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Allostatic load and women's brain health: A systematic review

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ABSTRACT

Allostatic load represents the 'wear and tear' of chronic stress on the brain and body that may differ between men and women. A small but growing number of studies are assessing allostatic load in relation to mental health. The objective of this systematic review was to (1) assess sex differences in allostatic load and (2) identify allostatic load associations that are specific to women. We systematically searched for allostatic load studies that included psychosocial causes and/or psychiatric consequences. Our search focused on allostatic load studies that disaggregated by sex and that include women. Sixty-two studies were included in this systematic review. First, men appear to have higher allostatic load than women. Second, women show gender-specific variation for numerous factors such as age, race/ethnicity, adversities, social support, and health behaviors that influence associations between allostatic load and mental health. Recommendations are made to guide researchers advance sex and gender approaches.

1. Introduction

Stress is experienced and exhibited differently for females and males. Among humans, women self-report more psychosocial distress on questionnaires, yet men are more biologically responsive to stressors (Kajantie and Phillips, 2006). Acute stress responses include the *sympathetic-adrenal-medullary* (SAM)-axis release of catecholamines (e.g., adrenalin) and the *hypothalamic-pituitaryadrenal* (HPA)-axis production of glucocorticoids (e.g., cortisol) that mobilize energy needed to adapt to environmental stressors (Sapolsky et al., 2000). In laboratory stress reactivity paradigms, male-typic cortisol responses are double that of women (Kirschbaum et al., 1992; Kudielka and Kirschbaum, 2005); however, women show considerable variation as a function of contraception (Kirschbaum et al., 1995b), menstruation (Kirschbaum et al., 1999), and pregnancy (Nierop et al., 2006). These variations are related to the *hypothalamic–pituitary–gonadal* (HPG)-axis secretion of gonadal hormones (e.g., estrogen, testosterone) that is also involved in stress responses (Juster et al., 2016b; Viau, 2002). Moving beyond sex differences in acute stress, we review sex differences in physiological dysregulations related to chronic stress.

1.1. Sex and gender considerations

Sex differences in stress responsivity are clearly influenced by biological sex-based factors (Kudielka and Kirschbaum, 2005). Evolution may have preserved a male-typic 'fight-or-flight' response and a female-typic 'tend-and-befriend' pattern that involves nurturing and socializing behaviors meant to protect against the demands of pregnancy, nursing, and childcare (Taylor et al., 2000). In addition to sex, socio-cultural gender-based factors also modulate within-sex variations in stress response patterns. While *sex* refers to a multi-dimensional construct involving genes, anatomy, gonads, and hormones, *gender* refers to a spectrum of implicit and explicit dissimilarities among men, women, and gender diverse people in their socially constructed roles, identities, orientations, and expressions (Johnson and Repta, 2011). For example, *gender-roles* represent a person's masculine and feminine behaviors and *gender relations* refer to interpersonal dynamics and power structures that contribute to pervasive inequalities (e.g., gender pay gap).

Sex and gender interactively influence the salience or "sex/gender-specificity" of stressor exposures. This in turn modulates how the sexes adapt to and cope with distinct stressors to ensure self-preservation (Dickerson and Kemeny, 2002; Mason, 1968). For example, men are more distressed by achievement-based stressors like public speaking, while women may be more sensitive to affiliation-based stressors like

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social rejection (Stroud et al., 2002). Social support is an excellent example of a gendered construct that appears to modulate acute stress reactivity in humans. In one fascinating study, women showed high cortisol reactivity when supported by their male partners, while men showed low cortisol responses when supported by their female partner (Kirschbaum et al., 1995a). This shows how gender-based social factors can influence stress responses that can become toxic when cumulatively strained.

1.2. Allostatic load

Pioneering work by the late Bruce S. McEwen (Galea et al., 2020) and his colleagues has shown that stress mediators (e.g., adrenalin, cortisol) exert 'wear and tear' on the brain and body through a pathogenic process called allostatic load (McEwen and Stellar, 1993). Allostatic load represents physiological dysregulations related to chronic stress that progressively disrupts interconnected neuroendocrine, immune, metabolic, and cardiovascular biomarkers in a multisystemic cascade (McEwen, 1998). Allostatic load is measured by indexing the sub-clinical and clinically significant dysregulations of multiple biomarkers connected to stress physiology (Beckie, 2012; Seeman et al., 1997). Abnormal SAM-axis function, HPA-axis function and elevated allostatic load are therefore viewed as important biological bellweathers that predict diverse somatic and/or psychiatric conditions (McEwen, 2003).

The allostatic load model has successfully been applied in transdisciplinary health research to better explain how chronic stress contributes to disease and death. A plethora of factors are related to increased allostatic load: increased age, lower socio-economic status, non-White race/ethnicity, poor social support, psychiatric symptoms, and many more that are consistent with the stress-disease literature (Juster et al., 2011). In addition to sex, these factors can synergize in an interactive way. *Intersectionality* represents the multiple identities (e.g., older Black woman) that can collectively strain health (Johnson et al., 2011). As can be seen holistically in Fig. 1, many of the antecedents of allostatic load are inherently gendered such as socio-economic status, unhealthy behaviors, and social support networks.

To date, we do not yet know if allostatic load differs between men and women. Furthermore among women, it not clear which mechanisms link allostatic load to health outcomes such as cardiovascular disease, metabolic problems, and premature mortality (Juster et al., 2010). While allostatic load is predictive of numerous physical conditions, more recent research has shown that allostatic load is also linked to psychiatric symptoms (Bizik et al., 2013). It is therefore imperative to consider both sex- and gender-based variation of allostatic load in order to advance this field forward, especially in the area of biological psychiatry (Juster et al., 2019).

1.3. Rationale and objectives

After nearly thirty years, it is not yet known whether allostatic load differs by sex or gender. The objective of this systematic review is to answer the following questions: (1) are there sex differences in allostatic load and (2) what are the causes and consequences of allostatic load in women? In the spirit of this Special Issue on Women's Brain Health, we systematically searched for allostatic load studies that included psychosocial causes and/or psychiatric consequences. Following recommendations for rigour and reproducibility (Clayton and Tannenbaum, 2016), we focus on allostatic load studies that provide analyses disaggregated by sex and that include women. Understanding how sex and gender relate to risk and protection to allostatic load will help us better identify the pathways whereby chronic stress strains the health and wellness of women.

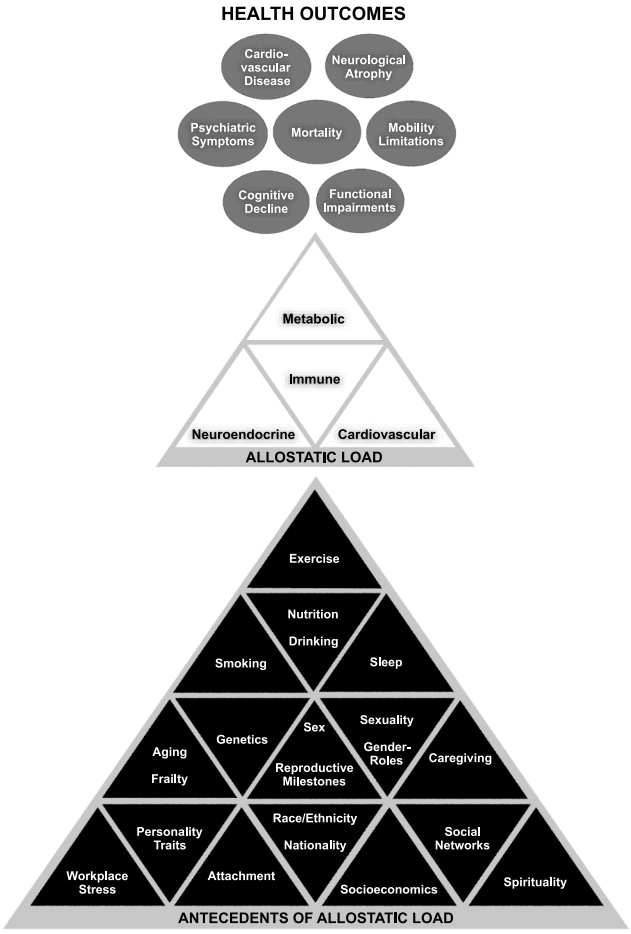

Fig. 1. Transdisciplinary summary of the allostatic load literature (Juster et al., 2016c; Juster et al., 2016d). In accordance with earlier review articles (Beckie, 2012; Juster et al., 2011; Juster et al., 2010), black triangles represent the identified antecedents of allostatic load, white triangles represent the biological systems that have traditionally been used to index allostatic load, and the gray circles represent health outcomes correlated with or predicted by allostatic load.

2. Methods

2.1. Study selection

No review protocols were registered prior to this systematic review. To reiterate, the aim of this systematic review was to assess the literature on (1) sex differences in allostatic load and (2) to assess health-promoting or health-damaging factors related to allostatic load among women across the lifespan in studies that included psychosocial and psychiatric variables. The allostatic load theoretical framework was first proposed by McEwen & Stellar in 1993. As such, only studies that were published in the English or French language between the years 1993–2019 were included. Study selection was done by an information specialist (MD) that conducted a library search query on August 22nd, 2019, using the PubMed, EMBASE, PsycInfo and CINAHL databases. It should be noted that we did not perform forward searches, nor did we inquire our network for unpublished datasets that met our inclusion criteria. However, three authors (PK, SK, MR) performed backward searches over the course of the screening procedure described in Fig. 2.

To ensure transparency, a detailed account of our search strategy, including queried variables, specifications and limitations for each search are provided in the Supplementary Material. The procedure for this systematic review followed the Preferred Reporting Items for

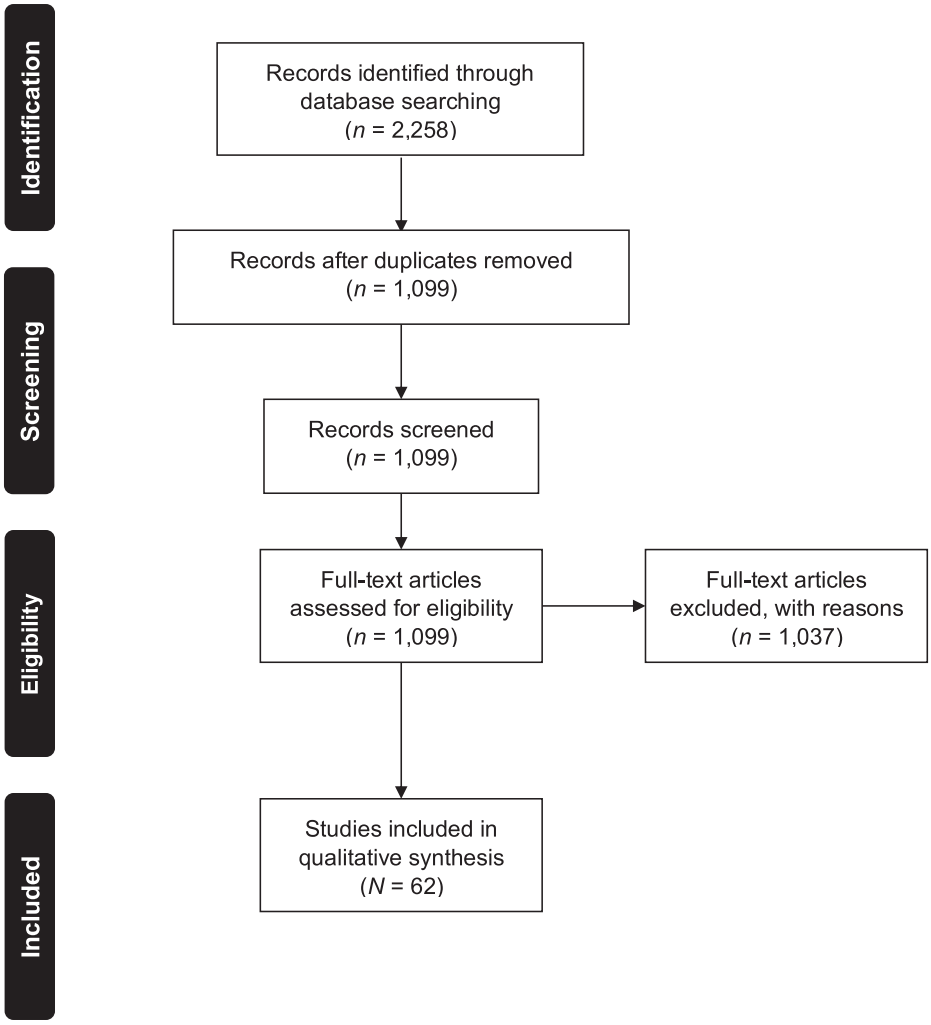

Fig. 2. Flow diagram of literature search and study inclusion.

Systematic Reviews and Meta-Analysis guidelines or PRISMA (Liberati et al., 2009). However, it should be noted that we did not consult our network for any unpublished data that could have met our inclusion criteria.

2.2. Inclusion and exclusion criteria

Inclusion criteria were: (1) empirical human studies, (2) authors had performed stratification of analyses by sex or reported effects of study outcomes in women and that (3) used an allostatic load index formulation with ≥6 biomarkers. Exclusion criteria were: (1) animal studies, (2) studies that only included men in their sample, (3) studies that did not perform stratification of analyses by sex, (3) review articles, theoretical articles, editorial/commentaries and book chapters. Three authors (PK, SK and MR) then screened the full text of the articles for suitability. We used the same criteria for both our research objectives, as articles were systematically screened for all inclusion/exclusion criteria – that is, if authors reported sex differences in allostatic load and/or women-specific factors that influenced allostatic load. Finally, the principal investigator (RPJ) performed a final assessment of the studies included to ensure consistency in data extraction.

2.3. Data extraction

For studies meeting our inclusion criteria, we extracted information on authors, year of publication, nationality/type of sample, number of participants, age (mean, standard deviation or standard error mean, range), sex distribution, race/ethnicity of participants, number and type of biomarkers included in the allostatic load algorithm (e.g., neuroendocrine, immune, cardiovascular, metabolic) (Seeman et al., 1997), as well as covariates or adjustments used in statistical analyses were extracted.

3. Results

3.1. Search results

Our search strategy identified 2,258 articles from four databases (Fig. 2). A total of 1,159 duplicate records were flagged and removed automatically during data importation. In addition, 18 duplicate records were removed manually. In total, we excluded 1,037 records in accordance with our inclusion and exclusion criteria described below. The final remaining 1,099 full-text articles were retrieved and three co-authors (PK, SK, MR) then assessed eligibility for inclusion in this systematic review.

3.2. Biomarker selection and measurement

Allostatic load index formulations included between 6 and 23 biomarkers (M = 11.61, SD = 3.38). In accordance with theory and practice, allostatic load biomarkers represented neuroendocrine, immune, cardiovascular and metabolic systems.

3.3. Study characteristics

In our final sample of 62 full-text articles, screening and assessment of eligibility was completed in a double-blind fashion to maximize objectivity. Three authors independently extracted data from the records: PK (n = 32), SK (n = 15) and MR (n = 15). Given the objectives of this special issue on women's brain health, only results linking study outcomes on allostatic load and psychosocial functioning and mental health that included women were included in the qualitative synthesis of this systematic review. Once data had been extracted from the reports, the senior author (RPJ) assessed records for consistency in data extraction from the original reports.

Risk of bias in individual studies was assessed at the study level and at the outcome level. At the study level, variability in bioassay methods used (e.g., sampling tissues, assay kit detection threshold, diverse allostatic load index formulations) or self-reported assessment of similar psychosocial constructs (e.g., depressive symptoms as measured by the BDI-II or the PHQ-9) may account for a proportion of inter-study variability in our results. At the outcome level, we have substantially reduced positive publication bias by including studies that found (or not) effects between study outcomes and allostatic load and psychosocial functioning of women. Moreover, because we used the same search strategy for both our objectives, it should be noted that this may potentially induce bias in our search results. In a preliminary analysis, we assessed inter-rater agreement for three raters by calculating (Fleiss, 1971; Fleiss et al., 2003) Fleiss' kappa. Results from this preliminary analysis yielded an overall Fleiss kappa of 0.654 (p < 0.001, CI95%: 0.618–0.69), which suggests moderate inter-rater agreement (Cohen, 1960). To limit discrepancies, the three authors who did the screening procedures reviewed all articles and decided if articles met inclusion/exclusion criteria until a consensus was agreed upon.

In studies that employed multiple regression models, only results from the most comprehensive models are presented in the qualitative synthesis of our systematic review. Specifically, findings of significant effects between allostatic load and study outcomes were sometimes lost or muddled when covariates (e.g., sex as a covariate) were added but not explored directly. In addition, the allostatic load model has often been used to assess physiological dysregulation in large populational and cohort-based quantitative studies. As such, results presented in this systematic review are often derived from among same samples.

In our systematic review (N = 62 studies), the statistical indices reported included odds ratio, relative risk ratio, bivariate correlations, structural equation models, multiple regressions, differences in means and chi-square. Some studies were derived from the same dataset; however, we did not combine this information nor conduct additional analyses as would be customary for a meta-analysis, sensitivity or subgroup analysis, or meta-regression.

3.4. Sex differences in allostatic load

Table 1 summarizes key findings from 62 allostatic load studies that assessed risk and protective factors with women included. Globally, we found that sex as a factor is inconsistently reported. Indeed, a substantial number of studies only added sex as a covariate for statistical analyses (n = 64) but did not perform stratification of analyses by sex or determine sex as a main effect. Of those that reported sex differences, very few reported effect sizes for differences.

Among those studies that did report on the effects of sex on allostatic load and health outcomes, seven found no sex differences (Brody et al., 2013; Chen et al., 2014; Christensen et al., 2019; Glei et al., 2013b; Gustafsson et al., 2011; Smith et al., 2009; Westerlund et al., 2012). By contrast, nine studies showed that women had lower allostatic load than men (Carlsson et al., 2017; Dich et al., 2015b; Dich et al., 2015c; Gale et al., 2015; Hawkley et al., 2011; Juster et al., 2016a; Kinnunen et al., 2005; Roepke et al., 2011; Schnorpfeil et al., 2003). Importantly, none of the studies to find sex differences reported higher allostatic load among women relative to men. In conclusion, men appear to have higher allostatic load than women in studies with sex differences.

3.5. Risk and protective factors among women.

Exploring individual characteristics that may prevent or precipitate adverse health outcomes among women are summarized next. Our goal here is to provide gendered insights into this mixed literature. According to the allostatic load model, normally adaptive physiological responses begin to falter under conditions of chronic stress and cumulative strain. As such, previous reviews have shown that individual factors (e.g., age, race/ethnicity, marital status, income, early childhood adversity) and environmental factors (e.g., country of birth, workplace stress) are major sources of chronic stress that contribute to allostatic load and adverse health outcomes (Beckie, 2012; Juster et al., 2011; Juster et al., 2010). Critically, the nature of the stressor and the amplitude of effects that these stressors exact on health differs significantly for men and women (Choleris et al., 2018). In particular, women face overt and covert stressors due to gender inequalities that are pernicious and unfortunately still pervasive worldwide. Identifying the specific gendered factors that are associated with allostatic load among women is crucial and described thematically below.

3.5.1. Allostatic load and health outcomes

Allostatic load is viewed as the biological culmination of 'wear and tear' of chronic stress that is related to various somatic and/or psychiatric problems. Critically, both somatic (e.g., musculoskeletal) and psychiatric (e.g., depression, anxiety) disorders disproportionately affect women when compared with men (Choleris et al., 2018; Galea et al., 2017). The causal pathways that lead to stress-related diseases also seem to differ. For example, studies found that higher allostatic load was related to decreased ratings of subjective health (Barboza Solis et al., 2016) and predicted future physical frailty in both men and women (Ding et al., 2017). However, dysregulated immune functioning was more strongly associated with decreased subjective health among women, while this was not the case for men (Barboza Solis et al., 2016). Another study showed that disrupted neuroendocrine and metabolic functioning was more strongly associated with somatic symptoms for women (Kinnunen et al., 2005). In line with this, individuals with allostatic load scores greater than 2 also showed increased severity of pain symptoms (Beckie et al., 2016). Psychosomatic symptoms also appear to be more severe among women compared with men, especially if these women self-report more masculine gender-roles (Juster and Lupien, 2012).

Individuals with high allostatic load face increased odds of experiencing depression (Bey et al., 2018a; Rodriquez et al., 2019) and comorbidities (Tampubolon and Maharani, 2018). However, one study failed to replicate associations between symptoms of stress, anxiety and depression with allostatic load (Adynski et al., 2019). Among depressed individuals, allostatic load was negatively associated with positive affect and this association has also been seen in schizophrenic patients (Nugent et al., 2015; Savransky et al., 2018). This is also the case for parents of children with developmental disorders, where caregiving parents with decreased positive affect show elevated allostatic load (Song et al., 2014). In sum, symptoms of depression, anxiety, and psychosis are repeatedly linked to allostatic load in the literature on biological psychiatry.

Stressful life events and circumstances can influence biomarker levels in men and women. Interestingly, this can be the case without changing overall allostatic load indices (Dich et al., 2015b). For example, one study found that higher metabolic and cardiovascular burden in allostatic load indices was associated with depressive symptoms among women, but this was not the case for men (Gillespie et al., 2019). Here, metabolic burden was also associated with an 88% increased risk of coronary heart disease, and this was mediated by

Table 1
Qualitative synthesis of allostatic load (AL) findings.

Authors	Nationality	*N*	Sex F/M	Age *M* *SD/SE* Range	Race/Ethnicity	# AL Biomarkers	Covariates/ Adjustments	AL Main Findings	Additional Associations
(Adynski et al., 2019)	American Low-Income Mothers	2,510	F	25.60 5.67 18-40	White (22.0%) Black (53.8%) Hispanic (24.2%)	10 BMI, HDL, TC/ HDL, HR, SBP, DBP, Waist-to-hip ratio, HbA1c, CRP, Diurnal cortisol	N/A	AL was not a significant predictor of depressive symptoms, stress symptoms or anxiety symptoms	↑ Odds of elevated stress symptoms in mothers with income below 100% of poverty line and/or experiencing interpersonal violence ↓ Odds of elevated stress symptoms in mothers who perceived food security ↑ Odds of elevated anxiety symptoms in mothers experiencing interpersonal violence and/or perceived food insecurity ↑ Odds of elevated depressive symptoms in mothers born outside of the United States of America, experiencing interpersonal violence, and perceiving food insecurity
(Allsworth et al., 2005)	American NHANES-III	2,470	F	23.6 N/A 17-30	White (28.0%) Black (33.1%)Hispanic (34.4%)	11 DBP, SBP, HbA1c, BMI, Triglycerides, HDL, TC, Albumin, CRP, Peak flow, Creatinine clearance	Age, Race/ ethnicity, Education, Poverty-income ratio, Smoking status, depression	↑ Odds of falling within high-risk AL group for women reporting early age of menarche (33.1% *vs.* 17.6%)	N/A
(Barboza Solis et al., 2016)	British 1958 British Birth Cohort	6,365	3,295 F 3,070 M	N/A	N/A	14 Salivary cortisol, CRP, Fibrinogen, IgE, IGF-1, HDL, LDL, Triglycerides, HbA1c, SBP, DBP, HR, Peak flow	Early life socioeconomics at birth Early adulthood socioeconomics Adulthood socioeconomics, Health behaviors confounders	↑ AL with ↓ subjective health index among men and women For women, ↑ fibrinogen, ↑ CRP were more strongly associated with ↓ subjective health index	↓ Paternal occupational status with ↓ subjective health index ↑ Income with ↑ subjective health index Smoking, alcohol abstinence, ↑ BMI with ↓ subjective health index
(Beckie et al., 2016)	American Women Veterans	81	F	47.0 10.0 24-71	White (54.3%) Black (29.6%)Hispanic (14.8%)Mixed/ other (16.0%)	12 TC, HDL, LDL, TC/HDL, Triglycerides, Glucose, BMI, Waist circumference, SBP, DBP, IL-6, CRP, Hair cortisol	N/A	↑ AL in women who experience 2 + categories of sexual assault AL score ≥ 2 with ↑ trend with pain symptoms	↑ Experiences of sexual assault during childhood, civilian or military service with ↑ Somatic symptoms, ↑ Depressive symptoms, ↑ PTSD symptoms
(Bellingrath et al., 2009)	German Women Teachers	104	F	45.0 9.75 25-61	N/A	17 Cortisol, Epinephrine, Norepinephrine, DHEA-S, Waist-to-hip ratio,	Age	↑ AL with ↑ effort-reward imbalance and ↑ age	↑ Vital exhaustion with ↑ effort-reward imbalance and ↑ burnout symptoms

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Table 1 (*continued*)

Authors	Nationality	*N*	Sex F/M	Age *M* *SD/SE* Range	Race/Ethnicity	# AL Biomarkers	Covariates/ Adjustments	AL Main Findings	Additional Associations
						HbA1c, HDL, TC/HDL, SBP, DBP, CRP, TNF-α, Fibrinogen, D-dimer, % Body fat, Triglycerides, Glucose			
(Bey et al., 2018a)	American NHANES 2005–2010	6,431	3,127 F 3,304 M	41.0 13.98 18-64	White (68.8%) Black (31.2%)	9 SBP, DBP, HR, BMI, TC, HDL, HbA1c, Albumin, CRP	Age, Family poverty-to-income ratio, AL biomarkers	↑ CRP was associated with ↑ odds of depression among Caucasian women, but not African American women ↑ TC was associated with depression among African American women	Half of Black women were obese, while the prevalence of obesity ranged from 30% to 34% in the other three groups Black people and women were more likely to report elevated depressive symptoms
(Bey et al., 2018b)	American NHANES 2005–2010	6,431	3,127 F 3,304 M	41.0 13.98 18-64	White (68.8%) Black (31.2%)	9 SBP, DBP, HR, BMI, HbA1c, HDL, TC, Albumin, CRP	Age, Family Poverty-to-income ratio	Black women were more likely to have ↑ AL (32%) ↑ AL was significantly associated with depression only among White women and Black menIndividuals with ↑ AL had increased odds (1.7x) of being depressed	Black women were more likely to be depressed (15%)
(Boneva et al., 2019)	AmericanWomen with Chronic Fatigue Syndrome (CFS) & Endometriosis (EM) – Wichita Cohort	36	F	51.1 1.0 27-69	White (88.9%) Black or Native American (11.1%)	11 DBP, SBP, Aldosterone, Waist-to-hip ratio, Albumin, CRP, IL-6, Serum/ Urinary cortisol DHEA-S, Epinephrine, Norepinephrine	Age, BMI	AL biomarkers were all within normal ranges ↑ Hemoglobin and hematocrit in CFS + EM relative to CFS-only patients ↓ TNF-α in CFS + EM relative to CFS-only patients	↑ Endometriosis in CFS patients (36%) relative to non-fatigued controls (17%) Patients with CFS + EM had ↑ CFS symptoms relative to CFS only patients Non-menstrual, chronic pelvic, or lower abdominal pain was reported significantly more by CFS + EM relative to CFS-only patients CFS + EM had increased odds (9x) to be menopausal and menopause onset was approximately a decade earlier relative to CFS-only patients ↑ Negative life events in CFS + EM relative to CFS-only patients ↑ Obstructive Apnea Events in CFS + EM relative

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Table 1 (*continued*)

Authors	Nationality	*N*	Sex F/M	Age *M* *SD/SE* Range	Race/Ethnicity	# AL Biomarkers	Covariates/ Adjustments	AL Main Findings	Additional Associations
									to CFS-only patients
(Brody et al., 2013)	Youth	489	259 F 230 M	T1 11.2 N/A N/A T2 19.2 N/A N/A	Black (100%)	6 Urinary cortisol, Epinephrine, Norepinephrine, SBP, DBP, BMI	Sex, Health problems	Sex was not associated with AL ↑ AL among individuals with both ↑ self-control/ competence and ↑ SES-related risk	↓ Externalizing problems among women Depressive symptoms were lower among individuals with ↑ self-control/ competence and ↑ SES-related risk Externalizing problems were associated with ↑ health problems and ↓ self-control/ competence Externalizing problems were lower among individuals with both ↑ self-control/ competence and ↑ high SES-related risk
(Carlsson et al., 2017)	Danish Organizational Change, Stress and Health Study	359	265 F 94 M	N/A	N/A	13 SBP, DBP, HbA1c, HDL, TC, Waist-to-hip ratio, BMI, Cortisol at awakening, CAR, DHEA-S, CRP, IL-6, Fibrinogen	Baseline biomarkers, markers of perceived psychosocial work environment, Psychological distress, Sex	↓ Baseline AL among women relative to men Immune system values were generally higher among women, whereas neuroendocrine and cardiovascular values were generally ↑ among men ↑ AL in workplace reorganization group relative to controls	N/A
(Chen et al., 2014)	American NHANES 2005–2008	3,330	1,581 F 1,749 M	N/A N/A 18+	White (47.8%) Black (21.4%)Hispanic American (19.07%)Other (11.71%)	9 SBP, DBP, HR, TC, HDL, BMI, HbA1c, CRP, Albumin	Age, Race/ ethnicity, Marital status, Education level, Poverty-income ratio, Country of birth, Physical activity, Alcohol consumption, Smoking	No sex differences in the prevalence of ↑ AL ↑ AL among individuals who were 60 + years old ↑ AL among widowed, separated or divorced relative to married or living with a partner ↑ AL in US born individuals relative to foreign individuals ↑ AL among individuals with less than high school education Prevalence of ↑ AL was highest among African Americans (26.3%), followed by Hispanic Americans	↑ Prevalence of insomnia and short sleep duration in African American individuals

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Table 1 (*continued*)

Authors	Nationality	*N*	Sex F/M	Age *M* *SD/SE* Range	Race/Ethnicity	# AL Biomarkers	Covariates/ Adjustments	AL Main Findings	Additional Associations
								(20.3%), Caucasian (17.7%) and other race/ ethnic groups (13.8%) ↑ Prevalence of high AL among individuals with diagnosed sleep apnea, snoring, snorting/stop breathing, insomnia, short sleep duration, diagnosed sleep disorders than those without sleep disturbances	
(Chiu and Lin, 2019)	Taiwanese Social Environment and Biomarkers of Aging Study 2000–2006	483	166 F 317 M	64.7 7.07 54-80	N/A	11 SBP, DBP, TC, HDL, Triglycerides, HbA1c, Cortisol, Epinephrine, Norepinephrine, Waist-to-hip ratio, DHEA-S	Age, Chronic disease, Education level, Sex	↓ Spousal health was associated with ↑ AL in women ↑ AL in women whose spouse's health remained poor	N/A
(Christensen et al., 2019)	Danish Copenhagen Aging and Midlife Biobank	5,512	1,730 F 3,782 M	N/A N/A 49-63	N/A	14 IL-6, TNF-α, CRP, SBP, DBP, LDL, HDL, TC, BMI, Waist-to-hip ratio, Glucose, Triglycerides, HbA1c, % Body fat	Age, Sex, Time of day of blood draw, Fasting status, Education level, Occupational social class, Smoking status, Alcohol consumption, Leisure time activity	No sex differences in AL ↑ Conscientiousness was associated with ↓ AL in women ↑ Education level was associated with ↓ AL in women	↑ Neuroticism, openness, agreeableness, education level, weekly alcohol consumption leisure time activity, time of blood draw among women
(Chyu and Upchurch, 2011)	American NHANES 1999–2004	5,765	F	N/A N/A 18-70+	White (80.6%) Black (12.1%)Hispanic American (7.3%)	10 SBP, DBP, HR, Homocysteine, CRP, Albumin, HbA1c, HDL, TC, BMI	N/A	Black women 40–49 years old had AL scores 1.14 higher than White women 50–59 years old Hispanic American women who were not born in the US had ↑ AL than those who were born in the US	N/A
(Dich et al., 2015b)	Danish Copenhagen Aging and Midlife Biobank	5,309	1,670 F 3,639 M	54.0 N/A 49-63	N/A	9 SBP, DBP, CRP, IL-6, Triglycerides, HDL, TC, HbA1c, Waist-to-hip ratio	N/A	↑ AL in men ↑ Stressful events and circumstances were associated with changes in biomarker levels, but not overall AL among women	↑ Stressful events and circumstances during childhood/ adolescence and adulthood among women relative to men
(Dich et al., 2015c)	British Whitehall II	7,007	2,102 F 4,905 M	49.0 5.80 N/A	N/A	9 BP, BMI, Insulin, Glucose, HDL, LDL, Triglycerides, CRP, IL-6	Age, Sex, Marital status, Social class, Baseline illness	↑ AL among men ↑ Caregiving burden was associated with ↑ AL and this effect was higher among individuals who reported ↑ job strain (no significant interaction)	Being a caregiver was associated with ↑ likelihood of reporting ↑ job strain Reporting ↑ job strain was associated with ↑ likelihood of being a woman, single, being a professional or executive and to

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Table 1 (*continued*)

Authors	Nationality	*N*	Sex F/M	Age *M* *SD/SE* Range	Race/Ethnicity	# AL Biomarkers	Covariates/ Adjustments	AL Main Findings	Additional Associations
									report baseline illness Caregivers were more likely to be older and to be women, relative to non-caregivers ↑ Caregiving burden was associated with ↓ SES
(Dich et al., 2015a)	Danish Copenhagen Aging and Midlife Biobank	181	87 F 94 M	N/A N/A 49-51	N/A	8 BP, Triglycerides, HDL, TC, HbA1c, BMI, CRP, IL-6	Age, Caregiving rewards, SES	Meaningful work with ↑ AL in women, but not men Rewards were associated with ↑ AL in women, but not men ↑ AL with emotional strain and ↓ physical strain in men, but not women	Meaningful work was associated with ↓ depressive symptoms for both men and women Reporting any caregiving responsibilities with ↑ depressive symptoms in women, but not men ↑ Emotional strain with ↑ depressive symptoms and ↑ perceived stress among women, but not men
(Ding et al., 2017)	British English Longitudinal Study of Ageing	4,638	2,568 F 2,070 M	74.0 6.30 65-89	N/A	9 SBP, DBP, HbA1c, Triglycerides, CRP, Fibrinogen, Peak flow, Waist-to-hip ratio, BMI	Age, Sex, Smoking history, High alcohol intake, Low education level, Low wealth	↑ AL with ↑ future physical frailty All study outcomes were not moderated by AL among women, but a small proportion were for men	↑ Rates of physical frailty among women and individuals of 75 years and older ↑ Obesity and depressive symptoms among women ↑ Chronic diseases, low physical activity, depressive symptoms, cognitive impairment, poor social support, poor social integration with ↑ future physical frailty among men and women
(Ellis et al., 2019)	American MIDUS	1,255	688 F 567 M	54.52 11.71 34-84	White (91.4%) Hispanic (3.6%)Black (2.6%) Native American (1.2%)Asian/ Pacific Islander (0.29%)	23 Urinary Epinephrine, Urinary Norepinephrine, RMSSD, Low & high frequency spectral power, Urinary cortisol, DHEA-S, CRP, IL-6, e-Selectin, ICAM-1, Fibrinogen, SBP, Pulse pressure, HR, Fasting blood glucose, HbA1c, HOMA-IR, Triglycerides, HDL, LDL, BMI, Waist-to-hip ratio	Age, Sex, Race/ ethnicity	↑ Perceived stress with ↑ AL ↓ Global sleep quality with ↑ AL ↓ Global sleep quality with ↑ inflammatory, cardiovascular, glucose & lipid metabolism burden ↑ Glucose & lipid metabolism burden among women	↑ Emotional regulation (suppression) was associated with ↑ perceived stress, ↓ global sleep quality↑ Emotional regulation (cognitive reappraisal) was associated with ↓ perceived stress

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Authors	Nationality	*N*	Sex F/M	Age *M* *SD/SE* Range	Race/Ethnicity	# AL Biomarkers	Covariates/ Adjustments	AL Main Findings	Additional Associations
(Gale et al., 2015)	Scottish The West of Scotland Twenty-07 Study	705	381 F 324 M	36.6 0.42 16-36	N/A	9 CRP, HbA1c, Albumin, TC, HDL, SBP, DBP, HR, Waist-to-hip ratio	General Health Questionnaire score, Parental social class, Educational attainment, Smoking status, Current alcohol consumption, Physical activity	↓ Processing speed at age 16 predicted ↑ AL at age 36 ↑ Depressive/ anxiety symptoms, ↑ parental socioeconomic disadvantage with ↑ AL	Female sex was a predictor for the association between ↓ processing speed and ↑ depressive/ anxiety symptoms ↓ Processing speed at age 16 predicted ↑ parental socioeconomic disadvantage, ↓ mental health at age 36, ↓ educational attainment, ↑ smoking, alcohol consumption and exercise
(Gale et al., 2016)	Scottish Lothian Birth Cohort 1936	876	443 F 433 M	70.0 N/A N/A	N/A	9 Fibrinogen, Triglycerides, TC/HDL ratio, Albumin, HbA1c, CRP, BMI, SBP, SBP	IQ, Sex, Father's occupation, Home environmental deprivation, Social class, Educational attainment, Frailty status, Smoking status, Alcohol consumption, Physical activity	Being a women with ↓ AL ↑ AL with ↓ IQ at age 11, ↑ frailty, ↑ father in professional/ managerial social class, being in professional/ managerial social class, ↑ frailty status, ↑ smoking status, ↓ educational attainment, ↓ alcohol consumption, ↓ physical activity	↓ IQ at age 11, ↑ Father in professional/ managerial social class, being in professional/ managerial social class, ↓ educational attainment, ↑ smoking status, alcohol consumption with ↑ frailty status
(Gillespie et al., 2019)	American Jackson Heart Study	2,670	1,762 F 908 M	53.4 12.50 21-94	N/A	10 Waist circumference, Triglycerides/ HDL ratio, LDL, HbA1c, HR, SBP, DBP, CRP, Serum cortisol, Serum aldosterone	Age, Sex, Education level, Occupation, Smoking status, Physical activity	↑ Depressive symptoms with ↑ metabolic AL among women, but not men ↑ Depressive symptoms with ↑ cardiovascular AL parameters among women, but not men ↑ Metabolic AL with ↑ 88% risk of coronary heart disease ↑ Neuroendocrine AL with ↑ 39% risk of coronary heart disease ↑ Composite AL with ↑ 130% risk of coronary heart disease Metabolic AL mediated the association between depressive symptoms and coronary heart disease among women, but not men	↑ Depressive symptoms with ↑ coronary heart disease
					N/A				N/A

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Authors	Nationality	*N*	Sex F/M	Age *M* *SD/SE* Range	Race/Ethnicity	# AL Biomarkers	Covariates/ Adjustments	AL Main Findings	Additional Associations
(Glei et al., 2013a)	Russian (SAHR) Taiwanese (SEBAS) American (MIDUS)	1,763 1,036 1,054	2,018 F 1,872 M	68.6 10.15 N/A 65.5 9.2 N/A 58.1 11.65 N/A		15 SBP, DBP, TC, HDL, Triglycerides, HbA1c, BMI, Waist circumference, CRP, Fibrinogen, DHEA-S, 12 h Urinary cortisol, IL-6, Urinary epinephrine, Urinary norepinephrine	Sex, Country, Age, Education level	For both sexes, AL was highest in Russians and lowest in Taiwanese ↑ Perceived stress with ↑ AL in Russians for both sexes, US women, but not Taiwanese ↑ Perceived stress with ↓ AL in Taiwanese men	
(Glei et al., 2013b)	Taiwanese SEBAS	539	224 F 315 M	64.9 7.20 54-86	N/A	17 Hypertension, HDL, Triglycerides, Waist circumference, Fasting glucose, IL-6, CRP, Soluble intercellular adhesion molecule 1, Soluble E-selectin, DHEA-S, Cortisol, Epinephrine, Norepinephrine, IGF-1, Creatinine clearance, Albumin, Homocysteine	Age, Sex, Urban residence, Education level, Social integration, Perceived availability of social support, Personal mastery	No significant effects on AL among women	N/A
(Glover et al., 2006)	American Mothers of children diagnosed with cancer	28	F	N/A 100%	N/A	10 BMI, SBP, DBP, Serum DHEA-S, Serum HDL, TC, HbA1c, Urinary cortisol, Urinary epinephrine, Urinary norepinephrine	Age, self-reported sleep quality, substance use	Dose-response effect on ↑ AL between healthy controls, no PTSD mothers of children diagnosed with cancer and PTSD mothers of children diagnosed with cancer ↑ AL with ↑ number of PTSD symptoms and ↑ severity of PTSD symptoms	N/A
(Groer et al., 2016)	American	81	F	46.5 10.60 18-70 100%	White (54.3%) Black (29.6%)Asian/ Pacific Islander (1.2%)Mixed (4.9%)Inuit/ Native American (1.2%)Other (8.6%)	17 TC, Triglycerides, HDL, LDL, Random glucose, CRP, IL-10, IL-4, IL-6, IFN-γ, TNF-α, IGF-I, SBP, DBP, Waist circumference, BMI, Hair cortisol	Age, Demographic variables, biological variables (not otherwise specified)	Women reporting childhood sexual assault had ↑ TC, LDL, Triglycerides, Hair cortisol than women who did not report childhood sexual assault	Childhood sexual assault was reported by 33% of the sample Women reporting childhood sexual assault were ↑ unemployed, disabled and/or financially supported by someone elseWomen reporting childhood sexual assault also reported ↑ civilian sexual assault relative to women who did not report childhood sexual assault

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Table 1 (*continued*)

Authors	Nationality	*N*	Sex F/M	Age *M* *SD/SE* Range	Race/Ethnicity	# AL Biomarkers	Covariates/ Adjustments	AL Main Findings	Additional Associations
									(70.3% *vs.* 18%) Women reporting childhood sexual assault reported ↑ perceived chronic stress, ↑ depressive symptoms, ↑ fatigue symptoms
(Gustafsson et al., 2011)	Swedish Northern Swedish Cohort	855	412 F 443 M	N/A	N/A	12 SBP, DBP, BMI, Waist circumference, TC, HDL, Triglycerides, Apolipoprotein A1, Apolipoprotein B, Glucose, CRP, Cortisol	Age, Sex, Current health behaviors at 43 years old (smoking, snuff, alcohol, inactivity), SES	No sex differences in AL ↑ AL with ↑ unhealthy behaviors in men, but not women ↓ SES at 16 and 43 years old with ↑ AL among women	N/A
(Hampson et al., 2009)	American Hawaii Personality and Health Cohort	470	243 F 227 M	Women: 50.0 2.0 N/A Men: 50.3 2.0 N/A	White (29.0%) Japanese American (42.0%) Native Hawaiians (17.0%)European Americans (12.0%)	11 SBP, DBP, TC, TC/HDL ratio, Triglycerides, Fasting blood glucose, BMI, Waist-to-hip ratio, Urinary protein, Cholesterol medication use, Blood pressure medication use	N/A	↑ Smoking, ↓ healthy food preparation with ↑ AL among men and women ↑ AL with ↓ self-rated health	N/A
(Hawkley et al., 2011)	American CHASRS	208	N/A	58.4 N/A 51-69	White (37.5%) Black (34.6%)Hispanic (27.9%)	9 SBP, DBP, Urinary Norepinephrine, Urinary Epinephrine, Waist circumference, Cortisol, HDL, TC, HbA1c	Age, Sex, Race/ ethnicity	↑ AL among men ↑ SES and ↑ Years of education with ↓ AL ↓ Sleep quality and ↑ hostility mediated association between SES and AL	N/A
(Horan and Widom, 2015)	American prospective cohort of neglected and abused children from juvenile and adult criminal courts	620	339 F 281 M	Phase 1 29.0 N/A N/A Phase 2 40.0 N/A N/A Phase 3 41.0 N/A N/A	White (67.6%) Black (32.4%)	9 SBP, DBP, HDL, TC, HbA1c, CRP, Albumin, Creatinine clearance, Peak Flow	Age, Sex, Race/ ethnicity	↑ Childhood abuse and neglect ↑ AL in middle adulthood among women ↑ Perceived social support with ↓ AL among women ↑ Perceived social support ↑ AL among men	N/A
(Hux et al., 2017)	American Pregnant women	103	F	29.8 5.0 18-45 100%	White (75.7%) Black (17.5%)Other (6.8%)	9 SBP, DBP, Pulse, Pre-pregnancy BMI, TC, HDL, Triglycerides, TNF-α, IL-6	Perceived stress	↑ AL with Pittsburgh Sleep Quality Index ↓ AL among college-educated women ↑ AL among African American women relative to non-African American women	N/A
(Johansson et al., 2007)	Swedish Individual Development and Adaptation Research Program	369	F	N/A 100%	N/A	7 SBP, DBP, TC, HDL, HbA1c, Peak flow, Waist-to-hip ratio	N/A	No AL differences for life-career patterns	Differences between life-career patterns for women in job satisfaction, work-to-family, life satisfaction and mental distress

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Table 1 (*continued*)

Authors	Nationality	*N*	Sex F/M	Age *M* *SD/SE* Range	Race/Ethnicity	# AL Biomarkers	Covariates/ Adjustments	AL Main Findings	Additional Associations
(Juster and Lupien, 2012)	Canadian	30	19 F 11 M	45.4 2.12 27-65	White (89.7%)	15 Plasma cortisol, DHEA-S, Insulin, HbA1c, Creatinine, Albumin, Pancreatic Amylase, CRP, Fibrinogen, Triglycerides, TC, HDL, SBP, DBP, Waist-to-hip ratio	Age, Sex, Gender-Roles	↑ AL with ↑ Masculine gender-roles for both sexes ↑ Physical complaints associated with ↑ AL	↑ Physical complaints among women
(Juster et al., 2013a)	Canadian Montreal Workers	199	118 F 81 M	Women 42.8 11.38 N/A Men 39.4 11.30 N/A	White (86.5%)	15 SBP, DBP, HRV, Insulin, Glucose, HOMA, HDL, LDL, Triglycerides, CRP, TNF-α, IL-6, BMI, Waist-to-hip Ratio, Salivary Cortisol	N/A	↑ Age with ↑ AL↓ Occupational status with ↑ AL (men)↑ Occupational status with ↓ AL (women) ↑ Psychological demands with ↓ AL	↑ Psychological demands and ↓ Decisional latitude with ↑ Anxiety symptoms ↑ Social support with ↓ Anxiety symptoms
(Juster et al., 2016a)	Canadian Montreal Workers	204	144 F 60 M	40.4 0.90 N/A	N/A	20 Diurnal CAR, Cortisol diurnal bedtime, Cortisol TSST, DHEA-S, TNF-α, IL-6, CRP, Fibrinogen, Triglycerides, LDL, HDL, Insulin, Hb1Ac, Creatinine, Albumin, HR, SBP, DBP, Waist-to-hip ratio, BMI	Age, Sex hormones, Chronic stress, Sexual orientation, Mental health conditions	↓ AL in women relative to men	Undifferentiated gender-role profiles with ↓ Self-Esteem, ↓ Well-Being, ↑ Depressive symptoms
(Juster et al., 2013b)	Canadian	87	40 F 47 M	24.61 0.61 18-45	White (71.3%)	21 Cortisol AM Slope, Cortisol PM Slope, DHEA-S, Adrenalin, Noradrenalin, Dopamine, TNF-α, IL-6, CRP, Fibrinogen, Insulin, HbA1c, Creatinine, Albumin, Triglycerides, Total Cholesterol, HDL, SBP, DBP, Waist-to-hip Ratio, BMI	Age, Awakening time, Chronic stress	AL did not differ between heterosexual and lesbian/bisexual women AL did not vary as a function of sexual orientation disclosure status ↑ AL in heterosexual men compared to gay/ bisexual men	↑ Depressive symptoms in lesbian or bisexual women ↑ Anxiety/ Depressive/ Burnout symptoms in individuals with non-disclosed sexual orientation
(Kinnunen et al., 2005)	Finnish Jyväskylä Longitudinal Study of Personality and Social Development	117	55 F 62 M	Women 41.6 N/A N/A Men 41.8 N/A N/A	N/A	8 DHEA-S, Urinary norepinephrine, HDL, Triglycerides, HbA1c, SBP, DBP, Waist-to-hip ratio	Sex, Occupational status, Health behaviors	↑ AL among men Men ↑ mean values for secondary AL biomarkers (except HDL) Women ↑ mean values for norepinephrine and ↓ DHEA-S Women fall more into the high risk quartiles except Waist-to-hip ratio Men fall more into the high risk quartiles for Waist-to-hip ratio	Stable career more frequent among men than women Men more often blue-collar workers and less often white-collar Women drink and smoke less often than men

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Authors	Nationality	*N*	Sex F/M	Age *M* *SD/SE* Range	Race/Ethnicity	# AL Biomarkers	Covariates/ Adjustments	AL Main Findings	Additional Associations
								↑ AL ↑ Psychosomatic symptoms	
(Lindfors et al., 2006)	Swedish Individual Development and Adaptation Research Program	200	F	43.0 N/A N/A	N/A	7 DBP, SBP, HbA1c, HDL, TC, Waist-to-hip ratio, Peak flow	Demographic characteristics (not otherwise specified)	↑ AL with ↑ Clinical risk ↑ AL associated with ↓ sense of coherence and less meaningfulness	Clinical risk associated with less meaningfulness
(Mauss et al., 2015)	German Mannheim Industrial Cohort Study	3,797	785 F 3,012 M	41.0 11.40 15-64	N/A	15 SBP, DBP, Fasting plasma glucose, HbA1c, TC, HDL, LDL, Triglycerides, Waist-to-hip ratio, Waist circumference, BMI, Leukocytes, CRP, RMSSD, Urinary albumin	Age, Sex, Smoking, Leadership responsibility, Present diseases	Perceiving work stress with ↑ AL ↓ Effort-reward ratio with ↑ AL Men more likely to perceive high stress levels Highest tertile AL index participants have higher perceived work stress ↑ AL odds ratio for work stress among men than women ↑ Age ↑ AL	N/A
(Mellner et al., 2005)	Swedish Individual Development and Adaptation Research Program	222	F	43.0 N/A N/A 100%	N/A	10 SBP, DBP, HR, Waist-to-hip ratio, HR, TC, HbA1c, Salivary cortisol, Urinary norepinephrine, Urinary HDL	N/A	Women with ↑ AL have ↑ HR and ↑ cortisol Women with ↓ AL have ↑ Urinary norepinephrine on a work free day evening at 8 PM	N/A
(Nugent et al., 2015)	American Schizophrenia (SZ) patients and controls	50	26 F 29 M	33.0 12.0 18-57	Healthy controls:White (55%)Black (35%)Other (5%) Schizophrenia (SZ) patients:White (50%)Black (47%)Other (3%)	13 Overnight 12H urine cortisol, Epinephrine, Norepinephrine, fasting blood DHEA, Fasting HDL, TC, BMI, Waist-hip ratio, Resting SBP, Resting DBP, HbA1c, CRP, Resting HR	Age, Smoking, Marital status	No sex differences in AL among healthy controls or SZ ↑ Age ↑ AL in both SZ and controls ↑ AL in married controls ↑ AL in SZ with less and more 5 years duration of illness ↑ AL ↓ functional capacity in SZ ↑ AL ↑ Positive symptoms in SZ ↑ AL in SZ taking antidepressants	N/A
(Rodriquez et al., 2018)	American NHANES	12,272	6,369 F 5,903 M	55.6 0.19 40-79	White (48%) Hispanic (27%) Black (25%)	10 SBP, DBP, BMI, HbA1c, TC, HDL, TC/HDL ratio, CRP, Albumin, Creatinine clearance	Age, Sex, Education level	AL associated with unhealthy behaviors and varies by individual behavior and/or ethnicity	Smoking highest among Black people Excessive binge drinking greater among Hispanic people Black and Hispanic people did not meet recommendations for physical activity and reported poorer diet. They also reported engaging in 3–4 unhealthy behaviors Hispanic and Black people have higher risk for

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Authors	Nationality	*N*	Sex F/M	Age *M* *SD/SE* Range	Race/Ethnicity	# AL Biomarkers	Covariates/ Adjustments	AL Main Findings	Additional Associations
									depressive disorder Higher odds of risk for depressive disorder in women
(Rodriquez et al., 2019)	American National Archive of Computerized Data on Aging	1,789	1,044 F 745 M	70.6 7.10 60-79	U.S. born Hispanic (49%) Foreign born Hispanic (51%)	10 SBP, DBP, Waist-hip circumference ratio, TC, HDL, TC/HDL ratio, IL-6, CRP, Albumin, Estimated creatinine clearance	Age, Birthplace, Sex, Educational attainment, Household income, Language preference	AL associated with obesity in foreign and U.S. born groups ↑ AL associated with current smoking in foreign born Hispanic people ↑ AL associated with ↑ odds ratio of engaging in one and two unhealthy behaviors ↑ AL associated with follow-up depressive symptoms	High unhealthy behaviors associated with follow-up depressive symptoms Participants with depressive symptoms at baseline more likely to have follow-up depressive symptoms Individuals that report more depressive symptoms at follow-up: − 80 + years of age - Men - College or higher education U.S. born − 9th grade-high school education foreign born
(Roepke et al., 2011)	American Spousal caregivers of patients with Alzheimer's and non-caregiving controls	130	88 F 42 M	Caregivers 74.3 7.80 N/A Non-caregivers74.9 6.80 N/A	Caregivers:White (95.4%) Non-caregivers: White (88.4%)	10 SBP, DBP, BMI, TC/HDL ratio, HDL, Plasma norepinephrine, Plasma epinephrine, DHEA-S, HbA1c, Urinary cortisol	Age, Sex, Years of participants smoking history, Antihypertensive drug use, Cholesterol-lowering drug use	↑ AL in men ↑ AL in caregivers relative to non-caregivers when ↑ mastery ↑ AL with ↓ Depression	Higher depressive symptoms, less mastery and overload among caregivers
(Rosemberg et al., 2019)	American	49	F	40.0 11.0 21-59 100%	White (0.06%) Black (28.6%)Hispanic (55.1%) Native American/ Alaska Native/ Asian (0.04%) Mixed (0.04%)	9 Serum CRP, HDL, HbA1c, Cortisol, SBP, DBP, HR, Waist-to-hip ratio, HR, BMI	Age, Foreign born, Marital status, Education level, Hourly wage, Insurance	↑ AL among housekeepers experiencing ↑ job strain ↑ AL among housekeepers with at least one chronic disease	↑ Job strain and daily discrimination have medium to large size effects on AL Housekeepers with at least one chronic disease have ↑ AL
(Savransky et al., 2018)	American Schizophrenic (SZ) patients and controls	92	31 F 61 M	Healthy controls 35.26 14.03 N/A Schizophrenia 36.13 14.33 N/A	N/A	13 SBP, DBP, BMI, Waist-to-hip ratio, HR, HDL, TC, HbA1c, CRP, DHEA, Epinephrine, Norepinephrine, Cortisol, HR	Age, Sex, Metabolic syndrome	↑ AL in SZ relative to healthy controls ↑ AL among men and women SZ relative to healthy controls ↑ AL in SZ with more than 5 years duration of illness relative to healthy controls ↑ AL among chronic SZ ↑ AL in early stage, but not chronic SZ ↑ AL with ↓ positive symptoms in early stage patients AL ↑ with earlier	↑ Immune subcomponent in early stage SZ

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Authors	Nationality	*N*	Sex F/M	Age *M* *SD/SE* Range	Race/Ethnicity	# AL Biomarkers	Covariates/ Adjustments	AL Main Findings	Additional Associations
								age of illness onset	
(Schenk et al., 2018)	Netherlands	45,225	26,408 F 18,817 M	45.0 11.9 N/A	N/A	12 CRP, SBP, DBP, HR, TC, Triglycerides, LDL, HDL, Albumin, Glucose, HbA1c, Waist circumference	Age, Sex, Negative affect, Health behaviors	↑ AL with ↓ positive affect in MDD, Somatic disease, and healthy controls Association between AL and positive affect stronger among women Health behaviors associated with AL ↑ AL ↓ negative affect except among MDD	N/A
(Schnorpfeil et al., 2003)	German Employees of a manufacturing plant for airplane parts	324	N/A	N/A	N/A	14 SBP, DBP, Waist-hip ratio, BMI, TC, HbA1c, Urinary cortisol, Urinary norepinephrine, Urinary epinephrine, Urinary albumin, CRP, TNF-α, HDL, DHEA-S	N/A	↑ AL in men ↑ AL with ↑ job demands	N/A
(Seeman et al., 2002)	American WLS cohort MAC cohort	106,765	49 F 57 M 389 F 376 M	58.5 0.80 58-59 74.2 2.80 70-79	White (100%) White (81.7%)	10 SBP, DBP, Waist-hip ratio, HDL, TC, HbA1c, DHEA-S, Urinary cortisol, Urinary Norepinephrine, Urinary epinephrine	N/A	Cardiovascular components contribute to AL among men, whereas neuroendocrine components contribute to AL among women WLS cohort: "Intellectual/ recreational" interactions were associated with significant AL differences for women, whereas low *vs.* high "mother caring" was marginally significant for men↑ Positive relationship pathways with ↓ mean AL scores (significant for women and marginally significant for men) MAC cohort:↑ Social ties with ↓ AL scores (significant for men, not for women)↑ Emotional support with ↓ AL (significant in men, not in women) ↑ Criticism/	N/A

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Authors	Nationality	*N*	Sex F/M	Age *M* *SD/SE* Range	Race/Ethnicity	# AL Biomarkers	Covariates/ Adjustments	AL Main Findings	Additional Associations
								demands from one's spouse with ↑AL for both men and women ↑ Social integration with ↓ AL for both men and women ↑ Emotional support with ↓ AL (significant in men, not in women) ↑ Negative interactions with family with ↑ AL score for both men and women	
(Sjors et al., 2013)	Swedish	170	87 F 83 M	N/A	N/A	13 BMI, Waist-to-hip ratio, SBP, DBP, HDL, TC/ HDL ratio, LDL, Triglycerides, CRP, Insulin, Glucose, HbA1c, Cortisol	Age, Antidepressant use	Significant difference between patients and controls in glucose for both men and women (stronger effect in women)	↓ Plasma glucose concentrations among women non-users relative to women antidepressant users
(Smith et al., 2009)	American	182	145 F 37 M	50.7 8.70 26-69	White (100%)	12 SBP, DBP, CRP, Albumin, IL-6, Aldosterone, Waist-to-hip ratio, Urinary cortisol, DHEA-S, Epinephrine, Norepinephrine	Age, Sex, BMI, Fatigue status	No sex differences in AL ↑ Age with ↑ AL The T allele of ACE rs4968591 was associated with an ↑ AL	Level of CRP and urinary cortisol varied significantly by genotype only among women
(Soltani et al., 2018)	American	N/A	F	N/A N/A 20-64	N/A	10 Urinary cortisol, Urinary epinephrine, Urinary norepinephrine, SBP, DBP, Waist-to-hip ratio, HDL, TC, DHEA-S, HbA1c	Age, BMI, Education level	↑ Healthy eating index for sodium consumption with ↓ in AL, independently of diet group DGA diet with ↑ in AL and TAD diet with ↓ in sodium consumption	↑ Healthy eating index for vegetable consumption with ↓ in perceived stress, independent of diet group
(Song et al., 2014)	American MIDUS	76	46 F 30 M	55.11 11.13 36-83	N/A	11 SBP, DBP, HDL, TC/HDL ratio, HbA1c, Waist-to-hip ratio, Urinary cortisol, Norepinephrine, Epinephrine, Serum DHEA, CRP	Age, Sex, Smoking status, Negative affect	Fathers had ↑ AL than mothers Older parents had ↑ AL Among parents of children with developmental disorder, ↓ reported level of positive affect had ↑ AL	Significant parenting status × positive affect interaction.
(Sun et al., 2007)	Chinese Employees	1,219	585 F 634 M	38.08, 9.17 23-58	N/A	13 BMI, Waist-to-hip ratio, SBP, DBP, HbA1c, IGR, Triglycerides, TC/HDL ratio, Fibrinogen, CRP, Urinary cortisol, Adnephrin	Age, Sex, Education level, Marital status, Smoking status, Alcohol consumption, Exercise	The strength and the type of association between job stress and AL differed by sex Men scored ↑ on the secondary cardiovascular and metabolic health outcomes The associations appear to have been greater in the	N/A

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Authors	Nationality	*N*	Sex F/M	Age *M* *SD/SE* Range	Race/Ethnicity	# AL Biomarkers	Covariates/ Adjustments	AL Main Findings	Additional Associations
								primary biological parameters for females Men scored ↑ on the total AL score Decision latitude was negatively and job demands were positively related to AL Individuals with type A personality had a ↑ AL score ↑ AL with ↑ age ↑ AL with ↓ educational level	
(Tampubolon and Maharani, 2018)	American The U.S. Health and Retirement Study English The English Longitudinal Study of Aging	15,583 14,765	8,796 F 6,787 M 8,044 F 6,721 M	N/A	N/A	8 SBP, DBP, HbA1c, TC/HDL ratio, Waist circumference, cystatin C, CRP 10 SBP, DBP, HbA1c, TC/HDL ratio, Waist circumference, BMI, Triglycerides, Fibrinogen, CRP	Age, Sex, Height, Medication use	Female have ↓ AL than male before 70 years in ELSA and 80 years in HRS, but after female have ↑ AL Female have ↓ AL throughout later life Married, better-educated, and wealthy participants have ↓ AL AL ↑ with age AL ↓ with ↑ rigorous physical exercise AL ↑ with ↑ comorbidities	N/A
(Tanner Stapleton et al., 2016)	American CCHN cohort	163	F	N/A	N/A	10 BMI, Waist-to-hip ratio, SBP, DBP, HR, CRP, HbA1c, HDL, TC/HDL ratio, Diurnal cortisol	Race/ethnicity, Poverty	AL is positively associated with four preliminary CCHN Life Stress Interview domains (neighborhood, family, partner relationship, and co-parenting with baby's father), and not associated with two (no partner and co-parenting with a new partner)	The CCHN LSI demonstrated consistent, moderate positive associations with several well-validated measures of stress All domains ratings on the LSI were significantly associated with all three indicators of mental health, with the exception of co-parenting with a new partner
(Tomasdottir et al., 2015)	Norwegian The Nord-Trondelag Health Study (HUNT)	37,612	20,338 F 17,274 M	N/A N/A 30-69	N/A	12 Waist-to-hip ratio, BMI, SBP, DBP, Pulse pressure, CRP, TC, Non-fasting glucose, Creatinine, HR, Height, Waist	Age, Sex	The mean values of 8 of the 12 allostatic parameters differed according to the participants' description of their childhood Women reporting a difficult childhood had ↑ non-fasting blood glucose, but not men Men had a significant trend towards ↓ diastolic	The prevalence of individual disease ↑ with ↑ degrees of childhood difficulty for all diseases except hypertension and cancer

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Authors	Nationality	*N*	Sex F/M	Age *M* *SD/SE* Range	Race/Ethnicity	# AL Biomarkers	Covariates/ Adjustments	AL Main Findings	Additional Associations
								blood pressure, but not women	
(Turner et al., 2016)	American	1,252	588 F 664 M	45.98 N/A N/A	White (53%) Black (47%)	10 Epinephrine, Norepinephrine, Cortisol, DHEA-S, SBP, DBP, TC, HDL, HbA1c, Waist-to-hip ratio	Probability of inclusion in the study	Men and Black people have a ↑ risk as estimated by AL Only parental occupational level and the stress dimensions of adult trauma and chronic stress significantly predicted AL AL is predicted by childhood socioeconomic position, but not by childhood trauma	Childhood socioeconomic position is negatively associated with poor health Childhood trauma is positively associated with poor health
(von Thiele et al., 2006)	Swedish Female employees of two public health care organizations	241	F	N/A	N/A	13 SBP, DBP, HR, HDL, LDL, LDL/HDL ratio, Waist-to-hip ratio, TC, Triglycerides, Glucose, HbA1c, Prolactin, DHEA-S	Age, Education level, Children living at home	Both age and cluster membership (recovered, non-recovered, or fatigued) reliably predicted the odds of ↑ AL ↑ Age increases the risk of ↑ AL and was associated with worse values on all biomarkers (except HR)	N/A
(Westerlund et al., 2012)	Swedish The Northern Swedish Cohort	673	343 F 330 M	N/A	N/A	12 SBP, DBP, BMI, Waist circumference, Fasting glucose, TC, HDL, Triglycerides, Apo A1, Apo B, CRP, Cortisol	Sex, SES	Adversity in adolescence was positively associated with AL in women but not in men but became not significant also in women after inclusion of the interaction between adversity in adolescence and job strain Job strain is associated with ↓ AL in men but not in women Women and men did not differ significantly in AL	Adversity in adolescence was negatively associated with SES and positively associated with job strain at age 43 in women, but not in men
(Ye et al., 2017)	Chinese Women with metastatic breast cancer	226	F	N/A	N/A	14 BMI, Waist-to-hip ratio, Resting HR, Standard deviation of R-R intervals, SBP, DBP, White blood cell count, Red blood cell count, Hemoglobin, Serotonin, Cortisol, CRP, IL-6, CD4+/CD8+	N/A	Participants in the Intervention Group (IG) determined as "Resilient" (i.e. from normal to high and back to normal in a short time) and a Control Group (CG) did not differ in AL	More participants exhibited "Resilient" types in IG than in CG on anxiety instead of depression

depressive symptoms among women but not men (Gillespie et al., 2019). Identifying sex differences in (sub)clinical biomarker thresholds will help us better explain individual differences in allostatic load (Juster et al., 2016a; Seplaki et al., 2005). Critically, delineating which subjective measures of mental health correlate the most with objective measures of allostatic load will be helpful in future research.

3.5.2. Sociodemographic and psychosocial factors

3.5.2.1. Age. Increased age is a consistent predictor of allostatic load for both sexes (Bellingrath et al., 2009; Chen et al., 2014; Juster et al., 2013a; Mauss et al., 2015; Sun et al., 2007). One study found that earlier age of menarche was also associated with increased risk of showing elevated allostatic load (Allsworth et al., 2005). Critically, allostatic load levels also vary *between and within* men and women of diverse age strata (Juster et al., 2013a; Tampubolon and Maharani, 2018; von Thiele et al., 2006) but also as a function of exposures to chronic stressors throughout lifespan development. In summary, increased age is one of the most important predictors of allostatic load; however, allostatic load is amplified by interactions between age and many other factors described below that differ by sex/gender.

3.5.2.2. Early adversity. Early adversity is related to allostatic load. In particular, childhood abuse and neglect have been associated with higher allostatic load among middle aged women (Horan and Widom, 2015). In another study, experiencing two or more categories of childhood sexual assault was associated with higher allostatic load among women and allostatic load scores greater than 2 were positively associated with pain symptoms (Beckie et al., 2016). In yet another study, women who reported childhood sexual assault showed higher total cholesterol, LDL cholesterol, triglycerides, and hair cortisol (Groer et al., 2016). Women who report childhood sexual abuse are also at higher risk of being unemployed, disabled or financially supported by someone else (Groer et al., 2016). Importantly, these factors may act as chronic stressors that contribute to higher allostatic load and disease risk from early life onwards. In line with this, women who experience adversity during adolescence show higher allostatic load relative to men. In addition, this trajectory is predicted by socioeconomic status-related risk in adulthood in women but not men (Westerlund et al., 2012). In conclusion, the associations between early adversity and allostatic load appears to be stronger among women.

3.5.2.3. Race and ethnicity. Associations between allostatic load and health outcomes differ between men and women as well as in interaction by race and ethnicity. For example, the prevalence of high allostatic load scores (e.g., ≥3 AL score) and the strength of associations between allostatic load biomarkers and depressive symptoms differs as a function of sex, but also race/ethnicity (Bey et al., 2018a; Bey et al., 2018b; Brody et al., 2013; Chen et al., 2014; Chyu and Upchurch, 2011; Hux et al., 2017; Turner et al., 2016). Specifically, large epidemiological studies have shown higher allostatic load in Black (26.3%) and Hispanic (20.3%) Americans when compared to White (17.7%) and other race/ethnic groups (13.8%) (Chen et al., 2014).

Sex and race/ethnic differences also vary considerably when assessing individual biomarkers in relation to psychiatric symptoms. For instance, increased levels of C-reactive protein are associated with increased odds of depression among White, but not Black women (Bey et al., 2018b). Moreover, allostatic load was positively associated with depression only in White women and Black men (Bey et al., 2018a). Importantly, *intersectionality* (e.g., bearing more than one marginalized status) also influences allostatic load. That is, Black women show higher allostatic load when compared with non-Black women (Hux et al., 2017). The compounding of multiple minority identities creates unique sources of stress and stigma that increase allostatic load.

In line with an intersectional perspective, one study found that relative to White women, Black women showed increased grade of membership for higher allostatic load (Bey et al., 2018b). Moreover, another study found the Black women aged 40–49 years old and White women aged 50–59 exhibited similar allostatic load levels, suggesting a 10-year precarious physiological 'wear and tear' among Black women (Chyu and Upchurch, 2011). Furthermore, allostatic load was significantly associated with depression among White women and Black men, but this gradient was not found among other groups (Bey et al., 2018b). Taken together, these findings on sex and race/ethnicity supports an intersectionality hypothesis, whereby bearing multiple minority statuses exerts additively or multiplicatively higher strain that contribute to allostatic load. Considering more environmental and macro-level factors will help us better explain intersectional gradients in allostatic load, health, and wellness. In conclusion, Black women show higher risk for elevated allostatic load in comparison to other race and ethnic groups.

3.5.2.4. Place of birth and nativity. Broader macro-level socio-cultural factors vary as a function of geopolitical context and act as drivers of social and health inequalities among men and women. For example, an individual's country of birth will be inherently different in socio-cultural factors like legislation, education, policies, political climate, and forms of structural stigma that collectively modulate allostatic load. For example, one study showed that allostatic load was highest among Russians followed by American and Taiwanese citizens, respectively (Glei et al., 2013a). Importantly, a subsequent study from this cohort found sex differences in the associations between levels of perceived stress and allostatic load with regards to country of birth. Specifically, perceived stress was associated with allostatic load among Russian men and women, while this was only the case for American women and not for Taiwanese men and women (Glei et al., 2013b).

Beyond one's country of birth, studies have shown that nativity influences allostatic load gradients. For example, one study showed that Hispanic Americans who were not born in the US had higher allostatic load than those who were born in the US (Chyu & Upchurch, 2011). While purely speculative, immigration may preclude harmful effects of country-specific chronic stressors (e.g., political climate, socioeconomic status, political turmoil, wars), while also representing an important stressor in itself through the challenges of acculturation. In conclusion, place of birth and nativity are important factors that influence allostatic load.

3.5.2.5. Personality traits. Personality traits can also influence an individual's threat perception and hence modulate how chronic stress affects health (Lazarus and Folkman, 1984). As such, conscientiousness has been negatively associated with allostatic load among women (Christensen et al., 2019). Conversely, one study has shown increased allostatic load in workers with type A personality (Sun et al., 2007), as well as women with both high self-control/competence and socioeconomic status-related risk (Brody et al., 2013). This suggests differential psychosocial pathways through which personality traits may modulate both physiological and behavioural responses. However, more research is needed to explain how personality traits relate to sex and gender in the allostatic load literature.

3.5.2.6. Gender-roles. The past half century has been pivotal in the advancement of women's rights. As such, women now represent nearly half the labour force in most industrialized countries. However, societal expectations regarding the endorsement of masculine and/or feminine gender-roles influence a person's likelihood of engaging in caregiving, child rearing and home responsibilities. Moving from traditional family structures where men were 'breadwinners' and women 'caretakers' toward modern, dual earner family structures can lead to role stress, which may strain health differently for men and women (Lundberg, 2005). In order to break glass ceilings and social inequalities worldwide, women have had to appropriate and enact masculine-typed gender-roles, which reflect attitudes and behaviors (e.g.,

assertiveness, leadership, dominance) that were once typically endorsed more by men (Juster et al., 2016a; Juster et al., 2016d).

Central to research conducted by our group, we found that gender-roles influenced allostatic load and health outcomes differently among men and women. For example in small study, masculinity was positively associated to higher allostatic load among men and women; however, severity of pain symptoms was higher among high masculine women when compared with men (Juster and Lupien, 2012). Moreover, androgyny – that is, simultaneous endorsement of both highly masculine and high feminine gender-roles – exerts protective effects on mental health, independent of one's sex (Juster et al., 2016a). Specifically, androgynous men and women show lower severity of depressive symptoms, while reporting higher degrees of well-being and self-esteem. However, this study by our group also showed that androgynous gender-role profiles only had beneficial effects on allostatic load for working men, as this effect was not found among working women with different gender-role profiles (Juster et al., 2016a). In conclusion, exploring more macro-level gender factors at work and at home should help better explain allostatic load gradients among working men and women (Juster et al., 2019).

3.5.2.7. Workplace stress and occupational status. Chronic exposure to adverse psychosocial work characteristics (e.g., job strain, effort-reward imbalance) also has deleterious effects on physiological functioning and health (Mauss et al., 2015). Importantly, work-related stressors affect working men and women's health in ways that differ considerably across the world. Indeed, the workplace stress literature on allostatic load is well represented internationally. This may partially explain why associations between job strain and allostatic load are inconsistently reported, since working conditions differ makedly.

Perceiving higher levels of workplace stress has been associated with higher allostatic load. This appears to be specific to men who perceive higher workplace stress when compared with women (Mauss et al., 2015). Another study found that job strain was positively associated with allostatic load among men but not women (Schnorpfeil et al., 2003). Consistent with this finding, two studies showed that decisional latitude was negatively associated with allostatic load in working women and men (Juster et al., 2013a; Sun et al., 2007). However, increased psychological demands have been shown to have protective effects on allostatic load among women, whereas it had damaging effects for men.

At the individual level of workplace overcommitment, higher effort-reward imbalance has been associated with higher allostatic load in German schoolteachers (Bellingrath et al., 2009). Moreover, occupational status - a measure of attainment and prestige related to one's position in the workplace hierarchy - affects allostatic load differently across men and women of diverse age groups (Juster et al., 2013a). That is, higher occupational status and increased psychological demands in the workplace were associated with lower allostatic load among women. Nevertheless, women are still more frequently found in occupations of lower occupational status, which may hinder women's health (Kroger, 2016). In addition to this, however, seemingly positive psychosocial work characteristics, such as more meaningful work and higher perceived work-related rewards have been shown to be associated with increased allostatic load in women but not men (Dich et al., 2019). In conclusion, sex differences in workplace stress are related to allostatic load; however, associations are not uniform and generally do not consider home and family factors that might compound gendered stress.

3.5.2.8. Socioeconomic status. Individual-level factors related to socioeconomic status modulate allostatic load and health in men and women across studies. The most consistent effect is related to education. For example, lower educational attainment (Christensen et al., 2019; Hux et al., 2017) is associated with higher allostatic load among women or for both sexes (Chen et al., 2014; Gale et al., 2016; Hawkley et al., 2011; Sun et al., 2007; Tampubolon and Maharani, 2018). Similarly, but less often shown, lower income is associated with higher allostatic load. Early life socioeconomic conditions can also exert long-term effects. For example, lower paternal occupational status is associated with lower subjective health, but not with allostatic load (Barboza Solis et al., 2016). Parental socioeconomic disadvantage can even predict decreased processing speed in adolescence (Gale et al., 2015). These effects can be pernicious (Turner et al., 2016): lower socioeconomic status in adolescence and in adulthood was associated with increased allostatic load in Swedish women (Gustafsson et al., 2011). In conclusion, lower socioeconomic status is related with higher allostatic load.

3.5.2.9. Interpersonal factors. An extensive body of literature has shown that marital status and caregiving responsibilities (e.g., child rearing, spousal care) affect health and wellness (Roepke et al., 2011). Importantly, these associations appear to have a stronger influence on women's health. Specifically, being married or living with a partner is associated with lower levels of allostatic load among women (Chen et al., 2014; Chiu and Lin, 2019; Tampubolon and Maharani, 2018). By contrast, individuals who are widowed, separated or divorced show higher allostatic load (Chen et al., 2014). This effect may be modulated by perceived social support, which has beneficial effects on allostatic load for both the sexes (Seeman et al., 2002). Notwithstanding, providing additional socioeconomic or psychosocial resources for divorced women should help partially alleviate strain on health.

On the other hand, caring for a spouse or children with poor health has also been associated with higher allostatic load among women (Chiu and Lin, 2019; Glover et al., 2006). Specifically, caring for a spouse with poor health had an effect that was dependent on the spouse's health status remaining poor or not over time (Chiu and Lin, 2019). An important increase in child rearing and household responsibilities is seen among men; nevertheless, women still carry a greater part of this burden. Importantly, one study showed that higher caregiving burden was associated with higher allostatic load and this effect was stronger among people with high job strain, although this interaction did not attain significance thresholds (Dich et al., 2015c). In conclusion, social support and gendered responsibilities may be appropriated differently from women in ways that intersect with additional stressors related to caregiving and workplace stress.

3.5.2.10. Health behaviors. Chronic stress and unhealthy behaviors synergistically exert *wear and tear* on the brain and body to increase allostatic load (for a recent systematic review on allostatic load and health behaviors, see Suvarna et al., 2020). Critically, gendered sociocultural expectations may modulate an individual's propensity to engage in unhealthy behaviors and therefore contribute to health inequalities in men and women. In this systematic review, we found that associations between unhealthy behaviors and allostatic load were generally stronger among men when compared with women (Gustafsson et al., 2011). The following describes some findings related to sleep, medication use, nutrition, and smoking.

Prevalence of sleep disorders is higher among women when compared with men and higher allostatic load is found among individuals diagnosed with poor sleep quality and/or sleep disorders (Chen et al., 2014; Ellis et al., 2019; Hux et al., 2017). Importantly, this may disproportionately predispose women to increased disease risk. Importantly, sex differences in sleep-wake cycles differ across age groups and are influenced by sex hormones, such as estrogen, testosterone and progesterone (Carrier et al., 2017). To date, however, sleep behaviors have yet to be studied objectively in the allostatic load literature.

Medication use is often used as an exclusion criterion or as a covariate in psychoneuroendocrine studies of stress (Kerr et al., 2020). In one study, antidepressant users showed lower plasma glucose levels than non-users and this effect was stronger among women when compared with men (Sjors et al., 2013). In a recent study by our group, we

found that psychotropic medication users showed higher allostatic load in a sample of psychiatric hospital workers (68% women) (Kerr et al., 2020). Critically, a secondary finding from this study supported the notion that psychotropic medication use was more likely to occur among women but was also associated with higher feminine gender-roles, independent of sex. Because women are at higher risk of developing specific somatic and/or psychiatric pathologies, it is important to understand how pharmacological treatment relates to sex and gender differences in allostatic load and health.

Studies have also shown that healthy food intake is associated with decreased allostatic load among men and women (Hampson et al., 2009; Soltani et al., 2018). Moreover, smoking status is frequently entered as a covariate in analyses because of their well-documented effects on stress physiology (Hampson et al., 2009; Rodriquez et al., 2018). Alcohol consumption does not appear to be consistently damaging in the allostatic load literature, but more research is needed. In conclusion, health behaviors are important to consider in allostatic load studies.

4. Discussion

The aim of this systematic review was to (1) synthesize literature on sex differences in allostatic load and brain health as well as (2) identify pathways specific to women. In line with recommendations to disaggregate analyses by birth-assigned sex (Clayton and Tannenbaum, 2016), we searched for allostatic load studies that provided sex-specificity and that therefore included women. First, we find evidence that allostatic load is higher among men; however, this result may be confounded by measurement issues that we will discuss. Second, certain causes and consequences of allostatic load show patterns that are specific to women but not men. In the spirit of this Special Issue on Women's Brain Health, we discuss our general findings and propose recommendations for future research on allostatic load that consider sex and gender together.

This systematic review has several limitations that warrant discussion outright. First at a review-level, many allostatic load studies were not included in our review simply because our search strategy was specific to psychosocial and psychiatric variables (see Supplementary Materials for all search criteria and results). This was done in order to tailor results to this Special Issue on Women's Brain Health. As such, the vast majority of allostatic load studies focus on physical health that do indeed assess sex differences of sex-specific associations that were not retrieved as part of our search strategy. This therefore also creates a report bias in our systematic review that could be expanded upon in future reviews that assess sex/gender differences more broadly. We believe that the time has come for a meta-analysis of sex differences in the allostatic load literature as they related to both physical and mental health.

4.1. Sex and allostatic load

The first objective of this systematic review was to identify whether allostatic load is higher or lower among women compared to men in studies assessing brain health. Among those studies that accounted for sex as a factor, seven studies found no differences (Brody et al., 2013; Chen et al., 2014; Christensen et al., 2019; Glei et al., 2013b; Gustafsson et al., 2011; Smith et al., 2009; Westerlund et al., 2012) and nine studies showed that women had lower allostatic load than men (Carlsson et al., 2017; Dich et al., 2015b; Dich et al., 2015c; Gale et al., 2015; Hawkley et al., 2011; Juster et al., 2016a; Kinnunen et al., 2005; Roepke et al., 2011; Schnorpfeil et al., 2003). While men appear to have higher allostatic load than women in studies with sex differences, more evidence is required since there is nearly equal evidence that allostatic load does not differ by sex. Moreover, few studies report the effect sizes of sex differences. More generally, analytic strategies that include stratification of statistical analyses based on biological sex are rarely implemented in psychoneuroendocrine research (Galea et al., 2017). As we will describe below, we argue that allostatic load formulations that do not account for sex differences in biomarker distributions may be lacking in sensitivity to identify meaningful results.

4.2. Gender and allostatic load

Beyond sex differences in allostatic load, our second objective was to identify within-gender or sex-specific variation among women. Of the 62 studies reviewed (see Table 1), there is considerable evidence of female-specific associations regarding the causes and consequences of allostatic load. Take for example poorer subjective health that is associated with higher allostatic load and is predictive of physical frailty for men and women (Barboza Solis et al., 2016; Ding et al., 2017). Interestingly among women, impaired immune functioning (Barboza Solis et al., 2016) and neuroendocrine functioning (Kinnunen et al., 2005) appeared to better account for the aforementioned associations. Other examples identified in our review are depressive, psychosomatic, and traumatic symptoms in women in relation to allostatic load.

We argue that it may be necessary to breakdown which systems or clusters of biomarkers drive associations among women. This has been explored by others in studies applying more sophisticated statistics to understand the factor structure of allostatic load (Wiley et al., 2016). We suggest that future studies apply greater delineation of sex-specific pathways for health conditions that appear to disproportionately affect more women than men (e.g., pain, depression). In addition, identifying which psychosocial factors are most strongly associated with mental health and allostatic load among women will help us identify modifiable factors to intervene. Lastly, one of the most important observations in this systematic review is that sex is often treated only as a covariate in statistical models which is limiting. In the following sub-sections, we will provide recommendations based on our interpretation of the systematic review and our reflections.

4.2.1. Sex-specific allostatic load formulation

It is highly likely that sex differences in allostatic load have not been previously identified because of the way allostatic load is calculated without regard for sex-specific biomarker variation. In general, the traditional count-based formulation uses high-risk cut-offs based on a given sample's biomarker distribution for both men and women together. Depending on the research questions, this might be problematic when we consider that the sexes differ in their values for many individual biomarkers. Applying sex-specific biomarker cut-offs have been suggested (Juster et al., 2016a; Seplaki et al., 2005); however, this formulation is very rarely applied in the allostatic load literature. We therefore recommend that studies apply sex-specific allostatic load calculations for studies deriving cut-offs on the sample's distribution. Future allostatic load studies should consider sex-specific formulations as an alternative approach that need not necessarily replace other approaches. One can think of this as a sensitivity analysis to ensure that sex-specific effects are not ignored. This will ensure that allostatic load algorithms represent biomarker variation specific to the sexes. In addition, applying a sex-specific allostatic load algorithm will allow for greater understanding of within-sex variation related to socio-cultural gender (Juster et al., 2016a).

4.2.2. Intersectionality

In addition to sex-specific allostatic load formulations, it could be informative to also consider variation by age, race/ethnicity, and other sociodemographic factors in the calculation of allostatic load. For example, allostatic load sex differences are also influenced by age differences (Juster et al., 2013a; Tampubolon and Maharani, 2018; von Thiele et al., 2006) and race/ethnic differences (Bey et al., 2018b; Hux et al., 2017). These sub-group differences are consistent with an intersectional framework that could be applied to the conceptualization of allostatic load. As stated in our Introduction, *intersectionality* is a

research framework that recognizes how individuals are members of multiple social groups with diverse identities that collectively influence health and wellness (Johnson et al., 2011). Intersectionality could therefore be used conceptually to inform the calculation and measurement of allostatic load, for instance, by using formulations that combine sex-, age-, race/ethnic-specific cut-offs.

On the other hand, intersectionality as a philosophical framework may have more relevance in understanding the broader socio-cultural causes of allostatic load. Indeed, intersectional theory was originally conceptualized to represent the multidimensional nature of intersecting identities such as the compounding discrimination faced by Black women (Crenshaw, 1989). Our review clearly provides evidence for an increased allostatic load among this population and therefore provides evidence for intersectionality. In terms of international generalizability, note that European allostatic load studies rarely report on race or ethnicity, which is not the case in North American studies. Taken together, differences among the sexes clearly *intersect* according to age cohorts, race/ethnicity, socio-economic status, culture, and geographic locations that require further study.

4.2.3. Lifespan development and health behaviors

Allostatic load among women is shaped by a myriad of factors spanning the life course. Early life adversities such as childhood abuse (Horan and Widom, 2015) and sexual assault (Beckie et al., 2016; Groer et al., 2016) are associated with allostatic load later on in adulthood. Sadly, these early life adversities can shape socio-economic patterns in adulthood in a manner that is especially problematic for women (Groer et al., 2016; Gustafsson et al., 2011; Westerlund et al., 2012). For example, women who receive less education appear to experience disproportionately higher allostatic load than men (Chen et al., 2014; Gale et al., 2016; Hawkley et al., 2011; Sun et al., 2007; Tampubolon and Maharani, 2018). In working adulthood, women are exposed to different occupational stressors that are distinctly related to allostatic load and mental health (Bellingrath et al., 2009; Dich et al., 2019; Juster et al., 2013a; Mauss et al., 2015; Schnorpfeil et al., 2003; Sun et al., 2007).

The sexes also appear to engage in health behaviors differently such as rates of smoking (Hampson et al., 2009; Rodriquez et al., 2018) or medication use (Kerr et al., 2020). As yet another example, sleep problems are higher among women and related with higher AL (Chen et al., 2014; Ellis et al., 2019; Hux et al., 2017). By contrast, healthy diets are associated with lower allostatic load among both sexes (Hampson et al., 2009; Soltani et al., 2018). Allostatic load and health behaviors synergize each other (Suvarna et al., 2020). Future research would should combine information on lifespan development and health behaviors in sex-specific analyses.

4.2.4. Sex- and gender-based analysis

Health inequalities among the sexes have compelled federal granting agencies to promote the inclusion of sex as a biological variable and gender as a socio-cultural variable in health research (Johnson et al., 2014; Sharman and Johnson, 2012; Tannenbaum et al., 2019). This has simply made for better science and practice. Disentangling the effects of biological factors that differ between the sexes (e.g., sex hormones) has been underlined in particular as an important area of investigation to better explain inconsistencies found in studies linking physiological stress biomarkers to adverse health (Juster et al., 2016b; Marrocco and McEwen, 2016). This is complimented by research that assesses socio-cultural gender factors as well. Research that includes both sex and gender together (Clayton and Tannenbaum, 2016) will further refine our understanding of the mechanism whereby allostatic load relates to health inequalities.

A sex- and gender-based approach provides a powerful framework to help solve health problems that cannot be easily explained by focusing solely on binary sex differences. Our group has shown that gender-role profiles based on masculine and feminine dimensions are related to allostatic load in sex-specific ways (Juster and Lupien, 2012; Juster et al., 2016a). That is, women with high masculinity have high allostatic load and psychosomatic complaints, while androgynous men (high masculinity and high femininity) show low allostatic load. The latter finding was only possible by using a sex-specific allostatic load formulation. This provides the first evidence for a sex- by gender interaction and supports our recommendation for the use of sex-specific allostatic load formulations when aiming to understand sex/gender-specific variation (Juster et al., 2019).

Recommendations for applying a sex- and gender-based analysis (Johnson et al., 2007) that can be adapted to allostatic load research could include: (1) revisiting and reanalyzing existing data by performing secondary analysis such as assessing sex differences and by disaggregating significant associations by sex in order to identity sex-specific effects (Tannenbaum, 2020); (2) refining an existing research design by including additional measures that represent sex (e.g., sex hormones) and gender (e.g., gender identity, gender roles); and (3) ensuring that sex and gender are considered from the very beginning of the research design. This systematic review provides clear support for the importance of both sex and gender in allostatic load research. Because we are at the very beginnings of this field, we will need great effort from future allostatic load researchers to further integrate sex or gender in their research.

Future allostatic load studies will need to further nuance socio-cultural gender measures in particular. There is especially a need for allostatic load research that investigates gender identity (Rich et al., 2020). To date, there are no published works that assess allostatic load among transgender and gender diverse people; however, this is currently in development (Dubois, 2012; DuBois et al., 2017; Rich et al., 2020). Orthogonal to gender but still related, sexual orientation is also related to sex-specific differences in allostatic load. Here, it seems that gay men show low allostatic load compared to heterosexual men but bisexual men show the highest allostatic load (Juster et al., 2013b; Mays et al., 2018). Note that these studies did not find sexual orientation differences in allostatic load among women nor did they tease apart what psychosocial factors could explain these within-sex/gender associations. At an interpersonal level, *gender relations* refer to dynamics among men, women, and gender diverse people that also appears to be indirectly related to allostatic load. For example, marital status (Chen et al., 2014; Chiu and Lin, 2019; Tampubolon and Maharani, 2018), caregiving (Chiu and Lin, 2019; Glover et al., 2006), and social support (Seeman et al., 2002) are all related to sex-specific patterns of risk or protection to allostatic load. We encourage researchers to be creative and resourceful in measuring gender and applying it to the study of allostatic load.

4.3. Conclusions

Our systematic review provides preliminary evidence for sex differences and gender diversity in allostatic load and mental health research. While men seem to have higher allostatic load than women, women show considerable gender-based variation related to numerous stress-related factors. With regards to health behaviors, smoking status was exclusively assessed for cigarette smoking; however, this could be expanded to other substances, such as cannabis and their effects on the endocannabinoid system which has been shown to interact with HPA-axis responses in animal studies (Evanson et al., 2010).

It is important to underline, that our search results may have been biased because we did not inquire our network for unpublished data that could have reported sex differences in allostatic load. Indeed, some authors may have performed analyses to investigate sex differences that were not reported. Because of positive publication biases, these may have not been included in the published literature. Also, some articles identified in our search did report sex differences – nevertheless, they did not correspond to other inclusion criteria and were therefore not reported in our systematic review. Studies included in our systematic

review also rarely reported effect sizes when stating sex differences and therefore, this limits our understanding of the significance of these differences and should be addressed in future studies investigating sex differences in allostatic load and health.

In conclusion, we have provided recommendations for approaches to further tease apart the role of sex and gender on allostatic load and brain health. The reviewed studies applying a gendered lens to the study of allostatic load are promising; however, researchers will need to develop creative ways to measure sex, gender and sexuality in diverse ways to further expand this emerging field. At the very minimum, future allostatic load studies should endeavour to treat sex as more than a covariate since this provides limited insights into elusive health pathways.

5. Dedication

We wish to dedicate this work to our dearly departed colleague and mentor Bruce S. McEwen who has shaped this field and the careers of exceptional scientists of both sexes and many genders.

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Appendix A. Supplementary material

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