PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Leptin status in adolescence is associated with academic performance in high school: A cross-sectional study in a Chilean birth cohort
AUTHORS	Correa Burrows, Paulina; Blanco, Estela; Reyes, Marcela; Castillo, Marcela; Peirano, Patricio; Algarin, Cecilia; Lozoff, Betsy; Gahagan, Sheila; Burrows, Raquel

VERSION 1 - REVIEW

REVIEWER	Soumyabrata Munshi, MBBS, MD. Rosalind Franklin University of Medicine and Science, United States of America.
REVIEW RETURNED	01-Feb-2016

GENERAL COMMENTS	In the study entitled "Leptin status in adolescence is associated with academic performance in high-school students", the authors have correlated the serum leptin levels with the academic performance for 16-year-old adolescents of middle to low socioeconomic status in a specified demographic region. Although a highly elaborative work, I have the following concerns regarding the study: 1. Leptin acts in the brain via the leptin receptor isomers (Ob-R) of which Ob-Rb is the predominant form in the hippocampus, and the latter structure is an important site involved in the physiology of memory. Of the various downstream signaling cascades (like MEK/ERK, SIRT1, JAK/STAT, PIP3 etc.) that mediate the effects of leptin in the brain, NMDAR signaling is a significant one which modulates LTP in the hippocampus responsible for dendritic remodeling and subsequently affecting memory and cognition. Additionally, integration of glutamatergic input from the ventral hippocampus to the prefrontal cortex plays a pivotal role in the processes of cognition. Various neuropsychiatric disorders are known to affect the NMDAR signaling in the brain, especially in the hippocampus and prefrontal cortex, thereby altering the integration of synaptic signaling in the hippocampus. Thus leptin effect on memory and cognition might be confounded by co-existence of neuropsychiatric disorders including depression, schizophrenia and substance abuse disorders; and these are likely to affect the outcome of the academic performance studied. However, the prevalence of these neuropsychiatric conditions have not been included in the study and this might have severely confounded the results seen in the present study. The authors mentioned that weight status, dietary and physical activity habits, sex, maternal education as proxy of SES and secondary education type were used as covariates. Also only one cardiovascular risk factor has been mentioned (fasting blood glucose) but its importance has not been clearly stated in the article. Taken together, the conclusion of the

	study remains questionable. 2. Assessment of academic performance using only high-school grades and GPA remains rather incomplete and weak. These two parameters would not reflect the neuropsychological outcomes with regards to cognition and memory as a whole. Specific neuropsychological outcome data with regards to the assessment of cognition and memory functions (like MMSE, CANTAB etc.) should have provided better insight into the problem. This omission failed to evaluate the functional outcome in the subjects. 3. The statistical analysis used in the study is highly recommended to be reviewed by an expert statistician. 4. The objective of the study has not been clearly defined. Only the hypothesis has been mentioned. 5. The abstract should correct the age of the subject by mentioning the range (and not only as 16-year-old) since the average age mentioned in the results is 16.8 (and not 16). It should also mention the objective clearly. 6. The comparison made with the conversion table as mentioned in the text (heading "Academic performance") could not be recognized from the reference mentioned. It could have been described in details in the text. Same applies for GPA conversion. 7. The PA questionnaire using accelometry-based activity as administered was previously used in under 10 years subjects as mentioned in the reference (Godard et al., 2012). It remains questionable as to if it is applicable in the present study where 16 years old are the subjects of study. 8. Authors should have mentioned the reference(s) used for the socioeconomic stratification used in the study (three categories used). 9. Serum separation/storage procedure should be detailed in terms of centrifugation conditions (speed, temperature, instrument used) and storage time. 10. BMI should be defined clearly as weight (kg)/{height(m)}2. The reference used for nutritional status definitions should be mentioned. 11. Ref. 31 title is not matching properly with the original article. This should be checked. The cut-off values should be mentioned. 12. Ref. 22 is not described in the ref. list. Hence the enrolment details of the study remain ambiguous. 13. The cut-offs used to divide the participants into three groups of physical activity patterns should be clearly stated. 14. The population studied was 16 year old as mentioned in the study samples and throughout the article, while the result shows the mean as 16.8. Hence the range of the population studied should be mentioned throughout, and not the fixed value as 16. 15. The table 1 should specify whether it is the SD or the percentage values across individual row (parameters); otherwise it is confusing

	whether the value used in the column (SD or Percentage) is an SD or a Percentage. 16. The table 2 should specify the name of the parameter (as Grade or Final GPA) in the column titled "Mean difference". 17. The authors' claim that the results support the notion of "leptin as a cognitive enhancer" is debatable. The study does not show any cause-effect relationship; it has only attempted to show association. Hence whether leptin enhances cognition remains questionable from this study. 18. References 22, 23, 30 are not detailed in the ref. list. 19. Long-term potentiation has been mistakenly typed as LPT in place of LTP several times. 20. Grammatical errors, errors in punctuations and errors in sentence constructions should be seriously taken care of.

REVIEWER	Alexander J. Rodriguez Monash University, Australia
REVIEW RETURNED	17-May-2016

GENERAL COMMENTS	This study analysed leptin concentrations in adolescent Chileans from low-to-middle SES backgrounds and related this to academic performance. Whilst there was a clear trend for those with higher leptin levels to have poor academic performance, the use of the term "leptin resistance" (LR) needs to be questioned. Cutpoints from the HELENA study were used to define LR. I believe this to be inappropriate because (1) the HELENA study is not representative of the present study and (2) there was no hard end-point in the HELENA study, it produced normative values for their cohort. As there is no HOMA-IR type test for leptin it is inappropriate to arbitrarily define leptin resistance. I would suggest use of the term hyperleptinemia. Perhaps a simple linear regression of leptin and scores, adjusted for sex and fat tissue would help in stratifying your cohort into above and below a median/mean. Other comments: - The sample was based on an existing cohort, please provide some details into the aims and exclusions of this cohort - Many citations refer to review studies, please cite original primary literature to ensure that claims made in the paper are properly sourced - Page 8 line 28 - to which questionnaires are being referred to. Are they appropriate for your cohort and aims? Page 10 Lines 35-42: why wasn't height included in regression models? Leptin has powerful anabolic capacity during puberty and this may explain some of the findings. Further, are these any body composition and insulin/glucose data available as these important aspects can affect leptin levels and may better explain the results. Results need to be adjusted for an objective measure of fat. Table 1: describe within-group differences (eg. in leptin resistant group, was the concentration of leptin similar across groups of BMI?) - Provide further details into the food questionnaire - how does the questionnaire assess eating habits? Page 22 line 5 "the"

	- Page 23 line 41 - please include the impact of the survey results on educational performance. The authors did not relate these results to academic achievement Page 23 Line 11 - results were independent of leptin status - does this not invalidate your previous claims?

REVIEWER	Alfgeir L. Kristjansson West Virginia University, School of Public Health, WV, USA
REVIEW RETURNED	30-May-2016

GENERAL COMMENTS	This is an interesting study on an important and emerging topic. Authors provide evidence for an association between Leptin profiles and academic achievement in a sample of 16 year old adolescents from Chile. My comments follow the order of sections in the paper. Abstract Based in the Objective section, leptin resistance is bad for academic performance. However, the way the story line is formulated it can easily be understood that LR is positively related to academic achievement (see lines 41-44. This is due to the coding of key variables as well as reporting odds ratios that are protective against a positive outcome. I suggest the authors rewrite this section and the results more generally so that it is clear LR is bad for academic achievement. This should be achieved by coding the binary variables always with the exposure category as = 1. In the conclusion section of the abstract the authors switch to the word choice of "high levels of leptin" but before use the terms "leptin resistant" and "leptin sensitive". Please just make sure that non-biology trained researchers, for example, education scientists can understood the study and its conclusions. This is far from clear from reading the abstract and after reading it I was still left wandering whether leptin was in fact good or bad for achievement. Strengths and limitations page First bullet point. There is nothing about "energy balance regulation" in this study. I suggest to the authors to stick to their main questions. Introduction P.6, first sentence, LR is bad. Please do not use the word "learning" which has a very specific and process oriented meaning in educational sciences and cannot be assessed in a correlational study. Instead, I suggest just using "gpa" or "grades". P6, lines 10-12. Sentence that begins with "We aimed.." is incomplete. Please do not assume that the reader will understand what is meant - just complete the sentences. Last line of Introduction. not sure that "comprise the ability" means. Better to just state that "LR negatively impacts" or "is negatively related with.." or something similar. Methods Study sample. 1) Please state the sampling frame and response rates. 2) Please state which of the data waves you were using in the

	present analysis. If only using the final wave (16 year olds) please state that clearly. After reading the paper I am still not sure which waves of data were used in the analysis. Measure subsection All this section needs updated. Please insert an adequate description for all measures so that others can replicate the study simply by reading the paper. For Leptin status at 16. The large difference in Leptin status between males and females is unexplained and unchallenged throughout the study. This cries for explanation and elaboration in the Methods, Results, and Discussion sections. Academic Performance. The transformation of the grades into scores ranging from 210 to 825 is meaningless unless more explained. BMI. 1) First line. Please explain what you mean by standardized methods. 2) the breakdown into under-, normal, over-, obese is odd. With BMI means differing between populations the divide into these subgroups by SDs is not the appropriate method for BMI distribution. Also, there are specific cut-off values used for BMI grouping with underage minors. 3) BMI status does not equal "Nutritional status" as stated in this paragraph. SES. It is a large problem that neither "family structure" or "father's education" are used as covariates in the study. In studying correlates to academic achievement these are pretty basic. It the authors have access to such data please rerun the data by including those variables. Otherwise please add this issue to the limitations section. Analysis subsection. In the Results and Discussion sections there is mentioning of odds ratios but these are not mentioned in the analysis subsection. Please make sure that all parts of the Methods are explained in adequate detail so that the study can be replicated by any potential reader. Results Page 14. Sentence: "The grades mean difference varied from 49 points to 27 points". Throughout you should thrive to describe impact in an ascending manner. The same goes for variable relationships, GPA differences, etc.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Leptin effect on memory and cognition might be confounded by co-existence of neuropsychiatric disorders including depression, schizophrenia and substance abuse disorders; and these are likely to affect the outcome of the academic performance studied. However, the prevalence of these neuropsychiatric conditions have not been included in the study and this might have severely confounded the results seen in the present study. The authors mentioned that weight status, dietary and physical activity habits, sex, maternal education as proxy of SES and secondary education type were used as covariates. Also only one cardiovascular risk factor has been mentioned (fasting blood glucose) but its importance has not been clearly stated in the article. Taken together, the conclusion of the study remains questionable.

Due to data constraint, we did not consider the mediating effect of other important influences, like the

prevalence of neuropsychiatric conditions and learning disorders which may impact student's academic functioning. We reckoned this as a major limitation.

Assessment of academic performance using only high-school grades and GPA remains rather incomplete and weak. These two parameters would not reflect the neuropsychological outcomes with regards to cognition and memory as a whole. Specific neuropsychological outcome data with regards to the assessment of cognition and memory functions (like MMSE, CANTAB etc.) should have provided better insight into the problem. This omission failed to evaluate the functional outcome in the subjects.
This study was conceived as a translational study. Thus, assessments of cognition and memory functions in relation with leptin status in adolescence is beyond the scope of this paper. We reinforced this idea in the Strength and Limitations section, and, also, we included a sentence stating that further studies should approach this in the future using neuropsychological outcomes.

The statistical analysis used in the study is highly recommended to be reviewed by an expert statistician.
The statistical analysis was reviewed and endorsed by statisticians at the Institute of Nutrition and Food Technology, University of Chile.

The objective of the study has not been clearly defined. Only the hypothesis has been mentioned.
An objective was included in the last paragraph of the Introduction section.

The abstract should correct the age of the subject by mentioning the range (and not only as 16-year-old) since the average age mentioned in the results is 16.8 (and not 16). It should also mention the objective clearly.
Corrections were made accordingly.

The comparison made with the conversion table as mentioned in the text (heading "Academic performance") could not be recognized from the reference mentioned. It could have been described in details in the text. Same applies for GPA conversion.
The reference was corrected to match the text. Also, a link to access to the tables was provided.

The PA questionnaire using accelerometry-based activity as administered was previously used in under 10 years subjects as mentioned in the reference (Godard et al., 2012). It remains questionable as to if it is applicable in the present study where 16 years old are the subjects of study.
Both questionnaire validation (Godard 2008) and cutoffs estimations for the Chilean school-age population (Burrows et al. 2008) were performed in elementary and high school students.

Authors should have mentioned the reference(s) used for the socioeconomic stratification used in the study (three categories used)
In our analysis, five standard hierarchic levels were defined according to the 2011 International Standard Classification of Education (ISCED). Then, we merged these categories into two. The reference is provided.

Serum separation/storage procedure should be detailed in terms of centrifugation conditions (speed, temperature, instrument used) and storage time
The manuscript was modified to include this information.

BMI should be defined clearly as weight (kg)/{height(m)}2. The reference used for nutritional status definitions should be mentioned.
The manuscript was modified accordingly.

Ref. 31 title is not matching properly with the original article. This should be checked. The cut-off values should be mentioned.
The reference description was corrected and the cut-off values were reported.

Ref. 22 is not described in the ref. list. Hence the enrolment details of the study remain ambiguous.
Some references were omitted to allow blind peer-review. In this new version they were provided in case the editors or the reviewers want to check them.
The cut-offs used to divide the participants into three groups of physical activity patterns should be clearly stated.
Cut-off values were included in the manuscript.

The population studied was 16 year old as mentioned in the study samples and throughout the article, while the result shows the mean as 16.8. Hence the range of the population studied should be mentioned throughout, and not the fixed value as 16.
In this new version of the paper, participants' age was is reported as a range (16 to 17y)

The table 1 should specify whether it is the SD or the percentage values across individual row (parameters); otherwise it is confusing whether the value used in the column (SD or Percentage) is an SD or a Percentage.
Table 1 was modified accordingly

The table 2 should specify the name of the parameter (as Grade or Final GPA) in the column titled "Mean difference".
Table 2 was modified accordingly

The authors' claim that the results support the notion of "leptin as a cognitive enhancer" is debatable. The study does not show any cause-effect relationship; it has only attempted to show association. Hence whether leptin enhances cognition remains questionable from this study.
That's right. To avoid any confusion we decided to remove anything that might suggest a cause-effect relation. The study design does not allow reaching such a conclusion.

References 22, 23, 30 are not detailed in the ref. list.
All these references were included in the Reference section. In the former version of the manuscript, they were omitted for peer-review purpose. Now they have been added.

Long-term potentiation has been mistakenly typed as LPT in place of LTP several times.
This was corrected. Now Long-term potentiation is LPT.

Grammatical errors, errors in punctuations and errors in sentence constructions should be seriously taken care of.
The manuscript was revised by three native English speakers.

Reviewer 2
Whilst there was a clear trend for those with higher leptin levels to have poor academic performance, the use of the term "leptin resistance" (LR) needs to be questioned. Cutpoints from the HELENA study were used to define LR. I believe this to be inappropriate because (1) the HELENA study is not representative of the present study and (2) there was no hard end-point in the HELENA study, it produced normative values for their cohort. As there is no HOMA-IR type test for leptin it is inappropriate to arbitrarily define leptin resistance. I would suggest use of the term hyperleptinemia.

In this new version of the manuscript we no longer use the term leptin resistance unless fully necessary. We now use abnormally high levels of leptin or hyperleptinemia. However, we decided to

keep using the cutoff values from the HELENA Study because: (1) these are the only cutoffs published for the adolescent population; (2) These cutoffs were estimated for healthy 16 years old adolescents. (3) In spite of being a Latin-American nation, Chile is in the last stages of the epidemiological transition, like many European countries,

Perhaps a simple linear regression of leptin and scores, adjusted for sex and fat tissue would help in stratifying your cohort into above and below a median/mean.
Because we are assessing the influence of a biological variable (leptin status) on a multifactorial outcome (school performance), it is important to consider the effect of other sociodemographic determinants. Some of them were available in our study (e.g. parental educational attainment), so, we'd like to keep these variables as covariates. Second, we include the influence of lifestyles (e.g. diet and physical activity habits) because in the same sample we found an association with academic results. Those results are already published or were presented in scientific meetings.

The sample was based on an existing cohort. Please provide some details into the aims and exclusions of this cohort.
In the new version of the manuscript, a description of enrolment and retention rates over the course of the study is provided.

Many citations refer to review studies, please cite original primary literature to ensure that claims made in the paper are properly source.
Because the neurocognitive effects of leptin have been less explored than its effects on energy regulation, we aimed to provide as much evidence as possible by using review articles. In the Introduction section we kept most of the references used in the former version of the manuscript. However, we replaced many reviews with original articles in the Discussion section.

Page 8 line 28 - To which questionnaires are being referred to. Are they appropriate for your cohort and aims?
We provided more details about the questionnaires being used for diet and physical activity assessment.

Page 10 Lines 35-42: Why wasn't height included in regression models? Leptin has powerful anabolic capacity during puberty and this may explain some of the findings. Further, are these any body composition and insulin/glucose data available as these important aspects can affect leptin levels and may better explain the results? Results need to be adjusted for an objective measure of fat.
All participants in our sample had completed their pubertal development, so height should not be affected by leptin levels at 16y. Besides, despite these kids are from middle to low SES, they do not suffer from undernutrition in infancy or toddlerhood. Also, height has not been related to our main outcome in the analysis. As for body composition and insulin/glucose measured, weight status and insulin sensitivity were entered into the models. Both haven related to cognition and academic performance.

Table 1: Describe within-group differences (eg. in the leptin resistant group, was the concentration of leptin similar across groups of BMI?)
An additional table (Table 2 in the revised version) was provided to report serum leptin levels across groups of BMI.

Provide further details into the food questionnaire. How does the questionnaire assess eating habits?

Page 23 line 41 - Please include the impact of the survey results on educational performance. The authors did not relate these results to academic achievement.
Unlike the Health Behaviour in School-aged Children, that covers 45 countries in Europe and North

America, the Global School-Based Health Survey does not include information on objective or reported measures of academic results.

Page 23 Line 11 - Results were independent of leptin status - does this not invalidate your previous claims
There is growing evidence on the impact of overconsumption of saturated fats and simple carbs on cognitive function and academic attainment. Models in both, animals and humans, report direct and effects of these macronutrients on cognitive and academic outcomes. Thus, the effect of diet on school grades may be independent of leptin status.

Reviewer 3

Comments on the Abstract: Based in the Objective section, leptin resistance is bad for academic performance. However, the way the story line is formulated it can easily be understood that LR is positively related to academic achievement (see lines 41-44. This is due to the coding of key variables as well as reporting odds ratios that are protective against a positive outcome. I suggest the authors rewrite this section and the results more generally so that it is clear LR is bad for academic achievement. This should be achieved by coding the binary variables always with the exposure category as = 1.
We rewrite both the abstract and paragraph 3 in the Introduction section to make sure that is clear for readers that leptin in the physiological range serves as a cognitive enhancer, but elevated plasma leptin levels or hyperleptinemia may act as a pathophysiological marker for impaired cognitive function.

In the conclusion section of the abstract the authors switch to the word choice of "high levels of leptin" but before use the terms "leptin resistant" and "leptin sensitive". Please just make sure that non-biology trained researchers, for example, education scientists can understood the study and its conclusions. This is far from clear from reading the abstract and after reading it I was still left wondering whether leptin was in fact good or bad for achievement.
In this new version of the manuscript we no longer use the term leptin resistance unless fully necessary. We now use abnormally high levels of leptin or hyperleptinemia. We made this decision based on the suggestion of Reviewer n°2 and due to the fact that use a cutoff based on statistical criteria, which are the only cutoffs published for the adolescent population.

Strengths and limitations page: First bullet point. There is nothing about "energy balance regulation" in this study. I suggest to the authors to stick to their main questions.
We modified the bullet accordingly.

Please do not use the word "learning" which has a very specific and process oriented meaning in educational sciences and cannot be assessed in a correlational study. Instead, I suggest just using "GPA" or "grades".
In this new version, we no longer use the word ‘learning’ unless we referred to learning process from a biological point of view.

Introduction: P6, lines 10-12. Sentence that begins with "We aimed..." is incomplete. Please do not assume that the reader will understand what is meant - just complete the sentences.
We modified the manuscript accordingly. As suggested by this reviewer, we were assisted by a social scientist to make sure that he was able to understand both the study and the conclusions.

Last line of Introduction. Not sure that "comprise the ability" means. Better to just state that "LR

negatively impacts" or "is negatively related with…" or something similar.
We modified the manuscript accordingly.
Methods: Study sample. 1) Please state the sampling frame and response rates. 2) Please state which of the data waves you were using in the present analysis. If only using the final wave (16 year olds) please state that clearly. After reading the paper I am still not sure which waves of data were used in the current analysis.
In this revised version of the manuscript, we provide much more details on how the sample was obtained. Also, in the Measurements subsection, we use headings to differentiate which wave the data came from.

Methods >> Measure subsection. All this section needs updated. Please insert an adequate description for all measures so that others can replicate the study simply by reading the paper.
This section was fully rearranged to facilitate reading of the paper.

Methods >> Measurements >> For Leptin status at 16. The large difference in Leptin status between males and females is unexplained and unchallenged throughout the study. This cries for explanation and elaboration in the Methods, Results, and Discussion sections.
Because leptin is produced in the fat tissue, we may assume that females tend to have higher odds for hyperleptinemia. However, leptin levels are also dependent on other determinants, such as insulin sensitivity and overconsumption of sucrose and fructose. In our sample, males and females had similar prevalence of excess weight and insulin resistance, but the proportion of adolescents having a fair diet (a diet high in simple sugars, mostly sucrose and fructose from candies and sugar sweetened soda) significantly higher) was significantly higher among males. We provide comments on this fact in the revised version of the manuscript.

Methods >> Measurements >> Academic Performance. The transformation of the grades into scores ranging from 210 to 825 is meaningless unless more explained.
We transform grades in scale 1-7 into scores because schools may have differed in grading policies, so the Ministry of Education use these method to account for these differences. We explained this in the Measurements section.

Methods >> Measurements >> BMI. 1) First line. Please explain what you mean by standardized methods. 2) The breakdown into under-, normal, over-, obese is odd. With BMI means differing between populations the divide into these subgroups by SDs is not the appropriate method for BMI distribution. Also, there are specific cut-off values used for BMI grouping with underage minors. 3) BMI status does not equal "Nutritional status" as stated in this paragraph
We provided more details on the anthropometric assessment and, thus, we removed the notion of standardized methods. As for the cutoffs used to define weight status in the sample, we used those proposed in the 2007 WHO references for the population aged 5-17y. To avoid any confusion, we also provide the reference (De Onis et al. 2007). Last, we replaced ‘nutritional status’ with ‘weight status’.

Methods >> Measurements >> SES. It is a large problem that neither "family structure" or "father's education" are used as covariates in the study. In studying correlates to academic achievement these are pretty basic. It the authors have access to such data please rerun the data by including those variables. Otherwise please add this issue to the limitations section.
We added information on father’s educational attainment. However, we had no information on family structure for the full subset, thus, we recognized this as a limitation.

Methods >> Analysis subsection >> In the Results and Discussion sections there is mentioning of odds ratios but these are not mentioned in the analysis subsection. Please make sure that all parts of

the Methods are explained in adequate detail so that the study can be replicated by any potential reader.
We took care that every step of the analysis performed is well described in the Analysis subsection

Results >> Page 14 >> Sentence: "The grades mean difference varied from 49 points to 27 points". Throughout you should thrive to describe impact in an ascending manner. The same goes for variable relationships, GPA differences, etc.
We modified the manuscript accordingly.

VERSION 2 – REVIEW

REVIEWER	Soumyabrata Munshi Rosalind Franklin University of Medicine and Science, USA.
REVIEW RETURNED	23-Jul-2016

GENERAL COMMENTS	All my concerns were addressed in the rebuttal. Thank you.

REVIEWER	Alexander J. Rodriguez Monash University, Australia
REVIEW RETURNED	17-Jul-2016

GENERAL COMMENTS	The study is listed as a cohort study - it is a cross-sectional analysis. I would still like to see the relationship between serum leptin and scores in a linear regression adjusting for fat tissue. Height is still important, at 16y growth would not be fully completed. Pg 23, Line 11 - further to previous comment if diet effect on grades is independent of leptin - can the authors comment on what is mediating the relationship?

REVIEWER	Alfgeir L. Kristjansson West Virginia University, WV, USA
REVIEW RETURNED	20-Jul-2016

GENERAL COMMENTS	The authors have addressed reviewer comments to my satisfaction

VERSION 2 – AUTHOR RESPONSE

Reviewer 2
The study is listed as a cohort study it is a crosssectional analysis.
The reviewer is right, this is a cross-sectional study conducted in a birth cohort. To avoid any confusion, we decided to put this point clear both in the title and the abstract.

I would still like to see the relationship between serum leptin and scores in a linear regression adjusting for fat tissue.
We run linear regression, adjusting for fat mass, and estimated coefficients for the relation of serum leptin levels and school grades are provided in Table 3.

Height is still important, at 16y growth would not be fully completed.
Participants in our sample did not differed in height at 16-17y (z-score and percentile) after controlling for leptin status, sex and weight status. We provide height data in Table 1 (Descriptive Stats) expressed as z-score and percentile and additional comparisons are provided in the table below:

Table S1 Height statistics of participants in the sample (n=568)

Control variable	Height (WHO z-score) Mean (SD)	P value*
Leptin status at 16y		
Normal leptin levels	-0.47 (0.8)	N.S.
Hyperleptinemia	-0.35 (0.8)	
Sex		
Male	-0.42 (0.8)	N.S.
Female	-0.48 (0.9)	
Weight Status		
Normal weight	-0.45 (0.8)	N.S.♠
Overweight	-0.48 (0.9)	
Obesity	-0.41 (0.8)	
Height (CDC z-score) Mean (SD)		
Leptin status at 16y	-0.50 (0.8)	N.S.
Normal leptin levels	-0.37 (0.8)	
Hyperleptinemia		
Sex		
Male	-0.47 (0.8)	N.S.
Female	-0.50 (0.9)	
Weight Status		
Normal weight	-0.49 (0.8)	N.S.♠
Overweight	-0.51 (0.9)	
Obesity	-0.44 (0.9)	
Height (CDC percentile) Mean (SD)		
Leptin status at 16y		
Normal leptin levels	34.5 (24.8)	N.S.
Hyperleptinemia	37.8 (24.2)	
Sex		
Male	35.2 (23.6)	N.S.
Female	34.8 (25.7)	
Weight Status		
Normal weight	34.4 (24.0)	N.S.♠
Overweight	35.9 (26.7)	
Obesity	36.2 (23.9)	

Height was expressed as z-score (WHO and CDC) and percentile. *Two-tailed Student's t test for independent samples, except as indicated. ♠ One-way ANOVA with Bonferroni adjustment. Normal weight: BMI z ≤ 1 SD. Overweight: BMI z > 1SD and ≤ 2 SD. Obesity: BMI z > 2 SD. Hyperleptinemia defined according to the cutoffs published by Köster-Webber et al.

In addition, we ran linear regressions to test the association of height with our main outcome. Height was not significantly associated with school grades and GPA (see Table S2 below). Due to a lack of association in our sample and because height has not been related to academic performance in previous studies (only height as part of BMI), we decided not to include height in the models. Yet

Table 3 Regression coefficients of the association between height at 16-17y and academic performance (transformed school grades) in high school (n=568)
Intercept Coef. Robust SE R2
9th grade
Height (WHO z-score) 444.7*** 8.41 5.32 0.04
Height (CDC percentile) 431.2*** 0.28 0.30 0.04
10th grade
Height (WHO z-score) 445.3*** -0.25 5.41 0.02
Height (CDC percentile) 445.4*** -0.003 0.18 0.02
11th grade
Height (WHO z-score) 426.3*** -3.37 5.32 0.03
Height (CDC percentile) 431.4*** -0.10 0.18 0.03
12th grade
Height (WHO z-score) 437.8*** -0.64 5.46 0.03
Height (CDC percentile) 437.7*** 0.008 0.18 0.03
HS GPA
Height (WHO z-score) 438.9*** 1.23 4.66 0.03
Height (CDC percentile) 436.6*** 0.05 0.16 0.03
HS GPA: High school grade-point average. Standard errors (SE) are robust to heteroscedasticity. *P<0.05. **P<0.01. ***P<0.001. Models were adjusted for sex and parental education.

Pg 23, Line 11 further to previous comment if diet effect on grades is independent of leptin can the authors comment on what is mediating the relationship?
We provided further comments on this point. In the new version of the manuscript they can be founded in page 25, lines 10 to 12.

VERSION 3 – REVIEW

REVIEWER	Alexander J. Rodriguez Monash University, Australia
REVIEW RETURNED	31-Aug-2016

GENERAL COMMENTS	The manuscript is most improved and I am pleased to see the results in Table 3. No further comments.