



Early life stress, air pollution, inflammation, and disease: An integrative review and immunologic model of social-environmental adversity and lifespan health



Hector A. Olvera Alvarez^{a,*}, Laura D. Kubzansky^b, Matthew J. Campen^c, George M. Slavich^d

^a School of Nursing, University of Texas at El Paso, Health Science and Nursing Building, Room 359, 500 West University Avenue, El Paso, TX, USA

^b Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, MA, USA

^c Department of Pharmaceutical Sciences, University of New Mexico, Albuquerque, NM, USA

^d Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA, USA

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ABSTRACT

Socially disadvantaged individuals are at greater risk for simultaneously being exposed to adverse social and environmental conditions. Although the mechanisms underlying joint effects remain unclear, one hypothesis is that toxic social and environmental exposures have synergistic effects on inflammatory processes that underlie the development of chronic diseases, including cardiovascular disease, diabetes, depression, and certain types of cancer. In the present review, we examine how exposure to two risk factors that commonly occur with social disadvantage—early life stress and air pollution—affect health. Specifically, we identify neuroimmunologic pathways that could link early life stress, inflammation, air pollution, and poor health, and use this information to propose an integrated, multi-level model that describes how these factors may interact and cause health disparity across individuals based on social disadvantage. This model highlights the importance of interdisciplinary research considering multiple exposures across domains and the potential for synergistic, cross-domain effects on health, and may help identify factors that could potentially be targeted to reduce disease risk and improve lifespan health.

1. Introduction

Socially disadvantaged individuals, such as those with low educational attainment or income, or who belong to racial or ethnic groups that have historically experienced discrimination, systematically experience relatively worse health across the lifespan, compared to those in more socially advantageous circumstances (Adler and Stewart, 2010). The determinants of these health disparities include both social and physical environmental factors that interact to influence a broad range of psychological, biological, and behavioral processes that in turn affect health (Braveman and Gottlieb, 2014). Although it is well documented that individuals in socially disadvantaged conditions are more likely to be exposed to harmful social and physical environments compared to those in better social conditions, research on the interaction of these factors is limited.

A harmful exposure common among socially disadvantaged populations is psychosocial stress during childhood (Andersen and Blosnich, 2013; Slopen et al., 2016). Indeed, early life exposure to psychosocial stress has been identified as a determinant of social disparities in health

that emerge over the life course (Miller et al., 2011; Shonkoff et al., 2012), and a large body of research now suggests that early life stress increases adulthood risk for cardiovascular disease, stroke, diabetes, autoimmune disease, and certain cancers, in addition to substance abuse and depression (Brown et al., 2013; Carroll et al., 2013; Chapman et al., 2004; Dube et al., 2009; Felitti et al., 1998). Moreover, the effects of severe early life stressors that cause repeated biological stress responses or prolonged biological dysregulation, such as poverty, abuse, neglect, isolation, discrimination, humiliation, or violence, appear to be particularly deleterious for lifespan health (Goodman et al., 2005; Horwitz, 2002; Nurius et al., 2013).

Like early life stress, exposure to air pollution is also patterned by social disadvantage. In the United States, for example, land values decrease substantially near highways and industrial sites, which are major sources of air pollution (Boehmer et al., 2013). Consequently, poor communities tend to be comprised of socially disadvantaged individuals who are commonly exposed to high levels of air pollution. This is notable since exposure to air pollution is also strongly associated with poor lifespan health, causing an estimated seven million premature

* Corresponding author.

E-mail address: holvera@utep.edu (H.A. Olvera Alvarez).

deaths worldwide each year, primarily due to inflammation-related diseases such as cardiovascular disease, chronic obstructive pulmonary disease, and lung cancer (World Health Organization, 2014). Inflammation is central to the biological machinery that links air pollution with adverse health outcomes (Du et al., 2016; Mostafavi et al., 2015). Consequently, alterations in inflammatory activity that are caused by early life stress may be one key mechanism that potentiates the negative effects that air pollution has on health over the lifespan.

In the present review, we integrate research from several fields—especially psychoneuroimmunology, epidemiology, environmental toxicology, and genomics—to elucidate how early life stress may influence immune system processes to increase vulnerability to air pollution and risk for inflammation-related chronic illness. To accomplish this, we first summarize studies linking early life stress and poor lifespan health. Second, we review research suggesting that psychosocial stress may promote poor health in part by initiating chronic, low-grade inflammation. Third, we examine toxicology studies linking exposure to particle air pollution and inflammation, and connect this work to related research on psychosocial stress and inflammation. Fourth, based on these literatures, we propose an integrated, multi-level model of early life stress, air pollution exposure, and lifespan health. This model suggests that stressors occurring during childhood program a “defensive” immunologic phenotype characterized by increased inflammatory reactivity to air pollution. As a result, individuals exposed to high levels of stress early in life may have more potent inflammatory responses upon exposure to a range of harmful social and physical factors, including air pollution, and thereby be at high risk of inflammation-related diseases and conditions (Gouin et al., 2012; Miller and Chen, 2007, 2010; Steptoe et al., 2002b). Finally, we suggest some possible avenues for future research.

2. Early life stress and lifespan health

The notion that early life stress can affect health has been around for centuries (Monroe and Slavich, 2016; Slavich, 2016). This idea was further concretized in 1998 when the Adverse Childhood Experiences (ACE) study revealed a strong dose-response relationship between exposure to different forms of childhood adversity and increased risk for several of the leading causes of death among adults in the United States (Felitti et al., 1998). Specifically, individuals experiencing four or more types of childhood adversity were found to have a 1.4- to 1.6-fold increase in physical inactivity and severe obesity compared to individuals experiencing none of these types of adversity, and a 4- to 12-fold increase in risk for smoking, self-rated health complaints, alcoholism, drug abuse, depression, heart disease, and suicide (Anda et al., 2008; Dong et al., 2004; Dube et al., 2009; Felitti et al., 1998). In this context, the terms *early life stress* or *early adversity*, have referred to different types of stressors, including violence, poverty, maltreatment, abuse, and neglect, as well as parental substance abuse or mental illness (Carroll et al., 2011; Dube et al., 2001; Hughes et al., 2017; Infurna et al., 2016; Lacey et al., 2014; Lindert et al., 2014; McCrory et al., 2011; Miller and Chen, 2010; Norman et al., 2012; Pollitt et al., 2007; Sripada et al., 2014; Varese et al., 2012; Zatti et al., 2017). It has been estimated that more than 60% of adults in the United States experience at least one these significant life stressors during childhood (Felitti et al., 1998). Such exposures have been found to reduce overall life expectancy by up to 4.5 years and active (i.e., non-functionally impaired) life expectancy by up to 6.6 years (Felitti et al., 1998; Montez and Hayward, 2014). Moreover, studies have shown that many of these stressors are more common among socially disadvantaged populations, suggesting that these exposures may contribute to structuring social disparities in health (Slopen et al., 2016).

Since the publication of the ACE study and others, the list of adverse health outcomes linked with childhood adversity has grown considerably (Table 1). Indeed, early adversity has been linked with increased risk for a wide variety of mental and physical health problems

in addition to those identified above, including asthma, rheumatoid arthritis, cardiovascular disease, type 2 diabetes, certain types of cancer, and accelerated cognitive decline (Brown et al., 2010; Danese and McEwen, 2012; Fagundes et al., 2013; Huang et al., 2015; Palmier-Claus et al., 2018; Wolitzky-Taylor et al., 2017). As a result, early life stress exposure is now recognized as a critical public health concern across the world (Shonkoff, 2010).

3. Inflammatory mechanisms linking early life stress and health

Recent studies in health psychology and psychoneuroimmunology have focused on elucidating biological mechanisms that may explain how early life stress affects mental and physical health in later life (Shields and Slavich, 2017; Slavich, 2018). One of the most recent and potentially important discoveries in this context has involved the recognition that inflammation may be a key process linking stress and health (Table 2) (Miller et al., 2011; Slavich, 2015). At least two major lines of research support this possibility. First, high levels of chronic peripheral inflammation, indexed by circulatory inflammatory markers, have been associated with experiences of early life stress in both cross-sectional (Carroll et al., 2011; Dixon et al., 2009; Gouin et al., 2012; Grosse et al., 2016; Hartwell et al., 2013; Lacey et al., 2013; Lehto et al., 2012; Lin et al., 2016; Moreira et al., 2018; Munjiza et al., 2018; Packard et al., 2011) and longitudinal studies (Baldwin et al., 2018; Boch and Ford, 2015; Chen and Lacey, 2018; Danese et al., 2011, 2009, 2008, 2007; Lacey et al., 2014; Slopen et al., 2013). For example, Slopen et al. (2013) found that cumulative adversity from birth to 8 years of age, as well as acute adverse events experienced between 6 and 8 years of age were associated with higher circulatory levels of interleukin-6 and C-reactive protein (CRP) at age 10, and CRP at age 15. Researchers have also found associations between experiences of bullying in childhood (9–16 years) and elevated CRP levels in young adulthood (19–21 years) (Copeland et al., 2014), as well as exposure to victimization during childhood (birth–12 years) and elevated levels of CRP at age 18 years (Baldwin et al., 2018).

Moreover, elevated levels of inflammation appear to persist into adulthood, even among disease-free adults with a history of disadvantage or maltreatment during childhood (Juonala et al., 2006). In one longitudinal study, for example, Danese et al. (2007) followed individuals from birth until age 32 and found that risk of clinically relevant CRP levels in adulthood was higher among individuals that experienced maltreatment as children, and that this association was independent of the co-occurrence of other early life risks, stress in adulthood, adult health status, and adult health behaviors. Similarly, a longitudinal birth-cohort study of 7462 participants recently found that social isolation during ages 7–11 predicted higher levels of CRP at 44 years of age (Lacey et al., 2014). Moreover, this association was robust while controlling for obesity and cigarette smoking at 42 years of age, as well as social disadvantage at 42 years of age, educational attainment at 23 years of age, and stress in adulthood (23–42 years).

Second, early life stress has been associated with the types of health problems that are suspected of having an underlying inflammation-related etiology. Indeed, several psychiatric disorders including substance abuse, post-traumatic stress disorder, depression, and schizophrenia have been linked to both early adversity exposure and inflammation, as have many somatic conditions, such as metabolic, cardiovascular, neoplastic, and rheumatic diseases (Anda et al., 2008, 2006; Batten et al., 2004; Brown et al., 2013; Chapman et al., 2004; Dong et al., 2004, 2003; Dube et al., 2009; Felitti et al., 1998; Halonen et al., 2015; Kivimaki et al., 2006; Korkeila et al., 2010; Mantovani et al., 2008; Miller et al., 2011; Nanni et al., 2012; Packard et al., 2011; Scrivo et al., 2011; Slavich and Irwin, 2014; Wolitzky-Taylor et al., 2017). For instance, higher levels of inflammatory activity have been associated with cardiovascular disease, type 2 diabetes, Alzheimer's disease, depression, rheumatoid arthritis, and some cancers, as indexed by the inflammatory markers CRP and fibrinogen (an inflammatory protein), as

Table 1
Associations between early life stress and health problems in adulthood.

Citation	Cited association	Type of study	Population	Sample size	Key metrics
Anda et al. (2008)	Association between childhood adversity and Chronic Obstructive Pulmonary Disease (COPD)	Quasi-prospective	Adults	15,472	Adverse Childhood Experiences (ACE; retrospective at baseline), COPD self-report, COPD incidence at follow-up, medication use at follow-up
Brown et al. (2010)	Association between childhood adversity lung cancer	Quasi-prospective	Adults	17,337	ACE (retrospective at baseline), hospital discharge at follow-up, mortality records at follow-up, adult smoking as mediator
Dong et al. (2004)	Association between childhood adversity and ischemic heart disease (IHD)	Retrospective	Adults	17,337	ACE, self-report of IHD, IHD risk factors (e.g., physical activity) as mediators
Dube et al. (2001)	Association between childhood adversity and suicide attempt	Retrospective	Adults	17,337	ACE, self-report suicide attempt, illicit drug use, depression, and alcoholism as mediators
Dube et al. (2009)	Association between childhood adversity and autoimmune diseases (AD)	Retrospective	Adults	15,357	ACE, hospitalization for 21 types of AD after baseline measurement of ACE, AD immunopathology grouping
Felitti et al. (1998)	Association between childhood adversity, health risk behaviors, obesity, and depression	Retrospective	Adults	9,508	ACE, health risk behaviors and disease from self-report and health screening
Miller and Chen (2010)	Association between early life harsh family climate and pro-inflammatory phenotype in adolescence	Prospective	Female adolescents	135	Harsh family climate, cytokine response to in-vitro bacterial challenge, sensitivity of glucocorticoid receptor
Montez and Hayward (2014)	Association between childhood adversity and active life expectancy	Retrospective	Adults	30,671	Childhood health and SES, mortality, activities of daily living (ADL), educational attainment as mediator
Norman et al. (2012)	Association between childhood adversity and physical and mental health problems	Meta-analysis	Mixed	> 500,000	Physical abuse, sexual abuse, emotional and psychological abuse, neglect, depressive disorder, anxiety, alcohol abuse
Sripada et al. (2014)	Association between childhood poverty and stress reactivity in adulthood	Case-control	Adults	52	Childhood poverty, Trier Social Stress Test, salivary cortisol
Hughes et al. (2017)	Association between childhood adversity an poor health in adulthood	Meta-analysis	Mixed	253,719	ACE, cancer, heart disease, mental illness, drug use, and interpersonal and self-directed violence
Varese et al. (2012)	Association between childhood adversity and psychosis in adulthood	Meta-analysis	Mixed	81,253	Childhood sexual abuse, physical abuse, emotional/psychological abuse, neglect, parental death, bullying, psychotic disorder, schizophrenia, schizoaffective disorder
Huang et al. (2015)	Association between childhood adversity and type 2 diabetes in adulthood	Meta-analysis	Mixed	87,251	ACE, type 2 diabetes
Infurna et al. (2016)	Association between childhood abuse and neglect and depression	Meta-analysis	Adults	4,372	Childhood experience of care and abuse (CECA), clinically assessed depression
Lindert et al. (2014)	Association between childhood sexual and physical abuse and depression	Meta-analysis	Mixed	115,579	Sexual and physical abuse prior to 16 years of age, depression and anxiety after 16 years of age
Palmier-Claus et al. (2018)	Association between childhood adversity and bipolar affective disorder	Meta-analysis	Mixed	> 1,000,000	Child abuse, neglect, bullying, loss of parent, trauma, bipolar disorder
Zatti et al. (2017)	Association between childhood trauma and suicide attempt	Meta-analysis	Children → Adults	6,612	Childhood sexual, physical, and emotional abuse, neglect, and suicide attempt

Table 2
Associations between early life stress and inflammation.

Citation	Cited association	Type of study	Population	Sample size	Key metrics
Baldwin et al. (2018)	Association between victimization in childhood and inflammation (CRP) in young adulthood	Prospective	Children and Young Adulthood	2,232	Childhood victimization, C-reactive protein (CRP), latent genetic risk score, socioeconomic status (SES), waist-hip ratio at age 18, body temperature
Baumeister et al. (2016)	Association between childhood trauma and adult inflammation	Meta-analysis	Adults	varied; 16,870-881	Adverse Childhood Experiences (ACE) Questionnaire; Childhood experiences of care and abuse; Childhood Trauma Questionnaire (CTQ) and CRP, tumor necrosis factor alpha (TNF- α), interleukin (IL)-6
Chen et al. (2008)	Graded association between adverse childhood experiences and inflammation (CRP, fibrinogen) in adulthood	Prospective	Children	7,464	ACE (0-16 years) and CRP, fibrinogen, Von Willebrand factor (vWF) at age 44-45 years, SES
Danese et al. (2007)	Association between childhood maltreatment and adult inflammation	Prospective	Adults (32 years old)	1,037	Childhood maltreatment between 3-11 years, CRP, depression, perceived stress, cardiovascular risk, smoking, physical activity
Danese et al. (2008)	Association between childhood maltreatment and the co-occurrence of depression and inflammation (CRP) in adulthood	Prospective	Adults	1,015	Childhood maltreatment, CRP, fibrinogen, white blood cell count, depression, childhood SES, adulthood SES, smoking, cardiovascular risk
Danese et al. (2009)	Association between adverse psychological childhood experiences and elevated levels of CRP	Prospective	Adults	1,037	Childhood maltreatment, childhood social isolation, adverse childhood experiences, childhood SES, CRP, depression, overweight, high blood pressure, total cholesterol, low high-density lipoprotein cholesterol, high glycated hemoglobin, and low maximum oxygen consumption levels adjusted for body weight
Danese et al. (2011)	Association between physical maltreatment and CRP in 12 year-old children	Prospective	Children	174	Physical maltreatment, CRP, depression, temperature, waist-hip ratio
Dixon et al. (2009)	Association of stress and TNF- α levels in children	Cross-sectional	Children	112	Stressful life events, TNF- α , body mass index (BMI), sex, family history of type 2 diabetes
Gouin et al. (2012)	Association between childhood abuse and inflammatory response, indexed by IL-6, to daily stressors	Cross-sectional	Older adults	130	CTQ, IL-6, TNF- α , and CRP assays, Center for Epidemiological Scale-Depression, Beck Anxiety Inventory, Pittsburgh Sleep Quality Index, Community Healthy Activities Model Program for Seniors (CHAMPS) Questionnaires, Older Adult Resources and Services
Grosse et al. (2016)	Association between childhood trauma and elevated cytokine (IL-6, TNF- α) levels in adults with major depression	Cross-sectional	Adults	394	CTQ, Threatening Experiences Questionnaire, IL-6, TNF- α , major depression, perceived stress
Hartwell et al. (2013)	Association between childhood traumatic experiences and elevated cytokine (IL-1 β , IL-6, TNF- α) levels	Cross-sectional	Adults	38	Early Trauma Inventory (ETI), IL-1 β , IL-6, TNF- α , CRP
Lacey et al. (2013)	Association between parental separation during childhood and increased inflammation (CRP) in adulthood	Cross-sectional	Adults	7462	Parental separation measured at 16 years, CRP and BMI levels measured at 44 years
Lehto et al. (2012)	Association between lower levels of anti-inflammatory marker adiponectin and history of childhood maltreatment in adults	Cross-sectional	Adults	147	Experiences of childhood maltreatment, adiponectin, resisting, depression, BMI
Lin et al. (2016)	Association between childhood adversity and CRP	Cross-sectional	Adults	11,198	Childhood adversity, CRP, adulthood trauma, education, smoking, BMI, alcohol use, physical activity
Miller and Chen (2010)	Inflammation between early life harsh family climate and pro-inflammatory phenotype in adolescence	Prospective	Female adolescents	135	Harsh family climate, cytokine response to in-vitro bacterial challenge, sensitivity of glucocorticoid receptor
Miller and Cole (2012)	Clustering of depression and inflammation (CRP, IL-6) in female adolescents exposed to childhood adversity	Prospective	Female adolescents (15-19 years old)	147	Depressive episodes Structured Clinical Interview for DSM-IV-TR (SCID) Axis I Disorders—Non-Patient Edition, childhood adversity index, CRP and IL-6
Munjiza et al. (2018)	Association between childhood abuse and IL-6 among depressed adults	Cross-sectional	Adults	64	CTQ, IL-6, Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HDRS), and Hamilton Anxiety Rating Scale (HARS)
Moreira et al. (2018)	Association between childhood trauma and higher levels of IL-6 and IL-10 among young adults with major depression	Cross-sectional	Young Adults	166	CTQ, IL-6, IL-10, TNF- α
Slopen et al. (2013)	Association between adverse events in childhood (ages 6-8 years) and CRP and IL-6 levels at age 10 years	Prospective	Children	4,647	Adverse life events, CRP, IL-6, BMI, depression

Table 3
Evidence of epigenetic embedding of early life stress.

Citation	Cited association	Type of study	Population	Sample size	Key metrics
Janusek et al. (2017)	Association between childhood adversity and DNA methylation of the interleukin (IL)-6 promoter	Experimental	Adults	34	Childhood Trauma Questionnaire (CTQ), household dysfunction, DNA methylation of IL-6 promoter, salivary IL-6 and cortisol, exposure to community violence, social support, anxiety, socioeconomic status (SES), health behaviors
Khulan et al. (2014)	Association between current mental state of men exposed to early-life stress (ELS) and DNA methylation	Case-control	Adult males	166	ELS in the form of separation from their parents during childhood, age at separation, length of separation, DNA methylation, current SES, education level, history of mental health disorders, glucose, insulin, IL6, TNF- α and CRP, depression
Labonté et al. (2012)	Association between childhood adversity and epigenetic alterations of genes in hippocampal neurons in suicide completers	Case-control	Adult males	41	Severe early-life abuse assessed via interviews, methylated DNA, gene expression
Levine et al. (2015)	Association between childhood stress and increased inflammatory gene expression later in life	Cross-sectional	Adults	114	Childhood trauma, gene expression levels for PTGS2, IL-1 β , and IL-8, childhood SES, childhood health, adult traumas, adulthood SES
Mehta et al. (2013)	Gene expression was associated with methylation differences in peripheral blood cells and childhood abuse among individuals with posttraumatic stress disorder (PTSD)	Case-control	Adults	169	CTQ, trauma events inventory, gene expression, DNA methylation, PTSD via symptomatic scale and clinician administered scale
Perroud et al. (2011)	Childhood sexual abuse, its severity and the number of maltreatments positively correlated with methylation of the glucocorticoid receptor gene (NR3C1) among individuals with borderline personality disorder (BPD)	Cross-sectional	Adults	101	CTQ, NR3C1 methylation, Screening Interview for Axis II Disorders BPD part, depression
Schwaiger et al. (2016)	Stress-responsive transcripts were enriched for genes involved in cytokine activity among individuals with history of childhood adversity	Experimental	Adults	60	CTQ, Early Trauma Inventory (ETI), genome-wide mRNA expression, Structured Clinical Interview for DSM Disorders (SKID I & II), Resilience Scale (RS-25), Brief Symptom Inventory, Trier Social Stress Test
Tyrka et al. (2012)	Parental loss, childhood maltreatment, and parental care, was associated with increased methylation of NR3C1	Cross-sectional	Adults	99	Parental Bonding Index, childhood parental loss, CTQ, methylation of NR3C1, Dex/CRH Test, plasma cortisol, Structured Clinical Interview for DSM-IV, Inventory for Depressive Symptoms, State-Trait Anxiety Inventory, Perceived Stress Scale
van der Knaap et al. (2014)	NR3C1 methylation rates were higher after exposure to stressful life events (SLEs) during childhood and after exposure to traumatic youth experiences	Prospective	Adolescents	468	Perinatal stress, SLEs and traumatic youth experiences, methylation of NR3C1
McGowan et al. (2009)	Methylation and gene expression of NR3C1 decreased in suicide victims with a history of childhood abuse compared with controls (victims of sudden, accidental death with no history of abuse)	Case-control	Adults	36	Childhood Experience of Care and Abuse Interview, NR3C1 methylation and gene expression, Structured Clinical Interview for DSM Disorders (III-R)
Klengel et al. (2013)	Decreased methylation of the glucocorticoid receptor regulator (FKBP5) was observed in individuals exposed to child abuse and carriers of a risk allele	Case-control	Adults	152	CTQ, methylation of FKBP5, genotyping, clinician-administered PTSD scale
Romens et al. (2014)	Physical maltreatment in children was associated greater methylation of NR3C1	Cross-sectional	Children (11-14 years)	56	Physical maltreatment, NR3C1 methylation, child SES, parent marital status, parent SES (employment status, educational attainment, and occupational prestige)

well as pro-inflammatory cytokines that drive the acute inflammatory response—namely, interleukin-1 β (IL-1 β), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF- α) (Fagundes and Way, 2014; Miller and Cole, 2012; Slavich and Auerbach, 2018).

Although numerous factors likely moderate the effects of early life stress on inflammation and health, gene-environment interactions likely play an important role in moderating the effects of early life stress on inflammation discussed above. In one case-control study of 262 cases of depression and 288 controls, childhood maltreatment interacted with single nucleotide polymorphisms in genes that regulate inflammation—namely, IL-6 [rs1818879] and CRP [rs3093077]—to predict increased risk of depression (Cohen-Woods et al., 2018). Indeed, genes involved in inflammation are well-known to influence the effects that life stress has on health (for a review, see Slavich and Cole, 2013).

4. Epigenetic embedding of a pro-inflammatory phenotype by early life stress

How might early life stress exposure initiate chronic, low-grade inflammation that persists into adulthood? One possibility is that early life stress becomes embedded in neural systems that regulate peripheral stress physiology (Nusslock and Miller, 2016; Slavich and Irwin, 2014) and in genes that coordinate the systemic inflammatory response (Slavich and Cole, 2013). Additionally, the bi-directional interaction between neural and immune systems may become more interconnected and self-promoting over time, allowing elevations in inflammatory activity to persist even after the initial provoking stimulus has passed (Nusslock and Miller, 2016; Slavich and Irwin, 2014).

Consistent with this possibility, growing evidence suggests that individuals reared in adverse childhood environments might tend to exhibit amplified (phenotypic-like) inflammatory responses to varied challenges including those that are both pathogen-related (e.g., bacteria) and threat-related (psychosocial stress). These pro-inflammatory patterns are evident after many types of challenges, and are marked by elevated circulating levels of the key pro-inflammatory cytokines IL-6 and TNF- α (Danese and McEwen, 2012; Gouin et al., 2012; Heim et al., 2002; Heleniak et al., 2016; Hornung and Heim, 2014; Levine et al., 2015; McLaughlin, 2016; Miller and Chen, 2010; Nusslock and Miller, 2016; Schwaiger et al., 2016; Slopen et al., 2013; Steptoe et al., 2002b, 2002a; Winzeler et al., 2017). For instance, adults exposed to early life stress have been found to exhibit greater IL-6 responses, and weaker anti-inflammatory cortisol responses, to real or simulated acute social stressors. Findings from simulated laboratory-based social stressors, such as the Trier Social Stress Test that induces an experience of psychosocial stress involving social evaluation and threat, are particularly interesting as they provide experimental evidence that social stress plays a causal role in activating inflammatory processes (Carpenter et al., 2007, 2010, 2009; Elzinga et al., 2008; Gouin et al., 2012). Similarly, adults reared in adverse childhood environments tend to exhibit exaggerated reactivity to standardized *in vitro* immunologic challenges, as indexed by greater TNF- α levels responses to *ex vivo* lipopolysaccharide (LPS) exposure (Baumeister et al., 2016).

In addition to these findings, lower family socioeconomic status in childhood has been associated with increased cellular inflammatory reactivity to *ex vivo* LPS exposure, as indexed by the cytokines IL-6 and TNF- α (Azad et al., 2012; Miller et al., 2009; Schreier et al., 2014; Wright et al., 2010). Likewise, a recent longitudinal study of female adolescents found that being raised in a harsh family environment was associated with a pronounced cytokine response to *ex vivo* LPS stimulation, as well as with declining glucocorticoid sensitivity, over time (i.e., cortisol became progressively less effective at suppressing LPS-evoked cytokine production; (Miller and Chen, 2010). Schreier et al. (2014) also observed that monocytes derived from adolescents from low socioeconomic status (SES) backgrounds exhibited a relative insensitivity to glucocorticoids. This altered sensitivity to glucocorticoids is potentially harmful for health given that glucocorticoids normally

down-regulate inflammation and promote recruitment and survival of anti-inflammatory monocytes that aid in resolving tissue injury. Finally, there is evidence that experiencing even one major life stressor involving social threat during adolescence can lead to greater upregulation of pro-inflammatory molecular signaling pathways (Murphy et al., 2013) and downregulation of anti-inflammatory pathways (Murphy et al., 2015).

Although the specific mechanisms by which early life stress becomes *biologically embedded* are not yet fully understood, at least one pathway likely involves early life stress-related programming of a *pro-inflammatory phenotype* via changes in the epigenetic regulation of gene expression (Table 3) (Khulan et al., 2014; Levine et al., 2015; Szyf and Bick, 2012)}. Consistent with this possibility, initial research has demonstrated associations between early life stress and genome-wide methylation in adulthood, which was in turn related to increased production of IL-6 following an immunologic challenge (Janusek et al., 2017; Lam et al., 2012). In human studies, early life stress has been associated with modifications of hypothalamic–pituitary–adrenal (HPA) axis- and neuroplasticity-related methylation patterns (Labonté et al., 2012; McGowan et al., 2009; Mehta et al., 2013). Specifically, early life stress was associated with increases in methylation of the glucocorticoid receptor gene (NR3C1; a key regulator of inflammatory activity) (McGowan et al., 2009; Romens et al., 2014; Tyrka et al., 2012; van der Knaap et al., 2014) as well as demethylation of the FKBP5 gene, which increases the expression of the FK506 protein, an important regulator of the stress hormone (Klengel et al., 2013). Increased methylation of the glucocorticoid receptor gene reduces its function and disturbs the feedback of the HPA axis, while binding of FKBP5 protein inhibits the glucocorticoid receptor (Tyrka et al., 2012). These epigenetic changes, which suppress the expression and function of the glucocorticoid receptor, can result in increased inflammatory activity.

The persistence of a phenotype into adulthood is also plausible as increased inflammatory activity can sustain and further exacerbate the impaired function of the glucocorticoid receptor (Miller et al., 2009; Pace et al., 2007; Zunszain et al., 2011). Because the glucocorticoid receptor is central to the regulation of TNF- α signaling, the connections identified between early life stress and pro-inflammatory responses indexed by TNF- α serve as further evidence of an underlying epigenetic mechanism (Van Bogaert et al., 2010). However, support for an epigenetic explanation of the biological embedding of early life stress is still in a preliminary state. Recently, for example, Marzi et al. (2018) conducted epigenome-wide analyses in peripheral blood from participants of the Environmental Risk (E-Risk) Longitudinal Study (Moffitt, 2002) and found no support for the hypothesis of robust changes in DNA methylation in young (18-year olds) individuals with history of victimization (Marzi et al., 2018).

Early life stress might also activate other epigenetic pathways to promote pro-inflammatory states, such as histone modification. For instance, in one animal model study with rats, the gene (GR/NR3C1) that encodes the glucocorticoid receptor exhibited differences in DNA methylation and histone acetylation (involved in chromatin remodeling) in the hippocampus of offspring of high versus low licking and grooming mothers (Weaver et al., 2004). These differences in DNA methylation and histone acetylation emerged very quickly over the first week of life and persisted into adulthood. Furthermore, these differences were reversed with cross-fostering. A causal relationship between epigenomic state, GR expression, and the maternal effect on stress responses in the offspring was supported by the removal of group differences in histone acetylation, DNA methylation, GR expression and HPA responses via central infusion of a histone deacetylase inhibitor (Weaver et al., 2004). In animals, maternal separation also affected gene regulation of both writer (histone acetyltransferases and histone methyltransferases) and eraser (histone deacetylases and histone lysine demethylases) classes of histone modifiers within the medial prefrontal cortex (mPFC), a key limbic brain region that regulates stress responses and mood-related behavior (Pusalkar et al., 2015).

Table 4
Associations between particle air pollution exposure, inflammation, and inflammation-related diseases in humans.

Citation	Cited association	Type of study	Population	Sample size	Key metrics
Akimtuye et al. (2016)	Association between fine particulate matter exposure and subclinical atherosclerosis	Meta-analysis	Adults	11,947 - 6,497	Exposure to PM _{2.5} , carotid intima media thickness, arterial calcification, ankle-brachial index
Balti et al. (2014)	Association between exposure to air pollution and increased risk of type 2 diabetes	Meta-analysis	Adults	385,395	Exposure to nitrous oxides (NOx), NO ₂ , PM ₁₀ , and PM _{2.5} , risk of type 2 diabetes
Behndig et al. (2006)	Increased interleukin (IL)-8 concentration in bronchial lavage was induced by diesel exhaust exposure	Experimental	Adults	15	Two-hour controlled exposure to PM from diesel exhaust and clean air, bronchoscopy performed 18 hours post exposure, IL-6, IL-8, lung function, endothelial adhesion molecules, vascular adhesion molecule, intracellular adhesion molecule
Bernatsky et al. (2016)	Association between exposure to PM _{2.5} and systemic autoimmune rheumatic diseases (SARDs)	Cross-sectional	Adults	> 1,000,000	Regional PM _{2.5} , systemic lupus, erythematous, Sjogren's syndrome, scleroderma, polymyositis, dermatomyositis, and undifferentiated connective tissue disease
Bobak (2000)	Association between prenatal exposure to sulfur dioxide (SO ₂) and low birth weight	Cross-sectional	Mother and child	108,173	Exposure to SO ₂ , NOx, total suspended particles (TSP) during each trimester of pregnancy, and low birth weight, prematurity, intrauterine growth retardation
Bowatte et al., (2017)	Association between exposure to traffic related air pollution (TRAP) and increased risk of atopy and wheezing	Cross-sectional	Children	1,405	Mean annual residential exposure to NOx, distance to nearest major road, lung function, asthma, atopy
Chen and Schwartz (2009)	Association between chronic exposure to PM ₁₀ and ozone and cognitive function	Cross-sectional	Adults	1,764	Exposure to PM10 and ozone, simple reaction time test (SRTT), basic measure of visomotor speed, symbol-digit substitution test (SDST) on coding ability, serial-digit learning test (SDLT) on attention and short-term memory, age, sex, race/ethnicity, SES
Dobrev et al. (2013)	Association between regional PM _{2.5} ambient levels and tumor necrosis factor alpha (TNF-α) and IL-10 in adolescents	Cross-sectional	Adolescents (18 years)	40	Regional PM ₁₀ , PM _{2.5} , SO ₂ , and NO ₂ levels, TNF-α, IL-6, IL12p40, IL-10
Ghio et al. (2000)	Acute exposure to concentrated ambient particles was associated with mild inflammation in lower respiratory tract as well as higher circulatory fibrinogen	Experimental	Adults	38	Two-hour exposure to PM _{2.5} (0.1–2.5 μm), cell count via bronchoalveolar lavage, fibrinogen, lung function
Gruzjeva et al. (2017)	Long-term exposure to PM ₁₀ and NO ₂ was associated with IL-6 in healthy children, and also with IL-10 in asthmatic children	Longitudinal	Children	670	Exposure to PM ₁₀ and NO ₂ , IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and TNF-α
Kim et al. (2016)	Association between long-term PM _{2.5} exposure and major depressive disorder	Longitudinal	Adolescents and adults	27,270	Long-term exposure to PM _{2.5} , major depressive disorder, household income, smoking, alcohol consumption, exercise
Kipen et al. (2011)	Association between exposure to fresh diesel-engine exhaust and reduced white and red blood cell protease activity	Experimental	Adult	38	Exposure to diesel exhaust, secondary organic aerosol, and clean air, platelet activation, nitric oxide metabolites, protease activity, endothelial function, heart rate variability
Lamichhane et al. (2015)	Association of exposure to particulate matter and adverse birth outcomes	Meta-analysis	Mother and child	> 1,000,000	Exposure to PM ₁₀ , and PM _{2.5} , birth weight, preterm birth
Ostro et al. (2014)	Association between prior-year exposure to PM _{2.5} and C-reactive protein (CRP)	Longitudinal	Adult women	1,923	Exposure to PM _{2.5} , CRP, diabetes, smoking, unmarried, income
Peters et al. (2001)	A high ambient-PM episode was associated with increased odds of observing increases in CRP in men	Prospective	Adult men	631	Exposure to total suspended particles, SO ₂ , and carbon monoxide (CO), CRP, body mass index (BMI), smoking
Pourazar et al. (2004)	Significant increase of IL-13 expression in bronchial epithelium cells induced by diesel exhaust exposure	Experimental	Adult	15	One-hour controlled exposure to diesel exhaust and clean air, bronchoscopy, IL-10, IL-13, IL-18
Requia et al. (2017)	Associations between respiratory diseases and PM _{2.5} exposure	Meta-analysis	Adults and children	> 1,000,000	Exposure to PM ₁₀ , PM _{2.5} , CO, SO ₂ , NO ₂ , ozone, mortality, hospital admissions, respiratory diseases, cardiovascular diseases
Rich et al. (2012)	Changes in air pollution levels during the Beijing Olympics were associated with acute changes in biomarkers of inflammation in healthy young persons	Quasi-experimental	Adults	125	Exposure to PM _{2.5} , CRP, fibrinogen, von Willebrand factor, soluble CD40 ligand (sCD40 L), soluble P-selectin (sCD62 P) concentrations, white blood cell count (WBC), heart rate, and blood pressure
Rueckert et al. (2007)	Association between increased circulatory IL-6 levels and acute exposure to ambient air particle levels in myocardial infarction survivors	Longitudinal	Adults	1,003	Exposure to PM ₁₀ , PM _{2.5} , ultrafine particles, black smoke, black carbon, CO, SO ₂ , NOx, and ozone, IL-6, CRP, blood pressure, BMI serum lipids, HbA1c
Seaton et al. (1999)	Association between personal three-day PM ₁₀ exposure and CRP	Cross-sectional	Older adult men	112	Personal exposure to PM ₁₀ , CRP, fibrinogen, hemoglobin, packed cell volume, platelets
Stieb et al. (2012)	Association of exposure to particulate matter and adverse birth outcomes	Meta-analysis	Mother and child	> 1,000,000	Exposure to PM ₁₀ , PM _{2.5} , CO, and NO ₂ , birth weight, preterm birth
Tomczak et al. (2016)	Increases in PM _{2.5} exposure were associated with elevated risk of lung cancer	Prospective	Adult women	89,234	Long-term exposure to PM _{2.5} , small cell carcinoma, adenocarcinoma, smoking
van Eeden et al. (2001)	Circulating levels of IL-1β and IL-6 were elevated in subjects exposed to high levels of PM ₁₀ during an episode of acute air pollution.	Longitudinal	Adult men	30	Exposure to PM ₁₀ , SO ₂ , NO ₂ , ozone, and CO during a forest fire, TNF-α, IL-1β, IL-6

(continued on next page)

Table 4 (continued)

Citation	Cited association	Type of study	Population	Sample size	Key metrics
Wang et al. (2014)	Association between exposure to air pollution and increased risk of type 2 diabetes	Meta-analysis	Adults	2,371,907	Exposure to NO ₂ , PM ₁₀ , and PM _{2.5} ; risk of type 2 diabetes
Wu et al. (2012)	Associations between PM _{2.5} chemical constituents and multiple biomarkers of inflammation	Longitudinal	Young adults	40	Exposure to PM _{2.5} , chemical composition, CRP, TNF- α , fibrinogen, plasminogen activator inhibitor type 1, tissue-type plasminogen activator, von Willebrand factor, soluble platelet selectin

Generally speaking, this shift toward a more pro-inflammatory phenotype has biological advantages, especially under conditions of acute threat of physical harm when inflammation is helpful for promoting wound healing and recovery. If persistently stimulated by inflammation-inducing factors such as pathogens, chronic psychosocial stress, or air pollution, however, the pro-inflammatory phenotype may become more self-promoting and prolonged, which could in turn promote low-grade, chronic inflammation that increases an individual's risk for disease (Slavich and Irwin, 2014). These effects are thus relevant for understanding how early life stress leads to poor health in general. Because exposure to stressors that trigger inflammation is socially patterned, however, these findings are also important for understanding how disparities in immunologic-related health outcomes may develop and persist over time (Miller et al., 2011).

5. Air pollution and health

The World Health Organization (WHO) presently considers air pollution the biggest environmental threat to health, with one of every nine deaths around the world attributed to air-pollution related conditions (World Health Organization, 2016). Ambient (outdoor) air pollution is commonly considered a combination of gaseous and particulate components, such as sulfur dioxide (SO₂), particulate matter (PM), ozone, nitric oxide (NO₂), carbon monoxide (CO), and lead, which have been individually demonstrated to have adverse impacts on health (Bose and Diette, 2016). Exposure to ambient air pollution alone is responsible for approximately 3 million deaths each year, mainly from cardiovascular diseases such as stroke and ischemic heart disease, as well as from respiratory conditions (24%) and lung cancer (6%) (World Health Organization, 2016). Importantly, this mortality is primarily due to exposure to particulate matter smaller than 10 microns in diameter (PM₁₀). Long-term exposure PM₁₀ or smaller (e.g., < 2.5 microns, PM_{2.5}), has also been associated with increased risk of adverse birth outcomes, respiratory disease, diabetes, and atherosclerosis, as well as poor neurodevelopment and cognitive function (Table 4) (Bobak, 2000; Bowatte et al., 2017; Calderón-Garcidueñas et al., 2015; Campen et al., 2012; Esposito et al., 2016; Malmqvist et al., 2011; Morgenstern et al., 2007; Thiering and Heinrich, 2015; Wang et al., 2016). Conversely, reductions in ambient PM_{2.5} concentrations across U.S. cities have been associated with significant increases in life expectancy, even after adjusting for changes in socioeconomic and demographic variables (Pope et al., 2009).

A recent study found significant evidence of adverse effects related to exposure to two common urban air pollutants (i.e., PM_{2.5} and ozone) even at concentrations below national standards and noted that these effects appeared most potent among socially disadvantaged individuals, such as racial minorities and people with low income (Di et al., 2017). Such findings hint that socially disadvantaged individuals may in fact be more vulnerable to air pollution. Throughout their lifespan, socially disadvantaged individuals tend to experience worse air quality (Bose and Diette, 2016; Frieden, 2011). However, although studies rarely account for exposure to both poor air quality and social disadvantage, the health impact of chronic exposure to poor air quality is closely intertwined with the negative health effects of social stressors that are also more concentrated among those who are socially disadvantaged, such as family dysfunction, violence, discrimination, and poverty (Evans and Kim, 2007; Kristiansson et al., 2015; Miller and Chen, 2013). Therefore, research is needed to understand how social and environmental factors interact in order to evaluate if and how synergy among these factors leads to social disparities in health. Understanding these interactions is essential for developing more effective interventions and policies to better protect susceptible populations, and in turn reduce health disparities and improve public health.

6. Inflammatory mechanisms linking air pollution and health

Toxicology research in humans and animal models shows that exposure to particle air pollution can result in both local and systemic inflammation (Table 4) (Ogino et al., 2017; Ostro et al., 2014; Riva et al., 2011). For example, inhaled traffic-related PM enters the lungs and causes a local inflammatory response from alveolar macrophage and bronchial epithelial cells (Bai and Sun, 2015); it is noteworthy that this response can be indexed by the production of the same pro-inflammatory cytokines that are triggered by life stress (Ghio et al., 2000; Peters et al., 2001; Pope et al., 1999; Seaton et al., 1999). At a cellular level, onset of this inflammatory response is initiated by the release of IL-1 β and TNF- α , which tend to be expressed as inactive proforms in resting cells and released without the activation of the transcriptional machinery (Schwarze et al., 2013). Subsequently, IL-1 β and TNF- α regulate the expression of various secondary cytokines and chemokines, including IL-6 and IL-8.

Release of these secondary cytokines and chemokines can also be activated directly (i.e., independent of IL-1 β and TNF- α) by traffic-related particle pollution through stimulation of the intracellular pro-inflammatory signaling pathways. One such pathway begins with oxidative stress that is induced by inhaled particle air pollution (Pope et al., 1999). In rats, for example, a three-hour exposure to particle matter smaller than 2.5 μm (PM_{2.5}) has been shown to lead to a rapid increase of reactive oxygen species (ROS) generation in the heart and lung (Gurgueira et al., 2002). Oxidative stress can then activate transcription factors such as nuclear factor (NF)- κ B and activator protein (AP)-1, which in turn upregulate the expression of genes coding for cytokines, chemokines, and other pro-inflammatory mediators (see Fig. 1) (Bennett et al., 2012). Notably, NF- κ B signaling is central to the human inflammatory machinery and can also be activated by toll-like receptor ligands of LPS (some of which can be attached to PM), hypoxic condition, and TNF- α . The localized pro-inflammatory mediators that result from NF- κ B activation then spill into the circulatory system and fuel a low-grade peripheral inflammatory state.

Activation of toll-like receptor 4 (TLR4) and NADPH oxidase in monocyte/macrophages by oxidized phospholipids may represent another potential pathway through which PM_{2.5} mediates systemic inflammation (Kampfath et al., 2011). Toll-like receptors and related

scavenger receptors, such as CD36 and lectin-like oxidized LDL receptor-1 (LOX-1), are the major immune sensors that recognize pathogen-associated and damage-associated molecular patterns arising from inflammation, infection, or cell stress, and these receptors have been mechanistically implicated as drivers of systemic inflammation following air pollution exposure (Aragon et al., 2017; Nergiz-Unal et al., 2011; Rao et al., 2014; Robertson et al., 2013). The scavenger receptor signaling pathways culminate in activation of NF- κ B (Kawai and Akira, 2007; Lund et al., 2011). TLR4 has also been involved in the recognition of PM and, similar to the scavenger receptors, has been shown to mediate the particle-induced production of TNF- α (Becker et al., 2002; Shoenfelt et al., 2009).

7. Inflammation as a common process triggered by early life stress and air pollution

Some epidemiologic studies have directly examined the extent to which psychosocial stress and air pollution have synergistic effects, and so far, this literature has revealed evidence that such effects may occur. For instance, Chen et al. (2008) studied the interaction between chronic exposure to chronic family stress and traffic-related air pollution in predicting biologic and clinical outcomes in 73 children with asthma (Chen et al., 2008). They found significant interactions, for instance children with high chronic family stress had elevated levels of IL-5, immunoglobulin E (IgE), and eosinophil counts as exposure to nitric dioxide decreased. Shankardass et al. (2009) studied 2497 children aged 5–9 years old from the Children's Health Study (McConnell et al., 2006; Shankardass et al., 2009), and looked at doctor-diagnosed new onset of asthma during a 3-year follow-up. They observed that risk of asthma attributable to exposure to traffic related air pollution (TRP) was significantly higher for children with high parental stress [Hazard Ratio (HR) = 1.51 across the interquartile range for TRP; 95% CI = 1.16–1.96] as compared to those with low parental stress (HR = 1.05, 95% CI = 0.74–1.49; interaction *P* value = 0.05). Although parental stress may have influenced the development of asthma in children through pathways other than psychosocial stress in these children, the pattern of susceptibility to air pollution based on stress was not explained by potentially relevant history of illness and a range of behavioral, socioeconomic, and environmental risk factors for

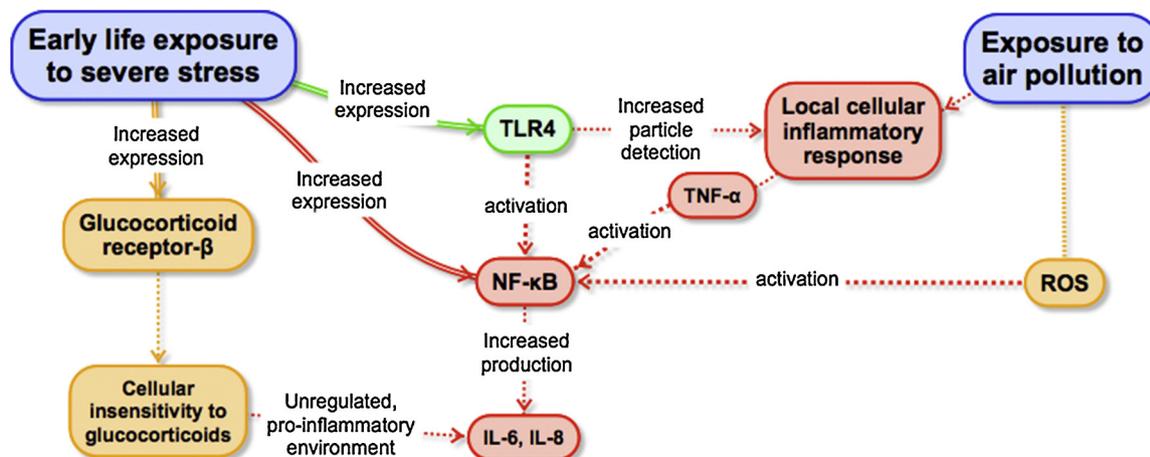


Fig. 1. An integrated multi-level model of early life stress, air pollution, and health. Depicted are the mechanisms through which early life stress exposure may affect the inflammatory response to air pollution exposure, leading in turn to poor lifespan health. Early life exposure to severe stress increases the expression of toll-like receptor 4 (TLR4), glucocorticoid receptor- β , and nuclear factor (NF)- κ B (Bennett et al., 2012; Fiordelisi et al., 2017; Miller et al., 2009). TLR4 is part of the air pollution recognition process that leads to the production of tumor necrosis factor alpha (TNF- α) and culminates in the activation of NF- κ B (Kampfath et al., 2011; Kawai and Akira, 2007; Lund et al., 2011; Becker et al., 2002; Shoenfelt et al., 2009). Exposure to air pollution increases reactive oxygen species (ROS) generation in the heart and lung (Gurgueira et al., 2002), which in turn also activates NF- κ B. Activation of NF- κ B upregulates the expression of genes coding for cytokines, chemokines, and other pro-inflammatory mediators such as interleukin-6 (IL-6) and interleukin-8 (IL-8) (Gurgueira et al., 2002; Bennett et al., 2012). Finally, increased expression of glucocorticoid receptor- β leads to insensitivity to glucocorticoids that creates a pro-inflammatory environment, which culminates in increased production of IL-6 and IL-8 (Cain and Cidlowski, 2015; Hamid et al., 1999).

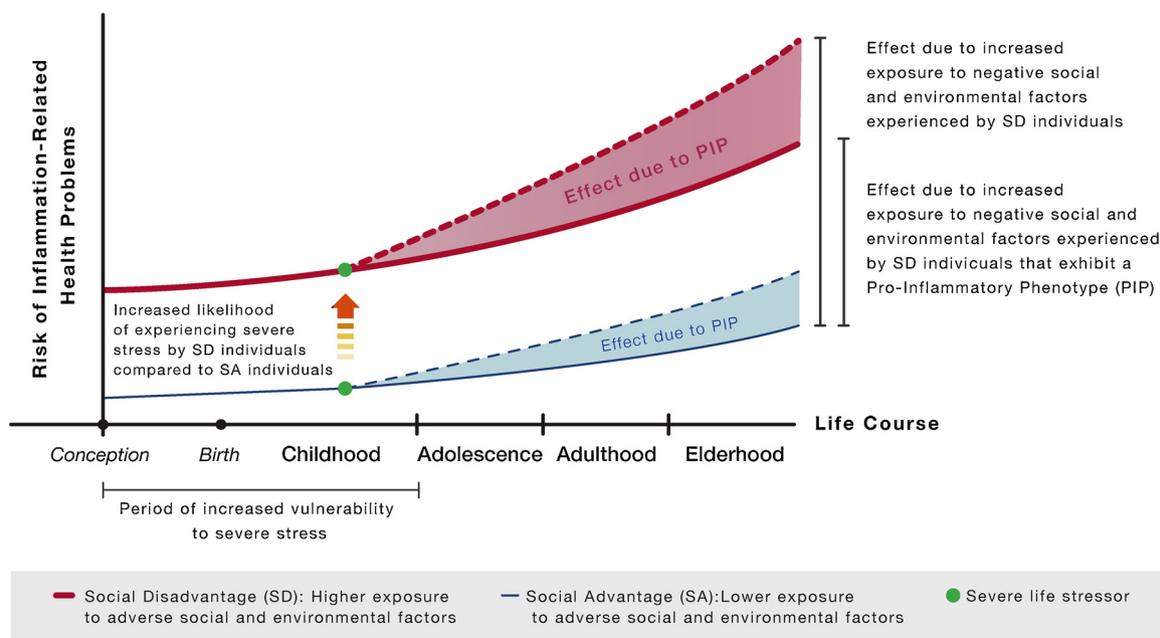


Fig. 2. The immunologic model illustrates a pathway through which specific social factors (i.e., early life stress exposure) and environmental factors (i.e., air pollution exposure) interact to increase the risk of developing inflammation-related health problems. It also describes how the accumulation of risk across the lifespan occurring as a function of higher exposure to these factors drives disparity across social strata. First, socially disadvantaged individuals are shown to be at particularly high risk for poor health, as compared to individuals in better social standing, due to a greater chance of experiencing severe stress during childhood (orange arrow) and greater exposure to air pollution -and other inflammation-inducing triggers- over the lifetime (shift between solid lines). Second, regardless of social circumstances, early life stress can program, via epigenetic mechanisms, a pro-inflammatory phenotype that ultimately results in vulnerability to inflammation-inducing triggers. As a consequence, individuals with this phenotype exhibit greater inflammatory reactivity to inflammatory triggers as compared to individuals without this phenotype. Over time, this pro-inflammatory phenotype increases individuals' risk of developing inflammation-related health problems as a function of exposure to inflammation-inducing triggers (shaded areas between solid and dotted lines). (For interpretation of the references to colour in the figure text, the reader is referred to the web version of this article).

asthma (Shankardassf et al., 2009). Using the same data set, Islam et al. (2011) reported that nitrogen oxide concentrations at home and school had a greater impact on lung function (e.g., FEV1 and FVC) among children of parents reporting higher perceived stress, after adjusting for household socioeconomic status (Islam et al., 2011). These findings are also broadly consistent with evidence showing that individuals from low socioeconomic backgrounds (which can give rise to stress) have greater air-pollution related mortality than their higher socioeconomic counterparts (Forastiere et al., 2007; Jerrett et al., 2004; Krewski et al., 2003).

Here, we posit that early life stress and air pollution are likely to have joint effects on health by way of stress exposure early in life increasing individuals' inflammatory response to particle air pollution across the lifespan. Evidence for this pathway comes from at least three lines of research. First, there is substantial overlap between the specific diseases that are strongly associated with particle air pollution and with early life stress exposure. These include disorders that cause substantial disease burden worldwide, including cardiovascular disease, autoimmune diseases, lung cancer, and depression (Bernatsky et al., 2016; Brunekreef and Holgate, 2002; Calderón-Garcidueñas et al., 2015; Lim et al., 2012). Second, many of these diseases have an underlying inflammatory component (Danese et al., 2009; O'Neill et al., 2007; Slavich and Irwin, 2014; Wellen and Hotamisligil, 2005). Moreover, psychosocial stress and particle air pollution seem to influence the same inflammatory processes, such as inducing oxidative stress, as well as activating NF- κ B and TLR4 (see Fig. 1); (Bennett et al., 2012; Fiordelisi et al., 2017).

In one study that sampled caregivers of brain-cancer patients, for example, exposure to chronic stress was associated with increased expression of transcripts with response elements for NF- κ B and reduced expression of transcripts bearing response elements for glucocorticoids (Miller et al., 2008). Another study with female adolescents found that

lower socioeconomic status early in life was associated with reduced expression of genes coding for glucocorticoid receptor and increased expression of TLR4 (Miller and Chen, 2007). The observed changes in the expression of these genes can lead to the improper regulation of inflammatory response.

Given that the inflammatory response to particle air pollution is mediated by the activation of NF- κ B via oxidative stress, a psychosocially induced increase in expression of NF- κ B could potentiate the inflammatory response to air pollution (Fiordelisi et al., 2017). Additionally, increased expression of glucocorticoid receptor- β can lead to cellular insensitivity to glucocorticoids, including in airway cells, creating a physiologic environment that favors the production of pro-inflammatory cytokines and increases systemic inflammation (Cain and Cidlowski, 2015; Hamid et al., 1999). Neither study evaluated possible interactions with air pollution. However, it is possible that risk of adverse outcomes is even greater than initially considered given the inflammatory response to fine particle air pollution, which is mediated by TLR4, is exacerbated by exposure to early life stress because such exposure increases expression of TLR4 (Kampfrath et al., 2011).

In sum, exposure to early life stress and to early life stress are socially patterned in very similar ways. Consequently, the aforementioned inflammatory pathway that links early life stress and air pollution exposure could help explain disparities in inflammation-related health problems during the lifespan for individuals in different socially disadvantaged groups.

8. An integrated multi-level model of early life stress, air pollution, and health

Based on the literatures synthesized in prior sections, we propose an integrated, multi-level immunologic model of how severe early life stress exposure combines with exposure to air pollution to structure

social disparities in inflammation-related health outcomes across the lifespan. Fixed factors that determine social disadvantage such as gender, race, and ethnicity are present from birth and persist across life. Factors such as poverty and SES although unfixable, also tend to persist across life (Chetty et al., 2014). Because individuals born into social disadvantage tend to remain in those circumstances into adulthood, they experience exposures across the lifespan that can interact to affect health and promote health disparities. One example of this is when individuals born into social disadvantage experience stress early in life and develop a sensitivity to air pollution characterized by a pro-inflammatory phenotype, while also being more likely to experience higher exposure to air pollution across the lifespan (Boehmer et al., 2013; Cicchetti and Toth, 2005; Evans, 2004). The model we propose in Fig. 2 describes this interaction and how it can promote health disparities by increasing a person's risk of developing health problems with an inflammatory component (e.g., depression, cardiovascular disease, diabetes).

As depicted in Fig. 2, our formulation highlights why compared to individuals in socially advantageous circumstances (blue lines), those in socially disadvantaged circumstances (red lines) are at particularly high risk of experiencing more inflammation-related health problems across the lifespan—namely, because:

- 1) Individuals in socially disadvantaged circumstances have greater risk of developing inflammation-related health problems due to exposure to higher levels of air pollution over the lifetime, as compared to those in socially advantageous circumstances (shift between solid blue and red lines).
- 2) Individuals in socially disadvantaged circumstances have a greater chance of experiencing severe stress early in life (orange arrow), and therefore of developing a pro-inflammatory phenotype that increases their inflammatory reactivity to air pollution exposure, as compared to individuals in socially advantageous circumstances (see also Fig. 1).
- 3) Independent of social condition, individuals who develop a pro-inflammatory phenotype experience greater risk of inflammation-related health problems due to increased inflammatory reactivity to air pollution exposure (shift between solid and dotted lines).
- 4) Disparity of inflammation-related health problems between individuals in socially advantageous circumstances and those in disadvantaged circumstances (shift between solid blue line and dotted red line), can result from differences in experiences of early life stress, sensitivity to air pollution due to the development of a pro-inflammatory phenotype, and exposure to higher levels of air pollution over the lifetime.

Our model describes how among socially disadvantaged individuals, an interaction between stress in childhood and air pollution across the lifespan, that is mediated by a pro-inflammatory phenotype, can result in a greater and compounded risk of developing inflammation-related health problems. The evidence discussed in previous sections also suggests that the pro-inflammatory phenotype results in increased inflammatory reactivity to inflammation-inducing factors, other than air pollution, such as psychosocial stress and pathogens (Baumeister et al., 2016; Carpenter et al., 2010, 2009, 2007; Elzinga et al., 2008; Gouin et al., 2012), to which socially disadvantaged individuals are also more likely to be disproportionately exposed during their life, compared to individuals in better social circumstances. For this reason, our model (shown in Fig. 2) was generalized to describe how severe stress experienced during childhood can drive disparity in inflammation-related health problems by programming a pro-inflammatory phenotype that increases the inflammatory response to social and environmental factors (that induce inflammation) and for which exposure is patterned by social advantage.

The immunological model proposed here is in alignment with the allostatic load model as it posits that historical factors (trauma/abuse,

stressful environments during childhood) induce a vulnerability to certain stressors by compromising allostatic mechanisms which result in the dysregulation of primary mediators; over-production of pro-inflammatory cytokines (e.g., IL-6, TNF α) and under-production of stress hormones (e.g., cortisol). Allostatic load as described by (McEwen and Stellar, 1993) refers to the “wear and tear” the body experiences in response to repeated allostatic activations caused by persistent perception of psychosocial stressors. The allostatic load model delineates that an individual's vulnerability or resiliency to stress is determined by their perception of threats and the subsequent activation of allostatic mechanisms, which in turn can be compromised by synergistic effects of primary mediators -stress hormones (epinephrine, norepinephrine, and cortisol) their antagonists, as well as pro- and anti-inflammatory cytokines (e.g., IL-6, TNF α)- on cellular activities (enzyme, receptor, ion channel, genomic) (Juster et al., 2010; McEwen, 1998; McEwen and Wingfield, 2003). Also, our model expands the allostatic load model by suggesting that allostatic load can result in vulnerability to environmental stressors such as air pollution.

Finally, our model emphasizes an interaction between stress early in life and air pollution exposure across the lifespan. However, there is also evidence of additive effects between psychosocial stress and environmental exposures (e.g., bacteria, virus, Pb) (Clougherty et al., 2014). The model also delineates a different risk of developing inflammation-related health problems at conception based on potential genetic susceptibilities passed on by parents, due to exposure to social and environmental factors associated with social advantage.

9. Future directions

Despite an evident overlap of social and environmental risk factors in society that is patterned by social disadvantage, insufficient research has focused on studying the interaction of these factors. Interdisciplinary research is urgently needed to determine how exposures, as they occur in the real world rather than in the siloed world of epidemiology, contribute to social disparities in health and, most importantly, how data along these lines can help scientists identify the factors that can be modified to prevent or manage these problems. To this end, we recently proposed a broad framework that accounts for a wide range of overlapping social and environmental exposures across the lifespan and delineates underlying biobehavioral pathways that lead to chronic illness (Olvera Alvarez et al., 2018). Along with this framework, a roadmap for research in this area was also delineated. Although this framework may generally guide research in this area, different combinations of exposures may require their own specific consideration to identify appropriate mechanisms and processes at play. For that reason, here we focus on a set of specific commonly co-occurring exposures, early life stress and air pollution, and consider how they may interact to affect health.

Research along several lines is needed to test and advance the hypothesis that a pro-inflammatory phenotype may help to understand the greater susceptibility of individuals who experience high levels of early life adversity, to adverse health effects of air pollution. First, research is necessary to understand which specific types of life stress most strongly trigger inflammation and lead to the development of a pro-inflammatory phenotype (Epel et al., 2018; Irwin and Slavich, 2017; Slavich et al., 2010). Second, there may be periods of vulnerability during childhood when stress exposure is more likely to promote a pro-inflammatory phenotype, but these periods presently remain unknown. Third, studies on the biological and physiological processes that characterize the pro-inflammatory phenotype, including the epigenetic markers such as the changes in methylation of specific genes at specific sites in specific cells, should be conducted to establish effective ways to assess the presence, persistence, and potential reversibility (if any) of this vulnerability. Such information may be used to identify individuals at risk earlier in the life course and may provide earlier opportunities for intervention.

Fourth, broad research efforts are necessary to determine the most pervasive factors that may induce inflammation to which individuals with a pro-inflammatory phenotype are vulnerable. Understanding these factors (e.g., certain foods, or specific forms of stress) could help direct efforts to minimize deleterious exposures. Relatedly, greater understanding of the social and environmental contexts in which exposure to factors that induce inflammation occurs is also important. Although it is clear that social disadvantage is broadly associated with greater exposure to harmful social and environmental risk factors, it is likely that substantial variation in vulnerability and risk also exists among those who are socially disadvantaged. For example, being part of an ethnic minority group or in low-SES does not imply an automatic constant risk. In this regard, future research should consider alternative pathways that may confound the associations between early life stress and adult health outcomes, such as access and quality of health care. Similarly, among socially disadvantaged populations, subgroups of intense risk also exist (e.g., very poor, individuals in isolation, minorities within very segregated communities), which need to be identified and prioritized in intervention efforts. In this regard, research efforts should focus primarily on identifying modifiable factors that could help reduce exposure to factors that induce inflammation among vulnerable populations.

Fifth, research is needed to explore potential protective factors (e.g., social, psychological, immunologic) against severe early life stress and the programming of the pro-inflammatory phenotype. There is evidence for instance that positive parental attachment could protect children against some of the outcomes associated with early life stress exposure (Cameron et al., 2017; Okello et al., 2014), but this research has generally not considered the potential role of air pollution or inflammatory processes. Research on the availability or prevalence of protective factors across social groups could further reveal opportunity for interventions is also necessary.

In general, despite growing interest in examining the joint contribution of social and environmental determinants of health, conducting interdisciplinary research on this topic can be challenging, and a critical limiting factor presently involves a lack of knowledge about how to measure exposures outside of one own's primary discipline. As a starting point, therefore, stress researchers are referred to a set of reviews summarizing air pollution exposure assessment methods (Krzyzanowski, 1997; Mirowsky and Gordon, 2015; Zhang and Lioy, 2002; Zou et al., 2009), as well as the USEPA's online resources for human air pollution exposure. Environmental health researchers, in turn, are referred to a set of reviews summarizing early life stress measures (Appleton et al., 2017; Burgermeister, 2007), as well as lifetime stress exposure measurement (Shields and Slavich, 2017; Slavich, 2016; Slavich and Shields, 2018).

10. Conclusion

In summary, we believe there is relatively strong evidence, emerging from different lines of research, to suggest that social factors interact with environmental factors via biobehavioral pathways that in turn affect health. With the rich separate bodies of evidence linking early adversity and air pollution with both inflammation and inflammation-related chronic diseases, considering the combined effects of early adversity and air pollution provides a potent example of how these effects might play out. To date, empirical research exploring the full range of factors that may be relevant for developing a comprehensive understanding of this interplay is limited. To illustrate the promise of this work and more directly explore a plausible pathway by which social disadvantage gets under the skin to influence lifelong health, we integrated evidence from epidemiology, psychoneuroimmunology, toxicology, and genomics research to support the hypothesis that early life stress activates a pro-inflammatory phenotype, which in turn increases individuals' susceptibility to developing inflammation-related diseases over the lifespan. Because individuals in

socially disadvantaged circumstances are more likely to be exposed to major life stress during childhood, as well as stressors that may induce inflammation across the lifespan, we posit that the activation of this phenotype is a key determinant of social disparities in health. To the extent that this is true, a better understanding of how this pro-inflammatory phenotype develops, as well as what interventions might help reduce inflammation-related health risks, will be important for reducing health disparities and improving population health worldwide (Slavich, 2015).

Declarations of interest

None.

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