Author's response to reviews

Title: Cardiovascular disease risk factors and ventilatory function: A cross-sectional study in young adults

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Author's response to reviews: see over
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Ref: 1324856350136256 – resubmission of revised manuscript ‘Cardiovascular risk factors and ventilatory function in young adults’

Dear Dr Bjerg,

We are most grateful for the helpful and positive comments sent by the reviewers to our manuscript. We have incorporated all the suggestions made, which were largely related to editing of the text. Specific details with our replies to each of the comments are provided enclosed to this letter.

As you and one of the reviewers mention, we agree that this manuscript provides potentially important cross-sectional evidence of the early association between cardiovascular risk factors and lung function as observed in this population-based study in young adults.

We hope you will find the revised draft fits the recommendations made by the reviewers. I would be delighted to answer any further queries you may have.

Yours sincerely,

[Signature]

Dr Vanessa Garcia Larsen
Editors’ Comment:

This is an interesting and potentially important study, and the baseline methods seem well thought through. I would welcome a revision following the reviewers’ comments, please pay close attention to these as the paper can clearly be improved. This also includes a number of minor errors where the text does not seem to correspond to data in tables.

We are grateful for these positive comments and feedback. We have addressed all the suggestions sent by the reviewers and one of the co-authors (a native British speaker) has checked again the manuscript to ensure that the grammar and style are appropriate.

Reviewer 1

Reviewer’s report:
This manuscript describes the association between pulmonary function and both lipid markers and markers of dysglycaemia.

This is a well-designed, executed and analysed cross-sectional study. Bias from measurement of the exposure or outcomes seem very unlikely and the reporting makes it very easy for readers to see what data were collected and how these were analysed.

The reporting of associations in Tables 2 and 3 is especially clear, and avoid the “Table 2 Fallacy” described by Westreich and Greenland (doi:10.1093/aje/kws412). I agree with the authors that these associations have not previously been studied in a population in their 20s.

The main issues I have with the study are i) the possibility of residual confounding by cigarette smoke exposure, ii) some overly strong claims about the implications of the research in the discussion section.

Major compulsory revisions
1. Residual confounding as a result of unmeasured variation in cigarette smoke exposure seems likely. Even had the study included pack years residual confounding could not be excluded and, as only smoking status is recorded, residual confounding seems a distinct possibility. Rather than being reassuring, the fact that smoking status was not associated with FEV1 or FVC in this dataset increases the likelihood that there is residual confounding. In order to state that the associations are not due to confounding from cigarette smoke exposure an analysis in never smokers ought to be reported.

We have run analyses in never smokers only, and confirmed that none of the exposures included in this manuscript were related to either FVC or FEV1, and therefore residual confounding may be unlikely in this case. A point to be made is that although smoking habit was common in these adults (66.0% in men and 49.2% women), the amount of cigarettes smoked was low. We have added a sentence in the Results section (lines 190-191) and add in line 237 that possibly early life factors might also influence the associations found.

2. Discussion lines 237-238. It is suggested that “Our results would indicate that in young adults CVD risk factors, other than smoking, could explain a lower level of lung function.” This is possible, it is equally possible however, and in my view more likely, that foetal and early life factors are responsible for the association. This possibility should be addressed in the discussion. Similarly, lines 275-282 do not acknowledge this possible explanation.
We have improved our explanation in lines 237-38 by acknowledging that foetal development may be an explanation for the associations found. We also improved the limitations paragraph (lines 275-82) by explaining that future studies would benefit from examining early life risk factors.

3. Discussion lines 262-264. It is suggested that these findings can be used to identify patients with COPD at an early stage. It is not clear how this conclusion follows from the reported findings.

We agree with the reviewer and have removed this sentence.

4. Discussion lines 270-273. The statement that “Our findings suggest that modifying lifestyle behaviours that lead to prevent an increased insulin resistance, an unfavourable lipoprotein profile and MS may reduce the losses of lung function over time” goes well beyond the presented findings. An intervention study would be best suited to support this claim, or if this is not feasible, a Mendelian randomisation study. At the very least a study with longitudinal follow-up with repeated lung function measures is needed before such a claim can be ventured.

We appreciate this recommendation, and have rephrased this paragraph to reflect the length to which our cross-sectional findings can go, and the relevance of these findings to encourage future longitudinal and intervention studies.

Minor essential revisions

1. Table 1 FEV1 seems to have an extraneous carat symbol.

We used the ^ (carat symbol) to link the FEV\textsubscript{1} figure to the footnote that explains that we chose the highest of five measurements. We have changed it to # as a more conventional symbol (see line 427).

Reviewer 2

Reviewer's report
Title: Cardiovascular disease risk factors and ventilatory function: A cross-sectional study in young adults
Version: 3 Date: 22 September 2014
Reviewer: Stig Hagstad

Reviewer's report:
The authors have presented a paper on the relationship between lung function and cardiovascular risk factors in young subjects. While the subject is of interest and worthy of further studies, there are several points that need to be amended.

Major Compulsory Revisions:
1) There are numerous factual errors related to the numerical analyses in the manuscript that must be corrected.
For example: p2, row 38 "...FVC bLLN 7\%.". 7\% is among males only and should read 4.7\%.

We have corrected this and state in line 39, and report 4.7\% of prevalence of FVC bLLN in the whole sample. We also state the exact prevalence of MS (11.8\% instead of 12\%), following the reviewer’s advice in point 1 of section Minor revisions.

2) Page 8, row 175: "As expected, men had higher lung function than women".
Clearly incorrect. I presume the authors mean that men had larger lung volumes as compared to women. In continuation on row 175: "Over 7\% of men had lung
obstruction as indicated by FVC bLLN”. First, the term is airway obstruction. Second, using FVC alone is not a correct manner of establishing airway obstruction.

We have provided the exact prevalence of men and women with an FVC bLLN and have corrected the term to ‘larger lung volumes’ (see line 174). There are various criteria to define ‘airway obstruction’ and we are aware of the discrepancies and complexities of each of these definitions (e.g. Swanney MP et al 2008; Burney P, 2014). This argument is beyond the scope of the current manuscript, but we appreciate the advice from the reviewer and have modified this sentence to refer to the spirometric values only as an objective marker of lung function

3) Page 8, row 181-183: "a consistent trend for a lower FVC with higher tertiles of LDL and TGs in men only”. However, among the whole sample association between FVC and LDL was statistically significant, p=0.03.

We have reworded this paragraph to explain better the associations found in men and women separately (see lines 179-182)

4) Page 8, row 185-186: "...elevated levels of HOMA-IR had lower levels of FEV1 and FVC levels in the whole sample, as well as per gender (the association being weaker in females). The association between HOMA-IR and FEV1 in women is not statistically significant (p=0.43), which should be clearly stated. Subsequently the same conclusion should be drawn from the association between metabolic syndrome and FEV1 in females, where the association was not, as stated, weaker but not statistically significant.

We have re-written this paragraph to better explain the associations found between measures of lung function and HOMA-IR and MS in men and women (please see lines 185-189)

5) Page 11, row 261. "7% of the population....more marked in men than in women". Se comment 2. (32+14)/970= 4.7. The authors must be certain that their calculations are correct and are advised to redo them.

We have corrected this figure to 4.7% (please see line 263)

Minor revisions:

1)General comment: when presenting prevalence data, please give one decimal instead of rounding op/down. E.g. p2 row 38: "...prevalence of MS was 12%”, should read 11.8%. This error can be found throughout the manuscript and must be corrected.

We have replaced round figures to exact percentages and subsequent lines in the text (please see lines 39, 174-177

2) p2, row 31: "...a sample 998 adults...". Should read "..a sample of 998 adults"

This has been corrected.

3) p8, row 173 “over two thirds of males and half of women”. For men, prevalence of current smokers was 66.0%, i.e. almost two thirds. For women, 266/541 = 49.2 (not as stated in table 1 48.6%), i.e almost half. Please see major revision comment 5.
The exact percentages have been provided in the text (please see line 172) and the figure 49.2% has replaced 48.7% in Table 1

4) p8, row 178 "Nearly a third...". Should read "More than a third.."

(153+182)/970 =0.345.

The wording has been corrected as advised (please see line 177)

5) p10, row 221: "...fourth cause of death...". According to the reference used, COPD is now (2010) the third cause of Death globally. Please correct the text accordingly.

This has been amended (please see line 221)

Discretionary Revisions:
1) p 4, row 87: "not included in the study because of Death (3.2%)". As the study population consists of comparatively young subjects, this is surprisingly high. The authors should comment on this.

The 3.2% of deaths refers to those found in the total sample frame (i.e. 3,092 born babies between 1974 and 1978). In the early 70s childhood mortality was still an important issue of public health at a time when Chile was experiencing high levels of maternal and infant health problems (related to poor hospital facilities and a high prevalence of under-nutrition before the age of 5). We also report this figure (3.2%) in the study published in Thorax (Rona RJ et al, 2005). We have added a brief sentence on this in the Methods section (please see line 86)

References


2) Burney P. Coming off the GOLD Standard. Lancet Resp 2014; DOI: 10.1016/S2213-2600(14)70040-2

3) Rona RJ, Smeeton NC, Bustos P, Amigo H, Diaz PV. The early origins hypothesis with an emphasis on growth rate in the first year of life and asthma: a prospective study in Chile. Thorax2005; 60:549-54