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

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Keywords: allostatic load, chronic stress, biomarkers, socioeconomic position

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 operationalising 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.

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.[1–3] 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.[4–7] 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.[8–11] 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.[12] 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.[13]

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.[13,14] 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).[15–17] 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).[18] For clarity, in this paper AL index refers to the quantifiable variable, while allostatic load refers to the conceptual framework devised by McEwen & Stellar.[13]

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.[19] 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.[15,20–24]

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.

Methods

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).

FIGURE 1 HERE

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.[22–24] The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were followed with a focus on methodologies used to operationalise AL.[25]

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 analysed using Stata 14.1.

Results

Findings from the literature search

The search strategy outlined above identified 282 papers; four 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.

FIGURE 2 HERE

The majority of studies were cross-sectional, used US-based population datasets, 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.

TABLE 1 HERE

Biomarker selection and measurement

A total of 59 individual biomarkers were used in one or more 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 immune marker, while only 58% included an HPA axis marker.

TABLE 2 HERE

AL indices were most often calculated by summing the number of biomarkers for which the individual was determined to be "high risk". The majority of studies (73%) used quartile-based cutoffs for individual biomarkers, and the scores for each biomarkers would then be summed (with each biomarker equally weighted). Cortisol was the only biomarker that had different cutoffs from the other biomarkers. For example, 3 studies used quartile cutoffs for all biomarkers except cortisol, where the lowest and highest octiles were considered high risk, based on previous studies associating extremely low and extremely high levels of cortisol with adverse health outcomes.[26–28]

Rather than summing individual biomarkers, four studies summed the proportion of high risk markers by biological system.[29–32] For example, if a person was above the high-risk cutoff for two out of four cardiovascular biomarkers, they would receive a score of 0.5 for this system. This approach was used in studies analysing the Midlife in the US study where over 20 biomarkers were combined from five or more biological systems to calculate an AL index.

Most studies analysed AL index as a continuous outcome (e.g. a score ranging from 0-10), while others dichotomized the AL index into "high" (e.g. above three) and "low" (e.g. below or at three). Four studies included the same nine biomarkers from the immune response, cardiovascular and metabolic systems with no HPA axis biomarker.[33–36] Two studies included the same 24 biomarkers from the immune response, HPA axis, and cardiovascular, metabolic, respiratory and parasympathetic nervous systems.[31,32] All remaining 20 studies used different sets of biomarkers to calculate AL.

Analysis of shared biomarkers

To understand how biomarkers were shared between studies, each study (n=26) was paired with all other studies for a potential of 325 pair-wise combinations. Table 3 shows the total pairs of studies, according to the number of biomarkers the study pairs have in common. Also shown are how many pairs share distinct groups of biomarkers, referred to as unique combinations. For example, the last row of the table shows that 16 study pairs shared only one common biomarker, among which there were five unique biomarker combinations (in this case, five unique biomarkers). It was most common for two studies to share five biomarkers, with 55 pairs of studies (17% of all pairs) sharing exactly five biomarkers. Twenty-four of these pairs (44%) were unique combinations of biomarkers. Only five pairs of studies had 10 biomarkers in common, four of which (80%) were unique combinations.

TABLE 3 HERE

Substantial heterogeneity was observed across AL indices when comparing studies to each other. Across all the possible combinations of biomarkers shared by two studies, the most commonly shared group of biomarkers was waist to hip ratio, systolic blood pressure, diastolic blood pressure and high density lipoprotein cholesterol, which appeared in 11 pairs of studies. The other biomarkers used in these AL indices hardly overlapped and were often categorised in different biological systems. For example, one study appeared in nine of the 11 pairs and additionally included biomarkers from the metabolic system and the HPA axis.[37] Another study appeared twice and included metabolic system-related, immune response and HPA axis markers.[49] A sensitivity analysis in which closely related but distinct biomarkers (e.g. fasting and non-fasting glucose) were collapsed into fewer broader classes (e.g. glucose) did not change our findings (see Supplementary Table S4).

Association between AL and SEP

There was considerable heterogeneity in the measurement of SEP. Education, income and occupation were the most common measures, with six studies examining how changes in SEP over an individual's lifetime were associated with AL in adulthood. Linear and logistic regression were primarily used to evaluate associations. Because of the diversity of SEP measures, analytic methods and heterogeneity in the definition and method of calculation of AL indices we did not calculate a summary measure of association between AL and SEP. Instead, a qualitative description of the strength of association was assigned based the magnitude of effect measures. However, in almost all studies lower SEP groups had higher AL indices (Table 4), while three studies found evidence of effect modification. One study found the association between AL and SEP differed by ethnicity while two others found the association differed by gender (Table 4).[28,34,38] All three used different biomarkers, high-risk cut-off criteria, SEP measurement, and methods of statistical analysis from one another. See supplementary table 3 for specific effect measures.

TABLE 4 HERE

Discussion

We reviewed the methodologies used to operationalise the concept of allostatic load, a term intended to represent the biological "wear and tear" a person experiences throughout life. Our findings indicate there is no standard method of calculating an AL index in the literature on AL and SEP. Across the 26 studies in the literature review, there were 59 biomarkers combined in 20 different ways. Not only were studies dissimilar to one another, there was no study that used the same biomarkers as the original calculation of an AL index using the MacArthur study.[18] Additionally, fewer than 60% of studies included an HPA axis-related biomarker, a key component of the conceptual framework devised by Stellar & McEwen.[13]

Lastly, all but three studies found a negative association between AL and SEP, such that SEP decreased as AL increased.

Whether or not a biomarker was included in AL indices appeared to be dependent on which biomarkers were collected. Papers analysing the MIDUS study, for example, all included HPA-axis related biomarkers whereas none of the studies analysing the NHANES included such markers. The MIDUS study was designed to explore the psychosocial factors affecting health outcomes in ageing Americans and contained an extensive biomarker profile whereas the NHANES was focused on nutritional status and disease. Not all studies are equally well suited for calculating an AL index, however, many studies appropriated the term AL regardless of how closely their index matched with the original conceptual framework.

The substantial inconsistency in biomarkers used to operationalise AL and the lack of fidelity to its original conception as an index that captures the biological response to psychosocial stress is striking. This suggests that the empirical literature on AL is intrinsically flawed and without a strong conceptual basis. Cardiovascular- and metabolic-related markers were not only ubiquitous in AL definitions, but were also overrepresented in many studies relative to other biological systems. It is well known that cardiovascular- and metabolic-related risk factors for CVD increase for those of a lower SEP, and these biomarkers are also more closely related to health behaviors (e.g. smoking and an increase in blood pressure).[39–43] By contrast, HPA axis biomarkers were absent from nearly half of studies, which contradicts McEwen & Stellar's initial conceptual framework emphasizing the importance of HPA axis biomarkers as primary mediators. In fact, AL is defined as the result of the "heightened neural or neuroendocrine response resulting from repeated or chronic environmental challenge".[13] Other biological systems, such as kidney/liver function, have been added into AL indices, despite not being included in this original conceptualization. This divergence makes it difficult to know what is being measured by AL, let alone interpret findings that examine the association between SEP and AL.

Despite the considerable inconsistency in AL operationalisation, the vast majority of articles reviewed found a negative association between SEP and AL. It is not expected that a reworking of the operationalisation of AL would dramatically affect these associations. Rather, the lack of coherence makes it difficult to compare findings from different studies (for example, in comparing the strength of association between AL and different SEP indicators), and therefore hinders a better understanding of the biological mechanisms underlying poorer health amongst those of a lower SEP.

Strengths & limitations

This is the first systemic review of the methodologies used to calculate AL indices in studies examining the relationship between AL and SEP. This undertaking is particularly important in light of the growing number of studies analysing AL in population studies. The following limitations, however, should be considered.

This review was limited to studies analysing the association between AL and SEP and did not include studies analysing AL indices as a predictor of disease outcomes. However, the issues identified here are likely to also occur in the wider literature on AL, especially if these issues are reflective of the availability of biomarkers collected in population-based studies. Since these inconsistencies in AL operationalisation are a result of biomarker inclusion, a broader review would have likely led to the same conclusion.

Additionally, given the diversity of measures employed it was difficult to summarise the strength of associations observed across all studies in this review. The qualitative assessment of the associations observed between SEP and AL are therefore meant to describe the direction of observed associations, rather than calculate a single summary estimate of the association between SEP and AL.

Future directions

Consistency across methods of calculating AL indices is key for reproducibility and generalizability of findings. We suggest future research focuses on examining the relevance of individual biomarkers and biological systems in construction of AL, as supported by the AL conceptual framework and evidence relating to different pathways through which chronic stress is embodied physiologically.

It is important to note that the original concept of AL is not invalidated based on problematic operationalisation. Studies following the original concept, that is including an HPA biomarker (such as those using the MIDUS study), should be regarded as the standard for using the term AL. Future studies incorporating additional biomarker measures, such as DNA methylation or telomere length, should clearly state how their analysis differs from the original concept.

Efforts to translate the concept of AL into a quantifiable variable have been widespread, however, it is crucial to consolidate this information, as we have done here, to improve AL studies. By excluding the HPA axis, these studies do not contribute to our current understanding of AL.

Concluding remarks

In conclusion, this review identified substantial methodological inconsistencies in calculating AL indices and a clear divergence from the original conceptual framework in the literature on AL and SEP. In the nearly 20 years since AL was first operationalised, the literature has become increasingly heterogeneous in the way composite AL indices are calculated. Standardization of definitions is key for reproducibility and establishing the validity of the published literature, especially when adapting a relatively new conceptual framework to analysis in population studies. There is a clear interest in a comprehensive measure of

health that researchers can use to examine complex interactions in biological and psychosocial pathways to health. Interpreting AL and its association with SEP, however, is hindered due to the diverse nature of operational definitions. Ionnidis and colleagues have suggested that 85% of research resources are wasted, in part due to the lack of standardized definitions and reproducibility in research.[44] Developing a standardized, valid method for operationalizing AL in population studies is critical in order to ensure findings from future studies are valid and reproducible.

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Appendix A

The following search terms were used to capture studies operationalizing AL: “allostatic load” and biomarker* or “biological marker*”. The following map search terms were used to capture studies examining SEP in relation to 5 topics based on prior literature on SEP and health.[45–49]

Socioeconomic position: socio?economic status, socio?economic position, subjective social status, social class
Education: education*
Wealth: income, debt, asset*, poverty, depriv*, affluen*, financ*
Employment and occupation: job, work*, umeploy*, employ*
Contextual: Neighbo?rhood

Table 1. Summary characteristics of included studies analysing allostatic load in association with socioeconomic position

Characteristics	No. Studies (n=26)
Study design	
Cross-sectional	15
Longitudinal	9
Location of study population	
US	14
UK	2
Sweden	1
Nepal	1
Denmark	1
Canada	1
Poland	1
Sample size of analyses	
50-100	1
101-500	7
501-1000	5
1001-10,000	10
Over 10,000	3
Number of biomarkers in AL index	
6-10	16
11-15	7
16-20	1
21-25	3

Table 2. Biomarkers included in allostatic load indices by biological system. Overall there were 59 biomarkers representing seven biological systems.

Biological System	No. Studies (N=26)	Percentage of studies
Cardiovascular	**26**	**100%**
Blood pressure (systolic, diastolic, hypertension)	25	96%
Heart rate	11	42%
Metabolic	**26**	**100%**
HDL, low density lipoprotein (LDL), total cholesterol, triglycerides, apolipoproteins	24	92%
Blood sugar (glucose, HbA1c)	23	88%
BMI, waist circumference, WHR, percent body fat	24	92%
Insulin	7	27%
Immune Response	**22**	**85%**
C-reactive protein (CRP)	20	77%
Fibrinogen	8	31%
Interleukin-6 (IL6)	6	23%
Serum albumin	7	27%
Soluble adhesion molecules	3	12%
Tumour necrosis factor-alpha (TNF-□)	3	12%
White blood cell count	2	8%
HPA Axis	**15**	**58%**
Cortisol	13	50%
Epinephrine and norepinephrine	9	35%
DHEA-S	6	23%
Respiratory	**3**	**12%**
Peak expiratory flow	2	8%
Parasympathetic Nervous System	**5**	**19%**
Standard deviation of heartbeat to heartbeat intervals	5	19%
Low frequency spectral power	4	15%
High frequency spectral power	4	15%
Root mean square of successive heartbeat differences	4	15%
Kidney/Liver function	**3**	**12%**
Creatinine (creatinine, creatinine clearance)	3	12%

Table 3. Combinations of shared biomarkers in AL between pairs of studies; sharing 11-23 biomarkers omitted. The denominator for the percentage was 325, which is the total number of potential pair-wise combinations for 26 studies.

Number of shared biomarkers (n=59)	Number of pairs of studies [%]	Number of unique combinations of biomarkers (n=138)
24	1 [0.3]	1
10	5 [1.5]	4
9	16 [4.9]	7
8	22 [6.8]	15
7	33 [10.2]	15
6	53 [16.3]	25
5	55 [16.9]	24
4	35 [10.8]	16
3	25 [7.7]	11
2	21 [6.5]	9
1	16 [4.9]	5

Table 4. Socioeconomic position measure, direction and strength of association with allostatic load. Negative associations indicate allostatic load increases with lower socioeconomic position. Where relevant, associations within subgroups is described (n=26).

Primary Author	SEP Measure	Direction of Association	Strength of Association
L. D. Kubzansky[37]	Education	Negative	Strong
B. Singer[50]	Household income	Negative	Strong
G. Johansson[51]	Career and life-course patterns, and occupation	Negative	None for life course pattern, strong for occupation
C. M. Worthman[52]	Social class	Negative	Strong
G. W. Evans[53]	Proportion of life in childhood poverty	Negative	Strong
S. Stein Merkin[34]	NSES, SEP: income, education, poverty, unemployment	Negative	Strong for black Americans, but weak for white and Mexican Americans
C. E. Bird[33]	NSES	Negative	Strong
L. C. Gallo[26]	Financial strain, work stress, and housing problems	Negative	Strong
T. L. Gruenewald[30]	SEP in adulthood and childhood: education and income	Negative	Strongest in later adulthood
D. A. Hickson[38]	Education, income	Negative/Positive	Strongly negative for women, weakly negative for men with less education, weakly positive for men with lower income
K. P. Theall[54]	Individual SEP and NSES	Negative	Strong
B. Rainisch[55]	Income and education	Negative	Strong
RP Juster[28]	Occupational status	Negative/Positive	Strongly negative in women of lower occupational status, but the reverse in men
T. Robertson[36]	Social class in childhood, early adulthood, and adulthood	Negative	Strongest for early adulthood and childhood
T. E. Seeman[31]	Social rank	Negative	Strong
P. E. Gustafsson[27]	NSES and neighborhood adversity across life course	Negative	Strong
A.M. Hansen[56]	Occupation, vocational training, education	Negative	Strong for both men and women
A. Lipowicz[57]	Education, marital status, residence	Negative	Strong
E. M. Friedman[29]	Early life SEP: education and income	Negative	Strong
T. Robertson[35]	Occupational class	Negative	Strong
D. M. Upchurch[58]	Education and income	Negative	Strong
C.B. Solis[59]	Maternal education and paternal occupation	Negative	Strong
E. Chen[60]	Family economic hardship	Negative	Strong
C. R. Gale[61]	Childhood SEP	Negative	Strong
N. R. Hamdi[32]	Education	Negative	Strong
T. Robertson[62]	Education	Negative	Strong

Figure 1. Causal diagram linking socioeconomic position and allostatic load (scope of literature review in dashed black lined boxed)

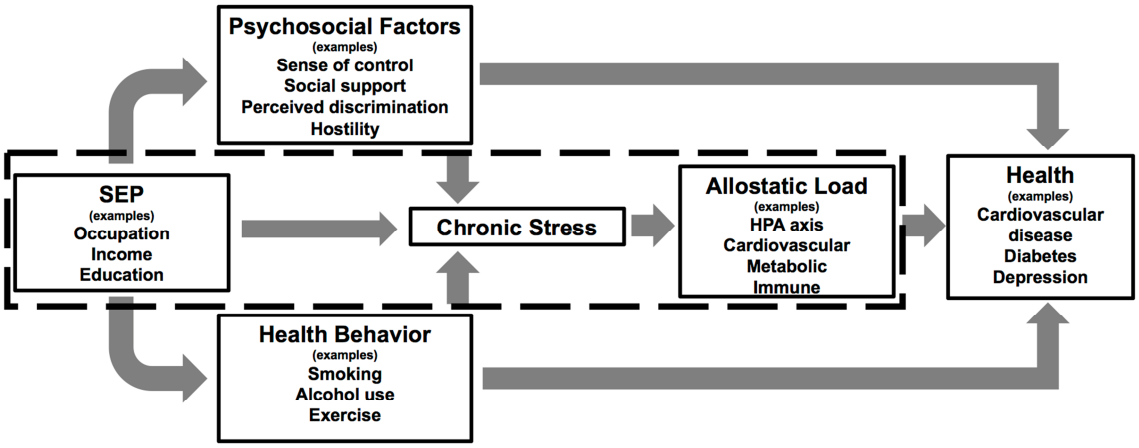
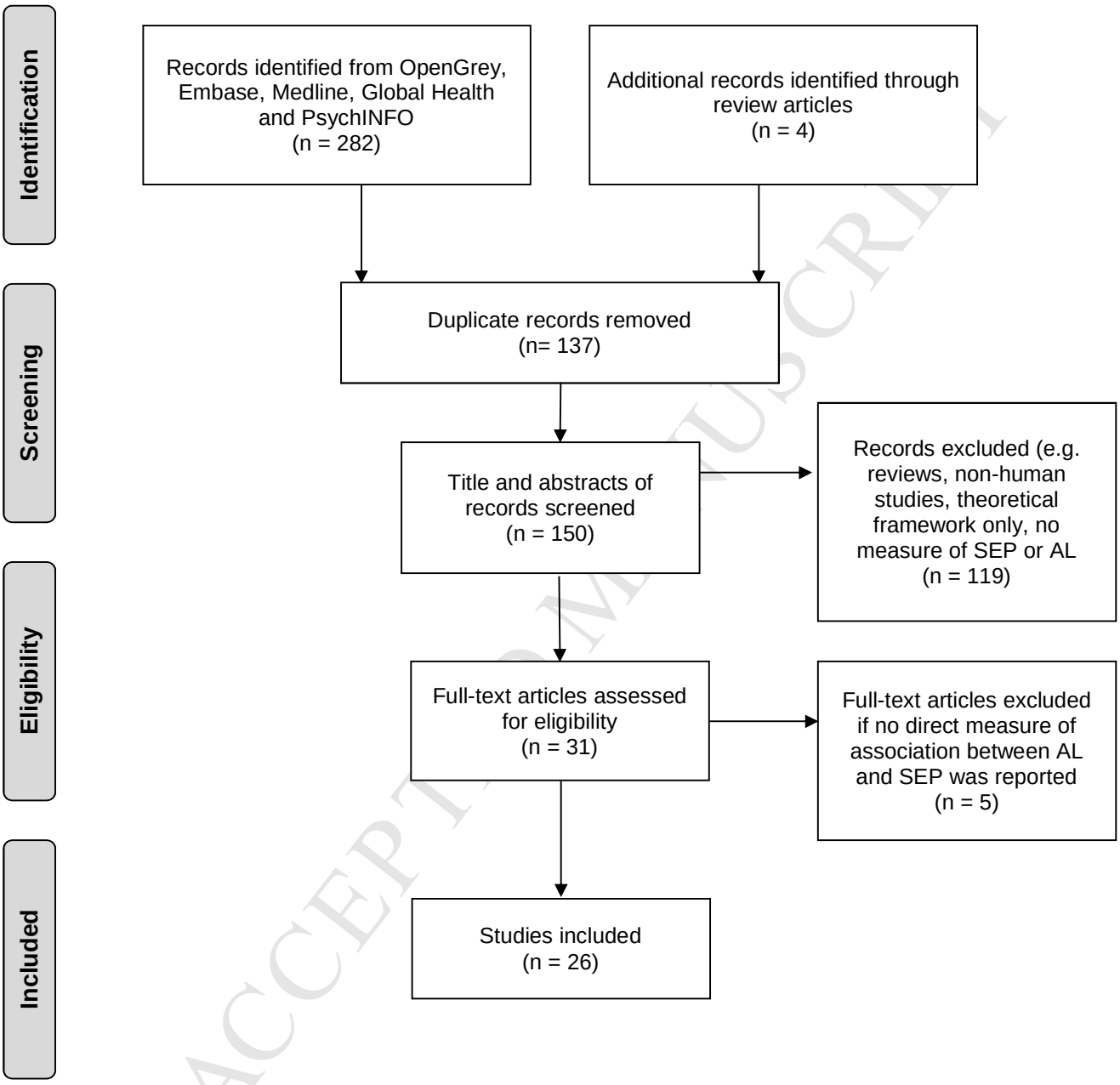


Figure 2. Flow chart of studies from literature search included in full data extraction[25]



- Allostatic load (AL) describes the biological effect of “cumulative wear and tear”
- The AL concept is operationalised through biomarker measurement
- AL is used to elucidate the biological basis of socioeconomic health differences
- Definitions are inconsistent and often show poor fidelity to the original concept
- Interpretation of AL should be subject to critical scrutiny