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Sociodemographic, behavioral and genetic determinants of allostatic load in a Swiss population-based study

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ABSTRACT

Allostatic load (AL) is a marker of physiological dysregulation which reflects exposure to chronic stress. High AL has been related to poorer health outcomes including mortality. We examine here the association of socioeconomic and lifestyle factors with AL. Additionally, we investigate the extent to which AL is genetically determined. We included 803 participants (52% women, mean age 48 ± 16 years) from a population and family-based Swiss study. We computed an AL index aggregating 14 markers from cardiovascular, metabolic, lipidic, oxidative, hypothalamus-pituitary-adrenal and inflammatory homeostatic axes. Education and occupational position were used as indicators of socioeconomic status. Marital status, stress, alcohol intake, smoking, dietary patterns and physical activity were considered as lifestyle factors. Heritability of AL was estimated by maximum likelihood. Women with a low occupational position had higher AL (low vs. high OR = 3.99, 95%CI [1.22;13.05]), while the opposite was observed for men (middle vs. high OR = 0.48, 95%CI [0.23;0.99]). Education tended to be inversely associated with AL in both sexes(low vs. high OR = 3.54, 95%CI [1.69;7.4]/OR = 1.59, 95%CI [0.88;2.90] in women/men). Heavy drinking men as well as women abstaining from alcohol had higher AL than moderate drinkers. Physical activity was protective against AL while high salt intake was related to increased AL risk. The heritability of AL was estimated to be 29.5% ±7.9%. Our results suggest that generalized physiological dysregulation, as measured by AL, is determined by both environmental and genetic factors. The genetic contribution to AL remains modest when compared to the environmental component, which explains approximately 70% of the phenotypic variance.

1. Introduction

Allostatic load (AL) is an indicator of biological dysregulation representing the cumulative physiological toll experienced by an organism when it fails to adequately respond to chronic psychosocial or physical challenges from the environment (Dowd et al., 2009; McEwen, 1998). Introduced in the early nineties by McEwen and Stellar (1993), AL is measured through a single index, resulting from a combination of biological markers reflecting the states of several axes including cardiovascular, metabolic, dyslipidemic, neuroendocrine, hypothalamus-pituitary-adrenal (HPA) and inflammatory (Nicod et al., 2014; Seeman et al., 2010). High AL has been related to several adverse health outcomes, including physical and cognitive functioning, symptoms of post traumatic stress disorder, risk of cardiovascular events (Crimmins et al., 2003; Juster et al., 2010; Seeman et al., 2001), and all-cause mortality (Seeman et al., 2004).

The concept of AL was originally introduced to represent the physiological consequences of chronic stress, itself influenced by

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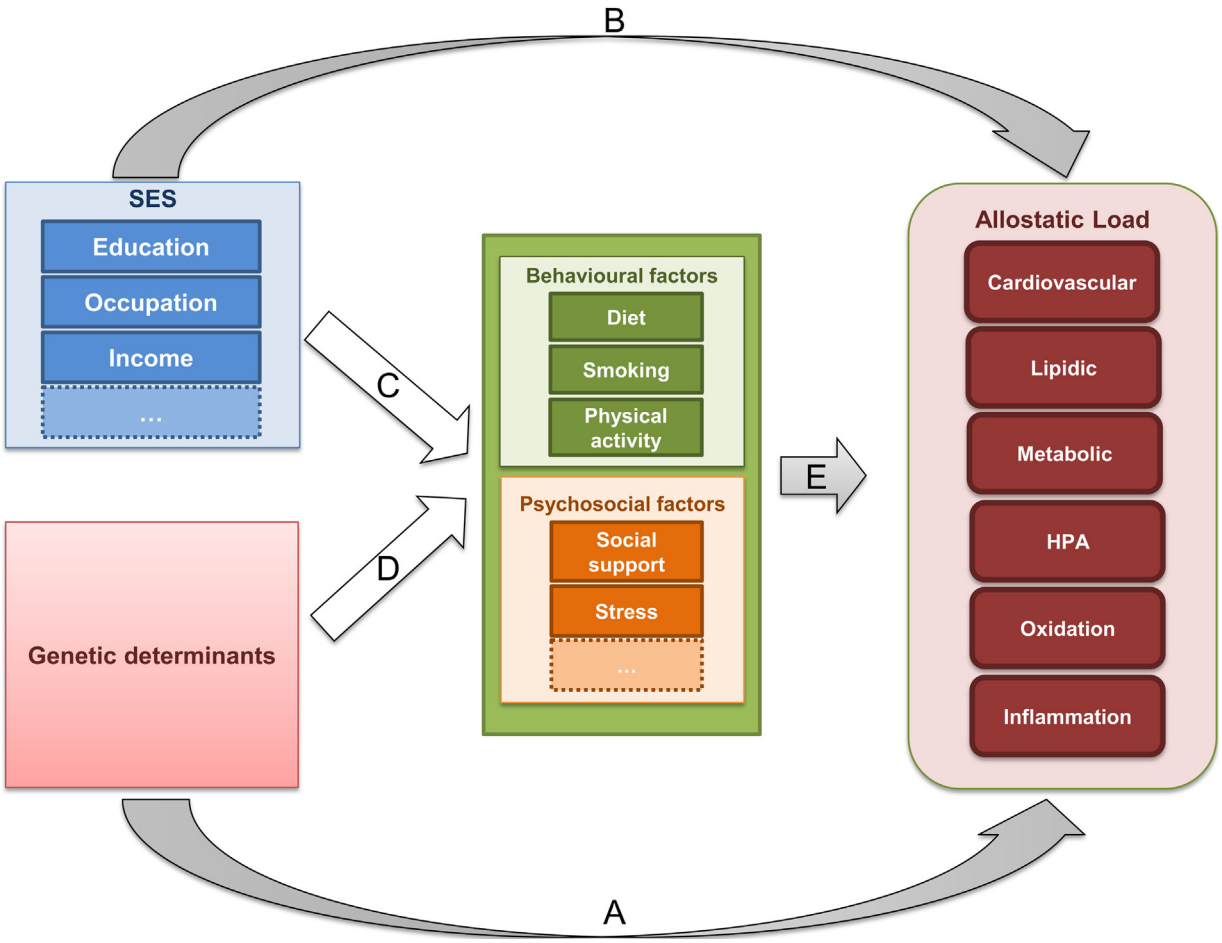

Fig. 1. Simplified conceptual framework for the determinants of allostatic load. AL is represented with its six homeostatic axes. It may be influenced directly by genetic factors (arrow A) and SES (B), or indirectly through behavioural and psychosocial factors (arrows C and D). Behavioural and psychosocial factors may also influence AL directly (E).

socioeconomic status (SES), health behaviors or psychosocial factors. In this context, many studies have found a strong association between low SES, as reflected by low education, adverse financial conditions or receiving social transfers, and high AL (Gruenewald et al., 2012; Nicod et al., 2014). The role of health behaviors in relation to chronic stress and health has also been investigated in previous research, which showed that individuals confronted to stressful daily life (i.e. poverty, crime) are prone to engage themselves into unhealthy behaviors such as smoking or overeating, which may help alleviate symptoms of psychological stress. However, despite these positive, short-term psychological effects, an unhealthy lifestyle has detrimental physiological consequences on the long term and thus results in increased morbidity and mortality (Jackson et al., 2010).

However, the associations between health behaviors and AL have not always been consistent across studies. Gallo et al. (2011) showed, for example, that moderate alcohol consumption was associated with decreased AL, whereas Crimmins et al. (2009) found no association between alcohol intake and AL. Similarly, results for the effect of smoking on AL were inconsistent (Crimmins et al., 2009; Hu et al., 2007). Finally, AL has mainly been studied as a consequence of chronic environmental demands, whereas a limited number of studies have examined the contribution of selected genetic determinants using a candidate gene approach to this phenotype (Brody et al., 2013; Cicchetti et al., 2011). The complex nature of AL suggests that this phenotype is influenced by more than one gene (i.e. a polygenic trait). However, previous studies have mainly focused on the role of specific genetic markers, which are involved in responses to contextual stress, including SES-associated risks, family or personal pressure and the response to physical abuse (Brody et al., 2013; Cicchetti et al., 2011). To date, two markers have been identified, the SLC6A4 serotonin transporter gene, whose shorter variant was associated with high AL, and CRHR1 corticotropin releasing hormone receptor 1 gene, which is involved in HPA axis regulation, and whose TAT variant was associated with high AL. However, to our knowledge, no study has yet investigated nor assessed heritability of AL, which allows the determine the overall genetic contribution to this phenotype, irrespective of the specific function of selected genes.

In this study, we examine the association of socioeconomic (education and occupation) and behavioral factors (marital status, smoking, alcohol consumption, physical activity, dietary patterns, and stress) with AL using data from a Swiss population-based study. Further, we investigate the extent to which AL is genetically determined by assessing narrow sense heritability. We hypothesize that AL is influenced by both environmental (socioeconomic and behavioral) and genetic factors (Fig. 1).

2. Methods

2.1. Study population and design

Data were drawn from the SKIPOGH study (Swiss Kidney Project on Genes in Hypertension), a multicenter family-based population

study initiated in 2009 to explore the genetic and environmental determinants of blood pressure (Alwan et al., 2014; Pruijm et al., 2013).

Study participants were recruited in the cantons of Bern and Geneva and the city of Lausanne. Recruitment began in December 2009 and ended in April 2013. Index cases were randomly selected from the population-based CoLaus study in Lausanne (Firmann et al., 2008), and from the population-based Bus Santé study in Geneva (Guessous et al., 2012). In Bern, index participants were randomly selected using the cantonal phone directory. Inclusion criteria were: (1) written informed consent; (2) minimum age of 18 years; (3) Caucasian origin; (4) at least one, and preferably three, first-degree family members also willing to participate. At the end of the recruitment period, the study population included 1128 participants. The SKIPOGH study was approved by the ethical committees of Lausanne University Hospital, Geneva University Hospital and the University Hospital of Bern (Ponte et al., 2014). Participants came from 271 distinct family structures (pedigrees), most of which included three generations and second degree links (i.e. cousins). The mean pedigree size (±SD) was 5.05 ± 2.26, with the largest nuclear family (parent–children only) including 8 members. These pedigrees led to 1444 parent–offspring pairs, 462 sibling pairs, 213 avuncular pairs, 310 grandparents–grandchildren pairs and 44 cousin pairs.

2.2. Clinical and biological data

Participants came for the study visit at one of the three medical centers in the morning, and filled in a standardized questionnaire at home. The questionnaire focused on a variety of issues including lifestyle habits as well as medical history. Body weight (kg), height (cm) and waist and hip circumferences (cm) were measured according to standard procedures. Body mass index (BMI) was defined as weight in kg divided by the square of height in meters. Blood pressure and heart rate were measured after 10 min of rest in the sitting position with a validated non-mercury auscultatory sphygmomanometer (A&D UM-101, A&D Company, Ltd., Toshima Ku, Tokyo, Japan). Each participant's office blood pressure and heart rate were the means of five consecutive readings. Venous blood samples were drawn after an overnight fast. Electrolytes, kidney and liver-function tests, blood glucose, cholesterol, triglycerides, insulin, C-reactive protein (CRP), serum uric acid, gamma-glutamyltransferase (GGT) and other biological markers were measured in local university laboratories using standard clinical laboratory methods. Participants were also asked to collect a 24-h urine sample for the measurement of urinary volume, urinary sodium and additional parameters (Alwan et al., 2014; Ponte et al., 2014; Pruijm et al., 2013).

2.3. Socioeconomic status (SES)

Two indicators of SES were used: educational level and occupational position. Highest level of education attained was self-reported and further classified into three categories: "High" (University education), "Middle" (Higher secondary education), and "Low" (Lower secondary education or lower). Occupational position was self-reported and grouped into three categories: "High" (Managers: liberal professions, directors, professors), "Middle" (Lower level executives: teachers, qualified technicians, nurses) and "Low" (Low qualified non-manuals and manuals: sales assistants, clerks, manual workers). Participants who were not currently working were assigned their past occupational position. Participants who had never worked (students and housewives) were not included in the analysis.

2.4. Lifestyle factors

Lifestyle factors were self reported. Marital status was categorized as "Living alone" or "Living in a couple". Alcohol consumption was assessed using questions on the number of alcoholic drinks usually consumed within a week, then categorized as "Abstainers" (0 unit/week; 1 unit = 10 g of pure alcohol) "Moderate" (1–21/1–14 units/week for men/women) or "Heavy drinking" (≥21/≥14 units/week for men/women). Smoking status was categorized as current and noncurrent smoking, the latter category including never smokers and ex-smokers. Physical activity was reported on a scale from 1 to 10, 1 corresponding to a complete sedentary lifestyle and 10 corresponding to manual work combined with sports practice. Based on this scale, three categories were subsequently defined: "Low" (1–4), "Moderate" (5), and "High" (6–10). Daily salt intake was assessed through 24-h urinary sodium excretion (mmol/24 h) and categorized as "Up to 5 g/day", "5–10 g/day" and " > 10 g/day". Weekly meat consumption was categorized as "Low" (Never–Once/week), "Moderate" (2–4 times/week) and "High" (5–7 times/week). Daily fruit and vegetable consumption was classified as "Low" (0–3 portions/day), "Moderate" (3 portions/day) and "High" (>3 portions/day). Perceived stress level (referred to as "Stress") was assessed through the question: "Please indicate on a scale from 1 to 10 the psychological tensions and stress to which you are exposed in your everyday life/*Veuillez noter sur une échelle de 1 à 10 les tensions psychologiques et le stress auxquel vous êtes confrontés actuellement dans votre vie quotidienne [FR]/Bitte beurteilen Sie anhand einer Skala von 1–10 Ihre tägliche Anspannung und Stress in Ihrem Alltag [DE]* " with possible answers on a scale from 1 to 10. It was further subdivided into "Low" (1–3), "Moderate" (4–6) and "High" (7–10).

2.5. Other covariates

Use of anti-hypertensive drugs (beta-blockers, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics), lipid-lowering drugs (statin, fibrates) and anti-diabetes drugs (oral anti-diabetics, insulin) was included as potential confounding effects in the association between SES and AL (sensitivity analyses).

2.6. Allostatic load

We analyzed the constituting risk factors of AL in groups corresponding to six physiological systems: cardiovascular, metabolism, hypothalamic-pituitary-adrenal axis (HPA), lipidic axis, inflammation and oxidative stress (Gallo et al., 2011; Nicod et al., 2014; Seeman et al., 2010). Compared to the markers usually included in the assessment of AL, we omitted autonomic nervous system parameters (i.e. adrenaline, noradrenaline) as they were not available in SKIPOGH. Moreover, we decided to include an oxidative stress axis as chronic oxidative stress has also been linked to generalized physiological dysregulation (Devaki et al., 2013; Nicod et al., 2014). Further, we separated the lipids from the metabolism axes contrary to previous studies. In total, we assessed 14 biological markers within 6 homeostatic dimensions: mean systolic blood pressure, mean diastolic blood pressure and heart rate (cardiovascular system); blood glucose, blood insulin, bmi and waist-to-hip ratio (metabolism); 24 h urine cortisol (HPA); high-density lipoprotein cholesterol, total cholesterol and triglycerides (lipidic axis), serum uric acid and GGT (oxidative stress) and CRP (inflammation). All physiological parameters composing AL were stratified by sex and are summarized in Supplementary Table 1 (online resource 1).

Each biological marker was dichotomized into high versus low-risk values (1–0) according to clinical thresholds as found in the literature (Ascaso et al., 2003; Dowd and Goldman, 2006; Dowd

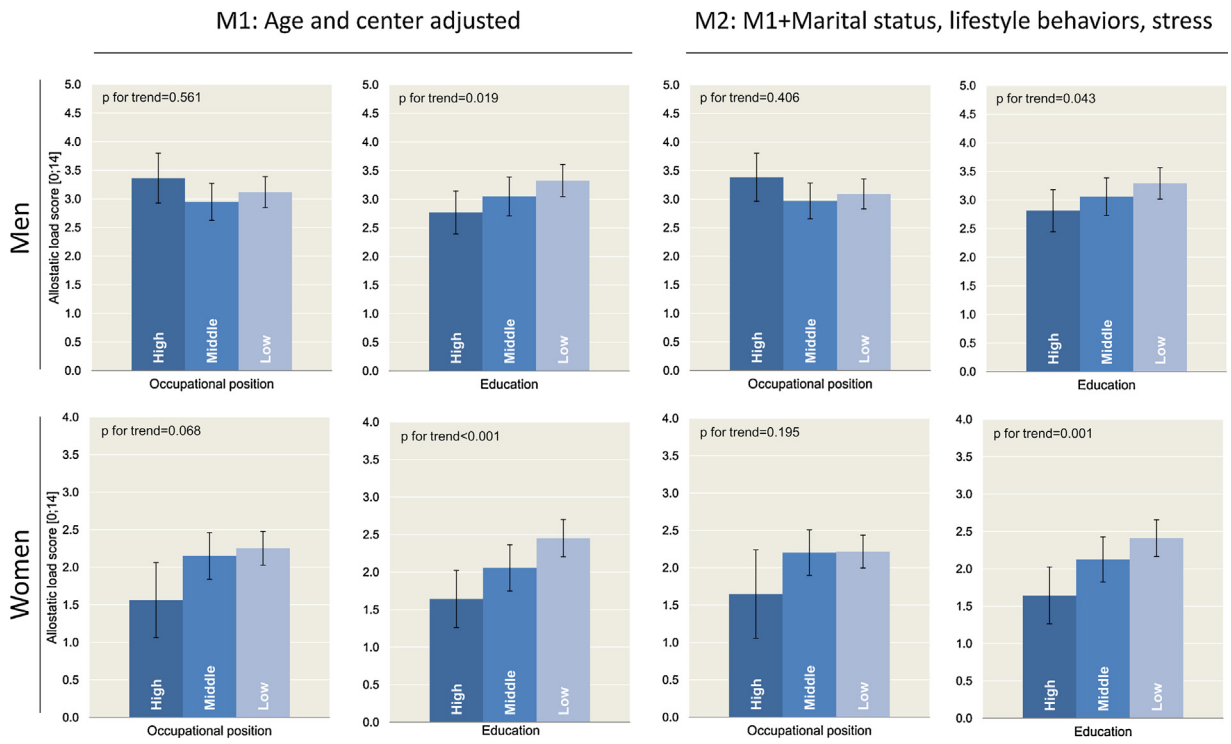

Fig. 2. Mixed linear regression adjusted means (±SE) for allostatic load by occupational position and education. Model 1 (M1) was adjusted for age and center and Model 2 (M2) was additionally adjusted for marital status, lifestyle behaviors and stress.

et al., 2009; Karlamangla et al., 2012; Krishnamurthy, 2013; Perk et al., 2012; Ridker, 2003; Zoppini et al., 2012). The AL score was computed by summing the dichotomized values and thus ranged between 0 and 14. The AL score and each of the six homeostatic dimensions were further dichotomized into high versus low risk by using as a cut-off the value closest to the median (Supplementary Table 2—online resource 2). This cut-off was chosen as previous studies have found that differences in morbidity or mortality occur between groups when AL was dichotomized at the median or at scores of 3–4 (Geronimus et al., 2006; Smith et al., 2009). ”

2.7. Statistical analyses

The associations of SES indicators and lifestyle factors with AL were analyzed using a minimally adjusted mixed logistic regression model and a fully adjusted model, which included additional adjustment for all factors. The association between SES and continuous AL score was further investigated through mixed linear regression models (M1: minimally adjusted and M2: fully adjusted) for which adjusted means were calculated. As the association of occupational position and several lifestyle factors with AL differed by sex (p for interaction <0.05), all analyses were stratified by sex. The associations of SES and lifestyle factors with AL were similar for the three centers (p for interaction >0.05), so data from the three centers were polled and all analyses were adjusted by center. Familial correlations were taken into account for all analyses. We assessed heritability as previously described (Pruijm et al., 2013). Heritability is a measure of familial resemblance that relies on the assumption that total phenotypic variance of a trait can be partitioned into independent genetic and environmental components. The genetic variance can further be subdivided into three components: an additive or polygenic genetic variance (1), a dominance variance (2) and an epistatic variance (3). The additive genetic component represents the average effects of individual alleles on a trait and reflects transmissible resemblance between relatives. Heritability in the narrow sense is defined as the ratio of the additive genetic variance to the total phenotypic variance. In this paper we refer to “heritability in the narrow sense” simply as heritability. We estimated the heritability of AL within a model which was adjusted for age, sex and center. For heritability measure, total phenotypic variance was subdivided into random (R), polygenic (P) (additive genetic variance) and marital (M) components. Sibship component was not included in the model as it did not significantly contribute to the total phenotypic variance. For heritability, the SAGE software (Statistical Analysis for Genetic Epidemiology) from the ASSOC program was used (Ponte et al., 2014). All other analyses were conducted in STATA 13, (Stata Corp., College Station, Texas, USA). A two-sided p-value < 0.05 was used as a significant threshold. Fig. 1 was generated using MSOffice PowerPoint and Fig. 2 was generated using MSOffice Excel and PowerPoint.

3. Results

Of the 1128 participants of the SKIPOGH study, 250 were excluded because of missing values or incomplete description on one or more covariates (N = 47 for education or occupational position, N = 171 for allostatic load and N = 32 for lifestyle factors) and 75 participants were excluded because they were not currently working and had no previous occupation (68 students and 7 housewives). In total, 803 individuals were included in the present study, of which 388 were men (48%). Excluded participants were younger (mean age 45 vs. 48 years, p < 0.05) and tended to have a lower education (13% vs. 23% in the high education group, p < 0.05) than those included in the study.

Table 1 summarizes the main characteristics of the sample. Women were more frequently in a low occupational position, were less frequently smokers, were more frequently alcohol abstainers and had healthier dietary patterns (lower meat consumption and daily salt intake and higher fruit and vegetable consumption) comparing to men (all p < 0.001).

Table 1
Baseline characteristics of participants included in the study.

	Men (*N* = 388)	Women (*N* = 415)	*p*-Value[a]
Age, mean (±SD, years)	48.28 (±16.51)	48.43 (±15.65)	0.893
Center			0.040
Lausanne	108 (28%)	150 (36%)	
Geneva	168 (43%)	156 (38%)	
Bern	112 (29%)	109 (26%)	
Educational attainment			0.379
High	95 (24%)	86 (21%)	
Middle	116 (30%)	123 (30%)	
Low	177 (46%)	206 (50%)	
Occupational position			<0.001
High	70 (18%)	32 (8%)	
Middle	130 (34%)	127 (31%)	
Low	188 (48%)	256 (62%)	
Marital status			0.241
Living alone	97 (25%)	119 (29%)	
Living in couple	291 (75%)	296 (71%)	
Smoking			<0.001
No	271 (70%)	333 (80%)	
Yes	117 (30%)	82 (20%)	
Alcohol consumption			<0.001
Moderate	249 (64%)	191 (46%)	
Abstainers	91 (23%)	192 (46%)	
Heavy drinkers	48 (12%)	32 (8%)	
Physical activity			0.053
Low	121 (31%)	143 (34%)	
Moderate	92 (24%)	119 (29%)	
High	175 (45%)	153 (37%)	
Daily fruit and vegetables consumption			<0.001
Low	168 (43%)	90 (22%)	
Moderate	129 (33%)	166 (40%)	
High	91 (23%)	159 (38%)	
Meat consumption			<0.001
Low	27 (7%)	58 (14%)	
Moderate	204 (53%)	250 (60%)	
High	157 (40%)	107 (26%)	
Salt intake			<0.001
Up to 5 g/day	32 (8%)	88 (21%)	
5–10 g/day	194 (50%)	253 (61%)	
> 10 g/day	162 (42%)	74 (18%)	
Stress level			0.752
Low	110 (28%)	124 (30%)	
Moderate	174 (45%)	189 (46%)	
High	104 (27%)	102 (25%)	

Data are *N* (%) unless otherwise specified.
[a] *p*-Value was computed according to Chi2 test was between each variable and sex.

Table 2
Association between socioeconomic indicators and allostatic load.

		Men (*N* = 388)				Women (*N* = 415)			
		Adjusted for age and center		Adjusted for age, center, lifestyle factors		Adjusted for age and center		Adjusted for age, center, lifestyle factors	
		OR (95% CI)	*p*[a]	OR (95% CI)	*p*[a]	OR (95% CI)	*p*[a]	OR (95% CI)	*p*[a]
Occupational position	High (Ref.)	1.00	0.600	1.00	0.480	1.00	0.042	1.00	0.190
	Middle	0.48 [0.23;0.99]		0.43 [0.19;0.94]		3.39 [1.00;11.48]		3.19 [0.88;11.56]	
	Low	0.69 [0.34;1.38]		0.62 [0.30;1.31]		3.99 [1.22;13.05]		3.23 [0.92;11.36]	
Education	High (Ref.)	1.00	0.107	1.00	0.137	1.00	<0.001	1.00	0.004
	Middle	1.07 [0.57;2.00]		1.13 [0.58;2.20]		2.30 [1.08;4.89]		2.50 [1.11;5.63]	
	Low	1.59 [0.88;2.90]		1.61 [0.84;3.10]		3.54 [1.69;7.40]		3.40 [1.53;7.57]	

OR, odds ratio; CI, confidence interval; Ref., reference level.
[a] *p*-Value for linear trend across >2 categories.

Table 3
Association between lifestyle factors and allostatic load.

		Men ($N = 388$)				Women ($N = 415$)			
		Adjusted for age and center		Adjusted for age, center, education and occupation		Adjusted for age and center		Adjusted for age, center, education and occupation	
		OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a
Marital status	Living alone (Ref.)	1.00	0.387	1.00	0.389	1.00	0.160	1.00	0.187
	Living in a couple	1.30 [0.72;2.37]		1.31 [0.71;2.41)]		0.68 [0.40;1.16]		0.70 [0.41;1.19]	
Smoking	No (Ref.)	1.00	0.137	1.00	0.143	1.00	0.617	1.00	0.949
	Yes	1.51 [0.88;2.59]		1.51 [0.87;2.63]		1.17 [0.63;2.15]		1.02 [0.56;1.85]	
Alcohol consumption	Abstainers	0.83 [0.47;1.47]	0.195	0.79 [0.44;1.40]	0.209	1.90 [1.14;3.17]	0.116	1.72 [1.03;2.85]	0.166
	Moderate (Ref.)	1.00		1.00		1.00		1.00	
	Heavy drinkers	2.28 [0.98;5.27]		2.41 [1.02;5.72]		1.09 [0.43;2.77]		1.11 [0.44;2.83]	
Physical activity	Low (Ref.)	1.00	0.011	1.00	0.006	1.00	0.008	1.00	0.003
	Moderate	0.41 [0.21;0.81]		0.37 [0.18;0.74]		0.86 [0.49;1.51]		0.79 [0.45;1.38]	
	High	0.44 [0.24;0.80]		0.40 [0.21;0.74]		0.45 [0.25;0.81]		0.43 [0.24;0.75]	
Fruits and vegetables	Low (Ref.)	1.00	0.289	1.00	0.408	1.00	0.106	1.00	0.325
	Moderate	0.77 [0.45;1.33]		0.84 [0.48;1.48]		0.77 [0.42;1.41]		0.81 [0.44;1.47]	
	High	0.74 [0.40;1.36]		0.77 [0.41;1.46]		0.60 [0.33;1.12]		0.72 [0.39;1.36]	
Meat	Low (Ref.)	1.00	0.346	1.00	0.372	1.00	0.310	1.00	0.375
	Moderate	1.92 [0.75;4.96]		1.82 [0.67;4.91]		1.94 [0.91;4.11]		1.80 [0.86;3.78]	
	High	1.98 [0.75;5.22]		1.90 [0.69;5.21]		1.77 [0.76;4.08]		1.64 [0.72;3.75]	
Salt intake	Up to 5 g (Ref.)	1.00	0.087	1.00	0.184	1.00	0.055	1.00	0.064
	5–10g	1.77 [0.71;4.42]		1.69 [0.67;4.28]		0.95 [0.52;1.73]		0.96 [0.53;1.76]	
	>10g	2.26 [0.90;5.70]		1.99 [0.78;5.08]		2.26 [1.03;4.95]		2.20 [1.00;4.86]	
Stress	Low (Ref.)	1.00	0.921	1.00	0.785	1.00	0.803	1.00	0.775
	Moderate	0.88 [0.49;1.59]		0.83 [0.45;1.51]		1.33 [0.76;2.31]		1.42 [0.82;2.44]	
	High	0.96 [0.50;1.84]		0.90 [0.46;1.77]		1.06 [0.55;2.05]		1.06 [0.55;2.04]	

OR, odds ratio; CI, confidence interval; Ref., reference level.
[a] p-Value for linear trend across >2 categories.

Table 4
Total variance partition and narrow sense heritability for allostatic load.

Variance component	Estimate (±SD)	*p*-Value
Random (R)	0.35 (±0.08)	<0.001
Polygenic (P)	0.21 (±0.06)	<0.001
Marital (M)	0.14 (±0.06)	0.01
Total (T)	0.71 (±0.03)	<0.001
Heritability (P/T)[a]	29.55% (±7.96%)	<0.001

[a] Narrow sense heritability (polygenic/total).

Table 2 shows results for the association of SES indicators with AL. Men in the middle vs. high occupational position had lower AL (OR = 0.48, 95%CI [0.23;0.99]) while those with a low vs. high education tended to have higher AL (OR = 1.59, 95%CI [0.88;2.90]). Women in the lowest vs. highest occupational and educational group had higher AL (OR = 3.99, 95%CI [1.22;13.05] for occupational position and OR = 3.54, 95%CI [1.69;7.4] for education). The association of occupational position with AL in women was partly attenuated after adjusting for lifestyle factors (OR = 3.23, 95%CI [0.92;11.36]). Further, we observed a dose-response association between education and AL in men and women (Fig. 2 all $p < 0.05$).

Results for the association of lifestyle factors and stress with AL are shown in Table 3. Heavy drinking tended to be associated with increased AL in men (OR = 2.28, 95%CI [0.98;5.27]), whereas abstaining was associated with higher AL in women (OR = 1.90, 95%CI [1.14;3.17]). Participants who were physically active had a decreased risk of high AL: OR = 0.44, 95%CI [0.24;0.80]/0.45, 95%CI [0.25;0.81] in men/women. High salt intake was associated with high AL in women (OR = 2.26, 95%CI [1.03;4.95]), and tended to be associated in men (OR = 2.26, 95%CI [0.90;5.70]). People consuming a high amount of fruit and vegetable had a lower AL, but the difference was not significant, whereas high meat consumption and smoking tended to be associated with high AL.

Estimated heritability measures for AL are presented in Table 4. Heritability for allostatic load was 29.5% ± 7.9% in the model adjusted for age, sex and center. Random, polygenic (additive) and marital variances significantly contributed to the total phenotypic variance (T).

In Supplementary Tables 4–8 (online resources 4–8), we present results for the association of SES indicators, lifestyle factors and stress with each homeostatic dimension. Lower education tended to be associated with high risk of all homeostatic axes, except for HPA and lipids. Lower occupational position tended to be associated with increased dysregulation of the metabolic and HPA axes. These associations were generally stronger in women than in men. High physical activity was associated with lower dysregulation of cardiovascular, metabolic, lipidic axes and tended to be associated with low oxidative stress. Heavy drinking was associated with deleterious dysregulation of cardiovascular and oxidative stress axes. Increased fruit and vegetable consumption was associated with low risk of metabolic dysregulation. Finally, high salt intake was associated with high risk of dysregulation of metabolic and HPA axes.

4. Sensitivity analyses

We conducted a sensitivity analysis to assess whether medication intake (anti-hypertensive, lipid-lowering, anti-diabetic drugs, entered as separate dummy variables) could confound or attenuate the association between SES and AL. We observed that an additional adjustment for these compounds attenuated the association between occupational position and AL in women (adjusted for age, sex, center OR = 3.99 95%CI[1.22;13.05]; + lifestyle factors 3.23[0.92;11.36]; + medication 3.03[0.85;10.78]) but not in men. We also observed an attenuation for the association between occupational position and the oxidative stress axis in women but not in men.

5. Discussion

In this multicentric population and family-based Swiss study, we found a strong association between SES, several lifestyle factors, and AL, a measure of generalized physiological dysregulation and a strong predictor of morbidity and all-cause mortality (Seeman et al., 2001). Occupational position and education were negatively related with AL in women, while the associations in men tended to be positive for occupational position and negative for education. Physical activity was negatively associated with AL, salt intake was positively associated, whereas the association between alcohol consumption and AL was dependent on sex. Finally, our results show a significant genetic component for AL, as measured by heritability, independently of age, center, SES and lifestyle factors.

Occupational position was negatively related to AL in women, with women with a low occupational position having a higher risk of high AL than their more advantaged counterparts, in line with results from other studies (Gallo et al., 2011; Juster et al., 2013). However, this association was reversed in men. A possible explanation for these results is that men in high occupational positions may have high-demand jobs with long working hours and considerable professional responsibilities, potentially leading to higher stress, comparing to men occupying non-manual intermediate occupations characterized by lower demand and at the same time not involving physical efforts. On the other hand, the adverse health effects of low occupational position may be particularly severe in women as they generally have to combine the physical and psychosocial strain of manual, less paid jobs (Bonjour and Gerfin, 2001) to that of household responsibilities (Artazcoz et al., 2004). For example, in a previous study partly based on the same population of our study(Alwan et al., 2014), women with a low occupational position were more affected by sleep deprivation than men regardless of social class. Sex differences in the association between occupational position and AL have been reported in a previous study in Montreal (Juster et al., 2013). A proposed explanation for this reversed association was that work related psychosocial factors, such as psychological demands, decision latitude and social support interact in sex-specific ways with AL (Juster et al., 2013). However, we must point out that the majority of studies in this field report a negative association between occupational position and AL for both sexes (Gustafsson et al., 2011). Participants with a low education experienced higher physiological dysregulation as measured by AL, in line with previous research (Howard and Sparks, 2015; Nicod et al., 2014; Seeman et al., 2004) including a study performed in a Swiss population (Nicod et al., 2014). This may be related to several factors such as health-related knowledge on detrimental behaviors (Kenkel, 1991; Nocon et al., 2007), use of health preventive services such as screening (Adler et al., 1993), availability of psychosocial resources such as social support, and better ability to cope with everyday hassles and stressful situations in individuals with high vs. low education (Adler and Snibbe, 2003; Seeman, 1996). All these factors may translate into better behaviors and lower exposures to chronic stress in individuals with high education. However, in our study lifestyle factors (including marital status and stress only) slightly attenuated the association between SES indicators and AL. Other factors such as work-life balance, social support, psychosocial factors, early life conditions and better measurements of stress and financial strain can potentially contribute to explain the observed social differences in physiological dysregulation (Gallo et al., 2011; Hawkley et al., 2011; Hu et al., 2007; Kubzansky et al., 1999). In terms of education results were more consistent than for occupational position (Hu et al., 2007; Nicod

et al., 2014; Seeman et al., 2004). A previous study performed by Nicod et al. (2014) also found a negative association between this indicator and AL, in a Swiss population from which a subset of the participants were also included in SKIPOGH.

Several lifestyle factors were also related to physiological dysregulation in our study. Moderate alcohol consumption was protective against high AL in both men and women, in line with results from Gallo et al. (2011). This may be related to the beneficial effects of moderate alcohol consumption on several axis included in the AL index such as lipidic, and to the detrimental effect of heavy drinking on the cardiovascular axis. Women abstaining from alcohol were also at increased risk of high AL. However, individuals might restrain from alcohol consumption due to medical conditions or other reasons such as past drinking (Gallo et al., 2011; Hu et al., 2007). Consistently with previous research showing the beneficial effects of physical activity on various physiological processes (Warburton et al., 2006), we found that men and women reporting high physical activity had lower AL and lower dysregulation of several physiological axes including metabolism, cardiovascular axis, lipidic profile and oxidative stress. We also observed that high salt intake was associated with increased AL in women and tended to be positively associated in men. These results are supported by previous research showing that an increased salt consumption causes an increase in the glomerular filtration rate in the kidneys thus contributing to high AL (Berge-Landry and James, 2004).

Surprisingly, we did not find an association between stress and AL, even though previous research has placed chronic stress as a major determinant of AL (Gallo et al., 2011; McEwen and Seeman, 1999). This is probably related to the rough measurement of stress in our study, where individuals were asked to rate their perceived stress on a 10-level scale, whereas research focusing on AL generally examines stressful events, conditions and experiences (Gruenewald et al., 2012; McEwen, 1998) or uses more elaborate and accurate tools, such as the Perceived Stress Questionnaire (Levenstein et al., 1993). Moreover, although previous research has found an association between smoking and increased AL (Crimmins et al., 2009), smoking tended to be weakly and not significantly associated with high AL in our study.

AL was a significantly heritable trait, after adjustment for age, sex and center. To our knowledge, this is the first study to demonstrate heritability of such a phenotype. However, despite statistical significance, the genetic contribution to AL remains modest when compared to the environmental component, which explains approximately 70% of the phenotypic variance.

It remains however to be clarified whether the heritability of AL comes from the individual contribution of each of its components (Bartels et al., 2003; Christian et al., 1976; Elbein et al., 1999; Loomba et al., 2010; McIlhany et al., 1975; Retterstol et al., 2003), most of which are known to be heritable, or from a "master-regulator" genetic process that affects several physiological parameters simultaneously.

In addition to the research that has investigated determinants of AL in Western populations, several studies have also been conducted in Asian countries such as Japan, Taiwan or Nepal, and may therefore provide an interesting ethnic or cultural contrast for the study of determinants of AL (Hu et al., 2007; Kusano et al., 2015; Worthman and Panter-Brick, 2008). Kusano et al. (2015) have shown that in elderly Japanese, high alcohol intake was associated with high AL, and increased vegetable consumption was associated with lower AL, a tendency which was also observed in our study. On the other hand, while we found a strong association between education or occupation and AL in our study, no relation was found for these SES indicators in a Japanese population. Moreover, other Asian studies have shown similar or different tendencies for the determinants of AL (Hu et al., 2007). However, at this point, it remains difficult to determine whether the similarities or differences in the associations between SES or lifestyle behaviors and AL are due to the genetic background or to cultural factors (Glei et al., 2013), and additional studies focusing on different ethnicities shall be conducted to clarify this point.

5.1. Strengths and limitations

Our study has several strengths, the first being the richness of the physiological, genetic and lifestyle data on a population-based sample of a Swiss population of European descent. This allowed us to compute dysregulation indexes for specific physiological axes and a generalized index of physiological dysregulation (AL score). In addition, the significant heritability of AL also suggested that data quality was high within our study, since measurement errors tend to reduce heritability (Pruijm et al., 2013).

Our study also has some limitations. First, except for dietary salt intake, the assessment of lifestyle factors is likely to be imprecise and subjective, as they were self-reported by study participants and assessed with basic questions. Second, the notion of AL as a marker of physiological dysregulation still requires further experimental and clinical validation. Even though this marker has been increasingly used (Steptoe et al., 2014), this concept remains somewhat arbitrary, relatively complex, and lacks absolute consensus in the way it is computed throughout studies (Karlamangla et al., 2012; Nicod et al., 2014). It would therefore be desirable to establish a widely accepted and precise definition for AL, as it is the case for frailty, which is a similar notion (Guessous et al., 2014). One of the issues regarding AL in our study is the lack of additional markers of inflammation and the total absence of neuroendocrine axis markers, such as adrenaline or noradrenaline (Karlamangla et al., 2012). This also raises the question of whether different homeostatic axes and their components shall be weighted differentially when generating the AL score. Further, the limited sample size may have led to statistical power issues for some of the associations. Finally, our findings are only valid for the Swiss population of European descent, and may not be generalized to other populations.

6. Conclusion

In summary, our findings indicate that SES acts as a strong determinant of AL, especially among women, and that this association is not necessarily attenuated by lifestyle behaviors, which affect AL independently. Moreover, despite that fact that the concepts of allostasis and AL were meant to express the consequences of chronic environmental demands, heritability analyses showed that there is a significant genetic predisposition for AL.

Author contributions

SS, MBo and DP designed the study. BP, ND, MP, GE, DA, IG, SEY, APB, BV, MM, PYM, FP, MBu and MBo actively contributed to data acquisition. DP, SS, EP, MBo analyzed the data. SS, DP, EP, BP, ND, MP, DA, IG, FP, MBu and MBo critically revised the manuscript.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2016.02.003.

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