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Maternal anaemia and risk of neonatal and infant mortality in low- and middle-income countries: a secondary analysis of 45 national datasets

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ABSTRACT

Background Anaemia in pregnancy has been recognised worldwide as a growing public health concern and an important cause of adverse neonatal outcomes. However, only a limited number of studies have been done in low-income settings, which have the highest prevalence of anaemia. We aimed to investigate the association between maternal anaemia and neonatal and infant mortality in low- and middle-income countries.

Methods Secondary analysis of pooled data from 45 national demographic and health surveys (2010–2020). We included all women between 15 and 49 years old, who had singleton live birth within 1 year preceding the survey, with a valid maternal measurement of haemoglobin. We used logistic regression models to estimate the crude and adjusted OR (aOR) with 95% CIs of the association between maternal anaemia (measured at the time of the survey) and the risk of neonatal and infant mortality.

Results Among 106 143 women included in our analysis, there were 53 348 (50.5%) women with no anaemia, 24 670 (23.2%) with mild anaemia, 25 937 (24.3%) with moderate anaemia and 2188 (2.0%) with severe anaemia. Overall, there were 2668 (2.5%) neonatal and 3756 (3.5%) infant deaths. Moderate (aOR 1.20; 95% CI 1.06 to 1.35) and severe (aOR 1.89; 95% CI 1.46 to 2.44) maternal anaemia were associated with increased odds of neonatal mortality, respectively. Similar estimates were observed for moderate and severe anaemia and infant mortality. No increased risk was noted for mild anaemia.

Interpretation Moderate and severe maternal anaemia in low- and middle-income settings are associated with increased risks of neonatal and infant mortality. Future research should examine how targeted interventions for prepregnancy and antenatal treatment of anaemia in reproductive-age women can enhance maternal and child health in low- and middle-income settings.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Few studies, mainly in high-income or upper-middle-income countries, have explored the link between maternal anaemia and neonatal mortality, yielding conflicting results.
⇒ Prior studies also used small sample sizes when examining the association of maternal anaemia with neonatal and infant mortality.

WHAT THIS STUDY ADDS

⇒ In this cross-sectional survey study, we analysed data from 45 low- and middle-income countries and found that severe maternal anaemia was associated with higher odds of neonatal and infant mortality, with severe anaemia increasing the odds of early neonatal mortality by nearly twofold and infant mortality by 1.6 times.
⇒ Mild anaemia showed no significant association with mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings provide evidence that the level of maternal haemoglobin, especially those with moderate and severe anaemia is associated with an increased risk of neonatal and infant death.
⇒ Our findings need to be replicated with prospectively collected data and possible mechanisms explaining this association need to be identified.

INTRODUCTION

Over the past three decades, reducing maternal, neonatal and child mortality has been a top global development priority and a key Millennium Development Goal.[1] From 2000 to 2020, neonatal deaths declined by 44%, but newborn deaths still accounted for 47% of under-five deaths in 2022.[1] Despite this achievement, the rate of infant mortality is still alarming, with 6700 newborns dying every day.[2 3] The majority of these deaths happen during the first 28 days of life, making the neonatal period the most crucial for a child's survival.[3] Pre-existing maternal conditions like undernutrition or pregnancy-induced conditions like pre-eclampsia and gestational hypertension are associated with increased risks of preterm birth, stillbirth and infant death.[4 5]

Anaemia in pregnancy has been recognised worldwide as a growing public health issue and a significant contributor to adverse outcomes for both the mother and the neonate.[5–8] Depending on age, sex and geography, a wide range of underlying risk factors can cause anaemia,[9] including malnutrition (deficiency of iron, folate or B12), parasitic and chronic infections such as malaria and HIV.[7] However, iron deficiency has been associated predominantly with anaemia in women of reproductive age, a potentially reversible cause with appropriate supplementation through diet or medications.[10] Even though great progress has been achieved in several settings, the overall reduction of anaemia prevalence across the globe seems insufficient.[11] Consequently, one of the goals of the World Health Assembly and the United Nations Sustainable Development Goals is the reduction of anaemia in women of reproductive age (15–49 years) by 50% by the end of 2025 and 2030, respectively.[11 12]

Few studies have explored the association between maternal anaemia and neonatal mortality, mostly in high-income or upper-middle-income countries, with conflicting results: some studies reported an increased risk,[5 6] while others an absence of association or even a protective effect on perinatal mortality.[7 13 14] Therefore, we aimed to investigate the association between maternal anaemia and risk of neonatal and infant mortality, using pooled data from 45 low- and middle-income countries provided by the Demographic and Health Surveys (DHSs) Programme. We hypothesised that the risk for neonatal and infant mortality will be higher for women with severe anaemia during pregnancy.

METHODS

The study was conducted by pooling data from the most recent standard DHS, namely phases six, seven and eight (VI, VII and VIII) between 2010 and 2020. DHS data have been widely used by 44 sub-Saharan African countries, 15 in South and Southeast Asia, 15 in Latin America and the Caribbean, 11 in North Africa/West Asia/Europe, five in Central Asia and two in Oceania. The standard DHSs are nationally representative cross-sectional surveys, conducted typically every 5 years and obtain information for a wide range of health indicators primarily using model questionnaires.[15] The details of sampling methods are presented elsewhere (https://dhsprogram.com/What-We-Do/Survey-Types/DHS-Methodology.cfm).

The target population for these surveys is all women of reproductive age between 15 and 49 years old, men aged 15–59 and their children under 5 years of age.[16] Since 1995, DHS has started to collect information for more than 50 countries for several biomarkers using field-friendly technologies such as height and weight, blood pressure and haemoglobin.[17] The age of death of the offspring was reported in days if it was <1 month, in months if it was <2 years and otherwise in years. DHSs have been shown to have high validity for low- and middle-income settings, and extensive data editing and imputation are performed to address incomplete and inconsistent data reporting.[18] The eligible population for this study were women between 15 and 49 years old, who had singleton live birth within 1 year preceding the survey, with a valid maternal measurement of haemoglobin. We conducted a complete case analysis, and thus, singletons with missing values in other covariates were excluded from the regression models.

Exposure variable

Information on maternal haemoglobin measurements during pregnancy was not available; therefore, we only included the outcome of the most recent live birth for each woman with available haemoglobin measurement who delivered within the last year preceding the survey (index birth), as a proxy for haemoglobin level during pregnancy. Haemoglobin was measured via finger prick test using the HemoCue blood haemoglobin testing, and the results were available immediately alongside information on anaemia prevention.[19] Maternal anaemia status was classified according to the WHO recommendation[20] as: non-anaemia (haemoglobin count ≥12.0 grams per decilitre for non-pregnant and ≥11.0 grams per decilitre for pregnant women), mild anaemia (haemoglobin count between 11.0 g/dL and 11.9 g/dL for non-pregnant and between 10.0 g/dL and 10.9 g/dL for pregnant women), moderate anaemia (haemoglobin count between 8.0 g/dL and 10.9 g/dL for non-pregnant and between 7.0 g/dL and 9.9 g/dL for pregnant women) and severe anaemia (haemoglobin <8.0 g/dL and <7.0 g/dL). We also considered haemoglobin as a continuous variable. Since the oxygen concentration is lower at a higher altitude (lower oxygen partial pressure), an adjustment has been made by DHS for the altitude in the haemoglobin level, when necessary. In addition, haemoglobin concentration was adjusted for cigarette smoking status using a formula provided by the US Centres for Disease Control and Prevention.[21]

Outcome variable

Infant mortality was defined as death within the first year of life (0–12 months). Neonatal mortality was defined as death in the first 27 completed days of life. Given that the aetiology of neonatal mortality varies based on the timing of neonatal death,[22] we further classified neonatal mortality into early neonatal mortality (deaths that occurred in the first six completed days of life) and late neonatal deaths (death between seven and up to 27 days of life).[23] Exposure and outcome data were collected simultaneously during the survey.

Covariates

DHS interviews collect information on the mother's current age, infant's sex, place of residence (urban or rural) and highest maternal education (categorised as no education, primary, secondary or higher). DHS recorded the relative wealth index, the birth order in which the child was born, the time elapsed since birth

Table 1 Distribution of maternal anaemia by country and region (n=106 143)

Countries	No.	Maternal anaemia category N (%)			
		No anaemia	Mild anaemia	Moderate anaemia	Severe anaemia
Sub-Saharan Africa					
Benin	1545	674 (43.8)	425 (27.4)	424 (27.3)	22 (1.5)
Burundi	1426	807 (54.1)	299 (21.7)	306 (23.2)	14 (1.0)
Burkina Faso	1597	770 (47.8)	341 (21.9)	440 (27.4)	46 (2.9)
Cameroon	1113	669 (59.9)	247 (21.7)	187 (17.5)	10 (0.9)
Ethiopia	2246	1438 (70.4)	339 (14.2)	392 (12.8)	77 (2.6)
Gambia	992	477 (54.9)	266 (24.9)	229 (19.0)	20 (1.2)
Guinea	905	471 (49.6)	210 (24.7)	207 (23.8)	17 (1.9)
Lesotho	382	280 (70.4)	55 (15.3)	45 (13.9)	<5
Liberia	676	335 (53.5)	186 (25.4)	147 (20.1)	8 (1.0)
Ghana	648	386 (58.6)	141 (21.6)	119 (19.5)	<5
Mali	1067	395 (36.8)	269 (25.0)	350 (32.9)	53 (5.3)
Malawi	1209	788 (66.2)	233 (17.8)	177 (15.0)	11 (1.0)
Nigeria	2767	1136 (41.2)	761 (27.8)	815 (28.6)	55 (2.4)
Rwanda	850	740 (87.1)	80 (9.6)	29 (3.2)	<5
Sierra Leone	1099	500 (46.6)	261 (22.5)	315 (29.0)	23 (1.9)
Tanzania	2225	1118 (51.9)	532 (24.2)	526 (22.0)	49 (1.9)
Uganda	1081	691 (65.1)	217 (18.9)	157 (14.5)	16 (1.5)
South Africa	245	172 (66.3)	37 (20.8)	34 (12.2)	<5
Zambia	2101	1468 (69.8)	372 (17.4)	243 (11.7)	18 (1.1)
Zimbabwe	1160	840 (74.3)	163 (13.4)	137 (10.8)	20 (1.5)
Congo	1131	547 (48.2)	300 (25.8)	276 (25.4)	8 (0.6)
Cote d'Ivoire	837	375 (43.5)	204 (24.0)	241 (30.3)	17 (2.2)
Congo Democratic Republic	2109	1280 (62.7)	427 (20.0)	386 (16.7)	16 (0.6)
Gabon	957	429 (45.9)	238 (23.2)	275 (29.7)	15 (1.2)
Mozambique	2483	1193 (45.3)	566 (23.7)	677 (29.0)	47 (2.0)
Niger	1295	711 (54.7)	303 (23.3)	258 (20.7)	23 (1.3)
Namibia	546	429 (76.9)	66 (13.1)	48 (9.3)	<5
Togo	723	436 (57.9)	152 (22.0)	132 (19.7)	<5
North Africa/West Asia/Europe					
Albania	553	435 (78.7)	78 (12.4)	39 (8.8)	<5
Armenia	357	297 (83.5)	50 (13.8)	10 (2.7)	0
Egypt	1185	853 (70.9)	251 (21.5)	79 (7.4)	<5
Jordan	1138	606 (55.2)	251 (21.9)	277 (22.5)	<5
Yemen	1060	205 (22.8)	208 (19.0)	536 (49.0)	111 (9.2)
Central Asia					
Tajikistan	1240	675 (53.1)	302 (24.1)	247 (21.6)	16 (1.2)
Kyrgyz Republic	1058	633 (59.5)	210 (20.2)	197 (19.2)	18 (1.1)
South & Southeast Asia					
Cambodia	1032	520 (48.7)	292 (29.2)	214 (21.5)	6 (0.6)
India	52 677	22 211 (42.0)	13 533 (25.9)	15 575 (29.6)	1358 (2.5)
Maldives	582	269 (39.2)	175 (31.6)	136 (28.4)	<5
Myanmar	995	522 (48.6)	269 (29.2)	189 (20.1)	15 (2.1)
Nepal	529	284 (52.2)	127 (24.7)	116 (22.8)	<5
Timor-Leste	547	401 (71.1)	82 (15.8)	58 (11.8)	6 (1.3)

Continued

Table 1 Continued

Countries	No.	Maternal anaemia category N (%)			
		No anaemia	Mild anaemia	Moderate anaemia	Severe anaemia
Latin America & Caribbean					
Honduras	2299	1930 (84.9)	257 (10.7)	107 (4.2)	5 (0.2)
Guatemala	2624	2098 (81.5)	344 (12.2)	172 (6.0)	10 (0.3)
Peru	1892	1388 (76.4)	335 (15.9)	158 (7.3)	11 (0.4)
Haiti	960	466 (47.1)	216 (23.3)	255 (27.2)	23 (2.4)
All countries					
Pooled	106 143	53 348 (50.5)	24 670 (23.2)	25 937 (24.3)	2188 (2.0)

Unweighted data (n) are presented and sample weights were used for the proportions (%).

(in months) and whether the last child was born with a caesarean section. Maternal body mass index (BMI) was calculated as the weight (in kg) divided by height (in m^2). BMI (kg/m^2) was classified according to WHO as underweight (BMI <18.5), normal weight (18.5–24.9), overweight (25.0–29.9) and obesity (≥30.0).

Statistical analysis

Birth and individual women's files of the 45 countries were extracted, appended and analysed using Stata 17 (StataCorp, College Station, TX) statistical software. The overall prevalence of anaemia among women aged 15–49 years in the included countries was calculated and compared with those who gave birth in the year preceding the survey. Descriptive statistics were conducted to explore the different anaemia categories in each country and were presented as unweighted count numbers and as weighted frequencies to adjust for sampling probabilities and response rates, applying individual-level survey weights provided with the original DHS data. We used logistic regression models to estimate crude and adjusted ORs with their corresponding 95% CIs adjusting for infant sex, maternal age, maternal BMI, place of residence, wealth index, birth order, maternal education and mode of delivery. Confounders were included in the final model based on previous literature.[24 25] The complex survey design was taken into consideration to restore the representativeness of the actual population and to adjust for non-response,[26] using the *svy* command in Stata. We performed logistic regression models with linear and non-linear terms for maternal haemoglobin levels. To assess potential non-linear associations between maternal haemoglobin and neonatal and infant mortality, we derived non-linear terms with restricted cubic spline models with three knots. Given that iron deficiency anaemia is the most common type in pregnancy and among women of reproductive age,[10] we further estimated whether the association is modified by iron supplementation during pregnancy. We tested the cross-product interaction terms between maternal anaemia and iron supplementation with the use of a Wald χ^2 test.

Sensitivity analysis

We examined the association between maternal anaemia and neonatal and infant mortality by region, categorised according to DHS, 'Sub-Saharan Africa', 'North Africa/West Asia/Central Asia/Europe', 'South & Southeast Asia' and 'Latin American & Caribbean'. To account for any possible changes in haemoglobin levels after the index birth, we further adjusted for the time elapsed between index birth and the survey. Given the Hemocue test's sensitivity (72%) and specificity (70%) for detecting anaemia in females,[27] we conducted a quantitative bias analysis to address potential non-differential misclassification of the exposure. Correction for exposure misclassification was accomplished based on the following assumptions: (1) the misclassification of maternal anaemia was assumed non-differential with respect to the outcome of interest; (2) the sensitivity and specificity for anaemia were assumed to range between 0.72 and 1.00, and between 0.70 and 1.00, respectively, derived from an earlier validation study[27] and (3) the simulations were performed assuming a uniform distribution. We estimated the bias-corrected median OR and 95% CI based on 10 000 replications. The probabilistic bias analysis was performed, using the *episens* command in Stata.

Patient involvement

This study was based on secondary analysis of information from survey data, and no patients were involved in designing the research question or the outcome measures, nor were they involved in developing plans for implementation of the study. No patients were asked to advise on interpretation or writing up of results.

RESULTS

In a sample population including 1 069 657 reproductive-age women (15–49 years) from 45 low- and middle-income countries with available information on haemoglobin, the overall weighted prevalence of mild anaemia was 22.6%, moderate anaemia 22.5% and severe anaemia 2.02%, very similar to our study population (online supplemental figure S1 and table S1). Among this sample

Table 2 Maternal and infant characteristics by maternal anaemia at the most recent birth (n=106 143)

	Total population	No anaemia	Mild anaemia	Moderate anaemia	Severe anaemia
	N (%)	N (%)	N (%)	N (%)	N (%)
Pooled	106 143 (100)	53 348 (50.53)	24 670 (23.17)	25 937 (24.32)	2188 (1.97)
Maternal age group (years at the time of interview)					
15–19	10 178 (9.84)	5123 (9.90)	2367 (9.90)	2484 (9.68)	204 (9.65)
20–24	36 394 (35.14)	17 444 (33.51)	8 741 (36.22)	9 460 (37.44)	749 (36.02)
25–29	31 087 (29.31)	15 682 (29.65)	7293 (29.20)	7453 (28.73)	659 (29.10)
30–34	16 689 (15.14)	8841 (15.96)	3675 (14.37)	3841 (14.21)	332 (14.64)
35–39	8462 (7.61)	4484 (7.88)	1857 (7.50)	1941 (7.16)	180 (7.51)
40–44	2777 (2.48)	1516 (2.68)	586 (2.27)	621 (2.27)	54 (2.48)
45–49	556 (0.48)	258 (0.42)	151 (0.55)	137 (0.51)	10 (0.59)
Type of place of residence					
Urban	28 957 (29.94)	15 992 (32.61)	6461 (28.80)	6105 (26.29)	399 (20.08)
Rural	77 186 (70.06)	37 356 (67.39)	18 209 (71.20)	19 832 (73.71)	1789 (79.92)
Relative wealth index					
Poorest	27 486 (23.80)	12 284 (20.91)	6587 (24.42)	7822 (28.34)	793 (34.51)
Poorer	24 391 (22.07)	11 910 (21.14)	5670 (22.30)	6277 (23.52)	534 (25.37)
Middle	21 119 (20.51)	10 733 (20.55)	4988 (21.01)	4981 (20.00)	417 (19.62)
Richer	18 227 (18.61)	9856 (20.25)	4128 (18.09)	3956 (16.10)	287 (13.80)
Richest	14 920 (15.01)	8565 (17.15)	3297 (14.18)	2901 (12.04)	157 (6.69)
Birth order					
First birth	34 083 (32.68)	17 305 (33.08)	7963 (32.80)	8227 (32.19)	588 (27.47)
Para 2–3	45 108 (42.77)	22 453 (42.30)	10 646 (43.27)	11 077 (43.26)	932 (42.87)
Para 4–5	16 567 (15.01)	8377 (15.10)	3706 (14.53)	4058 (14.95)	426 (18.91)
Para≥6	10 385 (9.54)	5213 (9.52)	2355 (9.40)	2575 (9.60)	242 (10.75)
Maternal education					
No education	29 094 (27.11)	12 374 (23.16)	7070 (28.46)	8718 (32.73)	932 (43.25)
Primary only	24 727 (22.91)	13 682 (25.37)	5363 (21.10)	5281 (19.98)	401 (17.10)
Secondary	41 995 (39.54)	21 774 (40.37)	9936 (40.52)	9621 (37.54)	664 (31.57)
Higher	9267 (9.39)	5313 (10.63)	2093 (9.06)	1781 (7.64)	80 (3.18)
Missing	1060 (1.05)	205 (0.47)	208 (0.86)	536 (2.11)	111 (4.90)
BMI category					
Underweight (<18.5 kg/m^2)	16 659 (16.22)	6521 (12.94)	4206 (17.55)	5370 (21.01)	562 (25.82)
Optimum (18.5–24.9 kg/m^2)	66 820 (62.01)	32 742 (60.41)	15 872 (63.56)	16 802 (63.75)	1404 (63.37)
Overweight (25–29.9 kg/m^2)	15 214 (14.45)	9210 (17.23)	3157 (12.83)	2697 (10.81)	150 (6.91)
Obese (≥30 kg/m^2)	5104 (5.06)	3280 (6.37)	1015 (4.33)	768 (3.25)	41 (2.25)
Missing	2346 (2.26)	1595 (3.05)	420 (1.73)	300 (1.18)	31 (1.65)
Mode of delivery					
Vaginal delivery/no caesarean section of last birth	92 316 (85.38)	45 432 (83.58)	21 510 (85.57)	23 292 (88.23)	2082 (94.16)
Caesarean section of last birth	13 704 (14.54)	7843 (16.33)	3138 (14.37)	2617 (11.71)	106 (5.84)
Missing	123 (0.08)	73 (0.09)	22 (0.06)	28 (0.06)	0 (0.00)
Infant's sex					
Male	54 910 (51.87)	27 483 (51.54)	12 822 (52.18)	13 468 (52.30)	1137 (51.27)
Female	51 233 (48.13)	25 865 (48.46)	11 848 (47.82)	12 469 (47.70)	1051 (48.73)

Unweighted data (N) are presented and sample weights were used for the proportions (%).

Table 3 Association of maternal anaemia with neonatal and infant mortality at the most recent birth, stratified by timing of neonatal death (n=102 626)

Neonatal and infant death	n	Neonatal or infant deaths	Weighted rate*	Crude OR (95% CI)
Days 0–6				
No anaemia	51 479	996	19.5	1.00 (reference)
Mild anaemia	24 022	440	18.7	0.96 (0.83 to 1.11)
Moderate anaemia	25 078	618	24.2	1.25 (1.10 to 1.42)
Severe anaemia	2047	89	39.7	2.08 (1.59 to 2.73)
Days 7–27				
No anaemia	50 483	200	4.2	1.00 (reference)
Mild anaemia	23 582	94	3.8	0.90 (0.66 to 1.22)
Moderate anaemia	24 460	133	5.0	1.19 (0.90 to 1.57)
Severe anaemia	1958	15	7.5	1.79 (0.88 to 3.64)
Days 0–27				
No anaemia	51 479	1196	23.6	1 (reference)
Mild anaemia	24 022	534	22.4	0.95 (0.83 to 1.08)
Moderate anaemia	25 078	751	29.1	1.24 (1.10 to 1.40)
Severe anaemia	2047	104	46.9	2.04 (1.58 to 2.63)
Haemoglobin (as continuous variable)	102 626	2585	25.1	0.88 (0.85 to 0.90)
Infant mortality (0-12 months)				
No anaemia	51 479	1693	33.7	1 (reference)
Mild anaemia	24 022	801	33.6	0.99 (0.89 to 1.10)
Moderate anaemia	25 078	1018	39.3	1.17 (1.06 to 1.30)
Severe anaemia	2047	126	59.8	1.82 (1.45 to 2.30)
Haemoglobin (as continuous variable)	102 626	3638	35.5	0.89 (0.86 to 0.91)

*Rate is expressed per 1000.

population, 106 143 gave birth to a singleton 1 year preceding the survey and were eligible to be included in the study (online supplemental figure S1, table 1). The rates of anaemia in our study sample were similar to the rates observed in the population of reproductive-age women (online supplemental figure S2). The largest sample in our study was from India with 52 677 women and the smallest with 245 eligible women from South Africa (table 1).

The rates of anaemia varied markedly between different regions and countries (table 1); South and Southeast Asia had the highest rates of anaemia, whereas Latin America and the Caribbean had the lowest. Women with anaemia were more likely to be older (45–49 years), living in rural areas, and belonging to the poor relative wealth index. Additionally, women with anaemia were more likely to have no education, deliver vaginally and were underweight (BMI <18.5 kg/m^2; table 2).

Overall, there were 2668 neonatal deaths and 3756 infant deaths corresponding to weighted rates of 25.2 and 35.6 per 1000 live births for neonatal and infant mortality, respectively. Models with linear terms for haemoglobin levels showed that each 1 unit g/dL increase in maternal haemoglobin was associated with a 12% decrease in unadjusted odds of neonatal mortality and an 11% decrease in infant mortality (table 3). Restricted cubic splines with three knots showed that increasing haemoglobin levels were associated with reduced adjusted odds for neonatal and infant mortality (figures 1 and 2). In the adjusted models, compared with offspring of mothers with normal haemoglobin, offspring of mothers with severe anaemia had 1.94-fold higher odds of early neonatal mortality (0–6 days) (95% CI 1.47 to 2.55) and 1.62-fold higher odds of infant mortality (95% CI 1.28 to 2.05) (figure 3). Moderate anaemia was also associated with higher odds of neonatal and infant mortality. Maternal mild anaemia was not associated with higher odds of neonatal and infant mortality. We found no association between maternal anaemia and late neonatal mortality (7–27 days).

In the stratified analysis, the association between moderate and severe anaemia and neonatal and infant mortality tended to be stronger among women who reported taking iron supplementation (table 4). However, we did not find a significant interaction on the multiplicative scale (p value >0.05).

Sensitivity analyses

In the stratified analysis by region, severe maternal anaemia was associated with higher odds of infant mortality in 'South & Southeast Asia' and 'Sub-Saharan

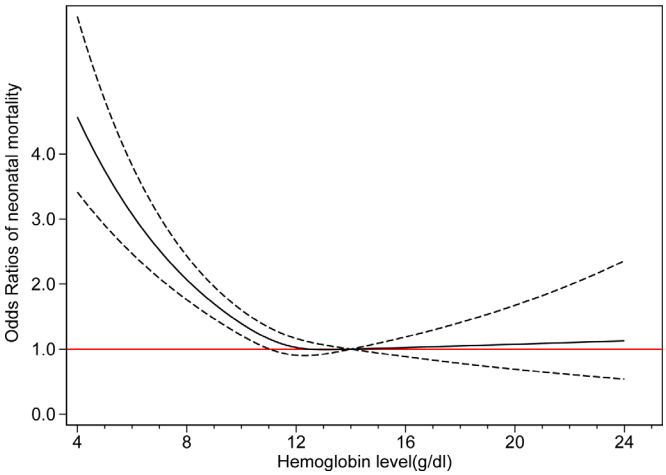

Figure 1 Adjusted ORs (black line) and 95% CI (black dashed lines) for neonatal mortality by maternal haemoglobin level (g/dL) modelled with restricted cubic splines. Three knots were placed at values 9.8, 11.9 and 13.7 of the haemoglobin distribution. Estimates are from a logistic regression model with linear and spline terms for haemoglobin as predictors, with 14 as the reference value.

Africa', although the latter did not reach statistical significance (online supplemental table S2). Furthermore, in 'South & Southeast Asia', mild anaemia was associated with lower odds of neonatal and infant mortality. In Latin America and the Caribbean, even mild anaemia was associated with an increase in OR for neonatal and infant death (online supplemental table S2). Controlling for the time elapsed between the index birth and the survey did not change our results (online supplemental table S3). The probabilistic bias analysis suggests that once the reported associations were corrected for exposure misclassification, the strength of the ORs for moderate and severe anaemia and neonatal and infant

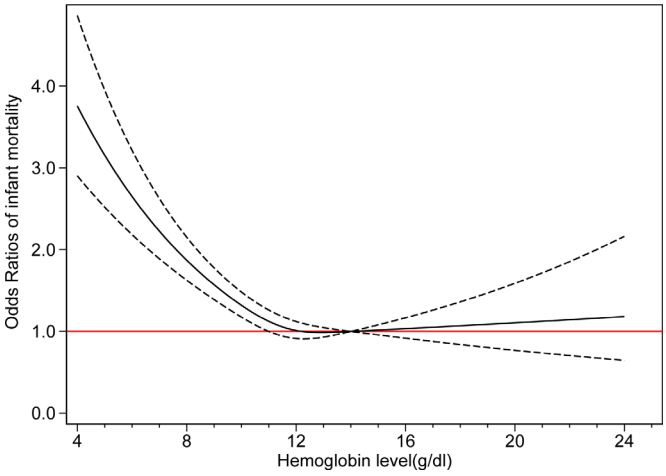

Figure 2 Adjusted ORs (black line) and 95% CI (black dashed lines) for infant mortality by maternal haemoglobin level (g/dL) modelled with restricted cubic splines. Three knots were placed at values 9.8, 11.9 and 13.7 of the haemoglobin distribution. Estimates are from a logistic regression model with linear and spline terms for haemoglobin as predictors, with 14 as the reference value.

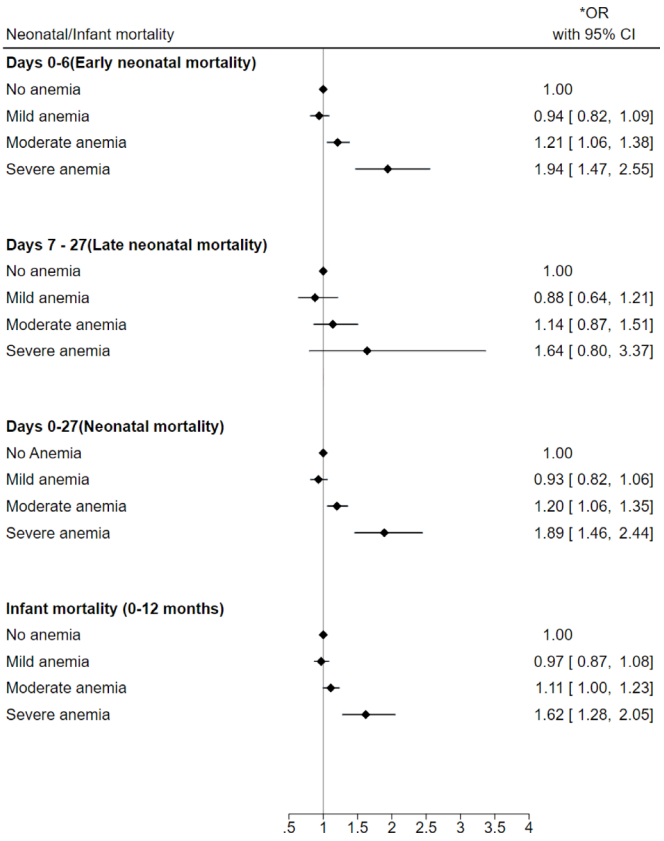

Figure 3 Adjusted ORs with 95% CIs for the association between maternal anaemia and neonatal and infant mortality. *Adjusted for maternal age, BMI, education, birth order, wealth index, mode of delivery, area of residence and infant's sex. BMI, body mass index.

mortality were higher compared with the conventional model (online supplemental table S4). For example, for moderate anaemia and neonatal mortality, the bias-corrected OR was 1.53 (95% CI 1.27 to 3.14) in contrast to the estimate of the conventional unweighted model of 1.30 (95% CI 1.18 to 1.42).

DISCUSSION

In this secondary data analysis of 45 cross-sectional surveys from low- and middle-income countries, we found significant regional variation in anaemia rates, with South and Southeast Asia having the highest rates, while Latin America and the Caribbean had the lowest. Moderate and severe levels of maternal anaemia were associated with higher odds of neonatal and infant mortality, with severe anaemia increasing the odds of early neonatal mortality by nearly twofold and infant mortality by 1.6 times. In contrast, mild anaemia showed no significant association with mortality.

Maternal anaemia can have severe consequences not only for the suffering mother but also, as highlighted by the current study, for the survival of her offspring. In our study, 49.5% of women had anaemia, which is in line with other studies examining the prevalence of anaemia during pregnancy in low- and middle-income

Table 4 Maternal anaemia and risk of neonatal and infant mortality stratified by iron supplementation during pregnancy, the most recent birth

	Neonatal mortality		Infant mortality	
Iron supplementation status	No. (rate/1000)*	Adjusted OR† (95% CI)	No. (rate/1000)*	Adjusted OR† (95% CI)
With iron supplementation				
No anaemia	840 (21.3)	1.00 (reference)	1187 (30.3)	1 (reference)
Mild anaemia	373 (20.1)	0.93 (0.80 to 1.10)	544 (29.7)	0.96 (0.84 to 1.10)
Moderate anaemia	526 (26.7)	1.23 (1.07 to 1.43)	705 (35.6)	1.14 (1.01 to 1.29)
Severe anaemia	74 (47.8)	2.16 (1.58 to 2.96)	88 (60.1)	1.85 (1.40 to 2.46)
Without iron supplementation				
No anaemia	345 (31.4)	1.00 (reference)	490 (45.2)	1 (reference)
Mild anaemia	158 (30.2)	0.93 (0.74 to 1.18)	250 (46.4)	0.99 (0.82 to 1.20)
Moderate anaemia	220 (36.2)	1.10 (0.88 to 1.37)	306 (50.1)	1.04 (0.87 to 1.26)
Severe anaemia	29 (42.9)	1.32 (0.84 to 2.09)	37 (57.3)	1.18 (0.78 to 1.78)

*Weighted rate per 1000 live births.
†Adjusted for maternal age, maternal BMI, place of residence, wealth index, birth order, maternal education, mode of delivery and infant's sex.
BMI, body mass index.

settings.[7 8 28] Low maternal haemoglobin levels have been associated with adverse neonatal and maternal mortality and morbidity in low-, middle- and high-income countries.[5 6 29–31] Regardless of the severity, maternal anaemia is independently associated with postpartum haemorrhage due to decreased uterine perfusion and uterine muscle strength, leading to maternal mortality.[32] Anaemia has been additionally linked with placenta-related complications, such as placental abruption, which consequently can lead to preterm delivery.[30]

Our results provide further evidence supporting previous literature on the theory of a reverse J-shaped association between the severity of maternal anaemia and risk of neonatal and infant deaths.[6 30] In agreement with previous research,[6 30] we showed that only in South & Southeast Asia, mild anaemia in mothers could potentially offer a protective effect on the offspring's risk of neonatal and infant death. With plasma volume expansion, a reduction of maternal haemoglobin might reduce blood viscosity and peripheral arterial resistance, thus increasing uteroplacental blood flow and perfusion, favouring fetal oxygen supply, growth and survival.[30] In contrast to these physiologic adaptations, moderate and severe anaemia might confer a health burden on the fetus and surpass the compensation ability, resulting in adverse maternal and fetal outcomes.[6 30]

Prevalence of anaemia varies markedly between low/middle-income countries, with the highest proportion in our study being reported in South and Southeast Asia and the lowest prevalence in Latin America and the Caribbean, in line with previous research.[33] Countries in Central America and the Caribbean, like Peru, have made significant progress in declining anaemia prevalence, with targeted interventions to vulnerable subpopulations.[33] Therefore, it is plausible that the increased odds between mild maternal anaemia and neonatal and infant death in this region might be explained by a constellation of health disorders in those women leading to anaemia during pregnancy. It could also be a random finding due to the small number of cases in this region.

In our study, mothers who reported taking iron supplementation appear to show stronger estimates for infant and neonatal death. However, these findings could be explained by the greater statistical power in the group of women on medication, as well as the small number of cases in the group without iron supplementation, since the majority of women in our study population (77%) were receiving iron supplementation. It is also possible that iron supplementation is a common effect of maternal anaemia and some unmeasured confounders; thus, conditioning the analysis on iron supplementation could introduce bias. Further, the anaemic mothers who took iron supplements might have more severe levels of anaemia and comorbid conditions, which might be responsible for a stronger association in this selected group. The early neonatal period conferred a higher and statistically significant increase in the odds of neonatal death compared with the late neonatal period, suggesting a proportionality in the risk of neonatal death closer to the delivery time.

Our study has several strengths. First, pooling data from 45 national datasets created a large sample with enough statistical power to examine the association between anaemia and neonatal and infant mortality. Furthermore, DHS intends to produce high-quality data with good reliability by editing and imputing inconsistent or missing values before the release. Additionally, we adjusted for several important confounders, such as educational level, place of residence and relative wealth index. Hence, the vital aspect of social vulnerability, possibly implicated in the pathway between maternal anaemia and neonatal death due to limited access to good quality healthcare

or undernutrition, was considered. Lastly, the ascertainment of haemoglobin was done using the HemoCue blood haemoglobin testing, providing a relatively accurate diagnostic tool for anaemia screening comparable with the laboratory method.[19 34] However, the results need to be interpreted with caution due to methodological limitations, some of which arose as a result of the cross-sectional design. Haemoglobin measurement was not done during pregnancy, but at the time that the questionnaire was distributed. However, we restricted our study to women who gave birth in the last 12 months prior to the survey as a proxy for haemoglobin levels during pregnancy. Nevertheless, this timing of measurement remains a major limitation of our study that cannot be addressed without prospective data collection. Prospective studies with ascertainment of haemoglobin value during pregnancy need to be conducted to establish a causal association by confirming that maternal anaemia temporally precedes neonatal or infant death. Anaemia's impact on neonatal outcomes may also vary by trimester[35 36] and requires further research. Countries with large populations, particularly India, may have influenced the results. However, stratified analysis by region produced similar estimates to the pooled data, minimising this bias despite some regional heterogeneity in prevalence and associations. To capture haemoglobin levels near those of their most recent pregnancy, we included only women who gave birth in the last year preceding the survey, which might limit the generalisability to all women of reproductive age. Quantitative bias analysis suggested potential underestimation of estimates due to Hemocue's sensitivity and specificity; however, we only accounted for the non-differential misclassification between anaemia and no anaemia, but not between anaemia severity levels. Lastly, we considered infant mortality as death between 0–12 months of life instead of 0–11 months, to avoid an underestimation and negative bias of the infant mortality, due to a heaping of age of death at 12 months.[37]

In summary, our study shows that anaemia in pregnancy, especially moderate and severe anaemia, is associated with early neonatal and infant mortality. With appropriate nutrition supplementation (eg, when there is a deficiency in ferrous, folate acid or B12 vitamin) or with proper medication (eg, HIV infection, malaria, or parasitic infection), anaemia might be a modifiable and reversible condition. Future research should examine how targeted interventions for prepregnancy and antenatal treatment of anaemia could minimise the burden of anaemia and improve maternal and child health in low- and middle-income settings.

Contributors Drs ET and NR had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analyses. Study concept and design: ET and NR. Acquisition of data: NR. Drafting of the manuscript: ET. Critical revision of the manuscript for important intellectual content: NR, TA and MZH. Statistical analysis: ET. Obtained funding: NR and TA. Study supervision: NR. Guarantor: NR.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Ethics approval The DHS received government permission and followed ethical practices including informed consent and assurance of confidentiality. Permission to study this dataset for secondary data analysis was approved by the DHS Program. We did not require separate ethics approval to analyse these secondary datasets. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The datasets generated and analysed during the current study are available by the DHS after appropriate ethical approval. DHS datasets are available from the DHS programme upon request at https://dhsprogram.com/data/available-datasets.cfm.

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