Childhood Violence Exposure and Inflammatory Disease Processes

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PART 1 of the briefing paper: The evidence base

1.**What is the psychobiological outcome? (e.g., neuropsychological functioning, immune functioning, telomere erosion). Define and describe it briefly.**

INFLAMMATION. Inflammation is part of the innate immune response, a powerful defense mechanism that enables recognition of evolutionarily-conserved microorganisms' antigens and triggers rapid, non-specific response against them without any prior contact. This is possible because innate immune receptors have been shaped through contact with common pathogens by natural selection during our evolutionary past and are encoded through the germ line. Thanks to innate immunity, newborns are protected from pathogens in the environment since birth (1). Inflammation is triggered by 'inducers', which could be both exogenous and endogenous (2). The exogenous inducers include the above-mentioned microbial pathogen-associated molecular patterns (PAMPs) and non-microbial factors, such as allergens, irritants, foreign bodies, and toxic compounds. The endogenous inducers include different biological signals produced by stressed, damaged, or otherwise malfunctioning tissues. In response to these signals, the innate immune system develops a non-specific response involving blood vessels, white blood cells, and the so-called acute-phase proteins: the inflammatory response (2). A successful inflammatory response will achieve the elimination of the signals that originated the response (i.e., inducers), the resolution of the response, and the repair of damaged tissues.

2. Is the psychobiological outcome important for physical health? Explain why.

If the resolution phase does not occur, the protective, acute inflammatory response becomes a detrimental, chronic inflammatory state. Because the inflammatory response is non-specific, the effectors of the inflammatory response are unable to discriminate between inflammation inducers (e.g., microorganisms) and surrounding tissues. Collateral damage during chronic inflammatory states may therefore lead to significant tissue damage leading to age-related disease, such as cardiovascular disease, type-2 diabetes, and dementia (3-5). For example, inflammation contributes to the progression of atherosclerosis, the basic pathophysiological process underlying cardiovascular disease (3, 6). Toxic factors, such as oxidized-LDL and free radicals accumulated in the arteries' walls are endogenous inducers of the inflammatory response, and experimental evidence from knocked-out mice with impaired inflammation activation showed that the magnitude of the inflammatory response triggered by these inducers is proportional to the speed of atherosclerosis progression (7-9). In humans, a meta-analysis of the longitudinal-epidemiological studies suggests that even mild elevation in plasma inflammation biomarkers, such as CRP, fibrinogen, and white blood cells count (WBC), predicts elevated risk for cardiovascular disease (10). Inflammation could similarly influence the pathophysiology of other age-related diseases, such as type-2 diabetes and dementia (4, 5). Elevated inflammation levels have also been linked to risk for psychopathology. Although inflammation has been associated with several psychiatric disorders, findings are arguably more established with regard to depression (11). Meta-analyses have shown that depression is associated with high levels of pro-inflammatory cytokines and acute-phase proteins, such as C-Reactive Protein (CRP) (12, 13). Inflammation and depression appeared to show a two-way interaction, with longitudinal studies showing that baseline inflammation levels predict risk of depressive episodes (14) but also that baseline depressive symptoms predict later increase in inflammation levels (15, 16). The causal

influence of inflammation on depression is supported by findings from randomized controlled trials (17-19) and experimental work in animal models (20).

3. How much literature is there linking juvenile violence victimization to the psychobiological outcome? Comment on the size and nature of the evidence base. There are several possible answers to this question:
(a) A lot: If so, please summarize it.

(b) None: if so, please note what research needs to be done.

(c) Some. We recognize that in some areas of research, there may actually be little evidence about violence victimization and the outcome of interest. Instead, there may be evidence about cognate exposures. For example, there may be very little on childhood violence victimization per se and DNA methylation, but much more work on stress in general and methylation. Likewise, there may be no literature on childhood violence exposure and your outcome, but more on adult violence exposure and your outcome, perhaps in the PTSD literature. If you need to bring in this cognate literature because you think it's a key, please do. But we ask that you label it as such, and say how it is possible to extrapolate from it to make inferences about juvenile violence exposure.

There is some direct evidence regarding the influence of juvenile violence victimization on inflammation, both in children and adult individuals. Our team reported initial evidence of innate immune system changes in young people exposed to adverse psychosocial experiences (21). Among 12-year old participants of the UK Environmental Risk (E-Risk) Twin Longitudinal study, we observed that maltreated children experiencing current depression already exhibited elevated inflammation levels in childhood. This finding could not be explained by potential confounders, such as family socio-economic circumstances, obesity, or current infections. Furthermore, both post-institutionalized children living in adoptive homes and children with substantiated cases of physical abuse still residing with their families showed elevated secretory IgA for Herpes Simplex Virus compared to controls (22), indicating impairment in the acquired immune response that normally contains the reactivation of this latent virus. Immune abnormalities have also been described in adult individuals with a history of childhood maltreatment. Our team tested the association between a prospectively-collected measure of childhood maltreatment and circulating inflammation biomarkers at age 32 years among participants of the Dunedin Multidisciplinary Health and Development Study (23). We observed that children who had been exposed to maternal rejection, harsh parenting, disruptive caregiver changes, physical abuse or sexual abuse were almost twice as likely as non-maltreated children to show greater levels of multiple clinically-relevant inflammation biomarkers, such as C-reactive protein, fibrinogen, and white blood cells count, in adulthood. These findings were independent of the influence of co-occurring early life risks, stress in adulthood, adult health and health behavior, and current active infections. Furthermore, maltreatment accounted for more than 10% of cases of low-grade inflammation in the population. The findings of elevated inflammation levels in adults with a history of maltreatment have been replicated in several other papers (24-26). Maltreated individuals showed not only elevated basal levels of inflammation but also heightened inflammatory response to psychosocial stress. Compared to non-depressed individuals, patients with major depression and increased early life stress showed greater interleukin-6 secretion and NF-kB DNA-binding in response to the Trier Social Stress Test (27). Moreover, adult individuals with a history of childhood maltreatment but no current psychopathology showed greater interleukin-6 secretion and maximum interleukin-6 concentration in response to the Trier Social Stress

Test (28). Consistent with the evidence in children, immune abnormalities in adults with a history of childhood maltreatment are not limited to innate immunity but also extend to adaptive immunity. For example, adults with a history of childhood maltreatment and current PTSD diagnosis showed greater delayed-type hypersensitivity than control individuals (29), a phenomenon mediated by T cells in the skin.

4. What does the research literature show? Here focus on major points and conclusions.

Juvenile violence victimization is linked to abnormal immune system functioning with elevated inflammation levels. The effects of juvenile violence victimization appeared to be independent of the influence of several correlated risk factors. Furthermore, these effects may onset in childhood and persist into adult life. These findings have important implications for health, as detailed below.

5. Establishing causality. Does the empirical evidence support the inference that juvenile victimization actually 'causes' the psychobiological outcomes? If this evidence is missing and work still needs doing, say so.

(a) Is there experimental work? If yes, most of this will probably involve model organisms.

(b) Do any research studies establish the unique, independent effects of violence victimization on the psychobiological outcome? This can take the form of ruling out confounding effects by relying on sibling designs, by using propensity matching, etc.

(c) Do any research studies rule out selection effects (i.e., child characteristics that lead to violence victimization)? This can take the form of ruling out selection effects by relying on studies of within-individual change, discordant MZ-twin designs, etc.

Experimental work in animal models supports the observational findings that stressful experiences, such as juvenile violence victimization, are linked to elevated inflammation levels. In 1968, Solomon et al (30) were among the first to report that early psychosocial experiences could have enduring effects on the immune function. They reported that pulps that were separated repeatedly for brief periods from their dams in the first days of life showed greater immune (antibody) response against flagellin polymer than non-handled pulps. Several other examples of immune consequences of early experiences have been reported both in mice and non-human primates (31-33). With regard to inflammation, Avitsur et al (34) reported that pulps that were separated repeatedly for brief periods from their dams in the first days of life showed greater expression of genes for pro-inflammatory cytokines IL-1, IL-6, and TNF-alpha in response to infection with influenza virus in later life. Similarly, maternal separation has been associated with potentiation of colic inflammation after treatment with dextran sulfate sodium, as indicated by secretion of pro-inflammatory cytokines interferon-gamma and TNF-alpha, and by inflammatory reduction in colon length (35). Furthermore, maternal separation has been linked with potentiation of airways inflammation after sensitization with ovalbumin (36, 37).

The experimental findings from animal models point to the effects of early life stress on long-term functioning of the immune system, and particularly inflammation. Experimental findings are consistent with evidence in humans. Observational findings in humans

appeared to meet several criteria suggestive of causal association between childhood maltreatment and adult inflammation (23, 38). First, longitudinal-prospective observations showed that violence victimization measured in childhood is associated with inflammation measured in adult life, suggesting that the exposure to violence preceded the outcome. Second, greater severity of juvenile violence victimization appeared to predict greater elevation in inflammation levels, suggesting the presence of a dose-response relation. Third, the association between juvenile violence victimization and inflammation remained significant in multivariate regression models, suggesting that findings were independent of key potential intervening variables, such as co-occurring early life risks, stress in adulthood, adult health and health behavior, and current active infections. Fourth, the association between juvenile violence victimization and inflammation was biologically plausible and consistent with pre-clinical and clinical data suggesting that juvenile violence victimization is associated with impaired functioning of anti-inflammatory hormones, glucocorticoids (39). Nevertheless, it is possible that residual bias or confounding may account for the long-term association between juvenile violence victimization and inflammation described in observational studies. In particular, no study has, so far, directly tested the possibility of selection bias, that is, that elevated inflammation levels could have preceded and possibly caused violence victimization. Furthermore, it is possible that unmeasured variables could account for the findings. Findings from animal models described above suggest that selection and confounding bias are not likely.

Preclinical findings do not clarify whether juvenile violence victimization has a unique influence on inflammation or whether similar effects could also be observed as a consequence of other stressful life experiences in childhood. Observational studies in humans suggest that other adverse childhood experiences, such as socio-economic disadvantage and social isolation, may also predict adult inflammation (40, 41). Adverse childhood experiences appeared to exert independent and cumulative effect on adult inflammation (41). Therefore, the association between adverse childhood experiences and inflammation does not appear to be sensitive to the type of adversity encountered but rather could be generalized to multiple indicators of stress in childhood. Although no clear qualitative differences have been described, it is possible that juvenile violence victimization could exert quantitatively greater effect on inflammation than other adversities. However, because adversities are often correlated in the population, it is challenging to test this hypothesis in observational studies. Furthermore, different mediating mechanisms could underlie the effects of different adverse childhood experiences on inflammation.

6. Effect moderation: Why do some children who are victimized develop the psychobiological outcome whilst others do not? If this evidence is missing and work still needs doing, say so.
For example, some of the factors that have been proposed to moderate the influence of violence victimization on mental health are:
Genetic vulnerability
The quality of children's relationships with their parents / social support
Intelligence

There is no clear and direct evidence of factors modifying the effect of juvenile violence victimization on inflammation levels or immune functioning. However, it is possible to extrapolate findings suggesting that age and concurrent psychopathology might moderate this relationship. We found elevated inflammation levels in both maltreated-only and maltreated+depressed members of the Dunedin Study at age 32 years (42). However, we

found elevated inflammation levels in maltreated+depressed but not in maltreated-only members of the E-Risk Study at age 12 years (21). These divergent findings may be due to between-study differences in age or in concurrent psychopathology. However, several other factors could clearly have accounted for the divergent results in the Dunedin and the E-Risk studies. More studies are needed to identify moderators of the association between juvenile violence victimization and inflammation.

7. Effect mediation: What accounts for the influence of victimization on the psychobiological outcome? If this evidence is missing and work still needs doing, say so. For example, some of the mediating factors that have been proposed in the area of research on the effects of violence victimization on mental health.
Revictimization
Attributional styles
Threat perception
Neurobiological alterations
Developmental and phenotypic cascades

Research in animal models and humans has begun to uncover the biological and molecular mechanism through which exposure to juvenile violence victimization could be translated into abnormalities in immune system functioning. It is useful to review here the systemic mechanisms through which the inflammatory response is activated and inhibited under conditions of perceived threat. Sensory experiences are continuously, and often unconsciously, monitored by a neurobiological network including the thalamus, the sensory cortex, and the amygdala (43). In conditions of perceived threat, the amygdala triggers firing in the locus coeruleus, which in turn induces the activation of the sympathetic nervous system - the 'fight or flight' response. The sympathetic activation triggers an inflammatory response under conditions of acute psychosocial stress (44-46), presumably conferring an evolutionary advantage by preparing the body to face potential tissue damage and infection. When the inflammatory response is not needed, it should be rapidly terminated to avoid unnecessary damage. Inflammation could be inhibited by the activation of the parasympathetic nervous system (47). Furthermore, inflammation could be inhibited by the activation of the hypothalamic-pituitary-adrenal (HPA) axis through the secretion of anti-inflammatory hormones, glucocrticoids (48). Individuals with a history of childhood maltreatment showed impaired functioning of the glucocorticoid hormones, and weakening of the anti-inflammatory HPA axis could promote chronic elevation in inflammation levels (49).
Significant abnormalities in HPA axis functioning have been described in both maltreated children and adults with a history of childhood maltreatment (39, 50). Basal (unstimulated) levels of cortisol were higher, and the normal circadian variation in cortisol levels - with peak in the morning and low value at bedtime - was blunted in maltreated children compared to non-maltreated children. HPA axis abnormalities have also been described in the context of reactivity tests. Maltreated children showed blunted cortisol response to standard psychosocial stress tasks (e.g., public speaking, mental arithmetical calculation). Maltreated children also showed blunted adrenocorticotropic hormone (ACTH) and normal cortisol response to pharmacological stimulation with corticotropin-releasing hormone (CRH), suggesting the presence of compensatory mechanisms to high basal cortisol levels. However, maltreated children with concurrent depression diagnosis showed heightened ACTH response to CRH, suggesting disruption of these compensatory mechanisms. Adult individuals with a history of childhood maltreatment showed similar abnormalities in HPA axis functioning, with higher basal activation measured through CRH

levels in the cerebrospinal fluid. Maltreated adults showed a blunted cortisol response to psychosocial stress tasks when free of psychiatric disorders but greater cortisol response compared to non-maltreated individuals when presenting with concurrent psychiatric disorders (e.g., depression). Similarly, maltreated adults showed a blunted ACTH and cortisol response to combined dexamethasone/CRH test when free of psychiatric disorders but greater responses compared to non-maltreated individuals when presenting with concurrent psychiatric disorders. Overall, this body of research suggests that individuals exposed to childhood maltreatment show greater cortisol secretion under basal conditions and blunted response to psychosocial and pharmacological stimuli than non-maltreated individuals. Experimental studies in animal models suggested that disruption in HPA axis functioning following early life stress might be due to epigenetic changes in the glucocorticoid receptor gene (51).
In addition to insufficient glucocorticoid signalling, other physiological changes could contribute to the elevated inflammation levels observed in individuals with a history of juvenile violence victimization. Additional mediating pathways include the imbalance between sympathetic and parasympathetic nervous system activation and the disruption in other stress-sensitive neuroendocrine pathways. However, more research is needed to clarify the contribution of these alternative pathways.

PART 2 of the briefing paper: Implications for prevention and intervention.

The next three sections encourage you to examine in the briefing paper how knowledge about the effects of juvenile violence victimization on the psychobiological outcome can be used to develop effective interventions. This part uses the evidence in part 1 as a "jumping-off point" to launch ideas about how to improve victim's health and reduce population health burden.

(a) Implications for primary prevention of juvenile violence exposure.
(b) Implications for secondary prevention and treatment of health outcomes among children and adolescents who have been victimized.
(c) Implications for secondary prevention and treatment of health outcomes among adults who have a history of violence victimization in their juvenile backgrounds.

For example, you might wish to suggest that CBTs to reduce depression in people with maltreatment histories should routinely collect biomarker data on inflammation. Or, you might wish to recommend public health campaigns, from television spots to giving out rope hammocks to encourage use of relaxation techniques. (Just kidding, but you get the idea, think creatively!)

Some questions to consider are:
(a) Is there any evidence that interventions can normalize development among victimized children?

There are several effective treatments that could reduce inflammation levels. Several classes of medications have anti-inflammatory effects. Commonly used non-steroidal anti-inflammatory drugs (NSAIDs) include salicylates (e.g., aspirin), propionic acid derivates (e.g., ibuprofen, naproxen), acetic acid derivates (e.g., diclofenac), enolic acid derivates (e.g., piroxicam), and selective COX-2 inhibitors (e.g., celecoxib). Exogenous glucocorticoid hormones are frequently used as potent (steroidal) anti-inflammatory drugs. Other drugs including antidepressant medications also have anti-inflammatory effects (11).

Furthermore, dietary intake of omega-3 poly-unsaturated fatty acids (PUFA) and physical exercise have shown anti-inflammatory effects (52, 53). Complementary and alternative medical therapies, such as acupuncture and meditation, may also have anti-inflammatory properties (54, 55). Finally, intial evidence suggests that psychotherapy could reduce pro-inflammatory gene expression (56).

(b) Is there potential for reversing the effects of juvenile violence victimization on the psychobiological or health outcome?

Reversing the effect of juvenile violence victimization on inflammation could prevent a large health burden owing to both physical and psychiatric disorders. Inflammation has been linked to elevated risk of chronic, age-related disease, such as cardiovascular disease, type-2 diabetes, and dementia (3-5). The influence of inflammation on the pathophysiology of age-related disease is likely to begin in childhood, well before the onset of clinical symptoms. Already in childhood, inflammation levels are positively correlated to the extent of atherosclerosis (57). Therefore, the stress-related elevation in inflammation levels linked to juvenile violence victimization could promote the pathophysiology of age-related disease, which will only become clinically apparent years after victimization. Consistent with the association of juvenile violence victimization with inflammation and the influence of inflammation on age-related disease, adult individuals with a history of maltreatment have greater risk of developing age-related disease than non maltreated individuals (58).
Inflammation has also been linked to elevated risk of psychiatric disorders including depression (11). The causal influence of inflammation on depression is supported by findings from randomized controlled trials (17-19) and experimental work in animal models (20). Elevated inflammation levels may also predict poor response to treatment with antidepressant medications (59). Consistent with the association of juvenile violence victimization with inflammation and the influence of inflammation on depression, adult individuals with a history of maltreatment have overall greater risk of developing depression than non-maltreated individuals (60). In particular, maltreated individuals are at elevated risk of developing the most impairing forms of depression, with recurrent and persistent depressive episodes, and to show poor response to treatment (61).
Because juvenile violence victimization may influence long-term clinical outcomes through elevation in inflammation levels, reversing the effect of victimization on inflammation could prevent large health burden.

(c) What new data should be collected in the context of randomized clinical trials to evaluate the effects of interventions on psychobiological outcomes?

Randomized clinical trials evaluating the impact of interventions to buffer the effect of juvenile violence victimization (62) should routinely assess inflammatory biomarkers, such as acute-phase proteins (CRP, fibrinogen), pro- and anti-inflammatory cytokines, and pro- and anti-inflammatory mediators, such as adipokines (leptin, adiponectin) and glucocorticoids. Routine collection of these biomarkers could shed light on the mechanisms through which victimization affects the immune system, and inform on effective treatments. However, in order to enable clinicians to routinely obtain inflammatory biomarkers, it is important to develop technology that allows minimally-invasive collection methods including assays for salivary and dried blood spot analysis (63, 64).

(d) What does the research about the effects of juvenile violence victimization on the psychobiological outcome suggest with regard to the timing of interventions?

There is only initial evidence to inform the debate about the relevance of timing of interventions in this area. We reported that, among 12-year-old members of the E-Risk Study, only maltreated children experiencing current depression showed elevated inflammation levels. In contrast, inflammation levels were not elevated in non-depressed maltreated children or in non-maltreated depressed children compared to controls (21). This may be interpreted to suggest that interventions targeted at reducing depression in maltreated children are effective in preventing elevation in inflammation levels. However, as discussed above, it is also possible that inflammation may lead to depression or that inflammation and depression could cluster together because of shared etiological factors, such as childhood maltreatment. Further research is needed to inform about the best timing of intervention to prevent the effects of juvenile violence victimization on inflammation.

(e) What does the research about the effects of juvenile violence victimization on the psychobiological outcome suggest with regard to shaping the content of therapy?

As detailed above, several treatment options might be effective to normalize development among victimized children. Classical anti-inflammatory medications, antidepressant medications, diet, physical activity, acupuncture, meditation, and psychotherapy all showed anti-inflammatory properties and might therefore be used to normalize inflammation in maltreated children. However, juvenile violence victimization could affect multiple inter-related biological pathways and focus on inflammation alone could not address all observed biological abnormalities. For a broader understanding of the biological abnormalities linked to juvenile violence victimization, it may be important to consider the suggested evolutionary contribution of early experiences to child development (49). Early experience could profoundly affect the maturation of biological systems, which largely takes place in early life. The influence of early experiences on biological system could be aimed at improving child survival until reproductive age (65) regardless of health outcomes at older ages, which are less important for evolutionary fitness (66). Therefore, children exposed to threat early in life may undergo multiple biological changes aimed to improve survival in the context of likely harm, such as a potentiated inflammatory response. However, as the context becomes less noxious, the priorities shift from immediate to long-term goals, and the responses persist for years after the threat has ceased, the biological changes induced by threatening early experiences may become detrimental (49). In order to effectively prevent the negative health outcomes linked to juvenile violence victimization, it may therefore be important to focus on central aspects of threat perception and emotion regulation in young people.

(f) What does the research about the effects of juvenile violence victimization on the psychobiological outcome suggest with regard to management of patients?

First, clinicians may consider that the routine inquiry about juvenile violence victimization is not harmful (67) and could add important prognostic information to their assessment (61). Second, because patients reporting victimization may be at high risk of comorbidity between psychiatric and medical disorders (42), clinicians may consider carrying out more holistic enquiries while working with this population.

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