Title: Anemia etiology in Ethiopia: assessment of nutritional, infectious disease, and other risk factors in a population-based cross-sectional survey of women, men, and children

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Short title: Anemia etiology in Ethiopia

Abbreviations:

AnemEE, Anemia Etiology in Ethiopia
CRP, C-reactive protein
EFCT, Ethiopian Food Composition Table
pPAR%, partial population attributable risk percentage
RR, risk ratio
SNNP, Southern Nations Nationalities and Peoples
WHO, World Health Organization

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Abstract

Background: While the causes of anemia at an individual level (such as certain nutritional deficiencies, infections, and genetic disorders) are well defined, there is limited understanding of the relative burden of anemia attributable to each cause within populations.

Objective: To estimate the proportion of anemia cases attributable to nutritional, infectious disease, and other risk factors among women, men, and children in six regions of Ethiopia.

Methods: A population-based cross-sectional study was conducted. Data were obtained from 2,520 women of reproductive age (15-49 years), 1,044 adult men (15-49 years), and 1,528 children (6-59 months). Participants provided venous blood samples for assessment of hemoglobin concentration, ferritin, folate, vitamin B12, C-reactive protein, and malaria infection. Stool samples were collected to ascertain helminth infection status. Sociodemographic questionnaires and a 24-hour diet recall were administered. Population-weighted prevalences of anemia and risk factors were calculated. Multivariable-adjusted associations of risk factors with anemia and partial population attributable risk percentages (pPAR%) were estimated using generalized linear models.

Results: Anemia prevalence was 17% (95% CI: 13%, 21%) among women, 8% (6%, 12%) among men, and 22% (19%, 26%) among children. Low serum ferritin contributed to 11% (-1%, 23%) of anemia cases among women, 9% (0%, 17%) among men, and 21% (4%, 34%) among children. The proportion of anemia attributable to low serum folate was estimated at 25% (5%, 41%) among women and 29% (11%, 43%) among men. Dietary iron intake was adequate for nearly all participants, while inadequacy was common for folate and vitamin B12. Inflammation and malaria were responsible for less than one in ten anemia cases.

Conclusions: Folate deficiency, iron deficiency, and inflammation appear to be important contributors to anemia in Ethiopia. Folic acid food fortification, targeted iron interventions, and strategies to reduce infections may be considered as potential public health interventions to reduce anemia in Ethiopia.

Key words/phrases: anemia, etiology, Ethiopia, folate, iron, infection, population attributable percentage

Introduction

Anemia remains a major public health challenge in low- and middle-income countries. In 2016, an estimated 44.6% of children aged <5 years and 35.1% of non-pregnant women aged 15-49 years globally were anemic.(1) Anemia is associated with increased mortality among children and pregnant women, impaired cognitive development among children, and reduced productivity among adults.(2-5) As a result, it was estimated that in 2010 anemia was responsible for 8.8% of global years lived with disability, more than major depression, chronic respiratory disease, or injuries.(6)

The underlying causes of anemia at the individual-level are relatively well-understood, including nutritional deficits (e.g. iron, folate, vitamin B12, vitamin A), infections (e.g. malaria, hookworm, HIV), and hemoglobinopathies (e.g. thalassemias, sickle cell).(7) However, it is important for public health policy-makers to understand the relative contribution of each of these causes at the population level when planning programs and allocating resources. Modeling studies have attempted to identify the proportion of anemia cases in the population attributable to each cause by assembling data from multiple sources on risk factor prevalence and the strength of the association between the risk factor and anemia.(6) However, it is rare for

population-representative participant-level data on multiple risk factors to be collected in a single study and used to directly estimate the proportion of anemia cases due to each cause. It is well known that with multi-factorial diseases such as anemia, attributable risk estimates are biased when only one risk factor at a time is considered.(8)

In Ethiopia, several studies have collected countrywide data on anemia prevalence or some risk factors, but there is no study which contains a broad set of biomarkers, infection, diet, and socioeconomic data, nor which estimates the proportion of anemia attributable to each cause. The 2015 Ethiopian National Micronutrient Survey collected blood specimens to assess the prevalence of anemia and serum micronutrient levels but did not assess diet and some infectious causes of anemia.(9) The 2013 Ethiopian National Food Consumption Survey administered a 24-hour dietary recall questionnaire to participants to estimate iron and other nutrient intake, but hemoglobin and non-dietary risk factors for anemia were not assessed.(10) The 2016 Demographic Health Survey assessed anemia prevalence and malaria, but not micronutrient status.(11) As a result, gaps in data availability in each of these surveys has not allowed for a complete and valid assessment of the contribution of diet, micronutrient status, infections and other risk factors jointly to anemia prevalence in Ethiopia.

This population-based study assessed the prevalence of anemia along with risk factors including dietary intake, nutritional and infectious disease blood biomarkers, malaria and helminth infections, and socioeconomic factors among women of reproductive age, adult men, and children 6-59 months in six regions of Ethiopia. The relative contribution of risk factors to the burden of anemia was estimated in order to inform decision-making on anemia control strategies.

Methods

Study population and sampling

The Anemia Etiology in Ethiopia (AnemEE) study is a population-based cross-sectional study conducted among women, men, and children. Detailed methods of the survey have been published elsewhere.(12) Sampling was

stratified across six regions (Addis Ababa, Afar, Amhara, Oromia, Southern Nations Nationalities and Peoples [SNNP], and Tigray). The six regions included in the study are estimated to account for 91% of the total population of Ethiopia.(13) Within each region a multi-stage sampling design was employed using administrative divisions (zones, woredas, and kebeles). Households were randomly selected within each kebele and were eligible for inclusion if they included a woman of reproductive age (15-49 years; pregnant women were not excluded). A target sample size of seventeen women of reproductive age, seven men (15-49 years), and ten children (6-59 months) were selected for data collection in each kebele. The total sample size was selected to have regionally representative anemia estimates for children, adult women, and adult men in the six selected regions. The assumptions used to calculate sample size were: anemia prevalence (by age, sex, and region) equal to the 2016 Demographic and Health Survey, 10% precision overall, 90% participation at the household, 90% participation at the individual-level, and a design effect of 2.0. The survey was undertaken twice in the same kebele – once from January to March 2019 and again from June to August 2019 and included different participants from each kebele by round to capture seasonal variation.

Data collection

Data were collected via a standardized questionnaire, 24-hour diet recall and blood and stool collection. Questionnaires were administered by trained enumerators following standard operating procedures and using tablet-based software (Survey CTO, Dobility Inc, Cambridge MA). Data quality was ensured through random spot-checks performed by field supervisors and by central-level weekly monitoring of data submissions. Blood and stool samples were collected by experienced phlebotomists and fieldworkers.

A household questionnaire was administered to collect information on sociodemographic characteristics, household infrastructure, health behaviors, and morbidity. Diet was assessed using a 24-hour recall tailored to the dietary characteristics of Ethiopia. A multiple-pass method was used to maximize recall accuracy of items consumed, their quantity, and their preparation method.(14) A second 24-hour recall was administered to a subset of participants to assess diet variability.(15) Venous blood was collected; 2 mL were used to assess

hemoglobin level and malaria infection and 5 mL were used to measure serum concentrations of ferritin (an indicator of iron deficiency), C-reactive protein (CRP; an indicator of inflammation), folate, and vitamin B12. Due to the constraints of specimen collection in community settings it was not possible to have participants fast before blood was drawn or to have blood drawn at the same time of day for all participants, although any diurnal variations in blood markers would likely result in non-differential measurement error. Participants who refused a blood draw were requested to provide finger-prick capillary blood to assess hemoglobin status. Stool samples were collected to assess the presence of intestinal helminths. Since household eligibility was based on the presence of a woman of reproductive age, a larger number of women of reproductive age were contacted than was needed in order to achieve the target sample size for men and children. For the women who fell above the target sample size for serum nutrient analysis (approximately half of women in each kebele), questionnaire-based data and a venous blood sample for hemoglobin and malaria assessment were collected.

Defining anemia and risk factors

Hemoglobin values were assessed using HemoCue 201+ analyzers (HemoCue AB, Angelholm, Sweden). Hemoglobin values were adjusted for altitude using a regression approach and then categorized as anemic according to World Health Organization (WHO) cutoffs; cutoffs used in this study are provided in **Supplementary Table 1**.(16, 17) Serum ferritin concentrations were adjusted for inflammation (measured by CRP).(18) Serum folate and serum vitamin B12 were categorized as low according to WHO criteria and standard clinical guidance, respectively, and serum ferritin was categorized as low or high according to WHO criteria.(19-21) Inflammation was defined using CRP >5 mg/L.(22) Presence of malaria infection (due to either P. falciparum or P. vivax) was assessed using a rapid diagnostic test (CareStart™ Malaria HRP2/pLDH [Pf/Pv] COMBO). Microscopic evaluation of Kato–Katz slides of stool specimens were examined for the presence of intestinal helminths and categorized as helminth-infected if they contained ova for roundworm (Ascaris lumbricoides), hookworm (Ancylostoma duodenale), whipworm (Trichuris trichiura), or tapeworm (Hymenolepis nana or Taenia species).

Dietary intake was assessed using the food items and quantities reported in the 24-hour recall. Nutrient intake was calculated by matching the consumed food items and their quantity to a dataset based on the Ethiopian Food Composition Table (EFCT).(23) For nutrient values not listed in the EFCT, food composition tables from Uganda, Tanzania, and the United States were used.(24-26) The value for iron content in injera – a commonly consumed food item and important source of iron – was taken from a study that accounted for soil contamination that occurs during teff grain processing.(27) Cutoffs for inadequate nutrient intake of iron, folate, and vitamin B12 were defined as consumption less than the age- and sex-specific Estimated Average Requirement of nutrient intake and assuming a low bioavailability of iron absorption (5%).(28)

Heavy menstruation is a risk factor for anemia among women of reproductive age.(29) Women were asked three questions based on a previously validated questionnaire: how heavy they perceived their period to be, how much pain they experienced, and the duration of their period.(30) These questions were combined into a single variable using principal components analysis and the highest ten percent of this new variable were classified as having heavy menstruation. Symptoms of diarrhea, cough, and fever during the previous two weeks were self-reported for adults or reported by the caregiver for children. Use of an unimproved source of water and unimproved sanitation was defined according to criteria by the WHO.(31) An asset index was calculated by conducting principal components analysis using a list of items owned by households and then dividing participants into quintiles. Data collection occurring between June and August was defined as the wet season for all regions except Afar, where the climate was hot and dry during this period.

Ethics

The AnemEE protocol was approved by the Harvard T. H. Chan School of Public Health Institutional Review Board (Ref. No. IRB18–0236) and the Addis Continental Institute of Public Health Institutional Review Board (Ref. No. ACIPH/IRB/005/2018). A support letter was also obtained from the Ethiopian Federal Ministry of Health (Ref. No.1/49/44/671). All adult participants were asked to provide written informed consent for study participation. Mothers or guardians provided informed written consent for children.

Statistical analysis

The prevalence of overall anemia by region and season for women, men, and children was estimated. The prevalence of mild, moderate, and severe anemia was also estimated by region. Standard errors were adjusted for correlated outcomes (within kebeles, woredas, and zones) and for stratification by region and season. Estimates of anemia prevalence aggregated across all six regions were weighted according to their relative age and sex-specific population sizes.(13) The prevalence of risk factors in the weighted sample was calculated among both anemic and non-anemic participants and compared using Pearson's design-based F statistic. Possible bias due to missing dietary and specimen collection among participants was accounted for using inverse probability of censoring weights (see **Supplementary Methods 1** for details).(32)

Estimates of usual diet were calculated using the Iowa State University methodology for prevalence measures, and based on mixed regression models for risk ratios and partial population attributable risk percentages (pPAR%).(33, 34) Estimates of usual dietary intake were obtained by estimating within- and between-person variation in intake by participant type and calculated using data from repeat 24-hour recalls taken for a subset of the sample (n=309, 6.3% of the total sample). Additional information on the methods and results of usual dietary intake estimation are presented in **Supplementary Methods 2**. Confidence intervals for these nutrient analyses using predicted values of usual diet were calculated using bootstrapping (see **Supplementary Methods 3** for details).(35) The prevalence of inadequate intake of iron was nearly zero, and the prevalence of inadequate vitamin B12 was nearly one hundred percent, so binary cutoffs for dietary intake were not used in the model for these nutrients. Instead, quartiles of nutrient intake adjusted for total energy intake using the residual method were used.(36) For iron and vitamin B12 intake, risk ratios and pPAR% were calculated comparing the lowest three quartiles of consumption to the highest quartile, whereas for folate a binary indicator defined by the Estimated Average Requirement was used.

Risk ratios for the association of risk factors with anemia were calculated using generalized linear models with a log link, Poisson distribution, and robust standard error.(37) Clustering due to the complex survey sampling

design was accounted for using Stata's "svyset" command applying standard methods.(38, 39) A proximal, medial, and distal risk factor model was estimated for each participant type (women, men, and children; **Figure 1**). The proximal model – which contains risk factors that most immediately precede anemia (serum biomarkers and infections) – includes only participants with complete blood and stool data. The medial models include intermediate risk factors (such as usual diet and morbidity symptoms) and the distal models include socioeconomic risk factors (such as sanitation and assets) plus age. Medial and distal models include participants with hemoglobin data. All estimates are adjusted for the other risk factors in the model. To control for potential confounding, the proximal and medial models each include all risk factors included in the distal model. Partial population attributable risk percentages were estimated from multivariate models.(40, 41) Risk ratios and pPAR% were weighted to represent the population distribution aggregated across the six sampled states.(13)

Results

There were 2,520 women, 1,044 men, and 1,528 children who consented for study participation and completed a household questionnaire (**Figure 2**). Among these, 2,229 women (88%), 917 men (88%), and 1,162 children (76%) had hemoglobin concentration data. Among women, 1,274 were randomly selected for serum micronutrient and inflammatory biomarker specimen collection while all 917 men and 1,162 children were eligible for biomarker assessment. Stool samples were obtained for 891 women, 674 men, and 796 children (respectively, 70%, 74%, and 73% of those eligible for stool collection). Among women included in the study, 192 (8.6%) reported that they were pregnant.

The prevalence of anemia among women was 14.9%, among men was 8.1%, and among children was 22.0% (**Table 1**). No statistically significant differences in anemia prevalence were observed by season (**Supplementary Table 2**). Significant differences were observed between regions among women, with Afar showing the highest prevalence. The majority of anemia cases were mild (**Supplementary Table 3**). The

prevalence of iron deficiency anemia (i.e. concurrent anemia and low serum ferritin) was 3.7% in women, 1.4% in men, and 9.5% in children (**Supplementary Table 4**). When excluding pregnant women from the analysis, the prevalence of anemia among women was 15.2% (**Supplementary Table 5**).

Analysis of serum samples demonstrated that folate deficiency was the most common micronutrient deficiency identified among women (41.2%) and men (39.3%), and was also common among children (21.3%; **Table 2**). The prevalence of low serum ferritin, an indicator of iron deficiency, was 25.3% among children and 13.8% among women, but not as high among men (4.6%). Low serum vitamin B12 was prevalent in about one in four adults and one in five children. High levels of inflammation were seen in 7-8% of women, men, and children. Malaria prevalence was uncommon, appearing in less than 2% of the population. Helminth infections were also rare, appearing in 5% or less of the population. Inadequate amounts of folate were consumed by 42% of women, 30% of men, and 26% of children. Inadequate dietary vitamin B12 consumption was observed in 100% of women, 98% of men, and 40% of children. The prevalence of risk factors varied by region (**Supplementary Table 6**). Mean intakes of dietary intake of iron and folate appear in **Supplementary Table 7.** High dietary iron consumption is presented in **Supplementary Table 8**.

The proximal model examined the association and contribution to anemia of serum biomarkers and infections. After adjustment for other risk factors in the proximal model for anemia among women, positive associations were observed between anemia and low serum ferritin, low serum folate, high CRP, and malaria; **Table 3**. The same set of risk factors were found in the proximal risk factor model for men (**Table 4**). For children, low serum ferritin, low serum folate, and high C-reactive protein were associated with increased risk of anemia (**Table 5**).

After adjustment for other proximal risk factors and potential confounders, the proportion of anemia estimated to be attributable to low serum ferritin among women was 11%, among men was 9%, and among children was 21%. Low serum folate was estimated to contribute to more than a quarter of anemia cases among women and men. High CRP contributed to about one in ten anemia cases among women and men, and

to one in twenty anemia cases among children. While malaria had strong relative risks for anemia among women and men, the low prevalence of malaria at the population-level resulted in only 3% of anemia cases attributed among women and 8% attributed among men. Low serum vitamin B12 was found to have a protective association with anemia among women and men. Risk factors in the proximal model that were significantly associated with increased anemia were together responsible for 34% of anemia cases among women, 42% among men, and 25% among children (**Supplementary Table 9**).

The medial model examined the contribution of dietary and morbidity risk factors. After adjustment for other medial risk factors and potential confounders, dietary intake of iron, folate and vitamin B12 were not associated with the risk of anemia for any participant group. Anemia was associated with cough among women and diarrhea among children. Heavy menstruation was not found to be an anemia risk factor among women.

The distal risk factor model examined the relation of socioeconomic, geographic, and seasonal variables with anemia. Water and sanitation were found to be important factors for adults. Use of an unimproved water source among women and use of unimproved sanitation among men were associated with increased anemia. For proximal, medial, and distal risk factors among women, men, and children, similar results were obtained in sensitivity analyses that did not adjust anemia for altitude (**Supplementary Table 10**). Similar results for anemia etiology were also observed after excluding pregnant women from the analysis (**Supplementary Table 11**).

Discussion

This population-based cross-sectional survey is among the few studies to estimate the proportion of anemia attributable to risk factors using individual-level data. The study found that more than a quarter of anemia cases among men and women across the six study regions were estimated to be attributable to low serum folate. Low serum ferritin, an indicator of iron deficiency, was associated with about one in ten cases among adults and one in five cases of anemia among children. Based on 24-hour recall data, nearly all men, women

and children met the recommended dietary intake levels for iron, while inadequate intake of folate and vitamin B12 was relatively common. Inflammation was also a contributor to anemia among women and children, although malaria and soil-transmitted helminths infections did not contribute to a large share of anemia cases.

Fourteen percent of women, 5% of men, and 25% of children had low serum ferritin (after adjustment for inflammation), an indicator of iron deficiency. These figures are similar to those found in the nationally-representative Ethiopian National Micronutrient Survey conducted in 2015.(9) Iron deficiency can result from blood loss, inadequate dietary iron intake, or insufficient absorption. Helminth infection prevalence was low and not associated with anemia, which suggests that this is not a substantial cause of blood loss. The prevalence of inadequate dietary iron intake using the WHO recommended daily intake was virtually zero for men, women and children. In fact, iron intake in the study population (55.1 mg/d for women, 63.3 mg/d for men, and 29.5 mg/d for children) is quite high from a global perspective (for example, iron intake in this study is two to three times higher than the average daily intake from food in the United States).(42) Yet low serum ferritin explained 9-21% of anemia (depending on the participant group), which suggests that efforts to improve dietary iron absorption could be important interventions to reduce anemia. This apparent disparity between the findings for serum ferritin and dietary iron may be explained by poor bioavailability of consumed iron. Inadequate absorption could result from high levels of inhibitors such as phytate and polyphenols which are present in many plant-based Ethiopian foods, or from low levels of meat, fish, and poultry consumption.(43) Fortification of staple food items with iron is a common policy intervention globally to improve iron status, but is not currently implemented at scale in Ethiopia. It is critical that a population-level intervention such as fortification does not result in iron overload among individuals who already consume adequate iron. Data from this study shows that 5.0% of women and 8.9% of men had excess levels of serum ferritin; in Addis Ababa and Tigray high serum ferritin was seen among approximately one in four men (**Supplementary Table 12**). Clinical sequelae and tissue damage due to iron overload typically occur at levels

significantly above the WHO criteria for high serum ferritin (e.g. SF 500>μg/L); only 1 woman (0.1%) and 8 men (0.9%) in the study population had serum ferritin above this threshold. Nevertheless, population-based interventions to increase iron intake (like iron fortification) may place those who already have elevated levels of SF at greater risk of clinical sequelae.(44) Targeted interventions – such as point-of-use iron fortification for children or iron supplementation for women – could be pursued as an alternative to population-based strategies.(45, 46)

Low serum folate was highly prevalent among women (41%), men (39%), and children (21%). By contrast, the Ethiopian National Micronutrient Study found that only 17% of women had low serum folate; the reason for this discrepancy is unclear.(9) Among women and men, low serum folate was associated with increased anemia, and was estimated be responsible for approximately a quarter of anemia cases. Notably, no significant risk of anemia was associated with low serum folate among children, which is why low serum folate did not explain a significant proportion of anemia among children despite the fact that 21% of children had low serum folate. Dietary assessment of folate consumption indicated that 26-42% of participants consumed inadequate quantities. As a result, food fortification with folic acid may be warranted as a national strategy to control anemia across all groups. In addition to benefits for anemia reduction, interventions to improve folate status are likely to improve other health outcomes such as neural tube defects and stroke, which are also notable public health problems in Ethiopia.(47-51) Dietary interventions may also be considered. For example, behavior-change communication to promote cooking legumes (an important source of dietary folate) for short periods of time without pre-soaking, or the consumption of steamed as opposed to boiled vegetables.(52-54)

Low serum vitamin B12 was observed in 20-26% of women, men and children, and participants reported negligible dietary intake of vitamin B12 on most recall days. Vitamin B12 is primarily found in animal food products (such as meats, eggs, and dairy), which all participant groups reported having rarely consumed; as a result, estimates of insufficient dietary intake of vitamin B12 (which were higher than levels of low serum vitamin B12) may be overestimated, due to a limited number of repeated 24-hour dietary recalls. Vitamin B12

deficiency is an established cause of macrocytic anemia, and therefore our finding that low serum B12 was associated with a reduced risk of anemia among women and men is counterintuitive. A potential explanation is that serum vitamin B12 concentrations were confounded by an unmeasured variable. Milk, which contains vitamin B12, has been noted as a potential cause of anemia among children due to mechanisms (i.e. the inhibition of non-heme iron absorption by calcium and casein) that may apply to adults as well, so this may be a confounder.(55) As a sensitivity analysis, a binary indicator of milk consumption was added to the proximal models, but this did not substantially attenuate the association between serum vitamin B12 and anemia. Another alternative explanation is that households raising livestock, and hence more likely to have better vitamin B12 status, may be exposed to environmental pathogens resulting in environmental enteric dysfunction and anemia.(56) Nevertheless, the biomarker data suggest that vitamin B12 deficiency does not appear to be a major contributor to anemia in Ethiopia.

Inflammation (as measured by high CRP) was found among less than one in ten participants and was associated in multivariate models with an increase in the risk of anemia among women and children. This study's findings on the proportion of children with elevated CRP are similar to those of the Ethiopian National Micronutrient Survey.(9) Overall, 10% of anemia cases among women and 5% among children were attributed to this cause. CRP is associated with the acute phase of inflammation, may be an indication of subclinical infection, and peaks especially with bacterial infections.(57) Tuberculosis infection can cause increased levels of CRP and anemia, but the low prevalence of active tuberculosis infections (0.3%) suggests this is not a primary cause of inflammation in the population.(58) Bacterial causes of bloody diarrhea (such as E. coli or Shigella) or other infections may be a more plausible explanation.

The burden of malaria and helminth infection was found to be low among men, women, and children. Malaria was strongly associated with anemia in adults, but due to the low prevalence of infection at the population-level only 3% of anemia cases in women and 8% in men were estimated to be attributable to malaria.

Helminth infections were not found to be associated with anemia in this study. However, prior research has

shown that deworming programs are associated with significant improvements in hemoglobin.(59) Ethiopia has programs for deworming and malaria control with high levels of population coverage.(60, 61) Although malaria and helminth infections are not currently major contributors to the existing burden of anemia in the country, current programs should be maintained to prevent a potential increase in anemia due to these causes. We also found that social determinants were important contributors to anemia risk, as has been observed in other studies.(62) Socioeconomic risk factors were associated with a significant proportion of anemia cases, including use of an unimproved water source for women and unimproved sanitation for men. These findings emphasize that poverty reduction and increased access to improved water and sanitation are potential interventions to produce reductions in anemia.

A major strength of this study is that it was population-based, so the distribution of risk factors represents the target population for public health interventions. Furthermore, data on multiple risk factors and covariates was collected, which enhances the ability to disentangle the individual contributions to anemia of multiple correlated risk factors. Serum nutrient data was collected in addition to dietary intake, which allowed for a comparison of results between nutrition indicators. A limitation is that the cross-sectional nature of this study cannot identify whether the measured risk factors occurred before the outcome of anemia; however, the risk factors evaluated in this study have been established as causes in prior research, and it is generally unlikely that anemia would have caused any of these risk factors. Another limitation is that dietary assessment methods which use reference values for the nutritional content of foods may be subject to error, as recipes and preparation methods can vary between households. This study used a set of standard Ethiopian recipes to calculate nutrient intake. Furthermore, serum biomarkers taken at a single time point may be subject to measurement error relative to their usual value. Finally, tests of genetic causes of anemia were not done for this study, though the prevalence of sickle cell and thalassemias in Ethiopia is low.(63, 64)

This study estimated that proximal risk factors explained 25% of all anemia cases among children, 34% among women, and 42% among men. One potential reason that a large proportion of cases remained unexplained is

the use of binary cutoffs for risk factors, since biological mechanisms of causality are rarely binary; however, binary cutoffs are often used in clinical practice and to maintain statistical modelling parsimony. A second reason could be unmeasured interactions between risk factors, which can impact estimates of the pPAR%. Finally, some risk factors that were not included in this analysis, such as vitamin A, may play a role in anemia in Ethiopia.

Folate deficiency, iron deficiency, and inflammation are important contributors to anemia in Ethiopia to varying degrees among men, women and children. Folate fortification in Ethiopia could lead to enhanced folate status and result in reduced risk of anemia and other adverse health outcomes. Targeted iron supplementation, particularly for women and children, should be considered as means to address anemia. Behavior change interventions to improve dietary intake of bioavailable nutrients and address social determinants of anemia are also important. While the risk factors identified in this study are supported by prior research and are generalizable to other contexts, analyses such as this study are critical in order to identify the key factors that contribute to anemia etiology for a specific context. As a result, other countries beyond Ethiopia will likely benefit from carrying out similar studies of anemia etiology.

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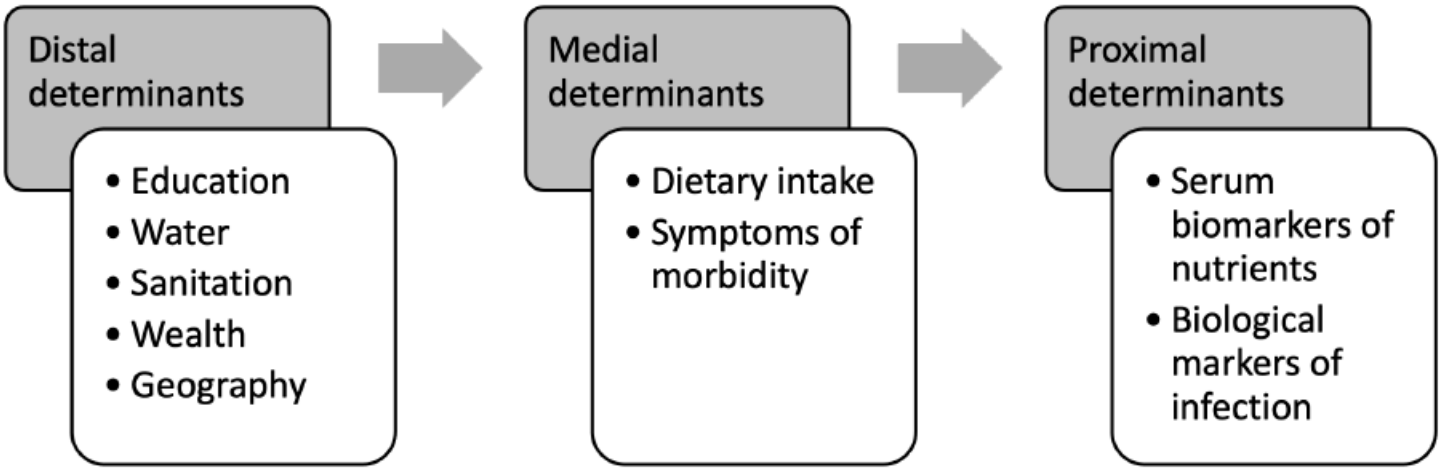

Figure 1. Conceptual framework for analysis of anemia etiology among women 15-49 y, men 15-49 y, and children 6-59 mo in Ethiopia.

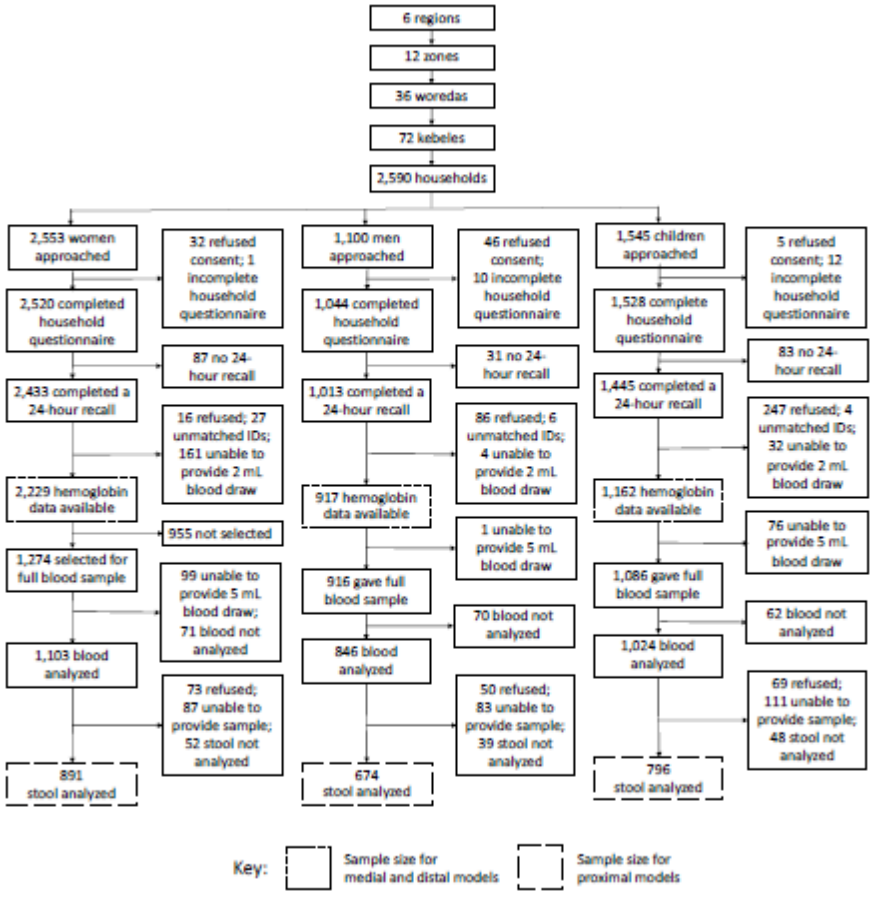

Figure 2. Flowchart of participant data collection and study inclusion for study of anemia etiology among women 15-49 y, men 15-49 y, and children 6-59 mo in Ethiopia.

Table 1. Prevalence of anemia in Ethiopia among women aged 15-49 y, men aged 15-49 y, and children aged 6-59 mo by region and time of data collection.[1]

		Overall				Dry season				Wet season		
Participant	**Region**	*n anemic*	*n total*	*weighted % (95% CI)*		*n anemic*	*n total*	*weighted % (95% CI)*		*n anemic*	*n total*	*weighted % (95% CI)*
Women	All regions[2]	376	2229	14.9 (11.0, 19.8)		192	1136	12.1 (9.1, 15.9)		184	1093	17.7 (11.1, 26.9)
	Addis	36	378	9.6 (7.9, 11.7)		20	175	11.5 (11.1, 11.8)		16	203	7.9 (4.9, 12.5)
	Afar	135	371	36.8 (33.0, 40.7)		79	183	43.6 (39.2, 48.1)		56	188	29.9 (23.4, 37.3)
	Amhara	52	357	14.7 (6.5, 29.9)		24	193	12.6 (7.3, 20.8)		28	164	16.8 (4.1, 48.8)
	Oromia	58	368	16.7 (10.3, 25.9)		22	191	11.8 (6.8, 19.6)		36	177	21.5 (11.2, 37.3)
	SNNP	44	404	10.8 (7.6, 15.1)		17	200	8.3 (3.4, 19.0)		27	204	13.4 (11.6, 15.7)
	Tigray	51	351	15.1 (12.8, 17.6)		30	194	15.4 (12.7, 18.5)		21	157	14.8 (11.3, 19.0)
Men	All regions[2]	87	917	8.1 (5.7, 11.5)		46	467	7.8 (5.8, 10.4)		41	450	8.5 (4.5, 15.5)
	Addis	3	125	2.2 (0.9, 5.5)		1	52	1.8 (0.2, 14.8)		2	73	2.7 (0.6, 11.3)
	Afar	25	187	12.8 (7.5, 20.9)		16	94	17.0 (9.3, 29.1)		9	93	9.5 (3.5, 23.0)
	Amhara	14	148	9.3 (7.9, 11.0)		9	81	10.9 (5.7, 19.8)		5	67	7.4 (2.7, 18.9)
	Oromia	8	151	5.6 (1.6, 17.8)		4	81	5.3 (2.1, 12.7)		4	70	5.9 (1.6, 19.1)
	SNNP	18	162	10.9 (8.7, 13.6)		7	82	8.5 (3.5, 18.9)		11	80	13.5 (6.8, 25.1)
	Tigray	19	144	13.6 (6.1, 27.7)		9	77	12.3 (5.7, 24.8)		10	67	15.4 (6.2, 33.3)
Children	All regions[2]	267	1162	22.0 (18.5, 25.9)		124	566	20.7 (14.5, 28.7)		143	596	23.1 (20.3, 26.2)
	Addis	29	135	20.9 (12.5, 32.7)		7	42	17.2 (5.4, 43.2)		22	93	23.4 (14.4, 35.8)
	Afar	67	216	31.3 (17.6, 49.4)		36	120	30.2 (13.8, 54.0)		31	96	32.7 (13.0, 61.2)
	Amhara	47	202	23.4 (20.7, 26.4)		19	103	18.2 (14.4, 22.7)		28	99	28.1 (25.2, 31.1)
	Oromia	48	190	24.5 (18.0, 32.4)		26	102	25.3 (13.3, 42.9)		22	88	23.7 (22.6, 24.9)
	SNNP	32	219	14.6 (9.5, 21.8)		11	96	11.5 (9.5, 13.8)		21	123	17.3 (8.5, 31.9)
	Tigray	44	200	22.1 (13.9, 33.6)		25	103	24.2 (9.4, 49.7)		19	97	20.2 (16.2, 24.9)

[1] There is a statistically significant difference in anemia prevalence across regions among women ($p<0.01$), but not between seasons. There are no statistically significant differences by region or season for men and children. See Supplementary Table 2 for details.

[2] Average weighted by regional population size.

Abbreviations: SNNP, Southern Nations Nationalities and Peoples

Table 2. Anemia risk factors among women aged 15-49 y, men aged 15-49 y, and children aged 6-59 mo in six regions of Ethiopia.

		All		Anemic		Non-Anemic		
Participant	**Risk factor**	*%*	*95% CI*	*%*	*95% CI*	*%*	*95% CI*	**p-value**
Women		*n=891*		*n=141*		*n=750*		
	Low serum ferritin	13.8	(9.2, 20.1)	22.3	(10.0, 42.8)	12.2	(7.9, 18.4)	0.12
	Low serum folate	41.2	(33.1, 49.7)	58.0	(41.9, 72.5)	38.1	(31.2, 45.5)	0.002
	Low serum vitamin B12	25.8	(14.3, 42.0)	15.3	(6.0, 33.5)	27.7	(15.4, 44.6)	0.07
	High C-reactive protein	6.5	(5.4, 7.9)	14.6	(6.8, 28.4)	5.1	(3.8, 6.8)	0.03
	Helminth infection	4.5	(1.8, 11.1)	1.0	(0.2, 4.8)	5.2	(2.0, 13.0)	0.03
	Malaria	1.5	(0.3, 6.6)	2.9	(0.5, 14.3)	1.2	(0.3, 4.9)	0.003
		n=2229		*n=376*		*n=1853*		
	Inadequate dietary iron	0.5	(0.2, 1.5)	0.3	(0.0, 2.6)	0.6	(0.2, 1.6)	0.52
	Inadequate dietary folate	42.2	(39.2, 45.3)	43.2	(32.6, 54.3)	42.0	(39.1, 45.0)	0.83
	Inadequate dietary vitamin B12	100.0	(99.9, 100.0)	100.0	--	100.0	(99.8, 100.0)	0.67
	Heavy menstruation	23.6	(21.5, 25.8)	20.9	(17.0, 25.3)	24.1	(21.3, 27.3)	0.29
	Diarrhea	7.5	(6.2, 9.1)	8.1	(5.6, 11.6)	7.4	(5.7, 9.5)	0.70
	Cough	16.3	(14.4, 18.5)	20.7	(13.1, 31.2)	15.5	(13.8, 17.4)	0.22
	Fever	27.7	(26.2, 29.2)	32.0	(25.6, 39.2)	26.9	(24.6, 29.3)	0.20
	Woman has not completed primary education	69.5	(64.2, 74.4)	74.2	(69.7, 78.2)	68.6	(62.8, 73.8)	0.02
	Unimproved water source	16.3	(11.7, 22.4)	26.5	(18.2, 36.9)	14.3	(9.5, 20.9)	0.02
	Unimproved sanitation	72.9	(70.0, 75.7)	77.9	(72.6, 82.5)	71.9	(68.4, 75.2)	0.06
Men		*n=674*		*n=63*		*n=611*		
	Low serum ferritin	4.6	(3.4, 6.1)	12.8	(6.2, 24.6)	3.8	(2.2, 6.5)	0.03
	Low serum folate	39.3	(29.3, 50.3)	52.4	(39.9, 64.6)	38.1	(28.0, 49.4)	0.007
	Low serum vitamin B12	23.4	(7.7, 52.8)	13.1	(4.7, 31.8)	24.3	(8.0, 54.4)	0.06
	High C-reactive protein	8.1	(6.9, 9.5)	14.8	(6.0, 32.4)	7.5	(6.1, 9.1)	0.13
	Helminth infection	4.3	(2.3, 7.9)	7.4	(2.9, 17.3)	4.1	(2.2, 7.3)	0.05
	Malaria	1.0	(0.2, 5.3)	7.3	(1.4, 30.9)	0.4	(0.1, 2.3)	<0.001
		n=917		*n=87*		*n=830*		
	Inadequate dietary iron	0.0	--	0.0	--	0.0	--	n/e
	Inadequate dietary folate	29.7	(23.8, 36.4)	28.8	(19.3, 40.7)	29.8	(23.4, 37.1)	0.86

	Inadequate dietary vitamin B12	97.9	(97.4, 98.4)		98.4	(94.0, 99.6)		97.9	(97.3, 98.4)	0.65
	Diarrhea	5.8	(4.5, 7.5)		9.4	(3.3, 24.0)		5.5	(4.4, 6.9)	0.25
	Cough	14.6	(12.3, 17.2)		15.8	(7.0, 31.6)		14.5	(12.0, 17.3)	0.81
	Fever	19.6	(14.2, 26.4)		25.9	(19.4, 33.6)		19.0	(13.3, 26.4)	0.14
	Woman has not completed primary education	69.8	(63.5, 75.4)		67.9	(54.4, 79.0)		70.0	(63.8, 75.5)	0.66
	Unimproved water source	18.1	(9.5, 31.9)		21.5	(8.9, 43.4)		17.9	(9.5, 31.0)	0.30
	Unimproved sanitation	72.9	(65.2, 79.5)		84.7	(77.0, 90.1)		71.9	(64.0, 78.6)	<0.001
Children		*n=796*			*n=168*			*n=895*		
	Low serum ferritin	25.3	(18.7, 33.4)		42.1	(24.6, 61.8)		21.1	(15.0, 28.9)	0.02
	Low serum folate	21.3	(16.3, 27.3)		31.8	(23.9, 40.8)		18.7	(14.1, 24.4)	<0.001
	Low serum vitamin B12	19.9	(12.5, 30.2)		19.0	(11.4, 30.1)		20.1	(12.4, 31.0)	0.75
	High C-reactive protein	8.4	(5.5, 12.7)		14.2	(10.0, 19.9)		7.0	(4.2, 11.4)	<0.001
	Helminth infection	5.1	(1.8, 13.1)		1.2	(0.3, 5.1)		6.0	(2.1, 16.2)	0.04
	Malaria	1.6	(0.2, 10.3)		0.1	(0.0, 0.5)		2.0	(0.3, 13.2)	0.007
		n=1162			*n=267*			*n=628*		
	Inadequate dietary iron	0.7	(0.6, 0.8)		0.4	(0.1, 3.5)		0.8	(0.5, 1.1)	0.62
	Inadequate dietary folate	25.8	(22.8, 29.0)		27.0	(23.7, 30.5)		25.4	(21.2, 30.2)	0.65
	Inadequate dietary vitamin B12	40.4	(38.4, 42.4)		35.6	(29.7, 42.0)		41.7	(38.0, 45.6)	0.18
	Diarrhea	13.7	(11.4, 16.5)		26.0	(20.1, 33.0)		10.3	(8.0, 13.2)	<0.001
	Cough	24.2	(20.4, 28.5)		34.2	(25.4, 44.2)		21.4	(16.0, 28.0)	0.06
	Fever	23.2	(20.6, 26.0)		35.6	(27.8, 44.4)		19.7	(15.6, 24.5)	0.007
	Woman has not completed primary education	70.8	(64.4, 76.6)		77.0	(68.0, 84.1)		69.1	(62.4, 75.1)	0.04
	Unimproved water source	16.6	(9.4, 27.7)		18.4	(11.5, 28.2)		16.1	(8.1, 29.5)	0.66
	Unimproved sanitation	73.8	(68.7, 78.4)		78.2	(70.6, 84.3)		72.6	(65.2, 78.9)	0.32

Table 3. Estimated proportion of anemia cases attributable to risk factors among women aged 15-49 years in six regions of Ethiopia.[1,2]

	Risk ratio			Partial population attributable percent	
	RR	*95% CI*		*%*	*95% CI*
Proximal factors model					
Low serum ferritin	2.06	(0.94, 4.49)		11	(-1, 23)
Low serum folate	1.77	(1.09, 2.86)		25	(5, 41)
Low serum vitamin B12	0.53	(0.30, 0.95)		-13	(-23, -4)
High C-reactive protein	2.88	(1.60, 5.18)		10	(2, 16)
Malaria	2.49	(1.63, 3.79)		3	(2, 4)
Helminth infection	0.30	(0.07, 1.31)		-2	(-4, 0)
Medial factors model					
Lower three quartiles of dietary iron intake	0.84	(0.68, 1.46)		-13	(-31, 25)
Insufficient dietary folate intake	1.08	(0.74, 1.37)		3	(-13, 13)
Lower three quartiles of dietary vitamin B12 intake	1.24	(0.88, 2.02)		16	(-1, 44)
Heavy menstruation	0.93	(0.47, 1.07)		-2	(-13, 2)
Diarrhea	0.99	(0.38, 1.79)		0	(-5, 5)
Cough	1.28	(1.01, 2.31)		4	(0, 14)
Fever	1.16	(0.74, 1.57)		4	(-7, 12)
Distal factors model					
Not completed primary education	1.14	(0.86, 1.50)		9	(-9, 24)
Unimproved water source	1.65	(0.98, 2.78)		10	(-1, 21)
Unimproved sanitation	1.15	(0.85, 1.56)		10	(-10, 27)
Lower four quintiles of household asset index	1.15	(0.52, 2.55)		12	(-69, 55)
Region					
Addis					
Amhara	1.17	(0.44, 3.10)		4	(-18, 21)
Afar	2.41	(1.23, 4.71)		3	(2, 4)
Oromia	1.25	(0.54, 2.86)		9	(-25, 34)
SNNP	0.92	(0.51, 1.67)		-1	(-10, 7)
Tigray	1.35	(0.84, 2.18)		2	(0, 4)
Wet season	1.49	(0.91, 2.43)		20	(-5, 38)

[1] Sample size for proximal model is 891, and for medial and distal models is 2,229.

[2] All models are multivariate adjusted. See Methods for details.

Abbreviations: SNNP, Southern Nations Nationalities and Peoples

Table 4. Estimated proportion of anemia cases attributable to risk factors among men aged 15-49 years in six regions of Ethiopia.[1,2]

	Risk ratio			Partial population attributable percent	
	RR	*95% CI*		*%*	*95% CI*
Proximal factors model					
Low serum ferritin	3.43	(1.20, 9.81)		9	(0, 17)
Low serum folate	2.21	(1.35, 3.60)		29	(11, 43)
Low serum vitamin B12	0.31	(0.16, 0.57)		-30	(-46, -16)
High C-reactive protein	2.61	(0.80, 8.53)		9	(-6, 22)
Malaria	14.59	(5.03, 42.33)		8	(3, 13)
Helminth infection	0.96	(0.39, 2.35)		0	(-7, 6)
Medial factors model					
Lower three quartiles of dietary iron intake					
Insufficient dietary folate intake	2.00	(0.71, 5.53)		40	(-28, 73)
Lower three quartiles of dietary vitamin B12 intake	0.92	(0.28, 1.44)		-2	(-29, 10)
Diarrhea	2.05	(0.76, 5.61)		45	(-23, 78)
Cough	1.65	(0.14, 2.96)		4	(-7, 6)
Fever	0.79	(0.23, 1.59)		-4	(-22, 8)
	1.54	(0.56, 3.10)		9	(-9, 22)
Distal factors model					
Not completed primary education	0.80	(0.37, 1.70)		-17	(-87, 26)
Unimproved water source	1.26	(0.78, 2.06)		4	(-5, 13)
Unimproved sanitation	2.03	(1.07, 3.85)		43	(6, 65)
Lower four quintiles of household asset index	1.77	(0.86, 3.64)		41	(-8, 68)
Region					
Addis	ref				
Amhara	2.40	(0.94, 6.16)		17	(2, 30)
Afar	2.97	(0.92, 9.56)		3	(0, 5)
Oromia	1.34	(0.36, 5.00)		7	(-27, 32)
SNNP	3.00	(1.25, 7.21)		19	(7, 29)
Tigray	3.57	(1.20, 10.65)		7	(0, 14)
Wet season	1.07	(0.55, 2.05)		3	(-31, 28)

[1] Sample size for proximal model is 674, and for medial and distal models is 917.

[2] All models are multivariate adjusted. See Methods for details.

Abbreviations: SNNP, Southern Nations Nationalities and Peoples

Table 5. Estimated proportion of anemia cases attributable to risk factors among children aged 6-59 months in six regions of Ethiopia. [1,2]

	Risk ratio			Partial population attributable percent	
	RR	*95% CI*		*%*	*95% CI*
Proximal factors model					
Low serum ferritin	1.96	(1.20, 3.22)		21	(4, 34)
Low serum folate	1.24	(0.86, 1.79)		6	(-3, 15)
Low serum vitamin B12	0.83	(0.57, 1.21)		-4	(-11, 3)
High C-reactive protein	1.54	(1.11, 2.15)		5	(1, 9)
Malaria	0.09	(0.02, 0.48)		-1	(-2, -1)
Helminth infection	0.28	(0.05, 1.68)		-3	(-5, -1)
Medial factors model					
Lower three quartiles of dietary iron intake	1.05	(0.59, 1.61)		4	(-50, 31)
Insufficient dietary folate intake	1.00	(0.70, 1.48)		0	(-9, 11)
Lower three quartiles of dietary vitamin B12 intake	1.01	(0.65, 1.79)		0	(-37, 37)
Diarrhea	1.73	(1.52, 3.38)		11	(8, 28)
Cough	1.13	(0.79, 1.85)		4	(-9, 21)
Fever	1.27	(0.77, 1.97)		8	(-10, 22)
Distal factors model					
Not completed primary education	1.36	(0.91, 2.04)		20	(-5, 40)
Unimproved water source	1.10	(0.55, 2.18)		2	(-10, 12)
Unimproved sanitation	1.26	(0.78, 2.03)		16	(-18, 40)
Lower four quintiles of household asset index	0.84	(0.34, 2.06)		-17	(-100, 43)
Region					
Addis	ref				
Amhara	1.12	(0.53, 2.37)		2	(-12, 15)
Afar	1.41	(0.54, 3.63)		1	(-1, 3)
Oromia	1.18	(0.60, 2.32)		8	(-23, 31)
SNNP	0.70	(0.29, 1.73)		-6	(-22, 8)
Tigray	0.99	(0.47, 2.06)		0	(-4, 4)
Wet season	1.16	(0.84, 1.60)		8	(-8, 21)

[1] Sample size for proximal model is 796, and for medial and distal models is 1,162.

[2] All models are multivariate adjusted. See Methods for details.

Abbreviations: SNNP, Southern Nations Nationalities and Peoples