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Is early life adversity a trigger towards inflammageing?

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Abstract

There are many 'faces' of early life adversity (ELA), such as childhood trauma, institutionalization, abuse or exposure to environmental toxins. These have been implicated in the onset and severity of a wide range of chronic non-communicable diseases later in life. The later-life disease risk has a well-established immunological component. This raises the question as to whether accelerated immune-ageing mechanistically links early-life adversity to the lifelong health trajectory resulting in either 'poor' or 'healthy' ageing. Here we examine observational and mechanistic studies of ELA and inflammageing, highlighting common and distinct features in these two life stages. Many biological processes appear in common including reduction in telomere length, increased immuno-senescence, metabolic distortions and chronic (viral) infections. We propose that ELA shapes the developing immune, endocrine and nervous system in a non-reversible way, creating a distinct phenotype with accelerated immuno-senescence and systemic inflammation. We believe that ELA acts as an accelerator for inflammageing and age-related diseases. Furthermore, we now have the tools and cohorts to be able to dissect the interaction between early life adversity and later life phenotype. This should, in the near future, allow us to identify the ecological and mechanistic processes that are involved in 'healthy' or accelerated immune-ageing.

Keywords: early life adversity; stress; psychosocial stress; hypothalamus-pituitary-adrenal axis; ageing; immuno-senescence; inflammageing; Developmental origins of health and disease.

1. Introduction

The delicate balance between health and disease as we age has long been a subject of interest to a wide variety of disciplines. Traditionally, research in this field has proven difficult due to the high intra-individual variability of the ageing process that necessitates large, labour intensive, expensive and time-consuming longitudinal cohort studies. Consequently, a more mechanistic approach was developed that focusses on common biological patterns, or *'hallmarks of ageing'* (Lopez-Otin et al., 2013). Through extensive research in this area, it has become clear, that ageing and long-term health are influenced by a variety of interconnected variables, with an incredible variance in their intensity, onset and duration.

A negative or poor social environment during critical periods such as early life has been shown to have exaggerated, negative, life-long health effects. Outside these periods it has a lesser effect that accumulates along the lifespan. The work of David Barker showed that many diseases of later life may have their origins in this early life period (Barker et al., 1989). This led to the development of the 'Barker Theory' or the 'developmental origins of health and disease (DOHaD)', describing their effects over the life-span, and emphasising the importance of the overall life trajectory. Although examining the effect and transmission of the social environment is complicated, recent data gathered in an interplay between social sciences, psychology, biology, and medicine focussing on longitudinal studies coupled with advanced bioinformatical tools has started to disentangle the different (psychological and societal) environmental elements, present new insights into the origins of health and disease.

In this paper, we review the mechanistic and immunological connection between a poor early-life environment, either through early life adversity (ELA) or low socioeconomic status, and chronic diseases later in life. Furthermore, we propose a model by which ELA accelerates the normal process of immune-ageing, especially inflammageing.

2. Early life adversity (ELA)

2.1 ELA and the associated long term effects

> *'[…] I am not talking about failing a test or losing a basketball game. I am talking about threats that are so severe or pervasive that they literally get under our skin and change our physiology. […]'*
>
> – Nadine Burke Harris, Surgeon General of California, on TED talks 2019

ELA is as a collective term to describe adverse social and ecological events occurring during pregnancy and early childhood (Fig.1). Prominent examples for ELA include institutionalization, calorie intake restriction, and psychosocial stress due to natural disasters, as well as forms of mental and physical abuse. While the initial work of David Barker focussed on the pre- and immediate post-natal periods rather than the entire span of childhood (Barker et al., 1993), this is slowly being expanded to 0-17 years (Merrick et al., 2018). This broader timeframe is particularly relevant for the more complex mode of operation of the social components of health (Ben-Shlomo and Kuh, 2002, Haas, 2013). The window of developmental sensitivity to the biological components of adversity (nutrition, pathogens) appears to be from the formation of organs during pregnancy to the final phases of brain development in young children (motor function, recognition, speech). While enhanced cerebral plasticity and synaptic connectivity during the first five years of life [reviewed in (Stiles and Jernigan, 2010)] clearly increases its' susceptibility to environmental influences, studies in post-traumatic stress disorder (PTSD) or occupational burnout have shown that extreme psychological trauma and chronic stress affect brain structure and stress hormone release in adults [reviewed in (Szeszko et al., 2018, Rothe et al., 2020)].

While there is no definitive temporal or constituent definition of *early life adversity*, the widely used consensus is that it covers approximately the first 1000 days of life, from conception to about 2 years of age.

There is a long history of using natural experiments or the normal variability in either human biology or the environment to dissect the role of the early-life environment. The earliest systematic studies on the effects of ELA were carried out by psychologists in the middle of the 20th century. Initially they reported severe developmental delays in institutionalised children and connected these observation with the lack of emotional attachment, mental stimulation and social interactions that a conventional ‘mother and child’ setting usually provided [reviewed in (Gunnar and Reid, 2019)].

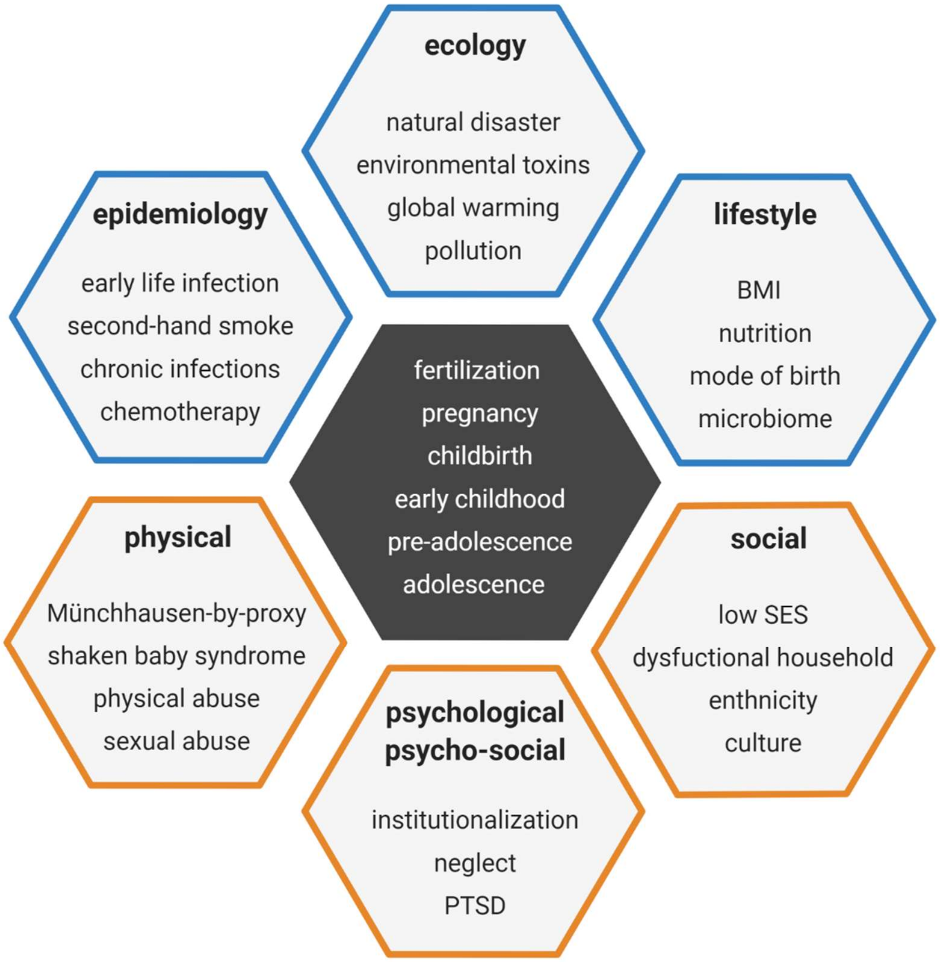

Figure 1. Components of early life adversity. Potential origins of early life adversity (ELA) are separated into categories with related examples. According to the ‘1000 days theory’ environmental/biological sources which may be of more importance in very early stages of life are lined in blue whereas societal/social sources are lined in orange. Often several components are present simultaneously. Stages of human development (middle) do not specifically correspond to

social or biological components, but represent stages of heightened susceptibility to environmental stimuli. [SES= socioeconomic status; PTDS= post-traumatic stress disorder, BMI= body mass index]

In the 1970s, British epidemiologist and medical doctor David Barker, discovered a link between children's birthweight and the development of cardiovascular disease in adulthood. In his seminal work Barker hypothesized that an adverse environment during pregnancy was linked to the risk to develop chronic diseases later in life (Barker et al., 1989) This led to the development of "Barker's Hypothesis" or the "developmental origins of health and disease (DOHaD)". Barker later extended his theory to span the risk for diabetes, high blood pressure and other chronic diseases (Barker et al., 2009). Since the publication of Barker's theory the number of publications linking early life adversity to lifelong health trajectories has grown almost exponentially. Despite initial scepticism, the original "Barker hypothesis" is now considered the "Barker theory".

The corner stone for such investigations was laid during the 1944 German-imposed food embargo in the Netherlands, the Dutch Hunger Winter (Susser and Lin, 1992). This and other natural disasters (Ahmed, 2010, Stein et al., 1975), including the most current findings from the 1998 Quebec Ice Storm (Laplante et al., 2004, Cao-Lei et al., 2014), have shown the severe impact of prenatal maternal stress on the children's long-term cognitive and physical development. Although natural disasters present a very clear and often well-defined form of ELA, by far the most common origins of childhood stressors are dysfunctional households as well as emotional, physical and sexual abuse (Ports et al., 2019, Merrick et al., 2018). The Adverse Childhood Experiences (ACE) study was one of the largest studies addressing long term health effects of childhood abuse, neglect and household dysfunction (Felitti et al., 1998). Over 17.000 insurance subscribers completed self-reports on their adverse childhood experiences and social behaviours that was subsequently integrated with their medical records. Over 50% of respondents reported at least one form of adversity, while 12% had encountered four or more. By integrating health, social and medical data a clear correlation between high adversity–scores and long-term negative health outcomes (Merrick MT, 2019), mental disease (Brown et al., 2019) and social misfortune (Metzler et al., 2017) was identified. While ELA is, in general, a clearly delineated and quantifiable entity, low socioeconomic status (SES) has similar effects. Early-life SES, is a generic life-history measure that includes the exposure to a milieu of increased stressors (psychosocial, psychological, and financial), adverse lifestyle factors (BMI, smoking, alcohol) as well as pathogens, allergens, pollutants, irritants, and many other noxious stimuli (Turner, 2018). Low SES in early life is, in itself, a form of ELA. Although often studied separately, individual components of ELA are inextricably linked and must be considered holistically. This has also broadened our definition of ELA as a range of potentially negative ecological, social and psychological factors. Since the DOHaD model was initially presented by David Barker it has continued to evolve. Initially the early life period was considered almost exclusively, however, it is currently conceptualised as a 'three hit model', whereas the '*hits'* are defined as (1) the genetic predisposition fixed at conception, (2) early life environment/adversity and (3) environmental challenges later in life (Daskalakis et al., 2013, Grova et al., 2019).

2.2 Biological components and consequences of ELA

Observational studies (such as the ACEs study) have shown a clear association between ELA and the long term risk to develop mental or chronic diseases including cardiovascular disease, diabetes, obesity and depression (Hertzman and Boyce, 2010), but the pathophysiological and mechanistic pathways behind these observations are only partially understood. ELA, in very simple terms, acts as a physiological or psychological stressor (or both) in the early phases of life. Stress is the body's reaction to a disruption of homeostasis provoked by an external (e.g. immediate physical danger, an approaching deadline at work, video games (Porter and Goolkasian, 2019)) or internal stimulus (e.g. viral infections, depression, sports (Selye, 1936, Selye, 1956, Kellmann and Günther, 2000)). This results in the rapid activation of the sympathetic nervous system (SNS) and the slower activation of the hypothalamic pituitary adrenal (HPA) axis and the release of adrenaline and cortisol respectively. Cortisol, the end product of the HPA axis is the result of cascading hypothalamic corticotropin-releasing factor (CRF), adrenocorticotropic hormone (ACTH) from the pituitary gland, and then cortisol release from the adrenal glands. Cortisol then acts via a negative feedback loop inhibiting CRF and ACTH release, downregulating further cortisol release [reviewed in (Herman et al., 2005)]. As cortisol levels rise blood sugar levels also rise through gluconeogenesis. The secretion of hormones and the state of hyper-mental awareness ends when the stressor is removed or the body's energy has been depleted (Chrousos and Gold, 1992).

ELA affects the long-term stress reaction: The increased incidence of many stress-related disorders after ELA (Batten et al., 2004, McCauley et al., 1997) has long suggested that the HPA axis and autonomic nervous system are not only immediately activated, but they are functionally impacted over the long-term. Long-term modification of HPA axis functioning may play a role in the pathophysiological effects of ELA (Barton et al., 2016). ELA models, such as maternal deprivation (MD) in monkeys (Sanchez, 2006), induce hyporeactivity of the HPA axis, resulting in lower cortisol levels in response to subsequent stressors, while rodent MD models induced HPA hyperactivity (Aisa et al., 2007). The human institutionalisation-adoption paradigm, similar to the maternal deprivation models, perturbs the HPA axis for many years post ELA (Gunnar et al., 2009, Hengesch et al., 2018, Meaney, 2001). The data are contradictory, both a hyper- and a hypo- responsive HPA axis have been reported (Hyperresponsive: (Heim et al., 2000, Pesonen et al., 2010); hyporesponsive: (Carpenter et al., 2007, Voellmin et al., 2015)). In our EpiPath institutionalisation-adoption cohort we observed a hyporesponsive HPA axis that was uniquely decoupled from the cardiovascular stress response that is governed by the autonomic nervous system (ANS), which remained unaffected (Hengesch et al., 2018). The mechanism by which ELA leaves a mark on, or '*programs*', the HPA axis response are currently not well understood, but neuronal inflammation play a central role in inducing epigenetic changes (Pierre et al., 2020). Epigenetic changes are most visible in the glucocorticoid receptor (GR) gene promoter and subsequent GR signalling in the central tissues of the GC feedback loop (Koss and Gunnar, 2018). Differential methylation of the GR has been associated with adverse maternal environment (Stonawski et al., 2019), diet (Ke et al., 2020), early life stress (Holmes, 2019), exposure to environmental toxins (Meakin et al., 2019), chronic stress (Rowson et al., 2019) and institutionalisation (Elwenspoek et al., 2019) among other sources. Epigenetic modification of the GR and related genes presents the best biomarker of ELA up to date, but these methylation changes might only occur in brain regions, making them inaccessible for preventive medicine (Lewis et al., 2020), since the peripheral GR does not appear to be functionally or transcriptionally altered (Elwenspoek et al., 2019).

ELA affects the normal development of the brain: Exposure to ELA not only leads to the increased risk of developing mental health problems including depression and schizophrenia, but is also associated with physical changes in the developing brain e.g. grey matter volume and white matter organization (Agorastos et al., 2019, Pagliaccio and Barch, 2016). Furthermore, it affects behaviour, emotion and attention, HPA axis activity, and autonomic nervous system functioning (Bick and Nelson, 2016). At birth, the human brain is not fully developed, and development continues for many years (Rice and Barone, 2000). Adversity and stress during this period not only affect the development, but also the long-term functioning of the brain and neuronal circuits. This may be partly mediated by brain-resident immune cells. Exposure to ELA (or low SES) reduces the volume of the amygdala (Luby et al., 2013) and increases reactivity to emotional stimuli (McCrory et al., 2013). Furthermore the connectivity between the amygdala and regions such as the ventrolateral and dorsolateral pre-frontal cortex, which provides top-down regulation, was altered (Kim et al., 2013), persisting into adulthood (Nusslock and Miller, 2016) and increasing the risk of anxiety-related psychopathologies. In rats exposed to maternal separation, these changes were sex-specific. They were stronger and occurred more rapidly in females, resulting in a stronger anxious phenotype, and the first evidence of sex specific differences in brain anatomy and function after ELA (Honeycutt et al., 2020). ELA also has significant long-term effects on hippocampus-mediated process including memory and learning. ELA directly affects not only the connectivity of the hippocampus, but also the neuronal structure and synapse number as well as dendritic arborisation increasing local CRF levels. Blocking the CRF receptor (CRF receptor type-1, CRFR1) abrogated the long-term memory and potentiation effects of ELA, although it did not affects anxiety-related behaviour (Short et al., 2020). These data suggest that ELA plays a '*programming'* role, and potentiates the effect of later-life expose to severe stress. Furthermore, after exposure to ELA later-life stressors induced a clear inflammatory response in the prefrontal cortex and hippocampus. This suggests a clear role for the immune system in the programming of the long-term effects of ELA on the brain (Ferle et al., 2020). This link is reinforced by the association of differential methylation of neuronal development genes in PBMCs after ELA (Esposito et al., 2016), and the epidemiological link between sepsis in new-borns and long term brain development (Alshaikh et al., 2013).

Dissecting the effects of ELA are complicated by ELA increasing the subsequent negative health-risk behaviours (HRBs) including increased cigarette smoking, substance abuse (including alcohol), risky sexual behaviours, sedentary lifestyles and obesity (Felitti et al., 1998). HRBs are either modelled on caregivers (Alcala et al., 2017), part of a coping strategy in stressful or conflictual environments (Rothman et al., 2008), or a challenge to reduced caregiver attention (Repetti et al., 2002). However, these HRBs may be a consequence of, and compensate, neurobiological differences in the brain induced by adversity in the developmental period. ELA appears to have a sustainable effect emotional reactivity/regulation, reward responsivity, and delay discounting (Duffy et al., 2018). Decreased amygdala volume and increased connectivity to e.g. the pre-frontal cortex after ELA are associated with increased emotional reactivity to e.g. negative emotional images throughout childhood (Duffy et al., 2018), adolescence and even into adulthood in a manner dependent on the severity of the adversity (McLaughlin et al., 2015, Maheu et al., 2010). This leads to increased emotional (Heleniak et al., 2016) and physiological responses (e.g. cardiovascular responses (Heleniak et al., 2016)) to environmental cues or stimuli. This in turn contributes to increased rates of depression and anxiety-related disorders (Mc Elroy and Hevey, 2014, Su et al., 2015) as well as deficits in long-term emotion-regulation strategies (Morris et al., 2007) that are compensated by negative HRBs. Reward responsivity is the degree to which "one experiences pleasure in the anticipation and presence of a potential reward". ELA exposure reduces reward responsivity in financial reward paradigms (Dennison et al., 2019), probably through reduced ventral striatum (VS) reactivity (Hanson et al., 2016) and reduced dopamine-2 receptor (D2R) levels (Blum et al., 1996). Subsequently, health-risk behaviours are adopted to palliate the reduced reward responsivity. Furthermore, ELA increases delay discounting, the psychological process by which smaller rewards are accepted sooner in preference to a larger reward later (Simmen-Janevska et al., 2015). This is associated with a reduced activation of the dorsolateral prefrontal cortex (McClure et al., 2004), and potentially the increase in health-risk behaviours for the immediate 'reward' provided.

ELA, obesity, insulin resistance, diabetes: Although there are few recent data, there is a well-established link between ELA, microbiome disturbances (Dong and Gupta, 2019) and obesity. Adults reporting prior childhood trauma / abuse have a strong dose-dependent increase in the relative risk for developing adult obesity (risk ratio 1.3 to 1.8 for 1 to 4 elements of abuse present), and inversely, 17% of morbidly obese patients report prior adversity (Williamson et al., 2002). Using the broader definition of '*neglect'* the association with obesity was stronger than any other psychological or sociological variable including parental occupation, housing or educational attainment (Lissau and Sorensen, 1994), or low SES (Surachman et al., 2020). Once childhood obesity is established, it is associated with metabolic changes and a meta-inflammatory phenotype that persists into adulthood (Singer and Lumeng, 2017). ELA and obesity play a role in the subsequent development of insulin resistance and type 2 diabetes (T2D). Low SES in early life induces a diabetogenic metabolic profile in adulthood, while current SES does not appear to do so (Hostinar et al., 2017, Horner et al., 2018). Furthermore, exposure to ELA is a major risk factor for T2D, as well as cardiovascular disease and "a significant proportion of the cardio-metabolic and diabetic disease burden may be attributable to maltreatment"(Chandan et al., 2020). As reviewed in (Holuka et al., 2020), it would appear that low SES transcriptionally programs inflammatory pathways shared with T2D including genes such as: *F8*, *CCL1, CD1D*, *KLRG1*, *NLRP12*, and *TLR3* as well as *AVP, FKBP5, and OXTR* (Holuka et al., 2020). This transcriptional inflammatory link is further re-enforced by the observation that elements of the ELA immunophenotype described below such as the accumulation of senescent CD8+ CTLs with increased levels of systemic inflammatory markers (Lau et al., 2019, Yi et al., 2019).

Ecological and Epidemiological influences in the context of ELA: Low SES and increased ELA are intimately associated with many other elements in the ecological environment in mediating long term health. Early life lead exposure though drinking water contamination disrupts heme synthease (ferrochelatase) and toxicity levels are proportional to body mass, exaggerating the effects during early life (Hammond and Dietrich, 1990). Other cause/effect relationships are more difficult, however, a 2019 report from the European Environment Agency (EEA) identified air quality, noise, soil and water pollution as a significant burden, affecting the social disadvantaged especially hard (EEA, 2019). Furthermore the World Health Organization (WHO) estimated that in 2012 up to 13% of all deaths in the Europe Union could be attributed to environmental pollution (WHO, 2016). While toxic chemicals often have very specific short-term effects on the body (poisoning), the long-term effects of low-dose environmental toxins (e.g. pesticides) are not well known, although the association between exposure and the loss of gene associated methylation patterns suggests epigenetic mechanisms may be involved (Wang et al., 2020). Consequently, high-income countries are experiencing an increase in behavioural disorders, diabetes and noncommunicable diseases, while low-income countries are suffering from respiratory infections, diarrheal diseases and preterm birth. (Landrigan et al., 2016). In line with this, it has been suggested, that ELA leads to an overall higher vulnerability for infectious diseases (Avitsur et al., 2015) such as human immunodeficiency virus (HIV) (Siegel et al., 2014) or cytomegalovirus (CMV) (Elwenspoek et al., 2017c, Reid et al., 2019), which might be partly explained by a tendency to engage in HRBs in individuals with ELA (Dube et al., 2002).

Throughout the plethora of long-term effects that have been epidemiologically, functionally or pathophysiologically linked to ELA, there is common theme. In almost all cases, it would appear that there is a role for immune cells, and in particular a role for the inflammatory system. Inflammation plays an important role in the aetiology and pathophysiology of all of the consequences that have so far been identified: cardiovascular disease (Lorenzatti and Servato, 2019), hypertension (Agita and Alsagaff, 2017), type 2 diabetes (Calle and Fernandez, 2012), depression (Beurel et al., 2020) and obesity (Cox et al., 2015).This has led over the last few years to a determined effort to determine the detailed ELA induced immunophenotype that will be described in the following section, and how it is implicated in disease development.

2.3 ELA immuno-phenotype

The ELA immunophenotype is characterized as pro-inflammatory and detrimental to overall wellbeing. Studies addressing immune cell specific effects are slowly emerging, enabling a more comprehensive picture on the effects of ELA on the innate and adaptive immune system (see Text Box – Innate and Adaptive Immunity). Independent studies in human adoptee cohorts found alterations in T cells, especially cytotoxic (CD8+) T cells. The overall number of CD8 cells was higher in individuals with ELA (Elwenspoek et al., 2017a) , shifting the CD4/CD8 balance in favour of CD8 T cells (Reid et al., 2019, Esposito et al., 2016) indicative of overall immune dysfunction and often associated with chronic viral infections such as HIV. The CD8 cells were not only more frequent in the ELA group, but also showed higher major histocompatibility complex two (MHC-II) dependant activation (HLA-DR+CD8+), and reduced early activation (CD8+CD69+) (Elwenspoek et al., 2017a) suggesting elevated T cell stimulation. Furthermore, regulatory CD8 cells (CD8+CD25+) and replicatively senescent terminally differentiated CD8 cells (CD8+CD57+) had significantly higher frequencies after ELA suggesting accelerated ageing (Elwenspoek et al., 2017a, Reid et al., 2019). These findings are concordant with early separation studies in rats, where the percentage of CD8 T cells increases after liposaccharide (LPS) challenge (Obi, 2019). ELA was also positively correlated with higher numbers of senescent CD4 (CD4+CD57+) (Reid et al., 2019) and $T_{helper}17$ cells (CD4+CCR4+CXCR3−CCR6+) (Elwenspoek et al., 2017a). Although the HPA axis and the immunomodulatory GC response were altered, this was not responsible for the changes in the immune system (Elwenspoek et al., 2019). Interestingly, an overall lower percentage of B cells was associated with ELA in both human and animal studies (Esposito et al., 2016, Naumova et al., 2012, Obi, 2019), without clear causal explanation.

However, several of the observations in immune populations of ELA subjects could be explained by latent herpes virus infection (Schmeer et al., 2019). Indeed, cytomegalovirus (CMV) antibody titres largely mediated the CD57 expression in formerly institutionalized adults (Elwenspoek et al., 2017c, Reid et al., 2019). Latent herpes viruses, like CMV or Epstein-Barr virus (EBV) are often acquired during childhood and are thought to reactivate under psychological stress (Glaser et al., 1991). Although the general prevalence for herpes infections in the population is high, a recent study also showed a higher incidence of virus re-activation in adolescents with prior early-life family instability (Schmeer et al., 2019). In animal studies, where latent infections are not an issue, frequencies of CD8 T cells were increased only after immune challenge with LPS or by hypertension (Obi, 2019).

Chronic infections such as HIV or herpes lead to higher lymphocyte activation, cytokine production and can accelerate immunosenescense (De Francesco et al., 2019, Ford et al., 2019). The effect of early-life acute infections is more difficult to determine, although during the perinatal period they affect brain development (Alshaikh et al., 2013) and immune activation (Cornet et al., 2020) lifelong. Although the molecular mechanisms linking the immune and nervous system are currently unclear, they communicate bi-directionally to maintain homeostasis. In rodents, maternal separation increased the number of microglia and inflammatory cytokine expression in several brain regions, as well as decreasing astrocyte numbers (Banqueri et al., 2019). Microglia and astrocytes are the principal immune cells found in the central nervous system (CNS). Systemic pro-inflammatory cytokines can cross the blood-brain barrier leading to neuroinflammation (Nettis et al., 2020), impacting both microglia and astrocytes and potentially brain development and function (Bilbo and Schwarz, 2009) (Fig. 2). In line with this, ELA in form of physical discipline correlated with higher circulating inflammatory markers [CRP, IL-6] and lower IQ scores in children (Holland et al., 2020); indicating a disruption of the immune – CNS homeostasis by ELA.

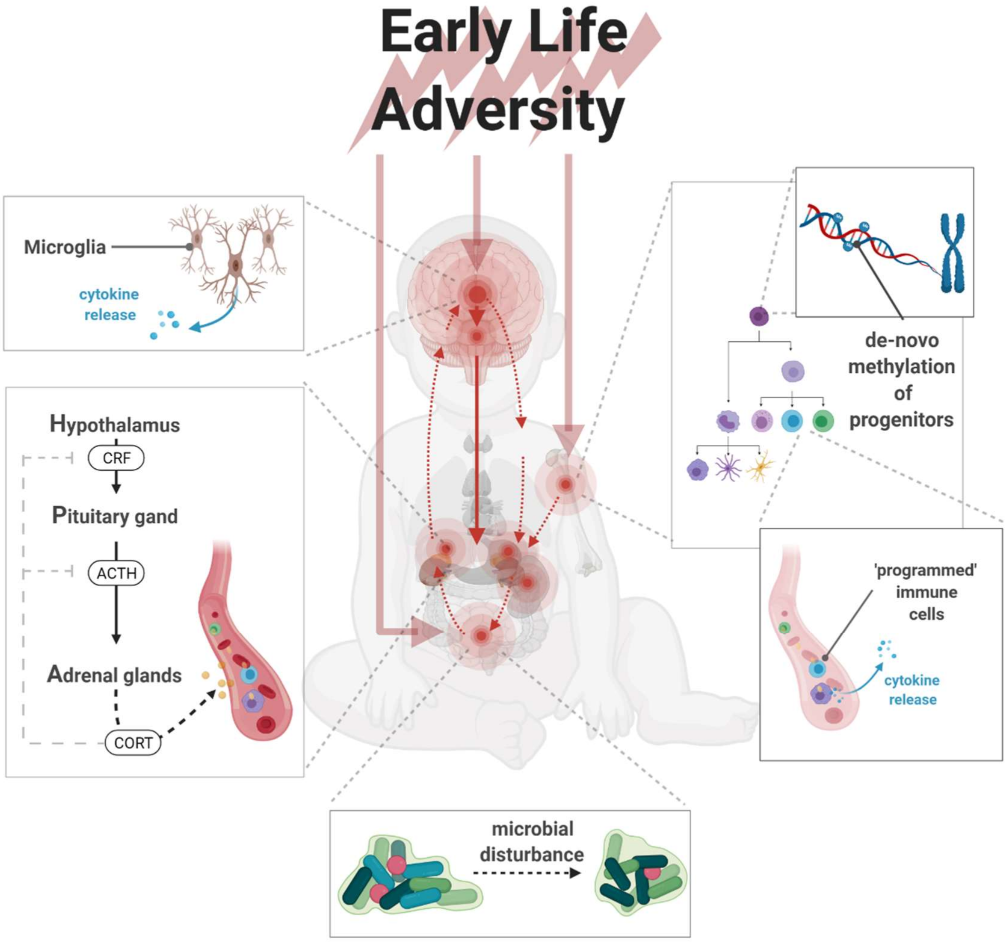

Figure 2. Biological consequences of early life adversity (ELA). ELA (especially stress) has been associated with an altered hypothalamic–pituitary–adrenal (HPA) axis and impaired negative feedback loop thereof. Leukocytes and their progenitor cells can be epigenetically '*programmed* by early life systemic inflammation, leading to enhanced cytokine production. Circulation cytokines and/or HPA products stimulate cytokine release by microglia, potentially leading to cognitive impairment during development. Furthermore, stress and inflammation lead to a loss in microbiome complexity. All of these factors can kick-off and enhance systemic inflammation, feeding of each other. [CRF= corticotropin releasing factor; ACTH= adrenocorticotropic hormone; CORT= cortisol]

The HPA axis is perceived to be the bridging element between the neuroimmune response and the circulating leukocytes. Indeed, genes involved in HPA axis function are permanently altered after

ELA (Silva et al., 2021, Gerritsen et al., 2017). GCs released after HPA axis activation regulate cytokine activity (Kunz-Ebrecht et al., 2003). Although the interaction of the two systems is not well understood, GC and cytokines are thought to be involved in the decrease of cognitive function (Sudheimer et al., 2014). A disruption in the expression of pro-inflammatory cytokines [IL-1β, IL-10] in the brain after prenatal GC has recently been shown in birds (Walker et al., 2019a) and pigs (Bruckmann et al., 2020). System wide elevated levels of cytokines might also explain the skewed T cells function associated with the ELA immunophenotype.

Then inflammatory markers most commonly measured are C-reactive protein (CRP) and interleukin-6 (IL-6) (Kuhlman et al., 2020). CRP, a diagnostic marker of inflammation is produced in the liver as a result of IL-6 stimulation. IL-6 is produced by a variety of cells as a result of early immune signalling and helps mediate the signalling among innate and adaptive immune cells (Mauer et al., 2015). Both markers are generally associated with systemic inflammation and immune activation. Pre-clinical models identified tumour necrosis factor-alpha (TNF-α), interleukin-10 (IL-10), IL-1β and IL-8 as immune-markers of ELA (Bruckmann et al., 2020, Obi, 2019), although they performed poorly in human studies (Shalev et al., 2020). The source of inflammation and inflammatory markers remains unknown (Baumeister et al., 2016, Kuhlman et al., 2020). Nevertheless tissue resident macrophages such as microglia are thought to be directly affected by inflammatory crosstalk between the immune and the nervous system [reviewed in (Nusslock and Miller, 2016)]. Indeed, psychological stress has proven to act directly on macrophages influencing their differentiation, proliferation, migration potential and total number (Desgeorges et al., 2019). While GC generally suppress the production of inflammatory cytokines, repeated exposure, especially during early life, might change the cellular programming of macrophages. In vivo experiments in zebrafish have shown a decreased phagocytic ability of macrophages after early life treatment with synthetic GC, leading to increased severity of bacterial infection (Xie et al., 2020). Ex-vivo experiments on endometrial macrophages stimulated with cortisol changed gene expression in these cells, potentially related to repair mechanisms (Thiruchelvam et al., 2016). Furthermore, in whole peripheral blood *ex vivo*, cortisol became progressively less effective at suppressing cytokine production in children and adolescents with low-SES (Miller and Chen, 2010, Schreier et al., 2014).

While we do not currently know the exact mechanisms by which ELA acts on the immune, nervous and endocrine system (Fig. 2), the assumption has to be made that the three systems are in homeostasis (Black, 1994) and a disruption in one could disrupt them all, although it remains possible that they are independently and concurrently affected (Elwenspoek et al., 2017b)

3. The immune system in development and ageing

The immune system develops, adapts and changes throughout life from naïve and uneducated at birth, the gradual construction of the adaptive immune system, especially the polarization towards T-helper 1 (Th1) cells through to the fully differentiated, but permanently resting, immune cells in the elderly that contribute to a pro-inflammatory aged-environment.

3.1 Immunity during development and early life

Before birth, the foetus is protected by the mother's immune system; therefore, maternal wellbeing during pregnancy is vital for the overall development of the baby and its immune system. In monkeys, cytokine production and lymphocyte proliferation was reduced after prenatal stress (Coe and Lubach, 2005). Prenatal exposure to bacteria might also have an influence on the postnatal gut microbiome composition. In turn, the gut microflora and immune system function are connected

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(Tourneur and Chassin, 2013, Zheng et al., 2020). After birth, the new-born immune system is vulnerable due to the low numbers of functional innate and adaptive immune cells. Additionally, naïve T cells are epigenetically biased towards T_{helper} 2 (T_h2) function (Dowling and Levy, 2014). These circumstances have often been described an '*immaturity*' of the immune system, however, this has more recently been suggested to serve as a period of plasticity for environmental adaptation (Kollmann et al., 2017, Danese and J Lewis, 2017). As such, it would appear that the environment before and after birth shapes not only the immediate development of the immune system, but its long-term trajectory.

One example of early life plasticity and adaption of the immune system to the external environment is the hygiene hypothesis. Here, contact with the broadest possible range of microorganisms and during childhood is necessary to establish immune tolerance. In the absence of this stimulation and tolerance induction, the risk of allergies and auto-immune diseases increases (Strachan, 1989, Okada et al., 2010, Alexandre-Silva et al., 2018). Importantly, it is the contact with the non-pathogenic microorganisms that is important, as early-life exposure to pathogens may increase the risk of allergy. Similarly, children from low-SES backgrounds, exposed to higher levels of indoor allergens, dust mites and air pollution have increased sensitization for asthma and allergies (Gaffin and Phipatanakul, 2009, Burbank et al., 2017).

Text Box 1: Basic principles of innate and adaptive immunity

Innate immunity

The innate immune system presents the first line of defence against pathogens, foreign objects (e.g. open wound) and dead cells. It is highly evolutionary conserved between species and can be simplified as providing three main functions: phagocytosis, cytokine production, and antigen presentation. Innate immunity is conveyed by tissue resident immune cells and white blood cells. Tissue resident cells are static and often form anatomical barriers (e.g. skin, mucus) to prevent pathogens from entering the body in the first place. Epithelial make up most of the surface of the outer and inner of organs and blood vessels. They are joined by fibroblasts (main source of collagen and connective tissue), goblet cells (secrete mucus to protect the cell surface layer) and several specified tissue specific and resident macrophages (e.g. microglia in the brain) and dendritic cells. White blood cells, so called leucocytes, are more mobile since they 'travel' through blood vessels and can therefore act systemically. The innate fraction of leukocytes is mainly composed of mast cells, neutrophils, monocytes (which are precursors to macrophages and dendritic cells), and natural killer (NK) cells. Possibly the most important feature of tissue resident immune cells and innate leukocytes is the ability to identify molecules as foreign invaders or self-produced. Most pathogens (e.g. viruses, bacteria) carry highly conserved molecule patterns on their surface. These patterns, referred to as damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), are recognized by the pattern recognition receptors (PRRs) on the surface of innate immune cells and activate them, resulting in the release of inflammatory mediators, such as cytokines, hormones, and reactive oxygen species (ROS). These signal molecules are essential to attract other immune cells to the site of inflammation. Subsequently innate *immune cells will engulf the foreign particle (or cell debris) and begin breaking it down (phagocytosis), in order to 'kill and clean' and for the communication with T- or B lymphocytes through antigen presentation (Janeway and Medzhitov, 2002).*

Adaptive immunity

T- and B-lymphocytes (short: T cells, B cells) are the key protagonists of the adaptive immune system. Their most distinctive feature is the random V(D)J recombination, which only occurs in lymphocytes. This produces a highly divers repertoire of T cell receptors (TCR) and surface antibodies on maturating T- and B cells, which enable these cells to mount a very effective response to pathogens (Tonegawa, 1983). After activation through antigen presentation, T- and B cells will rapidly expand and migrate to the site of inflammation. During this time, which lasts about one week, CD4 and CD8 T-cells will differentiate into effector T_{helper} *sub-sets (CD4+) and cytotoxic T-lymphocytes (CD8+), to eliminate pathogens above the capacity threshold of innate immune cells. While* T_{helper} *1 (*T_h*1) cells mainly regulate cellular responses by producing the antiviral and anti-suppressing cytokine INF-γ,* T_h*2 cells secrete high amounts of IL-4 and IL-5 abundantly found in allergic diseases (Romagnani, 1997).* T_h*17, named after their main cytokine signature [IL-17], are required for promoting inflammation during infections and autoimmune disease. They also have been found to play a vital part in the maintenance of mucosal barriers and cancer progression (Chang, 2019). Another T cell subset, regulatory T cells (*T_{reg}*), assists in the modulation of* T_{helper} *cell response, by secreting inhibitory cytokines [IL-35, IL-10, TGF-β, Granzyme B] towards the end of the immune response (Shevach, 2000). After the source of inflammation is eradicated most of the recently expanded T- and B-cells will undergo activation-induced cell death, a process for regulating cell numbers and managing immune homeostasis. The last phase of the adaptive immune response is the retention of some of those (now highly specialized) cells; a phenomenon called 'immunological memory' or memory T cells. Memory cells are long-lasting cells which remain dormant within the immune repertoire, but can rapidly be activated when the same (or a highly similar) pathogen is re-encountered (Ahmed and Gray, 1996). As such, the T cell life cycle is naïve, central memory, followed by effector memory, and ending in terminally differentiated (T)EMRA cells.*

3.2 Ageing and the immune system

Ageing is the gradual decrease of mental and physical capability (World Health Organization, 2018, Feb 05). Contrary to the linear progression of chronological age, the biological advancement of ageing is dependent on several cell-intrinsic factors that make up the "hallmarks of ageing" including: cellular senescence, impaired intracellular communication, alterations of the genome and epigenome, telomere shortening, deregulation of protein homeostasis, nutrient availability and the microbiome composition. These have been extensively reviewed elsewhere (Lopez-Otin et al., 2013, Rebelo-Marques et al., 2018, García-Velázquez L., 2020). While the ageing process of an individual is not a straight, pre-determined path, many of the factors that drive biological ageing accumulate with chronological age.

One of the major contributing factors to ageing is the time dependent accumulation of cellular damage leading to the irreversible end of proliferative potential, or cellular senescence (Hayflick and Moorhead, 1961). The most common cause for cellular senescence in the gradual shortening of telomeres with each cell division, also called replicative senescence (Harley et al., 1990). However, other factors like excessive mitogen signalling, oncogene expression or oxidative stress can also contribute to cellular senescence [reviewed in (Calcinotto et al., 2019, Gorgoulis et al., 2019)]. Although cellular senescence is associated with ageing, it is not the simple "ageing of the cell". It is an intrinsic program that restricts the proliferation of exhausted or damaged cells. Normally, when a cell reaches the end of its proliferative capacity it undergoes apoptosis and is cleared by immune cells. However, persistent senescent cells escape apoptosis and remain metabolically and transcriptionally active within their normal environment. These cells secrete a specific pattern of pro-inflammatory proteins and cytokines [such as IL-6, IL-8] (Coppé et al., 2008) termed the senescence-associated secretory phenotype (SASP) (Rodier et al., 2009). The SASP attracts immune cells [macrophages, NK cells, neutrophils and CD4 T cells] but can escape clearance by them (Pereira et al., 2019). The accumulation of senescent cells and their SASP is presumed to be a major contributor to many age-related diseases and a source of chronic low grade inflammatory markers [reviewed in (Campisi et al., 2019, Kirkland and Tchkonia, 2017)].

Similar to cellular senescence, immuno-senescence simply describes the inability of immune cells to proliferate any further, but the term is also confusingly used to describe the aged and therefore less efficient immune system as a whole. Immuno-senescence characterizes the insufficient immune answer the aged immune system can mount in response to pathogens. The IMM-AGE study, a longitudinal cohort, identified several immune subsets [e.g. naïve CD4+, naïve CD8+, CD8+PD1+, CD8+CD57+, CD4+$_{EM}$, CD161-CD45RA+T$_{reg}$] with declining frequencies directly correlated with the advancement of biological age. The correlation to the immune-age, or immune-senescence, was thereby greater as with chronological age (Alpert et al., 2019).

Cytomegalovirus (CMV) and other latent viral infections accelerate immuno-senescence by repeatedly activating T cells; forcing expansion and formation of CMV-specific memory cells. Regular CMV reactivation exhausts memory T cells, and their repeated expansion depletes the diversity of the memory cell pool. (Griffiths et al., 2015, Brunner et al., 2011). CMV infection may occur at any point and seropositivity steadily increases with age, reaching over 90% of the population by the age of 80 (Staras et al., 2006). By targeting T cells and overloading the memory reservoir, CMV is thought to accelerate immunsencesence and biological ageing (Bauer and Fuente, 2016). However, CMV infection in centenarians has not been shown to negatively impact their life expectancy (Sansoni et al., 2014).

Another hypothesized accelerator for biological ageing is long-term stress. While short periods of acute stress, like physical exercise (Dhabhar, 2014), even tattooing (Lynn et al., 2020), have been associated with an immune boost and general biological fitness, chronic stress has been associated with a shift in type1/2 cytokine balance, by disrupting HPA homeostasis. Time and duration of the stress determine the long-term consequences for the immune system. While acute stress is associated with enhanced number in infiltrating leukocytes, elevated levels of IL-2, INF-γ and TNF-α; chronic stress is accompanied by suppressed antibody production, leukocytes proliferation and T cell activity (Dhabhar, 2014).

Apart from the accumulation of memory cells and a decline in cellular ability, ageing is most often accompanied by a low-grade systemic chronic inflammation, also called '*inflammageing*' (Franceschi et al., 2000). Inflammageing is characterized by a slow but steady increase of circulatory inflammatory markers in the peripheral blood and organs and is considered the strongest driving factor in many age-related disease (Franceschi and Bonafè, 2003). It has been shown, that the levels of circulating cytokines [such as IL-6 and TNF-α] are 2- to 4-fold higher in adults older than 65 years than in young adults (Ferrucci and Fabbri, 2018). There is a broad range of detrimental stimuli which initiate and sustain inflammageing They can be categorized as '*non-self*', '*quasi-self*' and '*self*' (Franceschi et al., 2018). *Self*-stimuli comprise all body intrinsic stimuli such as cell debris, misplaced or altered molecules (Franceschi and Campisi, 2014), senescent cells and their SASP, microRNAs and immune cell defects but also oxidative stress. Reactive oxygen species (ROS) are chemically reactive oxygen molecules produced by intracellular metabolism and act as signalling molecules, but can cause chronic oxidative stress and damage to cells when accumulated (Franchina et al., 2018). Accumulation of ROS and oxidative damage has been reported in many age-related pathologies [reviewed in (Venkataraman et al., 2013, Zuo et al., 2019)]. Although most ROS are of endogenous origin (*self*), there are certain exogenous ROS sources (*non-self, quasi-self*) of ROS (e.g. drugs, UV radiation, pollutants) acquired from the environment and subsequently metabolized into free radicals (Liguori et al., 2018). Pollutants and pathogens are generally considered '*non-self*' as they are acquired in a passive manner through the individuals' environment. Metabolic products from the gut microbiome or nutrients acquired through the diet form the '*quasi-self*' category, since the individual has at least some influence on calorie intake and food choice. These different stimuli are recognized by pattern recognition receptors (PRRs) on the surface of innate immune cells leading to the release of pro-inflammatory cytokines; further supporting the pro-inflammatory environment (Franceschi et al., 2017). The pro-inflammatory environment of inflammageing is thought to be the involved in the manifestation of age-related diseases like Alzheimer's disease, cardiovascular diseases, cancer and frailty (Fülöp et al., 2016, Fulop et al., 2018).

There is considerable health variability and diversity in the elderly. The outcome of ageing ranges from healthy ageing to the rapid development of frailty. Frailty is characterised by "sedentariness, fatigue, weight loss and poor muscle strength, and it increases the risk of adverse outcomes, such as falls, disability, hospitalization and even death" (Pansarasa et al., 2019) together with loss of homeostasis in many physiological systems and physiological decline. It would appear that changes in the immune system underlie the trajectory towards either frailty or healthy ageing (Pansarasa et al., 2019). Frail individuals have higher levels of circulating interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-alpha), C-reactive protein (CRP) and fibrinogen [reviewed in (Singh and Newman, 2018, De Maeyer and Chambers, 2021)]. Although circulating inflammatory markers do not appear to predict frailty (Soysal et al., 2016) inflammation in midlife, calculated from Factor VIII, lymphocyte count, von Willebrand factor, and fibrinogen, or maintaining CRP levels above 3mg/L would appear to promote and predict the development of frailty (Walker et al., 2019b). Furthermore, the T cell populations appear to be biased towards a pro-inflammatory type-1 phenotype with higher numbers of CCR5 expressing naïve CD8 cells (Kohlmeier et al., 2008, De Fanis et al., 2008). Additionally, frailty is associated with increased number of circulating CD8 cytotoxic T cells, however, they are mainly CD8+CD28− (Semba et al., 2005). CD28 is necessary for T-cell activation, and is principally present on naïve, effector memory and central memory T cells, suggesting an accumulation in the later (T)EMRA subsets (Rufer et al., 2003). Although CD28 levels on both CD4 and CD8 T cells naturally decline with age (Teteloshvili et al., 2018) the loss appears to be accelerated in frailty. Moreover, senescent T lymphocytes express the surface protein CD57, indicating their inability for further proliferation (Kared et al., 2016). Both, senescent T cells and natural killer (NK) cells, increasingly express the killer cell lectin-like receptor G1 (KLRG1) in elderly (70 years and older) and frail individuals, resulting in an inhibition of cell function(Akbar, 2017). While there is an increase in CD8 cytotoxic T cells, the numbers of naïve CD4 and T_{helper} cells decrease with age, partly mediated trough involution of the thymus gland. Furthermore, innate immune populations phagocytic activity, contributing to the accumulation of cell debris and SASP. Similarly the overall amount of B cells declines with age [reviewed in (Esme et al., 2019)], leading to a loss of

B cell diversity (Tabibian-Keissar et al., 2016), and reduced memory repertoires, that may explain increased susceptibility to infections and lower vaccine responses in elderly patients that is accentuated with frailty (Yao et al., 2011, Marttila et al., 2014). Contrary to most adaptive immune cells, the total amount of macrophages and NK cells increases with ageing. However, both cell types loose immunomodulatory function and change to a more auto-inflammatory state, which is characterized by the change in expressed surface markers (Gounder et al., 2018, De Maeyer and Chambers, 2021) (see Fig. 3).

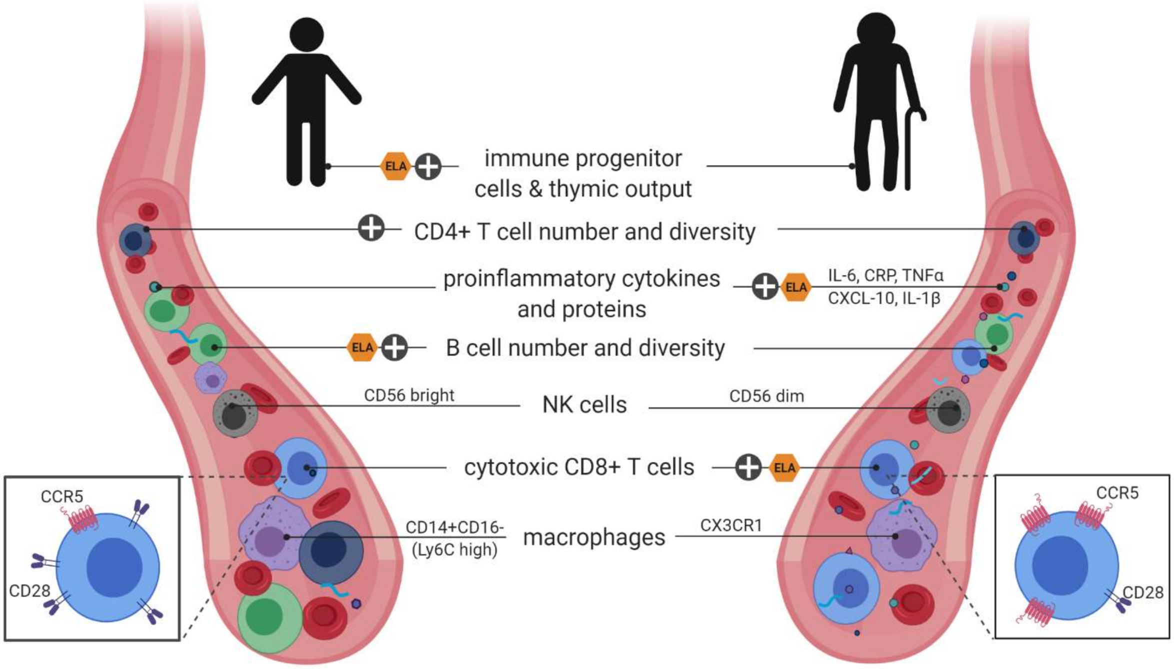

Figure 3. Immune changes associated with ageing and frailty. There are less bone marrow progenitor cells, CD4 and B lymphocytes in the elderly, while cytotoxic CD8 T cells are in abundance. NK cells and macrophages switch function and become pro-inflammatory. Changes in abundance between a ‘young’ and ‘aged’ immune system are marked with directional plus signs. Reported similarities with immune composition after ELA are marked with orange hexagons. [Mouse Ly6C^{high} macrophage marker is the equivalent to human CD14+CD16- macrophages]

4. Discussion

Immunosenescence and inflamm-ageing are not just the driving forces behind the ageing immune system, but also biological ageing as a whole (Khalatbari-Soltani et al., 2020). Despite the current perception, the immune system may be not only central to the long-term effects of ELA and the ageing process, but the driving mechanism. Many authors have connected social or biological components of ELA with the increased risk for clinical pathologies through a programmed HPA axis [reviewed in (Miller et al., 2009)]. Subsequent changes in gene expression patterns and inflammation are then thought to be dependent on neuroendocrine mediators. In this paradigm, the immune system is often characterized as either a ’means to an end’ or another consequence of the early life programming.

The HPA axis, the nervous system, the immune system and the gut, act as a multi-directional and integrated, intercommunicating system. In this sense, pathogens and some pollutants are known to be recognized first by the immune system, which in turn activates the HPA axis and stimulates GCs release (Heyner et al., 2019, Bauer et al., 2012, Badry et al., 2020).

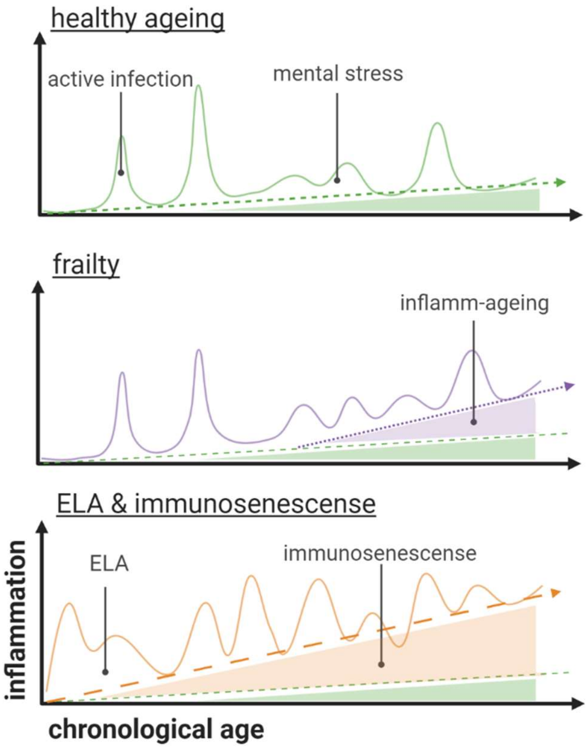

Figure 4. Early-life adversity changes the overall healthy trajectory. Healthy ageing is associated with punctual inflammation spikes during active infections or periods of high stress. In inflammageing this pattern disrupted by a persistent low-grade inflammation associated with advanced chronological age. ELA acts as an early spike in inflammation and does not enable it to recede. Additional stressors during ageing worsen this effect.

We suggest that ELA can act through the immune system, priming and accelerating for inflammageing, skewing the overall heath trajectory from the earliest periods of life towards a lifelong inflammatory immunophenotype (see Fig.4). Furthermore, we hypothesise that the exposure to adversity in the first 1000 days of life sets the individual on a negative trajectory that, in the later decades of life will manifest as frailty, and in this revised paradigm, the early life period may actually determine the morbidity and mortality of age-related immune mediated diseases.

In the following section we examine the literature for common and uncertain features between ELA and inflammageing, showing some uncanny parallels between the outcomes of ELA and common diseases associated with frailty.

4.1 Common features

Acute and chronic infections: It is well known, that the overall decline in immune function makes the elderly population more susceptible to acute infections [reviewed in (Gardner, 1980, Sadighi Akha, 2018)], but can infections also accelerate the ageing process? Persistent viral infections, especially cytomegalovirus (CMV) and HIV, have repeatedly been associated with immuno-senescence and accelerated ageing (Griffiths et al., 2015, Brunner et al., 2011). CMV contributes to a steady expansion of CMV-specific memory T cells, essentially filling up the '*space*' for other memory T cells (Brunner et al., 2011). Although the prevalence of CMV infection gradually increases with age, over 50% of children are likely to contract the virus under the age of six (Staras et al., 2006); leading to an overall longer time period of exposure. Interestingly, ethnicity, household income and early life stress have been linked to CMV prevalence in children (Ford et al., 2019, Staras et al., 2006), and the virus re-activation is higher in an unstable home environment (Schmeer et al., 2019). Latent infections can lead to a drastic acceleration in immune ageing (Bauer and Fuente, 2016). The detrimental effects are not limited to chronic infections: acute infections, such as neonatal sepsis (a bacterial bloodstream infection in new-borns) can result in long-term neurodevelopmental problems (Alshaikh et al., 2013) and early life respiratory infections, pollutants and microbes have been correlated with the risk of developing asthma and respiratory allergies (Burbank et al., 2017, Malinczak et al., 2020, Tregoning and Schwarze, 2010). A study in zebrafish found that an early life bacterial infection significantly altered the expression profiles in several inflammation-related genes [*mpx, tfa, ptgs2a*] and that the age at time of infection was a crucial factor for modulating the adult immune response (Bilbo and Schwarz, 2009). One suggested mode of environmental '*programming'* works through DNA methylation. It has recently been shown, that LPS treatment (mimicking an acute infection) can induce long term methylation changes in several genes associated with immune regulation [*HDAC4, AKT1,* and *IRAK1*] in endothelial cells (Jhamat et al., 2020). Furthermore, Fonseca and colleagues demonstrated that early life pathogen exposure could lead to epigenetic modifications in bone marrow progenitor cells, irreversibly shaping the immune system (Fonseca et al., 2020). Given the higher prevalence for infections in combination with ELA, and the increased hazard for stress mediated re-activation, we see CMV (and other infections) as accelerators for immune-ageing; heavily driven by the early-life environment (see Fig. 5).

Telomere length: The effects of ELA and ageing on telomere length are both somewhat inconsistent. While ELA (Ridout et al., 2018) and ageing (Campisi, 2014, Muñoz-Lorente et al., 2019) have been associated with telomere shortening and a positive rearing environment correlated with increased telomere length in rhesus monkeys (Schneper et al., 2016), we and others found no significant correlation between telomere length and ELA in human cohorts (Elwenspoek et al., 2017c, Verhoeven et al., 2015). This might be due to the very heterogeneous background in humans, as a very recent study in adult monozygotic twins found causal relation between leukocyte telomere length and stressful life events (which were not restricted to early life) (Gerritsen et al., 2020). Shorter telomere length is associated with active depression (Whisman and Richardson, 2017) and psychiatric disorders (Darrow et al., 2016, 2020). While several authors have connected telomere length to adverse pregnancy (Entringer et al., 2018) and childhood events (Epel and Prather, 2018), the argument could also be made that telomere length is connected to repeat stress rather than early life stress itself (Shalev et al., 2013, Rentscher et al., 2020), and that ELA enhances the risk to suffer from low SES and chronic stress in adulthood (Gur et al., 2019). Other studies have associated differing telomere length with overall health status in the elderly (Arai et al., 2015, Tedone et al., 2019). It does not seem far-fetched to assume, individuals encountering less stress might also lead happier and healthier lives. Telomerase, the enzyme generating telomere ends on chromosomes, is known to be most active in gametes and stem cells. In somatic tissue resident cells telomerase activity is rather low (apart from cancer cells), but genetic mutations in telomerase dependent genes are known to be associated with premature-aging symptoms (Armanios and Blackburn, 2012). Regular dividing cells and their progenitors, like lymphocytes, are strongly affected by telomerase activity and telomere shortening, affecting their potential for differentiation potential (Hodes et al., 2002). Recent publications showed that cellular ageing and immune proliferation have distinct effects on telomere length (Fali et al., 2019), with CD4 T cells stronger affected by ageing (Patrick et al., 2019) [reviewed in (Razgonova et al., 2020)]. We suggest that telomere length in leucocytes is likely determined by repeated immune activation, with overall '*healthy'* lifestyles preserving telomere length. Immune activation can be triggered by acute and chronic infections (e.g. CMV), psycho-social stress and other environmental factors (e.g. chemotherapy, pesticide exposure). The duration and intensity of the adversity is likely to play a critical role in telomere shortening.

Immuno-senescence: We and others have found several immune populations [CD8+CD57+, CD8+CD25+, CD8+ CM, CD8+ EM, T_h17] to be significantly affected by ELA (Elwenspoek et al., 2017a, Reid et al., 2019). Similar subsets [Th17, CD8+CD57+, CD8 EM] have been found to be (immune-) age dependant in the IMM-AGE cohort after CMV sero-positive correction (Alpert et al., 2019). Diverting form the original conclusion, these finding were not only mediated by CMV infection (Elwenspoek et al., 2017c), but appear to be genuine markers of immunosenescence. Furthermore, T cell differentiation towards a pro-inflammatory T_h17 phenotype has been shown to prevail in the elderly, and is likely the result of defective mitophagy (autophagy of the mitochondrion) within lymphocytes (Bharath et al., 2020). While a lower frequency of B cells was associated with ELA (Esposito et al., 2016, Naumova et al., 2012, Obi, 2019) an accelerated B cell immune ageing (see Fig. 3) has been linked to obesity. In-vitro leptin stimulated B cells switched to a pro-inflammatory phenotype, expressing *TNF-α, IL-6* and *IL-8* along with *TLR4* and cyclin-dependent kinase inhibitor 2A (*CDKN2A*), a cell division suppressor. Leptin is mainly secreted by adipocytes and therefore high in obese individuals, but also in the lean elderly (Frasca et al., 2020). Changes in immune subsets, activation and response are among the 'hallmarks of ageing'. Apart from accelerated telomere shortening in immune cells by repeated activation, age associated hyper- or hypomethylation of CpG islands can lead to impaired immune cell function (Tserel et al., 2015, Gowers et al., 2011) [reviewed in (Nardini et al., 2018)]. Early exposure to radiation, for example, was associated with significantly altered T_h1 cell methylation and increase in inflammatory cytokines several years later (Daniel et al., 2018) and exposure to stress changed the methylation in several genes associated with immune pathways in an ELA model of salmon (Uren Webster et al., 2018). Both, ELA and frail, negative ageing trajectories are characterized by a pro-inflammatory environment and several circulating cytokines (Kuhlman et al., 2020, Campisi et al., 2019, Baumeister et al., 2016) (see Fig.5). Whether elderly individuals (60 years+) that experienced ELA many decades earlier have overall higher levels of cytokines than those without is, to our knowledge, currently not known, as most studies addressing the mechanisms of biological ageing are not designed to assess ELA as well.

ROS and mitochondria: Reactive oxygen species (ROS) are unstable oxygen molecules, which often occur as intracellular by-products of oxygen metabolism. The mitochondrion at the centre of oxygen metabolism is not just the biggest source of intracellular ROS, but also a potential target for DNA damage caused by oxidative stress. Damaged mtDNA and reduced metabolic efficiency during ageing are thought to be major contributors to immunosenescense, inflammageing and frailty

(Mikhed et al., 2015, Ventura et al., 2017). Furthermore, exogenous sources, such as pollutants, tobacco smoke or a high fat diet which are encountered during life, often increase intracellular ROS by redirecting antioxidant capacity, which is also thought to diminish with ageing (Inal et al., 2001). Furthermore, immune cells, such as neutrophils and macrophages, are known to use ROS to effectively kill pathogens in a process called respiratory burst [reviewed in (Dahlgren and Karlsson, 1999)]. As ROS can damage proteins, enzymes and cell membranes by lipid oxidation, they are linked to the development of many chronic diseases [reviewed in (Alfadda and Sallam, 2012, Liguori et al., 2018)]. The role of ROS in immunomodulation and immunosenescense is a relatively young field of interest [reviewed in(Muri and Kopf, 2020)] and research concentrating on the connection between ELA and ROS are only slowly emerging, however, mitochondrial function and oxygen metabolism are negatively affected by ELA (Zitkovsky et al., 2021, Horn et al., 2019, Boeck et al., 2016). Using ELA animal models it also became clear, that ROS can cause axonal damage of neurons and thereby increase the risk for neuroinflammation and -degeneration (di Penta et al., 2013, Soares et al., 2020, Nouri et al., 2020), an important factor for the onset and progression of diseases like Parkinson's and Alzheimer's, perennially associated with ageing [reviewed in (Kandlur et al., 2020)].

Thymic involution: The involution of the thymus is directly connected to a decreased output of naïve T cells, impeding T cell receptor diversity and leading to immunosensecense. Furthermore there is an increase in autoreactive immune cells coming from the aged thymus, which can cause tissue damage and chronic inflammation (Thomas et al., 2020). Interestingly thymic involution, a well-known feature of ageing, is also linked to ELA. Adverse effects of ageing were more prominent in male rat thymi than female (Nacka-Aleksić et al., 2019). Similarly, severe ELA significantly accelerated thymic involution in young children in a dose-dependent manner. At the highest levels of ELA this was accompanied by both splenic and lymph node atrophy (Fukunaga et al., 1992).

Lifestyle and HRBs: Obesity, smoking, long-term stress, chronic infections, the lack of physical activity and alcohol consumption have been implicated to contribute to accelerated biological ageing (Furman et al., 2019). These HRBs closely mirror those adopted after ELA. As outlined above, there are clear neuropsychological reasons why those exposed to ELA undertake HRBs, particularly smoking and alcohol consumption. The data is growing that these lead to allostatic load, and accelerate the epigenetic clock, and that even in twins, differences in HRBs will strongly determine the risk of many non-communicable diseases (Turner et al., 2020). There are other lifestyle factors such as nutrition and physical activity that are, potentially modifiable lifestyle choices, that are epigenetic modifiers that when corrected may contribute to 'ageing well' and 'tailoring lifestyle to fit biology' (Wallace et al., 2018) (see Fig.5).

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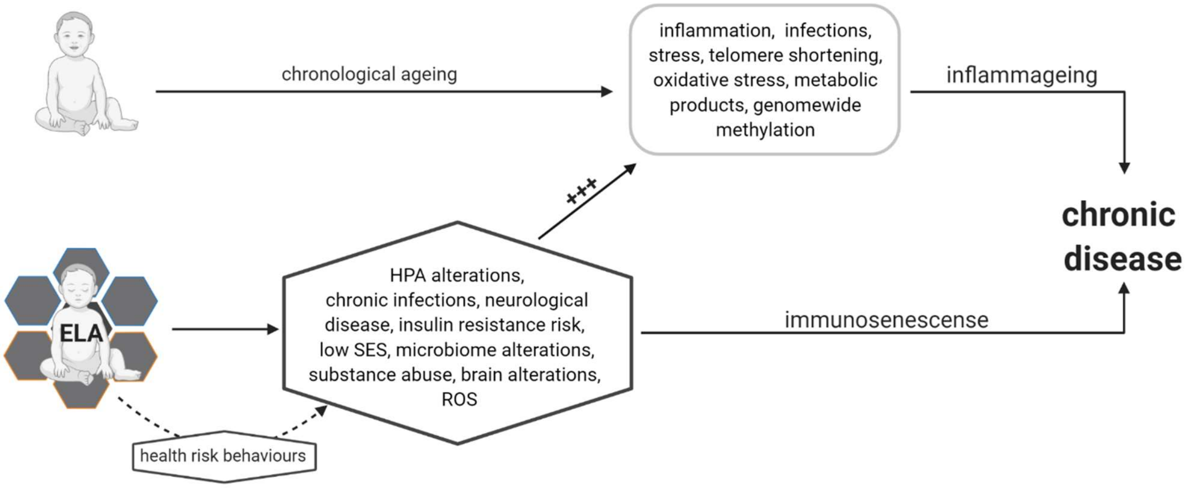

Figure 5. Early life adversity acts as an accelerator for inflammageing and immuno-senescence. Chronological ageing is inherently connected to biological components which accumulate over the lifetime of the individual. While several factors can accelerate the biological ageing progress, ELA heavily promotes this process on several levels. The ELA associated health-risk behaviour might support this further.

Diet and microbiome: Microbiome dysbiosis has recently been proposed as an additional hall mark of ageing (Bana and Cabreiro, 2019) as microbial changes have been reported in many age associated diseases (García-Peña et al., 2017). At the same time, specific diets (e.g. mediterrean (Critselis and Panagiotakos, 2020)) have been associated with 'healthy' ageing and increased quality of life (Foscolou et al., 2020). This effect is likely to be mediated through the gut microbiome. Indeed, a dietary intervention of just a few months has been shown to change microbiome composition in the elderly (Ghosh et al., 2020). Specific dietary metabolites, as well as calorie restriction, have also been shown to counteract ROS accumulation (Kurniawan et al., 2020, Vatner et al., 2020) and therefore beneficial for 'healthy' ageing. The gut microbiome and its metabolites are known to modulate immune fuction and contribute to metabolic diseases and inflammation (Shanahan and Sheehan, 2016, Sittipo et al., 2018). Long lasting alterations of the gut microbiome after ELA are a subject of rising interest as they clearly correlate with later health oucomes (Tamburini et al., 2016). In this way, the influence of an early life western style diet (McNamara et al., 2021), the mode of birth (Akagawa et al., 2019) and neonatal antibiotic treatment (Eck et al., 2020) have been shown to reduce microbial diversity and have adverese health effects. Reid and collegues have recently correlated microbial diversity with immune subsets in a human cohort of early life institutionalization (Reid et al., 2020), emphasizing on the role of microbiota in ELA associated pahtologies . Resent research suggests that bacterial diversity is at least partly inherited trough genetics: mtDNA variants are highly correlated with microbial composition, even if animals were reared in a different environment (Yardeni et al., 2019), resulting in altered ROS production. This is of high interest as ELA has repeatedly been associated with altered mitochondrial function and mtDNA copy number (Tyrka et al., 2016, Debray et al., 2018, Zitkovsky et al., 2021).

Psychosocial stress and mental health: The ELA induced risk of developing anxiety-related and depressive psychopathologies will clearly interact with the ageing process. It is clear that serious mental disorders decrease life expectancy and concurrently increase the relative risk of age-related pathologies such as dementia, and cardio-metabolic diseases, as well as accelerated immune ageing (Liu et al., 2017). This has resulted in the shift from considering many severe psychiatric disorders as only diseases of the to a more holistic multi-system, or even ‘whole body’ entity, of which ‘accelerated biological aging’ is an essential element (Wolkowitz et al., 2011). Here, accelerated biological ageing has been reported an significant shortening of leukocyte telomere length as well as an acceleration of epigenetic age measure by DNA methylation (Wolkowitz, 2018). In line with this, ELA has also repeatedly been associated with methylation changes in genes related to HPA axis function (Alexander et al., 2018), the immune system and in certain brain structures (Catale et al., 2020). Recent animal models of ELA have shown significant changes in gene expression associated with stress and inflammatory signalling long after exposure (Lopizzo et al., 2021, Lutz et al., 2020). Obesity, often seen after ELA as well as in the elderly, has been shown to drive cellular senescence and induce anxiety in a mouse model (Ogrodnik et al., 2019), showing another possible link between health behaviours and mental health. Psychological distress has also been implicated in accelerated ageing and lower life quality (Moore et al., 2020), while chronological ageing itself increases the perception of stress (Osmanovic-Thunström et al., 2015) and the risk for depression (Lee et al., 2020). While this seems like a self-perpetuating cycle, the extend of the immune component in mental health is not well defined. Given the literature about the emotional response to chronic diseases [reviewed in (D'Acquisto, 2017)], it raises the question if dysfunction of the immune system is a consequence or a driving factor to mental health, or both.

4.2 Uncertain features

Sex specificity: The pro-inflammatory environment of inflammageing is higher overall in men, contributing to their general lower life expectancy (Clutton-Brock and Isvaran, 2007). Early life adversity on the other hand has been reported inconsistently to have a stronger effect on women (Honeycutt et al., 2020, Power et al., 2012) or men (Appelmann et al., 2021). Self-reporting and retrospective reporting biases make these conclusions unreliable (Reuben et al., 2016), although, no significant bias was reported for self-reported vs reimbursed medication (Brown et al., 2007) or test-retest reliability (Dube et al., 2004) in the ACE study. Furthermore, ELA studies of institutionalisation (Gunnar et al., 2007, Rutter et al., 2004, van Ijzendoorn et al., 2011, O'Connor and Rutter, 2000) have shown that the psychological and physiological impact on children tends to correlate with the duration of institutionalisation and can therefore be considered an unbiased measurement. Information bias for observational (e.g. questionnaires) as well as experimentation parameters (e.g. only limited material collected) (Althubaiti, 2016) is inherent in all human research. However, certain biological components (e.g. hormones) are markedly different between the sexes. Estradiol and progesterone have been implicated to confer protection from oxidative stress and neuronal injury (Ishihara et al., 2015), which is also of interest in the scope of ELA, as steroid levels in the immature brain are higher than those in the adult brain (Konkle and McCarthy, 2011). In animal studies, without economic and social cofounders, males often fare less well. In a multiple-hit rat study, males displayed increased anxiety-like and anti-social behaviour (Bonapersona et al., 2019). Furthermore, the negative impact of ELA on the microbiome has been demonstrated to be higher in males (Rincel et al., 2019). Female sex hormones have also been found to have “immunoenhancing effects after infection or circulatory stress” (Angele et al., 1999). An enhanced immune response, evolutionary conserved in females, may partially explain this sexual dimorphism (Jaillon et al., 2019).

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HPA-axis: Literature on the effects of ageing on the HPA axis, and consequently stress response, are highly inconsistent. Several studies reported rising, stagnant or decreasing levels of cortisol associated with chronological ageing [reviewed in (Gaffey et al., 2016)]. In an animal model of aged rats, Glucocorticoid (GC) secretion was enhanced due to degenerative changes in brain connectivity (Sapolsky et al., 1986, Gardner et al., 2019), while GCs and cortisol have repeatedly been shown to have a 'blunted' response to acute stress after ELA (Lovallo et al., 2018, Hengesch et al., 2018). A recent study in mice has shown lower GC levels to be correlated with higher levels of inflammatory cytokines, ROS and macrophage activation, in accordance with inflammageing (Valbuena Perez et al., 2020). It remains to conclude that, while HPA dysregulation is often reported in combination with ageing (Gupta and Morley, 2014), the molecular mechanisms responsible remain largely unknown.

5. Future directions

We have shown many biological features shared between ELA, frailty, and inflammageing. Often we do not know, through which mechanistic pathways ELA acts on the body and mind, but the clear inflammatory driven phenotype is without question. Both, ELA and ageing, have repeatedly been associated with a decline in mental health and an increase in systemic inflammation. While telomere shortening is associated with both ageing and ELA, it might be more impacted by chronic stress, and the concrete influence of sex hormones in ageing or ELA remains elusive. Immunosenescence, which has often been reported after ELA, seems a valid connection for most features mentioned, and after all it is a so-called 'hallmark of ageing'. However, this perspective might change with emerging new foci in the research surrounding ELA and ageing: two underexplored areas, ROS and the microbiome will most likely emerge as essential in maintaining immune homeostasis and mental health.

As we and others have recently highlighted (Holuka et al., 2020), we need to start considering both socioeconomic and early life environment data as genuinely important medical information that should be routinely collected. It is important that the retrospective life-trajectory data is collected, even under the risk of recall bias. Studies done to assess the effect of ageing, in health or disease, usually do not retrospectively assess the early life environment of their participants. The ELA literature is clear: adversity is associated with accelerated immunological and biological ageing (Sun et al., 2020, Nettle et al., 2017, Hamlat et al., 2021). Well-established ELA cohorts such as the Dutch Hunger Winter, or survivors of the holocaust that are now in their 7th or 8th decade of life. Taking lessons from the ELA literature, natural experiments such as these may provide a perfect window into the role of ELA on ageing. In these cohorts the adversity suffered was clearly defined, and we know much about their susceptibility to non-communicable diseases and their overall trajectories. It remains now to be seen what effect this has had on the overall ageing process, and the ageing phenotype in such cohorts.

Nevertheless, early life exposure and lifetime accumulated allostatic load will remain hard to differentiate. Monodisciplinary approaches, of which we are also guilty, will ultimately have to make way for multi-system-studies, integrating observational parameters with experimental measurements in a holistic manner. As such data becomes available, it will necessitate the integration of the metadata with patients' medical records and many multi-omics and high-dimension datasets together with cooperation between disciplines (medicine, biology, psychology, social sciences, and computational sciences). Animal models and in-vitro immune assays will have to identify the mechanisms in a controlled environment.

Lastly, the ongoing SARS-CoV-2 virus and COVID-19 pandemic will have an enormous impact on the life of many people, including new-born children and pregnant women, as a source of ELA. It is also a unique opportunity to study the immune response to a completely novel pathogen in either an aged immune system, or an immune system that has been exposed to ELA many years ago. If our position outlined here that ELA accelerates immune-ageing is correct, prior ELA exposure will have significant consequences on the subsequent response to a novel pathogen to which the immune system is completely uneducated. There are many cohorts available worldwide from children and adolescents only recently exposed to ELA, or octogenarians that were exposed nearly 8 decades ago. Here the prior ELA has been characterised, and a wide variety of cross-sectional studies can be conceived that would investigate the effect of this exposure to ELA many decades ago on the relative morbidity and mortality of COVID-19 in these population. It has already been highlighted (Holuka et al., 2020) that the ELA immunophenotype may play a significant role in determining the outcome of COVID-19 disease. In summary, exposure to early life adversity would appear to not only produce a specific immunophenotype, but to accelerate the overall immune-ageing and inflammageing processes. We now have the tools to be able to dissect this interaction, and to potentially identify the ecological and mechanistic processes that are involved in 'healthy' or accelerated immune-ageing.

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Abbreviations

ACE: adverse childhood experiences
ACTH: adrenocorticotrophic hormone
BMI: body mass index
ELA: early life adversity
ELS: early life stress
CMV: Cytomegalovirus
EBV: Epstein-Barr virus
CRF: corticotrophin releasing factor
CT: childhood trauma
CTL: cytotoxic T lymphocyte
CTQ: Childhood Trauma Questionnaire
GCs: Glucocorticoids
HPA: Hypothalamus-pituitary Adrenal axis
HRBs: Health-risk behaviours
SASP: Senescence-associated secretory profile
DAMPSs: damage-associated molecular patterns

PAMPs: pathogen-associated molecular patterns
PRRs: pattern recognition receptors
ROS: reactive oxygen species
DOHaD: developmental origins of health and disease
LPS: Lipopolysaccharide

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