PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Adjuvant effects of vitamin A and vitamin D supplementation on treatment of children with attention-deficit/hyperactivity disorder: a study protocol for a randomised, double-blinded, placebo-controlled, multicentric trial in China
AUTHORS	Zhou, Ping; Wolraich, Mark; Cao, Ai-hua; Jia, Fei-Yong; Liu, Bin; Zhu, Lin; Liu, Yongfang; Li, Xiaoli; Li, Chao; Peng, Bin; Yang, Ting; Chen, Jie; Cheng, Qian; Li, Tingyu; Chen, Li

VERSION 1 – REVIEW

REVIEWER	Prof Con Stough Centre for Human Psychopharmacology
REVIEW RETURNED	09-Jul-2020

GENERAL COMMENTS	This is an important study. I comment the researchers in planning this study. The protocol paper could be improved significantly: The style and english language needs to be professionally edited Specify the hypotheses Specify the primary and secondary outcomes outline the power analyses, particularly how the sample size was calculated and the effect size needed to show an improvement

REVIEWER	Motahar Heidari-Beni Assistant Professor. Child Growth and Development Research Center Research Institute for Primordial Prevention of Non-communicable Disease Isfahan University of Medical Sciences Isfahan,Iran
REVIEW RETURNED	12-Jul-2020

GENERAL COMMENTS	1- the structure of the abstract should be corrected 2- novelty and importance of topic should be justifies 3-background part is too long 4-the result and discussion part is very incompleted 5- with which references dose and duration of supplements were selected

REVIEWER	Jeanette Johnstone Oregon Health & Science University, USA
REVIEW RETURNED	22-Jul-2020

GENERAL COMMENTS	Thank you for the opportunity to review the study protocol, Adjuvant effects of vitamin A and vitamin D supplementation on treatment of children with Attentiondeficit/hyperactivity disorder: a

	study protocol for a randomized, double-blinded, placebo-controlled, multicentric trial in China. Authors should be commended for writing the protocol and for undertaking the proposed study; ClinicalTrials.gov: NCT04284059 My overall comment is that the manuscript would benefit from editing for English language usage. I have mentioned a few of the many instances where wording was unclear or incorrect. From the abstract: I have concerns about the single, constant dose of methylphenidate. 18mg is a low dose, particularly for older children who weigh more. I recommend dose by weight, as used in Mohammadpour, Nakisa, et al. "Effect of vitamin D supplementation as adjunctive therapy to methylphenidate on ADHD symptoms: A randomized, double blind, placebo-controlled trial." Nutritional Neuroscience 21.3 (2018): 202-209. Completion date of December 2020 does not seem realistic. I'm not clear about exposure time and body part to sun; use of sunscreen – how to rate or compare that between participants Adverse Events – how will they be asked about? Pg 9, Line 38 – vit D level (is it 2000 IU/day or 2100) - not consistent with NCT registry Pg 10, line 35: Lay a foundation for mechanisms – in what way? This was not described Pg 14, lines 25-27 "However, it's required for patients with ADHD to adjust the stimulants dose or apply for nonstimulants on the basis of the therapeutic effect" that's why I think one dosage of methylphenidate for everyone will not be ideal. Pg 15, line 20 the word "companied" is not correct – diagnosed with? Pg 16, line 25 "promoting" is not the right word – positive effect on ADHD symptoms? Why using Wechsler Intelligence Scale? To rule out IQ <70? If so, say so. It's not necessary for ADHD diagnosis Will the participants be medication naïve before starting the study? If so, mention that; if not, they can only take 18mg of methylphenidate? Pg 18 line 46 - Exclusion criteria - what is meant by a "cortisol drug?" Pg 19 line 10 – Exit/termination criteria – what side effects constitute Vit A poisoning? Why is rickets considered a side effect? Maybe a side effect of being on placebo, but if supplemented with vit D, that would prevent rickets

	Pg 19 line 20 – “inform content” should be “informed consent” “according to their willing” is more accurately stated, “if willing” What family history will be collected? Medical history is the child’s medical history? Pg 19 line 35 ‘the exposure time and body part to sun and using of sunscreen cream” – more definition is needed here – what is the question(s) to be asked? What are the exclusion criteria? Pg 22 line 22 “a side-effect reporting scale” please say more about how potential side effects or adverse events will be asked about and reported. Pg 22 Lines 38-56 for the WISC, if the only purpose in giving it is to determine IQ for inclusion, you could use an abbreviated version – the Weschler Abbreviated Scale comprised of verbal and perceptual reasoning to estimate IQ – much faster and shorter Pg 23 lines 4-28 QCD - I believe this is the Chinese version of the SDQ – the Strengths and Difficulties Questionnaire. If that’s true, I would mention it so that future readers will know it is comparable and the data may be used as such. Pg 23 lines 33 – determination of Vit A and D will be conducted via blood draw? If so, mention that. The levels will be assessed and if the participant does not meet criteria, she or he will not be enrolled?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Con Stough
Institution and Country: Centre for Human Psychopharmacology
1. Please state any competing interests or state ‘None declared’: none declared

Response: Thank you for your kind suggestions. We have added the Competing interests section in the middle of page 25, following the Funding statement.

2. Please leave your comments for the authors below
This is an important study. I comment the researchers in planning this study. The protocol paper could be improved significantly:

Response: Thank you for your affirmation. We have edited the English language in the manuscript by a professional copyediting service. Responses to other comments have been provided below.

3. The style and English language needs to be professionally edited.

Response: We apologize to have caused you trouble in reading the manuscript. We have edited the English by a professional copyediting service to increase readability as much as possible.

4. Specify the hypotheses

Response: Thank you for this proficient suggestion. We have added the paragraph about hypotheses as follows:

Aside from the exiting data, a prospective study assessing the adjuvant effects of vitamin A and vitamin D administered with methylation in the ADHD population will be performed simultaneously, under the hypothesis vitamin A and vitamin D could expedite the therapy effects of therapy on ADHD symptoms. Previous studies conducted by Mohammadpour N, Dehbokri N, Elshorbagy HH, et al. have found that ADHD symptoms significantly were relieved under vitamin D supplementation [25-27]. Experiments conducted on rats revealed that high vitamin A intake during pregnancy has long-lasting programming effects on the dopamine system of the offspring[28]. Based on these findings, identifying the effects of vitamin A and vitamin D on the therapy of ADHD is highly essential, as ADHD patients may be excellent candidates for vitamin A and vitamin D combination therapy.

5. Specify the primary and secondary outcomes, outline the power analyses, particularly how the sample size was calculated and the effect size needed to show an improvement

Response: Thank you for your suggestion. We have added this part into the manuscript, specified as follows.

1) About the primary and secondary outcomes:
Primary outcomes:
We will use the Vanderbilt parent assessment scale and Vanderbilt teacher assessment scale to estimate the symptoms of various ADHD subtypes (predominantly inattentive, predominantly hyperactivity/impulsive, and combined) at baseline. We will use the Vanderbilt parent follow-up scales and Vanderbilt teacher follow-up scales to estimate the changes in ADHD symptoms at weeks 4 and 8, respectively. Moreover, we will assess problems in the daily life of children at particular times of the day by Questionnaire - Children with Difficulties (QCD).
Secondary outcomes:
The serum concentrations of vitamin A and vitamin D will be measured through high performance liquid chromatography using peripheral blood.

2) Regarding the sample size, we calculated it using the software PASS 2020. There are currently no previous research reports in the literature that we can use as references. The only previous studies concerning vitamin D supplementation on ADHD have been derived from small sample sizes and their outcome, ADHD symptoms changes, is assessed using an evaluation questionnaire (CPRS) different from the one used in our study. In our study, we considered Vanderbilt assessment scales to be as effective as the CPRS in assessing the changes in ADHD symptoms. Based on the hypothesis that vitamin A and vitamin D promote improvement of ADHD symptoms, we concluded that a total number of 504 patients will be enrolled in our study. Because patient recruitment has yet to begin, we are not able to complete power analyses.
The detailed description provided in the main manuscript is as follows:

Based on an alpha of 0.05, power of 80%, and a dropout rate of 10%, we adopted an ANOVA F-Test by using the PASS software 2020 to evaluate the sample size. This study is a randomised double-blind controlled trial. Intervention groups are vitamin AD group and vitamin D group, while the control is the placebo group. The primary outcome index is changes in ADHD symptoms as evaluated by Vanderbilt assessment scales at weeks 4 and 8 compared with that at baseline. In the study conducted by Mohammadpour N et al.[25], where the score generated using Conner's Parent Rating Scale (CPRS) was considered the main outcome, the mean ± standard deviation (SD) of ADHD index in CPRS was 55.84 ± 10.20 for the vitamin D + methylphenidate group (n = 25), and 56.79 ± 9.60 for the placebo + methylphenidate group (n = 29). The Vanderbilt assessment scale is considered as effective as the CPRS in assessing the changes of ADHD symptoms. Based on the hypothesis described above, vitamin A, along with D, promotes the improvement of ADHD symptoms. We cautiously presume that the mean score ± SD for vitamin AD + methylphenidate group is lower than that of vitamin D + methylphenidate group, while the control group scores the highest using the

Vanderbilt assessment scales, with a score of 54.00 ± 9.88 for the vitamin AD + methylphenidate group, 55.84 ± 10.20 for the vitamin D + methylphenidate group, and 56.79 ± 9.60 for the control group. The number of subjects to be enrolled in the study is 504.

Reviewer: 2
Reviewer Name: Motahar Heidari-Beni
Institution and Country: Research Institute for Primordial Prevention of Non-communicable Disease Isfahan University of Medical Sciences, Isfahan, Iran

Please leave your comments for the authors below
1. the structure of the abstract should be corrected

Response: Thank you for your suggestion. The corrected structure of the abstract is specified as follows.
Abstract
Introduction
Approximately 7.2% of children in the world suffer from attention-deficit/hyperactivity disorder (ADHD). Due to the availability of the osmotic-release oral-system methylphenidate, ADHD currently has a remission rate of up to 30.72%. Nevertheless, it has been reported that patients with ADHD tend to exhibit vitamin A and vitamin D deficiency, which may aggravate the symptoms of ADHD. This study aims to determine the effect of vitamin A and vitamin D supplementation as adjunctive therapy to methylphenidate on the symptoms of ADHD.
Methods and analysis
This is a parallel, prospective, interventional multicentric study. Patients will be enrolled from the southern, central, and northern parts of China. A target of 504 patients will be followed for 8 weeks. They will be allocated into 3 groups (vitamin AD, vitamin D, placebo) and administered the interventions accordingly. Data on changes in the symptoms of ADHD, as well as changes in the serum concentrations of vitamin A and vitamin D will be recorded. Both responders and non-responders based on the sociodemographic and clinical data will also be described to assess selection bias.

1. novelty and importance of topic should be justifies

Response: Thank you for this suggestion. We have added the novelty and importance of the topic in the section regarding Strengths and limitations of this study.
1) Designed as a multi-centre study across China, thereby increasing the generalisability of the study results.
2) First trial to examine vitamin A plus vitamin D supplementation on ADHD.
3) Classification of ADHD will elucidate the differential effects of vitamins A and D on ADHD subtypes and provide evidence regarding vitamin A and vitamin D supplementation in patients with ADHD.
4) The effects of vitamin A are unclear as the effect of vitamin A alone on ADHD was not investigated.
5) Methylphenidate may mask the effects of vitamin A and vitamin D owing to its strong and numerous effects.

2. background part is too long
Response: Thank you for your suggestion. We have appropriately shortened the original background and added a discussion section to the revised manuscript.

3. the result and discussion part is very incompleted

Response: Thank you for your feedback. We have revised the manuscript to be as specific as possible. More information regarding the result is provided in the section of the manuscript discussing

Primary outcomes and Secondary outcomes, and the Sociodemographic and clinical data and the discussion are written in the manuscript as follows:
Discussion
To our knowledge, this is the first trial to examine vitamin A plus vitamin D supplementation in ADHD. The study is expected to provide more substantial findings regarding the potential use of vitamin A and vitamin D in addition to methylphenidate in cases of ADHD complicated by vitamin A and vitamin D deficiency, and to provide supporting data to supplement and help revise the current ADHD clinical guidelines.

As the study will be carried out in the southern, central, and northern parts of China, regional differences will be minimized. This study design not only verifies the effect of vitamin D on the treatment of ADHD using a larger sample size[25-27], but also explores whether vitamin A along with vitamin D is effective in the treatment of ADHD. At the same time, the classification of ADHD will be conducted to further elucidate the effects of vitamin A and vitamin D on ADHD and to lay a foundation to explore the mechanism underlying this condition. Although the sample size is calculated by referring to the CPRS scale rather than the Vanderbilt assessment scales, our study proposes a much larger sample size than previous studies in the literature, reducing selection bias as much as possible. There are still some limitations in our study. We will not be administering vitamin A alone as our intervention due to the restrictions on pharmaceutical production, which may pose limitations in determining the exact effect of vitamin A. Considering ethical conditions, we will be enrolling all patients with deficiency or insufficiency in vitamin A and vitamin D and administer methylphenidate along with these vitamins to improve patient adherence. As a result, we cannot conclude the effect of vitamin A or vitamin D on ADHD patients with normal serum concentrations of vitamin A and vitamin D. Furthermore, methylphenidate may mask the effects of vitamin A and vitamin D owing to its strong and numerous effects. However, these restrictions are not the Achilles' heel of this study, and the topics of the study remains to be further investigated, as the mechanism of action of vitamins A and D on ADHD should be explored based on its promise shown in current literature.

4. with which references dose and duration of supplements were selected

Response: Thank you for your question. In fact, we have previously repeatedly discussed this issue with researchers, and selected the current research dose to maintain consistency. However, your question gave us the opportunity to re-examine this problem. Considering the treatment effect and compliance of children, as well as using previous studies as reference, we chose the following dosage used in Chinese clinical practice. All patients receive methylphenidate (trade name Concerta) 18–54 mg/day once a day (began with 18 mg/day for a week and titrated gradually to the optimum dose not more than 54 mg/day). These corrections are reflected in the original manuscript.

Reviewer: 3
Reviewer Name: Jeanette Johnstone
Institution and Country: Oregon Health & Science University, USA
1. Please state any competing interests or state ‘None declared’: None declared

Response: Thank you for your kind suggestion. We have added the Competing interests section to the middle of page 25, following the Funding statement.

2. Thank you for the opportunity to review the study protocol, Adjuvant effects of vitamin A and vitamin D supplementation on treatment of children with Attention deficit/hyperactivity disorder: a study protocol for a randomized, double-blinded, placebo-controlled, multicentric trial in China.

Authors should be commended for writing the protocol and for undertaking the proposed study; ClinicalTrials.gov: NCT04284059

Response: Thank you for your comment. We have updated the trial registry and the protocol to make them consistent. We will carry out the study according to the protocol. We will also inform BMJ Open and update the trial registry if we encounter any difficulties during the implementation of the protocol that result in a change of these plans.

3. My overall comment is that the manuscript would benefit from editing for English language usage. I have mentioned a few of the many instances where wording was unclear or incorrect.

Response: We apologize to have caused you trouble in reading the manuscript. We had the manuscript edited by a professional copyediting service to increase readability as much as possible. Thank you again for your patience in reading the manuscript.

4. From the abstract: I have concerns about the single, constant dose of methylphenidate. 18mg is a low dose, particularly for older children who weigh more. I recommend dose by weight, as used in Mohammadpour, Nakisa, et al. "Effect of vitamin D supplementation as adjunctive therapy to methylphenidate on ADHD symptoms: A randomized, double blind, placebo-controlled trial." Nutritional Neuroscience 21.3 (2018): 202-209.

Response: Thank you for your question. In fact, we have previously repeatedly discussed this issue with researchers, and selected the current research dose to maintain consistency. However, your question gave us the opportunity to re-examine this problem. Considering the treatment effect and compliance of children, as well as using previous studies as reference, we chose the following dosage used in Chinese clinical practice. All patients receive methylphenidate (trade name Concerta) 18–54 mg/day once a day (began with 18 mg/day for a week and titrated gradually to the optimum dose not more than 54 mg/day). These corrections are reflected in the original manuscript.

5. Completion date of December 2020 does not seem realistic.

Response: Thank you for raising this important question. After discussing with fellow researchers about this problem, referring to the advice of other experts, and considering the problems that have emerged this year, we have changed the primary completion date from December 2020 to May 30,2021, and the study completion date from April 30, 2021 to August 30, 2021.

6. I'm not clear about exposure time and body part to sun; use of sunscreen – how to rate or compare that between participants

Response: Thank you for your comment. We have discussed this problem with other researchers. This was included in our study because our target group is mainly school-aged children, very few Chinese children wear sunscreen when they go to school, and the sample collection time of the project is mainly concentrated in the winter and spring, with considerable coverage of the skin with clothing, resulting in less skin exposure. The children are usually at school from 8:00 to 16:00 every day, and classes are mainly conducted indoors, unlike in some foreign countries where there may be more frequent field trips or outdoor breaks. In addition, Chongqing, Jinan city in Shandong province and Changchun city in Jilin province are not cities with strong ultraviolet rays, and the clouds are relatively thick, which is the reason for the relatively high deficiency rate of vitamin D. Considering these reasons and previous literatures, we thought the time of sun exposure will not bias the result. Therefore, we have deleted the related content from the manuscript.

a) Adverse Events – how will they be asked about?

Response: We will use a detailed self-generated questionnaire to ask about adverse events during

follow-up appointments with patients, using the following questions: Did you experience any discomfort while taking the medication? Can you please specify the kind of discomfort? How long did this discomfort last? How do you relieve this discomfort? Can you endure this kind of discomfort? Does this discomfort occur regularly? Have you ever experienced this kind of discomfort prior to enrolling in the study? Have you ever seen a doctor because of this discomfort?

7. Pg 9, Line 38 – vit D level (is it 2000 IU/day or 2100) - not consistent with NCT registry

Response: The unit of vitamin D is 700 IU/capsule and the patient must take 3 capsules a day. The vitamin AD capsule is made of 2000 IU of vitamin A and 700 IU of vitamin D and the patient must take 3 capsules a day. We have checked the related contents of the NCT registry to ensure that the information in the protocol and the NCT registry are consistent.

8. Pg 10, line 35: Lay a foundation for mechanisms – in what way? This was not described

Response: Thank you for your detailed reading. We have changed the sentence “The classification of ADHD will be conductive to further elucidate the effects of vitamin A and vitamin D on ADHD and lay a foundation for mechanism exploration.” into “Classification of ADHD will elucidate the differential effects of vitamins A and D on ADHD subtypes and provide data evidence regarding vitamin A and vitamin D supplementation in patients with ADHD.”

9. Pg 14, lines 25-27 “However, it’s required for patients with ADHD to adjust the stimulants dose or apply for nonstimulants on the basis of the therapeutic effect” that’s why I think one dosage of methylphenidate for everyone will not be ideal.

Response: Thank you for this insightful suggestion. We apologize for our lack of consideration of this point. Considering the treatment effect and compliance of the child, as well as referring to previous studies, we chose the following dosage used in Chinese clinical practice. All patients will receive 18–54 mg/day methylphenidate (trade name Concerta) once a day (began with 18 mg/day for a week and titrated gradually to the optimum dose not more than 54 mg/day). We also made these corrections in the original manuscript.

10. Pg 15, line 20 the word “companied” is not correct – diagnosed with?

Response: Thank you for your suggestion. We have changed the word from “companied” to “diagnosed”.

11. Pg 16, line 25 “promoting” is not the right word – positive effect on ADHD symptoms?

Response: Thank you for your suggestion. We have changed the word from “promoting” to “positive”.

12. Why using Wechsler Intelligence Scale? To rule out IQ <70? If so, say so. It’s not necessary for ADHD diagnosis

Response: Yes, this scale was used to rule out the patients with IQ <70. We have deleted the scale for the ADHD diagnosis in the original manuscript and added it into the exclusion criteria

13. Will the participants be medication naïve before starting the study? If so, mention that; if not, they can only take 18mg of methylphenidate?

Response: Yes, the participants will be medication naïve before starting the study. The changed dose of the medication is detailed as follows: All patients will receive 18–54 mg/day methylphenidate (trade

name Concerta) once a day (begin with 18 mg/day for a week and titrated gradually to the optimum dose not more than 54 mg/day).

14. Pg 18 line 46 - Exclusion criteria - what is meant by a “cortisol drug?”

Response: We apologize for causing you confusion. We mean hydrocortisone — cortisol in nature, and a steroid hormone in the glucocorticoid class of hormones. This glucocorticoid would influence the absorption of vitamin D so we excluded the patients using hydrocortisone. We have replaced the term “cortisol drug” in the original manuscript with hydrocortisone.

15. Pg 19 line 10 – Exit/termination criteria – what side effects constitute Vit A poisoning? Why is rickets considered a side effect? Maybe a side effect of being on placebo, but if supplemented with vit D, that would prevent rickets

Response: Thank you for your helpful suggestions. Vitamin A poisoning includes toxicity to the liver, visual impairment, bone and muscle pain. We added this to the manuscript. The side effect about rickets has been deleted from the original manuscript.

16. Pg 19 line 20 – “inform content” should be “informed consent” “according to their willing” is more accurately stated, “if willing” What family history will be collected? Medical history is the child’s medical history?

Response: Thank you for your kind suggestion. We have changed the word “inform content” to “informed consent”. The family history includes records of neuropsychiatric disorders, including epilepsy, depression, ASD and ADHD, congenital diseases and metabolic diseases in her or his family, and this is a part of questions that are routinely asked during clinical interviews. The medical history refers to the child’s past medical history. We have added this part to the original manuscript.

17. Pg 19 line 35 ‘the exposure time and body part to sun and using of sunscreen cream” – more definition is needed here – what is the question(s) to be asked? What are the exclusion criteria?

Response: We had previously considered this a confounding factor that is difficult to exclude completely. Thank you for raising this question. We have discussed this problem with other researchers. This was included in our study because our target group is mainly school-aged children, very few Chinese children wear sunscreen when they go to school, and the sample collection time of the project is mainly concentrated in the winter and spring, with considerable coverage of the skin with clothing, resulting in less skin exposure. The children are usually at school from 8:00 to 16:00 every day, and classes are mainly conducted indoors, unlike in some foreign countries where there may be more frequent field trips or outdoor breaks. In addition, Chongqing, Jinan city in Shandong province and Changchun city in Jilin province are not cities with strong ultraviolet rays, and the clouds are relatively thick, which is the reason for the relatively high deficiency rate of vitamin D. Considering these reasons and previous literatures, we thought the time of sun exposure will not bias the result. Therefore, we have deleted the related content from the manuscript.

18. Pg 22 line 22 “a side-effect reporting scale” please say more about how potential side effects or adverse events will be asked about and reported.

Response: Thank you for this question. The side effects are derived from the Vanderbilt Assessment Follow-up—PARENT and TEACHER Informant. The following table includes more detailed information. We have added part of this information regarding side effects to the manuscript.
Side Effects: Has your child experienced any of the following side effects or problems in the past week?

Are these side effects currently a problem?
None Mild Moderate Severe
Headache

Stomach ache

Change of appetite—explain below

Trouble sleeping

Irritability in the late morning, late afternoon, or evening—explain below

Socially withdrawn—decreased interaction with others

Extreme sadness or unusual crying

Dull, tired, listless behaviour

Tremors/feeling shaky

Repetitive movements, tics, jerking, twitching, eye blinking—explain below

Picking at skin or fingers, nail biting, lip or cheek chewing—explain below

Sees or hears things that are not there

19. Pg 22 Lines 38-56 for the WISC, if the only purpose in giving it is to determine IQ for inclusion, you could use an abbreviated version – the Weschler Abbreviated Scale comprised of verbal and perceptual reasoning to estimate IQ – much faster and shorter

Response: Thank you for your suggestion. The reason why we use WISC in our research is not only to determine IQ for inclusion, but also to exclude children who have unique differences in their intelligence which have affected their learning ability, such as children with severe memory deficits or language impairment. In addition, our hospital only has copyright of this version of WISC. If possible, would you kindly consider sharing this scale with us, which we believe will be of great help to our clinical and scientific research? Thank you again for your extremely helpful suggestion.

20. Pg 23 lines 4-28 QCD - I believe this is the Chinese version of the SDQ – the Strengths and Difficulties Questionnaire. If that's true, I would mention it so that future readers will know it is comparable and the data may be used as such.

Response: Thank you for your question. The QCD questionnaire is indeed the Chinese version of Questionnaire – Children with Difficulties (QCD). It is a social function assessment questionnaire developed by a Japanese professor and has been known to be a reliable and valid Chinese version of the questionnaire. The following article contains more detailed information and can be used as a reference.
Zheng Y, Du Y, Su LY, et al. Reliability and validity of the Chinese version of Questionnaire - Children with Difficulties for Chinese children or adolescents with attention-deficit/hyperactivity disorder: a cross-sectional survey. Neuropsychiatr Dis Treat. 2018;14:2181-90. doi:10.2147/ndt.S166397.

21. Pg 23 lines 33 – determination of Vit A and D will be conducted via blood draw? If so, mention that. The levels will be assessed and if the participant does not meet criteria, she or he will not be enrolled?

Response: Yes, the levels of vitamin A and vitamin D will be conducted via peripheral blood draw. If the participant does not meet the criteria, she or he will not be enrolled. We also wanted to recruit more patients, including those patients with normal concentrations of vitamin A and vitamin D, as in previous studies reported in the literature. It is regrettable that our ethics committee rejected this proposal.

VERSION 2 – REVIEW

REVIEWER	Motahar Heidari-Beni Dr. Motahar Heidari-Beni, Assistant Professor. Child Growth and Development Research Center Research Institute for Primordial Prevention of Non-communicable Disease Isfahan University of Medical Sciences Isfahan,Iran
REVIEW RETURNED	21-Sep-2020

GENERAL COMMENTS	1- The abstract part does not consist of results and conclusion part. These parts should be added. 2- Several studies showed the effects of vitamin D and vitamin A on ADHD. What is the novelty and importance of the present study? When vitamin A and vitamin D separately affect ADHD, it seems that the assessment of their combination is not important. 3- Participant consumed 3 capsules per day. It is high dose of vitamin D and A. Which references support theses dosage 4- What are the components of placebo? 5- The potential mechanism of the effect of vitamin A and D on ADHD should be more explained in the discussion part. 6- You can implement study and after the end of it, you can report your results as a research paper. I suggest the RCT paper do not need methodology paper

VERSION 2 – AUTHOR RESPONSE

1.The abstract part does not consist of results and conclusion part. These parts should be added.

Response: Thank you for your kind suggestion. We wrote the manuscript based on the Submission Guidelines of BMJ OPEN. The guideline about Protocol requires the abstract only concludes Introduction; Methods and analysis; Ethics and dissemination.

2. Several studies showed the effects of vitamin D and vitamin A on ADHD. What is the novelty and importance of the present study? When vitamin A and vitamin D separately affect ADHD, it seems that the assessment of their combination is not important.

Response: Thank you for your deep consideration about the question. Actually, during the search

for the studies about vitamin A on ADHD, no published studies or protocols have been found. Also, there are only three articles about adjunctive effects of vitamin D on ADHD, which were carried out in the western countries with small sample. Basic research found that vitamin A influences vitamin D by binding to acceptors of vitamin D in vivo (Riccio & Rossano, 2018). Based on the above mechanism, we assume that the combined supplement of vitamin A and vitamin D is more effective in the adjuvant treatment of ADHD than that of vitamin D alone. Therefore, our team designed such a RCT study, hoping to further confirm our hypothesis. Due to the design requirements of the sample size, in order to ensure that a sufficient number of subjects meeting the inclusion criteria are enrolled in the study and successfully complete the experiment, the single group with vitamin A supplementation is not added at present. If the study goes well, we plan to further discuss whether there is adjuvant effect of vitamin A on ADHD according to your suggestions in the near future.

Reference:

Riccio, P., & Rossano, R. (2018). Diet, Gut Microbiota, and Vitamins D + A in Multiple Sclerosis. Neurotherapeutics, 15(1), 75-91. doi:10.1007/s13311-017-0581-4

3. Participant consumed 3 capsules per day. It is high dose of vitamin D and A. Which references support theses dosage

Response: Thank you for your kind suggestion. The dose of vitamin D -2100IU- isn't higher than the previous study, neither the reported 3000 IU/day of vitamin D lasting for 12 weeks in the study of Dr. Hatem Hamed Elshorbagy [1], nor 50,000 IU/week of vitamin D lasting for 6 weeks in the study of Dr. Nadia Dehbokri [2], and is as similar as 2000IU/day lasting for 8 weeks from Nakisa Mohammadpour[3]. Additionally, according to the category criterion of WHO, China is still a country with mild VA deficiency. Data from the Chinese Dietary Reference Intakes shows the UL (tolerable upper intake levels) of vitamin A in children above 4 years old is 6600IU/day [4]. Furthermore, the Nelson textbook of pediatrics 21st edition showed that 'Chronic daily intakes of 15,000 μg and 6,000 μg can be toxic in adults and children, respectively'[5]. And the reported chronic toxic dose in Chinese pediatrics textbook is 50,000 IU/day-100,000 IU/day for children, more than 6 months [6]. Considering the proportion of vitamin A and D dosage forms in China, we chose 6000IU/day of vitamin A during 3 months observation period in our study, which is lower than UL and chronic toxic dose. It's safe dose.

The following are the references:

1) Elshorbagy HH, Barseem NF, Abdelghani WE, et al. Impact of Vitamin D Supplementation on Attention-Deficit Hyperactivity Disorder in Children. Ann Pharmacother. 2018;52(7):623-31. doi:10.1177/1060028018759471.

2) Dehbokri N, Noorazar G, Ghaffari A, et al. Effect of vitamin D treatment in children with attention-deficit hyperactivity disorder. World J Pediatr. 2019;15(1):78-84. doi:10.1007/s12519-018-0209-8.

3) Mohammadpour N, Jazayeri S, Tehrani-Doost M, et al. Effect of vitamin D supplementation as adjunctive therapy to methylphenidate on ADHD symptoms: A randomized, double blind, placebocontrolled trial. Nutr Neurosci. 2018;21(3):202-09. doi: 10.1080/1028415X.2016.1262097.

4) Chinese Nutrition Society. Chinese dietary reference intakes [M].Xinhua Publishing House. 2013. 322.

5) Robert M. Kliegman & Joseph St. Geme. Nelson textbook of pediatrics[M].2019(21).1938.

6) Gui yonghao, Xue xindong. Pediatics[M].People's Medical Publishing House Co.,LTD. 2015-08-06(3). 84.

4. What are the components of placebo?

Response: The placebo capsule consists of oily liquids which are same with the basic ingredients contained in the capsules of vitamin A and D, while no vitamin A and vitamin D are contained in the placebo capsule. It was produced in strict accordance with China's drug management and packaging requirements for placebo by Shandong DYNE Marine Biopharmaceutical Co.,Ltd in China. Placebo, vitamin AD and vitamin D capsules are identical in appearance and odour to guarantee blinding.

We also has stressed the detailed information about placebo in the "Patient and public involvement" in the page 14 of the manuscript.

5. The potential mechanism of the effect of vitamin A and D on ADHD should be more explained in the discussion part.

Response: Thank you for your kind suggestion. If possible, we are glad to mention part of the potential mechanism of the effect of vitamin A and D on ADHD in the discussion part in order to demonstrate the protocol more fluent and clear. We are planning to add this sentence , 'Based on the known theoretic foundation-vitamin A binding to the vitamin D receptors to influence the metabolism of vitamin D,' in the first paragraph in the discussion part. The final demonstration is

as follows,

To our knowledge, this is the first trial to examine vitamin A plus vitamin D supplementation in ADHD. Based on the known theoretic foundation-vitamin A binding to the vitamin D receptors to influence the metabolism of vitamin D, the study is expected to provide more substantial findings regarding the potential use of vitamin A and vitamin D in addition to methylphenidate in cases of ADHD complicated by vitamin A and vitamin D deficiency.

What's more, we mention part of the potential mechanism of effect of vitamin A and D on ADHD in the part of introduction as our theoretical basis, and we indicate the strengths and limitations of this study in the discussion part according to the format purpose of protocol. Once the research results are obtained, we will publish the results in the form of a paper, and further analyze the potential mechanism in the discussion section of the paper.

6. You can implement study and after the end of it, you can report your results as a research paper. I suggest the RCT paper do not need methodology paper

Response: Thank you for your kindly reminder. When we retrieve the keyword of "RCT" and "protocol" on the website of BMJ OPEN, the searching interface notices there are 4,824 results for term "RCT" and "protocol". As far as I am concerned, the protocol could give other persons reference before the end of study, about the feasibility and reasonability. Other researchers could trace the progress of the study, monitor implementation process and give some advices to enrich the study. So we basically think it is necessary to write a methodology paper. If honored, we sincerely invite you to give suggestions and participate in the supervision of our project.

Above is our detailed explanation. What's more, we want to inform editors and reviewers that we have changed the number of capsules taken in the vitamin D group from 3 capsules per day for 8 weeks to 6 capsules per day, 2 weeks plus 5 capsules per day for 6 weeks, as the dose of vitamin D has changed from 700IU/capsule planned to 400 IU/capsule actually produced.

Apart from the fact that all the patients are diagnosed, treated alone and they all take medicine separately at home, the staff dispensing the drugs does not participate in the patient's diagnosis and treatment process. Therefore, the results of the study are not be biased even though the oral amount of vitamin D capsules is different from that of the other groups.

We have indicated this in the revised manuscript.

We would like to show our gratitude to the editors and reviewers for your time spending on our article.