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Review article

A systematic review of allostatic load in relation to socioeconomic position: Poor fidelity and major inconsistencies in biomarkers employed

Sarah C. Johnson [a, *], Francesca L. Cavallaro [b], David A. Leon [c, d]

[a] Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA, USA
[b] Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK
[c] Department of Non-Communicable Disease Epidemiology, Faculty of Epidemiology and Population Sciences, London School of Hygiene & Tropical Medicine, London, UK
[d] Department of Community Medicine, UiT Arctic University of Norway, Tromsø, Norway

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ABSTRACT

Background: The association between disease and socioeconomic position (SEP) is well established. Allostatic load (AL), or physiological 'wear and tear', is a concept that aims to elucidate the biological consequences of stress that may underlie these associations. The primary objective of this paper is to review the biomarkers and methods used to operationalise the concept of AL in studies analysing the association between AL and SEP.

Methods: Four databases (Embase, Global Health, MEDLINE, and PsychINFO) were searched using terms related to AL, biomarkers and SEP. Data extraction focused on the methods used to calculate AL indices. The frequency of pair-wise combinations of biomarkers were used to assess the level of overlap in AL definition between studies.

Results: Twenty-six studies analysing the association between AL and SEP were included. There was no consistent method of operationalizing AL across studies. Individual biomarkers and biological systems included in the AL index differed widely across studies, as did the method of calculating the AL index. All studies included at least one cardiovascular- and metabolic-related biomarker in AL indices, while only half of studies included at least one hypothalamic-pituitary-adrenal (HPA) axis biomarker and approximately one third an immune response-related biomarker. All but three studies found evidence of an association between lower SEP and higher AL.

Conclusions: Many studies lacked fidelity to the original concept of AL in which stress was considered central. The considerable variation in biomarkers used makes studies in this review difficult to compare. A more critical approach should be taken in the calculation of AL indices in particular to how far it captures the biological effects of psychosocial stress that may underlie socioeconomic differences in health.

1. Introduction

The social underpinnings of disease have been long acknowledged and an extensive body of literature has linked lower socioeconomic position (SEP) with adverse health outcomes (Marmot et al., 1991; Sapolsky, 2004; Taylor et al., 1997). The underlying mechanism for some diseases is better understood than others. For example, it is well established that in high income countries those of a lower SEP are more likely to smoke, be hypertensive and have increased cholesterol, which in turn results in an increased risk of cardiovascular disease (CVD) events (Fuller et al., 1983; Sterling and Eyer, 1981; Lynch, 2006; Kivimäki et al., 2008). However, the extent to which stress plays a role in the specific mechanisms through which social factors influence disease has remained elusive. Two key areas of research have emerged: one focused on how stress is related to behavioral mechanisms of disease and the other on the biological mechanisms responsible for translating stress into disease (Harbuz, 1999; Friedman et al., 1958; Kornitzer and Kittel,

* Corresponding author.
E-mail address: scharlottej13@gmail.com (S.C. Johnson).

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1986; Shah and Cole, 2010). The latter has emphasized understanding how the body internalizes an external stressor on a physiological level and how well a person can adapt to changes in his or her environment. Allostasis is a concept describing the normal process of how the human body adapts in response to a given stimulus (Sterling and Eyer, 1988). Allostatic load (AL) is defined as the physiological "wear and tear" a person experiences across his or her life, for instance chronically elevated blood pressure resulting from a lifetime of occupational strain (McEwen and Stellar, 1993).

According to the original AL framework, stress hormones controlled by the hypothalamic-pituitary-adrenal (HPA) axis (e.g. cortisol, epinephrine, and norepinephrine) are the "primary mediators" of AL, which in turn mediate "secondary effectors" such as blood pressure, lipid metabolism, and inflammation (McEwen and Stellar, 1993; Smith and Vale, 2006). Poor health conditions resulting from extreme values of primary mediators and secondary effectors are "tertiary outcomes" (e.g. coronary heart disease, decreased physical capacity, obesity or severe cognitive decline) (Karlamangla et al., 2002; Gruenewald et al., 2006, 2015). In the first study to calculate an AL index, measurements of 10 biomarkers were combined from three biological domains (cardiovascular and metabolic systems, and HPA axis) (Seeman et al., 1997). For clarity, in this paper AL index refers to the quantifiable variable, while allostatic load refers to the conceptual framework devised by McEwen & Stellar (McEwen and Stellar, 1993).

Since the term allostatic load was first introduced in 1993, the number of studies on AL have grown considerably. Between 2010 and 2017 the number of papers in PubMed mentioning AL have more than tripled, with 110 studies published in 2016 alone (Corlan, 2004). However, researchers have not taken a consistent approach to the way they have operationalised the concept. If AL is intended to measure the physiological response to stress, then the inclusion of primary mediators, such as HPA axis biomarkers (or equivalent), in an AL index is intrinsic to its definition.

These methodological inconsistencies make comparisons across studies challenging. There is therefore a need to determine how researchers define AL in the literature and to see how different definitions affect associations between stress, AL, and disease. No prior study has quantified the heterogeneity in AL indices. Previous reviews of AL, health disparities and outcomes have been performed, but none had a methodological focus, although some attention has been given to comparing different methods for how levels of constituent biomarkers should be arithmetically combined into a single index (Karlamangla et al., 2002; Seplaki et al., 2005; Seeman et al., 2001; Dowd and Simanek, 2009; Beckie, 2012; Mauss et al., 2015).

In this systematic review we have aimed to provide a comprehensive overview and discussion of the biomarker content and methods used to calculate AL in studies that have looked at its association with SEP. A secondary aim was to describe the associations of AL with SEP.

2. Methods

2.1. Search strategy & data extraction

The scope of this review was limited to the biological internalization of SEP and the effects of this stressor on AL, highlighting AL as a mechanism on the causal pathway between SEP and health outcomes (Fig. 1).

The literature review was restricted to peer-reviewed publications of human population studies that calculated an AL index and analysed the association between SEP as the main exposure and AL as the main outcome. Reviews, protocols, conference abstracts, and theoretical discussions were excluded. We sought to find all studies including the phrase "allostatic load", "biomarker", and SEP. Specific search terms can be found in Appendix A. Five electronic databases were searched (Embase, Global Health, MEDLINE, and PsychINFO) to identify articles published up to July 7th, 2017, with no language restrictions. Additionally, previous reviews of AL and social factors were cross-referenced to check the sensitivity of the search strategy (Dowd and Simanek, 2009; Beckie, 2012; Mauss et al., 2015). The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were followed with a focus on methodologies used to operationalise AL (Moher et al., 2015).

2.2. Analyses

We reviewed the biomarkers included in AL indices according to biological system, as defined by the study, and then looked at the frequency of papers in which each biomarker was included. Biomarkers that were measured differently were included as separate biomarkers; for instance, fasting glucose measures and non-fasting glucose measures were categorised as two separate biomarkers. A sensitivity analysis was also performed, where closely related biomarkers with minor differences were collapsed into one biomarker.

We quantified the extent to which papers used the same set of biomarkers in their AL index using a pair-wise approach in which the biomarker set of each study was compared to that of every other study. For every pair-wise comparison we counted the number of biomarkers that they used in common. This could vary between zero and total number of discrete biomarkers observed across all included papers. In addition we identified every unique biomarker combination observed, and counted the number of studies using any unique combination.

We analysed the data using MS Excel and Stata 14.1.

3. Results

3.1. Findings from the literature search

The search strategy outlined above identified 282 papers; five additional papers were included from cross-referencing previous systematic reviews resulting in 287 articles screened (Fig. 2). Thirty-one full text articles were reviewed after duplicate removal and title and abstract screening. Of these, five articles were excluded due to not reporting a direct measure of the association between AL and SEP, leaving a total of 26 articles. Of these 26, four analysed the National Health and Nutrition Examination Survey, three that used the Midlife in the US survey, and two that used the West of Scotland Twenty-07 study.

The majority of studies were cross-sectional, used US-based population datasets, and had a sample size between 1000 and 10,000 observations (Table 1). See Supplementary Table S1 for full data extraction. Studies identified were published between 1999 and 2016, with most appearing after 2009.

3.2. Biomarker selection and measurement

A total of 59 different biomarkers were used across all studies. The number of biomarkers used to create an AL index ranged between 6 and 25 (Table 1), with a mode of 9. There were 20 biomarker combinations observed across the 26 studies included in the literature review. Table 2 summarizes the number of studies including each biomarker organized by biological system. Biomarkers appearing in only one study are listed in Supplementary Table S2. All studies included at least one cardiovascular and one metabolic marker; the majority of studies (85%) included one