

Caesarean delivery and anaemia risk
in children in 45 low- and middle-
income countries

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Title: Caesarean delivery and anaemia risk in children in 45 low- and middle-income countries

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ABSTRACT

Caesarean delivery (CD) may reduce placental transfusion and cause poor iron-related haematological indices in the neonate. We aimed to explore the association between CD and anaemia in children aged < 5 years utilising data from Demographic and Health Surveys conducted between 2005 and 2015 in 45 low- and middle-income countries (N = 132 877). We defined anaemia categories based on haemoglobin levels, analysed each country's data separately using propensity-score weighting, pooled the country-specific odds ratios (ORs) using random effects meta-analysis, and performed meta-regression to determine whether the association between CD and anaemia varies by national CD rate, anaemia prevalence, and gross national income. Individual-level CD was not associated with any anaemia (OR 0.95, 95% confidence interval (CI) 0.86 to 1.06; $I^2 = 40.2\%$), mild anaemia (OR 0.91, 95% CI 0.81 to 1.02; $I^2 = 24.8\%$), and moderate/severe anaemia (OR 0.97, 95% CI 0.85 to 1.11; $I^2 = 47.7\%$). CD tended to be positively associated with moderate/severe anaemia in upper middle-income countries and negatively associated with mild anaemia in lower middle-income countries, however, meta-regression did not detect any variation in the association between anaemia and CD by the level of income, CD rate, and anaemia prevalence. In conclusion, there was no evidence for an association between CD and anaemia in children younger than 5 years in low- and middle-income countries. Our conclusions were consistent when we looked at only countries with CD rate > 15% with data stratified by individual-level wealth status and type of health facility of birth.

Keywords: Anaemia, child nutrition, demographic and health survey, haemoglobin, caesarean section, low- and middle-income countries

INTRODUCTION

The proportion of caesarean deliveries (CD) in the world has increased to unprecedented levels (Betran et al., 2016). This global trend is to a certain extent driven by non-medical factors (Murray, 2000, Arikan et al., 2011, Cotzias et al., 2001) rather than by medical indication, and potentially unnecessary CDs even in settings with low access have been reported (Maaloe et al., 2012). An ecological study revealed that population level CD rates higher than 10% are not associated with reductions in maternal and newborn mortality rates (Ye et al., 2016). In a recent statement on CD rates, however, the World Health Organization did not recommend any population-level CD rate threshold, highlighting the gaps in knowledge (World Health Organization, 2015).

CD has been linked to adverse maternal, neonatal, and perinatal outcomes (Villar et al., 2006) and to long-term effects such as childhood-onset type 1 diabetes and asthma in the offspring (Thavagnanam et al., 2008, Cardwell et al., 2008). The rising CD rates and the potential risks to offspring health have prompted calls to consider the risks of CD on long-term child health (Blustein and Liu, 2015).

Anaemia is a major public health problem among pregnant women and children (Kassebaum et al., 2014). Globally, about 43% of children under 5 years old are anaemic (Stevens et al., 2013). Anaemia in children is caused by many factors that act during the prenatal and postnatal periods. These include malaria infection, human immunodeficiency virus infection, intestinal helminths, poor maternal nutrition, poor child nutrition, micronutrient deficiencies, sickle cell disorders, and thalassemias (Crawley, 2004b, Kassebaum et al., 2014). Most anaemia cases are due to iron deficiency (Kassebaum et al., 2014). Iron deficiency anaemia in infants is associated with potentially irreversible diminished mental; motor; and behavioural development (Lozoff et al., 2006, Lozoff et al., 1991).

CD may reduce placental transfusion and cause poor iron-related haematological indices in the neonate (Zhou et al., 2014). Despite this risk and the rising CD rates worldwide, only a few studies have assessed the relationship between CD and anaemia in children. In two large Chinese birth cohorts, CD was associated with anaemia in children at 12 and at 58 months (Li et al., 2015). Cross-sectional studies have shown inconsistent results with some suggesting no association between CD

and anaemia (Wilunda et al., 2016) and others showing increased anaemia risk among children born by CD (Cotta et al., 2011, Granado et al., 2013). We aimed to investigate the association between CD and anaemia in children under 5 years old in low- and middle-income countries (LMICs) and to explore whether this association varies by country level CD rate, anaemia prevalence, and per-capita gross national income (GNI).

KEY MESSAGES

- Caesarean delivery (CD) may reduce placental transfusion and cause poor iron-related haematological indices in the neonate.
- Overall, in this study, there was no evidence for an association between CD and any anaemia, mild anaemia, and moderate/severe anaemia among children aged < 5 years.
- These results were consistent when the analysis was restricted to countries with CD rates > 15% with data stratified by individual-level wealth status and by type of health facility of birth.
- The effect estimates vary moderately across countries but this is uninfluenced by national CD rate, anaemia prevalence, and affluence level.

METHODS

Data source

This study utilised datasets from standard Demographic and Health Surveys (DHS) conducted between 2005 and 2015 in LMICs. All countries with data on both CD and haemoglobin (Hb) measurement were included (supplementary Table 1). The detailed methodology of DHS is available on the program's website (<http://dhsprogram.com>). In brief, DHS utilise stratified multistage cluster sampling method to select participants. In the first stage, clusters are selected from a list of enumeration areas using stratified random sampling. The second stage involves systematically sampling households in selected clusters. Eligible persons include all women aged 15-49 years and their children aged 0-59 months. Blood samples are collected in all the households or in a random subset of selected households based on considerations such as the required sample size and financial costs. Data are collected using interviewer-administered questionnaires.

Study population

The study population was singleton children aged less than 5 years and their mothers. The analysis was restricted to the most recent birth to avoid clustering of children at the woman level, to minimise recall bias, and because some covariates applied only to the most recent birth.

Variables

The outcome variable was anaemia defined based on altitude adjusted Hb levels as follows: none [Hb $\geq$ 11.0 grams/decilitre (g/dL)], mild (Hb 10-10.9 g/dL), moderate (Hb 7.0-9.9 g/dL), and severe (Hb $<$ 7.0 g/dL) (World Health Organisation, 2011). Because the number of children with severe anaemia in most countries was small, the last two categories were combined. In the DHS program, Hb levels are measured in a standardized way (Sharman, 2000): blood specimens are collected from children aged less than 5 years using a microcuvette from a drop of blood taken from a finger or heel prick, and Hb analysis is carried out on-site using a portable HemoCue® analyser; a highly valid method when compared to standard laboratory methods (Nkrumah et al., 2011).

The exposure variable was the mode of delivery [CD or vaginal delivery (VD)] ascertained by asking the respondent whether a child born five years preceding the survey was born by CD.

In propensity score weighting of individual participant's data (described below), we considered, *a priori*, the following variables to be potential confounders based on previous studies (Wilunda et al., 2016, Mishra and Retherford, 2007, Kyu et al., 2010): region within the country, residence (urban/rural), wealth index quintile, mother's age at childbirth, mother's education, parity, births in the preceding 5 years, number of antenatal visits, prenatal iron supplementation, prenatal deworming, mother's height, use of biomass for cooking, birth size (or birthweight if available), child's sex, child's age at Hb measurement, and caste (for India). Definitions of the potential confounders are available in supplementary file S1. In meta-regression (described below), we included the following national level covariates: per capita GNI based on the Atlas method (2016 US\$) (The World Bank, 2016), CD rate, anaemia prevalence in children younger than 5 years, year of the survey, and geographic region. For these variables, we used published data that corresponded to the year of the respective DHS.

Statistical analyses

After excluding children from households not selected for Hb measurement, those without Hb measurement, visitors, non-last-born children, multiple births, and those with missing data on childbirth mode, the final samples of mother-child dyads included in the study are as shown in supplementary Table S1. For all the countries, only the following variables had any missing data: number of antenatal visits, birth size (or birth weight), mother's height, prenatal deworming, prenatal iron supplementation, and use of biomass for cooking. The proportion of missing values for any of these variables was generally low and varied by country (supplementary Table S2). There was no association between the indicators for the missing values and anaemia. Thus, we performed single imputation of missing values using chained equations (StataCorp, 2013). The imputation model included all the variables included in the propensity score model (explained below) plus anaemia. For Albania, Armenia, Jordan, Kyrgyz Republic, Moldova, Namibia, Peru, Rwanda, and Sao Tome and

Principe, >90% of children had data on birth weight and we used this variable instead of birth size when computing propensity scores.

The main analysis consisted of three steps: 1) propensity score weighting to obtain country specific logarithms of odds ratios (ORs) and standard errors; 2) meta-analysis to obtain pooled ORs with 95% confidence intervals (CIs); and 3) meta-regression to assess whether the relationship between CD and anaemia varies by country level: CD rate, anaemia prevalence, and per capita GNI.

Propensity score weighting

Propensity score, defined as the probability of being assigned to a treatment group given an individual's observed covariate values (D'Agostino, 1998), was used to ensure that the CD and VD groups in the study were comparable in terms of potential confounders. Because of the complex sampling design used in DHS, we used the approach of propensity score weighting for complex surveys (Dugoff et al., 2014). First, we generated propensity scores by including sample weight as one of the covariates. Sample weights are adjustments applied to survey data to correct for oversampling, undersampling, and differences in survey response rates (<http://dhsprogram.com/faq.cfm>). We then assessed whether the scores were balanced across the CD and VD groups within blocks of the propensity score. Next, we weighted the CD and VD groups by the propensity score based on the inverse probability of treatment weighting method using doubly robust estimation (Funk et al., 2011). Each child born by CD received a weight equal to the inverse of the propensity score, and each comparison child received a weight equal to the inverse of one minus the propensity score (Garrido et al., 2014). The resultant propensity score weight was then multiplied by the sample weight to obtain a 'composite' weight. We then 'svyset' the dataset by the 'composite' weight variable, the cluster, and the strata. We used either multinomial logistic regression (for anaemia categorized as none, mild, moderate/severe) or binary logistic regression [for any degree of anaemia (hereafter any anaemia) categorized as yes or no], using the 'svy' prefix, to obtain country specific log odds ratios for the association between CD and anaemia, with adjustment for any covariate that did not meet the propensity score balancing property.

Meta-analyses

To account for moderate heterogeneity (assessed using the I^2 statistic) in the effect estimates across countries, we performed random effects meta-analyses to obtain summary ORs for the association between CD and any anaemia, mild anaemia, and moderate/severe anaemia. The unit of analysis was the country. We assessed for any bias in the selection of countries included in this study using a funnel plot and tested for the plot's symmetry using the Egger's test.

Meta-regression

We performed meta-regression to determine whether the association between CD and any anaemia varies by national level CD rate, anaemia prevalence, and GNI per capita. These variables were entered into the model as predictors whilst the country specific logarithms of ORs was the outcome.

Stratified and subgroup analyses

Because CD rates tend to be higher among wealthier women (Ronsmans et al., 2006) and those who deliver in private health facilities (Vieira et al., 2015), we performed two sets of stratified analyses among countries with national CD rate > 15%. We stratified children by wealth status (lower two wealth quintiles or upper two wealth quintiles) and by type of health facility of birth (public sector or private sector) and assessed for the association between CD and anaemia in these strata. Because the risk of anaemia in children varies by child's age (Crawley, 2004a), for each country, we stratified children by age (< 23 months or 24-59 months) and repeated the analyses in each age stratum using the same approach and variables as in the main analyses.

All statistical analyses were performed using STATA 14 (StataCorp, College Station, TX, USA).

Ethics

Country-specific DHS protocols were approved by relevant ethics committees and authorities in each country by ICF International institutional review board. Because this study utilised de-identified open source datasets, it did not require ethical review.

RESULTS

This study included 45 countries; a majority (23/45) were in the low-income group (Table 1). Seven and 18 of the countries had national CD rates of $> 15\%$ and $< 5\%$, respectively. Supplementary Table S1 presents sample characteristics of mother-child dyads included in the study.

Of the 132 877 children studied, 80 375 had any anaemia, 32 617 had mild anaemia, and 47 758 had moderate/severe anaemia. The pooled ORs showed no evidence for an association between individual-level CD and any anaemia (OR 0.95, 95% confidence interval (CI) 0.86 to 1.06; $I^2 = 40.2\%$, Figure 1), mild anaemia (OR 0.91, 95% CI 0.81 to 1.02; $I^2 = 24.8\%$, supplementary Figure S1), and moderate/severe anaemia (OR 0.97, 95% CI 0.85 to 1.11; $I^2 = 47.7\%$, Figure 2) in children under 5 years of age. There was moderate heterogeneity in the ORs across the countries. There was no association between CD and any anaemia in strata defined by country-level variables and between CD and mild anaemia and moderate/severe anaemia within the region, national CD rate, and anaemia prevalence strata (Table 2). CD was, however, positively associated with moderate/severe anaemia in upper middle-income countries (OR 1.22, 95% CI 1.01 to 1.47; $I^2 = 0.0\%$) and negatively associated with mild anaemia in lower middle-income countries (OR 0.84, 95% CI 0.74 to 0.95; $I^2 = 0.0\%$). CD was not associated with moderate/severe anaemia in low-income and lower middle-income countries and with mild anaemia in upper middle-income and low-income countries (Table 2).

There was no evidence of bias in the selection of countries included in this study as assessed based on any anaemia ($p = 0.549$, supplementary Figure S2). Meta-regression showed that the ORs for any anaemia did not vary by national CD rate; anaemia prevalence; and per capita GNI (Table 3). Supplementary Figure S3 further shows no evidence for an association between national income level on a continuous scale and the log odds ratio for anaemia.

Stratified and subgroup analyses

Among 64 037 children aged < 2 years, 16 684 had mild anaemia and 29 015 had moderate/severe anaemia. In this age group in which CD would potentially have the greatest effect on anaemia, there was no association between individual-level CD and any anaemia (OR 1.01, 95% CI 0.86 to 1.18; $I^2 =$

45.4%, supplementary Figure S4), mild anaemia (OR 0.98, 95% CI 0.98 to 1.14; $I^2 = 25.2\%$, supplementary Figure S5), and moderate/severe anaemia (OR 1.07, 95% CI 0.88 to 1.30; $I^2 = 51.3\%$, supplementary Figure S6).

Among 68 840 children aged 2-5 years, 15 933 had mild anaemia and 18 743 had moderate/severe anaemia. In this age group, there was no association between individual-level CD and any anaemia (OR 0.88, 95% CI 0.78 to 1.00; $I^2 = 22.6\%$, supplementary Figure S7), and moderate/severe anaemia (OR 0.86, 95% CI 0.74 to 1.01; $I^2 = 23.9\%$, supplementary Figure S8). However, children born by CD tended to have a reduced mild anaemia risk (OR 0.81, 95% CI 0.68 to 0.95; $I^2 = 40.4\%$ supplementary Figure S9) compared to those born by VD.

In subgroup analyses restricted to countries with CD rate of $> 15\%$, we did not find any association when data were stratified by wealth quintile and by type of health facility (private or public) (supplementary Table S3).

DISCUSSION

Overall, we did not observe any association between CD and any degree of anaemia, mild anaemia, and moderate/severe anaemia among children aged less than 5 years in LMICs. These findings were consistent when we restricted our analyses to countries with CD rate higher than 15% with data stratified by children's wealth status and by type of health facility of birth. There was moderate heterogeneity in the effect estimates across countries but the associations did not vary by national CD rate, anaemia prevalence, and per capita GNI. However, we noticed that CD tended to be more positively associated with moderate/severe anaemia in upper middle-income countries and more negatively associated with mild anaemia in lower middle-income countries. Similarly, there was no evidence for an association between CD and any anaemia and moderate/severe anaemia when children were stratified by age (younger than 2 years and 2-5 years).

In a meta-analysis of seven observational studies, Hb levels were 0.51 g/dL lower in neonates born by CD compared with those born vaginally (Zhou et al., 2014). CD may reduce Hb and other haematological indices in neonates through different mechanisms. CD may be associated with a shortened period of placental transfusion due to immediate umbilical cord clamping (Shirvani et al., 2010). Indeed, delayed cord clamping for at least 60 seconds after birth results in better haematological indices in neonates (McDonald et al., 2013) and WHO strongly recommends late cord clamping (performed about 1 to 3 minutes after birth) for all births (World Health Organisation, 2012). A recent trial in Nepal (Ashish et al., 2017) has found improved haemoglobin levels at 8 and 12 months, improved iron status at 8 months, and low risk of iron deficiency anaemia at 8 months after delayed cord clamping. However, a study in Sweden (Andersson et al., 2014) did not find an association between cord clamping and iron status at 12 months. Lack of/insufficient uterine contraction and vaginal squeeze during CD (Jain and Eaton, 2006), lower maternal blood pressure associated with the use of anaesthesia (Klohr et al., 2010), and delayed onset of respiration associated with CD (Redmond et al., 1965) may result in a weaker placental transfusion force. Additionally, delayed microbiota acquisition in children born by CD can affect their immunophysiological

development and increase the risk of infections (Gronlund et al., 1999), which would decrease iron absorption (Hurrell, 2012) or even cause anaemia. CD may also increase the risk of anaemia in children by disrupting breastfeeding (Prior et al., 2012) and maternal general health (Villar et al., 2006). A higher amount of intrapartum and postpartum blood loss associated with CD (Bateman et al., 2010) may cause maternal anaemia (Butwick et al., 2017) and reduce the amount of iron in breast milk.

Although an improvement in iron stores may persist up to six months in infants whose cord clamping was delayed (McDonald et al., 2013), it is plausible that differences in Hb concentration found shortly after birth due to the timing of cord clamping and mode of delivery may not persist into early childhood (McDonald et al 2013). This might partly explain the overall lack of association between CD and anaemia in children under 5 years of age or even in those under 2 years of age. Moreover, routine early-childhood anaemia control interventions such as iron supplementation, exclusive breastfeeding, and adequate nutrition may eliminate any differences in Hb concentration between CD and VD groups.

A study in China found that CD was weakly associated with increased anaemia risk in children aged 12 months and 58 months but not among those aged 6 months (Li et al., 2015). The authors, however, did not give a reason for this inconsistency. Two cross-sectional studies from Brazil (Cotta et al., 2011, Granado et al., 2013) have also reported an increased risk of anaemia among children born by CD. Of note is that China and Brazil are upper middle-income countries. We observed a higher moderate/severe anaemia risk among children born by CD in upper middle-income countries. This seems to be consistent with the findings in previous studies (Li et al., 2015, Cotta et al., 2011, Granado et al., 2013). Although we observed a reduced mild anaemia risk among children in the lower middle-income countries and among those aged 2-5 years, the forest plots (supplementary Figures S9 and S10) show that the number of children born by CD in each country was generally small and extreme odds ratios were more likely to be observed among countries with smaller numbers of children born by CD than in countries with larger samples. Thus, the observed negative associations could be by chance.

To our knowledge, this is the first single study on the relationship between CD and anaemia in children in LMICs using nationally representative data. Our study is based on a large sample of children from multiple countries included in the DHS program. The DHS program uses standardised data collection methods and is often considered to be the best available source of data for many health, nutrition, and demographic indicators in LMICs. We used propensity score weighting to adjust for confounding, and incorporated country- and individual-level data in the analyses. In propensity score weighting, we used doubly robust estimation which combines outcome regression and propensity score approaches to obtain unbiased effect estimators (Funk et al., 2011). The use of data from a large number of countries with varying levels of CD rates, affluence, and anaemia burden together with the lack of evidence of bias in the selection of the countries increases the generalisability of our findings to LMICs. This study, however, has limitations. First, we assumed that anaemia in childhood reflects iron status. However, anaemia is not a specific indication of iron deficiency. Thus, the association between CD and iron related anaemia could have been masked by the presence of anaemia due to other factors. Second, although we adjusted for many potential confounders in the analysis of individual level data, the results are still subject to unmeasured confounding by factors such as mother's prenatal anaemia status, pregnancy complications, and the practice of delayed cord clamping (DHS did not collect data on these variables). Moreover, we could not obtain national level data on cord clamping practices to account for this factor in meta-regression. The degree to which the unmeasured confounding might have affected our results remains uncertain. Third, information related to the prenatal period was ascertained retrospectively and may have been affected by recall bias. To minimise this bias, we limited our analysis to the youngest child. Finally, only seven countries had Hb data of children aged < 6 months. Given that CD would potentially have the most influence on anaemia among younger children because iron acquired before birth is the main source of iron for infants during the first months of life (Chaparro, 2008), and given that any effect of CD on anaemia is likely to be short term, lack of association between CD and anaemia in the present study could partly be because the participants were mainly aged 6-59 months. Nonetheless, a previous study did not find an association between CD and anaemia in infants aged 6 months (Li et al., 2015).

In conclusion, overall, there is no evidence for an association between CD and anaemia in children younger than 5 years in LMICs, although moderate differences in the associations exist across countries. Even though we cannot infer causality, our findings are reassuring in this era of increasing CD rates globally. Nevertheless, further and better-designed studies are needed to explore the relationship between CD and anaemia especially in upper middle-income countries and to elucidate the likely mechanism of any observed association.

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Tables and Figures

Table 1 Characteristics of the included countries

Characteristic	Frequency (n=45)	Percent
Year of survey		
2005-2008	9	20.0
2009-2011	15	33.3
2012-2015	21	46.7
Income level		
Low	23	51.1
Lower middle	17	37.8
Upper middle	5	11.1
National Anaemia prevalence in children		
< 40%	11	24.4
40-60%	15	33.3
>60%	19	42.2
Region ^a		
NA/WA/CA/E	8	17.8
SSEA	4	8.9
SSA	28	62.2
LA&C	5	11.1
National CD rate		
> 15%	7	15.6
5-15%	20	44.4
< 5%	18	40.0

^aModelled on the WHO classification of regions.

NA/WA/CA/E, North Africa/Western Asia/Central Asia/Europe; SSEA, South and South East Asia; SSA, Sub-Saharan Africa; LA&C, Latin America and the Caribbean; CD, cesarean delivery

Table 2 Summary odds ratios for the associations between CD and any anaemia, mild anaemia and moderate/severe anaemia in children aged under 5 years in low- and middle-income countries stratified by national characteristics

	Any anaemia		Mild anaemia		Moderate/severe anaemia	
	OR (95% CI)	I ²	OR (95% CI)	I ²	OR (95% CI)	I ²
Overall	0.95 (0.86 to 1.06)	40.2%	0.91 (0.81 to 1.02)	24.8%	0.97 (0.85 to 1.11)	47.7%
Region						
NA/WA/CA/E	0.87 (0.69 to 1.11)	44.3%	0.86 (0.66 to 1.11)	33.4%	0.95 (0.74 to 1.22)	27.6%
SSEA	0.86 (0.70 to 1.06)	0.0%	0.92 (0.73 to 1.17)	0.0%	0.89 (0.51 to 1.56)	73.1%
SSA	1.06 (0.89 to 1.27)	42.7%	0.99 (0.81 to 1.22)	32.8%	1.03 (0.84 to 1.27)	49.0%
LA&C	0.86 (0.68 to 1.09)	53.1%	0.85 (0.67 to 1.06)	37.5%	0.90 (0.67 to 1.22)	56.2%
National CD rate						
More than 15%	0.96 (0.84 to 1.10)	38.4%	0.93 (0.80 to 1.08)	25.9%	1.08 (0.89 to 1.33)	49.1%
5-15%	0.92 (0.78 to 1.09)	36.5%	0.89 (0.76 to 1.04)	4.8%	0.91 (0.75 to 1.11)	44.6%
Less than 5%	1.04 (0.78 to 1.37)	49.2%	0.95 (0.69 to 1.31)	43.2%	0.98 (0.71 to 1.34)	51.5%
Anaemia prevalence ^a						
Less than 40%	0.97 (0.82 to 1.15)	51.1%	0.94 (0.76 to 1.16)	58.0%	1.07 (0.94 to 1.22)	0.0%
40-60%	0.99 (0.78 to 1.25)	46.1%	0.91 (0.72 to 1.16)	18.5%	1.00 (0.73 to 1.38)	63.5%
More than 60%	0.92 (0.77 to 1.11)	40.2%	0.89 (0.76 to 1.05)	0.0%	0.89 (0.72 to 1.11)	44.8%
National income level						
Upper middle	1.12 (0.97 to 1.29)	0.0%	1.07 (0.90 to 1.27)	0.0%	1.22 (1.01 to 1.47) ^b	0.0%
Lower middle	0.89 (0.78 to 1.01)	14.1%	0.84 (0.74 to 0.95) ^c	0.0%	0.93 (0.75 to 1.14)	48.5%
Low	0.96 (0.78 to 1.18)	52.1%	0.90 (0.72 to 1.12)	37.8%	0.93 (0.74 to 1.17)	50.6%

^aIn children aged less than 5 years; ^bP=0.043; ^cp=0.007

The odds ratios are adjusted for region within the country, residence (urban/rural), wealth index, mother's age at childbirth, mother's education, parity, births in the past 5 years, number of antenatal visits, prenatal iron supplementation, prenatal deworming, mother's height, use of biomass for cooking, size of the baby at birth or birth weight, sex of the baby, and child's age in months.

CI, confidence interval; OR, Odds ratio. The other abbreviations are as under Table 1

Table 3 Meta-regression with odds ratios of any degree of anaemia as the dependent variable and national-level caesarean delivery rate, anaemia prevalence and per-capita gross national income as independent variables

Covariate	Unadjusted OR (95% CI)	Adjusted ^a OR (95% CI)
National CD rate		
Less than 5%	1	1
5-15%	0.94 (0.69 to 1.29)	0.87 (0.57 to 1.30)
More than 15%	0.99 (0.71 to 1.37)	1.09 (0.58 to 2.07)
Anaemia prevalence		
Less than 40%	1	1
40-60%	1.00 (0.74 to 1.35)	0.82 (0.51 to 1.31)
More than 60%	0.95 (0.71 to 1.25)	0.77 (0.48 to 1.22)
Income level		
Low	1	1
Lower middle	0.98 (0.79 to 1.21)	1.14 (0.77 to 1.67)
Upper middle	1.24 (0.97 to 1.59)	1.34 (0.82 to 2.20)

^aAdjusted for all the three group level covariates plus region and year of survey

CD, cesarean delivery; CI, confidence interval; OR, Odds ratio.

Figure 1 Association between caesarean delivery and any anaemia in children aged under 5 years in low- and middle-income countries

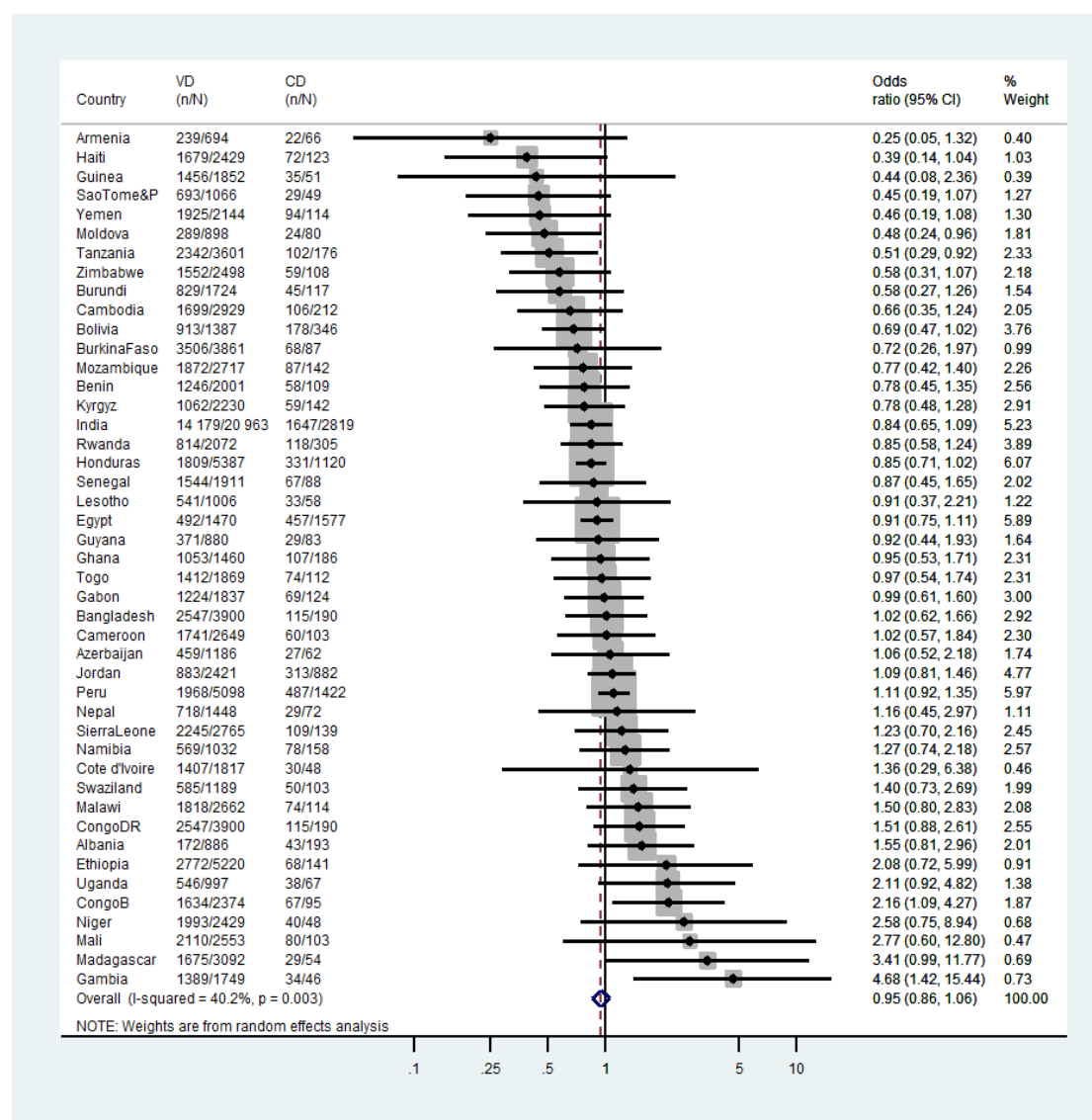


Figure 1 legend: VD: Vaginal delivery; CD: Caesarean delivery; n: any anaemia cases; N: number of children. Propensity score weighting was used to adjust the odds ratios for region within the country, residence (urban/rural), wealth index, mother's age at childbirth, mother's education, parity, births in the past 5 years, number of antenatal visits, use of iron supplements during pregnancy, use of deworming drugs during pregnancy, mother's height, use of biomass for cooking, size of the baby at birth or birth weight, sex of the baby, and child's age in months. We did not adjust for use of biomass for cooking for some countries either because almost all or no household used this fuel (Burundi, Rwanda, Gabon, Guinea, Madagascar, Malawi, Mali, Sierra Leone, Tanzania, Togo, and Uganda), or data were not collected (Jordan and Egypt). Armenia, Bangladesh, Bolivia, Jordan, Lesotho, and Tanzania did not have data on prenatal deworming. Yemen lacked data on woman's education and Bangladesh lacked data on prenatal iron supplementation.

Figure 2 Association between caesarean delivery and moderate/severe anaemia in children aged under 5 years in low- and middle-income countries

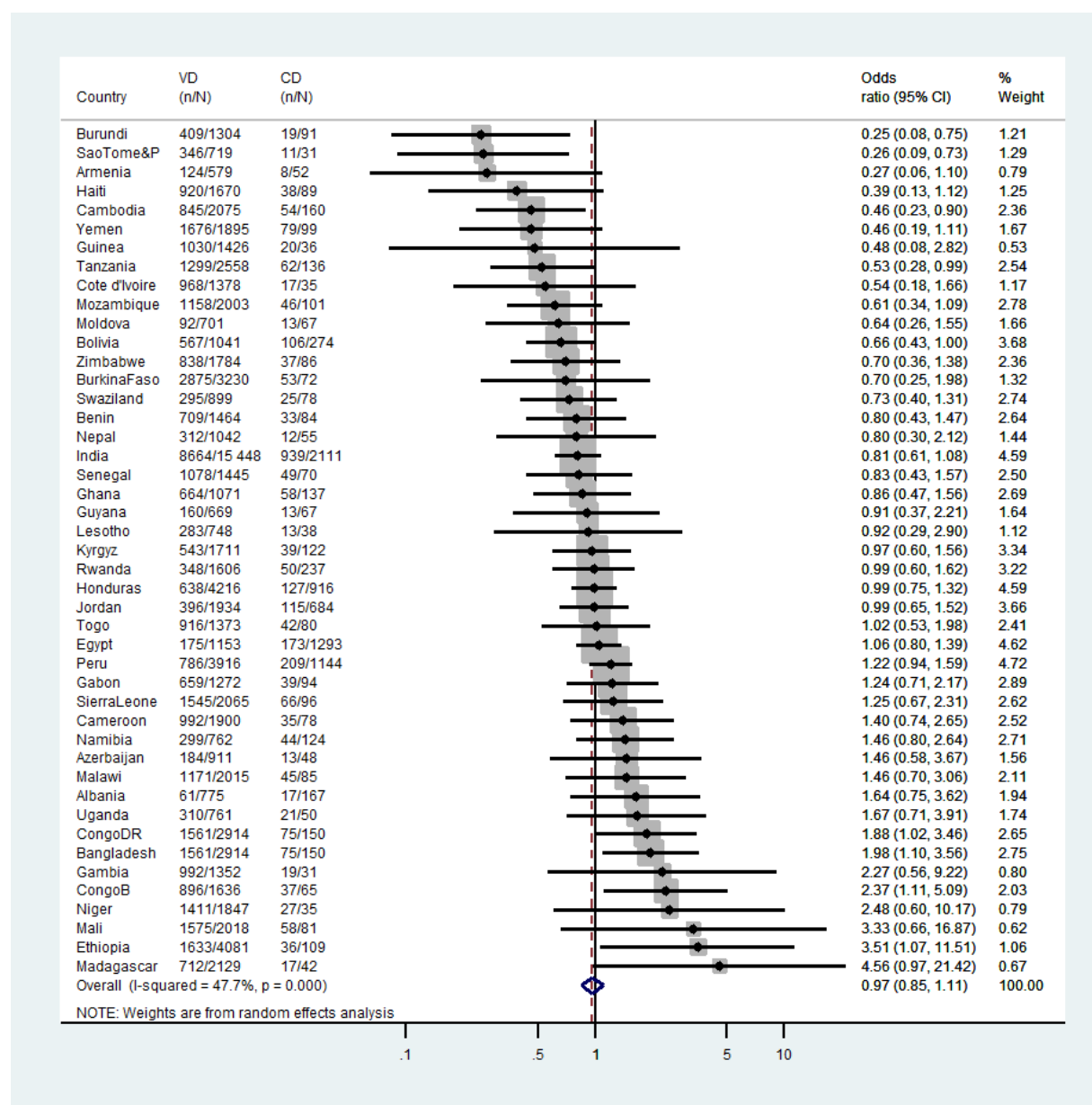
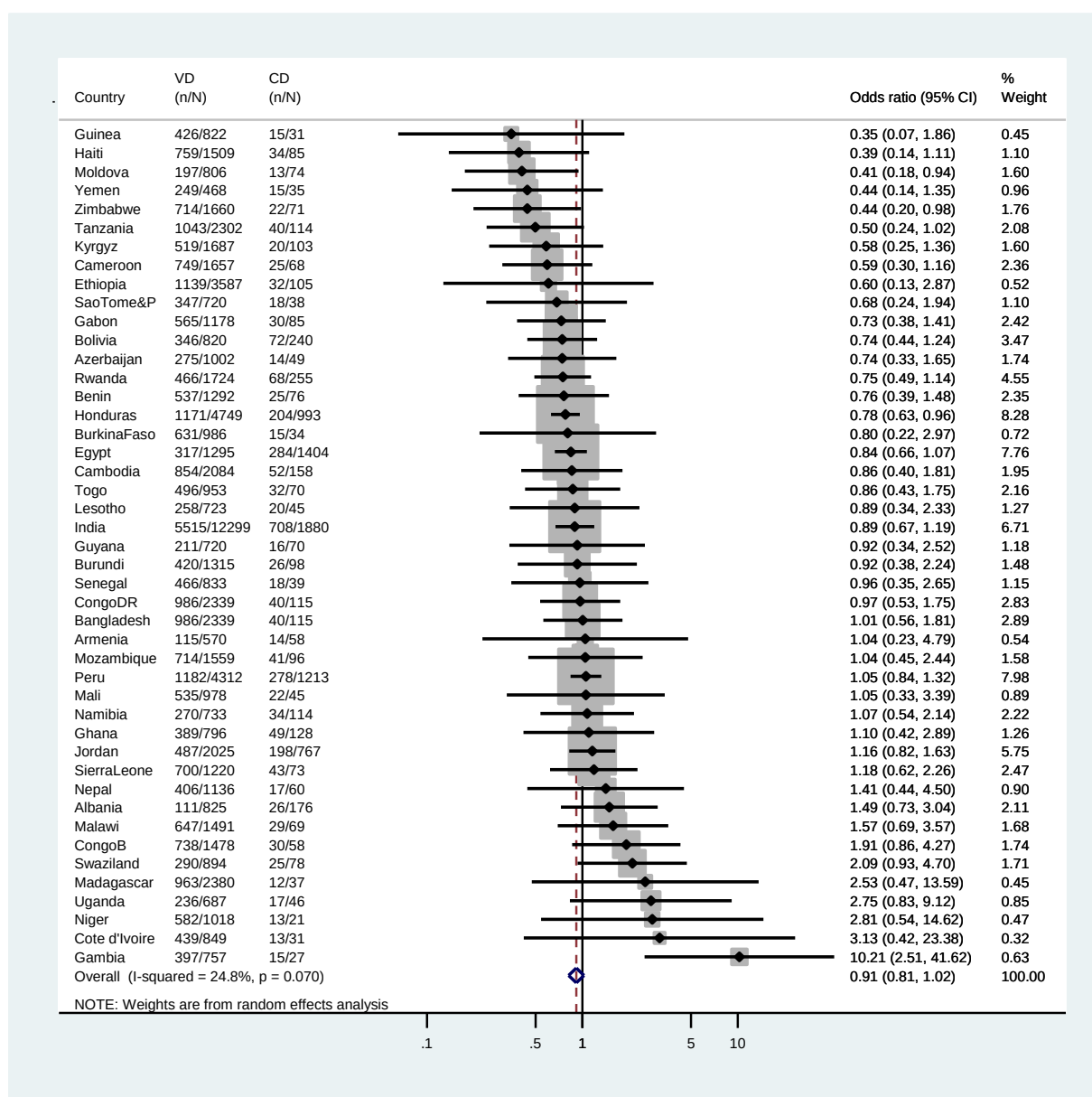


Figure 2 legend: VD: Vaginal delivery; CD: Caesarean delivery; n: moderate/severe anaemia cases; N: number of children. The other details are as provided in Figure 1 legend.

Caesarean delivery and anaemia risk in children in 45 low- and middle-income countries

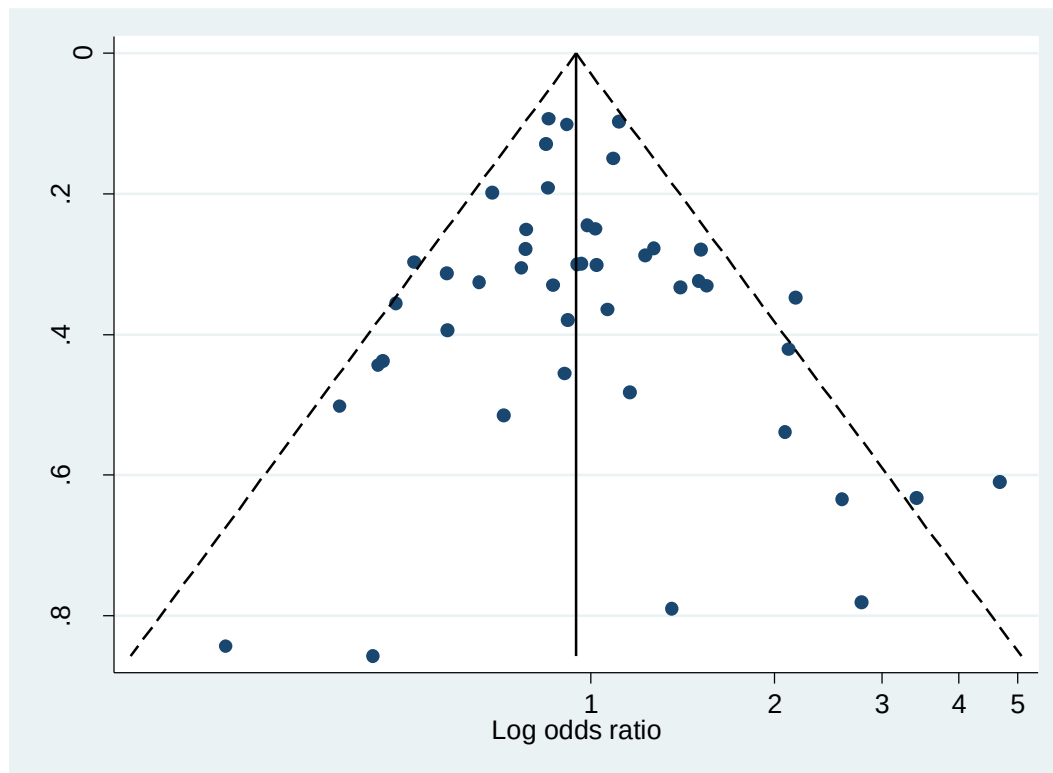
Supplementary figures

Supplementary Figure S1 Association between caesarean delivery and mild anaemia in children aged under 5 years in 45 low- and middle-income countries



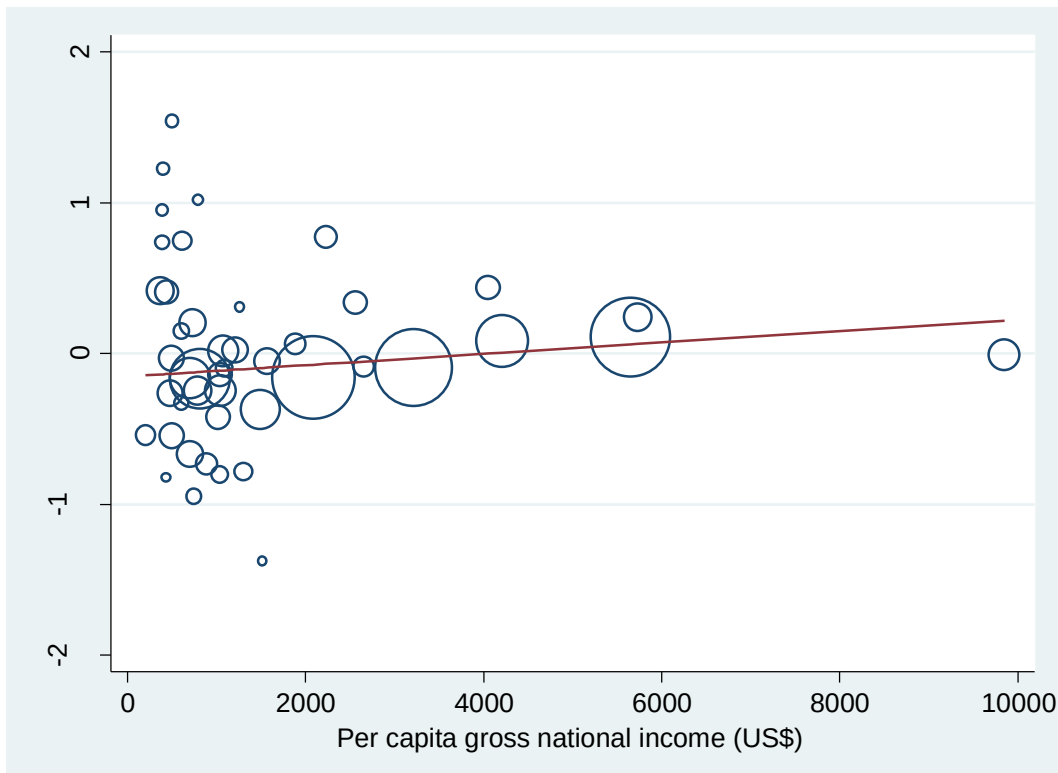
VD: Vaginal delivery; CD: Caesarean delivery; n: mild anaemia cases; N: number of children. Propensity score weighting was used to adjust for region within the country, residence (urban/rural), wealth index, mother's age at childbirth, mother's education, parity, births in the past 5 years, number of antenatal visits, use of iron supplements during pregnancy, use of deworming drugs during pregnancy, mother's height, use of biomass for cooking, size of the baby at birth or birth weight, sex of the baby, and child's age in months. We did not adjust for use of biomass for cooking for some countries either because almost all or no household used this fuel (Burundi, Rwanda, Gabon, Guinea, Madagascar, Malawi, Mali, Sierra Leone, Tanzania, Togo, and Uganda), or data were not collected (Jordan and Egypt). Armenia, Bangladesh, Bolivia, Jordan, Lesotho, and Tanzania did not have data on prenatal deworming. Yemen lacked data on woman's education and Bangladesh lacked data on prenatal iron supplementation.

Supplementary Figure S2 A funnel plot with pseudo 95% confidence intervals for the relationship between CD and any anaemia in children in 45 low- and middle-income countries.



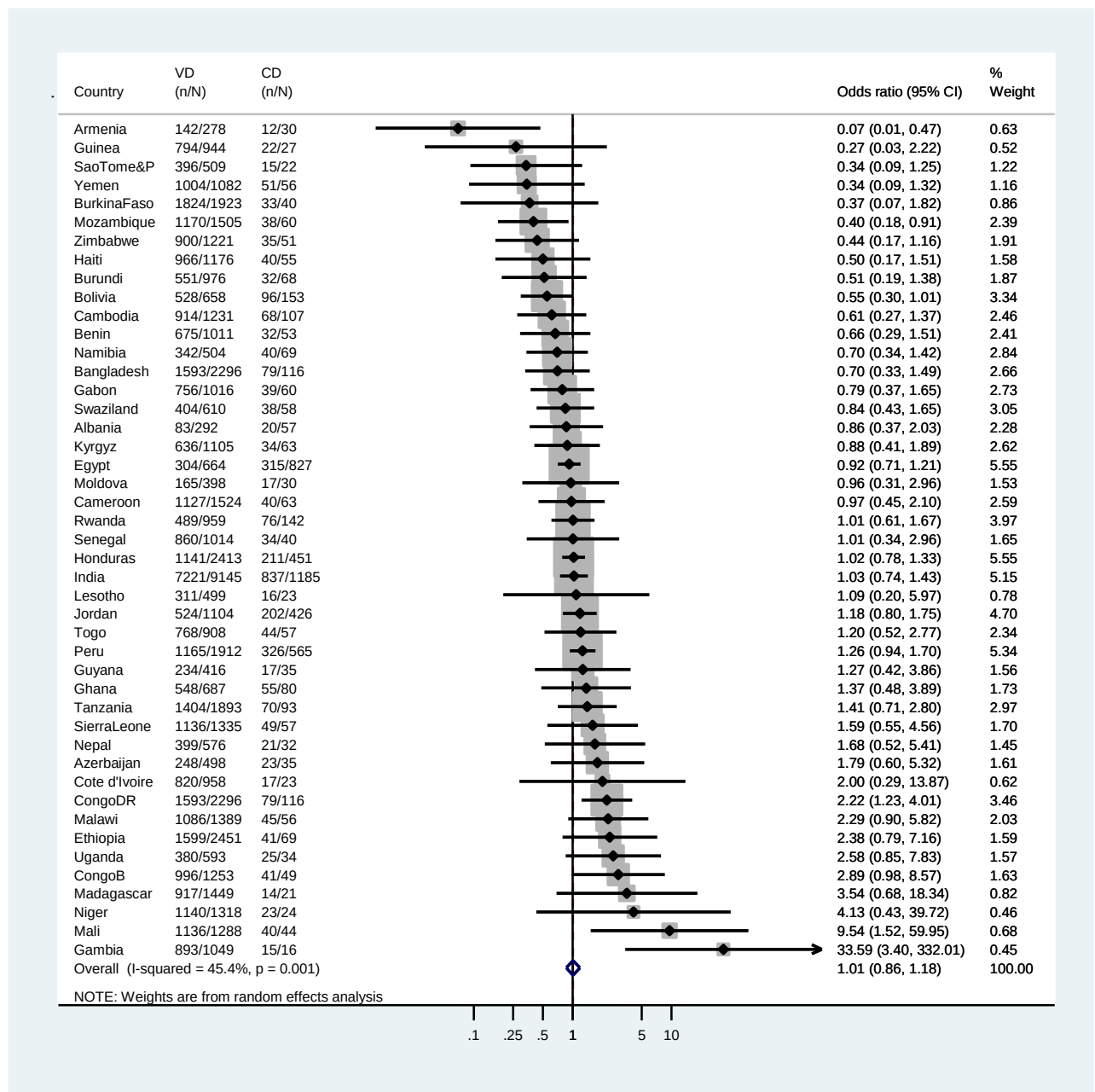
Note: Results from small studies are scattered widely at the bottom of the graph and the spread narrows among larger studies. In the absence of bias, the plot will resemble a symmetrical, inverted funnel.

Supplementary Figure S3 Association between the national income level and the log odds ratio for anaemia in children under 5 years in 45 low- and middle-income countries



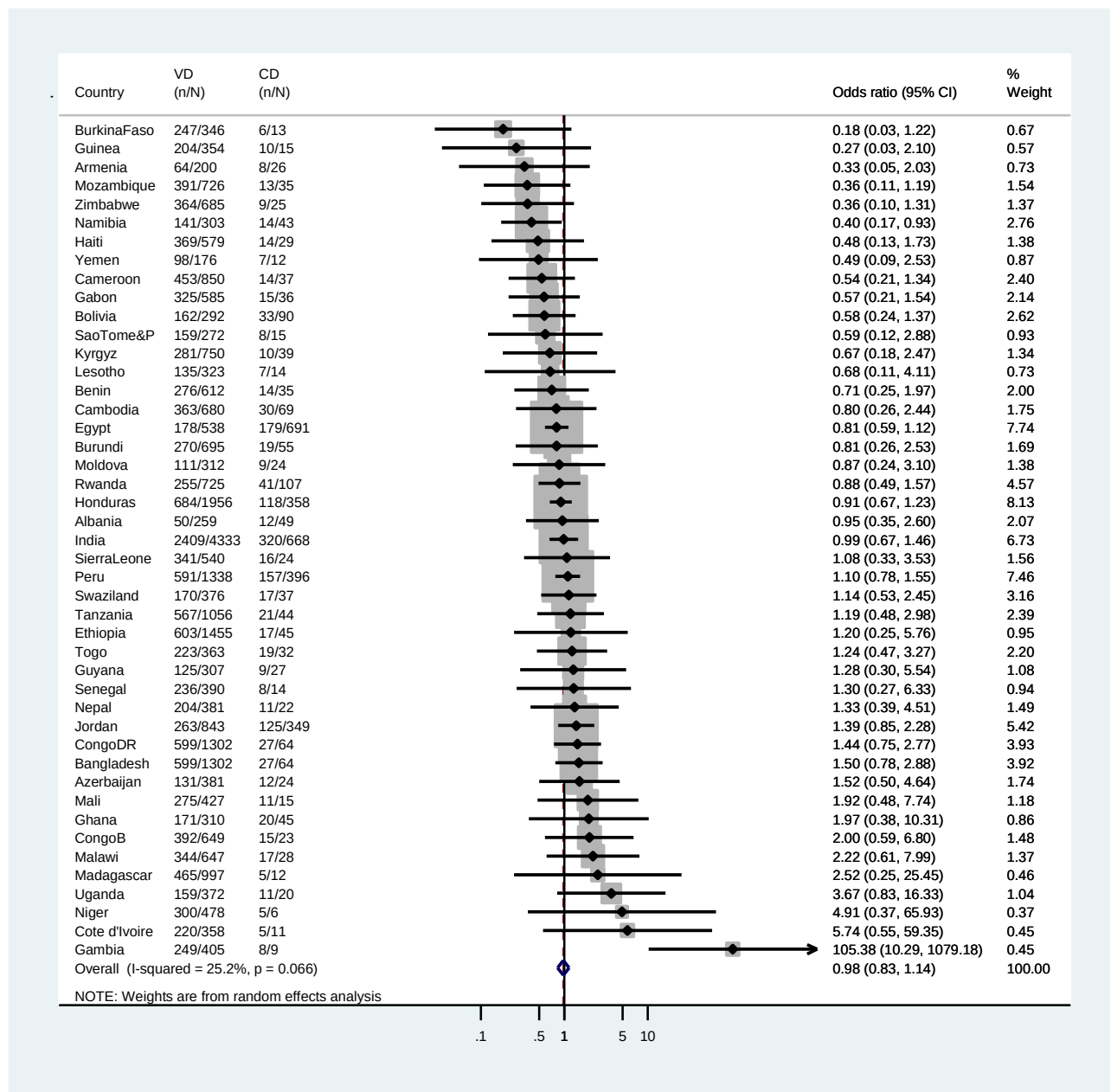
The graph shows a fitted regression line together with circles representing the estimates from each country; the size of each circle indicates the precision of each estimate. For every one US\$ increase in national income, the odds ratio for anaemia is multiplied by 1.00 ($p=0.096$)

Supplementary Figure S4 Caesarean delivery and any anaemia risk in children aged under 2 years in 45 low- and middle-income countries



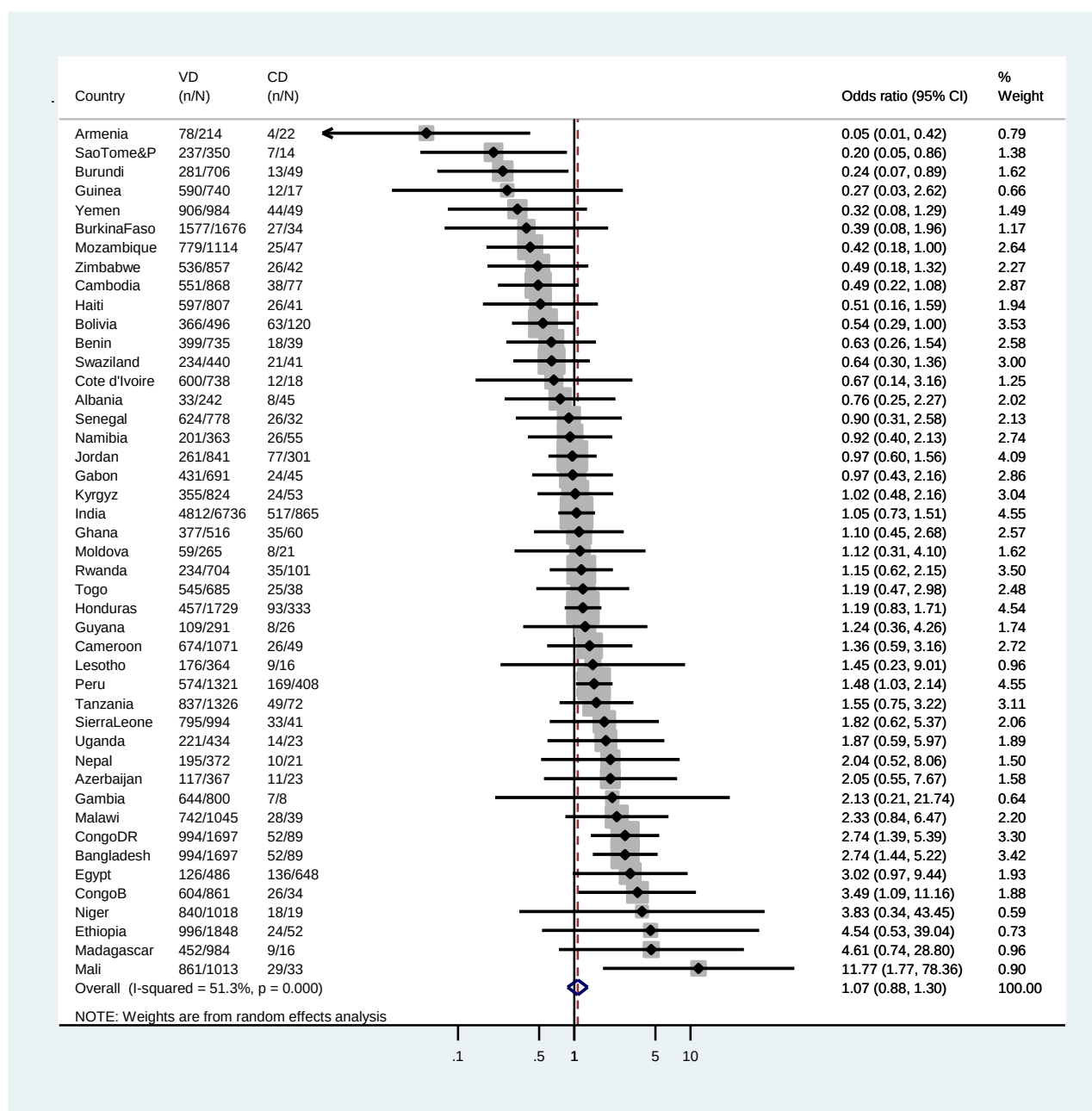
VD: Vaginal delivery; CD: Caesarean delivery; n: any anaemia cases; N: number of children. Other details are as presented in Supplementary Figure S1 legend

Supplementary Figure S5 Caesarean delivery and mild anaemia risk in children aged under 2 years in 45 low- and middle-income countries



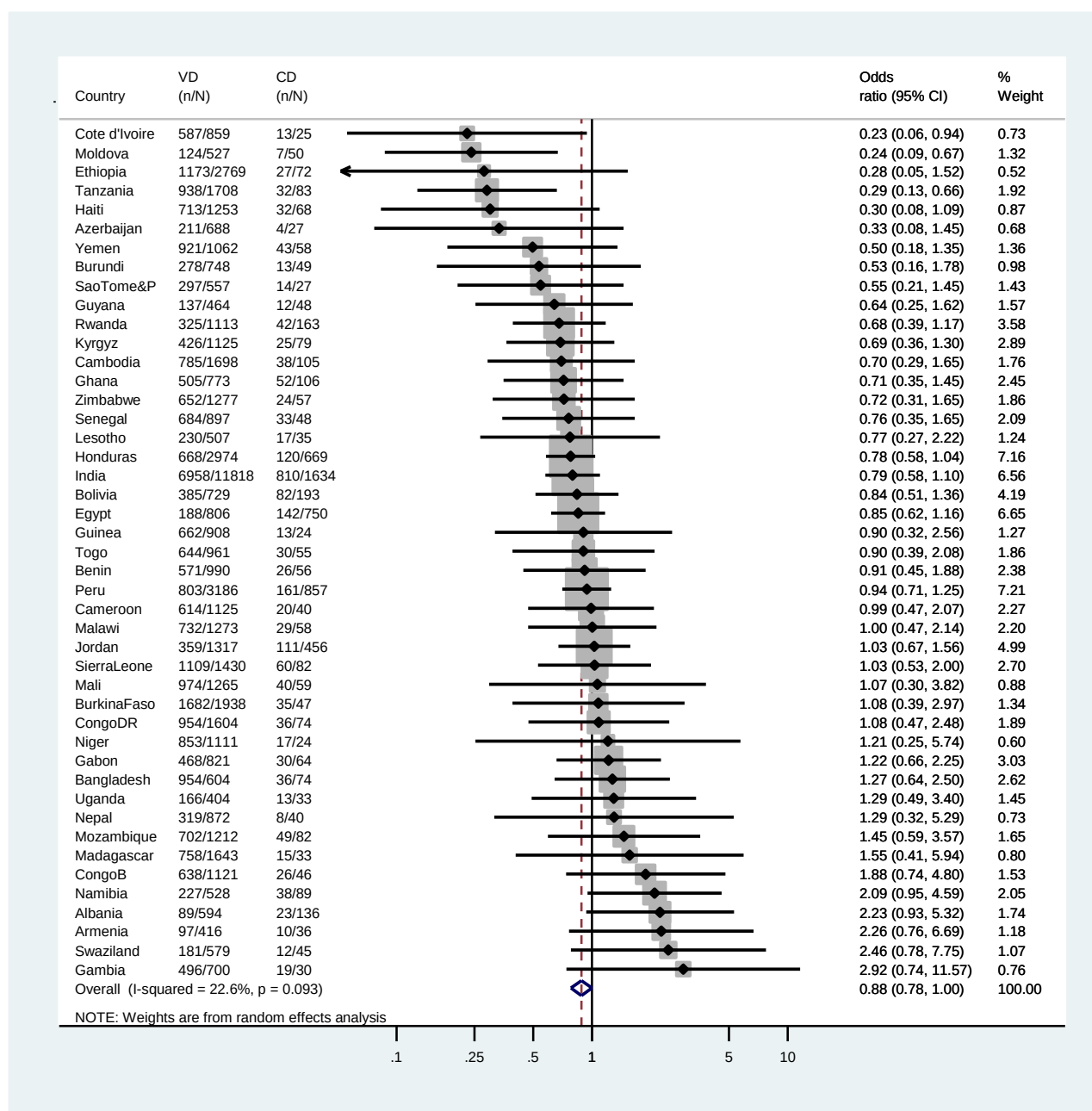
VD: Vaginal delivery; CD: Caesarean delivery; n: mild anaemia cases; N: number of children. Other details are as presented in Supplementary Figure S1 legend

Supplementary Figure S6 Caesarean delivery and moderate/severe anaemia risk in children aged under 2 years in 45 low- and middle-income countries



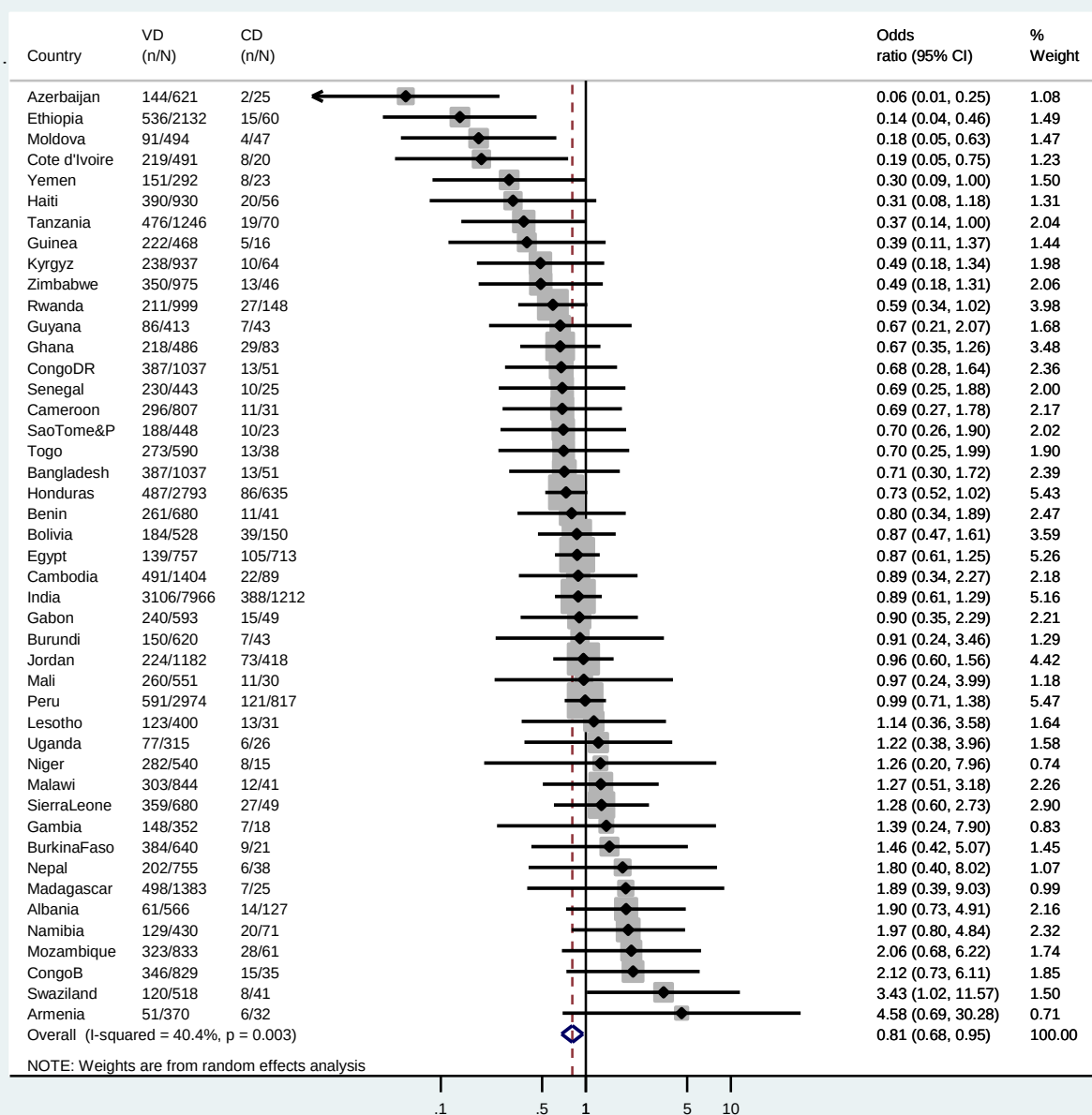
VD: Vaginal delivery; CD: Caesarean delivery; n: moderate/severe anaemia cases; N: number of children. Other details are as presented in Supplementary Figure S1 legend

Supplementary Figure S7 Caesarean delivery and any anaemia risk in children aged 2-5 years in 45 low- and middle-income countries



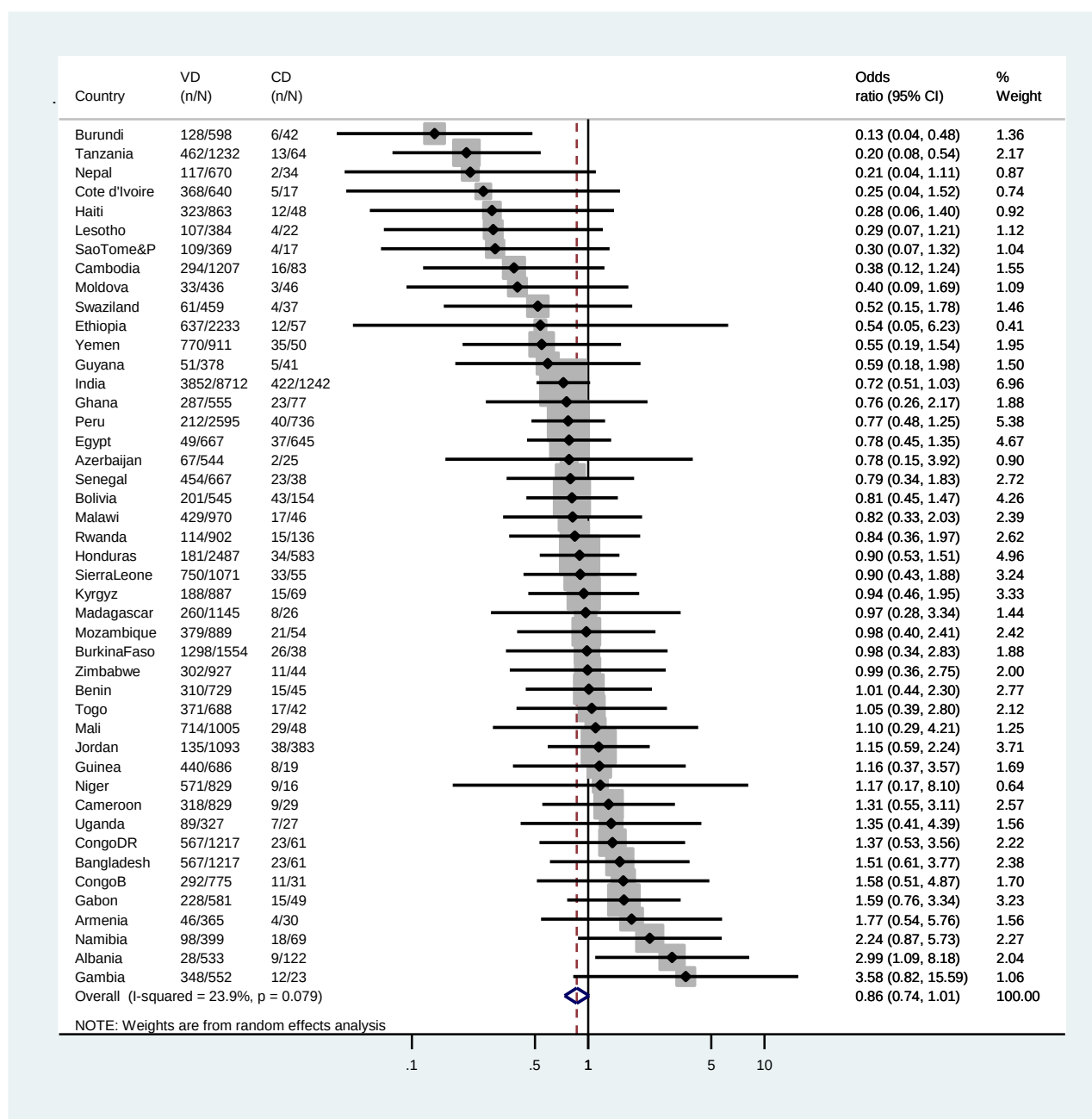
VD: Vaginal delivery; CD: Caesarean delivery; n: any anaemia cases; N: number of children. Other details are as presented in Supplementary Figure S1 legend

Supplementary Figure S8 Caesarean delivery and moderate/severe anaemia risk in children aged 2-5 years in 45 low- and middle-income countries



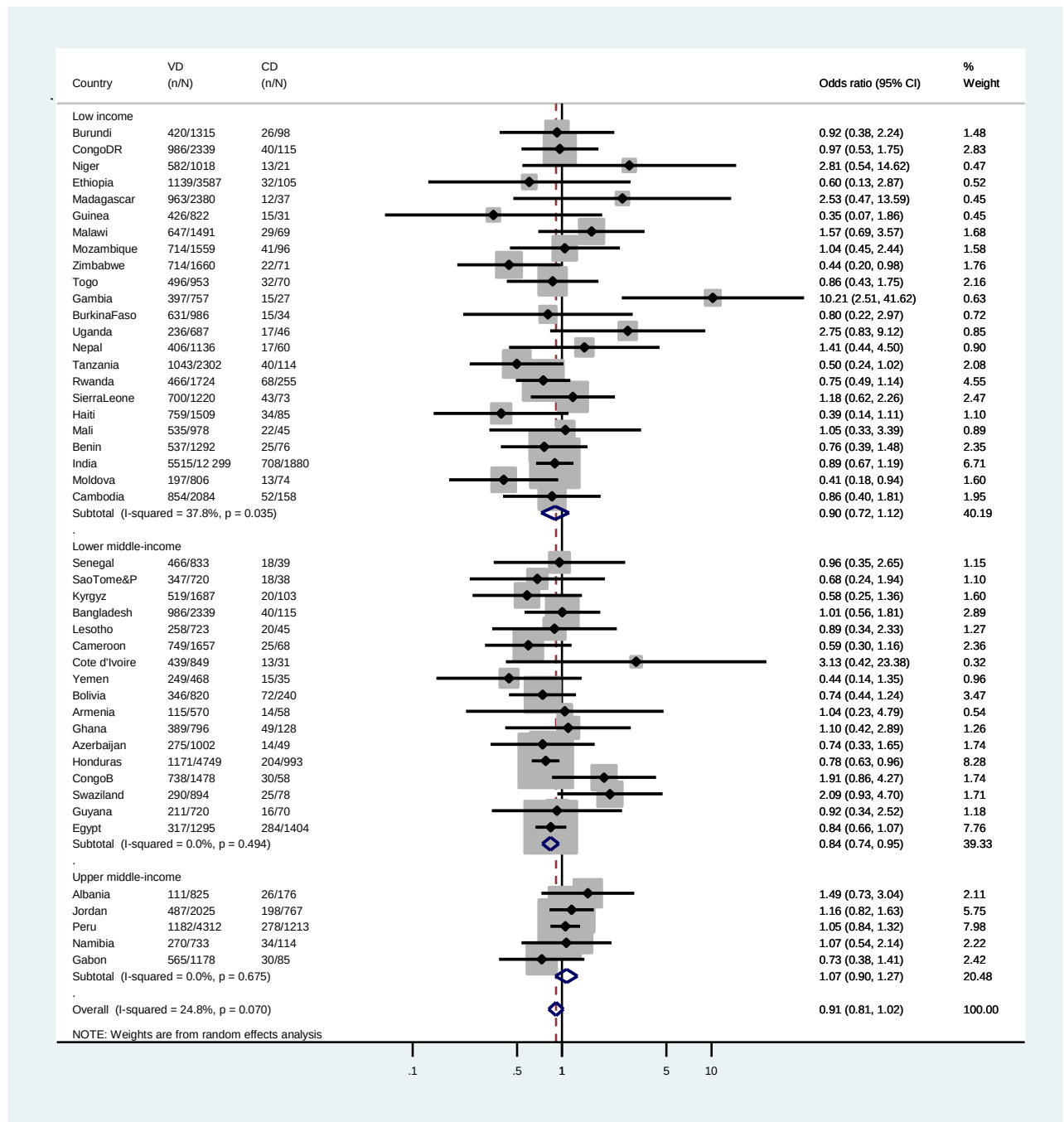
VD: Vaginal delivery; CD: Caesarean delivery; n: moderate/severe anaemia cases; N: number of children. Other details are as presented in Supplementary Figure S1 legend.

Supplementary Figure S9 Caesarean delivery and mild anaemia risk in children aged 2-5 years in 45 low- and middle-income countries



VD: Vaginal delivery; CD: Caesarean delivery; n: mild anaemia cases; N: number of children. Other details are as presented in Supplementary Figure S1 legend.

Supplementary Figure S10 Association between caesarean delivery and mild anaemia in children aged under 5 years in 45 low- and middle-income countries, stratified by national income level



The countries are assorted in ascending order by their per capita gross national income. Other details are as presented in the Supplementary Figure S1 legend.

Caesarean delivery and anaemia risk in children in 45 low- and middle- income countries: Supplementary tables

Supplementary Table S1 Sample characteristics of the study participants by country

	Country	N	Age at delivery Mean (SE)	Maternal Education (%)				Urban (%)	Parity Median (IQR)	Height, m Mean (SE)	Antenatal visits Median (IQR)	Prenatal Iron supplementation (%)	Male child (%)	Child's age in months Mean (SE)
				None	Primary	Secondary	Higher							
1	Albania	1079	27.9 (0.2)	0.8	63.6	25.1	10.5	42.0	2 (1-3)	1.61 (0.00)	5 (3-6)	32.2	51.5	33 (0.6)
2	Armenia	760	25.2 (0.2)	0.0	1.0	76.3	22.7	61.9	2 (1-2)	1.58 (0.00)	5 (3-7)	18.7	55.9	28.6 (0.7)
3	Azerbaijan	1248	26.2 (0.2)	1.3	1.7	83.1	13.9	52.4	2 (1-3)	1.59 (0.00)	3 (1-6)	23.0	57.2	27.7 (0.5)
4	Bangladesh	4090	27.9 (0.1)	19.8	41.6	37.1	1.5	30.0	4 (2-6)	1.56 (0.00)	3 (1-5)	59.5	50.8	22.9 (0.2)
5	Benin	2110	28.2 (0.2)	70.4	16.1	12.4	1.2	40.6	3 (2-5)	1.60 (0.00)	4 (3-6)	80.5	52.2	25.6 (0.3)
6	Bolivia	1733	27.4 (0.2)	4.0	52.0	31.2	12.9	57.4	3 (1-4)	1.52 (0.00)	5 (3-7)	78.2	51.8	27.8 (0.5)
7	BurkinaFaso	3948	28.1 (0.1)	81.9	12.0	5.8	0.3	18.9	5 (2-6)	1.63 (0.01)	3 (3-4)	92.6	51.5	25.2 (0.2)
8	Burundi	1841	29.1 (0.2)	54.2	39.4	5.9	0.5	8.5	4 (2-6)	1.55 (0.00)	3 (3-4)	74.4	51.5	23.7 (0.3)
9	Cambodia	3141	27.0 (0.1)	12.9	55.3	29.6	2.3	14.1	2 (1-3)	1.53 (0.07)	5 (4-7)	95.8	51.4	29.2 (0.4)
10	Cameroon	2752	26.9 (0.2)	26.2	39.3	31.3	3.3	46.4	3 (2-5)	1.60 (0.00)	4 (3-6)	81.8	49.6	23.6 (0.3)
11	CongoDR	4090	27.9 (0.1)	19.8	41.6	37.1	1.5	70.0	4 (2-6)	1.57 (0.00)	3 (2-5)	59.5	50.8	22.9 (0.2)
12	CongoB	2469	27.3 (0.2)	6.5	30.1	59.22	4.1	0.62	3 (2-3)	1.59 (0.00)	5 (4-6)	85.0	47.5	25.1 (0.4)
13	Cote d'Ivoire	1865	27.2 (0.2)	63.4	26.2	9.5	0.9	38.7	3 (2-5)	1.59 (0.00)	3 (2-5)	78.3	47.2	24.8 (0.5)
14	Egypt	3047	27.5 (0.1)	17.5	9.8	56.1	16.7	32.3	2 (2-3)	1.59 (0.00)	8 (5-12)	66.5	53.7	27.2 (0.3)
15	Ethiopia	5361	27.8 (0.1)	68.4	27.8	2.4	1.5	13.8	4 (2-6)	1.56 (0.00)	0 (0-3)	17.1	50.6	26.5 (0.4)
16	Gabon	1961	27.4 (0.2)	7.6	24.9	60.6	6.9	86.1	3 (1-4)	1.60 (0.00)	6 (4-7)	90.0	51.7	26.0 (0.5)
17	Gambia	1795	27.9 (0.2)	58.2	13.7	25	3.1	47.7	3 (2-5)	1.63 (0.00)	5 (4-6)	96.8	52	23.4 (0.4)
18	Ghana	1646	29.4 (0.2)	27.5	19.9	49.7	2.9	47.1	3 (2-5)	1.59 (0.00)	6 (5-8)	92.3	53.1	26.9 (0.5)
19	Guinea	1903	27.2 (0.2)	78.1	12.0	8.8	1.0	26.7	3 (2-5)	1.60 (0.00)	4 (2-6)	81.4	52.7	24.8 (0.4)
20	Guyana	963	26.3 (0.3)	3.5	21.0	68.7	6.8	22.4	2 (1-4)	1.56 (0.00)	7 (5-10)	82.3	50.8	27.9 (0.6)
21	Haiti	2552	28.1 (0.2)	21.3	41.0	34.6	3.1	35.7	2 (1-4)	1.59 (0.00)	5 (3-7)	76.1	50.6	26.7 (0.4)
22	Honduras	6507	26.0 (0.1)	4.8	59.0	31.7	4.5	45.7	2 (1-3)	1.53 (0.00)	7 (5-8)	57.7	52	28.7 (0.2)

Supplementary table S1 continued from previous page

	Country	N	Age at delivery Mean (SE)	Maternal Education (%)				Urban (%)	Parity Median (IQR)	Height, m Mean (SE)	Antenatal visits Median (IQR)	Prenatal Iron supplementation (%)	Male child (%)	Child's age in months Mean (SE)
				None	Primary	Secondary	Higher							
23	India	23782	25.0 (0.5)	47.6	14.2	32.5	5.6	25.9	2 (2-4)	1.52 (0.00)	3 (1-5)	65.9	54.9	28.3 (0.1)
24	Jordan	3303	30.1 (0.2)	1.7	6.1	63.3	28.9	81.8	3 (2-5)	1.58 (0.00)	9 (7-10)	84.0	54.2	28.4 (0.4)
25	Kyrgyz	2372	28.0 (0.2)	0.0	0.3	56.9	42.8	29.3	2 (1-3)	1.59 (0.00)	6 (5-8)	45.0	52.3	26.8 (0.3)
26	Lesotho	1064	26.0 (0.2)	1.8	53.6	40.6	4.1	19.9	2 (1-3)	1.57 (0.00)	5 (3-6)	46.5	49.9	27.0 (0.5)
27	Madagascar	3146	27.1 (0.2)	24.0	54.6	20.7	0.7	11.5	3 (2-5)	1.53 (0.00)	3 (3-4)	59.6	49.4	27.0 (0.3)
28	Malawi	2776	26.8 (0.1)	16.3	67.9	15.3	0.5	16.1	3 (2-5)	1.56 (0.00)	3 (3-4)	90.4	50.1	25.4 (0.3)
29	Mali	2656	27.4 (0.2)	82.4	9.4	7.6	0.7	19.1	4 (2-5)	1.62 (0.00)	3 (0-4)	66.9	51.2	25.2 (0.3)
30	Moldova	978	25.5 (0.2)	0.3	0.7	81.1	18.0	37.5	2 (1-2)	1.61 (0.00)	8 (6-10)	70.6	52.0	29.4 (0.5)
31	Mozambique	2859	27.0 (0.2)	35.8	50.5	13.1	0.6	28.7	3 (2-5)	1.55 (0.00)	4 (3-5)	81.3	49.5	23.9 (0.3)
32	Namibia	1190	27.9 (0.2)	5.8	21.7	66.9	5.6	46.3	2 (1-4)	1.61 (0.00)	6 (4-8)	89.7	48.4	27.0 (0.5)
33	Nepal	1520	25.5 (0.2)	45.5	19.7	29.4	5.4	9.6	2 (1-3)	1.51 (0.00)	3 (2-5)	78.0	51.6	29.3 (0.5)
34	Niger	2477	28.0 (0.2)	84.2	10.9	4.5	0.4	14.8	5 (3-7)	1.60 (0.00)	3 (2-4)	81.6	49.9	22.6 (0.3)
35	Peru	6520	28.0 (0.1)	2.8	27.6	45.8	23.8	66.8	2 (1-3)	1.52 (0.00)	9 (7-11)	87.5	52.1	30.5 (0.3)
36	Rwanda	2377	28.7 (0.1)	14.6	72.5	10.9	2.0	16.3	3 (1-4)	1.57 (0.00)	3 (3-4)	78.6	50.8	26.8 (0.3)
37	SaoTome&P	1115	27.7 (0.3)	4.2	71.2	24.4	0.3	49.4	3 (2-5)	1.59 (0.00)	6 (4-7)	92.9	49.6	26.6 (0.6)
38	Senegal	1999	28.2 (0.2)	69.0	20.9	9	1.1	42.6	3 (2-5)	1.64 (0.00)	4 (3-4)	94.4	47.8	25.5 (0.5)
39	Sierra Leone	2904	28.0 (0.2)	68.6	13.0	17.5	0.9	26.2	3 (2-5)	1.58 (0.00)	6 (5-10)	94.4	48.4	25.8 (0.3)
40	Swaziland	1292	26.4 (0.2)	8.4	36.7	48.9	6.0	17.1	2 (1-4)	1.59 (0.00)	5 (4-6)	90.1	51.0	25.8 (0.5)
41	Tanzania	3777	28.0 (0.2)	23.6	69.4	6.8	0.2	21.3	3 (2-5)	1.56 (0.00)	3 (3-4)	59.7	49.4	25.4 (0.3)
42	Togo	1981	28.6 (0.2)	40.1	37.2	20.9	1.8	35.9	3 (2-5)	1.59 (0.00)	4 (3-5)	86.7	51.5	26.7 (0.3)
43	Uganda	1064	28.2 (0.2)	12.8	64.0	18.6	4.5	15.2	4 (2-7)	1.59 (0.00)	3 (3-4)	76.0	49.5	23.3 (0.5)
44	Yemen	2258	28.2 (0.2)	xx	xx	xx	xx	31.4	4 (2-6)	1.54 (0.00)	1 (0-3)	71.1	50.8	25.4 (0.4)
45	Zimbabwe	2606	26.3 (0.1)	2.2	31.9	63.6	2.3	25.3	2 (1-4)	1.60 (0.00)	4 (3-6)	49.8	50.6	26.4 (0.3)

xx means that the variable was not used/not available. The percentages, means, and medians are weighted. Standard errors are adjusted for clustering

Supplementary Table S2 Percent of the missing data by country

Country	N	% missing data							
		Biomass for cooking	Prenatal iron supplementation	Prenatal deworming	Birth size	Birth weight	Mother's height	Number of antenatal care visits	caste
Albania	1079	0.00	1.39	0.37	xx	3.44	0.19	0.83	xx
Armenia	760	0.00	0.00	xx	1.18	xx	0.92	0.92	xx
Azerbaijan	1248	xx	2.72	0.64	16.02	xx	0.56	3.77	xx
Bangladesh	4090	0.00	xx	xx	1.40	xx	0.90	0.00	xx
Benin	2110	0.00	1.90	3.36	8.10	xx	1.52	6.35	xx
Bolivia	1733	0.00	0.00	xx	0.81	xx	1.15	0.40	xx
BurkinaFaso	3948	0.10	0.05	0.85	0.17	xx	0.50	0.10	xx
Burundi	1841	xx	0.05	0.22	1.30	xx	0.76	0.38	xx
Cambodia	3141	0.00	0.10	1.66	0.45	xx	0.13	0.45	xx
Cameroon	2752	0.00	0.15	2.65	0.62	xx	0.33	0.66	xx
CongoDR	4090	0.00	0.66	0.90	1.40	xx	0.90	0.91	xx
CongoB	2469	0.00	0.69	0.24	1.58	xx	0.77	0.61	xx
Cote d'Ivoire	1865	0.05	1.93	4.02	2.68	xx	1.39	0.54	xx
Egypt	3047	xx	0.62	0.53	0.46	xx	0.23	0.49	xx
Ethiopia	5361	0.00	0.28	0.71	0.13	xx	0.50	0.32	xx
Gabon	1961	0.05	0.66	1.78	4.9	xx	0.76	1.22	xx
Gambia	1795	0.00	0.06	2.45	0.22	xx	1.95	0.28	xx
Ghana	1646	0.00	0.67	2.43	0.12	xx	0.18	0.49	xx
Guinea	1903	xx	0.11	1.26	0.21	xx	0.42	0.32	xx
Guyana	963	0.21	1.35	2.70	1.97	xx	0.42	14.54	xx
Haiti	2552	0.00	0.04	2.27	0.08	xx	0.12	0.39	xx
Honduras	6507	0.00	0.28	0.28	0.11	xx	0.17	0.15	xx
India	23782	0.02	0.48	0.93	1.59	xx	0.39	1.00	4.57

Supplementary Table S2 continued from previous page

Jordan	3303	xx	0.24	xx	xx	0.79	0.12	0.00	xx
Kyrgyz	2372	0.08	0.17	1.77	xx	0.63	0.21	2.70	xx
Lesotho	1064	0.00	3.10	xx	0.56	xx	0.47	1.60	xx
Madagascar	3146	xx	1.11	0.92	1.27	xx	0.54	0.29	xx
Malawi	2776	xx	0.00	0.40	1.66	xx	0.61	0.79	xx
Mali	2656	xx	0.34	5.10	3.66	xx	0.91	1.33	xx
Moldova	978	0.00	24.00	xx	xx	0.41	0.2	3.68	xx
Mozambique	2859	0.00	0.28	3.88	3.64	xx	0.35	1.50	xx
Namibia	1190	0.08	0.50	3.45	xx	10.76	1.85	21.09	xx
Nepal	1520	0.00	0.00	1.05	0.07	xx	0.2	0.00	xx
Niger	2477	0.00	0.12	1.33	2.58	xx	1.41	0.52	xx
Peru	6520	0.00	0.06	0.12	xx	6.54	0.14	0.11	xx
Rwanda	2377	xx	0.13	0.25	xx	6.6	0.08	0.00	xx
SaoTome&P	1115	0.00	0.27	2.60	xx	18.12	1.35	5.29	xx
Senegal	1999	0.00	0.300	4.20	0.4	xx	1.75	1.80	xx
Sierra Leone	2904	xx	0.41	2.00	1.96	xx	1.17	11.05	xx
Swaziland	1292	0.08	1.32	5.73	2.32	15.56	0.7	2.71	xx
Tanzania	3777	xx	0.21	xx	2.86	xx	0.21	0.45	xx
Togo	1981	xx	0.61	3.28	0.61	xx	0.05	0.20	xx
Uganda	1064	xx	0.94	1.32	2.16	xx	0.56	1.88	xx
Yemen	2258	0.58	1.33	0.62	0.27	xx	0.80	0.58	xx
Zimbabwe	2606	xx	0.65	0.31	2.0	xx	0.35	1.11	xx

xx means that the variable was not used

The percentages are unweighted

Supplementary Table S3 Summary odds ratios for the associations between CD and any anaemia, mild anaemia, and moderate/severe anaemia among children younger than 5 years in countries with national CD rate >15%, stratified by wealth and place of delivery

	Any anaemia		Mild anaemia		Moderate/severe anaemia	
	OR (95% CI)	I ²	OR (95% CI)	I ²	OR (95% CI)	I ²
Wealth index quintiles						
Lower two	1.11 (0.82 to 1.50)	67.1%	0.94 (0.76 to 1.17)	21.9%	1.26 (0.87 to 1.89)	69.9%
Upper two	0.96 (0.82 to 1.13)	0.0%	0.89 (0.74 to 1.07)	0.0%	1.07 (0.82 to 1.41)	16.7%
Place of delivery						
Public sector	0.96 (0.83 to 1.12)	31.0%	0.88 (0.77 to 1.01)	0.0%	1.10 (0.91 to 1.34)	21.2%
Private sector	1.00 (0.82 to 1.23)	0.0%	1.01 (0.78 to 1.30)	0.0%	1.01 (0.77 to 1.33)	0.0%

Countries included in the analyses were Albania, Bangladesh, Bolivia, Egypt, Honduras, Jordan, and Peru. Albania was excluded from the analysis stratified by place of delivery because almost all the women delivered in the public sector. Propensity score weighting was used to adjust for region within the country, residence (urban/rural), wealth index, mother's age at childbirth, mother's education, parity, births in the past 5 years, number of antenatal visits, prenatal iron supplementation, prenatal deworming, mother's height, use of biomass for cooking, size of the baby at birth or birth weight, sex of the baby, and child's age in months. The summary odds ratios were obtained by pooling country specific odds ratios using random effects meta-analysis.