

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Do changing levels of maternal exercise during pregnancy affect neonatal adiposity? Secondary analysis of the Babies After SCOPE: Evaluating the Longitudinal Impact Using Neurological and Nutritional Endpoints (BASELINE) birth cohort (Cork, Ireland)
AUTHORS	Norris, Tom; McCarthy, Fergus; Khashan, Ali; Murray, Deidre; Kiely, Mairead; Hourihane, Jonathan; Baker, Philip; Kenny, Louise

VERSION 1 – REVIEW

REVIEWER	Allison L B Shapiro University of Colorado Anschutz Medical Campus, USA
REVIEW RETURNED	15-Jun-2017

GENERAL COMMENTS	<p>ABSTRACT</p> <p>General: There are no statistical methods described in the abstract. Please add a brief description of the models you ran (multivariable linear and logistic).</p> <p>Line 16: Please spell out “percent body fat” (%BF) before using the acronym.</p> <p>Line 21: You do not specify on which outcome there is no effect. Please add that there was no effect on “either birth weight, %BF, or risk of >90th centile infant”. Or something to that effect.</p> <p>METHODS</p> <p>General: The statistical analysis section is unorganized. Please first state your methods for descriptive comparisons (Tables 1 and 2). Then your methods for the first models that were run with linear regression, using birthweight and %BF as continuous outcomes. Then your methods for the final models you ran with logistic regression, and how you defined the bivariate outcomes of >90th or <10th adiposity centiles.</p> <p>Line 27: Please begin with your descriptive comparison methods. What statistical analysis did you use to generate the p-values in Table 2?</p> <p>Lines 40 – 44: This sentence is not clearly describing your method of creating a binary outcome variable for percentile of adiposity. See general comment above.</p> <p>Line 8 (page 8): Given the emphasis on the use of a DAG, please include the DAG as a supplementary figure.</p>
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	<p>RESULTS</p> <p>Lines 3 – 24 (page 13): Please use a sub-header to distinguish this results section as your “Sensitivity Analyses”.</p> <p>DISCUSSION</p> <p>Lines 10 – 17 (page 16): The measurement of physical activity, while self-reported, does not induce recall bias or the risk of recall bias in this cohort because of the prospective nature of the data collected (PA before birth outcomes). Further, recall bias due to PA self-report would only occur if the women who had bigger/more adipose babies systematically answered the PA questionnaire differently than the women with less adipose babies, and that this systematic difference was related somehow to the birth outcomes. The self-report of the PA measure is only likely to result in random error due to women not accurately remembering their PA levels. However, as you mention, the short duration of the recall period for PA is likely to reduce this random error.</p> <p>Lines 17 – 43 (page 17): It is not necessary to discuss issues of statistical power here. You found a significant result, therefore it appears that you had enough power (1-Type-II error) to detect the effect. However, you could discuss Type 1 error due to the number of models that you ran, which could increase the likelihood of finding something significant. Please comment on whether there were any p-value adjustments made.</p> <p>CONCLUSION</p> <p>General: Please comment on how this data suggest the increase/continued need for women to be encouraged to maintain or increase their level of exercise in pregnancy.</p>
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REVIEWER	Izzuddin M Aris Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research
REVIEW RETURNED	21-Jun-2017

GENERAL COMMENTS	<p>This is a well-written manuscript investigating the relationship between changes in levels of exercise during pregnancy with neonatal adiposity. Given that exercise during pregnancy is potentially modifiable through behaviour change interventions, this study makes an important contribution in to the current literature in understanding the potential determinants of neonatal adiposity. Below are my comments to the authors:</p> <p>Abstract - As this is only an association study, it is inappropriate to utilize the term “effects” in describing the results and conclusion, which is suggestive of causation. Would suggest the authors to describe their results and conclusions more conservatively</p> <p>Introduction - Well written, and gives a holistic view of the previous studies that have been conducted relating maternal exercise during pregnancy with birth size and its potential mechanisms.</p>
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- The hypothesis however, reads more like an aim/objective. The authors should be more specific on their hypothesis and state clearly the directions of the hypothesised associations (e.g. higher intensity of maternal exercise during pregnancy is associated with lower neonatal adiposity)

Methods

- With regards to the questionnaire used to determine the level of exercise, has it been validated before in a separate population, or at least in a separate cohort within the same population? This information should be described in the Methods

- Is there any information collected on blood glucose levels during pregnancy?

- Is there any information collected on gestational weight gain?

Results

- Well-written.

- The last paragraph however, should be moved to the top of the Results section; this would give the readers a better idea of the differences between the included and excluded subjects at the start.

Discussion

- There shouldn't be any reporting of effect estimates in the Discussion (first paragraph of Discussion)

- The use of the term "sensitive period" (first paragraph and in other parts of the Discussion) is a misnomer in the context of the study's findings. As described by Kuh D et al (PMID: 14573579), a "sensitive" period is one in which an exposure period has a larger effect than exposure during other periods; in other words, the same exposure outside this "sensitive" period may still be significantly associated with increased risk, but is weaker than during the sensitive period. The findings of this study however, shows that significant associations were only apparent between 15 and 20 weeks, but not prior to 15 weeks. Would suggest the authors to rephrase accordingly to properly reflect the findings

- Recent meta-analyses (Russo LM et al, PMID: 25730218; Sanabria-Martínez G et al, PMID: 26036300) have described that physical activity in pregnancy provides a protective effect against the development of gestational hyperglycemia, and reduces gestational weight gain. Gestational hyperglycemia and weight gain in turn, are well-known risk factors for increased neonatal adiposity (Farrar D et al, PMID: 27624087; Poston L, PMID: 22406744). The lack of measurements of maternal glycemia and gestational weight gain in this study, to potentially explain the observed associations, presents a great limitation which should be discussed and addressed

REVIEWER	Isabelle Marc Laval University Québec, PQ, Canada
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	<p>This study is a secondary analysis from the previous birth cohort SCOPE. The aim of the current study was to assess the effects of changes in maternal PA during pregnancy on the infant's adiposity.</p> <p>This is a very interesting question. However the impact of this paper is limited by:</p> <ul style="list-style-type: none"> - Definition and measure of the exposure: exercise was not assessed using validated questionnaire or objective measurements, so assessment of the changes in exercise is really subjective. It is a major problem of this study not having quantitative measures of PA. - Assessment of exercise only takes into account the time per week they engage in vigorous PA. Moreover the definition of vigorous activity is unclear: does it take into account only the part of PA the women is "breathing harder" or the whole time they engage in an activity including some vigorous activity? - Comparison of the effect of changes in exercise does not take into account the baseline levels. What is the impact of the women who perform no PA at the two assessments on the infant's adiposity? They cannot be classified as decreasing their PA levels? - How the authors consider the effects of PA changes after 20weeks and PA in late pregnancy on the results? - What is the rationale for the impact of this very specific and short period between 15 and 20 weeks for an impact on infant's adiposity? <p>There is no sample size calculation.</p>
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REVIEWER	Kai Ling Kong State University of New York at Buffalo, USA
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	<p>This paper aimed to assess whether changing levels of exercise during pregnancy are related to altered neonatal adiposity. This paper has many strengths which include: the longitudinal nature, the use of PEA POD for the body fat measurement and a large sample size. This can bring significant contribution to the field where data of this type is rare. However, there are some minor issues that should be addressed by the authors to strengthen this paper.</p> <p>Abstract: Please define BF% at the first use</p> <p>Methods:</p> <ul style="list-style-type: none"> - Cite as where the cut point for the BF% >90th as high and BF% < 10th as low coming from? - Why the authors decided to use dichotomous variable instead of reporting on the continuous variable for the BF%. I would like to see the continuous outcome variable being included in the paper. <p>Conclusion:</p> <ul style="list-style-type: none"> - This section is too long. The authors need to be concise in discussing their strengths and limitations (no more than 2/3 of the page). - More literature should be cited and reported on the topic of the effects of exercise during pregnancy on infants outcomes (i.e. weight status, % body fat, birth weight).
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

We are grateful for the constructive feedback provided, especially regarding the structuring of the 'statistical analysis' section and the issue of recall bias. Our specific responses are below.

ABSTRACT:

Comment: General: there are no statistical methods described in the abstract. Please add a brief description of the models you ran (multivariable linear and logistic)

Response: we have now added the following sentence "Multivariable linear and logistic regression models were used to investigate the relationship between exercise and the respective outcomes" (page 2 of track changed document within 'main outcome measures').

Comment: line 16: please spell out "percent body fat" (%BF) before using the acronym.

Response: this has now been done (page 2 of track changed document within 'main outcome measures').

Comment: line 21: you do not specify on which outcome there is no effect. Please add that there was no effect on "either birth weight, %BF, or risk of >90th centile infant". Or something to that effect".

Response: we have now amended the first sentence of the results section of the abstract to 'Crude analysis revealed no association between a changing level of exercise (since becoming pregnant) at 15 weeks' gestation and any of the outcomes (%BF, low adiposity, high adiposity)'.

METHODS:

Comment: general: The statistical analysis section is unorganized. Please first state your methods for descriptive comparisons (Tables 1 and 2). Then your methods for the first models that were run with linear regression, using birthweight and %BF as continuous outcomes. Then your methods for the final models you ran with logistic regression, and how you defined the bivariate outcomes of >90th or <10th adiposity centiles.

Response: the statistical analysis section (page 7 of track changed document) now starts with 'Descriptive statistics (frequencies and percentages) of the different levels of exercise were summarised and are shown in table 1. We generated a 'no exercise' binary variable with a value of 1 indicating women who reported doing no vigorous nor moderate nor recreational walking activity per week.'

The following sentence then refers to the second table looking at differences in maternal characteristics/birth outcomes: 'Differences in maternal characteristics and birth outcomes, stratified by change in exercise level, were explored using one way analysis of variance for continuous variables (with scheffe test for post-hoc pairwise comparisons) and chi2 test for categorical variables (table 2 of track changed document)'.

Comment: Line 27: Please begin with your descriptive comparison methods. What statistical analysis did you use to generate the p-values in Table 2?

Response: this is addressed above

Comment: Lines 40 – 44: This sentence is not clearly describing your method of creating a binary outcome variable for percentile of adiposity. See general comment above.

Response: we have changed this to 'We subsequently generated separate binary variables (0=no; 1=yes) indicating the presence of either low or high adiposity. Low and high adiposity was defined as below/above the gestational age- and sex-specific 10th/90th adiposity centiles respectively, according to the centiles produced by Hawkes et al (2011).²⁶ The effect of changes in physical activity on these dichotomous variables was investigated using logistic regression models' (page 8 of track changed document).

Comment: Line 8 (page 8): Given the emphasis on the use of a DAG, please include the DAG as a supplementary figure.

Response: this has now been added as supplementary figure 1.

RESULTS:

Comment: Lines 3 – 24 (page 13): Please use a sub-header to distinguish this results section as your "Sensitivity Analyses".

Response: we have now added a sub-heading 'descriptive statistics of the sample (and those omitted)' at the start of the results section (page 10 of track changed document). We don't feel this is a sensitivity analysis, i.e. we were not performing analyses in the two separate groups to see if the associations were maintained, rather, we were just describing the sample included to gauge its representativeness.

DISCUSSION:

Comment: Lines 10 – 17 (page 16): The measurement of physical activity, while self-reported, does not induce recall bias or the risk of recall bias in this cohort because of the prospective nature of the data collected (PA before birth outcomes). Further, recall bias due to PA self-report would only occur if the women who had bigger/more adipose babies systematically answered the PA questionnaire differently than the women with less adipose babies, and that this systematic difference was related somehow to the birth outcomes. The self-report of the PA measure is only likely to result in random error due to women not accurately remembering their PA levels. However, as you mention, the short duration of the recall period for PA is likely to reduce this random error.

Response: we have removed all references to recall bias, instead referring to 'error'... 'This potentially introduced error into the exercise variables due to women not accurately remembering their exercise levels (e.g. due to social desirability of reporting higher levels or age). Whilst the recall period was relatively short (5-15 weeks), thus reducing the extent of the error introduced' (page 19 of track changed document second paragraph). The authors debate whether this error is only random error though, as it may be related to variable such a SES, such that those with higher SES may be more likely to over-report levels of exercise as it is more desirable to be seen as physically active. It may be that these women with higher SES may also carry a differing risk for the delivering an infant with high/low adiposity.

Comment: Lines 17 – 43 (page 17): It is not necessary to discuss issues of statistical power here. You found a significant result, therefore it appears that you had enough power (1-Type-II error) to detect the effect. However, you could discuss Type 1 error due to the number of models that you ran, which could increase the likelihood of finding something significant. Please comment on whether there were any p-value adjustments made.

Response: we have removed the clause 'whilst this will have reduced the statistical power of the study' (page 21 para 1) and the sentence 'A complete case analysis would, however, reduce the statistical power of the analysis' (page 21 para 1 of track changed document)

CONCLUSION:

Comment: General: Please comment on how this data suggest the increase/continued need for women to be encouraged to maintain or increase their level of exercise in pregnancy.

Response: we have added the following 2 sentences (page 22 para 2 of track changed document): 'The data presented here suggest that a reduction in exercise levels may lead to less favourable outcomes in terms of neonatal adiposity. As such, and given the evidence of maintaining pre-pregnancy exercise levels^{43 44}, we advocate the continuation of pre- and early pregnancy exercise levels into later pregnancy'.

Reviewer 2

We thank this reviewer for the detailed review and for the constructive feedback. The reviewer raised important points and we have sought to address these by either adding new material or clarifying material already in the manuscript. Our detailed responses are below.

ABSTRACT:

Comment: As this is only an association study, it is inappropriate to utilize the term "effects" in describing the results and conclusion, which is suggestive of causation. Would suggest the authors to describe their results and conclusions more conservatively

Response: we completely agree with this point and have replaced all instances of the word with 'associations'.

Introduction:

Comment: The hypothesis however, reads more like an aim/objective. The authors should be more specific on their hypothesis and state clearly the directions of the hypothesised associations (e.g. higher intensity of maternal exercise during pregnancy is associated with lower neonatal adiposity)

Response: we have modified this sentence, which now reads 'Consequently, we hypothesise that maternal exercise in pregnancy will be associated with altered neonatal adiposity, such that an increasing/decreasing exercise level in pregnancy will be associated with a reduction/increase in adiposity, respectively' (page 5 para 2 of track changed document).

METHODS:

Comment: With regards to the questionnaire used to determine the level of exercise, has it been validated before in a separate population, or at least in a separate cohort within the same population? This information should be described in the Methods.

Response: Whilst the questionnaire regarding physical exercise was not validated for any population, the definition of vigorous exercise (daily exercise leading to heavy breathing or being out of breath) has previously been used in other studies such as Bell RJ, Palma SM, Lumley JM. The effect of vigorous exercise during pregnancy on birth-weight. Aust N Z J Obstet Gynaecol 1995;35:46–51.

Comment: is there any information collected on blood glucose levels during pregnancy?

Response: Consistent blood glucose levels during pregnancy were not available as women in SCOPE/BASELINE were recruited and reviewed at 15 and 20 weeks' gestation and not later in pregnancy.

Comment: is there any information collected on gestational weight gain?

Response: These data were not collected. We have added couple of sentences in the 'discussion' section on this point... 'We were unable to adjust our estimates for the likely mediating role of gestational hyperglycaemia as these data were not available. Similarly, we did not adjust our estimates for the effect of gestational weight gain. In line with the published literature^{4 5 41 42}, these variables are likely to operate along the causal pathway between maternal exercise and neonatal adiposity. While adjusting for them may mask part of the association between exercise and adiposity, it would have been of benefit to conduct a priori analysis to examine whether a change exercise was associated with neonatal adiposity independently of pre-pregnancy obesity, gestational weight gain or impaired glycaemic control. Acknowledging these data gaps, the current paper did not aim to elucidate possible mechanisms by which the association between exercise and adiposity is enacted, rather, we aimed to identify whether an association existed at all' (page 20, para 2).

RESULTS:

Comment: The last paragraph however, should be moved to the top of the Results section; this would give the readers a better idea of the differences between the included and excluded subjects at the start.

Response: this has now been moved to the beginning of the results section (page 9 of track changed document)

Discussion:

Comment: There shouldn't be any reporting of effect estimates in the Discussion (first paragraph of Discussion)

Response: we have removed this (page 18 para 1 of track changed document)

Comment: The use of the term "sensitive period" (first paragraph and in other parts of the Discussion) is a misnomer in the context of the study's findings. As described by Kuh D et al (PMID: 14573579), a "sensitive" period is one in which an exposure period has a larger effect than exposure during other periods; in other words, the same exposure outside this "sensitive" period may still be significantly associated with increased risk, but is weaker than during the sensitive period. The findings of this study however, shows that significant associations were only apparent between 15 and 20 weeks, but not prior to 15 weeks. Would suggest the authors to rephrase accordingly to properly reflect the findings

Response: we agree with the authors and although we were referring informally to the period as 'sensitive' i.e. not in terms of its use in lifecourse epidemiology, we appreciate this could have been ambiguous. Accordingly we have now referred to it as a 'potential critical period', in line with the glossary provided by Kuh et al (2003): 'Thus, we define a critical period as a limited time window in which an exposure can have adverse or protective effects on development and subsequent disease outcome.

Outside this developmental window there is no excess disease risk associated with exposure', e.g. we found an association with the exposure in this time window but no association outside of it. It is important to emphasise the use of the word 'potential' as we have only test two time points in

pregnancy and thus not the whole period and thus there may be other periods in which the association with the exposure may be greater.

Comment: Recent meta-analyses (Russo LM et al, PMID: 25730218; Sanabria-Martínez G et al, PMID: 26036300) have described that physical activity in pregnancy provides a protective effect against the development of gestational hyperglycemia, and reduces gestational weight gain. Gestational hyperglycemia and weight gain in turn, are well-known risk factors for increased neonatal adiposity (Farrar D et al, PMID: 27624087; Poston L, PMID: 22406744). The lack of measurements of maternal glycemia and gestational weight gain in this study, to potentially explain the observed associations, presents a great limitation which should be discussed and addressed

Response: In line with the previous comment about gestational glycaemia/weight gain, these data were not available. We do agree with the reviewer that identifying the (mediating) effect of these variables on the association between exercise and adiposity is indeed a very interesting question, however, we were unable to look at this.

Reviewer 3

Thank you for your feedback on our manuscript. We found this particularly useful for clarifying points, especially regarding the sample size calculation.

Comment: Definition and measure of the exposure: exercise was not assessed using validated questionnaire or objective measurements, so assessment of the changes in exercise is really subjective. It is a major problem of this study not having quantitative measures of PA.

Response: we completely agree with the reviewer that the subjective nature of the exercise variables is a limitation and have discussed this in detail in the discussion section. Whilst acknowledging that, a recent systematic review found that self-reported physical activity measures were the most common assessment method in pregnant women. Whilst the questionnaire regarding physical exercise was not validated for any population, the definition of vigorous exercise (daily exercise leading to heavy breathing or being out of breath) has previously been used in other studies such as 'Bell RJ, Palma SM, Lumley JM. The effect of vigorous exercise during pregnancy on birth-weight. Aust N Z J Obstet Gynaecol 1995;35:46–51'.

Comment: Assessment of exercise only takes into account the time per week they engage in vigorous PA. Moreover the definition of vigorous activity is unclear: does it take into account only the part of PA the women is "breathing harder" or the whole time they engage in an activity including some vigorous activity?

Response: the exercise questions asked at 15 and 20 weeks asked about the number of times per week spent engaged in a) vigorous activity b) moderate activity and c) recreational activity, not just vigorous activity. The time spent doing each of the activities was not recorded, rather if a woman reported any activity that made her 'breathe harder or puff or pant' (for vigorous activity), regardless of for how long, this would be classed as one instance of vigorous activity.

Comment: Comparison of the effect of changes in exercise does not take into account the baseline levels. What is the impact of the women who perform no PA at the two assessments on the infant's adiposity? They cannot be classified as decreasing their PA levels?

Response: women who performed no exercise at both time points would be classed as 'unchanged'

Comment: How the authors consider the effects of PA changes after 20weeks and PA in late pregnancy on the results?

Response: we agree with the reviewer that it would have been interesting to look at the effect of exercise (changes) in later pregnancy, however, the measurement schedule of the SCOPE/BASELINE study only allowed for investigation into the effects at 15 weeks and 20 weeks' gestation.

Comment: What is the rationale for the impact of this very specific and short period between 15 and 20 weeks for an impact on infant's adiposity?

Response: The impact of these findings suggest that altered levels of exercise over relatively short periods in pregnancy is associated with altered BF%. Potential mechanisms could include effects on maternal glucose metabolism or functioning of the placenta as it is around this time that the placenta's development is being completed. We agree with the reviewer that identifying the mechanism through which the association is enacted needs to be identified.

Comment: There is no sample size calculation.

Response: As a secondary analysis, it was not possible to conduct a pre-emptive sample size calculation. However, we have since conducted a retrospective power calculation using Stata's powersim command and using the complete case sample of 1200, for the binary outcome of high or low adiposity (vs not), it was shown that power was >0.9 for an effect size ranging from OR=0.4-2.0 and thus we are confident we had enough power to detect relevant effects.

Reviewer 4

We are grateful to the reviewer for the suggested changes, particularly the addition of more discussion on the association of PA on adiposity in childhood. The detailed responses are listed below.

ABSTRACT:

Comment: please define BF% at the first use

Response: this has now been done (page 2 abstract of track changed document)

METHODS:

Comment: Cite as where the cut point for the BF% >90th as high and BF% < 10th as low coming from?

Response: this is in the manuscript at the top of page 8: 'Low and high adiposity was defined as below/above the gestational age- and sex-specific 10th/90th adiposity centiles respectively, according to the centiles produced by Hawkes et al (2011)26'

Comment: Why the authors decided to use dichotomous variable instead of reporting on the continuous variable for the BF%. I would like to see the continuous outcome variable being included in the paper.

Response: the continuous outcome has been analysed and is included in the manuscript. We have discussed it in the methods (page 7 para 3 of track changed document) and is included in descriptive table 2 and table 3, which shows the coefficients for the association of the outcomes with the exercise variables.

CONCLUSION:

Comment: This section is too long. The authors need to be concise in discussing their strengths and limitations (no more than 2/3 of the page).

Response: we acknowledge that the strengths/limitations section is detailed. However, we felt (as did two reviewers) that this section is important given the limitation of the subjective exercise measure. If the editor wishes us to condense this further we will happily oblige but feel the content is currently appropriate.

Comment: More literature should be cited and reported on the topic of the effects of exercise during pregnancy on infants outcomes (i.e. weight status, % body fat, birth weight).

Response: we have added the following 'For example, it has been shown that the associations between maternal pregnancy exercise levels and offspring adiposity present at birth extend into childhood, with children of women who exercised during pregnancy observed to have a reduced fat mass at age 5 years (37mm ± 1 vs. 44mm ± 4) compared children whose mothers were inactive⁴⁵.' (page 22 para 2).

VERSION 2 – REVIEW

REVIEWER	Allison L B Shapiro University of Colorado Anschutz
REVIEW RETURNED	02-Aug-2017

GENERAL COMMENTS	The authors have adequately addressed the reviewers' suggestions and concerns.
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REVIEWER	Izzuddin M Aris Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore Division of Chronic Disease Across the Lifecourse Department of Population Medicine, Harvard Medical School, Boston, Massachusetts, USA Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research, Singapore
REVIEW RETURNED	25-Aug-2017

GENERAL COMMENTS	My comments to the authors have been addressed, and the manuscript is much improved. I have no further comments
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REVIEWER	Kai Ling Kong State University of New York at Buffalo, United States
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	No
REVIEW RETURNED	03-Aug-2017

GENERAL COMMENTS	<p>1. Authors should change the word "effect" throughout the manuscript including title of tables.</p> <p>2. Authors responded to my comment to include the continuous adiposity outcome to the analysis, but they should take a step further by discussing it. This continuous variable does not support their finding. Based on the reported 95% CI, it doesn't seem like the association is significant.</p>
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VERSION 2 – AUTHOR RESPONSE

We thank the reviewer for the additional comments on the manuscript. We completely agree with the reviewer that the use of the word 'effect' is misleading and we have changed this throughout the manuscript, including the tables.

We have also commented in the discussion (page 15, first paragraph) about the effect of a decreasing exercise level and the continuously measured adiposity outcome (%BF). However, we don't agree that this does not support the finding of the binary outcome (>90th centile). Although the 95% confidence does indeed include the null, which we have included in the added text, the association is consistent in both the univariate and multivariable analysis, after adjusting for confounders. Obviously if the 95% CI completely straddled the null (for example, -1 to +1), suggesting that we cannot be sure whether the association could either be positive or negative, we would not make such a conclusion. However, as both 95% CIs (unadjusted and adjusted) are predominantly on the positive side of the null (e.g. -0.05 to 1.13 and -0.03 to 1.15), we are more confident in our suggestion that a positive association is likely.

VERSION 3 – REVIEW

REVIEWER	Kai Ling Kong University of Buffalo, New York, United States
REVIEW RETURNED	05-Sep-2017

GENERAL COMMENTS	The authors appropriately addressed all of my comments. I do not have any further comments.
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