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Cumulative toll of exposure to stressors in Canadians: An allostatic load profile

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Abstract

Background: The cumulative toll of exposure to stressors (psychosocial, chemical, physical) can contribute to disease processes. The concept of allostatic load, essentially the cost of maintaining physiological stability in response to environmental demands, may be useful in assessing broad population health impacts of stressors beyond morbidity and mortality. In the present study, allostatic load scores were generated for Canadians and associations with age, sex, education and household income were examined.

Methods: Data from cycles 1, 2, and 3 (2007 to 2013) of the Canadian Health Measures Survey (CHMS) were used to generate a composite index of cumulative health burden (allostatic load score) for adults aged 20 to 79 (n=8,678) based on risk thresholds for nine biological measures: diastolic blood pressure, systolic blood pressure, heart rate, high-density lipoprotein (HDL), total cholesterol, glycated hemoglobin (HbA1c), waist-to-hip ratio, C-reactive protein (CRP), and albumin. Logistic regression models that included age (continuous), sex, education and household income were fit to generate model-adjusted predicted allostatic load scores.

Results: The most prevalent individual risk factors were elevated waist-to-hip ratio, elevated CRP, total cholesterol, and low HDL. Allostatic load scores increased with age. Males generally exhibited higher scores than females. Lower educational attainment and lower household income were found to be significantly associated with higher allostatic load scores after taking account of the effects of age and sex.

Interpretation: Age and socioeconomic gradients are associated with differences in allostatic load scores in the Canadian population. This composite measure of multisystem dysfunction, generated from a nationally representative survey that includes measurement of numerous health-relevant behaviours, biomarkers, and chemical levels, can be used in future to quantify sub-clinical impacts on health.

Keywords: allostatic load, Canadian Health Measures Survey, stress, age, sex, socioeconomic position
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Chronic diseases are the leading cause of death and the greatest burden on health care systems in Canada and around the world.[1,2] In addition to age and heredity, determinants of morbidity and mortality include behavioural factors (e.g., diet, tobacco use, physical activity levels) and environmental stressors (e.g., neighbourhood socioeconomic deprivation, exposure to pollutants, noise). Gradients in health associated with individual and societal factors have prompted investigation of underlying mechanisms to inform risk assessment and management initiatives. Estimating cumulative or combined impacts of stressors is a significant challenge for risk assessment; there are multiple pathways to morbidity and mortality, and resulting health impacts may depend on the nature, timing, magnitude, and duration of exposures as well as individual susceptibility factors. A key knowledge gap hampering assessment of cumulative and combined effects of stressors (broadly defined and encompassing psychosocial, physical, and chemical) is the lack of metric or metrics to characterize risk due to interactions of multiple stressors in the human population.[3,4] Moreover, inter-individual differences in stress response and resilience present a further complication, as these are rarely captured in epidemiological studies and may modify the effects of a given stressor.

One theoretical concept that could be useful in integrating cumulative impacts of chemical and non-chemical stressors is allostatic load. Allostatic load refers to the wear-and-tear on the body as various physiological systems respond to demands imposed by the environment.[5] While the response of innate defence systems to acute stressors is critical for survival, adaptation may come at a cost. Repeated or chronic exposure may shift systems out of their normal operating range, resulting in dysfunction that can predispose to poorer health. To encompass diverse impacts of chronic exposure to stressors, efforts to operationalize the concept of allostatic load have typically used composite indices that comprise variables from several major physiological regulatory systems to generate an allostatic load index (ALI) score.[6]

Notwithstanding the considerable heterogeneity of the variables—often selected based on availability—used to estimate allostatic load,[7] studies have generally shown that allostatic load scores tend to increase (worsen) with age,[8] and with individual[9] and neighbourhood[10] socioeconomic deprivation. Higher allostatic load scores are predictive of future declines in health, including increased probability of cardiovascular disease, cognitive and physical decline, and mortality.[11-14] Composite measures of allostatic load have been found to better predict subsequent morbidity and mortality than individual components.[14,15] This suggests that the index is indeed capturing some overall measure of physiological dysfunction. Importantly, by assessing the physiological outcome of stressor exposure through impacts on multiple biological systems, allostatic load indices incorporate inter-individual differences in stress response and, as a result, consider both stress exposure and sensitivity.

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What is already known on this subject?

- Allostatic load, or the wear and tear of responding to cumulative stressors, is a measure of chronic physiological stress and a predictor of future health problems.
- While allostatic load scores have been assessed in national studies elsewhere, there have been no comparable studies in Canada to date.

What does this study add?

- Using data from the Canadian Health Measures Survey (2007 to 2013), allostatic load scores were generated for a nationally representative population of Canadian adults.
- Allostatic load scores were higher for males than females, increased with age, and were highest in those with lower educational attainment and household income.
- This measure of physiological dysfunction can be used in future to quantify subclinical health impacts of exposure to a variety of stressors and behaviours.

A number of studies have used national survey data (in particular the National Health and Nutrition Examination Survey (NHANES) in the United States) to assess factors that affect the allostatic load profile of the population (reviewed in [7]). At present, there have been no comparable studies conducted in Canada. Distinct characteristics of the Canadian population, such as its composition, social programs, and health coverage, may impact overall population health.[16] This suggests that investigating the relationship between allostatic load and stressors in this population is warranted. The Canadian Health Measures Survey (CHMS) is a nationally representative survey that collects information on the health and health habits of Canadians, as well as direct physical measures, including biological samples to assess chemical exposures and biomarkers of health and nutritional status. Importantly, the data collected include measures used to calculate cumulative biological dysfunction in a number of previous studies (e.g., [10,12,17-19]). In this study, measures from CHMS cycles 1, 2 and 3 (2007 to 2013) were used to estimate allostatic load. Associations between this measure of cumulative biological dysfunction and sex, age, and socioeconomic indicators were then examined.

Table 1
Clinical and empirically defined percentile criteria for biological risk factors

	Empirical cut-off (75th or 25th percentile)	Clinical cut-off†	Unit
Diastolic blood pressure	>77	90	mm Hg
Systolic blood pressure	>120	140	mm Hg
Heart rate	>74	90	Bt/min
Waist-to-hip ratio	>0.95	Males >0.90 Females >0.85	
Total cholesterol	>5.5	>6.208	m mol/L
C-reactive protein	>3.0	>3	mg/L
Glycated hemoglobin (HbA1c)	>5.8	>6.4	%
Albumin	<42	<38	g/L
High-density lipoprotein	<1.1	<1.0344	m mol/L

†As described in Seeman et al. 2008. <=less than; >=greater than.
Source: Canadian Health Measures Survey, cycles 1, 2 and 3, 2007 to 2013.

Data and methods

Survey

The CHMS is a nationally representative survey that collects information on Canadians' health and health habits. It involves a personal interview to collect demographic and socioeconomic data, and detailed health, nutrition, and lifestyle information, as well as direct physical measures that are taken during a visit to the mobile examination centre. The survey excludes individuals living on reserves and in other Aboriginal settlements, full-time members of the Canadian Forces, institutionalized individuals, and residents of certain remote areas. Detailed information about the CHMS is available in the CHMS data user guides.[20-23] Data from CHMS cycles 1, 2 and 3 covering 16,606 people were used, with a focus on the adult subset of the survey, that is, individuals aged 20 to 79 (n=10,360). This was to enable comparison with prior work using NHANES, and because appropriate risk cut-offs may differ between children and adults. Pregnant women and any person with a missing indicator or factor were excluded. This resulted in a sample of 8,678 individuals.

Allostatic load score

The following measures were used to generate the allostatic load score: total cholesterol, high-density lipoprotein (HDL), glycated hemoglobin (HbA1c), waist-to-hip ratio, systolic blood pressure, diastolic blood pressure, resting heart rate, C-reactive protein (CRP), and serum albumin. This is consistent with previous efforts to operationalize allostatic load.[10,18] The high-risk thresholds were defined according to clinical guidelines (Table 1). As an alternate approach, risk thresholds were also determined empirically as above the 75th percentile for all variables except HDL and albumin; for these two, values below the 25th percentile were considered high-risk (Table 1). Empirically defined cut-offs enabled examination of whether socioeconomic gradients were associated with health biomarker gradients, regardless of whether the values surpass risk thresholds. This can be rationalized on the basis that stressors may move biological measures toward less optimal values relative to the rest of the population.

Dichotomous indicators were created for each measure. A value of "1" was assigned for high-risk, and a value of "0"

Table 2
Characteristics of the study population (cycles 1, 2 and 3 (2007 to 2013) of the Canadian Health Measures Survey)

	All adults				Modelled adults				Excluded adults			
			95% confidence interval				95% confidence interval				95% confidence interval	
	Number	Percent	from	to	Number	Percent	from	to	Number	Percent	from	to
Age group												
20 to 39	3566	38	37	38	2950	37	36	38	616	41	37	46
40 to 59	3550	40	40	41	3019	41	40	42	531	37	33	40
60 to 79	3244	22	22	22	2709	22	21	23	535	22	20	24
Sex												
Female	5455	50	50	51	4451	49	48	50	1004	58	54	62
Male	4905	50	49	50	4227	51	50	52	678	42	38	46
Cycle												
Cycle 1	3517	30	28	32	2493	25	23	26	1024	59	52	65
Cycle 2	3659	37	36	38	3337	40	39	41	322	19	14	24
Cycle 3	3184	33	32	34	2848	35	34	37	336	22	16	28
Personal education												
Less than high school	1418	13	11	14	1158	12	10	14	260	16	13	19
High school	1764	19	17	21	1489	19	18	21	275	19	15	22
Some postsecondary	553	6	5	6.9	457	6	5	6.9	96	6.1	4	8.2
Postsecondary	6516	62	59	65	5574	63	59	66	942	60	54	65
Household size												
1	2218	15	14	17	1907	16	14	18	311	13	10	16
2	3367	36	34	38	2801	36	34	39	566	35	30	39
3	1738	20	18	21	1425	19	18	21	313	22	18	26
4	2021	17	16	18	1707	17	16	18	314	16	14	19
5	687	7.5	6.5	8.6	568	7.3	6.2	8.4	119	8.7	6.1	11
6+	329	4.2	3.3	5.1	270	4	3	4.9	59	5.5	3.1	7.9
Household income												
1st quintile	2296	20	18	22	2015	19	17	22	281	26	19	33
2nd quintile	1875	20	18	22	1688	19	17	21	187	24	19	29
3rd quintile	1823	19	18	21	1661	19	18	21	162	19	14	23
4th quintile	1879	21	19	23	1734	21	19	23	145	18	12	24
5th quintile	1700	20	18	23	1580	21	19	24	120	13	9.7	16
Household income adjusted for household size												
1st quintile	2136	20	18	23	1854	19	17	22	282	29	22	36
2nd quintile	2004	20	18	21	1823	20	18	21	181	21	17	26
3rd quintile	1795	19	17	21	1619	19	17	21	176	20	15	24
4th quintile	1928	21	19	23	1782	21	19	23	146	19	12	25
5th quintile	1710	20	18	22	1600	21	18	23	110	12	8.5	15

Notes: "N" is the unweighted sample size. Percentages were calculated using weighted counts in combined cycles.
Source: Canadian Health Measures Survey, cycles 1, 2 and 3, 2007 to 2013.

was assigned for all other measurements. A simple count metric was employed to create the allostatic load score, resulting in scores in which higher values were considered to represent greater physiological dysregulation. Measures were weighted equally, in keeping with most of the past efforts to operationalize allostatic load and as a pragmatic approach to capturing health-relevant inputs from a variety of pathways without initial knowledge of which components may be most closely linked to stressor exposure or most important to contribute to health impacts in a given population. Prior studies have varied in how they handle medication use, which could influence levels of one or more biological measures. Because the theoretical concept of allostatic load focuses on the physiological impact of dysregulation, and given that prior work has shown that analyses that considered medication use were consistent with the actual levels of the measure,[18] the actual values were used to categorize measures as high-risk or not. For modelling purposes and to ensure an adequate sample size for each ALI score, individuals with scores greater than 4 (clinical cut-off analysis) were collapsed into the new group "5+", while those with scores greater than 7 (percentile analysis) were collapsed into the new group "8+".

Analyses

Ordinal and nominal logistic regression models were applied to the clinical and percentile allostatic load scores. As both models produced similar results (data not shown), results from ordinal regression models are presented because they had fewer convergence issues. Models included continuous age, sex, education and adjusted household income. Educational attainment was an individual variable divided into the categories "less than high school," "high school," "some postsecondary," and "postsecondary" (defined as having been awarded a diploma or degree). A household weight factor was used to adjust household income for household size as previously described.[24] Essentially, household members were assigned weights (first member = 1, second member = 0.4, third and subsequent members = 0.3), with the household weight factor determined by the sum of these weights. Household income was divided by the household weight, and the adjusted household incomes were grouped into quintiles, each representing one-fifth of the population. Age-squared was also included to allow for the possibility of non-linear relationships between age and allostatic load score, although it was removed if it was not significant in the model.

The potential for age- or sex-dependent differences in the impact of socioeconomic variables was assessed by including interactions in the model (i.e., age x education, age x income, sex x education, sex x income), then iteratively removing interactions that were not significant. As age x sex interactions were significant, each sex was modelled separately, and results are presented from sex-specific models. Model-adjusted predicted allostatic load index (ALI) scores were calculated using the following equation:

$$E(ALI) = \sum_{i} i \times P(ALI = i \,|\, x),$$

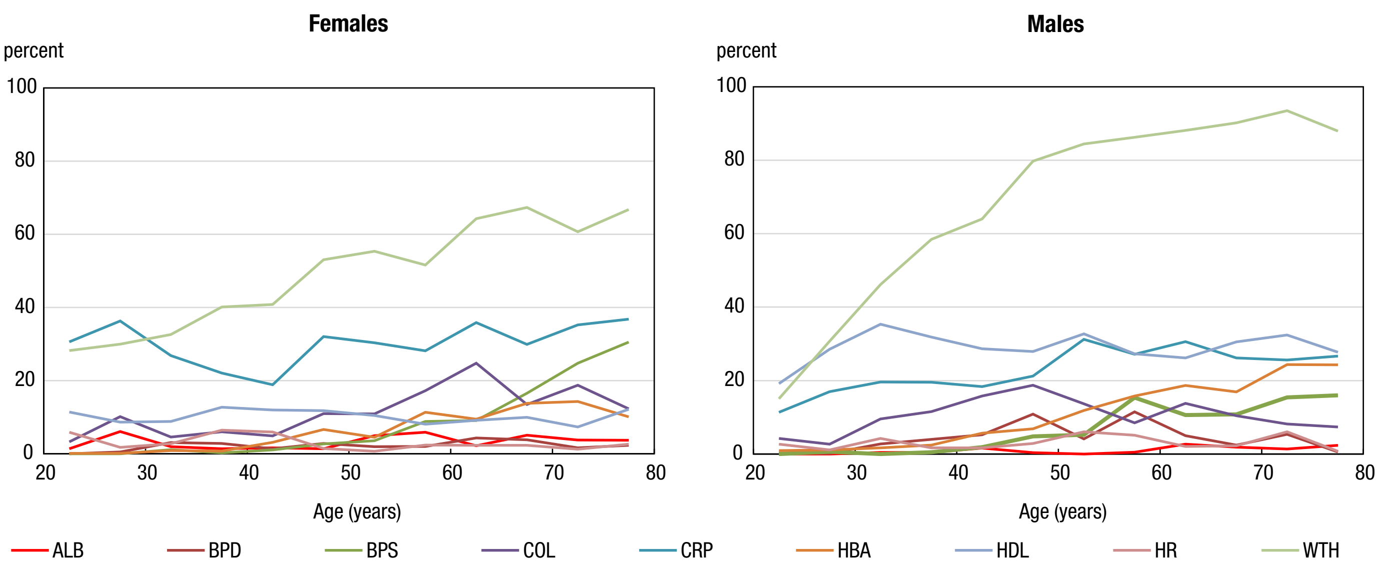
where P is the modelled probability of each ALI score (0, 1, 2…) and x represents the covariates. All analyses were conducted in SAS EG version 5.1 (SAS, Institute Inc., Cary, NC, USA) and R[25], and used the survey and bootstrap weights provided by Statistics Canada. Pearson correlations were estimated between each continuous biological measure and age, as well as between biological measures. Variance estimation for all tests, models and estimates followed the Balanced Repeated Replicates approach and used the combined bootstrap weights for cycles 1, 2 and 3 supplied with the CHMS and 35 degrees of freedom, as specified by the guides and instructions, for combining multiple cycles.[20,21,22,23] Satterthwaite-adjusted F statistics were used to determine the significance of model parameters. All results were rounded to two significant figures and assessed for data quality by means of the coefficient of variation (CV), as per the CHMS guidelines.[20,21,22,23]

Results

Table 2 presents descriptive information on the population in the analyses compared with the overall CHMS population and those excluded from the analyses because of missing data or pregnancy. The sample analyzed is broadly representative of the overall CHMS population with respect to age, sex and sociodemographic variables.

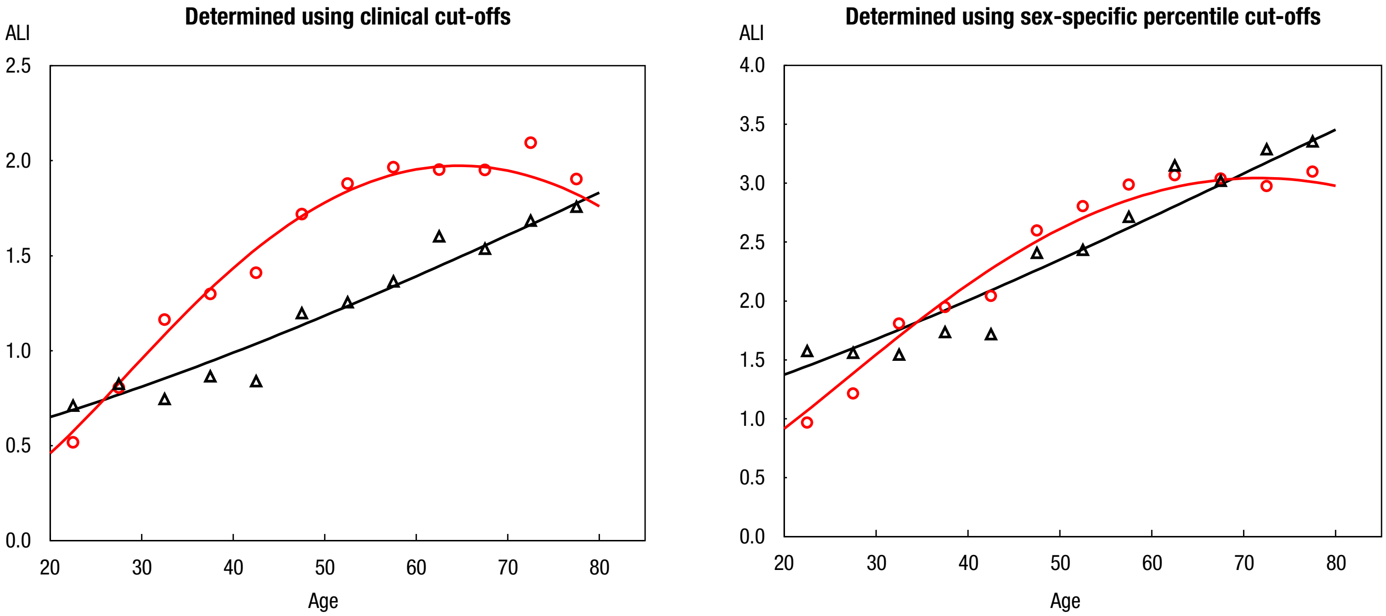
Individual risk factors, determined according to clinical cut-offs, differed in their population prevalence as a function of age for each sex (Figure 1). A high waist-to-hip ratio was the most prevalent (56% of population), followed by high C-reactive protein (25%), low HDL cholesterol (19%), and high total cholesterol (11%). Most measures exhibited statistically significant trends toward less optimal values with age: age was positively correlated with waist-to-hip ratio (r=0.37), systolic blood pressure (r=0.47), diastolic blood pressure (r=0.17), HbA1c (r=0.30), and total cholesterol (r=0.18), and negatively

Figure 1
Population prevalence of high-risk values for measures used to generate the allostatic load scores



Notes: ALB=albumin; BPD=diastolic blood pressure; BPS=systolic blood pressure; COL=cholesterol; CRP=C-reactive protein; HBA=glycated hemoglobin; HDL=high-density lipoprotein; HR=heart rate; WTH=waist-to-hip ratio.
Source: Canadian Health Measures Survey, cycles 1, 2 and 3, 2007 to 2013.

Figure 2
Allostatic load index (ALI) score as a function of age and sex



Notes: The points (triangles=female; circles=male) indicate mean scores by age for 5-year age categories. Curves indicate model-adjusted predicted values for females and males.
Source: Canadian Health Measures Survey, cycles 1, 2 and 3, 2007 to 2013.

correlated with albumin (r=-0.27) (all $p<0.001$).

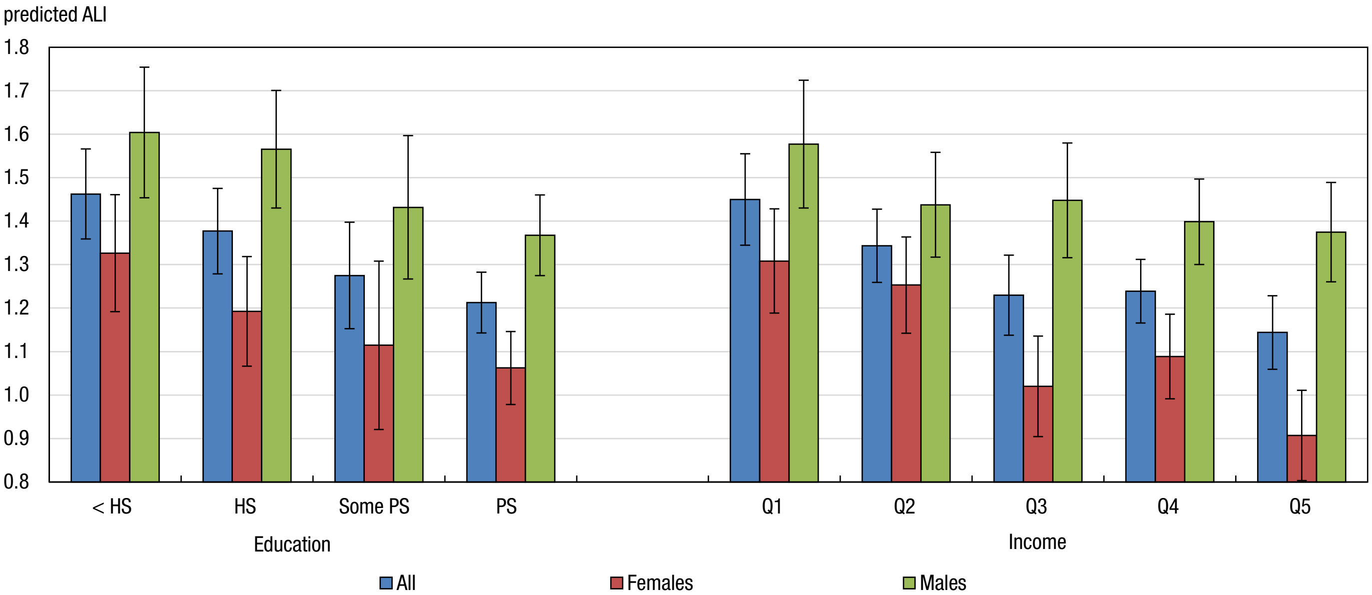
Mean allostatic load scores determined according to clinical cut-offs tended to increase with age (Figure 2A). Fitting separate quadratic curves to data for males and females showed that models fit the data reasonably well and presented some evidence of sex-dependent differences in shape. Males exhibited higher allostatic load scores at virtually all ages, with mean scores levelling at approximately 55 years, compared with females, for whom levelling was less pronounced. Similar profiles were generated using empirically-determined percentile cut-offs based on the population as a whole (data not shown). As the most prevalent risk factor (high waist-to-hip ratio) exhibited a similar sex-dependent profile as a function of age (Figure 1), this single measure was tested for whether it accounted for the differences between sexes. Removing the waist-to-hip ratio from the determination of allostatic load did not significantly alter the shape of the relationship between age and allostatic load score for each sex (data not shown). However, analyses that used sex-dependent percentile cut-offs produced more comparable profiles for males and females (Figure 2B). Similar results were obtained when modelling as a function of 10-year age categories instead of continuous age (data not shown).

Next, socioeconomic indicators were assessed for whether they were associated with differential allostatic load scores. In models that included age, age-squared, sex, education and adjusted household income, lower individual education and lower household income were significantly associated with higher predicted allostatic load scores (Figure 3). In fully adjusted models, the association with household income was significant for females, while the association with education was significant for males. Results were similar for analyses that used percentile cut-offs (data not shown). Because the societal value of educational attainment may vary as a result of historical differences in access to education, interactions among age, sex, educational attainment and household income were also tested. The only significant interaction was between age and sex, and the lack of interactions between age and socioeconomic variables persisted when modelling males and females separately (data not shown).

Discussion

Although a number of studies have used nationally representative health surveys to examine relationships between various factors and allostatic load, data were not available to conduct similar national studies in Canada until recently. The Canadian Health Measures Survey, which was initiated in 2007 to collect health data on the Canadian population, now provides the opportunity to complete an initial assessment of factors influencing allostatic load in Canada. The allostatic load score was found to increase with age and subsequently level off, a result consistent with the literature.[8,26] This flattening is attributable to a survival effect, with death removing the contribution to risk factor prevalence of those with the highest allostatic load scores. Lifestyle, societal and medical interventions that have led

Figure 3
Association of educational attainment and household income with allostatic load index (ALI) score



HS=high school
PS=postsecondary
Q=quintile
<=less than

Notes: Models included continuous age and age-squared (except in females, where age-squared was not significant and was removed from the model), sex, education and adjusted household income. For analyses in all adults ("All"), the model also included "age x sex" and "age-squared x sex" interaction terms. Data are presented as predicted means with 95% confidence intervals. P-values are for Satterthwaite-adjusted F tests of the main effect of education and income in the model (Education: All, p=0.003; Females, p=0.11; Males, p=0.03. Income: All, p=0.003; Females, p=0.002; Males, p=0.35).
Source: Canadian Health Measures Survey, cycles 1, 2 and 3, 2007 to 2013.

to reductions in mortality, but which nevertheless may increase the length of time individuals live with one or more risk factors, may also impact the profile. Indeed, there is evidence that declines in mortality from chronic disease have not been accompanied by an increase in the proportion of years of healthy living.[27,28] It would be expected that such patterns would also be observed in allostatic load scores, as these are generally thought to represent integrated measures of multiple physiological systems critical for health and relevant to disease processes.

The analyses revealed certain differences in the profiles for males and females, with males exhibiting an initial steeper climb and more pronounced leveling off than females. Few prior studies have presented separate allostatic load scores by sex as a function of continuous age. Geronimus et al.[29] displayed age x sex plots of allostatic load for a population aged 18 to 64 where the relationship showed some signs of flattening at the oldest ages. However, different variables were used to estimate allostatic load, and the lack of older adults (aged 65 to 79) hampers direct comparison. The differences in allostatic load score profiles for each sex in this study were robust to an alternative approach to defining risk groups (i.e., empirically defined using the entire sample) and to removing the most prevalent risk factor, high waist-to-hip ratio. The overall conservation of the sex-dependent shape in the age-allostatic load relationship supports the contention that the allostatic load index captures the cumulative impacts of aging that may appear through effects on different measures according to individual susceptibility, rather than simply reflecting the profile of a single risk factor. However, use of empirically defined sex-specific cut-offs reduced the contrast in profiles. This highlights the need for caution in interpreting sex-dependent differences in the relationship of age and allostatic load, as these differences appear sensitive to how risk thresholds are defined. There were clear sex-dependent differences in the prevalence of high-risk values for several of the biological measures across age. In males, the prevalence of high diastolic blood pressure and, to a lesser extent, high total cholesterol tended to be lower in the surviving population at higher ages, whereas the prevalence of these and other measures continued to increase in females, contributing to the differential allostatic load profiles.

Socioeconomic gradients are associated with health disparities that could be related to a range of factors, including differential exposure to stressors and support resources. The results, which show higher allostatic load scores for individuals with lower educational attainment and household income, are consistent with the notion that socioeconomic deprivation contributes to poorer health by imposing a load on biological systems that may manifest over time in physiological dysregulation and initiation or acceleration of disease processes.[9] The results indicate that adults in lower socioeconomic quintiles are more likely to experience higher levels of allostatic load earlier in life than those in higher socioeconomic quintiles. It is important to note that gradients were observed across all education and household income levels, which is consistent with previous reports from the United States (e.g.,[18]), This suggests that socioeconomic gradients continue to predict health even in populations that are generally not considered "deprived."

Direct comparison of results from the analyses using CHMS data and prior allostatic load analyses in NHANES is complicated by differences in survey design and the different data collection periods (data collection for NHANES precedes the CHMS). Notwithstanding these considerations, the observations were broadly consistent with relationships observed in NHANES.[18] A basic comparison of the CHMS data with previously published work using the same or similar clinical cut-offs in NHANES (from 1988 to 1994 and from 1999 to 2004[18,26]), albeit using BMI rather than waist-to-hip ratio in [26], suggests that the Canadian population generally exhibited lower mean ALI at each age interval and education level. Differences in disease rates between Canada and the United States have been attributed to a variety of factors, including access to health care and differences in poverty and inequality.[16] Allostatic load estimates would be expected to be similarly impacted by these factors. A systematic (and temporally matched) comparison of Canadian and American populations that accounts for survey differences would be needed in order to more completely assess similarities and differences between these populations in the relationship between socioeconomic factors and allostatic load.

Several aspects of the study should be considered in interpreting the findings. Strengths include the large and representative population examined. Associations between sex, age, education, household income, and allostatic load score were broadly consistent with previous work based on a national U.S. survey. As income was imputed for 13% of modelled participants, the entire analysis was repeated excluding all imputed income, and similar results were obtained (data not shown). Different models (nominal and ordinal logistic regression) and different means of assigning high-risk cut-offs (clinical vs. empirically defined) yielded similar results, increasing confidence in the relationships. The study is cross-sectional, so it was not possible to assess how allostatic load changes with time in relation to stressor exposure. The biomarkers used to estimate allostatic load, while consistent with others used in national surveys, were constrained by availability and restricted to measures generally considered secondary mediators. Nevertheless, the cardiovascular, metabolic, and inflammatory mediators included here have been linked to stress processes and biological dysfunction (e.g., [26]). Primary mediators (such as cortisol and epinephrine) that may be more directly linked to a stress response were not available. However, these mediators exhibit significant temporal variability and responsiveness to acute stressors, which may add considerable noise to the data by not reflecting chronic effects of cumulative exposure to stressors.[30,31] Clearly, allostatic load scores may be influenced by a vast number of factors not considered in this study. Generating a composite index of cumulative biological dysfunction using Canadian survey data offers the potential to examine relationships between psychosocial, physical and chemical stressors (as well as combined exposures to such stressors), behaviours, and early (pre-clinical) indicators of poor health at the population level.

There is a growing appreciation that environmental exposures impact a wide range of biological functions. For example, adverse health outcomes associated with exposure to air pollution, a stressor to which population exposure is virtually ubiquitous, now extend beyond respiratory and cardiovascular morbidity and mortality to include metabolic diseases (type 2 diabetes, obesity, metabolic syndrome), neurological/psychiatric disorders (impaired cognition, dementia, depression), and reproductive effects (low birth weight), among other diseases that have a strong stress component.[32]

Composite indices such as the one presented here offer a tool to measure multisystem impacts of exposures. In doing so, they may—at least to a degree—capture how exposure manifests in a variety of adverse effects, as determined by individual susceptibilities and concurrent or prior exposures, and therefore may provide a more comprehensive measure of health impacts. Risk assessment initiatives are increasingly recognizing the need to assess possible impacts of multiple exposures. By encompassing distal measures that represent effects on multiple converging biological pathways, allostatic load indices provide a tool for assessing the cumulative impacts of stressors that can act through a variety of pathways as a function of individual variability in exposure and susceptibility. It is important to note that the index can be used to quantify subclinical effects. As a result, the effects of stressors can be examined in the entire population, leading to a more complete characterization of population health impacts, one that goes beyond hospital admissions and mortality. ■

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