

Ethnic variation in causes of stillbirth in high income countries: A systematic review and meta-analysis

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Abstract

Background: Inequities in stillbirth rate according to ethnicity persist in high income nations. **Objectives:** To investigate whether causes of stillbirth differ by ethnicity in high-income nations. **Search strategy:** Medline, Embase, Scopus, CINAHL, Cochrane Library, and Global Health databases since their inception to 1 February 2021. **Selection criteria:** Cohort, cross-sectional, and retrospective studies investigating the causes of stillbirth in various ethnic groups. **Data collection and analysis:** Systems of classification and causes of stillbirth were aligned to the International Classification of Disease 10 for Perinatal Mortality (ICD10-PM) and pooled estimates were derived by meta-analysis. **Main results:** Fifteen reports from 3 countries (72,555 stillbirths) were included. Seven ethnic groups – “Caucasian” (n = 11 studies, n = 37,578 stillbirths), “African” (n = 11 studies, n = 17,883 stillbirths), “Hispanic” (n = 7 studies, n = 12,810 stillbirths), “Indigenous Australian” (n = 4 studies, n = 1,117 stillbirths), “Asian” (n = 2 studies, n = 15 stillbirths), “South Asian” (n = 2 studies, n = 55 stillbirths), and “American Indian” (n = 1 study, n = 27 stillbirths) – were identified. There was an overall paucity of recent, high-quality data for many ethnicities. For those with the greatest amount of data – Caucasian, African, and Hispanic – no major differences in the causes of stillbirth were identified. **Conclusion:** There is a paucity of high-quality information on causes of stillbirth for many ethnicities. Improving investigation and standardising classification of stillbirths is needed to assess whether causes of stillbirth differ across more diverse ethnic groups.

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Abbreviated title: Ethnic variation in causes of stillbirth

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Conclusion: There is a paucity of high-quality information on causes of stillbirth for many ethnicities. Improving investigation and standardising classification of stillbirths is needed to assess whether causes of stillbirth differ across more diverse ethnic groups.

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Tweetable abstract: Data investigating ethnic variation in causes of stillbirth is limited but our review does not suggest any differences between ethnicities.

INTRODUCTION

Stillbirth is a devastating pregnancy outcome that not only has emotional, psychological and financial consequences for affected women and families,¹ but also impacts individual healthcare workers, health care networks and the wider society.² The global stillbirth rate is estimated to be 18.4 per 1,000 births, equating to approximately 2.6 million stillbirths every year.³ The World Health Organisation’s (WHO) *Every Newborn: An Action Plan to End Preventable Deaths* aims to reduce the stillbirth rate to ≤ 12 per 1,000 births by 2030 worldwide.⁴ For countries already meeting this target, mostly high-income nations, the *Every Newborn* initiative aims to reduce equity gaps within the population.^{4, 5}

Despite similar access to healthcare services,⁶ inequities in stillbirth rates continue to persist in high income nations, especially in certain minority ethnic groups. For example, women of ethnic minorities who birth in Australia or Europe have stillbirth rates 2-3 times higher than Caucasian women.⁷⁻⁹ A similar trend is observed in women of African ancestry compared to their Caucasian counterparts in the United States.^{10, 11} A higher incidence of modifiable risk factors associated with stillbirth are observed in some minority ethnic groups¹² and may contribute, at least partly, to the higher rates of stillbirth observed. Given increasing international migration to high-income countries,¹³ it is pertinent to understand the ethnic variation in causes of stillbirth in order to address the persistent equity gaps.

A recent systematic review by Reinebrant and colleagues¹⁴ evaluated the causes of stillbirth according to geographical region and economic development around the world. Others have evaluated risk factors associated with stillbirth in various ethnic groups.¹² However, whether differences in the *actual* causes of

stillbirth between ethnicities exist is unknown. The aim of this study, therefore, was to perform a systematic review of the literature to investigate the causes of stillbirths in various ethnic groups in high income countries. This will assist in deepening the understanding of possible ethnic differences in causes of stillbirth and work towards the WHO's goal to reduce equity gaps in stillbirth.

METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Appendix S1) and MOOSE guidelines (Appendix S2) and was registered on PROSPERO [CRD42021224100]. A protocol was not prepared for this review. Two authors (SB and NB) independently conducted the literature search, screened studies for eligibility, extracted data, and performed the quality assessment.

Search strategy and information sources

A systematic literature search up to 1 February 2021 was conducted in Medline, Embase, Scopus, Cumulative Index of Nursing and Allied Health (CINAHL), Cochrane Library, and Global Health databases since their inception without language restrictions using the search terms outlined in Appendix S3. Reference lists of eligible studies were manually scanned to identify additional relevant publications.

Eligibility criteria

Cohort, cross-sectional, and retrospective studies investigating the causes of stillbirths in singleton pregnancies in various ethnic groups in high income countries were eligible for inclusion. Studies that only reported risk factors associated with stillbirth in various ethnic groups but did not investigate the actual cause of foetal death were excluded. Reports were also excluded if they did not provide data on causes in an extractable format. Given the considerable heterogeneity in the definition of stillbirth between studies, we did not specify a pre-determined definition to use as an eligibility criterion.

Data extraction

The following data were extracted into pre-piloted forms where available: period of data collection, country, setting (population/national, multicentre hospital, or single centre hospital), study design, mean maternal age, mean gestational age, total number of births, total number of stillbirths, stillbirth rate, stillbirth definition, stillbirth classification system used, proportion of stillbirths classified, data source, examination rate (autopsy, placental histology), and cause of stillbirth. Discrepancies were resolved by consensus or by involvement of a third independent reviewer (SMB). Missing data were reported as such and any corresponding authors were contacted for unclear information.

Quality assessment

Quality of the included studies was evaluated using the modified Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data tool as described previously.¹⁴ An overall quality rating was derived for each report as low, medium, or high quality.

Data analysis

Each reported cause of stillbirth was mapped to the relevant International Classification of Disease of perinatal mortality (ICD-10-PM) category. The ICD-PM includes five major maternal conditions categories (M1-5) and thirteen foetal categories, six with antepartum timing (A1-6), seven with intrapartum timing (I1-7), and others with unknown timing. For the Unknown (U) timing category, we included those categories described previously for consistency. Categories of stillbirth causes were represented as proportions of the total number of stillbirths for various ethnicities. Results for each ethnicity from different studies were statistically pooled using random effects meta-analysis using the *metaprop* command in STATA (version 16, Stata Corp, TX, USA) for binomial data. Pooled estimates were calculated after Freeman-Tukey double arcsine transformation of data to stabilise the variances and enable studies with estimated proportions of 0 or 1 to be retained.¹⁵ I^2 values were not reported as measures of heterogeneity as such statistics may be

less informative in meta-analyses of cohort/observational studies where sample sizes are relatively large and the within-study variation correspondingly small.¹⁶ Data were tabulated as pooled estimate of proportion (95% confidence interval).

RESULTS

Study characteristics

Of 791 studies identified in our search, 15 met inclusion and exclusion criteria and were included for analysis (**Figure 1**).¹⁷⁻³² Five studies were excluded as they either did not provide data in an extractable format or used language spoken at home or country of birth as a surrogate for ethnicity.³³⁻³⁷ Characteristics of the included studies are presented in **Table S1**. These fifteen studies encompassed 72,555 stillbirths, equating to a stillbirth rate ranging from 0.35% to 6.8% of all births. Seven were conducted in the United States of America, five in Australia, and three in the United Kingdom. Most ($n = 10$) were conducted more than 10 years ago and of these, six had data collected more than 20 years ago. Three studies were limited to a single institution, seven were multicentred, and five were conducted at a population or national level. Only eight of the included studies provided an indication of the autopsy rate. In these studies, the autopsy rate ranged from 37.6% to 100%. While the definition of stillbirth varied slightly between studies, a majority of studies defined stillbirth as death of foetus of at least 20 weeks' gestation. The classification system used to describe the cause of stillbirth varied widely, with four studies using the ICD system, three studies using INCODE, two studies using PSANZ, and six using a classification system unique to the study. Most studies were either retrospective cohort studies ($n = 7$) or cross-sectional in nature ($n = 4$), three were case-control, and one was prospective. Only one study was deemed to be of high quality; the rest were deemed to be either medium ($n = 7$) or low ($n = 7$) quality (**Table S2**).

Causes of stillbirth

Mapping of the causes of stillbirth to the ICD10-PM classification system revealed a total of 23 unique causes of stillbirths. Overall, maternal categories of causes of stillbirth (M1-M5) had higher frequencies compared to foetal causes and were thus used to present data. This may be explained by the fact that there are only five maternal categories of causes of stillbirth and thirteen foetal categories in the ICD-10-PM classification system. Of these, "complications of placenta, cord and membrane with no foetal cause (M1)", "maternal medical and surgical conditions with no foetal cause (M4)", and "other foetal cause with no maternal condition identified (M5U6)" were the most common causes of stillbirth in our pooled analyses.

Ethnic variation in causes of stillbirth

Data for six ethnic groups were available from the included studies. These included African ($n = 11$ studies), Caucasian ($n = 11$ studies), Hispanic ($n = 7$ studies), Asian ($n = 2$ studies), South Asian ($n = 2$ studies), and American Indian ($n = 1$ study) populations. Within the Australian context, data were also available for the Indigenous population ($n = 4$ studies). The pooled proportion of cases based on ethnicity for each mapped cause of stillbirth is shown in **Table S3**. Pooled causes of stillbirth for each ethnicity according to the maternal categories of ICD-10-PM are presented as pooled estimates (95% confidence intervals) in **Figure 2** with detailed results shown in **Table 1** and **Table S4**. Pooled causes of stillbirth for Indigenous Australians and non-Indigenous Australians are presented in **Table S5**. Caucasian and Hispanic ethnicities showed similar proportions attributable to various maternal causes in the ICD-PM classification system (**Figure 2**). By comparison, African women had a higher proportion of stillbirths caused by other complications of labour and delivery (M3) and fewer due to complications of placenta, cord and membranes (M1) compared to Caucasian and Hispanic women. Similarly, compared to non-Indigenous Australians, Indigenous Australians had a higher proportion of stillbirths caused by other complications of labour and delivery (M3). Women of Asian and South Asian ethnicities had a different profile of causes of stillbirth, with the majority of stillbirths caused by complications of placenta, cord and membranes (M1).

DISCUSSION

Main findings

This systematic review and meta-analysis identified 15 studies investigating the causes of stillbirth in various ethnic groups in high income nations. Despite over 70 thousand stillbirths included in this review, there was an overall paucity of recent, high quality studies investigating the causes of stillbirth in many ethnic groups. While proportions of stillbirth attributable to various ICD-10-PM causes appeared largely comparable between ethnic groups for which data were available, a significant proportion of stillbirths were either unexplained or fell into the *other* category, highlighting one of the key challenges in achieving the WHO's *Every Newborn* stillbirth target. Our results support the need for additional appropriately designed autopsy studies that utilise a consistent stillbirth classification system to further investigate the causes of stillbirth in ethnic groups poorly represented in our study.

Strengths and limitations

To the best of our knowledge, this is the first systematic review that synthesised data on the ethnic variation of the causes of stillbirth in high income nations and to standardise reporting of outcomes using the ICD-10-PM classification. To increase the accuracy of identified causes, we included only those studies that reported foetal autopsy and/or placental pathology data to determine the *actual* cause of stillbirth³⁸ rather than associated risk factors, and excluded studies that used surrogate markers of ethnic identity such as mother tongue or language spoken at home. Mapping disparate causation data from individual studies to the ICD-10-PM and subsequently pooling results by meta-analysis allowed improved interpretation of findings and easier comparison between ethnic groups.

Results from this study should be interpreted in the context of some limitations. First, exclusion of studies reporting only associations between various risk factors and stillbirth may have resulted in loss of information and limited our ability to assess the full value of the ICD-PM. Second, use of crude categories to define ethnicity may be limited by being only proximal guides to experiences, practices, and beliefs of individuals and may not capture the associated complex and interrelated socioeconomic determinants such as education and employment that may be driving disparities in stillbirth rates.^{27, 39-44} Inequalities in stillbirth between various ethnic groups have been shown to reduce after acculturation and adoption of host nationality,⁴⁵ highlighting the limitation in interpreting stillbirth data segregated by ethnicity. Third, differences in causes of stillbirth between studies may be a consequence of differences in classification rather than any important differences in pathological processes per se. This is especially pertinent in the context of the myriad classification tools available and used in various studies, making regional and global comparisons difficult. The ICD-PM itself faces challenges including insufficient differentiation of causes from associated conditions and insufficient detail on maternal conditions. Fourth, most data used in our analyses were collected more than 10 years ago and may not reflect recent migration patterns and demographic changes, and current socioeconomic and health care environments. Finally, despite including studies investigating the *causes* of stillbirths, we found considerable variation in autopsy rate between studies with some studies reporting rates as low as 38%. Previous studies have shown that ethnic minority groups have lower rates of being asked for consent for a post-mortem study, and also lower rates of consent when asked.^{46, 47} This may be due to assumptions and/or actual differences in religious or cultural observances and may reflect an inherent limitation in studies involving minority ethnic groups and causes of stillbirth. Due to this limitation it is also worth considering alternatives to post-mortem examination which may be accessible in high income counties, such as MRI,⁴⁸ to assist in assigning cause of death when post-mortem examination is declined.

Interpretation

Reinebrant and colleagues' seminal work¹⁴ provided a comprehensive overview of the causes of stillbirth around the globe. In our review, we built upon this foundation by investigating ethnic variation of causes of stillbirth in high-income countries. While perinatal outcomes in some ethnic minority groups appear to have improved over time, disparities in stillbirth rates based on ethnicity continue to persist in the majority of reported cases.^{7-9, 34, 36, 39, 40, 49-59} Ethnicities with the largest sample sizes (Caucasian, African and Hispanic) overall showed similar proportions in the causes of stillbirth. Compared to non-Indigenous Australians, Indigenous Australian women showed higher frequencies of stillbirth attributed to other complications of labour and delivery. This category includes stillbirth that has been attributed to malpresentation, forceps delivery,

vacuum delivery, caesarean delivery or induction of labour. This is in agreement with a population-based study from the Northern Territory, Australia which demonstrated higher rates of emergency caesarean and malpresentation in Indigenous mothers compared to non-Indigenous,⁶⁰ but contrary to the study by Kildea and colleagues who found Indigenous Australian to have lower rates of instrumental delivery and induction of labour.⁶¹ In our review, Asian and South Asian ethnicities showed a larger proportion of stillbirths attributed to complications of placenta, cord and membranes, in line with previous work showing higher rates of placental insufficiency⁶² and placenta praevia⁶³ in women of Asian heritage. However, the utility of the interpretation of differences observed in Indigenous Australian, Asian and South Asian women is limited due to their small sample sizes.

Our findings imply that the higher incidence of stillbirths observed in minority ethnic groups in previous studies are likely to be a consequence of factors other than intrinsic differences such as culturally inappropriate antenatal care⁶⁴ and higher incidence of modifiable risk factors such as obesity, maternal smoking, hypertension, and diabetes.¹² The effect of the migration experience and the associated socioeconomic disadvantage migrants may face is difficult to dissect from intrinsic differences between various ethnic groups, if any, with regards to stillbirth outcomes.^{24, 65-67} Gibson-Helm and colleagues⁶⁸ found that after adjusting for confounding factors such as age, parity, BMI and relative socio-economic disadvantage, the difference in stillbirth rates between migrants and women from host countries disappeared. These results, together with findings from our study, suggest that socio-cultural-economic factors may be more important in explaining the disparities in stillbirth rates between ethnic groups rather than intrinsic differences.

Conclusion

It has long been postulated whether there were underlying differences in causes of stillbirths in different ethnic groups, as disparities in stillbirth rates and perinatal outcomes continue to persist in many high-income nations. Understanding the ethnic variation in stillbirth rate and causes is crucial to bringing us a step closer to achieving the WHO's *Every Newborn* initiative. Results from this review suggest that while no obvious differences are apparent in causes of stillbirths in those ethnicities with sufficient data, important gaps in our knowledge persist. Future studies in high-income countries should aim to investigate causes of stillbirth in minority ethnic groups poorly represented in this review by using high quality placental histology and foetal autopsy data. To enable global comparisons, monitor trends, and clearly ascertain underlying causes, a widely accepted tool such as the ICD-PM that can capture more detailed information in data-rich settings should be used. Comprehensive testing across diverse settings and in as many ethnic groups as possible will enable focussed use of healthcare resources and corresponding policy changes.

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Nil

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SB and SMB were involved in conception and planning. SB and NB carried out the search, extracted data, and drafted the manuscript. SB analysed the data.

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Table 1: Pooled estimate of causes of stillbirth based on the ICD 10-PM classification in various ethnic groups. CI, confidence interval; ICD, International Classification of Diseases; M1, complications of placenta, cord, and membranes; M2, maternal complications of pregnancy; M3, other complications of labour and delivery; M4, maternal medical and surgical conditions; M5, no maternal condition identified; PE, pooled estimate.

Ethnicity	ICD-10-PM Code	References	Studies (n)	Stillbirths (n)	Total births (n)
Caucasian	M1	17, 18, 20-23, 25, 28-30	10	10,917	38,079
	M2	17, 22, 23, 25	4	4,775	37, 271
	M3	20	1	41	183
	M4	17, 18, 20, 22, 23, 25, 30	7	2,555	37,551
	M5	17, 18, 20, 22, 23, 25, 30, 31	9	19,186	37,970
African	M1	17, 18, 20-23, 25, 28-30	10	4,787	18,221
	M2	17, 22, 23, 25	4	3,016	17,584
	M3	20	1	50	115
	M4	17, 18, 20, 22, 23, 25, 30	7	2,030	17,743
	M5	17, 18, 20, 22, 23, 25, 30, 31	9	8,000	17,992
Hispanic	M1	20-23, 25	6	6,276	13,593
	M2	22, 23, 25	3	1,875	12,915
	M3	20	1	44	176
	M4	20, 22, 23, 25	4	1,003	13,091
	M5	20, 22, 23, 25, 31	5	6,276	13,267
Indigenous Australians	M1	19, 27, 32	3	92	768
	M2	19	1	2	47
	M3	27	1	110	527
	M4	19, 27, 32	3	103	768
	M5	19, 26, 27, 32	4	472	1,121
Asian	M1	18, 30	2	6	17
	M2	-	-	-	-
	M3	-	-	-	-
	M4	30	1	1	10
	M5	18, 30	2	8	17
South Asian	M1	18, 28	2	21	55
	M2	-	-	-	-
	M3	-	-	-	-
	M4	18	1	6	39
	M5	18, 28	2	21	55
American Indian	M1	17	1	7	27
	M2	17	1	4	27
	M3	-	-	-	-
	M4	17	1	3	27
	M5	17	1	13	27

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