PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between psychosocial work-related factors at midlife and arterial stiffness at older age in a prospective cohort of 1,736 white-collar workers
AUTHORS	Massamba, Victoria; Talbot, Denis; Milot, Alain; Trudel, Xavier; Dionne, Clermont E; Vézina, Michel; Mâsse, Benoit; Gilbert-Ouimet, Mahée; Dagenais, Gilles; Pearce, Neil; Brisson, Chantal

VERSION 1 – REVIEW

REVIEWER	Moreno, Claudio University of Sao Paulo
REVIEW RETURNED	07-Jun-2023

GENERAL COMMENTS	The study is relevant because arterial stiffness and its association with work-related factors have been poorly studied. Thus, the originality and relevance of the study are positive factors. I just have a couple of considerations regarding the way the study was presented. Firstly, none of the study variables were collected at T1 (baseline), meaning there is no data on arterial stiffness (collected only at T3) and psychosocial factors (collected at T2). Therefore, the study design is a result of data collection at only two time points, despite being presented as a cohort that started in 1991. It is actually a two-wave cohort that started in 1999. This should be made explicit from the abstract onwards to avoid giving the reader a mistaken idea about the study's timeline. One of the limitations of the study resulting from what I mentioned earlier is that arterial stiffness data were not collected at T2, which means that the cases found in the study could have already exhibited arterial stiffness since T2 due to aging or other factors. This fact should be clearly presented as a limitation of the study. Additionally, the discussion should address this issue. In addition, I suggest that Figure 1 should clearly indicate the year in which the study began. Finally, line 12 has a typo error.

REVIEWER	Boutouyrie, Pierre INSERM, U970
REVIEW RETURNED	08-Jun-2023

GENERAL COMMENTS	In the present study, the authors tested the relation between arterial stiffness, a biomarker of early vascular aging and cardiovascular damage, and work parameters. They took advantage of a large white collar working class cohort (1736) and measurement of carotid to femoral PWV, the gold standard for aortic stiffness to test their hypothesis. The main finding is that job

	strain is associated with higher stiffness in hypertensives, and lower in normotensives after long follow-up (16 years). The population is representative of civil servants in Canada, the rate of acceptance is good, the extensive investigations, including adequate questionnaires were applied at 3 time points, allowing prospective multiple analyses. The questionnaire for job strain is extensive, and included the demand and control dimensions, as previously validated for CV risk, resulting in 4 contrasted groups LD/LC, LD/HC, HD/LC and HD/HC. Stiffness is correctly measured using gold standard à T3, as outcome ariables. All meaningful covariates were included in the analysis. The analysis by subgroups (high BP or nor) was prespecified. Results are quite strong in amplitude, +1.38 m/s in the hypertensives exposed to high job strain is meaningful. Results are clearly presented and highly interesting, by showing the interaction between blood pressure and external factors such as job strain on early vascular aging. In particular, the time window chosen (16 years) allows to put in evidence the long term effects of factors which would have appeared as minor on shorter term. Minor points: how precisely was measured carotid to femoral distance? Did the authors apply the 0.8 correction factor? If so, then PWV could be translated into vascular age by using references values (EHJ 2010) The authors did not discuss physical activity. Climie et al 2019 showed that occupational physical burden had adverse effect on arterial stiffness, contrary to leisure physical activity (positive i.e. reduced arterial stiffness), which could be meaningful to interpret this data. Figure S1 could be included in the paper or as a graphical abstract

VERSION 1 – AUTHOR RESPONSE

Comment 1 – Reviewer 1

Firstly, none of the study variables were collected at T1 (baseline), meaning there is no data on arterial stiffness (collected only at T3) and psychosocial factors (collected at T2). Therefore, the study design is a result of data collection at only two time points, despite being presented as a cohort that started in 1991. It is actually a two-wave cohort that started in 1999. This should be made explicit from the abstract onwards to avoid giving the reader a mistaken idea about the study's timeline.

Response 1 – Reviewer 1

We have clarified the study design:

- We have provided clarification in the abstract (page 2 of the marked copy of the main document): **"**Association between psychosocial work-related factors from the job strain and effort-reward imbalance (ERI) models assessed at study baseline (1999-2001) with validated instruments and arterial stiffness assessed using carotid-femoral pulse wave velocity at follow-up, on average 16 years later (2015-2018).".
- We have provided further clarification in the method section (page 5-6 of the marked copy of the main document): "We used data from a prospective cohort study. This cohort was initiated in 1991-1993 among 9,188 white-collar workers (participation proportion: 75%) from 19 public organizations in Quebec City with two subsequent phases of data collection (1999-2001 and 2015-2018) (13). The current study baseline was set in 1999-2001, since ERI exposure was firstly assessed at that time. Arterial stiffness was assessed at follow up (2015-2018).".
- Throughout the paper, we have replaced "T2" with "baseline", "T3" with "follow-up" and "T1" with "in the original cohort initiation".

We would also like to clarify that we used the data measured at cohort initiation (1991-1993) to calculate the weights used in the inverse probability weighting method. We have therefore specified this in the analysis section as follows (page 8 of the marked copy of the main document): “Covariates measured at the initiation of the original cohort (in 1991-1993) were used in the calculation of the weights that were used for inverse probability weighting in order to minimize the potential selection bias resulting from losses to follow-up between cohort initiation and subsequent time points.”
Thank you for the comment.

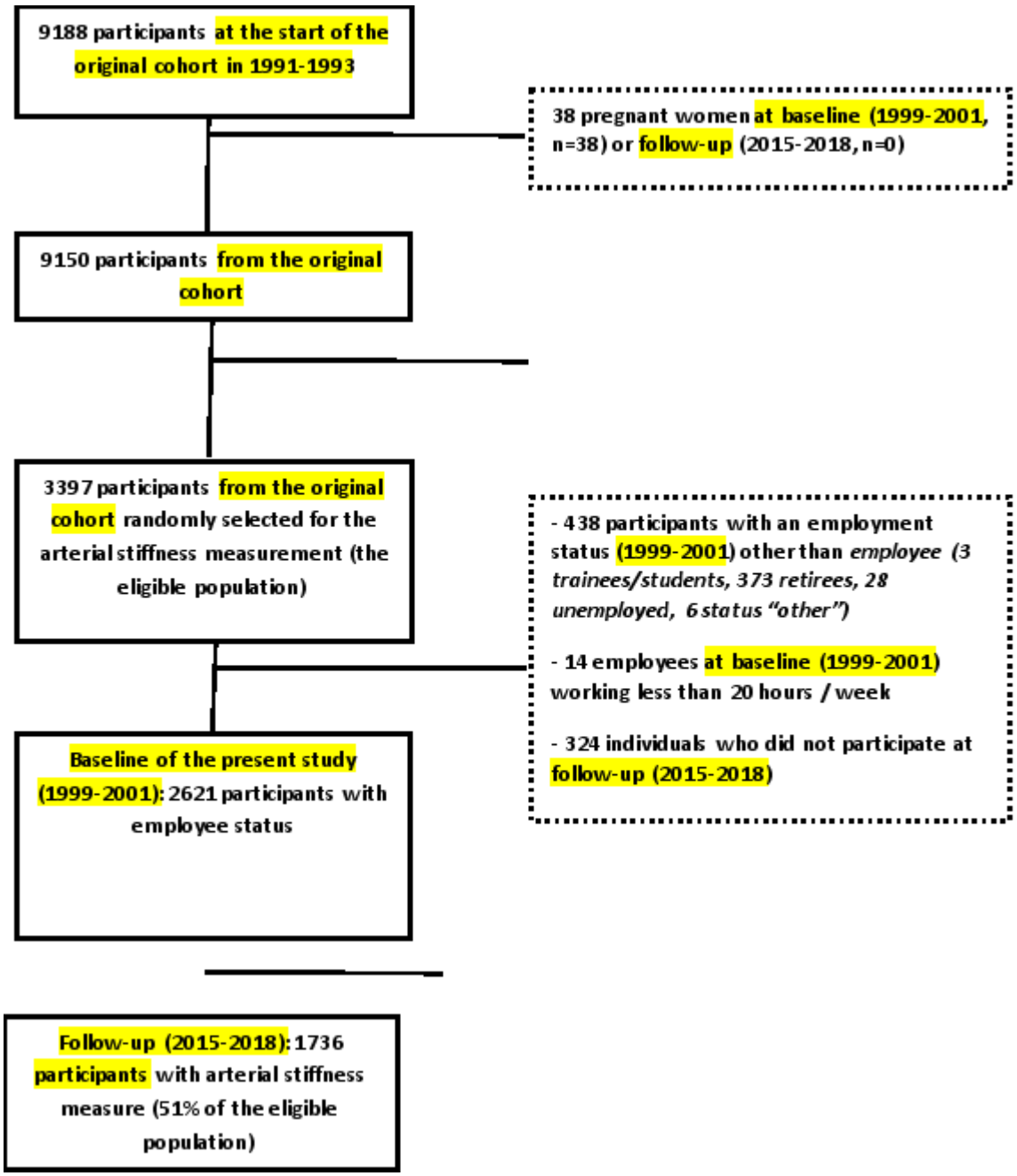
Comment 2 – Reviewer 1

One of the limitations of the study resulting from what I mentioned earlier is that arterial stiffness data were not collected at T2, which means that the cases found in the study could have already exhibited arterial stiffness since T2 due to aging or other factors. This fact should be clearly presented as a limitation of the study. Additionally, the discussion should address this issue.

Response 2– Reviewer 1
We agree. We have added additional information in the discussion to clarify (page 13 of the marked copy of the main document): “Fifth, arterial stiffness was measured at a single time point (at follow-up only). Therefore, stiffness progression over time could not be assessed limiting the possibility to draw causal inferences. However, data on several other major cardiovascular risk factors (age, blood pressure, cholesterol, smoking, etc.) were controlled for, which minimized the possibility for participants in compared group to substantially differ regarding their overall cardiovascular profile at baseline.”

Comment 3 – Reviewer 1
In addition, I suggest that Figure 1 should clearly indicate the year in which the study began.
Response 3– Reviewer 1
Thank you for your comment. We have clarified the measurement times of our study in figure 1 as follows:

Figure 1. Flow chart


9188 participants at the start of the original cohort in 1991-1993
38 pregnant women at baseline (1999-2001, n=38) or follow-up (2015-2018, n=0)
9150 participants from the original cohort
3397 participants from the original cohort randomly selected for the arterial stiffness measurement (the eligible population)
- 438 participants with an employment status (1999-2001) other than employee (3 trainees/students, 373 retirees, 28 unemployed, 6 status "other")
- 14 employees at baseline (1999-2001) working less than 20 hours / week
- 324 individuals who did not participate at follow-up (2015-2018)
Baseline of the present study (1999-2001): 2621 participants with employee status
Follow-up (2015-2018): 1736 participants with arterial stiffness measure (51% of the eligible population)

Comment 4 – Reviewer 1
Finally, line 12 has a typo error.
Response 4– Reviewer 1
To be determined, the reviewer has been contacted by the editorial office to clarify

Comment 1-Reviewer 2
Minor points: how precisely was measured carotid to femoral distance? Did the authors apply the 0.8 correction factor? If so, then PWV could be translated into vascular age by using references values (EHJ 2010)

Response 1– Reviewer 2
We estimated carotid-femoral pulse wave velocity (cfPWV) using the following formula (1, 2) :
cfPWV = 0,8*dL/dt
Where dL is the distance between the right common carotid artery and the right femoral artery, and dt is the time taken for the pulse wave to travel this distance. We did apply the value 0.8 (correction coefficient) to the distance, as the direct carotid-femoral distance (uncorrected) overestimates the distance effectively covered by the pulse wave by 25.4%.(3). The 0.8 x dL value is very close to the actual distance measured by magnetic resonance imaging (2).

Based on the references values (EHJ 2010), we have translated our results into vascular age and have added information in the discussion (page 12 of the marked copy of the main document):
“The observed association between psychosocial work-related factors and cfPWV can be translated into vascular age. For example, among participants with elevated DBP, those exposed to job strain (mean age: 63.1) had a mean cfPWV of 9.4 m/s, which is compatible with a vascular age of 50-59 years (27, 28). However, participants with elevated DBP in the low strain category (mean age: 64.9) had a mean cfPWV = 7.9 m/s, which is compatible with a vascular age of 30-39 years (27, 28)**.** The observed difference in cfPWV among participants exposed to job strain within this subgroup is therefore compatible with a decade discrepancy in vascular age.”

Comment 2-Reviewer 2
The authors did not discuss physical activity. Climie et al 2019 showed that occupational physical burden had adverse effect on arterial stiffness, contrary to leisure physical activity (positive i.e. reduced arterial stiffness), which could be meaningful to interpret this data.

Response 2– Reviewer 2
Thank you for your comment. Our study population comprises exclusively white-collar workers. The fact that our sample is composed exclusively of white-collar employees limits potential confounding by occupational physical burden. It would have been important to adjust for occupational physical burden if, for example, our study sample also included blue-collar workers, a category of worker frequently exposed to occupational physical burden. We have added this in the discussion (page 13 of the marked copy of the main document): “The fact that our sample is composed exclusively of white-collar

employees limits potential confounding by occupational physical burden (repetitive movements, lifting heavy loads, long walking distance …)"
Comment 3-Reviewer 2
Figure S1 could be included in the paper or as a graphical abstract
Response 2– Reviewer 2
We've moved Figure S1 in the paper. This figure thus becomes Figure 2 in the paper. Thank you.

References

1. Van Bortel ML, Laurent USS, Boutouyrie DP, Chowienczyk DP, Cruickshank DJK, De Backer DT, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. Journal of Hypertension. 2012;30(3):445-8.
2. Laurent S, Boutouyrie P. Mesure de la rigidité artérielle. Fiche technique. 2013.
3. Huybrechts AMS, Devos GD, Vermeersch JS, Mahieu LMD, Achten ME, De Backer MT, et al. Carotid to femoral pulse wave velocity: a comparison of real travelled aortic path lengths determined by MRI and superficial measurements. Journal of Hypertension. 2011;29(8):1577-82.
1

VERSION 2 – REVIEW

REVIEWER	Boutouyrie, Pierre INSERM, U970
REVIEW RETURNED	22-Aug-2023

GENERAL COMMENTS	I am satisfied with the responses