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Sex, Gender Factors and Cardiovascular Health in Canadian and Austrian Populations

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Brief Summary

This cross-sectional survey design study demonstrated that greater gender score (characteristics typically ascribed to women), associated with poorer cardiovascular health and higher risk of heart disease in Canadian and Austrian populations. This is while, female sex was associated with better CVH and lower prevalence of heart disease in both populations.

Abstract:

Backgrounds: Evidence differentiating the effect of biological sex from psycho-socio-cultural factors (gender) in different societies and its relation to cardiovascular diseases is scarce. We explored the association between sex, gender, and cardiovascular health (CVH) amongst Canadian (CAN) and Austrian (AT) populations.

Methods: Canadian Community Health Survey (CCHS) (n=63,522, 55% Females) and Austrian Health Interview Survey (AT-HIS) (n=15,771, 56% Females), were analyzed in a cross-sectional, survey design study. CANHEART index, a measure of ideal CVH composed of 6 cardiometabolic risk factors (smoking, physical activity, fruit and vegetable consumption, overweight/obesity, diabetes and hypertension; range: 0-6; higher scores reflecting ideal CVH) was calculated for both databases. A composite measure of psycho-socio-cultural gender was computed for each country (range=0-1, higher score identifying characteristics traditionally ascribed to women).

Results: Median CANHEART 4 [3-5] and CAN gender scores 0.55 [0.49-0.60] were similar to median ATHEART 4 [3-5] and AT gender scores 0.55 [0.46-0.64]. Although higher gender scores (CCHS: β=-1.33, 95%CI (-1.44,-1.22); AT-HIS: β=-1.08, 95%CI (-1.26,-0.89)) were associated with worse CVH; female sex (CCHS: β=0.35, 95% CI (0.33,0.37); AT-HIS: β=0.60, 95%CI (0.55,0.64)) was associated with better CVH in both populations. Additionally, higher

gender scores were associated with increased prevalence of heart disease, compared to female sex. The magnitude of this risk was higher in Austrians.

Conclusions: Our results demonstrate that individuals with characteristics typically ascribed to women, reported poorer cardiovascular health and higher risk of heart disease, independent of biological sex and baseline CV risk factors in both countries. Female sex exhibited better CV health and a lower prevalence of heart disease than males in both populations. However, gender factors and magnitude of gender impact varied by country.

Keywords: Gender score, Cardiovascular health, Psycho-socio-cultural factors, Sex

INTRODUCTION

Cardiovascular diseases (CVD) continue to represent the leading cause of mortality and morbidity amongst women and men worldwide [1]. While the importance of sex differences (biological characteristics in females and males) in the prevention, diagnosis, and treatment of CVD are being increasingly recognized, the impact of sociocultural gender has yet to be determined [2-4]. Sociocultural gender refers to psycho-socio-cultural roles, behaviors and identities. It influences people's perception of themselves and their interaction with each other and contributes to the distribution of power in different societies [4-13].

Biological differences between the sexes such as anatomical and physiological variations in coronary arteries and autonomic nervous system, alter the development and progression of cardiovascular disease. [14]. For example, smoking has been shown to have more adverse effect on females than males possibly due to difference in nicotine metabolism. Indeed, females who smoke have a 25% higher risk of ischemic heart disease compared to males [15, 16]. Sociocultural

gender also contributes to sex differences observed in cardiovascular health, including lifestyle behaviors such as exercising, or accessibility to cardiac rehabilitation [17-21]. Females are more likely to follow a healthy diet compared to males [22], however, they are less physically active [23, 24]. The rise in incidence of premature acute coronary syndrome especially in females in the last decades, can be attributed to changes in family dynamics, social, and institutional roles. Nevertheless, few studies differentiate biological sex from sociocultural gender with respect to cardiovascular risk [5, 6, 25-29]. As such, whether the effect of sex and gender differ based on country of residence remains to be determined.

In this study, we therefore sought to detangle the impact of sociocultural gender from biological sex in their association with cardiovascular health of Canadian and Austrian populations.

METHODS

Study Design

This cross-sectional, survey design study is part of the "Gender Outcomes INternational Group: to Further Well-being Development (GOING-FWD)" which is a five-country multidisciplinary consortium that was co-funded by the Canadian Institutes of Health Research, and GENDER-NET plus (http://gender-net-plus.eu/joint-call/funded-projects/going-fwd/). The overarching aims of the consortium are to integrate sex and gender aspects in health research and to evaluate their impact on outcomes in noncommunicable diseases including cardiovascular disease.

Data from two independent community health surveys administered in 2014 in Canada and Austria were analyzed (Supplementary Appendix S1, and S2). The Canadian Community Health Survey (CCHS 2014, n=63,522) is a cross-sectional survey that collected population-level

information on social determinants of health, health status and the healthcare resource utilization in the Canadian population. This survey began in 2001 and data has been collected annually since 2007. The Austria Health Interview Survey (AT-HIS 2014, n=15,771) was conducted as part of European Health Interview Survey (E-HIS) series in order to gather comparable statistical health data (i.e. population health status, health determinants, health care use and access, and sociodemographic information) from various European countries.

The GOING-FWD Methodology to Merge Data from the Canadian and Austrian Surveys

The GOING-FWD systematic multistep approach for retrospective studies was used to identify gender related variables and outcomes in both databases as well as to analyze the data. Briefly, gender-related factors were identified using Women Health Research Network's gender framework (i.e. gender identity, gender roles, gender relationships and institutionalized gender) [8], and comparable outcomes were subsequently selected. A retrospective data harmonization was performed using the Maelstrom Research guidelines [30], and finally based on the data structure of the 2 survey databases final analyses were performed locally and results were compared.

Gender Score Construction

After the identification of gender-related variables in both databases and their harmonization, the GENESIS-PRAXY methodology was used to generate a composite measure of gender [5, 6].

Outcome Measurements

The primary endpoints of this study were the cardiovascular health of the population using the CANHEART/ATHEART indices and prevalence of overt heart disease. To measure

the cardiovascular health of the population, we used the previously published CANHEART health index [31]. This index is a measure of cardiovascular health, composed from the sum of the ideal metrics for 6 cardiometabolic health factors and behaviors (i.e., smoking, physical activity, fruit and vegetable consumption, overweight/obesity, diabetes and hypertension), which range from 0 (worse) to 6 (best or ideal cardiovascular health). With our data we composed the CANHEART index and used a similar method to synthesize an index to measure the cardiovascular health of Austrian population (ATHEART) (Figure1).

Heart disease in the Canadian health survey was a self-reported measure of chronic heart disease diagnosed by health care professional, whereas in the Austrian population health survey, it was defined as having history of coronary heart disease or angina pectoris in the past 12 months.

Statistical Analysis

Descriptive statistics were reported as mean (standard deviation) for continuous variables and frequency (percentage) for categorical variables. In order to ensure statistical power for all analysis, case analysis (pairwise deletion) approach was used for dealing with missing data.

The detailed methodology of calculating the gender score has been reported in our previous publication [5, 6]. In this novel method, principal component analysis (PCA), was used to choose from a large number of relevant psychosocial variables extracted from the CCHS and AT-HIS databases. The PCA method helps reduce dimensionality and facilitate data compression to select the unique set of covariates to use in the predictive model. (Details of the method is reported in Supplementary Table S2, S3). Ultimately, components that accounted for a cumulative variance of greater than 60% of the data were selected. Factor loadings (correlation between original variables and factors) with values of 0.4 and more were used to select the best

set of variables. The optimized set of gender-related variables from the selected components in the PCA (Supplementary Table S2, S3) were then used to create a multivariable logistic model with biological sex as the dependent variable and gender-derived components as covariate. A gender index was then calculated through the construction of a propensity score, which was derived from coefficient estimates in the final logistic regression model. The propensity score for each person was defined as the conditional probability of being a female versus a male based on gender-related variables. This score ranges from 0-1, with higher scores relating to characteristics traditionally ascribed to women".

Multivariable linear regression was applied to assess the association between gender score, biological sex, and cardiovascular health measured by CANHEART/ATHEART indices (including smoking, physical activity, fruit and vegetable consumption, overweight/obesity, diabetes and hypertension) in both populations. The models were adjusted for age. The same approach was used for testing the association with overt heart disease. Multivariable logistic regression was used to assess the relationship between sex, gender and overt heart disease. These models were adjusted for age, CANHEART /ATHEART indices. A 2-way sex-by-gender score interaction was assessed in all models.

Data analysis was performed using R software (Version 1.2.5042). P-values of less-than or equal-to 0.05 were considered as statistically significant.

RESULTS

The CCHS Cycle 2014 included 63,522 respondents with 55.3% female composition (n=35,114, 42.3% younger than 50 years) while the AT-HIS Cycle 2014 included 15,771 respondents, of which 55.7% were females (n=8,786, 53.86% younger than 50 years). About

45% of Canadians and 53% of Austrians had normal body mass index (BMI<25). Rate of diabetes was double in Canadians, whereas rate of smoking was double in Austrian population (Supplementary Table S1a, S1b, S4a, 4b).

Amongst all gender-related variables, household size, perceived life stress, education level, sense of belonging to community, marital status, and household income were selected from the first 6 components of the CCHS based on their factor loadings. In AT-HIS, frequency of negative emotions, education level, marital status and household income were gender related variables selected from retained components. The first 6 components accounted for 84% of total variance in the CCHS, while a combination of the first 3 components in AT-HIS constituted 61% of total variance in the dataset. A gender score was calculated for all participants using propensity scores with biological sex as dependent variable (Table 1). While greater household size, perceived life stress, higher education, sense of belonging to community, being divorced or widowed and lower household income was associated with female sex in the Canadian population, lower education, greater frequency of having negative emotion, being divorced or widowed and having a lower household income were associated with being female in the Austrian population. Higher scores represent characteristics traditionally ascribed to women in these countries. The mean gender score in Canadian and Austrian populations were 0.55±0.09 (0.53, IQR: 0.49,0.60), and 0.55±0.12 (median 0.54, IQR: 0.46,0.64), respectively.

Figure 2 represents the distribution of gender score in males and females. The blue color demonstrates gender score in females, the red color males, and the purple color shows the overlap of the score in males and females. Higher gender score shows more feminine characteristics. The distribution of the gender score in men and women did not entirely overlap

with biological sex in both populations which shows their partially independent effect (Figure 2:I).

The mean cardiovascular health score was 3.88±1.3, with median of 4 (IQR: 3,5) in the Canadian population) while that in the Austrian population was 3.78±1.23 with median of 4 (IQR: 3,5). The cardiovascular health scores were significantly higher in females in both populations (Austria: male: 3.4 vs female: 4.02, Canada: male: 3.74 vs female: 3.99, p<0.001). While a higher gender score (B=-1.33, 95%CI (-1.44, -1.22), p<0.001) was associated with worse cardiovascular health, female sex (B=0.35, 95%CI (0.32, 0.37), p<0.001) was associated with better cardiovascular health in the Canadian population when adjusted for age (Table 2, Figure 2:II). Similar trend was observed in the Austrian cohort, where higher gender score (more traditionally feminine characteristics, Beta=-1.08, 95%CI (-1.26, -0.89), p<0.001) was associated with worse cardiovascular health, whereas, female sex (0.60, 95%CI (0.55, 0.64), p<0.001) was associated with better cardiovascular health when adjusting for age (Table 2, Figure 2: II).

The prevalence of heart disease was 8.7% (n=2,453) and 2.14% (n=150) in males and 6.3% (n=2,212) and 1.59% (n=140) in females in Canadian and Austrian populations, respectively. Higher gender scores were associated with a higher risk of heart disease when compared to female sex in both populations (Table 3). This association was stronger in the Austrian population (Austria: OR=22.14 (7.28, 68.17), vs Canada: 3.87 (2.71, 5.52)).

There was no significant interaction between sex and gender score in predicting cardiovascular health (CANHEART/ATHEART indices) of Austrian and Canadian populations (AT: P=0.5, CA: P=0.09). However, there was a statistically significant interaction between sex and gender for predicting the occurrence of overt heart disease, only in the Canadian population (P=0.04).

DISCUSSION

The results of the present study conducted in population-based samples of Canadians and Austrians demonstrate that, sociocultural gender, referring to personality traits and social characteristics typically ascribed to women, is associated with poorer cardiovascular health and a higher prevalence of heart disease regardless of sex. In contrast, females exhibited better cardiovascular health and a lower prevalence of heart disease than males in both populations independent from baseline CV risk factors.

In this study, we reported a composite measure of gender by creating a gender index in Canadian and Austrian populations. Previous literature [5-7, 32-34] has highlighted the need for building a composite measure to assess the impact of psychosocial variables due to the inherent statistical difficulties associated with addressing the large amount of variables. This study showed that a gender score can be created by different gender-related factors depending on the study population. Though there are a number of overlapping variables such as education, marital status and household income, factors such as perceived life stress and household size were specific to the Canadian population, while frequency of negative emotions was only reported for the Austrian database. Importantly, despite the different components that contribute to the construction of the gender score, the results of the PCA revealed a very similar distribution of the gender score in both countries.

In both populations, females experienced better cardiovascular health, and had a lower prevalence of cardiovascular disease. This finding is similar to the result of the study by Maclagan et al. [31] that also reported better cardiovascular health in females than males and further reported that males had poorer healthy behaviors compared to females except for physical

activity. Some studies have suggested that caregiver status and family commitments are barriers to physical activity in females, which may explain the observed discrepancy in this variable [35, 36]. In contrast, people with characteristics ascribed to women (higher gender scores) experienced worse cardiovascular health and higher risk of heart disease in both populations. The magnitude of this risk was greater in the Austrian population compared to Canada.

Gender Inequality Index (GII), a measure of institutionalized gender, is an index generated by the United Nations and measures gender inequality in three areas: reproductive health, empowerment and economic status [37]. The GII is standardized such that 0 indicates perfect gender equality and 1 indicates perfect inequality (in favour of males) Canada (0,083) and Austria (0,073) have a similar low Gender Inequality Index. Hence the difference in the impact of gender could rather be attributed to differences in sociocultural characteristics, healthcare system or institutionalized structures (education, income) of both populations (Supplementary Table S4b). For example, cultural differences in social support or mother-role expectations could lead to the slight difference between Canada and Austria. [38]

Our findings are consistent with the findings reported by Pelletier et al [5, 6], where a higher risk of adverse cardiovascular outcomes after a premature acute coronary syndrome was evident in patients with personality traits and social roles traditionally ascribed to women, independent of biological sex. Cardiovascular health is determined by various factors, most of which are interacting with living conditions and environment of the individual. Our study explored the impact of classical risk factors such as hypertension, dyslipidemia, diabetes mellitus, smoking and overweight/obesity, in addition to psychosocial factors such as depression, anxiety, chronic life stress, lack of social support and socioeconomic factors like low educational level and low income on cardiovascular disease [39-44].

Currently, one can find studies investigating the effect of some components of our gender index on cardiovascular health. The relationship between a multigenerational household and the risk of suffering a coronary artery incident has also been reported in a study by Ikeda et al [45]. In this study, living with a spouse and children/parents compared to a spouse alone increased the risk of developing coronary artery disease by two folds. Being divorced or separated was an additional factor that was considered in the gender score. While studies have demonstrated a better prognosis after myocardial infarction in married men, middle-aged married females demonstrated a higher fatality risk than unmarried females [46].

Evidence for the role of psychosocial distress and social/environmental adversity on cardiovascular outcomes have been discussed in a variety of disciplines [27, 47]. Our study reveals the importance of psychosocial and gender-related factors in cardiovascular health. Further prospective studies are warranted to assess the multidimensionality of such factors and their impact on cardiovascular disease outcome. Such investigation would facilitate the development of gender-based promotion strategies with the goal of endorsing healthy behaviours in order to further improve the cardiovascular health within the population [4, 27, 29, 31].

There are number of limitations with the current study. The first limitation is the difference in definition of heart disease in the two countries. The CCHS reported heart disease as chronic heart disease diagnosed by a health care professional, whereas AT-HIS definition was history of coronary heart disease or angina pectoris within the past 12 months. That could be the reason why we see differences in the magnitude of higher cardiovascular risk in people with characteristics ascribed to women between the two countries. Additionally, due to the harmonization of both databases some granularity of information was lost. For example, we had

to use household income instead of personal income, since AT-HIS only reported household income.

CONCLUSION

The results of the current study demonstrate that individuals with characteristics typically ascribed to women have poorer cardiovascular health and higher risk of heart disease, independent of biological sex and difference in baseline CV risk factors in both Canadian and Austrian populations. This is while female biological sex exhibited better cardiovascular health and a lower prevalence of heart disease than males in both populations. The study represents a practical approach to assess the complexity of the role of sociocultural gender (i.e. role, identity, relation, institutionalized gender), in a country-specific manner. Current investigations revealed that the magnitude of gender impact varied by country, greater in the Austrian than the Canadian population. This study highlights the need for the consideration and implementation of country specific gender-related factors to improve cardiovascular health.

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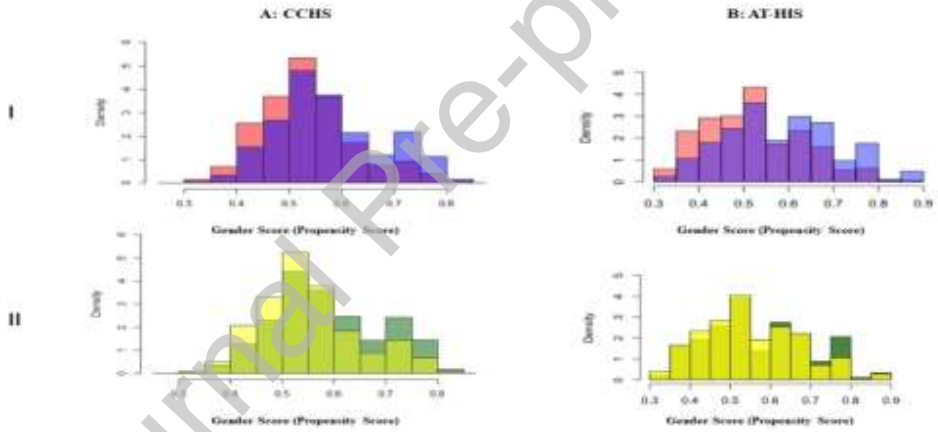
Disclosures:

The authors disclose no conflict of interest related to this study.

Figure Legends:

	CANHEART: Canadian population	ATHEART: Austrian population
Smoking	Non-Smoker or former daily or occasional smoker who quit more than 12 months	Non-Smoker or former daily or occasional smoker who quit more than 12 months
Overweight/obesity	BMI<25	BMI<25
Leisure physical activity	Energy expenditure ≥1.5 kcal/kg/d equivalent to ≥30 minutes of walking per day	number of days doing leisure physical activity for at least 10 min, >3 days a week
Fruit and vegetable consumption	≥5 times per day	1 or more times per day
Hypertension	No self-reported HTN diagnosed by health professional	No self-reported HTN diagnosed by health professional
Diabetes	No self-reported diabetes diagnosed by health professional	No self-reported diabetes diagnosed by health professional

1. Definitions of ideal cardiovascular health in Canadian and Austrian populations (CANHEART and ATHEART indices)



2. Density Plot: Y Axis: probability density of gender, X Axis: gender score
I: Gender score distribution in male and females in Canadian (Left: A) and Austrian populations (Right: B). Red: Gender score in males, Blue: Gender score in females, Purple: Overlapping of Gender score in both groups. Higher gender score demonstrates more feminine characteristics in the population. The distribution of the gender score in men and women did not entirely overlap with biological sex in both populations which shows their partially independent effect.

II: Gender score distribution in CANHEART /ATHHEART index <3 and >=3 in Canadian (Left: A) and Austrian populations (Right: B). Dark green: Gender score in CANHEART/ATHHEART index <3 (i.e., worst CV health), Yellow: Gender score in CANHEART/ATHHEART score >=3 (i.e., ideal CV health), Light green: overlapping of gender score in both groups. Higher gender score, and more feminine characteristics demonstrates worst CV health in both populations.

References:

1. Virani Salim S, Alonso A, Benjamin Emelia J, et al. Heart Disease and Stroke Statistics—2020 Update: A Report From the American Heart Association. *Circulation.* 2020;141:e139-e596.
2. Norris CM, Yip CYY, Nerenberg KA, et al. State of the Science in Women's Cardiovascular Disease: A Canadian Perspective on the Influence of Sex and Gender. *Journal of the American Heart Association.* 2020;9:e015634.
3. Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, et al. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *European heart journal.* 2016;37:24-34.
4. Bartz D, Chitnis T, Kaiser UB, et al. Clinical advances in sex-and gender-informed medicine to improve the health of all: a review. *JAMA Internal Medicine.* 2020;180:574-583.
5. Pelletier R, Khan NA, Cox J, et al. Sex versus gender-related characteristics: which predicts outcome after acute coronary syndrome in the young? *Journal of the American College of Cardiology.* 2016;67:127-135.
6. Pelletier R, Ditto B, Pilote L. A composite measure of gender and its association with risk factors in patients with premature acute coronary syndrome. *Psychosomatic medicine.* 2015;77:517-526.
7. Lippa R, Connelly S. Gender diagnosticity: A new Bayesian approach to gender-related individual differences. *Journal of Personality and Social Psychology*. 1990;59:1051.
8. Johnson JL, Greaves L, Repta R. *Better science with sex and gender: A primer for health research*: Women's Health Research Network Vancouver; 2007.
9. Carothers BJ, Reis HT. Men and women are from Earth: Examining the latent structure of gender. *Journal of personality and social psychology.* 2013;104:385.
10. Unger RK. Toward a redefinition of sex and gender. *American Psychologist.* 1979;34:1085.
11. CIHR. Online Training Modules: Integrating Sex & Gender in Health Research: CIHR; 2019. Vol 20202019.
12. Phillips SP. Defining and measuring gender: a social determinant of health whose time has come. *International journal for equity in health.* 2005;4:11-11.
13. WHO. A conceptual framework for action on the social determinants on health. Vol 20202010.
14. Huxley VH. Sex and the cardiovascular system: the intriguing tale of how women and men regulate cardiovascular function differently. *Adv Physiol Educ.* 2007;31:17-22.
15. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet (London, England).* 2011;378:1297-1305.
16. Peters SA, Huxley RR, Woodward M. Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes. *Stroke.* 2013;44:2821-2828.
17. Spence JD, Pilote L. Importance of sex and gender in atherosclerosis and cardiovascular disease. *Atherosclerosis.* 2015;241:208-210.
18. Izadnegahdar M, Singer J, Lee MK, et al. Do younger women fare worse? Sex differences in acute myocardial infarction hospitalization and early mortality rates over ten years. *Journal of women's health (2002).* 2014;23:10-17.
19. Sozzi FB, Danzi GB, Foco L, et al. Myocardial infarction in the young: a sex-based comparison. *Coronary artery disease.* 2007;18:429-431.
20. Kawase K, Kwong A, Yorozuya K, Tomizawa Y, Numann PJ, Sanfey H. The attitude and perceptions of work-life balance: a comparison among women surgeons in Japan, USA, and Hong Kong China. *World journal of surgery.* 2013;37:2-11.

21. Winham SJ, de Andrade M, Miller VM. Genetics of cardiovascular disease: Importance of sex and ethnicity. *Atherosclerosis.* 2015;241:219-228.

22. Forouzanfar MH, Afshin A, Alexander LT, Anderson HR, Bhutta ZA, Biryukov S. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet.* 2016;388:1659-1724.

23. Lee SK, Khambhati J, Varghese T, et al. Comprehensive primary prevention of cardiovascular disease in women. *Clinical cardiology.* 2017;40:832-838.

24. Shiroma EJ, Lee IM. Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. *Circulation.* 2010;122:743-752.

25. Lacasse A, Pagé MG, Choinière M, et al. Conducting gender-based analysis of existing databases when self-reported gender data are unavailable: the GENDER Index in a working population. *Canadian Journal of Public Health.* 2020:1-14.

26. Norris CM, Murray JW, Triplett LS, Hegadoren KM. Gender roles in persistent sex differences in health-related quality-of-life outcomes of patients with coronary artery disease. *Gender medicine.* 2010;7:330-339.

27. Chida Y, Steptoe A. Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: a meta-analysis of prospective evidence. *Hypertension.* 2010;55:1026-1032.

28. Peterson PN. JAHA Spotlight on Psychosocial Factors and Cardiovascular Disease. *Journal of the American Heart Association.* 2020;9:e017112.

29. White-Williams C, Rossi LP, Bittner VA, et al. Addressing Social Determinants of Health in the Care of Patients With Heart Failure: A Scientific Statement From the American Heart Association. *Circulation.* 2020;141:e841-e863.

30. Fortier I, Raina P, Van den Heuvel ER, et al. Maelstrom Research guidelines for rigorous retrospective data harmonization. *International journal of epidemiology.* 2017;46:103-105.

31. Maclagan LC, Park J, Sanmartin C, et al. The CANHEART health index: a tool for monitoring the cardiovascular health of the Canadian population. *CMAJ.* 2014;186:180-187.

32. Koch CG, Mangano CM, Schwann N, Vaccarino V. Is it gender, methodology, or something else? *The Journal of thoracic and cardiovascular surgery.* 2003;4:932-935.

33. Whittaker KS, Krantz DS, Rutledge T, et al. Combining psychosocial data to improve prediction of cardiovascular disease risk factors and events:: The NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study. *Psychosomatic medicine.* 2012;74:263.

34. Glynn RJ, Schneeweiss S, Stürmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic & clinical pharmacology & toxicology.* 2006;98:253-259.

35. Pilote L, Dasgupta K, Guru V, et al. A comprehensive view of sex-specific issues related to cardiovascular disease. *Cmaj.* 2007;176:S1-44.

36. King AC, Castro C, Wilcox S, Eyler AA, Sallis JF, Brownson RC. Personal and environmental factors associated with physical inactivity among different racial-ethnic groups of U.S. middle-aged and older-aged women. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association.* 2000;19:354-364.

37. PROGRAMME UND. Gender Inequality Index (GII). Vol 20202019.

38. Tandon A, Murray CJ, Lauer JA, Evans DB. Measuring overall health system performance for 191 countries. *Geneva: World Health Organization.* 2000.

39. Greenland P, Knoll MD, Stamler J, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *Jama.* 2003;290:891-897.

40. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. *Jama.* 2003;290:898-904.

41. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation.* 1999;99:2192-2217.

42. Dorner T, Kiefer I, Kunze M, Rieder A. [Gender aspects of socioeconomic and psychosocial risk factors of cardiovascular diseases]. *Wien Med Wochenschr.* 2004;154:426-432.

43. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. *Circulation.* 1993;88:1973-1998.

44. Diez Roux AV, Merkin SS, Arnett D, et al. Neighborhood of residence and incidence of coronary heart disease. *N Engl J Med.* 2001;345:99-106.

45. Ikeda A, Iso H, Kawachi I, et al. Living arrangement and coronary heart disease: the JPHC study. *Heart.* 2009;95:577-583.

46. Kilpi F, Konttinen H, Silventoinen K, Martikainen P. Living arrangements as determinants of myocardial infarction incidence and survival: a prospective register study of over 300,000 Finnish men and women. *Social Science & Medicine.* 2015;133:93-100.

47. Greaney JL, Surachman A, Saunders EF, Alexander LM, Almeida DM. Greater daily psychosocial stress exposure is associated with increased norepinephrine-induced vasoconstriction in young adults. *Journal of the American Heart Association.* 2020;9:e015697.

TABLES

Table1: Multivariate logistic model for assessing association of gender variables with biological sex as dependent variable

CCHS		AT-HIS	
Gender Variables	**OR (95%CI)**	**Gender Variables**	**OR (95%CI)**
Household size		**Frequency of negative emotions**	
(Reference:1Person)	-	(Reference:1=Never)	-
2 Persons	1.22(1.15-1.30)	2=Not often	1.62 (1.49-1.75)
3 Persons	1.25(1.17-1.34)	3= Intermittently	2.57 (2.33-2.83)
4 Persons	1.37(1.28-1.47)	4= Often	2.71 (2.33-3.15)
5 & 5+ Persons	1.36(1.25-1.47)	5= Always	2.03 (1.41-2.93)
Perceived life stress:			
stress during the day		**Education**	
(Reference: 1=not at all)	-	(Reference: <Secondary)	-
2=not very	1.37(1.29-1.44)	Secondary	0.57(0.51-0.62)
3=a bit	1.57(1.49-1.66)	Post secondary	0.65(0.58-0.69)
4=quite a bit	1.76(1.66-1.88)	>Post secondary	0.51(0.45-0.59)
5=Extremely	1.81(1.62-2.03)		
Education		**Marital Status**	
(Reference: <Secondary)	-	(Reference: Single)	-
Secondary	1.23(1.17-1.30)	Divorced/widowed	2.14 (1.92-2.38)
Post secondary	1.12(1.03-1.22)	Common-in-law/married	1.18 (1.1-1.27)
>Post secondary	1.20(1.15-1.26)		
Sense of belonging to community		**Household Income**	
(Reference:1=very weak)	-	(Reference: High)	-
2=somewhat weak	1.03(0.96-1.11)	Medium	1.20(1.1-1.31)
3=somewhat strong	1.16(1.08-1.24)	Low	1.24(1.15-1.34)
4=very strong	1.19(1.10-1.28)		
Marital Status	-		
(Reference: Single)	2.62(2.47-2.77)		
Divorced/widowed	1.16(1.11-1.22)		
Common-in-law/married			
Household Income	-		
(Reference: High)			
Medium	1.37(1.32-1.43)		
Low	1.81(1.69-1.94)		

Gender index was calculated through the construction of a propensity score, which was derived from coefficient estimates in the final logistic regression model with biological sex as dependent variable and gender related variables as covariates. The propensity score for each person was defined as the conditional probability of being a female versus a male based on gender-related variables. This score ranges from 0-1, with higher scores relating to characteristics traditionally ascribed to women.

Table 2: Association between cardiovascular health with biological sex and gender in Canadian and Austrians populations

	Cardiovascular health in Canadians (CANHEART score)			Cardiovascular health in Austrians (ATHEART score)		
	Unstandardized Coefficient (β)	95% CI	P-value	Unstandardized Coefficient (β)	95% CI	P-value
Gender score	-1.33	-1.44, -1.22	<0.001	-1.08	-1.26, -0.89	<0.001
Sex (Female)	0.35	0.33, 0.37	<0.001	0.6	0.55, 0.64	<0.001
Age groups						
<20 (reference)	-	-	-	-	-	-
20-29	-0.49	-0.53, -0.44	<0.001	-0.5	-0.62, -0.37	<0.001
30-39	-0.65	-0.70, -0.61	<0.001	-0.83	-0.95, -0.71	<0.001
40-49	-0.88	-0.92, -0.83	<0.001	-0.86	-0.97, -0.74	<0.001
50-59	-1.14	-1.18, -1.10	<0.001	-1.1	-1.22, -0.99	<0.001
60-69	-1.23	-1.27, -1.19	<0.001	-1.2	-1.34, -1.10	<0.001
>=70	-1.24	-1.29, -1.20	<0.001	-1.19	-1.31, -1.07	<0.001

Table 3: Associations between sex, gender and heart disease in Canadian and Austrian populations

	Canadians			Austrians		
Predictors of Heart Disease	**Odds Ratio (OR)**	**95% CI**	**P-value**	**Odds Ratio (OR)**	**95% CI**	**P-value**
CANHEART score (Canadians) ATHEART score (Austrians)	0.73	0.71,0.75	<0.001	0.77	0.69, 0.86	<0.001
Gender score	3.87	2.71,5.52	<0.001	22.14	7.28, 68.17	<0.001
Sex (Female)	0.58	0.54, 0.62	<0.001	0.61	0.46, 0.82	0.002
Age groups						
<20 (reference)	-	-	-	-	-	-
20-29	0.95	0.62, 1.48	0.96	0.94	0.2, 4.42	0.70
30-39	0.70	0.45, 1.1	0.12	0.32	0.07,1.67	0.08
40-49	1.82	1.26, 2.68	0.001	0.53	0.16, 2.38	0.21

50-59	4.62	3.34, 6.60	<0.001	2.14	0.77, 8.91	0.34
60-69	8.78	6.38, 12.47	<0.001	3.95	1.44, 16.36	0.04
>=70	19.45	14.16, 27.59	<0.001	7.28	2.32, 26.00	0.001