COMMENT AND DEBATE

Origins of heath inequalities: the case for Allostatic Load

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Abstract

In an opening paper Delpierre et al. explore the concept of allostatic load. The impact of the environment on our biological systems is summarised by the concept of embodiment. The biological embedding of social conditions could therefore be a relevant mechanism to partly explain the social gradient in health. A key issue is how to measure the 'physiological reality' – the biological expression of embodiment at individual and population levels. Allostatic load (AL) has been proposed as a measure of the overall cost of adapting to the environment and may be a relevant tool or concept for measuring the way we have embodied our environment. Social inequalities in health may be partly explained by the embodiment of social environments, and AL may allow us to measure and compare embodiment between socioeconomic groups. However, before operationalising AL, a number of issues deserve further exploration. Among these, the choice of biological systems, and variables within each system, that should be included to remain 'loyal' to the theory of biological multisystem wastage underlying AL and the most appropriate methodological approach to be used to build an AL score, are particularly important. Moreover, studies analysing the link between adverse environments (physical, chemical, nutritional, psychosocial) across the life course and AL remain rare. Such studies require cohorts with data on socioeconomic and psychosocial environments over the life course, with multiple biological measures, made at various stages across the life span. The development and maintenance of these cohorts is essential to continue exploring the promising results that could enhance our understanding of the genesis of the social gradient in health by measuring embodiment. These points are then debated in commentaries by Linn Getz and Margret Olafia Tomasdottir, Tony Robertson and Per Gustafson. The commentaries are followed by a response from the authors of the opening paper.

Keywords

Allostatic load, embodiment, social epidemiology

Allostatic load as a measure of social embodiment: conceptual and empirical considerations

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Introduction

The impact of the environment on our biological systems is summarised by the concept of embodiment. Krieger (2005) described embodiment as "how we, like any living organism, literally incorporate, biologically, the world in which we live, including our societal and ecological circumstances". The notion of embodiment refers to the fact that every human being is both a social and a biological organism that incorporates the world in which (s)he lives.

In consequence, an adverse socioeconomic environment may be implicated in the development of future diseases by modifying certain biological processes especially when exposures occur early in life. In the 1990s Barker (1990) showed that intrauterine growth retardation was associated with an increased risk of cardiovascular and metabolic diseases in adulthood, introducing the foetal origin of disease hypothesis. This postulates that environmental conditions during specific windows of development can have long-term effects on organogenesis, and metabolic and physiological processes. However, embodiment is a continuous process that occurs throughout life, with some periods of life being more sensitive than others to changes induced by the environment. As a phenomenon occurring over the life course, embodiment may partly explain the social gradient observed for the vast majority of chronic diseases. Hertzman (1999) wrote "the process whereby differential human experiences systematically affect the healthfulness of life across the life cycle has been termed *biological embedding*". If embodiment, or biological embedding, refers to the concept of environmental adaptation shared by living beings, a key question is how to measure the physiological reality, the biological expression of embodiment at individual and population levels?

Recently, we showed that psychosocial adversity during childhood (child spent time in care, physical neglect, parental contact with the prison service, parental separation including by death or divorce, family experience of mental illness, family experience of substance abuse) increased twofold the risk of cancer diagnosis and all-cause mortality before 50 years of age, after adjusting for several confounding factors like socioeconomic characteristics at birth, birth weight and breastfeeding. Including mediating factors in the model, like health behaviours or adult socioeconomic position, only slightly decreased the effect of childhood psychosocial adversity (Kelly-Irving et al., 2013a; Kelly-Irving et al., 2013b). Of course, there are a number of possible explanations for these results, such as methodological flaws in design and analysis, or not including an *a priori* confounding or mediating factor. However, one possible explanation is that the childhood psychosocial environment might have resulted in changes to biological systems during development that may alter health over time.

Due to immaturity at birth, humans, as with other altricial mammals, mature in constant interaction with the environment. Our environment

is highly variable requiring the permanent adaptation of physiological systems. This adaption through changes is crucial for survival and refers to allostasis (Sterling & Eyer, 1988). Three main systems, nervous, endocrine and immune, are involved in the allostasis processes, all of which mature during the postnatal period and into adulthood (Adkins, Laclerc and Marshall-Clarke, 2004; Gogtay et al., 2004). Chronic exposures to psychosocial stressors and inter-individual differences in the susceptibility to stress are both associated with a prolonged activation of these allostatic systems. This may lead to an allostatic overload with potentially detrimental health consequences. Allostatic load (AL) is therefore the price paid by the body over time for adapting to challenges. It refers to the concept of biological multisystem wastage, whereby "the strain on the body produced by repeated ups and downs of physiologic response, as well as by the elevated activity of physiologic systems under challenge, and the changes in metabolism and the impact of wear and tear on a number of organs and tissues, can predispose the organism to disease" (McEwen & Stellar, 1993).

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, Singer, Rowe, Horwitz & McEwen, 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 sulphate (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). 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, Epel, Gruenewald, Karlamangla & McEwen, 2010). These various scores of AL have been shown to be better predictors of mortality and functional limitations than the metabolic syndrome or any of the individual components used to measure AL when analysed separately (Seeman, McEwen, Rowe & Singer, 2001). 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; Danese et al., 2009; Shonkoff & Garner, 2012).

As a measure of the global cost of adapting to (and coping with) the environment, AL may be a relevant tool or concept for measuring the way we have embodied our environment. As the way in which human populations embody their environment may partly explain social inequalities in health, we guess that AL may be a relevant and useful tool for measuring and comparing embodiment between population and socioeconomic groups. However, some important issues regarding AL deserve consideration:

Representing multiple biological systems

There is increasing evidence that many chronic diseases are related: this disease interrelatedness, or human disease network, is well established for metabolic diseases like obesity, diabetes and vascular diseases, and more recently for Alzheimer's disease/dementia, and cancer (Barabasi, Gulbahce & Loscalzo, 2011). There is biological plausibility behind the observed associations between these diseases that exemplify health decline and aging processes over the life course. Endocrine physiology and inflammatory processes are shared and many of the same risk factors, such as hyperglycaemia, inflammatory responses or health behaviours, are common to these pathologies. Further progress in understanding therefore requires the development of a measure representing the physiological systems relevant to these diseases. However the AL scores most commonly used are strongly focused on the cardiovascular or metabolic systems. The conceptualisation of AL as a dysregulation across

multiple physiological systems requires that the measure includes a balance of relevant systems, as well as the cardiovascular or metabolic ones. For instance, the inflammatory and immune systems that are involved in various chronic diseases ought to be represented. A main question is therefore how to decide which systems to represent. One of the solutions is to adopt an *a priori* definition of the systems that should be included in the measure of AL by choosing major regulatory systems known to be involved in chronic stress responses. An alternative may be to select major biological systems affecting health (Seeman et al., 2010) with the risk to be limited for studying the link between AL and subsequent health, if health is included in AL score. It may be possible that one single combination of markers do not equally predict different chronic diseases like cardiovascular or metabolic diseases, cancer or Alzheimer's disease, so that our measure of embodiment may need to be adapted according to the health condition under investigation.

Choosing relevant biological markers in each system

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 summarise the state of that system. Moreover, AL markers could be drawn from several very different physiological 'levels' from epigenetic regulations (DNA methylation, telomere length) to 'health outcomes' (illness, BMI, waist-hip ratio). The cascade of events linked to stress responses, physiological burden and disease thus needs 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 rhythm 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.

Building a score

Considering the two previous points, the question of how to go about summarising, 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 uses a summary measure representing the number of biomarkers within a high risk percentile defined from the biomarkers' distribution in the studied population (Juster, McEwen & Lupien, 2010). Maybe more critical than questions on how to define 'subclinical' thresholds representative in various populations, 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 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. However, using such an approach raises issues about the capability of such a score to 'truly' measure global physiological wear and tear. 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 best to 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 (Seeman et al. 2010; Booth, Starr & Deary, 2013; McCaffery, Marsland, Strohacker, Muldoon & Manuck, 2012). These methods, based on the covariation of biomarkers, present several advantages including: the possibility of testing an *a priori* hypothesised 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 the 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.

Allostatic load across the life course

Taking a life course approach to studying health raises questions regarding how best to measure wear and tear over the life span. AL is by definition the consequence of a cumulative adaptive response to challenges. Thus this is a dynamic process and therefore its 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, and are likely to have an impact on physiological stress reactivity (Lupien, McEwen, Gunnar & Heim, 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 each deserve further investigation (Bale, 2011).

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, not many studies analyse the link between adverse environments (physical, chemical, nutritional, psychosocial) and AL, taking a life course approach. Very 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, Janlert, Theorell, Westerlund & Hammarstrom, 2011; Gustafsson, et al. 2012; Merkin, Karlamangla, Roux, Shrager & Seeman, 2014; Robertson, Popham & Benzeval, 2014). These studies justify that 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 necessitates rich longitudinal datasets with long follow-ups. Socioeconomic position being a proxy for various exposures, datasets with large panels of variables on socioeconomic and psychosocial environment are particularly precious to disentangle which aspects contained in socioeconomic position influence both health and AL. Another essential ingredient in these datasets is the inclusion of biological samples, repeatedly collected to represent the dynamic nature of AL.

Conclusion

Here, we consider AL as a useful conceptual tool in measuring the biological effect of embodiment that can play a role in the production of the social gradient of many chronic diseases. Measures of the way people cope with their environment, from early life onwards, offer 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 remain loyal to the theory behind AL we highlight that measures used should be constructed, where possible, to represent multiple biological systems. In order to achieve this, good quality stable biological markers of the different physiological systems are needed, as well as data on the psychosocial and socioeconomic environment. All these questions are therefore conditioned by the availability of such markers in human cohorts. The development and maintenance of these cohorts is

essential, including information on socioeconomic and psychosocial environments over the life course, with multiple biological measures, made at various stages across the life span.

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Commentary by

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Introduction

The paper by Delpierre and colleagues on 'Allostatic load as a measure of social embodiment' offers an interesting and timely discussion of allostatic load as a mediating mechanism of embodiment, a way to scientifically conceptualise the interrelatedness of life-time experiences and human health. From an epidemiological perspective the authors see a need to operationalise allostatic load in a consensual manner for future application across different populations.

The general practice research group to which we belong has for years taken an interest in allostatic load. The presented connection between allostatic load and the phenomenon embodiment (Krieger, 2005) is highly concordant with our thinking (Getz, Kirkengen, & Ulvestad, 2011; Kirkengen, 2001, 2010; Kirkengen et al., 2015; Kirkengen & Thornquist, 2012; Mjolstad, Kirkengen, Getz, & Hetlevik, 2013; Thornquist & Kirkengen, 2015; Tomasdottir et al., 2014; Tomasdottir et al., 2015; Vogt, Ulvestad, Eriksen, & Getz, 2014). The interrelatedness of human biology and biography has long been evident to experienced doctors in general practice (GPs) who encounter individuals over time across varying circumstances and stages of life (Kirkengen, 2005). Until recently it has been very hard to think and communicate professionally about the topic. We have simply been short of an adequate, non-dualistic terminology. The concepts *embodiment* and *allostatic load* are now gaining momentum as conceptual tools to help establish and consolidate new and relevant medical knowledge. Much work will however be needed before these concepts are likely to influence significantly the mainstream of medical thought and practice.

We support the authors who see a need to further develop 'allostatic load' as an empirical construct. In the initial, tentative phases of allostatic load research (including our own) somewhat differing variables and algorithms have indeed been applied, to a large extent reflecting practical availability of data in each case. Theoretical consensus and empirical rigor are now needed to consolidate and advance this important field.

But we see a lot more to the concept allostatic load than a quantifiable score. We see it as a potential keystone in coherent, integrative (in the sense of non-dualistic) thinking in future medicine (Tomasdottir et al., 2015; McEwen & Getz, 2013). From this perspective, we argue that the concept allostatic load needs more than algorithmic refinement. We must also tend to it as a philosophical concept, and to its associated metaphors.

Before elaborating further on these thoughts we comment on two concrete arguments found in the index paper. Firstly, we will consider the vision of a finite allostatic load score (AL score) in view of ongoing mega-projects in systems biology, captured by the keywords '–omics' and 'big data'. Secondly, we will comment on the existing level of knowledge pertaining to the social gradient in health, and the current implications of this knowledge.

Building an allostatic load score in the age of systems biology

The paper for debate asks which aspects of human physiology ought to be included in the AL score, and whether different algorithms might be useful, depending on the outcome(s) in question. Looking at these questions from a different angle, it seems likely that the search for finite AL algorithm(s) will soon be located in a whirlpool of biological data downstream of techno-scientific megaprojects such as 'the virtual physiological human' (http://www.vph-institute.org/) and 'the 100K wellness project' (www.systemsbiology.org/research/100k-wellness-project/). These prestigious projects aim to mathematically model the human body as a complex system, and are as such in full concordance with the approach of allostasis research. The systems biology projects, however, are not geared towards demarcated, finite algorithms. Their approach is based on high-throughput analysis of 'big data' involving billions of datapoints for each individual attempting to monitor even the faintest

reflections from the individual's norms (Chen et al., 2012; Hood, Lovejoy, & Price, 2015; Hood & Tian, 2012).

The term allostatic load has recently started to appear in association with '-omics' projects (Ghini, Saccenti, Tenori, Assfalg, & Luchinat, 2015) and the idea of applying *systems biology to medicine* has definitely been launched (Boissel, Auffray, Noble, Hood, & Boissel, 2015; Bousquet et al., 2011). In light of this development we wonder how long allostasis research will be based on parameters of the type currently involved in AL scores, e.g. as outlined by McEwen (2015). The new systems biology projects aim to elicit data on all conceivable '–omics levels' of the human organism, from genomics via transcriptomics and metabolomics 'upwards' in the direction of clinical and even behavioural data. From a relative distance we assume that future evaluations of allostatic load will involve '–omics' data/patterns. The optimal way of characterising 'wear and tear' in an organism might in fact evolve as new candidate markers/patterns surface from the hi-throughput analyses. The AL score thereby becomes 'a moving target'.

As we see it the 'billion datapoints' scenario of systems biology represents both an opportunity and a threat to the idea of allostasis as a keystone concept in medical thought and practice. In this state of ambivalence we think that what matters most is to safeguard the philosophical (conceptual) meaning of allostatic load in a way that makes it relatively inert in the face of techno-scientific and political trends and commercial pressure (Diamandis, 2015; James, 2014; Karlsen & Strand, 2009).

Current knowledge – an imperative for action

Our second immediate response to the index paper relates to the existing level of knowledge about the social gradient in health. From the perspective of scientific incompleteness we agree that there is a lot we still do not know and would like to find out. However, we argue that the overall picture is already quite clear, and this fact must not be understated (Forssen, Meland, Hetlevik, & Strand, 2011; Heath, 2010; Marmot, 2010). We have access to hundreds of high quality publications from epidemiology, clinical cohorts, the basic sciences, and neuroimaging, as well as the social sciences and other sources. The term 'the biology of disadvantage' has been used to sum up our existing insight in how social adversity undermines human health (McEwen & Getz, 2013). In the post-genomic era (Hayden, 2010) it has become easier to promote and stimulate knowledge about the impact of social and relational adversity on health across various disciplines. To illustrate the emergence of new and fruitful collaborations we note three publications that emerged independently of each other in 1998. The first introduced the physiological concept allostatic load to a broad medical audience (McEwen, 1998). The second presented the Adverse Childhood Experiences Study, based on clinical-epidemiological data collected by Kaiser Permanente in Southern California (Felitti et al., 1998). The third was a qualitative medical study rooted in phenomenology, later published as *Inscribed bodies - the health impact of childhood sexual abuse* (Kirkengen, 2001). Since then an immense amount of concordant evidence on the detrimental impact of early life adversity has become available (Getz et al., 2011; Kirkengen, 2010). In our research unit – the General Practice Research Unit at the Department of Public Health and General Practice, Norwegian University of Science and Technology – we apply insight from these different perspectives to deal with the conundrum of multimorbidity (Tomasdottir et al., 2014, 2015). So while agreeing that more research would strengthen existing knowledge, we acknowledge that it is possible to pave a good way for public health and primary care with the knowledge we already possess.

Allostatic load and human stories

We observe how the discourse related to allostatic load has started to dismantle walls between traditional "knowledge silos" and unify the perspectives of researchers/clinicians from various areas, including neuroscientists, endocrinologists, immunologists, psychologists, epidemiologists, public health and primary care researchers/practitioners. We believe such "breakthroughs" are facilitated by the fact that allostatic load can be addressed both in everyday metaphorical language ("wear and tear") and as a scientific-empirical construct (Heath, 2013). This seems to draw the individual experts' attention in the same direction, away from fragmented sub-systems in direction of the whole and undividable, living, striving organism . In the context of medicine,

and especially primary health care, the organism in question can best described as *a person*, with reference to physician-philosopher Eric Cassell (E. J. Cassell, 2010).

Already in 1992 Cassell (1992) pointed out that (personal) human agency must necessarily involve the whole human being, all the way down to the mitochondria . Today the basic sciences have reached a point where we can view both Cassell's argument and the mitochondria in terms of allostatic load (Picard, Juster, & McEwen, 2014). This convergence of philosophical and physiological perspectives opens new perspectives on narrative in medicine and the medical relevance of attending to human stories in the clinical encounter (Behforouz, Drain, & Rhatigan, 2014; McEwen & Getz, 2013; Scannell, 2012). It is hardly a coincidence that Nancy Krieger's (2005) erudite discussion of embodiment, the departing point of the index paper, revolves around the term "story", as does anthropologist and systems thinker Gregory Bateson's seminal work *Mind and Nature – a necessary unity* (Bateson, 1979): «But I come with stories – not just a supply of stories to deliver to the analyst but stories built into my very being».

Reflecting on human stories in the light of allostatic load we should keep in mind that such narratives evolve around the past, the present and, not the least, an imagined future. We now possess considerable knowledge about the biological processes by which past and present experiences become embodied. Schulkin (2011) reminds us that yet another essential determinant of a person's allostatic load lies in the person's own view of the future, the anticipation of that which has yet to come.

The metaphors of allostasis: from 'wear and tear' to 'gains and drains'?

Based on the metaphor "wear and tear," the concept *allostatic load* can effectively accommodate knowledge pertaining to the pathogenetic impact of socioeconomic disadvantage and adverse lifetime experiences (Tomasdottir et al., 2014). However, between the lines of the allostasis literature we also encounter considerations pertaining to salutogenetic factors which promote and uphold health. An explicit focus on resilience can be found in recent key publications about allostasis (Ghini et al., 2015; Karatsoreos & McEwen, 2013; McEwen, Gray, & Nasca, 2015). Consequently, we suggest that a metaphorical expression of the fundamental idea of *allostasis* should involve both detrimental (”draining”) and health promoting (”gaining”) phenomena (Kirkengen, 2010; Tomasdottir et al., 2014). Depiction of an existential balance between drains (adversity) and gains (buffering support) is in fact needed to grasp the very essence of the terms ”positive,” ”tolerable” and ”toxic stress” which have become tightly connected to the concept of allostatic load (Shonkoff, Boyce & McEwen, 2009. See also http://developingchild.harvard.edu/). In order to further refine the metaphors of allostasis it is also important to keep underlining the fundamental difference between an *exposure* (objectively categorized) and an *experience* (subjectively lived) (Kirkengen & Thornquist, 2012; Seery, 2011; Tomasdottir et al., 2015; Ulvestad, 2012; Vie, Hufthammer, Holmen, Meland, & Breidablik, 2014; Waller, 2015).

Closing remark

Clinical evaluation of allostatic load might obviously involve a quantifiable score. Although not explicitly defined as such, most risk factors currently monitored in primary health care represent allostatic variables (McEwen, 2015), including blood pressure, lipid profile, glucose metabolism and body composition. As we have discussed, it will be interesting to see what happens to the AL score in the era of systems medicine based on big data. But whatever algorithms are used, it takes more than de-contextualised measurements to appreciate the balance between gaining and draining factors in a clinically meaningful and ethically responsible way (Evans, 2003; Juster et al., 2015; Repetti, Robles, & Reynolds, 2011; Upchurch et al., 2015). From the clinical viewpoint we might speak of a capacity for integrative perception that might at some point become conceptually linked to professional empathy (Ferrari, 2014). The word *gestalt* comes to mind in relation to the perception of another person's allostatic balance, in the sense of being-in-the-world as an embodied *person* (Cassell, 2010). We are indeed speaking of "a structure, configuration, or pattern of physical, biological, or psychological phenomena so integrated as to constitute a functional unit with properties not derivable by summation of its parts" (definition of *gestalt* in Merriam-Webster dictionary, acc. June 30, 2015).

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Commentary by

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Introduction

In this edition of the journal Delpierre et al. open a discussion on the use of the allostatic load concept as means to measure the term 'embodiment' (also referred to as 'biological embedding'), essentially how our cultural, social and economic circumstances 'get under the skin' to eventually damage our physiological systems and play a role in disease development (Adler & Ostrove, 1999). As described by Delpierre and colleagues the allostatic load concept has a long history starting in the late 1980s (Sterling & Eyer, 1988), but it truly came into being as a concept and research tool a decade later with the merging of the theory and a practical score (McEwen, 1998; Seeman, McEwen, Rowe, & Singer, 2001; Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). Delpierre and colleagues summarise the concept and operationalisation of allostatic load, including its strengths, weaknesses and some future considerations, eloquently enough to avoid unnecessary repetition here. However, there are three points linked to those issues raised that I would like to discuss further.

Gaining credibility

The use of concepts such as allostatic load to try and better understand how the environments we live in can affect our physiology and health falls under a holistic approach, in contrast to the more reductionist approach often sought in epidemiology. While the reductionist approach has great value, especially in trying to elucidate causal mechanisms underpinned by theory and biological plausibility, this approach can feel somewhat incongruous given the complex milieu in which we live our day-to-day lives. In addition, given the strong evidence for almost all chronic diseases being socially patterned and following a social gradient (those with lower socioeconomic position having poorer health), the concept of common biological pathways, as offered with allostatic load, in helping explain this patterning is enticing (Adams & White, 2004; Robertson, Benzeval, Whitley, & Popham, 2015). However, in the pursuit of a better understanding of the 'black box' that links our socioeconomic circumstances and our health, this embodiment/embedding/common biological pathways approach, as measured by allostatic load, introduces a type of black box itself. Are we simply combining individual biomarkers that are easy to measure and available together with no strong theory for linking them? How do we intervene at social and healthcare levels to reduce damage across multiple physiological pathways? Is measuring a patient's allostatic load any more helpful than the seemingly ill-fated NHS Health Checks (Capewell, McCartney, & Holland, 2015), or simply more of the same?

What is clear, and of greatest value in getting wider support for the concept, is the evidence that supports allostatic load as a better predictor of morbidity and mortality as compared with the individual biomarkers that comprise the score (Borrell & Crawford, 2011; Duru, Harawa, Kermah & Norris, 2012; Gruenewald, Seeman, Ryff, Karlamangla & Singer, 2006; Hwang et al., 2014; Karlamangla, Singer & Seeman, 2006; Seeman et al., 2004). Recent analyses found that allostatic load shows similar socioeconomic patterning to chronic disease outcomes, including across the life course, with childhood and adolescence/early adulthood representing particularly sensitive periods for poorer socioeconomic circumstances impacting on allostatic load (Gruenewald et al., 2012; Gustafsson, Janlert, Theorell, Westerlund & Hammarstrom, 2012; Gustafsson et al., 2014; Robertson, Popham & Benzeval, 2014). Furthermore, the association between socioeconomic position and allostatic load appears to be largely mediated by material factors (e.g. income, ownership of goods), but not behavioural and psychological factors (Robertson et al., 2015). This indicates that policies and programmes targeted at more downstream factors (such as health behaviours) may have minimal returns in reducing health and physiological inequalities, as shown for morbidity and mortality (Acheson, 1998; Adler & Stewart, 2010; Macintyre, 2007; Marmot, 2010; Marmot, Friel, Bell, Houweling & Taylor, 2008; Scott et al., 2013). As Delpierre and colleagues discuss, it is through this type of evidence, supported by more multi-disciplinary, longitudinal and life course research that also

incorporates causal inference, that the allostatic load concept will not only gain support, but will also be challenged further and naturally improved also.

Biological ageing: A competing or complementary concept?

Many of the ideas and theoretical pathways linking allostatic load and embodiment discussed by Delpierre and colleagues and earlier in this commentary can also be represented by another common biological pathway – biological ageing. This is "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" (Robertson et al., 2013). However, the rate at which this ageing occurs will differ given the (socioeconomic) circumstances in which we live. Increased exposures to physical and psychological insults, along with more unhealthy behaviours, have the potential to increase cellular and genomic damage, thereby accelerating biological ageing (Adams & White, 2004). People in more disadvantaged circumstances, where these insults are more prevalent (Adler & Stewart, 2010), would therefore be expected to be 'biologically' older than their more affluent counterparts of the same chronological age (Robertson et al., 2012). Like the allostatic load concept, identifying biomarkers of ageing that can completely encompass the theory has proved difficult and there remain several questions over how biomarkers could and should be combined (Der et al., 2012). The most promising marker of biological ageing to date has been white blood cell telomere length. Telomeres are protective structures present at the ends of chromosomes that typically erode over time to protect against irreversible chromosomal damage, so that their length is a potential predictor of biological ageing (de Lange, 2002). Therefore, this represents accumulated damage over time that goes across large parts, if not the whole, of the body and is strongly influenced by social and economic circumstances and particularly the stress response. Sound familiar?

It has been proposed that markers such as telomere length are simply alternatives to the allostatic load model currently used (multiple physiological markers linked to health conditions in middle and later-ages), especially at younger ages (Theall, Brett, Shirtcliff, Dunn & Drury, 2013). Biomarkers of ageing have been defined as biological measures that "either alone or in some multivariate composite will, in the absence of disease, better predict functional capacity at some late age than will chronological age" (Baker & Sprott, 1988). Allostatic load could claim to be such a marker, although it has not yet been tested in such a fashion as telomere length (Der et al., 2012). Alternatively, would adding measures such as telomere length to the allostatic load construct add some predictive power over the current operationalisation? Again, this is a feature which has not been explored. Finally, is biological ageing/telomere length more of an outcome of allostatic load and somewhat further down the causal chain? In my opinion, this is difficult to answer given current data (see below), but both allostatic load and biological ageing incorporate what can be considered primary (e.g. cortisol vs. oxidative stress) and secondary (e.g. blood pressure vs. telomere length) physiological markers. In addition, our biological systems are active and dynamic, potentially being responsive to changes in our environments and repairing themselves to some degree (Epel, 2012). Hence, there is not really an end-point where one could say someone has reached, for example, allostatic *overload* and that could be considered a true outcome. So, where do we go from here?

Bio-social collaborations

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 collecting simultaneous 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. So far, much of the evidence is based on cross-sectional data or comes from biomarkers measured once, but with longitudinal social data for the same individuals. These emerging longitudinal measures will help us to better understand how our physiologies change over time and at different stages in life, exploring the importance of relative change within individuals (i.e. is it a high allostatic load that matters or the change in allostatic load score over time?). We must also begin to embrace theories and methods from

other fields, such as 'system dynamics' (Ford, 1998) and 'complexity theory' (Byrne, 1998). The increase in data linkage to routinely collected data records (e.g. health surveys and hospital admissions) is allowing us to research the long-term health consequences of socioeconomic circumstances, even after studies and surveys have ceased. It may also be possible in the future to link into biomarker data that are collected as is now done with hospital admissions and death records. There are obviously challenges and negatives linked to these ideas, but they offer possibilities to broaden our knowledge of the social determinants of health and to help design better policies and programmes for reducing inequalities and improving health.

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Commentary by

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Introduction

The authors give a thoughtful and incisive outlook on the theory and study of allostatic load (AL). In addition to a number of specific and concrete contributions I particularly welcome the general attention the authors pay to conceptual clarity, both with regard to the conceptual framing of the AL, and to its operationalisation. I believe that the conceptual ideas suggested by the authors have merit, and also that there are several details that invite further thought and discussion. Therefore, in this commentary I aim to highlight certain conceptual issues relevant for two links the authors explore; first, the one between the concept of AL and its operationalisation; and second, the link between the concepts of AL on one hand and embodiment on the other. I hope that my reflections will be helpful in furthering the endeavors the authors have initiated.

In the article, the authors mention the need to remain *loyal,* more precisely loyal to the theory of AL in the process of operationalising the concept. I think that describing it as a matter of (conceptual) loyalty is a very apt expression for situations where you aim to keep in concordance to an underlying theory (or belief system or ideology). I also think it may be a heuristic term to illustrate some of the complexities that may arise when dealing with concepts. My commentary can be viewed as an exploration of some conceptual loyalties, disloyalties and conflicts of loyalties in play in the operationalisation and conceptual framing of AL discussed by the authors.

Loyalty in operationalisation

I will start by commenting on loyalty in the sense the authors use it; that is, as staying true to the concept in the process of operationalisation. The authors make several constructive points here that if followed, would promote conceptual loyalty. For example, the observations that the definition of thresholds deviates from the concept of AL, the interesting possibility of constructing different AL scores for different manifest diseases, and the consequences of the heterogeneous stability of AL components. I also appreciate that they revitalise the idea of the causal ordering of the mediators and effects, which I regard as an important part of AL theory, but which unfortunately has received comparatively little empirical attention.

I would also like to comment on a specific issue where I do not seem to agree with the authors; or more specifically, where I do not see how their reasoning promotes loyalty to the concept of AL. The issue concerns the authors' discussion on selection of the multiple biological systems. Here, the authors seem to frame loyalty to the theory of AL only with respect to the degree AL operationalisations (or the set biological systems) predict manifest disease. Yet AL was developed as a concept and a measure designed to connect the social and the biological worlds or realities, with AL acting as a link between stressful experiences and the pathogenesis of manifest disease (McEwen, 1998). The theory of AL thus makes assumptions on both the predictor and outcome side of AL, and AL could be said to have the putative causal status of a mediator or intervening variable between environmental exposures on one hand, and manifest disease outcomes on the other. While the 'disease criterion' (AL as a predictor of manifest disease) is commonly considered in discussions and empirical examinations of AL operationalisations, the 'environmental criterion' (AL as an outcome of environmental exposures) has been given less consideration in operationalisations of AL, but instead is left as an empirical question to be examined subsequent to and independently from the operationalisation of AL. This emphasis is also reflected in the present article.

My question is then; should not a conceptually loyal AL measure need to reflect accurately the biological impact of the (social, physical) environment to the same degree as it accurately predicts manifest disease? If no, why not; what in the theory of AL suggests that the environmental criterion is secondary to the disease criterion?

To me, this emphasis of the disease criterion in the operationalisation of AL reflects a disloyalty to parts of AL theory. I also believe that this disloyalty may have unfortunate consequences for our understanding of the role of AL. An approach considering only, or mostly, the disease criterion in

the operationalisation of AL can be expected to result in AL measures which indeed are good predictors of manifest disease, but which do not necessarily play an important role in explaining social causes of disease. This kind of approach will therefore yield poor AL measures for the purpose the authors state; AL playing an integral role in explaining social gradients in health. Ultimately, we risk ending up with the empirical results and conclusions suggesting that AL does not play a role in explaining social health differentials. However, such inferences would be laden with the repercussions of bias we introduced in our operational approach – our initial disloyalty to the theory of AL.

To the degree that such empirical considerations should influence the operationalisation of AL, I wonder if a more loyal approach should give equal consideration to both criteria; to both sides of the causal chain in which AL is supposedly a link. This would mean choosing the physiological markers most accurately reflecting environmental conditions, in addition to those that most accurately predict disease. As a statistical representation (or simply a heuristic illustration) of this dual consideration, estimates such as the 'indirect effect' used in classic regression-based mediation analysis (Baron & Kenny, 1986) could be used, as it takes the mediator's associations to both the exposure and outcome equally into account. Selecting biological systems and also individual markers guided by such a (data-driven or theory-based) approach would result in conceptually loyal AL measures, which also are given a fair chance to empirically explain social inequalities in health.

Loyalty in conceptualisation

Conceptual loyalty becomes even more intricate under situations of dual loyalty, which is the case when we seek to integrate different concepts or frameworks. Conceptual integration can of course be straightforward. Maybe the entities to be integrated have been developed in the same scientific-historical context, maybe they share a phenomenon under study, and maybe they have similar conceptual goals and terminology. But conceptual integration of two or more concepts may also be trickier than first anticipated. We might be caught in conflicts of loyalty.

In their article, the authors propose integration of two concepts. First, the concept of *allostatic load*, which was born in the scientific context of physiology and stress research, based on the writing of Sterling and Eyer (1988) on allostasis and developed by McEwen and Stellar (McEwen, 1998; McEwen & Stellar, 1993). Second, the concept of *embodiment,* which has a more diverse history and which has been used (often implicitly) with widely different meanings in the health sciences literature (Hammarstrom, et al., 2014), e.g. by the sociologist Raewyn Connell (Connell, 2011), or within the phenomenological tradition (Bullington, 2009). In the present paper the authors use the embodiment concept of Nancy Krieger, who developed her own formulation of embodiment within a distinctly social epidemiological context during the 1990s and 2000s, as one central concept within the larger theoretical framework of *ecosocial theory* (Krieger, 1994, 2005, 2011).

At a glance, the purposes of the AL and embodiment concepts may seem readily commensurable. Both concepts are dealing with the same general phenomenon of environment and biology, and could be viewed as existing, at least partly, within the family of theories relevant to social determinants of health. Both focus on different areas of this phenomenon, but also encompass the area of the other, and both mention life course perspectives as one central tenet (but without delving into the details) (Krieger, 1994; McEwen, 1998). But what would the point be in doing such an integration? What do the two perspectives have to offer each other?

For AL theory, I would say that framing allostatic load under embodiment does have the potential to put the theory of AL into a well-developed theory of societal structure and population patterns of health and disease, in this case ecosocial theory. This I see as a substantial and much-needed conceptual gain for the theory of AL. Sure, references to society and social inequalities have always been present within AL theory, but they have generally taken the form of vague hints to frameworks without a detailed conceptual integration (Juster, McEwen, & Lupien, 2010; McEwen, 1998), or empirical examinations (Dowd, Simanek & Aiello, 2009; Seeman, Epel, Gruenewald, Karlamangla & McEwen, 2010; Szanton, Gill & Allen, 2005). Moreover, in the same way that societal structure has not been the main focus of the theory of AL, formulating specific intermediate links or health outcomes has not been a high priority within ecosocial theory. From

ecosocial theory's point of view, allostatic load could therefore contribute with a specific, concrete and operationalisable summary construct capturing a range of structural exposures that are relevant for the process of embodiment.

So, in such an integration, what do we need to pay attention to? Here, I think that we do need to clarify where our conceptual loyalties are, and also where they should be. With regard to the latter, from my point of view, conceptual loyalty should be mutual and equal towards each of the concepts or frameworks that are to be integrated. With regard to the former, in reading the article, I notice a strong conceptual loyalty towards the concept of AL, but a more tenuous one towards embodiment. This I interpret as a conflict of loyalty.

To exemplify my point, the authors title their paper, 'Allostatic load as a measure of social embodiment'. This view, where embodiment seems to be construed as something that can be captured by AL, is also expressed in parts of the paper ('AL may be a relevant and useful tool for measuring and comparing embodiment'). In other places in the article, however, the relationship between the two concepts is described as something which appears to be substantively different from in the first view; AL is described as the *biological expression* or *effect* of embodiment ('the 'physiological reality', the 'biological expression of embodiment', 'measuring the biological effect of embodiment'). My interpretation here is that AL is construed as something other than, causally subsequent to, or part of, embodiment. Thus, it seems to me that the article comprise two different conceptualisations of embodiment in relation to AL; one where the latter is an example of the former, and one where the latter is a result of the former. Here, I reminisce about the oft-cited quote referencing Hans Selye's stress theory: "Stress in addition to being itself, was also the cause of itself, and the result of itself." (Rosch, 1998).

So, which of the conceptualisations is more loyal to the concept of embodiment? With regard to the first conceptualisation I wonder whether embodiment really can be reduced to a physiological measurement. In what way are we, by summarising a number of cardiovascular risk factors and neuroendocrine markers, capturing 'how we literally incorporate, biologically, in societal and ecological context, the material and social world in which we live'? In relation to this question it is worth noting that Krieger emphasises that embodiment is not equivalent to, but encompasses more than, 'how society gets under the skin' or 'biological embedding' (Krieger, 2011, p. 222). Specifically, I interpret embodiment as not primarily reflecting how the proximal environment becomes embodied (as is the case in stress frameworks such as AL), but more how societal structure and dynamics become embodied and thereby create population patterns of disease. Here, embodiment is an alternating macro-micro-macro process, and as such by necessity a multilevel phenomenon. This does not seem to correspond well to the first conceptualisation of embodiment in the article, where embodiment is reduced to a much more limited construct, which seems to be guided more by loyalties to the theory of AL than to loyalties to the theory of embodiment. This expresses the loyalty conflict, and I would say that in this restricted sense the concept of embodiment adds little to the theory of allostatic load which was not already contained in the theory of AL. Consequently, I would advise against this conceptualisation of embodiment.

In the second conceptualisation of embodiment in the article, AL is instead construed as an effect of embodiment. Here, there are no restraints put on the concept of embodiment and what it represents; it just positions AL as one (possibly of many) biological effects of the (possibly complex and multilevel) phenomenon that is embodiment. Therefore, I regard this view of embodiment as more loyal to the concept of embodiment, and a more fruitful starting point for a conceptual integration of the two concepts.

Still, as noted above, embodiment is one concept within the larger theoretical framework of ecosocial theory, where ecosocial theory cannot be reduced to embodiment, and embodiment does not capture the entirety of ecosocial theory. To stay loyal towards the concept of embodiment I therefore think it should not be picked out as a single concept, disentangled from its theoretical context. Instead, I would rather approach the integration by framing AL within the complete ecosocial theory. This would for example mean construing AL as a phenomenon which is part of the societal arrangements of power and property; of current and changing societal patterns of disease; and for which we as researchers who study social inequalities in health, as well as those in power, are

explicitly held to account (Krieger, 2011). By using the entirety of ecosocial theory we could stay loyal to both the theories of embodiment and AL. I also believe this has a greater potential to lift the theory of AL from its individual and micro-focus, to include the grander macro-level narrative of society and its flourishing inequities. Such a perspective is offered by ecosocial theory and I believe is necessary for the theory of AL to be able to play an important role, not only in empirically explaining social gradients in health, but also in the theoretical context of equity in health.

While I hold that no theory or framework is holy or deserves our loyalty simply by its existence, I do believe that the ideas (e.g. theories, frameworks or concepts) on which we base our research are particularly important for us to articulate and scrutinise, or else our research, and the understanding we believe that we gain from it, runs the risk of simply reflecting our initial errors in thought. In this commentary I have sought to keep in line with the attention to conceptual detail of the original article, by highlighting a few problems of conceptual loyalty I perceived, as well as giving my thoughts on how to possibly solve or avoid them. Together, I hope these small reflections can contribute to further thought and discussion on the theory of AL, and I am sincerely looking forward to the authors' response.

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Response by

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We thank the authors who commented on our paper and discuss some of the most salient points they raised.

Firstly, regarding the many methodological considerations we mentioned, Getz and Tomasdottir in their comment point towards the burgeoning fields of biological systems research for potential answers. We agree that this area is promising in terms of understanding further the complexities of our biological systems and finding the most suitable way of measuring them. Indeed, the combined forces of methodological developments in the areas of bioinformatics, 'omics' research and biological systems will probably render redundant a simplified cumulative score, such as the ones typically used to measure allostatic load (AL). A more optimal method of measuring multi-system wear and tear due to stress may well emerge from these fields allowing the identification of biomarkers with a predictive or diagnostic value. A possible caveat of the increasingly accessible technologies around biological data and methodological developments within bioinformatics, is the risk of becoming overly focused on molecular-level details. Though a measure of cumulative wear-and-tear may benefit from such developments, we must not be tempted to stray too far into the attractive rabbit hole of detailed biological data and away from the original intent of the AL concept. The purpose of the measurement developed by McEwen et al (McEwen & Stellar, 1993; Seeman et al., 1997) was to capture, in one summary score, the physiological consequences of adaptations to the environment via the stress response pathways. Our aim should be to describe and capture these adequately enough to demonstrate the modifiable factors within the environment – in its broadest sense – that may be used to alter processes affecting socially structured groups of the population and leading to health inequalities. There is a risk of forgetting these important facets when faced with new and attractive methodologies.

Secondly, as mentioned by Robertson, it is relevant to question whether by attempting to understand mechanisms producing health inequalities and opening a black box, have we not formulated a new one with the concept of AL. We would argue that unlike many 'black boxes' AL has a well formulated conceptual foundation linking the environment to physiological processes via the stress response systems. Telomere length may be an interesting component of these processes, possibly to be included within an AL measure with its multi-system specificity. The links between AL and biological ageing are indeed clear. We would maintain that physiological wear-and-tear captures one set of processes potentially implicated in a wider notion of biological ageing wherein the link with stress is fundamental. Both the concepts of AL and biological ageing may deserve to be explored together, where AL is one among other potential mechanisms of biological ageing. Both concepts also deserve to be disentangled relative to the wider notions of embodiment and the framework of ecosocial theory, as pointed out by Gustafsson.

Indeed Gustafsson highlights that we were ambiguous regarding the position of the concept of AL relative to that of embodiment within the theoretical framework of 'ecosocial theory' (Krieger, 2001). We define embodiment as a dynamic concept, consisting of: i) responses to past environments and ii) an ongoing response to the present environment. The elements and mechanisms leading to the responses may vary in their nature, intensity and cadence over the life course. We suggest that AL captures one process of embodiment linking the environment, stress responses, and possible chronic damage to physiological systems, and as such this fits wholly

into the framework of ecosocial theory. Of course many other mechanisms of embodiment deserve further exploration in terms of environmental conditions across the life course, such as behavioural and psychological factors, socioemotional changes or cognitive function.

We agree with Gustasfsson that our desire to maintain an AL measure that is 'loyal' to a balance of physiological systems should be applied equally to the environmental factors that the measure attempts to capture. Now that a number of openly accessible longitudinal datasets collecting a large array of environmental and biological variables are available, it has become possible to specify plausible hypotheses to test and unpick many of the concepts raised here (Kelly-Irving, Tophoven & Blane, 2015). With this in mind, the ecosocial determinants of AL deserve to be deliberately defined and explored across contexts. Specific hypotheses that may link ecosocial factors at different environmental strata to AL need to be defined and tested using comparable data within different populations and at different stages of the life course.

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Referencing

The debate should be referenced as:

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