Author’s response to reviews

Title: Chronic disease and malnutrition biomarkers among unemployed immigrants and Canadian born adults

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Author’s response to reviews:

Dr. Olivier Bruyère

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Dear Dr Bruyère,

We would like to thank the reviewers for their thorough critics and comments concerning our manuscript "Chronic disease and malnutrition biomarkers among unemployed immigrants and Canadian born adults" (AOPH-D-19-00156). The manuscript has been revised according to the comments of our reviewers and we have addressed all their questions.

Our answers are written in italics under each comment made by the reviewers and the changes related to these comments are presented in the text of the article, highlighted in yellow.
Reviewer #1:

The authors report here some biological interesting findings in Canadian born and immigrants living in Canada. In such large studies, shortcomings are difficult to avoid and this study has some of them, acknowledged by the authors.

A major one is that the term "immigrants" is used for both refugees and people who migrate to Canada in a positive program of immigration. Indeed, Canada has a policy of positive immigration and these two types of "immigrants" are probably totally different, regarding level of education, employment rate and health status. Also, incomes are totally different, as well as access to healthy food and activities, social behaviour and employment. I thus think that a stratification should be made between refugees and immigrants. The social status, even in Canadian citizens, is quite different and this should be taken into consideration to fine-tune the analysis.

Response: We agree with this comment. This is a limitation that we have recognized. We have now added (at page 15 in yellow color) that Refugees represented 16.4% of all immigrants admitted to Canada between 1991-2000.


The authors use CRP as an inflammatory marker, but they have actually measured hs-CRP, which is rather a cardiovascular risk factor. The results should be analysed accordingly. Another major issue is the use of CRP, defined as an "inflammatory marker". Indeed, the authors used hsCRP (actually, this information does not figure in the text, but only in the table). At these levels, hsCRP is a marker of cardiovascular risk, not inflammation. This should be corrected.

Response: We have specified hsCRP in the abstract and noted in the text that “Plasma was used to assess high-sensitivity C-reactive protein,...” at page 7 in yellow color. We considered HsCRP as an inflammatory marker. As showed by Pearson TA, Mensah GA, Alexander RW, et al, (Circulation 2003;107:499-511), there is evidence of the association between several inflammatory markers (high-sensitivity C-reactive protein, white blood cell count, fibrinogen, etc) and cardiovascular diseases. HsCRP is also a low-grade inflammatory marker, and as such, it is a marker of cardiovascular risk (Adeli K, Higgins V, Nieuwesteeg M, et al. Clinical Chemistry 2015;61:1063; Ferrucci L, Fabbri E, Nat Rev Cardiol. 2018 Sep;15(9):505-522)
Reviewer #2

This preliminary study found very small differences in biomarkers in immigrant, female, and unemployed subjects.

The topic is interesting, but differences in health status due to socioeconomic reasons are a well-known topic.

Response: Yes, we have estimated small differences in the means of the population distributions of these biomarkers but relatively small shifts in the population distributions may have substantial impact in the number of individuals identified at risk of clinical disease. We have compared means because a distribution that is shifted to the left or right relative to another distribution would be reflected in a comparison of means (Menke A et al, Ann Epidemiol. 2014 February;24(2): 83–89).

Social determinants of health and socioeconomic factors have been analyzed in many papers including the influential 2008 WHO report (https://www.who.int/social_determinants/thecommission/finalreport/en/). Some of those papers have focused on immigration as a determinant of population health, another set of papers have focused on unemployment and health and a rather large literature body has been related to gender-related risk factors for health since gender is related to social context. (See page 5 in yellow color) The current paper encompasses these three social determinants of health and examines how they interact to increase vulnerability to chronic diseases as assessed by blood biomarkers of nutritional, metabolic and inflammatory markers. We have included this reasoning in the background section at end of page 5 and top of page 6 in yellow color.

The methodology used is not clear. Health, nutritional status, and inflammation are complex, multidimensional conditions and these preliminary results are based on small differences obtained in blood tests and demographic data, without taking into account food intake, clinical history, physical examination, or any anthropometric measurement. The assessment is incomplete in its present form.

Response: The differences that we have detected are small at the individual level but could be significant at the population level. Together they show that deviations of normal values are clustered in subpopulations.

We are examining how population distributions of blood biomarkers of nutrition, metabolism and inflammation vary in populations defined by gender, immigration and employment status. We are not examining mechanisms such as those implied by food intake, clinical history, physical examination or anthropometric measurements. However, our estimates, coefficients in
the equations, are adjusted by age, education, place of residence, body mass index, physical activity and smoking.

In the study, the survey was administered to the respondents, and later, blood test was proposed. Did all respondents agree to the blood extraction?

Response: Approximately 85% of respondents who completed a household interview in cycle 1 agreed to go to the Mobile examination centre (MEC). We added this statement in the text in the methods section at page 6 in yellow color.

How was the measurement of fasting glucose levels ensured?

Response: The measurement of fasting glucose based on VITROS GLU Slide method was performed using the VITROS GLU Slides and the VITROS Chemistry Products Calibrator Kit 1 on VITROS Chemistry Systems (as noted in table 1). To make sure that respondents were in the fasting state, a morning appointment were required that respondents fast overnight and shorter eating restrictions were imposed on those with afternoon appointments (see the last sentence in the method section at page 6 in yellow color).

The use of an isolated determination of glucose to determine inflammation or health status should be discussed.

Response: We discussed this issue in the discussion section page 15 (in yellow color) as follows: “Finally, as CHMS is a cross-sectional survey, we used one fasting blood glucose measurement to assess risk of diabetes and doing so, could introduce a measurement bias in the results. However, others authors also used a single determination of glucose to assess diabetes using data from CHMS, or data from The National Health and Nutrition Examination Survey (NHANES)”.

Albumin is no longer recommended as a nutritional marker, but rather as a marker of inflammation; the thresholds used are higher than those recommended by ESPEN.

Response: We agree with the reviewer that we should use albumin as inflammatory biomarker, but at the time of data collection, this variable was collected as nutritional biomarker, and authors continue to use it as nutritional status marker (Corona LP et al. Geriatrics & Gerontology International 2018;18:177-82).
Moreover, the study does not define them by any validated tool (e.g., Mini-nutritional assessment) or updated definition, such as the European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines on definition and terminology of clinical nutrition (Cederholm et al., 2017), etc.

Response: We used secondary data collected by the Canadian Ministry of Health through Statistic Canada. These data are equivalent to The National Health and Nutrition Examination Survey (NHANES). The Canadian Health Measures Survey (CHMS) data and the measurements used are those chosen by Statistics Canada and validated for the population survey. We added the last sentence in the method section of the text page 7 in yellow color.

I would recommend that the authors clarify the statistical method used in order to make their findings more understandable and reach a wider audience. For example, the mean values in the different parameters of the blood tests obtained in the sample are within the ranges of normality indicators.

Response: We have recalculated the means presented in Table 3 for hsCRP, blood glucose and glycosylated hemoglobin because in the previous version of the manuscript the following biomarkers mean values were log transformed. Converting the differences back to the natural scale produces the real biological values which allow for a better interpretation of their biological meaning. For example, the calculations for glycosylated hemoglobin were done as follows: a) the intercept of glycosylated hemoglobin was (-2.9), indicating that the mean value for Canadian employed men was exp(-2.9)=5.5;b) The coefficient of unemployed immigrant men and women for glycosylated hemoglobin was 0.26, then the mean for that group would be exp(-2.9+0.26)=7.13 and the difference between groups would be 7.13-5.5=1.63, as shown in Table 3. (We added this statement in the results section at page 10 in yellow color).

The population distributions of these biomarkers are unimodal. To test for differences in their means by unemployment status, immigrant status and gender, we used multiple linear regressions estimating the means for the reference group (Canadian born employed men) as intercepts and deviations from these means as coefficients of the indicators of unemployment, immigrant status and gender. Multiple regressions were fitted in three steps: first, including these indicators whose interactions constitute our main hypothesis (main effects and the multiplicative interaction terms for the first order interactions between unemployment and immigration; unemployment and gender; immigration and gender; and the second order interaction terms between unemployment, immigration and gender); second, controlling for age, sex and education and third, controlling for body mass index, smoking and physical activity.
The results and table 3 showed significant differences between employed and unemployed men by the analysis of the mean deviation, this should be explained more clearly.

Response: Among Canadian born men, results are stated (Results section page 10 and 11 in yellow color) (The mean deviation of hsCRP for Canadian born unemployed men was 0.25 mg/L compared with Canadian born employed men and in another sentence: “For fibrinogen, Canadian born unemployed men had higher values than corresponding employed men, with a difference of 0.1 g/L”) and repeated the first sentence in the results section of the abstract (“Unemployment was associated with higher inflammation (hsCRP and fibrinogen) in Canadian born men”) For glucose, differences were shown for the unemployed: “Glucose was also significantly higher in unemployed men and women (both Canadian born and immigrant) compared with those employed” and restated in abstract:” Unemployment was associated with higher glucose”

The study focused on minimal changes in the values; it might be more interesting if the minimal clinically important difference were defined, analyzed, and discussed for each biomarker.

Response: We agree with the reviewer that we could have analyzed binary outcomes using, for example, the cutoff point for the highest decile in each biomarker distribution but our approach aimed at examining the shift in the whole distribution, that is a shift detected by a deviation of the means, using the strategy of preventive medicine proposed by Rose G (See: Sick individuals and sick populations, Bull World Health Organ. 2001;79(10):990-6) and expanded to vulnerable populations by Frohlich and Potvin (See: Transcending the known in public health practice: The Inequality Paradox: The Population Approach and Vulnerable Populations, Am J Public Health. 2008;98:216–221). Also, it has been showed that small shifts in population mean distribution, for instance for high blood pressure, made a clinically significant difference in the numbers at risk (See Laaser U, et al.. Can a decline in the population means of cardiovascular risk factors reduce the number of people at risk? Journal of epidemiology and community health 2001;55:179-84). We have added a paragraph in the discussion section (page 14) to address the significance of results for population preventive interventions with a quotation to Rose.

Background-populations and discussion should be based on scientific literature. I would recommend updating your references and reframing the article.

Response: We thank the reviewer for this comment. We have now reformulated the background section and the discussion according to his/her comments and we have included a more in depth explanation of our work in the framework of the WHO social determinants of health (See page 5) and the strategy of population preventive interventions that take into account the vulnerability of certain subgroups of populations (See page 14).
As we noted in the background section, few research efforts have simultaneously examined the social intersecting conditions of being unemployed and being an immigrant, and their combined effect on health in terms of biomarkers.

The study involves a large sample and could certainly have some value if the authors improve the methodology.

Response: We thank reviewer for his or her comments. The methodology has now been improved by clarifying the statistical method used. In addition, it is important to remind that the survey methods were those of the Canadian Ministry of Health – Statistics Canada.