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Allostatic load: how stress in childhood affects life-course health outcomes

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Summary

This working paper summarises current knowledge about the biological consequences of social disadvantage in the first decades of life and how these contribute to health inequalities. People's health varies depending on where they are on the 'social gradient'. People in more advantaged socioeconomic circumstances live longer – and in better health – than those experiencing less advantage. Understanding why this is the case is an important step in addressing health inequalities.

Health outcomes are a result of multiple exposures over a person's life. These exposures, whether they are chemical, physical, behavioural or psychosocial, are a consequence of social circumstances and lead to modifications in individuals' biological processes: a concept described as 'biological embodiment'.

During periods of rapid development, biological systems are more sensitive to exposures in the environment. While changes in the human brain occur more rapidly in childhood and adolescence, it should be noted that physiological adaptability and brain plasticity is retained throughout people's lives. Thus, it is never too early – or too late – to act to improve health.

Biological embodiment occurs because of either exogenous or endogenous exposures. In the former, biological systems become modified by the introduction of living or inert materials into the body. These exposures are socially patterned through, for example, the nature of the external environment. In the latter, biological and physiological responses arise due to stressors in the external environment, such as financial hardship. In practice, these two mechanisms are often interrelated.

The process of adaptation to exposures is referred to as allostasis. It involves changes in the nervous, endocrine and immune systems and results in both benefits and costs to the individual. It is part of the human species' key to survival. However, chronic exposure to psychosocial stressors – and differences in susceptibility to stress – leads to prolonged activation of allostatic systems. This strain on the body results in measurable impact on markers such as blood pressure, serum high density lipoproteins and urinary cortisol. The measurable impact of these physiological responses is referred to as 'allostatic load' and can be described as the price paid by the body for adapting to challenges.

Studies have shown that socioeconomic disadvantage is associated with higher allostatic load. In turn, increased allostatic load has been associated with multiple chronic diseases. The relationship between social position and the biological embodiment of physiological responses that results in allostatic load operates through several pathways including the effects of behaviour, psychosocial responses, education and material deprivation.

There is still much more to understand in this field. For example, the impact of social disadvantage in early childhood and allostatic load in later life has been found to be modified by individuals who display psychosocial resilience. The scientific research on the concept of biological embodiment – how we literally incorporate the social world in which we live into our bodies' cells, organs and systems – is still at an early stage. However, the evidence is consistent across the literature about the impact of socioeconomic disadvantages and stressful life conditions in childhood and adolescence on physiological and biological adaptive responses and the consequences of these for health outcomes.

Introduction

The aim of this working paper is to summarise and describe current knowledge about the biological consequences of social disadvantage experienced in the first decades of life, and how these contribute to constructing health inequalities. Before getting into the literature, there is an important point that needs to be underlined. This working paper will discuss the evidence about how human biology is transformed and changed by our social environment. We physically adapt to our environments, and this process of adaptation is more pronounced during the years of our lives when we are undergoing rapid development and maturation. This phenomenon is a key part of our 'success' as a species, capable of living in and adapting to most physical environments found on Earth, within a wide variety of social organisations. Our biological systems allow us to bend and sway to the rhythm of our everyday experiences, at least to some extent. This is a *neutral* phenomenon – to say that we are transformed negatively by negative experiences, or positively by positive experiences, is to caricature what happens. We simply respond to our environment.

This point is important because otherwise certain terminologies can come to be regarded as socially stigmatising. Over the last decade or so, new sources of data and advances in science have allowed us to understand how our bodies change and adapt to the environments we live in. The *Annals of the New York Academy of Sciences* published an important special issue in 2010 entitled 'The biology of disadvantage'.[1] While this title draws attention to an important issue – that social environments affect biology – it could also lead to the erroneous assumption that we only biologically respond to disadvantaged environments. Evidence does suggest that poverty changes our biology, but *all* environments affect us biologically, be they 'good', 'bad' or 'neutral'. The question this paper will explore is: which aspects of our social environments are most likely to lead to socially patterned biological differences that in turn contribute to, or exacerbate, health inequalities?

The working paper will describe how social-to-biological research helps us to understand the construction of health inequalities. It summarises how everyday human experiences in childhood and early adulthood may affect human biology, resulting in socially patterned biological phenomena that may contribute to observed social differences in health. First, the phenomenon of biological embodiment, and how it is likely to occur, is discussed. Second, how embodiment may be measured by physiological dysregulation through the concept originally called 'allostatic load' is explored. Third, a number of examples from the literature on how experiences in childhood or adolescence are associated with biological changes are provided. Finally, the complexities and challenges involved in this relatively recent field of research, and where gaps remain, are discussed.

Social determinants of health and biological embodiment

Understanding how and why health is socially patterned across populations, forming a social gradient, is a major societal challenge if we are to address health inequalities. While overall life expectancy has improved over recent decades, the life expectancy gap between the least and most socially disadvantaged has increased. From 2014 to 2016 in England, the least-deprived men at birth could expect to live 9 years longer than the most deprived, while for women the gap was 7 years.[2] The social gradient in health refers to the graded, and often stepwise, relationship between a measure of social stratification (for example, occupational social class) and health within a population. Across a social gradient in health, the most socially disadvantaged have the worst health, those who are less disadvantaged have better health than their disadvantaged counterparts (but worse health than the socially advantaged) and those who are most socially advantaged have the best health outcomes.

Through a life-course approach, human developmental processes occurring from early life are taken into account as they change over time within their social and physical context.[3] A life-course approach offers a framework for understanding health as the result of a combination of multiple socially structured exposures (for example, chemical, physical, behavioural and psychosocial) likely to modify biological processes. These modifications, in turn, favour the development of health and illness in the long term, and may contribute to the construction of the social gradient in health. The way in which different socially patterned exposures affect our biology refers to the concept of biological embodiment:[4] how we literally incorporate into our bodies' cells, organs and systems the social world in which we live.

Understanding embodiment as a dynamic helps us grasp how social and psychosocial elements, structured into different layers within the human environment, are related to physiologically measurable states, morbidity and mortality.[5] Therefore the embodiment dynamic represents the complexity of interrelated processes and mechanisms leading to the social structuring of human developmental states and health outcomes from early life. Embodiment may be viewed as the dynamic that leads to population patterns of health and illness. As such, understanding that these covert interactions occur from the early stages of the life course, before their emergence as health outcomes or healthcare trajectories, is fundamental to the success of any attempts to thwart the socioeconomic gradient in health.

Human social, emotional and biological development over the life course

The first two decades of human life are sometimes characterised as being 'critical' or 'sensitive' in determining adult life trajectories. The concept of 'critical or sensitive periods' is borrowed from notions originally identified in neurobiology and physiology.[6] During a phase of rapid development, a biological system is more sensitive to exposures in the environment and especially deviations from 'normal' exposures expected during that particular phase of development for that particular system.[7] No single sensitive period can be identified. Rather, degrees of sensitivity are constantly shifting for different systems, which in turn vary in their complexity. It is more relevant, therefore, to allude to the earlier decades of life as a sequence of multiple sensitive periods that overlap and are structured in hierarchical form.

Developmental processes occurring earlier in the human life course are linked to fundamental biological functions most basic for human existence. Observed sensitive periods of development are strongly influenced by the properties of neural circuits, the environmental inputs that influence them, and inter-individual differences.[8] Later, during the development of higher functions, such as socioemotional behaviours, sensitive periods are likely to be longer and vary greatly between individuals.[9] Lupien *et al.* refer to the 'life cycle model of stress', describing how the effects of stress at different life stages depend upon the brain areas that are developing or declining at the time of exposure.[10] A better understanding of sensitive periods may elucidate mechanisms that contribute to the production of health inequalities. However, overly deterministic views about how early life and adolescence affects us as adults may be harmful.[11] We must remember that we are talking in terms of probabilities and means, comparing population groups and not individuals. That childhood sets the stage for our future is a widely held belief, yet we also know that people can be resilient in the face of tribulation, making remarkable recoveries.

An example of the heightened sensitivity to environmental conditions during early human development is seen in neurocognitive synaptic overproduction during the first 7–8 years of life, followed by 'synaptic pruning'.[12]

The sequence of human developmental changes and our acquisition of skills is important. For example, the ability to process facial emotions requires first that the individual has the ability to perceive the visual input of facial stimuli.[13] While changes to the human brain occur more rapidly in childhood, we also retain physiological adaptability and brain plasticity across the life course.[13] Human development is characterised by both sequences of sensitive periods at certain times, as well as an ongoing flexibility. This is important in explaining why it is possible to simultaneously conceptualise the early decades of life as being 'deterministic' for the future, all the while defining humans as plastic and adaptable all across their life course. This is why, in terms of acting to improve population health, it is never too early and never too late.

Social identities and childhoods

Bartley *et al*. described 'socially critical periods' as phases where individuals make transitions between different states, or identities – a liminal position that renders them vulnerable within mainstream social structures.[14]

Parallel to the more biological milestones, human development needs to be seen in relation to socially constructed identities. Rowntree's 1902 'standard of living life cycle' provides an example: 'a labourer is thus in poverty and therefore underfed a) in childhood – when his constitution is being built up b) in early middle life – when he should be in his prime c) in old age'.[15] Thus, several of the 'standard of living life cycle's' phases of hardship occur in parallel with the important biological stages of human life.[16]

In high-income countries, the childhood and adolescent years are often characterised socially through respective childcare and educational systems: when a child enters formalised educational environments, when they start school, when they transition from primary to secondary school and so forth. Adolescence is often described as a period of

rapid social and biological change. And the relatively recently defined period of 'emerging adulthood', spanning late adolescence into the early twenties, has become important due to sociodemographic shifts where education is prolonged, and entry into the labour market, marriage and parenthood are delayed.[17]

Through the life-course interdisciplinary framework, there are many ways to examine the mechanisms and pathways involved in the embodiment dynamic. For example, the mechanism of attachment[18] may be an important process for understanding the nature of interpersonal relationships in psychology, or language acquisition in children may be key to a cognitive scientist. An anthropologist may wish to examine cultural processes, and a medical researcher may take an interest in pathological mechanisms.

No matter what our specific research question may be, if we are interested in understanding how social gradients in health are produced, we want to know more about the specific pathways along which social-to-biological associations are likely to operate. A growing body of research hypotheses on the specific pathways that may operate between different environmental factors and embodiment can be identified and tested, informing deductive methods and the rejection of hypotheses or formulation of new ones.[19] When taking an interest in how many of these different processes may affect the production of the social gradient in health, it is suggested that one or several biological mechanisms are always ultimately implicated.[5] Below, two major groups of biological mechanisms are outlined.

Biological mechanisms

The nature and cadence of the embodiment dynamic varies over the life course and may be made up of many different processes. However, it always encompasses at least one biological mechanism.[5]

Exogenous origin

Our biological systems may become modified by the introduction into our bodies of external entities. Blane *et al.* refer to these types of biological mechanisms as *material*, consisting of the 'living (bacteria, viruses) and inert (asbestos fibres, folic acid) materials that have an impact on the body's structure and immune system. Impact can be beneficial (essential gut flora; folic acid-dependent embryonic neural tube development), harmful but contained (antibodies; scar tissue) or pathological (respiratory tuberculosis; mesothelioma)'.[20] Included within this broad type of mechanism are certain behavioural factors, such as smoking, drinking alcohol and diet. These are all socioculturally contextualised behaviours that lead us to take substances into our bodies that affect our biological systems.

Social position, through its influence on the nature of the external environment we live in (such as the quality of housing or the type of occupation) may act on the probability of coming into contact with these exogenous factors that become incorporated. An example of this process is in Bartley *et al*.'s findings from the 1958 Birth Cohort Study, whereby financial hardship experienced in early life in Great Britain was associated over the life course with a lower lung function at the age of 45, after taking into account many other social and behavioural factors.[21] Through their models, the authors showed that financial hardship led

to an increased exposure to poor-quality, damp and overcrowded housing, which was the most plausible pathway linking social position and lung function.

A different example by Garès *et al.* identified poor quality and overcrowded housing as associated with an increased likelihood of infection from Epstein–Barr virus (EBV) in children by the age of 3.[22] This finding is worth contextualising further, since it is not an example of social disadvantage necessarily leading to poorer health outcomes. In fact, being infected with EBV *earlier* in childhood means that those individuals are less likely to develop diseases like infectious mononucleosis or multiple sclerosis, which may be triggered through acquiring EBV later on in adolescence or early adult life.[23] This instead shows how the social–material environment may affect the priming – or early construction – of the immune system, leading to functional differences in immunity that may be socially patterned.

Endogenous origin

This set of mechanisms refers to biological and physiological responses occurring within our bodies in response to environmental changes. These are essentially responses that work through the brain, be they via perceived everyday experiences and relationships, often referred to as 'psychosocial', but also through our other cognitive functions, including skills acquisition and educational processes. Perceptions, emotions, personality, self-efficacy and many other mechanisms located in the mind can lead to a cascade of responses from the neuroendocrine system to physiological stress responses in various biological systems (for example, neurological, inflammatory or hormonal).[10]

As was seen above, developmental sensitivity is more pronounced at certain times during childhood and adolescence, in which case the experience of acute or chronic physiological stress caused by stressors in the environment can induce several known biological responses.[24,25] These responses could have an impact on subsequent biological and behavioural functions, depending on the timing of initial exposures, and be mediated subsequently by later exposures. For this reason, exposure to physiological stress can be examined as a potentially important initial exposure on a pathway towards ill health, which is likely to be socially patterned. We will now focus on exploring these mechanisms of endogenous origin in the literature, and how the biological response to physiological stress may be measured.

Links between the two

These two broad types of mechanism are clearly related, but they help us understand the 'origin' of the social-to-biological pathway we aim to study. For example, financial hardship within a household may lead to tensions between the household members and exposure to chronic physiological stress. This would exemplify a socioeconomic exposure leading to a biological mechanism of endogenous origin. However, the physiological stress may lead to the uptake of other behaviours, such as smoking cigarettes, or eating fast food – both mechanisms of exogenous origin.

Mechanisms of exogenous or endogenous origin may implicate molecular-level transformations, such as epigenetic changes, which in turn may alter endogenous biological

mechanisms. The two types of mechanism may also interact and affect each other. Once an exogenous entity has become incorporated biologically, it may affect endogenous biological systems positively, negatively or neutrally. For example, humans became habituated to living in relative harmony with living 'pathogens' that infect us but remain harmless. According to Rook *et al*. 'the Old Friends mechanism states that mammals co-evolved with an array of organisms that, because they needed to be tolerated, took on a role as inducers of immunoregulatory circuits'.[26] These organisms include bacteria, helminths (worms), chronic infections and environmental organisms from animals and water that humans have evolved and lived with until recently.

Separating biological mechanisms into exogenous and endogenous types is of course merely a construct that might facilitate our understanding of the embodiment dynamic. In many pathological processes, both are likely to be at play. However, identifying the probable source of a social-to-biological process may facilitate our understanding about how to prevent disease and improve health by modifying our social environment.

Measuring embodiment: adaptive allostasis, allostatic load and physiological dysregulation

Our environment is highly variable, requiring the permanent adaptation of physiological systems. This adaption through changes is crucial for survival and refers to *allostasis*.[27] Three main systems – nervous, endocrine and immune – are involved in allostasis processes, all of which mature during the postnatal period into adulthood. Over time, this 'adaptive allostasis' allows us to respond to environmental challenges and elicits benefits and costs to the individual.

Chronic exposures to psychosocial stressors, but also interindividual differences in the susceptibility to stress, are associated with a prolonged activation of allostatic systems. This may lead to an allostatic overload with potentially detrimental health consequences. Over time, the effort required to adapt to environmental challenges leading to psychological stress responses takes its toll across multiple physiological systems. These changes, where the new 'norm' for physiological systems becomes reset, mean that overall physiological functioning continues, but becomes less than optimal. The cost may be minimal; however, if environmental challenges vary and require continual adaptation, the effect may build up. When the environmental challenges affect socially defined subgroups of the population, the biological cost will be observed at the group level. This 'cost' is biologically measurable to some extent, using different approaches.

Allostatic load is therefore the price paid by the body over time for adapting to challenges. It captures biological multisystem wastage or weathering, whereby 'the strain on the body produced by repeated ups and downs of physiologic response, as well as by the elevated activity of physiologic systems under challenge, and the changes in metabolism and the impact of wear and tear on a number of organs and tissues, can predispose the organism to disease'.[28]

An allostatic load score should be a composite measure, including various physiological systems, so as to capture subclinical overall physiological wear and tear. The MacArthur Study of Successful Aging was the first to propose an allostatic load score.[29] Items included:

- systolic and diastolic blood pressure (indexes of cardiovascular activity)
- waist–hip ratio (an index of more long-term levels of metabolism and adipose tissue deposition, thought to be influenced by increased glucocorticoid activity, serum high-density lipoprotein (HDL) and total cholesterol levels (indexes of long-term atherosclerotic risk)
- blood plasma levels of total glycosylated haemoglobin (an integrated measure of glucose metabolism during a period of several days)
- serum dehydroepiandrosterone sulphate (DHEA-S) (a functional hypothalamic pituitary adrenal (HPA) axis antagonist); 12-hour urinary cortisol excretion (an integrated measure of 12-hour HPA axis activity)
- 12-hour urinary norepinephrine and epinephrine excretion levels (integrated indexes of 12-hour sympathetic nervous system activity).

Some variants of the original items can be found in the literature, but the markers most commonly used are associated with cardiovascular and metabolic diseases (blood pressure, heart rate, blood glucose, insulin, blood lipids, body mass index (BMI), waist circumference), HPA axis (cortisol, dehydroepiandrosterone sulfate), sympathetic nervous system (epinephrine, norepinephrine, dopamine) and inflammation (C-reactive protein, IL-6).[30]

As well as representing multiple systems, the score is calculated most often in relation to the population sample, taking distributional cut-off points to identify people whose biomarkers are in a relatively ‘at risk’ group compared with those who are not. The thresholds for the score are not based on clinical definitions of disease but rather on a distributional definition of risk. This is an important point, because it means that the 25% at risk for each biomarker may not be clinically significant, but rather a predisposition to dysregulation and subsequent disease. It also means that subpopulation thresholds can be calculated for men and women, or for age groups, allowing appropriate, within-group allostatic-load scores to be calculated, rather than applying a blanket threshold to the whole population.

These various scores of allostatic load have been shown to be a better predictor of mortality and functional limitations than the metabolic syndrome or any of the individual components used to measure allostatic load when analysed separately.[31] Across studies, socioeconomic disadvantage has been associated with a higher allostatic load score, and in turn increased allostatic load has been associated with multiple chronic disease outcomes.[32]

However, it is important to note that allostatic load has its critics. It is not always measured consistently across studies, and in some cases the biomarkers used to calculate allostatic load do not remain faithful to important conceptual issues, such as the representation of multiple systems and subclinical thresholds.[33,34] To date, no consensus about biomarker selection and biological system representation has been drawn up. Most research using allostatic load has referred to the initial biomarkers mentioned above, and the most readily collected ones. This means that, for pragmatic reasons, the cardiovascular system may

often be over-represented since its classic biomarkers tend to be routinely collected, and some do not require blood samples (for example blood pressure, pulse).

Furthermore, the inconsistencies across allostatic load measures make it difficult to compare results across studies or over time. Since the original concept was developed, shifts have taken place. It was originally strongly linked to stress-related exposures, measuring a biological response to physiological stress. However, over time, it has become apparent that the measure appears to be capturing processes beyond the classic stress HPA axis. Increasingly, in the literature, the term 'allostatic load' is being abandoned in favour of measures using the same approach but called 'multi-system physiological burden' or 'multi-system physiological dysregulation'.[35]

Physiological consequences of social and psychosocial factors in early life

As a measure of the global cost of adapting to (and coping with) the environment, allostatic load, or multi-system physiological dysregulation, may be a relevant concept and tool for measuring the way we have embodied our social environment.

Growing evidence suggests that early-life socioeconomic position (SEP) is a determinant of physiological wear and tear through allostatic load.[36–40] Overall, disadvantaged socioeconomic circumstances early in life have been associated with increased physiological dysregulation later in adulthood. The measures used to capture early life or childhood SEP have varied – for example, authors have used parental education, occupation or household income as measures.

- Gustafsson *et al*. examined the influence of SEP over the life course on allostatic load[41,42] in a northern Sweden cohort follow-up for 27 years. The authors found that cumulative socioeconomic disadvantage over the life course measured using occupational social class (parental and own) was strongly related to allostatic load in adulthood, adjusting for classic confounders of health behaviours. Health behaviours largely explained the relationship for men but not for women. In women, they found that SEP during adolescence was independently related to allostatic load, suggesting a critical period effect of exposure to SEP on later allostatic load. For men, only current SEP (in adulthood) was associated with allostatic load independent of risky behaviours.[41] In a second study, Gustafsson *et al.* investigated whether an allostatic load measure at 43 years of age was influenced by the accumulation of unfavourable social exposures over the life course, rather than social class. The authors took into account and evaluated the influence of both material and social forms of adversity. They measured social adversity earlier in life using parental loss, residential stability and parental illness among other things. They found that social adversity during adolescence for women (and early adulthood for men) was associated with later allostatic load independent of health behaviours and adulthood adversities.

- Using data from the West of Scotland Twenty-07 Study, Robertson *et al*. compared the life-course models (critical periods, pathways, accumulation) using SEP measures from three life stages, modelled against allostatic load.[37] The authors

found that accumulated SEP across the lifespan was the best-fitting life-course model explaining the association between SEP and allostatic load within the cohort members aged 35 years and 55 years. However, the authors did not find an association between SEP and allostatic load in the cohort members aged 75 years.[37] In a subsequent study, Robertson *et al*. investigated the role of material, psychological and behavioural factors explaining the association between SEP and allostatic load. They proposed three principal mediating pathways between SEP and health: material factors (measured using income, employment status, car ownership); psychosocial and psychological factors (measured through a general health questionnaire describing mood states used to assess psychiatric morbidity); and health behaviours (smoking, alcohol consumption, diet and physical activity). The authors found that behavioural and material factors accounted for much of the association between SEP and allostatic load.[38]

- Gruenewald *et al*. also investigated the life-course hypothesis, explaining the association between SEP and allostatic load. In line with Robertson's study, they found that greater experience of socioeconomic adversity across the life course may accumulate to have a negative effect on biological functioning in later adulthood. They concluded that higher allostatic load may be one pathway through which greater life course socioeconomic adversity leads to greater risk of morbidity and mortality in later adulthood. They additionally found that alcohol, tobacco, poor diet and low social support explained a large proportion of the association.[39]

- Barboza Solis *et al*. used the UK 1958 British birth cohort to examine the relationship between SEP at birth as related to physiological dysregulation at age 45. The authors attempted to disentangle pathways between early-life conditions and biological wear and tear. [43] They highlighted the childhood material disadvantage pathway, the BMI pathway and the educational-attainment pathway as all being important ways in which early-life SEP affected later physiological dysregulation. Regarding exposure to psychosocial stress, a cross-sectional comparison of the Wisconsin Longitudinal study and the MacArthur study revealed that less social integration, less social support and more judgemental families were associated with higher allostatic load.[44] These findings reinforced the hypothesis that positive social experiences are associated with lower physiological wear and tear.

- Danese and McEwen investigated the empirical evidence suggesting a link between adverse childhood and later health, using allostatic load. They suggested early life exposure to adverse childhood experiences (ACEs), like trauma, abuse or maltreatment, has been linked to alterations in brain structure and neurobiological stress–response systems, which have consequences for health and emotional wellbeing.[45] They considered that the 'study of stress in childhood includes attention to the biological changes associated with adverse psychosocial experiences in children as well as to the progressive and cumulative wear and tear that is the essence of allostatic load'.

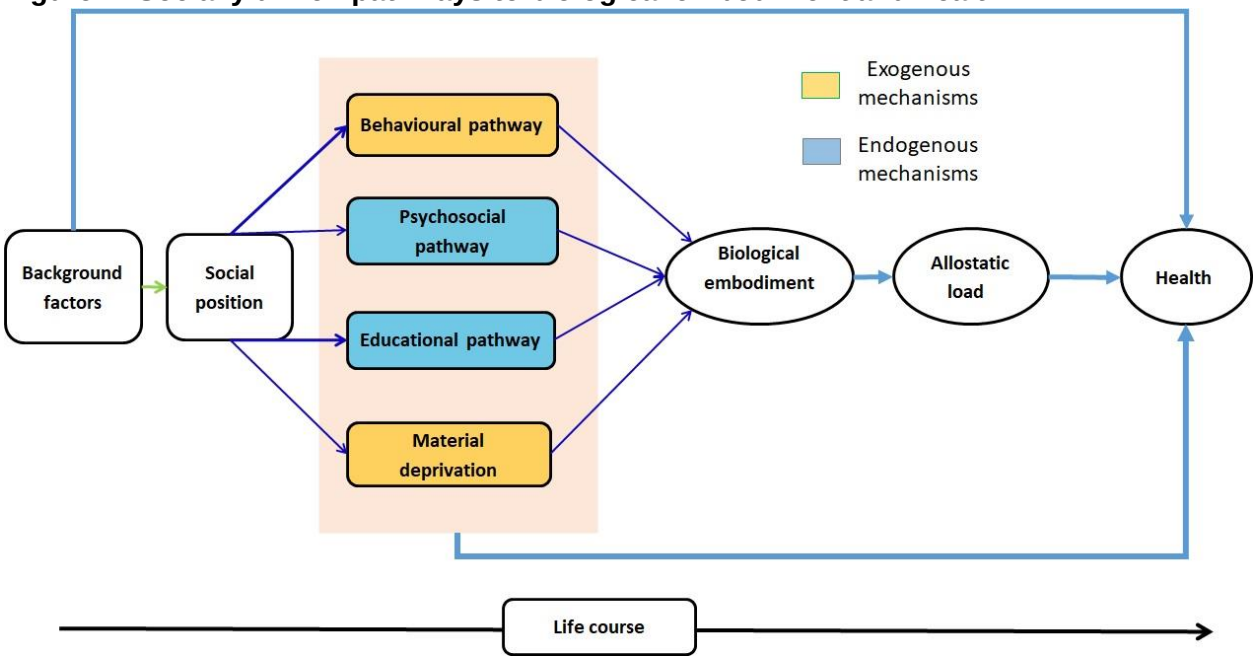
- Barboza Solis *et al*. also examined the association between ACEs at 7–16 years of age and subsequent physiological dysregulation at 45 years of age.[46] The authors found that respondents who had accumulated ACEs had a higher allostatic load in

adult life. They showed that this relationship seemed to work through health behaviours, such as smoking, BMI in women and subsequent socioeconomic processes like educational attainment and wealth accumulation.

- Lê-Scherban *et al.* recently examined early-life SEP using parental education and wealth, in tandem with adulthood SEP, to look at relative social mobility over the life course and the physiological stress response.[47] They established that having experienced a disadvantaged childhood and adulthood SEP was related to slower cortisol recovery after a cognitive-stress challenge. This means that people who had experienced social disadvantage across their life course were more likely to remain in a state of heightened stress reactivity, compared with those who had more advantaged trajectories. This is the mechanism most likely to be at the source of physiological dysregulation over time.

Figure 1 aims to simplistically summarise the potential pathways between social position, biological embodiment, allostatic load and health. Using the broad idea that exposures lead to biological mechanisms of exogenous or endogenous origin, the main general pathways towards biological embodiment and allostatic load are highlighted. These in turn are linked to health, however health is also affected by non-biological factors, including the health care system within the country of residence. The psychosocial pathway may involve how we perceive and experience the social structures or human relationships in our lives. Do we experience discrimination? Do we get support from our social network? The educational pathway remains to be unpacked through research, but involves the practical skills we learn, and whether we feel in control of our destiny (locus of control). All the pathways highlighted are mere summaries of the potential pathways, and are likely to heavily interact and entwine with one another at any one time, and over time.

Figure 1: Socially driven pathways to biological embodiment and health



Resilience strategies for coping with stressful social circumstances

Chen *et al*.[48] used parental education as a measure of early-life SEP, to examine whether a set of psychological resources, namely the 'shift and persist' strategy, was at play in the relationship between SEP and physiological wear and tear. The ability of individuals to change their response to the stressful aspects of socioeconomic disadvantage is described by the authors as entailing: 'both shifting (adjusting oneself to stressors through cognitive reappraisals and emotion regulation) and persisting (enduring life with strength by holding onto hopes for the future). This combination of approaches to dealing with life stressors is hypothesised to reduce physiological responses to stress acutely, and by doing so, mitigates the long-term progression of pathogenic processes that lead to chronic disease'.[48]

Their work showed that respondents displaying this ability in adulthood who had experienced relative social disadvantage in childhood had a lower allostatic load compared with those from the same type of disadvantaged background but who did not display the ability. Furthermore, their findings showed that this psychological faculty was of no advantage to people from socially advantaged early-life SEP backgrounds. The authors have since examined more specific biological outcomes, notably the inflammation process, inflammation being a key system within the multi-system allostatic dimensions.[49] This time they used parental income as the measure of early-life SEP, and found that the 'shift and persist' trait was a moderator of SEP on inflammatory biomarkers.[50]

The authors suggest that the shift-and-persist capacity 'may counteract the overabundance of inflammatory stimuli present in many low-[SEP] environments. These stimuli can be social (stress, violence, conflict) and physical (cigarette smoke, air pollution, high-fat diets) and, through repeated activation of monocytes and macrophages, foster the kind of low-grade, chronic inflammation that contributes to mental illnesses such as depression and to chronic diseases of aging. Shift-and-persist may alter how lower-SES individuals respond to these stimuli, both psychologically and immunologically'.[50]

These psychological-resilience factors require more in-depth examination to understand how they are constructed and how they may benefit individuals in the face of adversity. Many other factors within the social and psychosocial environment deserve similar attention, including different types of social networks and neighbourhood factors.

Other measures of biological embodiment

Epigenetics, specifically DNA methylation modifications, has been proposed as a biomarker of biological ageing and as one of the plausible mechanisms through which social exposures become biologically embodied, affecting physiological systems and cellular pathways leading to disease susceptibility.[51]

The 'epigenetic clock' is one measure recently developed based on age-related methylation changes.[52] It refers to specific sites on the genome where methylation levels change as the body ages and can therefore be used to predict chronological age with high accuracy.[53] The usefulness of this type of clock is that it can identify deviations between the epigenetic clock

and chronological age that may be driven by social exposures. This means that the biological ageing of one social group can be compared with another's, a useful tool when examining the socially driven differences in healthy ageing. Epigenetic mechanisms may also be involved in intergenerational terms, where a socially driven change in methylation status may be transmittable between parents and offspring.

It may be of interest to capture the overall cost of biological adaptive functioning through concepts like allostatic load, but also others that may capture more specific aspects, such as epigenetic mechanisms or inflammation. A wide literature refers to wide-ranging associations between markers of inflammation and many pathological processes leading to premature morbidity and mortality. As such, the term 'inflammaging' has emerged, referring to the role of the inflammatory system in ageing processes.[54] One of the big advantages of using biomarkers in health research is that they offer the opportunity to capture a range of processes underlying health states. Pathological conditions may be identified, but pre-disease and 'normal' or 'optimal' biological processes may be measured as well. This ultimately allows us to question what 'normal' is, how our biology functions under optimal conditions, and the early stages of biological deterioration.

What about genetics?

This is a question that is often asked. In some cases, the question emerges from a confusion between genetics and biology. It is important to clarify that genetics refers to our DNA, and therefore to a very specific sub-area of biology. Our DNA code is inherited from our parents and does not change throughout our life. The rest of our biology, which can be measured to some extent through biomarkers, is constantly changing in response to our experiences.

Some research does indeed explore the genetic characteristics of populations in terms of their social circumstances and attempts to identify genetically 'vulnerable' groups of the population who may be more likely to respond adversely to environmental exposures. We will not delve into this area here because, to improve population health, we cannot do anything about people's genes. They are immutable. However, the environment *is* changeable. Therefore, we will examine which aspects of the environment may lead to poor health. Epigenetics is another sub-area of biology that refers to gene expression, and is of interest to us because some epigenetic mechanisms may be driven by environmental factors, and these mechanisms in turn can affect biological functioning.

Interpreting the literature on social-to-biological research

Our understanding of how the social environment becomes biologically embedded is only just beginning. It has only been in the last decade that datasets containing quality social and biological variables have started to become available to researchers. The advent of open science and open data is also making this easier. So, on the one hand there has been an exponential increase in the research being published where social and biological variables are used together, making it a difficult area to navigate, while on the other hand much of the research has remained descriptive, and has not necessarily improved our understanding of causal mechanisms.

This is not unusual when a field of research opens itself up to more researchers and new analytical techniques. Many papers are validating or describing relationships that have already been published, but they are using different data, or new techniques. With the availability of high-throughput biological data (often called 'omics'), many papers seem to be exploring possible relationships between social variables and these biological outcomes. My advice for navigating the literature and papers on this topic is to read them while asking a number of questions.

- What is the hypothesis that the researchers want to test, or their research question?
- What is their reason for using the social variable(s) they chose?
- What is their biological measure, and why did they use that one?
- What is the social-to-biological reasoning they provide for their analysis?
- Is there a temporal order to the variables (were some variables collected before others)?
- From which population group does the data come, and why has it been used as the data source?

If the answers to these questions are not clear, then the paper is likely to be more exploratory or descriptive. It may be of interest, however it will not help to understand social-to-biological processes or mechanisms.

Mitigating the biological consequences of social disadvantage

The detailed scientific research about social-to-biological processes is still in its relative infancy, especially regarding our understanding of the biological mechanisms of different molecular systems. However, evidence is consistent across the literature about the impact of socioeconomic disadvantage and stressful life conditions in childhood on physiological and biological adaptive responses, and the consequence of these for health outcomes.

What we can say is that socioeconomic disadvantage exposes children and adolescents to multiple factors, resulting in biological mechanisms of exogenous and endogenous origin being instigated in response. Policy-level initiatives to relieve material disadvantage may serve to mitigate exposures to exogenous influences such as inert or living pathogens, and could also provide an environment that is less chronically stressful, or may at least contribute to buffer stressors occurring elsewhere. In recent years, the increase in life expectancy in the UK, the USA and other high-income nations has begun to stall. While it is difficult to make explicit causal links between the austerity policies implemented and this decrease in life expectancy, it is not surprising to those of us who work on health inequalities.

Simply put, if material capabilities are channelled towards those most in need in our society, namely children and young people living in socioeconomic disadvantage, this will facilitate and relieve their exposure to exogenous and endogenous factors that are bad for health all across the life course.

Knowledge gaps

The research discussed here shows that we have certainly moved beyond ‘blaming’ health inequalities on the health behaviours of disadvantaged populations. However, we are only beginning to understand how these social-to-biological processes work, and to what extent they are different or similar across human environmental contexts. There are a few areas where big gaps remain in our knowledge.

- When, in life-course and human-developmental terms, do biological processes start to be socially differentiated?
- Does the type of socially driven stressor lead to a specific type of biological response?
- What are the important resiliency factors allowing us to cope with social exposures: socioeconomic, community/neighbourhood, relational, educational?
- To what extent are sociocultural factors across different human societies involved in social-to-biological processes?
- Are social-to-biological processes transmitted across generations, and how?
- What are the causal relationships between biological markers of social conditions and health?

How can we move towards filling these gaps? In some cases, this will involve new research where specific efforts are made to improve our measurements and collect new data. For example, the way we currently measure and define stressors usually involves using survey methods measuring perceived stress or external events deemed to be stressful. If we were to examine these measures in relation to biological measures of stress (for example, through measuring the methylation levels of certain gene receptors), we may be able to get to grips with what our survey methods are measuring from a biological perspective. This would improve our knowledge about the measures.

We also need repeated biological measures over time from childhood to understand life-course social-to-biological shifts. In other cases, we have vast amounts of data and rich datasets at our disposal to examine many of the gaps. For example, resilience and sociocultural factors can already be examined with today’s data. This would involve going back to concepts and theories to develop appropriate measures with existing data and analysing them. Furthermore, a diversity of analytical approaches should be embraced from across disciplines, including economics, sociology and epidemiology, where both descriptive and causal inference analyses provide a new angle with which to unpick complex life-course processes.

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