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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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3 socioeconomic position: poor fidelity and major
4 inconsistencies in biomarkers employed

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

8

ACCEPTED MANUSCRIPT

9 Abstract

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

15
16 **Methods:** Four databases (Embase, Global Health, MEDLINE, and PsychINFO) were
17 searched using terms related to AL, biomarkers and SEP. Data extraction focused on the
18 methods used to calculate AL indices. The frequency of pair-wise combinations of bi-
19 omarkers were used to assess the level of overlap in AL definition between studies.

20
21 **Results:** Twenty-six studies analysing the association between AL and SEP were included.
22 There was no consistent method of operationalising AL across studies. Individual biomarkers
23 and biological systems included in the AL index differed widely across studies, as did the
24 method of calculating the AL index. All studies included at least one cardiovascular- and
25 metabolic-related biomarker in AL indices, while only half of studies included at least one hy-
26 pothalamic-pituitary-adrenal (HPA) axis biomarker and approximately one third an immune
27 response-related biomarker. All but three studies found evidence of an association between
28 lower SEP and higher AL.

29
30 **Conclusions:** Many studies lacked fidelity to the original concept of AL in which stress was
31 considered central. The considerable variation in biomarkers used makes studies in this re-
32 view difficult to compare. A more critical approach should be taken in the calculation of AL
33 indices in particular to how far it captures the biological effects of psychosocial stress that
34 may underlie socioeconomic differences in health.

35

36 Introduction

37 The social underpinnings of disease have been long acknowledged and an extensive body
38 of literature has linked lower socioeconomic position (SEP) with adverse health outcomes.¹⁻³
39 The underlying mechanism for some diseases is better understood than others. For
40 example, it is well established that in high income countries those of a lower SEP are more
41 likely to smoke, be hypertensive and have increased cholesterol, which in turn results in an
42 increased risk of cardiovascular disease (CVD) events.⁴⁻⁷ However, the extent to which
43 stress plays a role in the specific mechanisms through which social factors influence disease
44 has remained elusive. Two key areas of research have emerged: one focused on how stress
45 is related to behavioral mechanisms of disease and the other on the biological mechanisms
46 responsible for translating stress into disease.⁸⁻¹¹ The latter has emphasized understanding
47 how the body internalizes an external stressor on a physiological level and how well a
48 person can adapt to changes in his or her environment. Allostasis is a concept describing
49 the normal process of how the human body adapts in response to a given stimulus.¹²
50 Allostatic load (AL) is defined as the physiological “wear and tear” a person experiences
51 across his or her life, for instance chronically elevated blood pressure resulting from a
52 lifetime of occupational strain.¹³

53 According to the original AL framework, stress hormones controlled by the hypothalamic-
54 pituitary-adrenal (HPA) axis (e.g. cortisol, epinephrine, and norepinephrine) are the “primary
55 mediators” of AL, which in turn mediate “secondary effectors” such as blood pressure, lipid
56 metabolism, and inflammation.^{13,14} Poor health conditions resulting from extreme values of
57 primary mediators and secondary effectors are “tertiary outcomes” (e.g. coronary heart
58 disease, decreased physical capacity, obesity or severe cognitive decline).¹⁵⁻¹⁷ In the first
59 study to calculate an AL index, measurements of 10 biomarkers were combined from three
60 biological domains (cardiovascular and metabolic systems, and HPA axis).¹⁸ For clarity, in
61 this paper AL index refers to the quantifiable variable, while allostatic load refers to the
62 conceptual framework devised by McEwen & Stellar.¹³

63 Since the term allostatic load was first introduced in 1993, the number of studies on AL have
64 grown considerably. Between 2010 and 2017 the number of papers in PubMed mentioning
65 AL have more than tripled, with 110 studies published in 2016 alone.¹⁹ However, researchers
66 have not taken a consistent approach to the way they have operationalised the concept. If
67 AL is intended to measure the physiological response to stress, then the inclusion of primary
68 mediators, such as HPA axis biomarkers (or equivalent), in an AL index is intrinsic to its
69 definition.

70 These methodological inconsistencies make comparisons across studies challenging. There
71 is therefore a need to determine how researchers define AL in the literature and to see how
72 different definitions affect associations between stress, AL, and disease. No prior study has
73 quantified the heterogeneity in AL indices. Previous reviews of AL, health disparities and
74 outcomes have been performed, but none had a methodological focus, although some
75 attention has been given to comparing different methods for how levels of constituent
76 biomarkers should be arithmetically combined into a single index.^{15,20-24}

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

80 **Methods**

81 *Search Strategy & Data Extraction*

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

85 **FIGURE 1 HERE**

86 The literature review was restricted to peer-reviewed publications of human population
87 studies that calculated an AL index and analysed the association between SEP as the main
88 exposure and AL as the main outcome. Reviews, protocols, conference abstracts, and
89 theoretical discussions were excluded. We sought to find all studies including the phrase
90 “allostatic load”, “biomarker”, and SEP. Specific search terms can be found in Appendix A.
91 Five electronic databases were searched (Embase, Global Health, MEDLINE, and
92 PsychINFO) to identify articles published up to July 7th 2017, with no language restrictions.
93 Additionally, previous reviews of AL and social factors were cross-referenced to check the
94 sensitivity of the search strategy.^{22–24} The preferred reporting items for systematic reviews
95 and meta-analyses (PRISMA) guidelines were followed with a focus on methodologies used
96 to operationalise AL.²⁵

97 *Analyses*

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

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

109 biomarker combination observed, and counted the number of studies using any unique
110 combination.

111 We analysed the data using MS Excel and analysed using Stata 14.1.

112 Results

113 *Findings from the literature search*

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

121 **FIGURE 2 HERE**

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

126 **TABLE 1 HERE**

127 *Biomarker selection and measurement*

128 A total of 59 individual biomarkers were used in one or more studies. The number of biomarkers
129 used to create an AL index ranged between 6 and 25 (Table 1), with a mode of 9. There were 20

130 biomarker combinations observed across the 26 studies included in the literature review.
131 Table 2 summarizes the number of studies including each biomarker organized by biological
132 system. Biomarkers appearing in only one study are listed in Supplementary Table S2. All
133 studies included at least one cardiovascular and one metabolic marker; the majority of
134 studies (85%) included one immune marker, while only 58% included an HPA axis marker.

135 **TABLE 2 HERE**

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

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

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

156 *Analysis of shared biomarkers*

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

167 **TABLE 3 HERE**

168 Substantial heterogeneity was observed across AL indices when comparing studies to each
169 other. Across all the possible combinations of biomarkers shared by two studies, the most
170 commonly shared group of biomarkers was waist to hip ratio, systolic blood pressure,
171 diastolic blood pressure and high density lipoprotein cholesterol, which appeared in 11 pairs
172 of studies. The other biomarkers used in these AL indices hardly overlapped and were often
173 categorised in different biological systems. For example, one study appeared in nine of the
174 11 pairs and additionally included biomarkers from the metabolic system and the HPA axis.³⁷
175 Another study appeared twice and included metabolic system-related, immune response and
176 HPA axis markers.⁴⁹ A sensitivity analysis in which closely related but distinct biomarkers
177 (e.g. fasting and non-fasting glucose) were collapsed into fewer broader classes (e.g.
178 glucose) did not change our findings (see Supplementary Table S4).

179 *Association between AL and SEP*

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

193 **TABLE 4 HERE**

194 Discussion

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

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

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

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

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

236 *Strengths & limitations*

237

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

242

243 This review was limited to studies analysing the association between AL and SEP and did
244 not include studies analysing AL indices as a predictor of disease outcomes. However, the
245 issues identified here are likely to also occur in the wider literature on AL, especially if these
246 issues are reflective of the availability of biomarkers collected in population-based studies.

247 Since these inconsistencies in AL operationalisation are a result of biomarker inclusion, a
248 broader review would have likely led to the same conclusion.

249

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

255 *Future directions*

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

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

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

271 *Concluding remarks*

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

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

286

287

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428

429 **Appendix A**

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

434 Socioeconomic position: socio?economic status, socio?economic position, subjective
435 social status, social class

436 Education: education*

437 Wealth: income, debt, asset*, poverty, depriv*, affluen*, financ*

438 Employment and occupation: job, work*, umeemploy*, employ*

439 Contextual: Neighbo?rhood

440

441

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

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

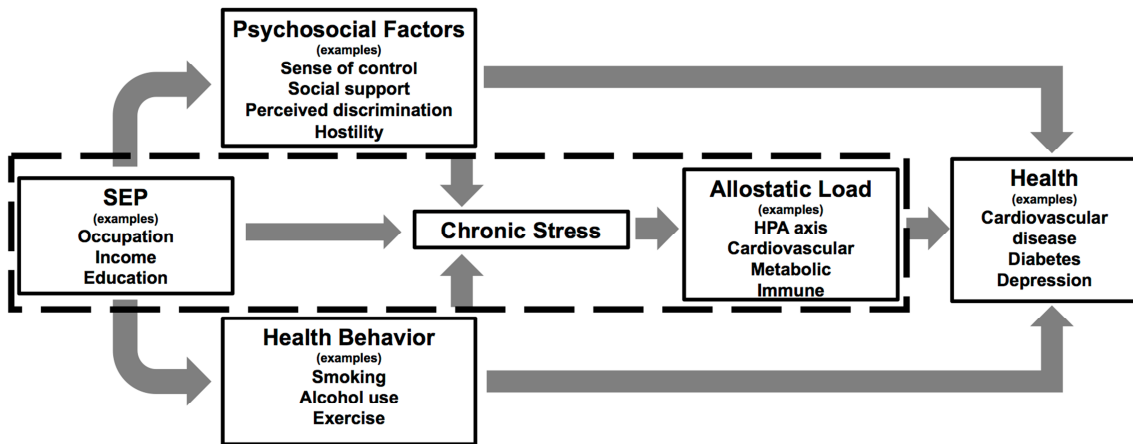
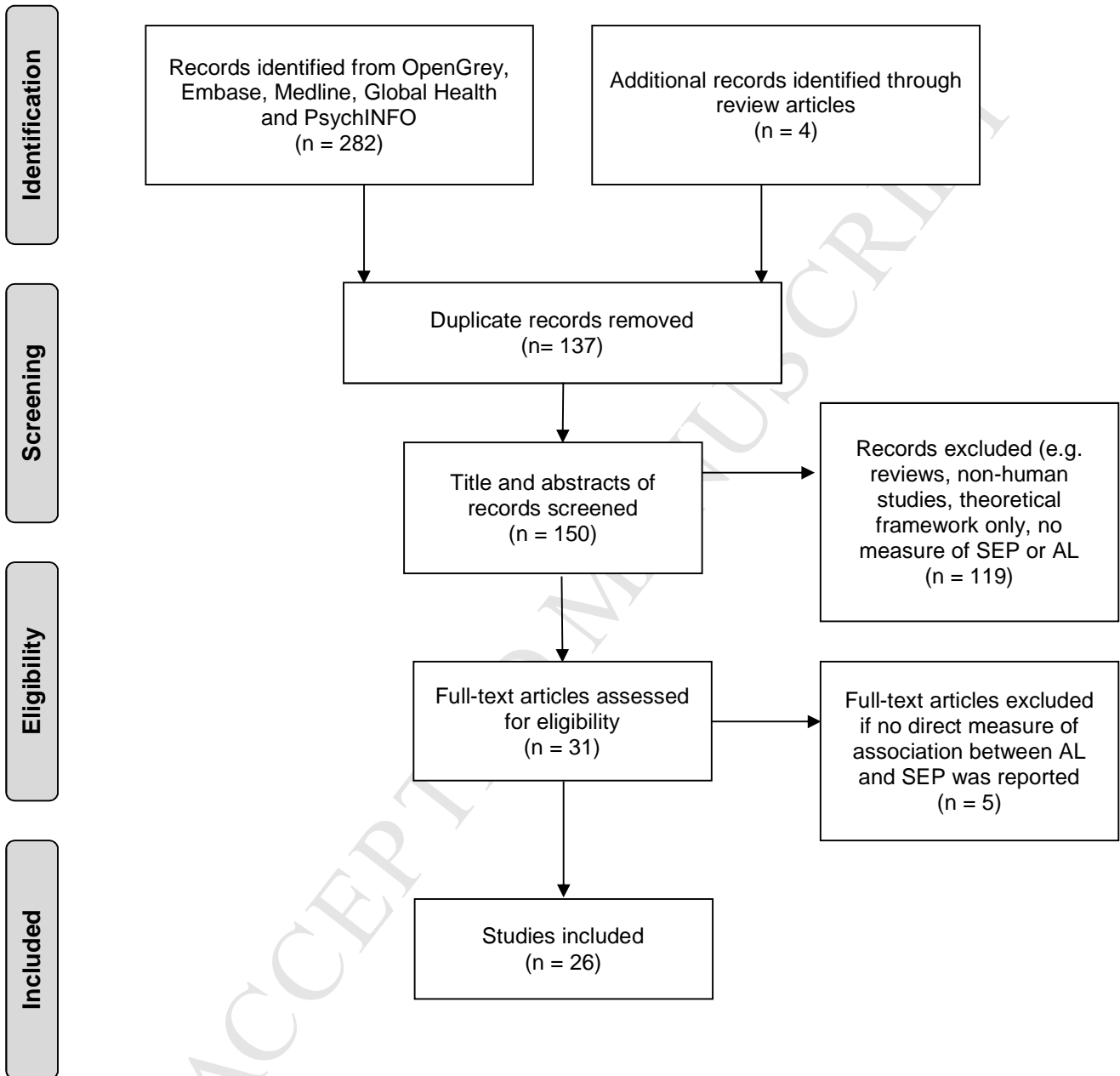


Figure 2. Flow chart of studies from literature search included in full data extraction²⁵

- 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

ACCEPTED MANUSCRIPT