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Victoria W. Konrad April 22, 2019

Association between National Mandatory Flour Fortification Legislation and Anemia Prevalence among Non-Pregnant Women of Reproductive Age: Findings from the Demographic and Health Surveys in Selected Countries.

By

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Global Epidemiology

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By

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Bachelor of Arts

Mercer University

2016

Faculty Thesis Advisors: Vijaya Kancherla, PhD, MS and Helena Pachón, PhD, MPH

An abstract of

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Abstract

Association between National Mandatory Flour Fortification Legislation and Anemia Prevalence among Non-Pregnant Women of Reproductive Age: Findings from the Demographic and Health Surveys in Selected Countries.

By Victoria W. Konrad

Background: Anemia affects more than 500 million women of reproductive age (WRA) worldwide and carries serious health consequences. Our multi-country analysis aimed at determining whether having national mandatory flour fortification policies for wheat or wheat and maize flour is associated with anemia prevalence among non-pregnant WRA.

Methods: We examined data from the Demographic and Health Surveys (DHS) from 11 countries (Armenia, Burundi, Ethiopia, Haiti, Malawi, Myanmar, Nepal, Tanzania, Timor-Leste, Uganda, and Zimbabwe). Accounting for the complex survey methods of DHS, we estimated the prevalence of anemia by country and conducted multivariable logistic regression considering residence in a country with (n=6) or without (n=5) mandatory flour fortification policy as a main predictor for anemia. Crude and adjusted prevalence odds ratios (cPOR, aPOR) and 95% confidence intervals (CIs) were estimated.

Results: A total of 193,463 non-pregnant WRA were examined from selected countries. Among countries with mandatory fortification for wheat or wheat and maize flour, pooled average anemia prevalence in countries with mandatory fortification was 36.72% (95% CI: 35.79, 37.64); and 34.64% (95% CI: 33.51, 35.77) in countries without fortification; the difference was not statistically significant ($P = 0.76$). Our multivariate analysis found that having a mandatory flour fortification policy was associated with marginally significantly reduced prevalence odds of anemia (aPOR: 0.92, 95% CI: 0.860, 0.999) after controlling for age, Human Development Index classification of the country, urban-rural status and body mass index.

Conclusions: Utilizing multinational DHS and global fortification data, our findings suggest that having a mandatory flour fortification policy for wheat or wheat and maize flour is associated with a marginally reduced prevalence odds for anemia in non-pregnant WRA. Future studies should examine the association based on longitudinal analyses, using biomarkers for anemia, and considering other potential confounders such as Human Immunodeficiency Virus (HIV) infection and malaria status in WRA that were not available in the DHS datasets.

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CHAPTER I

INTRODUCTION

Anemia is a disease characterized by a lack of hemoglobin, the protein found in red blood cells that is responsible for oxygen transport (1). It is the second leading cause of disability worldwide (2). Anemia affects more than 1.62 billion people, nearly one-fifth the global population (3). Poor cognitive development, pallor, fatigue, dizziness, and difficulty concentrating and completing daily tasks are among the myriad complications that result from anemia in non-pregnant populations (4).

The prevalence of anemia among non-pregnant women of reproductive age is an estimated 32.5% globally and 42.83% among lower middle income countries (5). While anemia is an often neglected health concern in the United States and other western societies, the burden of anemia severely affects the global south and has been labeled a “public health problem of global proportions” (6). In the United States, the National Institutes of Health (NIH) refer to anemia as an ‘easily’ treatable disease, and that treatment for some may be as simple as dietary change or taking iron supplements, which increase blood iron stores and promote hemoglobin production (7). This relatively low-cost intervention available in the west may not be available in low resource settings. Additionally causes of anemia may differ geographically, with areas of low resources having more hemoglobinopathies, blood disorders and diseases that affect red blood cells, such as intestinal helminths, sickle cell disease, and other non-nutritional factors (8). The global impact of anemia is substantial, and the condition is responsible for more than 68.4 million years of life lost (9). The World Bank estimates that, annually, 50 billion USD in global gross domestic product (GDP) is lost due to iron-deficiency anemia alone (5).

While anemia affects men and women of all ages, the consequences of disease are most devastating in the context of maternal and child health (10). Among women, pre-pregnancy anemia is associated with preterm birth and low birth weight (11). Improving baseline anemia levels among non-pregnant women of reproductive age decreases the risk of developing anemia in a future pregnancy, thereby reducing the risks of adverse birth outcome such as preterm birth and low birth weight, which affect children born to anemic mothers (11).

It is important to note, though, that the consequences of anemia extend far beyond the realm of maternal and child health, with one of its major known associations of severe fatigue and lack of productivity. The lack of hemoglobin in the blood prohibits oxygen transport and impedes normal body functions, increasing the amount of energy one must exert to perform basic tasks (12). This chronic fatigue is of critical concern, especially with regard to productivity. Studies have shown losses of 0.81% of gross domestic product associated with anemia and iron deficiency (13).

Fortifying foods, specifically wheat and maize flour, with iron and folic acid is considered a key mechanism to alleviate the burden of iron deficiency and anemia worldwide (14). A 2015 analysis found that, in countries with mandatory food fortification policies, odds of anemia in non-pregnant women of reproductive age decreased 2.4% each year after fortification (15). Our study serves as a response to Barkley et al., which recommended future studies to elucidate the impact of food fortification policies on anemia prevalence.

We used national cross-sectional survey data on women of reproductive age, collected by the Demographic and Health Surveys in selected countries which had required data needed for our study, and examined if anemia prevalence was lower in countries that have mandatory flour fortification policies compared to countries without mandatory flour fortification. We hypothesized that the there is a protective association between having mandatory folic acid fortification policy for wheat or wheat and maize flour in a country and anemia prevalence among non-pregnant women of reproductive age.

CHAPTER II

LITERATURE REVIEW

Anemia

Anemia, the second leading cause of disability worldwide, is characterized as a condition wherein a body's red blood cell count, or the hemoglobin protein of the red blood cells, has been reduced, leading to a decrease in oxygen delivery to body tissues (2). Poor cognitive development, pallor, fatigue, dizziness, and difficulty concentrating and completing daily tasks are among the myriad complications that result from anemia in non-pregnant populations (4). The majority of disability from anemia stems from severe fatigue, one of the most common complications of anemia, associated with lethargy and inabilities to complete daily tasks and normal functions (4). The World Health Organization (WHO) estimates that approximately 1.62 billion (95% CI = 1.50, 1.74) people globally had anemia, and 528.7 million women of reproductive age had anemia, of which, 20.2 million cases were severe (3, 16). The considerable global burden has resulted in WHO's second Global Nutrition Target for 2025: to decrease the global prevalence of anemia in women of reproductive age by 50% (14).However, UNICEF figures suggest that no country is on-track to meet its national anemia target by this date (14, 17).

Diagnosis of Anemia

Anemia can be diagnosed by complete blood cell count (CBC) tests, which measure a variety of blood features including hematocrit, the percentage of red blood cells in blood volume, and hemoglobin, the concentration of iron-rich protein that supports oxygen transportation (4). Globally, the most common point of care test (POCT) for anemia, and all hematology, is a hemoglobin concentration test (18). A common diagnostic tool, HemoCue, uses a simple finger prick to assess adults for anemia and is a sensitive, specific, and cost-effective method of diagnosis, often used when traditional lab testing is not possible (19, 20). The cut-points used to make anemia diagnoses are both population and altitude specific. For non-pregnant women of reproductive age (15-49 years), any anemia is classified by a hemoglobin (Hb) count <12.0 g/dl;

cutoffs for specific types of anemia are as follows: Hb ≥10.0 and ≤ 11.9 g/dl for mild anemia, Hb ≥7.0 and ≤ 9.9 g/dl for moderate anemia, and Hb <7.0 g/dl for severe anemia (19). Hemoglobin concentrations change by one's residential elevation and, because of such, adjustments must be made for Hb concentrations to reach a threshold of anemia (12). At higher altitudes, hemoglobin counts are decreased due to the lack of oxygen, therefore, one's altitude-adjusted hemoglobin level is less than it would be at a lower altitude, but the same reference numbers are used for anemia diagnoses (19).

Anemia and Pregnancy

In pregnancy, a woman's body requires more blood and therefore more nutrients to produce hemoglobin (1). The global prevalence of anemia among pregnant women was estimated by the World Health Organization (WHO) to be 41.8% (95% CI = 39.9, 43.8) (3). The common joint condition of pregnancy and anemia makes it difficult to study the impact of fortification initiatives in the entire female population; therefore, non-pregnant women of reproductive age are often used in such analyses. Women have higher iron demands during pregnancy to supply nutrients to their children and experience hemodilution, the loss of hemoglobin concentration in the blood (21).

Global Burden of Anemia

In 32 countries, anemia has been classified a severe public health problem among non-pregnant WRA (15-49 years), and a moderate public health problem for non-pregnant WRA in 109 countries (16). A systematic analysis found the worldwide prevalence of anemia was more than 32.9% in 2010 (9). The same study estimates that the years of life lost due to disability (YLD) due to anemia were 68.4 million (95% Uncertainty Interval [UI] = 41.0, 108), an increase of nearly 3 million from 1990 (9). The *Guidelines on Food Fortification with Micronutrients*, published by the WHO and the Food and Agricultural Organization of the United Nations (FAO) identified that more than 800,000 deaths each year are due to iron deficiency, about 1.5% of yearly global mortality (22). As with many disability-causing conditions, the largest burden of anemia is shouldered by low-income regions, with the highest numbers observed throughout Africa and Asia (16, 23). In high-income regions, the prevalence of anemia was less than 25%; by contrast, the prevalence in central Sub-Saharan Africa was more than 58% prevalence (9).

Consequences of Anemia

Though anemia exists in high income countries, the burden and consequences are much lower than in low income settings (9). Anemia is relatively simple to prevent and treat in high-income countries and is not considered a major health concern for the general population. In low and middle-income countries, however, the effects of anemia are substantial. Mild anemia may result in fatigue, pallor, weakness, and decreased productivity, while severe anemia may have more critical consequences such as shortness of breath, dizziness, weak and rapid pulse, and potential neurological damage (7).

In the United States, the prevalence of anemia is significantly higher in women than in men ($P < 0.001$) (24). WRA are considered a high-risk group for developing anemia (24). Many studies of anemia focus on either WRA (pregnant or non-pregnant) or children. WRA typically experience few symptoms from moderate anemia, but severe anemia is a cause for concern globally among WRA (1, 16).

Similarly to WRA, the primary mild and moderate anemia symptoms are shortness of breath and fatigue (25). The health risks of severe anemia for children under five years of age are profound. The disease has been associated with severe, sometimes irreversible, cognitive and physical impairment (9, 26). Seizures and strokes, as well as tachycardia and cardiac failure have been attributed to severe anemia in children (26).

Etiology of Anemia

Globally, an estimated 90,000 deaths were attributed to iron-deficiency anemia in 2013 (16). Anemia is caused by an array of infectious and non-communicable factors including inflammation, parasites, poor health conditions, pregnancy, and nutritional deficiencies (1). Anemia in low-income countries is often attributed to inadequate micronutrient intake, stemming from lack of diversity in diet and food shortages (14, 27). Anemia may be due to two or more concurrent etiologies.

Nutritional Anemias

Nutritional anemias include deficiencies of vitamin B12, folate, and iron (28). These may be caused by a variety of reasons including insufficient dietary intake of the micronutrients (28). Iron-deficiency anemia (IDA) is considered the most common cause and type of anemia worldwide, though the percentage of anemia attributable to IDA is contested, and is characterized by a lack of iron in the blood (1, 9). It is important to note that IDA is a type of anemia and should not be treated as the only kind of anemia, as the causes and sequelae may differ widely. IDA is a severe form of general iron deficiency.

The share of anemia due to iron deficiency is estimated at around 50%, but estimates vary widely by geography, age, and sex (23, 29). Petry et al. estimate that, specifically for women of reproductive age, the percentage of anemia associated with iron deficiency is 36.7%, with a range of 26.1% (South, East, and Southeast Asia region) to 59.0% (Latin America and the Caribbean region), rather than the commonly accepted figure of 50% (30). Assessing specific causes of anemia is vital for understanding the way to address and prevent anemia.

Malaria

Malaria is a known cause of anemia, especially in tropical regions (31). When a malaria-infected mosquito takes a blood meal, the parasite infects red blood cells, which eventually rupture; depletion of many red blood cells leads to anemia (32). While prevalence of anemia overall decreased from 1990 to 2010, prevalence of malarial anemia increased (9). In west-sub Saharan Africa Malaria was the cause of 24.7% of anemia (9). A systematic review of studies using malaria control interventions such as chemoprophylaxis, insecticide-treated nets, and residual spraying found that the relative risk for anemia in children in communities using anti-malarial interventions were 0.73 (95% CI = 0.64, 0.81) for mild anemia and 0.40 (95% CI = 0.25, 0.55) for moderate anemia compared to control groups who received no anti-malarial interventions (33). Iron deficiency and malaria are intertwined and exist as comorbid conditions in many patients (33).

HIV/AIDS

Anemia is a frequent complication of HIV/AIDS, affecting between 60-80% of those with symptomatic infections (34). The anemia seen in people living with HIV/AIDS is attributed to decreased and ineffective red blood cell production as well as increased red blood cell destruction, and not due to inadequate iron in the blood (34). Hemoglobin concentrations were significantly lower among HIV-positive women than HIV-negative women in a Rwandan study (35).

Food Fortification

Food fortification is the process of adding micronutrients to food. 'Premix,' a nutrient-dense supplement, is added to food products during food processing. Fortified foods deliver essential micronutrients to individuals. Food fortification uses existing delivery mechanisms to deliver micronutrients which increases one's micronutrient consumption without necessitating a shift in dietary habits (22). Fortification has been a public health tool to combat nutrient deficiencies since the early 1900s (36). WHO has guidelines for the fortification of wheat and maize flour with iron, folic acid, vitamin B12, vitamin A, and zinc (37). Wheat and maize flour are fortified with a variety of micronutrients in more than 81 countries globally (38). For nutrients involved in hemoglobin synthesis, their delivery into the body through fortified foods improves oxygen transportation throughout the body. Flour fortification may reduce anemia prevalence (39).

Mandatory fortification has been shown to be more effective than voluntary fortification for improving health outcomes (40). Fortified flour has been associated with decreases in neural tube defects, iron deficiency, and anemia (41) . Currently, 81 countries have a mandatory policy to fortify wheat flour with at least iron or folic acid, of these, 16 also have mandatory maize fortification policies (38). An assessment of cost savings of spina bifida prevention due to folic acid fortification in the United States found, that worst-case scenario of costs averted by fortification was an estimated US$299 million per year (42).

Mandatory food fortification policies may not necessarily translate to wide scale national implementation and national household coverage of fortified grains (43). Several barriers have been identified as reasons for poor national fortification coverage, including lack of expertise, capital investments/funding, lab capacities, and consumer demands, among others (43).

Nutrition Supplements

Recommended daily intake of micronutrients is often not achieved for people in low-income countries. Dietary supplements safely and effectively increase micronutrient supply, thereby decreasing risks associated with micronutrient deficiencies like nutritional anemia (44). While supplementation and fortification are recommended together to improve micronutrient status and decrease the burden of disease, the two forms of nutritional improvement have distinct differences (22). Dietary supplements provide a direct way of delivering needed doses of micronutrients to the individuals taking the supplements, food fortification, however, is a broad scale intervention that does not require any behavior or dietary change, but the levels of micronutrients each individual receives may not be as high (22).

Preconception Micronutrients

Preconception levels of micronutrients play an important role in the pre- and postnatal health of mother and baby (45). Iron and folic acid supplementation throughout pregnancy improves maternal hemoglobin levels at term and is associated with decreased low birth weight at term, though uptake and adherence to supplementation is low (46). Fortification programs are recommended to improve preconception levels of micronutrients to, among other things, improve fetal development and prevent birth defects (47). While mass fortification is an effective way to reach a wide population, it does not aim to meet the high iron needs of pregnant women; with fortification, we aim to help women enter pregnancy with a better nutritional status (48).

Flour Fortification and Anemia Prevalence

Pachón et al. (2015) conducted a systematic review of effectiveness studies of widespread, government-supported flour fortification programs to assess the impact of flour fortification on both iron and anemia status in subgroups of women of reproductive age and children of preschool age. Effectiveness studies, rather than the more common efficacy studies like randomized control trials, evaluate success and progress of interventions under real world scenarios. The review included 12 studies of WRA, both pregnant and non-pregnant, and 14 were included in the analysis for children. The study evaluated fortification policies to determine if flour fortification improves iron and anemia status (39). Only one third of the studies, in each subgroup, found a reduction in anemia (39). The authors acknowledged geographic and sample size limitations as well as those caused by a global lack of programmatic information. This review, the first to assess the effectiveness of flour fortification on anemia, encourages research to elucidate further the impact of flour fortification on anemia prevalence.

Barkley et al. (2015) utilized Demographic and Health Surveys and other national surveys to assess whether anemia in non-pregnant women of reproductive age was reduced after countries implemented fortification of wheat flour or maize flour with iron, folic acid, vitamin A, or vitamin B_{12}, nutrients that contribute to hemoglobin synthesis. The prevalence ratios determined by the surveys were analyzed using separate logistic regression models for countries that fortified and did not fortify flour. Exposure was coded as a continuous variable to reflect pre- and post-fortification status: years since fortification in countries with fortification (N=12), and in years since first available anemia survey in countries without fortification (N=20). Among countries that fortified flour, each year after fortification, the prevalence odds of anemia decreased by 2.4% (Prevalence Odds Ratio (POR) = 0.976, 95% Confidence Interval (CI) = 0.975, 0.978), when adjusting for Human Development Index and malaria. In countries without mandatory fortification policies, there was no statistically significant difference in anemia prevalence between the baseline (initial anemia survey) and most recent anemia survey (POR = 0.999, 95% CI = 0.997, 1.002) (15).

Urban-rural factors and their association with anemia and fortification

An analysis of anemia in thirty sub-Saharan African countries found that the impact of living in an urban rather than a rural area, urbanicity, was associated with decreased odds of anemia (OR = 0.76, 95% CI: 0.69, 0.84), when adjusting for the interaction of household wealth and education status (49). Urbanicity may also be associated with flour fortification. An eight low- and middle-income country large-scale food fortification assessment emphasized the potential impact of flour fortification in both urban and rural populations, but stressed that fortified foods reach everyone in the population, especially the most vulnerable, to make the most impact (50). Aaron et al. (2017) found that among rural populations, the coverage ratio (CR), or the proportion of coverage of fortified foods in vulnerable versus non-vulnerable households was highly variable, depending on country, and ranged from 0.2 (95% CI = 0.01, 0.03) to 2.5 (95% CI = 0.8, 7.2).

Education and its association with anemia and fortification.

Education is often considered a confounding factor in an exposure-disease relationship. A study also using multiple DHS found that education was significantly associated with anemia in 32 country-level surveys (23). A higher relative risk (RR) of anemia was seen among women with no education (RR = 1.08; 95% CI = 1.07, 1.10) and among women with primary education alone (RR = 1.04; 95% CI = 1.03, 1.05) compared to women with secondary education (23). In Mali, no education was found to be associated with higher odds of mild, moderate-to-severe, and any level of anemia (ORs = 1.31, 1.44, 1.35, respectively) when compared to any level of education (51). In a subnational analysis of Indian states, having a middle school education or more than a middle school education was associated with a decreased odds of anemia when compared to those who were illiterate (OR = 0.88; 95% CI = 0.86, 0.90 and OR = 0.77; 95% CI = 0.75, 0.79, respectively) (52). By contrast, the BRINDA project, which utilized 10 nationally representative cross-sectional surveys to assess biomarkers for inflammatory and nutritional anemia, found that education was not significantly associated with anemia in WRA in their pooled analysis of data from each of the 10 countries, but was associated in Laos (53).

Socioeconomic status and its association with anemia and food fortification.

Socioeconomic status (SES) has been associated with both anemia and food fortification. In Mali, the odds of moderate-to-severe anemia among women of medium wealth was 1.56-times that of women who were in the high wealth index group, when using a composite standard of living value for SES (51). Barkley et al. found that increasing human development index (HDI), the United Nation's measure of long and healthy life, standard of living, and knowledge, was associated with increased prevalence odds (POR = 3.89; 95% CI = 3.44, 4.39) of anemia in countries without flour fortification policies (19). The inverse association was found among countries that implemented flour fortification policies, the prevalence odds of anemia for each increase in HDI category (i.e.: low, medium, high) (POR = 0.04, 95% CI = 0.04, 0.05) (15).

Study Rationale

The current analysis addressed one of the limitations of Barkley et al. (19), which utilized existing national-level data to assess whether anemia in non-pregnant women of reproductive age was reduced after countries implemented mandatory wheat or wheat and maize flour fortification policies, also referred to as fortification status, by using individual-level anemia status. We hypothesized that the there is a protective association between having mandatory folic acid fortification policy for wheat or wheat and maize flour in a country and anemia prevalence among non-pregnant women of reproductive age.

CHAPTER III

METHODS

Demographic and Health Surveys (DHS)

We analyzed cross-sectional, nationally representative survey data from the DHS program. DHS surveys are nationally representative surveys of between 5,000 and 30,000 households administered in more than 90 countries approximately every 5 years (19). DHS surveys are standardized for comparison purposes, and include four questionnaires for each sampled household – household, woman's, man's, and biomarker questionnaires. We received permission to access DHS data files for each country used in this analysis (n=11) as well as two additional countries whose files did not contain anemia information. Each country file contained SAS datasets for each of the questionnaires. The woman's individual recode data file, which includes information from the woman's questionnaire as well as the biomarker questionnaire, was used for this analysis. Each questionnaire includes information for health and population characteristics with more than 1,000 variables collected for pregnant and non-pregnant women ages 15-49 years (19). DHS samples using a two-step cluster to ensure generalizability at national, residential, and regional levels (19). While most DHS data are self-reported, this analysis also includes information from biomarker data (hemoglobin) collected by trained study personnel.

Study Population

Our study population included non-pregnant women of reproductive age (WRA) living in selected countries with and without nationally mandated flour fortification policies. Data were obtained from all countries with available Demographic and Health Survey Programs (DHS) phase 7 re-codes including: Angola, Armenia, Burundi, Colombia, Ethiopia, Haiti, Malawi, Myanmar, Nepal, Tanzania, Timor-Leste, Uganda, and Zimbabwe. Surveys from Angola and Colombia were not used in the analysis as neither survey contains anemia or hemoglobin information. While individual-level information regarding consumption of wheat and maize flower was unknown, for the purpose of this analysis, women in countries with mandatory food fortification were assumed to consume fortified flour products, while those in countries without mandatory flour fortification were assumed not to consume fortified products. Information on nutrients included in fortification policies for wheat and maize flours are presented in Table 1. Study subjects who were eligible for the current analysis were residents of the eleven aforementioned countries. Our analytic sample consisted of only non-pregnant WRA with anemia information (n=193,463).

Study Design

By attributing national-level wheat or maize flour fortification policies to each individual in our dataset as our exposure of interest, we take an ecologic approach to analyzing retrospective cross- sectional data, with the outcome of individual-level anemia status and the primary exposure as whether or not the country had a national fortification policy for wheat or wheat and maize flour.

Outcome Measure

Among DHS participants, anemia is tested for and diagnosed using a finger prick HemoCue blood test that measures hemoglobin levels (DHS, 2019). The cut-points used to make anemia diagnoses are altitude-specific. For non-pregnant women of reproductive age (15-49 years), any anemia is classified by a hemoglobin (Hb) count <12.0 g/dl, mild anemia is Hb ≥10.0 and ≤ 11.9 g/dl, moderate anemia is Hb ≥7.0 and ≤ 9.9 g/dl, and severe anemia is Hb <7.0 g/dl (19). Hemoglobin concentrations increase by one's residential elevation and, because of such, adjustments must be made for Hb concentrations to reach a threshold of anemia (16). At higher altitudes, hemoglobin counts are decreased due to the lack of oxygen, therefore, one's altitude-adjusted hemoglobin level is less than it would be at a lower altitude, but the same reference numbers are used for anemia diagnoses (19). DHS utilizes this formula to adjust for altitude:

$$x = -0.032 \times y + 0.022 \times y^2 \text{ and } z = w - x \text{ (for } x > 0),$$

where x=adjustment, y= altitude, w=hemoglobin level, and z=adjusted hemoglobin level (19). DHS values for anemia were expressed as a four level categorical variable, mild, moderate, severe, and none. For the purpose of our analysis, we dichotomized anemia status as yes or no.

Exposure Assessment (Fortification status of a Country)

Flour fortification related information was obtained from the Global Fortification Data Exchange (GFDx) (https://fortificationdata.org/), which collects comprehensive worldwide data regarding legislation status, standards, availability, intake, industrially processed food, fortification quality, population coverage and monitoring protocols for wheat and maize flour, oil, rice, and salt. Legislation status (mandatory wheat or wheat and maize flour fortification: yes/no) and year of legislation were obtained from the accompanying file of the *Interactive Map: Fortification Legislation* in GFDx (54).

The primary exposure of interest was living in a country with a mandatory national wheat or wheat and maize flour fortification policy, since it is not possible to know an individual's consumption of fortified flour with data available in the current DHS surveys. For countries that had this legislation at the time of DHS data collection (n = 6), WRA were assigned a dummy variable coded as 1 for fortification while women who live in countries without mandatory legislation were assigned a value of 0. Haitian women were considered in the no fortification category, since they mandated flour fortification in 2017, after the survey was conducted.

Covariates

We considered the following covariates of interest based on our review of literature of anemia and fortification, as well as information available within the DHS dataset: age, body mass index (BMI), urbanicity, education, bed net usage, oral contraceptive usage, HIV status, and malarial status.

Our study was restricted to non-pregnant women of reproductive age, and we further categorized age into reproductive age cut-points of adolescence (15-19 years), 20-34 years, and advanced maternal age (35-49 years). Prevalence of anemia among WRA has been found to vary by age, and age has been found to be a predictor of anemia in older WRA (40-49 years), but not among younger WRA (15-39 years) (53).

BMI is collected by DHS as a continuous variable (19). We categorized the variable into: underweight (<18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25 – 29.9 kg/m^2), and obese (>30 kg/m^2), as BMI has been equivocally linked to anemia with some studies finding higher prevalence of anemia in underweight populations and others seeing this result among overweight and obese populations (55).

Human Development Index (HDI) is a measure of national human development for “a long and healthy life, being knowledgeable, and having a decent standard of living” that considers gross national income, expected years of schooling, and life expectancy (56). HDI information was obtained from the United Nations Development Programme Human Development Reports (56). HDI is measured on a continuous scale from 0-1 but also divided into multiple categorical units: low, medium, high, with low HDI representing the lowest category of national human development (56). Of the 11 countries, seven were in the low HDI category while three were in the medium HDI category. Armenia was the only country determined to be high HDI, and therefore was analyzed as a ‘medium/high HDI classification’ in our analysis. Each woman in a medium/high HDI country was given a value of 1 while those in low HDI countries were assigned 0.

Education, which prior studies using DHS data have indicated as a predictor for anemia, was included in the dataset as a multilevel, ordinal variable for no education, primary only, secondary only, or more than secondary education. No education has been associated with an increased relative risk (RR) of anemia among women with no education and primary education alone when compared to those with secondary education (23). Our dataset included only 4 missing values for education among the WRA.

DHS includes dichotomous urban/rural information for each survey participant's place of living (57). Urbanicity has been previously found to be associated with decreased anemia status (49).

Information on individual bed net usage at time of survey administration was available for the majority of WRA surveyed, though there were many missing values (n=34,295). Bed net usage was used as a proxy for malaria in a prior DHS study, even though we did not use bed nets as a proxy for malaria, we similarly dichotomized the variable for usage and no usage (51).

Information on primary birth control methods was available from DHS as a multilevel variable with information on oral contraceptive pills (OCPs), intrauterine device, injections, condoms and several others. We dichotomized birth control usage into current OCP use or otherwise based on a prior analysis of DHS data that found OCP usage is highly protective against anemia (58). Any missing values for OCP usage were classified as "nos" for current OCP usage.

Although both HIV and malaria were determined to be important factors influencing anemia status, these variables are not included in the Women's Recode DHS dataset used in this analysis (57). DHS conducts a malaria-specific survey, the Malaria Indicator Survey (MIS) but includes only pregnant women and children under 5 years (57). HIV datasets are only available for a subset of countries surveyed and require additional permission to access (57). Variables for HIV and malaria were not included in the available DHS datasets, and therefore could not be considered in the association calculations. Similar studies also faced this limitation. Similarly, nine of the countries we analyzed have endemic HIV, using the criteria of: "a male to female ratio of 2:1 or less, or HIV prevalence of 2% or greater among women receiving prenatal care, or a high prevalence of HIV infection in the adult population (1% or greater) with a predominant mode of heterosexual transmission" (all but Nepal and Timor-Leste) (59).

Statistical Analysis

All analyses were conducted accounting for DHS complex survey weights for nationally representative sampling procedures. The eleven individual country datasets were concatenated to create one analytic file that included each of the WRA (n=193,463). DHS recode files are standardized for methodology, variables, coding, and weighting, and have excluded any data outliers. Weight, stratum, and cluster information to account for sampling and national representation was available in the DHS dataset. We estimated prevalence of anemia in each country by using weighted frequency procedures and obtaining 95% confidence intervals using Poisson distribution methods.

We conducted a bivariate analysis to compare characteristics of WRA by country-level fortification and non-fortification status. Significant differences between the groups were summarized based on Rao-Scott Chi square tests ($P<0.05$). Crude PORs were estimated for the associations between mandatory country-level flour fortification status and anemia, and also age, education, OCP usage, bed net usage, BMI, HDI, and urban/rural status. We also conducted a descriptive analysis examining the associations between selected sociodemographic covariates and anemia.

We estimated crude adjusted prevalence odds ratios for the main effect (fortification status and anemia status). Our fully parameterized model included the dichotomized anemia status as the outcome, and living in a country with mandatory wheat or wheat and maize flour fortification as the main exposure, while adjusting for age, HDI, living in an urban/rural location, and BMI. Education was not included in the model, as not to over-adjust since education is a component included in HDI. Our final reduced model used to draw conclusions included age, and HDI. There was no difference in point estimates or 95% confidence intervals when adding urban/rural status. Covariates in the model were determined a priori. All analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina).

As information utilized from DHS were de-identified secondary data, the study was exempted from human subjects research review by the Emory University Institutional Review Board.

CHAPTER IV

RESULTS

Overall, unadjusted anemia prevalence among the WRA in our analysis ranged from 13.03% in Armenia to 46.55% in Myanmar **(Table 2)**. These numbers differ slightly from the national anemia prevalence reports available in DHS, as the complete country profiles consider both pregnant and non-pregnant WRA whereas our analysis considered only non-pregnant WRA. Among countries with mandatory fortification, pooled average anemia prevalence was 36.72% (95% CI: 35.79, 37.64); in countries without mandatory fortification it was 34.64% (95% CI: 33.51, 35.77) **(Table 2)**. The pooled prevalences for countries with and without mandatory flour fortification were not statistically significantly different ($P = 0.76$).

In our bivariate analysis examining associations between selected co-variables and mandatory fortification status, we found that maternal age, BMI, HDI, urbanicity, education, bed net usage, and oral contraceptive use were each significantly associated with mandatory fortification status **(Table 3**). For bivariate association examining association between selected co-variables and anemia status, the associations were significant for maternal age, BMI, education, bed net usage and oral contraceptive use **(Table 4**).

Our unadjusted logistic regression analysis for the main hypothesis showed that having mandatory flour fortification policy for wheat or wheat and maize flour was significantly associated with a decreased prevalence odds of anemia among WRA (cPOR = 0.91; 95%CI = 0.86, 0.97). However, in the multivariable analysis controlling for maternal age, HDI, urban/rural status, and maternal BMI, the magnitude of the association remained unchanged; however the confidence interval moved closer to null, indicating a marginally significant prevalence odds ratio (aPOR = 0.92, 95% CI = 0.860, 0.999) **(Table 5)**.

CHAPTER V

DISCUSSION

Utilizing multinational DHS and global fortification data, we found that anemia prevalence was lower in non-pregnant WRA in countries with mandatory flour fortification policies for wheat or wheat and maize flour, compared to anemia prevalence among those living in countries without these policies. We found that there is a marginally significant protective association between having a national mandatory wheat or wheat and maize flour fortification policy and anemia status in non-pregnant WRA. Our analysis was based on a large sample of about 200,000 women with individual anemia status, in comparison to previous studies where data were available only on national levels for anemia prevalence.

The prevalence of anemia that we calculated in each of the 11 countries we analyzed is similar to the prevalence of anemia described by other comparable countries that have participated in DHS. Any variations that we have seen were minor, and attributable to restricting our analysis to include only non-pregnant WRA. Our study was the first to examine the association between having a national mandatory fortification policy for wheat or wheat and maize flour and individual-level anemia status among non-pregnant WRA. Hence we are unable to compare our findings on the association with previous studies.

The cross-sectional approach of DHS methodology limits our ability to conclude on the causal association between having mandatory fortification policy and subsequent outcome of anemia reduction. Our findings should be interpreted with causation, and should be viewed as exploratory and a basis for future studies that can improve on methods. Systematic reviews on the association between anemia and fortification policy vary widely in terms of target group, food vehicle, and impact. Nevertheless anemia prevalence was reduced among WRA in three systematic reviews that included wheat and other cereal grains while an effectiveness study on wheat and maize flour showed limited results (60).

This is the first analysis using individual-level DHS data for anemia status in multiple countries as the outcome measure with mandatory flour fortification policy as an exposure. Though the attribution of fortification to each individual still generates an ecologic approach, having individual-level anemia status may improve the precision of the association. We utilized DHS data, as DHS is considered a gold standard for international public health research. We restricted our study to include only phase 7 of DHS surveys to ensure the same questions of the core modules were used in each of the countries. DHS utilizes complex sampling techniques that ensure the results are nationally representative for each country in the analysis. The recoded questionnaire datasets allowed for aggregation of data. Sample size was large with data from 193,463 non-pregnant women of reproductive age in the analytic sample.

Attributing national-level fortification policy information as an individual's exposure category may not be representative of a woman woman's dietary practice of consuming (or not consuming) foods made with fortified wheat or maize flour. Using fortification policy as a proxy limited our ability to adjust for confounding variables, as no available factors that may lead to anemia are also associated with national fortification policy. Finally, although DHS sampling is robust and the measure of anemia via hemoglobin testing is accurate, it is not able to account for one's cause of anemia (e.g., micronutrient deficiency, genetic, etc.). Fortification is only able to make improvements to nutritional anemias (39). As with all cross-sectional analyses, it is crucial to note that we have only assessed correlation not causation. It is possible that some of the factors we determined to be associated with anemia but could not include in the analysis, especially malaria status and HIV are distorting the true measure of association.

Global leaders in nutrition and fortification recommend that the next surveys administered by the DHS program, DHS-8, include a measure of household level consumption of fortified food (61). If available, a similar analysis using household level fortification status may yield more accurate information on the true association between fortification and anemia status. For countries with available data for HIV biomarkers a sub-analysis would allow better understanding of the role of fortification on anemia among those with HIV. A similar analysis for malaria should be conducted as well. We would have liked to have adjusted for individual malaria and HIV status as both affect one's anemia status, though the variables were not available. Further research could also be conducted considering national-level fortification exposure by assessing if a country follows World Health Organization recommendations for nutrients in standards for fortified flour.

The WHO recommendations supporting preconception nutrition encourage further work to reduce micronutrient deficiencies (37). This analysis, which specifically considered women of non-reproductive age, the population of interest for preconception care, suggests potential benefits of fortification for reducing anemia, some of which may be due to micronutrient deficiencies. Our findings further support the recommendations of food fortification from the World Health Organization and calls from global leaders in nutrition to promote mandatory wheat or wheat and maize fortification policies in the countries that do not yet have such requirements (61). With more than 100 countries that do not have mandatory wheat or maize flour fortification policies, our findings suggest there is tremendous potential for decreasing anemia status among non-pregnant women of reproductive age by establishing mandatory flour fortification policies (38).

In conclusion, our findings using a large multinational sample suggest that living in a country with mandatory wheat or wheat and maize flour fortification reduces the prevalence odds for anemia among non-pregnant WRA. These findings are based on an ecological and cross-section design. Our findings contribute further evidence showing the benefit of mandatory wheat and maize flour fortification polices to improve micronutrient intake among WRA and addressing anemia at a national level. Future studies should examine the association based on longitudinal analyses, using biomarkers for anemia, and considering other potential confounders such as HIV and malaria status in WRA that were not available in the DHS datasets.

CHAPTER VI

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CHAPTER VII

TABLES

Table 1. Nutrients included in standards for wheat and maize flour fortification among selected countries with mandatory fortification legislation, Global Fortification Data Exchange, 2019

Country	**Wheat Flour**	**Maize Flour**
Burundi	Folic acid, iron, niacin, riboflavin, thiamin, vitamin A, vitamin B_6, vitamin B_{12}, zinc	Folic acid, iron, niacin, riboflavin, thiamin, vitamin A, vitamin B_6, vitamin B_{12}, zinc
Malawi	Folate (B_9), iron, niacin, riboflavin, thiamin, vitamin A, vitamin B_{12}, zinc	Folate (B_9), iron, niacin, riboflavin, thiamin, vitamin A, vitamin B_{12}, zinc
Nepal	Folate (B_9), iron, vitamin A	Not applicable
Tanzania	Folate (B_9), iron, niacin, riboflavin, thiamin, vitamin A, vitamin B_6, vitamin B_{12}, zinc	Folate (B_9), iron, vitamin A, zinc
Uganda	Folate (B_9), iron, niacin, riboflavin, thiamin, vitamin A, vitamin B_6, vitamin B_{12}, zinc	Folate (B_9), iron, niacin, riboflavin, thiamin, vitamin A, vitamin B_{12}, zinc
Zimbabwe	Folate (B_9), niacin, riboflavin, thiamin, vitamin A, vitamin B_6, vitamin B_{12}, zinc	Folate (B_9), niacin, riboflavin, thiamin, vitamin A, vitamin B_6, vitamin B_{12}, zinc

Global Fortification Data Exchange. Fortification Legislation. 2019; Available from: http://www.fortificationdata.org. (54)

Table 2. Country specific anemia prevalence for non-pregnant women of reproductive age (15-49 years) by mandatory fortification policy for fortification of wheat or wheat and maize flour

Country Name	Total Subjects	Subjects with Anemia	Weighted Prevalence (%) of Anemia*	95% Confidence Interval for Prevalence of Anemia
Mandatory Fortification				
Burundi†	20,533	8,460	43.14	(40.92, 45.36)
Malawi†	20,775	6,662	30.77	(28.89, 32.64)
Nepal‡	12,579	5,005	40.77	(38.07, 43.47)
Tanzania†	33,958	15,356	43.70	(41.74, 45.67)
Uganda†	17,249	5,705	31.92	(29.70, 34.13)
Zimbabwe†	18,240	4,804	25.43	(23.76, 27.11)
TOTAL	123,334	45,992	36.72	(35.79, 37.64)
No Mandatory Fortification				
Armenia	8,280	1,074	13.03	(11.40, 14.67)
Ethiopia	13,436	3,534	23.20	(21.48, 24.93)
Haiti§	17,598	7,969	46.44	(44.34, 48.54)
Myanmar	21,602	9,814	46.55	(44.73, 48.36)
Timor-Leste	9,213	1,983	23.19	(20.71, 25.66)
TOTAL	51,674	17,876	35.37	(34.06, 36.68)

*Weighted prevalence due to Demographic and Health Survey sampling techniques (57)
†Wheat and maize flour fortification is mandatory (57)
‡Wheat flour fortification is mandatory (57)
§Wheat flour fortification in Haiti became mandatory in 2017 after the surveys were conducted. (57)

Table 3. Descriptive characteristics of non-pregnant women of reproductive age (15-49 years) by mandatory flour fortification of wheat or wheat and maize flour of the country, Demographic and Health Surveys, 2015-2017

Characteristics	Total Subjects		Fortification		No Fortification		Rao Scott P-value	Crude POR	95% CI
	n	%*	n	%*	n	%*			
Anemia†									
Yes	70,366	35.98	45,992	36.72	24,374	34.64		0.91	(0.86, 0.97)
No	123,097	64.02	77,342	63.28	45,755	65.36	0.0062	Referent	Referent
Age in years									
15-19	5,373	2.84	1,928	1.62	3,445	5.08		0.28	(0.25, 0.32)
20-34	76,533	40.18	51,158	41.86	25,375	37.1	<.0001	Referent	Referent
35-49	111,557	56.98	70,248	56.52	41,309	57.82		0.87	(0.82, 0.91)
BMI‡									
Underweight	20,574	10.59	11,809	9.64	8,765	12.32		0.71	(0.66, 0.77)
Normal	116,489	61.22	76,579	63.25	39,910	57.51	<.0001	Referent	Referent
Overweight	36,895	19.04	22,441	18.04	14,454	20.86		0.79	(0.73, 0.85)
Obese	17,815	9.16	11,395	9.07	6,420	9.31		0.89	(0.80, 0.99)
HDI§									
Low	141,789	74.23	110,755	90.02	31,034	45.37		10.87	(9.28, 12.72)
Medium/High	51,674	25.77	12,579	9.98	39,095	54.63	<.0001	Referent	Referent
Urban/Rural									
Urban	52,714	25.71	31,305	23.66	21,409	29.46	<.0001	Referent	Referent
Rural	140,749	74.29	92,029	76.34	48,720	70.54		1.35	(1.17, 1.55)
Education									
Primary	86,726	45.83	61,542	51.18	25,184	36.04		1.94	(1.76, 2.12)
Secondary	42,352	20.72	24,119	18.37	18,233	25.03	<.0001	Referent	Referent
Higher	9,184	4.74	2,845	2.32	6,339	9.17		0.34	(0.30, 0.39)
No	55,197	28.71	34,828	28.13	20,369	29.76		1.29	(1.15, 1.45)
Bed nets‖									
Yes	82,128	51.05	55,242	48.63	26,886	56.95	<.0001	Referent	Referent
No	77,040	48.95	55,513	51.37	21,527	43.05		1.40	(1.25, 1.56)
OCP Usage¶									
Yes	13,168	7.19	10,092	8.69	3,076	4.46		0.60	(0.54, 0.66)
No	180,295	92.81	113,242	91.31	67,053	95.54	<.0001	Referent	Referent

CI, Confidence Interval; POR, Prevalence Odds Ratio; BMI, Body Mass Index; HDI, Human Development Index; OCP, Oral Contraceptive Pills

*Weighted percent due to Demographic and Health Survey sampling techniques (19)

†Current anemia status; Hemoglobin (Hb) <12.0 g/dl (19)

‡BMI (kg/m^2): Underweight (<18.5 kg/m2), normal weight (18.5 – 24.9 kg/m2), overweight (25 – 29.9 kg/m2), and obese (>30 kg/m2) (19)

§Human Development Index (HDI) is a measure of national human development for "a long and healthy life, being knowledgeable, and having a decent standard of living" that considers gross national income, expected years of schooling, life expectancy (57). Low is the lowest level of human development.

‖Current bed net usage.

¶Current oral contraceptive usage.

Table 4. Descriptive characteristics of non-pregnant women of reproductive age (15-49 years) by individual anemia status, Demographic and Health Surveys, 2015-2017

Characteristics	Total Subjects		Subjects with Anemia		Subjects without Anemia		Rao Scott P-value	Crude POR	95% CI
	n	%*	n	%*	n	%*			
Fortification									
Yes	123,334	64.63	45,992	65.95	77,342	63.89		0.91	(0.86, 0.97)
No	70,129	35.37	24,374	34.05	45,755	36.11	0.0061	Referent	Referent
Age in years									
15-19	5,373	2.84	1,660	2.28	3,713	3.16		0.79	(0.72, 0.87)
20-34	76,533	40.18	26,226	37.86	50,307	41.48	<.0001	Referent	Referent
35-49	111,557	56.98	42,480	59.85	69,077	55.36		1.184	(1.13, 1.24)
BMI‡									
Underweight	20,574	10.59	8,876	12.50	11,698	9.51		1.23	(1.14, 1.32)
Normal	116,489	61.22	44,294	63.98	72,195	59.66	<.0001	Referent	Referent
Overweight	36,895	19.04	11,631	16.41	25,264	20.52		0.75	(0.70, 0.80)
Obese	17,815	9.16	5,072	7.10	12,743	10.31		0.64	(0.59, 0.71)
HDI§									
Low	141,789	74.23	52,490	74.67	89,299	73.98		1.04	(0.97, 1.11)
Medium/ High	51,674	25.77	17,876	25.33	33,798	26.02	0.3149	Referent	Referent
Urban/Rural									
Urban	52,714	25.71	17,567	24.91	35,147	26.16	0.0738	Referent	Referent
Rural	140,749	74.29	52,799	75.09	87,950	73.84		1.07	(0.99, 1.15)
Education									
Primary	55,197	28.71	22,942	32.47	32,255	26.59		1.56	(1.45, 1.68)
Secondary	86,726	45.83	32,183	46.85	54,543	45.25	<.0001	Referent	Referent
Higher	42,352	20.72	13,072	17.61	29,280	22.48		1.32	(1.24, 1.41)
No	9,184	4.74	2,169	3.07	7,015	5.68		0.69	(0.62, 0.77)
Bed nets‖									
Yes	82,128	48.95	32,016	52.51	50,112	50.16	0.0015	Referent	Referent
No	77,040	51.05	28,737	47.49	48,303	49.84		0.91	(0.86, 0.97)
OCP Usage¶									
Yes	13,168	7.19	3,437	5.17	9,731	8.33		0.60	(0.54, 0.66)
No	180,295	92.81	66,929	94.83	113,366	91.67	<.0001	Referent	Referent

CI, Confidence Interval; POR, Prevalence Odds Ratio; BMI, Body Mass Index; HDI, Human Development Index; OCP, Oral Contraceptive Pills

*Weighted prevalence due to Demographic and Health Survey sampling techniques (19)

†Current anemia status; Hemoglobin (Hb) <12.0 g/dl (19)

‡BMI (kg/m^2): Underweight (<18.5 kg/m^2), normal weight (18.5 – 24.9 kg/m^2), overweight (25 – 29.9 kg/m^2), and obese (>30 kg/m^2) (19)

§Human Development Index (HDI) is a measure of national human development for "a long and healthy life, being knowledgeable, and having a decent standard of living" that considers gross national income, expected years of schooling, life expectancy (57). Low is the lowest level of human development.

‖Current bed net usage.

¶Current oral contraceptive usage.

Table 5. Unadjusted and adjusted analyses examining the association between national mandatory fortification policy for wheat or wheat and maize flour and anemia status† of women of reproductive age (15-49 years) in selected countries, Demographic and Health Surveys, 2015-2017

Regression Models	**Prevalence Odds Ratio**	**95% Confidence Interval**
Fortification only	0.91	(0.86, 0.97)
Fortification + Age‡	0.92	(0.86, 0.98)
Fortification + HDI§	0.91	(0.84, 0.98)
Fortification + Education‖	0.96	(0.91, 1.03)
Fortification + Urbanicity	0.92	(0.86, 0.98)
Fortification + Age + HDI	0.92	(0.855, 0.992)
Fortification + Age + HDI + Urbanicity	0.92	(0.855, 0.991)
Fortification + Age + HDI + Urbanicity + BMI¶	0.93	(0.860, 0.999)

HDI, Human Development Index; BMI, Body Mass Index
†Current anemia status; Hemoglobin (Hb) <12.0 g/dl (19)
‡ Maternal age categorized into: 15-24 years, 25-34 years, and 35-49 years
§ Human Development Index (HDI) is a measure of national human development for "a long and healthy life, being knowledgeable, and having a decent standard of living" that considers gross national income, expected years of schooling, life expectancy (57). Low is the lowest level of human development.
‖Education categorized into: None, Primary, Secondary, or Higher education
¶BMI (kg/m^2): Underweight (<18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25 – 29.9 kg/m^2), and obese (>30 kg/m^2) (19)