PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Associations between lipid profiles of adolescents and their mothers based on a nationwide health and nutrition survey in South Korea
AUTHORS	Park, Eun-Cheol; Nam, Ji Hyung; Shin, Jaeyong; Jang, Sung-In; Kim, Ji Hyun; Han, Kyu-Tae; Lee, Jun Kyu; Lim, Yun Jeong

VERSION 1 – REVIEW

REVIEWER	Steven R. Jones Johns Hopkins University, United States.
REVIEW RETURNED	28-Jun-2018

GENERAL COMMENTS	This is a very well conceived study asking an important question of to what extent maternal genetics inlulence (correlate with) lipids in offspring. There is a significant shortcoming in the analysis. The authors would best consider constructing a more complex continuous multivariate approach to determining the portion of the variance attributable to the maternal lipids in the respective lipid levels of the offspring. Specifically, the dependent variable, each lipid variable of interest should be evaluated adjusted for both maternal and offspring confounding variables such as age, weight, glucose, smoking, etc. From this correlation, the proportion of variance attributable to the correlation between maternal and offspring can be determined. It will be very important to consider several subset analyses, probably most important is hypertriglyceridemic subjects (TG>150 mg/dL) where the abnormality may most likely be attributable to obesity, diet, inactivity, etc but where genetic influences are also significant. Similarly, in subjects with LDL-C in the range of >150 mg/dL or about the 80-90th percentile, there will be and increasing prealence of monogenic Familial Hypercholesterolemia or phenotypically equivalent polygenic hypercholesterolemia transmissible from mother to offspring. Additionally, similar analyses shoulf be constructed for the subset of low HDL-C, in the range of <35-40 mg/dL or the lower 10-20th percentile where genetics may have a greater role.

REVIEWER	Zhan KI,Sweden
REVIEW RETURNED	10-Jul-2018

GENERAL COMMENTS	The manuscript examined the relationship between lipid fractions in adolescents and the mothers. The topic is interesting and analyses were performed well. I only have minor comments. 1. TG is known to be skewed distributed. It is usually log-transformed before doing analyses. I would recommend the authors could follow this practice. 2. Could the plots and associations be reported by sex of kids? 3. Typoes and grammatical errors need to be corrected.

REVIEWER	Manisha Nair University of Oxford, UK
REVIEW RETURNED	19-Oct-2018

GENERAL COMMENTS	I was invited to conduct a statistical review of the paper. Below are my comments – 1. This is survey data – how did the authors control for design effect and clustering? This should be explained in the statistical analysis section. 2. Did the authors check whether the continuous variables were normally distributed? If not, the authors would need to transform the variables to get a normal distribution – example a log normal distribution. 3. I am worried about the results being a chance finding since a large number of models were tested – '16 possible combinations between four adolescents' and their mothers' lipid profiles', and various stratified analyses. The authors might need to adjust the models further to control for bias due to multiple testing, or justify that this bias is unlikely. 4. It looks like the authors used ordinary least square regression – did the authors look at the residual plots? R-squared indicates how well the model explains variability of the response data around its mean. It is not an accurate representation of goodness of fit for the models. Perfectly good models can have low R-squared and vice versa. In addition, why did the authors choose to look at the relationship between mothers and adolescents' lipid profile and not fathers'?

REVIEWER	Francesco Sera London School of Hygiene and Tropical Medicine
REVIEW RETURNED	19-Oct-2018

GENERAL COMMENTS	This is interesting paper evaluating associations between lipids profiles of adolescent and their mothers in a nationwide survey. I reviewed the statistical methods used in this paper. Overall the methods used to evaluate univariate and adjusted coefficients to measure association are coherent with the cross-sectional study design, but I have some concern on specific aspects of the analysis; these are the relation with the survey design, the treatment of missing data (especially on covariates), the problem of multiple testing and related to this how association for categorical variables and interactions (sub-group analysis) were tested. In particular 1. In the title and in the text the author refer to a nationwide survey, but in the analysis they didn't take into account of the

	sampling design (e.g. clustering or weights). I think the authors should give more information on the sampling design and the sampling design should be taken into account in the analysis using survey specific statistical methods. 2. The author perform a complete-case analysis on subject without missing data on covariate and outcome. There is evidence that this method could produce biased estimates. The authors could perform a sensitive analysis using multiple imputation techniques (considering the survey design) on the sample of 4148 subjects with lipid levels, or alternatively building a system of non-response weights (considering the full population of 5081 subjects) to combine with the survey weights. 3. In the multivariate analysis (Table 3) the authors report multiple tests (I counted 34 tests on the coefficients for the exposure and for categorical covariates for each of the 4 models). The multiple testing rise the problem of a high overall type-I error, and consequently on the interpretation of the findings. To attenuate this problem a global test for a covariate in the multivariate model cold be performed using Likelihood ratio (LR) test or Wald tests based procedures (using survey methods), e.g. to test the association between walking hours and TC the model with and without walking hours are compared and LR test calculated, or Wald test with null hypothesis that ALL the coefficients are zeros can be performed. 4. In table 4 the authors report the subgroup analysis, and they speculate that some of the coefficients were different according subgroups. To sustain this interpretation a formal test of interactions between mother characteristic and mother lipids level should be undertaken. On a more substantive terms it would be interesting to evaluate the association between mother bmi and dyslipidaemia with the other covariates exanimated. This set of association would help to understand the results for subgroups. Note that there is consensus on the statistical community to name multivariable models regression models with multiple covariates, and multivariate models to name regression models with multiple outcome.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

This is a very well conceived study asking an important question of to what extent maternal genetics influence (correlate with) lipids in offspring.

1. There is a significant shortcoming in the analysis. The authors would best consider constructing a more complex continuous multivariate approach to determining the portion of the variance attributable to the maternal lipids in the respective lipid levels of the offspring. Specifically, the dependent variable, each lipid variable of interest should be evaluated adjusted for both maternal and offspring confounding variables such as age, weight, glucose, smoking, etc. From this correlation, the proportion of variance attributable to the correlation between maternal and offspring can be determined.

Response: We appreciate your comments. We identified partial correlation coefficients, adjusted by mothers and adolescents factors, using partial correlations analysis, and confirmed partial variances of each adolescents and mothers lipid. We revised ‘abstract’, ‘statistical methods’, and ‘Results’ section based on the statistical results as follows, (All p values were still less than 0.001, and there was no

significant change in correlation coefficient and variance after using partial correlation analysis.)

[Page 2 (abstract), Line 38, 45-46]

We identified partial correlation coefficients (*r*) between the lipids.

Positive correlations between lipid levels of adolescents and mothers were observed for TC, TG, HDL-C, and LDL-C (*r,* 95% confidence interval = 0.271, 0.236–0.304; 0.204, 0.169–0.239; 0.289, 0.255–0.322; and 0.286, 0.252–0.319).

[Page 7, Line 174]

The correlation of lipid levels between adolescents and their mothers was analyzed using partial correlations (*r*) with 95% confidence interval (CI).

[Page 9, Line 213-220]
Adolescent TC level demonstrated a fair positive correlation with mother's TC level (*r,* 0.271; 95% confidence interval (CI), 0.236–0.304) (Supplementary Figure S1). TG, HDL-C, and LDL-C levels also had fair positive correlations between adolescents and their mothers, yielding *r* (95% CI) = 0.204 (0.169–0.239), 0.289 (0.255–0.322), and 0.286 (0.252–0.319), respectively. For reference, the correlations among the four adolescent lipid profiles demonstrated an almost perfect correlation between the TC and LDL-C levels (*r,* 0.915; 95% CI, 0.909–0.921; *P*<.001), and showed a significant negative correlation between HDL-C and TG (*r,* -0.329; 95% CI, -0.361–-0.296; *P*<.001).

2. It will be very important to consider several subset analyses, probably most important is hypertriglyceridemic subjects (TG>150 mg/dL) where the abnormality may most likely be attributable to obesity, diet, inactivity, etc but where genetic influences are also significant. Similarly, in subjects with LDL-C in the range of >150 mg/dL or about the 80-90th percentile, there will be and increasing prevalence of monogenic Familial Hypercholesterolemia or phenotypically equivalent polygenic hypercholesterolemia transmissible from mother to offspring. Additionally, similar analyses should be constructed for the subset of low HDL-C, in the range of <35-40 mg/dL or the lower 10-20th percentile where genetics may have a greater role.

Response: Just because the parameter estimates of multiple linear regression indicates a positive correlation between mothers' and offspring's lipids, this cannot represent the degree of correlation. Therefore, evaluating linear association among those with dyslipidemia has no special significance. Instead, we performed multivariate logistic regression based on the dyslipidemia (TG, LDL-C, HDL-C) or its absence (Supplementary Table S2), and added the related sentences at the end of the 'Results' section as follows,

[Page 11, Line 250-252]

When the lipid profiles were considered as binary outcomes, multivariate logistic regressions showed that adolescents' dyslipidemia was significant associated with mothers' dyslipidemia (Supplementary Table S2).

Supplementary Table S2 Adjusted odds ratios for risks of adolescents' dyslipidemia based on mothers' lipids

		Adolescents' lipids		OR	95% CI	*P* value
Mothers' lipids	TG (mg/dl)	≤150	>150			
	≤150	2266 (84.9)	157 (73.0)	ref		
	>150	403 (15.1)	58 (27.0)	2.15	1.52, 3.03	<.001
	LDL-C (mg/dl)	≤150	>150			
	≤150	2581 (90.8)	31 (72.1)	ref		
	>150	260 (9.2)	12 (27.9)	3.42	1.68, 7.00	<.001
	HDL-C (mg/dl)	<40	≥40			
	<40	84 (22.0)	215 (8.6)	ref		
	≥40	298 (78.0)	2287 (91.4)	0.33	0.24, 0.44	<.001

The other covariates (baseline and clinical characteristics, health behavioral factors) were adjusted for these regressions

CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; TG, triglyceride.

Reviewer 2:

The manuscript examined the relationship between lipid fractions in adolescents and the mothers. The topic is interesting and analyses were performed well. I only have minor comments.
1. TG is known to be skewed distributed. It is usually log-transformed before doing analyses. I would recommend the authors could follow this practice.

Response: We appreciate your comments. We checked whether the continuous variables were normally distributed, and mentioned it in the 'statistical methods' paragraph. The variables were transformed into log scales. We revised the *p* values in Table 1 and also relating sentences in the 1st paragraph of the 'Results' section as follows. There has been no significant difference in interpretation.

[Page 7, Line 170-171]

We checked whether the continuous variables were normally distributed, and used a log scale depending on the results.

[Page 8, Line 197]

Table 1 shows baseline characteristics and their associations with adolescent lipid levels, and all *P* values were shown on a log scale.

2. Could the plots and associations be reported by sex of kids?

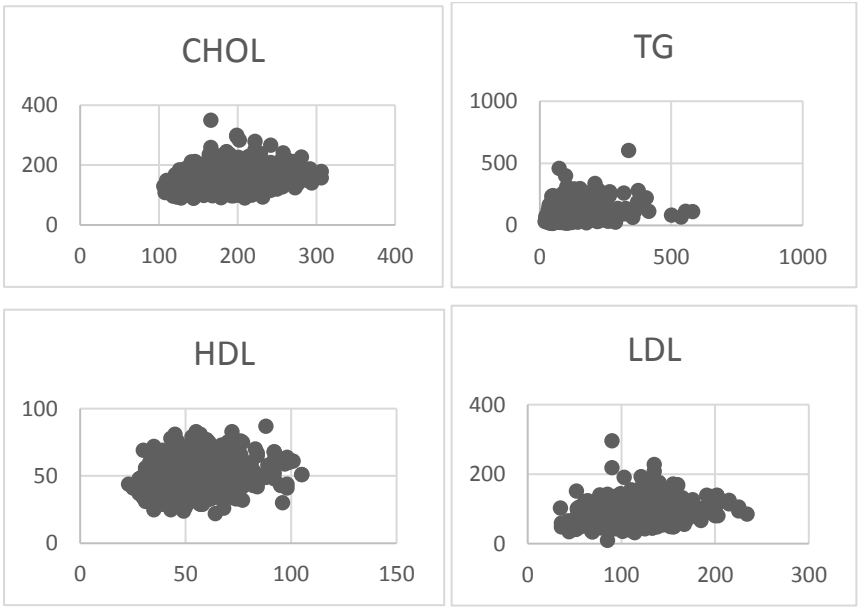
Response: We performed partial correlations analyses by sex of kids, and added relating sentence at the end of the 2nd paragraph of the 'Results' section as follows,

[Page 9, Line 220 – Page 10, Line 224]

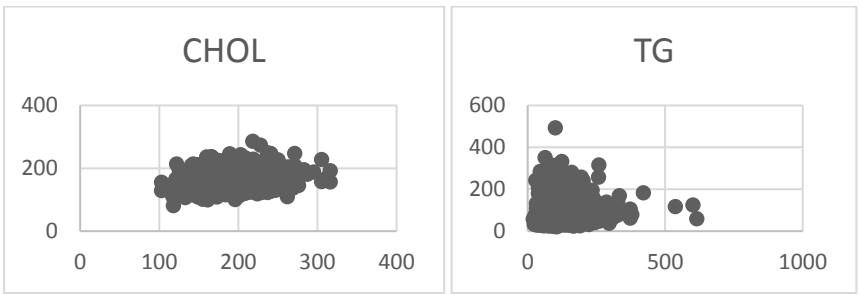
Meanwhile, the partial correlation coefficient (95% CI) for TC, TG, HLD-C, and LDL-C was 0.254 (0.206-0.301), 0.235 (0.186-0.282), 0.271 (0.224-0.317), and 0.267 (0.220-0.313) in males (n=1522), and it was 0.291 (0.241-0.339), 0.168 (0.116-0.220), 0.317 (0.268-0.364), and 0.309 (0.260-0.357) in females (n=1362). All *P* values were less than 0.001.

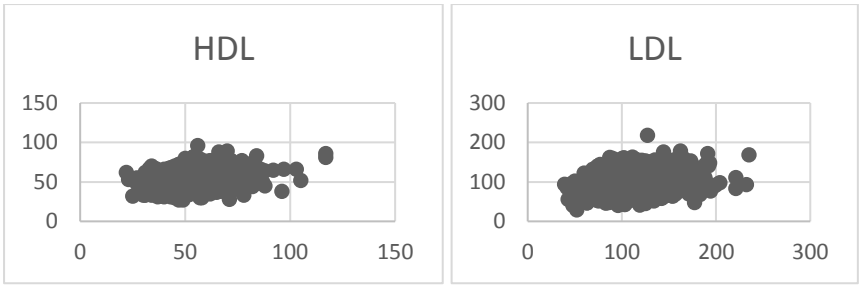
For reference, the scatter plots by sex were similar to that of the entire data (n=2,884) as follows,

(Male)



(Female)





3. Typos and grammatical errors need to be corrected.

Response: Thank you for your comments. According to your comment, we performed English proofreading again on the revised manuscript.

Reviewer 3:

I was invited to conduct a statistical review of the paper. Below are my comments –
1. This is survey data – how did the authors control for design effect and clustering? This should be explained in the statistical analysis section.

Response: We appreciate your comments. Our survey data was obtained from the stratified and clustered sampling, not from the simple random sampling. Thus, according to your comment, we used survey based statistical analysis and calculated design effect, and then revised the 'Methods' and 'Results' section as follows and also revised Table 2 & 3.

[Page 6, Line 136-137]

This survey used stratified and clustered sampling methods.

[Page 8, Line 179-180]

We used survey based statistical regression analyses, and the design effect relating survey sampling was calculated.

[Page 10, Line 228-229]

The design effect from survey sampling was 1.01, 1.43, 1.07, and 1.07 in TC, TG, HDL-C, and LDL-C respectively.

2. Did the authors check whether the continuous variables were normally distributed? If not, the authors would need to transform the variables to get a normal distribution – example a log normal distribution.

Response: According to your comments, we checked whether the continuous variables were normally distributed, and mentioned it in the 'statistical methods' paragraph. The variables were transformed into log scales. We revised the *p* values in Table 1 and also relating sentences in the 1st paragraph of the 'Results' section as follows. There has been no significant difference in interpretation.

[Page 7, Line 170-171]

We checked whether the continuous variables were normally distributed, and used a log scale depending on the results.

[Page 8, Line 197]

Table 1 shows baseline characteristics and their associations with adolescent lipid levels, and all *P* values were shown on a log scale.

3. I am worried about the results being a chance finding since a large number of models were tested – '16 possible combinations between four adolescents' and their mothers' lipid profiles', and various stratified analyses. The authors might need to adjust the models further to control for bias due to multiple testing, or justify that this bias is unlikely.

Response: We agree with your comments. We added related sentences in the limitations of the 'Discussion' section as follows,

[Page 15, Line 356-359]

Finally, our study might be vulnerable to bias originating from multiple testing. Especially, four dependent variables rise level of significance leading to the problem of high type-I error. However, even considering this, the *P* values for the associations are sufficiently significant.

4. It looks like the authors used ordinary least square regression – did the authors look at the residual plots? R-squared indicates how well the model explains variability of the response data around its mean. It is not an accurate representation of goodness of fit for the models. Perfectly good models can have low R-squared and vice versa.

Response: We agree with your comments. We added related sentences in the limitations of the 'Discussion' section as follows,

[Page 15, Line 359-362]

Additionally, R-squared indicates just how well the model explains variability of the response data. Although we chose four models, which showed high R-squared, it does not mean accurate representation of goodness of fit for the models.

5. In addition, why did the authors choose to look at the relationship between mothers and adolescents' lipid profile and not fathers'?

Response: There was no specific reason for choosing mothers' lipid. We aimed to evaluate the relationship of lipid levels between parents and offspring irrespective of mother or father. It will be interesting to compare the effect of mothers and fathers on offspring's lipids. We described sentences relating to this in the 'limitation' section as follows,

[Page 15, Line 350-352]

Fifth, we did not evaluate the father's lipid levels. If the father's lipid levels had also been considered, the genetic backgrounds of lipids might be emphasized more.

Reviewer 4:

This is interesting paper evaluating associations between lipids profiles of adolescent and their mothers in a nationwide survey.
I reviewed the statistical methods used in this paper. Overall the methods used to evaluate univariate and adjusted coefficients to measure association are coherent with the cross-sectional study design, but I have some concern on specific aspects of the analysis; these are the relation with the survey design, the treatment of missing data (especially on covariates), the problem of multiple testing and related to this how association for categorical variables and interactions (sub-group analysis) were tested. In particular
1. In the title and in the text the author refer to a nationwide survey, but in the analysis they didn't take into account of the sampling design (e.g. clustering or weights). I think the authors should give more information on the sampling design and the sampling design should be taken into account in the analysis using survey specific statistical methods.

Response: We appreciate your comments. Our survey data was obtained from the stratified and clustered sampling, not from the simple random sampling. Thus, according to your comment, we used survey based statistical analysis and calculated design effect, and then revised the 'Methods' and 'Results' section as follows and also revised Table 2 & 3.

[Page 6, Line 136-137]

This survey used stratified and clustered sampling methods.

[Page 8, Line 179-180]

We used survey based statistical regression analyses, and the design effect relating survey sampling was calculated.

[Page 10, Line 228-229]

The design effect from survey sampling was 1.01, 1.43, 1.07, and 1.07 in TC, TG, HDL-C, and LDL-C respectively.

2. The author perform a complete-case analysis on subject without missing data on covariate and outcome. There is evidence that this method could produce biased estimates. The authors could perform a sensitive analysis using multiple imputation techniques (considering the survey design) on the sample of 4148 subjects with lipid levels, or alternatively building a system of non-response weights (considering the full population of 5081 subjects) to combine with the survey weights.

Response: We performed sensitivity test using 4148 subjects according to your comment (Supplementary table S3), then, we also mentioned this in the 'Statistical analyses' of the 'Methods' section and at the end of the 'Results' section as follows,

[Page 8, Line 187-189]

Lastly, sensitivity test was done on 4,148 adolescents including 1,264 subjects who had inadequate baseline information or missing mothers' data to identify the baseline characteristics.

[Page 11, Line 252-254]

Finally, the sensitivity test on 4,148 adolescents showed comparable baseline characteristics with our study data (Supplementary Table S3).

Supplementary table S3 Sensitivity test: Demographics and lipid profiles in 4,148 adolescents aged 12-18 years

	No. (%)	TC			TG			HDL-C‡			LDL-C§		
		Mean	SD	*P* value†	Mean	SD	*P* value†	Mean	SD	*P* value†	Mean	SD	*P* value†
All (n=4148)		156.5	26.9		83.9	47.0		50.3	9.8		89.5	23.1	
Age (years)				0.252			0.459			0.013			0.996
12-14	1959 (47.2)	156.9	26.4		84.9	48.0		50.7	9.7		89.4	22.8	
15-18	2189 (52.8)	156.2	27.3		83.0	46.1		49.9	9.8		89.6	23.4	
Sex				<.001			0.313			<.001			<.001

Male	2215 (53.4)	151 .4	26 .8		84. 5	50 .1		48. 6	9. 4		86. 0	23 .1		
Female	1933 (46.6)	162 .4	25 .8		83. 3	43 .2		52. 3	9. 8		93. 4	22 .4		
BMI*				0.0 24			<.0 01			<.0 01			<.0 01	
<85%	3733 (90.0)	156 .0	26 .5		81. 1	44 .9		51. 0	9. 7		88. 8	22 .7		
≥85%	415 (10.0)	160 .9	30 .3		108 .8	57 .1		44. 1	7. 9		95. 0	26 .0		
Glucose (mg/dl)				0.1 66			0.1 34			0.7 65			0.1 42	
≤100	3935 (94.9)	156 .3	26 .6		83. 5	46 .7		50. 3	9. 7		89. 3	22 .8		
>100	213 (5.1)	160 .0	32 .5		90. 4	52 .7		50. 2	10 .2		92. 8	27 .9		

*Included 1264 adolescents who have no mothers' data or inadequate baseline information

†P values determined by log normal distributions

‡Included 42 missing data (n=4106)

§Included 43 missing data (n=4105)

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TC, total cholesterol; TG, triglyceride.

3. In the multivariate analysis (Table 3) the authors report multiple tests (I counted 34 tests on the coefficients for the exposure and for categorical covariates for each of the 4 models). The multiple testing rise the problem of a high overall type-I error, and consequently on the interpretation of the findings. To attenuate this problem a global test for a covariate in the multivariate model cold be performed using Likelihood ratio (LR) test or Wald tests based procedures (using survey methods), e.g. to test the association between walking hours and TC the model with and without walking hours are compared and LR test calculated, or Wald test with null hypothesis that ALL the coefficients are zeros can be performed.

Response: We agree with your comments. We added related sentences in the limitations of the 'Discussion' section as follows,

[Page 15, Line 356-359]

Finally, our study might be vulnerable to bias originating from multiple testing. Especially, four dependent variables rise level of significance leading to the problem of high type-I error. However, even considering this, the *P* values for the associations are sufficiently significant.

4. In table 4 the authors report the subgroup analysis, and they speculate that some of the coefficients were different according subgroups. To sustain this interpretation a formal test of interactions between mother characteristic and mother lipids level should be undertaken.
On a more substantive terms it would be interesting to evaluate the association between mother bmi and dyslipidaemia with the other covariates exanimated. This set of association would help to understand the results for subgroups.
Note that there is consensus on the statistical community to name multivariable models regression models with multiple covariates, and multivariate models to name regression models with multiple outcome.

Response: Thank you for your comments. We agree that subgroup analyses in our study should be interpreted taking into account the relationship of various factors. Therefore, we revised the interpretation of Table 3 results in abstract, and deleted or revised the related sentences in the text as follows and attached a table of the association between mother lipids and BMI according to your comments.

[Page 2, Line 49 – Page 3, Line 52]

The linear relationships were significant regardless of sex and mother characteristics.

Conclusions Mothers' lipid levels are associated with adolescents' lipids, therefore, it can serve as a reference for the screening of adolescent's dyslipidemia.

[Page 11, Line 261-262]

Moreover, we found that relationships between lipids of adolescents and their mothers were significant regardless of sex and mother characteristics.

[Page 13, Line 301-303]

Of course, this interpretation requires consideration of relationship between lipids and characteristics in mothers.

(Attached table)

Multivariate analyses of the association between lipids and baseline characteristics in mothers

Mothers' lipids	TC				TG			
	β	S.B.	S.E.	β	S.B.	S.E.		β
Age (years)								
30-39	Ref				Ref			
40-49	4.860	0.066	1.569	<.001	4.396	0.031	2.722	0.106
50-59	17.233	0.146	2.786	<.001	21.679	0.094	5.969	<.001
BMI (kg/m^2)								
<23	Ref				Ref			
23-24.9	3.877	0.052	1.434	0.007	18.568	0.128	2.511	<.001
≥25	10.351	0.145	1.472	<.001	43.485	0.311	3.002	<.001

Smoking, alcohol, education, income, working hours, and eating out were adjusted for these regressions.

Mothers' lipids	HDL-C				LDL-C			
	β	S.B.	S.E.	*P* value	β	S.B.	S.E.	*P* value
Age (years)								
30-39	Ref				Ref			
40-49	0.367	0.013	0.556	0.509	3.735	0.058	1.395	0.008
50-59	0.899	0.020	0.984	0.361	12.553	0.120	2.510	<.001
BMI (kg/m^2)								
<23	Ref				Ref			
23-24.9	-4.609	-0.164	0.527	<.001	4.707	0.071	1.258	<.001
≥25	-7.040	-0.260	0.496	<.001	8.832	0.139	1.318	<.001

Smoking, alcohol, education, income, working hours, and eating out were adjusted for these regressions.

VERSION 2 – REVIEW

REVIEWER	Francesco Sera London School of Hygiene and Tropical Medicine
REVIEW RETURNED	28-Dec-2018

GENERAL COMMENTS	The authors made an effort to answer to all the point I raised in my first review. Overall, I think the manuscript have improved from the submission version. There are some aspect of the method, and result sections that require more clarity: 1. It is not clear to me if log transformed outcome were used in the univariate analysis (Table 1) or also in the multivariable analysis (Table 2). I think if appropriate log transformed outcome should be used in both analysis. The first sentence of the results section (page 8 lines 196-197) should be changed as it appears that p values are in the log scale. 2. About the multiple testing problem I appreciate that the authors made an effort to answer to my concern, but the paragraph in the discussion section (page 15 line 356-359) doesn't have any sense to me. I suggest to remove it or change it with something similar with "Finally, the results of our study need to be evaluate with cautious as they might be vulnerable to family-wise type I error due to the multiple test involved in our analysis". 3. It would be good to have some more detail about the survey based regression methods used by the authors (e.g. definition of primary and secondary sampling units, weights, etc,,).

REVIEWER	Manisha Nair University of Oxford, UK
REVIEW RETURNED	20-Dec-2018

GENERAL COMMENTS	I was invited to comment on the statistical methods in the paper. The authors have addressed my concerns either by correcting the statistical methods or by noting in the limitations the methods that are not 100% adequate. I am happy for the journal to accept this version of the paper.

VERSION 2 – AUTHOR RESPONSE

Reviewer 4:

The authors made an effort to answer to all the point I raised in my first review. Overall, I think the manuscript have improved from the submission version.
There are some aspect of the method, and result sections that require more clarity:
1. It is not clear to me if log transformed outcome were used in the univariate analysis (Table 1) or also in the multivariable analysis (Table 2). I think if appropriate log transformed outcome should be used in both analysis. The first sentence of the results section (page 8 lines 196-197) should be changed as it appears that p values are in the log scale.

Response: Thank you for your comments. The log-transformed outcomes were clearly used in Table 1. According to your comment, we additionally used log-transformed outcomes in the multivariate analysis. We revised p values in Table 2 and relating sentences in 'Results' sections as follows,
[Page 9, Line 203]
Table 1 shows baseline characteristics and their associations with adolescent lipid levels, and it appears that P values are in the log scale.
[Page 10, Line 234]

Table 2 displays the multiple linear regressions of the four adequate models. It appears that P values are in the log scale.

2. About the multiple testing problem I appreciate that the authors made an effort to answer to my concern, but the paragraph in the discussion section (page 15 line 356-359) doesn't have any sense to me. I suggest to remove it or change it with something similar with "Finally, the results of our study need to be evaluate with cautious as they might be vulnerable to family-wise type I error due to the multiple test involved in our analysis".

Response: We appreciate your comment. We changed the sentence in Limitation as follows,

[Page 15, Line 362-364]
Finally, the results of our study need to be evaluate with caution as they might be vulnerable to family-wise type I error due to the multiple test involved in our analysis.

3. It would be good to have some more detail about the survey based regression methods used by the authors (e.g. definition of primary and secondary sampling units, weights, etc,,).

Response: According to your comment, we added relating sentences in 'Methods' section as follows,
[Page 6, Line 136-141]
This survey includes a representative sample of the population selected using a stratified, multi-stage, and clustered sampling method. Sampling units are district, survey area, and household. Stratification variables are city/province, district, and housing type. The sample is weighted to reflect sampling rate, response rate, and population demographics in order to estimate health consciousness, health behavior, and nutritional status on behalf of the population.

Reviewer 5:

I was invited to comment on the statistical methods in the paper. The authors have addressed my concerns either by correcting the statistical methods or by noting in the limitations the methods that are not 100% adequate.
I am happy for the journal to accept this version of the paper.

Response: We really appreciate your encouragement. Your comments have been a great help in improving our manuscript.

VERSION 3 – REVIEW

REVIEWER	Francesco Sera London School of Hygiene and Tropical Medicine
REVIEW RETURNED	14-Jan-2019

GENERAL COMMENTS	The authors answered positively to my last comments. I'm sorry perhaps there was a misunderstanding as I wasn't enough clear in my previous comments: 1) Legend in Table 1 and 2 should indicate that "P values were calculated considering log transformed outcome values" instead of "P values determined by log normal distributions". 2) The first sentence of the results section (page 9 lines 202-203) "and it appears that P values are in the log scale" should be changed with "and P values were calculated considering log transformed outcome values".

VERSION 3 – AUTHOR RESPONSE

1) Legend in Table 1 and 2 should indicate that "P values were calculated considering log transformed outcome values" instead of "P values determined by log normal distributions".

2) The first sentence of the results section (page 9 lines 202-203) "and it appears that P values are in the log scale" should be changed with "and P values were calculated considering log transformed outcome values".

Response) I appreciate your comments. I revised the Legends and Results section as follows,

[Page 22 & 24]

†P values were calculated considering log transformed outcome values.

[Page 9, line 202-203]

Table 1 shows baseline characteristics and their associations with adolescent lipid levels, and *P* values were calculated considering log transformed outcome values.