and placental programming, attachment disruption, and the cumulative biological toll captured by the allostatic-load and toxic-stress frameworks. Effects on grandchildren are well established for physical and metabolic outcomes in nutritional cohorts but remain more limited and heterogeneous for psychiatric outcomes specifically, and discrimination-related biological weathering extends the ancestral-trauma framework beyond discrete historical catastrophe to chronic structural adversity. The molecular pathology underlying biological transmission, principally DNA methylation at the glucocorticoid receptor and FKBP5 genes and altered sperm microRNA content, is real, measurable, and, based on preclinical evidence, in principle reversible rather than fixed, though this reversibility remains unestablished as a human treatment. The prenatal period emerges as the single most direct and intervenable window in this entire process. Encouragingly, treatment has been attempted and has succeeded at several points along the pathway: prenatal and infancy home visiting, attachment-focused caregiver coaching, dyadic parent-child treatment, task-shared treatment of maternal depression, and trauma-focused therapy for the affected parent generation have each demonstrated meaningful, replicated reductions in risk. Ancestral trauma is therefore best understood not as an unbreakable biological sentence but as a modifiable, multifactorial risk state, one for which a growing evidence base already identifies concrete, actionable points of prevention and intervention.

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