

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	IS NECK CIRCUMFERENCE AN APPROPRIATE TOOL TO PREDICT CARDIOVASCULAR RISK IN CLINICAL PRACTICE? A CROSS-SECTIONAL STUDY IN CHILEAN POPULATION
<b>AUTHORS</b>	Caro, Patricia; Guerra, Ximena; Canals, Andrea; Weisstaub, Gerardo; Sandaña, Carlos

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Luc Bruyndonckx Laboratory of Experimental Medicine and Pediatrics, University of Antwerp, Belgium
<b>REVIEW RETURNED</b>	03-Jan-2019

<b>GENERAL COMMENTS</b>	<p>Measuring neck circumference has been proposed as an easy way of assessing cardiovascular risk. However large studies were lacking investigating the correlation between neck circumference and cardiovascular risk. The manuscript is well written, I hope the authors take the following remarks in consideration.</p> <p>Strengths and limitations Please include a sentence stating that cardiovascular risk was not assessed directly by cardiovascular morbidity or mortality.</p> <p>Material/subjects and methods Was ethical approval given to this study? Who measured neck circumference (nurse? Physician?) Discussion How where Chilean cutoffs for neck circumference established?</p>
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<b>REVIEWER</b>	Vasilios Pergialiotis Greece
<b>REVIEW RETURNED</b>	21-Jan-2019

<b>GENERAL COMMENTS</b>	<p>The authors investigated in the present manuscript the efficacy of "NECK CIRCUMFERENCE as AN APPROPRIATE TOOL TO PREDICT CARDIOVASCULAR RISK IN CLINICAL PRACTICE". The manuscript is of scientific importance, however, certain clarifications are needed to increase its scientific merit in this field.</p> <ol style="list-style-type: none"><li>1) a bioethics committee approval is needed even in registry based studies.</li><li>2) statistical analysis section and results section are appropriately designed.</li><li>3) Discussion the main problem with this section is that the authors failed to identify the pathophysiological background that could implicate neck circumference as a marker of adiposity and increased cardiovascular risk. Are there any studies that suggest</li></ol>
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	that fat accumulation in neck is predominant among patients with CVD or metabolic syndrome. This should be stated in this section and analyzed in a separate paragraph. Also, implications for future research are also missing (potentially imaging analysis of fat distribution and CVD, or multivariable analysis that might take into consideration this parameter, together with vascular parameters) as well as guidance for current clinical practice (should it be used?).
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## VERSION 1 – AUTHOR RESPONSE

Reviewer: Luc Bruyndonckx

Comment 1: Strengths and limitations. Please include a sentence stating that cardiovascular risk was not assessed directly by cardiovascular morbidity or mortality.

Response: It was added in page 10, 3rd paragraph:

“Another limitation of the study is that cardiovascular risk was not assessed directly by cardiovascular morbidity or mortality, but through Framingham tables adapted for the Chilean population. However, tables and scores based on risk factors are widely recommended in clinical practice to measure cardiovascular risk (41)”

Comment 2: Material/subjects and methods. Was ethical approval given to this study?

Response: We added an ethical issues section in “Material/Subjects and Methods” (page 7, 2nd paragraph) in which we state that the Chilean National Health Survey 2009-2010 protocol was approved by the Research Ethics Committee of Pontificia Universidad Católica de Chile and also that our research was approved by the Scientific Ethics Committee of Universidad Mayor de Chile (C.R.I. N°195/161\_2019):

“Ethical issues

The present study is based on the analysis of the data resulting from the NHS 2009-2010, without direct intervention in human beings. The 2009-2010 NHS protocol was approved by the Research Ethics Committee of Pontificia Universidad Católica de Chile (September 1, 2009). The survey included the application of informed consent and information about the results of laboratory tests to individuals. The NHS database has open access to the Health Ministry of Chile web page (29). The present research was approved by the Scientific Ethics Committee of Universidad Mayor de Chile”

Comment 3: Material/subjects and methods. Who measured neck circumference (nurse? Physician?)

Response: In the description of neck circumference and waist circumference measurements (“Material/Subjects and Methods”>“Variables and measurements”) we added the sentence “Both measures were made by trained nurses” at the end of the paragraph (page 6, 2nd paragraph)”.

Comment 4: Discussion. How were Chilean cutoffs for neck circumference established?

Response: We selected cut-off values based on the best sensitivity and specificity to predict cardiovascular risk in Chilean population. This information was stated in “Material/Subjects and Methods”>“Statistical Analysis” (page 6, 5th paragraph), where we indicate that “Cut-off points for cervical obesity in each gender were selected based on the best performance of neck circumference to predict moderate/high CVR”. However, we have considered this comment and we have added the sentence “In this study, they were based on the best sensitivity and specificity of neck circumference to predict moderate/high CVR in each gender” in the paragraph in which we discuss these results (page 9, 3rd paragraph).

Reviewer: Vasilios Pergialiotis

Comment 1: A bioethics committee approval is needed even in registry based studies.

Response: We added an ethical issues section in "Material/Subjects and Methods" (page 7, 2nd paragraph) in which we state that the Chilean National Health Survey 2009-2010 protocol was approved by the Research Ethics Committee of Pontificia Universidad Católica de Chile and also that our research was approved by the Scientific Ethics Committee of Universidad Mayor de Chile (C.R.I. N°195/161\_2019):

"Ethical issues

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Comment 2: Discussion the main problem with this section is that the authors failed to identify the pathophysiological background that could implicate neck circumference as a marker of adiposity and increased cardiovascular risk. Are there any studies that suggest that fat accumulation in neck is predominant among patients with CVD or metabolic syndrome. This should be stated in this section and analyzed in a separate paragraph.

Response: We have complemented and deepened the second paragraph of discussion in which discuss the association between neck circumference and cardiometabolic risk factors (page 8, 4th paragraph and page 9, 1st paragraph):

"The results are in the same way as previous studies that have found a positive association between neck circumference and cardiometabolic risk factors (30). Neck circumference has been positively correlated with glucose and insulin resistance, systolic and diastolic blood pressure, free fatty acids, the production of very low-density lipoprotein cholesterol (VLDL-C) and triglycerides, while it would exist an inverse association with HDL cholesterol (24,30–33). It is possible to hypothesize that upper subcutaneous fat would have similar pathophysiological characteristics than abdominal visceral fat. In fact, neck circumference is also related to oxidative stress, endothelial cell dysfunction and vascular injury (24,31,32) and it is correlated with visceral adipose tissue, as measured by computed tomography (30,34,35). Therefore, neck circumference seems to be an important anthropometric marker for the identification of patients with a high cardiometabolic risk (36)."

Comment 3: Also, implications for future research are also missing (potentially imaging analysis of fat distribution and CVD, or multivariable analysis that might take into consideration this parameter, together with vascular parameters) as well as guidance for current clinical practice (should it be used?).

Response: We modified the last paragraph of discussion adding the implications suggested by the reviewer (page 10, 4th paragraph and page 11, 1st paragraph):

"... However, its good performance appears as an opportunity to use it in clinical practice when waist circumference measurement is difficult or eventually replace waist circumference measurement due to its easy technique.

Future research is needed in specific populations which have difficulties in cardiovascular risk estimation as extreme elderly people, multimorbidity patients or ethnic groups. It would be also recommendable to evaluate if a reduction of neck circumference post-bariatric surgery or loss weight is a good marker of cardiometabolic improvement and to incorporate imaging analysis of upper subcutaneous fat in these studies."

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Luc Bruyndonckx Translational Research in Immunology and Inflammation, University of Antwerp, Belgium
<b>REVIEW RETURNED</b>	07-Jul-2019

<b>GENERAL COMMENTS</b>	Previous remarks were well adressed in this manuscript
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<b>REVIEWER</b>	Vasilios Pergialiotis National and Kapodistrian University of Athens Greece
<b>REVIEW RETURNED</b>	22-Jun-2019

<b>GENERAL COMMENTS</b>	The authors successfully revised their manuscript.
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