Violence victimization in childhood and mental-health outcomes

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1. What is the psychobiological outcome?

This section focuses on psychiaric disorders (including substance-use disorders) and self-harming and suicidal behaviors.

2. Is the psychobiological outcome important for physical health?

The disability caused by psychiatric disorders is high, whether expressed in economic (dollar) or epidemiological (Years Lived with Disability; YLDs) terms. Four out of the ten leading causes of YLDs among 15-44 year olds are psychiatric disorders; in developed Western nations, where the burden of communicable diseases is now reduced, psychiatric conditions account for over 40% of all YLDs (World Health Report. Geneva: WHO, 2001).

3. How much literature is there linking juvenile violence victimization to the psychobiological outcome?

Today, childhood maltreatment is a scientifically accepted explanation of psychiatric disorder. But this is a recent historical development. Thirty years ago, the idea that childhood maltreatment causes psychiatric disorder was not widely integrated into etiological models in psychiatry, in part because many forms of maltreatment were considered to be sufficiently rare to account for population rates of disorder. Indeed, this is one of the reasons that many longitudinal-epidemiological studies that were launched as late as the 1970s never inquired about such risk factors. As a result, today we must rely on methodologically weaker retrospective studies to study the connection between childhood violence victimization and adult psychiatric disorder. The rapidly accumulated evidence-base thus bears scrutiny, for what is known, how it has become known, and what is not known.

4. What does the research literature show?

Violence victimization is a pleietropic risk factor that is related to many different psychiatric outcomes. It is difficult to identify a disorder to which violence victimization is not linked. Violence victimization in childhood is significantly associated with mood disorders (major depressive disorder, dysthymia, bipolor disorder), anxiety disorders (generalized anxiety disorder, panic disorder, specific phobia, social phobia, post-traumatic disorder), behavior disorders (conduct disorder as well as juvenile and adult crime), and substance-use disorders (tobacco, alcohol and drug dependence) (Scott et al., 2010; Green et al., 2010) (FIGURE BOX Figure 1). These associations have been reported in relation to childhood exposure to domestic violence, physical abuse, sexual abuse, emotional abuse, and neglect. The associations between childhood victmization and these psychiatric disorders is comparable across high-, middle-, and low-income

countries (Kessler et al., 2010). Research has also challenged the view that bullying victimization is normative and harmless, by documenting that bullying victimization increases the risk of psychiatric problems (Arseneault et al., 2010) and self-harming behaviors (Fisher et al., 2012; Winsper et al., 2012). A recent discovery is that violence victimization is also linked to schizophrenia, psychosis, and psychotic-like experiences and symptoms (Cutajar et al., 2010; Bebbington et al., 2011). The association with psychotic symptoms has been observed in clinical as well as in non-clinical populations, and among adults as well as young adolescents (Schreier et al., 2009; Toth et al., 2011). Importantly, the link between childhood trauma and psychotic symptoms is found for events that involve intentional harm, but not in relation to accidental harm (Arseneault et al., 2011).

Violence victimization is related to comorbid disorders. Comorbidity, the concurrent diagnosis of two or more mental disorders within the same individual, occurs with greater than chance frequency in child, adolescent, and adult populations; half of all persons with mental disorders have more than one diagnosable disorder (Kessler et al., 2005). The term comorbidity may be a misnomer, as meeting criteria for one disorder tends to predict meeting criteria for multiple other disorders. For this reason, the comorbidity phenomenon has been more accurately described as a multimorbidity phenomenon (Krueger & Markon, 2006). Violence victimization in childhood is associated with significantly greater odds of having two as well as multiple disorders (FIGURE BOX 1). It is not clear whether the association between violence victimization and comorbidity reflects etiological comorbidity, wherein victimization is a „pathological agent“ that causes different disorders, or whether comorbidity is the result of a primary condition leading to subsequent conditions.

Violence victimization is related to recurrent and persistent disorders. Course of psychiatric illness is typically defined by recurrence (e.g., number of episodes over a period of observation) or persistence (prolonged duration of uninterrupted illness). A meta-analysis of 16 studies revealed that childhood maltreatment predicts an unfavorable course of depression illness, as defined by both recurrence and persistence (Nanni et al., 2012). These associations do not appear to be simply a function of an earlier age-of-illness-onset among maltreated individuals, although this issue is difficult to resolve using retrospective self-reports about age-of-onset and episode duration (McLaughlin et al., 2010). Less evidence is available about the course of other psychiatric disorders. To address this knowledge gap, we tested the association between childhood maltreatment and recurrent disorders in the prospective Dunedin Longitudinal Study, a cohort of 1037 children followed from birth to age-38 years with minimal attrition (less than 10%) over 4 decades. Childhood maltreatment was significantly related to more recurrent major depressive disorders, anxiety disorders, alcohol-dependence disorders, and drug-dependence disorders (FIGURE BOX 2).

Violence victimization may be related to treatment-refractory disorders. A novel hypothesis is that childhood maltreatment may signal poor treatment response. A meta-analysis of 10 clinical trials of depression showed that childhood maltreatment was associated with either lack of response or with remission during treatment (Nanni et al.,

2012), possibly because maltreatment is associated with greater dysregulation in cognitive and biological vulnerabilities (Lupien et al., 2009) or because maltreatment is associated with unhealthy lifestyles and less social support that exacerbate depression. Less information is available about the link between childhood maltreatment and poor treatment response in other disorders.

What are we to make of the evidence that childhood maltreatment is associated with (a) risk of many different psychiatric disorders, (b) comorbidity, (c) unfavorable course of illness, and (c) poor treatment response? An intriguing possibility is that childhood maltreatment may confer non-specific risk for psychopathology rather than risk for any one specific disorder. To date, much of the research on childhood maltreatment and adult psychiatric disorders has focused on individual psychiatric disorders, studied one at a time. However, epidemiological research shows that observed patterns of comorbidity among psychiatric disorders reflect underlying liabilities to experience many different common psychiatric disorders (Kessler COP 2011). These liabilities are captured by two dimensions. An internalizing dimension indicates a liability to experience mood and anxiety disorders, including PTSD. An externalizing dimension indicates a liability to experience substance-use and behavioral disorders. Importantly, high scores on these latent liabilities are associated with indicators of disorder severity and impairment (Newman et al., 1998). Analysis of data from NESARC, a survey of over 30,000 U.S. adults, found that the association between childhood maltreatment and any specific psychiatric disorder operated through these two latent liabilities (Keyes et al., 2012). These findings have two implications. First, prevention of maltreatment may reduce multiple and different common mental disorders. Second, the causal mechanisms linking childhood victimization to adult psychiatric disorders are likely to be general and pan-disorder rather than disorder-specific.

5. Establishing causality.

It may seem heartless to challenge the hypothesis that maltreatment causes psychiatric problems, as there is a moral imperative to prevent violence against children. Irrespective of whether the statistical association between violence victimization and psychiatric disorder reflects a causal association, maltreated children require support and treatment. But there is also a scientific and societal imperative to evaluate threats to causal inference. For example, epidemiologists calculate population attributable fractions to estimate how much of the disease burden in the population could be reduced if certain causal factors were eradicated. Some estimates suggest that eradicating childhood adversities could reduce psychiatric disorders by nearly 30% (Kessler et al., 2010). Such estimates are intended to guide public policies and intervention efforts, but “from a public health perspective, estimation of the population attributable fraction is of most use when the factor of interest is clearly causally related to the end point” (Rockhill et al.,1998).There are three outstanding challenges to causal inference in research about the effects of childhood maltreatment on psychiatric disorders.

Separating the effects of maltreatment from the recollection of maltreatment. It is important to compare cohort studies that (a) prospectively ascertain whether children are victimized and (b) follow up these children to identify later mental health outcomes versus cross-sectional studies that (a) measure victimization retrospectively by interviewing adolescents or adults about their childhood experiences (b) at the same time as assessing their mental health. In general, retrospective measures of victimization are more strongly associated with disorder than are prospective measures of victimization; a methodological difference that is evident in within-study comparisons as well as in between-study comparisons (Gilbert et al., 2009) (FIGURE BOX 3). Retrospective reports pose interpretive difficulties because the temporal ordering of maltreatment and psychiatric disorders cannot be determined reliably and because it is not clear whether the recollection of childhood experiences is influenced by the victims' current emotional-cognitive appraisal of their past experiences. However, studies of maltreatment based on offical records (e.g., court-adjudicated cases or cases who come to professional attention) may not be representative of maltreatment in the population, leading to potential biases in estimating psychiatric outcomes. To be sure, there is converging evidence from both prospective and retrospective studies that childhood maltreatment is significantly associated with increased risk of psychiatric disorders. However, prospective and retrospective studies yield sufficiently large differences in the magnitude of association to flag concerns about which research designs will be most appropriate for discovering the biological, cognitive, and affective factors linking childhood maltreatment to subsequent psychiatric disorders.

Separating the effects of maltreatment from the wider context in which maltreatment occurs. Child maltreatment occurs in the context of other dysfunctional patterns of family interaction and in the context of many other stress-inducing social forces, including poverty (Belsky AP, 1980). To assess the independent influence of maltreatment, researchers rely on a variety of methods to statistically match „exposed" and „unexposed" individuals on factors that could influence the maltreatment-disorder association (Jafee et PB 2012). Converging evidence suggests that maltreated children have an increased risk of psychiatric disorder, and that this risk is not entirely a function of the context in which maltreatment occurs (Gilbert et al., 2009). However, there is no consensus about which factors need to be controlled, or how groups should be matched; different studies vary greatly in the reliability of their procedures and the comprehensiveness of their matching. Sibling controls may be more valuable than population controls for estimating the unique contribution of victimization to outcome. A sibling-control analysis compares siblings who are discordant for victimization, to test if the victimized sibling is more likely to develop the outcome than their non-victimized sibling, despite their shared family background. In this way, the family fixed-effect model *controls* for unobserved characteristics that are the same for both siblings (FIGURE BOX 4). The evidence from sib studies is mixed. Some sibling studies suggest that maltreatment has a direct effect on risk of developing psychiatric disorders (Kendler et al. 2000; Nelson AGP 2002) whereas other studies find that the association between maltreatment and risk of developing a disorder is attributable to other family-wide adversities that are shared by siblings (Young-Wolff PM 2011).

Separating the effects of maltreatment from correlated genetic risks. Correlations between genetic and environmental risks (rGE) occur when genetically-influenced attributes (e.g., personality, appearance, ability) contribute to, or have an influence over, exposure to environmental risks (Jaffee & Price, 2007). Two types of rGE threaten causal inferences about violence victimization in childhood.

A passive rGE occurs because children inherit both genotypes and environments from their parents. Parents' genotype influences the environments they provide for their children as well as their children's genetic liability to mental disorder. Passive rGE is an inferential threat specifically in research about victimization by parents and offspring psychiatric outcomes. In such research, the association between victimization and subsequent psychiatric outcomes must survive after controlling for parental psychopathology. However, information about parental psychopathology is seldom available in retrospective studies and inconsistently available in prospective studies. With information about family history of psychiatric disorder, we re-tested the association between childhood maltreatment and recurrent psychiatric disorder (see FIGURE BOX 2). The association between childhood maltreatment and recurrent depression and anxiety remained significant after controlling for family history of these conditions. However, the link between childhood maltreatment and recurrent substance-dependence disorders was no longer significant, suggesting that maltreatment may not have a direct or unique influence on the risk of developing substance-use disorders.

An evocative rGE occurs when heritable characteristics of children evoke victimization. For example, the association between maltreatment and children's disruptive behaviour disorders may arise because children with disruptive behavior disorders are more likely to attract harsh discipline. When a putative measure of the environment (e.g., maltreatment victimization) is assessed separately for each child in a family and the study design is genetically informative (e.g., a study of monozygotic [MZ] and dizygotic [DZ] twins), one can estimate the degree to which variations in victimization are accounted for by genetic and environmental factors (FIGURE BOX 5). If one finds that genetic factors account significantly for variation in maltreatment victimization, this suggests that heritable characteristics of the child influence the child's exposure to maltreatment. Three studies have used the twin design to evaluate genetic contributions to maltreatment by an adult, finding that genetic factors accounted for less than 10% of the variation in children's risk of such maltreatment (Jaffee et al., 2004; Schulz-Heik et al. 2009; Young-Wolff et al. PM 2011). In contrast, studies have discovered significant genetic contributions to children's risk of peer victimization (Arseneault et al., 2010). On the basis of this finding, we conclude that heritable characteristics of children may provoke peer victimization, but are less likely to provoke victimization by adults.

6. Effect moderation.

Although violence victimization in childhood is a potent risk factor for developing psychiatric disorders, there are substantial individual differences in outcome: many

individuals who are victimized during childhood remain healthy (Cicchetti & Rogosch, 2009). It is estimates that one-third to 50% of individuals who are abused will not exhibit psychiatric disorders (Fergusson & Mullen, 1999). It has been proposed that individual differences in vulnerability to victimization are partially genetically mediated. As such, the goal of genotype–environment interaction (GxE) research is to (a) account for heterogeneity in response at the genetic level with the hope to (b) better understand the neurobiological mechanisms underlying this variable response. Initial research documented that candidate genes in involved in neurotransmission moderated the effect of childhood maltreatment on subsequent antisocial behavior (Caspi et al., 2002) and depression (Caspi et al., 2003). Subsequent research has focused on hypothalamic-pituitary-adrenal (HPA) axis genes because the psychiatric sequelae of violence victimization involve activation and dysregulation of the HPA axis. Variants in the corticotropin-releasing hormone receptor gene (CRHR1) and in the *FKBP5* gene have been shown to moderate the development of stress-related disorders in persons with a history of childhood violence victimization (Bradley et al., 2008; Polanczyk et al., 2009; Binder et al., 2008; Zimmerman et al., 2011). These genetic variants also influence neuronal emotional processing and neuroendocrine responses to stress (Tyrka et al. 2009; Hsu et al., 2012; Binder et al., 2008) pointing to intermediate phenotypes that may mediate genetic susceptibility to stress-related disorders.

Epidemiologists and neuroscientists are working together to illuminate the black box of biology between the gene, victimization stress, and disorder. For example, evidence that variation in *5-HTT* may influence the development of stress-related disorders has led to more focused neuroscience research on a genetic susceptibility mechanism (Caspi et al. 2010). Future integrated multidisciplinary approaches must confront several challenges and opportunities.

First, detection of GxE has been shown to vary by how childhood violence victimization is measured (Uher & McGuffin, 2010), making it difficult to distinguish between false positive findings versus meaningful distinctions that represent valuable scientific leads. Second, detection of GxE has also been shown to vary by how psychiatric phenotypes are measured. For example, studies of depression using research designs that do not distinguish between persistent cases and single-episode cases of depression may underestimate GxE effects and contribute to replication failures in psychiatric genetics (Uher et al., 2011). Third, there is the possibility that some GxE effects may be sex-specific or race-specific. For example, variants in the MAOA gene that appear to exert a protective effect on abused and neglected Caucasian children from becoming antisocial and violent later in life do not have a comparable protective effect among non-whites (Widom & Brzustowicz, 2006). Fourth, characterization of genetic vulnerability versus resilience needs to move beyond single genetic polymorphisms. New approaches may incorporate information about genetic pathways into GxE studies in order to enhance explanatory power, although this will also present unique statistical challenges. Fifth, studies of individuals who have been exposed to violence may help to speed up gene discovery. Next generation sequencing and genome wide association studies of individuals exposed to violence could be applied, liked a magnifying glass, to reveal novel loci connected to stress-related disorders. Of course, this magnifying glass will be useful only for identifying genes whose connection to disorder operates via susceptibility

to victimization. However, given that childhood violence victimization is one of the most potent risk factors for adult psychiatric disorders--and that follow-back studies of adults with psychiatric disorders document high rates of childhood victimization--this strategy is promising.

7. Effect mediation.

Multiple pathways and mechanisms have been proposed to account for how associations between childhood maltreatment and later mental-health problems come about. First, the connection between childhood violence victimization and adult psychiatric disorders may reflect revictimization, which refers to the increased risk that victims of abuse will be victimized again later in life. Children who suffer one form of victimization are likely to experience diverse forms of victimization at later points, and there does not appear to be a specific 'gateway' to re-victimization (Finkelhor et al. 2007). Multiple explanations have been invoked to account for the phenomenon of revictimization, ranging from ecological systems theory (e.g., environmental factors that create victimization vulnerability are stable over victims' lives) to psychological theories (e.g., learned helplessness). Whatever the explanation, revictimization raises the possibility that childhood violence victimization does not have direct effects on adult psychiatric disorders, but indirect effects that operate by increasing exposure to additional forms of victimization and creating a greater cumulative stress load.

Second, violence victimization may sensitize people to respond more intensely to subsequent stressors. According to the 'sensitization' hypothesis, early victimization increases the risk that individuals will develop psychiatric disorder when they encounter new stressors later in life, even if these new stressors represent independent life events (Monroe & Harkness, 2005). It is possible that this sensitization may occur because early-life victimization permanently alters stress response systems (e.g., the HPA axis and the autonomic nervous system response to stress) (Gillespie & Nemeroff, 2007). It is not clear from the extant literature whether sensitization occurs among individuals who experienced prior trauma or among individual individuals who experienced prior trauma and who also exhibited a posttraumatic stress response following the initial exposure (Breslau et al., 1999, Breslau et al. 2008; Cougle et al., 2009).

Third, cognitive models of psychopathology posit that dysfunctional cognitive styles mediate the association between violence victimization and later psychiatric disorders, especially anxiety and depressive disorders (Gibb et al., 2001, 2008). Children form core beliefs about themselves and others in the context of early family relationships, and victimization experiences may influence the organization of these core beliefs. In particular, maltreated children develop tightly-connected negative schemas and loosely-connected positive schemas (ie., a depressotypic cognitive organization) that create a vulnerability for depression (Lumley & Harkness, 2009).

Fourth, violence victimization may affect how children process social and emotional information, and these social-information processing differences may shape their risk for developing behavioral and emotional disorders. For example, child abuse is associated

with children's hostile attribution biases and postive evaluations of aggression, and these in turn, predict later behavioral problems (Dodge et al., 1995) Abused children also differ from their non-abused peers in how they reason about, perceive, and understand cues representing emotions, whether the cues are visual or auditory. For example, abused children maintain anticipatory monitoring of angry conversations even after an angry exchange is resolved (Pollak et al., 2005). Differences in processing social and emotional information are also evident in studies that measure heightened neural reactivity to threat among children exposed to family violence (McCrory et al., 2011).

There are important outstanding issues in identifiying mediators that account for individual differences in the mental-health outcomes of victims of violence. First, are these putative mediators specific to some disorders or do they apply to multiple disorders? For example, does stress sensitization apply to depression or to substance dependence, as well? A persuasive theory must be able to either account for comorbidity or to document specificity. Second, are these putative mediators true mediators or are they part-and-parcel of the disorder? A compelling design must be able to test differences and compare four groups (Heim et al., 2000, 2001): a control group of individuals without psychiatric illness or a history of early-life victimization; individuals without a psychiatric disorder but who did experience early-life victimization; individuals with a psychiatric disorder but without early-life victimization; individulas with a psychiatric disorder who did experience early-life victimization.

8. Implications for prevention and intervention

Here I have listed key, broad questions that follow from the research I have reviewed. I will expand on each of these issues, and look forward to integrating other ideas/questions from the group.

If early-life victimization is very common, and the adverse mental-health consequences very pervasive, how can we develop strategies for expanding mental-health care? Is it feasible to turn to health workers to deliver treatment?

If violence victimization is embedded in the context of multipe other stress-inducing social forces, what special provisions needs to be made for treatment delivery?

If the consequences of early-life victimization are non-specific--and if the causal mechanisms linking childhood victimization to adult psychiatric disorders are general and pan-disorder rather than disorder-specific--how should treatment choices be structured/selected?

In order to develop interventions to alleviate the adverse consequences of early-life victimization, we need to identify the factors that account for how associations between childhood maltreatment and later mental-health problems come about. If stress sensitization is key, is there special benefit to cognitive and behavioral strategies that focus on coping with new, and even independent, events?

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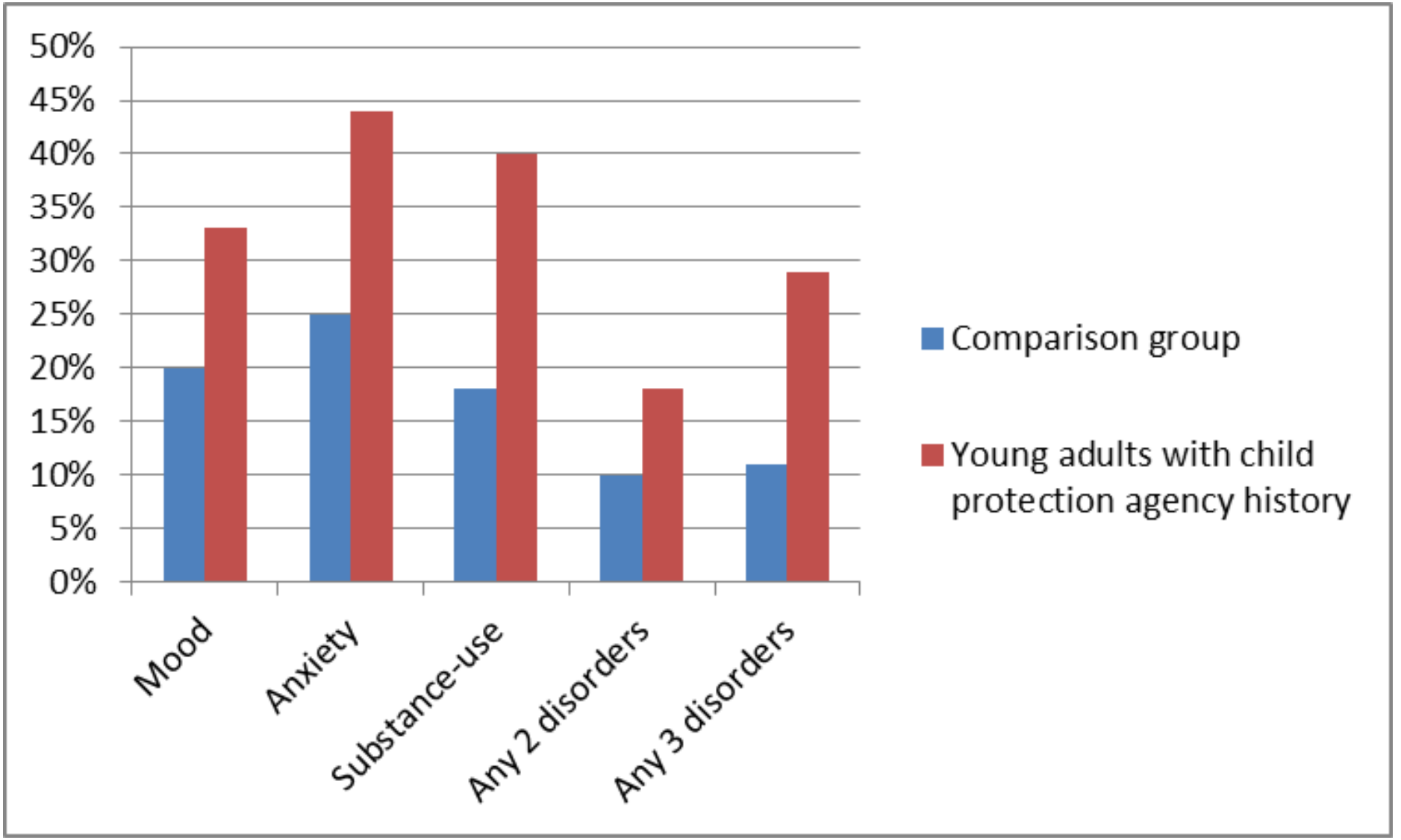
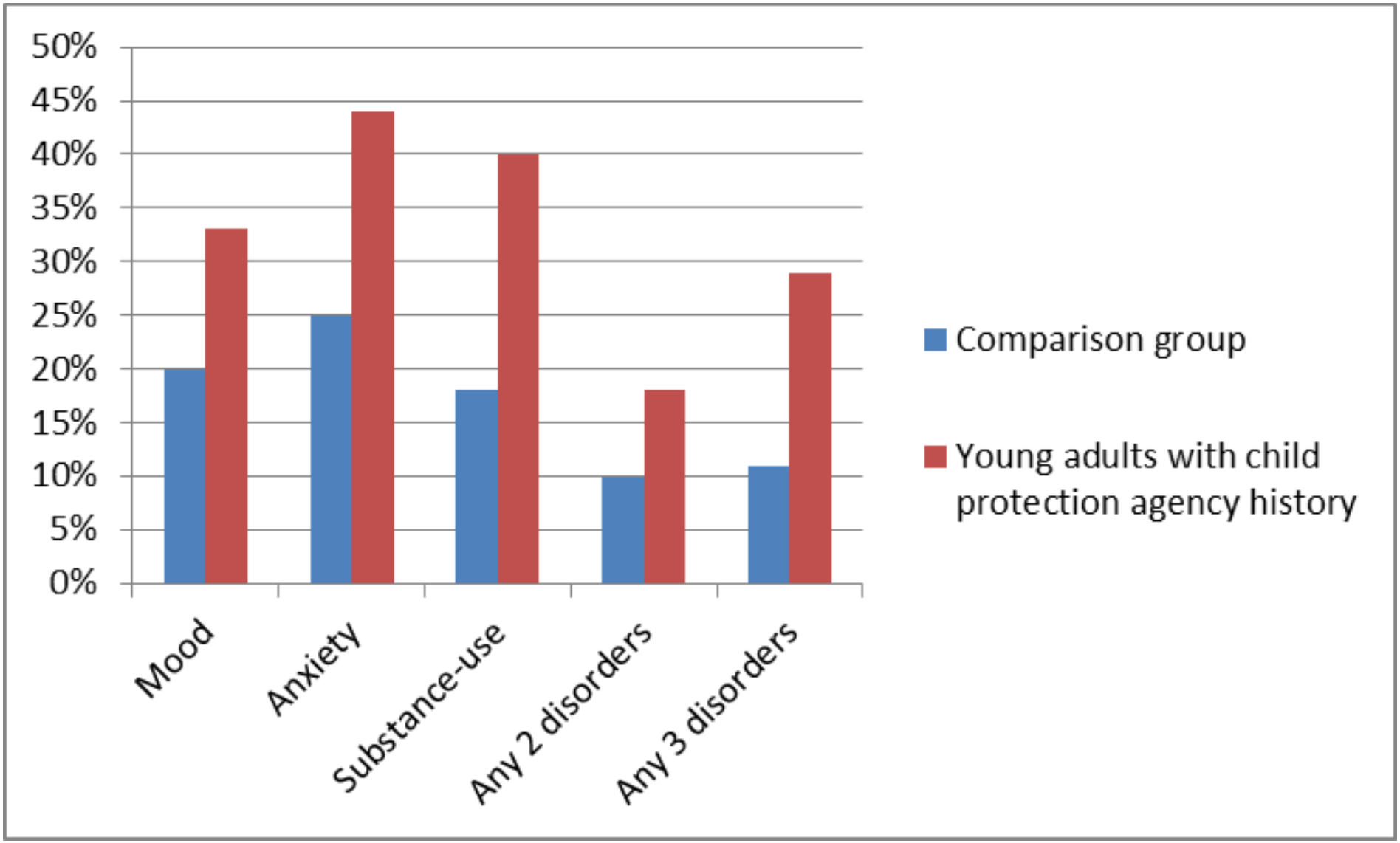
Lifetime DSM-IV Disorder Groups Among Adults With Child Protection Agency History*



*Data from Scott et al. (2010), Tables 5 and 6.

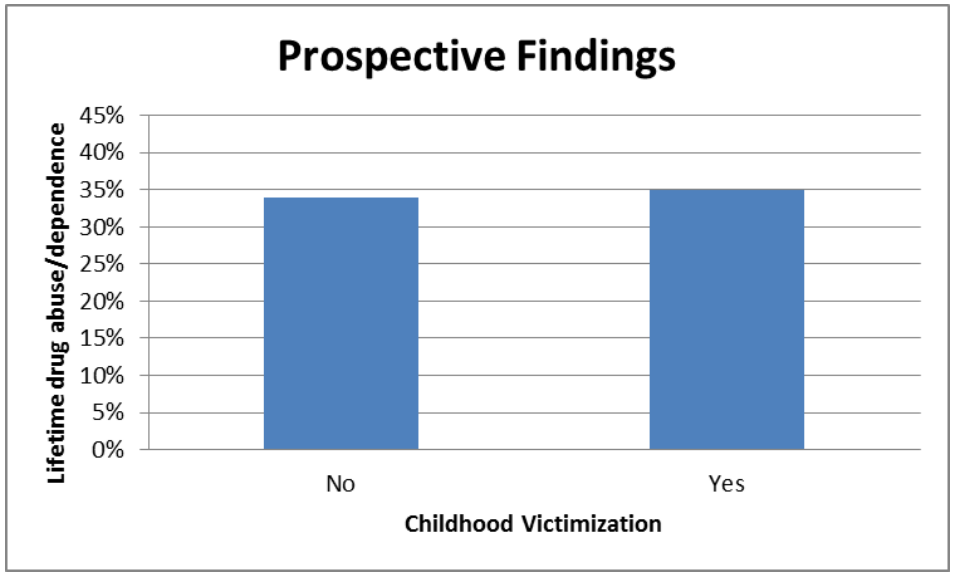
Figure 1.

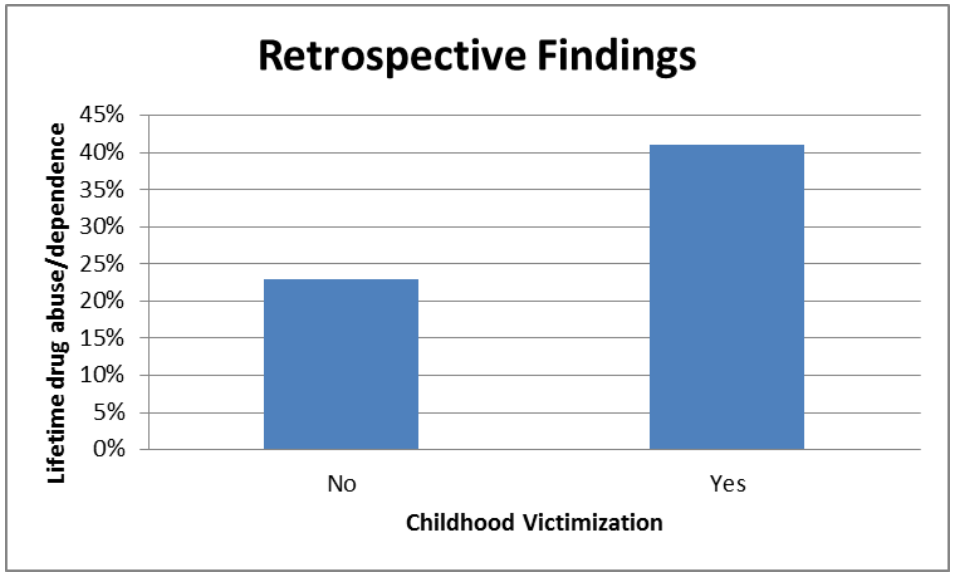
Recurrent DSM-IV Disorder Groups Among Adults with a History of Childhood Maltreatment*



*Data from The Dunedin Multidisciplinary Health and Development Study.

Figure 2.

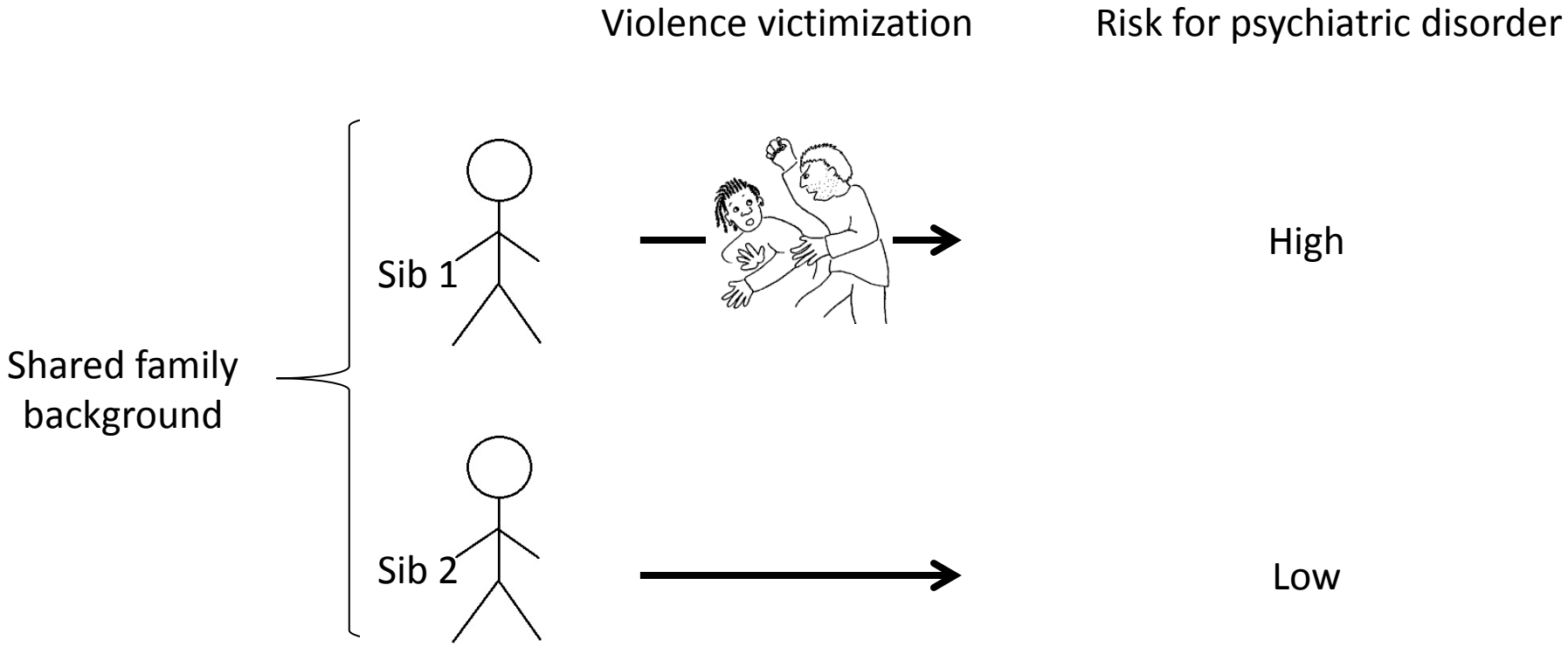




Prospective versus retrospective measurement of childhood victimization: Does it matter? Most measurement of childhood maltreatment involves colleting people's retrospective reports of their victimization. Retrospective assessment is necessary in psychopathology research because many important exposures occur years before the disorder (eg, childhood sexual abuse) or gradually over a period leading up to the disorder (eg, sustained, heavy alcohol consumption). The dangers of retrospective data are known: normal forgetting, revisionist recall, bias by respondents' knowledge of subsequent disease outcome, bias from respondents' cognitive dysfunction or low mood, and forward telescoping of recalled events. Widom et al.'s (1990) study examined whether childhood victimization increases risk for drug abuse using prospective and retrospective victimization information, in the same sample. Using prospective, official reports of childhood victimization, abused/neglected individuals were not at increased risk for drug abuse. In contrast, using retrospective self-reports of childhood victimization, abused/neglected individuals were at increased risk for drug abuse.

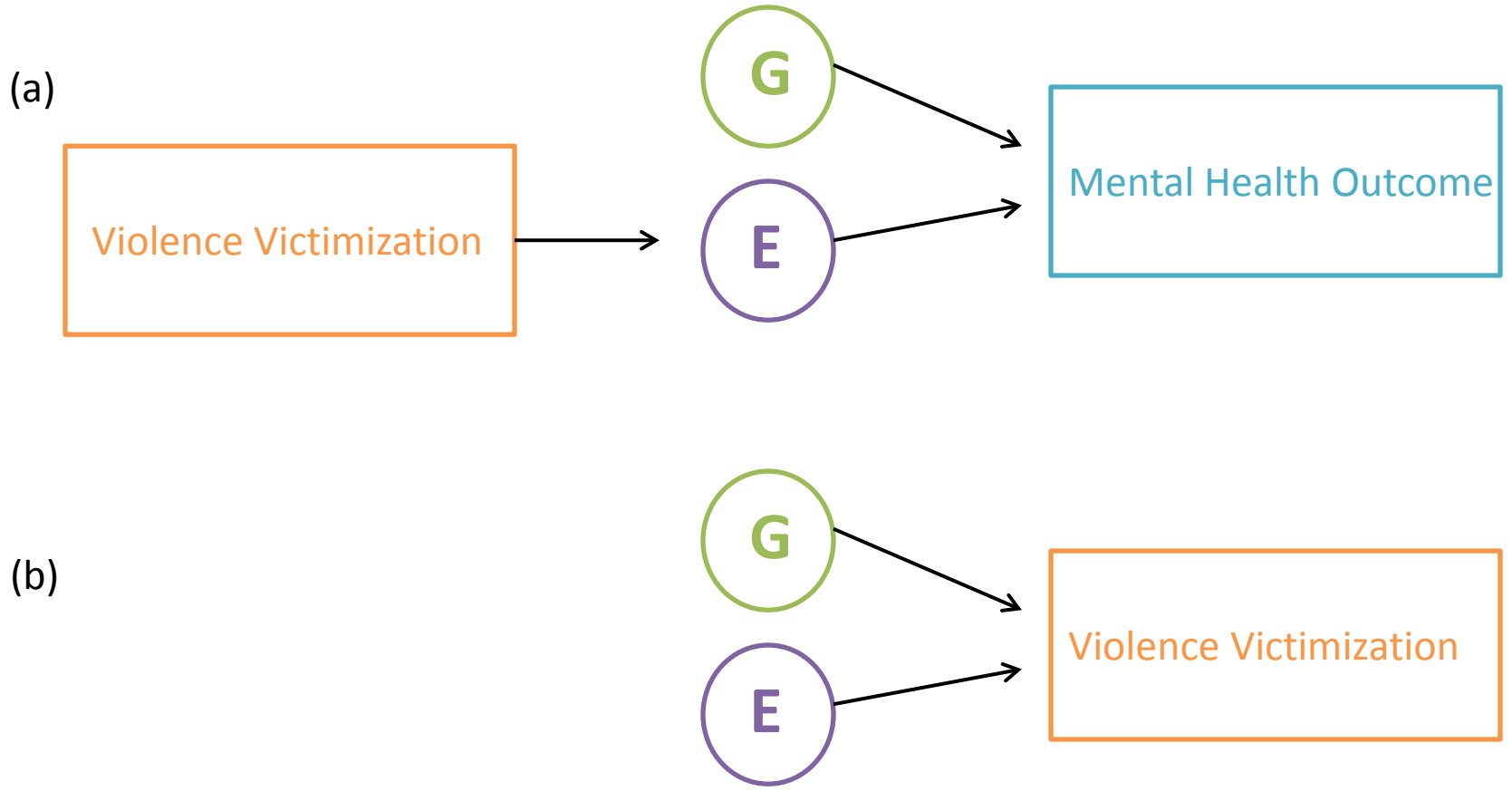
Data from Widom et al. (1999), Tables 4 and 5.

Figure 3.



A sibling-control analysis compares siblings who are discordant for victimization, to test if the victimized sibling is more likely to develop the outcome than their non-victimized sibling, despite their shared family background. For example, to rule out the influence of shared family background, Fisher et al. (2012) compared twins growing up in the same family to determine whether bullied twins were more likely to self-harm than their non-bullied age-matched and sex-matched co-twin.

Figure 4.



Genetic and environmental influences on victimization. Panel (a) shows the traditional perspective on environmental measures. An environmental measure (e.g., victimization) is assumed to index environmental influences (E) which contribute to variation in a phenotypic outcome. Panel (b) shows the radical perspective on environmental measures. When a putative measure of the environment (e.g., violence victimization) is assessed separately for each child in a family and the study design is genetically informative (e.g., a study of monozygotic [MZ] and dizygotic [DZ] twins), one can estimate the degree to which variation in victimization is accounted for by genetic and environmental factors. Adapted from Plomin (2004).

Figure 5.