



WHO analysis of causes of maternal death: a systematic review

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Summary

Background The reduction of maternal deaths is a key international development goal. Evidence-based health policies and programmes aiming to reduce maternal deaths need reliable and valid information. We undertook a systematic review to determine the distribution of causes of maternal deaths.

Methods We selected datasets using prespecified criteria, and recorded dataset characteristics, methodological features, and causes of maternal deaths. All analyses were restricted to datasets representative of populations. We analysed joint causes of maternal deaths from datasets reporting at least four major causes (haemorrhage, hypertensive disorders, sepsis, abortion, obstructed labour, ectopic pregnancy, embolism). We examined datasets reporting individual causes of death to investigate the heterogeneity due to methodological features and geographical region and the contribution of haemorrhage, hypertensive disorders, abortion, and sepsis as causes of maternal death at the country level.

Findings 34 datasets (35 197 maternal deaths) were included in the primary analysis. We recorded wide regional variation in the causes of maternal deaths. Haemorrhage was the leading cause of death in Africa (point estimate 33·9%, range 13·3–43·6; eight datasets, 4508 deaths) and in Asia (30·8%, 5·9–48·5; 11, 16 089). In Latin America and the Caribbean, hypertensive disorders were responsible for the most deaths (25·7%, 7·9–52·4; ten, 11 777). Abortion deaths were the highest in Latin America and the Caribbean (12%), which can be as high as 30% of all deaths in some countries in this region. Deaths due to sepsis were higher in Africa (odds ratio 2·71), Asia (1·91), and Latin America and the Caribbean (2·06) than in developed countries.

Interpretation Haemorrhage and hypertensive disorders are major contributors to maternal deaths in developing countries. These data should inform evidence-based reproductive health-care policies and programmes at regional and national levels. Capacity-strengthening efforts to improve the quality of burden-of-disease studies will further validate future estimates.

Introduction

The reduction of maternal deaths is a high priority for the international community, especially in view of the increased attention on the Millennium Development Goals.¹ Maternal deaths arise from the risks attributable to pregnancy and childbirth as well as from the poor-quality care from health services.² Effective services to improve overall maternal health need targeted health and social policies that are informed by reliable and valid epidemiological data. A comprehensive summary of the magnitude and distribution of the causes of maternal deaths is critical to inform reproductive health policies and programmes. The most widely referred source that is currently available³ dates back to the 1990s, although its methodology is not clear and it assumes a fixed distribution across all regions. Regional variations are likely to exist, although their magnitude and direction are unknown. A more recent WHO Global Burden of Disease estimate gave a breakdown by cause and region but the methodology and the data sources for cause attribution and regional differences were not reported.⁴

Systematic reviews are increasingly used to summarise descriptive epidemiological evidence to provide summary estimates for the extent of important public-health problems.^{5,6} We undertook a systematic review that

aimed to estimate incidence and prevalence of a range of maternal conditions, including maternal mortality and its causes.⁷ The aim of this study was to ascertain and map the distribution of causes of maternal deaths, to identify data gaps in regional coverage, and to explore the extent to which countries' development status, geographical location, and datasets' methodological features explain variable distribution of causes of deaths.

Methods

Our systematic review followed an a-priori protocol developed with a widely recommended methodology^{7–9} to generate a comprehensive, standardised, and reliable evidence summary for conditions contributing to maternal deaths worldwide. This process included the breakdown of causes of maternal deaths and examination of heterogeneity of causes.

Dataset selection

Participants included pregnant women or women within 1 year of the end of pregnancy who had maternal deaths. A maternal death is defined in the International Classification of Diseases, 10th edition (ICD-10) as the death of a woman while pregnant or within 42 days (or

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1 year for late maternal deaths) of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.¹⁰

We used datasets providing counts or proportions attributed to specific conditions leading to maternal death, from direct counting or from special surveys. We use the term dataset because some sources are research studies but others are direct counts or other forms of routine data collection (such as vital registration; webtable). We included only datasets that represented the populations in the final analysis. The population settings could be country, province, or city (or district).

Datasets were ineligible if data were taken before 1990, if part of the data was obtained before 1980 and disaggregation by year was not possible (in order to exclude data before 1980), or if data collection dates were not reported. In cases of partial data duplication with some data overlapping between different datasets, we selected the most recent and largest dataset.

To allow more stable and reliable estimation of proportions attributed to the various causes of maternal deaths, we excluded datasets with less than 25 maternal deaths in the series. The decision for this cutoff was arbitrary. Specifically for the joint distribution of cause analysis, we further excluded datasets that did not have a cause attributed to more than 25% of deaths, or did not include at least four of the following direct causes of death: haemorrhage, hypertensive disorder, sepsis, abortion, obstructed labour, ectopic pregnancy, and embolism.

Identification of data sources

We searched general and specialised bibliographic databases: MEDLINE, Popline, CAB, Sociofile, CINAHL, Econlit, EMBASE, BIOSIS, PAIS International, the Latin American and Caribbean Health Science Information (LILACS), African Index Medicus (AIM), Index Medicus for the Eastern Mediterranean Region (IMEMR), Index Medicus for the South-East Asian Region (IMSEAR), websites of ministries of health in all 192 WHO member states, and WHO Reproductive Health databases from 1997 to 2002, a time limit chosen to allow a review of recent data on causes of maternal deaths. Reference lists of the identified reports were screened and personal contacts were made with country representatives of WHO, non-governmental organisations (NGOs), and other organisations known to be active in the maternal-health field to find datasets not captured by bibliographic searches. Our search term combinations are described in detail elsewhere.⁷ We did not apply language restrictions in the search or in the selection process. Potentially eligible datasets included journal articles, registries, and published or unpublished information from government or other agencies, whether available in print or online.

Methodological quality assessment

The methodological quality of all eligible datasets was assessed to investigate internal validity (the extent to which the information is probably free of bias) with the following attributes:⁸ (1) reporting of maternal deaths definition to reduce bias in ascertainment of denominator data in the series (any published definition reported vs no definition); (2) adequacy of data source to ascertain a capture of denominator data that is as complete as possible (use of multiple data sources, special surveys, or clinical studies vs routine registration systems, in which adequate attribution of cause of death has been shown to be questionable for maternal deaths, leading to substantial underreporting);¹¹ (3) use of a robust approach to ascertain that the cause of death is a representation of the underlying condition that is as true as possible (confidential enquiries, verbal autopsies, use of multiple

See Online for webtable

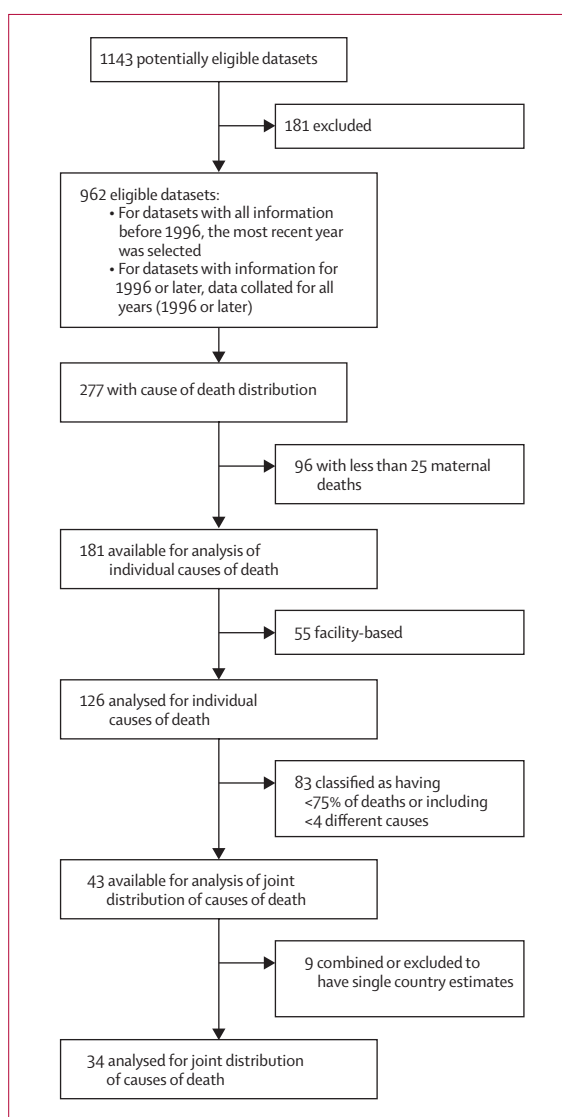


Figure 1: Dataset selection process

	Developed countries	Africa	Asia	Latin America and the Caribbean
Number of datasets	5	8	11	10
Number of maternal deaths	2823	4508	16 089	11 777
Haemorrhage	13.4% (4.7–34.6)	33.9% (13.3–43.6)	30.8% (5.9–48.5)	20.8% (1.1–46.9)
Hypertensive disorders	16.1% (6.7–24.3)	9.1% (3.9–21.9)	9.1% (2.0–34.3)	25.7% (7.9–52.4)
Sepsis/infections	2.1% (0.0–5.9)	9.7% (6.3–12.6)	11.6% (0.0–13.0)	7.7% (0.0–15.1)
Abortion	8.2% (0.0–48.6)	3.9% (0.0–23.8)	5.7% (0.0–13.0)	12.0% (0.0–32.9)
Obstructed labour	0.0%* (0.0–0.0)	4.1% (0.0–10.3)	9.4% (0.0–12.0)	13.4% (0.0–38.9)
Anaemia	0.0%* (0.0–0.0)	3.7% (0.0–13.2)	12.8% (0.0–17.3)	0.1% (0.0–3.9)
HIV/AIDS	0.0%* (0.0–0.0)	6.2% (0.0–13.3)	0.0%* (0.0–0.0)	0.0%* (0.0–0.0)
Ectopic pregnancy	4.9% (0.4–7.4)	0.5% (0.0–3.3)	0.1% (0.0–3.9)	0.5% (0.0–4.5)
Embolism	14.9% (0.0–21.2)	2.0% (0.0–5.6)	0.4% (0.0–51.0)	0.6% (0.0–8.4)
Other direct causes	21.3% (0.0–33.9)	4.9% (0.0–10.3)	1.6% (0.0–25.9)	3.8% (0.0–27.9)
Other indirect causes	14.4% (0.0–51.2)	16.7% (9.1–29.3)	12.5% (0.0–29.2)	3.9% (0.0–25.3)
Unclassified deaths	4.8% (0.0–22.9)	5.4% (0.0–21.8)	6.1% (0.0–16.2)	11.7% (0.0–20.4)

Data are pooled percentages (range), unless stated otherwise. *Zero indicates that the condition is not reported as a cause of death. Deaths from that cause could have occurred but listed under other or unclassified deaths.

Table 1: Joint distribution of causes of maternal deaths

	Haemorrhage	Hypertensive disorders	Sepsis	Abortion
Representative datasets (n)	74	61	48	66
Deaths due to specific cause (n)	12 725	9573	3281	5347
Total maternal deaths (n)	60 358	44 182	46 675	46 394
% of deaths due to cause (range)	1.4–49.6%	2.0–42.7%	0.5–15.1%	1.4–48.6%
Geographical variation*				
Unadjusted analysis				
Africa	1.74 (0.97–3.12)	0.74 (0.46–1.19)	2.71† (1.49–4.91)	0.74 (0.37–1.49)
Asia	1.40 (0.87–2.26)	0.93 (0.60–1.44)	1.91† (1.07–3.40)	0.65 (0.39–1.10)
Latin America and the Caribbean	0.92 (0.55–1.53)	1.93† (1.27–2.93)	2.06† (1.17–3.62)	1.18 (0.68–2.05)
Regional heterogeneity (p)	0.1237	0.0010	0.0108	0.1827
Adjusted analysis‡				
Africa	1.57 (0.80–3.07)	0.81 (0.46–1.43)	2.28† (1.04–5.01)	1.73 (0.86–3.46)
Asia	1.35 (0.82–2.21)	0.99 (0.61–1.60)	1.69 (0.86–3.34)	0.87 (0.55–1.39)
Latin America and Caribbean	0.91 (0.55–1.52)	1.95† (1.27–2.97)	2.01† (1.13–3.56)	1.06 (0.66–1.71)
Regional heterogeneity (p)	0.3354	0.0048	0.0826	0.2472
Methodological quality items§				
Unadjusted analysis				
Reporting of definition of maternal death	0.25 (0.05–1.28)	0.70 (0.25–1.94)	1.29 (0.25–6.60)	0.34 (0.06–1.92)
Reporting of confirmation of maternal deaths	1.41 (0.94–2.11)	0.71 (0.49–1.01)	1.68† (1.08–2.61)	0.33† (0.21–0.52)
Special data collection (vs routine data collection)	1.68† (1.12–2.51)	0.82 (0.57–1.18)	1.54 (0.98–2.41)	0.33† (0.20–0.53)
High quality (at least two of the above items) vs low quality (<2 of the above items)	1.41 (0.94–2.11)	0.71 (0.49–1.01)	1.68† (1.08–2.61)	0.33† (0.21–0.52)
Adjusted analysis				
High quality vs low quality (adjusted by region)	1.16 (0.73–1.84)	0.88 (0.59–1.32)	1.22 (0.68–2.20)	0.28† (0.16–0.48)

126 datasets were available for analysis of individual causes of death. Data (presented as odds ratios) derived from regression modelling, unless otherwise specified. *Data are odds ratios (95% CI) for geographic regions versus developed countries; odds ratios more than 1 indicate increased deaths due to cause in datasets from a developing region compared with developed countries. †p<0.05. ‡Adjusted by quality. §Data are odds ratios for each quality item independently; values more than 1 indicate increased deaths due to cause in datasets with quality features compared with datasets without quality features.

Table 2: Possible reasons for heterogeneity in proportion of deaths due to four major causes of maternal deaths

sources of death certification *vs* no special efforts to confirm cause); (4) sufficiently high proportion of cases with attributable cause of death established (<5% unclassified); and (5) identification of sufficiently large number of causes within a series to ensure that a fuller range of conditions have been included to reduce the risk of misclassification of cause of death (>5 causes was taken as a cutoff).

(4) and (5) are good-quality items relevant mainly to the joint cause of death analysis. For example, in a report that analysed deaths due to abortion only, a large proportion of deaths could be unclassified, but the report could still present a detailed and good-quality dataset for a specific cause if it complied with the quality items (1), (2), and (3). For this reason, in the appraisal of individual causes of death datasets, we only took three quality items into account. The datasets were classified into high-quality and low-quality groups, on the basis of compliance with at least two quality criteria.

Data extraction

Two reviewers independently assessed titles or abstracts from a randomly selected sample of citations identified by the electronic search that achieved 88.9% (95% CI 86.0–91.4) agreement (κ 0.60, 95% CI 0.52–0.69), a value corresponding to moderate to substantial concordance.¹² If one reviewer was unsure, the full text of the report was retrieved. In case of disagreement about the application of the selection criteria, the case was discussed with reference to the protocol criteria and, if needed, the full paper was retrieved. We extracted dataset characteristics, methodological quality information, and proportions of various causes among all maternal deaths.

Statistical analysis

We analysed two groups of population-based representative datasets: the joint cause of death distribution and the individual cause dataset. For the joint cause of death analysis, countries with several datasets for different times were combined to produce a nationally representative estimate per country. If estimates were from the same period because of overlapping settings, national data took precedence over data from provinces, states, or cities.

We obtained causes of death distribution within each geographical region by combining the estimates for all the countries within each region. For this purpose, the number of maternal deaths in countries with causes of death distribution was estimated and used to derive weights to be applied to the distribution of causes within each region. The number of maternal deaths were estimated with the maternal mortality ratio and the number of livebirths per country.¹³ The weights were based on the number of maternal deaths because this apportioned importance according to the disease burden contributed by each country. The traditional approach to

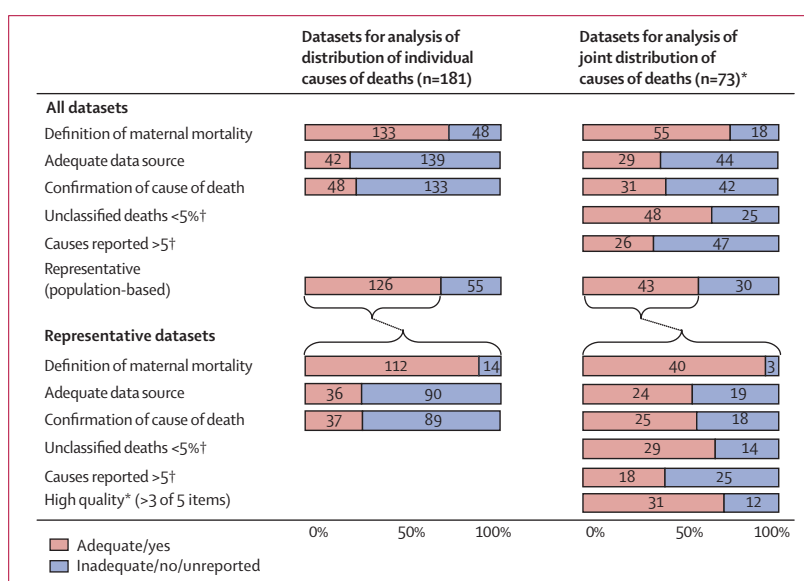


Figure 2: Methodological quality of datasets on causes of maternal deaths

*Of the 73 datasets, 43 were representative and used in the quality appraisal. A further nine representative datasets were combined or excluded because of the presence of another dataset from the same country, bringing the denominator to 34 for the statistical analysis. †Analysis restricted to joint-cause datasets.

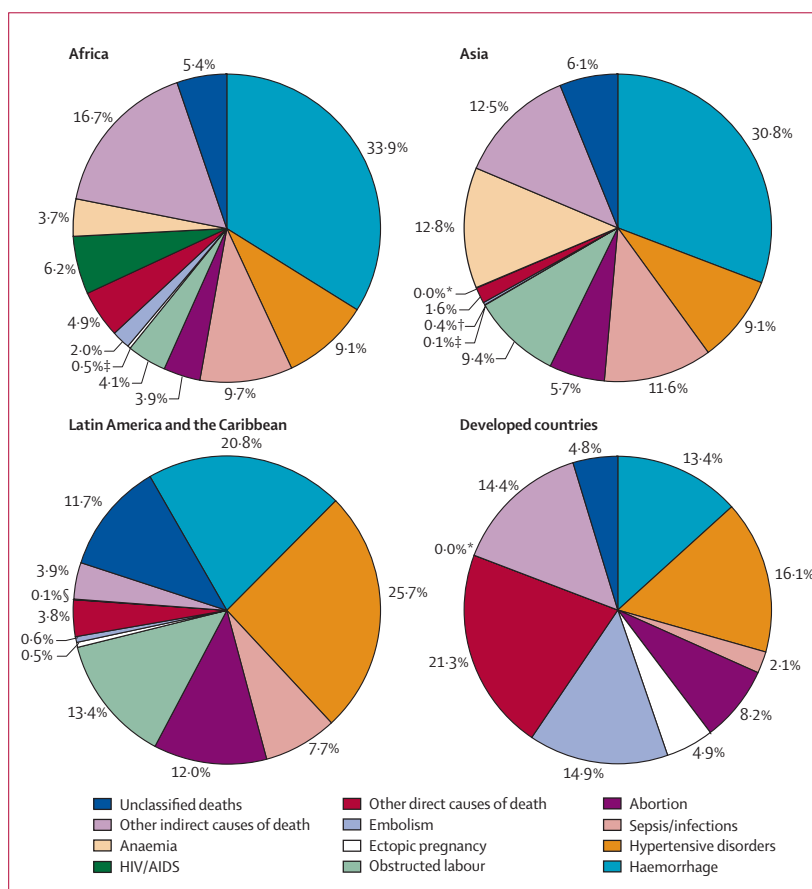


Figure 3: Geographical variation in distribution of causes of maternal deaths

*Represents HIV/AIDS. †Represents embolism. ‡Represents ectopic pregnancy. §Represents anaemia.

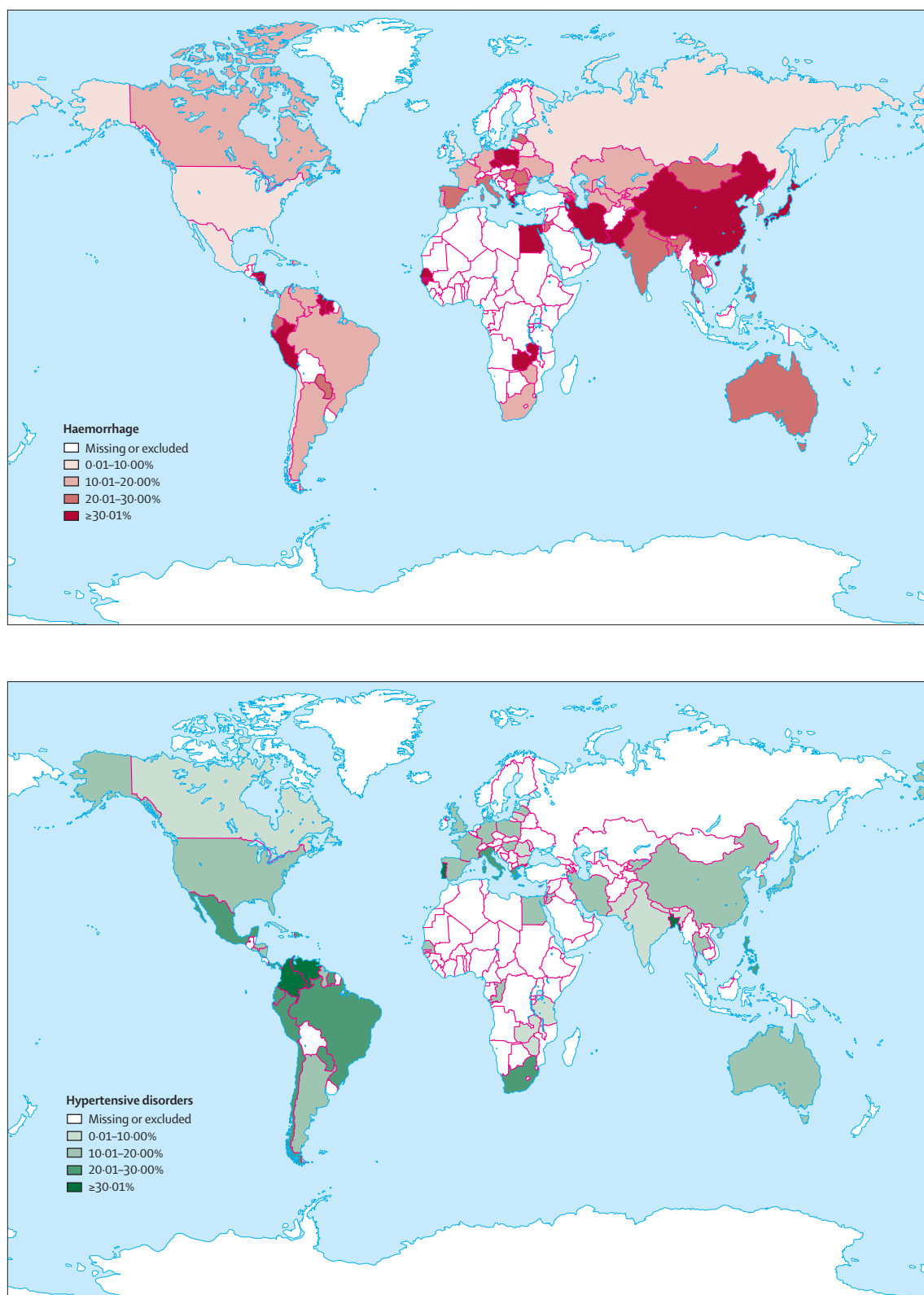
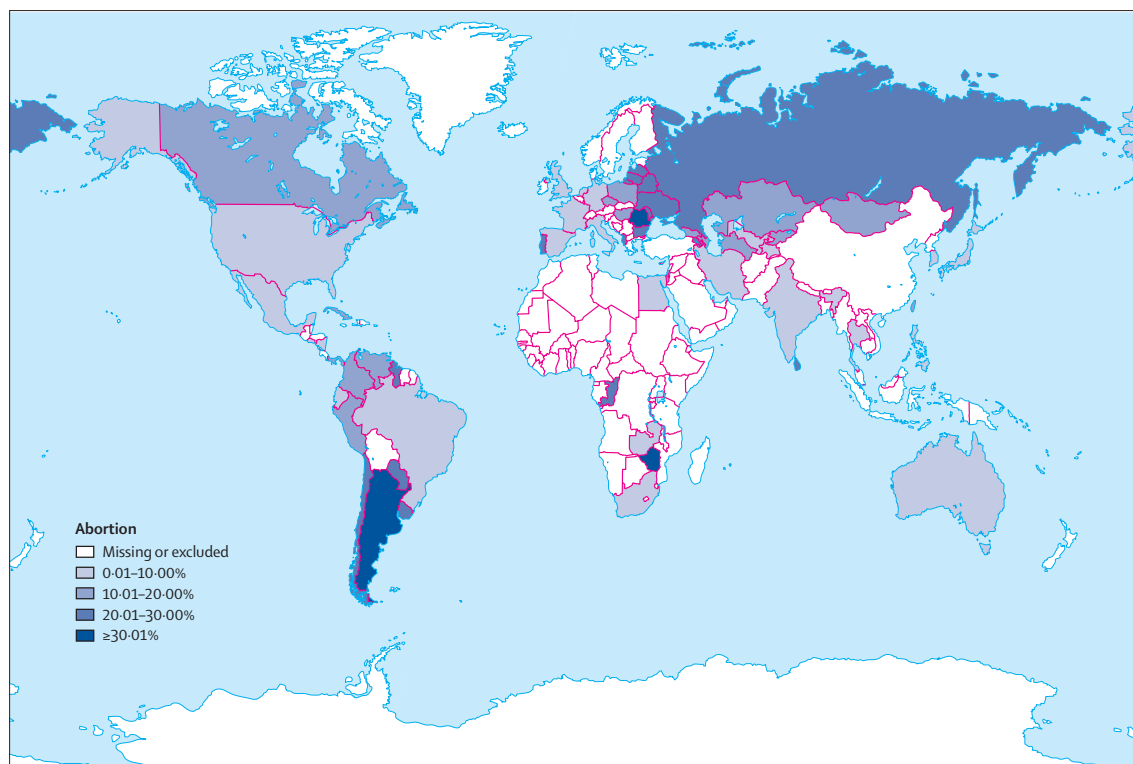
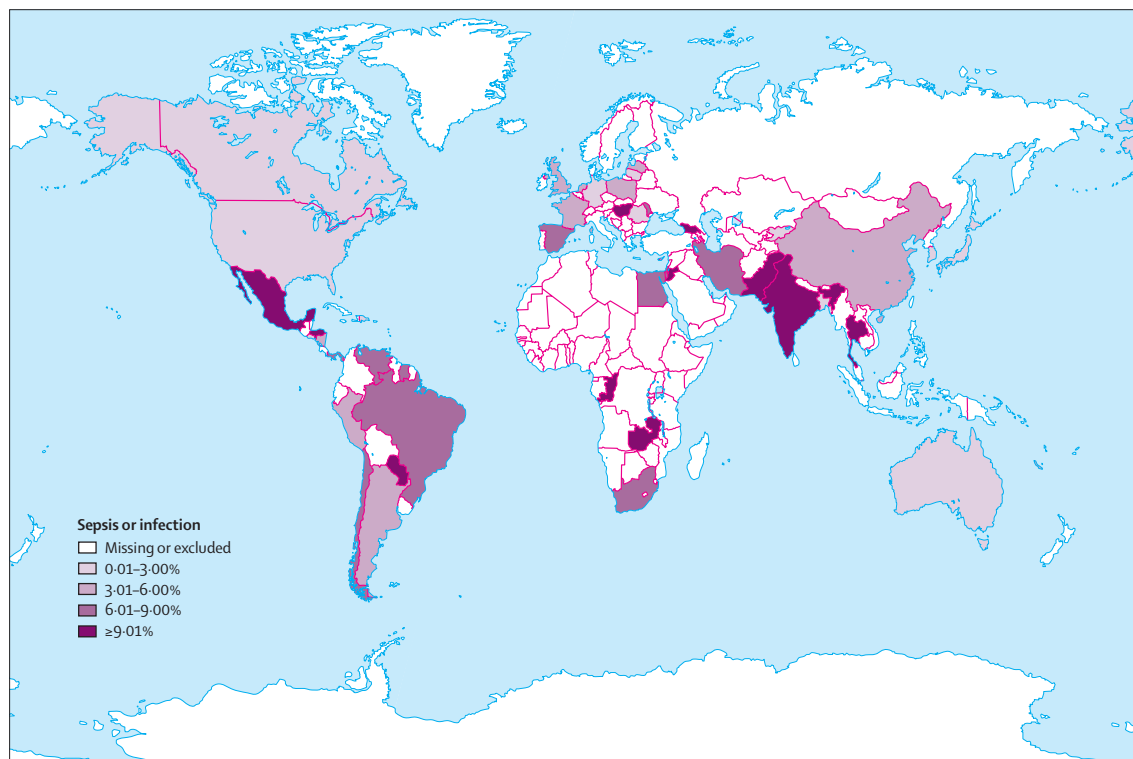


Figure 4: Country distribution of haemorrhage, hypertensive disorders, sepsis or infection, and abortion as causes of maternal deaths



See Online for webappendix and webfigure

weighting based on sample size or inverse variance has the disadvantage that it could apportion more importance to larger studies of causes of death distributions from smaller countries that make a small contribution to the overall disease burden.

We estimated the coverage of data for regions by calculating the proportion of estimated number of maternal deaths in areas for which cause distribution was analysed to total number of maternal deaths per year for each region. For geographical classification and development status, we used the UN classification system. Developing countries were grouped according to their geographical regions as Africa, Asia, and Latin America and the Caribbean. Developed countries from all regions were combined into a separate group, which included European countries, North America, Australia, New Zealand, and Japan.

For the individual cause of death analysis, the point estimates of proportions and their 95% CIs were represented in forest plots to explore heterogeneity and the possibility of the differences being due to chance were assessed statistically by Cochran *Q* test. To explore the presence of heterogeneity and its causes, regression models were adjusted to the proportions attributed to every individual cause of death.¹⁴ The proportions were previously transformed with the logit transformation.¹⁵ Explanatory variables considered in these models were: geographical region (which correlated with country development status) and dataset methodological quality items. The effect of methodological quality was assessed separately for individual items and for a summary score comparing high-quality with low-quality datasets. After univariate analysis, we did multivariable analysis to assess the unique effects of regional variation and methodological quality, adjusting for any interdependence between the two factors.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The search strategy yielded 64 585 citations for all defined maternal morbidity conditions and maternal mortality, of which 4606 were assessed in full-text form. Of these, 2581 reporting on a range of morbidities or mortality were included in the systematic review. 305 datasets provided information on causes of maternal deaths for 1 or more years or geographical locations (or both), with 1143 datasets (for a particular time or location) potentially eligible for this analysis. Figure 1 shows the detailed processing of these 1143 datasets for final inclusion in the analysis. The joint cause of death analysis was based on 34 population-based datasets representative for the

populations concerned (table 1). The countries from which data were analysed contributed 21·9% of estimated deaths per year in Africa, 78·1% in Asia, 31·5% in Latin America and the Caribbean, and 41·1% in developed countries. The webtable and webappendix provide further details of the 34 datasets.

The individual cause of death analysis was based on 126 population-based representative datasets, which were used for analysis of haemorrhage, hypertensive disorders, sepsis, and abortion complications (table 2). Quality assessment revealed deficiencies in many areas of methodology (figure 2). Joint cause of death datasets tended to have higher rates of causes confirmed and more use of adequate data sources than datasets included in the analysis for individual causes. Of the 43 representative datasets for the joint cause of death analysis that were critically appraised, 31 (72%) met 3 of 5 criteria for quality assessment.

In our analysis of joint causes of death, haemorrhage was the leading cause of maternal death in Africa and Asia (>30% of deaths; table 1, figure 3). Hypertensive disorders represent the highest cause of death in Latin America and the Caribbean. There was also wide variation within regions (webfigure). Other important regional differences included HIV/AIDS causing about 6% of deaths in Africa, and anaemia and obstructed labour each causing about a tenth of deaths in Asia. Abortion-related mortality was highest in Latin America and the Caribbean. Ectopic pregnancy was recorded as the cause in less than 1% of deaths in developing countries and almost 5% in developed countries.

As with the joint cause of death datasets, the individual cause of death datasets often had wide variability. However, these datasets allowed us to examine the distribution of four major causes in more detail (table 2). We investigated the variations in the percentages of the four major causes of deaths according to development status and methodological quality in individual cause of death datasets. Deaths due to hypertensive disorders and sepsis varied by development status. Compared with developed countries (reference group), sepsis was significantly more frequent in Africa, Asia, and Latin America and the Caribbean (table 2).

Methodological quality tended to produce variation in different directions for different individual causes of deaths. Compared with datasets with poor-quality features, high-quality datasets had a reduced percentage of deaths due to abortion, whereas they had an increased percentage of deaths due to haemorrhage and sepsis. Figure 4 shows the regional variation of haemorrhage, hypertensive disorders, sepsis or infections, and abortion, according to countries. Abortion-related deaths can exceed 30% in parts of Latin America and eastern Europe. We compared the contributions of the most common causes of maternal deaths reported in individual-cause datasets and joint-cause datasets and found these two data sources to be compatible (data not shown).

Discussion

As expected, our systematic analysis of the causes of maternal deaths, showed variation both across and within geographical regions. Our findings confirm the prominent role of haemorrhage as a cause of maternal death in developing countries. Hypertensive disorders are among the leading causes of deaths in Latin America and the Caribbean. In developed countries, most deaths are due to other direct causes, mainly complications of anaesthesia and caesarean sections. The contributions of sepsis and HIV in Africa, anaemia in Asia, abortion in Latin America and the Caribbean, and other direct causes (related to caesarean section and anaesthesia) and embolism in developed countries seem to be more region-specific.

Deaths due to abortion are high in Latin America and the Caribbean and some eastern European countries (figure 4). We can only speculate on possible reasons for the variation in abortion rates. The reasons for the relatively high contribution of abortion in Latin America could be because of fewer deaths due to other causes or restrictive abortion laws, compared with the other world regions. Abortion deaths are likely to be biased downwards by under-reporting and misclassification (as haemorrhage or sepsis). It is probably safe to assume that abortion deaths are most likely due to unsafe abortion. Abortion rates also seemed to be affected by methodological quality, because good-quality studies showed reduced rates, suggesting possible reporting bias in studies of low quality.

We believe this review has several strengths. Our search strategy was extensive, comprehensive, and reproducible, as required by systematic reviews of published work. We identified a large number of national reports and special surveys that might not have been accessible otherwise. We did a rigorous and transparent methodological quality assessment, and attempted to keep the risk of bias due to methodological weakness to a minimum by applying strict inclusion and exclusion criteria. We excluded datasets that were not representative of an administrative region (city or province or nation) from both analyses for individual and joint cause of death. This distinction is important because it is very difficult (if not impossible) to use facility-based data and adjust the results accordingly. The inclusion of facility-based datasets would have introduced potentially biased information and would have limited the generalisability of the whole analysis. Moreover, our approach of restriction to representative datasets limited the analysis for cause of death distribution to a subset of higher quality (figure 2), which adds to the internal validity of our inferences. Finally, we present the joint cause of death datasets (webfigure) with their descriptive details, quality assessments,⁹ and corresponding maternal mortality ratios (webtable), which made our approach as explicit as possible.

The results and conclusions of a systematic review can only be as robust as the data provided by the primary datasets. Confirmation of the cause of death is important for maternal mortality reports. However, only 37 of 126 datasets in the analysis for individual causes of death reported this confirmation. The joint cause of death datasets did better in this respect (25 of 43). Although the restrictions we imposed for the number of causes reported (>5) and unclassified (<5%) are arbitrary, we believe that they provide a fairly strict assessment.

The second limitation is the modest coverage of deaths within the regions, especially in Africa. Nevertheless, the eight datasets represent countries in north Africa (Egypt), west Africa (Senegal, another dataset covering seven countries), and east and south sub-Saharan Africa (Democratic Republic of Congo, South Africa, Tanzania, Zambia, Zimbabwe). This restricted coverage is partly because countries without a joint cause of death distribution were not included in the computation of the summary distribution for every region. This approach limits the power of our analysis, but also reduces the possibility of bias being introduced in the distributions of causes. Heterogeneity existed within and across regions. Logistic regression (table 2) showed that inadequacy of methods accounted for variation in rates of deaths due to haemorrhage, sepsis, and abortion.

We used UN definitions for the regions, which are commonly used in the classification of regions. Further subregional breakdown was not possible because of the restricted number of datasets. The regional estimates are useful as broad indicators of causes of deaths, but national and subnational data are also important to identify differentials due to emerging causes and other local characteristics, such as access to services. A specific example is the proportion of HIV/AIDS-related maternal deaths in Africa (figure 3). The 1998 South African Confidential Enquiries into Maternal Deaths identified HIV/AIDS as the cause in 14.5% of deaths. However, in three-quarters of all maternal deaths, the HIV/AIDS status was unknown, suggesting that had this information been available the contribution of HIV/AIDS might have been higher than had been reported.¹⁶

We followed most of the quality criteria for reviews of observational datasets.⁹ Despite the fact that the procedural guidelines we used were not necessarily developed for prevalence or incidence reviews, they do provide a framework for high-quality systematic reviews.

Our systematic review provides an up-to-date, critically appraised, and reproducible analysis of causes of maternal deaths. The commonly cited report¹ undertaken previously on cause distribution attributed 25% of maternal deaths to haemorrhage, 20% to indirect causes, 15% to infection, 13% to abortions, 12% to eclampsia, 8% to obstructed labour, and 8% to other direct causes globally.³ Our estimates agree that haemorrhage continues to be a major killer in Asia and Africa, and

they also highlight causes that have not been examined systematically before.

This systematic review highlights the need for increased emphasis on programmes relevant to specific settings such as the prevention and treatment of haemorrhage both prepartum and postpartum. At the very least, most postpartum haemorrhage deaths should be avoidable by appropriate diagnosis and management. Hypertensive disorders and sepsis continue to be a concern. Increased availability and use of magnesium sulphate should be a goal in all regions, especially in Latin America and the Caribbean. The regional variation in abortion-related deaths is a call for increased attention to access in those areas to services that can help women avoid unwanted births.

The absence of epidemiological information in many low-income countries should lead to efforts to increase capacity for data collection and reporting for vital statistics in those countries.¹⁷ Methodological studies are needed to improve our understanding of data synthesis in incidence and prevalence studies. Capacity-strengthening efforts to improve the quality of recording, reporting, and geographical coverage of burden-of-disease studies will increase the robustness of future estimates. This systematic review should be updated at regular intervals to record changes in the profile of causes of maternal deaths.

Contributors

A M Gülmezoglu and L Say planned the study design and did the systematic review. K S Khan, D Wojdyla, L Say, and A M Gülmezoglu planned the analysis. D Wojdyla maintained the database and did the analysis. A M Gülmezoglu and K S Khan coordinated the analysis and writing of the manuscript. P F A Van Look reviewed and provided input into the manuscript. All authors contributed intellectually to the work.

Conflict of interest statement

We declare that we have no conflict of interest.

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