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Maternal anemia and childhood cancer: a population-based case-control study in Denmark

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Abstract

Background: Childhood cancer risk is associated with maternal health during pregnancy. Anemia in pregnancy is a common condition, especially in low-income countries, but a possible association between maternal anemia and childhood cancer has not been widely studied.

Methods: We examined the relation in a population-based study in Denmark (N = 6420 cancer cases, 160,485 controls). Cases were taken from the Danish Cancer Registry, and controls were selected from national records. We obtained maternal anemia diagnoses from the National Patient and Medical Births registries. In a separate analysis within the years available (births 1995–2014),

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Naveen Qureshi: Writing – original draft, Formal analysis. **Helen Orimoloye:** Writing – review & editing, Formal analysis, Visualization. **Johnni Hansen:** Data curation, Writing – review & editing. **Jorn Olsen:** Writing - review & editing. **Xiwen Huang:** Formal analysis, Writing - review & editing. **Di He:** Formal analysis, Writing – review & editing. **Beate Ritz:** Writing - review & editing. **Julia E. Heck:** Conceptualization, Methodology, Supervision, Project administration, Writing – review & editing.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2022.102308.

we examined cancer risks among mothers taking prescribed vitamin supplements, using data from the National Prescription Register. We estimated the risks of childhood cancer using conditional logistic regression.

Results: The risks of neuroblastoma [odds ratio (OR= 1.83, 95% confidence interval (CI): 1.04, 3.22] and acute lymphoblastic leukemia (OR= 1.46, 95% CI 1.09, 1.97) were increased in children born to mothers with anemia in pregnancy. There was a two-fold increased risk for bone tumors (OR= 2.59, 95% CI: 1.42, 4.72), particularly osteosarcoma (OR= 3.54, 95% CI 1.60, 7.82). With regards to prescribed supplement use, mothers prescribed supplements for B12 and folate deficiency anemia (OR= 4.03, 95% CI 1.91, 8.50) had an increased risk for cancer in offspring.

Conclusion: Our results suggest that screening for anemia in pregnancy and vitamin supplementation may be an actionable strategy to prevent some cases of childhood cancer.

Keywords

Maternal anemia; Childhood cancer epidemiology; Folate; B12; Pregnancy

1. Introduction

Anemia occurs as a result of a decrease in the body's concentration of hemoglobin. During pregnancy, maternal anemia primarily arises due to folate, iron deficiency, and sometimes other causes such as vitamin B12 deficiency and chronic infections. Maternal anemia is common because of the natural increases in dietary needs of the mother during the pregnancy period. On average, a mother requires a daily intake of 400 μg folate, 2.20 μg of vitamin B12, and over the course of her pregnancy, a total of 1200 mg of iron [1]. Severe maternal anemia can affect the fetus because of its effects on placental structure, oxygenation of the developing fetal systems and organs, nutrient absorption, brain development, and formation of red blood cells [2].

The global prevalence of anemia during pregnancy is 41.8% and in Denmark, the World Health Organization estimates the prevalence of anemia to be 16% [3]. Maternal anemia is associated with negative birth outcomes such as low birth weight and preterm deliveries. Research also suggests that anemia may be linked to cancer in adults. Folate deficiency changes gene expression as a result of DNA hypomethylation, which can result in malignancies [4]. In Denmark, the Danish National Board of Health recommended universal iron supplementation among pregnant women (50–70 mg daily starting in week 20 of gestation) in 1998. Iron supplements are widely available over the counter, and an estimated 77% of Danish women ever take them during pregnancy [5]. Similarly, since 1997, the Danish Health and Medicines Authority recommended that Danish pregnant women take 0.4 mg of folic acid supplementation daily, beginning at least one month before conception and continued through the first 12 weeks of pregnancy. However, only 10.4% of Danish women adhere to this recommendation [6].

Cancer is the second leading cause of mortality in children in high-income countries [7]. Although the etiology of childhood cancers is largely unknown, known risk indicators

include low or high birth weight, older parental age, birth defects, genetic syndromes, and ionizing radiation. Exposures in-utero are believed to play an etiologic role [8–11].

The literature on the relations between maternal anemia and childhood cancers is sparse. While studies have been limited and results conflicting, the most consistent findings suggest associations between childhood leukemia, neuroblastoma, and retinoblastoma with maternal anemia during pregnancy [12–26]. The aim of the present study was to further examine the potential relation between maternal anemia during pregnancy and childhood cancers in a population-based study in Denmark.

2. Material and methods

The data were obtained by linking multiple Danish national registries, as previously described [8]. In brief, all residents in Denmark are given a unique 10-digit personal ID since 1968, including information on their date of birth and sex. This ID is used in all demographic and health registries in Denmark and allows linkage between registries. Using data from the Danish Cancer Register, we identified cancer cases (aged ≤ 19 years) diagnosed between 1977 and 2013. In the present analysis, we restricted to births 1977 + to have thorough information on pregnancy conditions as available from the Danish National Patient Register, which was established in that year. Controls were matched to cases (25:1 matching rate) by sex and birth date and selected at random from the Central Population Register; this database also includes information on vital status and place of birth and links children to their parents. In order to have thorough pregnancy information, all cases and controls included in the study were born in Denmark. Cancer cases were classified using the International Classification of Childhood Cancer (ICCC-1 and ICCC-3) [27], and we kept in the current analysis only cancer types for which there are at least five exposed cases (N = 6420). Fig. 1 shows a flowchart describing the selection of cases and controls.

We obtained information on maternal anemia during pregnancy from the Medical Births Registry and the National Patient Register. The Medical Births Registry contains pregnancy, labor, and gestational information, including certain maternal health conditions. Health conditions were classified using International Classification of Diseases, revision 8 (ICD-8) until 1993 and a Danish extended version of ICD-10 1993 +. The ICD-8 and ICD-10 codes used to identify anemia are shown in Supplementary Table 1. The time period of pregnancy was established using gestational age (days), which was taken from the Medical Births Registry. Because 3.9% of children were missing information on gestational age, we calculated it using multiple imputation. The details of the multiple imputation method were previously described [28].

We estimated cancer risk for children whose mothers had anemia during pregnancy via conditional logistic regression. The scientific literature guided the selection of additional variables for adjustment [8–11]. Covariates that were included in the final model included the mother’s age (continuous), parity (continuous), and the child’s place of birth (urban, small town, or rural). Other covariates considered for adjustment included maternal smoking, mother’s birthplace (Denmark/other Europe/other; a proxy for race/ethnicity), father’s age and father’s birthplace, and maternal pregnancy history of viral or bacterial

infections (using ICD codes identified by Atladottir [29]). However, adjustment for these variables changed estimates by < 10%; thus, these variables were left out of the final model [30]. We additionally examined adjustment for the mother's history of bleeding disorders (defined as menstrual disorders, hemophilia disorders, and Von Willebrand disease; disorders and their matching ICD codes are listed in Supplementary Table 2) but we left these out of the final model as they changed estimates by < 10%.

We conducted a number of sensitivity analyses. In order to determine whether any effect was dependent on maternal age, we also stratified by mother's age group (<24, 25–29, 30–34, and 35 or more) however, due to the small sample size for some specific cancer types, this was only done for acute lymphoblastic leukemia (ALL). In addition, because the first part of our study period only included inpatient records (1978–1997), possibly leading to lower ascertainment of some maternal health conditions such as anemia, we conducted sensitivity analyses restricting to the years 1998 +, when both inpatient and outpatient records were available. We additionally considered that certain types of anemia are strongly associated with cancer. For example, Fanconi anemia, a rare autosomal recessive disorder, is associated with acute myeloid leukemia (AML), but we did not have any mothers with a recorded Fanconi anemia in our sample. All analyses were performed using SAS 9.4 software (Cary, NC).

2.1. National Prescription Register

We used the National Prescription Register (1995 +) to examine whether there was an increased cancer risk with the use of anemia-treating medications in pregnancy (births 1995–2014 and cancer diagnoses 1996–2016). This register contains, on an individual basis, information on all prescribed pharmaceuticals from all pharmacies in Denmark. The Prescription Register data are maintained on the Statistics Denmark server; therefore, we conducted this analysis separately. Controls (matched by sex and date of birth) were randomly selected for the analysis. Medications were ascertained using Anatomical Therapeutic Chemical codes (Supplementary Table 1). We used conditional logistic regression to estimate the risk for cancer with anti-anemia medications, adjusting for the same covariates as the models for anemia risk. Additionally, we stratified by medication use in order to determine whether there was an increased risk of cancer dependent on medication use. Because our data source cannot ascertain over-the-counter supplements, and the prevalence of iron supplementation is high among Danish women [5], we did not examine the effect of iron supplements on childhood cancer risk.

The present study was approved by the Human Subjects Protection boards of the University of California, Los Angeles (#13–001904), Columbia University, the University of North Texas (IRB-21–469), and the Danish Data Protection Agency. This study used existing data, and a waiver of informed consent was received.

3. Results

Cases and controls were similar with regards to maternal age, parity, and the mother's place of birth (Table 1). A larger proportion of cases (3.6%) than controls (2.4%) had mothers with

anemia. Compared to controls, cases were slightly more likely to be born in an urban area of Denmark and have a mother with a bleeding disorder.

After adjustment for confounding variables, children of mothers with anemia had an increased risk for ALL, neuroblastoma, and malignant bone tumors, and marginal increases in central nervous system (CNS) tumors (Table 2).

When stratifying results by mother's age, we observed increased risks for ALL across all age groups, with overlapping confidence intervals (Supplementary Table 3). In our sensitivity analysis restricting to the years when outpatient records were available, we saw similar but slightly elevated results (Supplementary Table 4).

3.1. National Prescription Database

When stratifying by medication use, we observed an overall increase in cancers with maternal anemia (Table 3). Although increases in cancer risk were seen among children of mothers not prescribed supplements, a higher risk was seen among the children of mothers prescribed B12 and folate.

4. Discussion

In this study of Danish national registries, we found an overall association between maternal anemia and childhood cancer, which was not explained by Fanconi anemia. We observed elevated point estimates across multiple cancer types, although sample sizes were sometimes limited. Our study is the first to examine the association between maternal anemia and bone tumors.

The prevalence of anemia that we observed in controls, 3.6%, was smaller than the prevalence in Denmark estimated by WHO. The National Patient Register collects information from inpatient diagnoses as well as diagnoses from outpatient hospital-affiliated clinics, where visits to specialists take place. Anemia that was diagnosed solely in primary care would not be included. Hence, it is likely that the mothers with anemia had more severe disease which necessitated a referral for specialist care. Our results should be interpreted to reflect the impact of severe anemia. Underascertainment of anemia may also have occurred because not all of Denmark's clinics are included in the National Patient Register, as data are collected from hospital-affiliated clinics but not all private sector clinics; however, the private sector only accounts for 2% of patient visits [31]. Underascertainment of anemia could have biased our results to the null. Validation studies of the Danish National Patient Register for anemia diagnosed 2000–2009 showed a positive predictive value for anemia due to bleeding of 95% [32] and for vitamin B12 deficiency anemia between 31.5%– 36.8% [33].

Our findings for neuroblastoma are consistent with the results of two prior studies that reported that children whose mothers had maternal anemia were at an increased risk for neuroblastoma [21,25]. A weaker but still elevated association (OR=1.3, 95% CI 0.9, 1.9) was seen in a study that relied on self-report to ascertain anemia, whereas stronger effects were estimated in the current study and another study that used medical records to ascertain

anemia. However, a Washington state study that used both birth certificate records and hospital discharge records found a null association (OR= 0.69, 95% CI: 0.39, 1.21) [12]. As validation studies suggested, birth certificate records have low sensitivity to ascertain anemia (11–67%); the addition of hospital discharge records (available for a part of the Washington study) likely improved sensitivity, although these records presumably included the delivery rather than the entire prenatal period [34,35]. A separate study reported a greater risk of maternal anemia for metastatic neuroblastoma among children diagnosed at 18 months and older [36]. Metastatic neuroblastoma differs by age: when diagnosed in children younger than age 1, it is more often stage 4 S, which has the highest rate of spontaneous regression of any cancer and has considerably higher survival as compared to stage 4 neuroblastoma diagnosed at older ages; these different phenotypes appear to have distinct etiologies [37]. When we stratified by age, we observed that there was an increased risk for neuroblastoma with maternal anemia among those diagnosed 12 months and older (OR= 2.68, 95% CI: 1.47, 4.88), while the sample size of children diagnosed younger than one year of age was too small to estimate associations.

Our findings suggest an association between maternal anemia and risk for ALL. In five previous studies, mixed results were seen for the association between maternal anemia and leukemia [odds ratio (OR) range: 0.88 – 2.60] [14–17,38], with the majority of the prior studies [14–16] obtaining anemia information from medical records. A study by the Children's Oncology Group ascertained anemia via maternal recall but did not find any association between maternal anemia and leukemia [16]. A notable difference between the Children's Oncology Group study and the current study was that the prior study evaluated infant leukemia, whereas our study examined all childhood leukemia diagnosed to age 19.

Our stratified analyses showed that B12 and folate deficiency anemia was most strongly related to cancer risk. Anemia caused by vitamin B12 and folate deficiency is characterized mainly by macrocytic anemia, while iron deficiency anemia presents as microcytic anemia. Although obstetricians may not routinely perform tests to delineate the types of nutritional anemia in pregnancy, the Danish National Board of Health recommends that iron prophylaxis be given to pregnant women from 10 weeks of gestation. When we restricted our analysis to the years before 1998 when folate and iron supplementation was recommended in Denmark, there was no change in our results.

Sources of folate and vitamin B12 include dark leafy greens and dairy [39]. The literature is sparse on maternal pregnancy diet in relation to childhood cancer, but several studies have investigated foods, nutrients, and vitamins related to anemia. Three interview-based studies have examined maternal pregnancy diet in relation to ALL risk in offspring [40–42], and most found that consumption of vegetables and protein, specifically beef, was protective against ALL. In addition, two ecologic studies have examined regional changes in pediatric cancer incidence after implementing the folate supplementation of cereal grains; these reported lower neuroblastoma after supplementation [43,44]. Links between childhood cancer and inadequate folate levels have long been suspected and may also be suggested by the co-occurrence of neural tube defects among some cancer types [45].

If our results are due to low levels of maternal folate and B12, this would be in line with prior studies that indicated a lower risk for pediatric cancers with maternal vitamin supplementation in pregnancy, including studies of neuroblastoma, ALL, AML, and pediatric brain tumors [46]. In addition, a prior study found prenatal vitamins to be protective against osteosarcoma (OR: 0.70), which is in line with our results [47]. With regards to neuroblastoma, two studies found intake of vitamin supplements during pregnancy to be negatively associated (OR: 0.7, 95% CI: 0.5, 1.0; OR: 0.5 95% CI: 0.3, 0.7) [22,48]. However, one study found that vitamin or folate supplements were associated with an increased risk of neuroblastoma (OR = 1.50, 95% CI 1.06, 2.13) [49]. It may be difficult to differentiate any effect from the potentially protective factor (the supplement intake) versus an adverse effect due to the underlying condition (anemia), a problem generally referred to as confounding by indication. In our study, increased risks were seen among women with anemia, both when they took medication and when they did not, with higher point estimates for those women taking anti-anemia medication. However, anti-anemia medication use was likely related to anemia severity. Thus, we cannot discern whether the medication or the disease may be responsible for the high point estimates. Challenges to adequate vitamin supplementation include low tolerance to iron supplements and late recognition of pregnancy [50]. Hence, it is possible that women may not be taking the recommended supplement dose due to adverse side effects. This may explain varying results across studies.

Maternal anemia is associated with the insulin-like growth factor (IGF) system, including IGF-1, IGF-2, and IGFBP-3, as this system plays a modulatory role in increasing hematopoiesis and granulopoiesis [51,52]. The IGF system is crucial to fetal development and is involved in organogenesis [53]. The IGF system is involved in the pathogenesis of childhood leukemia [54] and solid tumors, including osteosarcoma, neuroblastoma, and Wilms tumor [55,56]. Iron deficiency anemia may stimulate hypoxia, enhancing DNA mutations [4]. There are multiple hypotheses involving the role of folate deficiency in cancer risk, including modifications of DNA methylation and the impairment of DNA [57]. Like folate deficiency, vitamin B12 deficiency contributes to atypical DNA methylation [58].

Further, iron deficiency anemia during pregnancy has been shown to increase placental weight, which may be related to some childhood cancer types [59]. A large placenta relative to fetal size has been associated with adverse birth outcomes, including Apgar score < 7, neonatal seizure, and respiratory morbidity [60].

Because childhood cancers are rare conditions, a limitation of our study was the small sample sizes for individual cancer types.

We lacked information on maternal diet or over-the-counter use of supplements among mothers. We could not account for maternal alcohol use as this information was not collected in Danish registries. Further, the race/ethnicity of mothers is related to anemia prevalence, and we were unable to adjust for that factor; however, adjustment for the maternal country of birth (a proxy for ethnicity) did not change the results.

One strength of our study is that our analysis included population-based registries with prospectively collected medical histories from the National Patient Register, limiting selection bias. Additionally, the use of medical records avoided differential or non-differential maternal recall errors but not non-differential misclassification due to errors in record keeping.

Early detection and adequate treatment of anemia using oral supplements can potentially lower anemia [61]. If the risk of maternal anemia can be reduced by prenatal vitamin supplementation, this would suggest an actionable strategy to prevent pediatric cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
IGF	insulin-like growth factor
ICCC	International Classification of Childhood Cancer

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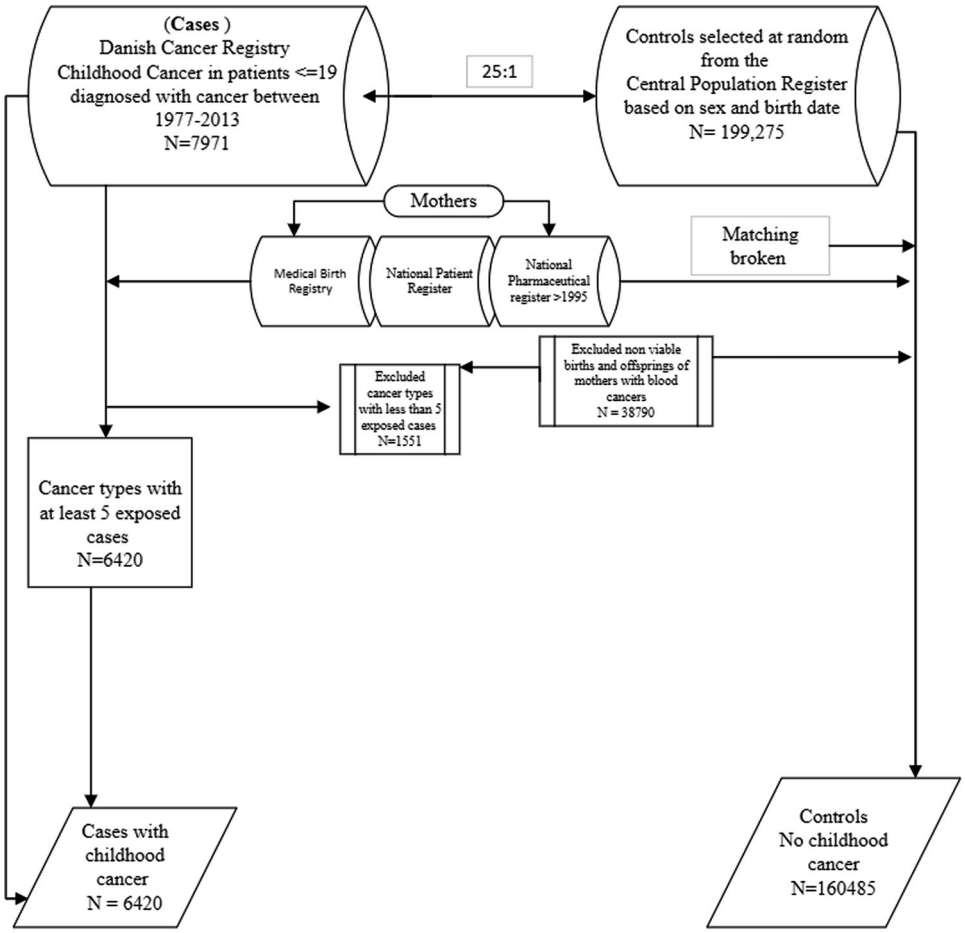

Fig. 1.
Flow chart showing the selection of cases and controls.

Table 1

Demographic characteristics of cases and controls in Denmark, birth years 1977–2013.

	Cases (N = 6420)	Controls (N = 160485)
	N (%)	N (%)
Maternal anemia during pregnancy	221 (5.1)	4143 (2.6)
Child's residence at birth		
Urban	2114 (32.9)	50982 (31.8)
Small Town	1808 (28.2)	46632 (29.1)
Rural	2498 (38.9)	62871 (39.1)
Maternal age in years (mean, SD)	28.4 (5.0)	28.2 (5.0)
Parity	1.8 (0.9)	1.8 (0.9)
Maternal Place of Birth		
Denmark	5853 (91.3)	146778 (91.6)
Europe (excluding Denmark)	201 (3.1)	5167 (3.2)
Non-Europe	354 (5.5)	8249 (5.1)
Missing	12	291
Bleeding disorder*	46 (11.1)	15728 (9.8)

*Bleeding disorders include menstrual irregularity, Hemophilia A, B, and C, and Von Willebrand disease.

Table 2

Odds ratios (and 95% CIs) for maternal anemia and childhood cancers in Denmark, birth years 1977–2013.

	Mothers with anemia N (%)	Total N	Crude OR (95% CI)	Adjusted OR (95% CI)*
Controls	4143 (2.6)	160485	1.00 (ref)	1.00 (ref)
Cancer	221 (3.4)	6420	1.35 (118, 1.55)	1.35 (1.18, 1.55)
Acute lymphoblastic leukemia	49 (4.0)	1223	1.45 (1.08, 1.96)	1.46 (1.09, 1.97)
Acute myeloid leukemia	8 (3.2)	250	1.29 (0.62, 2.68)	1.29 (0.62, 2.67)
Hodgkin lymphoma	10 (2.8)	352	1.29 (0.67, 2.50)	1.24 (0.64, 2.39)
Non-Hodgkin lymphoma**	13 (4.0)	219	1.42 (0.79, 2.52)	1.38 (0.78, 2.47)
Burkitt lymphoma	6 (5.8)	103	1.89 (0.80, 4.47)	1.93 (0.81, 4.58)
CNS tumors	51 (3.2)	1599	1.26 (0.94, 1.68)	1.24 (0.93, 1.66)
Gliomas	17 (2.2)	778	1.06 (0.64, 1.74)	1.06 (0.64, 1.74)
Neuroblastoma	14 (5.1)	276	1.86 (1.06, 3.27)	1.83 (1.04, 3.22)
Nephroblastoma	8 (3.9)	203	1.49 (0.71, 3.12)	1.48 (0.71, 3.10)
Malignant bone tumors	13 (4.8)	270	2.57 (1.41, 4.68)	2.59 (1.42, 4.72)
Osteosarcoma	8 (6.2)	130	3.64 (1.65, 8.03)	3.54 (1.60, 7.82)
Germ cell tumors	8 (2.4)	339	1.07 (0.52, 2.21)	1.06 (0.51, 2.20)

** Excludes Burkitt lymphoma

* Adjusted for child's place of birth, parity, maternal age, sex, and birth year

Table 3

Odds ratios (and 95% CIs) for maternal anemia and childhood cancers in Denmark, stratified by medication use (births after 1995 only).

	Cases (N = 2521)	Controls (N = 63025)	Crude OR (95% CI)	Adjusted OR (95% CI)*
No anemia in pregnancy	2390 (94.8)	60909 (96.6)	ref	ref
Anemia in pregnancy	131 (5.2)	2116 (3.4)	1.58 (1.32, 1.89)	1.58 (1.32, 1.89)
No anti-anemia medication prescribed	123 (4.9)	2051 (3.2)	1.53 (1.27, 1.84)	1.53 (1.27, 1.84)
Anti-anemia medications prescribed	8 (0.3)	65 (0.1)	3.14 (1.51, 6.56)	3.16 (1.51, 6.59)
B12 and folic acid	8 (0.3)	51 (0.1)	4.01 (1.90, 8.46)	4.03 (1.91, 8.50)

*Adjusted for child's place of birth, parity, maternal age