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

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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

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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 PM2.5, 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 individuals' 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 (SO_2), particulate matter (PM), ozone, nitric oxide (NO_2), 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 (PM_{10}). Long-term exposure PM_{10} 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-1β 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-1β 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-1β 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)-κB 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-κB 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-κB 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 (Kampfrath 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-κB (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 eosisophil 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

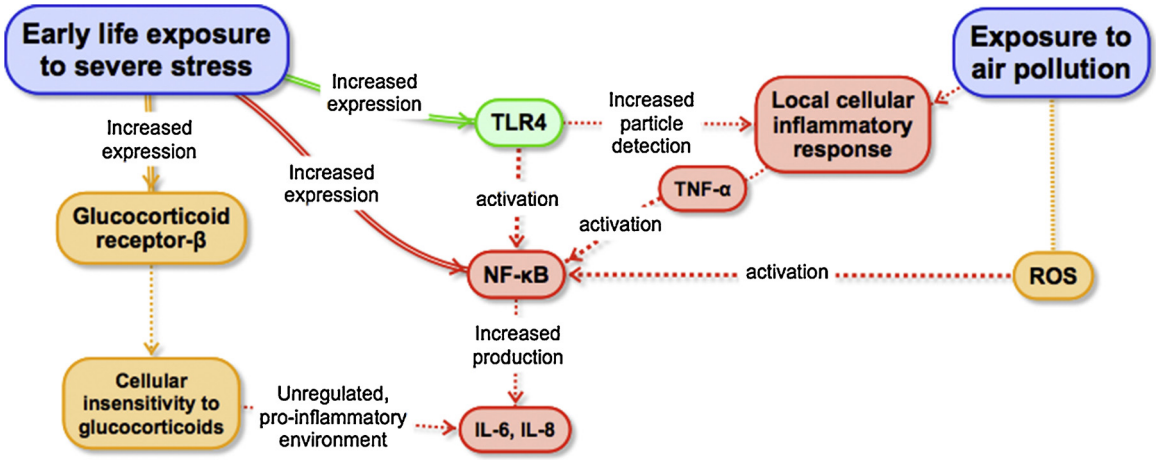

Fig. 1. An integrated multi-level model of early life stress, air pollution, and health. Depicted are the mechanisms through which early life stress exposure may affect the inflammatory response to air pollution exposure, leading in turn to poor lifespan health. Early life exposure to severe stress increases the expression of toll-like receptor 4 (TLR4), glucocorticoid receptor-β, and nuclear factor (NF)-κB (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-κB (Kampfrath 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-κB. Activation of NF-κB 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).

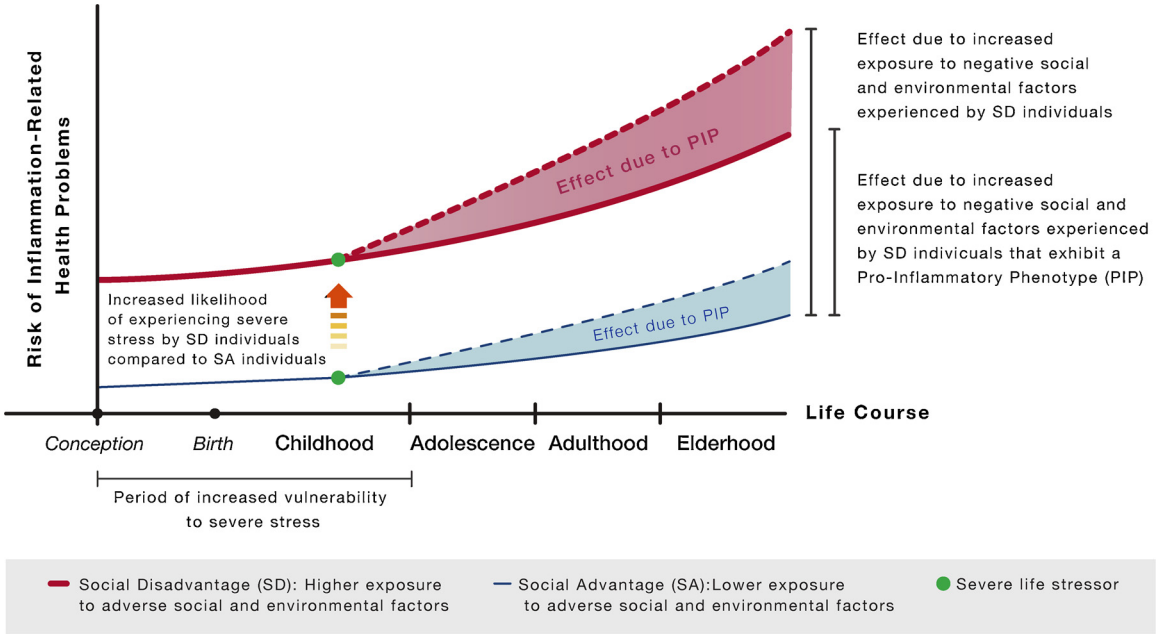

Fig. 2. The immunologic model illustrates a pathway through which specific social factors (i.e., early life stress exposure) and environmental factors (i.e., air pollution exposure) interact to increase the risk of developing inflammation-related health problems. It also describes how the accumulation 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-κB 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-κB 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-κB via oxidative stress, a psychosocially induced increase in expression of NF-κB 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 unfixed, 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 disadvantageous circumstances (red lines) are at particularly high risk of experiencing more inflammation-related health problems across the lifespan—namely, because:

1) Individuals in socially disadvantageous 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 disadvantageous 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 responsivity 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 disadvantageous 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, TNFα) 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, TNFα)- 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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