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# Life Course Epidemiology of Trauma and Related Psychopathology in Civilian Populations

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## Abstract

Traumatic events are ubiquitous exposures that interact with life course events to increase risk of acute psychopathology and alter mental health trajectories. While the majority of persons exposed to trauma experience mild to moderate psychological distress followed by a return to pre-trauma health, many persons exposed to trauma experience substantial distress that lasts for several years. Therefore, in an effort to understand why exposure to trauma can provoke such a range of reactions, we apply a life course approach that considers the complex accumulation and interaction of life experiences that range from social to biological factors, which occur over the life span—from gestation to death and across generations. We present this evidence in three categories: genetics and biology, individual exposures, and community experiences, followed by discussing challenges in existing research, and directions for future study.

### Keywords

Trauma; Posttraumatic stress disorder; PTSD; Epidemiology

## Introduction

The terms ‘traumatic event’, ‘potentially traumatic event’, and ‘trauma’ have been used in reference to a broad set of adverse experiences outside the ‘normal’ human experience. Exposure to these events is ubiquitous; seven out of ten respondents worldwide[1] and nine out of ten adults in the US [1-3] report experiencing one or more lifetime traumas. Traumatic event experiences include individually experienced and mass trauma events. Individual traumas that range from interpersonal violence to accidental injuries are highly prevalent. In addition, approximately 300 natural disasters [4, 5] and 30 armed conflicts [6] are part of the global experience annually. The majority of persons exposed to trauma endure mild to moderate psychological distress followed by a return to pre-trauma health shortly thereafter [7]. Nevertheless, a substantial proportion of persons exposed to traumatic

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events develop chronic pathological symptoms that may be debilitating and last for several years. We are therefore challenged to understand why exposure to trauma can provoke such a range of reactions.

In this paper, we consider traumatic events in accordance with DSM-IV [8] and DSM-5 [9] as an exposure that involves an actual or threatened harm to a person's safety, integrity, or life, and that are negative in impact and outcome. The characteristics of traumatic events can vary greatly across several dimensions, including type, chronicity, severity, expectedness, and timing. Type of trauma, for example, can range from individual (e.g., automobile accident) to natural disasters. Additional dimensions of traumatic events—including the persistence of the trauma ranging from acute to chronic, exposure severity from mild to severe, expected or unexpected, emotional or physical threat, and whether the trauma occurred during early or later life—can influence the consequences of traumatic events [10-12]. However, the production of psychopathology is unlikely to be explained by the trauma characteristics alone, but rather represents a consequence of the complex accumulation and interaction of life experiences that range from social to biological factors that occur over the life span—from gestation to death and across generations [13, 14]. Thus, we use a life course approach as an organizing paradigm through which we review the recent literature on traumatic events and their consequences, using key publications to illustrate how the life course paradigm can inform our understanding of the production of the consequences of traumatic events. By combining a focus on social determinants of health with a conceptual framework for understanding how early- and late-life genetics, biology, behavior, psychology, and environment interact, a life course approach can inform our understanding of how health trajectories are shaped over time and across levels of organization. Instead of focusing on individual risk factors as predictors of psychopathology after trauma, a life course epidemiology points to broad social, economic, and environmental vulnerabilities that are the underlying causes of the unequal distribution of psychopathology across generations and populations [15].

In this review, we consider the interplay between predisposing factors and trauma characteristics that cause psychopathology in civilians. We present this evidence following a life course perspective with focus on three categories: (1) genetics and biology, (2) individual exposures, and (3) community experiences. There is a substantial body of literature that informs our understanding of each of these three types of predisposing factors for the consequences of traumatic events. Recent reviews have comprehensively discussed the literature regarding several aspects of the production of the consequences of traumatic events, including genetic influences [16], biology [17], physical and psychological development [18, 19], disasters [20], and PTSD prevalence [21]. We do not aim here to replicate this work or to provide a systematic review of each section, but rather to selectively discuss key papers meant to illustrate how a life course perspective can illuminate a comprehensive understanding of the consequences of traumatic events. Finally, in this paper we focus on PTSD as the sentinel psychological injury after traumatic events, but include other psychopathology as relevant to complement the discussion.

## Genetics and biology

### Genetic determinants

There is little question that particular genetic variants are associated with greater risk of the psychological consequences of traumatic events. Indeed, genetic variation has been shown to explain from 30% to 72% of the liability for PTSD [17], underscoring the significance of genetics in understanding the psychological sequelae of trauma. There are at least 17 gene variants documented to be associated with PTSD [17]. Recognition that no single genetic determinant of the psychopathological consequences is likely to operate in isolation has resulted in a shift from focusing on single candidate genes, to examining polygenic risk scores that simultaneously assess several genes and PTSD [16]. This research has shown that polygenic risk scores may better explain PTSD risk than any single genetic variant alone [16, 17, 22]. While this has proven valuable for informing plausible mechanisms that biologically explain psychogenesis following trauma, it may lead to an oversimplification of our causal thinking, positioning genetics as the central driver of population patterns of psychopathology. Other work has, however, clearly shown that genes interact with environmental and behavioral exposures to produce psychopathology after traumatic events [23].

### Gene-environment interactions

Biological and social factors independently, cumulatively, and interactively increase psychopathology risk prior to the trauma experience. A life course epidemiology suggests that health trajectories are shaped over one's life. It is likely, however, that there are sensitive periods during which those exposed to traumatic events may be more vulnerable to eventual psychopathology. For example, those who experience traumatic events during periods of rapid development have a substantial increase in risk of psychopathology throughout life [24-35]. Binder and colleagues [36] therefore, investigated the interaction of early life (i.e., childhood abuse) and genetic (i.e., FKBP5) risk factors in the development of PTSD. Although no direct pathway between FKBP5 and PTSD was found, 4 FKBP5 single nucleotide polymorphisms (SNPs) were shown to interact with child abuse severity to predict PTSD [36]. Several studies have since confirmed this interaction between FKBP5 and early life abuse in the development of psychopathology [37-40].

The FKBP5 polymorphism is by no means the only evidence of gene-environment interaction in the development of psychopathology. Decades of research [41, 42] have implicated serotonin receptors in the mediation of PTSD symptoms and modulation of PTSD risk. Thus, investigation of the genetic variation in the promoter region of the serotonin transporter gene (5-HTTLPR) and PTSD has documented individual- (e.g., social support) and group-level (e.g., high unemployment neighborhood) exposures that interact with 5-HTTLPR in the development of PTSD [43, 44]. This literature has also led to more recent scholarship proposing a biological mechanism whereby trauma affects changes to the epigenome—DNA modifications that do not change the DNA sequence—that alter the expression of particular genotypes and that these changes may explain inter-individual differences in the consequences of traumatic events.

## Epigenetics

The burgeoning literature on lifetime experiences that alter the epigenome, and hence gene expression profiles, is one of the more exciting new areas of scholarship in the field of trauma research. Epigenetic changes include DNA methylation (DNAm) and histone modification [45], each of which are characterized by modifications to the regulation of the chromatin, the highly compressed DNA structure, and mediate gene expression in the individual. Epigenetics, therefore, have been leading to the suggestion of biologically plausible mechanisms by which the gene-environment interaction "gets under the skin" to affect the physiologic manifestations of illness [46-48].

Epigenetic changes, specifically DNAm, to the mechanisms involved in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis [46] and immune system [49] have been shown among individuals with PTSD. DNAm affects the accessibility of the DNA sequence for transcription into messenger RNA and its products [50]. In this manner, early life experiences mark the epigenome, which alter gene expression throughout the life course. Klengel and colleagues [51] showed that a childhood trauma activates glucocorticoid receptors in the HPA-axis that differentially induce DNAm changes in persons with a particular FKBP5 polymorphism [51]. Moreover, this increase in DNAm reduced neurogenesis, particularly in the right hippocampus [51], which is associated with depression and PTSD [27, 52, 53]. Although this finding leaves a "black box" association between hippocampal volume and psychopathology, this study suggested that (i) trauma exposure exerts the maximal effect only in childhood (i.e., similar effects were not shown for later life trauma exposure), (ii) creates long-lasting changes in gene function, and (iii) affects biological development and mental illness through the life course. Moreover, recent epigenetic studies have extended the influence of environmental exposures from individual directly exposed to their descendants and across generations [54-57].

Recent work suggests that epigenetic mechanisms are heritable and modifiable processes fundamental to the growth and sustainment of human life [45]. Epigenetic heritability, also called transgenerational inheritance, refers to alterations to the epigenome that are passed from one generation to another. While animal models have demonstrated that epigenetic variation acquired during the intrauterine period affects disease risk in adulthood [58, 56], recent studies have suggested that these alterations can influence several generations [54]. For example, Yao and colleagues [54] observed multigenerational inheritance whereby great-grandchildren of gestating female rats exposed to stress birthed pups of decreased weight and altered developmental behaviors [54], suggesting that individual trauma experience may be interacting with stress experiences across several generations to cause psychopathology.

In humans, differentiating the genetic and environmental origins of changes to the epigenome has been less clear. For example, children of women with PTSD are more likely to experience trauma than children of women without PTSD [55]. Thus, the mother's traumatic event could both cause her epigenetic changes and increase risk of a traumatic event that alters the child's epigenome—independent of the mother transmitting her epigenome to her child. Although the confirmation of transgenerational inheritance will

encounter substantial methodological challenges, recent work showing the effect of maternal smoking in DNA methylation [59, 60] provides early evidence in this regard.

## Individual Exposures

The psychological consequences of traumatic event experiences represent the culmination of an individual's biological, genetic, and life experiences prior to, during, and after a traumatic event. In this model, traumatic experiences never act in isolation. Rather, external stimuli affect biology and genetics to increase risk of psychopathology. In this section we will examine sensitive times during development when trauma may exert maximum influence on life course health trajectories. Second, we will discuss the potential for chains of risk that arise from the correlation between experiences. Third, we will discuss the role of event characteristics in the development of psychopathology. Fourth, we will discuss the contribution of post-event experiences in the risk and course of psychopathology.

### Frequency versus timing of events

In the US, 13% of children will experience a confirmed case of abuse or neglect by age 18 [61] and half will experience adversity that may include: parental death (3-7%), family violence (7-8%), parental substance abuse (11%), and parental criminality (26%) [62, 63]. The consequences of childhood adversity affect mental health well into adulthood. Indeed, experiencing one or more instances of adversity contributes to 80% of childhood/adolescent suicide attempts [64], 63% of drug dependence [65], and 54% of depression [66]. Evidence from several studies consistently demonstrates that a dose-response relationship exists whereby each additional event experienced in childhood increases the risk of mental illness [66], substance use [67, 68], and suicidal behaviors [64]. Based on this evidence, two models are proposed to explain this dose-response relationship between number of events and mental illness. First, there is evidence that sensitive stages of development exist when the effects of certain experiences, particularly traumatic events, are greater than during other periods [69]. Under this model, the event's timing during development drives both the acute response and alters biological processes that affect long-term mental health trajectories. Second, the 'chains of risk' hypothesis emphasizes the critical role that correlation between trauma and adversity plays in shaping life course mental health trajectories.

### Sensitive time periods

The sensitive time period model is grounded in an appreciation of developmental periods when events affect brain development and psychopathology differentially than other periods. Research that supports this model shows that the age sexual abuse is experienced during childhood differentially predicts regional changes in brain development. For example, a reduction in hippocampal volume is observed among those who experience sexual abuse between ages 3-5, while a reduction is observed in the corpus callosum and frontal cortex during ages 9-10 and 14-16, respectively [31]. Moreover, these differential changes in brain development paralleled differences in psychopathology, showing depression and PTSD symptoms are more likely among those who experience abuse respectively between ages 3-6 and 9-10 [31]. Alternatively, the correlation between events, as opposed to the timing of

events, may explain the dose-response relationship between trauma and mental illness risk throughout the life course.

## Chains of risk

Traumatic events happen repeatedly to the same people [2, 70, 71]. Several nationally representative surveys show that the majority of children and youth ages 2 to 17 years who report one or more traumas, report experiencing multiple events [71, 72], averaging three separate types of events [70, 73, 74]. This is not unique to children; we found that 62% of adults in urban Detroit experience three or more traumas in their lifetime (e.g., assaultive violence, serious motor vehicle crash, sudden unexpected death of a close friend or relative), while one in five experience eight or more traumas [2]. There are two primary pathways to explain this multiplicity of events. First, particular environments (e.g., neighborhoods) increase the likelihood of exposure to trauma and adversity. Importantly, this effect is more specific than urban versus rural [75], but particular to neighborhoods and high risk intra-urban areas [76-78]. Second, an initial trauma initiates a chain of risk whereby a cascade of adversity may follow [79, 80]. The second pathway will be the focus of this section.

Exposures can be either correlated or uncorrelated based on the probability of concurrent or sequentially associated occurrences of adverse experiences. Uncorrelated exposures, sometimes referred to as the single-hit model [81], are those that have effects on the outcome irrespective of a later exposure. This model is more akin to the evidence above showing sensitive time-windows for susceptibility for outcomes. However, many traumatic experiences are correlated exposures that can initiate a chain of risk throughout life. For example, while child abuse directly increases risk of psychopathology in the victim, victims of childhood trauma are substantially more likely to experience adulthood trauma [79, 80], suggesting this cycle of trauma may begin early and be perpetuated throughout the life course. Moreover, there is strong evidence that individuals experiencing interpersonal traumas at any age have a two to three fold higher risk of experiencing a second trauma [74]. For example, Daigle et al [82] reported that nearly one in four college rape victims report multiple instances of victimization in the past year, while nearly half (45%) of all rape reported in this sample occurred among the 3% of women who reported three or more sexual victimizations [82]. Thus, an incident trauma can initiate a long-term psychological chain of risk whereby an event increases risk of developing psychopathology, which increases risk of victimization.

## Trauma characteristics

In the previous sections we considered the role of individual factors, other than the trauma itself, in the production of psychopathology. However, in addition, degree of trauma severity has been observed to be consistently associated with development of disorders. Distance from event is one marker for severity of exposure. In the aftermath of the World Trade Center (WTC) (9/11) attacks, for example, we found that 7.5% of civilian survey respondents met criteria for PTSD in the 2-3 months after the attack [83]. The prevalence of PTSD, however, was substantially different based on location of residence prior to attack; respondents living south of Canal Street (less than 1 mile from WTC) were three times more likely to meet PTSD criteria than those who lived between Canal Street and 110$^{th}$ Street (1

to 7 miles from WTC). Moreover, in the 2-3 years following the attack, we found that 15% civilians survivors who worked in the towers met criteria for PTSD [84], compared to 12% who lived in the area south of Canal Street [85]. Other markers of trauma severity associated with development of psychopathology, include: injury [84, 86-88], intentionality [21], and witnessing horror and death [84].

### Secondary traumas

Post-exposure factors, also called secondary traumas, encompass a wide range of potentially traumatic events that may occur in conjunction with the primary trauma, including physical or sexual assault, loss of someone close, or a serious accident [89-92]. Consistent evidence [87, 89, 90, 93, 94] suggests that the natural disaster itself is often a lesser cause of psychopathology than the secondary traumas accompanying the disaster. For example, in a worldwide sample, examination of the effects of post-exposure factors following a natural disaster found that the association between the disaster itself and onset mental illness became insignificant in the presence of these secondary traumas [92]. Secondary traumas are examples of the risk cascades that are initiated by an incident trauma under the chains of risk model.

## Community Level Factors

Community-level factors are associated with the consequences of traumatic events over and above the role of individual-level factors. In the aftermath of mass trauma, disruption to a social environment frequently occurs in conjunction with the destruction of physical structures [95]. Community social cohesion, defined as willingness between individuals to cooperate with their community in the service of common values [76, 78], has been documented to affect mental health above and beyond individual-level characteristics [95-97]. As such, after traumatic events, community social cohesion is capable of both exacerbating mental illness risk in the presence of low social cohesion and encouraging recovery in communities characterized by high social cohesion [96]. For example, a socially cohesive community may be better positioned to mobilize post-trauma efforts to identify and assist those in need, disseminate information across the community, and advocate for outside aid [98, 99]. Conversely, displacement after trauma, which interferes with existing community social cohesion, has been associated with the development of psychopathology [95, 100].

These social factors do not act alone. Social factors modify the relationship between individual factors, trauma experiences, and psychopathology. For example, employing data from the 2004 Florida Hurricane Study, we showed that county crime rate modified the association between serotonin transporter genotype and risk of PTSD in adults [44], suggesting that these social factors act together with genetic/biological factors and individual characteristics to produce psychopathology in the presence of trauma. Therefore, explanation of trauma related psychopathology involves interplay among genetics and biology, individual factors, and social factors, i.e., the study of the consequences of trauma must focus on the pre-determinants of those consequences over the life course.

## Challenges in existing research, directions for future research

A life course perspective demands much from data. Centrally, time represents the most substantial challenge to assessing accurate lifetime trauma data. For example, since childhood traumatic event experiences significantly affect life course mental illness risk [19], the investigation of later life psychopathology requires the accurate measurement of early life trauma. However, our typical trauma assessment armamentarium, principally retrospective self-report and administrative records, has significant limitations. Nearly a third of people with documented cases of early life abuse do not report these incidents when surveyed as adults [101] and three times as many children are abused as reported to federal agencies in the US [102]. In addition, minor events are commonly forgotten [103], memories can be manipulated [104, 105], and administrative systems restrict identified access to these data for research.

Second, even if we could assume prefect recall and unlimited access to data, we require methods amply sensitive to identify influential experiences, yet granular enough to investigate factors across several levels of exposure. For example, in this paper alone, we discussed the consequences of trauma using examples from six different types of events that ranged across levels (i.e. individual [sexual assault, accidental injuries, child abuse] to mass trauma [natural disasters, terrorist attacks, armed conflicts]), time (i.e., childhood, adolescence, and later life), and severity (i.e., adversity [parental incarceration or death] to traumatic). The complexities inherent in these data require comprehensive measures that assess trauma characteristics specific to the question of interest, but robust enough for secondary analysis to assess the individual and cumulative effects of particular traumatic events.

Third, a life course epidemiology requires large prospective studies to investigate the complex accumulation and interaction of life experiences that range across levels and over time. To date, life course epidemiology has employed numerous small to moderately sized cohort studies to triangulate effects. The integration of findings across numerous studies, even employing analytical tools to account for methodological differences among studies (e.g., random-effects meta analyses [106]), remains beholden to the limitations of individual studies. Large scale longitudinal studies such as, for example, the Avon Longitudinal Study of Parents and Children (ALSPAC) [107] are one solution to this challenge. The ALSPAC is a large prospective study that enrolled in 1991, and has since followed, more than 13,000 pregnant women and their children who resided in the South West of England. While these data have greatly increased our understanding of life course health trajectories, the cohort is predominantly white (97.8%), affluent (79% home owners), and represents a sample of residents from one area of England [107]. Thus, additional life course epidemiologic studies in more diverse populations (e.g., US) are necessary to advance understanding of social and biological processes that alter life course health trajectories. While studies such as ALSPAC represent monumental efforts and costs, the interplay between individuals and societies over time are required to advance the field. In the absence of large prospective studies, best practices need to integrate data across several systems (e.g., electronic medical records, historical events) and methods (e.g., self-report, objective records) to triangulate trauma experiences throughout the life course.

The field also faces analytical challenges as it grapples with influences over multiple levels. Mervyn Susser wrote that "(i)f our disciple (epidemiology) is to rise to meet expectations, we shall have to command both the genies of molecules at the micro level, and of social forces at the macrolevel" [108]. Unfortunately, most extant analytical methods are not able to deal with the added complexity recent theoretical models have introduced, principally risk factors across levels and over time. A recent literature has introduced latent growth mixture models (LGMM) [see, 109] and multi-level regression into trauma epidemiology to respectively examine symptomology over time and across levels. However, regression based methods such as these assume there is no interaction between individual units [110]. Not only is this assumption unrealistic, the interaction between units that give rise to population-level phenomenon are of great interest to epidemiology. Thus, we have called for the adoption of complex systems approaches, including agent-based models, to examine complex disease etiologies in the study of epidemiology [111-113]. The interplay between levels of organization over time present in trauma research suggests these questions are well suited for analysis with complex systems approaches.

## Conclusions

Traumatic events are ubiquitous exposures that cause significant acute psychopathology and alter life course mental health trajectories. It is likely that we are currently underestimating the contribution of traumatic events to population health. A life course approach provides an important organizing principle to understand the interplay between traumatic events and the development of psychopathology. Future research that considers the complexity of interactions across levels of organization and over time is necessary to understand the full contribution of trauma to mental illness burden in the US and worldwide, with an aspiration towards mitigating the consequences of these events.

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** Of major importance

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