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Embodiment of early social adversity: the role of allostatic load in a life course perspective

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# Abstract

**Introduction**. The notion of embodiment proposes that every human being is both a social and a biological organism that incorporates the world in which (s)he lives. It has been hypothesized that early life socioeconomic position (SEP) can be biologically embedded, potentially leading to the production of health inequalities across population groups. Allostatic load (AL) is a concept that intends to capture the overall physiological wear-and-tear of the body triggered by the repeated activation of compensatory physiological mechanisms as a response to chronic stress. AL could allow a better understanding of the potential biological pathways playing a role in the construction of the social gradient in adult health.

**Objective**. To explore the biological embedding hypothesis, we examined the mediating pathways between early SEP and early adverse psychosocial experiences and higher AL at 44 years. We also confronted an AL index with a latent multidimensional and integrative measure of health status at 50y.

**Methods**. Data are from the 1958 British birth cohort (n=18 000) follow-up to age 50. AL was operationalized using data from the biomedical survey collected at age 44 on 14 parameters representing the neuroendocrine, metabolic, immune-inflammatory and cardiovascular systems.

**Results**. Overall, our results suggest that AL could be a suitable index to partially capture the biological dimensions of embodiment processes.

**Discussion**. Understanding how human environments affect our health by 'getting under the skin' and penetrating the cells, organs and physiological systems of our bodies is a key tenet in public health research. Promoting the collection of biological markers in large representative and prospective studies is crucial to continue to investigate on this topic. Replication studies could be part of the future research perspectives, to compare with other cultural context and to observe if an AL index can be 'universal'.

**Keywords**. allostatic load; embodiment; biological embedding; adverse childhood experiences; socioeconomic position; cohort study, social inequalities in health.

# Résumé

**Introduction.** La notion d'« embodiment » propose que chaque humain est à la fois un être social ainsi que biologique, intégrant le monde dans lequel il/elle vit. Nous faisons l'hypothèse que la position socioéconomique pendant l'enfance peut être biologiquement incorporée, conduisant à la production des inégalités sociales de santé entre les sous-groupes de population. La charge allostatique (CA) est un concept qui tente de capturer l'usure physiologique globale du corps liée à l'activation répétée des mécanismes physiologiques compensatoires en cas d'exposition à des stress chroniques. La CA pourrait permettre une meilleure compréhension des voies biologiques qui jouent un rôle potentiel dans la construction du gradient social de santé des adultes.

**Objectif**. Pour explorer l'hypothèse d'incorporation biologique, nous avons examiné les voies de médiation entre les adversités psychosociales et la position socioéconomique précoces et la CA à 44 ans. Nous avons également confronté l'indice de CA à une mesure multidimensionnelle de santé latente à 50 ans.

**Méthodes**. Les données sont issues de la cohorte Britannique de naissance de 1958 (n=18 000). La CA a été construite avec les données de l'enquête biomédicale conduite à 44 ans, comme une mesure physiologique synthétique, multi-système, à l'aide de 14 biomarqueurs représentant les systèmes neuroendocrinien, métabolique, immunitaire / inflammatoire et cardiorespiratoire.

**Résultats**. L'ensemble de nos résultats suggèrent que la CA pourrait être un indice approprié pour capturer partiellement la dimension biologique des processus d'embodiment.

**Discussion**. Comprendre comment l'environnement affecte notre santé en se « glissant sous la peau » et pénétrant dans les cellules, les organes et les systèmes physiologiques de notre corps est un principe clé dans la recherche en santé publique. Promouvoir le recueil de marqueurs biologiques dans des grandes études prospectives et représentatives est crucial pour continuer la recherche sur ce sujet. Les études de réplication pourraient faire partie des futures perspectives de recherche, pour comparer entre populations avec des contextes culturels différents pour observer si un index de CA peut être considéré comme «universel ».

**Mots clés**. charge allostatique ; embodiment ; incorporation biologique ; position socioéconomique ; étude de cohorte ; inégalités sociales de santé.

# List of abbreviations

| | |
|---|---|
| ACE | adverse childhood experiences |
| ACTH | adrenocorticotropic hormone |
| AL | allostatic load |
| ANS | autonomic nervous system |
| AVP | arginine vasopressin |
| BMI | body mass index |
| BSAG | Bristol social adjustment guide |
| CBG | corticosteroid binding globulin |
| CRF | corticosteroid releasing factor |
| CRP | C-reactive protein |
| DBP | diastolic blood pressure |
| DHEA-S | dehyrdroepiandrosterone sulphate |
| DNA | deoxyribonucleic acid |
| GR | glucocorticoid receptor |
| $HbA_{1c}$ | glycated haemoglobin |
| HDL | high-density lipoproteins |
| HPA | hypothalamic-pituitary-adrenal axis |
| HRQoL | health-related quality of life |
| IGE | immunoglobulin E |
| IGF-1 | insulin-like growth factor 1 |
| LDL | low-density lipoprotein |
| MAR | missing at random |
| ME | maternal education |
| MCAR | missing completely at random |
| MI | multiple imputation |
| MNAR | missing not at random |
| MR | mineralocorticoid |
| NCDS | national child development study |
| PCA | principal component analysis |
| PO | paternal occupation |
| PTSD | post-traumatic stress disorder |
| SAM | sympathic-adrenal-medullary axis |
| SBP | systolic blood pressure |
| SEBAS | social environment and biomarkers of aging study |
| SEP | socioeconomic position |
| SES | socioeconomic status |
| SNS | sympathetic nervous system |
| RGSC | registrar-general's social classes |
| UK | United Kingdom |
| USA | United States of America |
| WHO | World Health Organisation |

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# Foreword

This thesis stems from a continuing debate in epidemiological and biomedical research, about how the social world in which we live impacts our health. The health of populations reflects the social hierarchy and economic organization. To improve the health of populations we should systematically consider how the social world affects our daily lives. This is crucial for directing and giving a context to our research objectives, for a better implementation of effective public health interventions and for improving specific populations' health programs.

The expression of our genes, our cells, our organs, our physiology, and ultimately, our health, is influenced by the social strata. In this work we aimed to partially disentangle the mechanisms between the early social adversity, the biology, and later health, taking a life course framework.

We will start by a broad introduction, summarizing the global context in which we develop our research topic. In Part I, we will outline the theoretical framework, justification and rationale of our research question. We will describe some common notions comprised in our work. We will cover the concepts and empirical evidence related to the social gradient in health across populations, the life course framework, and we will focus on the role of early life in the genesis of health inequalities. We will introduce the hypothesis of social-to-biological transitions, or social causation, focusing in particular on the notions of embodiment and biological embedding. Subsequently we will address the conceptual framework of stress, homeostasis, allostasis and allostatic load focusing on the empirical evidence suggesting that allostatic load may be a useful indicator to measure social-to-biological transitions.

In Part II we will review the general methodology used in this work, concentrating in some common pitfalls and challenges. We will introduce the National Child Development Study, and the general sample on which we work. We will focus on several statistical methods, such as mediation analysis, multiple imputation models, sensitivity analysis and the implementation of a life course approach.

In Part III we will focus on the context, methods, results and methodology permitting to explore the question of the social determinants of allostatic load. We will present the findings of our first study investigating the psychosocial determinants of allostatic load. We will subsequently

introduce the findings of our second study aiming to disentangle the pathways by which early socioeconomic determinants influence allostatic load over the life course.

In Part IV we will concentrate on the question of allostatic load as a predictor of later health. We will investigate whether an index of allostatic load is linked with an overall measure of health. We will present the specific context and methodology used, as well as the main findings and conclusions.

In Part V we will discuss the general findings with regards to existing epidemiological research, to finally conclude with the future research perspectives.

*"It is the same cause that wears out our bodies and our clothes"*

*« C'est la même cause qui use nos corps et nos vêtements »*

*"Es la misma causa la que desgasta nuestros cuerpos y nuestra ropa"*

Bertolt Brecht

# PART I

# INTRODUCTION

# Résumé - Partie I

Les différences d'état de santé entre les groupes socio-économiques continuent de défier la recherche épidémiologique. Reconnues comme étant systématiques, socialement produites, modifiables et injustes, les inégalités sociales de santé (ISS) se retrouvent un large éventail d'indicateurs de la santé et de facteurs de risque pour la santé.

Des données empiriques ont montré l'existence et la persistance des ISS, historiquement et mondialement. La lutte contre les ISS à l'âge adulte peut être considérée comme une mesure d'urgence, et, pour être efficace, pourrait passer par l''identification des déterminants de la santé dès la petite enfance, afin de prévenir l'apparition des ISS.

Une littérature croissante suggère en effet que l'environnement (social, biologique, chimique, etc.) dans lequel nous grandissons peut être «incorporé» biologiquement, ce qui peut conduire à un moindre état de santé en cas d'exposition à un environnement défavorable. Selon Nancy Krieger, la notion d' « embodiment » se réfère à la façon dont les humains, comme tout organisme vivant, incorporent littéralement, biologiquement, le monde dans lequel ils vivent, y compris les circonstances sociales et écologiques. La charge allostatique (CA) est un concept qui tente de capturer l'usure physiologique globale du corps liée à l'activation répétée des mécanismes physiologiques compensatoires en cas d'exposition à des stress chroniques. La CA pourrait permettre d'approcher en partie ce phénomène d'incorporation biologique de l'environnement, notamment social, et ainsi permettre une meilleure compréhension des voies biologiques potentiellement impliquées dans la construction du gradient social de santé des adultes.

Dans cette thèse, nous définissons l'environnement social comme les éléments et les expositions résultant de la structure sociale, y compris les structures organisationnelles de la communauté, du quartier et la dynamique familiale, les hiérarchies de dominance, ainsi que les comportements, les réseaux sociaux, l'origine ethnique, la classe sociale et les conditions de logement.

Nous nous concentrons également sur trois voies principales qui explicitent comment l'environnement social peut devenir biologique : la voie matérielle / financière; la voie liée aux comportements à risque, et la voie psychosociale. Nous avons choisi ces voies à partir de données épidémiologiques et d'études empiriques suggérant un lien entre la position socioéconomique (SEP) et chaque chemin. Il a ainsi été suggéré que la santé est le résultat d'une accumulation d'expériences et d'expositions en lien avec le monde matériel. Les expositions biologiques (virus, bactéries) et les risques chimiques, sont plus fréquents dans les maisons et les quartiers moins favorisés, et dans certains statuts professionnels. Une relation inverse entre la position sociale (PS) et les comportements de santé à risque est par ailleurs largement démontrée dans la recherche empirique. L'adoption de comportements de santé peut être expliquée par des processus psychologiques complexes (par exemple l'autorégulation, auto-efficacité, le locus de contrôle) ou encore des explications en lien avec les normes, la tradition et les coutumes, qui dépendent des caractéristiques sociales. Enfin des recherches antérieures suggèrent que la PS peut influencer la santé à travers la perception qu'ont les individus de leur position dans la hiérarchie sociale. Ces perceptions peuvent produire des émotions négatives débuchant sur une moins bonne santé, via des mécanismes psycho-neuroendocrines liés aux systèmes physiologiques de réponse au stress.

Pour répondre à notre question de recherche, nous avons utilisé l'approche biographique, qui nous permet de prendre en compte ces différentes voies tout au long de la vie. En outre, il permet d'étudier les relations entre les expositions sociales, les réponses biologiques et les maladies à différents stades de développement de la vie. Une étape du développement humain qui semble être particulièrement importante lorsque l'on étudie les origines des inégalités de santé est la vie précoce (enfance, adolescence et jeune adulte).

De nombreux résultats suggèrent que l'organisme est sensible aux expositions environnementales, et cette sensibilité varie au cours de la vie. Le début de la vie, l'enfance et l'adolescence semblent être des moments particulièrement importants, sensibles aux demandes environnementales. Cette adaptation durant ces phases précoces de vie peut avoir des conséquences à long terme sur la santé. Un corps convergent de recherche de divers domaines tels que la neurobiologie et de l'épidémiologie, montrent qu'un stress chronique durant l'enfance peut affecter l'axe hypothalamo-hypophysaire (HPA), déclenchant une cascade de réactions impliqués dans l'inflammation, les réponses immunitaires, et ayant un impact au niveau des structures cérébrales et des fonctions neuronales. Cependant, pour l'étude d'autres périodes de la vie, comme à l'âge adulte ou chez les sujets âgés, les résultats restent peu concluants, et les études sont souvent contradictoires. Ces résultats posent des questions méthodologiques et théoriques intéressantes, dévoilant la nécessité d'une approche biographique pour analyser les effets à long terme d'un stress chronique sur la santé. La plupart des études sur la vie précoce fournissent des évidences importantes qui donnent une plausibilité biologique à l'hypothèse d'une incorporation biologique des expériences sociales précoces.

La charge allostatique (CA) pourrait être une mesure appropriée pour capturer partiellement la dimension biologique des processus d'incorporation biologique au cours de la vie de l'environnement social. Toutefois, deux conditions principales doivent être remplies. Premièrement, la CA doit être socialement déterminée ; et deuxièmement, la CA doit être un bon prédicteur de la santé ultérieure.

Pour explorer l'hypothèse que l'adversité psychosociale est une source de stress chronique, l'étude du lien entre les facteurs psychosociaux précoces et la CA est une étape centrale. Cependant cela n'a pas été encore étudié dans des recherches antérieures.

Les preuves suggèrent que la CA est socialement déterminée. Cependant, certaines questions restent mal comprises. Il n'est ainsi pas encore établi si différents déterminants sociaux durant la petite enfance jouent un rôle distinct sur la CA. Plus précisément, il n'est pas bien établi par quelles voies et mécanismes les déterminants sociaux pourraient agir sur la CA.

# Chapter I

# Social inequalities in health

In this chapter we provide a perspective on the topic of social inequalities in health. We will review the main developments on this theme, paying special attention to findings and hypothesis from epidemiological studies.

In section 1 we will lay out the main tenets of what we refer to as 'health inequalities'. One central focus in this section is the epidemiological evidence establishing the existence of a health gradient across populations and context, as well as the remaining theoretical and methodological challenges.

In section 2 we will present a contextual analysis of the notions of environments and exposures, to locate our research scope within this specific framework.

In section 3 we will propose the utility of using a life course framework to partially address some of these methodological questions raised from the study of health inequalities. We summarize the principles and models developed within the life course perspective from sociology to epidemiological studies.

Finally, in section 4 we will emphasise our approach on early life, as a developmental stage being described as a central phase for reaching our 'optimal' health potentiality. It has thus been proposed as an important moment in life for understanding health-diseases processes and for developing better adapted public health priorities.

## 1. The social gradient in health across populations

The differences in health status or in the distribution of health determinants between socioeconomic groups (World Health Organization) continue to challenge epidemiological research. Recognized as being systematic, socially produced, modifiable and unfair (Whitehead & Dahlgren, 2006), the social gradient in health affects a broad range of health indicators from risk factors to health outcomes; and as Hertzman noted,

> *"it is capable of replicating itself on new disease processes as they emerge in society"* (Hertzman, 1999).

Health status, usually measured by morbidity and mortality, follows a socioeconomic gradient in the large majority of the world's countries. Individuals in the bottom of social hierarchy are those who are more likely to experience unhealthy lives compared to those on the middle, and they in turn, have worse health than those at the top (Marmot et al., 2008). Hence, the social gradient is a continuous phenomenon that runs right across the social strata (Marmot & Wilkinson, 1999). On average, the lower one's socioeconomic position is, the worse one's health is. Here we are not interested in comparing extremes: the most precarious *versus* the most well-off. Therefore, we do not oppose the most disadvantaged groups, on extreme social and medical insecurity, against the rest of the population (Krieger, 2001).

Social inequalities in health are often described using the gradient observed according to socioeconomic characteristics of individuals, principally, education, social class and income (Galobardes et al., 2006a, b). With the publication of the Black Report 1980 in the United Kingdom, health inequalities were included in the public policy agenda. In the early XXI$^{th}$ century, health inequalities were recognized as a public health and research priority in western countries (Bartley, 2003a).

Here we define socioeconomic position (SEP) as

> "*an aggregate concept that includes both resource-based and prestige-based measures, as linked to both childhood and adult social class position. Resource-based measures refer to material and social resources and assets, including income, wealth, educational credentials; terms used to describe inadequate resources include 'poverty' and*

> *'deprivation'. Prestige-based measures refer to individual's rank or status in a social hierarchy, typically evaluated with reference to people's access to and consumption of goods, services, and knowledge, as linked to their occupational prestige, income, and education level*" (Krieger et al., 1997).

Differences in health status are generated within the social, economic and environmental spheres. Diseases related to 'free choices' and life style are systematically differentiated according to socioeconomic groups (Jarvis & Wardle, 1999). From this moment we will refer to 'social inequities', to incorporate the notion of unfairness and injustice (Whitehead & Dahlgren, 2006).

Empirical evidence has shown the existence and persistence of health inequities, historically and universally. Tackling health inequities in adulthood may be seen as an emergency measure, and might be less effective than identifying the health determinants from early life, to prevent inequities all over the life span (Wadsworth, 1999). According to Sen *et al*. good health with

> "*economic opportunities, political liberties, social powers, basic education, and the encouragement cultivation of initiatives*" are ways of promoting freedom, in both at the individual and at the society level (Sen, 2000).

Nowadays, health inequities continue to be widespread (Mackenbach et al., 2008). In Europe, most disadvantaged groups have worse health and higher mortality (for almost all the causes of mortality) (Mackenbach et al., 2008). A concrete example comes from France, were at 35 years, a non-manual worker can expect to live another 34 years without disabilities. On the contrary, a manual worker can expect to live 24 years without disability. Furthermore, the manual worker will not reach the retirement age (60 years) without disabilities, while the non-manual worker will benefit of a 9-years disability-free retirement (Cambois et al., 2008). Another example is in Brazil, where researchers identified the change of socioeconomic inequities in nutrition and anthropometrics measures in a country going through nutritional transition using three birth cohorts, showing the double burden of malnutrition -underweight and overweight- in the underprivileged compared to the more privileged (Matijasevich et al., 2012).

As we will further explained in Chapter II, section 1 and 2, the social gradient in health results from the accumulation over the life course of three main determinants: those related to the biomedical background (e.g. health care, preventive medicine), those related with socioeconomic determinants classified into material circumstances (e.g. income, physical, chemical factors) and psychosocial factors (e.g. social support, organizational work, stress, adverse experiences, etc.) (Marmot, 1999), and those related with life styles (e.g. smoking, alcohol consumption).

However, recent literature suggests that classic determinants of non-communicable diseases -mainly behavioural- are insufficient for explaining the large disparities observed in morbidity and mortality (Carlson & Chamberlain, 2005; Gallo et al., 2012). Gallo and colleagues recently showed that differences concerning mortality in nine European countries would be reduced by 23% among men and 16% among women if lowest risk level was attributed to all individuals. In other terms, the authors attributed to all the risk correspondent to the highest socio-economic levels regarding tobacco, alcohol use, body mass index, fruit and vegetable consumption and physical activity (Gallo et al., 2012). Moreover, 29% of cardiovascular deaths in men and 34% in women would be avoided if everyone would have been exposed to the risk of those with the highest level of education.

Stringhini and colleagues studied the effect of health behaviours in the association between SEP and mortality, comparing two European cohorts. The authors showed that the inclusion of health behaviours (smoking, alcohol, fruit and vegetable consumption, and physical activity) attenuated the association between socioeconomic level and mortality by 75% in the British civil servants Whitehall II cohort. However, this reduction was only of 19% in the French GAZEL cohort consisting of employees from the French national gas and electricity company, Electricité de France-Gaz de France (EDF-GDF) (Stringhini et al., 2010a). This suggests that

> "*the causal chain leading from* [SEP] *to health behaviours to mortality was not played out in a similar manner in the two contexts because of major differences in the social patterning of unhealthy behaviours*" (Stringhini et al., 2011).

Hence, the role of health behaviours explaining the social gradient is variable across countries, and more importantly, they do not allow to elucidate the social inequities observed in mortality

risk. In that sense health behaviours can be seen more as a consequence of SEP differences, rather than an actual 'explanation' for them.

An individual's health is therefore determined by important elements within the social, material, psychosocial, etc., environment. In the next chapter, we will contextualize our research according to the social environment and the respective social exposures.

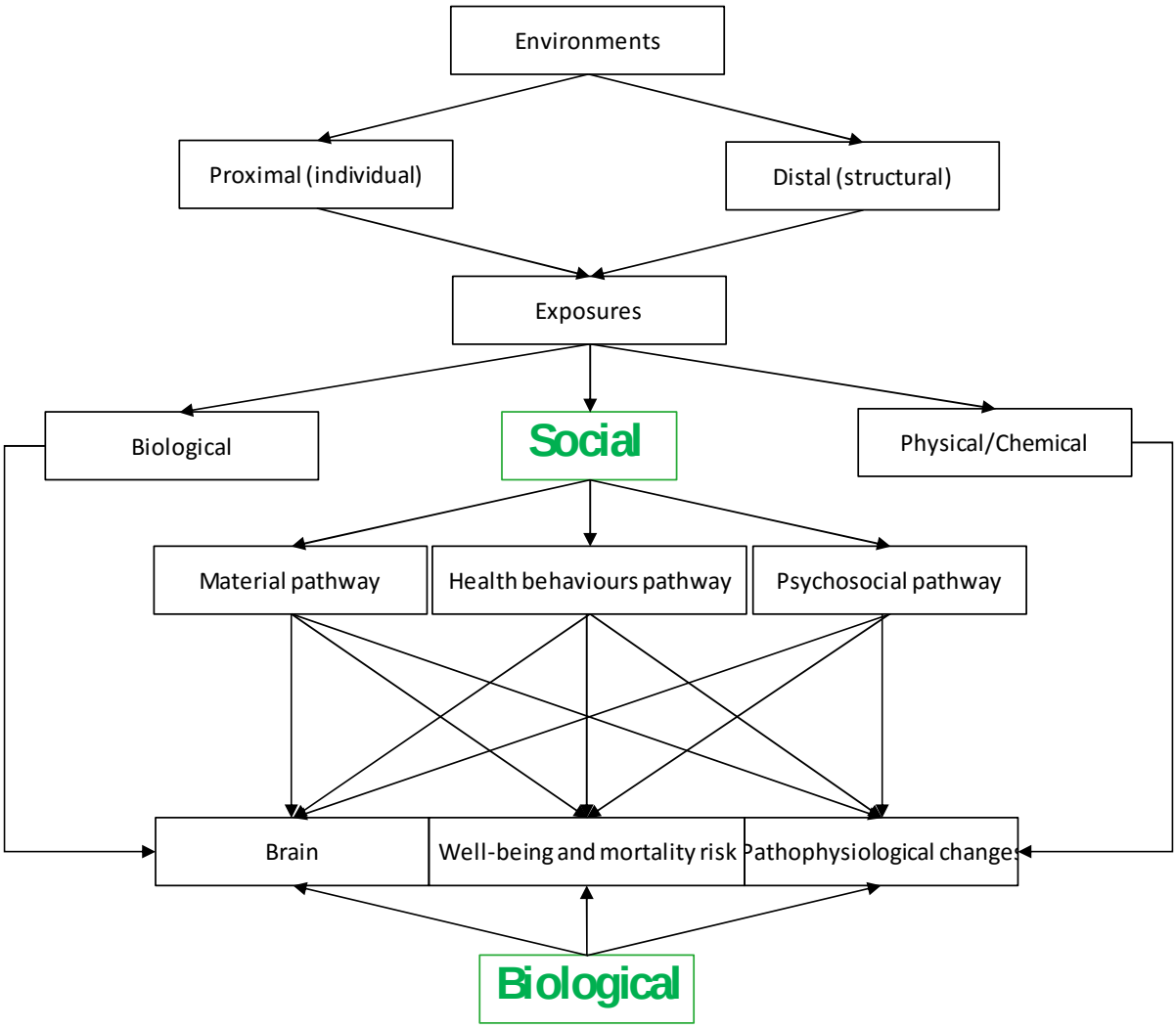
## 2. Environments and social exposures: a contextual analysis

There is a growing literature that argues that the environments in which we grow can be 'embodied'. Adverse exposures within the environment can result in poor physical and mental health, chronic diseases and a reduction in life expectancy (Krieger, 2005). We will pinpoint and define some terms to avoid to blend the distinction between what is social and what is biological as noted by Blane *et al*. (Blane et al., 2013), according to our hypothesis of social causation.

An individual will have numerous experiences within the environments in which s/he grows-up and will be continuously exposed throughout life –knowing that exposures may be harmful, neutral, or beneficial-. To illustrate, an individual will be exposed in subsequent concentric layers from the most proximal environments (at the individual level) to the most distal environments (at the structural level) (Figure 1). For clarity purposes, we do not show in the figure the potential link between each exposure or each pathway. Also, we do not make hypothesis regarding the hierarchical importance of exposures. For instance, we placed all three exposures as the same level (biological, social, chemical, physical) because we are focusing in this work only on social exposures.

For the purposes of this work we identified four concentric layers, we hypothesised that as groups of individuals, the more we move towards the outer distal layer, the less we are capable to control the 'forces' exerted by the structural level upon us (Figure 2.). This notion was coined by Durkheim's social facts theory. For Durkheim, the social facts have a coercive power. The social facts are imposed on individuals by the social rules, it is not the result of individual choices but rather of a combination of different elements such as social, economic, historical, geographical, political factors, etc. This combination imposes constraints to the individual. However, if the social fact is adequately 'internalized', the individual no longer feels these obligations as arduous or coercive (Durkheim, 1937).

Figure 1. Environments, social exposures and biological outcomes




This social constraint forces are based on informal rules (custom, tradition, moral, etc) and to transgress them is associated with a 'diffuse' sanction (ridiculous, collective disapproval, exclusion, etc.) (Durkheim, 1937). Based on this notion we illustrated the type of exposures we can be submitted to over the life course, highlighting the social pathways, which will be the focus on in this work Figure 2.

Figure 2 is inspired from Bronfenbrenner and shows the main exposures identified within each level (Bronfenbrenner, 1979), in our case, we are concentrating on social exposures, which we categorized into material, health behaviours and psychosocial (Blane et al., 2013).

Figure 2 illustrates the following four layers (Bronfenbrenner, 1979):

i) The individual (onto system according to Bronfenbrenner): Genetics, sex.

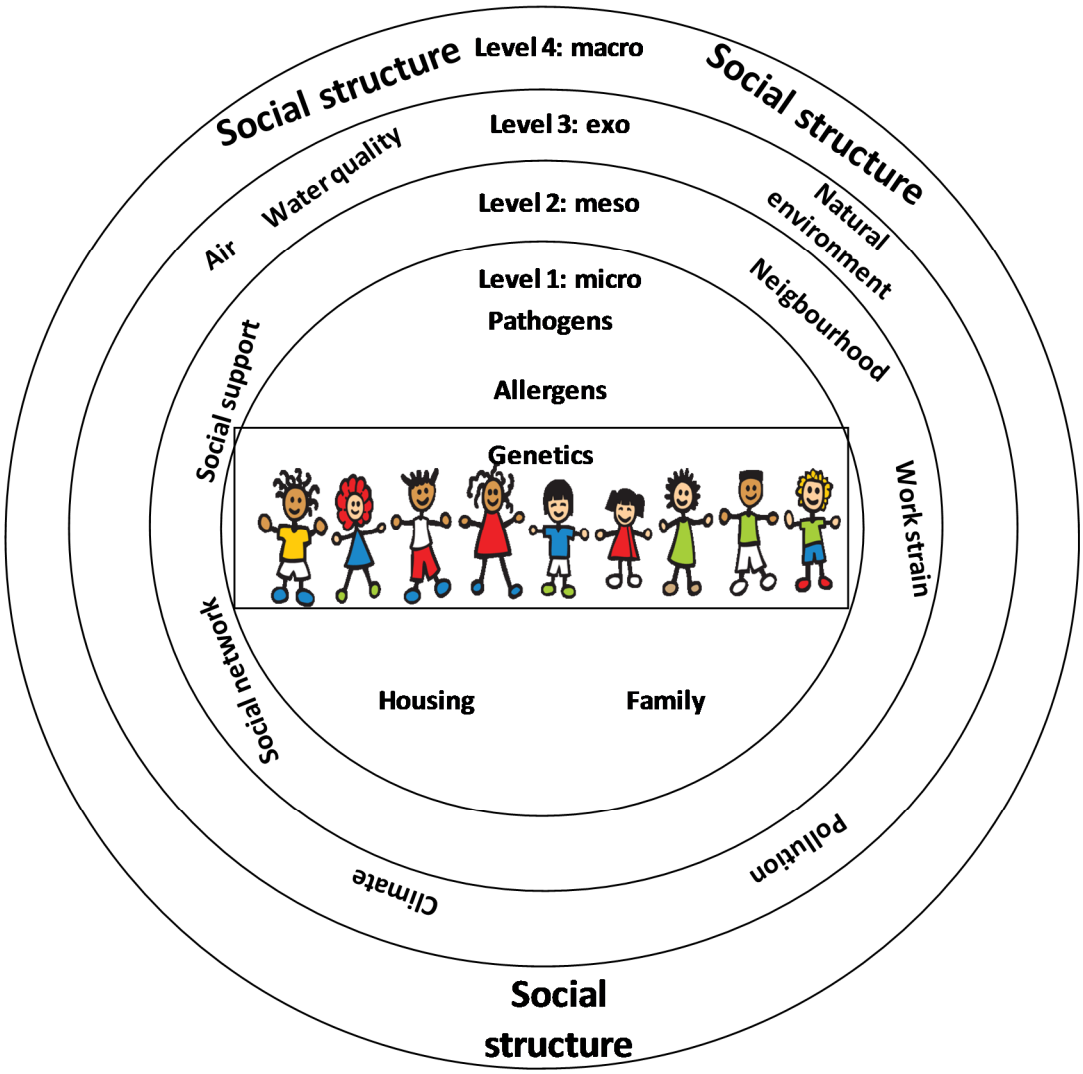
ii) Level 1 (micro system according to Bronfenbrenner): The individual level, represents an individual's proximal environment. We find biological exposures (pathogens: bacteria, viruses, allergens) and social exposures (socioeconomic exposures within the built environment like housing; and psychosocial exposures within the family circle, school, peers, etc).

iii) Level 2 (meso-system according to Bronfenbrenner): The neighbourhood, school and work level settings. We can identify once again the social exposures (socioeconomic exposures related to the neighbourhood conditions; psychosocial exposures due to social hierarchy and organisational work factors, work strain, social support and social network);

iv) Level 3 (exo-system according to Bronfenbrenner): we can identify the natural environment with chemical, biological and physical exposures (air quality, water quality, climate, weather, environment contaminants, etc.), the local government, local industry, etc.

v) Level 4 (macro-system according to Bronfenbrenner): Finally, in the most distal environment, the social structure, determining, constructing and socially patterning all the exposures an individual may be subject to, and the dominant beliefs and ideologies (coercive forces according to Durkheim) leaving a narrow room for manoeuvre. Within the social structure we can mention the exposures related to the social organisation and hierarchy, wealth distribution within a society, political context, cultural context, racism, discrimination, etc.

Figure 2. Concentric environments affecting populations' health inspired from (Bronfenbrenner 1979)




It is worth mentioning that regardless of the type of the exposure (e.g. chemical, biological), we consider them all socially patterned. Hence, the likelihood for some populations to be exposed to environmental challenges is not only greater, but also cumulative. This is why we are conceptualizing the 'social structure layer' as the final one, since the way individuals live and die according to social strata is indeed a biological, but also, a social justice issue.

Evidently, all the exposures interact with each other and a clear distinction between the proximal and distal environments is a complex task. For instance, even if we are classifying housing conditions within the proximal environment, because living in bad housing conditions will raise the probabilities of being exposed to biological hazards such as allergens, and other

pathogens; housing also depends on neighbourhood conditions and is manifestly a result of political and social priorities, from the structural social environment. In the same way, water quality could also been part of the proximal layer of exposures, since pathogens in drinking water could affect our health. However, having access to drinkable water is, in the most of the cases, a public policy issue.

The distinction between the proximal and the distal environment impacting health is important, essentially for the discussion of the most suitable intervention to prevent future disease development: at an individual level (e.g. medical treatment) or at a structural level (e.g. public policies). These diagrams attempt to locate our conceptual framework within the variety of environments and exposures, consistent with our social causation hypothesis (or causality chain). There is a broad literature that illustrates the organization of different environments, the most distinguished were the work of Bronfenbrenner in 1979 (Bronfenbrenner, 1979), Dahlgren & Whitehead in 1991 (Dahlgren & Whitehead, 1991), Susser & Susser in 1996 (Susser & Susser, 1996).

In summary, we define the social environment as the elements and exposures patterned according to social structure including populations' social context, community organizational structures, neighbourhood and family dynamics, dominance hierarchies (Hertzman & Boyce, 2010), as well as behaviours, social networks, ethnicity, social class, and housing conditions. We also recognize that these experiences *"may be subject to cognitive interpretation by the individual and vary according to context*" (Hertzman & Boyce, 2010).

We also illustrate the social causation hypothesis clarifying how the social environment may 'get under the skin':

i) the '**direct**' biological effect: impacting brain, physiology and ultimately determining well-being and mortality risk;
ii) the '**indirect**' hypothesis: explaining how socioeconomic circumstances potentially affect health, through health behaviours, occupational exposures (*via* physical, chemical), etc.

In this thesis we are focusing on three main pathways within the social environment that explicit how the social environment can become biological:

i) Materialist & financial pathway;

ii) Behavioural/life-styles pathway;

iii) Psychosocial pathway (equivalent to what Bartley called 'psychosocial', but also called 'interpersonal' by Blane and colleagues) (Blane et al., 2013).

The life course approach will allow us to take into account these pathways across the life span. A conceptual framework permitting to study the relationships between social exposures, biological responses and disease development in public health research was developed twenty years ago by Nancy Krieger in the ecosocial theory with the notion of embodiment, and by Clyde Hertzman with the notion of biological embedding. We will further explain this topic in Chapter II, section 2.

## 3. Life course approach, social inequities and health

*The Polish Peasant in Europe and America* published in 1918 to 1920 by William I. Thomas with collaboration of Florian Znaniecki, was a pioneer sociological study using what we would call today a life course perspective. The authors focused on the Polish immigrants, their families and their life conditions based on personal documents (e.g. autobiographies, life studies, letters, diaries), trying to integrate data analysis, the social context and the historical changes of country side. Thomas argued the need of a

> "*longitudinal approach to life history*" and to follow "*groups of individuals into the future, getting a continuous record of experiences as they occur*" (Elder et al., 2003).

Social scientists started to recognize the interest of studying groups of individuals life trajectories within the social structure when challenging social events occurred (Great Depression, World War II) (Elder et al., 2003).

Forsdahl investigated in the 1970s the role of poor living conditions during childhood in Norway to explain a higher risk of later cardiovascular disease (Forsdahl, 1977). He admitted the Darwin's theory of survival of the fittest within the individuals born in poor living conditions. Indeed the 'weaker' die at birth, however,

> "*the more fit survive and carry with them a life-long vulnerability because of the poor living conditions in early years*" (Forsdahl, 1977),

suggesting that a biological early effect and an accumulation of risk over the life course may be due to an early adverse living environment.

Blane *et al.* noted that the life course approach is the result of three strands of social and medical research (Blane et al., 2007). The first strand is biological 'programming'. In the 1990s David J. P. Barker *et al.* showed that prenatal growth predicted coronary heart diseases in adulthood (Barker, 2001). The authors suggested that poor nutrition or impairment during foetal development could 'permanently' affect organs grow and physiological systems leading to chronic diseases (Barker, 2002). The Barker's hypothesis of biological 'programming' *in utero* and infancy (Barker, 2001), will be discussed in more depth in Chapter I, section 4. The second strand relates with the accumulation of risk all over the life span. The third strand come from the health inequalities research, showing the social class differences in the prevalence of behavioural and other risk factors. These three mechanisms will be further explained in sections 3.1, 3.2 and 3.3.

Blane *et al.* mentioned that the social hierarchy is capable of structuring exposures to a range of behavioural and non-behavioural hazards,

> "*which are clustered cross-sectionally and accumulated longitudinally via advantage or disadvantage in various spheres of life*" (Blane et al., 2007).

The life course approach allows us to take into account a wider range of factors potentially impacting health. Thus, health is seen as a dynamic process that begins at conception and continues, following different paths, throughout life (Halfon et al., 2013). The need to disentangle the effects of differential exposures and experiences across life on subsequent health status have led to epidemiological studies based on a life course perspective. Life course studies demonstrate that an individual's health is the result of complex mechanisms combining genetics, lifestyle and the social and psychological environment acting from the youngest age. From a review of the life course approach in sociology and psychology, Alwin cited the Elder's five principles when it comes to life course approaches (Alwin, 2012):

i) The principle of lifespan development: human development and aging are lifelong processes;

ii) The principle of agency: individuals construct their own lives through the choices and actions they take within social structures (i.e. the opportunities and constraints of social arrangements) and historical circumstances;

iii) The principle of time and place: the lives of people are embedded and shaped by the historical times and places they experience over time;

iv) The principle of timing: the developmental consequences of events and transitions are conditional on their timing in people's lives;

v) The principle of linked lives: people's lives are lived interdependently and sociohistorical influences are expressed through networks of shared relationships (Elder, 1997).

More recently, the idea that the environment in which we grow-up and live can be 'embedded' throughout life started gaining strength with the work by Hertzman (Hertzman, 1999), Krieger (Krieger, 2005) and Kuh (Kuh et al., 2004a). The author's findings confirmed the need to describe how the social, cultural, and the psychological environment could 'get under the skin' influencing cells, organs and physiology. Three life course models have been suggested in biological and medical research:

i) Sensitive/critical periods, also called latent model;

ii) The accumulation model;

iii) The pathways model (Blane et al., 2007). For practical or public health priorities, latency and pathway models could be viewed as complementary to one another.

### 3.1. The critical/sensitive periods, or latent model

The critical period model suggests that during a phase of rapid development, a biological system is more sensitive to environmental exposures and to deviations from expected experiences - particularly *in utero* and early life- and have lasting effects on physiological functioning (Bruer, 2001). Hubel and Wiesel's experiments in the 1960s showed that kittens deprived of visual experience in one eye for six weeks after birth remained permanently blind of the deprived eye (Wiesel & Hubel, 1963). A critical period was therefore identified for the visual system in kittens: the brain 'expects' to be exposed to a visual input during a window of development, when the experience does not occur, the system is irreversibly damaged.

The **sensitive period** model refers to a longer moment in human development when a given experience will have important effects on the system in question during an specific timing, still allowing the system to adapt to later experiences and to reverse or modify the effect (Bailey et al., 2001).

According to Bruer, to establish a sensitive period, studies should demonstrate that

> "*an experience (or lack of it) during a given period in development has a more pronounced effect (positive or negative) on the organism than the exposure to that same experience at any other time during the organism's development*"(Bruer, 2001).

The vast literature on critical/sensitive periods suggests that it may exist a sensitive period for humans from gestation to three years after birth for certain systems (Bailey et al., 2001). A sensitive periods have been suggested for a first and a second language acquisition, as well as for the fundamental basis for social and emotional development (Bailey et al., 2001). It appears that for higher brain functions and socio-emotional behaviours the window of vulnerability may be longer, since the systems involved are more complex (Kelly-Irving, Mabile, et al., 2013).

The sensitive periods hypothesis underlie the notion of **neuroplasticity**, referring to

> "*the ability of the brain to be moulded by experiences or to remodel itself as a response to injury*" (Rutter, 2012)

Greenough and colleagues proposed a distinction between two types of brain plasticity; the **experience-expectant** with 'programming' effects; and the **experience-dependent** effects.

The experience-expectant refers to the periods of development that are contingent on the occurrence of experiences that are normally expected to be present (Rutter, 2012) (like the case of the visual system for kittens). Greenough and colleagues define it as a process

> "*designed to utilize the sort of environmental information that is ubiquitous and has been so throughout much of the evolutionary history of the species. Since the normal environment reliably provides all species members with certain experiences, such as seeing contrast borders, many mammalian species have evolved neural mechanisms that take*

> *advantage of such experiences to shape developing sensory and motor systems*"(Greenough et al., 1987).

The experience-dependent effects are those that allow the nervous systems to incorporate the environmental information when it becomes available. This means that some experiences do not have a critical or a sensitive period pattern, which allow our brain to be moulded according to experiences all over the life course. In other words, plasticity is present across the life course, however it may operate differently due to developmental processes. This means that humans are 'sensitive' to their environments, and this, across life. The brain is thus intrinsically plastic, and some learning experiences may be biologically embedded, not only during active brain growth (as for critical/sensitive periods) but all over the life span.

### 3.2. The pathways model

This model comes from the study of health inequities, characterized by a gradient producing health differences on morbidity and mortality according to social class. In this life course model, it is proposed that certain events occurring earlier in life may have pathways effect by setting a group of individuals in a particular life trajectory, influencing later opportunities, and exposures to health risk factors (Hertzman et al., 2001). Kuh and colleagues refer to 'social chains of risk' for explaining the early influences of childhood social conditions on later life experiences, impacting adult health (Kuh et al., 1997). These 'ongoing social processes' (Blane, 1999) or 'chain of risk', explains how an exposure will lead to another and impact body functions increasing disease risk (Kuh et al., 2004a). In practical terms, testing the pathways model empirically is difficult, since prospective studies are needed, with several time points data collections, permitting the continuous, lifelong operation of the pathway effects to be observed (Pollitt et al., 2005).

### 3.3. The accumulation model

This model proposes that long-term exposures across the life course can accumulate and have consequences on health. In practical terms, is difficult to disentangle this model from the pathways model. However, the accumulation model posits that an exposure may occur repeatedly over the life course, and it also may cluster with other concomitant exposures, cross-sectionally. In this model we 'add' the adverse events without following their sequence

and later influences. Hence, the impact of different life course events accumulate, but do not interact (Ben-Shlomo & Kuh, 2002). Concerning the study of the link between low socioeconomic position and non-communicable diseases, the accumulation model has been extensively used in empirical research (Gustafsson et al., 2014). Life course accumulation of socioeconomic disadvantage over life appears to cause cumulative damage to biological systems (Gustafsson et al., 2014). Galobardes *et al*. highlighted the accumulation processes concerning childhood socioeconomic circumstances. Children from low socioeconomic status could have lower birth weight, have poorer diets, be exposed to passive smoking, infectious diseases and so on (Galobardes et al., 2004).

In summary, as noted by Halfon and colleagues, the life course approach shows that (Halfon & Hochstein, 2002):

i) Health is a consequence of multiple determinants operating in nested genetic, biological, behavioural, social and economic contexts that changes a person develops.
ii) Health development is an adaptive process composed of multiple transactions between theses contexts and the biobehavioural regulatory systems that define human functions.
iii) Different health trajectories are the product of cumulative risk and protective factors and other influences that are programmed into biobehavioural regulatory systems during critical and sensitive periods.
iv) The timing and sequence of biological, psychological, cultural and historical events and experiences influence the health and development of both individuals and populations.

Critical/sensitive periods, pathways and accumulation models are intertwined, influence each other, are not mutually exclusive and may operate simultaneously (Kuh et al., 2004a). The life course framework allows to capture the sequence of psychosocial and material exposures, biological challenges and poor living conditions across the life course that could damage adult health (Koffijberg et al., 2012; Kuh et al., 2004b; Power & Hertzman, 1997).

Studying the origins of health inequities from early life and over the life span, remains a key tenet for public health priorities. In the mid-twentieth century were launched the first birth

cohort in western countries. It was until then that researchers could observe different life events potentially impacting health over the life course. With Barker's studies (Barker, 2002) that evolved throughout the hypothesis of foetal origins of adult disease, a special attention was given to early life. However it was rapidly acknowledge that risk factors accumulate and interact synergistically over the life course in very complex ways. Hence, for studying health inequities, the life course framework is particularly pertinent if we consider that health is a set of capabilities and resources, evolving throughout life, in a dynamic, complex and not–linear form.

## 4. Early life: comprehending biological and social processes of the genesis of health inequalities

Many studies have systematically documented the link between socioeconomic circumstances during childhood and later health during adulthood in both developed (Johnson & Schoeni, 2011; Maty et al., 2008; Osler et al., 2003; Pillas et al., 2014) and developing countries (Currie Janet & Vogl, 2013). Prenatal, childhood and adolescence appear to be important phases of human development for shaping the basis for later health (Wadsworth, 1999), well-being, and cognition; affecting later education and labour market success (Currie Janet & Vogl, 2013).

During childhood, the physiological systems and the brain are not fully mature (Juster et al., 2011a) and the developmental processes occurring, which may vary according to experience, can render children's physiological and cognitive functions more plastic and capable of adaptation (Kelly-Irving et al., 2013c). Childhood and adolescence are considered as developmental phases allowing experiences to 'get under the skin' (Kelly-Irving et al., 2013c). During this period, a number of experiences occur at specific times to attain an 'optimal' brain development. Early life has been described as a series of sensitive periods belonging to the domain of '**experience-expectant**' and '**experience dependant**' development, (see Chapter I, section 3.1) (Bailey et al., 2001). Thus, brain architecture is highly sensitive to environmental influences during early life, affecting health at this period, and all over the life span.

There are two main ways in which the socioeconomic factors from early life can affect adult health:

i) The '*biological chains of risk'* that involves the exposures suspected to be 'causal' factors during gestation, infancy, childhood, adolescence and early adulthood.

ii) The '*social chains of risk*', starting early in life but operating all over the life course and impacting in the long terms adult SEP (e.g. educational attainment), which influence the disease risk through hazard exposures to causal factors later in life (as we saw in the previous section 3.2) (Kuh et al., 1997).

Concerning the '*biological chain of risk'*, several researchers argue that these susceptibilities during early life relate to the rapid biological processes occurring during prenatal and infancy development. With Barker's model (Barker, 2002) of biological 'programming' in utero and infancy, it was emphasise the role of foetal undernutrition and body growth affecting later health. For Barker, the most important environmental factor determining health is undernutrition during pregnancy (Kuh & Davey-Smith, 1997). These studies contribute to the hypothesis of how an insult during a sensitive period of development can have lasting effects on the structure or function of the body. For instance, (De Boo & Harding, 2006) suggested that foetal nutrition leads to altered growth and maturation on foetal organs. This coupled to the permanent changes on the homeostatic regulation of the systems involved, will lead to increased risk of disease, especially if the individuals are later exposed to additionally nutritional stress (e.g. obesity). In this perspective, the notion of thrifty phenotype was also introduced

> "*in an attempt to explain the associations between poor foetal and infant growth and increased risk of developing impaired glucose tolerance and the metabolic syndrome in adult life*" (Hales & Barker, 2001).

The notion of 'programming' is also controversial for its 'deterministic' view, since it excludes the possibility of a later adaptation and plasticity. However this topic will not be reviewed here since it is beyond our scope.

Concerning the '*social chain of risk'*, and as we mentioned in the previous section 1, in most of studies investigating health inequities, health behaviours have not been found to explain all of the mortality differences. Lynch and colleagues studied the link between income and cardiovascular mortality in a population based study. For explaining the health inequities the authors took into account health behaviours, and additional psychological variables (e.g.

depression, hopelessness) and social risk factors (e.g. social connectedness, marital status) they could explain the mortality differences between the less well-off and the most well-off. This was important because it made evident the need of inclusion of psychosocial variables to better comprehend the health inequities observed (Lynch et al., 1996). Nevertheless, how can psychosocial circumstances affect health? One hypothesized mechanism linking early life and later disease relates to the biology of stress that we will further explored and define in Chapter II, section 2.

Bartley noted:

> "*In most of the psychosocial literature, the focus is on how feelings that arise because of inequality, domination or subordination may directly affect biological processes"* (Bartley, 2003a).

These finding are consistent with the literature indicating that repeated social insults in early life could program a 'defensive' phenotype (Miller et al., 2009). This phenotype will protect an individual by rapidly responding to mobilize energy, set immune and inflammatory systems to protect and adapt to difficult social environment conferring a survival advantage (Miller et al., 2009). However, this may have a cost for later health.

Being exposed to adverse social circumstances like crowding, material deprivation, social conflict, lack of social support, appear to alter stress response systems, impacting the **autonomic nervous system** (ANS), the **sympathetic system** and in turn the **Hypothalamo-Pituitary-Adrenal** (HPA) axis (this will be further explored in Chapter II, section 2). In addition, the biological conditions in utero appear to be linked to the mother's social factors and family circumstances, influencing mother's health before and during pregnancy. Pregnancy conditions are socially determined, such as life styles, smoking, and alcohol consumption; and they can impact foetal development (Wadsworth, 1999).

Concerning socio-emotional processes, attachment, or the establishment of a parent-infant bond at birth, appears to involve a sensitive period. An infant seems to need, for his/her emotional development an initial attachment relation with a consistent caregiver and a quality relationship of security. Attachment is important for human beings, since having a caregiver provides protection, assistance and support. It is also important for the development of psychosocial and psychological processes and contributes to stress management buffering the

secretion of stress hormones (Gunnar et al., 1996). Further details involving biological mechanisms linking social exposures in early life and later health will be treated in Chapter II, section 2.

In summary, early life is recognized as a window of vulnerability, but also of opportunity. During this period of life, an early form of socioeconomic gradient in health is set in place. A growing body of evidence points towards biological and social processes closely related, starting in early life and continuing across the life span. However, experiences can affect individuals differently. Over the life course a person is born, grows-up, works, and has social interactions with corresponding changes in cognition, emotional and physiological functions. Thus, to invest for children to achieve a better health during early life have important implications concerning population's future health, and therefore the society future potentiality.

Studies in animal models and humans have shown that the ability to adapt and embodying the environment in which we live can also continue in adulthood, even after brain development is completed. This reinforces the hypothesis that the embodiment of experiences is not limited to sensitive periods (Rutter, 2012). Regarding plasticity, these involve the '**experience-dependent**' brain plasticity mentioned before in section 3.1. It is clear, that the brain is intrinsically plastic throughout life, even if this plasticity is reduced with age (Rutter, 2012). Moreover, it appears that intense or sustained physiological activity could trigger existing molecular cascades for processes that underlie brain plasticity (Knudsen, 2004).

In conclusion, evidence of sensitive periods, mainly during early life, as a first window of opportunity for biological embedding is plentiful. However, the changes exerted during such periods are not necessarily fixed, immutable, or permanent. On the other hand, knowing that brain plasticity continues throughout adult life, even if it decreases with age, it is conceivable that health interventions could modify the environment where risk populations grow-up to prevent later disease. Hence, to comprehend biological and social causation is essential to contextualize the social-to-biological processes within the environment, where an individual will experience differential exposures throughout life.

# Chapter II

# Social-to-biological transitions: embodying health inequities over the life course

Two hypotheses have been mentioned for explaining social-to-biological transitions: a 'direct' hypothesis, also called biological 'programming', or biological chain of risk, explained in Chapter I; and the 'indirect' pathways, also called social chains of risk, that will be addressed in the present chapter.

In **section 1** we will mentioned the different social –'indirect'- pathways suspected to have an impact on health over the life course, identifying the psychosocial, material/financial, and health behaviours pathways. We will mentioned the specific epidemiological evidence suggesting a social causation between the social environment and later health.

Finally in **section 2** we will present the main epidemiologic thesis supporting the idea of social-to-biological transitions, based on the studies of Nancy Krieger and Clyde Hertzman. We will refer to the biology of stress and the stress response systems for explaining the main tenets regarding the also called 'biological chain of risk' or 'direct' hypothesis.

## 1. Proposed pathways between the early social environment and health: epidemiological evidence

According to Hertzman we can define health **pathways** as the

> "*experiences at one stage of life* [that] *influence the probability of others later in life, which then influence health and developmental outcomes*" (Hertzman & Boyce, 2010).

Several pathways have been proposed in epidemiological research to study the link between early social exposures and health across the life span [see (Bartley, 2003a; Blane et al., 2013)]. We will explore in this work three main indirect pathways: a health behaviours, a psychosocial, and a material/financial pathway.

## 1.1. Health behaviours pathway

The inverse relation between SEP and risky health behaviours have been largely demonstrated in empirical research (Lacey et al., 2011; Stringhini et al., 2011; Stringhini et al., 2010b). In the UK, the more a group of individuals is deprived, the greater is their likelihood of adopting unhealthy diets, smoking, being obese, to have a sedentary life style, and to drink heavily (Jarvis & Wardle, 1999). However the underlying causal mechanisms of such relationships remain misunderstood. Principally, since health behaviours involve more than the inability to purchase goods and services (Pampel et al., 2010). Bartley summarized the complex and wide theoretical elements that could clarify the association between SEP and health behaviours (Bartley, 2003b). Here we will highlighted the main explanations, and for further reading and details, please consult (Bartley, 2003b).

One explanation linking lifestyles and health is the 'direct' behavioural model, proposing that the adoption of health behaviours is due to personal capacities, assuming that people with lower SEP and worse occupational status are less endowed with some characteristics, such as, coping skills, psychological characteristics –e.g. locus of control-, etc. For instance, according to this theory, a person with internal locus-of-control, has 'the control of his/her life', and will reach the best positions in the social structure. A person with high self-control will, according to this theory, not adopt risky health behaviours. However, there is no evidence supporting this theory, and when tested, it has been showed that psychological characteristics are not as strong as material factors predicting health behaviours [(Bartley, 2003b), p.66) .

A second explanation relates to social norms, tradition, values, moral, laws and customs. In other terms, health behaviours are cultural and vary within a community social standards (Bartley, 2003a). Here we apply the Bourdieu's notion of habitus underlined by Bartley (p.69):

> "*as a collection of learned behaviours that are shaped by exposure to a certain social environment over the life course*".

The Bourdieu's idea of habitus highlights that people capture the 'common' behaviours s/he is use to see in her/his social environment. A child will therefore acquire some disposition toward a set of behaviours. In the case of high educated families, were 'good' behaviours are more frequent, children will reproduce these 'good' behaviours (p.70-71). Additionally, children from wealthy families are more likely to stay in the same advantage social position, which have some

habitus that include healthier life-styles. *Vice versa*, individuals from less educated background will also integrate the behaviours of his/her group, which, with regard to health –at least in western countries-, are to their disadvantage. Thus to engage in risky health behaviours is not a result of better cognitive performances, intelligence, or better psychological capacities.

(Bourdieu, 1984) also suggested the social distinction hypothesis (Bartley 2003 p.72-73). Health behaviours could be the result of an 'effort' one makes to resemble individuals in one's same social group. Thus, life-styles such as smoking, alcohol or diet are similar to clothes, books, music and fashion, a way of maintaining social distinction from other social groups. Bartley mentioned:

> "*Social differences in the adoption of healthy lifestyle do not have to be a result of explicit beliefs about health itself. As we have seen in the context of education, they may simply be part of what is viewed as appropriate behaviours for 'people like us' "* (p.73).

In epidemiology there are few studies investigating this hypothesis, mainly because the lack of measures of SEP based on social and friendship choices, like the Cambridge scale.

The cultural shift hypothesis, introduced by the studies of Kunst and colleagues when comparing European countries in terms of health inequities. They found greater health inequities in mortality and cardiovascular diseases in northern countries, which are *a priori* more socially equal, (Norway, Sweden) compared to southern countries (Italy, Portugal).

> Kunst is: "*The small* [social] *mortality differences in southern Europe are probably related to small or absent social gradients in several risk factors for ischaemic heart disease, including tobacco consumption and dietary factors. The southern European situation can further be understood in terms of 'delayed transition': the transition from positive to inverse gradients in ischaemic heart disease mortality, which occurred in the United States in the 1950s and in northern Europe in the 1960s, occurred in southern Europe in the 1980s or even later. This transition, and its slow diffusion to southern Europe, seems to be conditioned by cultural rather than socio-economic circumstances"* (Kunst, 1997).

An interesting comparative example is breastfeeding in Brazil and Europe. In western countries 30 years ago, long term breastfeeding was a behaviour more common among low SEP women, while high SEP women preferred not to breast feed. However, breastfeeding is nowadays a behaviour more common in well-off women. The evolution of breastfeeding in Brazil has shown that less well-off women are starting to breastfeed less on the first month of life than their counterpart, however, after twelve month of life is the disadvantage mothers that continue to breastfeed compared to the most advantaged one (Victora & Barros, 2006; Victora et al., 2008). This highlights an epidemiological transition in cultural trends.

Further research to comprehend the link between the social 'coercive pressures' on lifestyles is needed. However, it appears that the accumulation of social disadvantage over life could contribute to adopt risky behaviours, impacting physiological functioning (Adler & Stewart, 2010; Stringhini et al., 2011).

Finally, the self-regulation, or 'positive feedback' hypothesis was highlighted by Bartley (p.71) based on the studies of Siegrist, which encompasses some psychosocial elements. This work proposes that the social support find at work, the family circle, etc., will improve some characteristics like self-esteem and social acceptance. These personal psychological characteristics will create 'positive signals' on the shape of chemicals affecting the brain (such as serotonin). Siegrist explains that when a social component disappears –losing your job or divorcing- a source of self-regulation is removed and this

> "*may increase her or his susceptibility to adaptive breakdown. It may also reinforce a person's propensity to addictive behaviours as a means of compensating for unsuccessful self-regulation. Threats to core social roles and loss of roles are to be expected more frequently among people living in less favourable social circumstances, as defined, for example, by low socio-economic status, ethnic minority status, or residential segregation*" (Siegrist, 2000).

In this sense, it has been shown that health behaviours can result from early life adverse psychosocial exposures. Smoking and alcohol consumption, appear to be more likely in individuals who reported been exposed to adverse psychosocial experiences during childhood. The Adverse Childhood Study (ACE) explored the link between childhood trauma to long-term

effects on health *via* health risk behaviours such as alcohol consumption, smoking, and sexual behaviours, among others (Dube et al., 2002; Ford et al., 2011). Felitti et al. suggested that ACE could be a common pathway to social, emotional, and cognitive impairments that may lead to increased risky behaviours (Felitti, 2002).

### 1.2. Psychosocial pathway

As we mentioned in Chapter I, section 1, the gradient observed in mortality in the studies of health inequities is not entirely explained after adjustment for health behaviours (Stringhini et al., 2011). With the studies by Marmot and Wilkinson (Marmot & Wilkinson, 1999), one of the hypothesis that could partly explain the health differences relates to the psychosocial pathway. Researchers have extensively studied the mechanism between adverse psychosocial exposures and biological reactions. As mentioned by Upton:

> "*Social factors include general factors at the level of human society concerned with social structure and social processes that impinge on the individual. Psychological factors include individual-level processes and meanings that influence mental states*" (Upton, 2013).

Psychosocial is defined here as

> "*the interaction between people and their social environment involving psychological processes*" (Egan et al., 2008) or "*pertaining to the influence of social factors on an individual's mind or behaviour, and to the interrelation between of behavioural and social factors*" (Oxford English Dictionary).

Though we include in the psychosocial factors social support, loneliness, marriage status, social disruption, bereavement, work environment, social status, social integration (Upton, 2013), balance between efforts and rewards, balance between home and work (Bartley, 2003a), etc.

Epidemiological studies have integrated the notion of psychosocial factors in the 1990's. Siegrist puts forward the theory of effort-reward imbalance at work, proposed to assess adverse health effects of stressful experience at work (Siegrist, 1996), integrating the behavioural and psychosocial approaches. For Siegrist, as we already mentioned, the way

psychosocial exposures relate to later health is explained by changes on the brain chemicals, causing individual's to adopt risky health behaviours (Bartley, 2003c; Siegrist, 2000).

Another approach explaining how psychosocial factors may affect health is the direct impact on physiological processes, mainly during sensitive periods of life. The direct psychosocial explanation was born from the evolutionary theories of physiological reactions from an external threat. In this work we will call the external threat 'stressor' and the physiological reaction 'stress'.

Stress has been famously defined by Selye (1936) as

> "*a non-specific response of the body to any demand for change*" (The American Institute of Stress)

and deserves to be conceptually distinguished from a '**stressor**' which can be any condition or factor inducing a response. Here, we describe the physiological nature of stress, however, psychological processes are implicitly involved, which will be discussed below. Examples of stressor can include biological stressors (e.g. under/over nutrition) or social stressors (e.g. maltreatment, social isolation). Here we utilize an integrative approach that defines **stress**

> "*as a process that entails a stimuli, appraisal of it, and a response*" (Miller et al., 2011).

When an stimuli (better known as stressor) is evaluated as a threat, triggers a cascade of behavioural and biological adjustments called responses (Miller et al., 2011).

This physiological reactions combine responses of the Hypothalamic Pituitary Adrenal Axis (HPA), the central nervous system (CNS), the autonomic nervous system (ANS), and the sympathetic nervous system (SNS). We will further discuss this topic in Chapter II, section 2. For the moment, we will mentioned the epidemiological evidence suggesting a link between adverse psychosocial exposures during early life and later health.

Effects on health after exposure to psychosocial stressors is well described in literature. After the end of Nicolae Ceauşescu's regime in Romania in 1989, Rutter led the *English and Romanian Adoptees* (ERA) *Study Team* showing the profound effects of early physical and social deprivation on psychological and physiological development (Rutter et al., 2004). Among Rutter's research topics was his extended interest in maternal attachment theory. It appeared

that the establishment of a parent-infant bond at birth, as we mentioned in Chapter I, section 4, involved a sensitive period (Bailey et al., 2001).

The link between psychosocial factors and health has been investigated by the Adverse Childhood Study (ACE study). Felitti *et al*. examined in the 1990s a variety of psychosocial stressors during sensitive periods of development and their impact on later health .The authors proposed that exposure to maltreatment, child abuse, physical and emotional neglect can produce stress responses and, in the long term, impact adult health (Anda et al., 2006). Several studies suggested that exposure to chronic stress during sensitive periods of development may alter the maturation and responsiveness of physiological systems and have long-term effects on health (Ganzel & Morris, 2011; Hertzman, 1999, 2012). Early life exposure to trauma, abuse or maltreatment in childhood has been linked to alterations of the brain structure and the neurobiological stress response systems which may have long term consequences for health and emotional well-being (Anda et al., 2006; Felitti, 2002). Exposure to ACE could influence health through a broad range of behavioural, socioeconomic and physiological mechanisms (Felitti et al., 1998; Gustafsson et al., 2012; Kelly-Irving et al., 2013a; Kelly-Irving et al., 2013b). Longitudinal studies have found a relationship between ACE and cancer risk, behaviours, cardiovascular disease and mortality (Slopen et al., 2013).

Given this evidence, epidemiologists speculate that there might be a causal pathway by which stressful social circumstances, causing emotional and biological responses, may 'get under the skin', increasing the risk of later disease. However, to test the psychosocial pathways and its effects on biology is a complex task, mainly since ideally this requires blood sample collection on large number of study participants in representative prospective cohort studies.

### 1.3. Materialist/financial pathway

Researchers have consistently documented the link between low SEP and higher rates of later disease, disability, and mortality compared to their higher SEP counterpart (Adler et al., 1994). To measure the 'material' risk in epidemiological studies, income, household facilities, perceived financial insecurity, are frequently used. Evidently, having more money do not give a direct plausible causal pathway regarding health. The materialist path relates to the fact that people from more deprived background have more risk of health-damaging exposures in their everyday lives.

Lynch and colleagues suggested that health is the result of an accumulation of experiences and exposures due to the material world (Lynch et al., 2000). Biological (viruses, bacteria) and chemical hazards, are more likely in more deprived homes and neighbourhoods, and in some occupational statuses. The material/financial pathway plays an important role in health since it relates with material leaving standards, and toxic occupational and neighbourhood exposures (Bartley et al., 1996; Galobardes et al., 2006a).

### 1.4. SEP: connecting the behavioural, psychosocial and material pathways

As noted earlier in this chapter (Chapter I, section 2), most of the environmental exposures are socially patterned, it is not surprising that psychosocial adversity and health behaviours are not independent from the socioeconomic environment. Adler *et al.* in 1994 advanced several possible mechanisms linking SEP with health (Adler et al., 1994). The author proposed three main hypotheses: the spurious association, for not taking into account other possible explanations such as the underlying genetic factors; the drift hypothesis (or health selection), suggesting that the link reflects the influence of a prior disease state on SEP rather than SEP on disease; and finally the biological hypothesis hypothesizing that lower SEP can cause physical, mental and behavioural impairment, and increased the risk of cellular and genomic damage (Adler & Stewart, 2010). The first two hypothesis have already been largely studied, and both phenomenon unlikely explained the SEP-health relationship (see Marmot et al. 1984 (Marmot et al., 1984); Marmot et al. 1991 (Marmot et al., 1991), Blane et al. 1993 (Blane et al., 1993) for further details on this topic).

The third mechanism is biological, according to Adler and colleagues, suggests that SEP impacts biological functioning that in turn influence health (Adler et al., 1994). Low early life SEP might place individuals on a trajectory where they are more likely to experience psychosocial stress, being exposed to environmental hazard due to their material living standards or to engage in risky behaviours.

In summary, SEP relates to the material pathway by the financial component that could increase the risk of exposure to stressful and/or harmful situations relate to housing, work conditions, neighbourhood, etc. (toxins, allergens, overcrowding) (Gustafsson et al., 2012; Lannero et al., 2002; Robertson et al., 2015). SEP relates to behaviours by the group effect, the cultural and educational component, and also have a psychosocial explanation. The

psychosocial pathway is also determined by SEP. Individuals from higher SEP, enjoy of a better social standing, and thus, better social 'recognition'. Being in the highest social class allows individuals to enjoy a higher social network, with more social support compared to the most disadvantage. Another example is that parents from higher SEP may be likely to have certain parenting characteristics that ensures a 'safe' environment for the child (Danese et al., 2011; Fagundes et al., 2013; Miller et al., 2009). Parenting behaviours and the creation of a secure, warm social environment buffering stress responses, as well as the set-up of stress responses systems (Repetti et al., 2002; Shonkoff et al., 2012).

One particular dimension of SEP that we have not completely mentioned is education. According to Bourdieu education is closely linked to cultural capital (Bourdieu, 1979). It relates with health behaviours but also with, psychological resources such as coping resources, coping styles, self-esteem, self-efficacy providing advantages of the more educated (Dahl E., 1994). (Davey Smith et al., 1998) noted that education optimise the use of health services, the development of time preferences favourable to health maintenance, an increasing willingness to invest in human capital. In this sense, as a measure of SEP, education relates with the three pathways proposed between the social environment and health. Parental education may then influence educational outcomes in childhood. Hence, it is suggested that high educated parents may stimulate their children in a way that confers them with a greater adaptability to school or academic environments (Dubow et al., 2009; Kaplan G. A. et al., 2001).

What we propose here is a large conceptual framework, adapted to answer our research questions. To disentangle these pathways is probably impossible, however, to classify them and to propose differential mechanisms over the life course (or taking into account timing of exposures) allows us to explain that the social environment exerts an influence on all the three processes (behaviour, psychosocial and material). We do not seek to establish a hierarchy between them neither to hypothesised which path is the most important. However we can determine a 'timing priority', using the life course framework that will allow us to consider the notion of temporality, while taking a snapshot of an individual's life.

## 2. Can the social be embodied to become biological?

Social causation, or how social exposures become embedded and translated into disease, is complex. Hertzman *et al*. mentioned that social causation of disease involves several

characteristics, which differentiate it from the classic approach used for studying infectious diseases. Social causation is actually: nonlinear, nonspecific, iterative, involves everyday rather than exceptional exposures and implicates symbolic or semiotic processes (Hertzman & Boyce, 2010).

To take into account these characteristics, social epidemiologists use some theories and concepts to link the ecological and the biological integrity. The **ecosocial theory** aims to comprehend the social production of disease, taking additional insights of the evolutionary and developmental biology and ecology (Krieger, 2004).

Krieger *et al.* introduced this notion of disease distribution in 1994, defined as:

> "*one of the multilevel epidemiological frameworks that seek to integrate social and biological reasoning and a historical and ecological perspective so as to develop new insights into determinants of population distributions of disease and social inequalities in health. The central question for the theory is: 'Who and what is responsible for population patterns of health, disease, and well-being as manifested in social inequalities in health?' "* (Porta M, 2008).

The key constructs of the ecosocial theory include: embodiment; pathways to embodiment; cumulative interplay of exposure, susceptibility, and resistance across the life course; and agency and accountability (Krieger, 2004).

i) **embodiment** is a dynamic process that summarizes how our body becomes altered by our past experiences and is responding to the present, from how well we feel, down to the molecular modifications in our bodily structures. As Krieger noted, embodiment

> "*refers to how we, like any living organism, literally incorporate, biologically, the world in which we live, including our societal and ecological circumstances*" (Krieger, 2005);

ii) the pathways of embodiment involve multiple levels and mechanisms, and refer to the ways by which physical, chemical, biological, and social exposures interact

with an individual's bodies in context and following distinct trajectories according to the social hierarchy (e.g. material, health behaviours, psychosocial pathways);

iii) the cumulative interplay of exposure, susceptibility and resistance across the life course proposes that

> "*each factor and its distribution is conceptualized at multiple levels*" and is "*manifested in processes at multiple scales of time and space*";

iv) the agency and accountability

> "*expressed in pathways of and knowledge about embodiment, in relation to institutions (government, business, and public sector), communities, households, and individuals, and also to accountability and agency of epidemiologists and other scientists for theories used and ignored to explain social inequalities in health; a corollary is that, given probable complementary causal explanations at different scales and levels, epidemiological studies should explicitly name and consider the benefits and limitations of their particular scale and level of analysis*" (Krieger, 2005).

Hertzman introduced a concept called '**biological embedding**' that shares some similarities with the concept of embodiment of Krieger. The biological embedding is defined as:

> "*the processes by which human experience alters biological processes in stable and long-term ways that influence health over the life course*" (Hertzman & Boyce, 2010) .

For Hertzman, biological embedding takes place when four conditions are met (Hertzman, 2012):

i) Experience, metaphorically, 'gets under the skin' in ways that alter human biological and developmental processes;
ii) Systematic differences in experience in different social environments in society (especially early in life) lead to systematically different bio-developmental states.
iii) These differences are stable and long term;

iv) These differences have the capacity to influence health, well-being, learning, or behaviour over the life course.

Different developmental stages will offer different opportunities for biological embedding (Hertzman & Boyce, 2010). It is not surprising that biological effects depend on the time and the duration of the exposure. From animal models and human studies, researchers have investigated the biological mechanisms potentially involved in the social-to-biological transitions.

Lupien *et al.* reviewed evidence of the stress effects on brain, behaviour and cognition from the animal models as well as human studies (Lupien et al., 2009), taking evidence from prenatal, post-natal, adolescence, adulthood and elderly periods of life. This studies analysed prenatal exposures, since there has been a sensitive period suggested for brain and biological development starting after conception. In fact, for humans, early sensory stimulation activates specific genes, establishing sensory pathways that in turn affect neural pathways involved in activities like coping, language and cognition. The biological pathways could also be affected during that window of vulnerability, setting some biological parameters involving the immune and endocrine systems (Hertzman & Boyce, 2010). For instance, it has been suggested that stress could start a physiological response (Sapolsky et al., 1986), by releasing central neuropeptides, such as corticosteroid releasing factor (CRF), initiating a systemic stress response by activation of neuroendocrinological pathways such as the sympathetic nervous system, hypothalamic pituitary axis, and the renin-angiotensin system, with the release of what we called stress hormones (i.e., catecholamines, corticosteroids, growth hormone, glucagon, and renin) (Black, 2002).

Therefore, some physiological systems could represent a mediator between the social and the biological according to Hertzman's criteria (Hertzman, 2012). We will particularly focus on stress response systems as potential candidates for explaining how the social can become biological.

## 2.1. The hypothalamo-pituitary-adrenocortical (HPA) axis

One alleged mechanism explaining how experience can affect health relate to the theory of stress. The literature suggests that being exposed to an adverse environment during childhood and adolescence can alter an individual's stress response systems, making them vulnerable to subsequent exposures and disease (Bailey et al., 2001; Kelly-Irving et al., 2013a; Kelly-Irving et al., 2013c).

Exposure to hostile conditions results in a series of coordinated responses aimed at enhancing the probability of survival. Sapolsky *et al.* noted that the HPA axis, is by excellence, the stress response system. Activation of the HPA axis is necessary to meet and adapt to the environment (Figure 3). However, when the HPA axis is continuously activated, during chronic stress, it may be the cause of a fabric wear and may accelerate the pathophysiological processes (Sapolsky et al., 1986). The HPA axis is involved in restoring homeostasis and subsequent adaptation to real or perceived threats. Therefore, the activation of the HPA axis plays a pivotal role in the stress responses. While the short-term activation of the HPA axis allows for adaptive responses to the challenge, in the long term this can be deleterious for the organism. In particular, the chronic exposure to stressors occurring during periods of maturation (perinatal, adolescence) appear to have strong long-term effects on the subsequent behavioural and neuroendocrine response to stressors (McEwen & Seeman, 1999). Please see Figure 3.

We will review the evidence of the effects of environmental exposures on the HPA axis, giving special attention to the effects on cortisol secretion and the glucocorticoid receptor (GR). It is worth noting that HPA dysregulation may present either hypo or hyper-reactivity, with a U-shaped pattern of association, causing disparate and sometimes inconsistency on the evidence found.

Figure 3. The stress system according to Lupien and colleagues

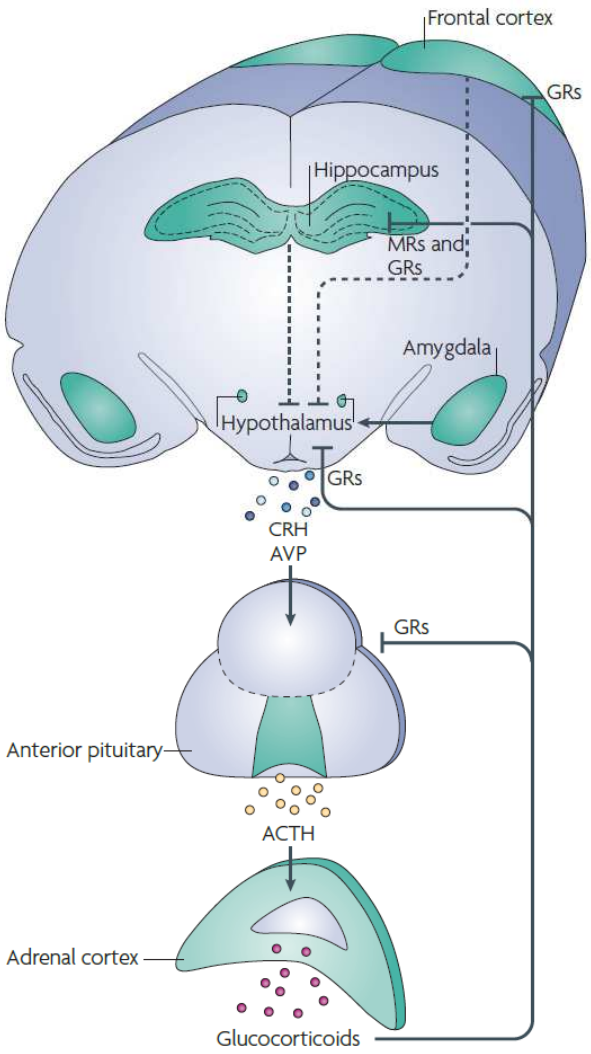



Figure 1 | **The stress system.** When the brain detects a threat, a coordinated physiological response involving autonomic, neuroendocrine, metabolic and immune system components is activated. A key system in the stress response that has been extensively studied is the hypothalamus-pituitary-adrenal (HPA) axis. Neurons in the medial parvocellular region of the paraventricular nucleus of the hypothalamus release corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). This triggers the subsequent secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, leading to the production of glucocorticoids by the adrenal cortex. In addition, the adrenal medulla releases catecholamines (adrenaline and noradrenaline) (not shown). The responsiveness of the HPA axis to stress is in part determined by the ability of glucocorticoids to regulate ACTH and CRH release by binding to two corticosteroid receptors, the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). Following activation of the system, and once the perceived stressor has subsided, feedback loops are triggered at various levels of the system (that is, from the adrenal gland to the hypothalamus and other brain regions such as the hippocampus and the frontal cortex) in order to shut the HPA axis down and return to a set homeostatic point. By contrast, the amygdala, which is involved in fear processing[142], activates the HPA axis in order to set in motion the stress response that is necessary to deal with the challenge. Not shown are the other major systems and factors that respond to stress, including the autonomic nervous system, the inflammatory cytokines and the metabolic hormones. All of these are affected by HPA activity and, in turn, affect HPA function, and they are also implicated in the pathophysiological changes that occur in response to chronic stress, from early experiences into adult life.

### 2.1.1. Chronic vs acute stress responses

According to the Center for Studies of Human Stress in Canada, there are two kinds of stress that can have different impacts on the mind and the body.

Acute stress results from specific events or situations that involve novelty, unpredictability, a temporary threat, and leave us with a poor sense of control. This type of stress can be positive, because the stress hormones released help our mind and body to deal with the specific situation, which may be perceived or interpreted as a threat. Acute stressors will activate, and will re-establish the internal equilibrium of the organism, without further physiological consequences.

Canon introduced the concept of '**fight-or-flight response**' in 1932 to describe the physiological reaction and behavioural responses when an organism faces threats. This theory proposed that

animals react to threats with a general discharge hormones within the sympathetic nervous system –principally adrenaline, noradreline- , priming the animal for fighting or fleeing (Canon, 1932). From this perspective, stress is a real or interpreted threat to an individual's physiological integrity that results in adaptive biological and behavioural response (McEwen & Seeman, 1999).

The ability of an organism to adapt to its environment is of vital importance. Brain-mediated responses to stress recruit a set of central and peripheral nervous system neuroendocrine and immune responses that promote adaptive 'survival' functions and, later, a return to equilibrium or homeostatic patterns. During the general alarm reaction numerous biological systems, starting with the neuroendocrine axis, are activated, and include the mobilization of energy (free fatty acids, glycerol, glucose, amino acids) from stored nutrients (triglycerides, glycogen, proteins) and a halt to further energy storage, an increase in cardiovascular/pulmonary tone to facilitate tissue delivery of oxygen and glucose, a slow-down of anabolic processes (which do not require oxygen), causing the suppression of digestion, growth, reproduction, and inflammatory and immune responses. Simultaneously, cognition is altered, with a tendency towards lowered sensory thresholds, which is a logical adaptation for coping with an emergency situation. In a second stage, negative feedback mechanisms are activated to counteract the physiological response (McEwen, 1998). This stage is thus essential for returning to the basal state in case of an acute stress, when the acute emergency has been survived.

Chronic stress on the other hand, results from repeated exposure to situations that lead to the release of stress hormones, continuously (Figure 3). This type of stress can cause wear-and-tear on the mind and body. It is hypothesised that the stress-related systems were not designed to be constantly activated. This overuse may contribute to the breakdown of many bodily systems. In this sense, once the stress response systems are activated, they automatically affect other systems, causing our bodily systems to dysregulate (Center for Studies on Human Stress).

Particularly during early life, chronic stress is defined as

> "*an experience where the stimuli remains present in a child's life over a lengthy period of time*" (Miller et al., 2011).

Maltreatment, nutritional and material deprivation, socioeconomic and financial disadvantage are examples of stressors that could linger over the lifespan. The National Scientific Council on

the Developing Child has proposed three different types of stress responses in children: positive, tolerable, and toxic (Center on the Developing Child Harvard University). The classification was built on the basis of their potential long term physiological damage.

'Positive stress' is brief and moderate. It can be socially buffered and represents an opportunity to adapt to adverse situations. 'Tolerable stress' produces temporary and potentially damaging stress responses that can be reversible and buffered in a supportive and secure social environment. 'Toxic stress' is characterized by the constant activation of the stress response systems -like the HPA axis- due to chronic or traumatic experiences in the absence of consistent social support, especially during childhood and adolescence (Shonkoff et al., 2012). According to the Center of Developing Child

> *"the extent to which stressful events have lasting adverse effects is determined in part by the individual's biological response (mediated by both genetic predispositions and the availability of supportive relationships that help moderate the stress response), and in part by the duration, intensity, timing, and context of the stressful experience*" (Center on the Developing Child Harvard University).

In summary, it appears that our physiology is well adapted to respond to acute stress, and this is in fact crucial for surviving. However, if the stressor remains –in the case of chronic stress- the negative feedback mechanisms can be dysregulated, and in the long term, promote vulnerability to ill health. As noted earlier, we focus in this work on the effects of chronic stress on health. In this case of 'over-solicitation', our stress response systems, not well designed for chronic stress, can be damaged and show dysregulated responses. McEwen illustrates the differences of stress responses in several systems (McEwen, 1998), as the reader can noted in the following Table 1.

Table 1. Interacting adaptive systems of the body[a] according to McEwen

| System | Acute response to challenge | Problems associated with chronic activity or inactivity[b] |
|---|---|---|
| Cardiovascular | Maintaining erect posture (avoiding a 'black out') | Hypertension, potential for stroke, myocardial infraction |
| Metabolic | Activating and maintaining energy reserves, including energy supply to the brain | Obesity, diabetes, atherosclerosis |
| Immune | Response to pathogens<br>Surveillance for tumors | Inflammatory[b], autoimmune disorders [b]<br>Immunosupression[b] |
| Brain, CNS | Learning, memory<br>Neuroendocrine and autonomic regulation | Neuronal atrophy, death of nerve cells |

[a]Mediators involved in modulating these adaptive systems consist of hormones (principally, but not confined to, adrenalin and noradrenalin, ACTH and glucocorticoids, insulin and glucagon) and cytokines (produced not only by immune cells but also by the liver and brain) [...].

[b]Elevated inflammatory cytokines or autoimmune responses reflect the inadequacy of other adaptive systems like adrenal steroids, which normally inhibit and contain these responses.

### 2.1.2. Timing and the HPA axis

**Timing** is another key topic to understand human development and health across the life course. The concept of timing leads to events or conditions taking importance or being unimportant at a given time point. The concept of timing is particularly important if we consider that social and biological elements change rapidly in the first two decades, but also towards the end of life. Vineis and colleagues considered three developmental stages in life to take into account when exploring the influence of timing on the responses of the different physiological systems (Vineis et al., 2016). The authors proposed a '**build-up**' stage that goes from conception and early intra-uterine life to late adolescence or early twenties. It is characterised by rapid successions of developmental stages. The second stage starts in early adulthood and finish in adulthood and is called '**maintenance** or **stability**'. The maintenance stage is characterized by a moment were function will remain 'steady' for several years. Finally comes the period of '**decline**' from maximum attained capacity to loss of function, incapacity, disease and death. The environment and behaviours during this stage can influence the rate at which functioning is lost. We hypothesised that the development of the HPA have a sensitive period, and it can be altered if the individual is submitted to chronic stress during childhood, adolescence and

early adulthood. We will further discuss these three stages in Part V, Discussion, Chapter III, section 2.

### 2.1.3. Prenatal stress

A large number of studies have analysed (*via* animal models) the effects of manipulating the foetal environment on later stress responses and behaviours (Kapoor et al., 2008; Matthews & Phillips, 2010). An example of a sensitive period having 'programming' effects on the HPA axis, is the glucocorticoid secretion and glucocorticoid receptor (GR) occurring *in utero*.

From animal models, De Boo *et al.* noted that

> "*intrauterine glucocorticoid exposure leads to a reduced numbers of glucocorticoids receptors in the hypothalamus, resulting on impairment on the negative feedback and hence long-term up regulation of HPA axis after birth. This can impact blood pressure and glucose tolerance*" (De Boo & Harding, 2006).

Lupien *et al.* noted that exposure of a pregnant female to stress, or increases in maternal glucocorticoids secretion, can pass through the placenta and reach the foetus. In rats this causes long-term hyper-reactivity of HPA axis (Lupien et al., 2009).

In human studies, Lupien *et al*. mentioned that it has been shown in retrospective studies a link between pregnant women experiencing psychosocial stress, adverse events, glucocorticoids treatment, stress, anxiety or depression with long-term neurodevelopmental effects, low birthweight, and increased basal HPA axis activity in offspring at different stages of life. Maternal stress has thus been associated with unsociable behaviour, sleep disturbance, drug abuse, and anxiety disorders in their offspring (Lupien et al., 2009).

### 2.1.4. Stress in early life

Using the maternal care models or maternal separation in rats, it has been suggested that maternal nurturance can act on glucocorticoids and the GR in multiple brain regions, including the hippocampus (McGowan et al., 2009). High maternal licking and grooming on pups, compared to those with low licking and grooming, showed increased GR expression, boosting negative-feedback sensitivity to glucocorticoids, reducing glucocorticoids releasing hormone

(CRF) expression in the hypothalamus and moderating adrenal responses to stress (Hertzman & Boyce, 2010; Weaver et al., 2004).

Another type of stress resulting from social deprivation was tested in rats by separating mothers from pups. To remove the mother over short periods of time triggered a hormone cascade, setting a dysregulated HPA axis, showing higher baseline levels and a blunted cortisol response to stress. These effects are created only during a narrow window in early life, which suggests that is a possible experience-dependent mechanism, were the stimulation or deprivation will be translated as brain and biological impairment, having long lasting effects throughout the life course (Franklin et al., 2010). At 24 months (elderly for rodents), rats separated from their mothers showed deterioration in memory, cognitive abilities and learning compared to those not separated. Other studies revealed that offspring of mothers with high licking and grooming showed increased hippocampal GR expression, negative feedback regulation over corticotropin releasing factor (CRF) and lower stress responses compared with offspring from low licking and grooming mothers (Turecki & Meaney, 2016).

In summary, these biological changes appear to be useful, in the short term, for survival and procreation. As Hertzman said, not being 'well handled' by the mother rat anticipates the fact that 'life is going to suck'. Therefore, being able to rapidly react to a threat, to rapidly mobilize sugar and energy to fight or fleeing, to develop the 'defensive' phenotype, will allow the adaptation to that adverse environment. However, this effects, in the long term, are going to be deleterious for learning, cognitive function, memory and ageing.

In human studies, early life adverse experiences have been linked with HPA axis impairment. The HPA axis is not fully mature at birth and shows important developmental changes throughout childhood, in both basal activity and cortisol reactivity (Gunnar & Donzella, 2002). Psychosocial stress during childhood appears to affect the glucocorticoids receptors (GR), regulating the negative feedback of the HPA axis. According to Miller and colleagues, living in a social disadvantage environment during early life may 'influence' the GR expression in a fashion that can diminish its sensitivity to cortisol-mediated signalling. Once the cortisol negative feedback is inhibited, it can dysregulate the HPA axis, showing a hyper-reactivity of the HPA axis with raised on diurnal cortisol output, or a hypo-reactivity of the HPA axis showing a flattened cortisol curve throughout the day (Miller et al., 2009).

Consider again the concept of attachment, mentioned in Chapter I, section 4. It has been suggested that a socially secure environment set in place with a consistent caregiver ensures the development of neural pathways. Conversely, a lack of the necessary sensitive inputs during infancy may have profound deleterious effects. Severe psychosocial deprivation may lead to stunting and even death, despite the adequate availability of material resources (Hertzman & Boyce, 2010). Evidence suggests that prefrontal cortex, the amygdala, and the hippocampus are regions in the brain particularly sensitive to psychosocial stress (McEwen, 2007). The treatment of Romanian orphans during the Ceausescu's regime was an example of a 'natural experiment' of the effects of extreme deprivation and neglect. Children adopted after more than eight months in their first years of life showed higher cortisol levels over the daytime hours than did the two control groups (early adopted ones, and children born and raised in their family of origin in Canada) (Gunnar et al., 2001). Another study suggested that prolonged institutional rearing caused cognitive impairment, quasi-autism, and disinhibited attachment (Kreppner et al., 2007).

Epidemiological studies have found associations between low SEP (and ethnicity) with flatter diurnal cortisol rhythms. In Whitehall II, lower SEP was also found to be associated with flattened cortisol secretion. Childhood maltreatment has already been found to dysregulate HPA axis, as well as having an impact on the developing human brain (Twardosz & Lutzker, 2010).

#### 2.1.5. Stress in adolescence

Adolescence and early adulthood is an important transitional period were hormone levels change rapidly. Taking a life course perspective, adolescence could represent a period were development may continue the same trajectory established in childhood or be transformed in significant ways (Gore et al., 1997).

From animal models, juvenile rats submitted to stressors showed prolonged activation of the HPA axis, compared with adult rats. Another study suggested that pre-pubertal rats had delayed glucocorticoid responses, but prolonged secretions due to an immaturity of the glucocorticoid negative feedback compared to adult rats. These findings suggest that during pubertal period experiences of chronic stress will expose the brain to a greater amount of

glucocorticoids compared to adult rodents submitted to similar experiences (Lupien et al., 2009).

In humans, adolescence is a complex period of life. Dhal explained the adolescence paradox as follows:

> "*Adolescence presents a striking paradox with respect to overall health statistics. This developmental period is marked by rapid increases in physical and mental capabilities. By adolescence, individuals have matured beyond the frailties of childhood, but have not yet begun any of the declines of adult ageing. Compared to young children, adolescents are stronger, bigger, and faster, and are achieving maturational improvements in reaction time, reasoning abilities, immune function, and the capacity to withstand cold, heat, injury, and physical stress. In almost every measurable domain, this is a developmental period of strength and resilience. Yet (…) overall morbidly and mortality rates increase 200% over the same interval of time. This (…) is not the result of cancer, heart disease, or mysterious infections. Rather, the major sources of death and disability in adolescence are relate to difficulties in the control of behaviour and emotion. It is the high rates of accidents, suicide, homicide, depression, alcohol and substance abuse, violence, reckless behaviours, eating disorders, and health problems related to risky sexual behaviours*" (Dahl R., 2004).

Moreover, regarding adolescence and health inequities we are confronted to the 'social equalization in youth' that suggests that social inequalities in health disappear or are attenuated in early adolescence possibly due to changing risk exposures (West, 1997). To evaluate health status and health inequities during adolescence appear to be a complex task.

Several researchers have tested the hypothesis that pubertal changes in HPA axis increase vulnerability to psychiatric disorders (Gunnar et al., 2009), arguing that stress can affect mental health, and cortisol affects neurodevelopment. Some studies in human adolescents support the idea that stress exposure during this period of life is linked with increased basal and stress-

induced activity of the HPA axis, however this changes may relate to sex steroids levels, influencing HPA axis activity (Lupien et al., 2009). These findings are quite consistent for girls, but less manifest for boys. Relatively few studies have sought to investigate the impact of a dysregulated HPA axis on adult health and the evidence for increases in stress reactivity of the HPA axis during this period is sparse and conflicting (Gunnar et al., 2009). However, empirical evidence has provided information to clarify the effects of stress on health. Adolescents from less well-off SEP backgrounds appear to have higher baseline glucocorticoid levels, as well as adolescents with mothers with depressive symptoms in early childhood. For instance, Gustafsson and colleagues showed that SEP in adolescence was associated with a more pronounced cortisol awakening response in adulthood, independently of later SEP (Gustafsson et al., 2010). Another study investigated whether perceived parenting and SEP impacted basal cortisol levels (measured as the area under the curve using three measures of saliva cortisol over day) or cortisol awakening response. Perceived parental emotional warmth was inversely correlated with basal cortisol levels. SEP showed an inverse U-shaped relation with both HPA-axis measures (Marsman et al., 2012). Concerning brain structure, there is no evidence of a link between stress and hippocampal volume, however it has been reported changes on grey matter volume, frontal cortex, and anterior cingulate cortex (Lupien et al., 2009).

#### 2.1.6. Stress in adulthood

From animal studies, stress appears to have different impacts depending on whether it is acute or chronic during adulthood. Acute stress, with small increases of glucocorticoids, affects hippocampus-mediated learning and memory. Larger glucocorticoids caused impaired hippocampal function. The inversely U-shaped correlation with acute stress appears to be an adaptive response, increasing vigilance and learning processes during limited environmental challenges. On the contrary, chronic stress appears to cause dendritic atrophy in rodents, interesting –and contrasting with chronic stress during early life- these changes take a longer period of time to be present, and more importantly, they disappear after a few days after the cessation of the stressor. Other studies have reported that chronic stress in rats can have impact in morphology in brain organs, such as, reduction of the hippocampal volume. Such a hippocampal changes have been reported to impact spatial learning. According to Lupien's review, the main difference with stress during early life –which have long lasting effects- in

animal models is that chronic stress in adulthood appears to be reversible after a few weeks of non-stress.

From human studies evidence remains inconsistent and hard to interpret. It appears to be differences between acute and chronic stress. The first show the same U-shaped pattern between glucocorticoids and cognitive functioning observed in animal models. Research has suggested that acute stress in this period of life appears to ameliorate memory related with emotional processes. Associations between chronic stress and morphologic changes of the hippocampus in humans without psychiatric or mental disorders have been reported by only a few studies. However, individuals reporting low self-esteem –suspected as an elevator of stress in humans- showed reduced hippocampal volume.

The main complexity when analysing stress reactivity and glucocorticoids effects on neurobiology is to disentangle the potential effects of early life. For instance, Lupien *et al*. reported studies showing a link between adults with Post Traumatic Stress Disorder (PTSD) and reduced basal cortisol levels. From other studies it has been suggested that exposure to trauma, abuse and neglect during childhood can cause low glucocorticoid concentrations. Thus, we can imagine that low cortisol levels may represent a risk for later PTSD in individuals who suffered strong adverse childhood experiences, and not that PTSD can cause low glucocorticoids concentrations. Another example reported a hyper-reactivity of the HPA axis in depressed or abused adults that suffered childhood abuse, while adults with PTSD showed hypo-reactivity. Furthermore, in individuals with PTSD or depression changes in the hippocampal volume have been reported.

As mentioned earlier, these findings in humans are difficult to interpret, in general these studies are limited to a relatively small period of time or are cross-sectional, with retrospective information about adverse experiences. These studies are highly variable and deserve further exploration since the effects of stress will depend on the type of the exposure, as well as timing, intensity and duration.

#### 2.1.7. Stress in older age

With the general reduction of physical and mental functioning in later life, studies have suggested that rodents submitted to long periods of exogenous glucocorticoids, developed memory deficiency and hippocampal reduction. Interestingly, maintaining artificially low levels

of glucocorticoids, prevented the emergence of memory deficits and hippocampal atrophy. Chronic stress appears to accelerate the signs of hippocampal ageing, and high levels of glucocorticoids appear to cause hippocampal dendritic atrophy. In monkeys, chronic treatment with glucocorticoids increased a pathological processes similar to Alzheimer's disease in humans (Lupien et al., 2009).

From human studies, evidence appears to associate stress and glucocorticoid secretion to the function of the nervous systems, particularly the ageing hippocampus (Sapolsky, 1999). According to Lupien's review, it appears that healthy older adults present a higher mean of diurnal cortisol than young people. Persons suffering of Alzheimer's disease have shown higher basal levels of cortisol compared with healthy individuals, and individuals with glucocorticoids treatment appear to further affect their cognition abilities.

#### 2.1.8. The neurotoxicity and vulnerability hypothesis

These findings have put forward two theories regarding the biological mechanism of how cortisol, as an important mediator of the stress responses cascade, can impact brain structure and morphology and have damaging neurobiological effects.

The **neurotoxicity hypothesis** advance that prolonged exposure to glucocorticoids reduces neurons capacities to resist insults. This may higher the risk of neurological damages coming from later toxic or ordinary exposures. The **vulnerability hypothesis** suggests that, an individual facing abuse, neglect, and adverse psychosocial adversities during a sensitive period of development -where specific systems of human biology are more susceptible to environmental challenges- can have structural and damaging effects on the brain and behaviour making them more vulnerable to later stress responses (Lupien et al., 2009).

Lupien noted:

> *"In contrast to the neurotoxicity hypothesis, the vulnerability hypothesis suggests that reduced hippocampal volume in adulthood is not a consequence of chronic exposure to PTSD, depression or chronic stress, but is a pre-existing risk factor for stress-related disorders that is induced by genetics and/or early exposure to stress. Unlike the neurotoxicity hypothesis, the vulnerability hypothesis can explain*

> *glucocorticoid hyposecretion in patients with PTSD. Indeed, studies in children facing significant adversity, such as abuse, report the development of glucocorticoid hyposecretion which might last until adulthood and confer vulnerability to developing PTSD as a result of trauma" (Lupien et al., 2009).*

### 2.1.9. Stress, inflammatory and immune processes

Numerous studies have highlighted a spectrum of age-associated diseases, such as, cardiovascular disease, osteoporosis, arthritis, type 2 diabetes, some cancers, Alzheimer's disease, periodontal disease, and frailty and functional, that may be influenced by pro-inflammatory processes (Kiecolt-Glaser et al., 2003). It has been shown that individuals suffering of depression and reporting negative emotions or stressful experiences presented higher levels of IL-6 and other pro-inflammatory cytokines. Both physical and psychological stressors can cause transitory increases in pro-inflammatory cytokines. Concerning the immune system, studies have suggested that persons having negative emotions and adverse psychosocial circumstances have greater risk for infection, prolonged infection, and delayed wound healing (Kiecolt-Glaser et al., 2003). Hence, inflammatory and immune dysregulation is also suspected as a potential pathway linking stressful early life events to physical health problems (Fagundes et al., 2013).

The epidemiological evidence suggests increased inflammatory markers –cytokines- in individual's with risky health behaviours, which are adversely affected by stress, increasing tobacco consumption, less physical activity, sleep impairment, and higher BMI (Vgontzas et al., 1997). Danese and colleagues found that children experiencing maltreatment and depression showed significantly elevated inflammation levels, after adjustment for socioeconomic status, and other classic confounders compared with non-maltreated children (Danese et al., 2011). A previous prospective study showed that children who were neglected during the first decade of life had higher CRP levels at age thirty-two compared with those who were not neglected. Another study showed the effects of stress on both the immune system and infection rates (Danese et al., 2009).

These findings suggest an impact of environmental stress on inflammatory and immune responses. From this perspective, inflammatory and immune processes are also candidate systems for the biological embedding of adverse experiences over the life course.

#### 2.1.10. Epigenetic processes

Epigenetic processes are suitable candidates to explain the environmental influences on gene expression. The environment itself does not change gene sequences, nevertheless it can regulate gene expression influencing DNA methylation of several genes (Roth & Sweatt, 2011). Growing evidence suggests that gene activity is highly sensitive to environmental factors as toxins, diet, stress and behavioural influences (Roth & Sweatt, 2011). A better understanding of these processes can contribute to the understanding embodiment processes starting early in life.

Epigenetics refers to any information heritable during cell division other than the DNA sequence itself (Feinberg, 2007). McGowan and Szyf defined it as:

> "*the combination of mechanisms that confer long-term programming to genes and could bring about a change in gene function without changing gene sequence*" (McGowan & Szyf, 2010).

Epigenetic mechanisms allow the strengthening or damping of gene expression and those affecting gene expression may be inherited, but are also acquired *via* the environment. A new area of exploration involves examining the permanence or temporary nature of epigenetic marks. Whether the timing of the occurrence of epigenetic marks appear to be important, their reversibility remain to be determined. Furthermore, early exposures may modify the rate of cell development, as well as the physical interactions between cells and organs. Research has been carried out establishing the link between psychosocial and socioeconomic exposures in early life and epigenetic modifications potentially leading to adverse health outcomes later in life (Borghol et al., 2011).

According to Rutter, there are several reasons to consider epigenetics as a key mediator of biological embedding. First, epigenetic changes are a set of mechanisms observed in several species (fish, bees, rodents, primates, etc.). Second, epigenetic changes appear to be evident in a wide range of experiences. Third, these changes appear to be highly stable to changes but

also show a high reactivity over time. Fourth, changes act as genetic influences, which would link the innate and acquired. Fifth, some epigenetic changes may remain through generations, however this have not been demonstrated for humans. Finally, Rutter indicates that studies of epigenetics have been subjected to rigorous analysis in the search for causal inference. Despite this, epigenetic changes are tissue-specific and developmental stage-specific, making research complex in humans (Rutter, 2012).

Studies analysing early life stress in rodents have revealed important and persistent alterations in gene expression and behaviour. Epigenetic mechanisms, including changes in DNA methylation is suspected. For instance, a recent review showed that increased maternal licking and grooming was associated with decreased methylation and increased hippocampal GR expression in all animal studies. When examining the GR gene methylation, 70% of the studies analysed in this review on rodents exposed to maternal separation reported a significant increase in methylation (Turecki & Meaney, 2016). Moreover, there is evidence in rodents that the prenatal influences on the HPA axis can be transmitted across generations through an epigenetic mechanism (Matthews & Phillips, 2010). In humans, (McGowan et al., 2009) found and epigenetic mechanisms causing decreased levels of glucocorticoid receptor in post-mortem hippocampus obtained from suicide victims with a history of childhood abuse.

However, as Hertzman noted,

> "*when it comes to the epigenetics of biological embedding in humans, the basic caveats must be acknowledged. Buccal and white blood cells are not neurons, association is not causation, DNA methylation is not gene expression, and the gene expression is not the occurrence of a positive or negative health or developmental outcome*" (Hertzman, 2012).

In conclusion, these findings suggest that an organism is sensitive to environmental exposures, and this sensitivity vary across the life course. Early life, childhood and adolescence appear to be important moments in life to adapt our biology to face environmental challenges. However, this adaptation may have long term consequences on health. A convergent body of research from diverse areas such as neurobiology and epidemiology, show that childhood stress can affect the HPA axis, triggering a cascade of biomarkers involved in inflammation, immune

responses, and impacting brain neural structures and functions (Rutter, 2012). However, for studying other periods of life, the results remain inconclusive, since human studies are rare, inconsistent, and present important methodological challenges. This is the case when analysing stress responses during adulthood and ageing, since is complex to disentangle the effects of early life stress from later effects on health. These findings yield interesting methodological and theoretical questions, showing the need of a life course approach to analyse the long term effects of stress in health. Most studies on early life, although spare, provide convincing biologic plausibility for the epidemiological hypothesis of embodiment of early social experiences (Anda et al., 2006). However, if early social adversity is indeed biologically embedded, how can we measure it for epidemiological, research and public health purposes?

# Chapter III

# Allostatic load and the empirical evidence

Human beings are biological and social animals, and human development occurs in specific contexts that shape our gene expression, molecules, cells and organs from conception to old age. The environmental contexts and social connections a person experiences throughout his/her lifetime significantly impact their development. Human biology comprises a number of systems directly interacting with the environment, this is one of the central characteristics permitting adaptation. Indeed in the short term, they are essential for adaptation, maintenance of homeostasis, and survival. However, over longer time intervals, they exact a cost that can accelerate disease processes.

In section 1 we will expose some physiological mechanisms that we believe are relevant for our research. We will focus on the 'fight-or-fight' response, and the theories of internal physiological regulation (homeostasis, allostasis) for finally introduced the concept of allostatic load.

In section 2, we will concentrate on the theories of allostasis physiological response and allostasis/allostatic load mediators.

In section 3 we will review some evidence of a link between different measures of allostatic load and potentially effects on brain structures

Finally we will conclude this chapter with section 4 by introducing the first measure of allostatic load used for epidemiological studies.

# 1. Development of a theory: stress, homeostasis, allostasis and allostatic load

## 1.1. Homeostasis, allostasis and allostatic load

To characterize the different ways in which chronic stress can damage human physiology, it is necessary to elucidate the adaptive control mechanisms. Claude Bernard introduced the notion of **homeostasis**, defined as the physiological mechanism that permits internal conditions to remain stable and relatively constant allowing a physiological balance. The purpose of homeostasis is to regulate and 'clamp' each internal parameter at a 'setpoint' by sensing errors and correcting them with negative feedback (e.g. temperature regulation) (Sterling, 2004). Based on this model, an internal mechanism is considered impaired when a parameter deviates from its 'norm'. From a clinical perspective, when such a dysregulation is diagnosed, the clinician will design therapies or medications to restore the 'normal' value.

However, in physiology, not all the parameters are constant, and their variations, rather than signifying error, are designed to reduce error (Sterling, 2004). **Allostasis** is the process whereby an organism maintains physiological stability by changing parameters of its internal milieu by matching them appropriately to environmental demands (Sterling & Eyer, 1988). This stress response is adaptive if it is transitory and shut off quickly with the help of feedback loops. However, in the long run, the suppression of anabolic processes, the depletion of energy stores and the suppression of the immune system can be devastating for the organism. Prolonged and/or uncontrollable sources of stress leads to the organism losing its resistance and entering a phase of exhaustion and ageing (Sapolsky et al., 1986). This process has been called **allostatic load (AL)**, and refers to the 'price' the tissue or organ pays for managing chronic stress responses; more precisely, allostatic load refers to the 'cost' of adaptation (McEwen, 2007). Such a physiological cost may express itself over time as illness and disease.

In the last two decades, epidemiological research has used the concept of allostatic load to explain how chronic stress can lead to physiological dysregulation and disease (Beckie, 2012; Juster, et al., 2010; Seeman, et al., 2001; Seeman, et al., 1997). Originating as a biopsychosocial model (Juster et al., 2011b),

> "*allostatic load is the wear-and-tear on the body and brain resulting from chronic dysregulation (i.e., over-activity or inactivity) of physiological systems that are normally involved in adaptation to environmental challenge*" (McEwen & Gianaros, 2010).

According to AL theory, cumulative and repeated activation of compensatory physiological mechanism in response to chronic stress can lead to a multisystem pre-disease state represented by a dysregulation of neuroendocrine, metabolic, inflammatory, or cardiovascular parameters (McEwen, 1998; McEwen & Seeman, 1999).

For (Sterling & Eyer, 1988), the allostatic model defines health as a state of responsiveness. The classic medical model defines health according to specific physiological thresholds. When a parameter presents values outside the normal range, it is considered abnormal and it is corrected with a treatment, often a pharmaceutical intervention. From the allostatic framework, a change in a parameter values is not necessarily consider as pathological, since it results from the physiological responsiveness controlled by a multitude of mutually reinforcing signals (Sterling, 2004). From this perspective

> "*pathology itself is a form of adaptation where, for instance, an individual develops hypertension in order to conciliate environmental demands, even if these processes are pathophysiological*" (Sterling, 2004).

Health is the result of predictive regulation assuring the adaptation to the environment. This model puts forward the idea that health and disease are complex processes, emphasizing on the holistic relationships between individuals and their environments. For these reasons, it makes sense to examine and identify subclinical states before they lead to disease (Juster et al., 2011a).

## 2. Stress, allostatic load and brain structures

Three main brain regions are involved in the stress responses: the hippocampus, the amygdala and the prefrontal cortex. According to McEwen & Gianaros these brain structures are

> "*anatomically networked components of a neural circuitry that coordinates behaviours, with neuroendocrine, immune and autonomic*

> *functions in the service of adaptively coping with environmental and psychosocial challenges*" (McEwen & Gianaros, 2010).

The brain structure more plausibly affected by social-related stress include the limbic brain areas (e.g. hippocampus, amygdala). There are mainly three reasons for believing that the hippocampus, the amygdala and the frontal cortex are key structures for embodying inequalities, and interestingly, all these three mechanisms are contained in the allostasis and allostatic load conceptual framework:

i) emotional and social information are largely processed in these systems;
ii) they regulate neuroendocrine, immune autonomic nervous system functions involved in both adaptation and pathophysiology;
iii) these brain areas express forms of neuroplasticity in association with conditions of chronic and acute stress in animal models (McEwen & Gianaros, 2010).

The hippocampus was the first area besides the hypothalamus to be recognize as a target of stress hormones. It is linked with memory and cognition as well as controlling the negative feedback regulation of the HPA axis. The amygdala, detects and responds to environmental threats and is involved in fear conditioning and emotional processing. The prefrontal cortex is involved in decision making processes, emotions regulation, impulsivity, cognition and coping strategies, and have autonomic and neuroendocrine functions (McEwen & Gianaros, 2010).

McEwen & Gianaros proposed that the neurobiological pathways linking psychosocial factors impacting allostatic load

> "*are likely to interact with genetic and dispositional individual differences to affect the neuroplasticity of limbic brain areas that regulate allostatic control systems. These brain areas include subdivisions of the prefrontal cortex (…), hippocampus (…), and the amygdala (…). Importantly, these limbic areas regulate neuroendocrine, autonomic, and immune systems, which are involved in the bidirectional allodynamic control of central and peripheral physiology. In adulthood and later life, psychosocial factors related to SES (e.g., meaningful employment and social integration) may similarly interact with individual difference and behavioural lifestyle factors to affect the*

> *neuroplasticity and aging of the same limbic systems mediating and targeted by allostatic control systems. To the extent that lower SES adversely affects limbic neuroplasticity via stress-related factors, then the regulation of key allostatic control systems may become impaired, leading to allostatic load on the body and brain and perhaps increased risk for ill health*" (McEwen & Gianaros, 2010).

Thus, an allostatic load index is a snapshot picture of the biomarkers involved in physiological wear-and-tear and would allow a better understanding of the occurrence of diseases linked to chronic stress.

## 3. Allostasis and allostatic load mediators

An important issue when it comes to allostasis and allostatic load is the measure of the concept. When trying to operationalise an allostatic load index, it is crucial to include the complex physiological cascade associated with stress responses systems.

According to Juster and colleagues, the dynamic and interaction of different biomarkers will take place in a three-time sequence. At first, perceived and interpreted stress will trigger the sympathic-adrenal-medullary (SAM) axis to immediately release **catecholamines** (adrenaline and noradrenaline) from the adrenal medulla on top of the kidneys. Subsequently, the HPA axis is activated within minutes to produce glucocorticoids. The production of **glucocorticoids** – mainly cortisol in humans- is the final result of a series of chemical signalling starting in the hypothalamus. HPA axis is a complex set of direct influences and feedback interactions involving the **hypothalamus**, the **pituitary** (or hypophysis) and the **suprarenal** endocrine glands. The hypothalamus activates the HPA axis through the **corticotrophin-releasing factor** (**CRF**), which 'connects' the hypothalamus to the hypophysis, where it signals the secretion of **adrenocorticotrophin hormone** (**ACTH**) from the anterior hypophysis. ACTH reaches the suprarenal glands viscerally where it binds to the receptor's tissue and stimulates cellular activity in the zona fasciculata of the adrenal cortex to produce glucocorticoids. Both, glucocorticoids and catecholamines trigger different biological reactions, as we mentioned earlier, permitting to fight or flee (Juster et al., 2011a)

In the case of chronic stress, allostatic load can be studied through biomarkers observing their interactions and their role in the establishment of certain health conditions (see Table 2). It has

been suggested that these biomarkers can be classified into a non-linear network, as following (Juster et al., 2011a):

i) Primary mediators: first, stressors will activate the primary mediators, chemical messengers that are released as part of allostasis. These are the stress-related hormones mainly from the neuroendocrine systems (cortisol, dehydroepiandrosterona, epinephrine, norepinephrine) and the inflammatory system (interleukin-6, tumor necrosis factor, insulin-like growth factor-I). Cortisol, for instance, is involved in the conversion of stored fats and proteins into carbohydrates; anti-inflammatory and immunosuppressive effects; increased blood pressure and heart rate; suppression of digestive, growth, and reproductive activities; and modulation of limbic and prefrontal regions upon traversing the blood–brain barrier. As we already mentioned in Chapter II, section 2, in the case of acute stress, feedback loops are triggered at various levels (e.g. hypothalamus hippocampus, frontal cortex), in order to shut the HPA axis down and return to a set homeostatic point (Lupien et al., 2009). Epinephrine, increases heart rate and glucose levels and decreases digestive and immune functions. Norepinephrine increases blood pressure, constricts blood vessels, and modulates brain activities (Juster et al., 2011a). In case of chronic stress, the GR receptors will diminished resulting in impairment on the negative feedback, and will lead to long-term up-regulation of the HPA axis.

ii) Secondary outcomes: the autonomic nervous system, the inflammatory cytokines and the metabolic hormones are affected by HPA axis activity, and in turn, affect HPA function. In response to chronic stress, primary mediators will be over activated, having effects on cell function that lead to a dysregulation of the secondary outcomes of the metabolic (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides), inflammatory (C-reactive protein, fibrinogen) and cardiovascular systems (systolic blood pressure, diastolic blood pressure, peak expiratory flow).

iii) Tertiary outcomes: the synergistic effect of the mediators causes the clinical manifestation of many diseases that share common inflammatory or immune roots

(e.g. disability, cognitive decline, cellular ageing, chronic diseases, and death) (see Table 2 including AL biomarkers classified as mediators and function).

However, there is currently no consensus regarding the construction of a score capable of capturing physiological wear-and-tear. More biomarkers from children are needed (e.g. primary teeth, hair cortisol). Moreover, the AL score created in empirical research remains limited by pragmatic issues such as variables availability and score composition. Although the concept of allostatic load is well defined, there is an on-going debate regarding the choice of relevant physiological systems, biomarkers, their interactions (linear relationships), their importance in the chain of physiological stress responses, as well as their measurement, combinations, weighting and the most suitable statistical analysis (Delpierre et al., 2016). Future research requires progress in the collection of biomarkers explicitly designed to assess allostatic load at multiple time points in longitudinal large representative samples (Beckie, 2012). Comparative studies are needed to better comprehend the age-related, sex/gender-related, ethnic-related differences in allostatic load (Beckie, 2012). Some of these remaining questions will be addressed in Part V, Discussion, Chapter II.

Table 2. Individual biomarkers commonly incorporated into the allostatic load index from Juster and colleagues (2011)

| Biomarker | Classification | Function |
|---|---|---|
| | | Neuroendocrine |
| Cortisol | Primary mediator | Glucocorticoid produced by the adrenal glands. Functions include the conversion of stored fats and proteins into carbohydrates; antiinflammatory and immunosuppressive effects; increased blood pressure and heart rate; suppression of digestive, growth, and reproductive activities; and modulation of limbic and prefrontal regions upon traversing the blood–brain barrier. |
| Dehydroepiandrosterone | Primary mediator | Androgen produced by the adrenal glands. Known functions include its role as an HPA-axis antagonist and its ability to convert into androgens and estrogens. It also suppresses inflammatory cytokines, improves lipid metabolism and lean muscle mass, decreases insulin resistance, and reduces oxidative brain damage. |
| Epinephrine | Primary mediator | Catecholamine produced by the adrenal glands and the brain. As part of the fight-or-flight response, it increases heart rate and glucose levels and decreases digestive and immune functions. |
| Norepinephrine | Primary mediator | Catecholamine produced by the brain. As part of the fight-or-flight response, it increases blood pressure, constricts blood vessels, and modulates brain activities. |
| Dopamine | Primary mediator | Catecholamine produced primarily in the brain and adrenal glands. It is a well-characterized neurotransmitter involved in many neurological activities (motivation, voluntary movement, cognition) and also increases blood pressure and heart rate. |
| Aldosterone | Primary mediator | Minerocorticoid produced by the adrenal glands. Functions by reabsorbing sodium, retaining water, and excreting potassium in the kidneys in order to maintain blood acidity, as well as to decrease blood volume and blood pressure. |
| | | Immune or Inflammatory |
| Insulin-like growth factor-1 | Primary mediator | Polypeptide protein hormone produced primarily in the liver and pancreas. Functions as a stimulator of cell growth and as an inhibitor of cellular apoptosis. |
| Interleukin-6 | Primary mediator | Cytokine produced by macrophages and T-cells. Functions in pro-inflammation and anti-inflammation by stimulating B cell and T cell differentiation that assist acute phase reactions to tissue damage. |
| Tumor necrosis factor | Primary mediator | Cytokine produced by macrophages. Functions in systemic inflammation by evoking mediators of acute phase reactions as well as in tumor apoptosis. |
| C-reactive protein | Secondary outcome | Protein synthesized in the liver. Functions by enhancing phagocytosis during acute phase reactions that promote inflammation. |
| Fibrinogen | Secondary outcome | Protein that synthesizes into fibrin in the liver. Upon synthesis, functions as a blood clotting factor that promotes coagulation but when excessive increases risk of thrombosis. |
| | | Metabolic |
| High-density lipoprotein cholesterol | Secondary outcome | Lipoprotein synthesized in the liver. Transports cholesterol to tissues that synthesize cell membranes and secretions. Commonly referred to as "bad cholesterol," because its low protein/high cholesterol form is more likely to be deposited in the walls of blood vessels and contribute to atherosclerosis. |
| Low-density lipoprotein cholesterol | Secondary outcome | Lipoprotein synthesized in the liver. Transports cholesterol from tissues to the liver. Commonly referred to as "good cholesterol," because its high protein/low cholesterol form is more easily removed by blood in the liver and excreted in bile. |
| Triglycerides | Secondary outcome | Glyceride formed from glycerol and three chains of fatty acids. Functions as an important source of energy and as a transporter of dietary fat. |
| Glycosylated hemoglobin | Secondary outcome | Hemoglobin used to index the average glucose concentration over many days, weeks, and even months. This proportion represents the amount of glucose that the analyzed hemoglobin has been exposed to during its cell cycle. |
| Glucose | Secondary outcome | Monosaccharide synthesized in the liver and kidneys. Functions as our main source of energy. |

(*continued*)

Table 2. continued

| Biomarker | Classification | Function |
|---|---|---|
| | | Metabolic |
| Insulin | Secondary outcome | Protein hormone produced in the pancreas. Functions by lowering glucose levels and promoting energy storage in the form of glycogen. |
| Albumin | Secondary outcome | Protein produced by the liver. Functions in the maintenance of blood volume regulation and as a carrier for molecules of low water solubility. |
| Creatinine | Secondary outcome | Nitrogeneous waste product of muscle creatine phosphate that is filtered and excreted by the liver. Creatinine clearance is a marker of glomerular filtration rate representing renal functioning. |
| Homocysteine | Secondary outcome | Amino acid biosynthesized from methionine and can convert into cysteine. Functions in remethylation and transsulfuration pathways that are in part dependent on the nutritional intake of folic acid and vitamin B12. Excessive homocysteine levels have been implicated in risk of cardiovascular disease. |
| | | Cardiovascular |
| Systolic blood pressure | Secondary outcome | Measured using a sphygmomanometer. Represents the maximal force exerted by blood against the blood vessel walls when the left ventricle is contracting during systole. |
| Diastolic blood pressure | Secondary outcome | Measured using a sphygmomanometer. Represents the minimal force exerted by blood against the blood vessel walls when the left ventricle is relaxed during diastole. |
| Peak expiratory flow | Secondary outcome | Measured using a peak flow meter. Represents the maximum speed of expiration and the degree of obstruction of airflow through the bronchi. |
| Heart rate/pulse | Secondary outcome | Measured at sites where arterial pulsation can be felt. Represents the number of palpations made by the heart within a period of time. |
| | | Anthropometric |
| Waist-hip ratio | Secondary outcome | Measure of waist circumference and hip circumference using measuring tape values that are than calculated into a ratio by dividing waist by hip. Higher levels represent greater adipose fat distribution of concern for obese individuals. Body shapes that are commonly referred to as apple shapes (greater waist size) are considered to be at greater risk of health problems than "pear shapes" (greater hip size). |
| Body mass index | Secondary outcome | Measure of weight and height that is then calculated into an index by dividing weight by height. Represents a proxy measure of an individual's relative body fat percentage ranging from severely underweight, underweight, normal, overweight, to three different classifications of obesity. |

## 4. Allostatic load first operationalization

The homeostasis process initiates with the release of chemical messengers, called 'mediators' by (McEwen, 2006; McEwen & Wingfield, 2003), exerting effects on tissues and organs *via* cellular activities (called primary effects). Mediators interact in a complex, non-linear and dynamic network, in which each mediator directly or indirectly influence each other. Neurotransmitters, neuropeptides, hormones and cytokines are involved not only in the successful adaptation of a system (*via* allostasis), but they also act as pathophysiological mediators (approached by allostatic load).

An AL score should, by definition, be a composite measure including various physiological systems in order to capture overall physiological wear-and-tear. The MacArthur Study of Successful Aging was the first to propose an AL score (Seeman et al., 1997). Parameters 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 sulfate (DHEA-S) (a functional 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). Each biomarker was then dichotomized into high risk versus low risk according to sex-specific quartiles. The high-risk quartile was the top quartile of all biomarkers, except for those for which a low level confers greater risk for poor health outcomes (e.g. HDL-C) (Seeman et al., 2001; Seeman et al., 1997). 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 or waist circumference), HPA axis (cortisol, DHEA-S), sympathetic nervous system (epinephrine, norepinephrine, dopamine) and inflammation (C-reactive protein, IL-6) (Seeman et al., 2010).

AL was a better predictor of mortality and physical functioning relatively to metabolic syndrome (Karlamangla et al., 2002; Karlamangla et al., 2006), and may be a useful measure of overall health, rather than considering each biomarker separately (Beckie, 2012; Carlson &

Chamberlain, 2005). AL score is also associated with an increased incidence of cardiovascular disease, and poorer cognitive function (Seeman et al., 1997). Recent research also suggests a link between early environment and AL (Danese & McEwen, 2012).

In the section, Part V, Discussion, Chapter II, we will discuss some issues relative to the operationalisation of AL, such as, the challenges for building the score, the biomarkers used, the lack of consensus in the scientific community, etc.

# Chapter IV

# Allostatic Load: a useful indicator to measure the biological embedding of social conditions?

From previous evidence, allostatic load appears to be a good measure of physiological wear-and-tear. In this chapter we will integrate the notion of SEP, since a remaining question is if AL is a suitable candidate to approach the biological embedding of the social environment over the life course. Therefore, allostatic load should be socially patterned and should be associated with later health status.

In section 1 we will review the empirical evidence evaluating allostatic load and the social determinants.

In section 2 we will summarize the evidence suggesting the potential relationship between AL and later health (allostatic load as a predictor of later health).

Finally in section 3 we will integrate the evidence suggesting allostatic load as useful measure to partially capture the social-to-biological transitions. The literature deployed in these three sections allows us to study if AL is a good candidate to approach biological embedding of social environment over the life course.

## 1. Allostatic load and the social determinants

Since the development of allostatic load theory, numerous studies sought to operationalize an AL index with two main purposes: to test the AL index prediction capacities and to describe AL determinants. In this section we will start reviewing evidence to clarify the socioeconomic, and the psychosocial determinants of allostatic load.

Growing evidence suggests that early life SEP is a distal determinant of AL (Chen et al., 2012; Dowd et al., 2009; Gruenewald et al., 2012; Robertson et al., 2015; Robertson et al., 2014), suggesting that poor socioeconomic circumstances early in life could set different population subgroups on life trajectories that are unfavourable for health, increasing their probability of being exposed to unhealthy environmental stressors and life-styles. Initially, the studies from the MacArthur Studies of Successful Aging highlighted the significant influences of SEP, the

psychosocial environment and sex differences on AL. Seeman *et al*. found that the AL index mediated 35% of the socioeconomic gradient in mortality. Particularly, the inflammatory markers and lung function were found to be the strongest mediators of the link between SEP and mortality, compared to the neuroendocrine markers. This suggested that a cumulative measure of biological dysregulation can provide additional information on sources of SEP-related differentials in mortality risk (Seeman et al., 2004).

Gustafsson examined the influence of SEP over the life course on AL (Gustafsson et al., 2011, 2012) in a northern Sweden cohort follow-up for 27 years. The authors found that cumulative socioeconomic disadvantage over the life course was strongly related to AL in adulthood, adjusting for classic confounders health behaviours. Health behaviours explained largely the relationship for men but not for women. In women, they found that SEP during adolescence was independently related to AL, suggesting a critical period effect of exposure to SEP on later AL. For men, only current SEP (in adulthood) was associated with AL independently of risky behaviours (Gustafsson et al., 2011). From a second study, Gustafsson and colleagues investigated whether an AL measure at 43 years of age was influenced by the accumulation of unfavourable social exposures over the life course. The authors took into account and evaluated the influence of material and social adversity. The authors measured social adversity earlier in life using parental loss, residential stability, and parental illness among others. It was found that social adversity during adolescence for women and during early adulthood for men was associated with later AL independently of health behaviours and adulthood adversities. Additionally these findings supported the idea of a cumulative risk, and a sensitive period life course models, but there was little support for a social pathway model. Sadly, the earliest adversity exposure was measured at age 16, which did not allow to test whether childhood social circumstances could represent a critical period (Gustafsson et al., 2012).

Using data from the West of Scotland Twenty-07 Study, Robertson and colleagues compared the life course models (critical periods, pathways, accumulation) using SEP measures from three life-stages, modelled against allostatic load (Robertson et al., 2014). The authors found that accumulated SEP across the life span was the best fitting life course model explaining the association between SEP and AL 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 of 75 years (Robertson et al., 2014). 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 AL (Robertson et al., 2015).

Gruenewald *et al.* also investigated the life course hypothesis explaining the link between SEP and AL. The authors found, as for Robertson's study, that greater experience of socioeconomic adversity across the life course may accumulate to have a greater negative effect on biological functioning in later adulthood. They concluded that higher AL 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 (Gruenewald et al., 2012).

Regarding exposure to psychosocial stress a cross-sectional comparison of the Wisconsin Longitudinal Study and the Mac Arthur Study revealed that less social integration, less social support, more judgemental families were related to higher AL (Seeman et al., 2002). These findings reinforced the hypothesis that positive social experiences are associated with lower physiological wear-and-tear.

Danese & McEwen investigated the empirical evidence suggesting a link between adverse childhood and later health, using the theoretical framework of allostasis and allostatic load (Danese & McEwen, 2012). They suggested that the application of these concepts could provide a powerful scientific basis for understanding how early environment may impact health in the long-term. As we already mentioned in Part I, Chapter I, section 4, early life exposure to adverse childhood experiences (ACE), 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 well-being (Anda et al., 2006; Lupien et al., 2009). 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*".

Studying chronic stress during sensitive periods –captured by Rutter's notion of Adverse Childhood Experiences- and evaluate its effects on an overall measure of physiological wear-and-tear could indeed provide a better understanding of social and biological transitions over the life course.

Overall these findings suggest that allostatic load is socially patterned (Dowd et al., 2009; Robertson et al., 2014; Seeman et al., 2010; Szanton et al., 2005), determined by socioeconomic position, material, psychosocial and behavioural factors all over the life span (Robertson et al., 2015). The allostatic load conceptual framework may contribute to clarify the biological component of the socioeconomic gradient observed in morbidity and mortality. However, some issues remain, which will be introduce later in Part V, Discussion, Remaining research challenges.

## 2. Allostatic load as a predictor of later health status

Growing evidence supports the idea that exposure to stressful conditions over life contributes to physiological dysregulation, subsequently translated into disease, through prolonged activation of stress response systems (McEwen & Seeman, 1999; McEwen & Stellar, 1993; Seeman et al., 2001). AL has been strongly correlated with subclinical conditions, cardiovascular events, physical and functioning decline and mortality (Juster et al., 2010; Karlamangla et al., 2002; Karlamangla et al., 2006). Beckie reviewed 185 articles to summarize the epidemiological evidence linking AL with health and health disparities, concluding that this literature supports the advantages of using AL for predicting subclinical states of numerous outcomes (Beckie, 2012). The studies from the MacArthur Studies of Successful Aging (Karlamangla et al., 2002) found in high functioning elderly individuals that AL was a predictor of later functional decline. Concerning mortality, they found that an increase of the AL score was linked with an increase of mortality risk 4.5 years later (Karlamangla et al., 2006). Seplaki and colleagues showed cross-sectionally that higher AL was correlated with self-rated health, activities of daily living,

mobility, as well as depressive symptoms, and cognitive impairment in Taiwanese elders of the Social Environment and Biomarkers of Aging Study (SEBAS) (Seplaki et al., 2006).

In 2010 a study investigated the association between AL with six chronic conditions (abdominal obesity, hypertension, diabetes, and self-reported cardiovascular disease, arthritis and cancer) in a cohort of Puerto Rican older adults living in the United States of America (USA). They additionally compared the results with a similar analysis using the metabolic syndrome. This study was interesting since racial and ethnic health disparities are a key tenet for comprehending the embodiment of our social environment. They found that AL was associated with abdominal obesity, hypertension, diabetes and self-reported cardiovascular disease and arthritis, but not with self-reported cancer. AL was also a better predictor of self-reported cardiovascular disease, arthritis and hypertension, and abdominal obesity, than metabolic syndrome. Only diabetes showed a stronger link when the metabolic syndrome was used as a predictor. Finally, neither allostatic load, nor the metabolic syndrome were predictors of reporting having cancer (Mattei et al., 2010).

In summary, this literature suggests a link between AL and several dimensions of health, such as cardiovascular morbidity and mortality. However, allostatic load has not yet be confronted with an overall measure of health. Moreover, some of this literature has focussed on elderly populations, and the relative importance of early life over the life course on AL and later health should be further explored.

## 3. AL as a measure of embodiment

In this section, we will summarize some evidence that justifies the use of AL as an indicator that could partially capture the embodiment processes over the life course.

Taking the example of adverse childhood experiences (ACE), Kelly-Irving and colleagues investigated recent evidence of the physiological embedding of stress causing chronic or acute stress responses that may alter fundamental biological functions. The authors proposed two main biological pathways through which the experience of ACE may get 'under the skin'. Stress induced by ACE could influence the onset of cancer *via*: (1) a 'direct' effect of stress on biological systems including neuroendocrine responses and epigenetic modifications, and (2) an 'indirect' biological effect of health behaviours as a response to early stress. Evidently, these pathways are intertwined and both mechanisms are likely to be set in place simultaneously

over time. They concluded that neuroendocrine, inflammatory responses and epigenetic modifications are potential biological mechanisms that may have an impact on both types of pathway.

McEwen & Gianaros reviewed evidence showing similar insights mentioned earlier: maltreatment, stressful life events and adverse physical and social conditions have an impact on structural and functional plasticity of the brain structures and ageing. An individual that grows-up, lives and ages in a low SEP may become more vulnerable to adverse social exposures impacting functionality of stress regulatory systems of the brain and the body (McEwen & Gianaros, 2010). The authors proposed that the cardiovascular system appears to be highly sensitive to stress. For instance, blood pressure has been reported to increase when individuals have repetitive jobs and time pressures, or if their work is undergoing structural changes. Metabolic disorders are also likely to be modified by social stressors, for instance, abdominal obesity is more important among the less well-off. An impaired immune system also appears to be vulnerable to stress within the context of lower SEP. These findings reinforce the idea that the systems that are most sensitive to stress are: the autonomic nervous system, the HPA axis, cardiovascular, metabolic and immune-inflammatory systems, all of which facilitate organisms to adapt to environmental challenges. It is noteworthy that the hippocampus and amygdala are anatomically and functionally connected and both have influences on the HPA axis, being the hippocampus generally inhibitory and the amygdala excitatory (McEwen & Gianaros, 2010).

Health behaviours, such as smoking, drinking, exercise, having a healthy diet and sleep are important features of how an individual copes with daily life challenges. Being frequently exposed to environmental stressors, failing to terminate adaptive responses to a particular environment may promote the adoption of adverse health behaviours. Concerning psychosocial factors, an important concept contained within the allostatic load framework is the notion of anticipation. These elements were originally introduced for explaining the physiological anticipation of environmental changes (for instance, preventing blacking out when getting out of bed in the morning). However, this may apply to psychosocial apprehension in some psychological states like anxiety, or cognitive preparation for an up-coming event. These kind of anticipation can trigger the allostasis mediators such as ACTH, cortisol and

adrenalin. If these conditions of anticipation remain in place over the long term, it is likely to cause an allostatic load state (McEwen & Gianaros, 2010).

Moreover, epidemiological evidence suggests that as a composite measure, AL performs as a better predictor of subsequent morbidity and mortality over and above each constituent biomarker when analysed individually (Karlamangla et al., 2002; Robertson et al., 2015; Seeman et al., 2001), or other composite indicators like the metabolic syndrome. These findings suggest that AL could represent a global physiological state and perhaps even a proxy for an outcome of the embodiment process.

Another reason for using AL as an indicator for partially capturing the embodiment processes is that the AL model, focussed on long-term accumulation and gradual development of physiological dysregulations, is conceptually compatible with life course influences on the social and biological transitions.

As a measure of the global cost of adapting to (and coping with) the environment, AL may be a relevant tool for measuring the way we have embodied our environment over life, partly explaining social inequalities in health. We consider AL as a relevant and useful tool for measuring and comparing embodiment between population and socioeconomic groups. However, some important issues regarding AL deserve consideration; which will be debated in the Part V, Discussion, Chapter II and Chapter III.

In conclusion, after reviewing evidence of allostasis and the allostatic load conceptual framework, as well as the neurobiological and epidemiological evidence, it seems that an allostatic load index may be a useful summary measure of embodiment processes. Here, we consider AL as a conceptual tool in measuring the biological effect of embodiment that plays a role in the production of the social gradient of many chronic diseases. From early life onwards, being able to measure the way in which people cope with their environment offers many possibilities regarding public health interventions both at a societal level by investing in childhood or in social environment, and at an individual level by preventing diseases through behavioural or treatment interventions. Before operationalising AL as a measure of embodiment, a number of issues deserve further exploration. To comprehend the theory behind AL we highlighted that measures used should be constructed, where possible, to represent multiple biological systems. In order to achieve this, good quality stable biological

markers (with multiple biological measures, made at various stages across the life span); as well as data on the psychosocial and socioeconomic environment are needed.

# Remaining research challenges

Two main conditions have to be fulfilled for considering allostatic load as a useful measure of embodiment of social conditions: allostatic load must be socially patterned, allostatic load should be a good predictor of later health.

After this literature review we will highlight the central challenges that remain concerning the use of the notion of allostatic load to evaluate the social-to-biological transitions from early life, and across the life course.

i) Hypothesizing that psychosocial adversity is a source of chronic stress, the study of the link between early psychosocial factors and allostatic load is a central step, using prospective data and by integrating additional pathways. However this was not thoroughly examined in previous research.

ii) Indeed, evidence suggests that allostatic load is socially patterned, however, some issues remain unclear. Typically, it is not yet well-establish if different social determinants from early life, with different theoretical meanings, play a distinct role on allostatic load. Specifically, it is not well-established whether different social determinants impact AL through the same pathways and mechanisms across the life course.

iii) Empirical research has investigated the link between AL and later health outcomes showing strong correlations with subclinical conditions, cardiovascular events and mortality risk. To a lesser extent, other aspects of health have been correlated with AL, like decline in cognitive and physical functioning. However, due to the global physiological effect captured by the AL concept, it is particularly pertinent to examine its association with subsequent health by taking a broad definition of the latter. To our knowledge, this step was not yet addressed by previous research.

# Chapter V

# Objectives and hypothesis

In this work, we seek to clarify the relevant theoretical notions of social causation, or how the social becomes biological, integrating theories regarding allostatic load, embodiment and biological embedding.

## 1. Objective

Our main objective is to investigate whether allostatic load, as a measure of physiological wear-and-tear, mediates the relationship between the early social environment and later biological responses. To address this question we adopted a life course framework, to identify and describe environmental factors in early life, childhood, adolescence and adulthood that may be implicated in the embodiment dynamic. We will investigate if allostatic load is a suitable index for capturing embodiment of social adversity from the youngest age, allowing for a better understanding of the genesis and accumulation of health inequities.

A secondary objective is to contribute to the development of an epidemiological research instrument capable of capturing the embodiment processes of social, material and psychosocial adversities and their impact on later health.

## 2. Hypotheses

Our key hypothesis is that allostatic load represents a physiological outcome partially capturing embodiment processes across the life course. Allostatic load is, by middle age, a biological reflection of some combination of sensitive period effects and pathways effects. The first influencing health 'directly', resulting from an insult during a sensitive period having a lasting impact in brain and physiological development. The second, influencing health 'indirectly', through socioeconomic circumstances, psychosocial factors and health behaviours accumulating over the life course. Finally we hypothesized that allostatic load is a useful measure for studying the environmental impact of life adversity on health, allowing the early identification, monitoring and surveillance of social determinants of health.

## 3. Axes of analysis

This thesis was structured around three axes of analysis, each contributing to meet the overall objective of the project.

Axis 1 aimed to investigate the psychosocial factors in early life linked with a later index of allostatic load (Part III, Chapter I).

Axis 2 studied the mediating pathways between parental SEP and later allostatic load (Part III, Chapter II).

Axis 3 explored whether allostatic load at 44 years, given its social pattern, was linked to an integrative latent variable of health status at 50 years (Part IV, Chapter I).

In Part II we will describe some common pitfalls concerning the sample and the general methodological issues of the three major axis.

In Part III we will sketch out the specific theoretical rationale, as well as the context, methods, results and discussion of axis 1 and axis 2.

In Part IV we will introduce research axis 3, which explores the association between allostatic load and later health.

The general discussion will be deferred in Part V. We will review and debate our main findings, and we will finally conclude with some recommendations in light of future research challenges and perspectives.

# PART II

# GENERAL METHODS: A LIFE COURSE APPROACH FOR ANALYSING EPIDEMIOLOGICAL DATA

# Résumé - Partie II : Méthodes

Notre projet de recherche a été conçu avec des données issues du National Child Development study (NCDS), une cohorte de naissance Britannique cohorte débutant en 1958. Cette étude comprend au total 18 558 personnes nées pendant une semaine de mars 1958 en Angleterre, en Ecosse et au Pays de Galles. La première vague correspondait à une étude sur la mortalité périnatale (PMS). Les participants de la cohorte ont été ensuite suivis huit fois jusqu'à l'âge adulte pour surveiller la santé des participants, leur niveau d'éducation, leur contexte économique et social. Ces enquêtes ont été réalisées en 1965 (7 ans), 1969 (11 ans), 1974 (16 ans), 1981 (23 ans), 1991 (33 ans), 1999-2000 (en 42 ans), 2004-2005 (46 ans) et 2008-2009 (50 ans). En outre, une enquête biomédicale a été menée entre 2002-2003 (44-45 ans) et du sang a été prélevé, afin d'obtenir des mesures de facteurs de risque biomédicaux. Pour ce travail, divisé en trois axes de recherche, nous avons utilisé plusieurs vagues : le PMS, vague 1, vague 2, vague 3, vague 4, vague 5, l'enquête biomédicale et la vague 8.

Concernant les méthodes utilisées dans ce travail pour atteindre nos objectifs, nous avons utilisé un modèle de médiation. Un médiateur peut être défini comme une variable qui a un rôle dans la chaine de causalité entre la variable d'exposition (variable indépendante) et le critère de jugement (variable dépendante). Pour l'axe 1 de recherche, nous avons effectué une analyse de médiation pour explorer les liens entre les adversités durant l'enfance (ACE en anglais) comme variable indépendante, et la charge allostatique (critère de jugement) comme variable dépendante. Notre objectif était d'explorer trois voies de médiation: i) une voie socio-économique / matérielle, ii) une voie psychosociale, et iii) une voie liée aux comportements de santé à risque. La voie «directe» (donc non médiée) entre les ACE et la CA a été calculée en utilisant une régression linéaire multivariée classique après ajustement sur les facteurs de confusion et les variables de médiation. Les voies «indirectes» (donc médiées) correspondaient à la partie de l'effet observé entre les ACE et le score de CA expliquée par les facteurs de médiation.

Pour l'axe 2 de notre recherche nous avons analysé les voies de médiation entre l'éducation maternelle et la CA; et par la suite entre la profession du père et la CA, chez les hommes et chez les femmes. Nous avons étudié quatre voies de médiation : i) une voie financière / matérielle, ii) une voie psychosociale / psychologique, iii) une voie éducationnelle, et iv) une voie liée aux comportements de santé et l'Indice de Masse Corporelle (IMC).

L'imputation des données manquantes a été utilisée pour les trois axes de recherche. Cette méthode est généralement utilisée pour la correction de la non-réponse partielle d'une enquête. Dans des études de cohorte, les données manquantes sont inévitables. Nous avons décidé dans notre étude d'utiliser les imputations multiples, ce qui permet utiliser toutes les données disponibles, la préservation de la taille de l'échantillon et la puissance statistique. Les données manquantes peuvent être distinguées comme « missing completely at random » (MCAR), « missing at random » (MAR), et « missing not at random » (MNAR). Dans cette étude, nous avons effectué trois modèles d'imputation, un pour chaque axe de recherche. Vingt bases de données ont été imputées en faisant l'hypothèse que les données étaient MAR. Chaque covariable avec des valeurs manquantes a été imputée. Le modèle d'imputation incluait tous les facteurs de confusion et de médiation du modèle multivarié. La variable d'exposition ainsi que la variable dépendante ont été exclues du modèle d'imputation.

Concernant l'opérationnalisation de la CA, parmi les biomarqueurs disponibles, nous avons sélectionné quatorze paramètres représentant quatre systèmes physiologiques : neuroendocrien (cortisol t1 (nmol/L), cortisol t1-t2 (nmol/L)); immun & inflammatoire (facteur de croissance insulino-mimétique (IGF-1 nmol/L), protéine C-réactive (CRP mg/L), fibrinogène (g/L), immunoglobuline E (IgE KU/L)); système métabolique (HDL (mmol/L), LDL (mmol/L), triglycérides (mmol/L), hémoglobine glyquée (%)); système cardiovasculaire & respiratoire (pression artérielle systolique (mmHg), pression artérielle diastolique (DBP mmHg), fréquence cardiaque (p/min), débit expiratoire de pointe (L/min)). Notre score correspondait à la somme des quatorze paramètres pour lesquels le sujet a été classé dans le quartile le plus à risque ( '1' vs faible risque '0'). Le quartile le plus à risque était le quartile supérieur pour tous les biomarqueurs, à l'exception de ceux pour lesquels un faible niveau confère un plus grand risque par rapport à la santé (HDL, cortisol salivaire t1-t2, IGF-1, débit expiratoire de pointe). Nous avons exclu de notre échantillon les personnes pour lesquelles aucun des quatorze biomarqueurs n'était disponible. Nous avons stratifié notre analyse par sexe.

Trois analyses de sensibilité ont été conduites pour évaluer la stabilité de nos résultats. La première était une série d'analyses de régressions sur chaque biomarqueur individuel pour étudier la stabilité du score de CA. Nous avons étudié s'il existait un paramètre ayant un poids plus élevé par rapport aux autres au sein du score. Étant donné que le nombre de personnes avec des données manquantes sur le score était plutôt élevée (> 3000), une deuxième analyse de sensibilité qui imputait les biomarqueurs manquants a été réalisée, pour garantir que les résultats n'étaient pas biaisés par les biomarqueurs manquants. Nous avons enfin construit un deuxième score de CA pour les axes 2 et 3 en calculant un score par système, ce qui donne un poids égal pour chaque système physiologique. Aucune différence significative n'a été observée en fonction des analyses réalisées confirmant la stabilité de nos résultats.

# Chapter I

# The National Child Development Study & sample

In this chapter we will present the cohort study used in this work in section 1, describing each data collection. In section 2 we will introduce the general sample specifically used to answer our research questions and in section 3 we will comment some ethical issues concerning the biological data.

## 1. The National Child Development Study (NCDS)

Our research project was conceived using The National Child Development Study (NCDS), a population based British birth cohort starting in 1958. It included a total of 18558 individuals. It comprised 17638 individuals born in one week in 1958 in England, Scotland and Wales recruited into the Perinatal Mortality Study (PMS); and additionally 920 immigrants born in the same week.

The original study aimed to identify social and obstetric factors linked to stillbirth and neonatal death. It is important to point out that the original survey was not planned as a longitudinal study. However, the National Children's Bureau was commissioned by the Central Advisory Council for Education to renewing a second survey when the participants were 7 years of age, with the objective to monitor their educational, physical, and social development (Power & Elliott, 2006).

After the PMS, cohort members were followed-up eight times (each follow-up is called a 'sweep') into adulthood to monitor participant's health, education, social and economic circumstances. These surveys were carried out in 1965 (age 7), 1969 (age 11), 1974 (age 16), 1981 (age 23), 1991 (age 33), 1999-2000 (age 42), 2004-2005 (age 46) and 2008-2009 (age 50). As part of the 1991 survey, information was additionally collected from co-resident partners and for a third of the sample, data was also collected from any co-resident natural or adopted children of the cohort member. Surveys of sub-samples of the cohort took place in 1976 (age 18), 1978 (age 20) and 1995 (age 37). The most recent sub-study, in 1995, involved conducting basic skills assessments with 10% of the cohort. Additionally, a biomedical survey was

conducted in 2002-2003 (age 44-45) in order to obtain objective measures of ill-health and biomedical risk factors (Brown et al., 2012).

For the objective of this work we used several sweeps from the NCDS 1958 birth cohort. For the different research axis we generally included the PMS, sweep 1, sweep 2, sweep 3, sweep 4, sweep 5, biomedical survey and the 8th sweep. Following we will briefly summarize the content of each sweep used in this thesis.

### 1.1. PMS survey at birth

At birth, the first survey of the NCDS cohort was completed by the mother's participants. Information about the social and family background, details of past obstetric history, antenatal care and abnormalities during pregnancy, length and abnormalities of labour, analgesia and anaesthesia as well as sex, weight, progress, management and outcome of the infant was collected.

### 1.2. First sweep at age 7

The 1965 survey comprised four parts. First, a parental interview, most commonly the mother alone, was interviewed in the home by an officer of the local authority, usually a Local Authority Health Visitor, using a structured interview schedule. Each child received a full medical examination from a Local Authority Medical Officer who also carried out some special tests and completed a medical schedule, additionally using some information available from medical records to help in compiling a medical history. A school questionnaire, was completed by the head teacher and class teacher(s) providing information on the school and on the study child. Finally, the child's direct contribution to the study, limited to the completion of tests administered in school (Center for Longitudinal Studies).

### 1.3. Second sweep at age 11

The 1969 survey followed the same structure that the previous one. However, the members' participation increased. The survey included at eleven years of age questions on leisure activities and attitudes to school. Each child was also asked to write a short composition on the life s/he imagined s/he would be leading at the age of 25. Different test were also performed: a general ability test -containing verbal and non-verbal items; a reading comprehension test -

constructed by the National Foundation for Educational Research in England and Wales (NFER) specifically for use in this study; and an arithmetic/mathematics test - constructed by NFER especially for use in this study (Center for Longitudinal Studies).

### 1.4. Third sweep at age 16

Conducted in 1974, this survey followed the same composition of the previous two. However, the questionnaire also included questions on participants attitudes to school and to methods of punishment in school, future educational and occupational expectations and aspirations, reasons for leaving school and choosing a job, school absences, self-ratings in school subjects, spare-time work, income and pocket money, intentions about marriage and having children, sex education and preparation for parenthood, leisure activities, family relationships, smoking and drinking and handedness (Center for Longitudinal Studies).

### 1.5. Fourth sweep at age 23

Conducted in 1981, the cohort members were experiencing major life transitions: from school to higher education or work, from parental dependency to independency and so on. Data on housing and household (e.g. overcrowding, sharing spaces/amenities, tenure of the accommodation, and type of accommodation), family income, savings and investment, employment, unemployment were collected. Apprenticeship and training, marriage, cohabitation, children, reported health state and health behaviours, psychological health, activity and leisure were collected (Center for Longitudinal Studies).

### 1.6. Fifth sweep at age 33

Conducted in 1991 this sweep followed the same composition of the previous one with additional information of the partner and child members of the family (Center for Longitudinal Studies).

### 1.7. Biomedical survey at age 44-45

Data collection was carried out on cohort members between birth and 50y. At age 44-45 a biomedical survey was conducted including a self-reported questionnaire, physical measurements, blood and saliva samples for a target sample of 12070 individuals of the original cohort and data were finally available for 9377. The purpose was to collect objective measures

of ill-health and biomedical risk factors in order to address a wide range of specific hypotheses relating to anthropometry, cardiovascular, respiratory and allergic diseases, visual and hearing impairment, and mental ill-health.

A large panel of biomarkers were collected from biochemical analyses of blood samples; physical measurements (e.g. blood pressure, heart rate, lung function, vision, hearing, etc); anthropometric measurements (e.g. height, weight, waist-hip circumference, etc); medical treatment (e.g. hormone replacement treatment for women); general and psychological health; and diet (Elliott et al., 2008).

### 1.8. Eighth sweep at age 50

Conducted from August 2008 to May 2009, this NCDS survey comprised in total 12316 cohort members with a final sample of 9790 participants interviewed. This survey was comprised of two parts: a 'core' face-to-face interview and a paper self-completion questionnaire. As in all recent follow-ups the main aim was to update information gathered in previous surveys in order to explore the factors central to the formation and maintenance of adult identity in each of the following domains: lifelong learning; relationships, parenting and housing; employment and income; health and health behaviours; citizenship and values (Brown et al., 2012).

Table 3 summarizes the initial target and final sample of each sweep of the NCDS 1958 birth cohort.

Table 3. Target and final sample of each sweep of the NCDS 1958 birth cohort

| Sweep | Age | Years | Cross-sectional target sample | Cross-sectional final sample |
|---|---|---|---|---|
| PMS | Birth | 1958 | 17 634 | 17 416 |
| 1 | 7 | 1965 | 16 727 | 15 425 |
| 2 | 11 | 1969 | 16 754 | 15 337 |
| 3 | 16 | 1974 | 16 901 | 14 647 |
| 4 | 23 | 1981 | 16 482 | 12 537 |
| 5 | 33 | 1991 | 16 240 | 11 407 |
| 6 | 42 | 2000 | 16 240 | 11 419 |
| Biomedical | 44-45 | 2003 | 12 037 | 9 377 |
| 7 | 46 | 2004 | 11 739 | 9 534 |
| 8 | 50 | 2008 | 12 316 | 9 790 |

## 2. General sample used in our work

From the data available from the biomedical survey (n=9377) we excluded from the analysis all the cohort members who had clinical conditions or medication potentially disturbing the biological measures. Under this criteria were excluded pregnant women, individual's taking anticoagulant medication, and those for whom blood was not obtained. Our sample included 4057 men and 4056 women. However for each axis, we worked on different samples. Figure 4 summarizes the general flow chart of each research axis of this study.

### 2.1. Axis 1 sample

For studying the Adverse Childhood Experiences and allostatic load, we worked on a final imputed sample of 3753 men and 3782 women. The complete case sample was 1867 men and 1984 women.

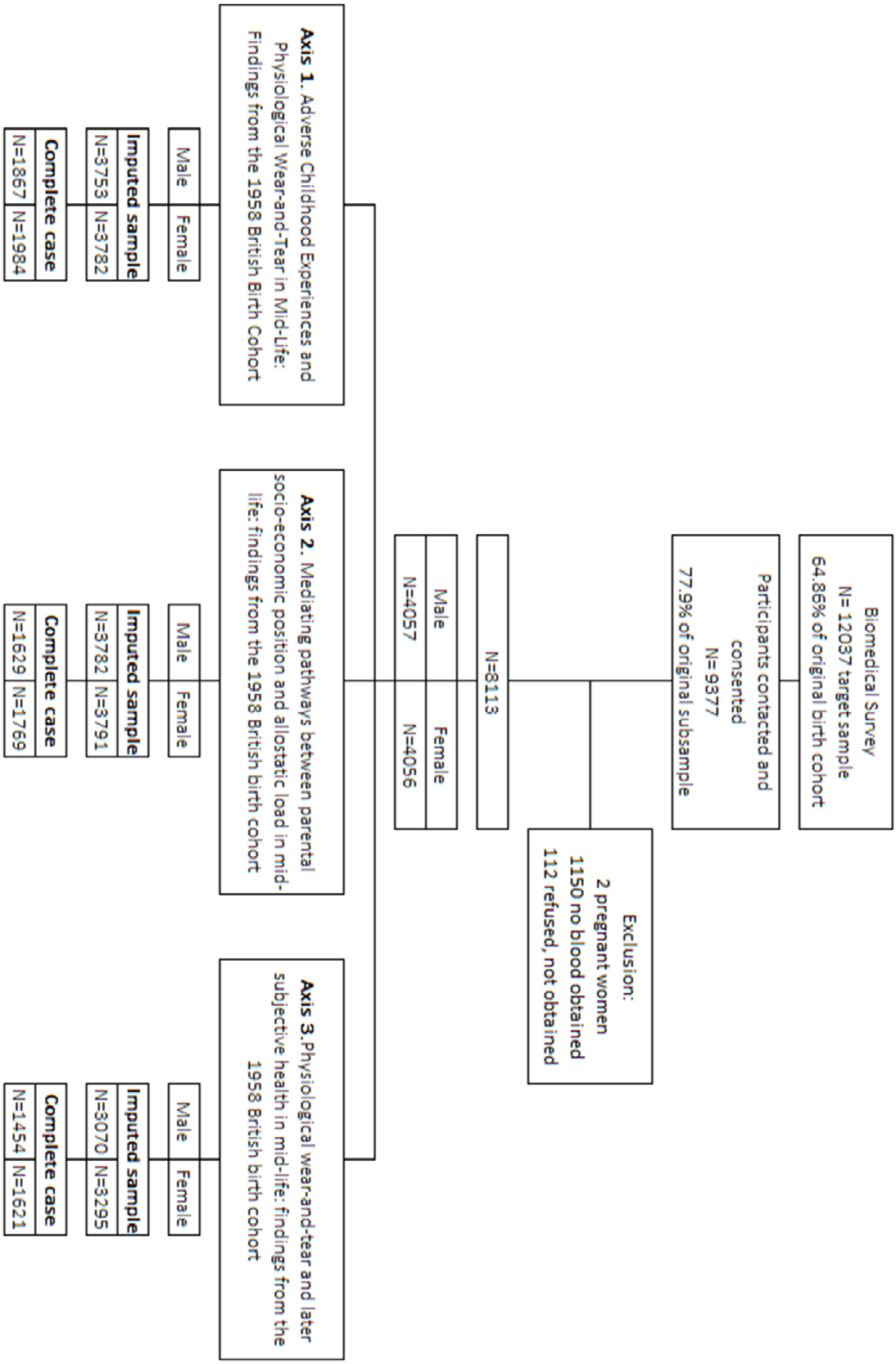
### 2.2. Axis 2 sample

For studying the mediating pathways between parental socioeconomic position and allostatic load in mid-life, we worked on a final imputed sample of 3782 men and 3791 women. The complete case sample corresponded to 1629 men and 1769 women.

### 2.3. Axis 3 sample

Finally for studying the mediating pathways between parental socioeconomic position and allostatic load in mid-life, we worked on a final imputed sample of 3070 men and 3295 women. The complete case was composed of 1454 men and 1621 women.

Figure 4. Diagram of inclusion and exclusion criteria for the analysis from the biomedical survey of the National Child Development Study. The sample imputed for missing data and used to run statistical analyses for each research axis is presented.



## 3. NCDS ethical approval and consent

Written informed consent was obtained from parents for childhood measurements and ethical approval for the adult data collection was obtained from the National Research Ethics Advisory Panel. NCDS data are open access and datasets are available to non-profit research organizations. Ethical approval for the age 44-45 year survey was given by the South East Multicentre Research Ethics Committee (MREC) (Shepherd, 2012). Table 4 lays out the ethical approval and consent for each sweep.

Table 4. NCDS 1958 birth cohort ethical approval and consent for each sweep

**NCDS ethical approval and consent**

| Sweep | Age | Year | Approval |
|---|---|---|---|
| PMS | Birth | 1958 | Internal review only * |
| NCDS 1 | 7 | 1965 | Internal review only * |
| NCDS 2 | 11 | 1969 | Internal review only ** |
| NCDS 3 | 16 | 1974 | Internal review only ** |
| NCDS 4 | 23 | 1981 | Internal review only ** |
| NCDS 5 | 33 | 1991 | Internal review only ** |
| NCDS 6 | 42 | 2000 | London MREC |
| Biomedical | 44-45 | 2002-2003 | South East MREC |
| NCDS 7 | 46 | 2004 | Internal review only *** |
| NCDS 8 | 50 | 2008 | London MREC |

*: Predates establishment of ethics committees in 1966

**: Predates establishment of MRECs in 1997

***: Not sought as telephone survey involved no medical assessment/measurement

Reference: Shepherd 2012

# Chapter II

# General statistical methods

In this chapter we will explain the common statistical methods used in our study. In **section 1** we will review the theoretical framework, the concept and the specific application to our work of the mediation analyses. Mediation analysis was used for addressing the methodological needs for research axis 1 and 2.

In **section 2** we will explain the multiple imputation analyses used in our study. This was used to answer a common statistical question regarding all three research axes.

Finally in **section 3** we will summarize the methodological issues regarding the use of a life course framework in our study.

## 1. Mediation analysis

### 1.1. Concept

The objective of a mediation model is to identify and elucidate the mechanisms or processes that underlie an observed relationship between an independent variable and a dependent variable *via* the inclusion of a third hypothetical variable, known as a mediator variable (also a mediating variable, intermediary variable, or intervening variable). The conceptual framework for the use of the mediation model was introduced by Baron and Kenny in 1986, they defined a mediator as follows:

> "*the mediator function of a third variable, which represents the generative mechanism through which the focal independent variable is able to influence the dependent variable of interest*" (Baron & Kenny, 1986).

Figure 5 illustrates the mediation concept.

According to Baron and Kenny, to establish a simple mediation, three conditions should be present:

i) the independent variable (X) must affect the mediator (M) in the first equation;

ii) the independent variable (X) must be shown to affect the dependent variable (Y) in the second equation;

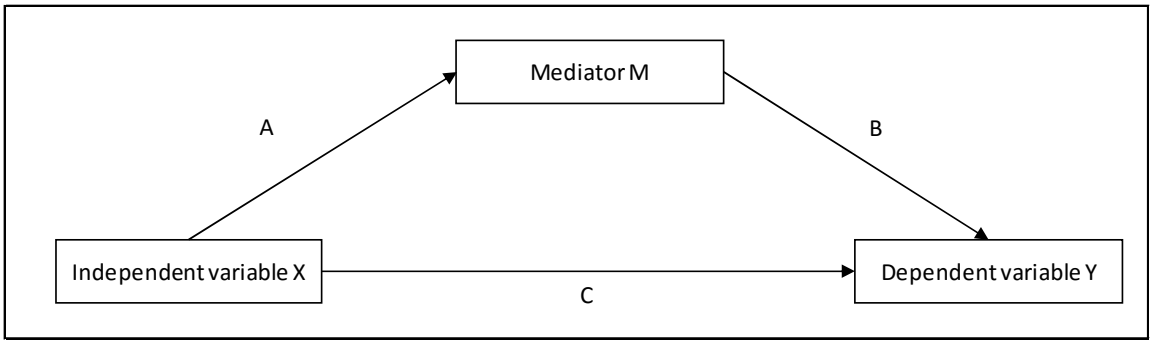
iii) the mediator (M) must affect the dependent variable (Y) in the third equation.

If these conditions hold in the predicted direction, then the effect of the independent variable (X) on the dependent variable (Y) must be less in the third equation than in the second. Perfect mediation holds if the independent variable (X) has no effect when the mediator is controlled.

The authors added:

> "*Because the independent variable is assumed to cause the mediator, these two variables should be correlated. The presence of such a correlation results in multicollinearity when the effects of independent variable and mediator on the dependent variable are estimated. This results in reduced power in the test of the coefficients in the third equation. It is then critical that the investigator examine not only the significance of the coefficients but also their absolute size. For instance, it is possible for the independent variable to have a smaller coefficient when it alone predicts the dependent variable than when it and the mediator are in the equation but the larger coefficient is not significant and the smaller one is"* (Baron & Kenny, 1986).

Figure 5. Simple mediation example




## 1.2. Path analyses & application to our work

In the case of our analyses we used the mediation framework as applied to the specific example of path analyses. Our analyses fit the case for a simple mediation framework and thus we are

faced the situation were an explaining variable have a significant effect on the outcome variable, which will be weakened, partially or totally, after adjustment for the mediator variable. Path analysis is defined as follows in epidemiological research:

> *"A mode of analysis involving assumptions about the direction of causal relationships between linked sequences and configurations of variables. This permits the analyst to construct and test the appropriateness of alternative models (in the form of a path diagram) of the causal relations that may exist within the array of variables included in the finite system studied. Identification of the less probable sequences of causal pathways may permit them to be eliminated from further consideration"* (Porta M, 2008).

To address the research questions of axes 1 and 2, the mediation effect was estimated through a linear regression for the statistical analyses using a path analysis. For the purposes of clarity we will call the remaining effect after adjustment for the mediator a 'direct' effect or 'direct' path, equivalent to path C in Figure 5. The effect explained by the mediators will be referred to as an 'indirect' effect or 'indirect' path, represented by path A + B in Figure 5. Hence, the path analysis allows us to disentangle and describe the 'indirect' effect pathways.

#### 1.2.1. Path analysis in axis 1

We conducted a path analysis using the variable representing Adverse Childhood Experiences (ACE) as the exposure variable to explore the relationships between ACE and allostatic load. We remind the reader that our objective was to explored three mediating pathways: i) a socioeconomic and materialist pathway, ii) a psychosocial pathway, and iii) a health behaviours pathway. The 'direct' pathway between ACE and AL was estimated using a classic multivariate linear regression after adjustment for confounders and mediation variables. The 'indirect' pathways corresponded to the part of the effect observed between ACE and AL score that was explained by the mediating factors.

#### 1.2.2. Path analysis for axis 2

We analysed the mediation paths between maternal education and AL; and subsequently between paternal occupation and AL; in both men and women. We investigated four mediating

pathways: i) a material/financial pathway, ii) a psychosocial/psychological pathway, iii) an educational pathway, and iv) a health behaviours & BMI pathway. As for Axis 1, the 'direct' path was the remaining effect after adjustments for the mediators and the 'indirect' path corresponded to the effect explained by the mediators.

### 1.3. Path analysis formulas

For disentangling the 'direct' and the 'indirect' path, we used the following formulas:

We note:

- y : the matrix (n x 1) describing the explaining variable (outcome)
- W: the matrix (n x $N_w$) describing the exposure variable
- X: the matrix (n x $N_x$) describing the confounders
- Z: the matrix (n x $N_z$) describing the mediation variables

We used the following formulas:

$$(1)\ \mathrm{y} = \beta_{01} + \beta_{11}\mathrm{X} + \beta_{21}\mathrm{W} + \varepsilon_1$$

$$(2\mathrm{i})\ \mathrm{y} = \beta_{02\mathrm{i}} + \beta_{12\mathrm{i}}\mathrm{X} + \beta_{22\mathrm{i}}\mathrm{W} + \beta_{32\mathrm{i}}\mathrm{Z_i} + \varepsilon_{2\mathrm{i}}$$

$$(3\mathrm{i})\ \mathrm{y} = \beta_{03} + \beta_{13}\mathrm{X} + \beta_{23}\mathrm{W} + \beta_{33\mathrm{i}}\mathrm{Z_i} + \beta_{43\mathrm{i}}\mathrm{Z_{(-i)}} + \varepsilon_3$$

Equation (1) allowed us to measure the coefficient $\beta_{21}$ that represented the total effect of W on y. $\beta_{21}$ was distributed between the direct effect $\beta_{23}$ (the linear coefficient after adjustment for confounder and mediators) and the indirect effect, through the mediating variables Z. The total indirect effect of exposure variable on our outcome *via* the mediating factors was equal to the total effect $\beta_{21}$ minus the direct effect $\beta_{23}$. To calculate separately each effect we proceeded as follows:

$$(4\mathrm{i})\ \text{Indirect effect of W } via\ \mathrm{Z_i} = (\beta_{21} - \beta_{22\mathrm{i}})/\beta_{32\mathrm{i}} * \beta_{33\mathrm{i}}$$

This calculation rose from the fact that including a term $Z_i$ associated with $\beta_{32i}$ in the model (1) affected the coefficient associated with W of ($\beta_{21}$ - $\beta_{22i}$). However, in the final model, the coefficient associated with $Z_i$ is no longer $\beta_{32i}$ but $\beta_{33i}$. Equations (4i) allowed us to separate each effect and we obtained:

$$\sum_{i=1}^{N_Z} \text{Indirect effect of W } via \text{ } Z_i = (\beta_{21} - \beta_{23})$$

We obtained an indirect effect of W by category of each variable in Z. For the variables with several categories, we present the sum of the indirect effects for each category.

All analyses were performed using STATA® V11 with a statistical significance level of 0.05.

## 2. Multiple imputation (MI) model

### 2.1. Concept

Sample loss and missing data are inevitable in longitudinal studies. Ad hoc approaches such as Last Observation Carried Forward and Complete Case analysis do not provide an underlying assumption for missingness, unnecessarily reduce statistical power and threaten study validity. 1976 Rubin provided a formal framework for the field of incomplete data. The author introduced three missing data mechanisms: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR). An MCAR mechanism is present when missingness is independent of both observed and unobserved variables. An MAR mechanism depends on the observed outcomes but missingness is independent of the unobserved outcomes. An MNAR mechanism depends on unobserved measurements and perhaps to covariates and or observed outcomes (Molenberghs & Kenward, 2007).

Multiple imputation (MI) was introduced by Rubin in 1978 and has become an influential approach for dealing with missing data. Instead of filling in a single value for each missing value, Rubin's multiple imputation procedure replaces each missing value with a set of *M* plausible values that represent the uncertainty about the right value to impute. According to Molenberghs,

> "*each value is a Bayesian draw from the conditional distribution of the missing observation given the observed data, made in such a way that the set of imputations properly represents the information about the missing value that is contained in the observed data for the chosen model. The imputation produce M 'completed' data sets, each of which*

*is analysed using the method that would have been appropriate had the data been complete*".

Hence two models can be identified, the one to produce the imputations is called 'imputation model' and the one for analysing the data is called the 'substantive model' (Molenberghs & Kenward, 2007).

Multiple imputation inference involves three distinct phases:

i) The missing data are filled in *M* times to generate *M* complete data sets.
ii) The *M* complete data sets are analysed by using standard procedures.
iii) The results from the *M* complete data sets are combined into a single inference.

A MI model uses all available data, preserving sample size and statistical power. According to Graham, when it comes to missing data in longitudinal studies, identifying the variables that most predict missingness later in the study is the best value for improving the missing data model (Graham, 2009).

## 2.2. Multiple imputation & application to our work

In this thesis we conducted three imputation models, one for each research axis. Twenty imputed data sets *M* were conducted taking the missing-at-random (MAR) assumption. Concerning the number of imputation in MI, missing data theorists have claimed that good inferences can be made with a number of data sets *M* of 3 to 5. However, recent research suggests that a larger set of *M* imputed data sets may be necessary if the statistical power is the main consideration. This approach is particularly important when detecting small effect size (Graham, 2009). For our research axes we decided to conduct 20 set of *M* imputed data sets.

In our study, each covariable with missing values was imputed including in the imputation model all confounders and mediators of the multivariate model. According to Graham, some strategies could be implemented for reducing attrition bias. The author proposed that auxiliary variables be included, or including information from follow-up data on a sample of those initially missing. We therefore tried to improve our imputation model by including additional variables from other sweeps correlated with the variable to impute. These variables from other sweeps were selected *a priori* and we kept only those that achieved the 5% significance cut-off. For instance, we imputed self-reported alcohol consumption at 23y using information on the

individual drinking at 16y, 33y and 42y. Table 5 summarizes the variables used to complement the multiple imputation model for each research axis.

We considered that the MAR assumption was plausible in the 1958 NCDS birth cohort, even though subjects who remained in the study most probably differ from those who dropped out, since it allows missingness to depend on observed data, such as baseline characteristics. However, the assumption of MAR is unverifiable and we cannot rule out that all the missing data are not MNAR (Coley et al., 2011). We include large numbers of predictor variables, a sufficient number of covariates in the multiple regression model and additional variables from previous or subsequent sweeps in the imputation model. This should help to make the MAR assumption more plausible and help to limit the impact of MNAR missingness (Coley et al., 2011). Some sensitivity analyses have been done in particular analyses on the sample with complete data to test the robustness of the results.

Table 5. Imputation model for each research axis

| Substantive model | Research axis | Imputation model | Variables included to improve the imputation model |
|---|---|---|---|
| Allostatic load at 44 y | 1 | Not included | |
| Adverse childhood adversities 7-16 y | 1 | Not included | |
| Subjective health at 50 y | 3 | Not included | |
| Mother's education level at birth | 1, 2 & 3 | Included in axis 1 & 3<br>Not included in axis 2 | Maternal grandfather's social class at birth, exam intentions at 16y, overcrowding at 11y, father's social class at 16y, mother's social class at 16y, mother's education level at 16y |
| Father's social class at birth | 1, 2 & 3 | Included in axis 1 & 3<br>Not included in axis 2 | Maternal grandfather's social class at birth, exam intentions at 16y, overcrowding at 11y, father's social class at 16y, mother's social class at 16y, mother's education level at 16y |
| Overcrowding | 1 | Included | Family moves since child's birth, maternal grandfather's social class at birth, overcrowding at 11y, child's position in the household |
| Mother's BMI | 1 & 2 | Included | |
| Mother smoking during pregnancy: | 1 | Included | Maternal grandfather's social class at birth, overcrowding at 11y, child's position in the household, mother's smoking status at 16y |
| Birthweight | 1 & 2 | Included | Maternal grandfather's social class at birth, exam intentions at 16y, child's position in the household, height at 23y |
| Mother's age at birth | 2 | Included | Smoking status at 16y, family moves since child's birth, maternal grandfather's social class at birth, exam intentions at 16y, overcrowding at 11y, child's position in the household, mother is alive at 23y |
| Breastfeeding | 1 & 2 | Included | Maternal grandfather's social class at birth, exam intentions at 16y, child's position in the household, mother's social class at 16y |
| Parity | 1 | Included | Family moves since child's birth, exam intentions at 16y, overcrowding at 11y, child's position in the household |
| Gestational age | 1 | Included | Overcrowding at 11y, child's position in the household, height at 23y |
| Childhood pathologies 7-16y | 1 | Included | Self-estimated health status at 33y, score of health at 23y |
| Parental involvement at 7y | 2 | Included | Household tenure at 42y, having a car at 42y, exam intentions at 16y, educational level at 33y, educational aspirations at age 16y |

*continued*

| Substantive model | Research axis | Imputation model | Variables included to improve the imputation model |
|---|---|---|---|
| BSAG* at 7y | 2 | Included | BSAG at 11y, household tenure at 42y, having a car at 42y, exam intentions at 16y, educational level at 33y, educational aspirations at age 16y |
| Motor ability at 7 y | 2 | Included | Motor ability at 11y |
| Childhood material factors at 7-16y | 2 | Included | Household tenure at 42y, having a car at 42y, exam intentions at 16y, educational level at 33y |
| Smoking status at 23y | 1 | Included | Smoking status at 16y, family moves since child's birth, maternal grandfather's social class at birth, exam intentions at 16y, overcrowding at 11y, father's smoking status at 16y, smoking status at 42y |
| Alcohol consumption at 23y | 1 | Included | Alcohol consumption at 16y, maternal grandfather's social class at birth, exam intentions at 16y, overcrowding at 11y, alcohol consumption at 42y, alcohol consumption at 33y |
| Physical activity at 23y | 1 | Included | Physical activity at 16y, physical activity at 33y, self-estimated health status at 33y, money spent in sports equipment at 16y |
| Health behaviours at 23y | 2 | Included | Alcohol consumption at 42y, smoking status at 16y, mother's smoking status at 16y, father's smoking status at 16y |
| Malaise inventory at 23y | 1 & 2 | Included | Malaise inventory at 42y, malaise inventory at 16y |
| Education level at 23y | 1, 2 & 3 | Included | Smoking status at 16y, family moves since child's birth, maternal grandfather's social class at birth, exam intentions at 16y, overcrowding at 11y, child's position in the household, education level at 33y |
| BMI at 23y | 1 & 2 | Included | Silhouette at 16y |
| Income at 23y | 2 & 3 | Included | Household tenure at 42y, having a car at 42y, exam intentions at 16y, educational level at 33y, educational aspirations at age 16y |
| Smoking status at 33y | 3 | Included | Smoking status at 16y, mother's smoking status at 16y, father's smoking status at 16y |
| Alcohol consumption at 33y | 3 | Included | Alcohol consumption at 42y |
| Physical activity at 33y | 3 | Included | Physical activity at 16y |
| BMI at 33y | 3 | Included | BMI at 23y |
| Social class/occupation at 33y | 1 & 3 | Included | Social class at 23y, first job, maternal grandfather's social class at birth, exam intentions at 16y, overcrowding at 11y, mother's social class at 16y |
| Wealth/household tenure at 33y | 1 & 3 | Included | Household tenure at 23y, household tenure at 42y, mother's social class at 16y, desire to buy a house at age 23y |
| Marital status at 33y | 1 & 3 | Included | Marital status at 23y, marital status at 42y |
| Social-security benefits at 33y | 3 | Included | Household tenure at 42y, having a car at 42y, exam intentions at 16y, educational level at 33y, educational aspirations at age 16y |
| Mortgage or rent arrears at 33y | 3 | Included | Household tenure at 42y, having+C8:F39 a car at 42y, exam intentions at 16y, educational level at 33y, educational aspirations at age 16y |

## 3. The life course model and statistical analysis

The life course model is largely implemented when it comes to analyse longitudinal studies. In our research work, taking into account the events across the life span became rapidly crucial, since we had a large panel of variables available, at different ages, which represented a strength, but also a limitation. The classic backward elimination stepwise -starting with all candidate variables, testing the deletion of each variable using a chosen model comparison criterion, deleting the variable (if any), improving the model, and repeating this process until no further improvement is possible- was not adapted for answering our research problematic. For our purposes, using a cohort study should represent a strength, and for accomplish that intention, we should take into account the chronology of life events.

Melchior and colleagues introduced a methodology, which could be applied to longitudinal studies, in a research article in 2007 testing the influence of childhood socioeconomic disadvantage on later health. First, they used a forward selection which involves starting with no variables in the model, testing the addition of each variable using a chosen model comparison criterion, adding the variable (if any) that improves the model the most, and repeating this process until none improves the model. Second, they compared the coefficient of the fully adjusted model with the coefficient of the unadjusted models and they calculate the percent change in the excess risk (Melchior et al., 2007).

This method could enlighten our research purposes because forward selection allowed us to consider all the chronological order of the variables chosen *a priori*; and also, this method re-joins the notion of mediation, we will be able to observe the effect of the later variables added to the model on the link between the first covariates added on the depend variable.

Therefore, for the three research axes explored here, this life course methodology on the multivariate models was used. The variables were entered chronologically as they would occur over the lifespan and to mimic life course experiences, we sequentially adjusted the multivariate linear regressions as follows:

i) Early life socioeconomic and material circumstances, as well as perinatal variables collected at birth;
ii) We controlled for childhood socioeconomic circumstances and psychosocial factors (in general at 7, 11 and 16 years of age);

iii) We adjusted the model for education, psychological malaise, and health behaviours at 23 years.

iv) If the research question required, we additionally adjusted the model for material, psychosocial and socioeconomic circumstances, as well as health behaviours and psychological malaise at 33 years of age.

Thus, we were able to observe the variation between the unadjusted links compared to the fully adjusted, and better appreciate the evolution of the link between the exposure variable and the independent variable.

Regarding empirical research, the mediating role of AL between socioeconomic position and mortality deserves in-depth examination. Though the link between AL and subsequent health is relatively well studied, there are few studies analysing the link between adverse environments (physical, chemical, nutritional, psychosocial, etc.) and AL, taking a life course approach. Recent studies using a life course approach have shown very promising results on the link between socioeconomic position over the life course and AL score (Gruenewald et al., 2012; Gustafsson et al., 2011, 2012; Merkin et al., 2014; Robertson et al., 2014). In order to identify mechanisms or causal chains linking environmental challenges, AL and subsequent health, a life course approach is required, particularly if interventions are to be implemented. To study such complex mechanisms, implicating direct and indirect effects of adverse exposures over time, we necessitate rich longitudinal datasets with long follow-ups. Socioeconomic position being a proxy of various exposures, datasets with large panels of variables on the socioeconomic and psychosocial environment over time are particularly precious to disentangle which aspects contained in socioeconomic position influence both health and AL. This justifies the use of a path analysis for axis 1 and 2, for disentangling the mediation effect of different life course variables.

# Chapter III

# Allostatic load biomarkers, methods & score construction

In the following section we will address the topic of data selection, variable construction and measurements in our work.

In the first major section 1 'Allostatic load at 44 years' we will present the allostatic load measure used in this thesis. We will introduce the biomarkers chosen, the high/low risk threshold implemented, as well as the statistical method used to summarize the biomarkers measures in one single score.

In section 2 we will explain the rationale for sex stratification and section 3 was dedicated to explain the sensitivity analysis conducted for demonstrating the stability of the score construction.

## 1. Allostatic load at 44 years.

Among available biomarkers, we selected fourteen parameters representing four physiological systems:

i) the neuroendocrine system: Participants were asked to collect two saliva samples on the first 45 min after awaking (time 1) and the second 3 hours later on the same day (time 2). For this study we used the cortisol awakening response (time 1: salivary sample taken 45 min after awaking) and the diurnal cortisol slope (t1-t2). We used two cortisol measures: salivary cortisol t1 (nmol/L) and salivary cortisol t1-t2 (nmol/L);

ii) the immune & inflammatory system: C-reactive protein (CRP mg/L), fibrinogen (g/L), immunoglobulin E (IgE KU/L), insulin-like growth factor-1 (IGF-1 nmol/L);

iii) the metabolic system: high density lipoprotein (HDL mmol/L), low density lipoprotein (LDL mmol/L), triglycerides (mmol/L), glycosylated hemoglobin (%);

iv) the cardiovascular & respiratory systems: systolic blood pressure (SBP mmHg), diastolic blood pressure (DBP mmHg), heart rate/pulse (p/min), peak expiratory flow (L/min).

These biomarkers were chosen based on previous measures of AL (Karlamangla et al., 2002; Karlamangla et al., 2006; Seeman et al., 1997) and according to evidence of their relationship to stressful conditions over life (Butland et al., 2008; Kumari M. et al., 2013; Kumari Meena et al., 2011; Kumari Meena et al., 2008). In accordance with the most classical AL operationalization proposed by Seeman and colleagues (Seeman, et al., 1997), our score was the sum of the fourteen parameters for which the subject was rated in the highest-risk quartile ('1' vs low risk '0') according to gender specific quartiles. The high risk quartile was the top quartile of all biomarkers, except for those for which a low level confers greater risk for poor health outcomes (HDL, salivary cortisol t1-t2, IGF1, peak expiratory flow). AL score was calculated by summing the fourteen dichotomized markers (ranged from 0-14). We excluded from our sample the persons for whom none of the fourteen biomarkers were collected. Some individuals did not have all the fourteen biomarkers available; in this case, we chose to adopt a conservative approach (maximum bias) systematically considering these people as not at risk for the biomarker with missing data.

Exclusion criteria for the analysis are shown in the flow chart (Figure 4, Chapter I, section 2). We additionally conducted the multivariate analysis using a different operationalization of AL score, by calculating a 0-1 risk score within each system (Carroll et al., 2015) and the results did not vary. We excluded from our sample 1264 individuals (pregnant women and those for whom blood was not obtained). 3104 individuals had at least one missing data for the fourteen biomarkers and on average 1.1.

Table 6 shows the descriptive statistics and high-risk cut-points for individual biomarkers of allostatic load score for men and women. Table 7 gives a full description of each biomarkers used for the construction of the allostatic load score with a brief overview of their function and measurement in the NCDS 1958 birth cohort.

Table 6. Descriptive statistics and high-risk cutpoints for individual biomarkers of allostatic load score for men and women

| Biomarker | N | Mean | Median | Min | Max | P25 | P75 | High-risk cutpoint |
|---|---|---|---|---|---|---|---|---|
| | | | | MEN | | | | |
| SBP (mmHg) | 3 732 | 132.7 | 131.3 | 93.0 | 198.0 | 122.3 | 141.0 | 141.0 |
| DBP (mmHg) | 3 732 | 81.9 | 81.0 | 51.0 | 129.3 | 75.0 | 88.3 | 88.3 |
| Heart rate (bmp) | 3 733 | 70.4 | 69.7 | 38.0 | 114.0 | 62.3 | 77.3 | 77.3 |
| Peak flow (L/min) | 3 664 | 573.6 | 581.0 | 69.0 | 971.0 | 496.0 | 655.0 | 496.0 |
| HDL (mmol/L) | 3 581 | 1.4 | 1.4 | 0.6 | 4.1 | 1.2 | 1.6 | 1.2 |
| LDL (mmol/L) | 3 272 | 3.6 | 3.5 | 0.7 | 8.0 | 2.9 | 4.1 | 4.1 |
| Triglycerides (mmol/L) | 3 577 | 2.5 | 2.1 | 0.3 | 25.3 | 1.4 | 3.0 | 3.0 |
| HbA1C (mmol/m) | 3 636 | 34.6 | 33.3 | 13.7 | 130.7 | 31.1 | 36.3 | 36.6 |
| IGF-1 (nmol/L) | 3 583 | 18.7 | 18.0 | 2.0 | 52.0 | 15.0 | 22.0 | 15.0 |
| CRP (mg/L) | 3 529 | 1.9 | 1.0 | 0.1 | 152.0 | 0.5 | 2.0 | 2.0 |
| Fibrinogen (g/L) | 3 519 | 2.9 | 2.8 | 1.0 | 5.9 | 2.5 | 3.2 | 3.2 |
| IgE (KU/L) | 3 521 | 114.3 | 35.0 | 0.0 | 2 000.0 | 14.0 | 96.0 | 96.0 |
| Cortisol t1 (nmol/L) | 2 652 | 20.9 | 18.8 | 2.1 | 97.2 | 13.1 | 26.4 | 26.4 |
| Cortisol t1-t2 (nmol/L) | 2 579 | 12.1 | 11.2 | -45.6 | 85.4 | 5.1 | 18.4 | 5.10 |
| | | | | WOMEN | | | | |
| SBP (mmHg) | 3 729 | 120.2 | 118.7 | 84.3 | 238.0 | 109.3 | 129.3 | 129.3 |
| DBP (mmHg) | 3 729 | 75.5 | 74.7 | 45.7 | 146.7 | 68.3 | 81.7 | 81.7 |
| Heart rate (bmp) | 3 729 | 72.7 | 72.3 | 39.3 | 114.3 | 65.7 | 79.0 | 79.0 |
| Peak flow (L/min) | 3 689 | 398.6 | 400.0 | 72.0 | 898.0 | 345.0 | 455.0 | 345.0 |
| HDL (mmol/L) | 3 606 | 1.7 | 1.6 | 0.7 | 5.2 | 1.4 | 1.9 | 1.4 |
| LDL (mmol/L) | 3 538 | 3.3 | 3.2 | 0.4 | 7.0 | 2.7 | 3.8 | 3.8 |
| Triglycerides (mmol/L) | 3 600 | 1.6 | 1.3 | 0.3 | 26.7 | 0.9 | 2.0 | 2.0 |
| HbA1C (mmol/m) | 3 658 | 33.2 | 32.2 | 12.6 | 128.4 | 30.1 | 34.4 | 34.4 |
| IGF-1 (nmol/L) | 3 607 | 18.7 | 18.0 | 0.0 | 66.0 | 15.0 | 22.0 | 15.0 |
| CRP (mg/L) | 3 555 | 2.4 | 1.0 | 0.1 | 77.4 | 0.4 | 2.6 | 2.6 |
| Fibrinogen (g/L) | 3 557 | 3.0 | 3.0 | 1.1 | 8.2 | 2.6 | 3.4 | 3.4 |
| IgE (KU/L) | 3 568 | 76.9 | 22.0 | 0.0 | 2 007.0 | 10.0 | 60.0 | 60.0 |
| Cortisol t1 (nmol/L) | 2 716 | 21.5 | 19.5 | 2.0 | 90.9 | 13.7 | 27.2 | 27.2 |
| Cortisol t1-t2 (nmol/L) | 2 677 | 13.7 | 12.4 | -43.10 | 78.8 | 6.2 | 20.0 | 6.2 |

Table 7. Biomarkers used for the construction of allostatic load score with a brief overview of their function and measurement in the NCDS 1958 birth cohort

| Biomarker | Function | Measure |
|---|---|---|
| *Cardiovascular* | | |
| SBP (mmHg) | Measure of cardiovascular activity. | The mean of three measures of systolic pressure was used. |
| DBP (mmHg) | Measure of cardiovascular activity. | The mean of three measures of diastolic blood pressure was used. |
| Heart rate (bmp) | Measure of cardiovascular activity. | The mean of three measures resting pulse. |
| Peak expiratory flow (L/m) | Measure of lung function. | The peak flow higher measure of three was used. |
| *Metabolic* | | |
| HDL (mmol/L) | Lipoprotein high levels are correlated with better cardiovascular health. | HDL was measured on non-fasting serum. |
| LDL (mmol/L) | Lipoprotein low levels are correlated with better cardiovascular health. | LDL cholesterol was measure on non-fasting blood sample and derived by the following formula: LDL = [Total chol] – (HDL + (Trig/2.2)). |
| Triglycerides (mmol/L) | Lipoprotein low levels are correlated with better cardiovascular health. | Triglycerides was measured on non-fasting serum. |
| $HbA_{1C}$ (%) | Identifies the average plasma glucose concentration. The proportion represents the amount of glucose that the analysed hemoglobin has been exposed to during its cell cycle. | HbA1c was measured on whole citrated blood on non-fasting blood sample. |
| *Immune & Inflammatory* | | |
| CRP (g/L) | Marker of acute inflammation. | C-reactive protein was measured on citrated plasma by high-sensitivity nephelometric analysis of latex particles coated with CRP-monoclonal antibodies. |
| Fibrinogen (g/L) | Functions as a blood clotting factor that promotes coagulation, in-excess, and increases risk of thrombosis. | Fibrinogen was measured on citrated plasma by the Clauss method using a MDA 180 coagulometer. |
| IgE (KU/L) | Mediate type 1 hypersensitivity responses. | IgE was measured on serum with positive and negative controls. Total IgE was assayed on all specimens, and allergen-specific IgE to house dust mite, mixed grasses, and cat fur, were measured on specimens with a total IgE concentration above the median (30kU/L). |
| IGF-1 (nmol/L) | Hormone produced primarily by the liver and pancreas. Stimulator of cell growth and inhibitor of cellular apoptosis. | Was measured on serum by chemiluminescence-immunoassay |
| *Neuroendocrine* | | |
| Cortisol t1 (nmol/L) | Measures the hypothalamic pituitary adrenal axis (HPA) function. Captures the post-waking peak cortisol concentration,* | Salivary cortisol sample taken 45 min after awakening. |
| Cortisol t1-t2 (nmol/L) | Measures the hypothalamic pituitary adrenal axis (HPA) function. Captures the decline following the post-waking peak. t1-t2 characterized the normative cortisol diurnal rhythm. ** | Salivary cortisol sample taken 3 hours after awakening. |

*A healthy HPA axis is typically characterised by high levels of cortisol concentration upon waking (30 to 45 minutes after waking up called the cortisol awakening response), and a subsequent decline over the day, reaching a low point around midnight. Raised saliva levels of cortisol t1 in the evening provide information about a potential hyperactivity of the HPA axis.
** t1-t2 give information about the diurnal cortisol rhythm. A "flat pattern" could suggest and HPA axis hypo-reactivity (Adam & Kumari, 2009).

## 2. Sex stratification

Studies using animal models have shown that sex differences exist when analysing some diseases, such as chronic non-communicable diseases. This sexual dimorphism begins to develop very early during pregnancy, the lactation period, and at childhood and adolescence (Gabory et al., 2012; Gabory et al., 2013; Gallou-Kabani et al., 2010). Differences in hormone regulation and epigenetics may also be strongly linked to sex. For example, sex differences have been observed from gestation in the cortisol response to stress, which appears to be consistently higher in males compared to female foetuses (Gabory et al., 2013). These studies showed that gene expression profiles and epigenetic marks are sex-specific in mice. The analyses conducted here took into account the potential differences between the sexes. Moreover, the perception, interpretation and physiological responses to chronic stress could have a differential impact in men and women. Additionally, some evidence suggests gender-related differences in biological markers (Goldman et al., 2004). Sexual dimorphism in allostatic load, has been relatively unexplored in the literature. Yang and Kozloski investigated sex differences in the age trajectories of different biomarkers across multiple systems and three summary indices including inflammation burden, metabolic syndrome, and allostatic load (Yang & Kozloski, 2011). The authors found significant sex differences, which is no that surprising contextualizing these findings in light of other studies, such as metabolic syndrome (McMillen & Robinson, 2005).

## 3. Sensitivity analysis

The allostatic load score was constructed as a sum of biomarkers, and several questions surround the methods concerning score operationalization. As we already indicated in previous sections, we based our score on previous measures and according to the most classic measures first suggested by Seeman and colleagues. However, we wished to confirm the stability of our results and the constancy of the allostatic load score. Therefore we additionally conducted two different sensitivity analyses.

### 3.1. First sensitivity analysis

The first sensitivity analysis was a series of regressions analyses of individual biomarkers for studying the AL score stability by identifying if within our score a parameter was having a

stronger effect relatively to the others. For the results of axis 1 please see Table 8 for men and 9 for women. For the results of axis 2 please see Table 10 for men and women.

We created fourteen different scores, the first score contained all the biomarkers except for cortisol t1. The second score contained all biomarkers except for cortisol t1-t2 and so on for each biomarker. We observed the β coefficients and significance variation of the link between the exposures variables (ACE, maternal education and paternal occupation) and allostatic load in a multivariate linear regression. We though created 14 different scores and we tested each new score in the same multivariate model of the original score (see Table 8, 9 for axis 1 results and Table 10 for axis 2 results below).

For axis 1 we observed that for men, the range of variation for 1 ACE was among 0.13 and 0.19, for 2 ACE or more the range of variation was between 0.36 and 0.45. For women was among 0.18 and 0.24 for 1 ACE, 0.28 and 0.39 for 2 or more ACE. These results allowed us to observe the interval fluctuation of ACE coefficient as well as their significance and we concluded that there was not enough variation, consequently our score using the fourteen biomarkers was stable.

In axis 2 we studied that mediating pathways between parental socioeconomic position and allostatic load at 44 years of age. As for axis 1, for axis 2 we reproduced the first sensitivity analysis studying our AL score stability (Table 10). For men, the β range of variation for maternal education was between 0.14 and 0.19. For paternal occupation the range of variation was between 0.05 and 0.16 for IIINM, 0.39 and 0.48 for IIIM, 0.57 and 0.66 for IV & V. For women (Table 11), the range of variation for maternal education was between 0.38 and 0.44. For paternal occupation, the range of variation for IIINM was between 0.20 and 0.27, for IIIM was between 0.51 and 0.61, and between 0.68 and 0.80. The interval fluctuation of parental SEP β coefficients as well as their significance allow us to conclude that our fourteen-biomarker score was stable.

### 3.2. Second sensitivity analysis

The second sensitivity analysis was run only for axis 1. Since the number of individuals who were missing 1 or more biomarkers was rather high (>3000), a second sensitivity analysis that imputed the missing biomarkers from other measured biomarkers was considered, to ensure that the results were not biased by the missing biomarkers. We ran a sensitivity analysis

imputing for the missing values for each biomarker using the multiple imputation program ICE in STATA® V11 (Table 11). No significant differences were observed confirming the stability of our results. Table 12 shows the sensitivity analyses imputing AL biomarkers *versus* complete case of AL biomarkers for men and women

### 3.3. Additional operationalization of allostatic load

We constructed a second AL score for axis 2 and axis 3 calculating a 0-1 risk score within each system, reflecting the proportion of biomarkers within the system for which the participant's values fall into the highest-risk quartile, allowing equal weight for each system (Carroll et al., 2015) and the results did not vary.

### 3.4. Evaluation of the association of individual biomarkers of allostatic load on later subjective health

For axis 3 we also evaluate which of the biomarkers was having the strongest link with the subjective health index. We therefore ran an additional multivariate model fully adjusted for the same confounders, taking each biomarker individually and previously divided into low '0'/high risk '1' in a sample without missing values for each biomarker (n=1781 for men, n=2110 for women) and ran the same multivariate analysis testing the link between each biomarker individually and later subjective health. In men, the biomarker showing the strongest link with the subjective health index was peak expiratory flow (-0.18SD, p<0.001) and HDL (-0.16SD, p<0.001). In women, CRP (-0.25SD, p<0.001) followed closely by fibrinogen (-0.21SD, p<0.001). For men, only four biomarkers were significantly related to subjective health index. For women half of the biomarkers were linked. Although, the AL score was linked to later subjective health index for both men and women (-0.02SD, p<0.001 for men, and -0.05SD, p<0.001 for women).

Table 8. Axis 1 sensitivity analyses for men (n=3753): AL score without one of its components and impact on its link with ACE

| | (-) Cortisol t1 | p | (-) Cortisol (t1-t2) | p | (-) Triglycerides | p | (-) LDL | p |
|---|---|---|---|---|---|---|---|---|
| *Adverse Childhood Experiences* | β | | β | | β | | β | |
| *None* | 0 | | 0 | | 0 | | 0 | |
| *One* | 0,191 (0,035 - 0,347) | 0,016 | 0,151 (-0,003 - 0,305) | 0,055 | 0,168 (0,020 - 0,315) | 0,026 | 0,168 (0,015 - 0,320) | 0,031 |
| *Two or more* | 0,408 (0,152 - 0,664) | 0,002 | 0,404 (0,151 - 0,656) | 0,002 | 0,371 (0,128 - 0,613) | 0,003 | 0,446 (0,196 - 0,696) | <0,001 |

| | (-) HDL | p | (-) Fibrinogen | p | (-) IgE | p | (-)IGF-1 | p |
|---|---|---|---|---|---|---|---|---|
| *Adverse Childhood Experiences* | β | | β | | β | | β | |
| *None* | 0 | | 0 | | 0 | | 0 | |
| *One* | 0,161 (0,010 - 0,311) | 0,036 | 0,130 (-0,015 - 0,275) | 0,079 | 0,145 (-0,005 - 0,296) | 0,058 | 0,153 (0,002 - 0,303) | 0,047 |
| *Two or more* | 0,358 (0,111 - 0,605) | 0,004 | 0,361 (0,123 - 0,599) | 0,003 | 0,371 (0,124 - 0,618) | 0,003 | 0,374 (0,127 - 0,622) | 0,003 |

| | (-) C-Reactive Protein | p | (-)$HbA_{1c}$ | p | (-) SBP | p | (-) DBP | p |
|---|---|---|---|---|---|---|---|---|
| *Adverse Childhood Experiences* | β | | β | | β | | β | |
| *None* | 0 | | 0 | | 0 | | 0 | |
| *One* | 0,156 (0,013 - 0,300) | 0,032 | 0,170 (0,022 - 0,319) | 0,024 | 0,166 (0,022 - 0,309) | 0,024 | 0,180 (0,034 - 0,325) | 0,015 |
| *Two or more* | 0,383 (0,148 - 0,619) | 0,001 | 0,397 (0,153 - 0,641) | 0,001 | 0,436 (0,199 - 0,672) | <0,001 | 0,427 (0,189 - 0,666) | <0,001 |

| | (-) Peak flow | p | (-) Heart rate/pulse | p |
|---|---|---|---|---|
| *Adverse Childhood Experiences* | | | | |
| *None* | 0 | | 0 | |
| *One* | 0,146 (-0,005 - 0,296) | 0,058 | 0,135 (-0,010 - 0,281) | 0,068 |
| *Two or more* | 0,375 (0,128 - 0,623) | 0,003 | 0,385 (0,145 - 0,624) | 0,002 |

(-): Results of Model 2, recreating the variable of AL score without one of its components. E.g.: (-) Cortisol t1 in Model 2, AL score constructed from 13 variables, cortisol t1 not included

Table 9. Axis 1 Sensitivity analyses for women (n=3782): AL score without one of its components and impact on its link with ACE

| | (-) Cortisol t1 | p | (-) Cortisol (t1-t2) | p | (-) Triglycerides | p | (-) LDL | p |
|---|---|---|---|---|---|---|---|---|
| *Adverse Childhood Experiences* | β | | β | | β | | β | |
| *None* | 0 | | 0 | | 0 | | 0 | |
| *One* | 0,199 (0,028 - 0,369) | 0,022 | 0,240 (0,071 - 0,409) | 0,005 | 0,178 (0,020 - 0,337) | 0,027 | 0,178 (0,015 - 0,342) | 0,033 |
| *Two or more* | 0,340 (0,058 - 0,622) | 0,018 | 0,391 (0,112 - 0,670) | 0,006 | 0,297 (0,035 - 0,559) | 0,026 | 0,368 (0,098 - 0,638) | 0,008 |

| | (-) HDL | p | (-) Fibrinogen | p | (-) IgE | p | (-)IGF-1 | p |
|---|---|---|---|---|---|---|---|---|
| *Adverse Childhood Experiences* | β | | β | | β | | β | |
| *None* | 0 | | 0 | | 0 | | 0 | |
| *One* | 0,195 (0,034 - 0,355) | 0,017 | 0,211 (0,053 - 0,369) | 0,009 | 0,210 (0,045 - 0,374) | 0,013 | 0,175 (0,012 - 0,337) | 0,035 |
| *Two or more* | 0,342 (0,077 - 0,608) | 0,011 | 0,333 (0,072 - 0,594) | 0,012 | 0,323 (0,051 - 0,596) | 0,020 | 0,336 (0,067 - 0,604) | 0,014 |

| | (-) C-Reactive Protein | p | (-) $HbA_{1c}$ | p | (-) SBP | p | (-) DBP | p |
|---|---|---|---|---|---|---|---|---|
| *Adverse Childhood Experiences* | β | | β | | β | | β | |
| *None* | 0 | | 0 | | 0 | | 0 | |
| *One* | 0,212 (0,058 - 0,367) | 0,007 | 0,191 (0,032 - 0,350) | 0,019 | 0,213 (0,055 - 0,370) | 0,008 | 0,189 (0,032 - 0,346) | 0,019 |
| *Two or more* | 0,338 (0,083 - 0,594) | 0,010 | 0,319 (0,055 - 0,582) | 0,018 | 0,381 (0,121 - 0,641) | 0,004 | 0,387 (0,127 - 0,646) | 0,004 |

| | (-) Peak expiratory flow | p | (-) Heart rate/pulse | p |
|---|---|---|---|---|
| *Adverse Childhood Experiences* | β | | β | |
| *None* | 0 | | 0 | |
| *One* | 0,188 (0,022 - 0,354) | 0,026 | 0,183 (0,022 - 0,345) | 0,026 |
| *Two or more* | 0,366 (0,092 - 0,640) | 0,009 | 0,344 (0,078 - 0,611) | 0,011 |

(-): Results of Model 2, recreating the variable of AL score without one of its components. E.g.: (-) Cortisol t1 in Model 2, AL score constructed from 13 variables, cortisol t1 not included

Table 10. Axis 2 sensitivity analyses of regressions on individual biomarkers for men: AL score without one of its components and impact on its link with maternal education, and each category of paternal occupation

| | Men (N=3782) | | | |
|---|---|---|---|---|
| | ME<br>*Left school before 14y* | PO<br>*III NM (skilled nonmanual)* | PO<br>*IIIM (skilled manual)* | PO<br>*IV & V (semi-unskilled)* |
| **(-) Cortisol t1**[1] | 0.18 (0.03 - 0.33) | 0.16 (-0.08 - 0.40) | 0.47 (0.29 - 0.64) | 0.66 (0.45 - 0.86) |
| p value | 0.017 | 0.201 | <0.001 | <0.001 |
| **(-) Cortisol (t1-t2)**[1] | 0.18 (0.03 - 0.33) | 0.13 (-0.11 - 0.37) | 0.48 (0.30 - 0.65) | 0.63 (0.42 - 0.83) |
| p value | 0.019 | 0.299 | <0.001 | <0.001 |
| **(-) Triglycerides**[1] | 0.19 (0.04 - 0.33) | 0.10 (-0.13 - 0.33) | 0.42 (0.26 - 0.59) | 0.58 (0.38 - 0.77) |
| p value | 0.010 | 0.389 | <0.001 | <0.001 |
| **(-) LDL**[1] | 0.19 (0.05 - 0.34) | 0.10 (-0.13 - 0.34) | 0.45 (0.28 - 0.62) | 0.63 (0.43 - 0.84) |
| p value | 0.009 | 0.385 | <0.001 | <0.001 |
| **(-) HDL**[1] | 0.19 (0.04 - 0.33) | 0.12 (-0.12 - 0.35) | 0.43 (0.26 - 0.60) | 0.58 (0.38 - 0.78) |
| p value | 0.011 | 0.324 | <0.001 | <0.001 |
| **(-) Fibrinogen**[1] | 0.17 (0.03 - 0.30) | 0.09 (-0.13 - 0.32) | 0.41 (0.25 - 0.57) | 0.59 (0.40 - 0.78) |
| p value | 0.021 | 0.417 | <0.001 | <0.001 |
| **(-) IgE**[1] | 0.18 (0.04 - 0.33) | 0.12 (-0.12 - 0.35) | 0.45 (0.28 - 0.62) | 0.63 (0.43 - 0.83) |
| p value | 0.013 | 0.332 | <0.001 | <0.001 |
| **(-)IGF-1**[1] | 0.19 (0.04 - 0.34) | 0.11 (-0.12 - 0.34) | 0.43 (0.26 - 0.60) | 0.57 (0.37 - 0.77) |
| p value | 0.011 | 0.360 | <0.001 | <0.001 |
| **(-) CRP**[1] | 0.18 (0.04 - 0.31) | 0.13 (-0.09 - 0.35) | 0.42 (0.26 - 0.58) | 0.59 (0.40 - 0.78) |
| p value | 0.013 | 0.243 | <0.001 | <0.001 |
| **(-)$HbA_{1c}$**[1] | 0.19 (0.05 - 0.34) | 0.13 (-0.10 - 0.36) | 0.42 (0.26 - 0.59) | 0.57 (0.37 - 0.77) |
| p value | 0.008 | 0.258 | <0.001 | <0.001 |
| **(-) SBP**[1] | 0.18 (0.04 - 0.32) | 0.13 (-0.10 - 0.35) | 0.43 (0.27 - 0.60) | 0.60 (0.40 - 0.79) |
| p value | 0.012 | 0.268 | <0.001 | <0.001 |
| **(-) DBP**[1] | 0.17 (0.03 - 0.31) | 0.11 (-0.11 - 0.34) | 0.41 (0.25 - 0.58) | 0.60 (0.41 - 0.80) |
| p value | 0.015 | 0.328 | <0.001 | <0.001 |
| **(-) Peak flow**[1] | 0.17 (0.03 - 0.32) | 0.05 (-0.18 - 0.28) | 0.39 (0.22 - 0.56) | 0.55 (0.35 - 0.75) |
| p value | 0.019 | 0.670 | <0.001 | <0.001 |
| **(-) Pulse**[1] | 0.14 (0.00 - 0.28) | 0.11 (-0.12 - 0.33) | 0.43 (0.26 - 0.59) | 0.60 (0.40 - 0.79) |
| p value | 0.050 | 0.359 | <0.001 | <0.001 |

(-): Results of Model 2 recreating the variable of AL score without one of its components, e.g.: (-) Cortisol t1: AL score constructed from 13 variables, cortisol t1 not included.

[1] β (IC 95%)

Table 11. Axis 2 sensitivity analyses of regressions on individual biomarkers for women: AL score without one of its components and impact on its link with maternal education, and each category of paternal occupation

| | Women (N=3791) | | | |
|---|---|---|---|---|
| | ME<br>*Left school before 14y* | PO<br>*III NM (skilled nonmanual)* | PO<br>*IIIM (skilled manual)* | PO<br>*IV & V (semi-unskilled)* |
| **(-) Cortisol t1**[1] | 0.44 (0.28 - 0.61) | 0.23 (-0.04 - 0.50) | 0.58 (0.39 - 0.78) | 0.77 (0.54 - 1.00) |
| p value | <0.001 | 0.093 | <0.001 | <0.001 |
| **(-) Cortisol (t1-t2)**[1] | 0.44 (0.27 - 0.60) | 0.27 (0.00 - 0.53) | 0.63 (0.43 - 0.82) | 0.80 (0.57 - 1.03) |
| p value | <0.001 | 0.046 | <0.001 | <0.001 |
| **(-) Triglycerides**[1] | 0.39 (0.24 - 0.55) | 0.21 (-0.04 - 0.46) | 0.51 (0.33 - 0.70) | 0.64 (0.43 - 0.85) |
| p value | <0.001 | 0.093 | <0.001 | <0.001 |
| **(-) LDL**[1] | 0.41 (0.25 - 0.57) | 0.22 (-0.04 - 0.47) | 0.56 (0.38 - 0.75) | 0.72 (0.50 - 0.94) |
| p value | <0.001 | 0.099 | <0.001 | <0.001 |
| **(-) HDL**[1] | 0.39 (0.23 - 0.55) | 0.22 (-0.03 - 0.47) | 0.53 (0.35 - 0.71) | 0.68 (0.46 - 0.90) |
| p value | <0.001 | 0.089 | <0.001 | <0.001 |
| **(-) Fibrinogen**[1] | 0.38 (0.23 - 0.54) | 0.20 (-0.05 - 0.45) | 0.53 (0.35 - 0.71) | 0.69 (0.48 - 0.90) |
| p value | <0.001 | 0.114 | <0.001 | <0.001 |
| **(-) IgE**[1] | 0.42 (0.26 - 0.58) | 0.24 (-0.02 - 0.50) | 0.59 (0.41 - 0.78) | 0.76 (0.54 - 0.99) |
| p value | <0.001 | 0.072 | <0.001 | <0.001 |
| **(-)IGF-1**[1] | 0.39 (0.23 - 0.55) | 0.21 (-0.05 - 0.46) | 0.55 (0.36 - 0.74) | 0.70 (0.48 - 0.92) |
| p value | <0.001 | 0.111 | <0.001 | <0.001 |
| **(-) CRP**[1] | 0.39 (0.24 - 0.54) | 0.21 (-0.04 - 0.45) | 0.51 (0.33 - 0.69) | 0.70 (0.49 - 0.91) |
| p value | <0.001 | 0.094 | <0.001 | <0.001 |
| **(-)$HbA_{1c}$**[1] | 0.42 (0.26 - 0.57) | 0.21 (-0.04 - 0.46) | 0.54 (0.36 - 0.72) | 0.67 (0.46 - 0.89) |
| p value | <0.001 | 0.104 | <0.001 | <0.001 |
| **(-) SBP**[1] | 0.41 (0.26 - 0.57) | 0.24 (-0.01 - 0.48) | 0.58 (0.40 - 0.76) | 0.77 (0.55 - 0.98) |
| p value | <0.001 | 0.059 | <0.001 | <0.001 |
| **(-) DBP**[1] | 0.41 (0.26 - 0.57) | 0.23 (-0.02 - 0.48) | 0.58 (0.40 - 0.76) | 0.74 (0.53 - 0.96) |
| p value | <0.001 | <0.001 | <0.001 | <0.001 |
| **(-) Peak flow**[1] | 0.40 (0.24 - 0.56) | 0.20 (-0.06 - 0.46) | 0.53 (0.34 - 0.72) | 0.68 (0.46 - 0.91) |
| p value | <0.001 | 0.123 | <0.001 | <0.001 |
| **(-) Pulse**[1] | 0.40 (0.25 - 0.56) | 0.24 (-0.01 - 0.49) | 0.61 (0.42 - 0.80) | 0.76 (0.54 - 0.98) |
| p value | <0.001 | 0.061 | <0.001 | <0.001 |

(-): Results of Model 2 recreating the variable of AL score without one of its components, e.g.: (-) Cortisol t1: AL score constructed from 13 variables, cortisol t1 not included.

[1] β (IC 95%)

Table 12. Axis 1 sensitivity analyses imputing AL score biomarkers vs complete case AL score for men and women

| Men<br>Imputed biomarkers | ß (CI 95%) | p |
|---|---|---|
| *ACE* | | |
| *None* | 0 | |
| *One* | 0,07 (-0,10 - 0,23) | 0,441 |
| *Two or more* | 0,18 (-0,10 - 0,45) | 0,205 |

| Men<br>Complete case | ß (CI 95%) | p |
|---|---|---|
| *ACE* | | |
| *None* | 0 | |
| *One* | 0,05 (-0,11 - 0,20) | 0,538 |
| *Two or more* | 0,18 (-0,08 - 0,43) | 0,177 |

| Women<br>Imputed biomarkers | ß (CI 95%) | p |
|---|---|---|
| *ACE* | | |
| *None* | 0 | |
| *One* | 0,15 (-0,02 - 0,33) | 0,090 |
| *Two or more* | 0,13 (-0,17 - 0,42) | 0,398 |

| Women<br>Complete case | ß (CI 95%) | p |
|---|---|---|
| *ACE* | | |
| *None* | 0 | |
| *One* | 0,09 (-0,08 - 0,26) | 0,299 |
| *Two or more* | 0,10 (-0,18 - 0,38) | 0,489 |

# PART III

# SOCIAL DETERMINANTS OF ALLOSTATIC LOAD:

# CONTEXT, METHODS AND DISCUSSION

# Résumé - Partie III : Les déterminants sociaux de la CA

Pour rappel les trois axes de recherche développés durant la thèse correspondaient à l'étude du lien entre les expériences adverses durant l'enfance (ACE) et le score de charge allostatique à 44 ans (axe 1), l'étude des liens entre la position socioéconomique des parents à la naissance et le score de CA (axe 2). Un point central dans ces deux premières sections sont les mécanismes de médiation.

Axe 1. Les ACE étaient associées à une CA supérieure pour les hommes et les femmes après ajustement sur les facteurs précoces de la vie et les pathologies infantiles. L'analyse de médiation a montré que l'association entre ACE et la CA était largement expliquée par des facteurs de médiation à 23 et 33 ans. Pour les hommes, l'effet total médié était de 59% (pour 2 ou plus ACE) principalement via les comportements de santé (tabac, IMC), le niveau d'éducation et le patrimoine. Pour les femmes, l'effet médié représentait 76% (pour 2 ou plus ACE) de l'effet total, principalement via le tabagisme, l'IMC, le niveau de l'éducation et de le patrimoine. Nos résultats indiquent que le stress psychosocial précoce pourrait avoir un impact durable sur l'usure physiologique via des liens indirects par les comportements de santé, l'IMC et les facteurs socio-économiques à l'âge adulte.

Axe 2. La position sociale des parents était liée à une CA supérieure. Nous avons de même investigué les chemins de médiations entre ME et PO. Nous avons montré que ME et PO étaient médiées par trois voies : matérielle / financière ; éducationnelle et par les comportements de santé tant pour les hommes comme pour les femmes. Nos résultats indiquent que la position sociale des parents peut augmenter le risque d'être exposé à différentes expositions au cours de la vie qui ont un impact sur la santé physiologique mesurée par la CA.

# Chapter I

# Psychosocial determinants of allostatic load

In the following chapter we lay out the main tenets concerning the psychosocial determinants of allostatic load. We will illustrate this topic by investigating the link between adverse childhood experiences (ACE) and an allostatic load score. One central focus in this section will be the mechanisms through which early psychosocial adversity may 'get under the skin'. In section 1 we will introduce the precise context and rationale justifying this research query. In section 2 we will introduce the specific methods, as well as the variables construction. We present in section 3 the main results of this analysis and finally, in the fourth section we will discuss the evidence that could clarify the pathways between ACE and AL.

Objective: To explore whether childhood psychosocial adversities were associated with elevated allostatic load in midlife after adjustment for classic social determinants. We additionally examined in what extent life course socioeconomic conditions and health behaviours explained such a relationship by three potential pathways between ACE and AL.

Hypothesis: chronic stress resulting from early psychosocial adversities may be biologically embedded and lead to a cumulative multisystem dysregulation *via* four broad and intertwined pathways across the life course: i) a socioeconomic and materialist pathway, ii) a psychosocial pathway, iii) a health behaviours pathway.

This work was the object of a publication in the *Journal Proceedings of the National Academy of Science of the United States of America* (PNAS) (Barboza Solis et al. 2014) and is presented in Appendix 1.

## 1. Context

Health disparities are observed for a wide range of health indicators from risk factors, incidence of chronic diseases and mortality across the world (Marmot et al., 2008). According to Hertzman, the socioeconomic gradient in health

> "*is capable of replicating itself on new disease processes as they emerge in society*" (Hertzman, 1999).

Recently, epidemiological studies have shown that classic determinants are not sufficient for explaining the social gradient in health. This may point toward the existence of other mechanisms influencing health, like a potential biological pathway. The notion of Allostatic Load (AL) may be useful to explore how experiences over the life course may 'get under the skin' and become biologically embedded (Hertzman, 1999; Krieger, 2005)

In the last two decades, epidemiological research has used the concept of AL to explain how chronic stress can lead to physiological dysregulation and disease (Beckie, 2012; Juster et al., 2010; Karlamangla et al., 2002; Karlamangla et al., 2006; Seeman et al., 2001; Seeman et al., 1997). AL is a measure of overall physiological wear and tear over the life course which could be the consequence of early life exposures (Danese & McEwen, 2012). According to AL theory, cumulative and repeated activation of compensatory physiological mechanism in response to chronic stress can lead to a multisystem pre-disease state represented by a dysregulation of neuroendocrine, metabolic, inflammatory or cardiovascular parameters (McEwen, 1998; McEwen & Seeman, 1999). Empirical evidence shows that AL has strong correlations to subclinical conditions, morbidity and mortality (Karlamangla et al., 2006; Seplaki et al., 2004) and may be a useful measure of overall health, rather than considering each biomarker separately (Beckie, 2012; Carlson & Chamberlain, 2005).

Several studies have suggested that exposure to chronic stress during sensitive periods of development may alter the balance and responsiveness of physiological systems and have long-term effects on health (Hertzman, 1999; Shonkoff et al., 2012). Early life exposure to Adverse Childhood Experiences (ACE), 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 well-being (Anda et al., 2006; Lupien et al., 2009). Exposure to ACE could influence health through a broad range of behavioural and socioeconomic mechanisms. For instance, the ACE study explored the relationship between ACE and health behaviours, linking childhood trauma to long-term effects on health *via* health risk behaviours such as alcohol consumption, smoking, sexual behaviours among others. Felitti *et al.* also suggested that ACE could be a common pathway to social, emotional, and cognitive impairments that may lead to increased risky behaviours (Felitti et al., 1998). It has been established that the adoption of health behaviours may also be explained by wide and complex psychological processes such as self-regulation, self-efficacy and self-management mechanisms (Bandura, 1998, 2005).

Furthermore, socioeconomic and material conditions in childhood appear to be linked to later brain development and cognition (Tomalski & Johnson, 2010). Lately, epidemiological studies have shown that ACE were associated with mortality and health even after adjusting for socioeconomic and behavioural factors, suggesting that a direct biological effect occurring from early life is plausible (Kelly-Irving et al., 2013a; Kelly-Irving et al., 2013b). It has been suggested that some psychosocial factors found in the rear environment could protect and buffer early adverse circumstances. Parental warmth and psychological resources may moderate physiological responses and mitigate disease processes (Carroll et al., 2013; Chen et al., 2012). However, only a few studies have analysed the influence of ACE on health over the life course by examining different pathways, and fewer have used an AL index to approach physiological wear-and-tear.

## 2. Methods

In this section we will present the construction of the outcome variable, covariates and measurements, as well as the statistical model used for investigating the link between early adverse psychosocial exposures and physiological wear-and-tear in mid-life, as measured by allostatic load.

### 2.1. Exposure variable: Adverse Childhood Experiences (ACE)

ACE were identified as a set of traumatic and stressful psychosocial conditions that are out of the child's control, that tend to co-occur (Rosenman & Rodgers, 2004) and often persist over time (Clark et al., 2010; Felitti et al., 1998). ACE were defined as intra-familial events or conditions causing chronic stress responses in the child's immediate environment. These include notions of maltreatment and deviation from societal norms, where possible to be distinguished from conditions in the socioeconomic and material environment. Since the NCDS has a large amount of prospective data we restricted ACE to intra-familial events or conditions in the child's immediate environment.

Information was extracted *via* variables collected at age 7, 11, 16 from questions asked to the child's parent or their teacher. Sources of adversity were divided into six categories:

i) Child in care: child has ever been in public/voluntary care services or foster care at age 7, 11 or 16.

ii) Physical neglect: child appears undernourished/dirty aged 7 or 11, information collected from the response from child's teacher to the Bristol Social Adjustment Guide.

Household dysfunction, as described by Felitti *et al*. (Felitti et al., 1998), is a dimension of adversity consisting of four categories each contributing to the score and describe as follows:

iii) Offenders: the child lived in a household where a family member was in prison or on probation (11y) or is in contact with probation service at 7 or 11y; the child has ever been to prison or been on probation at 16y.

iv) Parental separation: the child has been separated from their father or mother due to death, divorce, or separation at 7, 11 or 16y.

v) Mental illness: household has contact with mental health services at 7 or 11y; family member has mental illness at 7, 11 or 16y.

vi) Alcohol abuse: family member has alcohol abuse problem at 7y.

Exposure to adversity was identified by a positive response to any of the above categories. Respondents were excluded if they had missing data for all six categories. Respondents were considered as having no adversities if they answered 'no' to all the categories or if they answered 'no' to one or more category and the other categories were missing. ACE were measured by counting the reports of: child in care, physical neglect, offenders, parental separation, mental illness and alcohol abuse. A three category variable was then constructed (0 adversities, 1 adversity, 2 or more adversities).

### 2.2. Outcome variable: Allostatic load index

The outcome variable of interest in this study was a composite score of allostatic load as a measure of cumulative physiological wear-and-tear. Please see Part II, Chapter 3, section 1 for further details on the operationalization of the AL score.

### 2.3. Early life socioeconomic and biological confounders

To examine the relationship between ACE and AL, prior confounding variables potentially associated with both ACE and AL were included in the initial multivariate model. Among the variables available at baseline, collected from the cohort members' mothers *via* a questionnaire

at birth, we identified those most likely to be social or biological confounding factors based on the literature: household and parental characteristics [mother's education level (left school at 15y or later/before 14y), mother's partner's (or father's if unavailable) social class (non-manual/manual), overcrowded household (people per room >1.5 or ≤1.5)], maternal smoking during pregnancy (no smoking/sometimes/moderately/heavily), mother's BMI (self-reported pre-pregnancy weight and height measured after the birth): normal/underweight/overweight/obese (respectively 18.5–24.9, <18.5, 25–29.9 and ≥30kg/m2). Respondent's characteristics and birth variables were also included: birth weight (categorized in quartiles). We used the perinatal variables as proxies to better capture elements in the early environment potentially related to socioeconomic and psychosocial stressful conditions. These variables (mother's BMI, maternal smoking during pregnancy, and birth weight) may partly account for the association between ACE and AL acting as confounders. To control for health problems in childhood, a binary childhood pathologies variable was constructed using data collected at ages 7, 11 and 16 y. It was based both on mother's report and medical examinations including congenital conditions, moderate or severe disabilities, chronic respiratory or circulatory conditions, sensory impairments and special schooling (childhood pathology: yes/no).

### 2.4. Mediators across the life course

The variables taken into account to determine whether any observed associations between ACE and AL were due to adult mediating factors, covered the different pathways we have hypothesized. The following adult potential mediating factors were then added to the models: socioeconomic status [respondent's educational attainment at 23y (A level/O level/no qualification) and respondent's occupational social class at 33y (non-manual/manual active)]; socioeconomic status at 33y was described using a wealth variable constructed based on information about home ownership and the price of the house adjusted for economic inflation of the year of purchase and then divided in quartiles (not owner/Q1- owner lowest price/owner-Q2/owner-Q3/owner-Q4); and marital status at 33y (couple/single/divorced or widowed); health behaviours at 23y were considered as a proxy for behavioural patterns in early adulthood [physical activity (physically active/moderately active/inactive), alcohol consumption (moderate(women: between 1-14 units in the previous week, men: between 1-21 units in the previous week)/abstainers (reported not consuming any alcohol in the previous

week)/heavy drinkers (women: >14 units in the previous week, men: >21 units in the previous week) (House of Commons Science and Technology Committee, 2012) and smoking status (non-smoker/former smoker/smoker <10 cigarettes/smoker 10-19 cigarettes/smoker >20 cigarettes); BMI (normal/underweight/overweight/obese)]; a 'malaise inventory' that identifies symptoms of depression and/or anxiety. The individual was considered as having a psychological malaise if s/he reported experiencing more than seven out of twenty-four symptoms (no malaise/malaise) (Power & Manor, 1992; Rutter et al., 1970; Rutter et al., 1976).

### 2.5. Additional variables tested (not included in the final model)

We tested in our model the influence of adding other perinatal variables. We included other respondent's characteristics and birth variables: gestational age in weeks (39 to 41 weeks/ ≤38 weeks/ >41 weeks), mother's parity (primiparous/one/two or more), breastfeeding (no/one month or less/ more than one month), mother's age at birth (23 years or less/24 to 27 years/28 to 31 years/32 years or more), however we decided to exclude these variables according to statistical criteria. Their exclusion did not have an impact on the results of the multivariate analysis.

### 2.6. Statistical model & data analysis

Bivariate and multivariate analyses were carried out on the imputed data using linear regression. We performed a multivariate linear analysis that took a life course perspective, whereby variables were added to the model in chronological order. Then, to explore the relationships between ACE and AL, we conducted a path analysis using ACE as the exposure variable. For further details about imputation model, the life course model please refer to Part II, Chapter II, sections 1 and 3.

The variables were entered chronologically as they would occur over the lifespan:

i) Model 1 : Early life socioeconomic circumstances and perinatal variables;

ii) Model 2: M1 + childhood pathologies and ACE;

iii) Model 3: M2 + adulthood confounders at 23y (education, psychological malaise, and health behaviours);

iv) Model 4: M3 + adulthood socioeconomic confounders at 33y (wealth, social class and marital status).

Subsequently we used path modelling to examine all indirect associations between ACE and AL in adulthood. Path analysis allowed us to disentangle and describe indirect effect pathways (Israels, 1987). The direct pathway between ACE and AL was calculated using a classic multivariate linear regression after adjustment for confounders and mediation variables. The indirect pathways corresponded to the part of the effect observed between ACE and AL score that was explained by the mediating factors. For further details about path analysis and mediation analysis please refer to Part II, Chapter II, sections 1.

We performed two sensitivity analysis for this research axis. The first one was a series of regression analyses of individual biomarkers for studying the AL score stability by identifying if within our score a parameter was having a stronger effect relatively to the others. The second sensitivity analysis was to ensure that our results using a complete case AL score were not biased by missing values; we thus imputed the missing biomarkers from other measured biomarkers. For further details about sensitivity analysis please refer to Part II, Chapter II, sections 3.

All analyses were performed using STATA® V11 taking a statistical significance level of 0.05.

## 3. Results

Descriptive statistics of the non-imputed sample are presented in Table 13 for the subsample (N=3753 for men, N=3782 for women). Among respondents, 19.1% of men and 16.4% of women were classified as having an AL score equal to 3 at the age of 44. Only 7.5% of men and 8.3% of women had an AL score equal to zero. The majority of men (72.5%) and women (73.4%) were not identified as having ACE. The distribution of ACE was similar for both sexes, with 6.6% of men and 6.4% of women with two or more ACE.

Bivariate statistics (Table 14) for both men and women, showed a gradient relationship between ACE and AL [men: 1 ACE ($\beta$=0.30, p<0.001)/2ACE ($\beta$=0.67, p<0.001); women: 1 ACE ($\beta$=0.35, p<0.001)/2ACE ($\beta$=0.64, p<0.001)]. A significant graded relationship also appeared between the AL score and some confounding factors such as mother's education, parental

social class, overcrowding, mother's smoking status during pregnancy and childhood pathologies for both men and women.

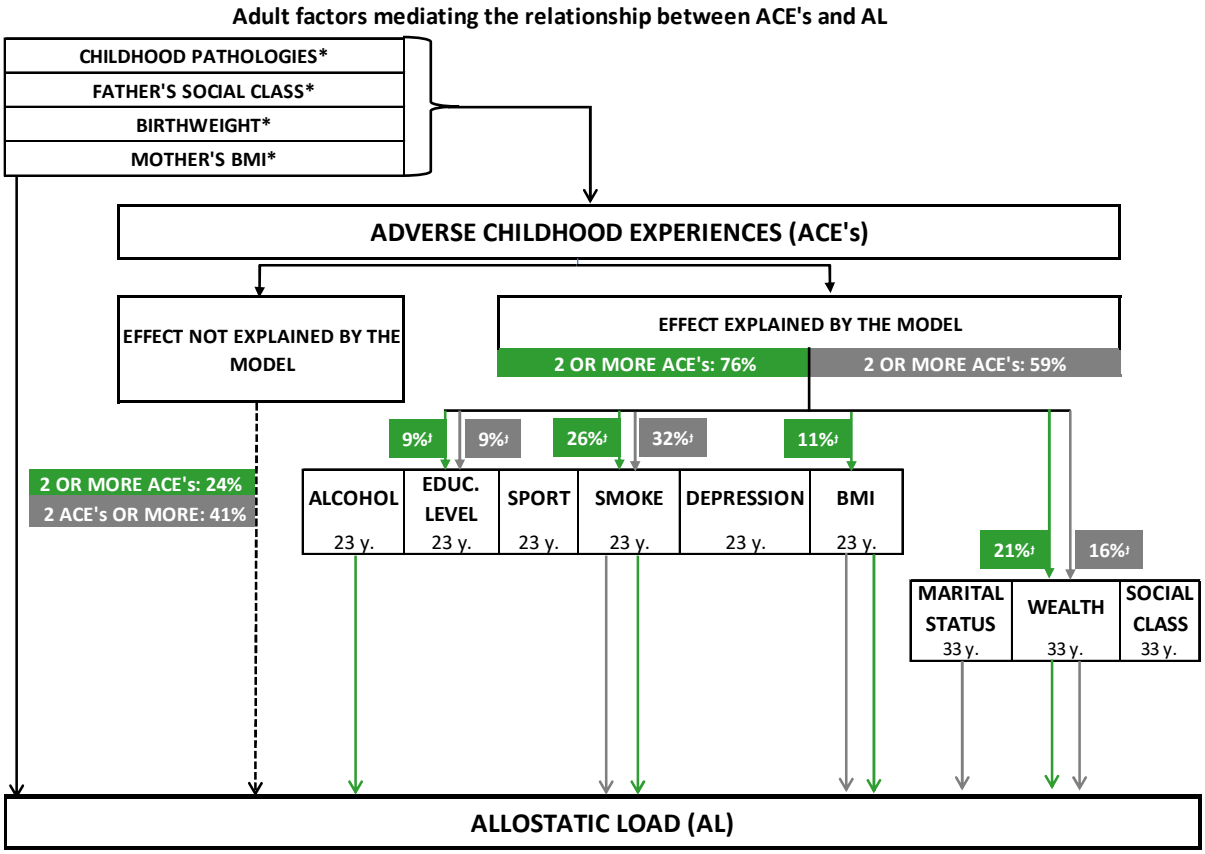
The multivariate analyses for men (Table 15) showed that mother's education, parental social class and childhood pathologies were associated with an increased AL score (Model 1). Mother's BMI and smoking heavily during pregnancy were positively associated with AL score. Birth weight was inversely associated to AL score: individuals in the highest quartile had a lower AL score compared to those into the lower quartile. With the inclusion of childhood pathologies and ACE (Model 2), the socio-economic variables at birth continued to be predictors of higher AL score, though these relationships were slightly attenuated. Compared to men with no ACE, those classified as having one ACE had an increased AL score (0.18, p=0.02), the increase was greater among men exposed to 2 or more ACE (0.46, p <0.01).The effect of ACE on AL score was strongly mediated by health behaviours at 23y, since the relationship between ACE and AL was no longer significant (Model 3). For men, childhood pathologies (β= 0.15, p <0.03), being a smoker (β= 0.40, p <0.001 for smoking between 10 to 19 cigarettes/β= 0.77, p <0.001 for heavy smokers), being physically inactive (β= 0.14, p =0.044), having a low educational level (β= 0.20, p= 0.07) and being overweight (β= 0.47 p<0.001) or obese (β= 1.16, p <0.001) were associated with an increased AL score compared to their counterparts.

The full model (Model 4) shows that the socio-economic variables at 33y were important mediators of the relationship between ACE and AL. Parental social class (manual), mother's BMI, birth weight, childhood pathologies, smoking heavily and being overweight or obese at 23y were associated with higher AL score even though the strength of these associations dropped slightly. Wealth was significantly related to a lower AL score (β= -0.43, p <0.01 for the highest quartile) and being single increased the AL score by 0.22 (p= 0.02). The path analysis, highlighting the direct and indirect effects between ACE and AL, for men showed that the association between ACE and AL was strongly mediated by health behaviours at 23y and socioeconomic status at 33y. Among men, 59% (for 2 or more ACE) of the total mediated effect was mediated by health behaviours (specially smoking), education level at 23 years and wealth at 33 years (Figure 6).

The multivariate analyses for women are shown in Table 16. Model 1 shows that mother's education, parental social class, mother's BMI (overweight) were positively and significantly associated with a higher AL score. Birth weight was inversely correlated with AL score. Children

of mothers who smoked sometimes and heavily during pregnancy had a significantly higher AL score. In Model 2, the same patterns were observed for the variables at birth even if the strength of these associations were weakened. Compared to women with no ACE, those with one ACE had an increased AL score (0.24, $p < 0.01$), as did those with 2 or more ACE (0.42, $p < 0.01$). The effect of ACE on AL score was strongly mediated by health behaviours at 23y, with the association between ACE and AL disappearing in Model 3 when the variables were entered into the model. Being a smoker, overweight or obese at 23y and having no qualification were associated with higher AL score. Being a heavy drinker was inversely associated to AL score. In the full model (Model 4), early life socioeconomic circumstances remained associated with AL score after controlling for mediators. Being a smoker, overweight or obese at 23 years and being a home owner at 33 years was significantly and positively associated to AL score at 44y. Finally the path analysis showed that the link between ACE and AL was strongly mediated by health behaviours and BMI at 23y as well as socioeconomic characteristics at 33y. ACE was associated with a higher AL score in mid-life mainly *via* smoking, wealth, BMI and education level (76% of the mediated effect for 2 or more ACE) (Figure 6).

Figure 6. Path analyses results for men and women.




* Childhood pathologies, Father's social class, Birthweight and Mother's BMI are linked to ACE's and to AL. The relationship with AL remains after including all adult variables.

Effect not explained by the model: not significant (p>0.05) in the final model.

Women: elevation of AL was associated with smoking (23 years), high BMI (23 years), low education level (23 years), and low wealth (33 years) for women (n=3,782). Smoking, alcohol, wealth and BMI were statistically significant in the final model for women.

Men: elevation of AL was associated with smoking (23 years), low education level (23 years), and low wealth (33 years) were factors mediating elevated AL for men (n=3,753). Smoking, BMI, wealth and marital status were statistically significant in the final model for men.

ǂ The sum of the mediated effect of adulthood variables corresponds to 76% for women and 59% for men. However we decided to include in this figure only those whose mediated effect was >8%.

Image by Cristina Barboza Solis and Romain Fantin

Table 13. Descriptive statistics on the subsample for men and women

| | Men 3753 [%] | Women 3782 [%] |
|---|---|---|
| Allostatic Load | | |
| *0* | 283 [7.54%] | 313 [8.28%] |
| *1* | 589 [15.69%] | 670 [17.72%] |
| *2* | 797 [21.24%] | 734 [19.41%] |
| *3* | 715 [19.05%] | 620 [16.39%] |
| *4* | 554 [14.76%] | 538 [14.23%] |
| *5* | 360 [9.59%] | 371 [9.81%] |
| *6* | 240 [6.40%] | 245 [6.48%] |
| *7* | 135 [3.60%] | 140 [3.70%] |
| *8* | 58 [1.55%] | 93 [2.46%] |
| *9* | 18 [0.48%] | 44 [1.16%] |
| *10* | 4 [0.11%] | 7 [0.19%] |
| *11* | 0 [0.00%] | 5 [0.13%] |
| *12* | 0 [0.00%] | 2 [0.05%] |
| Adverse Childhood Experiences | | |
| *None* | 2 721 [72.50%] | 2 775 [73.37%] |
| *One* | 786 [20.94%] | 764 [20.20%] |
| *Two or more* | 246 [6.56%] | 243 [6.43%] |
| Mother's education level | | |
| *Left school at 15 or later* | 963 [25.66%] | 971 [25.67%] |
| *Left school before 14* | 2 643 [70.42%] | 2 648 [70.02%] |
| *Missing* | 147 [3.92%] | 163 [4.31%] |
| Father's social class at birth | | |
| *Non-manual* | 1 063 [28.32%] | 1 037 [27.42%] |
| *Manual* | 2 534 [67.52%] | 2 568 [67.90%] |
| *Missing* | 156 [4.16%] | 177 [4.68%] |
| Overcrowding | | |
| *>1.5 people per room* | 385 [10.26%] | 448 [11.85%] |
| *≤1.5 people per room* | 3 146 [83.83%] | 3 103 [82.05%] |
| *Missing* | 222 [5.92%] | 231 [6.11%] |
| Mother's BMI | | |
| *Normal* | 2 514 [66.99%] | 2 472 [65.36%] |
| *Underweight* | 128 [3.41%] | 170 [4.50%] |
| *Overweight* | 652 [17.37%] | 665 [17.58%] |
| *Obese* | 144 [3.84%] | 140 [3.70%] |
| *Missing* | 315 [8.39%] | 335 [8.86%] |
| Mother smoked during pregnancy | | |
| *No* | 2 448 [65.23%] | 2 426 [64.15%] |
| *Sometimes* | 222 [5.92%] | 207 [5.47%] |
| *Moderately* | 514 [13.70%] | 550 [14.54%] |
| *Heavily* | 405 [10.79%] | 413 [10.92%] |
| *Missing* | 164 [4.37%] | 186 [4.92%] |

*(continued)*

Table 13. continued

| | Men 3753 [%] | Women 3782 [%] |
|---|---|---|
| **Birthweight** | | |
| *Q1 - Low weight* | 730 [19.45%] | 714 [18.88%] |
| *Q2* | 1 022 [27.23%] | 904 [23.90%] |
| *Q3* | 825 [21.98%] | 962 [25.44%] |
| *Q4 - High weight* | 939 [25.02%] | 956 [25.28%] |
| *Missing* | 237 [6.32%] | 246 [6.50%] |
| **Childhood pathologies** | | |
| *No* | 2 749 [73.25%] | 2 883 [76.23%] |
| *Yes* | 994 [26.49%] | 887 [23.45%] |
| *Missing* | 10 [0.27%] | 12 [0.32%] |
| **Smoking status at 23** | | |
| *Non-smoker* | 929 [24.75%] | 1 100 [29.09%] |
| *Former smoker* | 1 045 [27.84%] | 939 [24.83%] |
| *Smoker - Less than 10 cig.* | 221 [5.89%] | 336 [8.88%] |
| *Smoker - 10 to 19 cig.* | 437 [11.64%] | 493 [13.04%] |
| *Smoker - More than 20 cig.* | 576 [15.35%] | 467 [12.35%] |
| *Missing* | 545 [14.52%] | 447 [11.82%] |
| **Alcohol consumption at 23** | | |
| *Moderate* | 1 553 [41.38%] | 1 756 [46.43%] |
| *Abstainers* | 397 [10.58%] | 1 158 [30.62%] |
| *Heavy drinkers* | 1 256 [33.47%] | 420 [11.11%] |
| *Missing* | 547 [14.58%] | 448 [11.85%] |
| **Physical activity at 23** | | |
| *Physically active* | 1 389 [37.01%] | 797 [21.07%] |
| *Moderately active* | 587 [15.64%] | 474 [12.53%] |
| *Inactive* | 1 228 [32.72%] | 2 064 [54.57%] |
| *Missing* | 549 [14.63%] | 447 [11.82%] |
| **Malaise inventory at 23** | | |
| *No* | 3 093 [82.41%] | 3 003 [79.40%] |
| *Yes* | 110 [2.93%] | 329 [8.70%] |
| *Missing* | 550 [14.66%] | 450 [11.90%] |
| **Education level at 23** | | |
| *Passed A levels* | 788 [21.00%] | 762 [20.15%] |
| *Passed O levels* | 1 239 [33.01%] | 1 456 [39.56%] |
| *No qualifications* | 1 179 [31.42%] | 1 075 [28.42%] |
| *Missing* | 547 [14.58%] | 449 [11.87%] |
| **BMI at 23** | | |
| *Normal* | 2 522 [67.20%] | 2 673 [70.68%] |
| *Underweight* | 73 [1.95%] | 207 [5.47%] |
| *Overweight* | 502 [13.38%] | 334 [8.83%] |
| *Obese* | 60 [1.60%] | 83 [2.20%] |
| *Missing* | 596 [15.88%] | 485 [12.82%] |

(*continued*)

Table 13. continued

| | Men 3753 [%] | Women 3782 [%] |
|---|---|---|
| Social class at 33 | | |
| *Non-manual* | 1 649 [43.94%] | 2 249 [59.47%] |
| *Manual* | 1 464 [39.01%] | 950 [25.12%] |
| *Missing* | 640 [17.05%] | 583 [15.42%] |
| Wealth at 33 | | |
| *Not owner* | 732 [19.50%] | 777 [20.55%] |
| *Owner - Q1 (Low price)* | 637 [16.97%] | 637 [16.84%] |
| *Owner - Q2* | 610 [16.25%] | 663 [17.53%] |
| *Owner - Q3* | 633 [16.87%] | 632 [16.71%] |
| *Owner - Q4* | 595 [15.85%] | 645 [17.05%] |
| *Missing* | 546 [14.55%] | 428 [11.32%] |
| Marital status at 33 | | |
| *Couple* | 2 622 [69.86%] | 2 811 [74.33%] |
| *Single* | 453 [12.07%] | 312 [8.25%] |
| *Divorced or widowed* | 174 [4.64%] | 289 [7.64%] |
| *Missing* | 504 [13.43%] | 370 [9.78%] |

Table 14. Bivariate statistics on imputed data for men (n=3753) and women (3782)

| Variables | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | β | CI 95% | p | β | CI 95% | p |
| **Mother's education level** | | | | | | |
| *Left school after min age* | | | | | | |
| *Left school before min age* | 0.390 | [0.248 - 0.532] | <0.001 | 0.678 | [0.524 - 0.832] | <0.001 |
| **Father's social class at birth** | | | | | | |
| *Non-manual* | | | | | | |
| *Manual* | 0.535 | [0.398 - 0.671] | <0.001 | 0.694 | [0.543 - 0.846] | <0.001 |
| **Overcrowding** | | | | | | |
| ≥1.5 people per room | | | | | | |
| <1.5 people per room | -0.245 | [-0.445 - -0.044] | 0.017 | -0.429 | [-0.646 - -0.211] | <0.001 |
| **Mother's BMI** | | | | | | |
| Normal | | | | | | |
| Underweight | 0.224 | [-0.116 - 0.563] | 0.196 | 0.224 | [-0.114 - 0.563] | 0.194 |
| Overweight | 0.306 | [0.139 - 0.474] | <0.001 | 0.407 | [0.220 - 0.594] | <0.001 |
| Obese | 0.666 | [0.347 - 0.986] | <0.001 | 0.270 | [-0.093 - 0.632] | 0.144 |
| **Mother smoked during pregnancy** | | | | | | |
| No | | | | | | |
| Sometimes | 0.390 | [0.121 - 0.660] | 0.005 | 0.578 | [0.274 - 0.881] | <0.001 |
| Moderately | 0.189 | [0.005 - 0.374] | 0.044 | 0.191 | [-0.008 - 0.390] | 0.060 |
| Heavily | 0.324 | [0.120 - 0.527] | 0.002 | 0.327 | [0.105 - 0.550] | 0.004 |
| **Birthweight** | | | | | | |
| Q1 - Lowest weight | | | | | | |
| Q2 | -0.289 | [-0.465 - -0.113] | 0.001 | -0.172 | [-0.373 - 0.028] | 0.092 |
| Q3 | -0.281 | [-0.466 - -0.096] | 0.003 | -0.261 | [-0.456 - -0.065] | 0.009 |
| Q4 | -0.343 | [-0.521 - -0.166] | <0.001 | -0.407 | [-0.603 - -0.211] | <0.001 |

*(continued)*

Table 14. continued

| Variables | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | β | CI 95% | p | β | CI 95% | p |
| **Adverse Childhood Experiences** | | | | | | |
| *None* | | | | | | |
| *One* | 0.277 | [0.122 - 0.431] | <0.001 | 0.346 | [0.175 - 0.518] | <0.001 |
| *Two or more* | 0.667 | [0.413 - 0.921] | <0.001 | 0.644 | [0.364 - 0.924] | <0.001 |
| **Childhood pathologies** | | | | | | |
| *No* | | | | | | |
| *Yes* | 0.241 | [0.100 - 0.382] | <0.001 | 0.248 | [0.087 - 0.409] | 0.003 |
| **Smoking status at 23** | | | | | | |
| *Non-smoker* | | | | | | |
| *Former smoker* | -0.183 | [-0.353 - -0.014] | 0.034 | -0.243 | [-0.426 - -0.059] | 0.010 |
| *Smoker more than 10 cig.* | -0.038 | [-0.328 - 0.253] | 0.800 | -0.164 | [-0.414 - 0.086] | 0.199 |
| *Smoker 10 to 19 cig.* | 0.499 | [0.281 - 0.717] | <0.001 | 0.507 | [0.291 - 0.722] | <0.001 |
| *Smoker - More than 20 cig.* | 0.955 | [0.767 - 1.143] | <0.001 | 0.842 | [0.624 - 1.059] | <0.001 |
| **Alcohol consumption at 23** | | | | | | |
| *Moderate* | | | | | | |
| *Abstainers* | 0.100 | [-0.119 - 0.318] | 0.371 | 0.287 | [0.124 - 0.451] | <0.001 |
| *Heavy drinkers* | 0.134 | [-0.010 - 0.278] | 0.067 | -0.229 | [-0.462 - 0.003] | 0.053 |
| **Physical activity at 23** | | | | | | |
| *Physically active* | | | | | | |
| *Moderately active* | 0.116 | [-0.069 - 0.302] | 0.219 | -0.005 | [-0.240 - 0.231] | 0.969 |
| *Inactive* | 0.331 | [0.180 - 0.483] | <0.001 | 0.513 | [0.341 - 0.684] | <0.001 |

*(continued)*

Table 14. continued

| Variables | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | β | CI 95% | p | β | CI 95% | p |
| **Malaise inventory at 23** | | | | | | |
| *No malaise* | | | | | | |
| *Malaise* | 0.420 | [0.058 - 0.783] | 0.023 | 0.648 | [0.405 - 0.891] | <0.001 |
| *Passed A levels* | | | | | | |
| *Passed O levels* | 0.414 | [0.247 - 0.581] | <0.001 | 0.472 | [0.289 - 0.655] | <0.001 |
| *No qualifications* | 0.813 | [0.648 - 0.979] | <0.001 | 1.049 | [0.861 - 1.238] | <0.001 |
| **BMI at 23** | | | | | | |
| *Normal* | | | | | | |
| *Overweight* | 0.624 | [0.448 - 0.800] | <0.001 | 1.087 | [0.848 - 1.326] | <0.001 |
| *Obese* | 1.452 | [0.964 - 1.941] | <0.001 | 2.237 | [1.781 - 2.693] | <0.001 |
| **Social class at 33** | | | | | | |
| *Non-manual* | | | | | | |
| *Manual* | 0.488 | [0.351 - 0.624] | <0.001 | 0.529 | [0.372 - 0.687] | <0.001 |
| **Wealth at 33** | | | | | | |
| *Not owner* | | | | | | |
| *Owner - Q1 (Lowest price)* | -0.298 | [-0.496 - -0.100] | 0.003 | -0.557 | [-0.773 - -0.341] | <0.001 |
| *Owner - Q2* | -0.411 | [-0.615 - -0.206] | <0.001 | -0.858 | [-1.067 - -0.649] | <0.001 |
| *Owner - Q3* | -0.771 | [-0.972 - -0.570] | <0.001 | -1.025 | [-1.241 - -0.809] | <0.001 |
| *Owner - Q4* | -0.923 | [-1.131 - -0.716] | <0.001 | -1.230 | [-1.445 - -1.015] | <0.001 |
| **Marital status at 33** | | | | | | |
| *Couple* | | | | | | |
| *Single* | 0.283 | [0.098 - 0.468] | 0.003 | 0.189 | [-0.068 - 0.445] | 0.149 |
| *Divorced or widowed* | 0.358 | [0.070 - 0.646] | 0.015 | 0.333 | [0.071 - 0.596] | 0.013 |

Table 15. Life course multivariate linear regression using data obtained from multiple imputation: men (n=3753)

| Variables | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|
| | ß (SE) | p | ß (SE) | p | ß (SE) | p | ß (SE) | p |
| **Mother's education level** | | | | | | | | |
| *Left school at 15 or later* | 0 | | 0 | | 0 | | 0 | |
| *Left school before 14* | 0.17 (0.08) | 0.03 | 0.16 (0.08) | 0.04 | 0.07 (0.08) | 0.35 | 0.06 (0.08) | 0.44 |
| **Father's social class at birth** | | | | | | | | |
| *Non-manual* | 0 | | 0 | | 0 | | 0 | |
| *Manual* | 0.39 (0.08) | <0.01 | 0.37 (0.08) | <0.01 | 0.23 (0.08) | <0.01 | 0.22 (0.08) | <0.01 |
| **Overcrowding** | | | | | | | | |
| *>1.5 people per room* | 0 | | 0 | | 0 | | 0 | |
| *≤1.5 people per room* | -0.08 (0.10) | 0.46 | -0.03 (0.10) | 0.79 | 0.02 (0.10) | 0.84 | 0.04 (0.10) | 0.70 |
| **Mother's BMI** | | | | | | | | |
| *Normal* | 0 | | 0 | | 0 | | 0 | |
| *Underweight* | 0.13 (0.17) | 0.46 | 0.10 (0.17) | 0.58 | 0.19 (0.17) | 0.26 | 0.21 (0.17) | 0.22 |
| *Overweight* | 0.29 (0.08) | <0.01 | 0.29 (0.08) | <0.01 | 0.23 (0.08) | <0.01 | 0.22 (0.08) | <0.01 |
| *Obese* | 0.59 (0.16) | <0.01 | 0.55 (0.16) | <0.01 | 0.32 (0.16) | 0.05 | 0.30 (0.16) | 0.06 |
| **Mother smoked during pregnancy** | | | | | | | | |
| *No* | 0 | | 0 | | 0 | | 0 | |
| *Sometimes* | 0.29 (0.14) | 0.03 | 0.26 (0.14) | 0.05 | 0.16 (0.13) | 0.22 | 0.16 (0.13) | 0.24 |
| *Moderately* | 0.12 (0.09) | 0.19 | 0.11 (0.09) | 0.25 | 0.08 (0.09) | 0.39 | 0.08 (0.09) | 0.40 |
| *Heavily* | 0.22 (0.10) | 0.03 | 0.20 (0.10) | 0.06 | 0.09 (0.10) | 0.38 | 0.09 (0.10) | 0.39 |
| **Birthweight** | | | | | | | | |
| *Q1 - Low weight* | 0 | | 0 | | 0 | | 0 | |
| *Q2* | -0.27 (0.09) | <0.01 | -0.25 (0.09) | <0.01 | -0.24 (0.09) | <0.01 | -0.22 (0.09) | 0.01 |
| *Q3* | -0.26 (0.09) | <0.01 | -0.25 (0.09) | <0.01 | -0.26 (0.09) | <0.01 | -0.23 (0.09) | 0.01 |
| *Q4 - High weight* | -0.31 (0.09) | <0.01 | -0.28 (0.09) | <0.01 | -0.32 (0.09) | <0.01 | -0.30 (0.09) | <0.01 |

*(continued)*

Table 15. continued

| Variables | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|
| | ß (SE) | p | ß (SE) | p | ß (SE) | p | ß (SE) | p |
| **Childhood pathologies** | | | | | | | | |
| *No* | | | 0 | | 0 | | 0 | |
| *Yes* | | | 0.20 (0.07) | <0.01 | 0.18 (0.07) | 0.01 | 0.15 (0.07) | 0.03 |
| **Adverse Childhood Experiences** | | | | | | | | |
| *None* | | | 0 | | 0 | | 0 | |
| *One* | | | 0.18 (0.08) | 0.02 | 0.06 (0.08) | 0.47 | 0.05 (0.08) | 0.54 |
| *Two or more* | | | 0.46 (0.13) | <0.01 | 0.25 (0.13) | 0.05 | 0.19 (0.13) | 0.14 |
| **Smoking status at 23** | | | | | | | | |
| *Non-smoker* | | | | | 0 | | 0 | |
| *Former smoker* | | | | | -0.17 (0.09) | 0.05 | -0.16 (0.09) | 0.06 |
| *Smoker - Less than 10 cig.* | | | | | -0.06 (0.15) | 0.69 | -0.07 (0.15) | 0.64 |
| *Smoker - 10 to 19 cig.* | | | | | 0.42 (0.11) | <0.01 | 0.40 (0.11) | <0.01 |
| *Smoker - More than 20 cig.* | | | | | 0.79 (0.10) | <0.01 | 0.77 (0.10) | <0.01 |
| **Alcohol consumption at 23** | | | | | | | | |
| *Moderate* | | | | | 0 | | 0 | |
| *Abstainers* | | | | | -0.04 (0.11) | 0.73 | -0.08 (0.11) | 0.43 |
| *Heavy drinkers* | | | | | 0.06 (0.07) | 0.39 | 0.04 (0.07) | 0.54 |
| **Physical activity at 23** | | | | | | | | |
| *Physically active* | | | | | 0 | | 0 | |
| *Moderately active* | | | | | 0.09 (0.09) | 0.32 | 0.10 (0.09) | 0.28 |
| *Inactive* | | | | | 0.16 (0.08) | 0.03 | 0.14 (0.08) | 0.08 |
| **Malaise inventory at 23** | | | | | | | | |
| *No* | | | | | 0 | | 0 | |
| *Yes* | | | | | 0.06 (0.18) | 0.75 | 0.01 (0.18) | 0.95 |

*(continued)*

Table 15. continued

| Variables | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|
| | ß (SE) | p | ß (SE) | p | ß (SE) | p | ß (SE) | p |
| **Education level at 23** | | | | | | | | |
| *Passed A levels* | | | | | 0 | | 0 | |
| *Passed O levels* | | | | | 0.11 (0.09) | 0.20 | 0.09 (0.09) | 0.33 |
| *No qualifications* | | | | | 0.26 (0.10) | <0.01 | 0.20 (0.11) | 0.07 |
| **BMI at 23** | | | | | | | | |
| *Normal* | | | | | 0 | | 0 | |
| *Underweight* | | | | | -0.15 (0.21) | 0.46 | -0.24 (0.21) | 0.24 |
| *Overweight* | | | | | 0.48 (0.09) | <0.01 | 0.47 (0.09) | <0.01 |
| *Obese* | | | | | 1.22 (0.24) | <0.01 | 1.16 (0.24) | <0.01 |
| **Social class at 33** | | | | | | | | |
| *Non-manual* | | | | | | | 0 | |
| *Manual* | | | | | | | -0.03 (0.08) | 0.71 |
| **Wealth at 33** | | | | | | | | |
| *Not owner* | | | | | | | 0 | |
| *Owner - Q1 (Low price)* | | | | | | | -0.17 (0.10) | 0.10 |
| *Owner - Q2* | | | | | | | -0.15 (0.11) | 0.15 |
| *Owner - Q3* | | | | | | | -0.39 (0.11) | <0.01 |
| *Owner - Q4* | | | | | | | -0.43 (0.12) | <0.01 |
| **Marital status at 33** | | | | | | | | |
| *Couple* | | | | | | | 0 | |
| *Single* | | | | | | | 0.22 (0.10) | 0.02 |
| *Divorced or widowed* | | | | | | | 0.15 (0.14) | 0.28 |

Table 16. Life course multivariate linear regression using data obtained from multiple imputation: women (n=3782)

| Variables | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|
| | ß (SE) | p | ß (SE) | p | ß (SE) | p | ß (SE) | p |
| **Mother's education level** | | | | | | | | |
| *Left school at 15 or later* | 0 | | 0 | | 0 | | 0 | |
| *Left school before 14* | 0.45 (0.08) | <0.01 | 0.43 (0.08) | <0.01 | 0.31 (0.09) | <0.01 | 0.31 (0.09) | <0.01 |
| **Father's social class at birth** | | | | | | | | |
| *Non-manual* | 0 | | 0 | | 0 | | 0 | |
| *Manual* | 0.45 (0.08) | <0.01 | 0.43 (0.08) | <0.01 | 0.25 (0.08) | <0.01 | 0.22 (0.08) | <0.01 |
| **Overcrowding** | | | | | | | | |
| *>1.5 people per room* | 0 | | 0 | | 0 | | 0 | |
| *≤1.5 people per room* | -0.19 (0.11) | 0.10 | -0.15 (0.11) | 0.17 | -0.04 (0.11) | 0.68 | -0.03 (0.11) | 0.76 |
| **Mother's BMI** | | | | | | | | |
| *Normal* | 0 | | 0 | | 0 | | 0 | |
| *Underweight* | 0.10 (0.17) | 0.54 | 0.07 (0.17) | 0.70 | 0.11 (0.16) | 0.49 | 0.11 (0.16) | 0.51 |
| *Overweight* | 0.36 (0.10) | <0.01 | 0.37 (0.10) | <0.01 | 0.24 (0.09) | 0.01 | 0.24 (0.09) | 0.01 |
| *Obese* | 0.18 (0.18) | 0.32 | 0.16 (0.18) | 0.39 | -0.19 (0.18) | 0.29 | -0.21 (0.18) | 0.24 |
| **Mother smoked during pregnancy** | | | | | | | | |
| *No* | 0 | | 0 | | 0 | | 0 | |
| *Sometimes* | 0.41 (0.15) | <0.01 | 0.36 (0.15) | 0.02 | 0.19 (0.15) | 0.21 | 0.15 (0.15) | 0.31 |
| *Moderately* | 0.08 (0.10) | 0.44 | 0.07 (0.10) | 0.52 | -0.02 (0.10) | 0.87 | -0.04 (0.10) | 0.70 |
| *Heavily* | 0.21 (0.11) | 0.07 | 0.18 (0.11) | 0.11 | 0.01 (0.11) | 0.94 | 0.01 (0.11) | 0.96 |
| **Birthweight** | | | | | | | | |
| *Q1 - Low weight* | 0 | | 0 | | 0 | | 0 | |
| *Q2* | -0.17 (0.10) | 0.10 | -0.17 (0.10) | 0.10 | -0.12 (0.10) | 0.24 | -0.12 (0.10) | 0.21 |
| *Q3* | -0.21 (0.10) | 0.03 | -0.20 (0.10) | 0.04 | -0.17 (0.10) | 0.08 | -0.15 (0.10) | 0.11 |
| *Q4 - High weight* | -0.36 (0.10) | <0.01 | -0.35 (0.10) | <0.01 | -0.33 (0.10) | <0.01 | -0.33 (0.10) | <0.01 |

*(continued)*

Table 16. continued

| Variables | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|
| | ß (SE) | p | ß (SE) | p | ß (SE) | p | ß (SE) | p |
| Childhood pathologies | | | | | | | | |
| *No* | | | 0 | | 0 | | 0 | |
| *Yes* | | | 0.20 (0.08) | 0.02 | 0.13 (0.08) | 0.11 | 0.12 (0.08) | 0.12 |
| Adverse Childhood Experiences | | | | | | | | |
| *None* | | | 0 | | 0 | | 0 | |
| *One* | | | 0.24 (0.09) | <0.01 | 0.13 (0.08) | 0.12 | 0.10 (0.08) | 0.24 |
| *Two or more* | | | 0.42 (0.14) | <0.01 | 0.15 (0.14) | 0.27 | 0.10 (0.14) | 0.46 |
| Smoking status at 23 | | | | | | | | |
| *Non-smoker* | | | | | 0 | | 0 | |
| *Former smoker* | | | | | -0.20 (0.09) | 0.03 | -0.19 (0.09) | 0.04 |
| *Smoker - Less than 10 cig.* | | | | | -0.06 (0.12) | 0.61 | -0.10 (0.12) | 0.43 |
| *Smoker - 10 to 19 cig.* | | | | | 0.41 (0.11) | <0.01 | 0.35 (0.11) | <0.01 |
| *Smoker - More than 20 cig.* | | | | | 0.66 (0.11) | <0.01 | 0.57 (0.11) | <0.01 |
| Alcohol consumption at 23 | | | | | | | | |
| *Moderate* | | | | | 0 | | 0 | |
| *Abstainers* | | | | | 0.02 (0.08) | 0.77 | -0.02 (0.08) | 0.81 |
| *Heavy drinkers* | | | | | -0.36 (0.11) | <0.01 | -0.35 (0.11) | <0.01 |
| Physical activity at 23 | | | | | | | | |
| *Physically active* | | | | | 0 | | 0 | |
| *Moderately active* | | | | | -0.06 (0.11) | 0.61 | -0.05 (0.11) | 0.63 |
| *Inactive* | | | | | 0.16 (0.09) | 0.06 | 0.14 (0.09) | 0.12 |
| Malaise inventory at 23 | | | | | | | | |
| *No* | | | | | 0 | | 0 | |
| *Yes* | | | | | 0.22 (0.12) | 0.06 | 0.20 (0.12) | 0.09 |

*(continued)*

Table 16. continued

| Variables | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|
| | ß (SE) | p | ß (SE) | p | ß (SE) | p | ß (SE) | p |
| Education level at 23 | | | | | | | | |
| *Passed A levels* | | | | | 0 | | 0 | |
| *Passed O levels* | | | | | 0.08 (0.10) | 0.41 | 0.06 (0.10) | 0.51 |
| *No qualifications* | | | | | 0.26 (0.11) | 0.02 | 0.17 (0.12) | 0.15 |
| *BMI at 23* | | | | | | | | |
| *Normal* | | | | | 0 | | 0 | |
| *Underweight* | | | | | -0.26 (0.14) | 0.08 | -0.25 (0.14) | 0.08 |
| *Overweight* | | | | | 0.89 (0.12) | <0.01 | 0.85 (0.12) | <0.01 |
| *Obese* | | | | | 2.01 (0.23) | <0.01 | 1.88 (0.23) | <0.01 |
| Social class at 33 | | | | | | | | |
| *Non-manual* | | | | | | | 0 | |
| *Manual* | | | | | | | 0.04 (0.09) | 0.68 |
| Wealth at 33 | | | | | | | | |
| *Not owner* | | | | | | | 0 | |
| *Owner - Q1 (Low price)* | | | | | | | -0.35 (0.11) | <0.01 |
| *Owner - Q2* | | | | | | | -0.48 (0.11) | <0.01 |
| *Owner - Q3* | | | | | | | -0.50 (0.12) | <0.01 |
| *Owner - Q4* | | | | | | | -0.55 (0.12) | <0.01 |
| Marital status at 33 | | | | | | | | |
| *Couple* | | | | | | | 0 | |
| *Single* | | | | | | | 0.03 (0.13) | 0.81 |
| *Divorced or widowed* | | | | | | | -0.04 (0.13) | 0.74 |

## 4. Discussion

Psychosocial adversity during childhood was related to physiological wear and tear at 44 years after taking birth and childhood factors into account, in a large prospective cohort. For men and women, this association was strongly mediated by health behaviours at 23 years (principally smoking) and socioeconomic status (in particular education level at 23 years and wealth at 33 years). For women, BMI at 23 years also explained part of the link between ACE and AL.

Our hypothesis was that early psychosocial adversity can be embedded and impact later health. Our findings add to the literature by testing potential mediating pathways. We have proposed that biological embedding could be the result of three different pathways: two indirect pathways through health behaviours and socioeconomic/or psychosocial factors, and a third direct biological pathway. We used the conceptual framework of allostatic load as a measure of cumulative physiological wear-and-tear to examine our hypotheses. These results are suggestive of a link between stressful conditions in early life and health in adulthood largely explained by socioeconomic or behavioural factors but not entirely.

Our results showed that after controlling for confounders and mediators, a sizable part of the initial effect remained unexplained (24% to 41% in the whole population according to the level of ACE). The lack of statistical significance may be due to a lack of power, since we only had 246 men and 243 women with 2 or more ACE. These associations may be explained by measurement error or the omission of confounders, but it may also suggest the existence of a biological path that could have lasting effects over time (Kelly-Irving et al., 2013c)

Hertzman introduced the term of biological embedding as the processes whereby cumulative disadvantaged could metaphorically 'get under the skin' and alter human biological and developmental processes (Hertzman, 2012). In this context, the study of the relationship between ACE and AL can contribute to a better understanding of early origins of disease and social gradient in health. Recently, Kelly-Irving *et al* (Kelly-Irving, Lepage, Dedieu, Bartley, et al., 2013; Kelly-Irving, Lepage, Dedieu, Lacey, et al., 2013) showed an association between ACE and self-reported cancer as well as mortality, after adjusting for behavioural and socioeconomic factors suggesting a potential direct link. There is growing evidence the early environment could have an adverse effect on mental and physical health and ACE appeared to be associated

with increased activation in the nervous, endocrine and immune systems. To our knowledge, only one study has explored the influence of social adversity over the lifespan on AL independently of socioeconomic status (Gustafsson et al., 2012). However, health behaviours were not taken into account in this study and it remains unclear how to disentangle the potential pathways by which ACE could influence AL. The mechanisms underlying these observations remain unclear and deserve further research.

Our findings showed a link between birth weight and AL. This result is in accordance with Barker's hypothesis which suggested that exposure to undernutrition in utero was associated with developing coronary heart disease in adulthood (Barker, 2002). Subsequent work based on the developmental origins of adult disease points towards the existence of a sensitive periods mechanism, and in this case, that low birth weight has a lasting impact on health across the lifespan (Barker, 2007).

Regarding the mediating role of health behaviours, our findings were consistent with the literature. The common social pattern in health behaviour adoption potentially includes a number of processes that have been well describe in the literature. The psychological processes highlighted by Bandura *et al*. suggest that ACE may be related to health through a number of mechanisms. These may include poor self-regulation, self-efficacy and self-management mechanisms (Bandura, 1998, 2005). Furthermore, it has been suggested that individuals exposed to adversity-induced stress could adopt coping mechanisms by obtaining a pharmacological or psychological benefit from tobacco or alcohol use (Anda et al., 2006; Anda et al., 2002; Felitti et al., 1998). These results suggested an indirect mechanism of the embodiment of early life experiences *via* health behaviours, material and/or psychosocial circumstances in adulthood.

The main weakness of this study was related to attrition, missing data and selection bias. We therefore imputed the missing data in the eligible sample taking the missing at random (MAR) assumption in order to preserve important aspects of the distribution, variability and relationships between variables. According to this assumption, missingness depends on observed data, such as baseline characteristics and other measures occurring at different time points (Little R & DB, 1987). However, the assumption of MAR is unverifiable and we cannot rule-out that some data are 'missing not at random' (MNAR). Multiple imputation models, such as the one used on these data, included large numbers of covariates, helping to render the

MAR assumption more plausible and to limit the impact of MNAR missingness (Coley et al., 2011).

Another limitation was the measurement of allostatic load. Thought the concept of AL was consistent with our biological embedding hypothesis, our score remained limited by the pragmatism of variable availability. Our score was strongly focused on the cardiovascular system and we had a lack of 'primary' biomarkers (epinephrine and norepinephrine). However, there is currently no consensus regarding the choice of relevant physiological systems, of biomarkers, their interactions (linear relationships), their importance in the chain of physiological stress responses, as well as their measurement, combinations, weighting and the most suitable statistical analysis (Beckie, 2012). Furthermore, as physiological responses to stress may differ according to developmental stage over time, measure of AL may differ in terms of markers and risk thresholds.

It is likely that a number of confounders and mediators have not been taken into account for this analysis. Measurement error is likely in the variable characterizing ACE. Misclassification bias is possible where parents may have responded 'no' to any given question due to the sensitive nature of the data. Because of that, the ACE variable we built is also a conservative measure. Our ACE measurement was limited and it remains a proxy for severe circumstances that we hypothesized as being chronically stressful, and it took into account only the child's condition at age 7, 11 and 16.

Despite these limitations, this study has a number of strengths. It is a longitudinal population-based study collecting data prospectively across the life span. Most studies on childhood adversities use retrospectively collected information, which is highly sensitive and potentially open to a number of different reporting biases. A strength of the childhood adversity measure operationalized here is in its prospective nature, where information collected during childhood about potentially stressful events in the child's life was used to create the variable. Another important strength is in the sample size included in the biomedical survey, and the large number of biomarkers available. Finally, the array and detail of the variables within the cohort allowed us to control for a number variables of potential confounding and mediating factors.

## 5. Conclusion

These results, based on a path analysis showed that childhood adversity was associated with physiological wear-and-tear in mid-life as measured by allostatic load. This relationship was mediated, but not fully explained by later life variables. The path analysis suggested that childhood adversities were associated with an increased AL score in mid-life for men *via* health behaviours, education and wealth, and for women *via* wealth, education, smoking and BMI.

This research provides insight into the mechanisms of accumulation of health risk in adults. Groups who experienced adversities may carry the cost across their life expressed by physiological wear-and-tear in adulthood. For instance, men who experienced 2 or more ACE are more likely to have a lower education level, to smoke and drink at 23 years and to be less well-off at 33 years. Women were more likely to have a lower education level, smoke, be overweight and be less well-off. Nevertheless, this study remains a first approach to understand the potential biological mechanisms that associate ACE with AL. AL represents a useful conceptual tool in measuring the biological effect of biological embedding that can play a role in the production of the social gradient in health.

Childhood is recognized as a window of vulnerability, but also of opportunity. During this period of life, an early form of the socioeconomic gradient in health is set in place. Understanding the origins of health inequalities may lead us to conceptualise better adapted public policy priorities.

# Chapter II

# Mediating factors between early SEP and allostatic load over the life course

In the following chapter we focus on the early socioeconomic environment. In section 1 we will introduce the specific context, the rationale, and we will remind the readers of the objective and hypothesis of this research axis. In section 2 we will present the data and statistical methods as well as the construction variables. In section 3 we will present the main results and finally, in section 4 we will discuss the evidence that could clarify the life course pathways between parental socioeconomic position and offspring's allostatic load in mid-life.

Objective: To investigate the relationship between parental socioeconomic position –measured by maternal education and paternal occupation- and allostatic load at 44 years. We previously identified four pathways that potentially explain such a relationship.

Hypothesis:

PO may affect health through:

i) material resources (that determine material leaving standards);
ii) work privileges (i.e. social security);
iii) social standing (determining work control/autonomy and work based stress);
iv) toxic occupational exposures (Bartley et al., 1996; Galobardes et al., 2006a).

ME could affect health through:

i) higher score of knowledge/skills and thus cultural capital;
ii) material resources;
iii) by increasing the odds of acquiring better positions in occupation and higher income (Galobardes et al., 2006a).

We evaluated the role of four mediating pathways:

i) A material/financial pathway: we hypothesized that living in poor material/financial circumstances could increase the risk of exposure to stressful and harmful situations

related to housing, work conditions, neighbourhood, etc. (toxins, allergens, overcrowding) (Gustafsson et al., 2012; Lannero et al., 2002; Robertson et al., 2015).

ii) A psychosocial/psychological pathway: parental SEP could influence parenting and the creation of a secure social environment buffering toxic stress responses, as well as the set-up of stress responses systems (Repetti et al., 2002; Shonkoff et al., 2012).

iii) An educational pathway: higher parental SEP may influence educational outcomes in childhood, impact cognitive functions (Dubow et al., 2009; Kaplan G. A. et al., 2001) and later adult SEP.

iv) A health behaviours & BMI pathway: the accumulation of social disadvantage over life could contribute to adopt risky behaviours, impacting physiological functioning (Adler & Stewart, 2010; Stringhini et al., 2011).

## 1. Context

Redressing the social stratification of ill health is a major concern in public health research. Classic determinants of non-communicable disease, which are mainly behavioural, are insufficient for explaining the large disparities observed in morbidity and mortality (Gallo et al., 2012). The concept of embodiment (Krieger, 2005) and biological embedding (Hertzman, 2012) are similar, and may be useful tools for formulating hypotheses on how health inequalities are produced over the life course. In both concepts, how human environments affect our health by penetrating the cells, organs and physiological systems of our bodies, is a key tenet. Here, we conceptualize embodiment as a dynamic process that summarizes how we become altered by our past experiences and are responding to the present, from how well we feel, down to the molecular modifications in our bodily structures. The process of embodiment being socially stratified (Hertzman & Boyce, 2010) may therefore contribute for explaining the production of social gradients in health.

Growing evidence supports the idea that exposure to stressful conditions over life contributes to physiological dysregulation, subsequently translated into disease, through prolonged activation of stress responses systems (McEwen & Seeman, 1999; McEwen & Stellar, 1993; Seeman et al., 2001). Allostasis is the process where our body adapts to environmental challenges or stressful conditions in order to maintain physiological stability (McEwen & Wingfield, 2003; Sterling, 2012). The repeated activation of compensatory physiological

mechanisms as a response to chronic stress can lead to a physiological wear-and-tear, known as allostatic load (AL) (Juster et al., 2010; McEwen & Stellar, 1993; McEwen & Wingfield, 2003). AL has been strongly correlated with subclinical conditions, cardiovascular events, physical and functioning decline and mortality (Juster et al., 2010; Karlamangla et al., 2002; Karlamangla et al., 2006). As a composite measure, AL performs as a better predictor of subsequent morbidity and mortality over and above each constituent biomarker when analysed individually (Karlamangla et al., 2002; Robertson et al., 2015; Seeman et al., 2001), or other composite indicators like the metabolic syndrome. These findings suggest that AL could represent a global physiological state and perhaps even a proxy for an outcome of the embodiment processes.

Growing evidence suggests that early life socioeconomic position (SEP) is a distal determinant of AL (Chen et al., 2012; Dowd et al., 2009; Gruenewald et al., 2012; Robertson et al., 2015; Robertson et al., 2014), suggesting that poor socioeconomic circumstances early in life could set different population subgroups on life trajectories that are unfavourable for health, increasing their probability of being exposed to unhealthy environmental stressors and lifestyles. Early SEP is often measured using parental education and occupation at birth or in childhood, both of these measures being generally available in birth cohort studies. Education and occupation may operate through both similar and unique mechanisms to influence offspring health. In the current analysis, measures of parental education were limited to maternal education (ME), and occupation to paternal occupation (PO), due to variables availability and due to the historical context in which measures were assessed. However, in the social causation model, occupational status and education do not have the same theoretical meaning (Dahl E., 1994). Though the two variables may be highly correlated, the literature suggest that education and occupation do not impact health through the same pathways and should be analysed separately (Galobardes et al., 2007; Galobardes et al., 2006a).

The life course pathways linking early SEP to AL deserve to be disentangled, in particular the specific pathways involving ME and PO respectively. We aimed to address this question by exploring four pathways through which ME and PO may be differentially embodied during childhood, adolescence and early adulthood leading to physiological wear-and-tear, as measured by AL.

We selected these four pathways based on epidemiological evidence and on empirical studies suggesting a link between SEP and each path. Lynch *et al.* (Lynch et al., 2000) suggested that

health is the result of an accumulation of experiences and exposures due to the material world. Biological (viruses, bacteria) and chemical hazards, are more likely in more deprived homes and neighborhoods, and in some occupational statuses. An inverse relation between SEP and risky health behaviors has been largely demonstrated in empirical research (Stringhini et al., 2011). The adoption of health behaviors may be explained by complex psychological processes (e.g. self-regulation, self-efficacy, locus of control) (Bandura, 1991). Other explanations relate to social norms, tradition, and customs since lifestyle depends on social characteristics established by community social standards (Bartley, 2003a). Concerning the psychosocial path, previous research (Marmot & Wilkinson, 1999) suggests that SEP may relate to health through the perception individuals have of their position in a social hierarchy. These perceptions may produce negative emotions resulting in poorer health, through psycho-neuroendocrine mechanisms (Brunner & Marmot, 1999) linked to stress responses (and/or stress-related behaviors such as smoking). Regarding the educational path, Hackman & Farah, showed in a recent review that SEP is linked with neurocognitive performance, such as language and executive function. Cognitive ability appears to be affected by poverty, especially during childhood. Different mechanisms have been suggested (e.g. cognitive stimulation, nutrition, parenting styles).

## 2. Methods

In this section we will introduced the variables construction (outcome and covariates) and the statistical model and data analysis used for addressing this research axis.

### 2.1. Exposure variable: Parental SEP

We conceptualized parental SEP using ME and PO collected at birth. PO was constructed from the British Registrar General's social class system using mother's partner's social class (recoded into four categories: I-professional occupations & II-intermediate occupations/III-skilled occupations (non-manual)/III-partly skilled occupations (manual)/IV-partly skilled occupations & V-unskilled occupations.), and if this was unavailable the mother's father's social class was used. The only ME measure available was self-reported and ask if mother left school after legal minimal age (14y) or if the mother left school before legal minimal age. The theoretical differences between these two measures relate to their potential mechanisms affecting health.

### 2.2. Outcome variable: Allostatic load index

The outcome variable of interest in this study was a composite score of allostatic load as a measure of cumulative physiological wear-and-tear. Please see Part II, Chapter 3, section 1 for further details on the operationalization of the AL score.

### 2.3. Early life socioeconomic and biological confounders

Table 17 show the descriptive statistics of these axis. We selected from a questionnaire completed at birth by the participant's mother variables known to affect later health and representing socioeconomic markers. Birthweight (Barker, 2001, 2002; Gavin et al., 2012), maternal smoking during pregnancy (Jaakkola et al., 2001; Moussa et al., 2009; Raisanen et al., 2014), mother's body mass index (BMI) categorized as follows: normal: 18.5–24.9 /underweight: <18.5 /overweight: 25–29.9/obese: ≥30 kg/m2 (Cooper et al., 2013; Han et al., 2015; Perng et al., 2014) and mother's age at birth.

### 2.4. Educational pathway

Data on motor ability at 7y and educational attainment at 23y were collected. Motor ability was derived from the Copy-a-Design test at 7y, a measure of a child's capacity to reproduce geometrical figures and used in some studies as proxy of cognitive ability (Lacey et al., 2011). It ranged from 0 to 12, with higher scores relating to better perceptual motor skills and the child's ability to adapt to the school environment. Educational attainment was coded into three categories (passed A levels (highest)/passed O levels/No qualifications).

### 2.5. Psychosocial/psychological pathway

Extracted from the parental and teacher's questionnaires at ages 7, 11, and 16, we selected variables approaching parental involvement at 7y, Bristol Social Adjustment Guide (BSAG) at 7y and family structure at 7 & 11 and malaise inventory at 23y. Parental involvement was constructed *via* five variables evaluating the time spend with the child (mum outing, dad outing, mum reading, dad reading and paternal role in the management of the child) coded 0 if the activity occurred every week, 1 if occasionally, and 2 if hardly ever. The ten-category variable was divided in three final items: most frequent (0-2)/occasionally (3-4)/hardly ever (5-10). The BSAG is a teacher-rated measured that aims to characterize the child's behaviour in school

(Shepherd, 2013). Higher scores potentially indicate psychosocial and behavioural "maladjustment" (Stott, 1963). Family structure informed about parental separation at 7y and presence of a father figure at 11y. Rutter's Malaise Inventory comprise 24 yes/no items on both emotional and somatic symptoms (Rodgers et al., 1999). The individual was considered as having psychological malaise if s/he reported experiencing more than 7 out of 24 symptoms (Rutter et al., 1970).

## 2.6. Material/financial pathway

We selected variables characterizing material/financial deprivation at ages 7, 11 and 16, and income at 23y. From the parental and teacher's questionnaires childhood material deprivation included information about housing deprivation and financial adversity. This variable was first constructed using nonimputed data. After choosing, creating and imputing the new variables representing housing deprivation and financial adversity, a Principal Component Analysis (PCA) was conducted on the imputed sample. The PCA included two types of variables: housing deprivation and financial adversity.

### 2.6.1. Housing deprivation variable (nonimputed sample)

i) Type of accommodation at 7 & 11 y was coded for each sweep: '0'Whole house/ '1' Flat, maisonnette/'2' Rooms, caravan, other. We aimed to construct a variable for capturing at least one material negative exposure during the time reported. A three-category variable was finally created coded as followed: '0'Child always leaved in a whole house/'1' Child leaved at least one time in a flat, maisonette/'2' Child leaved at least one time in a room, caravan, other.

ii) Tenure of accommodation at 7 & 11 y was coded for each sweep: '0' Owner occupied/'1' Private rented/ '2'Rent free or tied/ '3' Council rented. As for type of accommodation, a final variable was created taking into account if the child leaved at least one time in the most depredated category relatively to the "superior" category: '0' Child always leaved in own tenure/ '1' Child leaved at least one time in a private tenure/ '2' Child leaved at least one time in a council rented or other type of tenure/ '3' Child leaved at least one time in a free rent residence.

iii) House amenities variable at 7, 11 & 16 created (if the variable was available and coded in the same scale), it included:

- Use of bathroom '0' Yes sole use/ '1' Shared/ '2' None at 7, 11 & 16. The precedent method was used to create a single variable. The final variable was coded as follows: '0' Child always had sole use of bathroom/ '1' Child used a shared bathroom at least one time/ '2'Child leaved at least one time in a house with no bathroom.

- Use of lavatory '0'Indoor sole use/ '1' Outdoor sole use/ '2'Shared/ '3' None at 7, 11 & 16. The final variable was coded '0'Child always had indoor sole use of lavatory/ '1' Child used at least one time an outdoor sole use lavatory/ '2' Child shared at least one time lavatory/ '3' Child didn't had any lavatory at least one time.

- Cooking facilities (at 7 & 11) we followed the same method explained above.

- Use of hot water (7, 11 &16) we followed the same method explained above.

- We included in the housing deprivation variable a measure to capture overcrowding during childhood and adolescence: sharing beds with at least one person at 11 & 16 (coded '0' yes/ '1' no).

iv) Household facilities variable at 16y including: availability of black & white television, colour television, refrigerator, deep-freeze, telephone, 2 or more cars, 1 car and central heating.

### 2.6.2. Financial adversity

i) Financial hardship: if parents reported being seriously troubled by financial problems in the past 12 months (yes/no at 11 & 16y).

ii) Free school meals: if the child was entitled to free school meals (yes/no at 11 & 16y).

iii) Family income at 16y: equivalent net family income, adjusted for family size, divided into quartiles.

We then imputed the variables created (type of accommodation, tenure of accommodation, housing deprivation, household facilities, financial hardship, free school meals and income) and ran a PCA on the imputed sample deriving one single component.

### 2.7. Health behaviours pathway

From a self-reported questionnaire a variable containing information about physical activity, alcohol consumption (House of Commons Science and Technology Committee, 2012), and smoking status was derived. We created a three-category variable considered as a proxy for life-style patterns in early adulthood. Each of these variables were coded '0' non exposed/ '1' moderately exposed/ '2' heavily exposed as follows:

i) Smoking status: '0' Non-smoker/ '1' Former smoker/ '2' Current smoker.
ii) Alcohol consumption: '0' Moderate (women: between 1 and 14 units in the previous week; men: between 1 and 21 units in the previous week)/ '1' Abstainers (reported not consuming any alcohol in the previous week)/ '2' Heavy drinkers (women: >14 units in the previous week; men: >21 units in the previous week)
iii) Physical activity: '0' Physically active/ '1' Moderately active/ '2' Inactive.

A six-category variable characterizing health behaviours at 23y was created: 'Least at risk' (0, 1, 2)/ 'Moderately at risk (3, 4)/ 'Most at risk (5, 6).

BMI was also added to the health behaviours path to represent nutritional/diet behaviours.

### 2.8. Additional variables tested (not included in the final model)

We tested our model for the influence of adding other variables of material circumstances at 23 years. At 23 years the cohort members were experiencing major life transitions: from school to higher education or work, from parental dependency to independency and so on. We decided not to include the housing deprivation variables (overcrowding, sharing spaces/amenities, tenure of the accommodation, and type of accommodation) based on the fact that material deprivation at that particular time was not the best marker of deprivation due to transient nature of the early adulthood life phase. We decided instead to include income at 23 to capture material circumstances in early adulthood.

### 2.9. Statistical model & data analysis

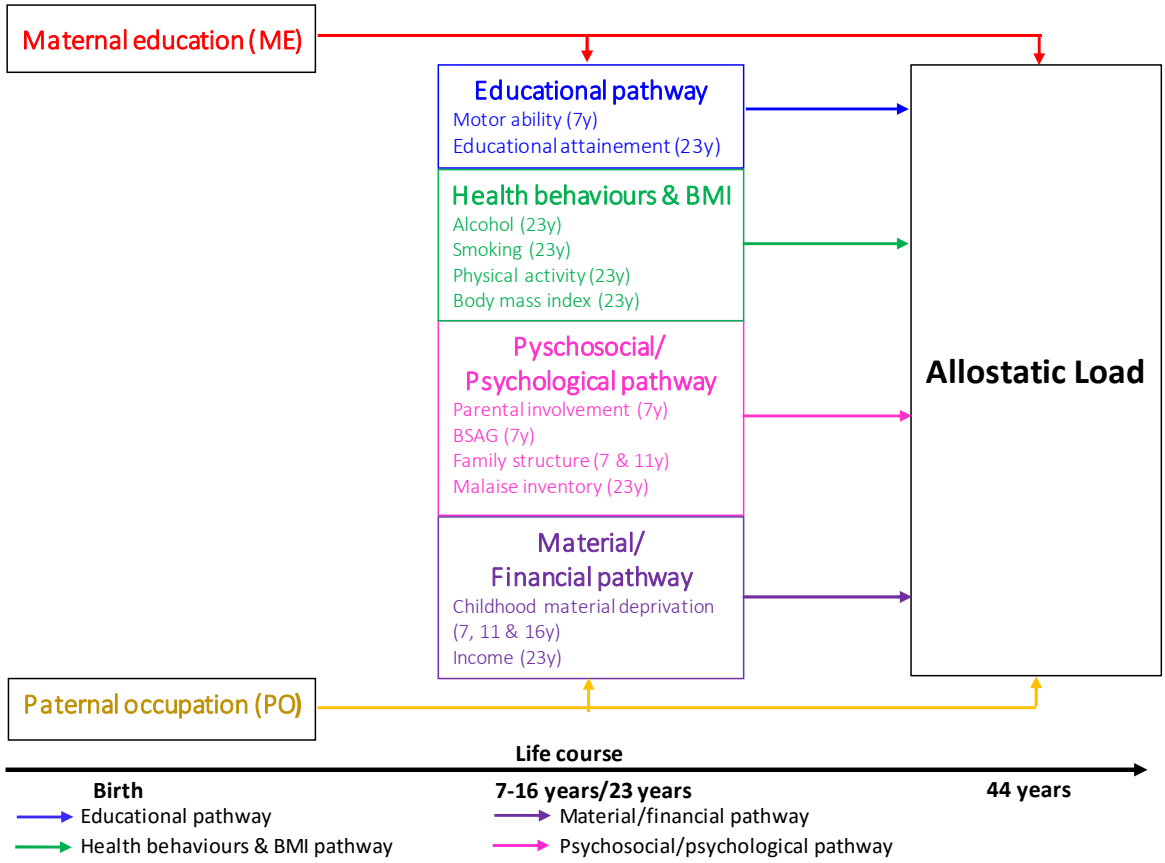
To control for possible bias due to missing data, we imputed data for covariates with missing data using the multiple imputation program ICE in STATA V11 and the analyses were stratified by sex (for further details about sex stratification see Part II, Chapter III, section 2). Descriptive statistics (Table 17) were carried out on nonimputed data. We used linear regression path modelling on imputed data to examine the relationship between parental SEP and AL (Barboza Solis et al., 2015; Israels, 1987). Path analysis allows us to disentangle and describe indirect mediating pathways. We analysed the mediation paths between ME and AL and subsequently between PO and AL, in both men and women. For further details about path analysis and mediation analysis please refer to Part II, Chapter II, section 1.

Figure 7 shows the indirect paths chosen *a priori* in this study. We tested all the mediating pathways, adjusting for ME, PO, confounders and mediators. Bivariate statistics (Table 18) and multivariate linear regression (Table 19) were carried out on imputed data. We constructed a second AL score calculating a 0-1 risk score within each system, reflecting the proportion of biomarkers within the system for which the participant's values fall into the highest-risk quartile, allowing equal weight for each system (Carroll et al., 2015) and the results did not vary. For further details about AL score operationalization please refer to Part II, Chapter III, sections 1. All analyses were performed using STATA V11 taking a statistical significance level of 0.05.

i) Model 1 : Parental SEP
ii) Model 2: M1 + perinatal factors
iii) Model 3: M2 + childhood factors
iv) Model 4: M3 + Early adulthood socioeconomic factors at 23y

It is noteworthy that for implementing the path analysis we used regression analyses for describing the 'indirect' paths. For instance, for analysing ME and PO, we compared model M2 (SEP + perinatal factors) and model M4 (M3 + Early adulthood socioeconomic factors at 23y) by calculating the difference between the β coefficient of M4 and M2 according to the formula presented in Part II, Chapter II, section 1. We run a second analysis comparing model M3 (M2 + childhood factors) and M4, using the same formula, for investigating the 'indirect' effect between childhood factors and AL. For instance, as we will present in the Results section, we analysed the 'indirect' effect between motor ability at 7y and AL at 44y only in men, and between childhood material deprivation (at 7, 11 and 16) and AL at 44y in men and in women.

Figure 7. Model tested in this study




## 3. Results

Descriptive statistics of the nonimputed sample are presented in Table 17 for the subsample (n=3782 for men; n=3791 for women). Figures 8 and 9 represent the path analyses results, showing only the mediating variables explaining > 5% of the total effect for men and women respectively, first between ME and AL, and second between PO and AL. The sum of all pathways is not equal to 1 due to other small or negative pathways not presented in the figures.

The path analyses for ME and AL showed for men that the link was mainly mediated by the educational pathway [represented by motor ability at 7y (6% of the total indirect effect) and educational attainment at 23y (31% of the total indirect effect)]. The second most important pathway was denoted by a component of the health behaviour path represented by BMI at 23y (13%). Finally the third path yields the role of material/financial factors captured by childhood material factors (9%). Overall, 45% of the total effect between ME and AL in men remained unexplained by those paths, after adjustment for confounder and mediators (Figure 8).

For women, 22% of the total mediated effect between ME and AL was explained by the educational path [represented by educational attainment at 23y (15%)] and by the material/financial path [represented by childhood material deprivation at 7y (7%)]. Overall, 63% of the total effect between ME and AL in women remained unexplained by those paths after adjusting for confounders and mediators (Figure 8).

The relationship between PO and AL in men was mainly mediated by the educational pathway [represented by educational attainment at 23y (IIIM=17%/ IV & V= 17%)]. The second path was denoted by health behaviours [represented by BMI (IIIM=8%/ IV & V= 9%)]. The third path was the material/financial [explained by childhood material deprivation at 7y (IIIM=6%/ IV & V=9%)]. For the III skilled-manual class 68% of the total effect remained unexplained by the paths, for the IV-V semi/unskilled manual this percentage was 57% (Figure 9).

PO for women was mainly mediated by the educational path (IIIM: 12%/IV & V: 14%), and by the health behaviours path [drawn by BMI (IIIM: 12%/IV & V: 14%)]. The third was denoted by the material/financial path [represented by childhood material deprivation (IIIM: 7%/IV & V: 9%)]. For the III skilled-manual class 58% of the total effect remained unexplained by those paths, for the IV-V semi/unskilled manual this percentage was 47% (Figure 9).

As we mentioned in the Methods, we additionally explored the pathways linking childhood material factors and AL in midlife for both men and women, and between motor ability and AL only for men. These two variables were analysed since they were the only childhood variables significantly linked to AL at the risk threshold of 5% in the full model, and that were also mediated by early adulthood variables.

For men, the link between motor ability and AL was mediated by the health behaviours path (6%), and the educational path (23%). Childhood material factor was also mediated by the health behaviours path (middle deprivation: 6%, high deprivation: 7%), and by the educational path (middle deprivation: 42%, high deprivation: 29%) (see Figure 10). It is noteworthy that we only report the categories of PO that remained significantly linked to AL at 5% in the full model.

For women, high material deprivation during childhood was mainly mediated by a psychosocial/psychological path represented by the malaise inventory (19%) at 23y, by the health behaviours path represented by BMI at 23y (6%), and by the educational path represented by educational attainment at 23 (5%) (see Figure 11).

Multivariate results are presented in Table 19 and Table 20 for men and women respectively. The full model showed that ME remained statistically linked to later AL only for women (0.39, P=0.004). PO for both men (IIIM: 0.27; P=0.004/ IV & V: 0.32; P=0.005) and women (IIIM: 0.29; P=0.005/ IV & V: 0.30; P=0.016) remained statistically associated with AL. Additionally for men, the full model showed that birthweight and mother's BMI had an important independent association with later AL. Health behaviours, BMI, education level and income at 23y were also found correlated to AL after adjustment for confounder and mediators. For women, variables from early life (birthweight, mother's BMI and mother's age at birth), from childhood/adolescence (BSAG, family structure and material deprivation) and all variables at 23y (except for income) remained independently associated with later AL.

Table 17. Descriptive statistics on the subsample for men (n=3782) and women (n=3791)

| | Sex | |
|---|---|---|
| Variable | Men n [%] | Women n [%] |
| Allostatic load | | |
| *0* | 287 [7.6%] | 312 [8.2%] |
| *1* | 614 [16.2%] | 669 [17.6%] |
| *2* | 789 [20.9%] | 727 [19.2%] |
| *3* | 720 [19.0%] | 617 [16.3%] |
| *4* | 560 [14.8%] | 532 [14.0%] |
| *5* | 359 [9.5%] | 380 [10.0%] |
| *6* | 236 [6.2%] | 251 [6.6%] |
| *7* | 136 [3.6%] | 144 [3.8%] |
| *8* | 61 [1.6%] | 99 [2.6%] |
| *9* | 16 [0.4%] | 44 [1.2%] |
| *10* | 4 [0.1%] | 9 [0.2%] |
| *11* | 0 [0.0%] | 5 [0.1%] |
| *12* | 0 [0.0%] | 2 [0.1%] |
| Maternal education | | |
| *Left school at 15 or later* | 1 017 [26.9%] | 1 017 [26.8%] |
| *Left school before 14* | 2 765 [73.1%] | 2 774 [73.2%] |
| Paternal occupation | | |
| *I & II (professional/managerial)* | 739 [19.5%] | 706 [18.6%] |
| *IIINM (skilled nonmanual)* | 378 [10.0%] | 388 [10.2%] |
| *IIIM (skilled manual)* | 1 902 [50.3%] | 1 904 [50.2%] |
| *IV & V (semi-unskilled)* | 763 [20.2%] | 793 [20.9%] |
| Birthweight | | |
| *Q1 - Low weight* | 792 [20.9%] | 849 [22.4%] |
| *Q2* | 1 037 [27.4%] | 1 002 [26.4%] |
| *Q3* | 973 [25.7%] | 913 [24.1%] |
| *Q4 - High weight* | 855 [22.6%] | 921 [24.3%] |
| *Missing* | 125 [3.3%] | 106 [2.8%] |
| Mother smoked during pregnancy | | |
| *No* | 2 537 [67.1%] | 2 517 [66.4%] |
| *Sometimes* | 230 [6.1%] | 215 [5.7%] |
| *Moderately* | 545 [14.4%] | 580 [15.3%] |
| *Heavily* | 428 [11.3%] | 438 [11.6%] |
| *Missing* | 42 [1.1%] | 41 [1.1%] |
| Mother's BMI | | |
| *Normal* | 2 618 [69.2%] | 2 591 [68.3%] |
| *Underweight* | 138 [3.6%] | 180 [4.7%] |
| *Overweight* | 679 [18.0%] | 685 [18.1%] |
| *Obese* | 148 [3.9%] | 141 [3.7%] |
| *Missing* | 199 [5.3%] | 194 [5.1%] |

*(continued)*

Table 17. continued

| Variable | Sex | |
|---|---|---|
| | Men n [%] | Women n [%] |
| **Mother's age at birth** | | |
| *23 years or less* | 976 [25.8%] | 1 023 [27.0%] |
| *24 to 27 years* | 1 073 [28.4%] | 1 043 [27.5%] |
| *28 to 31 years* | 848 [22.4%] | 821 [21.7%] |
| *32 years or more* | 884 [23.4%] | 900 [23.7%] |
| *Missing* | 1 [0.0%] | 4 [0.1%] |
| **Parental involvement at 7** | | |
| *Most Frequent* | 1 967 [52.0%] | 1 917 [50.6%] |
| *Occasionally* | 868 [23.0%] | 916 [24.2%] |
| *Hardly ever* | 548 [14.5%] | 584 [15.4%] |
| *Missing* | 399 [10.6%] | 374 [9.9%] |
| **BSAG* at 7** | | |
| *Q1 - Least disturbed* | 956 [25.3%] | 1 348 [35.6%] |
| *Q2* | 822 [21.7%] | 921 [24.3%] |
| *Q3* | 829 [21.9%] | 664 [17.5%] |
| *Q4 - Most disturbed* | 826 [21.8%] | 540 [14.2%] |
| *Missing* | 349 [9.2%] | 318 [8.4%] |
| **Family structure at 7 & 11** | | |
| *Presence of father figure/not divorced* | 3 533 [93.4%] | 3 492 [92.1%] |
| *No father figure or divorced* | 172 [4.5%] | 234 [6.2%] |
| *Missing* | 77 [2.0%] | 65 [1.7%] |
| **Motor ability at 7 (mean)** | 7.20 | 7.14 |
| *Missing* | 356 [9.4%] | 326 [8.6%] |
| **Childhood material factors at 7-16** | | |
| *Q1 - Low material deprivation* | 635 [16.8%] | 662 [17.5%] |
| *Q2* | 612 [16.2%] | 615 [16.2%] |
| *Q3* | 638 [16.9%] | 622 [16.4%] |
| *Q4 - High material deprivation* | 624 [16.5%] | 654 [17.3%] |
| *Missing* | 1 273 [33.7%] | 1 238 [32.7%] |
| **Health behaviours at 23** | | |
| *Least at risk* | 1 293 [34.2%] | 1 243 [32.8%] |
| *Moderately at risk* | 1 413 [37.4%] | 1 550 [40.9%] |
| *Most at risk* | 534 [14.1%] | 556 [14.7%] |
| *Missing* | 542 [14.3%] | 442 [11.7%] |
| **BMI at 23** | | |
| *Normal* | 2 542 [67.2%] | 2 677 [70.6%] |
| *Underweight* | 74 [2.0%] | 207 [5.5%] |
| *Overweight* | 510 [13.5%] | 341 [9.0%] |
| *Obese* | 62 [1.6%] | 84 [2.2%] |
| *Missing* | 594 [15.7%] | 482 [12.7%] |

*(continued)*

Table 17. continued

| | Sex | |
|---|---|---|
| Variable | Men n [%] | Women n [%] |
| *No* | 3 123 [82.6%] | 3 020 [79.7%] |
| *Yes* | 112 [3.0%] | 326 [8.6%] |
| *Missing* | 547 [14.5%] | 445 [11.7%] |
| Education level at 23 | | |
| *Passed A levels* | 789 [20.9%] | 762 [20.1%] |
| *Passed O levels* | 1 245 [32.9%] | 1 511 [39.9%] |
| *No qualifications* | 1 204 [31.8%] | 1 074 [28.3%] |
| *Missing* | 544 [14.4%] | 444 [11.7%] |
| Income at 23 | | |
| *Q1 - Low income* | 531 [14.0%] | 843 [22.2%] |
| *Q2* | 639 [16.9%] | 911 [24.0%] |
| *Q3* | 866 [22.9%] | 800 [21.1%] |
| *Q4 - High income* | 1 025 [27.1%] | 696 [18.4%] |
| *Missing* | 721 [19.1%] | 541 4.3%] |

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Table 18. Bivariate statistics on imputed data for men (n=3782) and women (3791)

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| Variables | β | CI 95% | p | β | CI 95% | p |
| Maternal education | | | | | | |
| *Left school at 15 or later* | 0 | | | 0 | | |
| *Left school before 14* | 0.39 | (0.25 - 0.53) | <0.001 | 0.67 | (0.52 - 0.83) | <0.001 |
| Paternal occupation | | | | | | |
| *I & II (professional/managerial)* | 0 | | | 0 | | |
| *IIINM (skilled nonmanual)* | 0.17 | (-0.07 - 0.41) | 0.166 | 0.36 | (0.10 - 0.63) | 0.007 |
| *IIIM (skilled manual)* | 0.55 | (0.38 - 0.71) | <0.001 | 0.79 | (0.60 - 0.97) | <0.001 |
| *IV & V (semi-unskilled)* | 0.74 | (0.54 - 0.93) | <0.001 | 0.99 | (0.77 - 1.21) | <0.001 |
| Birthweight | | | | | | |
| *Q1 - Low weight* | 0 | | | 0 | | |
| *Q2* | -0.28 | (-0.46 - -0.11) | 0.001 | -0.21 | (-0.40 - -0.01) | 0.036 |
| *Q3* | -0.26 | (-0.44 - -0.08) | 0.004 | -0.37 | (-0.56 - -0.17) | <0.001 |
| *Q4 - High weight* | -0.37 | (-0.55 - -0.19) | <0.001 | -0.48 | (-0.67 - -0.28) | <0.001 |
| Mother smoked during pregnancy | | | | | | |
| *No* | 0 | | | 0 | | |
| *Sometimes* | 0.37 | (0.11 - 0.64) | 0.006 | 0.61 | (0.31 - 0.91) | <0.001 |
| *Moderately* | 0.17 | (-0.02 - 0.35) | 0.073 | 0.18 | (-0.02 - 0.37) | 0.074 |
| *Heavily* | 0.31 | (0.11 - 0.51) | 0.002 | 0.33 | (0.11 - 0.55) | 0.003 |
| Mother's BMI | | | | | | |
| *Normal* | 0 | | | 0 | | |
| *Underweight* | 0.23 | (-0.09 - 0.56) | 0.163 | 0.25 | (-0.07 - 0.58) | 0.129 |
| *Overweight* | 0.32 | (0.16 - 0.49) | <0.001 | 0.43 | (0.25 - 0.61) | <0.001 |
| *Obese* | 0.55 | (0.23 - 0.87) | <0.001 | 0.29 | (-0.07 - 0.65) | 0.119 |

*(continued)*

Table 18. continued

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| Variables | β | CI 95% | p | β | CI 95% | p |
| Mother's age at birth | | | | | | |
| *23 years or less* | 0 | | | 0 | | |
| *24 to 27 years* | 0.04 | (-0.13 - 0.21) | 0.672 | -0.46 | (-0.65 - -0.27) | <0.001 |
| *28 to 31 years* | -0.05 | (-0.23 - 0.13) | 0.556 | -0.54 | (-0.74 - -0.34) | <0.001 |
| *32 years or more* | -0.08 | (-0.26 - 0.10) | 0.392 | -0.36 | (-0.56 - -0.17) | <0.001 |
| Parental involvement at 7 | | | | | | |
| *Most Frequent* | 0 | | | 0 | | |
| *Occasionally* | 0.01 | (-0.14 - 0.17) | 0.857 | 0.14 | (-0.02 - 0.31) | 0.096 |
| *Hardly ever* | 0.16 | (-0.02 - 0.35) | 0.075 | 0.29 | (0.09 - 0.49) | 0.005 |
| BSAG* at 7 | | | | | | |
| *Q1 - Least disturbed* | 0 | | | 0 | | |
| *Q2* | -0.02 | (-0.20 - 0.16) | 0.855 | 0.20 | (0.02 - 0.38) | 0.028 |
| *Q3* | 0.17 | (-0.01 - 0.35) | 0.059 | 0.46 | (0.26 - 0.65) | <0.001 |
| *Q4 - Most disturbed* | 0.35 | (0.17 - 0.53) | <0.001 | 0.65 | (0.44 - 0.86) | <0.001 |
| Family structure at 7 & 11 | | | | | | |
| *Presence of father figure/not divorced* | 0 | | | 0 | | |
| *No father figure or divorced* | 0.43 | (0.13 - 0.73) | 0.005 | 0.38 | (0.10 - 0.67) | 0.009 |
| Motor ability at 7 | -0.09 | (-0.12 - -0.05) | <0.001 | -0.14 | (-0.17 - -0.10) | <0.001 |
| Childhood material factors at 7-16 | | | | | | |
| *Q1 - Low material deprivation* | 0 | | | 0 | | |
| *Q2* | 0.12 | (-0.08 - 0.31) | 0.241 | 0.23 | (0.02 - 0.45) | 0.035 |
| *Q3* | 0.35 | (0.15 - 0.55) | <0.001 | 0.46 | (0.24 - 0.69) | <0.001 |
| *Q4 - High material deprivation* | 0.56 | (0.37 - 0.75) | <0.001 | 0.80 | (0.60 - 1.01) | <0.001 |

*(continued)*

Table 18. continued

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| Variables | β | CI 95% | p | β | CI 95% | p |
| **Health behaviours at 23** | | | | | | |
| *Least at risk* | 0 | | | 0 | | |
| *Moderately at risk* | 0.38 | (0.24 - 0.53) | <0.001 | 0.35 | (0.19 - 0.51) | <0.001 |
| *Most at risk* | 0.68 | (0.48 - 0.87) | <0.001 | 0.72 | (0.51 - 0.92) | <0.001 |
| **BMI at 23** | | | | | | |
| *Normal* | 0 | | | 0 | | |
| *Underweight* | -0.15 | (-0.60 - 0.30) | 0.505 | -0.15 | (-0.45 - 0.15) | 0.326 |
| *Overweight* | 0.63 | (0.45 - 0.81) | <0.001 | 1.12 | (0.88 - 1.35) | <0.001 |
| *Obese* | 1.28 | (0.76 - 1.80) | <0.001 | 2.29 | (1.82 - 2.76) | <0.001 |
| **Malaise inventory at 23** | | | | | | |
| *No* | 0 | | | 0 | | |
| *Yes* | 0.42 | (0.05 - 0.79) | 0.025 | 0.67 | (0.43 - 0.91) | <0.001 |
| **Educational attainment** | | | | | | |
| *Passed A levels* | 0 | | | 0 | | |
| *Passed O levels* | 0.39 | (0.22 - 0.56) | <0.001 | 0.51 | (0.33 - 0.69) | <0.001 |
| *No qualifications* | 0.80 | (0.64 - 0.97) | <0.001 | 1.13 | (0.93 - 1.32) | <0.001 |
| **Income at 23** | | | | | | |
| *Q1 - Low income* | 0 | | | 0 | | |
| *Q2* | -0.20 | (-0.42 - 0.01) | 0.062 | -0.16 | (-0.36 - 0.04) | 0.121 |
| *Q3* | -0.39 | (-0.60 - -0.18) | <0.001 | -0.36 | (-0.56 - -0.16) | <0.001 |
| *Q4 - High income* | -0.41 | (-0.61 - -0.21) | <0.001 | -0.58 | (-0.80 - -0.37) | <0.001 |

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Table 19. Life course multivariate linear regression using data obtained from multiple imputation: men (n=3782)

| Variables | Model 1: Parental SEP | | | Model 2: Perinatal factors | | | Model 3: Childhood factors | | | Model 4: Early adulthood factors | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ß | CI 95% | p | ß | CI 95% | p | ß | CI 95% | p | ß | CI 95% | p |
| **Maternal education level** | | | | | | | | | | | | |
| *Left school at 15 or later* | 0 | | | 0 | | | 0 | | | 0 | | |
| *Left school before 14* | 0.19 | (0.04 - 0.34) | 0.012 | 0.16 | (0.01 - 0.31) | 0.037 | 0.11 | (-0.04 - 0.27) | 0.146 | 0.07 | (-0.08 - 0.23) | 0.358 |
| **Paternal occupation** | | | | | | | | | | | | |
| *I & II (professional/managerial)* | 0 | | | 0 | | | 0 | | | 0 | | |
| *IIINM (skilled nonmanual)* | 0.12 | (-0.12 - 0.36) | 0.326 | 0.10 | (-0.15 - 0.34) | 0.441 | 0.04 | (-0.20 - 0.28) | 0.752 | 0.05 | (-0.19 - 0.29) | 0.679 |
| *IIIM (skilled manual)* | 0.46 | (0.29 - 0.64) | <0.001 | 0.39 | (0.22 - 0.57) | <0.001 | 0.34 | (0.15 - 0.52) | <0.001 | 0.27 | (0.09 - 0.45) | 0.004 |
| *IV & V (semi-unskilled)* | 0.64 | (0.44 - 0.85) | <0.001 | 0.56 | (0.35 - 0.77) | <0.001 | 0.43 | (0.21 - 0.65) | <0.001 | 0.32 | (0.09 - 0.54) | 0.005 |
| **Birthweight** | | | | | | | | | | | | |
| *Q1 - Low weight* | | | | 0 | | | 0 | | | 0 | | |
| *Q2* | | | | -0.26 | (-0.44 - -0.09) | 0.003 | -0.23 | (-0.40 - -0.06) | 0.009 | -0.23 | (-0.40 - -0.06) | 0.007 |
| *Q3* | | | | -0.23 | (-0.41 - -0.06) | 0.009 | -0.18 | (-0.36 - -0.01) | 0.042 | -0.21 | (-0.38 - -0.03) | 0.020 |
| *Q4 - High weight* | | | | -0.34 | (-0.52 - -0.15) | <0.001 | -0.28 | (-0.46 - -0.09) | 0.003 | -0.33 | (-0.51 - -0.15) | <0.001 |
| **Mother smoked during pregnancy** | | | | | | | | | | | | |
| *No* | | | | 0 | | | 0 | | | 0 | | |
| *Sometimes* | | | | 0.25 | (-0.01 - 0.52) | 0.059 | 0.20 | (-0.06 - 0.47) | 0.129 | 0.14 | (-0.13 - 0.40) | 0.310 |
| *Moderately* | | | | 0.09 | (-0.09 - 0.27) | 0.337 | 0.06 | (-0.12 - 0.24) | 0.543 | 0.03 | (-0.15 - 0.21) | 0.735 |
| *Heavily* | | | | 0.20 | (0.00 - 0.40) | 0.046 | 0.17 | (-0.03 - 0.37) | 0.102 | 0.10 | (-0.10 - 0.30) | 0.334 |
| **Mother's BMI** | | | | | | | | | | | | |
| *Normal* | | | | 0 | | | 0 | | | 0 | | |
| *Underweight* | | | | 0.15 | (-0.18 - 0.47) | 0.377 | 0.13 | (-0.19 - 0.46) | 0.415 | 0.16 | (-0.16 - 0.48) | 0.320 |
| *Overweight* | | | | 0.31 | (0.15 - 0.48) | <0.001 | 0.30 | (0.13 - 0.46) | <0.001 | 0.22 | (0.06 - 0.38) | 0.008 |
| *Obese* | | | | 0.48 | (0.16 - 0.80) | 0.003 | 0.46 | (0.14 - 0.77) | 0.005 | 0.26 | (-0.06 - 0.58) | 0.106 |
| **Mother's age at birth** | | | | | | | | | | | | |
| *23 years or less* | | | | 0 | | | 0 | | | 0 | | |
| *24 to 27 years* | | | | 0.11 | (-0.06 - 0.27) | 0.220 | 0.12 | (-0.04 - 0.29) | 0.150 | 0.14 | (-0.02 - 0.31) | 0.092 |
| *28 to 31 years* | | | | 0.00 | (-0.18 - 0.18) | 0.997 | 0.03 | (-0.15 - 0.21) | 0.760 | 0.06 | (-0.12 - 0.24) | 0.516 |
| *32 years or more* | | | | -0.05 | (-0.23 - 0.13) | 0.603 | -0.06 | (-0.23 - 0.12) | 0.533 | -0.01 | (-0.19 - 0.17) | 0.910 |
| **Parental involvement at 7** | | | | | | | | | | | | |
| *Most Frequent* | | | | | | | 0 | | | 0 | | |
| *Occasionally* | | | | | | | -0.06 | (-0.21 - 0.09) | 0.444 | -0.10 | (-0.25 - 0.05) | 0.207 |
| *Hardly ever* | | | | | | | -0.05 | (-0.24 - 0.13) | 0.577 | -0.12 | (-0.31 - 0.06) | 0.187 |

*(continued)*

Table 19. continued

| Variables | Model 1: Parental SEP | | | Model 2: Perinatal factors | | | Model 3: Childhood factors | | | Model 4: Early adulthood factors | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ß | CI 95% | p | ß | CI 95% | p | ß | CI 95% | p | ß | CI 95% | p |
| **BSAG* at 7** | | | | | | | | | | | | |
| *Q1 - Least disturbed* | | | | | | | 0 | | | 0 | | |
| *Q2* | | | | | | | -0.04 | (-0.22 - 0.14) | 0.647 | -0.08 | (-0.26 - 0.09) | 0.344 |
| *Q3* | | | | | | | 0.09 | (-0.08 - 0.27) | 0.306 | 0.01 | (-0.16 - 0.19) | 0.902 |
| *Q4 - Most disturbed* | | | | | | | 0.19 | (0.01 - 0.38) | 0.038 | 0.04 | (-0.14 - 0.23) | 0.643 |
| **Family structure at 7 & 11** | | | | | | | | | | | | |
| *Presence of father figure/not divorced* | | | | | | | 0 | | | 0 | | |
| *No father figure or divorced* | | | | | | | 0.26 | (-0.05 - 0.56) | 0.097 | 0.22 | (-0.08 - 0.51) | 0.153 |
| **Motor ability test at 7** | | | | | | | -0.05 | (-0.08 - -0.02) | 0.003 | -0.03 | (-0.07 - 0.00) | 0.056 |
| **Childhood material factors at 7-16** | | | | | | | | | | | | |
| *Q1 -Low material deprivation* | | | | | | | 0 | | | 0 | | |
| *Q2* | | | | | | | 0.00 | (-0.20 - 0.20) | 0.999 | -0.03 | (-0.22 - 0.16) | 0.769 |
| *Q3* | | | | | | | 0.13 | (-0.08 - 0.34) | 0.224 | 0.07 | (-0.14 - 0.27) | 0.524 |
| *Q4 - High material deprivation* | | | | | | | 0.26 | (0.05 - 0.46) | 0.014 | 0.15 | (-0.05 - 0.36) | 0.144 |
| **Health behaviours at 23** | | | | | | | | | | | | |
| *Least at risk* | | | | | | | | | | 0 | | |
| *Moderately at risk* | | | | | | | | | | 0.30 | (0.16 - 0.45) | <0.001 |
| *Most at risk* | | | | | | | | | | 0.54 | (0.35 - 0.73) | <0.001 |
| **BMI at 23** | | | | | | | | | | | | |
| *Normal* | | | | | | | | | | 0 | | |
| *Underweight* | | | | | | | | | | -0.26 | (-0.70 - 0.17) | 0.239 |
| *Overweight* | | | | | | | | | | 0.48 | (0.30 - 0.67) | <0.001 |
| *Obese* | | | | | | | | | | 1.00 | (0.48 - 1.52) | <0.001 |
| **Malaise inventory at 23** | | | | | | | | | | | | |
| *No* | | | | | | | | | | 0 | | |
| *Yes* | | | | | | | | | | 0.10 | (-0.27 - 0.46) | 0.602 |
| **Educational attainment at 23** | | | | | | | | | | | | |
| *Passed A levels* | | | | | | | | | | 0 | | |
| *Passed O levels* | | | | | | | | | | 0.15 | (-0.03 - 0.33) | 0.101 |
| *No qualifications* | | | | | | | | | | 0.31 | (0.12 - 0.51) | 0.002 |

*(continued)*

Table 19. continued

| Variables | Model 1: Parental SEP | | | Model 2: Perinatal factors | | | Model 3: Childhood factors | | | Model 4: Early adulthood factors | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ß | CI 95% | p | ß | CI 95% | p | ß | CI 95% | p | ß | CI 95% | p |
| Income at 23 | | | | | | | | | | | | |
| *Q1 - Low income* | | | | | | | | | | 0 | | |
| *2* | | | | | | | | | | -0.10 | (-0.31 - 0.10) | 0.329 |
| *3* | | | | | | | | | | -0.26 | (-0.47 - -0.06) | 0.013 |
| *Q4 - High income* | | | | | | | | | | -0.25 | (-0.45 - -0.06) | 0.011 |

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Table 20. Life course multivariate linear regression using data obtained from multiple imputation: women (n=3791)

| Variables | Model 1: Parental SEP | | | Model 2: Perinatal factors | | | Model 3: Childhood factors | | | Model 4: Early adulthood factors | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ß | CI 95% | p | ß | CI 95% | p | ß | CI 95% | p | ß | CI 95% | p |
| **Maternal education level** | | | | | | | | | | | | |
| *Left school at 15 or later* | 0 | | | 0 | | | 0 | | | 0 | | |
| *Left school before 14* | 0.44 | (0.27 - 0.60) | <0.001 | 0.39 | (0.22 - 0.55) | <0.001 | 0.30 | (0.13 - 0.46) | <0.001 | 0.24 | (0.08 - 0.41) | 0.004 |
| **Paternal occupation** | | | | | | | | | | | | |
| *I & II (professional/managerial)* | 0 | | | 0 | | | 0 | | | 0 | | |
| *IIINM (skilled nonmanual)* | 0.24 | (-0.03 - 0.51) | 0.079 | 0.19 | (-0.07 - 0.46) | 0.155 | 0.17 | (-0.09 - 0.44) | 0.204 | 0.12 | (-0.14 - 0.39) | 0.349 |
| *IIIM (skilled manual)* | 0.60 | (0.41 - 0.80) | <0.001 | 0.50 | (0.30 - 0.69) | <0.001 | 0.39 | (0.19 - 0.59) | <0.001 | 0.29 | (0.09 - 0.49) | 0.005 |
| *IV & V (semi-unskilled)* | 0.78 | (0.55 - 1.01) | <0.001 | 0.63 | (0.40 - 0.87) | <0.001 | 0.45 | (0.21 - 0.69) | <0.001 | 0.30 | (0.06 - 0.53) | 0.016 |
| **Birthweight** | | | | | | | | | | | | |
| *Q1 - Low weight* | | | | 0 | | | 0 | | | 0 | | |
| *Q2* | | | | -0.20 | (-0.38 - -0.01) | 0.041 | -0.17 | (-0.36 - 0.01) | 0.070 | -0.14 | (-0.32 - 0.04) | 0.138 |
| *Q3* | | | | -0.30 | (-0.49 - -0.10) | 0.003 | -0.26 | (-0.45 - -0.06) | 0.009 | -0.25 | (-0.44 - -0.05) | 0.012 |
| *Q4 - High weight* | | | | -0.41 | (-0.61 - -0.22) | <0.001 | -0.37 | (-0.57 - -0.18) | <0.001 | -0.37 | (-0.56 - -0.18) | <0.001 |
| **Mother smoked during pregnancy** | | | | | | | | | | | | |
| *No* | | | | 0 | | | 0 | | | 0 | | |
| *Sometimes* | | | | 0.43 | (0.14 - 0.73) | 0.004 | 0.38 | (0.08 - 0.67) | 0.012 | 0.28 | (-0.01 - 0.57) | 0.062 |
| *Moderately* | | | | 0.07 | (-0.13 - 0.26) | 0.504 | 0.02 | (-0.17 - 0.21) | 0.856 | -0.03 | (-0.22 - 0.16) | 0.741 |
| *Heavily* | | | | 0.22 | (0.00 - 0.44) | 0.049 | 0.16 | (-0.05 - 0.38) | 0.140 | 0.06 | (-0.15 - 0.28) | 0.555 |
| **Mother's BMI** | | | | | | | | | | | | |
| *Normal* | | | | 0 | | | 0 | | | 0 | | |
| *Underweight* | | | | 0.10 | (-0.22 - 0.42) | 0.543 | 0.12 | (-0.21 - 0.44) | 0.483 | 0.13 | (-0.19 - 0.45) | 0.414 |
| *Overweight* | | | | 0.40 | (0.22 - 0.58) | <0.001 | 0.41 | (0.23 - 0.59) | <0.001 | 0.29 | (0.11 - 0.46) | 0.001 |
| *Obese* | | | | 0.27 | (-0.09 - 0.63) | 0.138 | 0.21 | (-0.15 - 0.56) | 0.258 | -0.12 | (-0.48 - 0.24) | 0.505 |
| **Mother's age at birth** | | | | | | | | | | | | |
| *23 years or less* | | | | 0 | | | 0 | | | 0 | | |
| *24 to 27 years* | | | | -0.36 | (-0.55 - -0.18) | <0.001 | -0.33 | (-0.51 - -0.15) | <0.001 | -0.26 | (-0.44 - -0.08) | 0.004 |
| *28 to 31 years* | | | | -0.43 | (-0.62 - -0.23) | <0.001 | -0.39 | (-0.58 - -0.19) | <0.001 | -0.29 | (-0.49 - -0.10) | 0.003 |
| *32 years or more* | | | | -0.29 | (-0.49 - -0.10) | 0.003 | -0.28 | (-0.47 - -0.08) | 0.005 | -0.19 | (-0.38 - 0.00) | 0.050 |

*(continued)*

Table 20. continued

| Variables | Model 1: Parental SEP | | | Model 2: Perinatal factors | | | Model 3: Childhood factors | | | Model 4: Early adulthood factors | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ß | CI 95% | p | ß | CI 95% | p | ß | CI 95% | p | ß | CI 95% | p |
| **Parental involvement at 7** | | | | | | | | | | | | |
| *Most Frequent* | | | | | | | 0 | | | 0 | | |
| *Occasionally* | | | | | | | 0.04 | (-0.13 - 0.20) | 0.670 | 0.02 | (-0.14 - 0.18) | 0.795 |
| *Hardly ever* | | | | | | | 0.10 | (-0.10 - 0.30) | 0.316 | 0.04 | (-0.15 - 0.24) | 0.655 |
| **BSAG* at 7** | | | | | | | | | | | | |
| *Q1 - Least disturbed* | | | | | | | 0 | | | 0 | | |
| *Q2* | | | | | | | 0.11 | (-0.07 - 0.28) | 0.227 | 0.05 | (-0.12 - 0.23) | 0.537 |
| *Q3* | | | | | | | 0.28 | (0.09 - 0.48) | 0.004 | 0.21 | (0.02 - 0.40) | 0.033 |
| *Q4 - Most disturbed* | | | | | | | 0.36 | (0.15 - 0.58) | <0.001 | 0.17 | (-0.05 - 0.38) | 0.136 |
| **Family structure at 7 & 11** | | | | | | | | | | | | |
| *Presence of father figure/not divorced* | | | | | | | 0 | | | 0 | | |
| *No father figure or divorced* | | | | | | | 0.11 | (-0.18 - 0.39) | 0.470 | 0.04 | (-0.24 - 0.33) | 0.758 |
| **Motor ability test at 7** | | | | | | | -0.08 | (-0.12 - -0.04) | <0.001 | -0.05 | (-0.09 - -0.01) | 0.013 |
| **Childhood material factors at 7-16** | | | | | | | | | | | | |
| *Q1 -Low material deprivation* | | | | | | | 0 | | | 0 | | |
| *Q2* | | | | | | | 0.06 | (-0.15 - 0.27) | 0.582 | 0.05 | (-0.16 - 0.26) | 0.627 |
| *Q3* | | | | | | | 0.14 | (-0.09 - 0.37) | 0.229 | 0.09 | (-0.14 - 0.31) | 0.455 |
| *Q4 - High material deprivation* | | | | | | | 0.35 | (0.13 - 0.57) | 0.002 | 0.23 | (0.01 - 0.46) | 0.040 |
| **Health behaviours at 23** | | | | | | | | | | | | |
| *Least at risk* | | | | | | | | | | 0 | | |
| *Moderately at risk* | | | | | | | | | | 0.08 | (-0.08 - 0.23) | 0.347 |
| *Most at risk* | | | | | | | | | | 0.31 | (0.10 - 0.52) | 0.004 |
| **BMI at 23** | | | | | | | | | | | | |
| *Normal* | | | | | | | | | | 0 | | |
| *Underweight* | | | | | | | | | | -0.17 | (-0.46 - 0.12) | 0.243 |
| *Overweight* | | | | | | | | | | 0.88 | (0.65 - 1.11) | <0.001 |
| *Obese* | | | | | | | | | | 1.94 | (1.48 - 2.40) | <0.001 |
| **Malaise inventory at 23** | | | | | | | | | | | | |
| *No* | | | | | | | | | | 0 | | |
| *Yes* | | | | | | | | | | 0.29 | (0.05 - 0.53) | 0.019 |

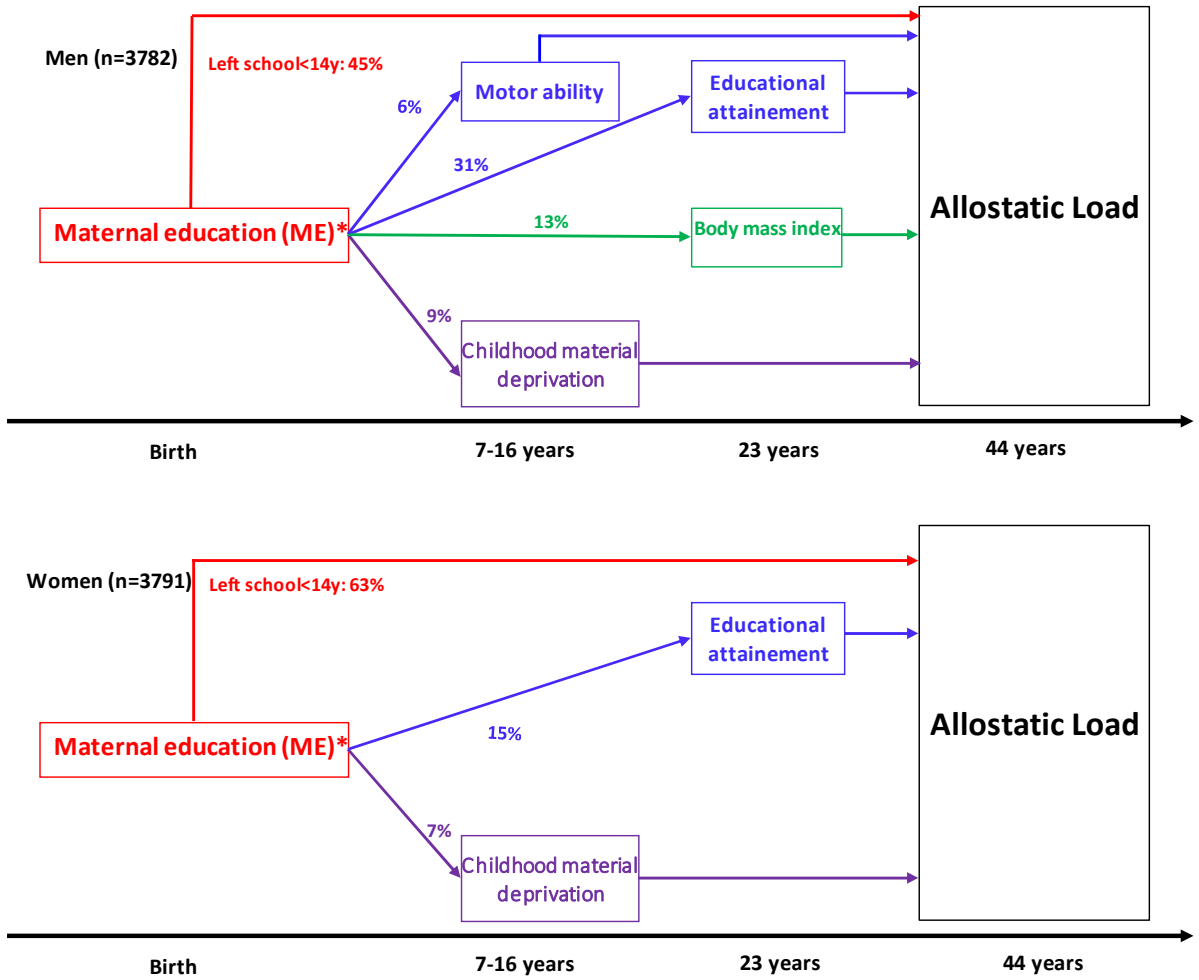
*(continued)*

Table 20. continued

| Variable | Model 1: Parental SEP | | | Model 2: Perinatal factors | | | Model 3: Childhood factors | | | Model 4: Early adulthood factors | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ß | CI 95% | p | ß | CI 95% | p | ß | CI 95% | p | ß | CI 95% | p |
| **Educational attainment at 23** | | | | | | | | | | | | |
| *Passed A levels* | | | | | | | | | | 0 | | |
| *Passed O levels* | | | | | | | | | | 0.12 | (-0.07 - 0.31) | 0.206 |
| *No qualifications* | | | | | | | | | | 0.36 | (0.13 - 0.59) | 0.002 |
| **Income at 23** | | | | | | | | | | | | |
| *Q1 - Low income* | | | | | | | | | | 0 | | |
| *2* | | | | | | | | | | -0.03 | (-0.23 - 0.16) | 0.733 |
| *3* | | | | | | | | | | 0.02 | (-0.18 - 0.21) | 0.879 |
| *Q4 - High income* | | | | | | | | | | -0.07 | (-0.29 - 0.14) | 0.517 |

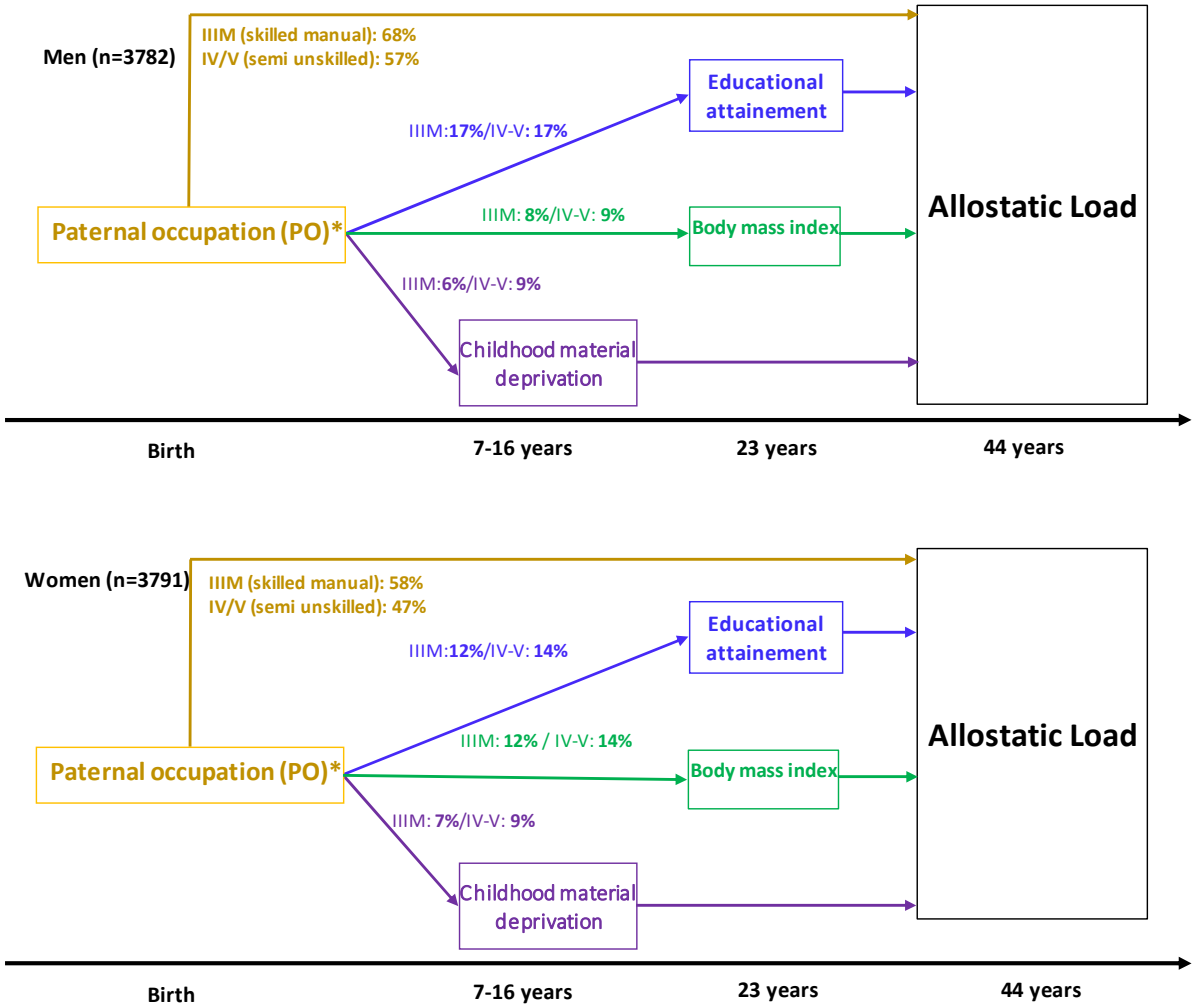
*Bristol Social Adjustment Guide

Figure 8. Mediating pathways between maternal education and AL for men (n=3782) and women (n=3791)




Were included in this figure only variables explaining 5% or above of the variability between ME and AL
Model adjusted for paternal occupation, birthweight, mother smoked during pregnancy, mother's BMIn mother's age at birth, parental involvement,
*The sum of all pathways are not equal to 1 due to other small or negative pathways not presented on this figure

Figure 9. Mediating pathways between paternal occupation and AL for men (n=3782) and women (n=3791)




Were included in this figure only variables explaining 5% or above of the variability between ME and AL
Model adjusted for paternal occupation, birthweight, mother smoked during pregnancy, mother's BMIn mother's age at birth, parental involvement,
*The sum of all pathways are not equal to 1 due to other small or negative pathways not presented on this figure

Figure 10. Mediating pathways between motor ability and childhood deprivation and AL for men

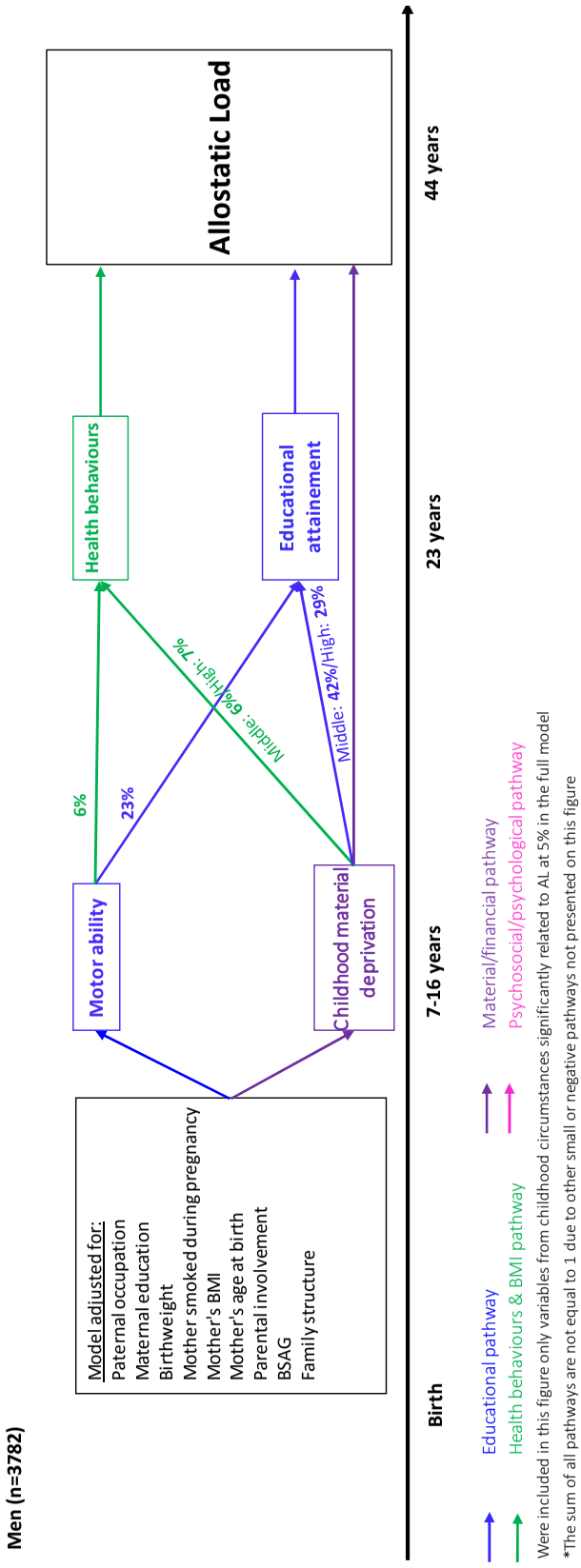
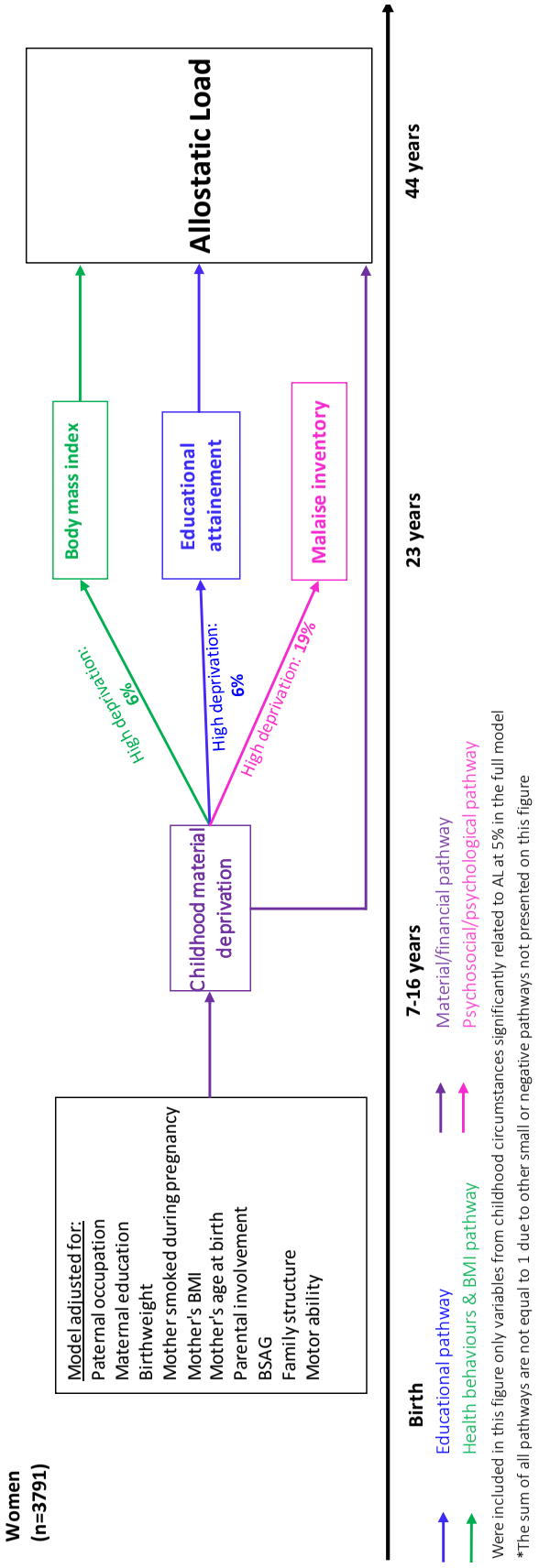


Figure 11. Mediating pathways between childhood deprivation and AL for women



## 4. Discussion

Lower maternal education and manual paternal occupation were associated with a higher allostatic load at 44 years, mainly *via* the educational, material/financial, and health behaviours pathways for both men and women. For the relationship between ME and AL, more than 60% of the link in women and 45% in men remained unexplained by the mediators. Around 50-60% of the relationship between PO and AL remained unexplained by the mediators in men and in women. In both relationships these pathways may represent differential early life embodiment processes or: i) an underrepresentation, underestimation of the four path we tested due to measurement errors or lack of availability of variables representing better these paths; ii) the lack of identification or omission of other possible paths, including cognitive functioning and social support (John-Henderson et al., 2015); iii) an early biological impact of parental SEP, having long lasting influence on physiology (Miller et al., 2009; Noble et al., 2015).

Up to 37% of the link between ME and AL observed in men was mediated by the educational path represented by motor ability at 7y (6%) and educational attainment at 23y (31%). The health behaviours path represented 13% of the total effect and the material/financial path 9%.

For women, only two paths appeared to be important in the relationship between ME and AL: 15% was explained by educational attainment and 7% by childhood material deprivation. The link between childhood material factors and AL for women was mainly mediated by psychological malaise in adulthood. Concerning the link between PO and later AL, men and women showed similar patterns: the main path was educational, followed by the health behaviours and the material/financial pathways.

The most important path revealed in this study for both ME and PO was the educational. This suggests a significant protective effect of education on a favourable health trajectory. Parental education might help and stimulate children, influencing cognitive abilities (Biedinger, 2011), favoured a good adaptation to school settings, influence offspring's receptivity to health education messages, and can impact health trough the material circumstances (better jobs, higher household incomes, and better housing) (Dubow et al., 2009; McKenzie et al., 2011).
The second main path was drawn by a particular dimension of adult health behaviours: BMI. The intergenerational influences of parental SEP have been reported to affect offspring's adult obesity (Laaksonen et al., 2004), suggesting that obesity trajectories may be set early in life.

Higher SEP could increase awareness concerning health messages, prevention, healthy eating, exercise and weight control efforts (Laaksonen et al., 2004).

The third path was the material/financial pathway. Gustafsson *et al.* suggested that early material circumstances

> "*might be mediated by physiological effects of their emotional and social meaning*" (Gustafsson et al., 2012),

it is also conceivable that they could impact AL increasing the probabilities of harmful exposures early in life (e.g. home/neighbourhood) (Robertson et al., 2015). Moreover, for men, motor ability and childhood material factors were mediated by health behaviours, consistent with the idea linking cognitive and material factors with the susceptibility for adopting later risky behaviours (Lacey et al., 2011). Interestingly, for women, the path analysis between childhood material factors and AL showed the importance of psychological distress at 23, a relationship observed elsewhere in the literature (Mensah & Hobcraft, 2008; Power et al., 2002).

When exploring the link between SEP and AL, Robertson *et al*. showed that behavioural and material factors accounted for much of the association (Robertson et al., 2015). They also revealed in a previous study that accumulated SEP across the life span was the best fitting life course model (Robertson et al., 2014). Gruenewald *et al*. found that alcohol, tobacco, poor diet and low social support explained an important amount of the link (Gruenewald et al., 2012). In this work we contributed to this discussion by testing diverse pathways, taking into account potential sex/gender differences and by testing two dimensions of parental SEP separately. We observed that ME and PO were overall mediated by the same pathways, nevertheless, some differences should be mentioned. For ME in men, motor ability had an important role, suggesting perhaps that ME could be positively associated with cognitive ability in offspring (Bartels et al., 2009). The health behaviours path had an important role through BMI (except for ME in women). We hypothesized that the possible impacts of ME and PO may operate through socially stratified parental behaviours and parenting styles, which may in turn impact future life styles in men and in women. For instance, it is known that heritability of BMI is high (Han et al., 2015), and parental socioeconomic factors have been linked with offspring's BMI (Chaparro & Koupil, 2014).

Other variables characterizing parental SEP were available in the NCDS. We selected ME and PO at birth, because we wanted to include in our analysis the earliest SEP markers available capturing the child social environment where s/he born into. We chose ME since literature suggests that it is a fundamental resource linked to children's health (Currie & Moretti, 2003; Gakidou et al., 2010). ME is strongly associated with improved health outcomes for children and it is inversely correlated with low birth weight and premature birth (Currie J. & Moretti, 2003). Moreover, at that time women were more likely to have traditional gender roles related to child-rearing in the household. Given the time she was likely to spend on household and childcare activities, we attempted to capture the mother's educational resources that may be transmitted to her children. Concerning occupation, because of gender ascribed social roles, women had less stable occupational trajectories, compared to men. Paternal occupation was the best variable that allowed us to capture the material conditions in the household at birth. In summary, our main goal was to explore the potential pathways through which parental education and occupational status may link to later health. However, due to measurement availability and historical context, the most appropriate measure available for education came from mothers, and likewise, occupation from fathers.

We observed that ME and PO were mediated by the same pathways. However, we expected to see differences concerning the importance of each path impacting AL. For instance, we hypothesized that PO could affect AL through mainly the material path and ME through mainly the educational path. However, our results were similar, suggesting that both may relate in similar ways with AL. Nevertheless, some differences should be mentioned. For ME in men, motor ability had an important role, suggesting perhaps that ME could be positively associated with cognitive ability in offspring (Bartels et al., 2009).

Concerning the path between PO and AL, there was no difference between the III-partly skilled occupations and the IV-V semi/unskilled manual categories. The RGSC is as a general measure of social standing, based on particular skills to perform an occupation. However, research on RGSC have showed a wide range of results sometimes difficult to interpret (Bartley et al., 1996). We speculate that the most important feature when it comes to occupational status and later physiological wear-and-tear is the psychosocial hypothesis of social standing. The psychosocial component may be underestimate using the RSGC, since it may better capture the material

advantages bestowed by the world of work. Future research may purposes measures of occupational status based on social standing or social interactions (e.g. Cambridge scale).

The health behaviors path had an important role through BMI (except for ME in women). We hypothesize that the possible impacts of ME and PO may operate through socially stratified parental behaviors and parenting styles, which may in turn impact future life styles in men and in women. For instance, it is known that heritability of BMI is high (Han et al., 2015), and parental socioeconomic factors have been linked with offspring's BMI (Chaparro & Koupil, 2014).

The main weakness of this study is related to attrition, and selection bias, common features related to longitudinal studies. Nevertheless, it has been shown that the NCDS 1958 birth cohort remain broadly representative of the surviving cohort on key childhood and adult characteristics (Atherton et al., 2008). We compared the biomedical survey participants included in our analyses to all of those involved in the cohort at baseline to ascertain differences due to missing data. We observed that the analyzed sample have more educated mothers (27% vs 23%), have fewer fathers in the semi/unskilled category of occupational class (21% vs 24%), are more likely to have a normal BMI at 23y (80% vs 75%), being less in the 'no qualification' at 23y category (34% vs 47%), are more likely to be former smokers (30% vs 25%) or to less smoke heavily (16% vs 20%), compared to their baseline counterparts. In this sense, our results might be rather conservative and they could underestimate the effects of early SEP on AL. Therefore, we imputed the data taking the MAR assumption to preserve important aspects of the distribution, variability, and relationships between variables. The ME variable is unprecise, however it has already been independently related in the NCDS 1958 birth cohort to later AL (Barboza Solis et al., 2015). Concerning the relative minor role of the psychosocial/psychological path, it is possible that we are underestimating its real impact, due to lack of robustness, to variable availability, variable construction, and more importantly, the incapacity to completely disentangle this path from others, especially the material/financial path (Robertson et al., 2015). With family structure, parental involvement, social adjustment and the malaise inventory we tried to capture the nature of the social environment (supportive and secure) that could reverse or buffer potentially damaging stress responses. Indeed, parental warmth, and a supportive social environment, could reduce the extent of physiological wear-and-tear (Carroll et al., 2013; Shonkoff et al., 2012). Additionally, depression and anxiety,

approached here with the malaise inventory, has already been found related with AL (McEwen, 2000).

Regarding the composite variable of health behavior, we want to note that the objective was to capture a general profile of lifestyles, hypothesizing that the accumulation of risky behaviors is more likely in socioeconomically deprived population subgroups. Poor population subgroups are more likely to smoke, to have a sedentary life, and to drink more heavily than their well-off counterparts (Jarvis & Wardle, 1999). It is possible that by building this variable we have misclassified individuals, and our statistical power may be decreased, leading to an underrepresentation of the health behaviors path.

We were limited by the availability of variables in our data set. There are some confounders and mediators that may be not taken into account in this analysis, that could better account for other potential mechanisms, like diet, environmental exposures, social support and cognitive skills (Gruenewald et al., 2012). We tried to capture cognitive ability by utilizing the Copy-a-Design test, a concept that aims to "recognize the principle governing different geometric forms and to reproduce them" (Schoon et al., 2002). Higher scores could represent the child's ability to follow instructions, remain concentrated and increasing their probabilities for educational success. Previous studies have used the motor skill test as a cognitive ability proxy (Lacey et al., 2011). A study showed that children whose mothers had no college education showed reduced effects of selective attention on early neural processing of speech and reduced ability to filter irrelevant information (Stevens et al., 2009). The social, material and behavioral exposures included are self-reported, thus measurement errors are probable. Our AL score remains limited by the pragmatism of variable availability, with a strong focus on the cardiovascular system. Our only available primary mediator biomarker was cortisol, other widely used primary biomarkers are epinephrine and norepinephrine (Juster et al., 2011a), however these were not available in the NCDS biomedical survey. With the two cortisol measures (t1 and t1-t2) we tried to characterize the diurnal pattern of the HPA axis. t1 was measure 45 min after wakening and t2, 3 hours later (Elliott et al., 2008). A healthy HPA axis is typically characterized by high levels upon waking and a subsequent decline over the day, reaching a low point around midnight (Adam & Kumari, 2009). We tried to capture the cortisol pattern using the t1-t2 measure, however we recognize that the lack of further measures underestimate the impact of the neuroendocrine system inside the AL score.

Additionally, there is currently no consensus regarding the choice of relevant physiological systems, of biomarkers, their interactions (linear relationships), their importance in the chain of physiological stress responses, as well as their measurement, combinations, weighting and the most suitable statistical analysis (Beckie, 2012). Furthermore, as physiological responses to stress may differ according to developmental stage over time, measures of AL may differ in terms of markers and risk thresholds (Barboza Solis et al., 2015). However, the two sensitivity analysis already mentioned showed the stability of the results. Concerning sex stratification, recent population-based studies suggest sex/gender differences in several biomarkers (Goldman et al., 2004; Lakoski et al., 2006), and a study has found sex differences in AL (Yang & Kozloski, 2011). Even if the results do not show large differences by sex, we consider these potential sexual dimorphism should be taking into account in the analyses.

Regarding the significance of each pathway, we used bootstraps on 1000 random samples, to calculate the p values for each mediating variable. However, the significance at 5% was not the main criteria for considering variable as clinically or epidemiologically "relevant" or significant, since we had a large sample and in these cases the statistical significance does not provide information on clinical relevance. It seems to us that in this case we should analyze the change in effect size (Chavalarias et al., 2016). Therefore, we decided to present the percentage for which each variable explained at least 5% of the total variability (Table S5 and S6).

Despite these limitations, this study has a number of strengths. We used a longitudinal population-based study collecting data prospectively across the life span. This study is further strengthened by analyzing separately two concepts of parental SEP by sex, exploring potential differences in the mechanisms. These findings enlighten us on the important relationship between education and physiological burden. Reducing inequalities in education could contribute to targeting population subgroups, less likely to be educated and at risk of developing physiological wear-and tear. Moreover, identifying sets of biomarkers for capturing embodiment processes early in life may be useful for conceptualizing and assessing early preventive intervention before the initiation of deleterious health trajectories.

## 5. Conclusion

We assessed in this research axis the contribution of a financial/materialist, psychological/psychosocial, educational, and health behaviours/BMI pathways over the life

course, in mediating the associations between maternal education, paternal occupation and AL. Maternal education and paternal occupation were mediated by three main pathways: educational, material/financial, and health behaviours, for both men and women. A better understanding of embodiment processes leading to disease development may contribute to developing adapted public policies aiming to reduce health inequalities.

# PART IV

# ALLOSTATIC LOAD AS A PREDICTOR OF LATER HEALTH: CONTEXT, METHODS AND DISCUSSION

# Résumé - Partie IV : La CA comme prédicteur de la santé ultérieure

Pour capturer partiellement la dimension biologique des processus d'incorporation biologique de l'environnement social, la charge allostatique se doit d'être un bon prédicteur de la santé ultérieure. L'axe 3 explore le lien entre le score de CA à 44 ans et l'état de santé global ultérieur, à 50 ans. Pour cette section nous avons introduit le contexte précis et le rationnel justifiant cet axe de recherche.

L'étude du lien entre la CA et une dimension ou mesure unique de l'état de santé pourrait ne pas être la meilleure façon d'approcher la notion d'usure physiologique globale contenue dans le concept de CA. Pour répondre à cette question, nous avons analysé l'association entre la CA mesurée à 44 ans, et une mesure multidimensionnelle de l'état de santé six ans plus tard chez 7573 membres de la cohorte britannique de naissance de 1958 suivi jusqu'à l'âge de 50 ans. La santé subjective, telle que la santé perçue ou la qualité de vie, a en effet la capacité de proposer une approche holistique de la santé et de prédire la morbi/mortalité générale. L'état de santé a été mesuré à partir des informations déclarées par les participants sur leur santé subjective et résumé en utilisant une analyse en composantes principales à partir des sept dimensions issues du questionnaire SF-36 de qualité de vie, la sous-échelle de sommeil de la Medical Outcomes Study, et un score de malaise (malaise inventory score) détectant les symptômes dépressifs. La CA a été construite comme une mesure physiologique synthétique, multi-système, à l'aide des mêmes 14 biomarqueurs précédemment décrits.

Des scores plus élevés de CA à 44 ans étaient associés à un plus mauvais score de santé subjective six ans plus tard, après prise en compte des facteurs de confusion classiques. Cette association était indépendante des variables socioéconomiques, considérées tout au long de de la vie, des comportements de santé et de l'indice de masse corporelle à l'âge adulte.

L'ensemble des résultats de ce travail de thèse supporte l'idée que la CA pourrait représenter une mesure physiologique du processus d'incorporation de son environnement social, et contribuer ainsi à une meilleure compréhension des origines des maladies et du gradient social de santé.

# Chapter I

# Allostatic load and later health: context, methods, results and discussion

As for the previous part, here we will introduce the specific context, methods, results and discussion of the limits and the forces of the third research axis; as well as the specific perspectives involving research in this field. In this Chapter we will discuss the evidence we found linking allostatic load and later health. In section 1 we will summarize existing evidence of a link between physiological wear-and-tear and health, concentrating on the specific findings concerning allostatic load. In section 2 we will explain the materials and methods implemented to answer this question. In the third section we will discuss the limitations of our work.

Objective: To explore the association between physiological wear-and-tear in mid-life and later health status. We aimed to address this question by studying the impact of allostatic load on an integrative latent variable of subsequent subjective health.

Hypothesis: physiological wear-and-tear, as measured by allostatic load, could influence health status in the long term, independently of common social determinants (Appendix 1).

## 1. Context

Krieger *et al*. defined the concept of embodiment as

> "*how we, like any living organism, literally incorporate, biologically, the world in which we live, including our societal and ecological circumstances*" (Krieger, 2005).

Growing evidence supports the idea that exposure to chronic stress over the life course contributes to physiological dysregulation, subsequently translated into disease (McEwen & Seeman, 1999; McEwen & Stellar, 1993; Seeman et al., 2001). Allostasis is the active process of adaptation where our body tries to maintain physiological stability in response to environmental challenges (Sterling, 2004, 2012). The repeated activation of compensatory physiological mechanisms as a result of chronic exposure to stress can lead to a physiological wear-and-tear, known as allostatic load (AL) (Juster et al., 2010; McEwen & Stellar, 1993;

McEwen & Wingfield, 2003). AL may be a useful conceptual tool in measuring the biological effect of embodiment.

Based on prospective data, used to capture the history of prior environmental insults (Seeman et al., 2010) researchers have studied the life course origins of AL development. They highlighted the role of social adversity (Gustafsson et al., 2012), and socioeconomic position (SEP) (Gustafsson et al., 2011) as predictors of AL, also identifying the mediating role of material, behavioural and psychosocial factors between SEP and later AL (Barboza Solis et al., 2015; Robertson et al., 2015; Robertson et al., 2014). These findings suggest that a) AL is socially patterned (Dowd et al., 2009; Robertson et al., 2014; Seeman et al., 2010; Szanton et al., 2005), determined by socioeconomic position, material, psychosocial and behavioural factors all over the life span (Robertson et al., 2015), b) AL conceptual framework may contribute to clarify the biological component of the socioeconomic gradient observed in morbidity and mortality (Carlson & Chamberlain, 2005; Gruenewald et al., 2012).

Empirical research has investigated the link between AL and later health outcomes (Beckie, 2012; Karlamangla et al., 2006). However, the conceptual framework of AL is constructed on the basis of a global effect of stress on health, *via* multiple physiological mechanisms and by impacting several systems and brain structures. Therefore, AL is not designed to be specific, but rather to show an overall effect on health. Several studies have shown links between AL and, diverse health outcomes (Juster et al., 2010; Karlamangla et al., 2002; Karlamangla et al., 2006). However, testing the link between AL and one specific aspect of health, for instance, cardiovascular disease, fragments the notion of overall physiological wear-and-tear. Therefore, due to the global physiological effect captured by the AL concept, it is particularly pertinent to examine its association with subsequent health by taking a broad definition of the latter, not only measured by the absence or presence of diseases.

Health status is indeed a multidimensional and integrative attribute, a latent concept, capturing subjective (e.g. self-rated health, well-being, quality of life, health related quality of life, happiness, life satisfaction); clinical (e.g. morbidity, functional decline); and biological (e.g. biomarkers) dimensions (Hyland et al., 2014). Health-related quality of life (HRQoL) –defined as the perception of the impact of health problems on different spheres of life, including physical, mental, and social aspects (Testa & Simonson, 1996)- have been used as measures of health status since they correlate to morbidity and mortality (Power et al., 1998). Subjective health

measures are then frequently used as surrogate endpoints of morbidity and mortality, where their main advantage is to define health through its various dimensions. In this study we aimed to investigate the link between AL at 44 years and a holistic/integrative latent measure of health using a subjective health variable integrating sleep patterns, physical and mental health at 50 years. We hypothesized that AL could influence health status in the long term, independently of social determinants and health behaviours.

## 2. Methods

In this section we analysed the predictive value of allostatic load, using a measure of overall subjective health at 50 years of age. The hypothesis tested in this axis was that AL could influence health status in the long term, independently of social determinants and health behaviours. Descriptive statistics are presented in Table 21. Bivariate statistics are introduced in Table 22. Multivariate statistics are presented in Table 23 and 24 for men and women respectively.

### 2.1. Outcome variable: Subjective health index at 50y

We conceptualize health status following an integrative approach incorporating three different dimensions of health from subjective health measures collected at the 8$^{th}$ sweep of the NCDS 1958 British birth cohort.

The *SF-36* is a general questionnaire measuring Health Related Quality of Life (HRQoL) (Ware, 2000) through its physical and mental components (Taft et al., 2001) that captures, for instance, the interference with work or other daily activities due to physical health, emotional problems, interference with normal social activities, symptoms associated with anxiety/depression and measures of positive affect (please see Appendix 5 for details of the 36 items of the SF-36 questionnaire). Each of the eight dimensions is ranged from 0 to 100 with higher scores related to better HRQoL. The SF-36 has been shown to be predictive of subsequent morbidity and mortality (Kaplan M. S. et al., 2007; Otero-Rodriguez et al., 2010; Rodriguez-Artalejo et al., 2005; Tsai et al., 2007).

A subscale of four items from twelve original *Sleep Scale of the Medical Outcomes Study* (MOS) was used in the NCDS to collect information about sleep patterns in the last four weeks measuring quality of sleep (Hays & Stewart, 1992). The original Sleep Scale of the Medical

Outcomes Study comprised 12-item instrument informing about sleep patterns in the last four weeks, with six scales: sleep disturbance (assessing trouble falling asleep, how long to fall asleep, sleep was not quiet, awaken during your sleep time and have trouble falling asleep again; sleep adequacy (informing about person getting enough sleep to feel rested upon waking in the morning, getting amount of sleep needed); daytime somnolence (asking about drowsy during day, having trouble staying awake during the day, taking naps); snoring; awaken short of breath or with headache; and quantity of sleep. Items are administered using a past 4-week recall interval. Quantity of sleep is scored as the average hours slept per night (Frech et al., 2011). Following we present the details of the self-completion sleep scale in the 8$^{th}$ sweep of the NCDS 1958 British birth cohort:

i) What was usual time taken to fall asleep in last 4 weeks (1: 0 - 15 minutes/2: 16 - 30 minutes/3: 31 - 45 minutes/4: 46 - 60 minutes/5: More than 60 minutes);
ii) Average number of hours sleep per night in last 4 weeks (continuous variable);
iii) How often woke-up and have trouble refalling asleep in past 4 weeks (1: All of the time/2: Most of the time/3: A good bit of the time/4: Some of the time/ 5: A little of the time/ 6: None of the time);
iv) How often slept enough to wake feeling rested in past 4weeks (1: All of the time/2: Most of the time/3: A good bit of the time/4: Some of the time/ 5: A little of the time/ 6: None of the time). These 4 variables were entered in the principal components analysis as continuous variables.

These four items capture three different dimensions of sleep problems, relating to quantity of sleep/optimal sleep duration, perceived sleep adequacy, and sleep disturbance (Chatzitheochari, 2013). Previous studies have provided evidence on the validity and reliability of the MOS sleep measures (Hays et al., 2005; Viala-Danten et al., 2008). Sleep patterns are known to be related to chronic diseases (diabetes, hypertension, cardiovascular), poor health-related quality of life and self-rated poor health (Chatzitheochari, 2013). In terms of physiological balance, sleep disturbances have an impact on metabolic and endocrine functioning (Spiegel et al., 1999).

Finally, the *malaise Inventory* which measures psychological distress, comprising a nine-item score from the original twenty four (Rutter et al., 1970), was included as a continuous variable

in a Principal Component Analysis (PCA), with higher scores relating to worst mental health. The questionnaire informed about:

i) Whether participant feels tired most of the time;
ii) Whether participant often feels miserable and depressed;
iii) Whether participant often gets worried about things;
iv) Whether participant often gets into a violent rage;
v) Whether participant often suddenly scared for no good reason;
vi) Whether participant is easily upset or irritated;
vii) Whether participant is constantly keyed up and jittery;
viii) Whether every little thing gets on participant's nerves;
ix) Whether participant's heart often races like mad

The malaise inventory score has been found to have acceptable internal validity in different socio-economic groups in the NCDS sample (Rodgers et al., 1999). Mental health has been found to correlate to later morbidity and mortality (Vogt et al., 1994).

We ran a Principal Components Analysis (PCA) to sum-up the information of the above self-reported variables using non-imputed data and deriving one single component. The PCA included three groups of variables:

i) The first group was created using seven dimensions of the SF-36 scale of HRQoL questionnaire (physical functioning, role-physical, bodily pain, general health, vitality, role-emotional, mental health). The social functioning subscale was excluded under statistical criteria when running the principal component analysis;
ii) Four items of the *Sleep Scale of the Medical Outcomes Study* included as ordinal continuous variables;
iii) The malaise inventory score ranged between 0 and 9.

PCA showed an adequate fit to the data (Component 1 eigenvalue=5.3; Overall Kaiser-Meyer-Olkin measure of sampling adequacy= 0.89; overall α Cronbach=0.81). Subsequently we standardized the distribution using *Z*scores separately by sex. Figure 12 shows the distribution of *Z*scores for men and women. Figure 13 shows the AL mean by deciles of subjective health index. All analyses were performed using STATA V14 taking a statistical significance level of 0.05.

Figure 12. Zscore distribution of the subjective health index at 50 years for men and women

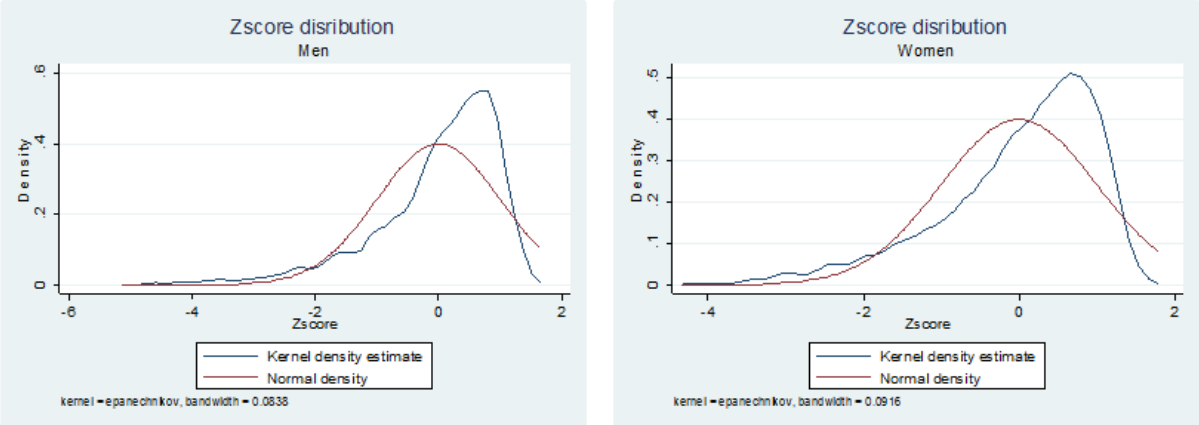
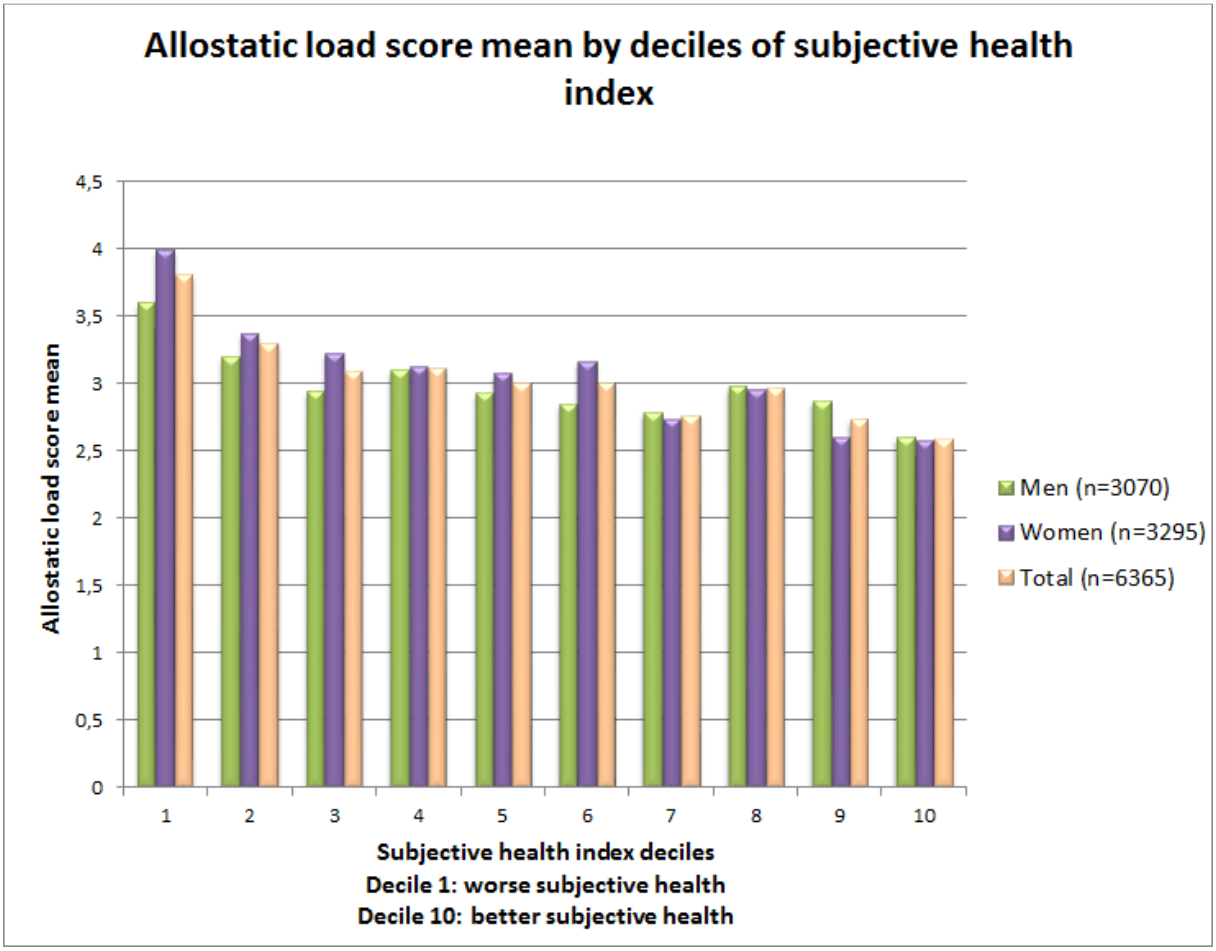



Figure 13. Allostatic load mean by deciles of subjective health index



### 2.2. Exposure variable: Allostatic load index

The outcome variable of interest in this study was a composite score of allostatic load as a measure of cumulative physiological wear-and-tear. Please see Part II, Chapter 3, section 1 for further details on the operationalization of the AL score.

### 2.3. Early life socioeconomic confounders

Information on participant's early life factors was collected *via* a questionnaire completed at birth by the participant's mother. Maternal education was self-reported (mother left school after legal minimal age/mother left school before legal minimal age). Mother's partner's (or father's if unavailable) occupation was classified in four categories: I-professional occupations & II-intermediate occupations/III-skilled occupations (non-manual)/III-partly skilled occupations (manual)/IV-partly skilled occupations & V-unskilled occupations.

### 2.4. Early adulthood socioeconomic confounders at 23y

The selected variables were: respondent's educational attainment (A level/O level/no qualification) and the equivalent net family income (adjusted for family size and composition with weightings from supplementary-benefit scale) (Power et al., 1998).

### 2.5. Adulthood socioeconomic confounders at 33y

To take the role of material circumstances into account, we investigated firstly household tenure (classified in two categories: owner occupiers/renters, other), whether the participant's or their partner were receiving social security benefits (income support, supplementary, or unemployment benefit), whether the participant declared having mortgage or rent arrears (never been 2 or more month behind/yes, ever been 2 or more moth behind) and occupation (classified in non-manual/manual). To capture social support, marital status was used grouped into the following categories: couple/single/divorced or widowed.

### 2.6. Adult health behaviours at 33y.

We investigated the smoking status (non-smoker/former smoker/current smoker), alcohol consumption [moderate (women: between 1 and 14 units in the previous week; men: between 1 and 21 units in the previous week)/abstainers (reported not consuming any alcohol in the

previous week)/heavy drinkers (women: >14 units in the previous week; men: >21 units in the previous week)] (House of Commons Science and Technology Committee, 2012), and physical activity (physically active/moderately active/inactive). To measure eating habits, we added BMI in the model (normal/underweight/overweight/obese).

### 2.7. Statistical analysis

To control for possible bias due to missing data, twenty imputations were conducted using the multiple imputation program ICE in STATA V14. We took a missing-at-random (MAR) assumption. For further details about multiple imputation please see Part II, Chapter II, section 2.

To observe the unadjusted link and better appreciate the evolution of the link between AL and later subjective health, the first model of the multivariate linear regression took only into account AL. Subsequently, and to mimic life course experiences, we sequentially adjusted the multivariate linear regression resulting in four models:

i) Model 1 : AL
ii) Model 2: M1 + Early life socioeconomic confounders at birth,
iii) Model 3: M2 + Early adulthood socioeconomic confounders at 23y,
iv) Model 4: M3 + Adulthood socioeconomic and health behaviours confounders at 33y,

As some evidence suggests gender-related differences in biological markers (Goldman et al., 2004) and potential sexual dimorphism in AL (Yang & Kozloski, 2011) or other biological measure (e.g. metabolic syndrome) (McMillen & Robinson, 2005), the analyses were stratified by sex (Goldman et al., 2004; Yang & Kozloski, 2011). For further details about sex stratification see Part II, Chapter III, section 2.

For further details about other AL score operationalization, please refer to Part II, Chapter III, section 1.

## 3. Results

Descriptive statistics of the non-imputed sample are presented in Table 1 for the subsample with complete data for subjective health and AL (n=3070 for men; n=3295 for women). Table S2 show the results for the bivariate statistics for both men and women. AL score was

associated with subjective health index in men (-0.14 standard deviation (SD); p<0.001) and in women (-0.21SD; p<0.001).

### 3.1. Allostatic load and subjective health

Multivariate results are presented in Table 23 and 24 for men and women respectively. Model 1 showed that AL was significantly associated with later subjective health. Men with higher scores of AL at 44 years had worst subjective health indexes (-0.07SD; p<0.001) at 50 years. The same pattern was observed for women, where higher scores of AL were correlated with worst subjective health index (-0.09SD; p<0.001). In model 2 and model 3 the link was slightly weakened after adjustment for early life and early adulthood socioeconomic circumstances. Model 4 showed that socioeconomic and health behaviours variables reduced the link for both men and women, however it remained significant: A one-point increase of the AL score was associated with a reduction of 0.04SD (p<0.001) and 0.05SD (p<0.001) in the health index for men & women respectively.

### 3.2. Early socioeconomic confounders at birth and later subjective health

For men, model 2 showed that individuals whose mothers left school before legal minimal age had their subjective health index reduced by 0.10SD (p=0.034). Lower occupational status, skilled manual and semi-unskilled, reduced the subjective health index of 0.10SD (p=0.039) and 0.12SD (p=0.046) respectively. These effects were no longer significant with the inclusion of the socioeconomic variables at 23y (model 3). For women, only paternal occupation (skilled manual: -0.11; p=0.026/semi-unskilled: -0.20; p=0.001) was found to be associated with later subjective health index in model 2. These links disappeared after adjustment for variables at 23y (model 3).

### 3.3. Early adulthood socioeconomic confounders at 23y and later subjective health

Model 3 showed that education level at 23y was associated with subjective health index at 50y: having no qualifications decreased the subjective health index of 0.22SD (p<0.001) for both men and women. However, after adjusting for confounders at 33 years (model 4), this effect disappeared in women, although for men, the association was reduced but remained significant (-0.14SD; p=0.025). Income was found to predict better subjective health. For men, having a

high income increases the subjective health index by 0.13SD, link that was no longer significant after adjusting for socioeconomic factors and behaviours at 33y (model 4). For women, model 3 showed a clear gradient between income at 23y and the subjective health index: the most the income increased, the better the subjective health index was (Q2: 0.14; p=0.005/Q3: 0.16; p=0.002/Q4: 0.33; p<0.001). In Model 4 having a high income (Q4) remained consistently associated with a better subjective health index after adjustment for socioeconomic confounders and health behaviours at 33y (0.23; p<0.001).

### 3.4. Adulthood socioeconomic and health behaviours confounders at 33y later subjective health

Worse material and socioeconomic circumstances at 33y were important independent factors associated with lower subjective health index. For both men and women, being a tenant (men: -0.14SD, p=0.019)/women: -0.16SD, p=0.004), receiving social-security benefits (men: -0.30SD, p=0.003/women-0.21SD, p=0.002) and declaring ever being two or more months behind mortgage or rent arrears (men:-0.23SD, p=0.007/women:-0.21SD, p=0.008) were significantly associated with a worse subjective health index compared to their counterparts. Model 4 also showed the important role of health behaviours and BMI predicting the subjective health index for both men and women. Being a current smoker (men: -0.10SD, p=0.034/women:-0.18SD, p<0.001), being classified as a heavy drinker for men (-0.20SD, p=0.002) or an abstainer for women (women:-0.12SD, p=0.002), and being obese (men:-0.15SD, p=0.026/women:-0.29SD, p<0.001), decreased the subjective health index relatively to those classified as non-smokers, moderate drinkers, or having a normal BMI respectively.

Table 21. Descriptive statistics on the subsample for men (n=3070) and women (n=3295)

| Variables | Men | Women | Total |
|---|---|---|---|
| Subjective health Z score at 50 | | | |
| n (min-max) | 3070 (-5.0-1.6) | 3295 (-4.2-1.7) | 6365 (-5.0-1.7) |
| mean (SD) | 0 (1.0) | 0 (1.0) | 0 (1.0) |
| Allostatic load score at 44 | | | |
| *0* | 244 (7.9%) | 277 (8.4%) | 521 (8.2%) |
| *1* | 505 (16.5%) | 578 (17.5%) | 1 083 (17.0%) |
| *2* | 649 (21.1%) | 656 (19.9%) | 1 305 (20.5%) |
| *3* | 574 (18.7%) | 560 (17.0%) | 1 134 (17.8%) |
| *4* | 464 (15.1%) | 452 (13.7%) | 916 (14.4%) |
| *5* | 280 (9.1%) | 313 (9.5%) | 593 (9.3%) |
| *6* | 190 (6.2%) | 219 (6.6%) | 409 (6.4%) |
| *7* | 97 (3.2%) | 108 (3.3%) | 205 (3.2%) |
| *8* | 56 (1.8%) | 83 (2.5%) | 139 (2.2%) |
| *9* | 9 (0.3%) | 37 (1.1%) | 46 (0.7%) |
| *10* | 2 (0.1%) | 9 (0.3%) | 11 (0.2%) |
| *11* | 0 (0.0%) | 1 (0.0%) | 1 (0.0%) |
| *12* | 0 (0.0%) | 2 (0.1%) | 2 (0.0%) |
| Maternal education | | | |
| *Left school at 15 or later* | 811 (26.4%) | 870 (26.4%) | 1 681 (26.4%) |
| *Left school before 14* | 2 107 (68.6%) | 2 239 (68.0%) | 4 346 (68.3%) |
| *Missing* | 152 (5.0%) | 186 (5.6%) | 338 (5.3%) |
| Paternal occupation | | | |
| *I & II (professional/managerial* | 624 (20.3%) | 612 (18.6%) | 1 236 (19.4%) |
| *IIINM (skilled nonmanual)* | 295 (9.6%) | 323 (9.8%) | 618 (9.7%) |
| *IIIM (skilled manual)* | 1 425 (46.4%) | 1 557 (47.3%) | 2 982 (46.9%) |
| *IV & V (semi-unskilled)* | 568 (18.5%) | 610 (18.5%) | 1 178 (18.5%) |
| *Missing* | 158 (5.1%) | 193 (5.9%) | 351 (5.5%) |
| Education level at 23 | | | |
| *Passed A levels* | 707 (23.0%) | 728 (22.1%) | 1 435 (22.5%) |
| *Passed O levels* | 1 021 (33.3%) | 1 319 (40.0%) | 2 340 (36.8%) |
| *No qualifications* | 925 (30.1%) | 860 (26.1%) | 1 785 (28.0%) |
| *Missing* | 417 (13.6%) | 388 (11.8%) | 805 (12.6%) |
| Income at 23 | | | |
| *Q1 - Low income* | 462 (15.0%) | 805 (24.4%) | 1 267 (19.9%) |
| *Q2* | 550 (17.9%) | 794 (24.1%) | 1 344 (21.1%) |
| *Q3* | 709 (23.1%) | 657 (19.9%) | 1 366 (21.5%) |
| *Q4 - High income* | 777 (25.3%) | 563 (17.1%) | 1 340 (21.1%) |
| *Missing* | 572 (18.6%) | 476 (14.4%) | 1 048 (16.5%) |

*(continued)*

Table 21. continued

| Variables | Men | Women | Total |
|---|---|---|---|
| Household tenure at 33 | | | |
| *Owner* | 2 130 (69.4%) | 2 361 (71.7%) | 4 491 (70.6%) |
| *Renter* | 341 (11.1%) | 463 (14.1%) | 804 (12.6%) |
| *Rent free, goes with job, equity sharer* | 23 (0.7%) | 37 (1.1%) | 60 (0.9%) |
| *Missing* | 576 (18.8%) | 434 (13.2%) | 1 010 (15.9%) |
| Social-security benefits at 33 | | | |
| *No* | 2 594 (84.5%) | 2 766 (83.9%) | 5 360 (84.2%) |
| *Yes* | 137 (4.5%) | 245 (7.4%) | 382 (6.0%) |
| *Missing* | 339 (11.0%) | 284 (8.6%) | 623 (9.8%) |
| Mortgage or rent arrears at 33 | | | |
| *Never been 2/+ month behind* | 2 579 (84.0%) | 2 818 (85.5%) | 5 397 (84.8%) |
| *Yes ever been 2/+ month behind* | 143 (4.7%) | 189 (5.7%) | 332 (5.2%) |
| *Missing* | 348 (11.3%) | 288 (8.7%) | 636 (10.0%) |
| Occupation at 33 | | | |
| *Non-manual* | 1 453 (47.3%) | 2 060 (62.5%) | 3 513 (55.2%) |
| *Manual* | 1 152 (37.5%) | 759 (23.0%) | 1 911 (30.0%) |
| *Missing* | 465 (15.1%) | 476 (14.4%) | 941 (14.8%) |
| In couple at 33 | | | |
| *Couple* | 2 204 (71.8%) | 2 474 (75.1%) | 4 678 (73.5%) |
| *Single* | 376 (12.2%) | 273 (8.3%) | 649 (10.2%) |
| *Divorced or widowed* | 140 (4.6%) | 250 (7.6%) | 390 (6.1%) |
| *Missing* | 350 (11.4%) | 298 (9.0%) | 648 (10.2%) |
| Smoking status at 33 | | | |
| *Non smoker* | 1 388 (45.2%) | 1 562 (47.4%) | 2 950 (46.3%) |
| *Former smoker* | 550 (17.9%) | 595 (18.1%) | 1 145 (18.0%) |
| *Current smoker* | 791 (25.8%) | 859 (26.1%) | 1 650 (25.9%) |
| *Missing* | 341 (11.1%) | 279 (8.5%) | 620 (9.7%) |
| Alcohol consumption at 33 | | | |
| *Moderate* | 1 984 (64.6%) | 1 758 (53.4%) | 3 742 (58.8%) |
| *Abstainers* | 476 (15.5%) | 1 105 (33.5%) | 1 581 (24.8%) |
| *Heavy drinkers* | 286 (9.3%) | 164 (5.0%) | 450 (7.1%) |
| *Missing* | 324 (10.6%) | 268 (8.1%) | 592 (9.3%) |
| Physical activity at 33 | | | |
| *Physically active* | 1 932 (62.9%) | 2 135 (64.8%) | 4 067 (63.9%) |
| *Moderately active* | 199 (6.5%) | 168 (5.1%) | 367 (5.8%) |
| *Inactive* | 84 (2.7%) | 88 (2.7%) | 172 (2.7%) |
| *Missing* | 855 (27.9%) | 904 (27.4%) | 1 759 (27.6%) |
| BMI at 33 | | | |
| *Normal* | 1 352 (44.0%) | 1 943 (59.0%) | 3 295 (51.8%) |
| *Overweight* | 1 047 (34.1%) | 695 (21.1%) | 1 742 (27.4%) |
| *Obese* | 261 (8.5%) | 280 (8.5%) | 541 (8.5%) |
| *Missing* | 410 (13.4%) | 377 (11.4%) | 787 (12.4%) |

Table 22. Bivariate statistics on imputed data for men and women

| | Men (n=3070) | | Women (n=3295) | |
|---|---|---|---|---|
| Variables | ß (CI 95%) | p | ß (CI 95%) | p |
| Allostatic load score at 44 | -0.07 (-0.08 - -0.05) | <0.001 | -0.09 (-0.10 - -0.07) | <0.001 |
| Maternal education | | | | |
| *Left school at 15 or later* | 0 | | 0 | |
| *Left school before 14* | -0.16 (-0.24 - -0.08) | <0.001 | -0.17 (-0.25 - -0.09) | <0.001 |
| Paternal occupation | | | | |
| *I & II (professional/managerial* | 0 | | 0 | |
| *IIINM (skilled nonmanual)* | -0.10 (-0.24 - 0.04) | 0.150 | 0.03 (-0.10 - 0.17) | 0.617 |
| *IIIM (skilled manual)* | -0.18 (-0.27 - -0.08) | <0.001 | -0.20 (-0.29 - -0.11) | <0.001 |
| *IV & V (semi-unskilled)* | -0.21 (-0.32 - -0.10) | <0.001 | -0.30 (-0.41 - -0.19) | <0.001 |
| Education level at 23 | | | | |
| *Passed A levels* | 0 | | 0 | |
| *Passed O levels* | -0.13 (-0.22 - -0.03) | 0.008 | -0.14 (-0.23 - -0.05) | 0.002 |
| *No qualifications* | -0.31 (-0.41 - -0.21) | <0.001 | -0.41 (-0.51 - -0.31) | <0.001 |
| Income at 23 | | | | |
| *Q1 - Low income* | 0 | | 0 | |
| *Q2* | 0.14 (0.02 - 0.27) | 0.022 | 0.19 (0.09 - 0.28) | <0.001 |
| *Q3* | 0.14 (0.03 - 0.26) | 0.016 | 0.26 (0.15 - 0.36) | <0.001 |
| *Q4 - High income* | 0.17 (0.06 - 0.28) | 0.002 | 0.44 (0.34 - 0.55) | <0.001 |
| Household tenure at 33 | | | | |
| *Owner occupiers* | 0 | | 0 | |
| *Renters/other* | -0.30 (-0.41 - -0.18) | <0.001 | -0.46 (-0.56 - -0.36) | <0.001 |
| Social-security benefits at 33 | | | | |
| *No* | 0 | | 0 | |
| *Yes* | -0.47 (-0.66 - -0.29) | <0.001 | -0.49 (-0.62 - -0.36) | <0.001 |
| Mortgage or rent arrears at 33 | | | | |
| *Never been 2/+ month behind* | 0 | | 0 | |
| *Yes ever been 2/+ month behind* | -0.40 (-0.56 - -0.23) | <0.001 | -0.44 (-0.59 - -0.29) | <0.001 |
| Occupation at 33 | | | | |
| *Non-manual* | 0 | | 0 | |
| *Manual* | -0.18 (-0.25 - -0.10) | <0.001 | -0.24 (-0.32 - -0.16) | <0.001 |
| In couple at 33 | | | | |
| *Couple* | 0 | | 0 | |
| *Single* | -0.14 (-0.25 - -0.02) | 0.017 | -0.15 (-0.28 - -0.02) | 0.022 |
| *Divorced or widowed* | -0.22 (-0.40 - -0.04) | 0.017 | -0.29 (-0.42 - -0.16) | <0.001 |
| Smoking status at 33 | | | | |
| *Non smoker* | 0 | | 0 | |
| *Former smoker* | -0.03 (-0.13 - 0.07) | 0.566 | -0.05 (-0.14 - 0.04) | 0.267 |
| *Current smoker* | -0.23 (-0.32 - -0.15) | <0.001 | -0.36 (-0.44 - -0.28) | <0.001 |

*(continued)*

Table 22. continued

| | Men (n=3070) | | Women (n=3295) | |
|---|---|---|---|---|
| Variables | ß (CI 95%) | p | ß (CI 95%) | p |
| Alcohol consumption at 33 | | | | |
| *Moderate* | 0 | | 0 | |
| *Abstainers* | -0.12 (-0.22 - -0.01) | 0.029 | -0.20 (-0.27 - -0.12) | <0.001 |
| *Heavy drinkers* | -0.27 (-0.39 - -0.15) | <0.001 | -0.05 (-0.21 - 0.11) | 0.564 |
| Physical activity at 33 | | | | |
| *Physically active* | 0 | | 0 | |
| *Moderately active* | -0.05 (-0.21 - 0.10) | 0.494 | -0.07 (-0.23 - 0.08) | 0.357 |
| *Inactive* | -0.07 (-0.30 - 0.17) | 0.564 | -0.09 (-0.30 - 0.12) | 0.381 |
| BMI at 33 | | | | |
| *Normal* | 0 | | 0 | |
| *Overweight* | -0.09 (-0.17 - -0.01) | 0.034 | -0.12 (-0.21 - -0.03) | 0.007 |
| *Obese* | -0.25 (-0.39 - -0.12) | <0.001 | -0.50 (-0.62 - -0.38) | <0.001 |

Table 23. Life course multivariate linear regression between AL and standardized subjective health index Zscores using data from multiple imputation : men (n=3070)

| | M1: AL | | M2: Socioeconomic factors at birth | | M3: Socioeconomic factors at 23y | | M4: Socioeconomic and behavioural factors at 33y | |
|---|---|---|---|---|---|---|---|---|
| Variables | ß (CI 95%) | p | ß (CI 95%) | p | ß (CI 95%) | p | ß (CI 95%) | p |
| Allostatic load score at 44 | -0.07 (-0.08 - -0.05) | <0.001 | -0.06 (-0.08 - -0.04) | <0.001 | -0.06 (-0.07 - -0.04) | <0.001 | -0.04 (-0.06 - -0.02) | <0.001 |
| Maternal education | | | | | | | | |
| *Left school at 15 or later* | | | 0 | | 0 | | 0 | |
| *Left school before 14* | | | -0.10 (-0.18 - -0.01) | 0.034 | -0.06 (-0.15 - 0.03) | 0.220 | -0.05 (-0.14 - 0.04) | 0.279 |
| Paternal occupation | | | | | | | | |
| *I & II (professional/managerial* | | | 0 | | 0 | | 0 | |
| *IIINM (skilled nonmanual)* | | | -0.07 (-0.21 - 0.07) | 0.306 | -0.05 (-0.19 - 0.08) | 0.437 | -0.05 (-0.19 - 0.09) | 0.455 |
| *IIIM (skilled manual)* | | | -0.10 (-0.20 - -0.01) | 0.039 | -0.06 (-0.16 - 0.04) | 0.256 | -0.06 (-0.16 - 0.05) | 0.273 |
| *IV & V (semi-unskilled)* | | | -0.12 (-0.24 - 0.00) | 0.046 | -0.05 (-0.18 - 0.08) | 0.450 | -0.03 (-0.16 - 0.10) | 0.634 |
| Education level at 23 | | | | | | | | |
| *Passed A levels* | | | | | 0 | | 0 | |
| *Passed O levels* | | | | | -0.08 (-0.18 - 0.02) | 0.119 | -0.05 (-0.15 - 0.06) | 0.369 |
| *No qualifications* | | | | | -0.22 (-0.32 - -0.11) | <0.001 | -0.14 (-0.27 - -0.02) | 0.025 |
| Income at 23 | | | | | | | | |
| *Q1 - Low income* | | | | | 0 | | 0 | |
| *Q2* | | | | | 0.11 (-0.01 - 0.23) | 0.080 | 0.05 (-0.07 - 0.17) | 0.396 |
| *Q3* | | | | | 0.10 (-0.01 - 0.21) | 0.078 | 0.03 (-0.09 - 0.14) | 0.645 |
| *Q4 - High income* | | | | | 0.13 (0.02 - 0.24) | 0.020 | 0.06 (-0.06 - 0.17) | 0.339 |
| Household tenure at 33 | | | | | | | | |
| *Owner occupiers* | | | | | | | 0 | |
| *Renters/other* | | | | | | | -0.14 (-0.26 - -0.02) | 0.019 |

*(continued)*

Table 23. continued

| | M1: AL | | M2: Socioeconomic factors at birth | | M3: Socioeconomic factors at 23y | | M4: Socioeconomic and behavioural factors at 33y | |
|---|---|---|---|---|---|---|---|---|
| | ß (CI 95%) | p | ß (CI 95%) | p | ß (CI 95%) | p | ß (CI 95%) | p |
| **Social-security benefits at 33** | | | | | | | | |
| *No* | | | | | | | 0 | |
| *Yes* | | | | | | | -0.30 (-0.49 - -0.10) | 0.003 |
| **Mortgage or rent arrears at 33** | | | | | | | | |
| *Never been 2/+ month behind* | | | | | | | 0 | |
| *Yes ever been 2/+ month behind* | | | | | | | -0.23 (-0.40 - -0.06) | 0.007 |
| **Occupation at 33** | | | | | | | | |
| *Non-manual* | | | | | | | 0 | |
| *Manual* | | | | | | | -0.01 (-0.10 - 0.09) | 0.912 |
| **In couple at 33** | | | | | | | | |
| *Couple* | | | | | | | 0 | |
| *Single* | | | | | | | -0.10 (-0.21 - 0.02) | 0.092 |
| *Divorced or widowed* | | | | | | | -0.13 (-0.31 - 0.05) | 0.151 |
| **Smoking status at 33** | | | | | | | | |
| *Non smoker* | | | | | | | 0 | |
| *Former smoker* | | | | | | | 0.00 (-0.10 - 0.10) | 0.973 |
| *Current smoker* | | | | | | | -0.10 (-0.19 - -0.01) | 0.034 |
| **Alcohol consumption at 33** | | | | | | | | |
| *Moderate* | | | | | | | 0 | |
| *Abstainers* | | | | | | | -0.04 (-0.15 - 0.06) | 0.436 |
| *Heavy drinkers* | | | | | | | -0.20 (-0.32 - -0.08) | 0.002 |

*(continued)*

Table 23. continued

| | M1: AL | | M2: Socioeconomic factors at birth | | M3: Socioeconomic factors at 23y | | M4: Socioeconomic and behavioural factors at 33y | |
|---|---|---|---|---|---|---|---|---|
| | ß (CI 95%) | p | ß (CI 95%) | p | ß (CI 95%) | p | ß (CI 95%) | p |
| **Physical activity at 33** | | | | | | | | |
| *Physically active* | | | | | | | 0 | |
| *Moderately active* | | | | | | | -0.04 (-0.19 - 0.10) | 0.549 |
| *Inactive* | | | | | | | -0.07 (-0.30 - 0.16) | 0.562 |
| **BMI at 33** | | | | | | | | |
| *Normal* | | | | | | | 0 | |
| *Overweight* | | | | | | | -0.04 (-0.12 - 0.04) | 0.275 |
| *Obese* | | | | | | | -0.15 (-0.29 - -0.02) | 0.026 |

Table 24. Life course multivariate linear regression between AL and standardized subjective health index Zscores using data from multiple imputation : women (n=3295)

| | Model 1: AL | | Model 2: Socioeconomic factors at birth | | Model 3: Socioeconomic factors at 23y | | Model 4: Socioeconomic factors and behavioural at 33y | |
|---|---|---|---|---|---|---|---|---|
| Variables | ß (CI 95%) | p | ß (CI 95%) | p | ß (CI 95%) | p | ß (CI 95%) | p |
| **Allostatic load score at 44** | -0.09 (-0.10 - -0.07) | <0.001 | -0.08 (-0.10 - -0.07) | <0.001 | -0.07 (-0.09 - -0.06) | <0.001 | -0.05 (-0.07 - -0.04) | <0.001 |
| **Maternal education** | | | | | | | | |
| *Left school at 15 or later* | | | 0 | | 0 | | 0 | |
| *Left school before 14* | | | -0.07 (-0.15 - 0.02) | 0.118 | -0.01 (-0.10 - 0.07) | 0.775 | -0.02 (-0.10 - 0.07) | 0.686 |
| **Paternal occupation** | | | | | | | | |
| *I & II (professional/managerial* | | | 0 | | 0 | | 0 | |
| *IIINM (skilled nonmanual)* | | | 0.09 (-0.05 - 0.22) | 0.204 | 0.10 (-0.03 - 0.23) | 0.147 | 0.11 (-0.03 - 0.24) | 0.113 |
| *IIIM (skilled manual)* | | | -0.11 (-0.21 - -0.01) | 0.026 | -0.06 (-0.16 - 0.04) | 0.212 | -0.03 (-0.13 - 0.07) | 0.520 |
| *IV & V (semi-unskilled)* | | | -0.20 (-0.31 - -0.08) | 0.001 | -0.11 (-0.23 - 0.01) | 0.072 | -0.06 (-0.18 - 0.06) | 0.314 |
| **Education level at 23** | | | | | | | | |
| *Passed A levels* | | | | | 0 | | 0 | |
| *Passed O levels* | | | | | -0.05 (-0.14 - 0.05) | 0.318 | 0.00 (-0.09 - 0.09) | 0.976 |
| *No qualifications* | | | | | -0.22 (-0.33 - -0.11) | <0.001 | -0.08 (-0.20 - 0.03) | 0.166 |
| **Income at 23** | | | | | | | | |
| *Q1 - Low income* | | | | | 0 | | 0 | |
| *Q2* | | | | | 0.14 (0.04 - 0.23) | 0.005 | 0.08 (-0.01 - 0.18) | 0.091 |
| *Q3* | | | | | 0.16 (0.06 - 0.27) | 0.002 | 0.07 (-0.03 - 0.18) | 0.171 |
| *Q4 - High income* | | | | | 0.33 (0.22 - 0.44) | <0.001 | 0.23 (0.12 - 0.33) | <0.001 |
| **Household tenure at 33** | | | | | | | | |
| *Owner occupiers* | | | | | | | 0 | |
| *Renters/other* | | | | | | | -0.16 (-0.26 - -0.05) | 0.004 |
| **Social-security benefits at 33** | | | | | | | | |
| *No* | | | | | | | 0 | |
| *Yes* | | | | | | | -0.21 (-0.35 - -0.08) | 0.002 |

*(continued)*

Table 24. continued

| | Model 1: AL | | Model 2: Socioeconomic factors at birth | | Model 3: Socioeconomic factors at 23y | | Model 4: Socioeconomic factors and behavioural at 33y | |
|---|---|---|---|---|---|---|---|---|
| | ß (CI 95%) | p | ß (CI 95%) | p | ß (CI 95%) | p | ß (CI 95%) | p |
| **Mortgage or rent arrears at 33** | | | | | | | | |
| *Never been 2/+ month behind* | | | | | | | 0 | |
| *Yes, ever been 2/+ month behind* | | | | | | | -0.21 (-0.36 - -0.06) | 0.008 |
| **Occupation at 33** | | | | | | | | |
| *Non-manual* | | | | | | | 0 | |
| *Manual* | | | | | | | -0.03 (-0.11 - 0.06) | 0.559 |
| **In couple at 33** | | | | | | | | |
| *Couple* | | | | | | | 0 | |
| *Single* | | | | | | | -0.11 (-0.24 - 0.02) | 0.088 |
| *Divorced or widowed* | | | | | | | -0.10 (-0.23 - 0.03) | 0.141 |
| **Smoking status at 33** | | | | | | | | |
| *Non smoker* | | | | | | | 0 | |
| *Former smoker* | | | | | | | -0.03 (-0.12 - 0.06) | 0.541 |
| *Current smoker* | | | | | | | -0.18 (-0.27 - -0.10) | <0.001 |
| **Alcohol consumption at 33** | | | | | | | | |
| *Moderate* | | | | | | | 0 | |
| *Abstainers* | | | | | | | -0.12 (-0.19 - -0.04) | 0.002 |
| *Heavy drinkers* | | | | | | | -0.02 (-0.18 - 0.14) | 0.802 |
| **Physical activity at 33** | | | | | | | | |
| *Physically active* | | | | | | | 0 | |
| *Moderately active* | | | | | | | -0.02 (-0.17 - 0.12) | 0.769 |
| *Inactive* | | | | | | | 0.02 (-0.18 - 0.22) | 0.823 |
| **BMI at 33** | | | | | | | | |
| *Normal* | | | | | | | 0 | |
| *Overweight* | | | | | | | -0.05 (-0.13 - 0.04) | 0.293 |
| *Obese* | | | | | | | -0.29 (-0.41 - -0.17) | <0.001 |

## 4. Discussion

Higher scores of allostatic load at 44 years were found to be associated with worse subjective health six years later in a large prospective cohort, after taking into account classic confounders. This association was independent of socioeconomic variables across the life course, adult health behaviours and BMI. These findings add some evidence to the hypothesis of a plausible biological underlying mechanism between the social environment and later overall health, via stress response systems. We deduce that AL may represent a physiological outcome of embodiment processes, contributing to a better understanding of susceptibility to poorer health and the production of social gradients in health.

There are several limitations in this study. First, since these analyses where performed using a birth cohort, an important weakness is related to attrition and selection bias. However, the surviving cohort remains broadly representative of the initial cohort key childhood and adult characteristics (Atherton et al., 2008). We additionally imputed the data for confounding variables taking the missing at random assumption to preserve important aspects of the distribution, variability, and relationships between variables. Second, we cannot conclude that AL provides an added value for predicting later subjective health, since to answer that question, we would need to adjust the model at baseline for subjective health measures. Unfortunately, our study lacks of the same instruments (SF-36, MOS sleep scale) we used for constructing the subjective health variable at previous sweeps. However, to address this question we decided to run a sensitivity analysis using self-rated health as an outcome at 50y, adjusted for self-rated health at 44y in the same imputed sample. Self-rated heath has the advantage of being available at both baseline and at 50 years; and it is a measure contained within the SF-36 score we used for our subjective health measure. We found that AL was independently associated with self-rated health at 50y after adjusting for self-rated health at 44y. This result reinforces the hypothesis that the association between AL and subjective health at 50y is not due to subjective health status at 44 years.

Third, our score remains limited by pragmatic issues regarding variable availability and operationalization. The biomarkers included in our AL score were derived from available data, as parameters of major regulatory systems with known or hypothesized links with stress responses. For example, our AL score lacks “primary” biomarkers and neuroendocrine

biomarkers (e.g. epinephrine and norepinephrine) (Juster et al., 2011a). Furthermore, the physiological relationship between biomarkers, and their relative importance in the physiological cascade of stress responses remains unclear (Beckie, 2012). AL operationalization continue to be a central debate around how to better approach physiological wear-and-tear. The operationalization we choose was pragmatic and it does not rigorously corresponds to the dynamic theory and definition of AL, and how it accumulates. In previous work we discussed some of the conceptual and empirical consideration regarding these questions (Delpierre et al., 2016). Several issues remain, for instance, the choice of biomarkers (DNA methylation, telomeres length, markers from -omics technologies; or larger molecules and physiological measures); or the best methodological tool to sum up these biomarkers (weighting, taking into account the dependency of each biomarker) and the measurement models more adapted (canonical correlation, recursive partitioning). Future research requires progress in the collection of biomarkers explicitly designed to assess allostatic load at multiple time points in longitudinal large representative samples (Beckie, 2012). Comparative studies are needed to better comprehend the age-related, sex/gender-related, ethnic-related differences in AL. Further research should propose and explore consistent theoretical explanations of the link between the biological mechanism, the system dynamic and the allostatic load measurement. We have previously attempted to raise and debate some of these issues (Delpierre et al., 2016) but many remain open and deserve further clarification, such as the concept of 'strain', 'cost', 'price' that have never being truly defined and that we could not incorporate in the AL operationalization. At this point, AL is capable of characterizing only a fragment of the causal path between social environment and later health. In our case, adding biomarkers to epidemiological research does not solve the 'black box' problem. We can only better 'trace' and hypothesize aspects of the biological component of the 'black box', by exploring the pathways of associations between the exposures, the biomarkers and the health outcome.

Third, we have a one-time AL measure available, which did not allow for a lifetime health trends analysis. Finally, our subjective health measure remains an ad-hoc index and its reproducibility is limited. Health is a latent variable that can be captured using different psychometric scales, as well as clinical and biological variables. We only integrated standardised and validated measures of subjective health which had already been related to later health and mortality risk. It is worth mentioning that in this study both AL and health measures are confined to a specific

social and cultural context. The subjective health measure used here is adapted to a Western population, and the questionnaires used were oriented towards a British population. The notion of well-being and psychological malaise, for instance, are confined to a particular social and cultural context (Ryff et al., 2014). Regarding AL, differences on the perception of stressful conditions may have consequences on the symptoms reported (Lock & Kaufert, 2001), and differences on the biomarkers average levels (Miyamoto et al., 2013). To think in terms of 'local biologies' will add some scientific bases when analysing the effects of environmental exposures and health outcomes (Lock & Kaufert, 2001). However, AL is structured to use the distribution of the sample in question, thus it is as local or as global as the sample allows in terms of multi-system wastage. We do believe that common underlying biological mechanisms are plausible, and these biological mechanisms can be captured using different measures according (and more adapted) to the specific social context. The possibility of comparing results from different contexts and to replicate the studies may allow us to observe if the underlying physiological responses, in particular physiological stress responses, are 'generalizable'.

Despite these limitations, our findings offer several insights with respect to previous studies. There is a growing amount of evidence that supports AL as a better predictor of morbidity and mortality (Gruenewald et al., 2006; Karlamangla et al., 2006; Seeman et al., 2001). Previous studies have concentrated their analysis on specific dimensions of health mainly using elderly population based studies, and though have a lack of prospective data concerning early life, adolescence and early adulthood circumstances. The main novelty of our study is to focus our analysis on the basis of a global effect of stress on health, using an integrative measure -that is not centered on the dichotomy absence/presence of disease- in middle aged adults that have been followed since birth. This allows us to take into account a variety of material, psychosocial, educational and life styles exposures from early life and across the life course.

We studied the link between a physiological measure and a subjective measure adjusted for a large panel of confounders which reduces the risk of a spurious link. In previous work, we investigated the socioeconomic determinants of AL, trying to disentangle the mediating pathways between early environment and AL (Barboza Solis et al., 2015). We intended to wed two major conceptual frameworks: AL theory –conceptualized in the stress and neuroendocrinology research- and ecosocial theory –conceptualize within the social epidemiology and health inequalities research- (Delpierre et al., 2016). We used a birth cohort

study to capture the physiological impact of embodiment over the life course using an AL index. We hypothesised that the exposure to stressful and challenging events may be embodied, leaving a physiological stamp, partially captured by AL. Here we show that AL predicts subsequent health status by conceptualizing health as a measure beyond the classic definition of pathology, taking into account self-reported measures that could capture health capacities and resources, rather than clinically diagnosed categories of pathology or mortality.

These findings may add a conceptual validity to the hypothesis that social challenges become biologically embedded. The results showed the important role of socioeconomic factors across the life course for both men and women, the most important variables affecting subjective health being behaviours and material circumstances at 33y (model 4). Material circumstances have previously been linked via low socioeconomic position, to different measures of health status, through exposures related to bad housing, work conditions, neighborhood characteristics, etc. (toxins, allergens, overcrowding) (Galobardes et al., 2006a). In terms of health behaviours, smoking, alcohol and BMI had the strongest effects on subjective health. Concerning BMI our findings are consistent with previous literature were BMI was found to correlate with well-being and health related quality of life (Ford et al., 2001). Obese individuals are more likely to suffer from low self-esteem, depression (Luppino et al., 2010) and discrimination with a well-established link between BMI and metabolic status, morbidity and mortality (Berrington de Gonzalez et al., 2010; Calle et al., 1999; Ferrucci & Alley, 2007).

## 5. Conclusion.

In this study we show evidence of a link between physiological wear-and-tear, as measured by allostatic load, and health status, captured by latent variable of subjective health. These findings add some evidence to the hypothesis of a plausible biological underlying mechanism between the social environment and later overall health, *via* stress response systems. Allostatic load may represent a physiological outcome of embodiment processes contributing to a better understanding of early disease processes and social gradients in health. Hence, using a physiological index to grasp how the environment in which we live can 'get under the skin' leading to poor health is of great interest in public health research.

# PART V

# DISCUSSION

*“Se lo comenté a don José Coronel Urtecho: en este libro que estoy escribiendo, al revés y al derecho, a luz y a trasluz, se mire como se mire, se me notan a simple vista mis broncas y mis amores.*
*Y a orillas del río San Juan, el viejo poeta me dijo que a los fanáticos de la objetividad no hay que hacerles ni puto caso:*
*—No te preocupés —me dijo—. Así debe ser. Los que hacen de la objetividad una religión, mienten. Ellos no quieren ser objetivos, mentira: quieren ser objetos, para salvarse del dolor humano.”*

*« J'en fis le commentaire à José Coronel Urtecho : dans le livre que j'écris, à l'endroit ou à l'envers, à la lumière du jour ou à contre-jour, qu'importe la façon de le regarder, se lisent clairement mes colères et mes amours.*
*Et à l'embouchure du fleuve San Juan, le vieux poète me dit que ces fanatiques de l'objectivité, il ne faut pas en faire le moindre cas :*
*Ne t'en fais pas, me dit-il. C'est ainsi que ça doit être. Ceux qui font une religion de l'objectivité mentent. Mensonge, ils ne veulent pas être objectifs : ils veulent être des objets pour se sauver de la douleur humaine. »*

*“I made the comment to José Coronel Urtecho: In this book I'm writing to the right or upside down, in daylight or against the light, no matter how you look at it, is clearly read my anger and my passion.*
*And the mouth of the river San Juan, the old poet told me that we had to ignore the fanatics of objectivity:*
*Those who make objectivity a religion are liars. They don’t want to be objective, it's a lie: they want to be objects, to save themselves from human pain.”*

Celebración de la subjetividad
Eduardo Galeano
El libro de los abrazos

# Résumé – Partie V

D'après nos résultats, nous pouvons conclure que la charge allostatique (CA) est en effet déterminée socialement. Nous avons également montré un lien entre la CA et la santé ultérieure, capturé par une variable latente.

Des analyses complémentaires ont confirmé ces analyses, en attirant l'attention sur les mécanismes sociaux impliqués. Les conditions psychosociales adverses durant l'enfance peuvent ainsi «pénétrer sous la peau» via les comportements de santé, l'éducation et le patrimoine à l'âge adulte. En outre pour les femmes un malaise psychologique à l'âge adulte a également joué un rôle important de médiation entre les expériences psychosociales adverses précoces et la CA.

Notre analyse sur le lien entre la position sociale des parents et la CA plus tard a confirmé l'importance des voies « indirectes », montrant qu'une éducation maternelle moins élevée et une profession manuelle du père étaient associées à une CA supérieure à 44 ans, principalement par l'intermédiaire de la voie l'éducationnelle, matérielle / financière, et des comportements de santé chez les hommes et les femmes.

Enfin, le lien trouvé entre la CA et une mesure multidimensionnelle de la santé, permet de mieux discuter l'hypothèse d'un mécanisme sous-jacent biologique global entre l'environnement social et de la santé ultérieure.

Dans l'ensemble, nos résultats nous ont permis de mieux comprendre que les expositions sociales défavorables précoces dès le début de la vie peuvent avoir un impact physiologique menant potentiellement à une usure multi-systèmes par deux mécanismes principaux. Le premier pourrait influencer la santé influençant la santé «indirectement» via des mécanismes socio-économiques, notamment liées aux facteurs psychosociaux, matériels / financier, éducatifs et les comportements à risque. Le second, «directement», - résultant d'une adversité (ou exposition adverse) au cours d'une période sensible du développement- ayant un impact durable sur le développement cérébral et physiologique.

Peu d'études ont étudié les déterminants sociaux de la charge allostatique, et son utilisation en tant que mesure d'incorporation biologique au cours de la vie est encore rare dans la littérature. Nous considérons notre étude importante puisque nous avons exploré certains processus sous-jacents de cette incorporation. La capacité de mesurer la façon dont les gens s'adaptent et font face à leur environnement avant le développement de la maladie offre de nombreuses possibilités en termes d'interventions de santé publique, tant au niveau populationnel (en investissant dans l'enfance ou dans l'environnement social), comme au niveau individuel (par la prévention des maladies par une meilleure compréhension des comportements de santé et par des traitements, pas forcément médicamenteux).

Néanmoins, de nombreuses questions de recherche demeurent. Promouvoir la collection de marqueurs biologiques dans des grandes études épidémiologiques représentatives de la population est un enjeu crucial pour continuer à explorer ce sujet. La possibilité de comparer avec d'autres études et de répliquer nos résultats dans des contextes culturels différents est indispensable pour nous permettre d'observer si les réponses physiologiques à des expositions psychosociales adverses sont «universelles».

# Chapter I

# General discussion of our results

In this chapter we will conclude with a general discussion of the contributions of this work.

In **section 1** we will summarize the main results of our three research axes.

In **section 2** we will recapitulate the main pathways proposed between the social and the biological.

In **section 3** we will summarise the evidence already mentioned in the Introduction section, confronting it to the nine Bradford Hill's criteria of causality.

## 1. Synthesis of the results

In the section Remaining research challenges, we underlined two main conditions that had to be fulfilled for considering allostatic load as a useful measure of the embodiment of social conditions: allostatic load should be socially patterned and allostatic load should be a good predictor of later health. Given our results we can conclude that AL is indeed socially determined; and we additionally showed evidence of a link between AL and health status, captured by a latent variable of subjective health.

Supplementary analyses confirmed the previous two premises, drawing attention on the social pathways. The results showed the important role of particular 'indirect' social mechanisms. Adverse psychosocial conditions may 'get under the skin' *via* adult health behaviours, education and wealth. For women, psychological malaise in adulthood also played an important role mediating early adverse psychosocial experiences and allostatic load.

Our analysis on parental SEP and later allostatic load confirmed the importance of the 'indirect' effect, showing that lower maternal education and manual paternal occupation were associated with a higher allostatic load at 44 years, mainly *via* the educational, material/financial, and health behaviours pathways for both men and women.

Finally, the link found between AL and a multidimensional measure of health, add some evidence to the hypothesis of a plausible biological underlying mechanism between the social environment and later health.

Overall, our results allowed us to better understand that adverse social exposures early in life could impact later physiological wear-and-tear by two main mechanisms.

The first influencing health '**indirectly**' -through socioeconomic circumstances, psychosocial factors and health behaviours accumulating over the life course-. In that sense, groups of individuals exposed to adverse social conditions (psychosocial or material) early in life may carry the cost across their life, putting them on different life trajectories increasing their odds of subsequent exposures related to their own future social position. Our results showed for example that children with psychosocial adversities during childhood had, on average, lower levels of education and were more prone to adopt risky health behaviours. Similarly, we have shown that children who were born in disadvantaged socioeconomic households were more likely to be obese adults and to have a lower level of education. This reinforces the idea that health behaviours may be a consequence of psychosocial and socioeconomic adversity; rather than an individual's 'free' choice. Therefore, at the populations level, differences in health behaviours are indeed health 'inequities' rather than health 'inequalities'.

Since our results were not completely explained by the indirect effects, the second mechanism, relates to the potential '**direct**' biological effect -resulting from an insult during a sensitive period- influencing health and having a lasting impact on brain and physiological development.

These results additionally suggest that AL could be a useful epidemiologic instrument for studying the environmental impact of life adversity on health, allowing the early identification, monitoring and surveillance of social determinants of health.

However, numerous limitations and challenges remain. In the next chapters (II and III) we will address some of them, which we believe are important to take into account for further research directions.

## 2. Theoretical pathways between the social and the biological

From our research results we can conclude that allostatic load could represent a useful measure partially capturing the biological processes of embodiment. We recognize that the index we used is limited, by biomarker availability as well as methodological and theoretical issues (that we will address later in Part V, Chapter II, section 1). However, we believe that the conceptual framework of physiological wear-and-tear across the life course may allow us to

represent the biological strain our bodies deal with according to the environment in which we grow-up.

Our findings allowed us to identify several theoretical pathways by which the social can become biologically embedded. We provided empirical evidence regarding the mediating pathways between early life and allostatic load in mid-life, analysing both psychosocial and socioeconomic determinants. This work has the potential to make a contribution to the literature addressing the multiple mechanisms through which early life may become embodied. The use of a life course framework, the concept of ACE, the separation of SEP in maternal education and paternal occupation, and the study of the link between AL and later health; provides further support to the growing literature on the link between the social environment and physiological burden.

Here we will summarize the hypothesized pathways by which early social environment can become embodied all over the life course:

i. Health behaviours pathway: damaging different organs and physiological function;
ii. Socioeconomic and materialist pathway: through chemical and biological exposures related to work, neighbourhood and housing conditions;
iii. Psychosocial pathway: 'directly', through a biological alteration of the stress responses systems; and 'indirectly', through health behaviours (e.g. by increasing the odds of adopting risky behaviours).
iv. Educational/cultural pathway: through cognitive development, psychosocial factors (e.g. social support, social network), behaviours (related with habitus, cultural customs) and since it relates with future job opportunities (therefore work hazards).

To separate these potential pathways remains an attempt at theoretical clarification. This is an important step, on one hand, for illustrating the different hypothesis we are testing. On the other hand, it is critical for a better operationalization of the variables, measurements, and to elucidate the methodological challenges of the research question. For instance, not having a school degree will not *per se* affect our health, is what it comes associated with the 'bad feelings' (psychosocial exposures) due to social standing, social opportunities (material resources allowing access to social security for instance), social relationships (habitus), and adverse exposures socially patterned (occupational hazards). Viruses and bacteria will have a

direct effect on our health, as well as the psychosocial effect related with the emotions generated by our social standing. Hence the psychosocial pathway, which relates with a 'direct' effect throughout stress responses systems, but can also affect health by a 'indirect' effect by increasing the odds of an individual exposed to psychosocial adversities early in life to adopt risky behaviours.

We used in our research often the terms '**direct'** and '**indirect'** when referring to these different pathways. This is somewhat confusing, since at the end, all the mechanisms will potentially impact health. For us the main difference relates to timing. The so called 'indirect effects' corresponds to a '**later effect**' on health, from exposures occurring after a sensitive period of life. The so called 'direct effects' may correspond to an '**early effect**' during a sensitive period of life that can have lifelong effects on health.

Regarding the 'early effects', some exposures during sensitive periods could alter physiological systems (e.g. hypothalamic-pituitary-adrenal axis) *via* stress responses, leading to modifications on brain structures (e.g. cognitive ability and cognitive functions). Other biological mechanisms (not related with stress responses) are also plausible, however we did not explore them in this work.

Research on stress impacting human physiology may appear 'deterministic'. However, it is important to clarify that the organism's plasticity is not fixed. On the contrary, adaptations are possible all across the life course, and the discussion on how to intervene in groups of individuals with an increased susceptibility during specific phases of development and in specific social spheres is essential. We have to keep in mind that the extent of the biological modification caused by stress exposures will depend on the severity, the length and the timing of the exposure. Childhood is mainly a window of opportunity to protect well-being and to promote current and future health.

Regarding these pathways, numerous questions remain. For instance, how to measure stress? How should we measure psychosocial exposures? Is socioeconomic disadvantage at the same level of adversity as maltreatment or social isolation? Do all the psychosocial exposures have the same impact on health? What types of exposures are more important regarding health (psychosocial, material, and educational)? How to measure and test resilience? How to

promote the best interventions? Different interventions will be needed to tackle each adverse childhood experience?

## 3. A plausible causal mechanism between allostatic load and health?

Our intention with this section was to summarize and classify some of the evidence concerning AL. According to the review of the literature presented in Introduction Part I, and according to our findings, we will confront the 'causal' mechanisms using the Bradford Hill's 9 criteria. We want to clarify upfront that our objective was not to conclude to the existence of a causal mechanism between allostatic load and health, mainly because allostatic load is not an exposure *per se*, but rather a biological outcome. However it is interesting to use these criteria to classify and to summarize the evidence of a physiological composite measure that may be adapted when analysing a dimension of health in epidemiological studies. Indeed, if allostatic load is a biological consequence of embodiment, it is not surprising that it will be linked with later health.

i. ***Demonstration of a strong association between the causative agent and the outcome.*** A large amount of evidence has shown a link between AL and numerous health outcomes (Beckie, 2012). We additionally showed with our work a link between AL and a global measure of subjective health.

ii. ***Consistency of findings across research sites and methods.*** Some studies across western populations (USA, UK) suggested the reproducibility of the results, and in other non-western countries like Taiwan (Hwang et al., 2014) or in a Porto Rican population in the USA (Mattei et al., 2010). However further research is needed.

iii. ***Specificity.*** As for other measures of stress, AL is not designed to be specific, but rather to show an overall effect and influence on health. For that reason it is not surprising that several studies have shown links between AL and numerous, but more importantly, diverse health outcomes (such as cardiovascular diseases, but also negative emotional responses, or subjective health) (Barboza Solís et al., 2016; Dich et al., 2014; Seeman et al., 1997). However, the conceptual framework of AL is constructed on the basis of a global effect of stress on health, *via* multiple physiological mechanisms and by impacting several brain structures.

iv. ***Temporal sequence.*** Using population-based prospective studies we have an idea of the temporality of the exposures. In our specific case, we know that AL precedes the health

measure. However, we cannot completely rule-out the possibility of an inverse relationship; and to include this issue in further research, repeated measures of biological data is needed. Because one variable is measured before another does not guarantee temporal sequence.

v. ***Biological gradient.*** The dose-response relationship between AL and later health outcomes is often graded. The higher the AL score, the higher is the risk of having the disease (Seeman, et al., 1997). In our case, the higher the AL was, the lower the health index was. Other studies have suggested that elevated AL on psychiatric disorders bring more evidence to the dose-response relationship (Glover, 2006).

vi. ***Biological plausibility.*** Studies from the neuroscience and physiology in animal models as well as in humans (Part I), integrated with the epidemiological research have increased the biological plausibility of the social-to-biological transitions. The specific mechanisms by which stress can 'get under the skin' is starting to be elucidated. Stress-related physiological systems, the structural changes in the brain and involvement of epigenetic marks appear to be good candidate mechanisms for explaining this topic.

vii. ***Coherence.*** Regarding the coherence with current biological knowledge and epidemiological sources, the AL framework remains somewhat innovative concerning the current vision of the health-diseases processes.

viii. ***Experimental evidence.*** As we already mentioned in Part I, Chapter II, section 2, studies in animal models appear to be consistent with this hypothesis. For ethical reasons, it is not possible to use randomized control trials to test the effects of stress on health. However, as we mentioned in Part I, Chapter 2, section 2, some human 'natural experiments' studied within the scientific community enlighten us, for example, in the case of ACE studies on the Romanian orphanages.

ix. ***Analogous evidence.*** The effect of similar factors may be considered, ACE studies brought some similar evidence, given additional support to the hypothesis of early life effects of stress on later health.

Evidently, if AL is a result of stress responses, the conclusion of this literature is that a causal link exists between stress and health, which is already suggested in existent literature. As we already mentioned, what is not that clear is the use of a composite measure, behind a concept of physiological wear-and-tear.

Using the Bradford Hill's 9 criteria to present and summarize the evidence allows us to put our research in perspective. In fact there is still a long way to go to show a coherent use of AL from theory to method to implementation and public health usefulness.

# Chapter II
# Methodological considerations around AL and biomarkers in epidemiological studies

If allostatic load heuristics are moderately accepted in research, the operationalization is contested. Our work is subject to several methodological limitations that we will address in this chapter. We will review the limits of the AL measure, biomarker selection, ethical considerations, and the remaining questions regarding the fact that AL may not be the best measure to capture embodiment processes in the era of biomarkers research. These discussions were the object of two publications:

- Delpierre, C., Barboza-Solís, C., Castagné, R., Lang, T., Kelly-Irving, M. (2016). « Environnement social précoce, usure physiologique et état de santé à l'âge adulte : un bref état de l'art ». Bulletin Epidémiologique Hebdomadaire.
- Delpierre, C., Barboza Solis, C., Darnaudery, M., Bartley, M., Blane, D., Kelly-Irving, M. (2015). "Allostatic Load as a measure of social embodiment: Conceptual and empirical considerations." Longitudinal and Life Course Studies.

In Part I, Chapter III, section 4, we introduced the first allostatic load index for analysing epidemiological studies. The purpose of the present chapter is to offer some insights regarding the operationalization of an allostatic load index. We will discuss the limits and the complexity of the allostatic load score construction.

In **section 1**, we will introduce the topics relating to the general issues regarding allostatic load operationalisation.

In **section 2** we will propose some solutions for moving forward.

In **section 3** we will raise the question and problematics of measuring health with biomarkers.

In **section 4** we will focus on the challenges regarding the biomarkers collection in large epidemiological studies

In **section 5** we will conclude the chapter with some ethical insights regarding the use of biological data in epidemiological studies.

# 1. Allostatic load as an epidemiological tool & its limitations

## 1.1. Choosing relevant biomarkers

After identifying the physiological systems relevant for inclusion in an AL score, it is necessary to define the biological markers within each system that are the most appropriate proxies to summarize the state of that system. Moreover, AL markers could be drawn from several very different physiological 'levels' from epigenetic regulations (DNA methylation, telomeres length) to 'health outcomes' (illness, BMI, waist hip ratio). The cascade of events linked to stress responses, physiological burden and disease therefore need careful consideration. Currently, some markers are presented as primary mediators (cortisol, DHEA-S, catecholamines), some others as secondary mediators (HDL, glucose level and more generally 'biological risk factors') and some others as tertiary mediators (diseases) (McEwen & Seeman, 1999). Furthermore, some mediators are more variable than others. In particular primary mediators, like cortisol, vary according to circadian rhythms and acute environmental challenges whereas secondary mediators, like HDL, are more stable. For primary indicators, multiple measures are required whereas for secondary or tertiary mediators, one measure may suffice. Furthermore, the total hormone level is not necessarily a good index of the active part of the hormone. In this case, transport proteins (such as CBG for cortisol) and salivary or urine assessment (free cortisol) should be measured. This issue raises general methodological considerations regarding AL score construction from various measures. Moreover this issue also raises questions on the feasibility of collecting such biomarkers in accessible samples like blood, saliva or urine. In Part I, Chapter III, Table 1 we presented a review drawn-up by (Juster et al., 2011a) of biomarkers used in the literature as potential candidates for constructing an allostatic load score.

## 1.2. Building a score

Considering the two previous points, the question of how to go about summarizing, in one single score, information contained from a number of biomarkers is fundamental. In practice an AL score is usually built pragmatically from available data. The most widely used method to build an AL score is then to use a summary measure representing the number of biomarkers within a high risk percentile defined from the biomarkers distribution in the studied population (Juster et al., 2010). Some biomarkers show an up-dysregulation as well as a down-dysregulation. This is the case of cortisol, which is a dynamic biomarker, and dysregulation can

lead to both hyper or hypocortisolemia (Adam & Kumari, 2009). Other biomarkers seem to show the same characteristics, such as, IGF-1 where both high and low appear to be related with greater mortality (Lara et al., 2015). Other biomarkers are characterized by their continued decrease with age, such is the case of DHEAS (Barrou et al., 1997). Therefore, it is possible that there is more than one allostatic load profile, and we do not know the health consequences of these potentially different and opposed changes on health and ageing.

Maybe more critical than questions on how to define 'subclinical' thresholds representative in various population, this approach is empirical and is in large part not based on a theoretical concept of AL. Consequently, some scores are composed of variables that lead to one physiological system being over-represented versus the others. This is often the case with the cardiovascular or metabolic systems that can be measured through several easily-collected variables (HDL, LDL cholesterol total, blood pressure, glucose and insulin level, waist hip ratio, BMI) whereas the HPA axis, sympathetic nervous system, inflammatory and immune systems tend to be represented using one or two variables. By simply summing these variables to build a score, it is likely that the score will be well correlated with cardiovascular diseases and less so with other diseases. It may be possible to weight the score according to the outcome measure of interest. The score would then be composed of the same variables weighted differently according to the disease studied. Other methods suggest that biomarkers included should be summarized according to their specific system. Thus the construct of an index will be based on the sum of the systems rather than the sum of individual biomarker. Additionally, such a method also raises questions related to the fact that these variables are not independent, some of them being linked by physiological pathways. In consequence how to best take the nature of these different relationships into account in the overall score is an important issue. In response to these questions, more sophisticated methods like recursive partitioning or canonical correlation analyses have been used to manage weighting and interrelation between biomarkers (Juster et al., 2010). More recently new approaches based on confirmatory factor analysis and structural equation modelling have been proposed which could be particularly relevant to 'capture' the concept of AL (Booth et al., 2013; McCaffery et al., 2012; Seeman et al., 2010). These methods based on the covariation of biomarkers present several advantages including: the possibility of testing an *a priori* hypothesized model or structure linking biomarkers and physiological systems which is relevant to analyse AL; the construction of AL

as a latent variable (metafactor) by modelling shared variance among biological systems which is in accordance with the general idea of wear and tear included in AL concept; testing factorial invariance which could be useful to test the stability of the AL score in various groups of the population (age, gender); the use of continuous variables; the fact that no assumption on weight is required as the weight of each parameter is defined empirically.

Other difficulties relate to individual variability, we do not know how we can account for individual differences in responses to stress. If we use AL as a population tool, the individual variability is less problematic. However, the capacities of a biomarker for distinguishing between groups of individuals may be reduced. For avoiding this potential misclassification, the source of variability should be identified. We are still ignorant about whether different profiles of allostatic load can differ by ethnicity and gender. These limitations result in important complexity when it comes to summarize all the biomarkers.

### 1.3. Allostatic load biomarkers and treatment: insights from our work

Another topic that we should able to take into account is the potential interaction with other exposures, such as, drugs and treatments (medication). Taking a treatment is an important issue when it comes to biomarker analysis. In our case, we measured AL at 44 years of age, when the number of individuals reporting taking medications was relatively low, therefore we were not completely confronted with the methodological problems imposed by taking medication. However, we observed the mean of AL biomarkers individually in treated participants and in non-treated participants. It was surprising to observe for the majority of biomarkers that the individuals taking a medication were in general, more at risk for each biomarker compared to those that were not taking a medication (see Table 24). Overall, the AL score in treated individuals was also higher compared to untreated individuals for men and women (AL mean=3.79 in treated men vs 2.89 in untreated/AL mean=3.63 in treated women vs 2.86 in untreated). At 44 years in the 1958 NCDS birth cohort, individuals taking a medication, potentially improving his/her individual physiological levels, remained 'rather sick' compared to the individuals not taking a medication. Additionally, we tested the effect of treatment in the cardiovascular system. We created two scores, a 'cardiovascular score'; and a 'other systems score' with the remaining biomarkers. We found that the group taking a medication for the cardiovascular system had an elevated mean for the cardiovascular score compared to non-medicated. Additionally, those taking a cardiovascular treatment had also an elevated mean for

the second score (taking into account the remaining biomarkers) compared to those who were not taking a cardiovascular medication. This may suggest that medication can also be a source of dysregulation. Sadly, in our data set we do not have sufficient reliable information regarding medication to formally test this hypothesis.

Several researchers, such as Robertson and colleagues created an AL score adjusted by medication. For instance, for those taking antihypertensive medication, systolic and diastolic blood pressures were adjusted by adding 10mmHG and 5mmHG, respectively, and so on for the other biomarkers (Robertson et al., 2014). However this a remaining challenge that deserves further research.

Table 25. Mean for each biomarker in treated and in untreated individuals for men and women

| | Men (n=4046) | | Women (n=4056) | |
|---|---|---|---|---|
| **Biomarker** | **Mean in treated (n=647)** | **Mean in non-treated (n=3399)** | **Mean in treated (n=1410)** | **Mean in non-treated (n=2631)** |
| Cortisol t1 | 20.5 | 21.1 | 21.1 | 21.8 |
| Cortisol t1-t2 | 9.2 | 9 | 8.3 | 7.8 |
| Triglycerides | 2.9 | 2.4 | 1.8 | 1.5 |
| LDL | 3.4 | 3.6 | 3.3 | 3.3 |
| HDL | 1.4 | 1.4 | 1.7 | 1.7 |
| HbA1c | 5.8 | 5.3 | 5.3 | 5.1 |
| Ige | 162.6 | 107.3 | 101.7 | 65.1 |
| IGF-1 | 18.3 | 18.7 | 17.9 | 19.1 |
| Fibrinogen | 18.3 | 18.7 | 17.9 | 19.1 |
| CRP | 2.4 | 1.8 | 3.4 | 1.8 |
| SBP | 135.3 | 132.2 | 121.9 | 119.2 |
| DBP | 83.6 | 81.6 | 76.9 | 74.7 |
| Pulse | 72 | 70.1 | 72.7 | 72.6 |
| Peak expiratory flow | 546.9 | 578.1 | 393.2 | 400.9 |
| **AL score** | **3.8** | **2.9** | **3.6** | **2.9** |

### 1.4. AL across the life course

A limitation of most prior work on the allostatic load model is that it has been based on measures of biomarkers collected at only one point in time. An essential ingredient in these datasets is the inclusion of biological samples, repeatedly collected to represent the dynamic nature of AL. Taking a life course approach for studying health raises questions regarding how to best measure wear-and-tear over the life span. This is a dynamic process and therefore an adapted measure should be dynamic as well. Moreover, the question of timing is key. The

physiological systems identified to measure AL, and how to measure them, are indeed likely to vary considerably according to age. The physiological responses to stress vary by developmental stage in early life, with sensitive periods of brain development and consequent physiological responses occurring well into late adolescence. Sensitive periods of brain change also occur in older age, which are likely to have an impact on physiological stress reactivity (Lupien et al., 2009). How to measure early stages of physiological wear-and-tear at different periods of life as well as differences in sex/ gender stress response deserve further investigation (Bale, 2011).

For implementing these ideas, we can suggest:

i) For characterizing a developmental stage, specific measures of AL need to explore (for instance, is childhood different from adulthood in terms of biomarker collection?).
ii) We should be able to test sex/gender differences by life-stage.
iii) To avoid part of these issues, repeated measures are needed from early life to adulthood and old age.

## 2. How to move forward and what can be done to improve AL measurements?

### 2.1. The advantages of allostatic load as an epidemiological instrument

The concept of allostatic load and physiological wear-and-tear is useful for understanding the interrelatedness of human biology and the environment. Robertson *et al.* noted

> "*The emergence of this field linking the biological and the social has grown over the last twenty years, but especially over the last decade, with the increasing inclusion of biomarkers in many large, population - based health and social surveys. This growth in* [simultaneously] *collecting biological and social data, longitudinally and across the life course, is key if we are to continue to advance our knowledge of the biological impacts of our environments and society*" (Robertson, 2016).

Additional questions remain regarding other measures largely used in clinical research. For instance, it remain unclear how measures of AL relate to other indices, such as healthy ageing, metabolic syndrome (MS) or the Framingham Risk Score. Seeman found that AL was a better predictor of mortality and physical functioning than MS. But MS was found a better predictor

of incident cardiovascular disease. One study examined both AL and MS (Seeman et al., 2001). Compared to MS, AL was a better predictor of self-reported cardiovascular disease, arthritis, hypertension, and abdominal obesity. In this study, MS was found to be a better predictor compared to AL for diabetes. Neither AL, nor the metabolic syndrome were predictors of reporting having cancer (Mattei et al., 2010). We can say that in terms of conceptual framework these measures were not designed for answering the same questions. MS is designed as a clinical diagnostic tool, at an individual level. From our point of view, AL could be used as a subclinical measure allowing the identification of different trajectories across the life course of diverse populations. However in terms of predictive value, further studies have to be made regarding this topic.

Regarding the emergence of high technology advances on human physiology, Getz and Tomasdottir have discussed the use of AL in relation to projects that aim to mathematically model the human body (Getz & Tomasdottir, 2016) ['the virtual physiological human' (VPH Institute) and the '100K wellness project' (Institute for Systems Biology)]. Computer models will be able to integrate the mechanical, physical and biochemical functions of a living human body. In parallel, other projects are gearing toward the analysis of big data and –'omics' projects; both, aiming to be descriptive, integrative and predictive of individual norms, however it remains uncertain if they offer advantages or further predictive values over well-established biomarkers (Vineis & Perera, 2007).

Our way of thinking today is confronted with several methodological issues, regarding how we treat the vast availability of data. This means that the concept of AL may be rather stable, however the specific ways in which we can measure it are likely to evolve constantly. The more we know about physiology at the molecular, cellular, organ and systems level, the more we can operationalize different measures, using different methodologies.

In this context, the central advantages conferred by an AL index can be divided in two: the advantages brought by its conceptual construct; and the advantages bestowed by its practical characteristics.

Regarding the advantages related with its conceptual framework, we can mention:

i) AL may correspond to the construct of physiological health, shaped by the influences of the environments;

ii) It corresponds to the idea of an overall measure of physiological health and cumulative biological risk. In this perspective AL could be an adapted tool for studying an integrative and holistic measure of health, rather than specific and separate outcomes.

iii) It corresponds to a better definition of health based on the resources and capacities conferred by health rather than disease and mortality.

Concerning the practical characteristics, we can mention:

i) AL, being by definition a subclinical measure, it is capable of detecting tendencies and health patterns from early in life and throughout the life course. Therefore, it allows a characterization of physiological wear-and-tear from early life, young adulthood, above and beyond clinical health decline. It precedes the processes of ageing and disease.

ii) It allows an analysis of physiological functioning all over the life course in large scale prospective studies;

iii) It allows the identification of population sub-groups at risk;

iv) It is a useful instrument that allows the assessment of physiological wear-and-tear on large population based studies (cross-sectionally and longitudinally);

v) It could allow interventions at the population level in groups identified as in risk.

vi) It allows temporal monitoring changes in risk factor profiles for predicting later health

Nowadays, clinical research seeks to better diagnose and treat patients according to their current symptoms. A strategy that has modest results -slowing the physiological decline-, relatively to measures that search to prevent appearance of disease. In the allostatic load framework, it seems more logical to consider acting upstream, prior to occur a profound impact on physiological or brain damage.

## 3. Measuring health with biomarkers or 'objectivizing' health

The use of biomarkers in epidemiology has provided important findings to the field. The study of risk factors in epidemiology has been referred as a 'black box' approach, when studies focussed on finding correlations between an exposure and an outcome. Biological data are important since they allow us to integrate in our analysis objective measures potentially related

to health, providing scientific basics to a particular biological dimension. Adding biomarkers to research in epidemiology, allows researchers to better 'trace' and hypothesize aspects of the biological component of the 'black box', by exploring the pathways of associations between the exposures, the biomarker and the health outcome (Grandjean, 1995). Biomarkers can partially reflect the spectrum of health-disease processes and allow researchers to monitor health through time. In that sense, biomarkers are useful for a better understanding of the natural history and prognosis of a disease (Mayeux, 2004).

In general, the studies on biomarkers have intended to capture some aspects of one or several biological pathways. Some authors argue that instead, we should be giving more attention to the causes of diseases. Rutter discusses this regarding psychopathology, saying that researchers should analyse DNA as a possible biomarker since it could be the 'source' of some psychiatric disorders (Rutter, 2014). However, the vast majority of human diseases have multifactorial causation. As we already mentioned, the environment 'guides' DNA expression. It is also because of multifactorial causation that we are not capable of identifying a single 'effective' biomarker capable of predicting later health. Moreover, adding biomarkers to epidemiological research does not solve the 'black box' problem. We are still observing correlations, and the exact biological mechanisms, in most cases, remain poorly understood. However, biomarkers add valuable information on how our human bodies cope with our environment. Biomarkers have proven to be useful in several dimensions. For instance, they allow:

i) A better elucidation of potential pathogenic mechanisms;
ii) To improve the etiologic classification of environmentally related-diseases;
iii) To recognize early effects in the natural history of the disease (Grandjean, 1995);
iv) To reduce misclassification of exposures or risk factors and disease (Mayeux, 2004);
v) To provide better interpretation of exposure-outcome associations;
vi) The observation of a specific dose-response effect;
vii) To be used as surrogated measures or proxies;
viii) To provide further information of causal and biological mechanisms (Schulte, 1992);
ix) To reduce recall bias (Mayeux, 2004);
x) Delineation of events between exposure and disease;
xi) Establishment of variability and effect modification;

xii) Enhanced individual and group risk assessments (Mayeux, 2004);

xiii) To develop interventions at the individual and population level

Throughout this thesis we have discussed what allostatic load is. Here we will discuss what allostatic load is not. Grandjean noted regarding biomarkers that

> "*to be useful in epidemiology, the measurable event in the human body should represent a subclinical change only*" (Grandjean, 1995).

From that perspective, neither biomarkers, nor allostatic load have been considered in this work as a diagnostic test at the individual level. For us, AL represents an indicator of an early biological alteration that may lead to clinically diagnosed disease. AL also implies that some of these changes can be reversible, and therefore, early preventive actions may be set in place.

We hypothesized that AL can partially capture the physiological pathway caused by the chronic activation of the stress responses. Therefore, allostatic load, as we measure it, does not entirely capture physiological wear-and-tear, it does not represent biological embedding itself and characterize only a fragment of the causal path between social environment and later health, as integrated in the notion of embodiment.

Health, as we noted earlier, is a larger concept that cannot be summarised using only 'objective' measures (e.g. biomarkers). Quite different from the original definition of health suggested by the WHO, Huber and colleagues proposed that health should be defined according to the ability of a person to adapt and self-manage in the face of social, physical, and emotional challenges. They take into account three main dimensions of health: physical health, mental health and social health. The author noted when describing the relation between health and the social domain:

> "*Health in this domain can be regarded as a dynamic balance between opportunities and limitations, shifting through life and affected by external conditions such as social and environmental challenges. By successfully adapting to an illness, people are able to work or to participate in social activities and feel healthy despite limitations*". (Huber et al., 2011).

Regarding the role of allostatic load, it could be a specific instrument for measuring aspects of health like the capacities of groups of individuals to cope and to adapt to a particular environment. In that sense, AL could make some contributions to research as a tool for measuring, or classifying, the 'strength' of a person in terms of physiological capacities to adapt, in other words, to identify some aspects of resilience.

In summary, health encompassed in several dimensions, notably, physical, mental and the social dimensions. The way in which we perceive the world in which we live is partially contained in the allostatic load concept. However, allostatic load is not health, and cannot capture it. AL is a notion that intends on capturing the physiological processes linked with stress responses.

### 3.1. Proposing a panel of biomarkers for measuring AL

Biological markers has been increasingly incorporated into large-scale, population-based studies. Rapidly, it became a challenge in epidemiological studies, since a large amount of biological data was collected on hundreds to thousands of people. Epidemiological studies provided the opportunity to test different biomarkers and/or sets of biomarkers by population subgroups, ethnicity, ages, and sex/gender.

In this section we will mention some biomarkers that we believe are interesting and that may be part of an AL index, according to age and sex/gender. However, this will remain an unaddressed question, since we have not executed a meta-analysis for analysing all the biomarkers suggested by literature showing a predictive validity according to different health outcomes. Our objective is to move beyond examination of how a single exposure (psychosocial, material, behavioural factor) influencing a single biological system or health outcome. We look forward to a more comprehensive view of the various profiles of dysregulation that may be developed.

Greater attention needs to be paid to primary mediators that can affect multiple other regulatory systems (e.g. cortisol, inflammatory cytokines and catecholamines) as well as to anabolic hormones (e.g. Igf-1, DHEA, testosterone, oestrogens). Some interesting research has found the effects of cortisol on other endocrine biomarkers, such as the thyroid hormones. It has been hypothesized that stress responses, and therefore cortisol, may cause some auto-immune diseases, such as Hashimoto and Graves diseases (Mizokami et al., 2004; Tsatsoulis,

2006). Another biomarker that has shown interesting characteristics are dopaminergic, associated with early ageing and neurodegenerative diseases such as Parkinsons, or blood melatonin (a serotonin metabolite). From the sympatho-adrenal biomarkers adrenaline and noradrenaline can also capture some physiological reaction from environmental stressors. It would be helpful to have better measurement of primary mediators, for instance, to capture the cortisol diurnal rhythm several measures are needed across the day. From the secondary biomarkers, lipid profile (metabolic system), heart rate, blood pressure (cardiovascular), IGF-1, CRP, cytokines (inflammatory), are interesting biomarkers, however from the research on cancer and metabolic disease, a large panel of biomarkers may also been considered.

## 4. Biomarkers assessment in large scale studies

Adam & Kumari analysed the collection of cortisol assessment in large scale epidemiological studies, which we believe can be transposable to other biological data in terms of the challenges raised including difficulties in sampling, data treatment and analysis. The authors noted the following regarding the advantages of large scale studies:

> "*The representative nature of sampling, and large samples sizes associated with population-based research offer high generalizability and power, and the ability to examine cortisol functioning in relation to: (a) a wide range of social environments; (b) a diverse array individuals and groups; and (c) a broad set of predisease and disease outcomes*." (Adam & Kumari, 2009).

However, even if the sample includes a large amount of participants, for studying some rare diseases, the sample needed could be even larger if we want to reach a power of 90% to detect a significant difference at 5% (see Table 26 below from Adam and Kumari 2009 for further details).

Table 26. Total number of study participants required to have power of 90% to detect a significance difference at 5% (two-sided) from (Adam and Kumari 2009)

| | Exposure prevalence (i.e. Top 50% vs. bottom 50%) | | | | | |
|---|---|---|---|---|---|---|
| | Rate ratio | | | | | |
| | 1.4 | 1.5 | 1.6 | 1.8 | 2.0 | 2.5 |
| Disease prevalence (in low risk group) | | | | | | |
| 5% | 6120 | 4094 | 2966 | 1804 | 1240 | 644 |
| 10% (overall prevalence) | 2868 (12%) | 1914 (12.5%) | 1382 (13%) | 836 (14%) | 572 (15%) | 292 (17.5%) |
| 20% (overall prevalence) | 1244 (24%) | 824 (25%) | 590 (26%) | 352 (28%) | 236 (30%) | 114 (35%) |
| 30% (overall prevalence) | 702 (36%) | 460 (37.5%) | 326 (39%) | 190 (42%) | 124 (45%) | ~100 |

*Note*. The sample size required to have a power of 90% to detect a significant difference at 5% (two-sided) is shown for varying disease prevalences and rate ratios. A rate ratio of 1.5 means that the expected rate of disease is 1.5 times greater in the at risk group compared to the low risk group.

Research on biomarkers could enlighten us for future research perspectives in terms of AL, incorporating a battery of biomarkers potentially related to many causes of disease development. However, the biomarkers collection should fulfilled some conditions:

i) Practical (collection should be possible at home),
ii) Easy to collect (rapidly, not painful),
iii) Least invasive possible,
iv) Economic

To be used effectively in epidemiology, allostatic load and it components, must be:

i) Valid
ii) Reliable
iii) Practical

For reaching these conditions, the epidemiological studies can collect blood, saliva, urine, hair and primary teeth.

Concerning the use of biomarkers in epidemiology (Schulte, 1992), that they should be able:

i) To detect earlier biologic changes presumptive of disease or disease risk,
ii) To identify a detailed continuum of events between an exposure and resultant disease.

The author added that to validate a biomarker for use at the population level must fulfil some requirements, such as, background prevalence, sample size, natural history, persistence, variability, and have good predictive value.

## 5. Ethics considerations when using biological data

Concerning the participants, some ethical questions can be discussed. One issue concerns the communication of the results to participants. As we already suggested, biomarkers during early life and childhood could be very useful to capture different biological trajectories. We also mentioned that one remaining challenge concerning AL relates to the possibility to implementing epidemiological studies in developing countries. These questions raise important ethical issues.

Some ethical topics that we can mentioned:

i) ***The responsibility toward participants in alerting them of their health status***. For epidemiological research, the vast majority of research findings do not indicate significant risk or clinical complications. First, because the results are uninterpretable on an individual level, only at a population level. Second because many biomarkers studies produce results with uncertain meaning. And finally, because epidemiological research on biomarkers has no clinical value (Schulte, 1992); and sometimes the scientific knowledge is insufficient to quantify a particular risk. However, we can imagine to provide some results at the community level, and individual results, relatively to the mean of the population results.

ii) ***Protecting confidentiality and privacy.*** Special permission should be requested, with an ethical commission that evaluates the objectives and purposes of the research. Privacy, and the anonymity have to be maintained, and the results should be confidential (Coughlin, 2006).

iii) ***Protecting vulnerable populations.*** Minimizing risks and potential harms and maximizing potential benefits are particularly important in epidemiological studies of vulnerable populations. This is particularly important in studies of children, prisoners, elderly people, marginalized or socioeconomically disadvantaged populations (Coughlin, 2006).

iv) ***Communicating the ethical requirements and obligations to the participants and the communities***. Obligations may include communicating the results, explaining the results to the communities involved after the studies has been validated by peer review (Coughlin, 2006).

v) ***Informed consent***. Submitting proposed studies for ethical review.

vi) ***Respecting cultural diversity.*** If the studies were carry out in different cultural populations, epidemiologists should respect and understand the local community values. They should communicate with members of the communities (as 'cultural mediators') to explain the results and to elucidate the best way to communicate the findings with the rest of the community involved in the study. For instance, some issues may arise if the funding is obtained in an economically developed country for conducting the research project in an economically developing country (Sly et al., 2009).

vii) ***Regarding research on children***. Usually the consent is given by the parents, however, and according to children's age, researcher should also take into account the wishes of the child about not participating in the study. This point raises the question of when a child is competent to provide consent. After the participants gain the age of legal majority, researchers should contact them to obtain an additional consent if the biological samples will be further used (Sly et al., 2009).

viii) In other issues we can mention the access to banked specimens, and the management of unexpected findings (incidental findings) potentially affecting health. Finally, AL could also be used unethically to classify and discriminate groups of individuals according to their potential health risks. Hence, ethical review is critical.

# Chapter III
# Embodiment, allostatic load & healthy ageing

For the present work we used the life course perspective as a framework to integrate three concepts: embodiment, biological embedding and allostatic load. 'Embodiment' is an essential notion of the ecosocial theory; 'biological embedding', was conceived in the Human's Development studies; and 'allostatic load' was developed in the field of neuroscience and neuroendocrinology. Each of these concepts have captured the attention of their specific field, nonetheless, an integration of the three as complementary concepts remain rare.

In section 1 we will summarize the advantages brought by these three frameworks in our work, individually.

We will additionally introduced the notion of healthy ageing in section 2, which we believe is connected to the notion of allostatic load as a measure of cumulative physiological dysregulation. We raise the question of the differences and similarities between allostatic load and healthy ageing –as well as their operationalisation since these two concepts may integrate similar biomarkers-. In this chapter we will review the literature of healthy ageing to put into perspective the concept and operationalisation of AL.

## 1. The value of integrating embodiment, biological embedding and allostatic load

The concepts of biological embedding and embodiment lead us to think that the environment exerts changes in our physiology. The brain is like a command centre that causes changes to respond to environmental demands. To illustrate, let's say that the brain and the body talk to each other continuously, *via* chemical signals, altering physiological parameters. The concept of allostatic load should allow us to partially capture these conversations. At the population level, we will be capable of assessing population risk.

With this work we have made manifest the need of an epidemiological tool for evaluating the health of population subgroups early in life, adolescence and young adulthood. For the moment, and with all the advances in biology, we are still not capable of differentiating groups of persons according to their current and previous health in childhood and early adulthood. And this may be the greatest contribution of allostatic load: to identify health trajectories, from

early life, throughout the life course. However, this raises further questions and limitations, such as, the potential structural interventions and the fact that for now, we don't know how to measure allostatic load across childhood.

In summary, we can hypothesize that a sort of 'hierarchy' exists between the conceptual framework of embodiment, biological embedding and allostatic load. The notion of embodiment explains how we literally incorporate the world (social, biological, chemical, etc.) in which we live. Biological embedding attempts to explicit the biological mechanisms of the embodiment processes. Finally, allostatic load, or physiological wear-and-tear, is a notion that aims to capture a specific dimension of biological embedding resulting from the mechanisms of stress responses. In other words, allostatic load may be one biological outcome, among others, of biological embedding.

In Table 27 we present a synthetic answers for the question: is AL a suitable measure for measuring the biological dimension of embodiment (How?, When?, What?, Where?).

Table 27. How?, When?, What?, Where?

| | |
|---|---|
| **How?** | Mechanisms: stress response-related systems |
| **When?** | Sensitive periods: pre-natal, childhood, adolescence, young adulthood<br>Pathways effect: different trajectories over the life course |
| **What?** | Early experiences matter, social trajectories matter |
| **Where?** | Brain and physiological systems |

In summary, few studies have investigated the life course origins of allostatic load and its use as a measure of the biological embedding of early life circumstances is still rare in the literature. We consider our study important since we explored some underlying processes of embodiment. The ability to measure the way in which people cope with their environment before disease development offers many possibilities regarding public health interventions both at a societal level, by investing in childhood or in social environment, and at an individual level by preventing diseases through behavioural or treatment interventions.

As Krieger noted:

> "*We humans are mortal, after all. It is no mystery that each of us will die. Yet how we live-and how we die, with what degree of suffering- is at once a profoundly social and biological question. It is biological because it involves our literal beings and the complex interplay, within our bodies and our embodied minds, of exposure, susceptibility, and resistance across the life course. It is social because current and changing population distributions of the burden of illness, disability, and premature mortality can yield evidence of the range of possibilities of human well-being and delimit the existence and degree of preventable suffering. And it is social AND biological because, as implied by the concept of "embodiment", what we manifest in our bodies-and how we ail and what therapies we can access-is simultaneously an expression of our experiences in the world and their literal incorporation within us."* (Krieger, 2004).

## 2. Healthy ageing and physiological wear-and-tear: competitive or complementary notions?

Healthy ageing has been frequently used as an index to evaluate health during old age (Kuh et al., 2014a; Mathers et al., 2012) and therefore the vast majority of research and biomarkers proposed are focus on elderly people. However, some authors have pointed out the importance of early life and life course trajectories. This is the case of Vineis and colleagues, which proposed healthy ageing as a continuous process starting after conception and evolving all over the life course. And such, early life accounts for a great deal of what happens next in adulthood and old age (Vineis et al., 2016). They propose that healthy ageing is a concept that can be measured at different life stages -called build-up, maintenance and decline- using different measures and biomarkers (Vineis et al., 2016).

Healthy ageing can be divided into two dimensions: biological ageing and well-being (Kuh et al., 2014b). (Robertson et al., 2013) defined 'biological ageing',

> "*as the incremental, universal, and intrinsic degeneration of physical and cognitive functioning and the ability of the body to meet the physiological demands that occur with increasing chronologic age"*

which appears to be complementary to the definition of AL. AL may represent the biological dimension of healthy ageing, hence, both concepts are part of the idea of an overall 'physiological wear-and-tear'.

Since healthy ageing and allostatic load 'share' similar biomarkers in their operationalisation (Lara et al., 2015), we proposed here to evaluate the concept of the former for putting into perspective the two notions. For instance, we can think that ageing is a consequence of allostatic load, hence allostatic load can affect ageing processes and lead to a reduced longevity, accelerated aging, and impaired health (Maestripieri & Hoffman, 2011). We believe that, according to the research question, we may rather use one, the other or a combination of both measures.

### 2.1. Healthy ageing: definition and context

Population ageing is a global process affecting all developed countries and it represents an emerging challenge in numerous developing countries (Kuh et al., 2014a). The age structure show a major demographic shift with increasing ratio between people aged 65 and older, and working age population (15-64 years) (Christensen et al., 2009; Harper, 2014). It is widely accepted that the major driver is falling fertility, which increases median ages and later demographic ageing (Harper, 2014). Other causes are frequently evoked, like improvements in life expectancy, falling mortality and increasing longevity (Harper, 2014; Kuh et al., 2014a). By 2050, the world population aged 80 and older is estimated to triple (Department of Economic and Social Affairs Population Division, 2013), and at the same time, the global burden of disease and disability appear to rise (Vos et al., 2012). Nevertheless, the gap between social groups in terms of mortality, morbidity and health decline is shaped early in life (Langie et al., 2012), and accumulates over the life span resulting in widening inequalities in ageing (Chandola et al., 2007). Consequently, healthy life expectancy and disability-free life expectancy reveal strong social inequalities in most developed countries (Guichard & Potvin, 2010).

Healthy ageing is a multidimensional notion, encompassing several dimensions, as suggested by Lara et al.

> "*the biological processes contributing to ageing per se; the socio-economic and environmental exposures across life which modulate ageing and the risk of age-related frailty, disability and disease; and the development of*

> *interventions which may modulate the ageing trajectory*" (Lara et al., 2015).

Epidemiological research of healthy ageing requires a broad conceptual framework based on interdisciplinary approaches. Using a life course perspective is central for studying and evaluating healthy ageing. Recent evidence show the important role from early life, intergenerational factors, that influence the probabilities of developing different chronic diseases later in life (Lupien et al., 2009) (please see Figure 14 regarding the life course functional trajectories according to Kuh and colleagues (Kuh et al., 2014a). Thus, this field of research can provide a powerful research framework for the identification of early life factors influencing healthy ageing, analysing the biological mechanisms, the social and psychosocial pathways.

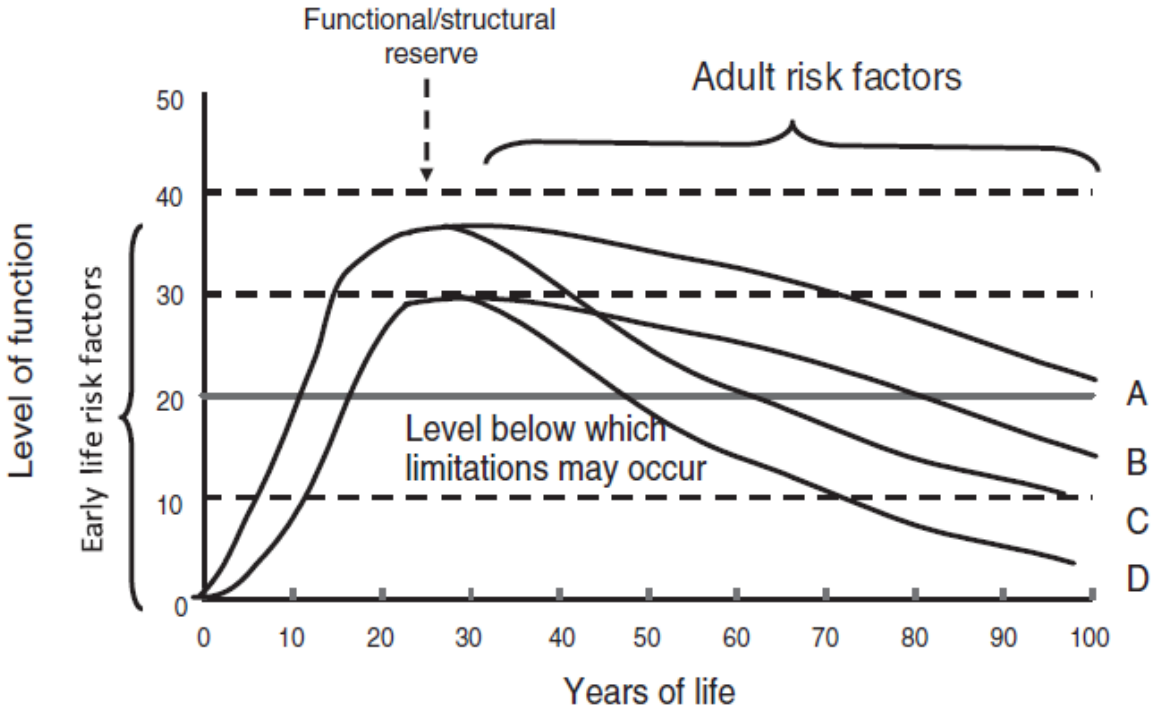
Kuh *et al*. defined biological ageing as

> "*the maintenance, post maturity, of optimal physical and cognitive functioning for as long as possible, delaying the onset and rate of functional decline*."

This notion incorporates other components like survival, delaying the onset of clinical disorders and chronic diseases (Kuh et al., 2014b).

Figure 14. Life course functional trajectories.

According to Kuh and colleagues, adapted from Yoav Ben-Shlomo and Diana Kuh, A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives, International Journal of Epidemiology, Volume 31, Issue 2, pp. 285-293, Copyright International Epidemiological Association 2001, by permission of Oxford University Press (Kuh, Cooper et al. 2014).




The use of biomarkers has become of great interest in epidemiology as a way to describe 'objective' health. The use of a set of biomarkers could better capture the complexity of ageing processes and the decline of physiological systems rather than using single biomarkers or self-reported measures. However, some of the findings mentioned above may suggest that biomarkers of healthy ageing, -as we have seen for allostatic load-, may be different according to age and sex/gender.

## 2.2. Measures and biomarkers of healthy ageing

We will mention in this section the proposed biomarkers for capturing healthy ageing according to the working group of Mathers and colleagues (Mathers et al., 2012).

### 2.2.1. Biomarkers of physical capacities

Grip strength, walking speed, chair rising time and standing balance are the main indicators of physical capability for providing evidence of their association with subsequent morbidity and mortality. These biomarkers are interesting since they complement self-reported health variables, they are more stable in time, and they can be compared, since they might be less susceptible to changes in cultural, language and education differences. There are also used to identify threshold with screening purposes and early interventions.

### 2.2.2. Biomarkers of cognitive function

Executive function, processing speed, verbal memory and learning, attention, working memory, crystallised ability, reasoning, visual memory and visuo-spatial ability are some of the biomarkers of cognitive function used in most of cohorts (Mathers et al., 2012). As for other biomarkers, some showed an inverted U-shaped pattern across the life course (e.g. executive function), and other diminishes progressively with age (e.g. processing speed).

### 2.2.3. Biomarkers of endocrine and immune function

In the endocrine markers we will find the same proposed for measuring AL, such as cortisol, sex hormones (e.g. testosterone, oestrogens, DHEAS), growth hormones (e.g. IGF-1). This working group of healthy ageing also propose to add biomarkers that are not related with the stress-response systems, such as melatonin, adipokines and thyroid hormones. These biomarkers show the same difficulty already discuss for AL (non-linear relations with ageing, both high and low levels associated with greater mortality risk, etc.) (Lara et al., 2015). Concerning the immune biomarkers, it has been included the classic inflammatory biomarkers also known for AL (cytokines, CRP, IL-6 and TNF-α).

### 2.2.4. 'Physiological' function biomarkers

Evidence suggests that there is an added value for the prediction of mortality in assessing different measures of physical capability in midlife (Lara et al., 2015). Additionally, biomarkers can be used as surrogate endpoints. Lung function, body composition, cardiovascular function, blood lipids, low skeletal muscle mass, blood pressure and glucose metabolisms are measures

that usually correlate with other health outcomes (e.g. cognitive function, cardiovascular diseases) and mortality (Lara et al., 2015).

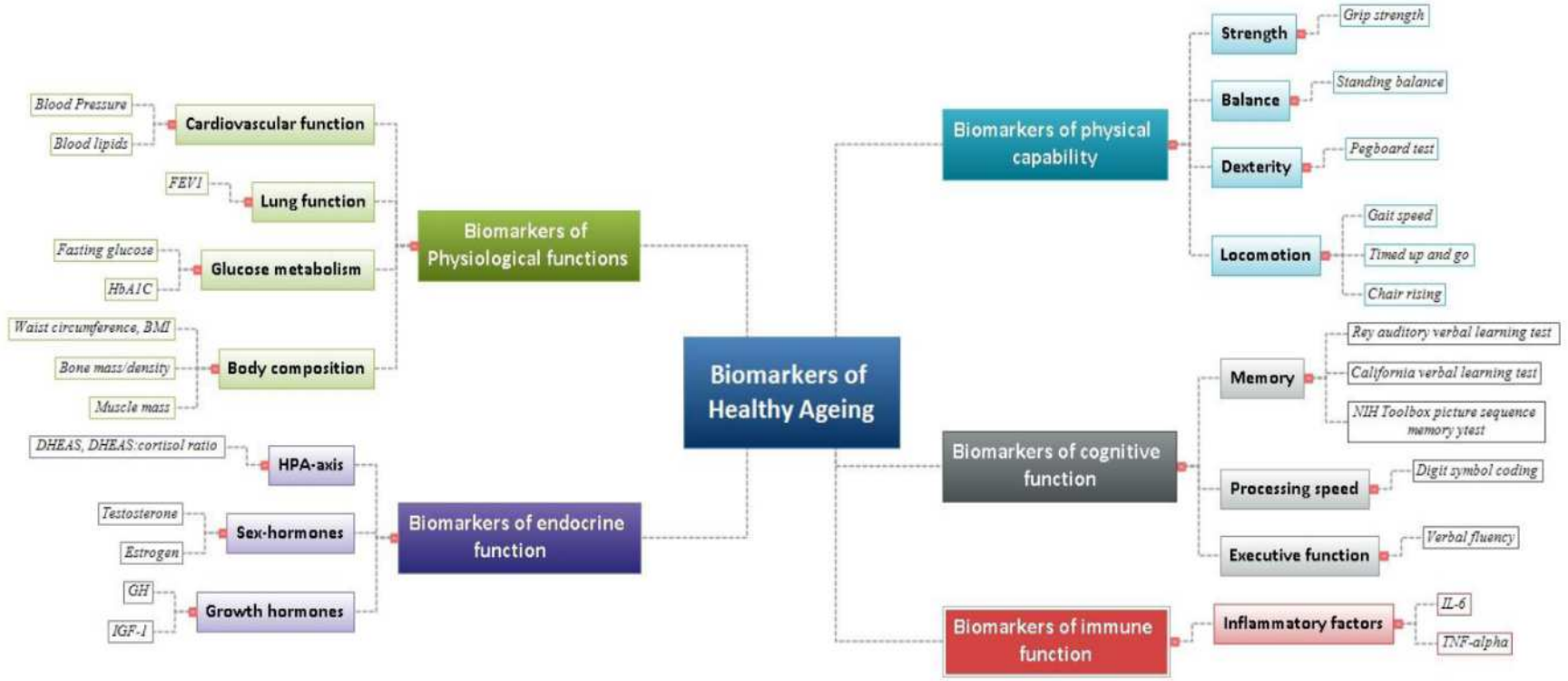
#### 2.2.5. Sensory functions

Lara and colleagues finally propose to evaluate the value of some sensory functions (e.g. audition, vision, and olfaction). These functions may be interesting, for instance, olfactory decline has been proposed as an indicator of brain integrity in elderly. It appears that smell dysfunction is a sign of some neurodegenerative diseases, such as, Alzheimer's and Parkinson and it is associated with mortality (Lara et al., 2015). If we take the perspective of healthy ageing as a process occurring all over the life course, we can imagine that some of this biomarkers can also be considered for measuring healthy ageing in early life when the brain architecture for these systems is founded. In Figure 15 we show the panel of biomarkers proposed by Mathers and colleagues (Mathers et al., 2012).

#### 2.2.6. Telomere length

Robertson *et al*. noted that one promising biomarker for approaching healthy ageing is telomere length (also suggested as a potential biomarker of AL) (Robertson et al., 2013). As the authors explain, telomeres are nucleoproteins present at the end of chromosomes, and help to maintain chromosomic integrity. Telomeres shorten with age, inflammation and oxidative stress (Masi et al., 2011). Some studies have shown that short telomeres are associated with a higher risk of diseases related to age. Telomere length in lymphocytes and monocytes has been correlated with ageing. However (Lara et al., 2015) noted that shortened telomeres is also a marker of infection frequency. The authors concluded that measuring telomere length in leukocytes may not be a reliable index of biological ageing. The evidence linking telomere length and health remain spare and mixed. Further analysis on large representative longitudinal studies using SEP measures allowing comparisons are needed (Robertson et al., 2013).

Figure 15. Proposed panel of biomarkers ok healthy ageing. From: Guidelines for biomarkers of healthy ageing (Lara, Cooper et al. 2015)



## 2.3. Healthy ageing and AL as measures of cumulative physiological wear-and-tear

People living in more disadvantage circumstances are more likely to present an earlier cellular and genomic biological ageing relatively to their counterparts (Adams & White, 2004). Healthy ageing concepts overlap with AL through the idea of cumulative physiological wear-and-tear over the life course. The notion of frailty refers to a state of increased vulnerability to stressors due to age-related declines in physiologic reserve across neuromuscular, metabolic, and immune systems (Walston et al., 2006), which is pretty similar to the framework of AL. As for AL, healthy ageing has come across some difficulties for purposing the 'ideal' set of biomarkers. As for AL, there is no gold standard for measuring healthy ageing.

There are several reasons for separating these two notions. One reason relate to the fact that it is difficult to sustain the notion of 'ageing' during early life, childhood and adolescence. Since studies of healthy ageing are frequently based on old age, the biomarkers classically proposed that better capture the current health status and better predict future morbidity and mortality in elderly individuals, may be not the best ones for characterizing healthy ageing in childhood and adolescence. From that perspective, AL biomarkers appear to be better adapted to measure health status during childhood and adolescence. However, as we mentioned before, the concept of healthy ageing encompasses several processes, and recent studies show that experiences across the life matter, and propose to measure healthy ageing early in life (Vineis et al., 2016). Kelly-Irving proposes the following statement to define healthy ageing, but especially, to discuss a potential operationalization:

> '*is the optimal state of performance and well-being capable for any particular phase of the life course that can be expected in a society, across all social and cultural groups of a population*'(Kelly-Irving, 2015).

In this sense, as for AL, questions about the biological markers more suitable for measuring ageing at a certain point in the life course, are probably not the same for evaluating current and future health status at another developmental stage.

For us, one of the main differences between allostatic load and healthy ageing, and the ensuing choice of biomarkers, relates to their conceptual framework. The AL theory closely relates to the effects of stress on physiology. Ageing is

> "*a gradual and progressive deterioration of integrity across multiple organ systems*"(Belsky et al., 2015).

Indeed, ageing may be interrelated with stress and stress systems, but not necessarily, and not exclusively. This is why it makes sense for ageing biomarkers to include a larger panel of biomarkers (like those evaluating physical functioning, e.g. grip strength) that are not directly part of the stress-response systems. Hence, healthy ageing is suitable for measuring cumulative biological risk over life.

As we mentioned before, (Vineis et al., 2016) have proposed three different stages shaping health over the life span: the build-up, the maintenance and the decline. Here we will suggest a set of biomarkers (AL, healthy ageing, or both) that could be useful for capturing a current health status and for predicting later health outcomes for each stage of live (see Figure 16). We will refer to the 'primary' and 'secondary' mediators of AL, (please see Part I Introduction, Chapter III, section 2 for further details). If we explored the possibility of ageing being an outcome of allostatic load, we can imagine that -according to AL theory- our bodies adapt to their environment first to survive, but our bodies pay a 'cost' for such adaptation. In that sense, the first biomarkers that become dysregulated will correspond to those interacting directly with our environment (HPA axis, SNS, neuroendocrine and cardiovascular systems, etc.). However, once these systems are dysregulated, functional decline and accelerated ageing may begin. In this case, the functional biomarkers of ageing will show strong correlations with current health compared to AL biomarkers.

We can speculate that AL biomarkers will be different according to age in terms of assessing current health and in terms of predictive value for evaluating future health outcomes.

i) Biomarkers during early life: considering again the AL framework (Part I, Chapter III, section 2) we can imagine that for the early years of life, the primary mediators (cortisol, adrenaline, noradrenaline, DHEAS, testosterone, oestrogens, etc.), will be the most important. Those biomarkers could be the first to be dysregulated when chronic stress is set in place (Figure 16).

ii) Biomarkers during young adulthood: once the primary biomarkers have been dysregulated, the secondary biomarkers (e.g. HDL, LDL, glycated haemoglobin, etc.) may be more robust in terms of assessing current and future health. However, a

composite measure of both, primary and secondary biomarkers may be the most adapted (Figure 16).

iii) Biomarkers during mid-adulthood: we can speculate that AL biomarkers and healthy ageing are in this stage complementary measures, encompassing different biological mechanisms (not only stress-responses). In this sense, biomarkers of function (e.g anthropometrics, glucose metabolism, blood lipids, blood pressure, etc.; will be suitable markers for representing current health and they could be good predictors of later health outcomes (Figure 16).

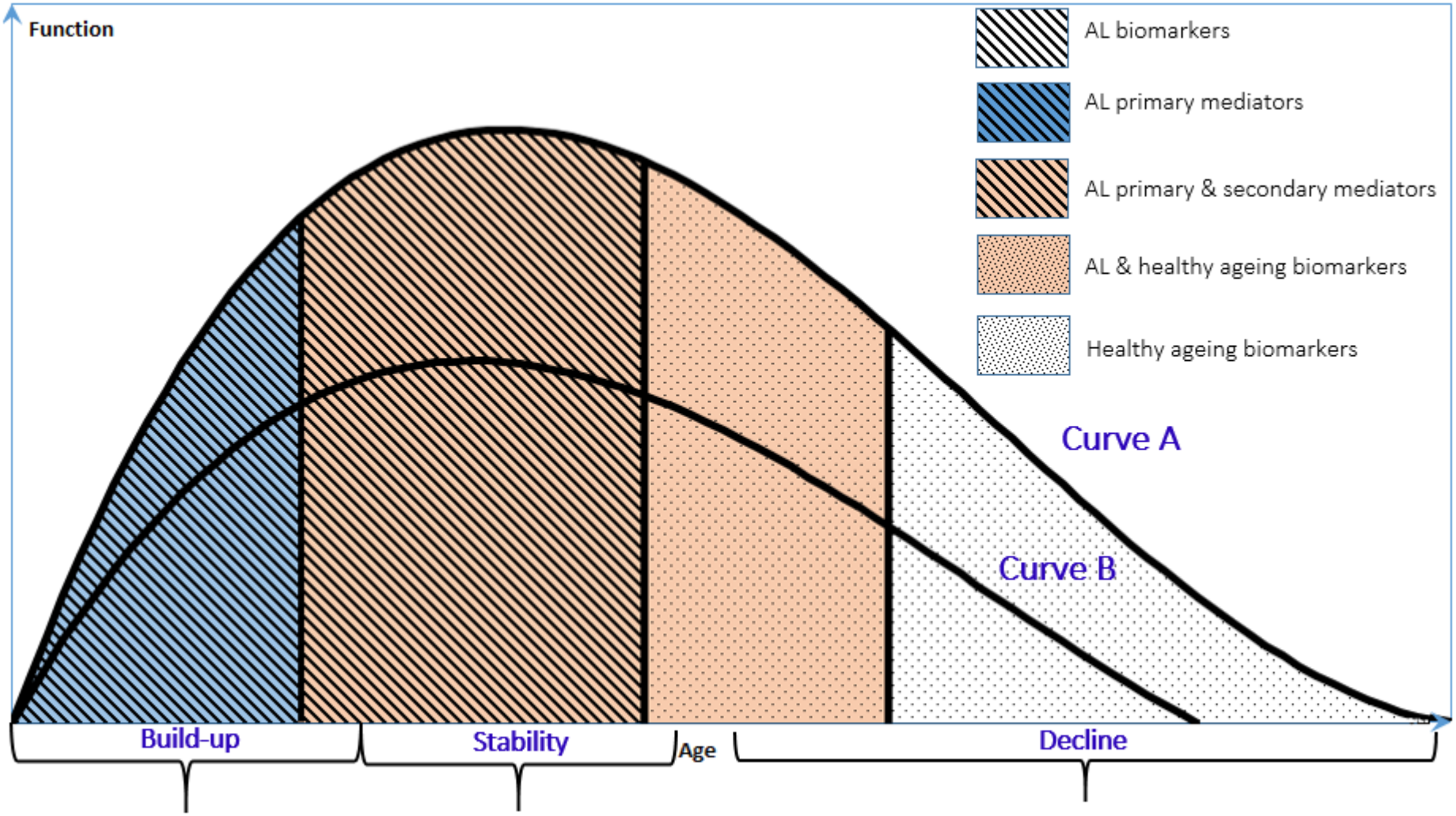
iv) Old-age: we can imagine that the functional components of the healthy ageing measures (e.g. grip strength, walking speed) will be the more adapted when it comes to evaluate current health and future health outcomes, particularly, mortality (Figure 16). Two processes may occur during old age that make the functional measures more suitable than AL measures. One is the mortality selection represented by curve B Figure 16. Early mortality will be more likely in individuals with several AL biomarkers dysregulated, selecting those with better physiological function. However if we analyse mortality during old age, not been able to walk or to get out of the bed will certainly be a good marker of future mortality or multi-comorbidities.

The notion of healthy ageing, using some of the biomarkers proposed in the literature (e.g. grip strength, chair rising, walking speed), are probably the most adapted for analysing the decline stage in health. The age or the specific moment when we start to decline in function is also an unaddressed question. A recent study of Belsky *et al*. showed difference in ageing trajectories from the second decade of life, suggesting that health decline (or an accelerated ageing processes) may be start -and be detected- in rather young individuals (Belsky et al., 2015).

In other words, allostatic load may be a better index when analysing differences in healthy groups of subjects, compared to healthy ageing classic biomarkers (grip strength, etc.). The classic biomarkers of healthy ageing are indeed more adapted for groups of subjects that (in theory) have starting the health decline process. It is noteworthy that in this perspective, allostatic load may better encompass the biological component of health, and not of illness. Using AL biomarkers we are analysing trends and differences between groups of individuals that (*a-priori*) have not been clinically diagnosed with a disease (see Figure 16). However,

(Vineis et al., 2016) working group proposes that healthy ageing should be, as for AL, a measure that can capture subclinical conditions at different stages of life.

Figure 16. Build-up, stability and decline: which biomarkers are more adapted? AL or healthy ageing?



In summary, there is no gold standard for assessing healthy ageing, nor allostatic load in a population level. Allostatic load could be one measure used to capture the early biological dysregulation linked with stress responses. Allostatic load may be a suitable measure for childhood adolescence, and early adulthood. As suggested by Seeman *et al.*

> "*if chronic stress disrupts allostatic load component systems sequentially, it may be more appropriate to look first at early alterations in neuroendocrine systems, later at elevations in inflammatory markers, and even later at markers of metabolic syndrome*"(Nielsen et al., 2007).

Healthy ageing encompasses a larger and more diverse biological mechanisms (not only related with stress responses) that are suitable for evaluating current health status and later mortality risk in individuals with some biological decline. However, if we consider the conceptual proposition of (Vineis et al., 2016), some healthy ageing measures can also be included for capturing early physiological wear-and-tear (in children for instance) like some anthropometric measures (e.g. birth weight, weight, height, or other 'sensory functions' as we mentioned earlier).

Overall, a sort of 'temporality' may be elucidated: first, an acute stressor will be followed by an acute physiological response. If the stressor remains, it will be followed by a chronic stress response *via* the stress response systems (AL biomarkers involved). This will be followed by a global physiological dysregulation (AL biomarkers and healthy ageing involved). Finally, different systems will be dysregulated, causing an overall cumulative biological risk that will be followed by an accelerating ageing, decline in function and early morbi-mortality (healthy ageing biomarkers involved).

# Chapter IV
# Research perspectives & conclusions

The future direction of research on social-to-biological transitions is difficult to state with clarity. Some directions can however be discerned, allowing researchers from different areas to point the way and to prioritize future research perspectives. Some questions remain unaddressed by this work, we will list some of them:

i) To further test the AL index in different cultural and social context,
ii) To further study the biological cascade of biomarkers,
iii) To further study the biological evidence linking the AL mediators,
iv) To determine the criteria by which new biomarkers should be evaluated for inclusion in research on physiological wear-and –tear,
v) To find a consensus regarding the best panel of biomarkers according to age, social context, across cultural and population social characteristics,
vi) To compare the predictive validity of AL biomarkers and new emerging ones that are consistent with AL framework of physiological wear-and-tear.
vii) To further investigate the cumulative physiological burden that relate to other biological mechanisms besides stress responses.
viii) To develop a measure of chronic stress that can put forward cumulative models of distress in prospective studies (e.g. traumatic events, major life events, perceptions of stress?)
ix) To better understand stress vulnerability and stress resilience

Regarding other research perspectives, there still some topics that have been moderately explored using the AL framework. For instance, the link between AL and cancer, neurodegenerative diseases, in different social and cultural context have been rarely explored.

In summary, numerous research questions remain regarding AL future perspectives. Promoting the collection of biological markers in large representative and prospective studies appear to be crucial to continue to investigate on this topic. The possibility to compare with other cultural context and to replicate the studies may allow us to observe if the underlying physiological responses are ‘universal’.

In conclusion we will refer rapidly to interventions in health. We believe that interventions should be based on collective actions creating favourable and dynamic environments. In terms of public health, obstacles should be identified and removed and

> "*to make the healthier choice the easier choice*" (British Department of Health, 2004).

The consideration of the social context as a whole should represent a real strategy in health policy and research programs. Some ideas may relate, as our findings suggest, with education, which relates to health in diverse ways.

The main challenge is twofold, because it is essential to ensure that these actions will not exacerbate health inequities (reaching the most favoured and excluding the least favoured), and to guarantee an equally distribution of social resources to all people at the service of social justice, as noted by Whitehead and Dahlgren, efforts to promote social equity in health should create opportunities, remove barriers allowing people to achieve their health potential (Whitehead & Dahlgren, 2006). For this, a fair distribution of social resources is needed.

In the Ottawa Charter for Health Promotion is noted:

> "*Health is created and lived by people within the settings of their everyday life; where they learn, work, play and love. Health is created by caring for oneself and others, by being able to take decisions and have control over one's life circumstances, and by ensuring that the society one lives in creates conditions that allow the attainment of health by all its members."*

*"Cuando creíamos que teníamos todas las respuestas, de pronto, cambiaron todas las preguntas."*

*«Quand nous avons cru avoir toutes les réponses, tout à coup, toutes les questions changèrent.»*

*"When we thought we had all the answers, suddenly, all the questions changed."*

Mario Benedetti

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# APPENDIX

# Appendix 1
# Publications in peer reviewed journals

- Barboza Solís, C; Kelly-Irving, M; Fantin, R; Darnaudéry,M; Torrisani, J; Lang, T; Delpierre, C. (2015). "Adverse childhood experiences and physiological wear-and-tear in mid-life: Findings from the 1958 birth cohort". *Proceedings of the National Academy of Sciences of the United States of America, 112*(7), E738-746. doi: 10.1073/pnas.1417325112

- Barboza Solís, C; Kelly-Irving, M; Fantin, R; Castagné, R; Lang, T; Delpierre, C. (2016). "Mediating factors between early socioeconomic position and allostatic load over the life course". (Under review after first revision). *Social Science & Medicine.*

- Barboza Solís, C; Kelly-Irving, M; Fantin, R; Delpierre, C. (2016). "Physiological wear-and-tear and later subjective health in mid-life: findings from the 1958 British birth cohort" (Under review after first revision). *Psychoneuroendocrinology*.

- Barboza Solis, C. (2015). "Incorporación de la Adversidad Psicosocial Precoz y la Carga Alostática Utilizando una Perspectiva Biográfica: Revisión de la Literatura". *Odovtos - International Journal of Dental Sciences*

1. Appendix: Publication in *Proceedings of the National Academy of Science of the United States of America*

# Adverse childhood experiences and physiological wear-and-tear in midlife: Findings from the 1958 British birth cohort

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**Allostatic load (AL) is a measure of overall physiological wear-and-tear over the life course, which could partially be the consequence of early life exposures. AL could allow a better understanding of the potential biological pathways playing a role in the construction of the social gradient in adult health. To explore the biological embedding hypothesis, we examined whether adverse childhood experiences (ACEs) are associated with elevated AL in midlife. We used imputed data on 3,782 women and 3,753 men of the National Child Development Study in Britain followed up seven times. ACEs were measured using prospective data collected at ages 7, 11, and 16. AL was operationalized using data from the biomedical survey collected at age 44 on 14 parameters representing four biological systems. We examined the role of adult health behaviors, body mass index (BMI), and socioeconomic status as potential mediators using a path analysis. ACEs were associated with higher AL for both men and women after adjustment for early life factors and childhood pathologies. The path analysis showed that the association between ACEs and AL was largely explained by early adult factors at age 23 and 33. For men, the total mediated effect was 59% (for two or more ACEs) via health behaviors, education level, and wealth. For women, the mediated effect represented 76% (for two or more ACEs) via smoking, BMI, education level, and wealth. Our results indicate that early psychosocial stress has an indirect lasting impact on physiological wear-and-tear via health behaviors, BMI, and socioeconomic factors in adulthood.**

allostatic load | adverse childhood experiences | biological embedding | health behaviors | cohort study

Health disparities are observed for a wide range of health indicators from risk factors, incidence of chronic diseases, and mortality across the world (1). According to Hertzman, the socioeconomic gradient in health "is capable of replicating itself on new disease processes as they emerge in society" (2). Recently, epidemiological studies have shown that classic determinants are not sufficient for explaining the social gradient in health (3). This may point toward the existence of other mechanisms influencing health, like a potential biological pathway. The notion of allostatic load (AL) may be useful to explore how experiences over the life course may "get under the skin" and become biologically embedded (2, 4, 5).

In the last two decades, epidemiological research has used the concept of AL to explain how chronic stress can lead to physiological dysregulation and disease (6–12). AL is a measure of overall physiological wear-and-tear over the life course, which could be the consequence of early life exposures (13, 14). According to AL theory, cumulative and repeated activation of compensatory physiological mechanism in response to chronic stress can lead to a multisystem predisease state represented by a dysregulation of neuroendocrine, metabolic, inflammatory, or cardiovascular parameters (15, 16). Empirical evidence shows that AL has strong correlations to subclinical conditions, morbidity, and mortality (12, 17), and may be a useful measure of overall health, rather than considering each biomarker separately (6, 18).

Several studies have suggested that exposure to chronic stress during sensitive periods of development may alter the balance and responsiveness of physiological systems and have long-term effects on health (2, 13, 14, 19–21). 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 well-being (22, 23). Exposure to ACE could influence health through a broad range of behavioral and socioeconomic mechanisms. For instance, the ACE study explored the relationship between ACE and health behaviors, linking childhood trauma to long-term effects on health via health risk behaviors such as alcohol consumption, smoking, and sexual behaviors, among others. Felitti et al. (24) also suggested that ACE could be a common pathway to social, emotional, and cognitive impairments that may lead to increased risky behaviors. It has been established that the adoption of health behaviors may also be explained by wide and complex psychological processes such as self-regulation, self-efficacy, and self-management mechanisms (25, 26). Furthermore, socioeconomic and material conditions in childhood ap-

## Significance

**The role of early life experiences on health is of major concern to research. Recent studies have shown that chronic stress may "get under the skin" to alter human developmental processes and impact later health. Our findings suggest that early negative circumstances during childhood, collected prospectively in a British birth cohort, could be associated with physiological wear-and-tear in midlife as measured by allostatic load. This relationship was largely explained by health behaviors, body mass index, and socioeconomic status in adulthood, but not entirely. These results suggest that a biological link between adverse childhood exposures and adult health may be plausible. Our findings contribute to the development of more adapted public health interventions, both at a societal and individual level.**

Author contributions: C.B.S., M.K.-I., and C.D. designed research; C.B.S., M.K.-I., R.F., and C.D. performed research; C.B.S., M.K.-I., R.F., M.D., J.T., T.L., and C.D. contributed new reagents/analytic tools; C.B.S., M.K.-I., and R.F. analyzed data; and C.B.S., M.K.-I., and C.D. wrote the paper.

The authors declare no conflict of interest.

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pear to be linked to later brain development and cognition (27). Lately, epidemiological studies have shown that ACEs were associated with mortality and health even after adjusting for socioeconomic and behavioral factors, suggesting that a direct biological effect occurring from early life is plausible (28, 29). It has been suggested that psychosocial factors could protect and buffer early adverse circumstances, such as parental warmth and psychological resources, reducing physiological responses and mitigating disease processes (30, 31). However, only a few studies have analyzed the influence of ACE on health over the life course by examining these different pathways, and fewer have used an AL index.

The main hypothesis tested in this study is that chronic stress resulting from ACE may be biologically embedded (2, 19) and lead to a cumulative multisystem dysregulation via three broad and intertwined pathways across the life course: (*i*) an indirect health behaviors pathway, (*ii*) an indirect socioeconomic/materialist and/or psychosocial pathway, (*iii*) through a direct biological pathway via alterations of physiological stress systems (e.g., hypothalamic-pituitary-adrenal axis) that could influence health in the long term. The aim of this paper is to explore whether ACEs are associated with elevated AL in midlife. We will examine whether cumulative socioeconomic conditions and/or health behaviors mediate such a relationship, and if the relationships still persists after adjusting for these mediating factors.

## Materials and Methods

**Participants.** Data are from the 1958 National Child Development Study (NCDS), which included all births during 1 wk in 1958 ($n$ = 18,558) in Great Britain. Data collection was carried out on cohort members between birth and 50 y. At age 44–45 y, a biomedical survey was conducted including a self-reported questionnaire, physical measurements, blood and saliva samples for a target sample of 12,070 individuals of the original cohort, and data were available for 9,377. The NCDS has been described in detail elsewhere (32).

**Ethics and Data.** Written informed consent was obtained from parents for childhood measurements and ethical approval for the adult data collection was obtained from the National Research Ethics Advisory Panel. NCDS data are open-access datasets available to nonprofit research organizations. Ethical approval for the age 45 y survey was given by the South East Multicentre Research Ethics Committee.

**Measures.**

***ACEs.*** ACEs were identified as a set of traumatic and stressful psychosocial conditions that are out of the child's control, that tend to co-occur (33), and that often persist over time (24, 34). ACEs were defined as intrafamilial events or conditions causing chronic stress responses in the child's immediate environment. These include notions of maltreatment and deviation from societal norms, where possible to be distinguished from conditions in the socioeconomic and material environment. Because the NCDS has a large amount of prospective data, we restricted ACE to intrafamilial events or conditions in the child's immediate environment.

Information was extracted via variables collected at ages 7, 11, and 16 from questions asked to the child's parent or their teacher. Sources of adversity were divided into six categories as follows: (*i*) Child in care: child has ever been in public/voluntary care services or foster care at age 7, 11, or 16. (*ii*) Physical neglect: child appears undernourished/dirty at age 7 or 11, information collected from the response from child's teacher to the Bristol Social Adjustment Guide. Household dysfunction, as described by Felitti et al. (24), is a dimension of adversity consisting of four categories each contributing to the score: (*iii*) offenders: the child lived in a household where a family member was in prison or on probation (11 y) or is in contact with probation service at 7 or 11 y; the child has ever been to prison or been on probation at 16 y. (*iv*) Parental separation: the child has been separated from their father or mother due to death, divorce, or separation at 7, 11, or 16 y. (*v*) Mental illness: household has contact with mental health services at 7 or 11 y; family member has mental illness at 7, 11, or 16 y. (*vi*) Alcohol abuse: family member has alcohol abuse problem at 7 y.

Exposure to adversity was identified by a positive response to any of the above categories. Respondents were excluded if they had missing data for all six categories. Respondents were considered as having no adversities if they answered "no" to all of the categories or if they answered "no" to one or more category and the other categories were missing. ACEs were measured by counting the reports of the following: child in care, physical neglect, offenders, parental separation, mental illness, and alcohol abuse. A three-category variable was then constructed (0 adversities, one adversity, two or more adversities).

***AL at 44 y.*** AL is a measure of cumulative physiological wear-and-tear. Among available biomarkers, we selected 14 parameters representing four physiological systems: the neuroendocrine system [salivary cortisol t1 (nanomoles per liter), salivary cortisol t1–t2 (nanomoles per liter)]; the immune and inflammatory system [insulin-like growth factor-1 (IGF1) (nanomoles per liter), C-reactive protein (CRP) (milligrams per liter), fibrinogen (grams per liter), IgE (kilounits per liter)]; the metabolic system [high-density lipoprotein (HDL) (in millimoles per liter), low-density lipoprotein (LDL) (millimoles per liter), triglycerides (millimoles per liter), glycosylated hemoglobin ($HbA_{1C}$) (millimoles per mole)]; the cardiovascular and respiratory systems: [systolic blood pressure (SBP) (millimeters of mercury), diastolic blood pressure (DBP) (millimeters of mercury), heart rate/pulse pulses per minute), peak expiratory flow (liters per minute)] (detailed information regarding the function and measure of each biomarker is provided in Table S1; descriptive information and high-risk cut points are provided in Table S2). These biomarkers were chosen based on previous measures of AL (11, 12) and according to the evidence of their relationship to stressful conditions over life and later morbidity and mortality (35–38). Each biomarker was then dichotomized into high risk versus low risk according to sex-specific quartiles. The high-risk quartile was the top quartile of all biomarkers, except for those for which a low level confers greater risk for poor health outcomes (HDL, salivary cortisol t1–t2, IGF1, peak expiratory flow). AL score was calculated by summing the 14 dichotomized markers. We excluded from our sample 1,264 individuals (pregnant women and those for whom blood was not obtained). A total of 3,155 individuals had at least one missing data for the 14 biomarkers and, on average, 2.6. We chose to adopt a conservative approach (maximum bias), systematically considering them as not at risk for the missing biomarker.

***Early life socioeconomic and biological confounders.*** We selected variables from a questionnaire completed at birth by the cohort member's mother that were likely to be social or biological confounders based on the literature: household and parental characteristics [mother's education level (left school at 15 y or later/before 14 y), mother's partner's (or father's if unavailable) social class (nonmanual/manual), overcrowded household (people per room >1.5 or ≤1.5)], maternal smoking during pregnancy (no smoking, sometimes, moderately, heavily), mother's body mass index (BMI) (self-reported prepregnancy weight and height measured after the birth): normal/underweight/overweight/obese (18.5–24.9, <18.5, 25–29.9, and ≥30 kg/m$^2$, respectively). Respondent's characteristics and birth variables were also included: sex, birth weight (categorized in quartiles). We used the perinatal variables as proxies to better capture elements in the early environment potentially related to socioeconomic and psychosocial stressful conditions. These variables (mother's BMI, maternal smoking during pregnancy, mother's age at birth and birth weight) may partly account for the association between ACE and AL acting as confounders. A binary childhood pathologies variable was constructed using data collected at ages 7, 11, and 16 y. It was based both on mother's report and medical examinations including congenital conditions, moderate/severe disabilities, chronic respiratory or circulatory conditions, sensory impairments, and special schooling.

***Mediators across the life course.*** The following adult mediating factors were added to the models: socioeconomic status [respondent's educational attainment at 23 y (A level/O level/no qualification) and respondent's occupational social class at 33 y (nonmanual/manual active)]; socioeconomic status at 33 y was described using a wealth variable constructed based on information about home ownership and the price of the house adjusted for economic inflation of the year of purchase and then divided in quartiles (not owner/Q1—owner lowest price/owner-Q2/owner-Q3/owner-Q4); and marital status at 33 y (couple/single/divorced or widowed); health behaviors at 23 y were considered as a proxy for behavioral patterns in early adulthood (physical activity [physically active/moderately active/inactive], alcohol consumption [moderate (women: between 1 and 14 units in the previous week; men: between 1 and 21 units in the previous week)/abstainers (reported not consuming any alcohol in the previous week)/heavy drinkers (women: >14 units in the previous week; men: >21 units in the previous week)] (39), and smoking status [nonsmoker/former smoker/smoker (<10 cigarettes/smoker; 10–19 cigarettes/smoker; >20 cigarettes)]; BMI [normal/underweight/overweight/obese]); a "malaise inventory" that identifies symptoms of depression and/or anxiety. The individual was considered as having a psychological malaise if

**Table 1. Descriptive statistics on the subsample for men and women**

| Variables | Men, 3,753 (%) | Women, 3,782 (%) |
|---|---|---|
| AL | | |
| 0 | 283 (7.54%) | 313 (8.28%) |
| 1 | 589 (15.69%) | 670 (17.72%) |
| 2 | 797 (21.24%) | 734 (19.41%) |
| 3 | 715 (19.05%) | 620 (16.39%) |
| 4 | 554 (14.76%) | 538 (14.23%) |
| 5 | 360 (9.59%) | 371 (9.81%) |
| 6 | 240 (6.40%) | 245 (6.48%) |
| 7 | 135 (3.60%) | 140 (3.70%) |
| 8 | 58 (1.55%) | 93 (2.46%) |
| 9 | 18 (0.48%) | 44 (1.16%) |
| 10 | 4 (0.11%) | 7 (0.19%) |
| 11 | 0 (0.00%) | 5 (0.13%) |
| 12 | 0 (0.00%) | 2 (0.05%) |
| ACEs | | |
| None | 2,721 (72.50%) | 2,775 (73.37%) |
| One | 786 (20.94%) | 764 (20.20%) |
| Two or more | 246 (6.56%) | 243 (6.43%) |
| Mother's education level | | |
| Left school at 15 or later | 963 (25.66%) | 971 (25.67%) |
| Left school before 14 | 2,643 (70.42%) | 2,648 (70.02%) |
| Missing | 147 (3.92%) | 163 (4.31%) |
| Father's social class at birth | | |
| Nonmanual | 1,063 (28.32%) | 1,037 (27.42%) |
| Manual | 2,534 (67.52%) | 2,568 (67.90%) |
| Missing | 156 (4.16%) | 177 (4.68%) |
| Overcrowding | | |
| >1.5 people per room | 385 (10.26%) | 448 (11.85%) |
| ≤1.5 people per room | 3,146 (83.83%) | 3,103 (82.05%) |
| Missing | 222 (5.92%) | 231 (6.11%) |
| Mother's BMI | | |
| Normal | 2,514 (66.99%) | 2,472 (65.36%) |
| Underweight | 128 (3.41%) | 170 (4.50%) |
| Overweight | 652 (17.37%) | 665 (17.58%) |
| Obese | 144 (3.84%) | 140 (3.70%) |
| Missing | 315 (8.39%) | 335 (8.86%) |
| Mother smoked during pregnancy | | |
| No | 2,448 (65.23%) | 2,426 (64.15%) |
| Sometimes | 222 (5.92%) | 207 (5.47%) |
| Moderately | 514 (13.70%) | 550 (14.54%) |
| Heavily | 405 (10.79%) | 413 (10.92%) |
| Missing | 164 (4.37%) | 186 (4.92%) |
| Birth weight | | |
| Q1: low weight | 730 (19.45%) | 714 (18.88%) |
| Q2 | 1,022 (27.23%) | 904 (23.90%) |
| Q3 | 825 (21.98%) | 962 (25.44%) |
| Q4: high weight | 939 (25.02%) | 956 (25.28%) |
| Missing | 237 (6.32%) | 246 (6.50%) |
| Childhood pathologies | | |
| No | 2,749 (73.25%) | 2,883 (76.23%) |
| Yes | 994 (26.49%) | 887 (23.45%) |
| Missing | 10 (0.27%) | 12 (0.32%) |
| Smoking status at 23 | | |
| Nonsmoker | 929 (24.75%) | 1,100 (29.09%) |
| Former smoker | 1,045 (27.84%) | 939 (24.83%) |
| Smoker: less than 10 cigarettes | 221 (5.89%) | 336 (8.88%) |
| Smoker: 10–19 cigarettes | 437 (11.64%) | 493 (13.04%) |
| Smoker: more than 20 cigarettes | 576 (15.35%) | 467 (12.35%) |
| Missing | 545 (14.52%) | 447 (11.82%) |
| Alcohol consumption at 23 | | |
| Moderate | 1,553 (41.38%) | 1,756 (46.43%) |
| Abstainers | 397 (10.58%) | 1,158 (30.62%) |
| Heavy drinkers | 1,256 (33.47%) | 420 (11.11%) |
| Missing | 547 (14.58%) | 448 (11.85%) |
| Physical activity at 23 | | |
| Physically active | 1,389 (37.01%) | 797 (21.07%) |
| Moderately active | 587 (15.64%) | 474 (12.53%) |
| Inactive | 1,228 (32.72%) | 2,064 (54.57%) |
| Missing | 549 (14.63%) | 447 (11.82%) |
| Malaise inventory at 23 | | |
| No | 3,093 (82.41%) | 3,003 (79.40%) |
| Yes | 110 (2.93%) | 329 (8.70%) |
| Missing | 550 (14.66%) | 450 (11.90%) |
| Education level at 23 | | |
| Passed A levels | 788 (21.00%) | 762 (20.15%) |
| Passed O levels | 1,239 (33.01%) | 1,496 (39.56%) |
| No qualifications | 1,179 (31.42%) | 1,075 (28.42%) |
| Missing | 547 (14.58%) | 449 (11.87%) |
| BMI at 23 | | |
| Normal | 2,522 (67.20%) | 2,673 (70.68%) |
| Underweight | 73 (1.95%) | 207 (5.47%) |
| Overweight | 502 (13.38%) | 334 (8.83%) |
| Obese | 60 (1.60%) | 83 (2.20%) |
| Missing | 596 (15.88%) | 485 (12.82%) |
| Social class at 33 | | |
| Nonmanual | 1,649 (43.94%) | 2,249 (59.47%) |
| Manual | 1,464 (39.01%) | 950 (25.12%) |
| Missing | 640 (17.05%) | 583 (15.42%) |
| Wealth at 33 | | |
| Not owner | 732 (19.50%) | 777 (20.55%) |
| Owner: Q1 (low price) | 637 (16.97%) | 637 (16.84%) |
| Owner: Q2 | 610 (16.25%) | 663 (17.53%) |
| Owner: Q3 | 633 (16.87%) | 632 (16.71%) |
| Owner: Q4 | 595 (15.85%) | 645 (17.05%) |
| Missing | 546 (14.55%) | 428 (11.32%) |
| Marital status at 33 | | |
| Couple | 2,622 (69.86%) | 2,811 (74.33%) |
| Single | 453 (12.07%) | 312 (8.25%) |
| Divorced or widowed | 174 (4.64%) | 289 (7.64%) |
| Missing | 504 (13.43%) | 370 (9.78%) |

s/he reported experiencing more than 7 out of 24 symptoms (no malaise/malaise) (40–42).

***Data analysis.*** To control for possible bias due to missing data, we imputed data for covariates with missing data using the multiple imputation program ICE in STATA V11. Twenty imputations were conducted taking the missing-at-random (MAR) assumption. Each covariable with missing values was imputed including all confounders and mediators used in the models as well as variables from other sweeps correlated with the variable to impute (*SI Materials and Methods*), but excluding the exposure variable (ACE) and AL. The sample used for this study is described in Fig. S1.

Descriptive statistics (Table 1) were carried out on nonimputed data. Bivariate (Table S3) and multivariate analyses (Tables 2 and 3) were carried out on the imputed data using linear regression. We performed a multivariate linear analysis that took a life course perspective, whereby variables were added to the model in chronological order. Then, to explore the relationships between ACE and AL, we conducted a path analysis using ACE as the exposure variable (Figs. S2 and S3).

We conducted two different sensitivity analyses (*SI Materials and Methods*). The first one was a series of regression analyses of individual biomarkers for studying the AL score stability by identifying if within our score a parameter was having a stronger effect relatively to the others (Table S4). The second sensitivity analysis was to ensure that our results using a

complete case AL score were not biased by missing values; we thus imputed the missing biomarkers from other measured biomarkers (Table S5).

Recent studies have shown that potential sex/sex differences may exist when analyzing the life course processes of disease development (43–45). When studying the lasting impact of stress-related diseases, the perception, interpretation, and physiological responses to chronic stress could have a differential impact on men and women (for further details, see *SI Materials and Methods*). Therefore, the multivariate linear analysis was run separately by sex. The variables were entered chronologically as they would occur over the life span. First, early life socioeconomic circumstances and perinatal variables were entered. In model 2, we controlled for childhood pathologies and ACE. Model 3 additionally controlled for education, psychological malaise, and health behaviors at 23 y. Finally, model 4 took into account the material and socioeconomic circumstances at 33 y: wealth, social class, and marital status.

Subsequently, we used path modeling to examine all indirect associations between ACE and AL in adulthood. Path analysis allows us to disentangle and describe indirect effect pathways (46) (Figs. S2 and S3). The direct pathway between ACE and AL was calculated using a classic multivariate linear regression after adjustment for confounders and mediation variables. The indirect pathways correspond to the part of the effect observed between ACE and AL score that is explained by the mediating factors. All analyses were performed using STATA V11 taking a statistical significance level of 0.05.

## Results

Descriptive statistics of the nonimputed sample are presented in Table 1 for the subsample ($n$ = 3,753 for men; $n$ = 3,782 for women). In *Materials and Methods*, we report the bivariate statistics (Table S3) for both men and women.

The multivariate analyses for men (Table 2) showed that mother's education, parental social class, and childhood pathologies were associated with an increased AL score (model 1). Mother's BMI and smoking heavily during pregnancy were positively associated with AL score. Birth weight was inversely associated to AL: individuals in the highest quartile had a lower AL score compared with those into the lower quartile. With the inclusion of childhood pathologies and ACE (model 2), the socioeconomic variables at birth continued to be predictors of higher AL score, although these relationships were slightly attenuated. Compared with men with no ACE, those classified as having one ACE had an increased AL score (0.18; $P = 0.02$); the increase was greater among men exposed to two or more ACEs (0.46; $P < 0.01$). The effect of ACE on AL score was strongly mediated by health behaviors at 23 y, because the relationship between ACE and AL was no longer significant (model 3). The full model (model 4) shows that the socioeconomic variables at 33 y were important mediators of the relationship between ACE and AL. Parental social class (manual), mother's BMI, birth weight, childhood pathologies, smoking heavily, and being overweight or obese at 23 y were associated with higher AL score even though the strength of these associations dropped slightly. Wealth was significantly related to a lower AL score ($\beta = -0.43$, $P < 0.01$ for the highest quartile) and being single increased AL score by 0.22 ($P = 0.02$). The path analysis, highlighting the direct and indirect effects between ACE and AL, for men showed that the association between ACE and AL was strongly mediated by health behaviors at 23 y and socioeconomic status at 33 y. Among men, 59% (for two or more ACEs) of the total mediated effect was mediated by health behaviors (especially smoking), education level at 23 y and wealth at 33 y.

The multivariate analyses for women are shown in Table 3. Model 1 shows that mother's education, parental social class, and mother's BMI (overweight) were positively and significantly associated with a higher AL score. Birth weight was inversely correlated with AL score. Children of mothers who smoked lightly during pregnancy had a higher AL score. The same patterns were observed for the variables at birth even if the strength of these associations were weakened (model 2). Compared with women with no ACE, those with one ACE had an increased AL score (0.24; $P < 0.01$), as did those with two or more ACEs (0.42; $P < 0.01$). The effect of ACE on AL score was strongly mediated by health behaviors at 23 y, with the association between ACE and AL disappearing (model 3) when these were entered into the model. Being a smoker, overweight, or obese at 23 y and having no qualification were associated with higher AL score. Being a heavy drinker was inversely associated to AL score. In the full model (model 4), early life socioeconomic circumstances remained associated with AL score after controlling for mediators. Being a smoker, overweight, or obese at 23 y and being a home owner at 33 y was significantly and positively associated to AL score at 44 y. Finally the path analysis showed that the link between ACE and AL was strongly mediated by health behaviors and BMI at 23 y as well as socioeconomic characteristics at 33 y. ACE was associated with a higher AL score in midlife mainly via smoking, wealth, BMI, and education level (76% of the mediated effect for two or more ACEs).

Table S4 shows the sensitivity analyses results on individual biomarkers. No significant variances between different AL scores constructed were observed confirming the stability of the 14 AL score. Table S5 reports the results of the second sensitivity analysis comparing the complete case AL score to the imputed AL score showing that missing values did not impact the stability of the AL score. We tested in our model the influence of adding other perinatal variables (mother's age at birth, parity, gestational age, and breastfed), and the results remained unchanged.

## Discussion

The main finding of this study was that psychosocial adversity in childhood was related to physiological wear-and-tear at 44 y after taking birth and childhood factors into account, in a large prospective cohort. For men and women, this association was strongly mediated by health behaviors at 23 y (principally smoking) and socioeconomic status (in particular education level at 23 y and wealth at 33 y). For women, BMI at 23 y also explained part of the link between ACE and AL.

Our hypothesis was that early psychosocial adversity can be embedded and impact later health. Our findings add to the literature by testing potential mediating pathways. We have proposed that biological embedding could be the result of three different pathways: two indirect pathways through health behaviors and socioeconomic/or psychosocial factors, and a third direct biological pathway. We use the conceptual framework of AL as a measure of cumulative biological wear-and-tear to examine our hypotheses. These results are suggestive of a link between stressful conditions in early life and health in adulthood largely explained by socioeconomic or behavioral factors but not entirely.

Our results show that, after controlling for confounders and mediators, a sizable part of the initial effect remains unexplained (24–41% in the whole population according to the level of ACE). The lack of statistical significance may be due to a lack of power, because we only have 246 men and 243 women with two or more ACEs. These associations may be explained by measurement error or the omission of confounders, but it may also suggest the existence of a biological path that could have lasting effects over time (47).

Hertzman introduced the term of biological embedding as the processes whereby cumulative disadvantaged could metaphorically "get under the skin" and alter human biological and developmental processes (19). In this context, the study of the relationship between ACE and AL can contribute to a better understanding of early origins of disease and social gradient in health. Recently, Kelly-Irving et al. (28, 29) showed an association between ACE and self-reported cancer as well as mortality, after adjusting for behavioral and socioeconomic factors suggesting

**Table 2. Life course multivariate linear regression using data obtained from multiple imputation: men ($n$ = 3,753)**

| | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|
| Variables | $\beta$ (SE) | $P$ | $\beta$ (SE) | $P$ | $\beta$ (SE) | $P$ | $\beta$ (SE) | $P$ |
| Mother's education level | | | | | | | | |
| Left school at 15 or later | 0 | | 0 | | 0 | | 0 | |
| Left school before 14 | 0.17 (0.08) | 0.03 | 0.16 (0.08) | 0.04 | 0.07 (0.08) | 0.35 | 0.06 (0.08) | 0.44 |
| Father's social class at birth | | | | | | | | |
| Nonmanual | 0 | | 0 | | 0 | | 0 | |
| Manual | 0.39 (0.08) | <0.01 | 0.37 (0.08) | <0.01 | 0.23 (0.08) | <0.01 | 0.22 (0.08) | <0.01 |
| Overcrowding | | | | | | | | |
| >1.5 people per room | 0 | | 0 | | 0 | | 0 | |
| ≤1.5 people per room | −0.08 (0.10) | 0.46 | −0.03 (0.10) | 0.79 | 0.02 (0.10) | 0.84 | 0.04 (0.10) | 0.70 |
| Mother's BMI | | | | | | | | |
| Normal | 0 | | 0 | | 0 | | 0 | |
| Underweight | 0.13 (0.17) | 0.46 | 0.10 (0.17) | 0.58 | 0.19 (0.17) | 0.26 | 0.21 (0.17) | 0.22 |
| Overweight | 0.29 (0.08) | <0.01 | 0.29 (0.08) | <0.01 | 0.23 (0.08) | <0.01 | 0.22 (0.08) | <0.01 |
| Obese | 0.59 (0.16) | <0.01 | 0.55 (0.16) | <0.01 | 0.32 (0.16) | 0.05 | 0.30 (0.16) | 0.06 |
| Mother smoked during pregnancy | | | | | | | | |
| No | 0 | | 0 | | 0 | | 0 | |
| Sometimes | 0.29 (0.14) | 0.03 | 0.26 (0.14) | 0.05 | 0.16 (0.13) | 0.22 | 0.16 (0.13) | 0.24 |
| Moderately | 0.12 (0.09) | 0.19 | 0.11 (0.09) | 0.25 | 0.08 (0.09) | 0.39 | 0.08 (0.09) | 0.40 |
| Heavily | 0.22 (0.10) | 0.03 | 0.20 (0.10) | 0.06 | 0.09 (0.10) | 0.38 | 0.09 (0.10) | 0.39 |
| Birth weight | | | | | | | | |
| Q1: low weight | 0 | | 0 | | 0 | | 0 | |
| Q2 | −0.27 (0.09) | <0.01 | −0.25 (0.09) | <0.01 | −0.24 (0.09) | <0.01 | −0.22 (0.09) | 0.01 |
| Q3 | −0.26 (0.09) | <0.01 | −0.25 (0.09) | <0.01 | −0.26 (0.09) | <0.01 | −0.23 (0.09) | 0.01 |
| Q4: high weight | −0.31 (0.09) | <0.01 | −0.28 (0.09) | <0.01 | −0.32 (0.09) | <0.01 | −0.30 (0.09) | <0.01 |
| Childhood pathologies | | | | | | | | |
| No | | | 0 | | 0 | | 0 | |
| Yes | | | 0.20 (0.07) | <0.01 | 0.18 (0.07) | 0.01 | 0.15 (0.07) | 0.03 |
| ACEs | | | | | | | | |
| None | | | 0 | | 0 | | 0 | |
| One | | | 0.18 (0.08) | 0.02 | 0.06 (0.08) | 0.47 | 0.05 (0.08) | 0.54 |
| Two or more | | | 0.46 (0.13) | <0.01 | 0.25 (0.13) | 0.05 | 0.19 (0.13) | 0.14 |
| Smoking status at 23 | | | | | | | | |
| Nonsmoker | | | | | 0 | | 0 | |
| Former smoker | | | | | −0.17 (0.09) | 0.05 | −0.16 (0.09) | 0.06 |
| Smoker: less than 10 cigarettes | | | | | −0.06 (0.15) | 0.69 | −0.07 (0.15) | 0.64 |
| Smoker: 10–19 cigarettes | | | | | 0.42 (0.11) | <0.01 | 0.40 (0.11) | <0.01 |
| Smoker: more than 20 cigarettes | | | | | 0.79 (0.10) | <0.01 | 0.77 (0.10) | <0.01 |
| Alcohol consumption at 23 | | | | | | | | |
| Moderate | | | | | 0 | | 0 | |
| Abstainers | | | | | −0.04 (0.11) | 0.73 | −0.08 (0.11) | 0.43 |
| Heavy drinkers | | | | | 0.06 (0.07) | 0.39 | 0.04 (0.07) | 0.54 |
| Physical activity at 23 | | | | | | | | |
| Physically active | | | | | 0 | | 0 | |
| Moderately active | | | | | 0.09 (0.09) | 0.32 | 0.10 (0.09) | 0.28 |
| Inactive | | | | | 0.16 (0.08) | 0.03 | 0.14 (0.08) | 0.08 |
| Malaise inventory at 23 | | | | | | | | |
| No | | | | | 0 | | 0 | |
| Yes | | | | | 0.06 (0.18) | 0.75 | 0.01 (0.18) | 0.95 |
| Education level at 23 | | | | | | | | |
| Passed A levels | | | | | 0 | | 0 | |
| Passed O levels | | | | | 0.11 (0.09) | 0.20 | 0.09 (0.09) | 0.33 |
| No qualifications | | | | | 0.26 (0.10) | <0.01 | 0.20 (0.11) | 0.07 |
| BMI at 23 | | | | | | | | |
| Normal | | | | | 0 | | 0 | |
| Underweight | | | | | −0.15 (0.21) | 0.46 | −0.24 (0.21) | 0.24 |
| Overweight | | | | | 0.48 (0.09) | <0.01 | 0.47 (0.09) | <0.01 |
| Obese | | | | | 1.22 (0.24) | <0.01 | 1.16 (0.24) | <0.01 |
| Social class at 33 | | | | | | | | |
| Nonmanual | | | | | | | 0 | |
| Manual | | | | | | | −0.03 (0.08) | 0.71 |

**Table 2. Cont.**

| Variables | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|
| | $\beta$ (SE) | *P* | $\beta$ (SE) | *P* | $\beta$ (SE) | *P* | $\beta$ (SE) | *P* |
| Wealth at 33 | | | | | | | | |
| Not owner | | | | | | | 0 | |
| Owner: Q1 (Low price) | | | | | | | −0.17 (0.10) | 0.10 |
| Owner: Q2 | | | | | | | −0.15 (0.11) | 0.15 |
| Owner: Q3 | | | | | | | −0.39 (0.11) | <0.01 |
| Owner: Q4 | | | | | | | −0.43 (0.12) | <0.01 |
| Marital status at 33 | | | | | | | | |
| Couple | | | | | | | 0 | |
| Single | | | | | | | 0.22 (0.10) | 0.02 |
| Divorced or widowed | | | | | | | 0.15 (0.14) | 0.28 |

a potential direct link. There is growing evidence the early environment could have an adverse effect on mental and physical health and ACE appeared to be associated with increased activation in the nervous, endocrine, and immune systems. To our knowledge, only one study has explored the influence of social adversity over the life span on AL independently of socioeconomic status (48). However, health behaviors were not taken into account in this study, and it remains unclear how to disentangle the potential pathways by which ACE could influence AL. The mechanisms underlying these observations remain unclear (13, 14, 49) and deserve further research.

Our findings showed a link between birth weight and AL. This result is in accordance with Barker's hypothesis, which suggests that exposure to undernutrition in utero was associated with developing coronary heart disease in adulthood (50). Subsequent work based on the developmental origins of adult disease points toward the existence of a sensitive-periods mechanism, and in this case, that low birth weight has a lasting impact on health across the life span (51).

Regarding the mediating role of health behaviors, our findings are consistent with the literature. The common social pattern in health behavior adoption potentially includes a number of processes that have been well described in the literature. The psychological processes highlighted by Bandura (25, 26) suggest that ACEs could be related to health through a number of mechanisms. These may include poor self-regulation, self-efficacy, and self-management mechanisms. Furthermore, it has been suggested that individuals exposed to adversity-induced stress could adopt coping mechanisms by obtaining a pharmacological or psychological benefit from tobacco or alcohol use (22, 24, 52). These results suggest an indirect mechanism of the embodiment of early life experiences via health behaviors and material and/or psychosocial circumstances in adulthood.

The main weakness of this study is related to attrition, missing data, and selection bias. We therefore imputed the missing data in the eligible sample taking the MAR assumption to preserve important aspects of the distribution, variability, and relationships between variables. According to this assumption, missingness depends on observed data, such as baseline characteristics and other measures occurring at different time points (53). However, the assumption of MAR is unverifiable and we cannot rule out that some data are "missing not at random" (MNAR). Multiple imputation models, such as the one used on these data, include large numbers of covariates, helping to render the MAR assumption more plausible and to limit the impact of MNAR missingness (54).

Another limitation is the measurement of AL. Although the concept of AL is consistent with our biological embedding hypothesis, our score remains limited by the pragmatism of variable availability. Our score is strongly focused on the cardiovascular system and we have a lack of "primary" biomarkers (epinephrine and norepinephrine). However, there is currently no consensus regarding the choice of relevant physiological systems, of biomarkers, their interactions (linear relationships), their importance in the chain of physiological stress responses, as well as their measurement, combinations, weighting, and the most suitable statistical analysis (6). Furthermore, as physiological responses to stress may differ according to developmental stage over time, measure of AL may differ in terms of markers and risk thresholds.

It is likely that a number of confounders and mediators have not been taken into account for this analysis. Measurement error is likely in the variable characterizing ACE. Misclassification bias is possible where parents may have responded "no" to any given question due to the sensitive nature of the data. Because of that, the ACE variable we built is also a conservative measure. Our ACE measurement is limited and it remains a proxy for severe circumstances that we hypothesized as being chronically stressful, and it takes into account only the child's condition at age 7, 11, and 16.

Despite these limitations, this study has a number of strengths. It is a longitudinal population-based study collecting data prospectively across the life span. Most studies on childhood adversities use retrospectively collected information, which is highly sensitive and potentially open to a number of different reporting biases. A strength of the childhood adversity measure operationalized here is in its prospective nature, where information collected during childhood about potentially stressful events in the child's life was used to create the variable. Another important strength is in the sample size included in the biomedical survey, and the large number of biomarkers available. Finally, the array and detail of the variables within the cohort allows us to control for a number variables of potential confounding and mediating factors.

## Conclusion

These results based on a path analysis show that childhood adversity is associated with physiological wear-and-tear in midlife as measured by AL. This relationship is mediated, but not fully explained, by later life variables. The path analysis suggests that childhood adversities are associated with an increased AL score in midlife for men via health behaviors, education, and wealth, and for women via wealth, education, smoking, and BMI.

This research provides insight into the mechanisms of accumulation of health risk in adults. Groups who experienced adversities may carry the cost across their life expressed by physiological wear-and-tear in adulthood. For instance, men who experienced two or more ACEs are more likely to have a lower education level, to smoke and drink at 23 y, and to be less well-off at 33 y.

**Table 3. Life course multivariate linear regression using data obtained from multiple imputation: women ($n$ = 3,782)**

| | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|
| Variables | $\beta$ (SE) | $P$ | $\beta$ (SE) | $P$ | $\beta$ (SE) | $P$ | $\beta$ (SE) | $P$ |
| Mother's education level | | | | | | | | |
| Left school at 15 or later | 0 | | 0 | | 0 | | 0 | |
| Left school before 14 | 0.45 (0.08) | <0.01 | 0.43 (0.08) | <0.01 | 0.31 (0.09) | <0.01 | 0.31 (0.09) | <0.01 |
| Father's social class at birth | | | | | | | | |
| Nonmanual | 0 | | 0 | | 0 | | 0 | |
| Manual | 0.45 (0.08) | <0.01 | 0.43 (0.08) | <0.01 | 0.25 (0.08) | <0.01 | 0.22 (0.08) | <0.01 |
| Overcrowding | | | | | | | | |
| >1.5 people per room | 0 | | 0 | | 0 | | 0 | |
| ≤1.5 people per room | −0.19 (0.11) | 0.10 | −0.15 (0.11) | 0.17 | −0.04 (0.11) | 0.68 | −0.03 (0.11) | 0.76 |
| Mother's BMI | | | | | | | | |
| Normal | 0 | | 0 | | 0 | | 0 | |
| Underweight | 0.10 (0.17) | 0.54 | 0.07 (0.17) | 0.70 | 0.11 (0.16) | 0.49 | 0.11 (0.16) | 0.51 |
| Overweight | 0.36 (0.10) | <0.01 | 0.37 (0.10) | <0.01 | 0.24 (0.09) | 0.01 | 0.24 (0.09) | 0.01 |
| Obese | 0.18 (0.18) | 0.32 | 0.16 (0.18) | 0.39 | −0.19 (0.18) | 0.29 | −0.21 (0.18) | 0.24 |
| Mother smoked during pregnancy | | | | | | | | |
| No | 0 | | 0 | | 0 | | 0 | |
| Sometimes | 0.41 (0.15) | <0.01 | 0.36 (0.15) | 0.02 | 0.19 (0.15) | 0.21 | 0.15 (0.15) | 0.31 |
| Moderately | 0.08 (0.10) | 0.44 | 0.07 (0.10) | 0.52 | −0.02 (0.10) | 0.87 | −0.04 (0.10) | 0.70 |
| Heavily | 0.21 (0.11) | 0.07 | 0.18 (0.11) | 0.11 | 0.01 (0.11) | 0.94 | 0.01 (0.11) | 0.96 |
| Birth weight | | | | | | | | |
| Q1: low weight | 0 | | 0 | | 0 | | 0 | |
| Q2 | −0.17 (0.10) | 0.10 | −0.17 (0.10) | 0.10 | −0.12 (0.10) | 0.24 | −0.12 (0.10) | 0.21 |
| Q3 | −0.21 (0.10) | 0.03 | −0.20 (0.10) | 0.04 | −0.17 (0.10) | 0.08 | −0.15 (0.10) | 0.11 |
| Q4: high weight | −0.36 (0.10) | <0.01 | −0.35 (0.10) | <0.01 | −0.33 (0.10) | <0.01 | −0.33 (0.10) | <0.01 |
| Childhood pathologies | | | | | | | | |
| No | | | 0 | | 0 | | 0 | |
| Yes | | | 0.20 (0.08) | 0.02 | 0.13 (0.08) | 0.11 | 0.12 (0.08) | 0.12 |
| ACEs | | | | | | | | |
| None | | | 0 | | 0 | | 0 | |
| One | | | 0.24 (0.09) | <0.01 | 0.13 (0.08) | 0.12 | 0.10 (0.08) | 0.24 |
| Two or more | | | 0.42 (0.14) | <0.01 | 0.15 (0.14) | 0.27 | 0.10 (0.14) | 0.46 |
| Smoking status at 23 | | | | | | | | |
| Nonsmoker | | | | | 0 | | 0 | |
| Former smoker | | | | | −0.20 (0.09) | 0.03 | −0.19 (0.09) | 0.04 |
| Smoker: less than 10 cigarettes | | | | | −0.06 (0.12) | 0.61 | −0.10 (0.12) | 0.43 |
| Smoker: 10–19 cigarettes | | | | | 0.41 (0.11) | <0.01 | 0.35 (0.11) | <0.01 |
| Smoker: more than 20 cigarettes | | | | | 0.66 (0.11) | <0.01 | 0.57 (0.11) | <0.01 |
| Alcohol consumption at 23 | | | | | | | | |
| Moderate | | | | | 0 | | 0 | |
| Abstainers | | | | | 0.02 (0.08) | 0.77 | −0.02 (0.08) | 0.81 |
| Heavy drinkers | | | | | −0.36 (0.11) | <0.01 | −0.35 (0.11) | <0.01 |
| Physical activity at 23 | | | | | | | | |
| Physically active | | | | | 0 | | 0 | |
| Moderately active | | | | | −0.06 (0.11) | 0.61 | −0.05 (0.11) | 0.63 |
| Inactive | | | | | 0.16 (0.09) | 0.06 | 0.14 (0.09) | 0.12 |
| Malaise inventory at 23 | | | | | | | | |
| No | | | | | 0 | | 0 | |
| Yes | | | | | 0.22 (0.12) | 0.06 | 0.20 (0.12) | 0.09 |
| Education level at 23 | | | | | | | | |
| Passed A levels | | | | | 0 | | 0 | |
| Passed O levels | | | | | 0.08 (0.10) | 0.41 | 0.06 (0.10) | 0.51 |
| No qualifications | | | | | 0.26 (0.11) | 0.02 | 0.17 (0.12) | 0.15 |
| BMI at 23 | | | | | | | | |
| Normal | | | | | 0 | | 0 | |
| Underweight | | | | | −0.26 (0.14) | 0.08 | −0.25 (0.14) | 0.08 |
| Overweight | | | | | 0.89 (0.12) | <0.01 | 0.85 (0.12) | <0.01 |
| Obese | | | | | 2.01 (0.23) | <0.01 | 1.88 (0.23) | <0.01 |
| Social class at 33 | | | | | | | | |
| Nonmanual | | | | | | | 0 | |
| Manual | | | | | | | 0.04 (0.09) | 0.68 |

**Table 3. Cont.**

| Variables | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|
| | $\beta$ (SE) | *P* | $\beta$ (SE) | *P* | $\beta$ (SE) | *P* | $\beta$ (SE) | *P* |
| Wealth at 33 | | | | | | | | |
| Not owner | | | | | | | 0 | |
| Owner: Q1 (low price) | | | | | | | −0.35 (0.11) | <0.01 |
| Owner: Q2 | | | | | | | −0.48 (0.11) | <0.01 |
| Owner: Q3 | | | | | | | −0.50 (0.12) | <0.01 |
| Owner: Q4 | | | | | | | −0.55 (0.12) | <0.01 |
| Marital status at 33 | | | | | | | | |
| Couple | | | | | | | 0 | |
| Single | | | | | | | 0.03 (0.13) | 0.81 |
| Divorced or widowed | | | | | | | −0.04 (0.13) | 0.74 |

Women were more likely to have a lower education level, smoke, be overweight, and be less well-off. Nevertheless, this study remains a first approach to understand the potential biological mechanisms that associate ACE with AL. AL represents a useful conceptual tool in measuring the biological effect of biological embedding that can play a role in the production of the social gradient in health.

Childhood is recognized as a window of vulnerability, but also of opportunity. During this period of life, an early form of the socioeconomic gradient in health is set in place. Understanding the origins of health inequalities may lead us to conceptualize better adapted public policy priorities.

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# Mediating pathways between parental socio-economic position and allostatic load in mid-life: Findings from the 1958 British birth cohort

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ABSTRACT

Understanding how human environments affect our health by "getting under the skin" and penetrating the cells, organs and physiological systems of our bodies is a key tenet in public health research. Here, we examine the idea that early life socioeconomic position (SEP) can be biologically embodied, potentially leading to the production of health inequalities across population groups. Allostatic load (AL), a composite measure of overall physiological wear-and-tear, could allow for a better understanding of the potential biological pathways playing a role in the construction of the social gradient in adult health. We investigate the factors mediating the link between two components of parental SEP, maternal education (ME) and parental occupation (PO), and AL at 44 years. Data was used from 7573 members of the 1958 British birth cohort follow-up to age 44. AL was constructed using 14 biomarkers representing four physiological systems. We assessed the contribution of financial/materialist, psychological/psychosocial, educational, and health behaviors/BMI pathways over the life course, in mediating the associations between ME, PO and AL. ME and PO were mediated by three pathways: educational, material/financial, and health behaviors, for both men and women. A better understanding of embodiment processes leading to disease development may contribute to developing adapted public policies aiming to reduce health inequalities.



## 1. Introduction

Redressing the social stratification of ill health is a major concern in public health research. Classic determinants of non-communicable disease, which are mainly behavioral, are insufficient for explaining the large disparities observed in morbidity and mortality (Gallo et al., 2012). The concept of embodiment (Krieger, 2005) and biological embedding (Hertzman, 2012) are similar, and may be useful tools for formulating hypotheses on how health inequalities are produced over the lifecourse. In both concepts, how human environments affect our health by penetrating the cells, organs and physiological systems of our bodies, is a key tenet. We conceptualize embodiment as a dynamic process that summarizes how we become altered by our past experiences and are responding to the present, from how well we feel, down to the molecular modifications in our bodily structures. The process of embodiment being socially stratified (Hertzman and Boyce, 2010) may contribute to explaining the production of social gradients in health.

Growing evidence supports the idea that exposure to stressful conditions over life contributes to physiological dysregulation, subsequently translated into disease, through prolonged activation of stress response systems (McEwen and Stellar, 1993). Allostasis is the process where our body adapts to environmental challenges or stressful conditions in order to maintain physiological stability. The repeated activation of compensatory physiological mechanisms as a response to chronic stress can lead to a physiological wear-and-tear, known as allostatic load (AL) (Juster et al., 2010; McEwen and Stellar, 1993). AL has been strongly correlated with subclinical conditions, cardiovascular events, physical and functioning decline and mortality (Juster et al., 2010; Karlamangla et al., 2002, 2006). As a composite measure, AL performs as a better predictor of subsequent morbidity and mortality over and above each constituent biomarker when analyzed individually (Karlamangla et al.,

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2002). These findings suggest that AL could represent a global physiological state and perhaps even a proxy for an outcome of the embodiment process.

Growing evidence suggests that early life socioeconomic position (SEP) is a distal determinant of AL (Gruenewald et al., 2012), suggesting that poor socioeconomic circumstances early in life could set different population subgroups on life trajectories that are unfavorable for health, increasing their probability of being exposed to unhealthy environmental stressors and lifestyles. Early SEP is often measured using parental education and occupation at birth or in childhood, both of these measures being generally available in birth cohort studies. Education and occupation may operate through both similar and unique mechanisms to influence offspring health. In the current analysis, measures of parental education were limited to maternal education (ME), and occupation to paternal occupation (PO), due to variables availability and due to the historical context in which measures were assessed. Literature suggests that education and occupation do not impact health through the same pathways and should be analyzed separately (Galobardes et al., 2006, 2007). PO may affect health through: i) material resources (that determine material leaving standards), ii) work privileges (i.e. social security), iii) social standing (determining work control/autonomy and work based stress), and iv) toxic occupational exposures (Bartley et al., 1996; Galobardes et al., 2006). ME could affect health through: i) higher score of knowledge/skills and thus cultural capital, ii) material resources, iii) increasing the odds of acquiring better positions in occupation and higher income (Galobardes et al., 2006).

The lifecourse pathways linking early SEP to AL deserve to be disentangled, in particular the specific pathways involving ME and PO respectively. We aim to address this question by exploring four pathways through which ME and PO may be differentially embodied during childhood, adolescence and early adulthood leading to physiological wear-and-tear, as measured by AL. (a) A material/financial pathway: we hypothesize that living in poor material/financial circumstances could increase the risk of exposure to stressful and harmful situations relate to housing, work conditions, neighborhood, etc. (toxins, allergens, overcrowding) (Gustafsson et al., 2012; Lannero et al., 2002; Robertson et al., 2015). (b) A psychosocial/psychological pathway: parental SEP could influence parenting and the creation of a secure social environment buffering toxic stress responses, as well as the set-up of stress responses systems (Repetti et al., 2002; Shonkoff et al., 2012). (c) An educational pathway: higher parental SEP may influence educational outcomes in childhood, impact cognitive functions (Dubow et al., 2009; Kaplan et al., 2001) and later adult SEP (d) a health behaviors & BMI pathway: the accumulation of social disadvantage over life could contribute to adopt risky behaviors, impacting physiological functioning (Adler and Stewart, 2010; Stringhini et al., 2011).

We selected these four pathways based on epidemiological evidence and on empirical studies suggesting a link between SEP and each path. Lynch et al. (Lynch et al., 2000) suggested that health is the result of an accumulation of experiences and exposures due to the material world. Biological (viruses, bacteria) and chemical hazards, are more likely in more deprived homes and neighborhoods, and in some occupational statuses. An inverse relation between SEP and risky health behaviors has been largely demonstrated in empirical research (Stringhini et al., 2011). The adoption of health behaviors may be explained by complex psychological processes (e.g. self-regulation, self-efficacy, locus of control) (Bandura, 1991). Other explanations relate to social norms, tradition, and customs since lifestyle depends on social characteristics established by community social standards (Bartley, 2003). Concerning the psychosocial path, previous research (Marmot and Wilkinson, 1999) suggests that SEP may relate to health through the perception individuals have of their position in a social hierarchy. These perceptions may produce negative emotions resulting in poorer health, through psycho-neuroendocrine mechanisms (Brunner and Marmot, 1999) linked to stress responses (and/or stress-related behaviors such as smoking). Regarding the educational path, Hackman & Farah, showed in a recent review that SEP is linked with neurocognitive performance, such as language and executive function. Cognitive ability appears to be affected by poverty, especially during childhood. Different mechanisms have been suggested (e.g. cognitive stimulation, nutrition, parenting styles).

## 2. Materials & methods

### 2.1. Study population

The National Child Development Study (NCDS) is a birth cohort that includes all children born during one week in 1958 (N = 18,558) in Great Britain. Subsequent data collection was carried out on cohort members between 7y and 50y. At age 44-45y a biomedical survey was conducted including a self-reported questionnaire, physical measurements, blood and saliva samples (Power and Elliott, 2006). The sample used for this study is described in Fig. S1. Details about ethics and data are given in Supplementary Material.

### 2.2. Allostatic load at 44y

Among available biomarkers, we selected fourteen parameters representing four physiological systems: neuroendocrine (salivary cortisol t1 (nmol/L), salivary cortisol t1-t2 (nmol/L)); immune & inflammatory (insulin-like growth factor-1 (IGF-1 nmol/L), C-reactive protein (CRP mg/L), fibrinogen (g/L), immunoglobulin E (IgE KU/L)); the metabolic system (high density lipoprotein (HDL mmol/L), low density lipoprotein (LDL mmol/L), triglycerides (mmol/L), glycosylated hemoglobin (%)); cardiovascular & respiratory: (systolic blood pressure (SBP mmHg), diastolic blood pressure (DBP mmHg), heart rate/pulse (p/min), peak expiratory flow (L/min)). These biomarkers were chosen based on previous measures of AL (Barboza Solis et al., 2015; Seeman et al., 1997) and according to evidence of their relationship to stressful conditions over life and later morbidity and mortality (Butland et al., 2008; Kumari et al., 2013, 2011, 2008). In accordance with the most classical AL operationalization proposed by Seeman et al., our score result from the sum of fourteen parameters for which the subject was rated in the highest-risk quartile ('1' vs low risk '0') according to gender specific quartiles (Seeman et al., 1997). The high risk quartile was the top quartile (cut-off at the 75th percentile) for most biomarkers, for those where a low level confers a greater risk of poor health outcomes (HDL, salivary cortisol t1-t2, IGF1, peak expiratory flow) the first quartile (cut-off at the 25th percentile) was used. Function for individual biomarkers of AL score and measurement in the NCDS 1958 birth cohort is given in Table S1. Table S2 show the descriptive statistics and high-risk cut-points for men and women. Individuals with missing data were considered as not at risk for the missing biomarker adopting a conservative approach (maximum bias). Exclusion criteria for the analysis is shown in the flow chart (Supplementary Material, Fig. S1).

### 2.3. Parental SEP

We conceptualized parental SEP using ME and PO collected at birth. PO was constructed from the British Registrar General's social class system (RGSC) using mother's partner's social class (recoded

into four categories: I-professional occupations & II-intermediate occupations/III-skilled occupations (non-manual)/III-partly skilled occupations (manual)/IV-partly skilled occupations & V-unskilled occupations.), and if this was unavailable the mother's father's social class was used. The only ME measure available was self-reported and ask if mother left school after legal minimal age (14y) or if the mother left school before legal minimal age. The theoretical differences between these two measures relate to their potential mechanisms affecting health.

### 2.4. Early life socioeconomic and biological confounders

We selected from a questionnaire completed at birth by the participant's mother variables known to affect later health and representing socioeconomic markers (Table S1): birthweight (Barker, 2001, 2002; Gavin et al., 2012), maternal smoking during pregnancy (Jaakkola et al., 2001; Moussa et al., 2009; Raisanen et al., 2014), mother's body mass index (BMI) (Supplementary Material) (Cooper et al., 2013; Han et al., 2015; Perng et al., 2014) and mother's age at birth.

### 2.5. Educational pathway

Data on motor ability at 7y and educational attainment at 23y were collected. Motor ability was derived from the Copy-a-Design test at 7y, a measure of a child's capacity to reproduce geometrical figures and used in some studies as proxy of cognitive ability (Lacey et al., 2011). It ranged from 0 to 12, with higher scores relating to better perceptual motor skills and the child's ability to adapt to the school environment. Educational attainment at 23y was coded into three categories: passed the Advanced Level (A level)//passed the Ordinary Level (O levels)/No qualifications. The O levels represents the minimum leaving school age and corresponds to age 15-16y. The A level represents the final high school degree, and corresponds to age 18 years.

### 2.6. Psychosocial/psychological pathway

Extracted from the parental and teacher's questionnaires at ages 7, 11, and 16, we selected variables approaching parental involvement at 7y, social adjustment (Bristol Social Adjustment Guide) at 7y and family structure at 7 & 11 and malaise inventory at 23y. Parental involvement was constructed *via* five variables evaluating the time spend with the child (mum outing, dad outing, mum reading, dad reading and paternal role in the management of the child) categorized into three final items: most frequent/occasionally/hardly ever (Supplementary Material). Social adjustment is a teacher-rated measured that aims to characterize the child's behavior in school (Shepherd, 2013). Higher scores potentially indicate psychosocial and behavioral "maladjustment" (Stott, 1963). Family structure informed about parental separation at 7y and presence of a father figure at 11y. Rutter's Malaise Inventory comprise 24 yes/no items on both emotional and somatic symptoms (Rodgers et al., 1999). The individual was considered as having psychological malaise if s/he reported experiencing more than 7 out of 24 symptoms (Rutter et al., 1970).

### 2.7. Material/financial pathway

We selected variables characterizing material/financial deprivation at ages 7, 11 and 16, and income at 23y. From the parental and teacher's questionnaires childhood material deprivation was derived using a principal components analysis including information about housing deprivation and financial adversity (Supplementary Material). The equivalent net family income, adjusted for family size and composition with weightings from supplementary-benefit (Power et al., 1998), was also added.

### 2.8. Health behaviors & BMI pathway

From a self-reported questionnaire a variable containing information about physical activity at 23y, alcohol consumption at 23y (House of Commons Science and Technology Committee, 2012), and smoking status at 23y was derived. We created a three-category variable: Least at risk (0–2)/Moderately at risk (3–4)/Most at risk (5–6) (Supplementary Material) considered as a proxy for lifestyle patterns at 23y ranged from 0 to 6. BMI measured at 23y was also added to the health behaviors path to approach nutritional/diet behaviors.

### 2.9. Statistical analysis

To control for possible bias due to missing data, we imputed data for covariates with missing data using the multiple imputation program ICE in STATA V11 (Supplementary Material) and the analyses were stratified by sex (Supplementary Material). Descriptive statistics (Table 1) were carried out on nonimputed data. We used linear regression path modelling on imputed data to examine the relationship between parental SEP and AL (Barboza Solis et al., 2015; Israels, 1987). Path analysis allows to disentangle indirect mediating pathways. We analyzed the mediation paths between ME and AL and subsequently between PO and AL, in both men and women. Fig. 1 shows the indirect paths chosen a priori in this study. We tested all the mediating pathways, adjusting for ME, PO, confounders and mediators. Bivariate (Table S3) and multivariate linear regression results (Table S4) are shown in Supplementary Material and were carried out on imputed data. Bootstraps on 1000 random samples were ran to calculate the p values for each mediating variable (Tables S5 and S6). We conducted two sensitivity analysis. The first one for studying the stability of the AL score by identifying whether within our score, a parameter was having a stronger association relatively to the others (Supplementary Material, Table S7). The second computed a different AL score calculating a 0–1 risk score within each system, reflecting the proportion of biomarkers within the system for which the participant's values fall into the highest-risk quartile, allowing equal weight for each system. This operationalization; first suggested by (Gruenewald et al., 2012), and later by (Brooks et al., 2014) and (Carroll et al., 2015); did not impact our original results. All analyses were performed using STATA V11 taking a statistical significance level of 0.05.

## 3. Results

Descriptive statistics of the nonimputed sample are presented in Table 1 for the subsample (n = 3782 for men; n = 3791 for women). Figs. 2 and 3 represent the path analyses results, showing only the mediating variables explaining >5% of the total effect for men and women respectively, first between ME and AL, and second between PO and AL. The sum of all pathways are not equal to 1 due to other small or negative pathways not presented in the figures (Tables S5 and S6).

The path analyses for ME and AL show that for men the link was mainly mediated by the educational pathway [represented by motor ability at 7y (6% of the total indirect effect) and educational attainment at 23y (31% of the total indirect effect)]. The second most important pathway was denoted by a component of the health behavior path represented by BMI at 23y (13%). Finally the third path yield the role of material/financial factors captured by childhood material factors (9%). Overall, 45% of the total effect

**Table 1**
Descriptive statistics on the subsample for men (n = 3782) and women (n = 3791).

| Variable | Sex | |
|---|---|---|
| | Men n [%] | Women n [%] |
| **Allostatic load** | | |
| 0 | 287 [7.6%] | 312 [8.2%] |
| 1 | 614 [16.2%] | 669 [17.6%] |
| 2 | 789 [20.9%] | 727 [19.2%] |
| 3 | 720 [19.0%] | 617 [16.3%] |
| 4 | 560 [14.8%] | 532 [14.0%] |
| 5 | 359 [9.5%] | 380 [10.0%] |
| 6 | 236 [6.2%] | 251 [6.6%] |
| 7 | 136 [3.6%] | 144 [3.8%] |
| 8 | 61 [1.6%] | 99 [2.6%] |
| 9 | 16 [0.4%] | 44 [1.2%] |
| 10 | 4 [0.1%] | 9 [0.2%] |
| 11 | 0 [0.0%] | 5 [0.1%] |
| 12 | 0 [0.0%] | 2 [0.1%] |
| **Maternal education** | | |
| Left school at 15 or later | 1017 [26.9%] | 1017 [26.8%] |
| Left school before 14 | 2765 [73.1%] | 2774 [73.2%] |
| **Paternal occupation** | | |
| I & II (professional/managerial) | 739 [19.5%] | 706 [18.6%] |
| IIINM (skilled nonmanual) | 378 [10.0%] | 388 [10.2%] |
| IIIM (skilled manual) | 1902 [50.3%] | 1904 [50.2%] |
| IV & V (semi-unskilled) | 763 [20.2%] | 793 [20.9%] |
| **Birthweight** | | |
| Q1 – Low weight | 792 [20.9%] | 849 [22.4%] |
| Q2 | 1037 [27.4%] | 1002 [26.4%] |
| Q3 | 973 [25.7%] | 913 [24.1%] |
| Q4 – High weight | 855 [22.6%] | 921 [24.3%] |
| Missing | 125 [3.3%] | 106 [2.8%] |
| **Mother smoked during pregnancy** | | |
| No | 2537 [67.1%] | 2517 [66.4%] |
| Sometimes | 230 [6.1%] | 215 [5.7%] |
| Moderately | 545 [14.4%] | 580 [15.3%] |
| Heavily | 428 [11.3%] | 438 [11.6%] |
| Missing | 42 [1.1%] | 41 [1.1%] |
| **Mother's BMI** | | |
| Normal | 2618 [69.2%] | 2591 [68.3%] |
| Underweight | 138 [3.6%] | 180 [4.7%] |
| Overweight | 679 [18.0%] | 685 [18.1%] |
| Obese | 148 [3.9%] | 141 [3.7%] |
| Missing | 199 [5.3%] | 194 [5.1%] |
| **Mother's age at birth** | | |
| 23 years or less | 976 [25.8%] | 1023 [27.0%] |
| 24–27 years | 1073 [28.4%] | 1043 [27.5%] |
| 28–31 years | 848 [22.4%] | 821 [21.7%] |
| 32 years or more | 884 [23.4%] | 900 [23.7%] |
| Missing | 1 [0.0%] | 4 [0.1%] |
| **Parental involvement at 7** | | |
| Most Frequent | 1967 [52.0%] | 1917 [50.6%] |
| Occasionally | 868 [23.0%] | 916 [24.2%] |
| Hardly ever | 548 [14.5%] | 584 [15.4%] |
| Missing | 399 [10.6%] | 374 [9.9%] |
| **Social adjustment at 7** | | |
| Q1 – Least disturbed | 956 [25.3%] | 1348 [35.6%] |
| Q2 | 822 [21.7%] | 921 [24.3%] |
| Q3 | 829 [21.9%] | 664 [17.5%] |
| Q4 – Most disturbed | 826 [21.8%] | 540 [14.2%] |
| Missing | 349 [9.2%] | 318 [8.4%] |
| **Family structure at 7 & 11** | | |
| Presence of father figure/not divorced | 3533 [93.4%] | 3492 [92.1%] |
| No father figure or divorced | 172 [4.5%] | 234 [6.2%] |
| Missing | 77 [2.0%] | 65 [1.7%] |
| **Motor ability at 7 (mean)** | 7.20 | 7.14 |
| Missing | 356 [9.4%] | 326 [8.6%] |
| **Childhood material factors at 7–16** | | |
| Q1 – Low material deprivation | 635 [16.8%] | 662 [17.5%] |
| Q2 | 612 [16.2%] | 615 [16.2%] |
| Q3 | 638 [16.9%] | 622 [16.4%] |
| Q4 – High material deprivation | 624 [16.5%] | 654 [17.3%] |
| Missing | 1273 [33.7%] | 1238 [32.7%] |
| **Health behaviours at 23** | | |
| Least at risk | 1293 [34.2%] | 1243 [32.8%] |
| Moderately at risk | 1413 [37.4%] | 1550 [40.9%] |
| Most at risk | 534 [14.1%] | 556 [14.7%] |
| Missing | 542 [14.3%] | 442 [11.7%] |
| **BMI at 23** | | |
| Normal | 2542 [67.2%] | 2677 [70.6%] |
| Underweight | 74 [2.0%] | 207 [5.5%] |
| Overweight | 510 [13.5%] | 341 [9.0%] |
| Obese | 62 [1.6%] | 84 [2.2%] |
| Missing | 594 [15.7%] | 482 [12.7%] |
| **Malaise inventory at 23** | | |
| No | 3123 [82.6%] | 3020 [79.7%] |
| Yes | 112 [3.0%] | 326 [8.6%] |
| Missing | 547 [14.5%] | 445 [11.7%] |
| **Educational attainment at 23** | | |
| Passed A levels | 789 [20.9%] | 762 [20.1%] |
| Passed O levels | 1245 [32.9%] | 1511 [39.9%] |
| No qualifications | 1204 [31.8%] | 1074 [28.3%] |
| Missing | 544 [14.4%] | 444 [11.7%] |
| **Income at 23** | | |
| Q1 – Low income (mean = 46.6[a]) | 531 [14.0%] | 843 [22.2%] |
| Q2 (mean = 93.0) | 639 [16.9%] | 911 [24.0%] |
| Q3 (mean = 131.4) | 866 [22.9%] | 800 [21.1%] |
| Q4 – High income (mean = 189.0) | 1025 [27.1%] | 696 [18.4%] |
| Missing | 721 [19.1%] | 541 [4.3%] |

[a] Pounds per week.

between ME and AL in men remained unexplained by those paths, after adjustment for confounder and mediators. For women, 22% of the total mediated effect between ME and AL was explained by the educational path [represented by educational attainment at 23y (15%)] and by the material/financial path [represented by childhood material deprivation at 7y (7%)]. Overall, 63% of the total effect between ME and AL in women remained unexplained by those paths after adjusting for confounders and mediators.

The relationship between PO and AL in men was mainly mediated by the educational pathway [represented by educational attainment at 23y (IIIM = 17%/IV & V = 17%)]. The second path was denoted by health behaviors [represented by BMI (IIIM = 8%/IV & V = 9%)]. The third path was the material/financial [explained by childhood material deprivation at 7y (IIIM = 6%/IV & V = 9%)]. For the III skilled-manual class 68% of the total effect remained unexplained by the paths, for the IV-V semi/unskilled manual this percentage was 57%. PO for women was mainly mediated by the educational path (IIIM: 12%/IV & V: 14%), and by the health behaviors path [drawn by BMI (IIIM: 12%/IV & V: 14%)]. The third was denoted by the material/financial path [represented by childhood material deprivation (IIIM: 7%/IV & V: 9%)]. For the III skilled-manual class 58% of the total effect remained unexplained by those paths, for the IV-V semi/unskilled manual this percentage was 47%.

Multivariate results are presented in Table S4 for men and women. The full model showed that ME remained statistically linked to later AL only for women (0.39, P = 0.004). PO for both men (IIIM: 0.27; P = 0.004/IV & V: 0.32; P = 0.005) and women (IIIM: 0.29; P = 0.005/IV & V: 0.30; P = 0.016) remained statistically associated with AL. Additionally for men, the full model shows that birthweight and mother's BMI had an important independent association with later AL. Health behaviors, BMI, education level and income at 23y were also found correlated to AL after adjustment for confounder and mediators. For women, variables from early life (birthweight, mother's BMI and mother's age at birth), from childhood/adolescence (social adjustment, family structure and material deprivation) and all variables at 23y (except for income) remained independently associated with later AL.

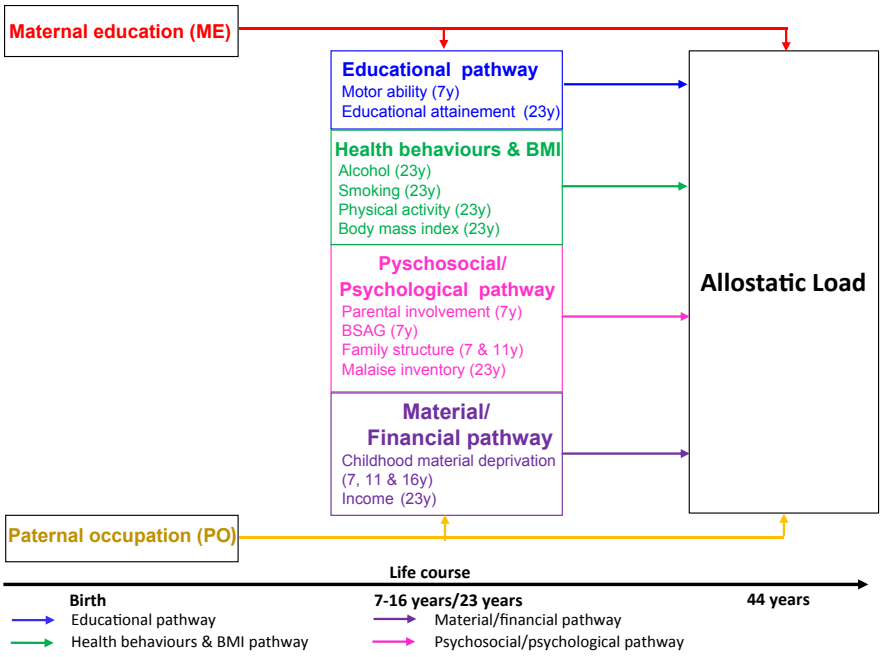
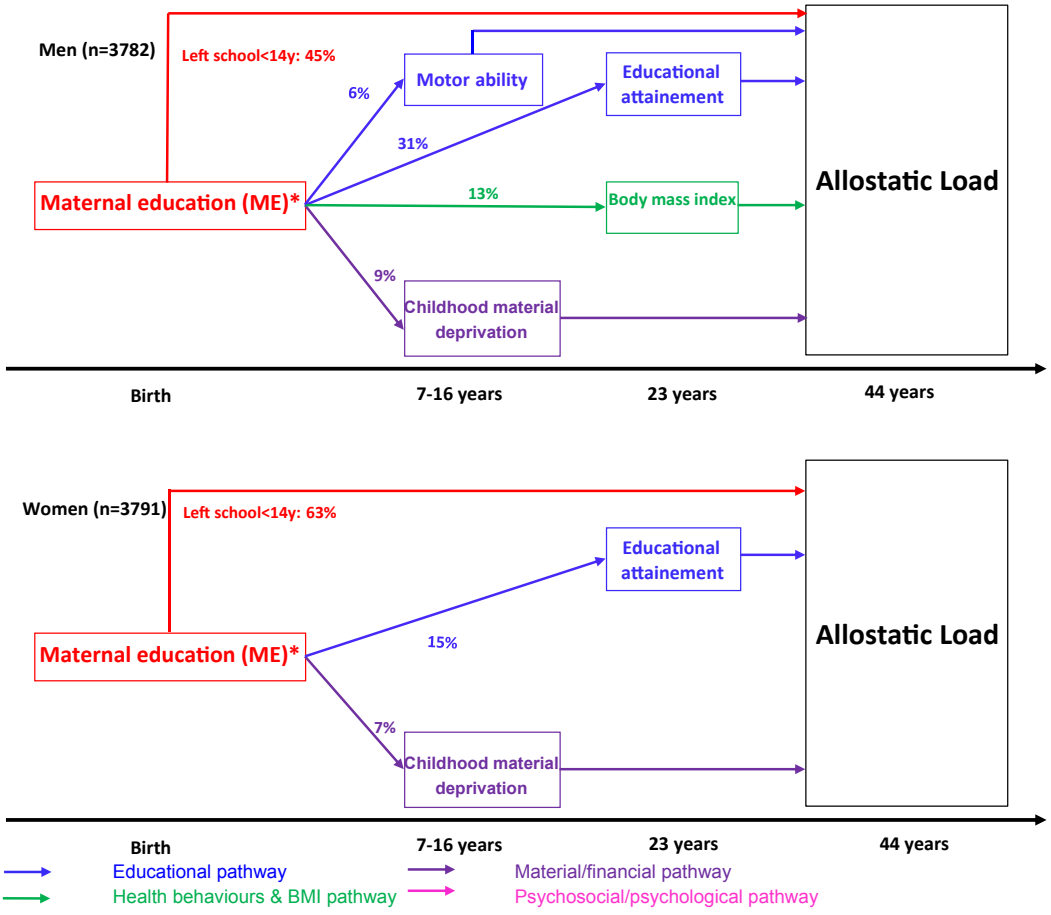



**Fig. 1.** Path analyses model tested in this work.




Were included in this figure only variables explaining 5% or above of the variability between ME and AL
Model adjusted for paternal occupation, birthweight, mother smoked during pregnancy, mother's BMIn mother's age at birth, parental involvement,
*The sum of all pathways are not equal to 1 due to other small or negative pathways not presented on this figure

**Fig. 2.** Path analysis results between ME and AL for men (n = 3782) and women (n = 3791).

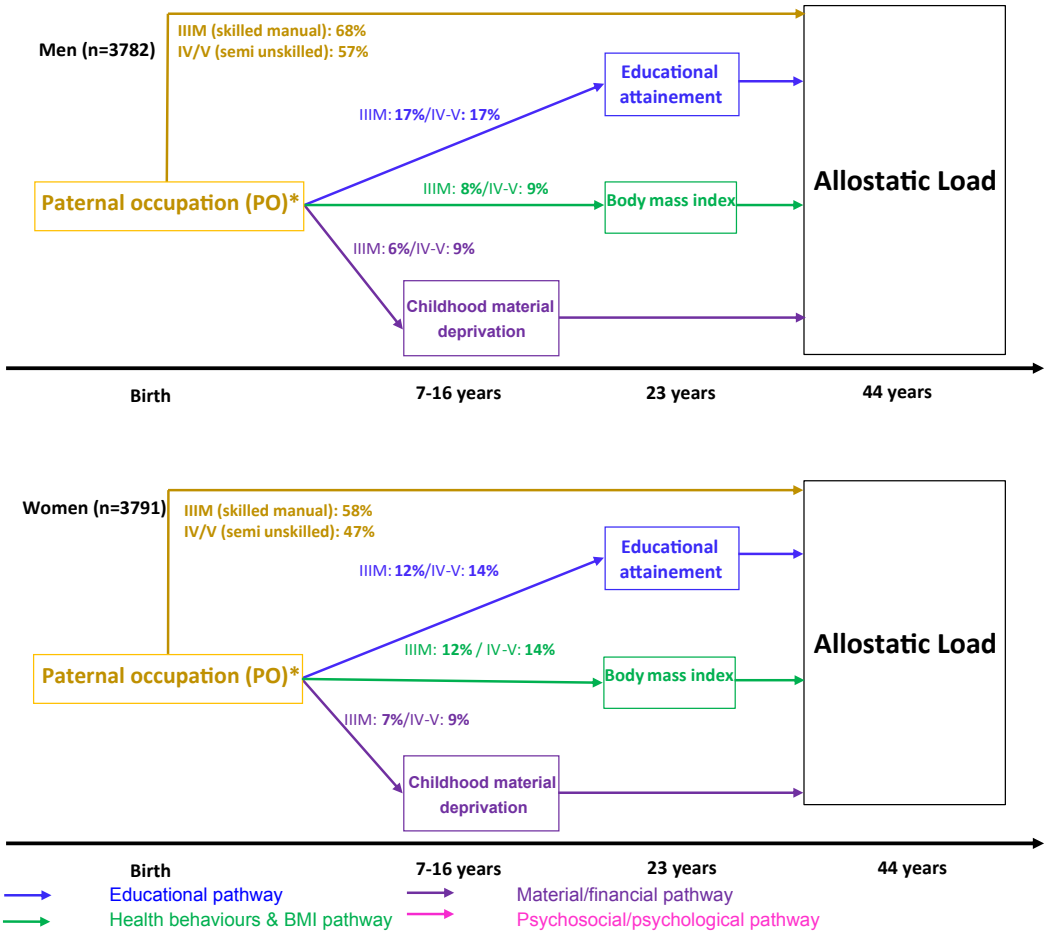



**Fig. 3.** Path analysis results between PO and AL for men (n = 3782) and women (n = 3791).

## 4. Discussion

Lower maternal education and manual paternal occupation were associated with a higher allostatic load at 44 years, mainly *via* the educational, material/financial, and health behaviors pathways for both men and women. For the relationship between ME and AL, more than 60% of the link in women and 45% in men, remained unexplained by the mediators. Around 50–60% of the relationship between PO and AL remained unexplained by the mediators in men and in women. In both relationships these pathways may represent differential early life embodiment processes or: i) an underrepresentation, underestimation of the four path we tested due to measurement errors or lack of availability of variables representing better these paths; ii) The lack of identification or omission of other possible paths (e.g. cognitive functioning and social support) (John-Henderson et al., 2015); iii) an early biological impact of parental SEP, having long lasting influence on physiology (Miller et al., 2009; Noble et al., 2015).

Up to 37% of the link between ME and AL observed in men was mediated by the educational path represented by motor ability at 7y (6%) and educational attainment at 23y (31%). The health behaviors path represented 13% of the total effect and the material/financial path 9%. For women, only two paths appeared to be important in the relationship between ME and AL: 15% was explained by educational attainment and 7% by childhood material deprivation. Concerning the link between PO and later AL, men and women showed similar patterns: the main path was educational, followed by the health behaviors and the material/financial pathways.

The most important path revealed in this study for both ME and PO was educational. This suggests a significant protective effect of a favorable health trajectory. Parental education might help and stimulate children, influencing cognitive abilities (Biedinger, 2011), favored a good adaptation to school settings, influence offspring's receptivity to health education messages, and can impact health trough the material circumstances (better jobs, higher household incomes, and better housing) (Dubow et al., 2009; McKenzie et al., 2011). We additionally found a strong correlation between motor ability at 7y and educational attainment at 23y. This provides further evidence suggesting an underlying construct cognitive characteristics, partially influenced by parental SEP early in life and having later consequences on educational attainment (Kaplan et al., 2001).

The second main path was drawn by a particular dimension of adult health behaviors: BMI. The intergenerational influences of parental SEP have been reported to affect offspring's adult obesity (Laaksonen et al., 2004), suggesting that obesity trajectories may be set early in life. Higher SEP could increase awareness concerning health messages, prevention, healthy eating, exercise and weight control efforts (Laaksonen et al., 2004). The third path was the

material/financial pathway. (Gustafsson et al., 2012) suggested that early material circumstances "might be mediated by physiological effects of their emotional and social meaning", it is also conceivable that they could impact AL increasing the probabilities of harmful exposures early in life (e.g. home/neighborhood) (Robertson et al., 2015).

When exploring the link between SEP and AL, (Robertson et al., 2015) showed that behavioral and material factors accounted for much of the association. They also revealed in a previous study that accumulated SEP across the life span was the best fitting life course model (Robertson et al., 2014). (Gruenewald et al., 2012) found that alcohol, tobacco, poor diet and low social support explained an important amount of the link. In this work we contribute to this discussion by testing diverse pathways, taking into account potential sex/gender differences and by testing two dimensions of parental SEP separately.

Other variables characterizing parental SEP were available in the NCDS. We selected ME and PO at birth, because we wanted to include in our analysis the earliest SEP markers available capturing the child social environment where s/he born into. We chose ME since literature suggests that it is a fundamental resource linked to children's health (Currie and Moretti, 2003; Gakidou et al., 2010). ME is strongly associated with improved health outcomes for children and it is inversely correlated with low birth weight and premature birth (Currie and Moretti, 2003). Moreover, at that time women were more likely to have traditional gender roles related to child-rearing in the household. Given the time she was likely to spend on household and childcare activities, we attempted to capture the mother's educational resources that may be transmitted to her children. Concerning occupation, because of gender ascribed social roles, women had less stable occupational trajectories, compared to men. Paternal occupation was the best variable that allowed us to capture the material conditions in the household at birth. In summary, our main goal was to explore the potential pathways through which parental education and occupational status may link to later health. However, due to measurement availability and historical context, the most appropriate measure available for education came from mothers, and likewise, occupation from fathers.

We observed that ME and PO were mediated by the same pathways. However, we expected to see differences concerning the importance of each path impacting AL. For instance, we hypothesized that PO could affect AL through mainly the material path and ME through mainly the educational path. However, our results were similar, suggesting that both may relate in similar ways with AL. Nevertheless, some differences should be mentioned. For ME in men, motor ability had an important role, suggesting perhaps that ME could be positively associated with cognitive ability in offspring (Bartels et al., 2009).

Concerning the path between PO and AL, there was no difference between the III-partly skilled occupations and the IV-V semi/unskilled manual categories. The RGSC is as a general measure of social standing, based on particular skills to perform an occupation. However, research on RGSC have showed a wide range of results sometimes difficult to interpret (Bartley et al., 1996). We speculate that the most important feature when it comes to occupational status and later physiological wear-and-tear is the psychosocial hypothesis of social standing. The psychosocial component may be underestimate using the RSGC, since it may better capture the material advantages bestowed by the world of work. Future research may purposes measures of occupational status based on social standing or social interactions (e.g. Cambridge scale).

The health behaviors path had an important role through BMI (except for ME in women). We hypothesize that the possible impacts of ME and PO may operate through socially stratified parental behaviors and parenting styles, which may in turn impact future life styles in men and in women. For instance, it is known that heritability of BMI is high (Han et al., 2015), and parental socioeconomic factors have been linked with offspring's BMI (Chaparro and Koupil, 2014).

The main weakness of this study is related to attrition, and selection bias, common features related to longitudinal studies. Nevertheless, it has been shown that the NCDS 1958 birth cohort remain broadly representative of the surviving cohort on key childhood and adult characteristics (Atherton et al., 2008). We compared the biomedical survey participants included in our analyses to all of those involved in the cohort at baseline to ascertain differences due to missing data. We observed that the analyzed sample have more educated mothers (27% vs 23%), have fewer fathers in the semi/unskilled category of occupational class (21% vs 24%), are more likely to have a normal BMI at 23y (80% vs 75%), being less in the 'no qualification' at 23y category (34% vs 47%), are more likely to be former smokers (30% vs 25%) or to less smoke heavily (16% vs 20%), compared to their baseline counterparts. In this sense, our results might be rather conservative and they could underestimate the effects of early SEP on AL. Therefore, we imputed the data taking the MAR assumption to preserve important aspects of the distribution, variability, and relationships between variables. The ME variable is unprecise, however it has already been independently related in the NCDS 1958 birth cohort to later AL (Barboza Solis et al., 2015). Concerning the relative minor role of the psychosocial/psychological path, it is possible that we are underestimating its real impact, due to lack of robustness, to variable availability, variable construction, and more importantly, the incapacity to completely disentangle this path from others, especially the material/financial path (Robertson et al., 2015). With family structure, parental involvement, social adjustment and the malaise inventory we tried to capture the nature of the social environment (supportive and secure) that could reverse or buffer potentially damaging stress responses. Indeed, parental warmth, and a supportive social environment, could reduce the extent of physiological wear-and-tear (Carroll et al., 2013; Shonkoff et al., 2012). Additionally, depression and anxiety, approached here with the malaise inventory, has already been found related with AL (McEwen, 2000).

Regarding the composite variable of health behavior, we want to note that the objective was to capture a general profile of lifestyles, hypothesizing that the accumulation of risky behaviors is more likely in socioeconomically deprived population subgroups. Poor population subgroups are more likely to smoke, to have a sedentary life, and to drink more heavily than their well-off counterparts (Jarvis and Wardle, 1999). It is possible that by building this variable we have misclassified individuals, and our statistical power may be decreased, leading to an underrepresentation of the health behaviors path.

We were limited by the availability of variables in our data set. There are some confounders and mediators that may be not taken into account in this analysis, that could better account for other potential mechanisms, like diet, environmental exposures, social support and cognitive skills (Gruenewald et al., 2012). We tried to capture cognitive ability by utilizing the Copy-a-Design test, a concept that aims to "recognize the principle governing different geometric forms and to reproduce them" (Schoon et al., 2002). Higher scores could represent the child's ability to follow instructions, remain concentrated and increasing their probabilities for educational success. Previous studies have used the motor skill test as a cognitive ability proxy (Lacey et al., 2011). A study showed that children whose mothers had no college education showed reduced effects of selective attention on early neural processing of speech and reduced ability to filter irrelevant information (Stevens

et al., 2009). The social, material and behavioral exposures included are self-reported, thus measurement errors are probable. Our AL score remains limited by the pragmatism of variable availability, with a strong focus on the cardiovascular system. Our only available primary mediator biomarker was cortisol, other widely used primary biomarkers are epinephrine and norepinephrine (Juster et al., 2011), however these were not available in the NCDS biomedical survey. With the two cortisol measures (t1 and t1-t2) we tried to characterize the diurnal pattern of the HPA axis. t1 was measure 45 min after wakening and t2, 3 h later (Elliott et al., 2008). A healthy HPA axis is typically characterized by high levels upon waking and a subsequent decline over the day, reaching a low point around midnight (Adam and Kumari, 2009). We tried to capture the cortisol pattern using the t1-t2 measure, however we recognize that the lack of further measures underestimate the impact of the neuroendocrine system inside the AL score.

Additionally, there is currently no consensus regarding the choice of relevant physiological systems, of biomarkers, their interactions (linear relationships), their importance in the chain of physiological stress responses, as well as their measurement, combinations, weighting and the most suitable statistical analysis (Beckie, 2012). Furthermore, as physiological responses to stress may differ according to developmental stage over time, measures of AL may differ in terms of markers and risk thresholds (Barboza Solis et al., 2015). However, the two sensitivity analysis already mentioned showed the stability of the results. Concerning sex stratification, recent population-based studies suggest sex/gender differences in several biomarkers (Goldman et al., 2004; Lakoski et al., 2006), and a study has found sex differences in AL (Yang and Kozloski, 2011). Even if the results do not show large differences by sex, we consider these potential sexual dimorphism should be taking into account in the analyses.

Regarding the significance of each pathway, we used bootstraps on 1000 random samples, to calculate the p values for each mediating variable. However, the significance at 5% was not the main criteria for considering variable as clinically or epidemiologically "relevant" or significant, since we had a large sample and in these cases the statistical significance does not provide information on clinical relevance. It seems to us that in this case we should analyze the change in effect size (Chavalarias et al., 2016). Therefore, we decided to present the percentage for which each variable explained at least 5% of the total variability (Tables S5 and S6).

Despite these limitations, this study has a number of strengths. We used a longitudinal population-based study collecting data prospectively across the life span. This study is further strengthened by analyzing separately two concepts of parental SEP by sex, exploring potential differences in the mechanisms. These findings enlighten us on the important relationship between education and physiological burden. Reducing inequalities in education could contribute to targeting population subgroups, less likely to be educated and at risk of developing physiological wear-and tear. Moreover, identifying sets of biomarkers for capturing embodiment processes early in life may be useful for conceptualizing and assessing early preventive intervention before the initiation of deleterious health trajectories.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.socscimed.2016.07.031.

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# Physiological wear-and-tear and later subjective health in mid-life: Findings from the 1958 British birth cohort

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ABSTRACT

*Objective:* Our body adapts continuously to environmental challenges and stressful conditions. Allostatic load (AL) is a concept that aims to capture the overall physiological wear-and-tear of the body triggered by the repeated activation of compensatory physiological mechanisms as a response to chronic stress. Growing evidence has shown a link between AL and later health decline, morbidity and mortality. However, due to the global physiological effect captured by the AL concept, it is particularly pertinent to examine its association with subsequent health by taking a broad definition of the latter. We examined the association between AL at 44 years and general health as measured by a latent multidimensional measure of subjective health at 50 years integrating sleep patterns, physical and mental health.
*Methods:* AL was constructed using 14 biomarkers representing four physiological systems on 7573 members of the 1958 British birth cohort. Health status was captured using self-reported information about subjective health and summarized using a principal component analysis including: seven dimensions of the SF-36 questionnaire of health-related quality of life, the sleep subscale of the Medical Outcomes Study characterizing quality of sleep patterns, and a malaise inventory score detecting depressive symptoms.
*Results:* Higher AL score was gradually associated with worse subjective health, after taking into account classic confounders.
*Conclusions:* Using a physiological index to grasp how the environment can "get under the skin" leading to poor health is of great interest, permitting a better understanding of life course origins of disease and social gradients in health.



## 1. Introduction

Krieger et al. defined the concept of embodiment as "how we, like any living organism, literally incorporate, biologically, the world in which we live, including our societal and ecological circumstances" (Krieger, 2005). Growing evidence supports the idea that exposure to chronic stress over the life course contributes to physiological dysregulation, subsequently translated into disease (McEwen and Seeman, 1999; McEwen and Stellar, 1993; Seeman et al., 2001). Allostasis is the active process of adaptation where our body tries to maintain physiological stability in response to environmental challenges (Sterling, 2004, 2012). The repeated activation of compensatory physiological mechanisms as a result of chronic exposure to stress can lead to a physiological wear-and-tear, known as allostatic load (AL) (Juster et al., 2010; McEwen and Stellar, 1993; McEwen and Wingfield, 2003). AL may be a useful conceptual tool in measuring the biological effect of embodiment.

Based on prospective data, used to capture the history of prior environmental insults (Seeman et al., 2010) researchers have studied the life course origins of AL development. They highlighted the role of social adversity (Gustafsson et al., 2012), and socioeconomic position (SEP) (Gustafsson et al., 2011) as predictors of AL, also identifying the mediating role of material, behavioural and psychosocial factors between SEP and later AL (Barboza Solis et al., 2015; Robertson et al., 2015, 2014). These findings suggest that (a) AL is socially patterned (Dowd et al., 2009; Robertson et al., 2014; Seeman et al., 2010; Szanton et al., 2005), determined by socioeconomic position, material, psychosocial and behavioural factors all over the life span (Robertson et al., 2015), (b) AL conceptual framework may contribute to clarify the biological component of the socioeconomic gradient observed in morbidity and mortality (Carlson and Chamberlain, 2005; Gruenewald et al., 2012).

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Empirical research has investigated the link between AL and later health outcomes (Beckie, 2012; Karlamangla et al., 2006). However, the conceptual framework of AL is constructed on the basis of a global effect of stress on health, via multiple physiological mechanisms and by impacting several systems and brain structures. Therefore, AL is not designed to be specific, but rather to show an overall effect on health. Several studies have shown links between AL and, diverse health outcomes (Juster et al., 2010; Karlamangla et al., 2002, 2006). However, testing the link between AL and one specific aspect of health, for instance, cardiovascular disease, fragments the notion of overall physiological wear-and-tear. Therefore, due to the global physiological effect captured by the AL concept, it is particularly pertinent to examine its association with subsequent health by taking a broad definition of the latter, not only measured by the absence or presence of diseases.

Health status is indeed a multidimensional and integrative attribute, a latent concept, capturing subjective (e.g. self-rated health, well-being, quality of life, health related quality of life, happiness, life satisfaction), clinical (e.g. morbidity, functional decline) and biological (e.g. biomarkers) dimensions (Hyland et al., 2014). Self-rated health and health-related quality of life (HRQoL) – defined as the perception of the impact of health problems on different spheres of life, including physical, mental, and social aspects (Testa and Simonson, 1996)- have been used as measures of health status since they correlate to morbidity and mortality (Power et al., 1998). Subjective health measures are then frequently used as surrogate endpoints of morbidity and mortality, where their main advantage is to define health through its various dimensions. In this paper we investigate the link between AL and a holistic/integrative latent measure of health using a subjective health variable integrating sleep patterns, physical and mental health at 50 years. We aimed to address this question studying the impact of AL measured at 44 years of age on a latent variable of subsequent subjective health measured at 50. We hypothesised that AL could influence health status in the long term, independently of social determinants and health behaviours.

## 2. Materials and methods

### 2.1. Participants

The National Child Development Study (NCDS) includes all children born during one week in 1958 (N = 18558) in Great Britain. Data collection was carried out on cohort members between birth and 50y. At age 44–45y a biomedical survey was conducted including a self-reported questionnaire, physical measurements, blood and saliva samples (Power and Elliott, 2006). The sample used for this study is described in Fig. S1.

### 2.2. Ethics & data

Written informed consent was obtained from parents for childhood measurements and ethical approval for the adult data collection was obtained from the National Research Ethics Advisory Panel. NCDS data are open access datasets available to non-profit research organizations. Ethical approval for the age 45 year survey (Gruenewald et al., 2012; Gustafsson et al., 2011) was given by the South East Multicentre Research Ethics Committee.

### 2.3. Measurements

#### 2.3.1. Allostatic load at 44y

Among available biomarkers, we selected fourteen parameters representing four physiological systems: the neuroendocrine system (salivary cortisol t1 (nmol/L), salivary cortisol t1-t2 (nmol/L)); the immune & inflammatory system (C-reactive protein (CRP mg/L), fibrinogen (g/L), immunoglobulin E (IgE KU/L), insulin-like growth factor-1 (IGF-1 nmol/L),); the metabolic system (high density lipoprotein (HDL mmol/L), low density lipoprotein (LDL mmol/L), triglycerides (mmol/L), glycosylated hemoglobin (%)); the cardiovascular & respiratory systems: (systolic blood pressure (SBP mmHg), diastolic blood pressure (DBP mmHg), heart rate/pulse (p/min), peak expiratory flow (L/min)). These biomarkers were chosen based on previous measures of AL (Barboza Solis et al., 2015; Karlamangla et al., 2002, 2006; Seeman et al., 1997) and according to evidence of their relationship to stressful conditions over life (Butland et al., 2008; Kumari et al., 2013, 2011, 2008). In accordance with the most classical AL operationalization proposed by Seeman et al. (1997), our score was the sum of the fourteen parameters for which the subject was rated in the highest-risk quartile ('1' vs low risk '0') according to gender specific quartiles. A full description of each parameter is given in Table S1. Individuals with missing data were considered as not at risk for the missing biomarker adopting a conservative approach (maximum bias). Exclusion criteria for the analysis is shown in the flow chart (Fig. S1). We additionally run the multivariate analysis using a different operationalization of AL score, by calculating a 0–1 risk score within each system and the results did not vary.

#### 2.3.2. Subjective health index at 50y

We conceptualize health status following an integrative approach incorporating three different dimensions of health from subjective health measures collected at the 8th sweep of the NCDS 1958 British birth cohort. The *SF-36* is a general questionnaire measuring Health Related Quality of Life (HRQoL) (Ware, 2000) through its physical and mental components (Taft et al., 2001) that captures, for instance, the interference with work or other daily activities due to physical health, emotional problems, interference with normal social activities, symptoms associated with anxiety/depression and measures of positive affect (Supplementary material). Each of the eight dimensions is ranged from 0 to 100 with higher scores related to better HRQoL. The SF-36 has been shown to be predictive of subsequent morbidity and mortality (Kaplan et al., 2007; Otero-Rodriguez et al., 2010; Rodriguez-Artalejo et al., 2005; Tsai et al., 2007).

A subscale of four items from twelve original *Sleep Scale of the Medical Outcomes Study* (MOS) was used in NCDS to collect information about sleep patterns in the last four weeks measuring quality of sleep (Hays and Stewart, 1992). Previous studies have provided evidence on the validity and reliability of the MOS sleep measures (Hays et al., 2005; Viala-Danten et al., 2008) (Supplementary material). The self-completion sleep scale included: usual time taken to fall asleep, average number of hours sleep per night, waking-up during night frequency and trouble falling back to sleep, and whether the respondents had slept enough, based on whether they felt rested upon waking. These four items capture three different dimensions of sleep problems, relating to quantity of sleep/optimal sleep duration, perceived sleep adequacy, and sleep disturbance (Chatzitheochari, 2013). Sleep patterns are known to be related to chronic diseases (diabetes, hypertension, cardiovascular), poor health-related quality of life and self-rated poor health (Chatzitheochari, 2013). In terms of physiological balance, sleep disturbances have an impact on metabolic and endocrine functioning (Spiegel et al., 1999).

Finally, the *malaise Inventory* which measures psychological distress, comprising a nine-item score from the original twenty four (Rutter et al., 1970), was included as a continuous variable, with higher scores relating to worst mental health (Supplementary material). The malaise inventory score has been found to have acceptable internal validity in different socio-economic groups in the NCDS sample (Rodgers et al., 1999). Mental health has been

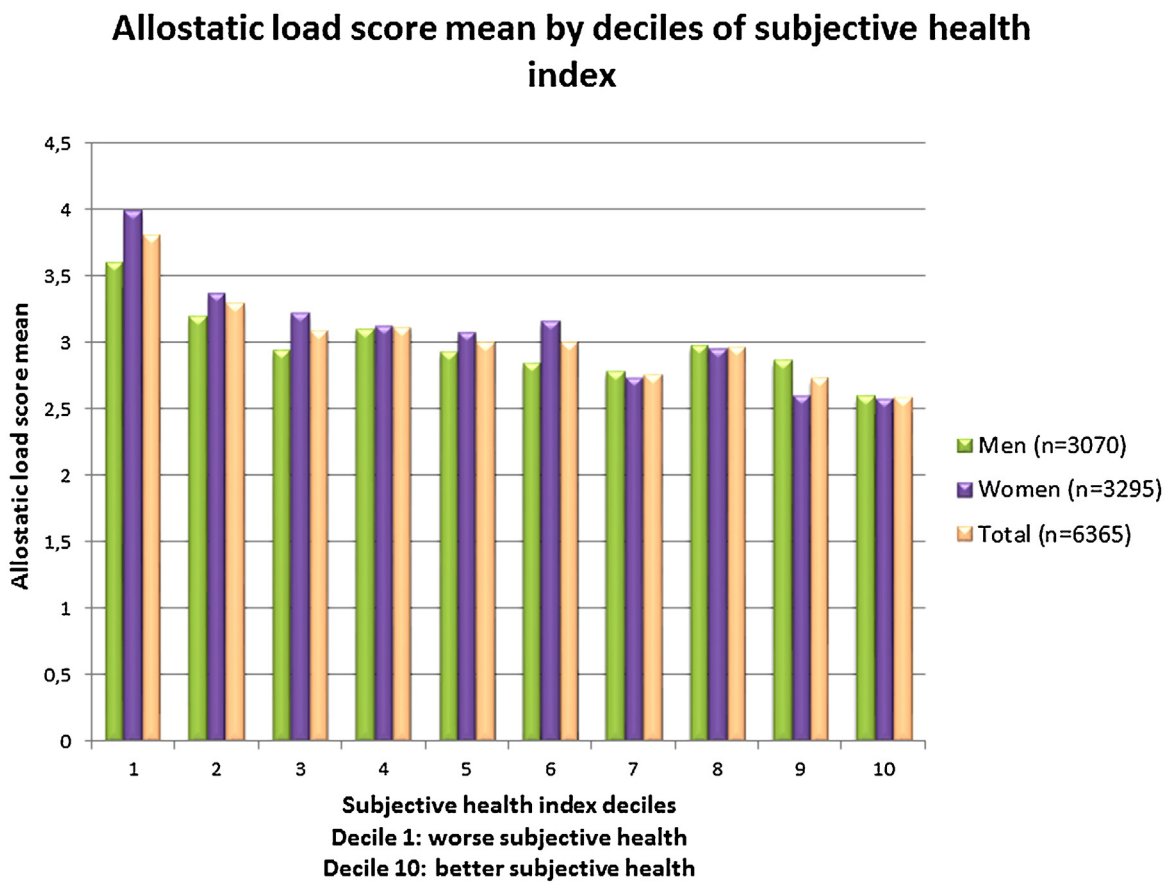


**Fig. 1.** Allostatic load score mean by deciles of subjective health.

found to correlate to later morbidity and mortality (Vogt et al., 1994).

We ran a Principal Components Analysis (PCA) to sum-up the information of the above self-reported variables using non-imputed data and deriving one single component. The PCA included three groups of variables: (i) the first group was created using seven dimensions of the SF-36 scale of HRQoL questionnaire (physical functioning, role-physical, bodily pain, general health, vitality, role-emotional, mental health). The social functioning subscale was excluded under statistical criteria when running the principal component analysis. (ii) Four items of the *Sleep Scale of the Medical Outcomes Study* included as ordinal continuous variables. (iii) The malaise inventory score ranged between 0 and 9. PCA show an adequate fit to the data (Component 1 eigenvalue = 5.3; Overall Kaiser-Meyer-Olkin measure of sampling adequacy = 0.89; overall $\alpha$ Cronbach = 0.81). Subsequently we standardized the distribution using *Z*scores separately by sex. Fig. S2 shows the distribution of *Z*scores for men and women (Supplementary material). All analyses were performed using STATA V14 taking a statistical significance level of 0.05.

*2.3.3. Early life socioeconomic confounders*

Information on participant's early life factors was collected via a questionnaire completed at birth by the participant's mother. Maternal education was self-reported (mother left school after legal minimal age/mother left school before legal minimal age). Mother's partner's (or father's if unavailable) occupation was classified in four categories: I-professional occupations & II-intermediate occupations/III-skilled occupations (non-manual)/III-partly skilled occupations (manual)/IV-partly skilled occupations & V-unskilled occupations.

*2.3.4. Early adulthood socioeconomic confounders at 23y*

The selected variables were: respondent's educational attainment (A level/O level/no qualification) and the equivalent net family income (adjusted for family size and composition with weightings from supplementary-benefit scale) (Power et al., 1998).

*2.3.5. Adulthood socioeconomic confounders at 33y*

To take the role of material circumstances into account, we investigated firstly household tenure (classified in two categories: owner occupiers/renters, other), whether the participant's or their partner were receiving social security benefits (income support, supplementary, or unemployment benefit), whether the participant declared having mortgage or rent arrears (never been 2 or more month behind/yes, ever been 2 or more moth behind) and occupation (classified in non-manual/manual). To capture social support, marital status was used grouped into the following categories: couple/single/divorced or widowed.

*2.3.6. Adult health behaviours at 33y*

We investigated the smoking status (non-smoker/former smoker/current smoker), alcohol consumption [moderate (women: between 1 and 14 units in the previous week; men: between 1 and 21 units in the previous week)/abstainers (reported not consuming any alcohol in the previous week)/heavy drinkers (women: >14 units in the previous week; men: >21 units in the previous week)] (2012), and physical activity (physically active/moderately active/inactive). To measure eating habits, we added BMI in the model (normal/underweight/overweight/obese).

### 2.4. Statistical analysis

To control for possible bias due to missing data, twenty imputations were conducted using the multiple imputation program ICE in STATA V14. We took a missing-at-random (MAR) assumption. Each covariable with missing values was imputed including all confounders used in the models as well as variables from other sweeps correlated with the variable to impute but excluding the exposures variable (AL) and the subjective health index (Supplementary material). To observe the unadjusted link and better appreciate the evolution of the link between AL and later subjective health, the first model of the multivariate linear regression took only into account AL. Subsequently, and to mimic life-course experiences, we sequentially adjusted the multivariate linear regression resulting in four models:

1. Model 1: AL
2. Model 2: M1 + Early life socioeconomic confounders at birth,
3. Model 3: M2 + Early adulthood socioeconomic confounders at 23y,
4. Model 4: M3 + Adulthood socioeconomic and health behaviours confounders at 33y,

As some evidence suggests gender-related differences in biological markers (Goldman et al., 2004) and potential sexual dimorphism in AL (Yang and Kozloski, 2011) or other biological measure (e.g. metabolic syndrome) (McMillen and Robinson, 2005), the analyses were stratified by sex (Goldman et al., 2004; Yang and Kozloski, 2011) (Supplementary material).

## 3. Results

### 3.1. Sample characteristics

Descriptive statistics of the non-imputed sample are presented in Table 1 for the subsample with complete data for subjective health and AL (n = 3070 for men; n = 3295 for women). Mean of AL for both men and women was equal to 3, ranged from 0 to 12. Table S2 shows the results for the bivariate statistics for both men and women. AL score was associated with subjective health index in men (−0.07 standard deviation (SD); $p < 0.001$) and in women (−0.09SD; $p < 0.001$).

### 3.2. Allostatic load and subjective health

Fig. 1 shows the AL score mean by deciles of subjective health index. A clear gradient is revealed, individuals in the 1st decile of subjective health index (worse health) had an AL score mean of 3.5 and 4 for men and women respectively. Men and women in the 10th decile of subjective health show an AL score mean of 2.5. Multivariate results are presented in Tables 2 and 3 for men and women respectively. Model 1 showed that AL was significantly associated with later subjective health. Men with higher scores of AL at 44 years had worse subjective health indexes (-0.07SD; $p < 0.001$) at 50 years. The same pattern was observed for women, where higher scores of AL were correlated with worse subjective health index (−0.09SD; $p < 0.001$). In model 2 and model 3 the link was slightly weakened after adjustment for early life and early adulthood socioeconomic circumstances. Model 4 showed that socioeconomic and health behaviours variables reduced the link for both men and women, however it remained significant: a one-point increase of the AL score was associated with a reduction of 0.04SD ($p < 0.001$) and 0.05SD ($p < 0.001$) in the health index for men and women respectively. As sensitivity analyses we constructed an additional AL score by calculating a 0–1 risk score within each system, reflecting the proportion of biomarkers within the system for which the participant's values fell into the highest-risk quartile, allowing an equal weight for each system (Carroll et al., 2015). The results did not vary. We also evaluate which of the biomarkers was having the strongest link with the subjective health index. We run an additional multivariate model fully adjusted for the same confounders, taking each biomarker individually and previously divided into low '0'/high risk '1' in a sample without missing values. For men peak expiratory flow and for women CRP and fibrinogen showed the strongest link (Supplementary material). For men, only four biomarkers were significantly related to the subjective health index, for women only half. This could reinforce the construct of AL, maybe measuring an overall physiological state that better predicts later health than each biomarker separately.

### 3.3. Life course socioeconomic confounders and later subjective health

From early life, mothers education (only for men) and lower paternal occupational status (skilled manual and semi-unskilled) reduced the subjective health index for both men and women, however these links disappeared after adjustment for socioeconomic variables in adulthood. The fully adjusted model yield additionally interesting findings. For men, having no qualifications at 23y decreased the subjective health index of 0.14SD ($p < 0.001$). Income was found to predict better subjective health only in women (0.23; $p < 0.001$). Worse material and socioeconomic circumstances at 33y were important independent factors associated with lower subjective health index. For both men and women, being a tenant (men: −0.14SD, $p = 0.019$)/women: −0.16SD, $p = 0.004$), receiving social-security benefits (men: −0.30SD, $p = 0.003$/women:−0.21SD, $p = 0.002$) and declaring ever being two or more months behind with mortgage or rent arrears (men:−0.23SD, $p = 0.007$/women:−0.21SD, $p = 0.008$) were significantly associated with a worse subjective health index compared to their counterparts. Model 4 also showed the important role of health behaviours and BMI. Being a current smoker (men: −0.10SD, $p = 0.034$/women:−0.18SD, $p < 0.001$), being classified as a heavy drinker for men (-0.20SD, $p = 0.002$) or an abstainer for women (women:−0.12SD, $p = 0.002$), and being obese (men:−0.15SD, $p = 0.026$/women:−0.29SD, $p < 0.001$), decreased the subjective health index relatively to those classified as non-smokers, moderate drinkers, or having a normal BMI respectively.

## 4. Discussion

Higher scores of allostatic load at 44 years were found to be associated with worse subjective health six years later in a large prospective cohort, after taking into account classic confounders. This association was independent of socioeconomic variables across the life course, adult health behaviours and BMI. These findings add some evidence to the hypothesis of a plausible biological underlying mechanism between the social environment and later overall health, via stress response systems. We deduce that AL may represent a physiological outcome of embodiment processes, contributing to a better understanding of susceptibility to poorer health and the production of social gradients in health.

There are several limitations in this study. First, since these analyses were performed using a birth cohort, an important weakness is related to attrition and selection bias. However, the surviving cohort remains broadly representative of the initial cohort key childhood and adult characteristics (Atherton et al., 2008). We additionally imputed the data for confounding variables taking the missing at random assumption to preserve important aspects of the distribution, variability, and relationships between variables.

**Table 1**
Descriptive statistics on the subsample for men (n = 3070) and women (n = 3295).

| Variables | Men | Women | Total |
|---|---|---|---|
| Subjective health Z score at 50 | | | |
| n (min–max) | 3070 (−5.0 to 1.6) | 3295 (−4.2 to 1.7) | 6365 (−5.0 to 1.7) |
| mean (SD) | 0 (1.0) | 0 (1.0) | 0 (1.0) |
| Allostatic load score at 44 | | | |
| 0 | 244 (7.9%) | 277 (8.4%) | 521 (8.2%) |
| 1 | 505 (16.5%) | 578 (17.5%) | 1083 (17.0%) |
| 2 | 649 (21.1%) | 656 (19.9%) | 1305 (20.5%) |
| 3 | 574 (18.7%) | 560 (17.0%) | 1134 (17.8%) |
| 4 | 464 (15.1%) | 452 (13.7%) | 916 (14.4%) |
| 5 | 280 (9.1%) | 313 (9.5%) | 593 (9.3%) |
| 6 | 190 (6.2%) | 219 (6.6%) | 409 (6.4%) |
| 7 | 97 (3.2%) | 108 (3.3%) | 205 (3.2%) |
| 8 | 56 (1.8%) | 83 (2.5%) | 139 (2.2%) |
| 9 | 9 (0.3%) | 37 (1.1%) | 46 (0.7%) |
| 10 | 2 (0.1%) | 9 (0.3%) | 11 (0.2%) |
| 11 | 0 (0.0%) | 1 (0.0%) | 1 (0.0%) |
| 12 | 0 (0.0%) | 2 (0.1%) | 2 (0.0%) |
| Maternal education | | | |
| Left school at 15 or later | 811 (26.4%) | 870 (26.4%) | 1681 (26.4%) |
| Left school before 14 | 2107 (68.6%) | 2239 (68.0%) | 4346 (68.3%) |
| Missing | 152 (5.0%) | 186 (5.6%) | 338 (5.3%) |
| Paternal occupation | | | |
| I & II (professional/managerial | 624 (20.3%) | 612 (18.6%) | 1236 (19.4%) |
| IIINM (skilled nonmanual) | 295 (9.6%) | 323 (9.8%) | 618 (9.7%) |
| IIIM (skilled manual) | 1425 (46.4%) | 1557 (47.3%) | 2982 (46.9%) |
| IV & V (semi-unskilled) | 568 (18.5%) | 610 (18.5%) | 1178 (18.5%) |
| Missing | 158 (5.1%) | 193 (5.9%) | 351 (5.5%) |
| Education level at 23 | | | |
| Passed A levels | 707 (23.0%) | 728 (22.1%) | 1435 (22.5%) |
| Passed O levels | 1021 (33.3%) | 1 319 (40.0%) | 2340 (36.8%) |
| No qualifications | 925 (30.1%) | 860 (26.1%) | 1785 (28.0%) |
| Missing | 417 (13.6%) | 388 (11.8%) | 805 (12.6%) |
| Income at 23 | | | |
| Q1 – Low income | 462 (15.0%) | 805 (24.4%) | 1267 (19.9%) |
| 2 | 550 (17.9%) | 794 (24.1%) | 1344 (21.1%) |
| 3 | 709 (23.1%) | 657 (19.9%) | 1366 (21.5%) |
| Q4 – High income | 777 (25.3%) | 563 (17.1%) | 1340 (21.1%) |
| Missing | 572 (18.6%) | 476 (14.4%) | 1048 (16.5%) |
| Household tenure at 33 | | | |
| Owner | 2130 (69.4%) | 2361 (71.7%) | 4491 (70.6%) |
| Renter | 341 (11.1%) | 463 (14.1%) | 804 (12.6%) |
| Rent free, goes with job, equity sharer | 23 (0.7%) | 37 (1.1%) | 60 (0.9%) |
| Missing | 576 (18.8%) | 434 (13.2%) | 1010 (15.9%) |
| Social-security benefits at 33 | | | |
| No | 2594 (84.5%) | 2766 (83.9%) | 5360 (84.2%) |
| Yes | 137 (4.5%) | 245 (7.4%) | 382 (6.0%) |
| Missing | 339 (11.0%) | 284 (8.6%) | 623 (9.8%) |
| Mortgage or rent arrears at 33 | | | |
| Never been 2/+ month behind | 2579 (84.0%) | 2818 (85.5%) | 5397 (84.8%) |
| Yes ever been 2/+ month behind | 143 (4.7%) | 189 (5.7%) | 332 (5.2%) |
| Missing | 348 (11.3%) | 288 (8.7%) | 636 (10.0%) |
| Occupation at 33 | | | |
| Non-manual | 1453 (47.3%) | 2060 (62.5%) | 3513 (55.2%) |
| Manual | 1152 (37.5%) | 759 (23.0%) | 1911 (30.0%) |
| Missing | 465 (15.1%) | 476 (14.4%) | 941 (14.8%) |
| In couple at 33 | | | |
| Couple | 2204 (71.8%) | 2474 (75.1%) | 4678 (73.5%) |
| Single | 376 (12.2%) | 273 (8.3%) | 649 (10.2%) |
| Divorced or widowed | 140 (4.6%) | 250 (7.6%) | 390 (6.1%) |
| Missing | 350 (11.4%) | 298 (9.0%) | 648 (10.2%) |
| Smoking status at 33 | | | |
| Non smoker | 1388 (45.2%) | 1562 (47.4%) | 2950 (46.3%) |
| Former smoker | 550 (17.9%) | 595 (18.1%) | 1145 (18.0%) |
| Current smoker | 791 (25.8%) | 859 (26.1%) | 1650 (25.9%) |
| Missing | 341 (11.1%) | 279 (8.5%) | 620 (9.7%) |
| Alcohol consumption at 33 | | | |
| Moderate | 1984 (64.6%) | 1758 (53.4%) | 3742 (58.8%) |
| Abstainers | 476 (15.5%) | 1105 (33.5%) | 1581 (24.8%) |
| Heavy drinkers | 286 (9.3%) | 164 (5.0%) | 450 (7.1%) |

Table 1 (*Continued*)

| Variables | Men | Women | Total |
|---|---|---|---|
| Missing | 324 (10.6%) | 268 (8.1%) | 592 (9.3%) |
| Physical activity at 33 | | | |
| Physically active | 1932 (62.9%) | 2135 (64.8%) | 4067 (63.9%) |
| Moderately active | 199 (6.5%) | 168 (5.1%) | 367 (5.8%) |
| Inactive | 84 (2.7%) | 88 (2.7%) | 172 (2.7%) |
| Missing | 855 (27.9%) | 904 (27.4%) | 1759 (27.6%) |
| BMI at 33 | | | |
| Normal | 1352 (44.0%) | 1943 (59.0%) | 3295 (51.8%) |
| Overweight | 1047 (34.1%) | 695 (21.1%) | 1742 (27.4%) |
| Obese | 261 (8.5%) | 280 (8.5%) | 541 (8.5%) |
| Missing | 410 (13.4%) | 377 (11.4%) | 787 (12.4%) |

Second, we cannot conclude that AL provides an added value for predicting later subjective health, since to answer that question, we would need to adjust the model at baseline for subjective health measures. Unfortunately, our study lacks of the same instruments (SF-36, MOS sleep scale) we used for constructing the subjective health variable at previous sweeps. However, to address this question we decided to run a sensitivity analysis using self-rated health as an outcome at 50y, adjusted for self-rated health at 44y in the same imputed sample. Self-rated heath has the advantage of being available at both baseline and at 50 years; and it is a measure contained within the SF-36 score we used for our subjective health measure. We found that AL was independently associated with self-rated health at 50y after adjusting for self-rated health at 44y. This result reinforces the hypothesis that the association between AL and subjective health at 50y is not due to subjective health status at 44 years.

Third, our score remains limited by pragmatic issues regarding variable availability and operationalization. The biomarkers included in our AL score were derived from available data, as parameters of major regulatory systems with known or hypothesized links with stress responses. For example, our AL score lacks "primary" biomarkers and neuroendocrine biomarkers (e.g. epinephrine and norepinephrine) (Juster et al., 2011). Measures of AL may differ in terms of biomarker choice, variable weight, statistical methods, and risk thresholds. Furthermore, the physiological relationship between biomarkers, and their relative importance in the physiological cascade of stress responses remains unclear (Beckie, 2012). AL operationalization continue to be a central debate around how to better approach physiological wear-and-tear. The operationalization we choose was pragmatic and it does not rigorously corresponds to the dynamic theory and definition of AL, and how it accumulates. In previous work we discussed some of the conceptual and empirical consideration regarding these questions (Delpierre et al., 2016). Several issues remain, for instance, the choice of biomarkers (DNA methylation, telomeres length, markers from -omics technologies; or larger molecules and physiological measures); or the best methodological tool to sum up these biomarkers (weighting, taking into account the dependency of each biomarker) and the measurement models more adapted (canonical correlation, recursive partitioning). Future research requires progress in the collection of biomarkers explicitly designed to assess allostatic load at multiple time points in longitudinal large representative samples (Beckie, 2012). Comparative studies are needed to better comprehend the age-related, sex/gender-related, ethnic-related differences in AL. Further research should propose and explore consistent theoretical explanations of the link between the biological mechanism, the system dynamic and the allostatic load measurement. We have previously attempted to raise and debate some of these issues (Delpierre et al., 2016) but many remain open and deserve further clarification, such as the concept of 'strain', 'cost', 'price' that have never being truly defined and that we could not incorporate in the AL operationalization. At this point, AL is capable of characterizing only a fragment of the causal path between social environment and later health. In our case, adding biomarkers to epidemiological research does not solve the 'black box' problem. We can only better 'trace' and hypothesize aspects of the biological component of the 'black box', by exploring the pathways of associations between the exposures, the biomarkers and the health outcome.

Third, we have a one-time AL measure available, which did not allow for a lifetime health trends analysis. Finally, our subjective health measure remains an ad-hoc index and its reproducibility is limited. Health is a latent variable that can be captured using different psychometric scales, as well as clinical and biological variables. We only integrated standardized and validated measures of subjective health which had already been related to later health and mortality risk. It is worth mentioning that in this study both AL and health measures are confined to a specific social and cultural context. The subjective health measure used here is adapted to a Western population, and the questionnaires used were oriented towards a British population. The notion of well-being and psychological malaise, for instance, are confined to a particular social and cultural context (Ryff et al., 2014). Regarding AL, differences on the perception of stressful conditions may have consequences on the symptoms reported (Lock and Kaufert, 2001), and differences on the biomarkers average levels (Miyamoto et al., 2013). To think in terms of 'local biologies' will add some scientific bases when analysing the effects of environmental exposures and health outcomes (Lock and Kaufert, 2001). However, AL is structured to use the distribution of the sample in question, thus it is as local or as global as the sample allows in terms of multi-system wastage. We do believe that common underlying biological mechanisms are plausible, and these biological mechanisms can be captured using different measures according (and more adapted) to the specific social context. The possibility of comparing results from different contexts and to replicate the studies may allow us to observe if the underlying physiological responses, in particular physiological stress responses, are 'generalizable'.

Despite these limitations, our findings offer several insights with respect to previous studies. There is a growing amount of evidence that supports AL as a better predictor of morbidity and mortality (Gruenewald et al., 2006; Karlamangla et al., 2006; Seeman et al., 2001). However, previous studies have concentrated their analysis on specific dimensions of health mainly using elderly population based studies, and though have a lack of prospective data concerning early life, adolescence and early adulthood circumstances. The main novelty of our study is to focus our analysis on the basis of a global effect of stress on health, using an integrative measure -that is not centered on the dichotomy absence/presence of disease- in middle aged adults that have been followed since birth. This allows us to take into account a variety of material, psychosocial, educational and life styles exposures from early life and across the life course. Here we analyzed health as an integrative measure in middle aged adults using a life course perspective allowing for a better

**Table 2**
Lifecourse multivariate linear regression between AL and standardized subjective health index Zscores using data from multiple imputation: men (n = 3070).

| Variables | Model 1: AL | | Model 2: Socioeconomic factors at birth | | Model 3: Socioeconomic factors at 23y | | Model 4: Socioeconomic and behavioural factors at 33y | |
|---|---|---|---|---|---|---|---|---|
| | ß (CI 95%) | p | ß (CI 95%) | p | ß (CI 95%) | p | ß (CI 95%) | p |
| Allostatic load score at 44 | −0.07 (−0.08 to −0.05) | <0.001 | −0.06 (−0.08 to −0.04) | <0.001 | −0.06 (−0.07 to −0.04) | <0.001 | −0.04 (−0.06 to −0.02) | <0.001 |
| Maternal education | | | | | | | | |
| Left school at 15 or later | | | 0 | | 0 | | 0 | |
| Left school before 14 | | | −0.10 (−0.18 to −0.01) | 0.034 | −0.06 (−0.15 to 0.03) | 0.220 | −0.05 (−0.14 to 0.04) | 0.279 |
| Paternal occupation | | | | | | | | |
| I & II (professional/managerial | | | 0 | | 0 | | 0 | |
| IIINM (skilled nonmanual) | | | −0.07 (−0.21 to 0.07) | 0.306 | −0.05 (−0.19 to 0.08) | 0.437 | −0.05 (−0.19 to 0.09) | 0.455 |
| IIIM (skilled manual) | | | −0.10 (−0.20 to −0.01) | 0.039 | −0.06 (−0.16 to 0.04) | 0.256 | −0.06 (−0.16 to 0.05) | 0.273 |
| IV & V (semi-unskilled) | | | −0.12 (−0.24 to 0.00) | 0.046 | −0.05 (−0.18 to 0.08) | 0.450 | −0.03 (−0.16 to 0.10) | 0.634 |
| Education level at 23 | | | | | | | | |
| Passed A levels | | | | | 0 | | 0 | |
| Passed O levels | | | | | −0.08 (−0.18 to 0.02) | 0.119 | −0.05 (−0.15 to 0.06) | 0.369 |
| No qualifications | | | | | −0.22 (−0.32 to −0.11) | <0.001 | −0.14 (−0.27 to −0.02) | 0.025 |
| Income at 23 | | | | | | | | |
| Q1 – Low income | | | | | 0 | | 0 | |
| 2 | | | | | 0.11 (−0.01 to 0.23) | 0.080 | 0.05 (−0.07 to 0.17) | 0.396 |
| 3 | | | | | 0.10 (−0.01 to 0.21) | 0.078 | 0.03 (−0.09 to 0.14) | 0.645 |
| Q4 – High income | | | | | 0.13 (0.02 to 0.24) | 0.020 | 0.06 (−0.06 to 0.17) | 0.339 |
| Household tenure at 33 | | | | | | | | |
| Owner occupiers | | | | | | | 0 | |
| Renters/other | | | | | | | −0.14 (−0.26 to −0.02) | 0.019 |
| Social-security benefits at 33 | | | | | | | | |
| No | | | | | | | 0 | |
| Yes | | | | | | | −0.30 (−0.49 to −0.10) | 0.003 |
| Mortgage or rent arrears at 33 | | | | | | | | |
| Never been 2/+ month behind | | | | | | | 0 | |
| Yes ever been 2/+ month behind | | | | | | | −0.23 (−0.40 to −0.06) | 0.007 |
| Occupation at 33 | | | | | | | | |
| Non-manual | | | | | | | 0 | |
| Manual | | | | | | | −0.01 (−0.10 to 0.09) | 0.912 |
| In couple at 33 | | | | | | | | |
| Couple | | | | | | | 0 | |
| Single | | | | | | | −0.10 (−0.21 to 0.02) | 0.092 |
| Divorced or widowed | | | | | | | −0.13 (−0.31 to 0.05) | 0.151 |
| Smoking status at 33 | | | | | | | | |
| Non smoker | | | | | | | 0 | |
| Former smoker | | | | | | | 0.00 (−0.10 to 0.10) | 0.973 |
| Current smoker | | | | | | | −0.10 (−0.19 to −0.01) | 0.034 |
| Alcohol consumption at 33 | | | | | | | | |
| Moderate | | | | | | | 0 | |
| Abstainers | | | | | | | −0.04 (−0.15 to 0.06) | 0.436 |
| Heavy drinkers | | | | | | | −0.20 (−0.32 to −0.08) | 0.002 |
| Physical activity at 33 | | | | | | | | |
| Physically active | | | | | | | 0 | |
| Moderately active | | | | | | | −0.04 (−0.19 to 0.10) | 0.549 |
| Inactive | | | | | | | −0.07 (−0.30 to 0.16) | 0.562 |
| BMI at 33 | | | | | | | | |
| Normal | | | | | | | 0 | |
| Overweight | | | | | | | −0.04 (−0.12 to 0.04) | 0.275 |
| Obese | | | | | | | −0.15 (−0.29 to −0.02) | 0.026 |

**Table 3**
Lifecourse multivariate linear regression between AL and standardized subjective health index Zscores using data from multiple imputation: women (n = 3295).

| Variables | Model 1: AL | | Model 2: Socioeconomic factors at birth | | Model 3: Socioeconomic factors at 23y | | Model 4: Socioeconomic factors and behavioural at 33y | |
|---|---|---|---|---|---|---|---|---|
| | ß (CI 95%) | p | ß (CI 95%) | p | ß (CI 95%) | p | ß (CI 95%) | p |
| Allostatic load score at 44 | −0.09 (−0.10 to −0.07) | <0.001 | −0.08 (−0.10 to −0.07) | <0.001 | −0.07 (−0.09 to −0.06) | <0.001 | −0.05 (−0.07 to −0.04) | <0.001 |
| Maternal education | | | | | | | | |
| Left school at 15 or later | | | 0 | | 0 | | 0 | |
| Left school before 14 | | | −0.07 (−0.15 to 0.02) | 0.118 | −0.01 (−0.10 to 0.07) | 0.775 | −0.02 (−0.10 to 0.07) | 0.686 |
| Paternal occupation | | | | | | | | |
| I & II (professional/managerial | | | 0 | | 0 | | 0 | |
| IIINM (skilled nonmanual) | | | 0.09 (−0.05 to 0.22) | 0.204 | 0.10 (−0.03 to 0.23) | 0.147 | 0.11 (−0.03 to 0.24) | 0.113 |
| IIIM (skilled manual) | | | −0.11 (−0.21 to −0.01) | 0.026 | −0.06 (−0.16 to 0.04) | 0.212 | −0.03 (−0.13 to 0.07) | 0.520 |
| IV & V (semi-unskilled) | | | −0.20 (−0.31 to −0.08) | 0.001 | −0.11 (−0.23 to 0.01) | 0.072 | −0.06 (−0.18 to 0.06) | 0.314 |
| Education level at 23 | | | | | | | | |
| Passed A levels | | | | | 0 | | 0 | |
| Passed O levels | | | | | −0.05 (−0.14 to 0.05) | 0.318 | 0.00 (−0.09 to 0.09) | 0.976 |
| No qualifications | | | | | −0.22 (−0.33 to −0.11) | <0.001 | −0.08 (−0.20 to 0.03) | 0.166 |
| Income at 23 | | | | | | | | |
| Q1 – Low income | | | | | 0 | | 0 | |
| 2 | | | | | 0.14 (0.04 to 0.23) | 0.005 | 0.08 (−0.01 to 0.18) | 0.091 |
| 3 | | | | | 0.16 (0.06 to 0.27) | 0.002 | 0.07 (−0.03 to 0.18) | 0.171 |
| Q4 – High income | | | | | 0.33 (0.22 to 0.44) | <0.001 | 0.23 (0.12 to 0.33) | <0.001 |
| Household tenure at 33 | | | | | | | | |
| Owner occupiers | | | | | | | 0 | |
| Renters/other | | | | | | | −0.16 (−0.26 to −0.05) | 0.004 |
| Social-security benefits at 33 | | | | | | | | |
| No | | | | | | | 0 | |
| Yes | | | | | | | −0.21 (−0.35 to −0.08) | 0.002 |
| Mortgage or rent arrears at 33 | | | | | | | | |
| Never been 2/+ month behind | | | | | | | 0 | |
| Yes, ever been 2/+ month behind | | | | | | | −0.21 (−0.36 to −0.06) | 0.008 |
| Occupation at 33 | | | | | | | | |
| Non-manual | | | | | | | 0 | |
| Manual | | | | | | | −0.03 (−0.11 to 0.06) | 0.559 |
| In couple at 33 | | | | | | | | |
| Couple | | | | | | | 0 | |
| Single | | | | | | | −0.11 (−0.24 to 0.02) | 0.088 |
| Divorced or widowed | | | | | | | −0.10 (−0.23 to 0.03) | 0.141 |
| Smoking status at 33 | | | | | | | | |
| Non smoker | | | | | | | 0 | |
| Former smoker | | | | | | | −0.03 (−0.12 to 0.06) | 0.541 |
| Current smoker | | | | | | | −0.18 (−0.27 to −0.10) | <0.001 |
| Alcohol consumption at 33 | | | | | | | | |
| Moderate | | | | | | | 0 | |
| Abstainers | | | | | | | −0.12 (−0.19 to −0.04) | 0.002 |
| Heavy drinkers | | | | | | | −0.02 (−0.18 to 0.14) | 0.802 |
| Physical activity at 33 | | | | | | | | |
| Physically active | | | | | | | 0 | |
| Moderately active | | | | | | | −0.02 (−0.17 to 0.12) | 0.769 |
| Inactive | | | | | | | 0.02 (−0.18 to 0.22) | 0.823 |
| BMI at 33 | | | | | | | | |
| Normal | | | | | | | 0 | |
| Overweight | | | | | | | −0.05 (−0.13 to 0.04) | 0.293 |
| Obese | | | | | | | −0.29 (−0.41 to −0.17) | <0.001 |

understanding of the causal sequence of events. We studied the link between a physiological measure and a subjective measure adjusted for a large panel of confounders which reduces the risk of a spurious link. In previous work, we investigated the socioeconomic determinants of AL, trying to disentangle the mediating pathways between early environment and AL (Barboza Solis et al., 2015). We intended to wed two major conceptual frameworks: AL theory – conceptualized in the stress and neuroendocrinology research- and ecosocial theory – conceptualize within the social epidemiology and health inequalities research- (Delpierre et al., 2016). We used a birth cohort study to capture the physiological impact of embodiment over the life course using an AL index. We hypothesised that the exposure to stressful and challenging events may be embodied, leaving a physiological stamp, partially captured by AL. Here we show that AL predicts subsequent health status by conceptualizing health as a measure beyond the classic definition of pathology, taking into account self-reported measures that could capture health capacities and resources, rather than clinically diagnosed categories of pathology or mortality.

These findings may add a conceptual validity to the hypothesis that social challenges become biologically embedded. The results showed the important role of socioeconomic factors across the life course for both men and women, the most important variables affecting subjective health being behaviours and material circumstances at 33y (model 4). Material circumstances have previously been linked via low socioeconomic position, to different measures of health status, through exposures related to bad housing, work conditions, neighborhood characteristics, etc. (toxins, allergens, overcrowding) (Galobardes et al., 2006). In terms of health behaviours, smoking, alcohol and BMI had the strongest effects on subjective health. Concerning BMI our findings are consistent with previous literature were BMI was found to correlate with well-being and health related quality of life (Ford et al., 2001). Obese individuals are more likely to suffer from low self-esteem, depression (Luppino et al., 2010) and discrimination with a well-established link between BMI and metabolic status, morbidity and mortality (Berrington de Gonzalez et al., 2010; Calle et al., 1999; Ferrucci and Alley, 2007).

## 5. Conclusion

In this study we show evidence of a link between physiological wear-and-tear, as measured by allostatic load, and health status, captured by latent variable of subjective health. These findings add some evidence to the hypothesis of a plausible biological underlying mechanism between the social environment and later overall health, via stress response systems. Allostatic load may represent a physiological outcome of embodiment processes contributing to a better understanding of early disease processes and social gradients in health. Hence, using a physiological index to grasp how the environment in which we live can “get under the skin” leading to poor health is of great interest in public health research.

## Conflict of interest

The authors declare no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2016.08.018.

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# Embodiment of Early Psychosocial Adversity and Allostatic Load Using a Life Course Perspective: A Review

## Incorporación de la Adversidad Psicosocial Precoz y la Carga Alostática Utilizando una Perspectiva Biográfica: Revisión de la Literatura

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ABSTRACT

The role of early life experiences on health is a major concern for research and public health interventions. Recent studies show that being exposed to chronic psychosocial stress during sensitive periods of development can have an impact on later health. It appears that children exposed to adverse conditions (economic, material and psychosocial) show a higher risk of adopting deleterious health behaviors (smoking, alcohol), heightened vulnerability to chronic diseases and mortality. Allostatic load (AL) is a measure of overall physiological wear-and-tear that can be the consequence of early life exposures. AL could allow for a better understanding of the potential biological pathways linking adverse exposures and later health. Here we review current evidence to discuss a biological embedding hypothesis, focusing on adverse psychosocial exposures during childhood and its effects on later AL, taking a life course perspective. Via a non-systematic review of recent literature, we examine whether adverse childhood experiences (ACE), causing chronic stress responses, may alter physiological functioning, as measured by AL. A better understanding of the biological mechanisms underlying psychosocial exposures could contribute to the development of more adapted public health interventions, both at a societal and individual level.

KEYWORDS

allostatic load, adverse childhood experiences, biological embedding, health behaviors, cohort study

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RESUMEN

El rol de las experiencias vividas durante la infancia sobre la salud genera gran interés y preocupación tanto a nivel de la investigación en salud como a nivel de las posibles intervenciones en salud pública. Estudios recientes muestran que haber estado expuesto al estrés psicosocial durante periodos sensibles del desarrollo podría impactar la salud a largo plazo. Ha sido sugerido que los niños(as) expuestos(as) a situaciones de adversidad (económica, material y psicosocial) muestran un mayor riesgo de adoptar comportamientos riesgosos (tabaco y alcohol), aumentando su vulnerabilidad a las patologías crónicas, acrecentando la mortalidad. La carga alostática (AL por sus siglas en inglés) representa el desgaste fisiológico global que podría ser la resultante de experiencias adversas vividas durante la infancia. La carga alostática podría permitir una mejor comprensión de los mecanismos biológicos implicados que relacionan el estrés psicosocial durante la infancia y la salud del adulto. En este artículo revisamos evidencia actual para discutir una hipótesis de incorporación biológica, centrándose en las exposiciones psicosociales adversas de la infancia y sus efectos sobre la carga alostática del adulto, tomando una perspectiva biográfica (a lo largo de la vida). Via una revisión no sistemática de la literatura reciente sobre el tema, examinamos si las experiencias adversas durante la infancia (ACE por sus siglas en inglés), causando respuestas al estrés crónico, son susceptibles de alterar el estado fisiológico global, medido por la carga alostática. Una mejor comprensión de los mecanismos biológicos subyacentes a las exposiciones psicosociales precoces podría contribuir al desarrollo de intervenciones en salud pública más adaptadas, tanto a nivel colectivo como individual.

PALABRAS CLAVES

carga alostática, experiencias adversas durante la infancia, incorporación biológica, comportamientos de riesgo, estudio de cohorte

## INTRODUCTION

Nancy Krieger described embodiment as “how we, like any living organism, literally incorporate, biologically, the world in which we live, including our societal and ecological circumstances” (Krieger, 2005). The notion of embodiment proposes that every human being is both a social and a biological organism that incorporates the world in which (s)he grows. The notion of embodiment or biological embedding (Hertzman, 1999, 2012) is a key concept within life course epidemiology; an interdisciplinary framework that analyses long-term biological, behavioral, and psychosocial processes linking early life exposures to health in later life via a number of mechanisms and processes (Kuh, Ben-Shlomo, Lynch, Hallqvist, & Power, 2003; Kuh, Ben-Shlomo, & Susser, 2004).

A growing literature shows the early life biological and social determinants of heart disease, diabetes, obesity, depression, premature mortality, among others (Hertzman & Boyce, 2010). In the early 1990s, Barker showed that exposure to undernutrition in utero was associated with developing coronary heart disease in adulthood (Barker, 2002). These findings opened an extensive field of research studying the early life origins of adult disease (Barker, 2002, 2007) recently known as Developmental Origins of Health and Disease (DOHaD). Since, other factors besides the intrauterine environment have been studied. Felitti et al. conducted in the late 1990s the “Adverse Childhood Experiences (ACE) study” showing that being exposed to psychosocial adversity during childhood -like child abuse, emotional and physical neglect- was strongly correlated with adult risky behaviors, cancer, and early mortality (Felitti, 2002; Felitti et al., 1998).

Evidence suggests that early psychosocial adversity could have an adverse effect on mental and physical health and appears to be associated with increased activation in the nervous, endocrine, and immune systems (Kelly-Irving, Mabile, Grosclaude, Lang, & Delpierre, 2013; Li, Power, Kelly, Kirschbaum, & Hertzman, 2007). Lupien et al. has shown the neurodevelopmental consequences of growing-up in poverty and adversity (Boyce, Sokolowski, & Robinson, 2012; Lupien, McEwen, Gunnar, & Heim, 2009). During childhood and adolescence, nervous, endocrine, and immune systems are not fully developed and show significant changes (Danese & McEwen, 2012). The identification of these mechanisms and their importance for brain and behavioral development starting early in life, support the hypothesis that exposure to chronic psychosocial stress, and its subsequent physiological reaction, can have enduring effects on health throughout the life span (Kelly-Irving, Mabile, et al., 2013).

In the last two decades, epidemiological research has used the concept of allostatic load (AL) to explain how chronic stress can lead to physiological dysregulation and disease (Beckie, 2012; Juster, McEwen, & Lupien, 2010; McEwen, 2006; Seeman, McEwen, Rowe, & Singer, 2001; Seeman, Singer, Rowe, Horwitz, & McEwen, 1997) . AL is a measure of overall physiological wear-and-tear over the life course, which could be the consequence of early life exposures (Danese & McEwen, 2012; Taylor, Way, & Seeman, 2011). According to AL theory, cumulative and repeated activation of compensatory physiological mechanism in response to chronic stress can lead to a multisystem predisease state represented by a dysregulation of neuroendocrine, metabolic, inflammatory, or cardiovascular parameters (McEwen, 1998; McEwen & Seeman, 1999). Current research exploring the link between socioeconomic exposures and later health is not consistent and the mechanisms by which psychosocial adversity "gets under the skin" and impact physiological pathways leading to disease remains unclear. The aim of this study is to discuss current evidence of how early psychosocial environment becomes biologically embedded and produces health differences across populations. The hypothesis discussed in this review is that allostatic load may be a suitable indicator of the physiological wear-and-tear produced by embodiment processes over the life course.

## CHRONIC STRESS & EARLY PSYCHOSOCIAL ENVIRONMENT

Here we utilize an integrative approach that define stress "as a process that entails a stimuli, appraisal of it, and a response" (Miller, Chen, & Parker, 2011). When an stimuli (better known as stressor) is evaluated as an unmanageable threat, triggers a cascade of behavioural and biological adjustments called responses (Miller, et al., 2011). In this review we focus on chronic psychosocial stress during childhood and its contribution to adulthood health. Chronic stress refers to "an experience where the stimuli remains present in a child's life over a lengthy period of time" (Miller, et al., 2011). Maltreatment, nutritional and material deprivation, socioeconomic and financial disadvantage are examples of stressors that could linger over the lifespan. The National Scientific Council on the Developing Child has proposed three different types of stress responses in children: positive, tolerable, and toxic (Center on the Developing Child Harvard University). The classification was built on the basis of their potential long term physiological damage. "Positive stress" is brief and moderate. It can be socially buffered and represent an opportunity to adapt to adverse situations. "Tolerable stress" produces temporary and potentially damaging stress responses that can be reversible and buffered in a supportive and secure social environment. "Toxic stress" is characterized by the constant activation of the stress response systems -like the hypothalamic-pituitary-adrenal (HPA) axis- due to chronic or traumatic experiences in the absence of consistent

social support, especially during childhood and adolescence (Shonkoff, Garner, Comm Psychosocial Aspects Child, Comm Early Childhood Adoption, & Sect Dev Behav, 2012). According to the Center on Developing Child "the extent to which stressful events have lasting adverse effects is determined in part by the individual's biological response (mediated by both genetic predispositions and the availability of supportive relationships that help moderate the stress response), and in part by the duration, intensity, timing, and context of the stressful experience" (Center on the Developing Child Harvard University).

Children can be exposed to a wide range of chronic stressors, nevertheless, recent literature showed the importance of psychosocial stress and their consequences on later health, specifically through the stress systems (Danese & McEwen, 2012; Danese & Tan, 2014). Psychosocial is defined here as "the interaction between people and their social environment involving psychological processes" (Egan, Tannahill, Petticrew, & Thomas, 2008) or "pertaining to the influence of social factors on an individual's mind or behavior, and to the interrelation between of behavioral and social factors"(Oxford English Dictionary). In this context the Adverse Childhood Study (ACE study) examined in the 1990s a variety of psychosocial stressors and their impact on health. The authors proposed that exposure to maltreatment, child abuse, physical and emotional neglect can produce toxic stress responses and, in a long term, impact adult health. It is known that the prefrontal cortex, the amygdala, and the hippocampus are regions in the brain particularly sensitive to psychosocial stress (McEwen, 2007). For instance, it has been showed that maltreated children present chronic activation of the HPA axis, blunted cortisol and neuroendocrine responses in specific laboratory tasks.

These findings suggest that an organism is capable of "programming" itself and adapting its biology to face environmental challenges, which make the embodiment of early psychosocial experiences plausible. Nevertheless, interesting methodological and theoretical questions are raised. How does childhood adversity "get under the skin" to become biological and how can we study processes of embodiment occurring throughout life?

## ACE EMBODIMENT & LIFE COURSE PERSPECTIVE: SENSITIVE PERIODS, ACCUMULATION AND PATHWAYS MODELS

The lifecourse approach is a conceptual framework well adapted for studying embodiment, a process occurring over the lifespan. Three lifecourse models have been suggested in biological and medical research. The first is the "biological programming" or sensitive/critical periods model, the second is the accumulation model, and the third is the pathways model (Blane, Netuveli, & Stone, 2007).

The critical/sensitive periods model suggests that during a phase of development, a biological system is more sensitive to environmental exposures and to deviations from expected experiences -particularly in-utero and early life- and have lasting effects on physiological functioning (Bruer, 2001). Hubel and Wiesel's experiments in the 1960s showed that kittens deprived of visual experience in one eye for 6 weeks after birth remained permanently blind of the deprived eye (Wiesel & Hubel, 1963). A critical period was therefore identified for the visual system: the brain expects to be exposed to a visual input during a window of development, when the experience does not occur, the system is permanently and irreversibly damaged. Barker et al. showed that prenatal growth predicted coronary heart diseases in adulthood. They suggested that poor nutrition or impairment during foetal development could affect permanently physiological systems and structures leading to chronic diseases (Barker, 2002). This hypothesis has been enlarged to include the

social environment, identifying important social transitions during human development (Blane, et al., 2007). A sensitive period refers to a longer moment in human development when a given experience will have important effects on the system in question during an specific timing, still allowing the system to adapt to later experiences and reverse or modify the effect (Bailey, Bruer, Symons, & Lichtman, 2001). The vast literature on critical/sensitive periods suggests the existence of a sensitive period for humans from gestation to three years after birth (Bailey, et al., 2001). Critical/sensitive periods have been suggested for a first and a second language acquisition, as well as for the fundamental basis for social and emotional development (Bailey, et al., 2001). It appear that for higher brain functions and socio-emotional behavior the window of vulnerability may be longer, since the systems involved are more complex (Kelly-Irving, Mabile, et al., 2013). A key socio-emotional process in human development is attachment, or the establishment of a parent-infant bond at birth, that involves a sensitive period. An infant seems to need, for his/her emotional development an, initial attachment relation with a consistent caregiver and a quality relationship of security. Attachment is important for human beings principally because having a caregiver provides protection, assistance and support. It is also important for the development of psychosocial and psychological processes and contributes to stress management buffering the secretion of stress hormones (Gunnar, Brodersen, Nachmias, Buss, & Rigatuso, 1996). Concerning ACE, the existence of a sensitive period may be plausible. Being exposed to trauma, maltreatment and physical neglect during childhood and adolescence can alter the individual's physiological responses making them vulnerable to subsequent exposures and disease (Bailey, et al., 2001; Kelly-Irving, Lepage, Dedieu, Bartley, et al., 2013; Kelly-Irving, Mabile, et al., 2013).

The accumulation model purposes that long-term exposures across the life course accumulate and have consequences on health. Concerning the study of the link between low socioeconomic position and non-communicable diseases, the accumulation model is the most used model in empirical research (Gustafsson et al., 2014). Lifecourse accumulation of socioeconomic disadvantage appears to cause cumulative damage to biological systems (Gustafsson, et al., 2014). Galobardes et al. highlighted the accumulation processes concerning childhood socioeconomic circumstances. Children from low socioeconomic status could present lower birth weight, have poorer diets, being exposed to passive smoking, infectious diseases and so on (Galobardes, Lynch, & Smith, 2004). There is a lack of research exploring ACE and the mechanisms of accumulation, however, when analysing the gradual accumulation of physiological dysregulation over the life course, the accumulation model seems appropriate (Seeman, Epel, Gruenewald, Karlamangla, & McEwen, 2010).

The pathways model arose from the study of health inequalities, characterized by a "fine-grained" gradient producing health differences on morbidity and mortality according to social class. Blane et al. posits that "the social structure was suggested as the mechanism that could produce this fine-grained distribution of mortality, by structuring exposure to a range of non-behavioral hazards, which are clustered cross-sectionally and accumulated longitudinally via advantage or disadvantage in the various spheres of life" (Blane, 1995; Blane, et al., 2007). This "chain of risk" model explains how an exposure will lead to another and impact function and increasing disease risk (Kuh, et al., 2004). Typically, the ACE study has shown that being exposed to psychosocial stress early in life, increases the odds of adopting risky behaviors, which in turns promotes the appearance of non-communicable diseases and early mortality (Shanta R. Dube et al., 2006; Felitti, 2002; Felitti, et al., 1998; Ford et al., 2011).

These three lifecourse models are intertwined, influence each other, are not mutually

exclusive and may operate simultaneously (Kuh, et al., 2004). Life course approach allows to capture the sequence of social risk, psychosocial and material exposures, biological challenges and inferior living conditions across the life course that could damage adult health (Koffijberg, Adami, Buskens, & Palme, 2012; Kuh, et al., 2004; Power & Hertzman, 1997).

Some challenges persist when studying ACE in a life course perspective to test the embodiment hypothesis. A first challenge involves ACE, the definition is complex, variable, there are non-linear relation with health, and it can captures other domains besides the psychosocial. The second remaining question is how to conceptualize a measure of embodiment. Should we focus on specific health outcomes, individual biomarkers with clinical thresholds? In this context McEwen et al. proposed the concept of allostatic load (AL), a measure of overall physiological wear-and-tear over the life course that may be the consequence of early psychosocial exposures. A notion that could capture the cumulative physiological burden on the body caused by stressful environmental challenges (McEwen & Wingfield, 2003).

## ADVERSE CHILDHOOD EXPERIENCES (ACE) & PHYSIOLOGICAL WEAR-AND-TEAR AS MEASURED BY ALLOSTATIC LOAD (AL)

Empirical evidence shows that allostatic load (AL) has strong correlations with subclinical conditions, morbidity, and mortality, and may be a useful measure of overall health, rather than considering each biomarker separately. The notion of AL may be useful to explore how psychosocial adverse experiences over the life course may become biologically embedded.

The first operationalization of an AL index was conceived by Seeman et al. in 1997 utilizing the MacArthur study of successful aging, a longitudinal study of 70 to 79-year-olds follow-up over 12 years. This AL index included 10 biomarkers of multisystem physiological dysregulation: DHEA-S, urinary free cortisol, epinephrine, norepinephrine, systolic blood pressure, diastolic blood pressure, waist-hip ratio, high-density lipoprotein cholesterol (HDL-C), the ratio of total cholesterol to HDL-C (TC/HDL-C) and glycosylated hemoglobin. Each biomarker was then dichotomized into high risk versus low risk according to sex-specific quartiles. The high-risk quartile was the top quartile of all biomarkers, except for those for which a low level confers greater risk for poor health outcomes (e.g. HDL-C) (Seeman, et al., 2001; Seeman, et al., 1997). This index of AL was a better predictor of mortality and physical functioning relatively to metabolic syndrome (Karlamangla, Singer, McEwen, Rowe, & Seeman, 2002; Karlamangla, Singer, & Seeman, 2006), and may be a useful measure of overall health, rather than considering each biomarker separately (Beckie, 2012; Carlson & Chamberlain, 2005).

In the last decade, researchers have explored the link between early childhood/adolescence and later AL (Barboza Solis et al., 2015; Robertson, Benzeval, Whitley, & Popham, 2015). Three main pathways have been put forward: (i) an indirect health behaviors pathway, (ii) an indirect socioeconomic/materialist and/or psychosocial pathway, (iii) through a direct biological pathway via early alterations of physiological stress systems (e.g., hypothalamic-pituitary-adrenal axis). In a recent study we showed that exposure to Adverse Childhood Experiences (ACE) can alter AL at 44 years, after taking birth and childhood factors into account (Barboza Solis, et al., 2015). We utilize the National Child Development Study, a British birth cohort (n=18000) followed-up since 1958 (Power & Elliott, 2006). The AL index was conceptualize using 14 biomarkers representing four physiological systems: the neuroendocrine [salivary cortisol t1, salivary cortisol t1–t2]; the immune/inflammatory [insulin-like growth factor-1, C-reactive protein, fibrinogen, IgE]; the metabolic system [HDL, LDL, triglycerides, glycosylated

hemoglobin]; the cardiovascular and respiratory systems: [systolic blood pressure, diastolic blood pressure, heart rate/pulse, peak expiratory flow] (Barboza Solis, et al., 2015). ACE were defined as a set of traumatic and stressful psychosocial conditions that are out of the child's control, that tend to co-occur (Rosenman & Rodgers, 2004), and that often persist over time (Clark, Caldwell, Power, & Stansfeld, 2010; Felitti, et al., 1998). ACE represent intrafamilial events or conditions causing chronic stress responses in the child's immediate environment taking 6 dimensions at 7,11 and 16 years: (i) Child in care: child has ever been in public/voluntary care services or foster care. (ii) Physical neglect: child appears undernourished/dirty. Household dysfunction, consisting of four categories each contributing to the score: (iii) Offenders: the child lived in a household where a family member was in prison or on probation or is in contact with probation service; (iv) Parental separation: the child has been separated from their father or mother due to death, divorce, or separation. (v) Mental illness: household has contact with mental health services; family member has mental illness. (vi) Alcohol abuse: family member has alcohol abuse problem (Kelly-Irving, Lepage, Dedieu, Bartley, et al., 2013; Kelly-Irving, Lepage, Dedieu, Lacey, et al., 2013).

The correlation was largely, but not fully explained, by health behaviors, body mass index, and socioeconomic status in adulthood. These results suggest that a biological link between adverse childhood experiences and adult health may be plausible (Barboza Solis, et al., 2015). In this study, the most important pathway linking ACE to AL was the indirect health behaviors path. Health behavior adoption includes a number of processes that have been well described in the literature. The psychological processes suggest that adverse experiences during childhood could be related to health through a number of psychological mechanisms. These may include poor self-regulation, self-efficacy, and self-management (Bandura, 1991, 2005). Furthermore, it has been suggested that individuals exposed to adversity induced stress could adopt coping mechanisms by obtaining a pharmacological or psychological benefit from tobacco or alcohol use (Anda et al., 2002; S. R. Dube, Anda, Felitti, Edwards, & Croft, 2002; Shanta R. Dube, et al., 2006). These results suggest an indirect mechanism of embodiment of early psychosocial experiences via health behaviors and material and/or psychosocial circumstances in adulthood. Nevertheless, these factors did not account for the entire effect, suggesting that other mechanisms could be involved and it deserves further research.

## CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

Current evidence suggests a link between psychosocial stressors during childhood and physiological dysregulation in adulthood, as measured by allostatic load, in favor of the hypothesis of a biological embodiment of early psychosocial exposures over the life course. Experiencing psychosocial adversity during childhood may influence the biological stress systems in development and make them more susceptible to later disease. Adverse childhood experiences appear to influence adult allostatic load increasing the likelihood of low socioeconomic status, high BMI, and a propensity to engage in unhealthy behaviors. This confirms the existence of an accumulation process, a "chain of risk"/pathway model but we cannot rule out a sensitive period effect.

Despite significant progress in the field of early life stress and biological embedding leading to disease, many challenges remain. Future research should improve quantification of early stress (psychological, social and economic). Starting by using quality prospective longitudinal data to reduce recall bias and lack of accuracy in self-reported experiences. Studies should control for early life health experiences, socioeconomic status, educational attainment and lifestyle factors in adulthood.

Concerning AL, there is currently no consensus regarding the construction of a score capable of capturing physiological wear-and-tear. More collection data with biomarkers from children are needed (e.g. primary teeth, hair cortisol). Moreover, the AL score remains limited by the pragmatic issues such as variables availability and score composition. Although the concept of AL is well defined, there is an on-going debate regarding the choice of relevant physiological systems, biomarkers, their interactions (linear relationships), their importance in the chain of physiological stress responses, as well as their measurement, combinations, weighting and the most suitable statistical analysis (Delpierre et al., 2015). Future research requires progress in the biomarkers collection explicitly designed to assess AL at multiple time points in longitudinal large population-representative samples (Beckie, 2012). Comparative studies are needed to better comprehend the age-related, sex/gender-related ethnic-related differences influences on AL (Beckie, 2012).

Epidemiological research could test other mediators of biological embedding. Epigenetics, neural structure and function, HPA axis and inflammatory processes represent other valuable mediators (Rutter, 2012). Epigenetics in particular is a suitable candidate to explain the environmental influences on genes. The environment itself does not change gene sequences, nevertheless it can regulate gene expression influencing DNA methylation of several genes (Roth & Sweatt, 2011). Growing evidence suggests that gene activity is highly sensitive to environmental factors as toxins, diet, stress and behavioral influences (Roth & Sweatt, 2011). A better understanding of these processes can contribute to the conceptualization of more adapted public health interventions at an individual and at a population level with the objective of reducing health inequalities.

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# Appendix 2
# International conferences

- Barboza Solis, C. “Adverse childhood experiences and physiological wear-and-tear in mid-life: Findings from the 1958 birth cohort”. *Society for Longitudinal & Lifecourse Studies International Conference.* Poster session. Lausanne, 9-11 October 2014.

- Barboza Solis, C. « Les adversités durant l’enfance et la charge allostatique à l’âge adulte: résultats de la cohorte de naissances britannique de 1958 ». *Colloque Santé et Société : « Quels déterminants de santé et quel système de soins pour la santé de toute la population ?* ». Toulouse, 11-13 May 2015.

- Barboza Solis, C. “Parental Socio-Economic Position and Offspring’s Allostatic Load in Mid-Life: a Life Course Approach Using the 1958 British Birth Cohort”. *Society for Longitudinal & Lifecourse Studies International Conference*. Dublin, 19-21 October 2015.

- Delpierre, C; Barboza Solis, C. « Usure physiologique globale et santé subjective à l'âge adulte : résultats de la cohorte de naissances Britannique de 1958 ». *Congrès ADELF-EPITER. Rennes 7-9 Septembre 2016.*

# Appendix 3
# Additional publications

- Cyrille Delpierre, Cristina Barboza-Solís, Raphaëlle Castagné, Thierry Lang, Michelle Kelly-Irving. (2016). « Environnement social précoce, usure physiologique et état de santé à l'âge adulte : un bref état de l'art ». *Bulletin Epidémiologique Hebdomadaire.*

- Delpierre, C., C. Barboza Solis, M. Darnaudery, M. Bartley, D. Blane, M. Kelly-Irving. (2015). "Allostatic Load as a measure of social embodiment: Conceptual and empirical considerations." *Longitudinal and Life Course Studies.*

- Delpierre, C; Fantin, R; Barboza Solis, C; Lepage, B; Darnaudery, M; Kelly-Irving, M (2016). "The early life nutritional environment and early life stress as potential pathways towards the metabolic syndrome in mid-life? A lifecourse analysis using the 1958 British Birth cohort". *BMC Public Health.*

- Fantin, R; Delpierre, C; Dimeglio, C; Lamy, S; Barboza Solís, C; Charles, MA; Kelly-Irving, M. (2016). "Disentangling the respective roles of the early environment and parental BMI in BMI change across childhood: A counterfactual analysis using the Millennium Cohort Study". *Preventive Medicine.*

# Appendix 4
# Lay communications

- Barboza Solis, C. (2015). Revista ABC Salud. “El estrés infantil perjudica la salud de adulto: La infancia es un periodo crítico para el desarrollo integral y óptimo de los sistemas fisiológicos”. http://www.abc.es/salud/noticias/20150204/abci-estres-infantil-salud-201502041251.html

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# Appendix 5
# SF-36 Questionnaire used for sweep 8 (50 years) in the NCDS British birth cohort

1. Self-assessment of health
2. Self-assessment of health compared to a year ago
3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
5. Lifting or carrying groceries
6. Climbing several flights of stairs
7. Climbing one flight of stairs
8. Bending, kneeling or stooping
9. Walking more than one mile
10. Walking half a mile
11. Walking 100 yards
12. Bathing or dressing yourself
13. Past 4 weeks physical health led to cut down amount of time spent on work/other activities
14. Past 4 weeks physical health led to accomplished less than would like
15. Past 4 weeks physical health led to limited in the kind of work or other activities able to do
16. Past 4 weeks physical health led to difficulty performing work/other activities
17. Past 4 weeks emotional problems led to cut down amount of time you spent on work or other activities
18. Past 4 weeks emo problems led to accomplished less than would like
19. Past 4 weeks emo problems led to not done your work/other activities as carefully as usual
20. Past 4 weeks, what extent has physical health/emotional problems in family, friend, etc.
21. How much bodily pain have you had during the past 4 weeks?
22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outs)
23. Did you feel full of life?
24. Have you been a very nervous person?
25. Have you felt so down in the dumps nothing could cheer you up?
26. Have you felt calm and cheerful?
27. Did you have a lot of energy?
28. Have you felt downhearted and low?
29. Did you feel worn out?
30. Have you been a happy person?

31. Did you feel tired?
32. Has you health limited your social activities (like visiting friends, relatives, etc.)?
33. I seem to get ill a little easier than other people
34. I am as healthy as anybody I know
35. I expect my health to get worse
36. My health is excellent

AUTEURE : Cristina BARBOZA SOLIS

TITRE : Incorporation biologique de l'adversité sociale précoce: le rôle de la charge allostatique dans une perspective biographique

TITLE: Embodiment of early social adversity: the role of allostatic load in a life course perspective

DIRECTEURS DE THESE : Cyrille DELPIERRE et Michelle KELLY-IRVING

LIEU ET DATE DE LA SOUTENANCE : Toulouse, le 16 septembre 2016

Résumé

L'« embodiment » propose que tout humain est à la fois un être social ainsi que biologique, intégrant le monde dans lequel il/elle vit. Nous faisons l'hypothèse que la position socioéconomique pendant l'enfance peut être biologiquement incorporée, conduisant à la production des inégalités sociales de santé entre les sous-groupes de population. La charge allostatique (CA) est un concept qui tente de capturer l'usure physiologique globale du corps liée à l'activation répétée des mécanismes physiologiques compensatoires en cas d'exposition à des stress chroniques. La CA pourrait permettre une meilleure compréhension des voies biologiques qui jouent un rôle potentiel dans la construction du gradient social de santé des adultes. Nous avons examiné les voies de médiation entre les adversités psychosociales et la position socioéconomique précoces et la CA à 44 ans. Nous avons également confronté l'indice de CA à une mesure multidimensionnelle de santé latente à 50 ans utilisant les données de la cohorte Britannique de naissance de 1958 (n=18 000). La CA a été construite avec les données de l'enquête biomédicale conduite à 44 ans, comme une mesure physiologique synthétique, multi-système, à l'aide de 14 biomarqueurs représentant les systèmes neuroendocrinien, métabolique, immunitaire / inflammatoire et cardiorespiratoire. Nos résultats suggèrent que la CA pourrait être un indice approprié pour capturer partiellement la dimension biologique des processus d'embodiment. Comprendre comment l'environnement affecte notre santé en se « glissant sous la peau » et pénétrant dans les cellules, les organes et les systèmes physiologiques de notre corps est un principe clé dans la recherche en santé publique. Mots clés. charge allostatique ; embodiment ; incorporation biologique ; position socioéconomique ; inégalités sociales de santé, étude de cohorte

Abstract

'Embodiment' proposes that every human being is both a social and a biological organism that incorporates the world in which (s)he lives. It has been hypothesized that early life socioeconomic position (SEP) can be biologically embedded, potentially leading to the production of health inequalities across population groups. Allostatic load (AL) is a concept that intents to capture the overall physiological wear-and-tear of the body triggered by the repeated activation of compensatory physiological mechanisms as a response to chronic stress. AL could allow a better understanding of the potential biological pathways playing a role in the construction of the social gradient in adult health. We examined the mediating pathways between early SEP and early adverse psychosocial experiences and higher AL at 44 years. We also confronted an AL index with latent multidimensional measure of health status at 50y using data of the 1958 British birth cohort (n=18 000) follow-up to age 50. AL was operationalized using data from the biomedical survey collected at age 44 on 14 parameters representing the neuroendocrine, metabolic, immune-inflammatory and cardiovascular systems. Our results suggest that AL could be a suitable index to partially capture the biological dimensions of embodiment processes. Understanding how human environments affect our health by 'getting under the skin' and penetrating the cells, organs and physiological systems of our bodies is a key tenet in public health research. Keywords. allostatic load; embodiment; biological embedding; adverse childhood experiences; socioeconomic position; social inequities in health, cohort study.

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