OPEN PEER REVIEW

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International Journal of Endocrinology and Metabolism
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Peer Review Report for "Familial-Related Risks for Congenital Hypothyroidism in Iranian Newborns: A Population-Based Case-Control Study"

Author(s): Shahin Yarahmadi, Nasrin Azhang, Mahmood Salesi, Khaled Rahmani

Review Timeline:

Submit Date: 12 May 2020
Revised Date: 19 Nov 2020
Accepted Date: 23 Dec 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | Revision (0) — 12 Jul 2020

Dear AE,
The manuscript has the potential for publication if the authors would provide more information in their manuscript and enrich their references as mentioned in the comments.
Thanks.

Koorosh Etemad: Reviewer | Revision (0) — 23 Aug 2020

Dear AE,
The name of the province is used for socioeconomic status; I didn't see this variable in the analysis as a variable. There are several problems with this using I think is not right.
- A screening test for the mother has been done after delivery, is it equal with the situation in pregnancy?
- Please explain the sampling design and how ascertained sample size is based on the population of the province. Did you use weighted analysis?
- What is the definition of employee in mothers and explain its measurement?
- What is the definition of smoking in mothers and explain its measurement?
Thanks.

Ladan Mehran: Reviewer | **Revision** (**0**) 24 Aug 2020

Dear AE,

The authors in a community-based case-control study assessed Familial-related risks for congenital hypothyroidism in Iranian newborns: a population-based case-control study. The following points should be addressed.

1. The introduction is written with too many unnecessary details e.g. regarding the symptoms of CH etc. Paragraph 1 and 2 should be summarized.

2. What the authors mean by the population-based incidence case control study, doesn't make sense. Please delete the word “incidence”

3. Refer to the following reference for this sentence in Introduction:

“The incidence of CH in Iran is much higher than in many other countries and the global average.”

⇥ Mehran L, Khalili D, Yarahmadi S, Amouzegar A, Mojarrad M, Ajang N, Azizi F.Worldwide Recall Rate in Newborn Screening Programs for Congenital Hypothyroidism. Int J Endocrinol Metab. 2017 Jun 25;15(3):e55451.

4. Methods are vague in some parts. For example, the authors claim that all mothers of participants were tested for thyroid function and mentioned it as an advantage of this study. If the answer is yes the authors should presents the details of laboratory measurements and definition of hypothyroidism in mothers.

5. In the Result section, some of variables are not at all important to be mentioned e.g. father’s smoking, or mother’s smoking which has a very low rate (1%)

6. In table 3, what is the meaning of genetic profile? and what is the difference between model 2 and 3? Although it is better to delete Father smoking as a confounders as there are many other important confounders which were not evaluated and considered.

7. Model 3: Genetic Profiles + Type of childbirth/delivery + Father smoking + Mother’s age (Variable level= Medical Universities, method: random intercept)

8. In Discussion, the first paragraph “showed that familial-related factors such as congenital anomalies, history of mental retardation in the family, mother’s hypothyroidism during pregnancy, intra-family marriage, gestational diabetes, having a hypothyroid child in the family, and twins or more, are considered as significant risk factors for the high incidence of CH in Iran.”

There are many other risk factors that have not been evaluated in the current survey. Therefore, the authors should rewrite the sentence to the following sentence: “Among familial-related factors, congenital anomalies, history of mental retardation in the family, etc…. are mostly associated with CH.”

9. “In general, the rate of intra-family marriage in Iranian society is high, “

Please indicate reference for this Statement in Iran, and even you can refer to Middle East countries.

10. Instead of twins substitute twin or multiple pregnancy

11. In the limitation indicates that the authors did not have the data to evaluate other important risk factors of CH e.g. maternal iodine status by urinary iodine measurement and iodine supplementation with iodofolic which are supported in many provinces in Iran from 4 years ago, As we know e.g in Markazi, Fars, Khuzestan, Khorasan razavi, iodine supplementation with iodofolic tablets have been routinely administered for pregnant women from 4 years ago.

In this part refer to the following references:

⇗ Mehran L, Yarahmadi S, Khalili D, Nazeri P, Delshad H, Abdollahi Z, Azhang N, Azizi F. The Impact of Iodine Status on the Recall Rate of the Screening Program for Congenital Hypothyroidism: Findings from Two National Studies in Iran. Nutrients. 2017 Oct 30;9(11):1194.
⇗ Mehran L, Khalili D, Yarahmadi S, Amouzegar A, Mojarrad M, Ajang N, Azizi F.Worldwide Recall Rate in Newborn Screening Programs for Congenital Hypothyroidism. Int J Endocrinol Metab. 2017 Jun 25;15(3):e55451.

12. Also the association of these risk factors with the type of CH to be permanent or transient was not evaluated.
13. Clarify that why Gestational diabetes was considered as a familial-related risk for congenital hypothyroidism, as there is no evidence in this regard???
Thanks.

REFEREE: Associate Editor | **Revision** (0) 25 Aug 2020

Dear EIC,
Given the issues raised by the reviewers, I recommend major revision for this manuscript.
Thanks.

REFEREE: EIC | **Revision** (0) 25 Aug 2020

Dear Author,
The reviewers' comments are mentioned. Please correct the details as mentioned above carefully according to reviewers' request.
Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear Prof. Fereidoun Azizi & Dr. Azita Zadeh-Vakili,

Editor-in-Chief of International Journal of Endocrinology and Metabolism,

Greetings,

Manuscript ID: 104889

Title: Familial-related risks for congenital hypothyroidism in Iranian newborn: a population-based case-control study

First of all, we would like to thank you and the respected reviewer whose technical comments helped us to improve and revise our manuscript. We made the required changes in the manuscript and highlighted them in the text; additionally in the table below we have listed the revisions and the responses to the comments.

Reviewer	Comments	Response
Reviewer 1	*1. The introduction is written with two much unnecessary details e.g. regarding the symptoms of CH etc. Paragraph 1 and 2 should be summarized.*	With respect to the reviewer's comments. The corrections were made to the manuscript.
	2. What the authors mean by the by the population-based incidence case control study, it doesn't make sense. Please delete the word "incidence"	Incidence case-control study is a type of case-control. Indeed, we have two types of case-control designs based on case selection: prevalence case or incidence case. In this study we used incidence cases.
	3. Refer to the following reference for this sentence in Introduction: "The incidence of CH in Iran is much higher than in many other countries and the global average." ¬ *Mehran L, Khalili D, Yarahmadi S, Amouzegar A, Mojarrad M, Ajang N, Azizi F.Worldwide Recall Rate in Newborn Screening Programs for Congenital Hypothyroidism. Int J Endocrinol Metab. 2017 Jun 25;15(3):e55451.*	We added this reference to the paragraph 3 introduction.
	4. Methods are vague in some parts. For example, the authors claim that the all mothers of participants were tested for thyroid function and mentioned it as an advantage of this study. If the answer is yes, the authors should present the details of laboratory measurements and definition of hypothyroidism in mothers.	For all studied mothers we checked the TSH and T4 hormones and categorized them into two groups: with and without hypothyroidism.
	5. In the Result section, some of variables are not at all important to be mentioned e.g. father's smoking, or mother's smoking which has a very low rate (1%)	Thank you for your attention, you are right. Although we assessed these factors but we did not highlight them in the results and discussion.

	6. In table 3, what is the meaning of genetic profile? and what is the difference between model 2 and 3? Although it is better to delete Father smoking as a confounder as there are many other important confounders which were not evaluated and considered.	Thanks for your comment. We changed genetic factor with familial factor. It should be noted that modeling and model selection are based on fitting evaluating method.
	7. Model 3: Genetic Profiles + Type of childbirth/delivery + Father smoking + Mother's age (Variable level= Medical Universities, method: random intercept)	I am afraid, I did not understand this comment.
	8. In Discussion, the first paragraph "showed that familial-related factors such as congenital anomalies, history of mental retardation in the family, mother's hypothyroidism during pregnancy, intra-family marriage, gestational diabetes, having a hypothyroid child in the family, and twins or more, are considered as significant risk factors for the high incidence of CH in Iran." *There are many other risk factors that have not been evaluated in the current survey. Therefore, the authors should rewrite the sentence to the following sentence: "Among familial-related factors, congenital anomalies, history of mental retardation in the family, etc…. are mostly associated with CH."*	This paragraph is changed based on mentioned comments.
	9. "In general, the rate of intra-family marriage in Iranian society is high, " *Please indicate reference for this Statement in Iran, and even you can refer to Middle East countries.*	Thanks for your attention, we referenced this sentence.
	10. Instead of twins' substitute twin or multiple pregnancy	It was done.
	11. In the limitation indicates that the authors did not have the data to evaluate other important risk factors of CH e.g. maternal iodine status by urinary iodine measurement and iodine supplementation with iodofolic which are supported in many provinces in Iran from 4 years ago, As we know e.g in Markazi, Fars, Khuzestan, Khorasan razavi, iodine supplementation with iodofolic tablets have been routinely administered for pregnant women from 4 years ago. *In this part refer to the following references:* *¬ Mehran L, Yarahmadi S, Khalili D, Nazeri P, Delshad H, Abdollahi Z, Azhang N,Azizi F. The Impact of Iodine Status on the Recall Rate of the Screening Program for Congenital Hypothyroidism: Findings from Two National Studies in Iran. Nutrients. 2017 Oct 30;9(11):1194.* *¬ Mehran L, Khalili D, Yarahmadi S, Amouzegar A, Mojarrad M, Ajang N, Azizi F.Worldwide Recall Rate in Newborn Screening Programs for Congenital Hypothyroidism. Int J Endocrinol Metab. 2017 Jun 25;15(3):e55451.*	Thanks for your recommendation, we added this limitation to the discussion in final paragraph and we used the mentioned references.

	12. Also the association of these risk factors with the type of CH to be permanent or transient was not evaluated.	To evaluate the association between these risk factors and permanent/transient CH, we have to wait to three years after birth while we did this study in first month after birth. In fact this is a weakness of our study.
	13. Clarify that why Gestational diabetes was considered as familial-related risks for congenital hypothyroidism, as there are no evidence in this regard???	Many thanks for your comments. We changed all sentences that have been considered gestational diabete as familial risk factors so that now we have GDM and familial-related risk factors separately.
Reviewer 2	*Name of province is used for socio economic status; I didn't see this variable in analysis as a variable. There are several problems for this using I think is not right.*	With respect to the comment, the name of province is not mean SES variable.
	Screening test for mother has been done after delivery, is it equal with situation in pregnancy?	Although this situation could not the pregnancy situation but it can a surrogate for measurement of this variable.
	Please explain about sampling design and how ascertained sample size based on population of province. Did you use weighted analysis?	Since we did not cluster sampling and also our work was not survey study, using the weighted analysis was not pertinent for the data.
	What is definition of employee in mothers and explain about it's measurement.	With respect to the reviewer's comment, we did not this term in our manuscript and we use occupied and unoccupied in order to mention the job of parents.
	What is definition of smoking in mothers and explain about it's measurement	This variable measured by asking from mothers about history of smoking during pregnancy and before.
Reviewer 3	*The manuscript has the potential for publication if the authors would provide more information in their manuscript and enrich their references as mentioned in the comments*	Many thanks and regards.

With Warmest Regards,
Khaled Rahmani,
Corresponding Author

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Ladan Mehran: Reviewer | **Revision (1)** 8 Nov 2020

Dear AE,
The responses to the following questions are not satisfying
1. Methods regarding thyroid function tests in mothers are vague. I think the investigators did not measure the thyroid hormones in mothers and these data were pre-existing data gathered from the laboratory measurements from many different, unknown labs all over the country. This causes bias in the research results due to differences in methods, techniques, equipment, and calibrations between laboratories. Please more clarify this issue in the method and also mention this in the limitations.
2. What is the difference between models 2 and 3 in Table 3? Please explain model 3 in the method (statistical analysis).
Model2: Genetic Profiles + Type of childbirth/delivery +Father smoking + Mother's age
Model 3: Genetic Profiles + Type of childbirth/delivery +Father smoking + Mother's age (Variable level= Medical Universities, method: random intercept)
3. Please change reference 13 to the following reference
13. Mehran L, Khalili D, Yarahmadi S, Delshad H, Mehrabi Y, Amouzegar A, Ajang N, Azizi F. Evaluation of the congenital hypothyroidism screening program in Iran: a 3-year retrospective cohort study. Arch Dis Child Fetal Neonatal Ed. 2019 Mar;104(2): F176-F181.
4. Please add the following reference as Ref. 26
*Mehran L, Khalili D, Yarahmadi S, Amouzegar A, Mojarrad M, Ajang N, Azizi F.Worldwide Recall Rate in Newborn Screening Programs for Congenital Hypothyroidism. Int J Endocrinol Metab. 2017 Jun 25;15(3):e55451.
Thanks.

REFEREE: Associate Editor | **Revision (1)** 14 Nov 2020

Dear EIC,
In addition to responses to comments of the reviewer, authors should consider a second revision of the manuscript in the following order:
1. Please add changes you have made in the manuscript with exact page and line numbers for each of your responses.
2. In accordance with comment No 2 of Reviewer 1, delete the word "incidence" before the case-control study.
3. Add all weaknesses and limitations addressed by reviewers that you agree with in the

limitations of the manuscript page 11, in particular, your response to comment No. 12 of Reviewer 1.
Thanks.

REFEREE: EIC | **Revision (1)** 17 Nov 2020

Dear Author,
Your article is reviewed by the reviewers carefully. According to their comments, this document needs minor revision. Please follow their comments as requested.
Thanks.

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear Prof. Fereidoun Azizi & Dr. Azita Zadeh-Vakili,

Editor-in-Chief

Greetings,

Manuscript ID: 104889

Title: Familial-related risks for congenital hypothyroidism in Iranian newborn: a population-based case-control study

First of all, we would like to thank you and the respected reviewer whose technical comments helped us to improve and revise our manuscript. We made the required changes in the manuscript and highlighted them in the text; additionally, in the table below we have listed the revisions and the responses to the comments.

Reviewer	Comments	Response
Reviewer 1	1. Methods regarding thyroid function tests in mothers are vague. I think the investigators did not measure the thyroid hormones in mothers and these data were pre-existing data gathered from the laboratory measurements from many different, unknown labs all over the country. This causes bias in the research results due to differences in methods, techniques, equipment, and calibrations between laboratories. Please more clarify this issue in the method and also mention this in the limitations.	با سلام و تشکر از دقت نظر داور محترم: این یک طرح کشوری بود که برا یهمه ماماران مورد بررسی بعد اززایمان و با کیت های استاندارد و یکسان آزمایش کارکرد غده تیروئید به عمل آمد و در واقع هیچ محدودیتی از نظر عدم یکسان بودن کیت و ... نداشتیم و برای همه ماماران تست انجام دادیم.
	2. What is the difference between model 2 and 3 in Table 3? Please explain about model 3 in the method (statistical analysis). Model2: Genetic Profiles + Type of childbirth/delivery +Father smoking + Mother's age Model 3: Genetic Profiles + Type of childbirth/delivery +Father smoking + Mother's age (Variable level= Medical Universities, method: random intercept)	The model 2 is a multiple Logistic Regression model adjusted for some of the covariates. But the model 2 is a multilevel multiple Logistic Regression model with similar covariates, in this model Universities have considered as level of sampling and run as random intercept model. We add this explain to the table 3 and highlighted it.
	3. Please change reference 13 to the following reference 13. Mehran L, Khalili D, Yarahmadi S, Delshad H, Mehrabi Y, Amouzegar A, Ajang N, Azizi F. Evaluation of the congenital hypothyroidism screening programme in Iran: a 3-year retrospective cohort study. Arch Dis Child Fetal Neonatal Ed. 2019 Mar;104(2):F176-F181.	It was done
	4. Please add the following reference as the Ref. 26 *Mehran L, Khalili D, Yarahmadi S, Amouzegar A,	This reference is used as reference 10.

	Mojarrad M, Ajang N, Azizi F.Worldwide Recall Rate in Newborn Screening Programs for Congenital Hypothyroidism. Int J Endocrinol Metab. 2017 Jun 25;15(3):e55451.	
Associate Editor's Comments:	1. Please add changes you have made in the manuscript with exact page and line numbers for each of your responses.	It was done.
	2. In accordance with comment No 2 of the Reviewer 1, delete the word “incidence” before case-control study	It was deleted.
	3. Add all weaknesses and limitations addressed by reviewers that you agree in the limitations of the manuscript page 11, in particular your response to comment No. 12 of Reviewer 1.	It was done.

With Warmest Regards,

Khaled Rahmani,
Corresponding Author

OPEN PEER REVIEW

Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (2) 23 Dec 2020

Dear EIC,
The authors have revised the manuscript satisfactorily. The manuscript is now suitable for publication in the IJEM.
Thanks.

REFEREE: EIC | **Revision** (2) 23 Dec 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.