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The Long-Term Impact of Early Adversity on Late-Life Psychiatric Disorders

Anda Gershon · Keith Sudheimer · Rabindra Tirouvanziam · Leanne M. Williams · Ruth O'Hara

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Abstract Early adversity is a strong and enduring predictor of psychiatric disorders including mood disorders, anxiety disorders, substance abuse or dependence, and posttraumatic stress disorder. However, the mechanisms of this effect are not well understood. The purpose of this review is to summarize and integrate the current research knowledge pertaining to the long-term effects of early adversity on psychiatric disorders, particularly in late life. We explore definitional considerations including key dimensions of the experience such as type, severity, and timing of adversity relative to development. We then review the potential biological and environmental mediators and moderators of the relationships between early adversity and psychiatric disorders. We conclude with clinical implications, methodological challenges and suggestions for future research.

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A. Gershon (✉) · K. Sudheimer · L. M. Williams · R. O'Hara
Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94305-5717, USA
e-mail: gershon@stanford.edu

K. Sudheimer
e-mail: ksudheim@stanford.edu

L. M. Williams
e-mail: leawilliams@stanford.edu

R. O'Hara
e-mail: roh@stanford.edu

A. Gershon · R. O'Hara
Sierra Pacific Mental Illness Research Education and Clinical Center (MIRECC), Palo Alto, Veterans Health Care System, Palo Alto, CA, USA

R. Tirouvanziam
Department of Pediatrics, Emory University School of Medicine, 2015 Uppergate Dr, Atlanta, GA 30322-1014, USA
e-mail: tirouvanziam@emory.edu

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Introduction

Numerous large-scale community-based studies have documented that exposure to adversity early in life is a robust predictor of psychiatric disorder onset including mood disorders, anxiety disorders, eating disorders, substance abuse or dependence, and posttraumatic stress disorder (PTSD) [1–11] as well as personality disorders [12]. Moreover, the risk for psychiatric disorders following early adversity appears to persist into old age [13–16], although the data are limited. However, not everyone who experiences an early adversity will subsequently develop a psychiatric disorder. There is some evidence that specific types of early adversity, such as abuse, may contribute more to risk for psychiatric disorders than others [17•]. Thus, there is increasing interest in understanding the mechanisms by which adversity leads to psychiatric disorders, and in identifying the factors that may modify these long-term effects. The goal of this review is to summarize the current knowledge pertaining to the psychiatric impact of exposure to early adversity, with a particular emphasis on the effects that persist into older age.

Early Adversity: Definitional Considerations

A wide array of experiences is subsumed under the term "early adversity," including abuse or assault, neglect, poverty, death of a parent (or primary caretaker), parental chronic physical or mental illness, alcohol or substance problems, or criminality, parental separation, physical illness or injury

during childhood, domestic violence, peer victimization, violence and/or criminal behavior in one's neighborhood or community, and involvement in a war or a natural disaster.

The definition of early adversity also varies considerably depending on whether one focuses on the stressful event itself or the response to the event. The term may refer to a psychological event (e.g., neglect), biological event (e.g., physical illness), psychological response (e.g., distress), or a biological response (e.g., activation of the sympathetic nervous system). Furthermore, the adversity may occur as a single acute event, repeated episodes or a chronic condition. The response may similarly be immediate or prolonged. Adversity may have components that are both physical/biological and psychological within the same event. Moreover, the psychological aspects of the adversity may lead to physiological consequences and vice versa. Failing to parse apart these differential sources of stress has led to substantial confusion within the field and difficulty in interpreting findings across studies.

Here we define early adversity as single or multiple, acute or chronic stressful events which may be biological or psychological in nature, occurring during childhood and resulting in a biological and/or psychological stress response. In addition to consideration of the above distinctions, the impact of early adversity on psychiatric risk also likely depends on several key dimensions of the experience, including type, severity, and timing of adversity relative to development.

Type of Early Adversity

Theoretical models have posited that specific adversity types may be uniquely related to specific psychiatric outcomes. A review of over 200 youth studies examining the relationship between exposures to a range of early adversities and internalizing versus externalizing symptoms found little evidence for such specificity [18]. Findings from the National Comorbidity Survey (N=5,692, 18 and older) indicate that while exposure to early adversities is associated with psychiatric illness in adulthood, this relationship also appears to be non-specific [2, 19]. Cross-national data from the WHO World Mental Health surveys conducted in 21 countries also indicates little evidence for specificity in the association between adversity type and psychiatric outcome [20]. Thus, studies with youth and adult samples suggest that while exposure to early adversity is associated with increased risk for psychiatric disorder, the risk is non-specific.

Severity of Early Adversity

Accumulating evidence from nationally representative studies of youth [21] and adults [2] suggests over half of those exposed to adversity suffer multiple and co-occurring adversities. Several studies support a dose–response relationship such that the probability of developing a psychiatric disorder is proportional to the number and severity of adversities experienced. Among adult community women (N= 732, ages 36–45 years), those who experienced multiple categories of childhood abuse were found to be at highest relative risk for depression, compared to women who reported one form of abuse, who were, in turn, at higher risk for depression than women with no abuse history [22]. Felitti et al. [23] similarly identified a strong dose–response relationship between the number of childhood exposures and risk for negative health outcomes, including alcohol or substance abuse, depression, and suicidality, in a large sample of HMO members (N=9,508, mean age=56.1 years). A dose–response effect between severity of childhood sexual abuse and risk for disorder was also found in a population-based sample of 1,411 female twins (ages 17–55 years) [3]. Similar patterns have been found for the effects of early adversity on neurocognitive impairment. Echoing the cumulative effect found for psychiatric disorders, Evans and Schamberg [24] showed that the greater the proportion of childhood spent in poverty, the poorer one's working memory as a young adult. The dose–response effect appears to persist into old age. In a sample of over 22,000 adults 60 years of age or older, the effects of experiencing both physical and sexual abuse in childhood was associated with worse outcomes than experiencing either form alone [25]. Thus, the initial data in older adults suggest that risk of developing a psychiatric disorder may, as at other stages of the lifespan, be proportionally related to the severity of adversity exposure.

Timing of Early Adversity

Theorists have argued that exposure to adversity during the critical developmental periods of late childhood and early adolescence may confer high vulnerability to particular forms of psychiatric disorders, perhaps owing to the rapid brain development that occurs during these ages [26, 27]. Exposure to sexual abuse after the age of 12 has been associated with an increased risk for PTSD in adulthood, whereas sexual abuse before the age of 12 was associated with an increased risk for depression [28]. In a birth cohort sample of 496 cases of court-substantiated abuse (mean age=39.5 years) the experience of abuse before age 12 was associated with increased risk for internalizing symptoms (e.g., depression, anxiety) in adulthood whereas the experience of abuse after age 12 was associated with externalizing symptoms (e.g., behavioral problems, inattention, impulsivity) [29]. Thus, the transition to puberty may be a critical developmental period which carries increased risk for particular forms of psychiatric disorders.

There is some evidence that the risk associated with adversity during stages of critical brain development persists into late life. Yehuda and colleagues [30] found that Holocaust survivors diagnosed with current PTSD (n=35) showed impaired ability to learn new information compared to survivors without a current PTSD diagnosis (n=26) or controls (n=40). Interestingly, the specific long-term cognitive impairments identified among Holocaust survivors differed from long-term cognitive impairments identified among Vietnam veterans. The authors speculate that these differences may relate to the timing in trauma exposure: While Vietnam veterans were exposed to trauma during early adulthood (military service) many Holocaust survivors were still children/adolescents during the exposure.

Mediators of the Relationship Between Early Adversity and Psychiatric Disorders

At least two broad pathways have been hypothesized to explain the impact of adversity on later psychiatric risk. First, exposure to early adversity may become "biologically embedded" [31], altering the development of key physiological systems (hypothalamic–pituitary–adrenal axis, HPA, and immune function). Second, exposure to early adversity may be a psychosocial index of continued stress exposure, such that those who experience adversity in childhood are more likely to suffer subsequent stress [32, 33].

Biological Mediators: HPA Function

Substantial evidence exists to support the hypothesis of the sustaining physiological effects of early adversity. Several types of acute stressors that occur in association with adversity can activate an immediate response of the HPA and sympathetic adrenal medullary axes beginning with the release of hypothalamic corticotropin releasing hormone (CRH), which initiates the endocrine response to stress. CRH then prompts the release of adrenocorticotropin (ACTH). ACTH promotes the release of glucocorticoids from the adrenal cortex. Glucocorticoids regulate the utilization of energy and provide negative feedback at the level of the hypothalamus and pituitary (for reviews see [34–36]). Glucocorticoids also affect the morphology and functionality of central nervous system target tissues, including those responsible for mood and cognitive functions relevant to psychiatric disorders [37–40].

Some types of early life adversity can negatively impact HPA responsiveness and regulation. Studies have shown that children raised in an environment of secure parental attachments and attentive care giving show lower stress-induced cortisol release [41]. By contrast, abused children show hallmarks of an HPA axis that has already adapted to a trauma, such as lower early morning cortisol secretion [42], reduced CRH-stimulated ACTH release, and reduced circadian production of ACTH [43].

Few prospective longitudinal studies have linked HPA response to adversity in youth with psychiatric risk in late life. However, retrospective studies suggest that early stressors can have an enduring influence on HPA axis activity. Adults with a history of early adversity, in the form of childhood abuse exhibit signs of HPA axis trauma adaptations, including flattened diurnal variability and lower early morning cortisol secretion [44], more robust dexamethasone suppression of cortisol [45], increased ACTH release and lower cortisol responses to either CRH administration [35] or a laboratory stressor [46]. Adult holocaust survivors with PTSD also show similar adaptations compared to adults that did not experience the holocaust [47]. In addition to trauma and PTSD, impaired HPA activity in later life has also been associated with depression (for a review see [48]).

HPA axis adaptations to a chronically high adversity environment or traumatic events may have short term survival advantages for living in dangerous environments but also carry the risk of long term effects on cognition and emotion and risk for psychiatric disorders later in life.

Biological Mediators: Immune Function

The HPA axis is not the only physiological system impacted by stress. The immune system encompasses a complex set of pro-inflammatory mediators, specifically cytokines, chemokines, and growth factors, all of which have been proposed as mediators of the relationship of adversity to psychiatric disorders. It is very difficult to investigate long-term effects of early adversity on immune function in adulthood, and animal models are often too simple with regards to the range of stressors and life episodes that can be tested. In animal models, stressors exerted to the mother (pre- or postnatally) and/or to the infant, in the form of nutritional imbalance, infectious agents and/or toxicants, physical restraint, or mother–infant separation can lead to long-lasting immune imbalances or altered "immune set points" [49–51]. Altered immune set points may lead to the chronic secretion of pro-inflammatory signals, contributing to heightened immune responsiveness. These altered set points are sometimes associated with changes in the HPA axis, notably glucocorticoid levels [52], emphasizing the functional link between the brain and the immune system [53]. Early stressors such as abuse can result in PTSD-like symptoms, and manifest as changes in the immune set points [54]. One of the only large-scale prospective longitudinal study of a birth cohort followed to age 32 has

shown that maltreatment in the first decade of life is associated with high-sensitivity C-reactive protein (hsCRP) levels, a biomarker of inflammation [55]. This effect was independent of potential confounds (e.g., low SES, depression, high levels of stress in adulthood, smoking, unhealthy diet), and findings support a dose–response relationship between severity of early adversity and inflammation.

Among healthy older adults who were dementia caregivers and non-caregivers (N=132, mean age=70), those who experienced childhood adversity showed greater proinflammatory cytokine levels, interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α, as well as telomere length, than those without such history. Effects were only partially attributable to caregiving, suggesting that early adversity influences immune function beyond the effects of the stress associated with caregiving [56]. In a follow-up study with this sample, Gouin and colleagues [57] found that those exposed to abuse, in particular, exhibited elevated IL-6 responses to daily stressors. Similar to findings on HPA, altered immune set points have the potential to be normalized, or "buffered," by positive influences such as social support [58]. Although it stands to reason that these effects could persist through adulthood, studies have not yet examined the role of social support in general for moderating long-term effects of early adversity.

Psychosocial Mediators: Adult Stressors

Theorists have articulated a transactional model of stress continuity, whereby exposure to early adversity alters psychosocial processes, generating further stress, and leading to increased psychiatric risk. Using data from a longitudinal survey of adults, Kessler and Magee [7] found that interpersonal stress in adulthood mediated the effect of childhood family violence on recurrence of depression. The authors speculated that exposure to family violence in childhood may have disrupted interpersonal functioning thereby increasing reactivity to future stressors and, in turn, depressive recurrence. Similarly, McLeod [59] found that marital strain in adulthood mediated the relationship between exposure to parental divorce in childhood and adult depression. On the other hand, some studies indicate adult stressors do not contribute to adult psychopathology over and above exposure to early adversity (e.g., [17•]).

Moderators of the Relationship Between Early Adversity and Psychiatric Disorders

Gender

Rates of exposure to childhood adversity vary between genders by type of adversity; Childhood sexual abuse is more prevalent in females whereas childhood physical abuse are is more prevalent in males [8, 9, 60, 61]. A recent literature review of community-based samples in which gender differences were specifically tested for found that nearly half of all studies report no gender differences in effects of childhood victimization on risk for psychiatric disorder across the lifespan. In studies that did observe gender differences, victimization tended to be associated with higher psychiatric risk in females in studies with adult samples, whereas in youth samples, victimization tended to be associated with higher psychiatric risk in males [62]. These results underscore the need for elucidating more precise age-specific paths for psychiatric disorders.

Genetic Susceptibility

Genetic markers may moderate the effects of early adversity on later psychopathology. A functional insertion/deletion polymorphism in the serotonin gene linked promoter region (5-HTTLPR) has repeatedly been found to moderate the influence of early adversity and stressful events on the development of psychopathology [63]. The 5HTT s allele may thus impact depression and anxiety via an interaction with fear circuits in the brain. Individuals with the s allele variant having experienced early adversity show hyperreactivity of the autonomic system and of the amygdala and anterior cingulate circuits in response to signals of fear [64]. Among adults with psychotic disorders (N=118), homozygotic s allele carriers who experienced childhood trauma showed greater cognitive impairment [65].

Most research in this area, however, is limited to younger samples. Caspi et al. [66] seminal study, which showed that the 5HTT s allele moderates the effect of childhood maltreatment on risk for depression, was limited to a relatively young sample of 26-year old males (N=1,037) [66]. The persistence of the interactive effect of 5HTT with early adversity on psychiatric risk across the lifespan is less clear. O'Hara and colleagues [67] found no interactive effects of stress, by analysis of cumulative life stress or early trauma, and the 5HTT s allele on cognitive function in older adults (N=154, mean age=71.1 years). However, significant interactions of the 5HTT with elevated levels of waking cortisol did predict lower memory performance and hippocampal volume. Further, there was a direct association of 5HTT genotype status and increased levels of waking cortisol suggesting that biological measures of stress may be more important in advanced age, than are self-reports of early life adversity and stress.

In another investigation which included older adults, Gillespie and colleagues [68] found no interactive effect of stressful events and 5HTT genotype on levels of depressive symptoms. However, in another large population-based study of older men and women (N=906, aged 65 years or older) a link was found between childhood adversity and

depression that was significantly stronger for those with the 22/23EK or the 9beta variant [69]. Additional polymorphisms, such as the FK506 binding protein 5 (FKBP5), an immunoregulatory factor, have been identified as moderators of the effect of early adversity on later psychopathology [70]. This suggests that several different pathways and mechanisms may subserve the interaction of early adversity and neurocognitive and neuropsychiatric outcomes in late life (Fig. 1).

Animal Models of Early Adversity and Associated Psychiatric Disorders

The impact of early adversity on later psychopathology is not an easy process to study in humans. Practical difficulties inherent to multi-decade long studies, the wide genetic diversity among humans, the cultural and generational biases in the perception and reporting of early adversity, and the variability of observed psychopathological outcomes are among the most significant barriers to such studies. Animal models can alleviate some of these barriers. Indeed, animal models significantly reduce the duration of experimental studies, due to the faster development of animals compared to humans. Animal models also offer better control over genetic backgrounds, especially when closely related control and mutant strains are available. For example, rodent studies have been conducted comparing control animals to test animals with abnormal serotonin [71] or cortisol response [72] due to intrinsic genetic differences. Animals can also be engineered to express polymorphisms replicating those found in humans, like in the anxiety-prone brain-derived neurotrophic factor (BDNF) Met "knock-in" mouse [73].

Furthermore, animal studies can use standardizable stressors to mimic early adversity, and objective outcome measures of later psychopathology. This is especially true for rodent models, in which well-controlled experimental stressors include neurochemical stress like prenatal alcohol exposure [74], emotional stress like maternal separation [72, 75, 76], and physical stress [77]. Finally, animal studies can leverage standardized psychopathological outcomes, including exploration / risk-taking / hyperactivity (e.g., open-field test), anxiety-like behavior (e.g., elevated maze test) and depressive-like behavior (e.g., forced swim test), as often used in rodent studies.

Animal models are well-suited to test the prevalent diathesis hypothesis [78] according to which a combined effect of genetic predisposition and environmental stressors (encountered during specific developmental windows) underlies the association between early adversity and psychopathology. For example, heightened cortisol levels in adult hypertensive rats were found to be associated with a protection against anxiety and depressive-like symptoms seen in adult control rats exposed to early adversity in the form of maternal separation [72]. In mice, maternal separation and early weaning leads to significant psychopathology in open-field (hyperactivity), elevated maze (increased anxiety) and forced swim (depression-like behavior) tests, in a genetically-controlled, strain-dependent way [75]. In another elegant study in rats, Wilkin and colleagues demonstrated that early adversity in the form of physical stress applied during early vs. late adolescence leads to opposite outcomes in adulthood, namely decreased and increased exploration / risk-taking behavior compared to unstressed controls, and that these effects are further modulated by gender [77].

Although they offer many practical and experimental advantages, animal models are not without limitations. Chief among these is the fact that psychopathology encapsulates complex, neurodevelopmental and behavioral processes that are, in large part, species-specific, sometimes putting into the question the very validity of animal models [79, 80]. To circumvent some of these limitations, it may be valuable to develop surrogate biomarker strategies that coincide with certain forms of anxiety and depression in both humans and animal models, such as anomalous blood transcript profiles [81]. Studies may also be conducted in more complex animal models than rodents, especially primates, which offer more extensive opportunities to test emotional stressors, due to more elaborate inter-individual relationships and group structures [82]. Primate models, however, are far less accessible and much more cost- and labor-intensive than rodent models.

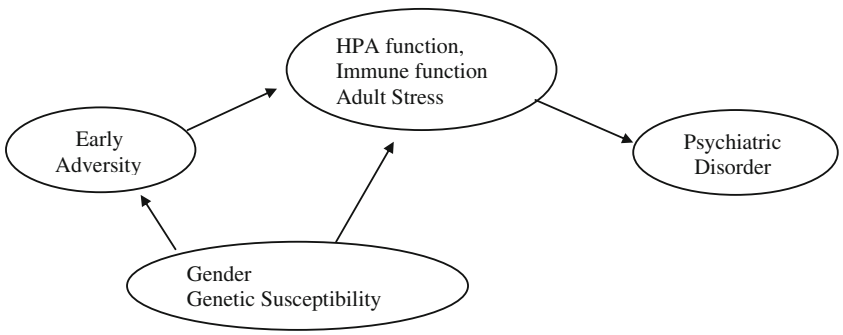

Fig. 1 Biological and environmental mediators and moderators of the relationships between early adversity and psychiatric disorders

Methodological Issues and Future Directions

Several improvements can be made with regard to assessment of adversity. It is critical for future research to assess adversity history comprehensively so that more precise delineations of the relationships among adversities, and their contributions to psychiatric disorders in late life, can be obtained [21]. Second, reporting bias continues to present a challenge particularly in studies with older samples [67]. It is possible that retrospective self-report measures misrepresent the levels of life stress, early adversity and trauma experienced by older adults. Older individuals often have recall difficulties, and evidence suggests that older adults are more likely to pay attention and remember positively valenced stimuli than negatively valenced stimuli [83•]. Psychological resilience in those who are able to survive early life adversity may also potentially attenuate the effect of adversity exposure on risk for psychiatric disorder. In addition, distal traumatic events may be less relevant to older adults than the chronic, ongoing daily stress they experience. While recall of lifetime events has been found to be fairly reliable in research on depression [84], reliability is vastly improved by use of interview measures [85] which are designed to enhance recall and minimize reporting bias. Interview measures, however, present challenges in cost, manpower, and participant burden.

With regard to study design, most of the knowledge regarding the relationship between exposure to early adversity and psychiatric disorders is based on cross-sectional retrospective data. Prospective studies, following participants from childhood into late adulthood with frequent assessments of adversity and symptoms, would be ideally suited to delineate longitudinal trajectories of risk. However, results would take decades to emerge, with the older adult stage of the lifespan spanning up to 40 years (60 years to 100 years). Structured, multi-cohort designs, such as accelerated longitudinal designs offer significant advantages for examining differential effects of early adversity by age of exposure, and thus for identifying critical periods in development that confer heightened risk for psychiatric disorders in late life [86].

The few studies that have had the ability to look at mediators in a longitudinal design indicate that some of the risk associations between childhood adversity and psychiatric disorders in older adults may be mediated by psychopathology developed in early adulthood [13]. Such findings further highlight the need for longitudinal designs such that psychopathology can be continually assessed over time to identify the points of emerging illness.

Conclusions

The findings of this review highlight that exposure to adversity early in life is capable of exerting long-term risk for a range of neuropsychiatric outcomes. Such findings underscore the need for better assessment of early adversity as well as for the implementation of widespread interventions to help prevent or reduce the adverse effects of early adversity. Early adversity needs to be considered as part of routine clinical and medical assessments. Given that a broad range of experiences are subsumed under the term "adversity," assessment needs to be comprehensive and to include measures of key dimensions of the experience such as severity, chronicity, and timing. Those identified with a history of early adversity may be candidates for more intensive psychiatric treatments to help prevent adverse effects associated with the exposure. As our understanding of the effects of adversity develops, treatments may be individually tailored to the type and timing of exposure. On a larger scale, community-based preventive interventions that improve the quality of family and neighborhood environments during childhood may have substantial long-term benefits in reducing the prevalence or incidence of psychiatric disorders in the general population. Parenting programs and intensive family-focused social services have been shown to effectively reduce the rates of child abuse and domestic violence in the community [87].

Little evidence has emerged for specificity between type of adversity and disorder outcomes, reflective of definitional and measurement issues that undermine the success of the field. There does appear to be a strong cumulative effect, such that more severe experiences are consistently associated with proportionally higher rates of disorders. Some periods of vulnerability have also been highlighted (e.g., transition to puberty). Further research is needed to identify the precise critical periods and the forms of adversity most damaging at each period.

Studies are limited by the lack of prospective longitudinal designs, particularly with older samples. Efforts to identify mediators of the relationship between adversity and psychopathology have been largely focused on HPA function, which is just one marker of stress function. Although emergent evidence points to immune function as a potential mediator, relatively few studies have been conducted in this domain [54, 76, 77]. Nevertheless, several groups are pursuing translational and clinical research studies to determine whether therapies targeting immunological and inflammatory pathways can indeed modulate psychological symptoms linked to depression, leading to significant benefit for patients (reviewed in [88]). Evidence for genetic moderators similarly suggest the need for greater focus on gene by environment interactions on psychopathology. Nevertheless, one of the most important lessons from this literature, particularly in samples of older adults [67], is that improved characterization and measurement of early adversity is needed before we can elucidate the mechanisms by which genetic susceptibility interacts with adversity, leading to increased risk for psychopathology.

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References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Bifulco A, Brown GW, Adler Z. Early sexual abuse and clinical depression in adult life. Br J Psychiatry. 1991;159:115–22.
2. Green JG, McLaughlin KA, Berglund PA, et al. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: associations with first onset of DSM-IV disorders. Arch Gen Psychiatry. 2010;67(2):113–23.
3. Kendler KS, Bulik CM, Silberg J, et al. Childhood sexual abuse and adult psychiatric and substance use disorders in women: an epidemiological and cotwin control analysis. Arch Gen Psychiatry. 2000;57(10):953–9.
4. Kendler KS, Gardner CO, Prescott CA. Toward a comprehensive developmental model for major depression in women. Am J Psychiatry. 2002;159(7):1133–45.
5. Kendler KS, Gardner CO, Prescott CA. Toward a comprehensive developmental model for major depression in men. Am J Psychiatry. 2006;163(1):115–24.
6. Kessler RC, Davis CG, Kendler KS. Childhood adversity and adult psychiatric disorder in the US National Comorbidity Survey. Psychol Med. 1997;27(5):1101–19.
7. Kessler RC, Magee WJ. Childhood family violence and adult recurrent depression. J Health Soc Behav. 1994;35(1):13–27.
8. MacMillan HL, Fleming JE, Streiner DL, et al. Childhood abuse and lifetime psychopathology in a community sample. Am J Psychiatry. 2001;158(11):1878–83.
9. Molnar BE, Buka SL, Kessler RC. Child sexual abuse and subsequent psychopathology: results from the National Comorbidity Survey. Am J Public Health. 2001;91(5):753–60.
10. Nelson EC, Heath AC, Madden PAF, et al. Association between self-reported childhood sexual abuse and adverse psychosocial outcomes: results from a twin study. Arch Gen Psychiatry. 2002;59(2):139–45.
11. Widom CS. Posttraumatic stress disorder in abused and neglected children grown up. Am J Psychiatry. 1999;156(8):1223–9.
12. Afifi TO, Mather A, Boman J, et al. Childhood adversity and personality disorders: results from a nationally representative population-based study. J Psychiatr Res. 2011;45(6):814–22.
13. Clark C, Caldwell T, Power C, et al. Does the influence of childhood adversity on psychopathology persist across the lifecourse? A 45-year prospective epidemiologic study. Ann Epidemiol. 2010;20(5):385–94.
14. Comijs HC, Beekman AT, Smit F, et al. Childhood adversity, recent life events and depression in late life. J Affect Disord. 2007;103(1–3):243–6.
15. Kivela SL, Luukinen H, Koski K, et al. Early loss of mother or father predicts depression in old age. Int J Geriatr Psychiatry. 1998;13(8):527–30.
16. Wilson RS, Krueger KR, Arnold SE, et al. Childhood adversity and psychosocial adjustment in old age. Am J Geriatr Psychiatry. 2006;14(4):307–15.
17. • Chu DA, Williams LM, Harrisa AWF, et al. Early life trauma predicts self-reported levels of depressive and anxiety symptoms in nonclinical community adults: relative contributions of early life stressor types and adult trauma exposure. J Psychiatr Res. 2013;47(1):23–32. *One of the few and largest studies to investigate how exposure to early life trauma contributes to depression and anxiety disorders in later life, using a fine-grained assessment of early life stress than is typical of epidemiological investigations. Findings underline the relative importance of early exposure to 'interpersonal violation' relative to other types of early stressors for future psychiatric risk.*
18. McMahon SD, Grant KE, Compas BE, et al. Stress and psychopathology in children and adolescents: is there evidence of specificity? J Child Psychol Psychiatry. 2003;44(1):107–33.
19. McLaughlin KA, Green JG, Gruber MJ, et al. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication II: associations with persistence of DSM-IV disorders. Arch Gen Psychiatry. 2010;67:124–32.
20. Kessler RC, McLaughlin KA, Green JG, et al. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. Br J Psychiatry. 2010;197(5):378–85.
21. Finkelhor D, Ormrod RK, Turner HA. Re-victimization patterns in a national longitudinal sample of children and youth. Child Abuse Negl. 2007;31(5):479–502.
22. Wise LA, Zierler S, Krieger N, et al. Adult onset of major depressive disorder in relation to early life violent victimisation: a case-control study. Lancet. 2001;358(9285):881–7.
23. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998;14(4):245–58.
24. Evans GW, Schamberg MA. Childhood poverty, chronic stress, and adult working memory. Proc Natl Acad Sci U S A. 2009;106(16):6545–9.
25. Draper B, Pfaff JJ, Pirkis J, et al. Depression and Early Prevention of Suicide in General Practice Study Group. Long-term effects of childhood abuse on the quality of life and health of older people: results from the Depression and Early Prevention of Suicide in General Practice Project. J Am Geriatr Soc. 2008;56(2):262–71.
26. Kaplow JB, Dodge KA, Amaya-Jackson L, et al. Pathways to PTSD, part II: sexually abused children. Am J Psychiatry. 2005;162(7):1305–10.
27. Rudolph KD, Flynn M. Childhood adversity and youth depression: influence of gender and pubertal status. Dev Psychopathol. 2007;19(2):497–521.
28. Schoedl AF, Costa MC, Mari JJ, et al. The clinical correlates of reported childhood sexual abuse: an association between age at trauma onset and severity of depression and PTSD in adults. J Child Sex Abus. 2010;19(2):156–70.
29. Kaplow JB, Widom CS. Age of onset of child maltreatment predicts long-term mental health outcomes. J Abnorm Psychol. 2007;116(1):176–87.
30. Yehuda R, Golier JA, Halligan SL, et al. Learning and memory in Holocaust survivors with posttraumatic stress disorder. Biol Psychiatry. 2004;55(3):291–5.
31. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol Bull. 2011;137(6):959–97.
32. Hazel NA, Hammen C, Brennan PA, et al. Early childhood adversity and adolescent depression: the mediating role of continued stress. Psychol Med. 2008;38(4):581–9.
33. Pearlin LI. The sociological study of stress. J Health Soc Behav. 1998;30(3):241–56.
34. Gunnar M, Quevedo K. The neurobiology of stress and development. Ann Rev Psychol. 2007;58:145–73.

35. Heim C, Newport DJ, Bonsall R, et al. Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. Am J Psychiatry. 2001;158(4):575–81.
36. Kaufman J, Plotsky PM, Nemeroff CB, et al. Effects of early adverse experiences on brain structure and function: clinical implications. BPS. 2000;48(8):778–90.
37. Abercrombie HC, Jahn AL, Davidson RJ, et al. Cortisol's effects on hippocampal activation in depressed patients are related to alterations in memory formation. J Psychiatr Res. 2011;45(1):15–23.
38. de Quervain DJ, Henke K, Aerni A, et al. Glucocorticoid-induced impairment of declarative memory retrieval is associated with reduced blood flow in the medial temporal lobe. Eur J Neurosci. 2003;17(6):1296–302.
39. Karst H, Nair S, Velzing E, et al. Glucocorticoids alter calcium conductances and calcium channel subunit expression in basolateral amygdala neurons. Eur J Neurosci. 2002;16(6):1083–9.
40. Mitra R, Sapolsky RM. Gene therapy in rodent amygdala against fear disorders. Expert Opin Biol Ther. 2010;10(9):1289–303.
41. Spangler G, Grossmann KE. Biobehavioral organization in securely and insecurely attached infants. Child Dev. 1993;64(5):1439–50.
42. King JA, Mandansky D, King S, et al. Early sexual abuse and low cortisol. Psychiatry Clin Neurosci. 2001;55(1):71–4.
43. De Bellis MD, Chrousos GP, Dorn LD, et al. Hypothalamic–pituitary–adrenal axis dysregulation in sexually abused girls. J Clin Endocrinol Metab. 1994;78(2):249–55.
44. Gerritsen L, Geerlings MI, Beekman AT, et al. Early and late life events and salivary cortisol in older persons. Psychol Med. 2010;40(9):1569–78.
45. Stein MB, Yehuda R, Koverola C, et al. Enhanced dexamethasone suppression of plasma cortisol in adult women traumatized by childhood sexual abuse. Biol Psychiatry. 1997;42(8):680–6.
46. Heim C, Newport DJ, Heit S, et al. Pituitary–adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA. 2000;284(5):592–7.
47. Yehuda R, Golier JA, Kaufman S. Circadian rhythm of salivary cortisol in Holocaust survivors with and without PTSD. Am J Psychiatry. 2005;162(5):998–1000.
48. Sudheimer K, Flournoy J, Gershon A, et al. HPA axis and late life depression. In: Lavretsky H, Sajatovic M, Reynolds CF, editors. Late-life mood disorders. New York: Oxford University Press; 2013.
49. Graham JE, Christian LM, Kiecolt-Glaser JK. Stress, age, and immune function: toward a lifespan approach. J Behav Med. 2006;29(4):389–400.
50. Langley-Evans SC, McMullen S. Developmental origins of adult disease. Med Princ Pract. 2010;19(2):87–98.
51. Merlot E, Couret D, Otten W. Prenatal stress, fetal imprinting and immunity. Brain Behav Immun. 2008;22(1):42–51.
52. Miller GE, Chen E, Fok AK, et al. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc Natl Acad Sci U S A. 2009;106(34):14716–21.
53. Bellinger DL, Lubahn C, Lorton D. Maternal and early life stress effects on immune function: relevance to immunotoxicology. J Immunotoxicol. 2008;5(4):419–44.
54. Bauer ME, Wieck A, Lopes RP, et al. Interplay between neuroimmunoendocrine systems during post-traumatic stress disorder: a minireview. Neuroimmunomodulation. 2010;17(3):192–5.
55. Danese A, Pariante CM, Caspi A, et al. Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci U S A. 2007;104(4):1319–24.
56. Kiecolt-Glaser JK, Gouin JP, Weng NP, et al. Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. Psychosom Med. 2011;73(1):16–22.
57. Gouin JP, Glaser R, Malarkey WB, et al. Childhood abuse and inflammatory responses to daily stressors. Ann Behav Med. 2012;44(2):287–92.
58. Macphee AG, Divol L, Kemp AJ, et al. Limitation on prepulse level for cone-guided fast-ignition inertial confinement fusion. Phys Rev Lett. 2010;104(5):055002.
59. McLeod JD. Childhood parental loss and adult depression. J Health Soc Behav. 1991;35:205–20.
60. Gorey KM, Leslie DR. The prevalence of child sexual abuse: integrative review adjustment for potential response and measurement biases. Child Abuse Negl. 1997;21(4):391–8.
61. MacMillan HL, Fleming JE, Trocme N, et al. Prevalence of child physical and sexual abuse in the community. Results from the Ontario Health Supplement. JAMA. 1997;278(2):131–5.
62. Gershon A, Minor K, Hayward C. Gender, victimization, and psychiatric outcomes. Psychol Med. 2008;38(10):1377–91.
63. Caspi A, Hariri AR, Holmes A, et al. Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. Am J Psychiatry. 2010;167(5):509–27.
64. Williams LM, Gatt JM, Schofield PR, et al. 'Negativity bias' in risk for depression and anxiety: brain–body fear circuitry correlates, 5-HTT-LPR and early life stress. NeuroImage. 2009;47(3):804–14.
65. Aas M, Djurovic S, Athanasiu L, et al. Serotonin transporter gene polymorphism, childhood trauma, and cognition in patients with psychotic disorders. Schizophr Bull. 2010;38(1):15–22.
66. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003;301(5631):386–9.
67. O'Hara R, Schroder CM, Mahadevan R, et al. Serotonin transporter polymorphism, memory and hippocampal volume in the elderly: association and interaction with cortisol. Mol Psychiatry. 2007;12(6):544–55.
68. Gillespie NA, Whitfield JB, Williams B, et al. The relationship between stressful life events, the serotonin transporter (5-HTTLPR) genotype and major depression. Psychol Med. 2005;35(1):101–11.
69. Bet PM, Penninx BW, Bochdanovits Z, et al. Glucocorticoid receptor gene polymorphisms and childhood adversity are associated with depression: new evidence for a gene–environment interaction. Am J Med Genet B Neuropsychiatr Genet. 2009;150B(5):660–9.
70. Binder EB, Bradley RG, Liu W, et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA. 2008;299(11):1291–305.
71. Lesch KP. When the serotonin transporter gene meets adversity: the contribution of animal models to understanding epigenetic mechanisms in affective disorders and resilience. Curr Top Behav Neurosci. 2011;7:251–80.
72. Sterley TL, Howells FM, Russell VA. Effects of early life trauma are dependent on genetic predisposition: a rat study. Behav Brain Funct. 2011;7:11.
73. Hariri AR. Genetic polymorphisms: a cornerstone of translational biobehavioral research. Sci Transl Med. 2010;2(18):18ps6.
74. Macrì S, Spinelli S, Adriani W, et al. Early adversity and alcohol availability persistently modify serotonin and hypothalamic–pituitary–adrenal–axis metabolism and related behavior: what experimental research on rodents and primates can tell us. Neurosci Biobehav Rev. 2007;31(2):172–80.
75. George ED, Bordner KA, Elwafi HM, et al. Maternal separation with early weaning: a novel mouse model of early life neglect. BMC Neurosci. 2010;11:123.
76. Baram TZ, Davis EP, Obenaus A, et al. Fragmentation and unpredictability of early-life experience in mental disorders. Am J Psychiatry. 2012;169(9):907–15.

77. Wilkin MM, Waters P, McCormick CM, et al. Intermittent physical stress during early- and mid-adolescence differentially alters rats' anxiety- and depression-like behaviors in adulthood. Behav Neurosci. 2012;126(2):344–60.
78. Harro J. Animal models of depression vulnerability. Curr Top Behav Neurosci. 2012. doi:10.1007/7854_2012_221.
79. Berton O, Hahn CG, Thase ME. Are we getting closer to valid translational models for major depression? Science. 2012;338(6103):75–9.
80. Dzirasa K, Covington 3rd HE. Increasing the validity of experimental models for depression. Ann N Y Acad Sci. 2012;1265:36–45.
81. Pajer K, Andrus BM, Gardner W, et al. Discovery of blood transcriptomic markers for depression in animal models and pilot validation in subjects with early-onset major depression. Transl Psychiatry. 2012;2:e101.
82. Pryce CR, Rüedi-Bettschen D, Dettling AC, et al. Long-term effects of early-life environmental manipulations in rodents and primates: potential animal models in depression research. Neurosci Biobehav Rev. 2005;29(4–5):649–74.
83. • Reed AE, Carstensen LL. The theory behind the age-related positivity effect. Front Psychol. 2012;3:339. doi:10.3389/fpsyg.2012.00339. *A striking finding from the field of aging is the* "*positivity effect*", *which refers to older adults*' *tendency to attend to and remember more positive than negative information*, *relative to younger adults*. *This article provides an overview of the theoretical basis of the positivity effect*, *discussing the implications of this phenomenon for consideration of emotional processing in older adults*.
84. Brewin CR, Andrews B, Gotlib IH. Psychopathology and early experience: a reappraisal of retrospective reports. Psychol Bull. 1993;113(1):82–98.
85. Brown GW, Harris TO. Social origins of depression: a study of psychiatric disorder in women (1st American ed.). New York: Free Press; 1998.
86. Thompson WK, Hallmayer J, O'Hara R. Design considerations for characterizing psychiatric trajectories across the lifespan: application to effects of APOE-epsilon4 on cerebral cortical thickness in Alzheimer's disease. Am J Psychiatry. 2011;168(9):894–903.
87. MacLeod J, Nelson G. Programs for the promotion of family wellness and the prevention of child maltreatment: a meta-analytic review. Child Abuse Negl. 2000;24:1127–49.
88. Haroon E, Raison CL, Miller AH. Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. Neuropsychopharmacology. 2012;37(1):137–62.