PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Preventive Antenatal Educational Program on Allergic Diseases (PAEPAD) versus standard antenatal care for prevention of atopic dermatitis: study protocol for a single-center, investigator blinded randomized controlled trial.
AUTHORS	zhao, mutong; Liang, Yuan; Song, Fengli; Ma, Lili; Wang, Ying; Gao, Wanli; Tian, Jing; Ying, Xiangji; Shen, Chunping; Wang, Shan; Jiao, Lei; Wang, Yang; Sun, Xiaoyan; Ma, Lin; Ma, Xiuhua

VERSION 1 – REVIEW

REVIEWER	Ohya, Yukihiro National Center for Child Health and Development, Tokyo, Allergy
REVIEW RETURNED	27-Mar-2021

GENERAL COMMENTS	General comments: As described well in Introduction and Discussion, education for patients is critically important for desirable outcome. The authors stated the stage change model of behavior (pre-contemplation, contemplation, preparation, to action and maintenance) applied for health education. This point of view is excellent for researchers and practitioners to improve adherence of participant in the intervention study like this, however, in the Intervention section (line 207 ~ 232), the authors did not describe the way how to apply the stage change model to this intervention. Specific comment line 160 – 167 The authors described as follows: 2) consent to biological sample collections of the mother that are non-invasive, including but not limited to the recollection of blood from routine pregnancy workups; 4) consent to biological sample collections of the child that are non-invasive, including but not limited to the recollection of blood from routine checkups; What items and how many volumes of blood sampling do “including but not limited to the recollection of blood from routine pregnancy workups and routine checkups” mean? line 219-221 The authors described 2) Skin care of the newborns with a practical demonstration on bathing and emollient application (20 min). Are participants in the intervention group provided specific emollient from the hospital or purchase it for themselves? How frequent are the participants in the intervention group advised to apply emollient for infants? Do they continue using it until the

	onset of atopic dermatitis? How are they checked their adherence of emollient use? How to bath and how to apply emollient for infantile skin are core educational contents in this study, however, no description was found in Intervention section. line 259-266 During the follow up period, do the participants in the intervention group receive skin care education such as the way of emollient application for infants? there are no description about it. About SPIRIT check list Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered. The authors indicated 8 Line 201, however, no sufficient detail to allow replication was described in the Intervention section. 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return,laboratory tests) The authors indicated 8 Line 201-6, however, no relevant description was found in Intervention section.

REVIEWER	Yan, Weili Children's Hospital of Fudan University
REVIEW RETURNED	08-May-2021

GENERAL COMMENTS	Abstract -Objective: “This study aims to evaluate the effect of an educational 30 intervention, i.e., the Preventive Antenatal Education Program on Allergic Diseases 31 (PAEPAD), on infantile allergic disease incidences” is not clear. It is better to “to evaluate the effect of an educational 30 intervention, i.e., the Preventive Antenatal Education Program on Allergic Diseases 31 (PAEPAD), on infantile allergic disease incidences compared with the standard care” -Although limited space, the eligibility of participants, experimental intervention can be more clear. Sample size -It is stated that this trial is an exploratory trial (line 141-142), however a detailed sample size calculation is presented, please make sure it is not a confirmative trial. -Sample size calculation will be determined based on the estimated difference in the primary outcome (accumulate incidence of AD), instead of an estimated incidence only. Randomization -Line 193-201: It is confusing, it is a “individual randomization” or “a block randomization”? Statistical analysis -Line 320-322. For the primary outcome, accumulate incidence % of AD, Chisquare test will not able to provide risk ratio or risk difference. -Line 341: An interim analysis is planned, therefore, the statistical analysis plan for the primary outcome should be consider it and make adjustment.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Yukihiro Ohya, National Center for Child Health and Development, Tokyo
Comments to the Author:
General comments:
As described well in Introduction and Discussion, education for patients is critically important for desirable outcomes. The authors stated the stage change model of behavior (pre-contemplation, contemplation, preparation, action and maintenance) applied for health education. This point of view is excellent for researchers and practitioners to improve adherence of participants in the intervention study like this, however, in the Intervention section (line 207 ~ 232), the authors did not describe the way how to apply the stage change model to this intervention.

Response: Thank you for bringing to our attention that important clarification was needed for the PAEPAD session. We have added details on how it's implemented in the supplementary material. The intervention is entirely educational, we hope to achieve behavioral changes over the postnatal period and further modify disease outcome. This would reflect the real-world scenario of how behavioral changes take place following patient education. As we have stated in the discussion, the lone-term adherence to the desirable behavior extending beyond treatment phase can be as low as 4% in the BEEP study (where emollients rather than education were provided), indicating that maintenance of behavior without consciousness-raising, environmental-reevaluation and self-evaluation, all of which can be accounted for presumably through education, is rather difficult. Herein, we set out to investigate how educational intervention can modify behavior and change disease outcomes. The outcome of our study included both disease incidence as evaluated by physician observations and knowledge and attitude change by survey questions.

Specific comment
(1)line 160 – 167
The authors described as follows:
2) consent to biological sample collections of the mother that are non-invasive, including but not limited to the recollection of blood from routine pregnancy workups;
4) consent to biological sample collections of the child that are non-invasive, including but not limited to the recollection of blood from routine checkups;
What items and how many volumes of blood sampling do "including but not limited to the recollection of blood from routine pregnancy workups and routine checkups" mean?

Response: The items, including blood volumes and how they are processed for storage are included in the supplementary material.

(2)line 219-221
The authors described 2) Skin care of the newborns with a practical demonstration on bathing and emollient application (20 min).
Are participants in the intervention group provided specific emollient from the hospital or purchase it for themselves?

Response: The PAEPAD session included a live demonstration of how bathing and moisturizing should be implemented, but no emollients are provided at the end of the session and nor are they provided at any subsequent visits. The intervention is purely educational. We clarified on this in line 240-242.

(3)How frequent are the participants in the intervention group advised to apply emollient for infants? Do they continue using it until the onset of atopic dermatitis? How are they checked their adherence of emollient use?
How to bath and how to apply emollient for infantile skin are core educational contents in this study, however, no description was found in Intervention section.
Response: We agree that details should be included for specific PAEPAD session topics and we provided a table of key recommendations on the four topics in the supplementary material.
To be specific, they are advised to use emollients within 5 minutes after bathing and a liberal use is recommended whenever xerosis become evident. Emollients are recommended for use for AD patients. We check for emollient usage during follow-up visits as an outcome measure rather than as an index for adherence as our intervention is antenatal education. We understand that this may confuse the reviewer, please refer to comment 6 for additional clarification.

(4)line 259-266
During the follow up period, do the participants in the intervention group receive skin care education such as the way of emollient application for infants? there are no description about it.
Response:
The participants do not receive further education during follow-up visits and we agree that this should be clarified within the manuscript (line 240-242).

(5)Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered.
The authors indicated 8 Line 201, however, no sufficient detail to allow replication was described in the Intervention section.
Response:
We agree that details should be included for specific PAEPAD session topics and we provided a table of key recommendations in the supplementary material.

(6)11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return,laboratory tests)
The authors indicated 8 Line 201-6, however, no relevant description was found in Intervention section.
Response:
We stated that “Any crossover and non-compliance will be surveyed by a research nurse at the beginning and end of the antenatal sessions.” and that “For those who failed to complete the intervention prior to admission into the OB department, a pre-recorded video will be played during their hospital stay.” These measures will help us identify adherers and non-adherers for the PAEPAD sessions.
We understand how this may confuse the reviewer in that if this was a behavioral intervention, i.e. emollients was provided as the intervention, specifying how emollients are dispensed and recording the emollient usage would be of paramount importance. However, as our intervention is education, we recorded emollient usage within the outcome matices as a secondary outcome rather than as an index for intervention compliance. We agree with the reviewer that this is of substantial importance in the stage of change model and have provided details on how this will be measured in Table 1.

Reviewer: 2
Dr. Weili Yan, Children's Hospital of Fudan University
Comments to the Author:
(1)Objective: “This study aims to evaluate the effect of an educational 30 intervention, i.e., the Preventive Antenatal Education Program on Allergic Diseases 31 (PAEPAD), on infantile allergic disease incidences” is not clear. It is better to “to evaluate the effect of an educational 30 intervention,

i.e., the Preventive Antenatal Education Program on Allergic Diseases 31 (PAEPAD), on infantile allergic disease incidences compared with the standard care"
Although limited space, the eligibility of participants, experimental intervention can be more clear.
Response: We agree that clarification on inclusion criteria and intervention is needed in the abstract and have made corrections accordingly.

(2)Sample size
It is stated that this trial is an exploratory trial (line 141-142), however a detailed sample size calculation is presented, please make sure it is not a confirmative trial.
Response: Thank you for raising the discussion about the difference between exploratory and confirmatory design. We agree that our study is more suitable for a confirmatory trial (line 148). We set out to investigate a desirable behavioral change that has been confirmed to be effective in small pilot studies[1-3]. Our agenda differs from previous studies in that we tested the effect of education, rather than the immediate behavior of applying emollient, on disease outcome. We believe that this bears a closer resemblance to the real world, where health education is regarded as a powerful tool that elicits behavioral change.

(3)Sample size calculation will be determined based on the estimated difference in the primary outcome (accumulate incidence of AD), instead of an estimated incidence only.
Response: We calculated sample size based on the incidence of the control group (0.2) and an estimated RR (0.75), corresponding to an estimated incidence of 0.15 for the treatment group, which is a conservative estimation of the effect size. We chose an estimated RR of 0.75 based on previous studies[1-3] and we elected to be conservative on the effect size due to the consideration that our intervention is entirely educational, which may not translate fully into immediate behavioral change.

Randomization
(4)Line 193-201: It is confusing, it is a "individual randomization" or "a block randomization"?

Response: We used block randomization, rather than simple randomization to allocate participants. We apologize for causing confusion over the wording of "individual" and have made corrections in the manuscript accordingly (line 203).

Statistical analysis
(5)Line 320-322. For the primary outcome, accumulate incidence % of AD, Chisquare test will not able to provide risk ratio or risk difference.
Response: We agree that this would cause confusion and have made corrections in the manuscript (line 347).

(6)Line 341: An interim analysis is planned, therefore, the statistical analysis plan for the primary outcome should be consider it and make adjustment.
Response: Thank you for bringing to our attention that type I error may increase with interim analyses. We intended to measure knowledge at 1 year postnatal as our interim outcome. As this is not the primary outcome (disease incidence at 2 years postnatal), nor is it necessarily correlated with the primary outcome, we came to realize that this would not warrant stop of recruitment and have made corrections accordingly. Please kindly let us know if there are other adjustments to be made.

References

1 Horimukai K, Morita K, Narita M *et al.* Application of moisturizer to neonates prevents development of atopic dermatitis. *The Journal of allergy and clinical immunology* 2014; 134: 824-30 e6.

2 McClanahan D, Wong A, Kezic S *et al.* A randomized controlled trial of an emollient with ceramide and filaggrin-associated amino acids for the primary prevention of atopic dermatitis in high-risk infants. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2019; 33: 2087-94.
3 Simpson EL, Chalmers JR, Hanifin JM *et al.* Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *The Journal of allergy and clinical immunology* 2014; 134: 818-23.

VERSION 2 – REVIEW

REVIEWER	Ohya, Yukihiro National Center for Child Health and Development, Tokyo, Allergy
REVIEW RETURNED	11-Sep-2021

GENERAL COMMENTS	Responses to the comments were adequate. In SPRIT table, Item NO description and line numbers were matched, however, line numbers were occasionally not.

REVIEWER	Yan, Weili Children's Hospital of Fudan University
REVIEW RETURNED	01-Sep-2021

GENERAL COMMENTS	The protocol looks nice for publication.