Risk of maternal mortality in women with severe anaemia during pregnancy and post partum: a multilevel analysis

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Summary

Background **Anaemia affects as many as half of all pregnant women in low-income and middle-income countries, but the burden of disease and associated maternal mortality are not robustly quantified. We aimed to assess the association between severe anaemia and maternal death with data from the WHO Multicountry Survey on maternal and newborn health.**

Methods **We used multilevel and propensity score regression analyses to establish the relation between severe anaemia and maternal death in 359 health facilities in 29 countries across Latin America, Africa, the Western Pacific, eastern Mediterranean, and southeast Asia. Severe anaemia was defined as antenatal or postnatal haemoglobin concentrations of less than 70 g/L in a blood sample obtained before death. Maternal death was defined as death any time after admission until the seventh day post partum or discharge. In regression analyses, we adjusted for post-partum haemorrhage, general anaesthesia, admission to intensive care, sepsis, pre-eclampsia or eclampsia, thrombocytopenia, shock, massive transfusion, severe oliguria, failure to form clots, and severe acidosis as confounding variables. These variables were used to develop the propensity score.**

Findings **312 281 women admitted in labour or with ectopic pregnancies were included in the adjusted multilevel logistic analysis, and 12 470 were included in the propensity score regression analysis. The adjusted odds ratio for maternal death in women with severe anaemia compared with those without severe anaemia was 2·36 (95% CI 1·60–3·48). In the propensity score analysis, severe anaemia was also associated with maternal death (adjusted odds ratio 1·86 [95% CI 1·39–2·49]).**

Interpretation **Prevention and treatment of anaemia during pregnancy and post partum should remain a global public health and research priority.**

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Introduction

As many as half of all pregnant women in low-income and middle-income countries are diagnosed with anaemia,[1,2] which affects 32 million pregnant women worldwide.[2] Women in low-income and middle-income countries are at increased risk of anaemia[1] because of the higher frequency of dietary iron deficiency, haemoglobinopathies, macronutrient deficiencies, and infections such as malaria, HIV, and hookworm infestation in those countries than in high-income countries.[3] Anaemia has been associated with increased prevalence of ante-partum and post-partum haemorrhage.[4]

WHO has recognised anaemia as a global problem with serious consequence for mothers and their babies.[5] Even though anaemia in pregnancy is readily treatable, data from several studies show an association between maternal anaemia and severe adverse maternal and perinatal outcomes.[2] The findings of these studies were not robust as a result of methodical limitations, including small sample sizes, use of surrogate outcome measures,[6] inconsistent definitions of severe morbidity,[7] and failure to adjust for relevant confounders. Thus, severe anaemia is strongly correlated with maternal morbidity secondary to known clinical and biological factors.[8] Furthermore, the crucially important outcome of maternal death is often not reported or is reported with low precision because of the rarity of events[9] in small and retrospective datasets.[4,10] As a result, the relation between severe anaemia and maternal mortality is not well understood.

The absence of robust evidence of severe anaemia and maternal mortality could affect prioritisation of anaemia as an important condition in its own right. We assessed the association of severe anaemia with maternal mortality in a large, multicountry dataset gathered via standardised procedures.

Methods

Survey methods and participants

The WHO Multicountry Survey was a large, cross sectional study in which data were collected for all

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Research in context

Evidence before this study

Anaemia in pregnancy is associated with severe maternal morbidity and an indirect cause of maternal death across pregnant populations in both low-income and high-income settings.

We searched MEDLINE and Embase with the terms "anaemia", "anemia", "anae*", "anem*", "pregnancy", "pregnan*", "mother", "mortality", "death", and "maternal mortality" for observational studies published in any language before June 19, 2017. We also searched in WHO's study registry. We did not identify any large international analyses of the association between severe anaemia and maternal death, but noted several small national or regional studies with methodological limitations, such as small sample size, in which the small number of events prevented development of a robust model with adequate adjustment for known confounding variables.

Added value of this study

To our knowledge, ours is the first study to explore the independent association of severe anaemia with maternal mortality. We noted an independent association to varying degrees in an ethnically and geographically diverse population. Because severe anaemia was recorded as a binary variable in our dataset (from the WHO Multicountry Survey), we could not examine whether a dose–response relationship exists between haemoglobin concentration and maternal mortality. Nonetheless, we identified an association that was present in several different regions and reproducible with different statistical techniques, even after adjustment for several known confounding variables.

Implications of all the available evidence

Irrespective of the cause, severe anaemia should be treated with vigour. Our findings support the use of haematological indices as outcome measures that are strongly associated with clinical outcomes. Our work also shows the need to prioritise the prevention and management of anaemia in pregnancy as a global public health and research priority.

delivery and severe maternal outcomes (ie, maternal death and maternal near-miss) with standardised methods at 359 health facilities in 29 countries across Latin America, Africa, the Western Pacific, eastern Mediterranean and southeast Asia between May, 2010, and December, 2011. The included countries were Afghanistan, Angola, Argentina, Brazil, Cambodia, China, Democratic Republic of the Congo, Ecuador, India, Japan, Jordan, Kenya, Lebanon, Mexico, Mongolia, Nepal, Nicaragua, Niger, Nigeria, Pakistan, Palestine, Paraguay, Peru, Philippines, Qatar, Sri Lanka, Thailand, Uganda, and Vietnam. They were chosen on the basis of their participation in the WHO Global Country Survey and on assessments of feasibility. Types of health-care facilities included government-funded regional and local hospitals, and community hospitals. Detailed explanations of the methods have been published previously.[11,12]

The WHO Multicountry Survey was based on a stratified multistage cluster-sampling approach to obtain a global sample of pregnancy complications. Within each region, two randomly selected provinces and the capital city of each country were sampled. Within each capital city and province, seven institutions with more than 1000 deliveries per year and the capacity for caesarean deliveries were randomly selected (if there were fewer than seven eligible institutions, all eligible institutions were included). Data were collected for 2 months in institutions with more than 6000 deliveries per year data, and for 3 months in institutions with fewer than 6000 deliveries per year. In countries where fewer than 3000 deliveries were anticipated per year, data were gathered for 4 months at all centres. Health-care facilities were the primary sampling level of the WHO Multicountry Survey, and thus individual level analyses could be affected by clustering.

The study population comprised all women giving birth in participating hospitals and their respective neonates; all maternal near-miss cases admitted to participating hospitals, irrespective of gestational age and delivery status; and all maternal deaths in participating hospitals, irrespective of gestational age and delivery status, during the data collection period. Those in whom severe outcomes were a result of miscarriage or ectopic pregnancy were also included. Data were gathered for all eligible individuals from admission to a health-care facility until 7 days post partum or post abortion, discharge, or death (whichever came first). Thus, complications that occurred before presentation, more than 7 days post partum, after discharge, or during a post-partum readmission were not recorded. Data were captured via a pre-tested individual data collection form. Trained data collectors reviewed medical records and abstracted data into the forms daily; there was no contact with eligible women. Clarification, when needed, was sought from clinical staff. Additionally, data collectors completed an institutional form in consultation with the head of the obstetric department, in which obstetric, neonatal, and intensive-care capacity, and capacity to identify a range of laboratory, clinical, and management severity indicators for mothers and neonates were captured. Data for both the individual and institutional forms were then entered into a web-based management system. Ethical approval for the original Multicountry Survey was granted by WHO's Ethical Review Committee, and was also sought in each contributing country. This specific analysis was approved by the

WHO Multicountry Survey Research Network after a review of our protocol.

Definitions and variables

Haemoglobin was measured in accordance with standard clinical practice. Severe anaemia was recorded as an independent pregnancy complication if the haemoglobin measurement in an antenatal or postnatal blood sample taken before the outcome was less than 70 g/L (in line with WHO's definition of near miss for women who experience severe complications of pregnancy or delivery and nearly die, but survive).[13] Women without anaemia and those with haemoglobin concentrations of 70–120 g/L were grouped together. Maternal death was defined as death any time after admission until the seventh day post partum or discharge (whichever came first). Our approach follows the standards used by the WHO Multicountry Survey Research Network and previous analyses of this dataset.[14] A list of the potential confounding variables and their respective definitions sought for adjustment within statistical models are provided in the appendix in accordance with reporting guidelines for regression models.[15]

Statistical analysis

In our analysis, we included all women admitted for delivery or ectopic pregnancy with or without severe anaemia at facilities where there were more than 100 cases (to avoid instability and problems of convergence related to small sample sizes). We explored the relation between severe anaemia and maternal death with two approaches: a multilevel logistic regression analysis and a propensity score regression analysis.

We fitted an explanatory multilevel logistic regression model with maternal death as the dependent binary outcome and severe anaemia as the main exposure. We defined a three-level model for women (first level) giving birth in facilities (second level) within countries (third level). We selected a set of potential confounding variables from the covariates captured by the data extraction form a priori. Covariates selected had to have a plausible biological relation to the association between severe anaemia and maternal death (appendix). Selection of covariates was an iterative process that involved informal discussions with clinicians, epidemiologists, and laboratory scientists. We aimed to adjust the association of severe anaemia with the outcome of maternal death. Thus, we defined a confounding effect as a change of greater than 10% between the adjusted and unadjusted or crude odds ratio (OR) for severe anaemia and maternal death. We used a non-automated backwards elimination strategy to select variables included in the final model. All variables that were significant (ie, $p<0·05$) in the adjustment were included in the final model.

Because we noted important differences in baseline clinical characteristics between women with and without severe anaemia, we did a second analysis based on propensity scores to mitigate confounding bias caused by the imbalance between the characteristics of the groups under comparison. We developed[16] a score that represents the propensity (ie, the conditional probability) of a woman to develop severe anaemia in view of her clinical characteristics. Compared with classic multivariate adjustments, the propensity score permitted finer adjustments for wider sets of covariates. To obtain the score, we fitted a logistic regression model, with severe anaemia as a binary dependent variable and adjusted with the same covariates used in the multilevel logistic regression analysis (appendix). We used the propensity score to match, without replacement, women with severe anaemia and women without severe anaemia in a 1:2 ratio, to optimise the precision of the estimate of association and limit bias.[17] Matched pairs were chosen from within countries. We established a caliper of 0·25 of the SD of the propensity score,[18] resulting in a small caliper but an excellent balance of women with severe anaemia and those without as matched samples. We computed standardised differences (ie, the difference in proportions divided by the SD) for all variables included in the propensity score before and after matching to assess the effect of matching on the imbalance. We deemed a 10% standardised difference as the limit for

See Online for appendix

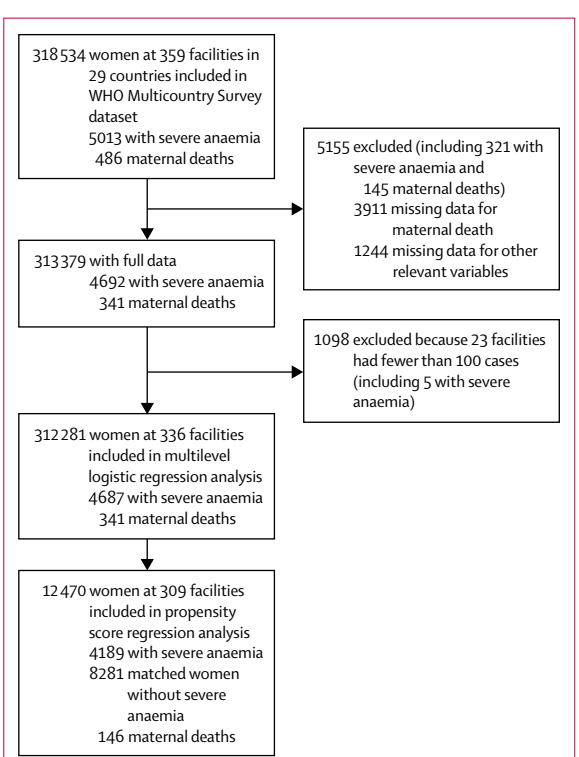

Figure 1: **Selection of sample from the WHO Multicountry Survey dataset**

	Women with severe anaemia (n=4687)		Women without severe anaemia* (n=307 594)		p value†
	Data available (n)	Finding	Data available (n)	Finding	
Maternal death	..	135 (3%)	..	206 (<1%)	<0·0001
Age, years	4679	26·7 (6·4)	306 684	26·6 (6·0)	0·118
Marital status	..	..	..	..	0·002
Single, separated, divorced, widowed, or other	..	411 (9%)	..	30 947 (10%)	..
Married or cohabitating	..	4244 (91%)	..	273 065 (89%)	..
Length of schooling, years	4473	7·3 (5·2); 8 (0–12)	282 316	8·5 (4·9); 9 (6–12)	<0·0001
Pregnancies (including current pregnancy)	4683	2·9 (2·2); 2 (1–4)	307 111	2·5 (1·8); 2 (1–3)	<0·0001
Previous births (excluding current delivery)	4684	1·6 (2·0); 1 (0–2)	306 991	1·3 (1·7); 1 (0–2)	<0·0001
Previous caesarean sections	4663	0·29 (0·7); 0 (0–0)	303 430	0·16 (0·5); 0 (0–0)	<0·0001

Data are n (%), mean (SD), or mean (SD); median (IQR). *The subset of women included in the propensity score regression analysis were taken from this group. †The student's *t* test was used to compare continuous variables; the χ^2 test was used for all other variables.

Table 1: **Demographic features of women included in analysis of the association between severe anaemia and maternal mortality**

	Odds ratio* (95% CI)	p value
Multilevel logistic regression†		
Crude	43·35 (35·03–53·65)	<0·0001
Adjusted		
Severe anaemia	2·36 (1·60–3·48)	<0·0001
General anaesthesia	1·85 (1·24–2·75)	0·003
Admission to intensive-care unit	5·38 (3·36–8·60)	<0·0001
Post-partum haemorrhage	3·35 (2·27–4·95)	<0·0001
Sepsis	13·85 (8·78–21·84)	<0·0001
Pre-eclampsia	6·62 (4·58–9·56)	<0·0001
Oliguria	17·72 (9·49–33·09)	<0·0001
Failure to form clots	2·84 (1·37–5·89)	0·005
Thrombocytopenia	3·27 (1·42–7·53)	0·005
Massive transfusion	0·36 (0·18–0·69)	0·002
Shock	85·55 (56·61–129·28)	<0·0001
Severe acidosis	10·40 (4·74–22·85)	<0·0001
Propensity score regression‡		
Cases with severe anaemia matched (1:2) with cases without severe anaemia	1·86 (1·39–2·49)	<0·0001

The appendix lists definitions of the covariates used in the multilevel logistic regression model. *Maximal model used to develop adjusted odds ratio includes severe anaemia, general anaesthesia, admission to intensive-care unit, post-partum haemorrhage, sepsis, pre-eclampsia, oliguria, failure to form clots, thrombocytopenia, massive transfusion, shock, severe acidosis, previous pregnancies, abnormal placentation, malaria, dengue, azotaemia, and dialysis; goodness-of-fit test for the adjusted final model χ^2 1536 (12 degrees of freedom; p<0·0001). †N=312 281, 4687 of whom had severe anaemia; 341 maternal deaths were recorded. ‡N=12 470, 4189 of whom had severe anaemia; 146 maternal deaths were recorded; the covariates used to identify matched women without severe anaemia are in the appendix.

Table 2: **Regression analyses of association between severe anaemia and maternal mortality**

a correct balance. We also computed the post-match C statistic to assess the degree of balance.[19] After matching, we compared maternal mortality between women with severe anaemia and those without severe anaemia as matched groups. We calculated an adjusted OR to quantify the association between severe anaemia and maternal death, and used univariate logistic regression fitted by generalised estimating equations to account for matched data.

To assess the effect of reducing severe anaemia on mortality, we calculated the population attributable fraction[20] to estimate the reduction in mortality that would occur if severe anaemia was completely eradicated in the study sample:

$$\text{Population attributable fraction} = \frac{P_c(aOR-1)}{aOR}$$

where P_c is the proportion of cases that are exposed and αOR is the adjusted OR for the effect of anaemia on mortality.

We used the non-random package in R (version 1.42) for the propensity score matching, and STATA/IC (version 15.0) for all remaining statistical analysis.

Role of the funding source

The funder had no role in study design; data collection, analysis, or interpretation; or writing of the Article. The corresponding author had access to all study data and responsibility for the decision to submit the paper for publication.

Results

312 281 pregnancies (including 96 ectopic pregnancies), 4687 cases of severe anaemia and 341 maternal deaths at 336 facilities were included in the multilevel analysis (figure 1). Table 1 shows the characteristics of included women with and without severe anaemia. 12 470 women—4189 women with severe anaemia matched with 8281 women without severe anaemia—from 309 facilities, and 146 maternal deaths were included in the propensity score analysis (figure 1). For 97 women with severe anaemia, only one match could be found (ie, they were matched 1:1 rather than 1:2).

The odds of maternal death was higher in mothers with severe anaemia than in those without severe anaemia in both the crude (OR 43·35 [95% CI

35·03–53·65], p<0·0001) and adjusted analyses (adjusted OR 2·36 [95% CI 1·60–3·48], p<0·0001; table 2). The propensity score matching algorithm largely reduced the initial imbalance between women with and without severe anaemia, with between-group standardised differences for all instances lower than the recommended 10% limit (figure 2, table 3). After matching, the C statistic was 0·506, which suggests almost-perfect matching. Overall, propensity score regression analysis showed an association between severe anaemia and maternal death (adjusted OR 1·86 [95% CI 1·39–2·49], p<0·0001; table 2). The population attributable fraction was 0·184.

We did sensitivity analyses for both the multilevel and the propensity score regression models. When cases of post-partum haemorrhage were removed from the multilevel regression model, the adjusted OR between severe anaemia and maternal death was more pronounced (4·58 [95% CI 2·87–7·31]). The association between anaemia and maternal mortality was unchanged when post-partum haemorrhage was classed as "none", "moderate", or "severe" according to use of medical and surgical management strategies (adjusted OR 2·41 [95% CI 1·63–3·55]). In the propensity regression analysis, changing the caliper between the cases with severe anaemia and those without severe anaemia did not affect the size or direction of the estimate (data not shown).

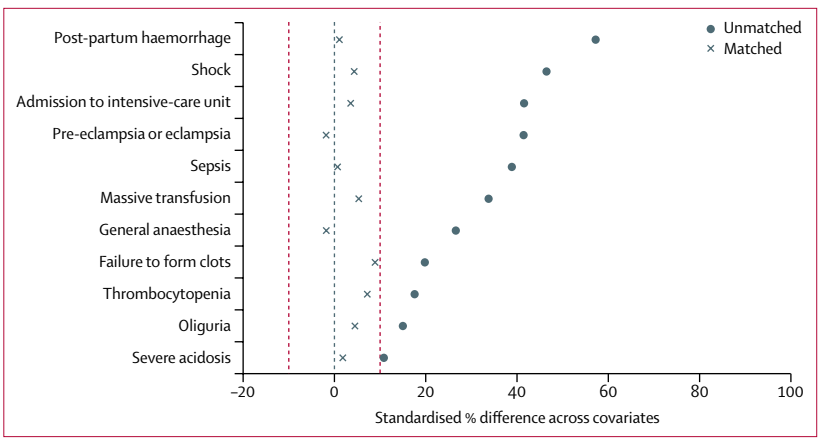

Figure 2: **Propensity score matching of cases of severe anaemia with cases without severe anaemia**
Red dotted lines denote 10% standardised difference between covariates. The appendix details the confounding variables included.

Discussion

In our analysis of a dataset of 312 281 pregnancies in 29 countries from the WHO Multicountry Survey, the odds of maternal death were twice as high in those with severe anaemia compared with those without severe anaemia. The association seemed to be moderately strong, temporal, and consistent and was reproducible in both multilevel and propensity score regression analyses. Previously published estimates of the relation between anaemia and maternal mortality were limited by low event rates, low geographical variability,[4] and residual confounding variables.[10] Furthermore, maternal death is rarely reported as an outcome in randomised studies, and therefore such analyses necessitate use of observational data.[10]

Our finding of a link between severe maternal anaemia and mortality challenges the assumption that haematological indices such as haemoglobin are not suitable outcome measures.[6] The insistence that clinical outcomes be used for assessment of effectiveness of iron interventions will necessitate larger, more complicated studies (possibly of composite outcomes) to ensure adequate power.[6] The implications of our findings are far reaching, because severe anaemia is globally prevalent.[2] The implementation of international recommendations on iron fortification,[21] targeted iron supplementation,[5] anthelminthic therapy programmes,[5] blood management strategies, and access to transfusion services should be vigorously reinforced. Importantly, maternal anaemia should remain an important priority, and merits renewed focus in terms of public health interventions and from clinicians caring for women during pregnancy and labour. Increased focus on effective prevention is needed, because approaches so far have not effectively addressed the problem.

Our study had several strengths. The dataset was large and diverse (both geographically and ethnically), with ample numbers of events and many available confounding variables, allowing for adjustment of statistical models without compromising the model's goodness-of-fit.[22] We used two types of regression analyses to ensure that our findings were not affected by our choice of statistical modelling. The confounding variables chosen were from an extensive list of data gathered within the original study.[12] We chose variables that had a plausible biological relation with severe anaemia and maternal death, those that, if present in the context of severe anaemia, worsen outcomes (appendix), and those that are associated with maternal death such as shock, admission to intensive care, and severe acidosis. The relevance of these variables helps to explain the great reduction from the crude OR after adjustment.

The association of anaemia with poor maternal outcomes, including increased morbidity related to post-partum haemorrhage,[23] antenatal sepsis, and postnatal sepsis, is well reported.[24] We are confident that our adjustment of the statistical models has a rational a-priori basis. We were, however, limited in our choice of variables for adjustment, by what was recorded within the original WHO study. 341 maternal deaths were recorded in the survey sample, and our adjusted model included 12 variables—well within the rule of thumb of one confounder per ten outcome events.[25]

Our study also had several limitations. Anaemia data were collected according to the WHO definition of severe adverse outcome.[12] Thus, anaemia was recorded as a binary variable (ie, present [haemoglobin <70 g/L] or absent [haemoglobin ≥70g/L]), and actual haemoglobin concentrations were not recorded. As a result, women

	Unmatched				Matched			
	Women with severe anaemia (n=4687)	Women without severe anaemia (n=307 594)	Standardised difference (%)	p value	Women with severe anaemia (n=4189)	Women without severe anaemia (n=8281)	Standardised difference (%)	p value
General anaesthesia	455 (9·7%)	9913 (3·2%)	26·6	<0·0001	293 (7·0%)	615 (7·4%)	–1·8	0·380
Admission to intensive-care unit	429 (9·2%)	1393 (0·5%)	41·6	<0·0001	260 (6·2%)	452 (5·5%)	3·6	0·089
Post-partum haemorrhage	804 (17·2%)	3840 (1·2%)	57·2	<0·0001	589 (14·1%)	1139 (13·8%)	1·1	0·640
Sepsis	397 (8·5%)	1691 (0·5%)	38·9	<0·0001	264 (6·3%)	510 (6·2%)	0·7	0·754
Pre-eclampsia or eclampsia	617 (13·2%)	7126 (2·3%)	41·5	<0·0001	570 (13·6%)	1166 (14·1%)	–1·8	0·471
Oliguria	57 (1·2%)	111 (<0·1%)	15·0	<0·0001	30 (0·7%)	30 (0·4%)	4·5	0·007
Failure to form clots	96 (2·0%)	131 (<0·1%)	19·8	<0·0001	57 (1·4%)	38 (0·5%)	8·9	<0·0001
Thrombocytopenia	78 (1·7%)	154 (0·1%)	17·6	<0·0001	49 (1·2%)	42 (0·5%)	7·2	<0·0001
Massive transfusion	262 (5·6%)	206 (0·1%)	33·8	<0·0001	75 (1·8%)	76 (0·9%)	5·3	<0·0001
Shock	481 (10·3%)	579 (0·2%)	46·5	<0·0001	216 (5·2%)	349 (4·2%)	4·3	0·017
Severe acidosis	30 (0·6%)	60 (<0·1%)	10·8	<0·0001	11 (0·3%)	13 (0·2%)	1·8	0·204

Data are n (%), unless otherwise specified.

Table 3: **Standardised differences between women with severe anaemia and those without severe anaemia included in propensity score analysis**

with mild-to-moderate anaemia were grouped with women without anaemia as the comparator. This grouping probably weakens the association identified, and also meant that we could not assess a potential dose–response relation between severe anaemia and maternal death. Furthermore, the timing of severe anaemia (antenatal or postnatal) was not recorded. However, with respect to temporality of association, all data for severe anaemia were gathered before maternal death occurred. Future similar research should explore haemoglobin as a continuous variable with maternal morbidity or mortality, or both, and whether higher haemoglobin concentrations are associated with adverse maternal outcomes.

More than 4000 cases were excluded from our analyses because of missing data. This issue was due to how data were gathered in the original survey[12] (ie, in a binary fashion), which meant that multiple imputation strategies could not be used.[26] Unfortunately, we could not examine in depth how these missing data affected the estimate of the relation between severe anaemia and maternal death.

We used propensity score regression analysis in addition to multivariable logistic models, because such analyses allow for comparisons of outcomes of interest from observational data via a scoring system for groups with similar characteristics, mimicking a randomised study.[27] In propensity score analysis, important differences between groups are minimised (eg, achieving similarity in baseline characteristics reduces the risk of selection bias), although we cannot completely exclude the possibility of residual confounding—some relevant variables could be inadvertently omitted from the score. The use of propensity score analysis for data from the WHO Multicountry Survey is novel and supported the main findings of the logistic regression model.

The availability of care varied between the individual facilities contributing data to the dataset. An analysis stratified by individual facilities was unfeasible and therefore was not done. We controlled for variables that could predispose women to postnatal anaemia in our multilevel and propensity regression analyses and did sensitivity analyses to establish whether the relation between severe anaemia and maternal death was solely related to post-partum haemorrhage within these data.

We are confident that our findings are a robust demonstration of an independent link between severe anaemia and maternal death. Although our data cannot explain a direct causal relation between severe anaemia and maternal death, examination of the extent to which causal criteria have been met by our work is worthwhile.[28] We noted a moderately strong association between severe anaemia and maternal death in the multilevel regression analysis on the basis of published criteria, with a point estimate (ie, adjusted OR) in the range of 2–5.[29,30] By these criteria, the association was weak in the propensity score regression analysis, but this statistical approach underestimates the strength of associations.[31] The association was temporal in that the exposure measurements (severe anaemia) were obtained before the occurrence of the outcome (death). This relation has biological plausibility,[28] because severe anaemia reduces tissue oxygen availability (via a reduction in circulating haemoglobin), reduces iron availability for DNA synthesis, and alters enzyme function,[2] all of which could contribute to an association between severe anaemia and maternal death. The relation between severe anaemia and maternal death was also consistently noted with varied statistical approaches.[28,32] We could not study if there was a biological gradient.

Our sensitivity analyses showed that, when cases of post-partum haemorrhage were removed from the multilevel regression model, the strength of the association between severe anaemia and maternal death increased. Thus, inclusion of post-partum haemorrhage in our models could have resulted in underestimation of the strength of the relation. Furthermore, our sensitivity analyses emphasise that severe anaemia in pregnant and postnatal women strongly and independently contributes to adverse outcomes, irrespective of the cause. Anaemia treatment and prevention in pregnancy should remain a global priority.

Contributors

JD, JZ, JV, and KSK planned the analyses. All authors refined the statistical analysis protocol. JD, JZ, and BMF-F did the statistical analyses. JD wrote the first draft of the Article, which was revised and critically reviewed by all authors. All authors contributed to the arguments presented, and approved the final version.

Declaration of interests

JZ has received financial support from Novartis and Astellas for lectures. All other authors declare no competing interests.

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