

PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Co-morbid anemia and stunting among children 2-5 years old in southern Ethiopia: a community based cross-sectional study
AUTHORS	Orsango, Alemselem Zebdewos Loha, Eskindir Lindtjørn, Bernt S. Engebretsen, Ingunn Marie

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Emmanouil Bagkeris Institution and Country: Imperial College London, National Heart and Lung Institute / Genomic and Environmental Medicine Competing interests: None
REVIEW RETURNED	18-Feb-2021

GENERAL COMMENTS	<p>This is a great piece of work. Congratulations to the authors. Below are some comments/recommendations:</p> <ol style="list-style-type: none">1. In the methods section, although information for the sample size calculation are provided, you did not specify what the recommended sample size from the sample size calculation was and whether it was achieved or not and why.2. Please explain the reason for the 2.6% drop-out from the 340 selected children.3. In table 1 the number of children currently breastfeeding does not add up to 331. Was breastfeeding missing for one child? Please edit the methods section to explain whether a complete case analysis was performed or not.4. Although the methods section suggests that along with means the standard deviations are reported, in the results section you report 95% CI for the number of people at home. Please be consistent. Moreover, state in the methods section that for all prevalence reported, 95% CIs are provided.5. In table 3 both for child age and for maternal/paternal education please specify what the unit was. I understand that it is years, but it is important to be explicit.6. What do the asterisks in table 3 mean? Please explain in footnotes. Why non-significant factor (own domestic animals) has an asterisk for the AOR?7. Throughout the results section, refer to higher/lower odds not to higher/lower risk. You did not perform a Poisson regression. The estimates are odds ratios not relative risks.8. Have you considered running a multinomial logistic regression instead of three multivariable models (combined outcome, anaemia, stunting)? Would the results be more coherent if you had a combined outcome (0=no anaemia/stunting, 1=anaemia,
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	2=stunting, 3=anaemia and stunting) using the first category (no anaemia/stunting) as the reference group?
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REVIEWER	Reviewer name: Mr. Abebaw Molla Institution and Country: Mizan-Tepi University, School of public health Competing interests: None
REVIEW RETURNED	

GENERAL COMMENTS	<p>Introduction</p> <p>Comments to the Author</p> <p>Title: Co-morbid anemia and stunting among children 2-5 years old in southern Ethiopia: a community based cross-sectional study</p> <p>Thank you for giving me the opportunity to review this article. The study uses a cross-sectional study design to determine prevalence and factors associated with co-morbid anemia and stunting among children 2-5 years old in southern Ethiopia: a community-based cross-sectional study. Some specific comments are as follows:</p> <p>Abstract</p> <p>Line 27 HAZ less than -2 what?? Doesn't give meaning Better to avoid using abbreviations/acronyms in the abstract section</p> <p>Introduction</p> <p>Since the manuscript is focused on 2-5 years, the first paragraph should emphasize the issue of comorbid anemia and stunt in this population, but the author focuses on under-five. Add the importance of Comorbid anemia and stunting in this population groups</p> <p>The author didn't show the link between anemia and stunting or the interaction of micronutrient deficiency and micronutrient deficiency, instead of reporting prevalence only it's important to show a link between anemia and growth faltering.</p> <ol style="list-style-type: none"> 1. Justification of the study is not strong enough, limited study isn't sufficient because there are studies done on comorbid anemia and stunting as the author stated. So the study needs strong justification. 2. The authors need to explain what is unique with the study that differentiates it from other studies including the EDHS analysis that can also be used to assess comorbid anemia and stunning including previous studies EDHS, or what this study adds or fill as compared with past studies done on the topic 3. Why author focus on these population groups? Because anemia and stunting are the highest among children aged 6-23 months as compared to children 2-5 years. 4. Please explain why measuring Comorbid anemia and stunting is important compared to only assessing anemia and stunting since both have almost similar conceptual frame work-UNICEF conceptual framework for malnutrition? 5. Line 48-50: the study area is characterized by poor economic status, inadequate health facilities, poor environmental hygiene and sanitation, and inadequate water supplies should be cited because it is difficult to conclude with such a statement without knowing currently available information regarding the existed services. 6. Author used EDHS 2011 prevalence of anemia to estimate sample size for the present study, why the author used this prevalence (EDHS 2011) over EDHS 2016 or recent studies done in the southern region? Plus prevalence of anemia used to estimate sample size took in the population group was 3-5 years why don't you used 2-5 years prevalence? 7. The study conducted in Cheffe Cote Jebessa Kebele which is a single kebele, but the author mentioned as 1689 2-5 years children were lived in these kebeles. This number is very unlikely and difficult to accept this figure. So the author should describe population demography in the study area and should be cited otherwise it's
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	<p>very difficult taking this large number of children 2-5 years living in one kebeles.</p> <p>8. Your exclusion criteria, what do you think about children taking vitamin A or iron supplementation and children taking deworming recently?</p> <p>9. Operational definition of indicators needs to be explained more clearly. For example, the questions in HFIAS questionnaires need to be explained in general before explaining how to define food secure and insecure households, Please add information on the response rate.</p> <p>10. Anthropometric and hemoglobin data</p> <p>Why author used ENA SMART for anthropometric data analysis over WHO Anthros? The author also presents all anthropometric measurement under descriptive section</p> <p>The author should describe standard quality control for hem cue analyzer during filed setting and describe a detailed procedure for hemoglobin measurement procedure and interpretation protocol. Author state superficially about anemia measurement procedure</p> <p>11. Tables: I recommend refining table presentation and try to format to save space, instead of two columns for frequency and % you can put both values in one column n (%).</p> <p>Statistical analysis</p> <p>12. I would like the authors to discuss the validity of their statistical approach ("Bi-variable logistic regression analysis was done to see the association between outcome variables and each independent variable. All covariates with p-value < 0.1 in the bi-variable analysis were entered into multivariable analysis to control possible confounders. The authors should discuss their approach more, with references, and consider revising their methods if they do not match general practice. They should also run sensitivity analyses (how do results vary when all variables are included in one large multivariate model ?)</p> <p>13. It is not clear from reading the paper which variables were omitted from the results because they were found to have p-values greater than 0.1 in the bivariate analysis.</p> <p>14. Please explain all the variables assessed for determinant analysis? Better to use education status as a categorical variable like in table 2 instead of analyzing continuous, similarly variable measurement in regression analysis is not clear such as maternal age, family size either, is it categorical, continuous or?</p> <p>3. Overall authors should describe all variables used in bi-variable analysis and variables used for adjustment should be described with its appropriate measurement.</p> <p>4. household food security status should be categorized into food secure and insecure because in authors' classification there is a small number in cells (5) which is difficult to estimate the odds of anemia and stunting with this number.</p> <p>3. How did confounders controlled. Did you test interaction effects between variables?</p> <p>Discussion</p> <p>1. Discussion looks like narration and restate the results, the author should rewrite discussion in a more in-depth manner including implication for policymakers and possible mechanism. Based on your findings what is/are the best recommendation that policymakers should consider for solving the existed problems? why are these findings important?</p>
REVIEWER	<p>Reviewer name: Dr. Muluken Azage</p> <p>Institution and Country: Bahir Dar University College of Medical and Health Sciences, Enviornmental Health</p>

	Competing interests: none
REVIEW RETURNED	26-Feb-2021

GENERAL COMMENTS	<p>Major concern</p> <p>The authors declared to identify context-based factors that are associated with CAS. However, they identified the common factors which are stated in previously conducted study? what is the contribution this paper for the readers or the scientific community? This is a part of larger study that aimed to evaluate the efficacy of home processed amaranth grain containing bread in the treatment of anaemia among two-to-five-year-old children in southern Ethiopia. How did the authors validity of the result by including only a singly kebele? The sample size calculation did not consider the second objective (to identify factors of CAS) or the stated sample size may not enough to consider the all factors that the authors want to identify?</p> <p>Abstract</p> <ul style="list-style-type: none"> • The associated factors like child age and family size are not explicitly stated. Which age group? What family size? <p>Method section</p> <ul style="list-style-type: none"> • How do you see the sample size calculated for measuring comorbidity of CAS can be used to answer the second objective? • Was the assumption for logistic regression checked? <p>Results</p> <ul style="list-style-type: none"> • The interpretation of odds ratio is not correct • Why some of the values in Table 3 are omitted? Example <p>Discussion</p> <ul style="list-style-type: none"> • Child age vs CAS is not discussed? • The authors stated that "Our study indicated that stunting prevalence was higher among anaemic children and height for age z-score increased when haemoglobin concentration increased in the children". The above statements is supported with evidence since the authors did logistic regression only for CAS.
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REVIEWER	<p>Reviewer name: Mr. Muhammad Umer</p> <p>Institution and Country: Aga Khan University, Pediatrics & Child Health</p> <p>Competing interests: None</p>
REVIEW RETURNED	01-Mar-2021

GENERAL COMMENTS	The study provides sufficient evidence regarding high prevalence of anemia and stunting. it provides insights into an important issue and it is useful to the people who make decisions.
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VERSION 1 – AUTHOR RESPONSE

Dear Editor and reviewers

We thank the editors and the four reviewers for their time and constructive comments which helped us to revise our manuscript entitled "Co-morbid anaemia and stunting among children 2-5 years old in southern Ethiopia: a community based cross-sectional study".

In the revised manuscript, we have carefully considered the editor's and reviewers' suggestions, and we adjusted and added some paragraphs on statistical analysis, results, and discussion especially the issue on multinomial logistic regression analysis. Furthermore, we addressed and responded to each of the points raised by the reviewers and editor. The reviewers' and editor's comments are below given in bold format followed by our answer in normal font.

With these changes, we would like to resubmit the paper to BMJ Paediatrics Open.

Yours sincerely,
On behalf of all authors
Alemselam Zebdewos Orsango
Hawassa, Ethiopia

Associate Editor

Comments to the Author:

The reviewers make a number of helpful suggestions to improve the paper.

I have a few additional comments and questions:

1. Under the "what this study adds" and "what is known" section, make explicit that these statements are about Ethiopia. For "what this study adds" list the important factors associated with co-morbid anemia/stunting in the statement.

Thank you very much. We appreciate your comment and now we list the important factors associated with 'co-morbid anaemia and stunting' (CAS) under 'what this study adds' and 'what is known about the subject.' (L 345)

What is known about the subject?

One-quarter of children 6 to 24 months of age had co-morbid anaemia and stunting (CAS) in Ethiopia based on the last Ethiopian Demographic and Health survey.

Vitamin A supplementation, consumption of vitamin A rich fruits, vegetables, meat, legumes, meal frequency, low household wealth, low caregivers' education level, male sex, age, history of infection, and low birth weight have been found associated with CAS in children less than 2 years of age in Ethiopia.

What this study adds

One in six children 2-5 years of age in Southern Ethiopia had co-morbid anaemia and stunting.

Food insecurity, child's age, iron supplementation during pregnancy, and father's educational status were associated with co-morbid anaemia and stunting in children 2-5 years of age.

2. In the introduction/discussion, some more interaction/comparison with the most recent DHS survey might be helpful. Presumably, anemia data exists in the DHS data set for 2-5-year-olds, and it's puzzling to me that the prior publications apparently only reported CAS for under 2-year-olds.

Thank you very much for your comment. We updated the background with recent findings on anemia and stunting independently among children 2-5 years of age. (L 64-66)

We understand you are puzzled by the prior findings on CAS among children under 2 only. EDHS presented anemia and stunting independently for children less than five years old but the prior study presented co-morbid anemia and stunting was used EDHS data to analyze CAS for only less than two years of age.

3. Table formatting could be significantly simplified for readability. Tables 1 and 2: descriptive categories can go indented under each variable name to eliminate that column; unless there is significant missing data for one of the variables the N is not needed (the total N is given at the top of the table). In the Regression table (Table 3) the distribution of CAS is not needed, just the columns with the crude and adjusted ORs. The table could be further simplified by removing the implied reference category for each analyzed variable (where the OR is 1)

Thank you very much for your comment. We simplified Tables 1 and 2 by indenting under each variable name. We eliminated a column and the total N and percentage are given at the top of the tables. We also took your advice and deleted information about missing value when that was negligible (set to < 1%). We changed the content of table 3 because of accepting multinomial analysis based on the comment given by the reviewers but still, we maintained only COR and AOR in the table. Also, we omitted to give the reference value = 1 for obvious categories (e.g. yes/no and boy/girls). (L202, L211, L237)

4. I do not understand this sentence in the statistical analysis section: "Factors were introduced to the

model step by step and based on their level of statistical significance." Prior to this the text states that factors were selected by expert knowledge and the UNICEF conceptual framework and then included if they had a bivariate p-value of <0.1 . But then this following sentence makes it sound like a stepwise approach was used to build the model. Please clarify. Overall pre-specifying factors based on the conceptual framework and expert knowledge, augmented by p-value checks, is a better approach than stepwise regression.

Thank you very much for your comment. Now we deleted the phrase "step by step". We have also taken your advice fully and checked the pre-specified factors based on the conceptual framework and expert knowledge augmented by p-value checks. (L 190-193)

A list of potential factors associated with CAS, anaemia, and stunting was identified based on the conceptual framework (Fig 1) and analyzed with multinomial bi-variable regression models. Variables associated with the outcome variable that had a P-value <0.2 in the bi-variable analysis were included in the multivariable analysis to control for possible confounders.

Editor in Chief

1. What this study adds: change to One in six children in Southern Ethiopia had both anaemia and stunting. Food insecurity was associated with co-morbid anaemia and stunting. Amend What is already known in a similar way

Thank you very much we accepted your comment and corrected it as follows (L 345)

What is known about the subject?

One in fourth children 6-24 months of age had anaemia and stunting in Ethiopia based on EDHS. Vitamin A supplementation, consumption of vitamin A rich fruit and vegetables, meat, legumes and meal frequency, low household wealth, low caregivers' education level, male sex, age, history of infection, and small birth size have been found associated with anaemia and stunting in children less than 2 years of age in Ethiopia.

What this study adds

One in six children 2-5 years of age in Southern Ethiopia had co-morbid anaemia and stunting (CAS). Food insecurity, child's age, iron supplementation during pregnancy and father's education status were associated with co-morbid anaemia and stunting in children 2-5 years of age in Ethiopia.

2. Abstract Results clarify age and family size in relation to CAS. I presume it is younger children and larger family size that are risk factors. This needs to be clearly stated.

Thank you very much for the comment. This is now specified, however, we chose to omit information about family size in the abstract as this was only borderline significant and that should be given an extra explanation (L51).

Reviewer: 1

This is a great piece of work. Congratulations to the authors. Below are some comments/recommendations:

Thank you very much for your constructive comments. Based on comments we have changed our analytical approach and present results based on multinomial regression.

1. In the methods section, although information for the sample size calculation is provided, you did not specify what the recommended sample size from the sample size calculation was and whether it was achieved or not, and why.

Thank you very much for this comment. Now we included more information regarding the recommended sample size in the sample size calculation paragraph and emphasized the assumptions for the baseline study as well as presented a post-hoc calculation for the present study. (L117-119)

A post-hoc sample size calculation done for this study was 281 assuming a 24% CAS prevalence, 95% confidence level, and +/-5% margin of error.

2. Please explain the reason for the 2.6% drop-out from the 340 selected children.

Thank you for the comment. We have now explained this at the beginning of the result section. The possible reason for this dropout was that the study involved blood sample collection from children and 9 mothers refused to provide the blood sample of their children. (L.196-198)

From a total of 340 children selected for the study, 331 (97.4%) participated in the study, and 9 (2.6%) of the mothers were refused to provide the written consent as the survey involve blood sample collection from their children.

3. In table 1 the number of children currently breastfeeding does not add up to 331. Was breastfeeding missing for one child? Please edit the methods section to explain whether a complete case analysis was performed or not.

Thank you for your observation. We had some missing information; it was one missing in the breastfeeding and three missings in the father's education variables. We report complete case analysis and we have specified that in the methods section. (L 189-190).

We were also told by the editor not to report missing in the descriptive tables when the numbers were small, we put a footnote which describes that the missing was not reported if <1%.

4. Although the methods section suggests that along with means the standard deviations are reported, in the results section you report 95% CI for the number of people at home. Please be consistent. Moreover, state in the methods section that for all prevalence reported, 95% CIs are provided.

Thank you very much for your comment. We have corrected this and only report 95% CIs for the prevalence estimates (L 182-183) and household size described with proportion (207-208)

5. In table 3 both for child age and for maternal/paternal education please specify what the unit was. I understand that it is years, but it is important to be explicit.

Thank you for the comment. Now we expressed child age in a month and maternal and paternal education status in school years (L 237).

6. What do the asterisks in table 3 mean? Please explain in footnotes. Why non-significant factor (own domestic animals) has an asterisk for the AOR?

Thank you.

Now the asterisk is defined in a footnote and the asterisks are removed from the domestic animal's ownership variable as that was an error (L 237).

7. Throughout the results section, refer to higher/lower odds, not to higher/lower risk. You did not perform a Poisson regression. The estimates are odds ratios, not relative risks.

Thank you very much, we agree. We have now changed the respective comparisons from 'risk' to 'odds'.

8. Have you considered running a multinomial logistic regression instead of three multivariable models (combined outcome, anaemia, stunting)? Would the results be more coherent if you had a combined outcome (0=no anaemia/stunting, 1=anaemia, 2=stunting, 3=anaemia and stunting) using the first category (no anaemia/stunting) as the reference group?

Thank you very much for your comment.

We have taken your advice and changed our analytical approach. We used a multinomial analysis for the four categories (no anemia or stunting, anemia only, stunting only, and anemia and stunting). This would intrinsically "reduce" the numbers for anemia and stunting, so the model presented differs for

those two categories alone, disregarding co-occurrence of the conditions. Of course, the CAS category is similar. The adoption of multinomial analysis made us to change descriptions in the abstract, methods, results and discussion. The changes presented as follows:-

In Method parts: (L 184-189)

Result (L 220-237)

Discussion (L284-292)

Reviewer: 2

Thank you very much for your constructive comments which helped us to improve the manuscript.

Based on your comment we clarified and improved the introduction, sample size, odds ratio reporting and we discussed age as a factor for CAS in the discussion part.

Major concern

1. The authors declared to identify context-based factors that are associated with CAS. However, they identified the common factors which are stated in previously conducted study? what is the contribution this paper for the readers or the scientific community?

Thank you very much. We elaborated more on this in the introduction. The previous study reported only for children less than two years of age and household food insecurity was not stated as a factor. Also, there is a controversial idea that anemia and stunting are independent conditions, so more research is needed on context-based findings in terms of risk factors and co-occurrence (L 93-94)

The previous study in Ethiopia reported an age group of less than two years and the factor also different from our finding. Household food insecurity, father education status, iron supplementation during pregnancy were not associated with the occurrence of co-morbid anaemia and stunting in under two years of age. So our finding produces more information in terms of factors associated with co-morbid anaemia and stunting in children 2-5 years of age. (L 345)

2. This is a part of larger study that aimed to evaluate the efficacy of home processed amaranth grain containing bread in the treatment of anaemia among two-to-five-year-old children in southern Ethiopia. How did the authors validity of the result by including only a singly kebele? The sample size calculation did not consider the second objective (to identify factors of CAS) or the stated sample size may not enough to consider the all factors that the authors want to identify?

Thank you very much for your comment.

a. Yes it is true we selected a single kebele and we mentioned it as one of the limitations of our study. The reason for the selection of a single kebele was due to the experimental study following this study which required sizable recourses, as we were planning to distribute bread daily to those eligible children. Owing to this, we concentrated on a single kebele but we minimized the selection bias by applying random sampling techniques within the kebele (L295-299).

b. We have elaborated more on the sample size calculation and made a post-hoc sample size calculation as if it was done for CAS only. (L116-118).

A post-hoc sample size calculation done for this study was 281 assuming a CAS prevalence 24%, 95% confidence level, and +/-5% margin of error. But we used a sample size of 340 for this study so it could be representative for all dependent variables.

3. Abstract

The associated factors like child age and family size are not explicitly stated. Which age group? What family size?

Thank you very much for the comment. Now we presented categorized child age in the abstract part (L51-53) and family size in the result part (L 207)

4. Method section

How do you see the sample size calculated for measuring co-morbidity of CAS can be used to answer the second objective?

Thank you for the comment. The calculated sample size by considering the anaemia prevalence was higher than that of the expected sample size based on CAS prevalence. Therefore, we believe that the sample size we used was sufficient to represent three of the variables: stunting, anemia, and co-morbid anemia and stunting. (L 115-118)

5. Was the assumption for logistic regression checked?

Thank you for the comment. We have now shifted our approach to a multinomial logistic regression and described the procedures in the methods part. (L186-193)

Before doing multinomial analysis, the dependent variable assumed nominal and mutually exclusive. The dependent variable consists of four nominal categories: 'no anaemia or stunting', 'stunting only', 'anaemia only' and 'stunting and anaemia together' (CAS). The 'no anaemia or stunting' category was set as the reference. Variance inflation factor, variance decomposition proportion and conditional indices were used to test multicollinearity among independent variables.

6. Results

The interpretation of odds ratio is not correct

Thank you for this comment, and we have now corrected this.

7. Why some of the values in Table 3 are omitted? Example

Table 3 is now deleted; however, the category for CAS will remain the same. We only proceeded with variables that had a p-value less than 0.2 in the multivariable analysis.

Also, we are providing supplementary tables that are providing all variables based on COR. (Supplementary Table 1)

Discussion

8. Child age vs CAS is not discussed?

Thank you for the comment, now we discussed it. (L278-283)

We have not seen this in other studies discussing CAS, but this is often reported regarding stunting, and shows more varying results with regard to anaemia.

9. The authors stated that "Our study indicated that stunting prevalence was higher among anaemic children and height for age z-score increased when haemoglobin concentration increased in the children". The above statements is supported with evidence since the authors did logistic regression only for CAS.

Thank you for the comment. Now we removed this part from our study.

Reviewer: 3

Comments to the Author

The study provides sufficient evidence regarding high prevalence of anemia and stunting. it provides insights into an important issue and it is useful to the people who make decisions.

Thank you very much for your constructive comment.

Reviewer: 4

Introduction

Comments to the Author

Title: Co-morbid anemia and stunting among children 2-5 years old in southern Ethiopia: a community based cross-sectional study

Thank you for giving me the opportunity to review this article. The study uses a cross-sectional study

design to determine prevalence and factors associated with co-morbid anemia and stunting among children 2-5 years old in southern Ethiopia: a community-based cross-sectional study. Some specific comments are as follows:

Thank you very much for your constructive comments. We used your comments to improve our manuscript.

1. Abstract

1.1. Line 27 HAZ less than -2 what?? Doesn't give meaning

Thank you for the comment.

Now we added -2 standard deviation. (L 45)

1.2. Better to avoid using abbreviations/acronyms in the abstract section

Thank you. We agree, but we chose to use the term CAS after the introduction as the term is lengthy and we considered that the abbreviation eased reading. We also used standard abbreviations for odds ratio.

2. Introduction

2.1 Since the manuscript is focused on 2-5 years, the first paragraph should emphasize the issue of co-morbid anemia and stunt in this population, but the author focuses on under-five. Add the importance of Co-morbid anemia and stunting in this population groups

Thank you for your comment. Now we added in the first paragraph the prevalence of anemia and stunting of children 2-5years of age but not for CAS as there is no data on the CAS for this age group. (64-66)

We understand the concern around reporting on children under 5, however, as this is the standard age group reported on in global health literature, we kept it in order to inform about the nutritional status in the country.

2.2. The author didn't show the link between anemia and stunting or the interaction of micronutrient deficiency and micronutrient deficiency, instead of reporting prevalence only it's important to show a link between anemia and growth faltering.

Thank you for your comment. We have now referred to a study explaining the described relationship between growth and anaemia (L67-71)

Chronic anaemia has a negative effect on linear growth during all stages of growth (infancy, childhood, and adolescence) and this indicated in the background part of the study.

Micronutrients important for optimal haematological status is also important for optimal growth, however, we chose not to give a physiological explanation as this is very complex and not in the scope of our objective also it is generally understood by a health-oriented audience.

2.3. Justification of the study is not strong enough, limited study isn't sufficient because there are studies done on co-morbid anemia and stunting as the author stated. So the study needs strong justification.

Thank you very much for the comment. We do believe co-morbid anemia and stunting should be investigated in more depth in studies providing that data to get a better evidence base for our understanding. The previous study reported only children less than two years of age and household food insecurity was not stated as a factor. Also, there is a controversial idea that anemia and stunting are independent conditions, so more research is needed both in terms of risk factors and co-occurrence. We have now elaborated more on our justification and referred to the literature showing inconsistent results. (L 92-94) and (L 345)

2.4. The authors need to explain what is unique with the study that differentiates it from other studies

including the EDHS analysis that can also be used to assess co-morbid anemia and stunting including previous studies EDHS, or what this study adds or fill as compared with past studies done on the topic.

Thanks for this comment, we have improved that section. The previous study in Ethiopia reported an age group of less than two years and the factor also different from our finding. Household food insecurity, father education status, iron supplementation during pregnancy were not associated with the occurrence of co-morbid anaemia and stunting in under two years of age in the previous study. So, our finding produces more information in terms of factors associated with co-morbid anaemia and stunting in children 2-5 years of age. This may help us to understand the factors of CAS somehow different in different age groups (L 345)

2.5. Why author focus on these population groups? Because anemia and stunting are the highest among children aged 6-23 months as compared to children 2-5 years.

Thank you for this question. (L 121-124)

Yes, it is true that anemia and stunting are more common in 6-23 months than 2-5 years. The explanation is that we used this study as a baseline for the larger experimental study following it. We selected 2-5 years age group for our experimental study as they would receive bread as part of the intervention. It was therefore necessary that they could chew and accept foods given to them.

4. Please explain why measuring Co-morbid anemia and stunting is important compared to only assessing anemia and stunting since both have almost similar conceptual frame work-UNICEF conceptual framework for malnutrition?

Thank you for this comment.

Yes, it is true that both share similar conceptual frameworks but the prevention strategy different for anemia and stunting. The anemia prevention strategy focuses on the supplementation program whereas stunting focuses on hygiene, diet, and simulation-based approaches. Therefore, we are interested in assessing the prevalence of co-morbidity of the two prevalent nutritional problems in the children and factors associated with it. We explained that in (L81-84)

The syndemic approach not only aggregates anaemia and stunting, but also acknowledges social and environmental factors that exacerbate the occurrence of stunting and anaemia. This approach can be more useful in resource-constrained settings as the prevention strategies focusing on stunting and anaemia differs.

5. Line 48-50: the study area is characterized by poor economic status, inadequate health facilities, poor environmental hygiene and sanitation, and inadequate water supplies should be cited because it is difficult to conclude with such a statement without knowing currently available information regarding the existed services.

Thank you for the comment. We provided more information about the conditions in the study area. We collected secondary information from the socio-economic profile of the area and also conducted a census of the study area prior to the study including field observation.

6. Author used EDHS 2011 prevalence of anemia to estimate sample size for the present study, why the author used this prevalence (EDHS 2011) over EDHS 2016 or recent studies done in the southern region? Plus prevalence of anemia used to estimate sample size took in the population group was 3-5 years why don't you used 2-5 years prevalence?

Thank you very much for this comment. We didn't find the prevalence for this specific age group in the region. So, we used EDHS data; now discussed this further under the limitation section of the discussion. (L 299-302-315)

Also, our sample size calculation based on the EDHS 2011 report since our proposal development and approval did before the release of the 2016 EDHS report. Furthermore, children aged 3-5 years of age were used for sample size calculation as EDHS was not reporting on the age group 2-5 years of age.

7. The study conducted in Cheffe Cote Jebessa Kebele which is a single kebele, but the author mentioned as 1689 2-5 years children were lived in these kebeles. This number is very unlikely and difficult to accept this figure. So the author should describe population demography in the study area and should be cited otherwise it's very difficult taking this large number of children 2-5 years living in one kebeles.

Thank you for your comment.

Before the survey, we conducted a census and we found that figure. As you mentioned the figure exceeds the national or regional average. This was possibly due to the study area which is in the expansion area of Hawssa city and may be characterized as a sub-urban poor area. (L104-107) According to a census we conducted before the start of our study in 2016, the population of the village was 23010 people within 3900 households, 2180 under-five children, and 1689 children aged 2-5 years old.

8. Your exclusion criteria, what do you think about children taking vitamin A or iron supplementation and children taking deworming recently?

Thank you for your comment. As deworming and Vit A is part of the regular national program we did not consider that for our models. We present the cross-sectional frequency but did not include it in our analytical models due to co-linearity and interpretation issues.

9. Operational definition of indicators needs to be explained more clearly. For example, the questions in HFIAS questionnaires need to be explained in general before explaining how to define food secure and insecure households, Please add information on the response rate.

Thank you for this comment. We have explained the HFIAS in more detail and 100% of the participants responded to the question. (L142-151)

10. Anthropometric and hemoglobin data

10.1. Why author used ENA SMART for anthropometric data analysis over WHO Anthro? The author also presents all anthropometric measurement under the descriptive section

Thank you for your suggestion.

We didn't have any special reason to use ENA SMART instead of WHO Anthro. We chose this due to it is user-friendly software. It is using the WHO Growth Standards too, so the results are the same as for the other software.

10.2. The author should describe standard quality control for hemocue analyzer during field setting and describe a detailed procedure for hemoglobin measurement procedure and interpretation protocol. Author state superficially about anemia measurement procedure

Thank you very much for your comment. We have now described this. (L164-169)

Using vein puncture, 3–5 ml of blood was collected by using a lithium heparin plasma separator test tube to measure haemoglobin. The blood was shaken slowly 6-8 times prior to measuring haemoglobin levels, which were determined immediately on-site using a HemoCue analyser 301 (Angelholm, Sweden) the HemoCue analysers were calibrated every morning before the start of data collection. Then haemoglobin corrected for altitudes, according to WHO standards. Anaemia was defined as altitude-adjusted haemoglobin values <11.0 g/dl.

11. Tables: I recommend refining table presentation and try to format to save space, instead of two columns for frequency and % you can put both values in one column n (%).

Thank you. The editor also commented on the tables and they have been adjusted.

Statistical analysis

12. I would like the authors to discuss the validity of their statistical approach ("Bi-variable logistic regression analysis was done to see the association between outcome variables and each independent variable. All covariates with p-value < 0.1 in the bi-variable analysis were entered into multivariable analysis to control possible confounders. The authors should discuss their approach more, with references, and consider revising their methods if they do not match general practice. They should also run sensitivity analyses (how do results vary when all variables are included in one large multivariate model?)

Thank you very much for this comment. We have now redone our analysis in line with other reviewer's suggestions and explained the statistical analysis and rationale for it in detail. Variable selection for the multivariable model is a very good point of discussion but with different suggestions, each with pros and cons. And advisable to consider different aspects at a time, in the current analysis we have followed UNICEF's conceptual framework and variables with $p < 0.2$ in bi-variable analysis to list candidates for the multivariable model. (L 190-193)

13. It is not clear from reading the paper which variables were omitted from the results because they were found to have p-values greater than 0.1 in the bivariate analysis.

Thank you very much for this comment, now we attached the supplementary table which contains all variable computed for bivariate analysis. (Supplementary table 1)

14. Please explain all the variables assessed for determinant analysis? Better to use education status as a categorical variable like in table 2 instead of analyzing continuous, similarly variable measurement in regression analysis is not clear such as maternal age, family size either, is it categorical, continuous or?.

Thank you for this comment. (L 237)

Now we categorized age, family size, and educational status to make it more understandable.

15. Overall authors should describe all variables used in bi-variable analysis and variables used for adjustment should be described with its appropriate measurement.

Thank you for the comment.

Now all variables are described in the supplementary table 1

16. household food security status should be categorized into food secure and insecure because in authors' classification there is a small number in cells (5) which is difficult to estimate the odds of anemia and stunting with this number.

Thank you for the comment, now we categorized it into food secured, mild and moderate food insecurity, and severe insecurity (L237).

17. How did confounders controlled. Did you test interaction effects between variables?

Thank you for your comment. We did not test the interaction effects as we did not expect it, but we checked for collinearity, and thus avoided an excess amount of variables. Also, we adjusted the analysis than taking confounding into account. (1190-193)

18. Discussion

1. Discussion looks like narration and restate the results, the author should rewrite discussion in a more in-depth manner including implication for policymakers and possible mechanism.

Based on your findings what is/are the best recommendation that policymakers should consider for solving the existed problems?

why are these findings important?

Thank you for your comments. We have elaborated our discussion and we are also giving directions for policymakers in our conclusion. (310-313)

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Dr. Peter Flom Institution and Country: Peter Flom Consulting, United States Competing interests: None
REVIEW RETURNED	21-Apr-2021

GENERAL COMMENTS	<p>I confine my remarks to statistical aspects of this paper. While the general approach is appropriate, I do have some issues to resolve before I can recommend publication.</p> <p>The big issue is categorization of variables. It is best not to do this for either dependent or independent variables. I can understand why you did it for the dependent variable, but doing this for independent variables increases type I and type II error rates and introduces a sort of "magical thinking" --- that something amazing happens at the cutoffs. Continuous independent variables should be left continuous. Splines can be used to investigate nonlinearity.</p> <p>For more on this issue see e.g. my paper https://medium.com/@peterflom/what-happens-when-we-categorize-an-independent-variable-in-regression-77d4c5862b6c</p> <p>Specific comments:</p> <p>p 2 line 37 "top two" is not useful. Top two on the basis of what list? Instead, give rates. (also line 88)</p> <p>line 38 Stunting cannot really be said to have an impact on growth, as stunting is defined in terms of growth. Or do you mean later growth? Adult height? Please clarify.</p> <p>p. 3 line 71 "linear" is not a great choice of words here -- it makes it sound like a linear (as opposed to quadratic or something) relationship. Do you mean height?</p> <p>p. 6 line 139 Don't make these groups</p> <p>p. 7 line 149 and line 159 Same comment</p> <p>p. 8 Good to do multinomial logistic regression and to look at collinearity. What were the results of the collinearity diagnostics? How were categorical variables handled? The results seem a bit odd, which could be a result of collinearity.</p> <p>line 190-193 This is known as bivariate screening and it is not recommended. It is best to use substantive knowledge to build the model. But if an automatic method has to be use, LASSO is better than bivariate screening. See e.g. Regression Modeling Strategies by Frank Harrell</p> <p>Table 3 - These results are quite odd. Several variables that are positive for anemia are negative for stunting, or vice versa. For instance, boys are less likely to have anemia with no stunting, but more likely to have stunting with no anemia and more likely to have both. Other variables switch sign when going from the crude to the adjusted model. This seems like some sort of specification error in the model. It might be collinearity (as noted above) or it might disappear if you don't categorize variables.</p> <p>Fig 2 I don't think this Venn diagram is that useful. Better would be a 2x2 table with "stunting yes/no" and "anemia yes/no". However, we can see that anemia and stunting have some relationship. If they were independent, then the proportion with CAS would be the</p>
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	<p>product of that with stunting and that with anemia. $0.32 \times 0.38 = 0.12$, but, actually, 18% (0.18) had both.</p> <p>Even more useful would be a scatterplot of the variables underlying anemia and stunting (that is, hemoglobin and growth z scores).</p> <p>Peter Flom</p>
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VERSION 2 – AUTHOR RESPONSE

Dear Editor and reviewers

We thank the editors and the reviewer for their constructive comments to our manuscript entitled "Co-morbid anaemia and stunting among children 2-5 years old in southern Ethiopia: a community based cross-sectional study".

In the revised manuscript, we have carefully considered the editor's and reviewers' suggestions, and we revised the analysis focusing on variable selection and using continuous variables in the multivariable analysis.

Furthermore, we addressed and responded to each of the points raised by the reviewer and editor. The reviewer's and editor's comments are given below.

With these changes, we would like to resubmit the paper to BMJ Paediatrics Open.

Yours sincerely,

On behalf of all authors

Alemselam Zebdewos Orsango

Hawassa, Ethiopia

Editor in Chief Comments to Author :

Please address the points raised by the statistical reviewer. Apologies for raising additional points, but it is important we get your paper correct before publication. It will be worth it

Thank you.

We have now addressed the additional points raised by the statistical reviewer about categorization, variable selection, and specific comments. We appreciate the statistical review.

Associate Editor

Comments to the Author:

This version of the paper is much improved and getting close. The statistical reviewer has a number of additional suggestions, however, which should be still addressed.

Thank you. The suggestion from the reviewer addressed mainly categorization, variable selection, and choice of model.

A few specific comments:

1. In the introduction, the new sentences about the "controversial idea" of the independence of stunting and anemia is important and should be elaborated a bit.

Thank you for your comment. We have now elaborated more on the idea (L 92-95).

Furthermore, a controversial idea was that a study from Asia reported that anaemia and stunting are independent conditions opposing a systematic review from low- and middle-income countries recommending that stunting and anaemia should be considered as a syndemic.

2. The statistical reviewer raises concerns about bivariate screening to build the model, and I raised a similar concern in the first round of reviews. It does seem that you've mostly used conceptual framework/knowledge to build your model, as you address in the response letter, but please double

check that nothing odd is being included just because of a p value. This is important because some of your coefficients are unexpected (as the stats reviewer notes) so make sure nothing is misspecified/included that doesn't have a good theoretical or practical reason to be in the model.

Thank you. We have now addressed the reviewer's comments specifically on variable selection. First we selected variables based on the conceptual framework. Then we used LASSO technique to screen variables (Line 184-188)

Twenty-three potential factors associated with CAS were identified based on a conceptual framework (Fig 1), and then ten variables were selected according to minimum lambda with using least absolute shrinkage and selection operator (LASSO) for multinomial logit model this was implemented using glmnet package of R (Supplementary Table 1).

Reviewer: 1

Dr. Peter Flom, Peter Flom Consulting

Comments to the Author

I confine my remarks to statistical aspects of this paper. While the general approach is appropriate, I do have some issues to resolve before I can recommend publication.

The big issue is categorization of variables. It is best not to do this for either dependent or independent variables. I can understand why you did it for the dependent variable, but doing this for independent variables increases type I and type II error rates and introduces a sort of "magical thinking" --- that something amazing happens at the cutoffs. Continuous independent variables should be left continuous. Splines can be used to investigate nonlinearity.

For more on this issue see e.g. my paper <https://medium.com/@peterflom/what-happens-when-we-categorize-an-independent-variable-in-regression-77d4c5862b6c>

Thank you. Now we used all continuous variables as continuous (paternal education, mother age, meal frequency, child age and household family size) as continuous independent variables. (Line 230)

Specific comments:

1. p 2 line 37 "top two" is not useful. Top two on the basis of what list? Instead, give rates. (also line 88)

Thank you now we corrected.

- In Ethiopia 38% of children, less than five years of age were stunted and 57% were anaemic. (L 37)
- Line 88. The comment is important, but now when we have given figures it may become a repetition if repeat it.

2. line 38 Stunting cannot really be said to have an impact on growth, as stunting is defined in terms of growth. Or do you mean later growth? Adult height? Please clarify.

Thank you. We accept your comment and we have specified that stunting (which is correctly used for children < 5 years of age) has an impact on physical growth later in life (Line 38)

Both have a negative impact later in life on physical growth and cognitive development and often co-exist.

3. p. 3 line 71 "linear" is not a great choice of words here -- it makes it sound like a linear (as opposed to quadratic or something) relationship. Do you mean height?

As we know the literature linear growth is often used as opposed to ponderal growth, but we replaced it with 'physical growth' now which we hope you find acceptable (Line 69).

4. p. 6 line 139 Don't make these groups, p. 7 line 149 and line 159 Same comment

Thank you, deleted.

5. p. 8 Good to do multinomial logistic regression and to look at collinearity. What were the results of the collinearity diagnostics? How were categorical variables handled? The results seem a bit odd, which could be a result of collinearity.

Thank you. We considered your comment on variable screening to use LASSO for the multinomial logit model. Lasso considers the multicollinearity, however, we rechecked multicollinearity that we didn't present to minimize redundancy. (Line 184-188)

6. line 190-193 This is known as bivariate screening and it is not recommended. It is best to use substantive knowledge to build the model. But if an automatic method has to be use, LASSO is better than bivariate screening. See e.g. Regression Modeling Strategies by Frank Harrell

Thank you. It is true that the automatic method for variable selection is decreases multicollinearity. So we did LASSO for the multinomial logit model to select independent variables. (Line 184-198)

Twenty-three potential factors associated with CAS were identified based on a conceptual framework (Fig 1), and then ten variables were selected according to minimum lambda with using least absolute shrinkage and selection operator (LASSO) for multinomial logit model this was implemented using glmnet package of R (Supplementary Table 1).

7. Table 3 - These results are quite odd. Several variables that are positive for anemia are negative for stunting, or vice versa. For instance, boys are less likely to have anemia with no stunting, but more likely to have stunting with no anemia and more likely to have both. Other variables switch sign when going from the crude to the adjusted model. This seems like some sort of specification error in the model. It might be collinearity (as noted above) or it might disappear if you don't categorize variables.

Thank you. Now we used all continuous variables without categorization (paternal education, meal frequency, child age, and household family size) (Line 230). But variables that are positive for anemia and negative for stunting or vice versa remain the same it is maybe due to sample size. Since our main outcome variable is stunting with anemia we focused on that.

8. Fig 2 I don't think this Venn diagram is that useful. Better would be a 2x2 table with "stunting yes/no" and "anemia yes/no". However, we can see that anemia and stunting have some relationship. If they were independent, then the proportion with CAS would be the product of that with stunting and that with anemia. $0.32 \times 0.38 = 0.12$, but, actually, 18% (0.18) had both. Even more useful would be a scatterplot of the variables underlying anemia and stunting (that is, hemoglobin and growth z scores).

Thank you for your observation. Present with table 3 (L 216)