PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from Archives of Disease in Childhood but declined for publication following peer review. The authors addressed the reviewers’ comments and submitted the revised paper to BMJ Paediatrics Open. The paper was subsequently accepted for publication at BMJ Paediatrics Open.

ARTICLE DETAILS

| TITLE (PROVISIONAL) | A SINGLE CENTRE CASE CONTROL STUDY INVESTIGATING THE ASSOCIATION BETWEEN ACANTHOSIS NIGRICANS, INSULIN RESISTANCE AND TYPE 2 DIABETES IN A YOUNG, OVERWEIGHT, UK POPULATION. |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AUTHORS            | Callanan, Niamh, Wright, Neil |

VERSION 1 – REVIEW

REVIEWER
Reviewer name: Dr. Melanie Kershaw
Institution and Country: Birmingham Children's Hospital NHS, United Kingdom of Great Britain and Northern Ireland
Competing interests: None
REVIEW RETURNED 20-Oct-2021

GENERAL COMMENTS
The grading of severity of acanthosis should refer to a standardised score
Given the retrospective methodology can the authors confidently state that all sites for acanthosis were examined in those recorded with no acanthosis.
Did the authors look at HbA1c
Whilst the sample size was small and subjects were matched for age ethnicity and sex, a table outlining the ethnic origins of the population and the representation of different ethnic groups in relation to the local population would enhance the paper. At present the cohort could include 90% SE asian population and this would have a bearing on the authors conclusions

REVIEWER
Reviewer name: Dr. Juan Lopez-Alverenga
Institution and Country: None
Competing interests: None
REVIEW RETURNED 01-Nov-2021

GENERAL COMMENTS
Paper titled: “A CASE-CONTROL STUDY INVESTIGATING THE EXTENT TO WHICH THE PRESENCE OF ACANTHOSIS NIGRICANS CONFERS ADDITIONAL RISK FOR INSULIN RESISTANCE AND TYPE 2 DIABETES WITHIN A YOUNG, OVERWEIGHT, UK POPULATION”.
This study brought the controversy if acanthosis nigricans (AN) could be an independent marker of insulin resistance (IR) or merely a reflection of obesity. The authors addressed the problem with a UK-based retrospective study design.
Strengths. The authors described their study design as a case-control using medical records. They collected information from 94 patients with AN matched for age, sex, and BMI with a control group without acanthosis. The researchers added another group of 42 participants to analyze the strength of association between AN and IR.
Version 1 – Author’s Response

Dear Miss Callanan:

archdischild-2021-323172 entitled “A case-control study investigating the extent to which the presence of acanthosis nigricans confers additional risk for insulin resistance and type 2 diabetes, within a young, overweight, UK population.”

Thank you for submitting the above paper to the Archives of Disease in Childhood. It has been considered carefully and unfortunately, we are unable to accept it for publication. We receive a high volume of manuscripts and unfortunately we cannot publish them all. This research did not meet the threshold for publication, particularly when considering impact on clinical practice. However, I hope the comments from the reviewers are helpful. You may want to look at the ethnicity of your cohort as this is not reported in your manuscript.

The comments of the reviewer(s) are included at the bottom of this letter.

I hope the outcome of this specific submission will not discourage you from the submission of future manuscripts.

If your article reports original research, you might like to consider BMJ Paediatrics Open, a new open access, peer-reviewed journal from the publishers of ADC. If you would like to transfer your paper, save
time by emailing info.adc@bmj.com. We will transfer your submission files and any peer reviews associated with them. Please note there is an Article Processing Charge (APC) for accepted articles, with a 25% discount for RCPCH members.

Sincerely,

Dr. Catherine Peters
Associate Editor, Archives of Disease in Childhood

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author
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Given the retrospective methodology can the authors confidently state that all sites for acanthosis were examined in those recorded with no acanthosis.
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Reviewer: 2

Comments to the Author
Paper titled: "A CASE-CONTROL STUDY INVESTIGATING THE EXTENT TO WHICH THE PRESENCE OF ACANTHOSIS NIGRICANS CONFERS ADDITIONAL RISK FOR INSULIN RESISTANCE AND TYPE 2 DIABETES WITHIN A YOUNG, OVERWEIGHT, UK POPULATION".
This study brought the controversy if acanthosis nigricans (AN) could be an independent marker of insulin resistance (IR) or merely a reflection of obesity. The authors addressed the problem with a UK-based retrospective study design.
Strengths. The authors described their study design as a case-control using medical records. They collected information from 94 patients with AN matched for age, sex, and BMI with a control group without acanthosis. The researchers added another group of 42 participants to analyze the strength of association between AN and IR.
Weakness. The paper needs to give a rationale for what is novel and needs more detail with the operational methods. If the authors can not accomplish this requirement, perhaps, they should consider a letter to the editor instead.
1. The description of the methods needs more work, but at the same time, what’s the novelty the authors are offering in this paper?
2. Please, describe the tolerance for matching. For example, in the case of age, a participant was matched with control within ±5 years old (or what you done).
3. How did the authors make the matched analysis?
4. Which other confounders did they consider, i.e.: waist circumference?
5. How the severity of AN was assessed? The authors just described mild and severe AN, but they did not give a clue about the classification they used.
6. The PPV and NPV are not informative as the study was matched (the prevalence was controlled). The authors should include some comments regarding this issue in the discussion section.
7. Table 1 and 2. The authors described they used the median values. Which method did the authors use to calculate the 95%CI? Please, add these descriptions in the methods/statistics section.
8. The results (added group) did not indicate how they analyzed the association between the degree of AN and IR. The results suggest the authors contrasted these variables using medians of HOMA. Perhaps they should make log-transformation and use a parametric approach.
9. In the conclusion the authors wrote: Individuals with both acanthosis nigricans and obesity had significantly greater degrees of insulin resistance (sic). Please, describe how this interaction was analyzed (or even discarded).
10. Other minor suggestions.
10.1. Redaction. The title just has to mention the presence of acanthosis nigricans (not with/without).
10.2. Define the acronym BMI SDS; i.e.: The body mass index z-score (BMI SDS).
10.3. The authors should clarify the inclusion criteria for cases that must have AN grade 1 or higher and control a score of 0 (and of course, the used criteria for classification).

If you elected during submission to send your article on to another journal the article will be transferred in 5 working days. If you intend to rebut this decision please notify us before then. The journal(s) (if any) you have selected at submission are: BMJ Paediatrics Open
If you want to speed up or stop this onward transmission please email the editorial office:
info.adc@bmj.com

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**VERSION 2 – REVIEW**

**REVIEWER**
Reviewer name: Dr. Juan Carlos Lopez-Alvarenga
Institution and Country: The University of Texas Rio Grande Valley, United States
Competing interests: None

**REVIEW RETURNED**
03-Jul-2022

**GENERAL COMMENTS**
This is an original paper on insulin resistance associated with AN in England sample. The case-control design helps to contrast metabolic disarrangements in participants matched by BMI. The researchers made changes in the paper to fill the suggestions we made. This study is remarkable for the studied population in U.K. The methods for matching the cases and controls are now well described. The authors decided to drop the AN severity, I agree with them because the severity in this study did not add knowledge but noise. Therefore, it was better to maintain a dichromic (yes/no) variable. The paper became clearer now. The authors addressed the limitation of the artificial prevalence due to the study design (case and control), but still has diagnostic relevance in PPV and NPV measurements.

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**REVIEWER**
Reviewer name: Dr. Rachel Mary Hilliam
Institution and Country: The Open University, United Kingdom of Great Britain and Northern Ireland
Competing interests: None

**REVIEW RETURNED**
28-Jun-2022

**GENERAL COMMENTS**
The authors have fully responded to the original comments by the reviewers. The paper will well written and has findings which the readers of this journal will find interesting. The statistics in the paper are appropriate for the data. It would be helpful if the limitations of the data were described more fully, but there is an adequate discussion.

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**Version 2 – Author’s Response**

15th July 2022

Dear Professor Imti Choonara,

Re: A case-control study investigating the extent to which the presence of acanthosis nigricans confers additional risk for insulin resistance and type 2 diabetes within a young, overweight, UK population (old title). A single centre case control study investigating the association between acanthosis nigricans, insulin resistance and type 2 diabetes in a young, overweight, UK population (new title).

Thank you for reviewing our manuscript. Changes have been made to the manuscript, following review
of the minor recommendations (documents attached). I hope these changes fulfil the comments made.

Please address all correspondence concerning this manuscript to me at callananniamh@gmail.com

Thank you again for your consideration of our manuscript.

Yours sincerely,

Miss Niamh Mary Callanan BMedSci MBChB
The University of Sheffield