Author's response to reviews

Title: Effect of External Airflow Resistive Load on Postural and Exercise-associated Cardiovascular and Pulmonary Responses in Pregnancy

Authors:

Jung-Hyun Kim (inr3@cdc.gov)
Raymond J Roberge (dtm0@cdc.gov)
Jeffrey B Powell (efe8@cdc.gov)

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Author's response to reviews:

Reviewer's report
Title: Effect of External Airflow Resistive Load on Postural and Exercise-associated Cardiovascular and Pulmonary Responses in Pregnancy
Version: 1 Date: 1 November 2014
Reviewer: Philip Harber
Reviewer's report:

MAJOR
The paper addresses a very relevant topic since many filtering facepiece respirator users are women. The results provide reassuring insight into the very limited adverse impact of respirator use.
Several aspects of the manuscript might be clarified so that readers without detailed knowledge of respirators would optimally benefit:

General Comments:

The paper provides very useful data about the potential impact of respirator use upon workers who might be pregnant. The data are generally reassuring. The entire discussion and introduction focus on resistance of the respirator. However, respirators also add dead space, thermal loading, and other effects. Thermal and moisture affects are generally particularly prominent for the class of respirators they studied here. The investigators have previously published several very insightful reviews of the physiologic impact of respirators, and they have been extremely useful when considering pregnant users. While they certainly should not repeat their entire previous publication, general readers would benefit from an explanation that resistance is not the only important fact.
Author Reply: We agree that there are factors other than just resistance that impact the wearer. We have added the following (lines 252-256): “It is important to note that it is not only EARL that impacts those who wear facial coverings; associated issues of facial heat and humidity, increased perceptions of total body heat, variable carbon dioxide retention, and psychological issues (e.g., anxiety, claustrophobic reactions) must also be taken into consideration (Roberge et al, 2010, Wu et al, 2011, Roberge et al, 2012).

Similarly, they use a single subjective factor, the relative perceived exertion (RPE). Aspects other than perceived exertion may also be important to respirator users. Perhaps they should mention other possible subjective factors of importance.

Author Reply: We agree that there can be other subject factors impacting the wearer. We have added the following (Lines 256 - 258): “We tested subjective responses only for perceptions of exertion (RPE), but other subjective factors such as thermal sensations and psychological reactions (e.g., anxiety, claustrophobia) to wearing facial coverings could affect results.”

81: They used two distinct models of N95 respirators. It appears that each subject only used a single type. While they indicate that the resistance of the two models was comparable, the functional dead space may become quite different with a flat fold and a cup type device. This would in turn significantly affect ventilation. The authors should indicate how many used each device and if there were differences depending upon the device type (even if not statistically significant because of the small sample size using each one).

Author Reply: We agree that dead space is an important issue and have added the following (Lines 78-79): “The static dead space of the three N95 FFR models was, respectively, 375 ml, 280 ml, and 210 ml.” While we agree that the issue of respirator dead space is, in general, an important one, it is the functional dead space (dead space while worn by the user), not the static deadspace, that is the important parameter and it was not possible to determine functional deadspace while worn by the study subjects. We have also added (Lines 258-261): “Although the static dead space volumes of the three N95 FFR models used in the current study differed by as much as 165 ml, the functional dead space that impacts breathing parameters could not be determined while the respirators were worn, so that no conclusions can be drawn with respect to dead space.” We have also indicated the number of subjects who utilized each model of N95 respirator (Lines 85 -85): “A passing score was achieved by 22 subjects with the 3M 9210 model, 7 subjects with the Moldex 2200 model, and 3 subjects with the Moldex 2201 model.” Lastly, we have added the following (Lines 263 - 267: “Further, from the standpoint of comparisons of the impact of different respirator styles on measured variables, the significantly greater number of subjects passing fit testing with the 3M 9210 (69%) precludes any meaningful comparisons with the
small numbers for the Moldex 2200 (21%) and Moldex 2201 (10%) models.

85: The investigators performed a quantitative fit test and excluded subjects with a fit factor <100. Since they mention numerous types of head coverings in their general comments, can they indicate which if any of the non-respirator head coverings could actually be considered in any way comparable to a respirator? (They reference a study done by their colleagues that investigated this specific topic). If the alternative forms of cloth devices did not achieve appropriate fits, do they believe the devices would impose any resistance or dead space comparable to the actual filtering facepiece respirators?

Author Reply: Some of the facial coverings mentioned in the general comments likely do not fit as tightly as the respirators used in the current study. However, although the resistance of the fabrics used for these coverings is less than noted for filtering facepiece respirators (see Rengasamy et al, 2010), the coverings adhere completely to the face (as opposed to only the sealing surface of respirators being attached to the face) and the warmed, expired air continually trapped in the facial covering may increase the breathing resistance to that seen with respirators. We have added the following (Lines 224 - 230): “It is likely that, given the lower resistance levels of various fabrics used for facial coverings (Rengasamy et al, 2010), and the fact that some facial coverings likely do not adhere as tightly to the face as N95 FFR, their impact on the wearers would be less than that noted in the current study for N95 FFR. However, the accumulation of significant amounts of expired moisture or sweat on facial coverings that adhere closely to the facial skin (e.g., niqab, balaclava, medical/surgical mask, etc.) could result in significant breathing resistance (Roberge et al, 2012b) that might equal that of some filtering facepiece respirators.”

112: The results might be more easily understood by the reader if a table of the results were presented. Since they used an analysis of variance approach, such a table should include the estimate for each factor as well as its DF.

Author Reply: We agree that a Table would be useful in understanding of the data and have added a Table with our results.

112: if they actually analyzed each minute rather than just the end of each activity time, a model other than ANOVA would seem appropriate since there is such a high correlation between results at time t and time (t-1)

The figure shows that there were apparent changes over time within each of the activity types (e.g, heart rate and relative perceived exertion to progressively increase within exercise time, and there were progressive declines while sitting). If so, this may violate the assumption of a steady-state or pseudo-steady-state
condition for which the last minute of each exercise type can be chosen to be indicative. (If they are predominantly concerned about health care workers, many of the respirator use durations are less than 15 min. when nurses enter/leave patient rooms).

The authors may wish to discuss whether they considered alternative statistical analyses (e.g., including every data point rather than just three for each subject, using time since initiating an activity type as a variable). The results may also be subject to an autoregressive component (results at one time may depend very heavily upon results upon the immediately preceding time).

Since the graphs seem to suggest that several physiologic variables have continued to change, the authors may wish to expand their excellent discussion section to indicate whether their results are applicable only for very short times or may be relevant to more prolonged use.

Author Reply: As described in the statistical analysis portion of the Materials and Methods section, all study variables were first averaged over one minute and then arranged for 10 minute intervals of each 20 minute study phase (standing, cycling, sitting), so that the analysis is not just for “the end of each activity time” but at 10 minute intervals (6 intervals in total over the course of one hour). The ANOVA is therefore an appropriate test for this data. With regard to the effects of each activity on heart rate and RPE, there are minimal changes noted on the graphs with standing, the expected increases in heart rate with exercise, and the expected decreases noted with sitting (that is analogous to a resting state). The total one hour period of mixed activity (standing, cycling, sitting) utilized for the study was meant to better reflect the normal fluctuation in daily activities that occur during a workday, as opposed to a pseudo-steady state condition that is likely not the norm. Thus, we feel that the statistical analysis we chose is appropriate for determining the effects of EARL on pregnant and non-pregnant subjects. We do agree with the reviewer that some mention should be made of the fact that our findings may not be reflective of EARL over periods of time that are greater than one hour. We have added the following (Lines 234 - 236): “The study trials were carried out for one hour periods, so that we cannot comment on the impact of similar levels of EARL over longer periods of time.”

MINOR

Abstract: The authors describe this as a "case-control" study. However, they did not actually match participants on an individual basis as is typically done in a case-control design. Rather, they compared a group of pregnant and nonpregnant volunteers. Comparing the same subjects with/without a respirator does not constitute a typical case-control study.

Author Reply: We agree that case-control may not be completely appropriate for
the current study which may be better defined as a Comparative Study.

47: “Face coverings” versus “respirator”: The introduction includes an innovative mention that face coverings are widely used for religious/cultural reasons as well as protection against inhaled materials, the relevance is uncertain since most of the women's head coverings are to prevent seeing the face rather than having a tight seal. Their study is narrowly focused on one particular type of standard clinical respiratory protective device. It is not clear from their references that these extended uses impose resistive or dead space loads since they are not tightly worn. Perhaps the authors could express this potential limitation.

Author Reply: As per the reply to “85” above, we have added (Lines 224 – 230): “It is likely that, given the lower resistance levels of various fabrics used for facial coverings (Rengasamy et al, 2010), and the fact that some facial coverings likely do not adhere as tightly to the face as N95 FFR, their impact on the wearers would be less than that noted in the current study for N95 FFR. However, the accumulation of significant amounts of expired moisture or sweat on facial coverings that adhere closely to the facial skin (e.g., niqab, balaclava, medical/surgical mask, etc.) could result in significant breathing resistance (Roberge et al, 2012b) that might equal that of some filtering facepiece respirators.” We have added the Roberge et al 2012b article to the reference list.

77: The research methods might be described in some more detail. Specifically, was the order of assignment to exercise with/without respirator randomly assigned to the subjects or did all complete one phase initially?

Author Reply: We mentioned in the Materials and Methods section that the phases of the study were contiguous, thus indicating that subjects carried out a non-stop, complete set of trials or control sessions. However, to more clearly indicate this, we have added (Line 112) “non-randomized” to the trials description in the Materials and Methods section (pg 6, para 1) so that it now reads (Lines 110 – 114): “The order of the trials (wearing an N95 FFR) and controls (not wearing an N95 FFR) was randomized; each trial and control consisted of three contiguous (non-randomized) 20 min phases of standing upright, pedaling a Kettler RX7 reclining bicycle ergometer (Ense-Parsit, North Rhine-Westphalia, DE) at 60 pedal cycles/min and 50 watts resistance, and sitting upright in a chair.”

90: The measurements of stroke volume and total peripheral resistance were made using a technique that estimates these noninvasively rather than by direct measurement. Since this method differs from the typical invasive (and therefore infeasible for studies such as this) approach, the authors may describe its mechanism and its strength/limitations in some more detail. For example, is it affected by the blood volume (which in turn is impacted by pregnancy)? Is the
accuracy of the indirect estimation of stroke volume and resistance impacted by body position? (E.g., standing may lead to reduced venous return). Or, by the authors confident that the stroke volume and TPR would not be affected by the exercise your body position, so that any differences would only reflect use of the respirator?

Author Reply: We have added the following in the Materials and Methods section (Lines 91 - 102): “The volume clamp method, as used in the FinoMeter, utilizes a cuff (clamp) with an inflatable bladder around the finger to maintain the diameter of a finger artery constant despite changes in arterial pressure with each heartbeat. With the volume of the artery then fixed, the pressure difference across the arterial wall (transmural pressure) is zero and intraarterial equals extraarterial pressure. The FinoMeter cuff contains an infrared plethysmograph that detects arterial volume changes with each heartbeat and infrared arterial pulsatile diameter changes that are used to alter the pressure in the cuff as needed to maintain the fixed volume. The cuff pressure then serves as an indirect measure of intraarterial pressure ((Bogert and van Lieshout, 2005). Utilizing the ModelFlow methodology, stroke volume is determined by a three-element model using aortic characteristic impedance, arterial compliance, and systemic vascular resistance (Wesseling et al, 1993). We have added the Bogert and Wesseling articles to the reference list.

In the Limitations section (Lines 261 – 263) we have added the following: “Finger arterial pressure can overestimate brachial artery systolic pressure due to pulse pressure amplification that occurs with differences in vessel compliance between larger and smaller arteries (Bogert and van Lieshout, 2005).”

It is possible that posture can influence vascular tone (for example, going from the supine to standing position). In order to prevent venous pooling in the legs that is common in pregnancy (with attendant decreased venous return), the pregnant subjects were instructed to perform 20-30 seconds of stationary walking every 5 minutes while standing and we have added the following to the Materials and Methods (Lines 114 - 116) section: “Pregnant subjects were instructed to perform stationary walking for 30 seconds every 5 minutes during the standing portion of the trials and controls to prevent venous pooling in the lower extremities.” In addition, reclining bicycle ergometers, of the type used in the study, are considered the safest exercise in pregnancy because they do not interfere with venous return (Durak EP, Jovanovic-Peterson L, Peterson CM. 1990. Comparative evaluation of uterine response to exercise on five aerobic machines. Am J Obstet Gyne 162:754-756), so that we do not think that body position had a major impact on the study results. Given that the work rate (exercise) was the same for both subject groups and differed between trials and controls only in the use of a respirator, we feel confident that our findings likely reflect only the difference in respirator use or non-use and are not impacted to any significant degree by body position or exercise.
111: Statistical methods: They collected a great deal of data with minute by minute measurements and 10 min. aggregates. Readers would benefit from a more clear explanation of the statistical approaches. It seems that they actually only used a single point from each of the exercise regimens (the last minute).

Author Reply: As in the response to 112 above, our reply is (Lines 124 – 125): “As described in the statistical analysis portion of the Materials and Methods section, all study variables were first averaged over one minute and then arranged for 10 minute intervals of each 20 minute study phase (standing, cycling, sitting)”, so that the analysis is not just for “the end of each activity time”.

158: For clarity, the major heading “vascular” might be better described as “cardiovascular” since most of the variables referred to the heart.

Author Reply: Agree, and have done so (Line 172).

188: The Results section includes only a brief summary of the actual findings. The reader is referred to the figures for many details. However, the figures do not include any symbols showing statistical significance test results, confidence intervals, etc. Since the ANOVA they performed presumably gave estimates for the effect of each of their variables (pregnancy status, activity type, and respirator condition), these estimates and their associated statistical significance and confidence intervals could easily be presented in a table.

Author Reply: With the inclusion of a Table (Table 2) to the manuscript, values that are statistically significant will be indicate, but due to the inclusion of so much data into a Table, space limitations preclude the addition of confidence intervals. Statistical significance would indicate that the values fall within the confidence intervals.

188 FF: Including a table of results would also help the reader ascertained the effects of pregnancy per se. While physiologic impact of pregnancy is not the focus of the paper, it would put the respirator and activity related changes in perspective.

Author Reply: We agree that the addition of the Table (see Table 2) will assist in putting the effect of pregnancy in perspective.

231: The conclusions focus only on resistance, but there may have been effects of temperature, dead space, or other factors as well. Please see general comments above
Author Reply – As in our reply to General Comments above, we had added (Lines 252 – 256): “It is important to note that it is not only EARL that impacts those who wear facial coverings; associated issues of facial heat and humidity, increased perceptions of total body heat, variable carbon dioxide retention, and psychological issues (e.g., anxiety, claustrophobic reactions) must also be taken into consideration (Roberge et al, 2010, Wu et al, 2011, Roberge et al, 2012).

The authors thank the reviewer for his insightful and useful comments.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I have received funding from the federal agency for which the authors work

Reviewer’s report
Title: Effect of External Airflow Resistive Load on Postural and Exercise-associated Cardiovascular and Pulmonary Responses in Pregnancy
Version: 1 Date: 9 December 2014
Reviewer: Michail Keramidas
Reviewer’s report:
Major Compulsory Revisions
The present study examined the effects of the N95 filtering facepiece respirators (EARL) on the haemodynamic responses measured with the Finometer in a group of pregnant and no-pregnant women during light exercise, and standing and sitting positions. The authors concluded that the EARL caused increases in the diastolic and mean arterial pressures, but the responses were not aggravated in the pregnant women.

The practical value of the study is clear. However, there are a few major concerns that need to be addressed, mainly including the poor development of the study rationale and the lack of a testable hypothesis. In fact, there is a lack of strong physiological clarity in the introduction: did the authors expect any different response in the pregnant women? If yes, why?

Author Reply: In the Introduction, our rationale for the study was put forward as (Lines 48 – 51), “a significant proportion of women wearing facial coverings will be pregnant, yet little scientific data is available on the effects of these low external airflow resistive loads (EARL) on pregnancy-associated cardiovascular and pulmonary responses (Silversides and Colman, 2007; Gee et al, 1967). We then went on to say that the purpose of the study was (Lines 52 – 58) “to
examine the cardiovascular and respiratory impact of EARL in pregnancy.” With regard to the lack of strong physiological clarity in the Introduction, we believe we have addressed this with citations of the scant related studies addressing this topic with our statement (Lines 43 – 48), “These facial coverings impose variable external resistive loads (~19.6 – 196.1 Pa [2 – 20 mm H2O] pressure) to the wearer, depending on fabric properties (e.g., fiber diameter, packing density, pore size, electrostatic charge, etc.) (Rengasamy et al, 2010; Schutz and Church, 2011) and how tightly the covering is applied to the face, that have been shown to negatively impact pulmonary function and cardiovascular responses (Carnevale and Ducharme, 1999; Alghadir et al, 2012). Based on the limited scientific data available on the topic, the authors were unaware if there would be any different responses in the pregnant subjects.

Moreover, the data presentation is somewhat “puzzling”, and the reader has difficulties to follow them. Namely, it is unclear whether the reported P values are referred to the main effects or to the post-hoc analyses – the authors need to be specific. In this context, the statistical significances should be clearly depicted in the graphs as well. There is no need to repeat the P values in the discussion.

Author Reply: In the Statistical Analysis area of the Materials and Methods Section of the manuscript we stated (Lines 124 – 128), “Repeated measures ANOVA in a mixed design (two within-subjects factors [condition × time] and one between-subjects factor [pregnancy]) was carried out to determine the main effect of EARL over time together with the effect of pregnancy on the variables” informing the reader that these were main effects. Also, F-values (as reported in the Results Section) are generally indicative of main effects relationships, not post-hoc results.

The authors report in the results section that “pregnancy was not associated with a significant effect on any of the measured variables compared with values for non-pregnant subjects”; however, HR, SV, CO and TPR were different, as it is reported in the discussion section and is outlined in the graphs.

Author Reply: We agree that the that “pregnancy was not associated with a significant effect on any of the measured variables compared with values for non-pregnant subjects” is not accurate as stated. What we meant to state was that there were no differences between controls and trials in the pregnant category and also in the non-pregnant category, not differences between categories as implied in the original sentence. We regret this oversight and have changed this sentence to now read (Lines 142 – 143), “No significant difference was noted for any measured variable between the control and trial portions of the study in either the pregnant study group or the non-pregnant study group.”

Minor comments
I recommend that the authors should replace “blood pressure” with “arterial
pressure”.

Author Reply: We are not sure why the reviewer recommends this change. These terms are generally considered interchangeable and numerous published articles on use of the FinoMeter refer to its measurements as “blood pressure” measurements, so that we believe it is acceptable to use the term “blood pressure”.

The continuous measure of arterial pressure is based on the venous-clamp method. However, an indication of the stroke volume, and hence the cardiac output, is provided by the Modelflow method, which computes an aortic flow waveform from the finger by simulating a non-linear three-element model of the aortic input impedance. This needs to be clarified in the methodology section. In this context, all the Modeflow-derived variables should be referred as indexes (i.e. index of cardiac output, index of stroke volume etc).

Author Reply: We agree, and as per our response to Reviewer #1, we have included (Lines 91 - 102), “Utilizing the ModelFlow methodology, stroke volume is determined by a three-element model using aortic characteristic impedance, arterial compliance, and systemic vascular resistance (Wesseling et al, 1993).” In addition, we have now changed the sentence to the following, “Utilizing the ModelFlow methodology, stroke volume is determined by a three-element model using aortic characteristic impedance, arterial compliance, and systemic vascular resistance (Wesseling et al, 1993), and cardiovascular parameters obtained from the ModelFlow methodology are appropriately referred to as indexes.”

I suggest that the changes in systolic arterial pressure (p = 0.06) should not be reported as not significant, but perhaps as a “statistical tendency for a higher SAP”.

Author Reply: In the Statistical Analysis of the Materials and Methods Section, we stated “A statistical significance was accepted when p<0.05…” thus, p<0.06 is not statistically significant and we have no way of knowing if, with greater subject numbers, the value would become statistically significant or even more non-significant. However, we are now stating (Lines 173 - 175), “The effect of EARL on the SBP of study subjects approached, but did not achieve, statistical significance (F=3.763. p=0.06), but the interaction of time and pregnancy was significant (F=2.645, p=0.03).”

The standard deviations should be added in the graphs.

Author Reply: With four values for each minute of the one-hour study trials, the use of standard deviations in the graphs would make the graphs essentially unreadable due to all the standard deviation bars’ overlap. The standard deviations, however, will be reported in Table 2.
In the limitation section, I do not understand the sentence “Due to not having pre-study data, it is possible that the SBP and DBP reported are higher than the subjects’ normal baseline due to the effects of relatively prolonged wear of the FinoMeter on the finger”. Please, clarify it.

Author Reply: It has been shown (Ristuccia HL, Grossman P, Watkins LL, Lown B. Incremenetal bias in Finapres estimation of baseline blood pressure levels over time. Hypertension 1997;29:1039-1043) that the use of FinoMeter for prolonged periods of measurement can result in elevated blood pressure values that may be related to: 1) interstitial fluid loss from the finger tissue under the cuff, 2) altered blood flow, 3) edema, or 4) altered finger temperature at the measurement site. For the purposes of clarity, we shall rephrase the sentence as (Lines 236 – 240), “Due to not having pre-study data, it is possible that the SBP and DBP reported are higher than the subjects’ normal baseline due to any of the possible effects of relatively prolonged wear of the FinoMeter on the finger (i.e., interstitial fluid loss from the finger tissue under the cuff, altered blood flow, edema, or altered finger temperature at the measurement site (Ristuccia HL, Grossman P, Watkins LL, Lown B. Incremenetal bias in Finapres estimation of baseline blood pressure levels over time. Hypertension 1997;29:1039-1043).”

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests.

The authors thank the reviewer for his insightful and useful comments.