Title: The contribution of modifiable risk factors to socioeconomic inequities in cardiovascular disease morbidity and mortality: a nationally representative population-based cohort study

Authors: Sara Nejatinamini MPH, PhD[1], David JT Campbell MD, MSc, PhD[2], Jenny Godley MA, PhD[1,3], Leia M Minaker MSc, PhD[4], Tolulope T Sajobi MSc, PhD [1], Gavin R McCormack MSc, PhD [1], Dana Lee Olstad MSc, PhD, RD [1*]

Affiliations: [1]Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada, [2]Departments of Medicine, Community Health Sciences & Cardiac Sciences, Cumming School of Medicine, University of Calgary, [3]Department of Sociology, University of Calgary, Calgary, Alberta, Canada, [4]School of Planning, University of Waterloo, Waterloo, Ontario, Canada.

*__Corresponding author:__ Dr. Dana Olstad, Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, 3E16, 3280 Hospital Drive NW Calgary, AB, Canada, T2N 4Z6. Email: dana.olstad@ucalgary.ca; Phone: 403-210-8673.

Word count of the main text: 3610

Word count of the abstract: 249

Abstract

This study examined the individual and joint effects of modifiable risk factors mediating the associations between socioeconomic position (SEP) and morbidity and mortality from cardiovascular diseases (CVD) in a nationally representative sample of adults in Canada.

Participants in the Canadian Community Health Survey (n=289,800) were followed longitudinally for CVD morbidity and mortality using administrative health and mortality data. SEP was measured as a latent variable consisting of household income and individual educational attainment. Mediators included smoking, physical inactivity, obesity, diabetes and hypertension. The primary outcome was CVD morbidity and mortality, defined as the first fatal/nonfatal CVD event during follow-up (median 6.2 years). Generalized structural equation modeling tested the mediating effects of modifiable risk factors in associations between SEP and CVD in the total population and stratified by sex.

Lower SEP was associated with 2.5 times increased odds of CVD morbidity and mortality (OR: 2.52, 95% CI: 2.28, 2.76). Modifiable risk factors mediated 74% of associations between SEP and CVD morbidity and mortality in the total population and were more important mediators of associations in females (83%) than males (62%). Smoking mediated these associations independently and jointly with other mediators. The mediating effects of physical inactivity were through joint mediating effects with obesity, diabetes or hypertension. There were additional joint mediating effects of obesity through diabetes or hypertension in females.

Findings point to modifiable risk factors as important targets for interventions along with interventions that target structural determinants of health to reduce socioeconomic inequities in CVD.

Keywords: Socioeconomic position; health inequities; modifiable risk factors; cardiovascular disease; mediation analyses

1. Introduction

Socioeconomic position (SEP), as assessed by factors such as income, educational attainment and occupational prestige, is strongly associated with morbidity and mortality from cardiovascular diseases (CVD) in Canada and other nations.[1–3] The World Health Organization (WHO) conceptual framework describes SEP as a fundamental determinant of health and health inequities because it shapes individuals' exposures and vulnerability to intermediary determinants of health such as material and psychosocial circumstances, along with health-related practices and biological factors. [4] This model provided an overarching framework for the current analyses.

Approximately 70% of CVD morbidity and mortality has been attributed to potentially modifiable health-related practices (smoking and physical inactivity) and biological risk factors (obesity, diabetes and hypertension).[5–7] All of these risk factors have been shown to individually mediate associations between SEP and a variety of health outcomes, including CVD.[8–16] To our knowledge, just four previous studies have examined associations between SEP and CVD mediated by health-related practices and biological risk factors.[13–16] However, important knowledge gaps remain. Most importantly prior studies have not examined potential mediating roles of multiple health-related practices and biological factors simultaneously in one model, including their joint mediating effects.[17,18] Second, prior studies tended to use single variables (e.g., income, occupation, education) to represent SEP, which only partly captures its multiple dimensions. Third, prior studies did not examine time-to-event outcomes, and therefore did not account for the different follow up times of each cohort member in their mediation analyses. Fourth, although two studies stratified their analyses by sex,[13,14] direct comparisons of their findings are difficult due to differences in indicators of SEP, mediators, and populations thus it remains unclear whether and to what extent mediators of associations between SEP and CVD differ between males and females. Finally, all prior studies were conducted in European nations, none of which used nationally representative samples. It is important to examine whether and how these pathways may differ in other contexts, given significant differences in political, economic, physical and social environments between nations.[19] Understanding the socially contingent nature of mediation pathways is essential for effective intervention.

In this study, we addressed these limitations by leveraging a large, nationally representative dataset to explore the individual and joint mediating effects of modifiable risk factors, including smoking, physical inactivity, obesity, hypertension and diabetes in associations between SEP and CVD morbidity and mortality among adults in Canada. We also examined whether the pathways linking low SEP with CVD morbidity and mortality differed for males and females.

2. Methods

2.1. Study design and participants

This study employed a population-based prospective observational cohort design whereby individuals who participated in the Canadian Community Health Survey (CCHS) - Annual between 2000/2001 and 2011 were followed longitudinally for CVD morbidity and mortality using administrative data. The cohort consisted of CCHS participants who consented to have their survey responses linked with administrative data (85.3%; n=614,774).[20] We excluded participants under 35 years of age, pregnant and breastfeeding women, those who self-reported having been diagnosed with heart disease or stroke at the time of survey administration, and those who resided in a province that did not report to the Discharge Abstract Database (DAD; Manitoba before 2004 and Quebec) (Figure 1). Thus, n=289,800 participants were included in the analyses. The follow-up period for each participant started from the completion date of the cycle of the CCHS to which the participant responded and ended on the date of the first CVD hospitalization, death, or 31 March 2013 (the endpoint of the study), whichever came first. The procedures followed were in accordance with the ethical standards of the Helsinki Declaration of 1975 as revised in 1983. The Conjoint Health Research Ethics Board at the University of Calgary deemed this study exempt from ethical approval because it involved secondary data analysis of a survey conducted by Statistics Canada.[21]

2.2. Data sources

We used a dataset that linked respondents from eight cycles of the CCHS (2000/2001 - 2011) to longitudinal administrative health/mortality data in the DAD (2000-2013) and the Canadian Mortality Database (CMDB; 2000-2013). This data set was used because the more recent 2000-2017 data set did not include imputed household income for all years. The accuracy and

completeness of the linkage process was confirmed by internal and external validations conducted by Health Canada.[22,23]

2.2.1. Canadian Community Health Survey

The CCHS is an ongoing nationally representative cross-sectional survey that uses a multistage, stratified cluster sampling strategy to collect health-related information from individuals living in Canada, including health status, health care utilization, health-related practices and health determinants. Details of the CCHS methodology have been described elsewhere. [20]

2.2.2. Discharge Abstract Database

The DAD captures administrative and clinical data for all patients discharged from acute care hospitals in Canada, except the province of Quebec and respondents from Manitoba before 2004. For consistency across survey cycles, International Classification of Diseases and Related Health Problems, 9th Revision (ICD-9) codes assigned for survey cycles before 2004 were converted to ICD-10-CA. Hospital admission date and the most responsible diagnosis (main diagnosis or condition that was the most responsible for the patient's hospital stay) were extracted for all hospitalizations between 2000 and 2013.

2.2.3. Canadian Mortality Database

The CMDB contains the cause of death (using ICD-10CA codes) reported by provincial and territorial Vital Statistics Registries to Statistics Canada. This analysis used data from the CMDB for the years 2000 to 2013.

2.3. Data collection

2.3.1. Exposures

Household income: Respondents reported total household income from all sources in the previous 12 months. Respondents were divided into deciles based on the adjusted ratio of their total household income to the low-income cut-off corresponding to their household and community size, as derived by Statistics Canada.[20] Missing data for household income were

imputed by Statistics Canada[24]. Income deciles were then dichotomized as lower (deciles 1-5) or higher (deciles 6-10).

Educational attainment: The respondent's highest educational attainment was dichotomized as completed secondary school or less or completed post-secondary education or above.

2.3.2. Mediators

Smoking: Self-reported tobacco smoking was dichotomized as current or never/former smoker.[25]

Physical inactivity: A physical activity index was derived based on responses to 22 leisure activities over the past 3 months. These responses represent the average daily energy expended on leisure-time physical activity.[26] Participants were dichotomized as active/moderately active (≥1.5 kcal/kg/d) or inactive (<1.5 kcal/kg/d).

Obesity: Self-reported body weight and height were used to calculate BMI, and respondents were dichotomized as having (BMI≥30 kg/m^2) or not having obesity (BMI<30 kg/m^2).

Diabetes: Respondents were dichotomized as having (self-reported ever being diagnosed with diabetes after age 30 years) or not having diabetes.[27]

Hypertension: Respondents were dichotomized as having (self-reported ever being diagnosed with high blood pressure) or not having hypertension.

2.3.3. Outcome

The primary outcome was CVD morbidity and mortality, defined as the first fatal or nonfatal CVD event that occurred during follow-up and dichotomized as presence or absence of CVD morbidity and/or mortality. CVD morbidities were identified from the DAD, and deaths due to CVD were identified through the CMDB. CVD was identified using diagnosis codes for ischemic

heart diseases, heart failure, stroke and peripheral artery disease (ICD-10CA I20/I25; I50; I63/I66; I70/I75 and ICD-9 428; 440/444; 433/437; 410/414).

2.3.4. Potential confounders

Potential confounders included in statistical models were sex (male, female), age (continuous) and race/ethnicity (white, non-white).

2.4. Data analysis

2.4.1. Statistical analyses

Generalized Structural Equation Modeling (GSEM) was performed to model pathways linking SEP with CVD morbidity and mortality mediated by modifiable risk factors (Figure 2).[28] In GSEM, it is possible to group inter-correlated variables into latent constructs, which reduces measurement error by having multiple indicators per latent construct. In this study, we used a latent variable for SEP consisting of household income and educational attainment.[17,29] The GSEM model was developed a priori based on the WHO Framework,[4] and included mediators shown to individually mediate associations between SEP and CVD in the literature.[8–16] We also tested bi-variate associations between the exposure, mediators and outcome in a step-wise manner and pathways were drawn between variables that were significantly associated ($p<0.05$) (Figure 2).[16] There were statistically significant interactions with sex in all bi-variate associations ($p<0.05$), hence all analyses were conducted in the total population and for males and females separately. To account for the fact that some mediators may be on the causal pathway for others, we allowed health-related practices (smoking and physical inactivity) to act as mediators individually and jointly through biological risk factors (obesity, diabetes and hypertension). Similarly, we examined obesity as a mediator individually and jointly through diabetes and hypertension. The model was adjusted for potential confounders by adding directional paths from them to all variables in the model. We compared two candidate models, one with smoking and physical inactivity as categorical mediators and another where all mediators were binary. The GSEM model with binary mediators was selected as it had smaller Akaike's information criterion (AIC) and Bayesian information criterion (BIC) values, indicating better model fit.

The GSEM model was fitted using the maximum-likelihood method assuming logit links and Bernoulli distributions (binary data) for all variables. We used dichotomized exposures and mediators to enable comparability of estimates between the various pathways we estimated. [30] Odds ratios (OR; exponentiated coefficients from Bernoulli distributions) and unstandardized coefficients of direct, indirect and total effects were calculated. Interactions between SEP and the mediators were not significant and were therefore not included in the final model.[37] The total effect was calculated as the sum of the direct (unmediated) and indirect effects (indirect effect of all mediators combined). The proportion mediated was calculated by dividing the coefficients of the total indirect effect by the total effect.[31] Differences in total, indirect and direct effects between males and females were tested by multi-group GSEM analysis using bootstrapped standard errors (500 replications).

The percentage of missing values for variables in our dataset was minimal (<5.2%) and handled by list-wise deletion. All analyses were conducted using Stata version 15 (Stata Corp, Texas, USA). P values <0.05 were considered statistically significant. Sampling weights created by Statistics Canada were used to adjust for those who did not agree to data sharing and linkage (~15% of the sample) and estimates were weighted to represent the population of Canada. Bootstrapping based on 500 replications was performed to derive 95% confidence intervals (CIs) for all mediation parameters.

2.4.2. Sensitivity analyses

We excluded CVD events that occurred within the first year of follow-up to reduce potential reverse causation. Furthermore, to account for differing observation times of participants in each cycle of the cohort, we conducted GSEM with time-to-event analysis. A Weibull distribution with a logit link was used to handle time to CVD morbidity and mortality, with logit links and Bernoulli distributions for all other variables. In this model, the exponentiated coefficients are hazards ratios. We also conducted a sensitivity analysis in which we additionally adjusted our models for a co-morbidity score (self-reported cancer, intestinal or stomach ulcers, chronic bronchitis, emphysema or chronic obstructive pulmonary disease at baseline). In addition, we examined household income and educational attainment as separate exposures to evaluate whether the estimated mediation effects were similar to that of the primary analysis.

3. Results

The study population comprised 289,800 CCHS participants, with a mean age of 53.3 ± 12.9 years at the time of survey administration (Table 1). During a mean follow-up time of 5.3 ± 3.3 years (median 6.2 years, IQR 2.25-8.25), 2.8% of participants were discharged from hospital with a CVD diagnosis and/or died from CVD, with significant differences by sex (1.9% in females *vs.* 3.6% in males; p<0.001).

Odds ratios of direct, indirect and total effects of SEP on CVD morbidity and mortality are presented in Table 2 and are described in the text to enable direct comparisons between the various mediating pathways. Unstandardized coefficients of the total, indirect and direct effects are presented in Supplementary Table 1.

3.1. Total effects of SEP

The total effects of SEP on CVD morbidity and mortality were significant in the total population (OR: 2.52, 95% CI: 2.28, 2.76) and among females (OR: 3.58, 95% CI: 3.00, 4.15) and males (OR: 2.04, 95% CI: 1.78, 2.29) (Table 2). The total effects of SEP on CVD morbidity and mortality were higher in females than in males (p<0.001).

3.2. Direct effects of SEP

In the total population, the odds ratio of CVD morbidity and mortality was higher among respondents of low SEP (OR: 1.27, 95% CI: 1.17, 1.37) (Table 2, Figure 2). Similar results were found for females and males (p<0.001).

3.3. Indirect effects of SEP

The proportion of the total effect of SEP mediated by all of the modifiable risk factors together was 73.9%, 83.4% and 61.9% in the total population, females and males, respectively (Table 2). The total indirect effects of SEP were higher in females than in males (OR: 2.89, 95% CI: 2.41, 3.37 *vs.* OR: 1.55, 95% CI: 1.31, 1.79; p<0.001). Smoking mediated associations between SEP and CVD morbidity and mortality in the total population (OR: 1.57, 95% CI: 1.46, 1.68) and among females and males. There was also evidence of joint mediating effects of smoking with

all other mediators in all groups, although the joint mediating effects of smoking with obesity or hypertension were not significant in females.

In the total population, physical inactivity mediated the effects of SEP on CVD morbidity and mortality through joint mediating effects with other mediators including: obesity (OR: 1.04, 95% CI: 1.02, 1.07), diabetes (OR: 1.04, 95% CI: 1.02, 1.06), hypertension (OR: 1.03, 95% CI: 1.02, 1.06), obesity and hypertension (OR: 1.08, 95% CI: 1.05, 1.10), and obesity and diabetes (OR: 1.10, 95% CI: 1.06, 1.14). Similar indirect effects were found among females and males, although the latter joint mediating effect was stronger in females than in males ($p<0.001$).

The indirect effect of SEP through obesity was significant in the total population (OR: 1.02, 95% CI: 1.01, 1.04) and among females and males (Table 2, Figure 2). Obesity also mediated the effects of SEP on CVD morbidity and mortality through its associations with diabetes or hypertension in females but not among males.

3.4. Sensitivity analyses

Similar results were found when we excluded CVD events that occurred within the first year of follow-up (Supplementary Table 2 and Table 3). Furthermore, results from the analysis with time to CVD morbidity and mortality as the outcome of interest were similar to the results of the main analyses (Supplementary Table 4 and Table 5). Sensitivity analyses in which we adjusted our models for co-morbidity score showed similar results (data not shown). When income and education were included as individual exposures, results were largely consistent with the primarily analysis with a few exceptions. First, the indirect effects of household income through physical inactivity were significant in the total population. Similar results were found in females when educational attainment was the exposure. Second, the total and indirect effects of educational attainment were larger than they were for household income and the latent SEP variable. Third, compared to when SEP was the exposure, the indirect effects of educational attainment through obesity were slightly higher, and the indirect effects of household income through obesity were slightly lower among males (Supplementary Table 6 and Table 7).

4. Discussion

This is the first study to investigate individual and joint mediating effects of modifiable risk factors in associations between SEP and CVD morbidity and mortality in a nationally representative prospective cohort. We assessed mediation by multiple modifiable risk factors simultaneously while taking into account that these factors may influence CVD morbidity and mortality jointly as well as through individual pathways. Results indicated that SEP was prospectively associated with CVD morbidity and mortality among adults ≥ 35 years of age living in Canada, with respondents in the low SEP group having 2.5 times higher likelihood of CVD morbidity and mortality relative to those in the high SEP group. Modifiable risk factors jointly mediated 74% of associations between SEP and CVD morbidity and mortality, with higher mediating effects in females than in males.

Smoking was an important mediator of associations between SEP and CVD morbidity and mortality, both individually and jointly with other mediators. Others have also found smoking to be an important mediator of these associations.[13,16,32] The mediating role of smoking in these associations is likely due to the fact that low SEP is associated with an increased risk of smoking initiation, progression to regular smoking and a reduced likelihood of cessation, along with the fact that smoking is one of the strongest risk factors for CVD.[7,33,34] These findings suggest that while tobacco control programs and policies have succeeded in reducing overall tobacco use in Canada, they do not appear to have reduced inequities in the negative health effects of smoking.[35]

Except for small mediating effects of obesity in the total population, there was no evidence that physical inactivity and obesity individually mediated associations between SEP and morbidity and mortality from CVD in females or males. Instead, our findings indicated that physical inactivity and obesity mediated associations between SEP and CVD morbidity and mortality through joint mediating effects with diabetes or hypertension. Prior studies found that obesity and/or physical activity individually mediated associations between education and CVD, however these studies did not consider joint mediating effects through these and other modifiable risk factors.[14,30] In support of our findings, Mora et al (2007)[38] found that associations between physical inactivity and CVD morbidity were mediated via obesity and hypertension, while others have found that diabetes and hypertension explained nearly one-half of associations between obesity and CVD morbidity and mortality.[39]

The total effects of SEP were higher in females than in males and there were some sex-specific patterns in indirect effects. These findings suggest that females may be more susceptible to the negative health effects of a lower SEP, which is consistent with previous studies.[40–42] Although participants in the CCHS reported biological sex, sex and gender are interrelated, and thus it is not possible to separate their effects. The mechanisms underpinning these sex/gender-specific differences are likely related to sex/gender differences in the socioeconomic patterning of modifiable risk factors that are both biological in nature and linked to gender identity and societal roles.[43,44] Our findings therefore suggest that strategies to reduce socioeconomic inequities in morbidity and mortality from CVD may require distinct approaches for males and females.

Our findings suggest that midstream interventions that address smoking, physical inactivity and obesity among lower SEP groups may be important leverage points for intervention to reduce the risk of developing diabetes and hypertension, and subsequent CVD. Our analysis highlights the linked nature of modifiable mediators and suggests that rather than addressing single mediators in isolation, a more useful approach could be to target multiple mediators simultaneously. This is consistent with the concept of 'health lifestyles,' which refer to constellations of health-related practices that co-occur, some of which may be more or less healthful.[45,46] These practices emerge from the interaction of agency and structure, whereby individuals choose those practices that are available and accessible to them based on their unique social locations and group memberships.[45,46] Addressing underlying 'health lifestyles' may therefore be essential to meaningfully change individuals' health trajectories. Nevertheless, although midstream interventions that target health-related practices and biological risk factors can be helpful, health inequities will persist so long as social inequities do. Therefore, it will ultimately be essential to tackle the social mechanisms that yield unequal access to the social determinants of health, including governance mechanisms, macroeconomic and social policies, cultural and societal values, among others.[4]

The large and nationally representative sample with prospective follow-up over a median of 6.2 years was an important strength of this study. In addition, we excluded individuals with self-reported CVD at baseline and conducted a sensitivity analysis excluding those who were diagnosed with CVD or died within the first year after completing the survey to minimize the potential for reverse causality. There are also limitations of this study. First, OR could

overestimates the risk ratio when the incidence of the outcome is high, so caution in interpretation is required. SEP and modifiable risk factors were only measured once at baseline and were not updated over time. In addition, SEP and all mediators were assessed at the same time, however education is very likely to have been stable for many years prior to baseline (i.e. adults were aged ≥ 35 years) and the CCHS requested household income in the previous 12 months. Therefore, there is a stronger case for the temporal ordering of our exposures and mediators, although the temporal associations between health-related practices and biological mediators are less certain. For this reason, we have referred to joint, rather than to sequential mediating effects throughout. By its very nature, modeling entails simplifying complex relationships. Finally, although we were able to explain 74% of associations between SEP and CVD, one quarter of the associations between SEP and CVD morbidity and mortality remained unexplained by our model. Future studies might assess the potential mediating role of factors such as dyslipidemia, dietary patterns, social support, stress, and food insecurity, among others, in accounting for the remainder of these associations.

5. Conclusion

In conclusion, low SEP was prospectively associated with 2.5 times increased odds of CVD morbidity and mortality among adults ≥ 35 years of age living in Canada. Modifiable risk factors mediated 74% of associations between SEP and CVD morbidity and mortality. Smoking was an important mediator of these associations, both individually and jointly with other risk factors. The mediating effects of physical inactivity and obesity operated through joint mediating effects with diabetes or hypertension. Some of these pathways differed in females and males. While these findings highlight modifiable risk factors as targets to alleviate inequities in CVD morbidity and mortality in the medium-term, effective long-term solutions must also address the structural upstream determinants of inequities in CVD morbidity and mortality to enhance health equity.

Funding

This study was funded by a Libin Cardiovascular Research Institute of Alberta Innovation Seed Grant and the Petro-Canada Young Innovator Award in Community Health. SN was supported by a Libin Cardiovascular Research Institute of Alberta/Cumming School of Medicine Postdoctoral Award.

CRediT authorship contribution statement

Sara Nejatinamini: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing - original draft **David JT Campbell:** Conceptualization; Writing - review & editing **Jenny Godley** Conceptualization; Writing - review & editing **Leia M Minaker** Conceptualization; Writing - review & editing **Tolulope T Sajobi** Conceptualization; Writing - review & editing **Gavin R McCormack** Conceptualization; Writing - review & editing **Dana Lee Olstad** Conceptualization; Investigation; Resources; Methodology; Supervision; Funding acquisition; Writing - original draft

Declaration of Competing Interest

DLO and DJTC have received research support from a Petro-Canada Young Innovator Award in Community Health. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data described in the article cannot be made available because the data are held by Statistics Canada. Statistics Canada permits approved researchers to access its data sets within its Research Data Centres (https://www.statcan.gc.ca/eng/microdata/data-centres).

Appendix A. Supplementary data

References:

1. Choinière R, Lafontaine P, Edwards AC. Distribution of cardiovascular disease risk factors by socioeconomic status among Canadian adults. *CMAJ*. Published online 2000.

2. Filate WA, Johansen HL, Kennedy CC, Tu J V. Regional variations in cardiovascular mortality in Canada. *Can J Cardiol*. Published online 2003.

3. Lee DS, Chiu M, Manuel DG, et al. Trends in risk factors for cardiovascular disease in Canada: Temporal, socio-demographic and geographic factors. *CMAJ*. Published online 2009. doi:10.1503/cmaj.081629

4. Solar, O. & Irwin A. *A Conceptual Framework for Action on the Social Determinants of Health. Discussion Paper for the Commission on Social Determinants of Health*.; 2010. doi:ISBN 978 92 4 150085 2

5. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet*. 2016;388(10046):761-775. doi:10.1016/S0140-6736(16)30506-2

6. Yusuf S, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364(9438):937-952. doi:10.1016/S0140-6736(04)17018-9

7. Yusuf S, Joseph P, Rangarajan S, Islam S, Mente A, Hystad P, Brauer M, Kutty VR, Gupta R, Wielgosz A, AlHabib KF, Dans A, Lopez-Jaramillo P, Avezum A, Lanas F, Oguz A, Kruger IM, Diaz R, Yusoff K, Mony P, Chifamba J, Yeates K, Kelishadi R, Yusufali A, Kha DG. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet*. 2020;395(10226):795-808.

8. Petrovic D, de Mestral C, Bochud M, et al. The contribution of health behaviors to socioeconomic inequalities in health: A systematic review. *Prev Med (Baltim)*. 2018;113:15-31. doi:10.1016/j.ypmed.2018.05.003

9. Hossin MZ, Koupil I, Falkstedt D. Early life socioeconomic position and mortality from cardiovascular diseases: An application of causal mediation analysis in the Stockholm Public Health Cohort. *BMJ Open*. 2019;9(6). doi:10.1136/bmjopen-2018-026258

10. Van Lenthe FJ, Gevers E, Joung IMA, Bosma H, Mackenbach JP. Material and behavioral factors in the explanation of educational differences in incidence of acute myocardial infarction: The globe study. *Ann Epidemiol*. Published online 2002. doi:10.1016/S1047-2797(01)00279-4

11. Kivimäki M, Lawlor DA, Smith GD, et al. Socioeconomic position, co-occurrence of behavior-related risk factors, and coronary heart Disease: The finnish public sector study. *Am J Public Health*. Published online 2007. doi:10.2105/AJPH.2005.078691

12. John Lynch, George Davey Smith, Sam Harper KB. Explaining the social gradient in coronary heart disease: comparing relative and absolute risk approaches. *J Epidemiol Community Heal*. 2006;60:436-441.

13. Woodward M, Oliphant J, Lowe G, Tunstall-Pedoe H. Contribution of contemporaneous risk factors to social inequality in coronary heart disease and all causes mortality. *Prev Med (Baltim)*. 2003;36(5):561-568. doi:10.1016/S0091-7435(03)00010-0

14. Nordahl H, Rod NH, Frederiksen BL, et al. Education and risk of coronary heart disease: Assessment of mediation by behavioral risk factors using the additive hazards model. *Eur J Epidemiol*. 2013;28(2):149-157. doi:10.1007/s10654-012-9745-z

15. Méjean C, Droomers M, Van Der Schouw YT, et al. The contribution of diet and lifestyle to socioeconomic inequalities in cardiovascular morbidity and mortality. *Int J Cardiol*. Published online 2013. doi:10.1016/j.ijcard.2013.07.188

16. Kershaw KN, Droomers M, Robinson WR, Carnethon MR, Daviglus ML, Monique Verschuren WM. Quantifying the contributions of behavioral and biological risk factors to socioeconomic disparities in coronary heart disease incidence: The MORGEN study. *Eur J Epidemiol*. 2013;28(10):807-814. doi:10.1007/s10654-013-9847-2

17. Gunzler D, Chen T, Wu P, Zhang H. Introduction to mediation analysis with structural equation modeling. *Shanghai Arch Psychiatry*. 2013;25(6):390-394. doi:10.3969/j.issn.1002-0829.2013.06.009

18. Van Der weele T, Vansteelandt S. Mediation analysis with multiple mediators. *Epidemiol Method*. 2013;2(1):95-115. doi:10.1515/em-2012-0010

19. Zheng H, George LK. Rising U.S. income inequality and the changing gradient of socioeconomic status on physical functioning and activity limitations, 1984-2007. *Soc Sci Med*. 2012;75(12):2170-2182. doi:10.1016/j.socscimed.2012.08.014

20. Statistics Canada. Canadian Community Health Survey—Annual Component (CCHS) Ottawa, ON: Statistics Canada. Published online 2018.

21. TCPS 2 (2018) – Chapter 2: Scope and Approach, 2018. *[https://ethics.gc.ca/eng/tcps2-eptc2_2018_chapter2-chapitre2.html#a]*.

22. Sanmartin C, Decady Y, Trudeau R, et al. Linking the Canadian community health survey and the canadian mortality database: An enhanced data source for the study of mortality. *Heal Reports*. Published online 2016.

23. Rotermann M. Evaluation of the coverage of linked Canadian Community Health Survey and hospital inpatient records. *Health Rep*. 2009;20(1):45-51.

24. Yeung CW TS. Income imputation for the Canadian Community Health Survey. Ottawa, Ontario: Household Survey Method Division, Statistics Canada; Published online 2013.

25. Kershaw KN, Droomers M, Robinson WR, Carnethon MR, Daviglus ML, Monique Verschuren WM. Quantifying the contributions of behavioral and biological risk factors to socioeconomic disparities in coronary heart disease incidence: The MORGEN study. *Eur*

J Epidemiol. 2013;28(10):807-814. doi:10.1007/s10654-013-9847-2

26. Bryan S, Walsh P. Physical Activity and Obesity in Canadian Women. *BMC Womens Health*. Published online 2004. doi:10.1186/1472-6874-4-s1-s6

27. McNeely MJ, Boyko EJ. Type 2 diabetes prevalence in Asian Americans: Results of a national health survey. *Diabetes Care*. 2004;27(1):66-69. doi:10.2337/diacare.27.1.66

28. Christ SL, Lee DJ, Lam BL, Zheng DD, Arheart KL. Assessment of the effect of visual impairment on mortality through multiple health pathways: Structural equation modeling. *Investig Ophthalmol Vis Sci*. 2008;49(8):3318-3323. doi:10.1167/iovs.08-1676

29. Chavance M, Escolano S, Romon M, Basdevant A, De Lauzon-Guillain B, Charles MA. Latent variables and structural equation models for longitudinal relationships: An illustration in nutritional epidemiology. *BMC Med Res Methodol*. 2010;10. doi:10.1186/1471-2288-10-37

30. Maron J, Gomes de Matos E, Piontek D, Kraus L, Pogarell O. Exploring socio-economic inequalities in the use of medicines: is the relation mediated by health status? *Public Health*. 2019;169:1-9. doi:10.1016/j.puhe.2018.12.018

31. Ditlevsen S, Christensen U, Lynch J, Damsgaard MT, Keiding N. The mediation proportion: A structural equation approach for estimating the proportion of exposure effect on outcome explained by an intermediate variable. *Epidemiology*. Published online 2005. doi:10.1097/01.ede.0000147107.76079.07

32. Stringhini S, Sabia S, Shipley M, et al. Association of socioeconomic position with health behaviors and mortality. *JAMA - J Am Med Assoc*. 2010;303(12):1159-1166. doi:10.1001/jama.2010.297

33. Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M. Causes of cancer in the world: Comparative risk assessment of nine behavioural and environmental risk factors. *Lancet*. 2005;366(9499):1784-1793. doi:10.1016/S0140-6736(05)67725-2

34. Gilman SE, Abrams DB, Buka SL. Socioeconomic status over the life course and stages of cigarette use: Initiation, regular use, and cessation. *J Epidemiol Community Health*. 2003;57(10):802-808. doi:10.1136/jech.57.10.802

35. Wang P. The Causal Relationship between Socioeconomic Status and Smoking Behavior: Evidence from Canada. 2018;51(Icemgd):44-56. doi:10.2991/icemgd-18.2018.9

36. Marmot MG, Shipley MJ, Hemingway H, Head J, Brunner EJ. Biological and behavioural explanations of social inequalities in coronary heart disease: The Whitehall II study. *Diabetologia*. 2008;51(11):1980-1988. doi:10.1007/s00125-008-1144-3

37. Strand BH, Tverdal A. Can cardiovascular risk factors and lifestyle explain the educational inequalities in mortality from ischaemic heart disease and from other heart diseases? 26 Year follow up of 50 000 Norwegian men and women. *J Epidemiol Community Health*. 2004;58(8):705-709. doi:10.1136/jech.2003.014563

38. Mora S, Cook N, Buring JE, Ridker PM, Lee IM. Physical activity and reduced risk of cardiovascular events: Potential mediating mechanisms. *Circulation*. 2007;116(19):2110-2118. doi:10.1161/CIRCULATIONAHA.107.729939

39. Lu Y, Hajifathalian K, Rimm EB, Ezzati M, Danaei G. Mediators of the effect of body mass index on coronary heart disease. *Epidemiology*. 2015;26(2):153-162. doi:10.1097/EDE.0000000000000234

40. Denton M, Walters V. Gender differences in structural and behavioral determinants of health: An analysis of the social production of health. *Soc Sci Med*. 1999;48(9):1221-1235. doi:10.1016/S0277-9536(98)00421-3

41. P. M, V W. Gender and health: Reassessing patterns and explanations. *Soc Sci Med*. 2001;52(4):547-559. http://ovidsp.ovid.com/ovidweb.cgi?T=JS%7B&%7DPAGE=reference%7B&%7DD=emed8%7B&%7DNEWS=N%7B&%7DAN=31000791

42. Backholer K, Peters SAE, Bots SH, Peeters A, Huxley RR, Woodward M. Sex differences in the relationship between socioeconomic status and cardiovascular disease: A systematic review and meta-analysis. *J Epidemiol Community Health*. 2017;71(6):550-557. doi:10.1136/jech-2016-207890

43. Twells LK, Gregory DM, Reddigan J, Midodzi WK. Current and predicted prevalence of obesity in Canada: a trend analysis. *C Open*. 2014;2(1):E18-E26. doi:10.9778/cmajo.20130016

44. Booth HP, Charlton J, Gulliford MC. Socioeconomic inequality in morbid obesity with body mass index more than 40 kg/m2 in the United States and England. *SSM - Popul Heal*. 2017;3:172-178. doi:10.1016/j.ssmph.2016.12.012

45. Cockerham WC. *Health Lifestyle Theory and the Convergence of Agency and Structure**. Vol 46.; 2005.

46. Mollborn S, Lawrence EM, Saint Onge JM. Contributions and Challenges in Health Lifestyles Research. *J Health Soc Behav*. 2021;62(3):388-403. doi:10.1177/0022146521997813