Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis

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Summary

Background Stillbirth rates in high-income countries have shown little or no improvement over the past two decades. Prevention strategies that target risk factors could be important in rate reduction. This systematic review and meta-analysis was done to identify priority areas for stillbirth prevention relevant to those countries.

Methods Population-based studies addressing risk factors for stillbirth were identified through database searches. The factors most frequently reported were identified and selected according to whether they could potentially be reduced through lifestyle or medical intervention. The numbers attributable to modifiable risk factors were calculated from data relating to the five high-income countries with the highest numbers of stillbirths and where all the data required for analysis were available. Odds ratios were calculated for selected risk factors, from which population-attributable risk (PAR) values were calculated.

Findings Of 6963 studies initially identified, 96 population-based studies were included. Maternal overweight and obesity (body-mass index >25 kg/m²) was the highest ranking modifiable risk factor, with PARs of 8–18% across the five countries and contributing to around 8000 stillbirths (≥22 weeks' gestation) annually across all high-income countries. Advanced maternal age (>35 years) and maternal smoking yielded PARs of 7–11% and 4–7%, respectively, and each year contribute to more than 4200 and 2800 stillbirths, respectively, across all high-income countries. In disadvantaged populations maternal smoking could contribute to 20% of stillbirths. Primiparity contributes to around 15% of stillbirths. Of the pregnancy disorders, small size for gestational age and abruption are the highest PARs (23% and 15%, respectively), which highlights the notable role of placental pathology in stillbirth. Pre-existing diabetes and hypertension remain important contributors to stillbirth in such countries.

Interpretation The raising of awareness and implementation of effective interventions for modifiable risk factors, such as overweight, obesity, maternal age, and smoking, are priorities for stillbirth prevention in high-income countries.

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Introduction

In high-income countries, one in every 200 pregnant women reaching 22 weeks' gestation will have a stillborn baby.[1] Although notable reductions in stillbirth rates in such countries have been achieved since the 1940s, rates have become stable or decreased only marginally in many regions over the past decade. Most stillbirths are now antepartum deaths, frequently associated with placental dysfunction and growth restriction,[1] and many remain unexplained.[2]

Risk factors for stillbirth are increasingly being investigated and reported. Identification of priorities for prevention from individual published studies, however, is problematic. We undertook a systematic review of studies relevant to present practice to clearly identify important risk factors for stillbirth in high-income countries. If some of these risk factors can be avoided or prevented, fewer parents will experience the intense grief and lasting psychosocial trauma of stillbirth.[3]

Methods

Search strategy

The search strategy is summarised in the panel.[4] In undertaking this study, we followed recommendations

***Panel:* Search strategy and selection criteria**

We searched Medline (PubMed and Ovid), CINAHL, and the Cochrane Database of Systematic Reviews for reports published between the years 1998–2009, using a sensitive methodological filter for aetiology studies. Search terms were "stillb*", "fetal death", "fetal mortality", and "pregnancy outcome*". We excluded reports not published in English, animal studies, and studies from low-income and middle-income countries. Bibliographies of relevant retrieved studies and recent reviews were hand-searched for additional publications. Where recent data on specific factors were missing, we searched back to 1990—this extended search was done for studies on education, indigenous status, primiparity, and hypertension.

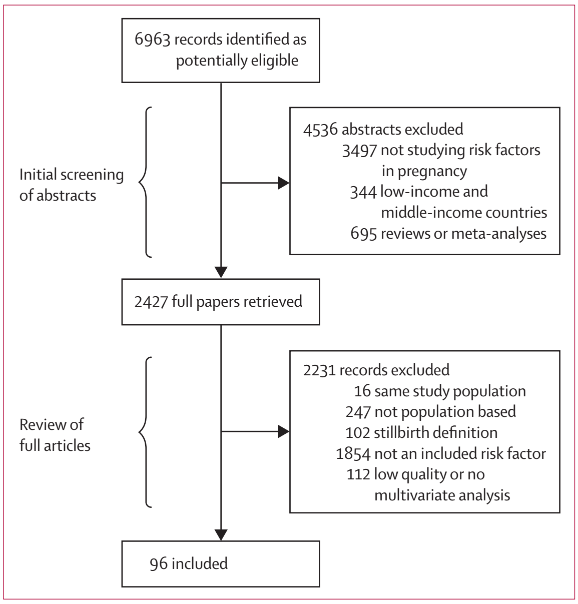

***Figure 1*: Inclusion and exclusion of studies for review**

made by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.[5]

Inclusion criteria

See Online for webappendix

Studies were included if they fulfilled the following criteria: they assessed at least one risk factor associated with stillbirth; they used a definition of stillbirth of 20 weeks' gestation or more, or a birthweight of at least 400 g; they were done in high-income countries (defined for the purposes of this study according to the World Bank country classification[6]); and they were of sufficient quality, according to the Newcastle-Ottawa scale.[7] We considered studies from all countries listed with the World Bank as high-income members of the Organisation for Economic Co-operation and Development. For studies that used the same study population as another or others, we selected the one of highest quality.

Through our search we identified factors that were frequently reported in relation to stillbirth risk. We chose to study factors relating to maternal demographics and lifestyle and maternal medical disorders and pregnancy complications, for which exposure to the risk factor or the risk associated with a factor could potentially be reduced through intervention. The relevant risk factors not related to pregnancy or medical disorders were as follows: maternal characteristics of ethnic origin, socioeconomic status, maternal and paternal age, education level, body-mass index (BMI), smoking, alcohol, and illicit drug use, caffeine intake, geographical remoteness; and adequacy of antenatal care. The following risk factors related to pregnancy and medical disorders of primiparity were selected: hypertension; diabetes; antepartum haemorrhage (specifically placental abruption and praevia); small size for gestational age and fetal growth restriction; use of assisted reproductive technology; multiple pregnancy; post-term pregnancy; and previous obstetric history (specifically stillbirth and caesarean section).

Data extraction and quality assessment

Study characteristics, adjusted effect estimates, and 95% CI were extracted for factors of interest and quality assessment was undertaken independently by at least two authors (LK, VF, PM, KG, and AG). Disagreements between authors with regards to data extraction were resolved by discussion. Quality assessment scores differed for eight studies and were resolved through discussion with a third author.

Data analysis and presentation

Where factors of interest were reported by two or more studies, effect estimates were combined with random effects meta-analyses in StataSE (version 10.1), which yielded pooled adjusted odds ratios (aOR) and associated 95% CIs. We prespecified use of the random effects model of DerSimonian and Laird[8] because we suspected a priori that studies would be from different populations and have different designs (eg, case-control *vs* cohort studies).

Heterogeneity between studies was assessed by comparison of study settings, populations, and design, supplemented with the I^2 statistic. A summary of sensitivity analyses and decisions made regarding heterogeneity is provided in webappendix p 5. Where data were not presented in a way that could be included in the meta-analysis or where only one study was identified for a risk factor, results of individual studies are presented.

Population-attributable risk (PAR)[9] was calculated for each risk factor with a significant association ($p<0 \cdot 05$) with stillbirth in the meta-analysis or in an individual study. We estimated the stillbirth burden of our chosen risk factors in and across the five high-income countries with the highest numbers of stillbirths and where all the relevant data required for analysis were available (Australia, Canada, Netherlands, UK, and USA). The total number of stillbirths attributed to each factor was calculated by multiplying the total number of stillbirths in the five high-income countries by the corresponding PAR. We used WHO's recommended definition of stillbirth for calculation of numbers of attributable stillbirths (>22 weeks' gestation or birthweight >500 g) for generalisability. Several identified studies, however, used the lower gestation and birthweight cutoffs (>20 weeks or >400 g) and, as we deemed the populations according to either definition to be comparable, we used the lower limit definition in the inclusion criteria. We further estimated the numbers of stillbirths attributable to each risk factor for all high-income countries. For this calculation we used a value of 50 820 stillbirths in high-income countries per year,

	aOR (95% CI)	Australia (n=1236 SB)			Canada (n=1885 SB)			USA (n=20 416 SB)			UK (n=4898 SB)			Netherlands (n=1153 SB)			Total preventable SB for five study HIC	Total preventable SB for all HIC
		P (%)	PAR	SB (n)	P (%)	PAR	SB (n)	P (%)	PAR	SB (n)	P (%)	PAR	SB (n)	P (%)	PAR	SB (n)		
BMI (kg/m²)																		
<25	1·0	57·6	12·3%	178	52·3	13·9%	304	41·6	17·6%	4056	57·4	12·2%	705	72·5	7·7%	108	5352	8064
25–30	1·2 (1·09–1·38)	28·7	··	··	31·3	··	··	34·2	··	··	29	··	··	20·5	··	··	··	··
>30	1·6 (1·35–1·95)	13·7	··	··	16·4	··	··	24·2	··	··	13·5	··	··	7·1	··	··	··	··
Maternal age (years)																		
<35	1·0	77·7	··	··	82	··	··	85·8	··	··	79·9	··	··	78·2	··	··	··	··
35–39	1·5 (1·22–1·73)	18·7	11·1%	99	15·1	9·1%	123	11·6	7·5%	1116	16·4	10·2%	367	19	10·6%	86	1790	4226
40–44	1·8 (1·4–2·3)	3·4	··	··	2·8	··	··	2·4	··	··	3·5	··	··	2·7	··	··	··	··
≥45	2·9 (1·9–4·4)	0·2	··	··	0·1	··	··	0·2	··	··	0·2	··	··	0·1	··	··	··	··
Any smoking	1·4 (1·27–1·46)	16·6	6·2%	77	13·4	5·1%	96	14·2	5·4%	1097	19	7·1%	346	10	3·9%	44	1660	2852
Primiparity	1·4 (1·42–1·33)	41·6	14·3%	176	44·4	15·1%	284	42·6	14·6%	2972	43	14·7%	719	45·1	15·3%	176	4328	7434
Medical disease																		
Pre-existing hypertension	2·6	4·6	6·9%	85	5·4	8·0%	151	4·8	7·1%	1451	9·8	13·6%	665	7·1	10·2%	118	2470	4242
Pre-existing diabetes	2·9	2·6	4·7%	58	2·1	3·9%	74	2·5	4·5%	914	2·2	4·0%	193	1·8	3·3%	39	1277	2194
Abruption	18·9	1	15·2%	188	1	15·2%	286	1	15·2%	3100	1	15·2%	744	1	15·2%	175	4492	7716

Five study HIC were those with the highest numbers of stillbirths and all relevant data for analysis available. aOR=adjusted odds ratio. SB=stillbirths. HIC=high-income countries. P=prevalence. PAR=population-attributable risk. SB (n)=number of SB attributed. BMI=body-mass index. The sources used to generate the data of this table are referenced in webappendix pp 34–35.

***Table 1*: Most important potentially modifiable risk factors and attributable stillbirth across selected HIC**

which was based on the estimate of Lawn and colleagues[10] of 36 300 late gestational age (≥28 weeks) stillbirths plus an additional 40% to account for those that occurred from 22 to 27 weeks.[1] Where robust prevalence data were not readily available across all five selected countries for factors of interest, we used population data to make best estimates of prevalence from which to calculate PAR.

Meta-analysis of observational studies has well known limitations, especially the effect of residual confounding. Additionally, calculation of PAR does not allow for interdependent risk effects. If multiple variables are interdependent, however, preventive interventions will still be effective, irrespective of whether they relate to one cause or the other.[11,12] Nevertheless, results of the meta-analysis were viewed with these limitations in mind and the estimates of PAR in this study were taken to be a general estimate of the effect of the reported factors.

Role of the funding source

The sponsors 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 literature searches yielded 22 691 studies. After review of the abstracts, 6963 studies were identified as potentially eligible for inclusion. After full review, 96 studies[13–108] were deemed eligible and were included in the study. The list of studies excluded and reasons for exclusion are shown in figure 1. Of the 96 included studies, 76 were cohort studies (six prospective and 70 retrospective) and 20 were case-control studies. All studies were of high quality (see webappendix p 7).

The definition of stillbirth varied across studies. More than half used a definition that included stillbirth from early gestational age (≥20 weeks' gestation in 42 studies, ≥22 weeks in five studies) or small birthweight (≥500 g in seven studies). Other studies used later gestational ages as the cutoff values for stillbirth (≥28 weeks in 20 studies, ≥24 weeks in 13, ≥26 weeks in two, >34 weeks in one, 37 weeks in two, and 40 weeks in one). 25 studies reported on antepartum stillbirth only. Women with multiple pregnancies were excluded from most studies (59 excluded all multiple pregnancies and another six

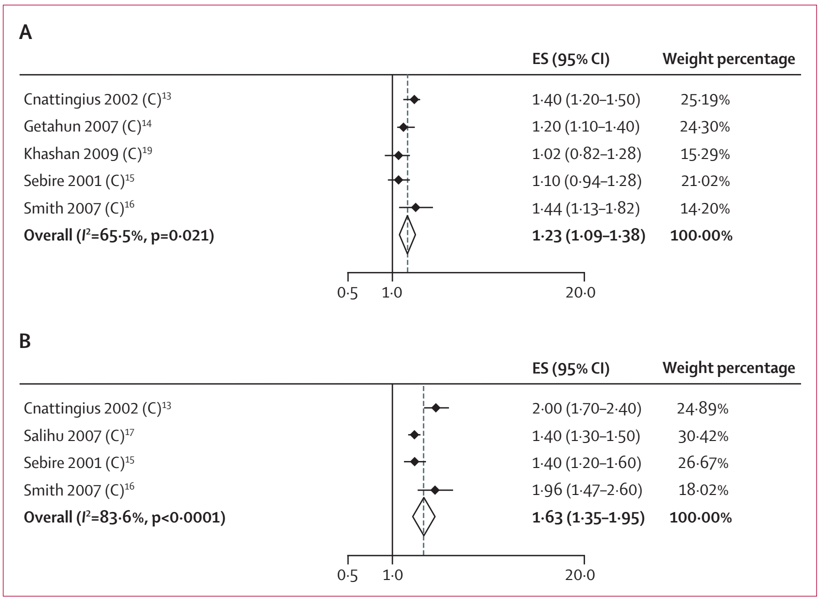

***Figure 2*: Association between maternal overweight, obesity, and risk of stillbirth**
(A) Overweight is classified as BMI 25–30 kg/m². (B) Obesity is classified as BMI >30 kg/m². Weight percentage values are from random effects analysis. ES=effect size. C=cohort study. BMI=body-mass index.

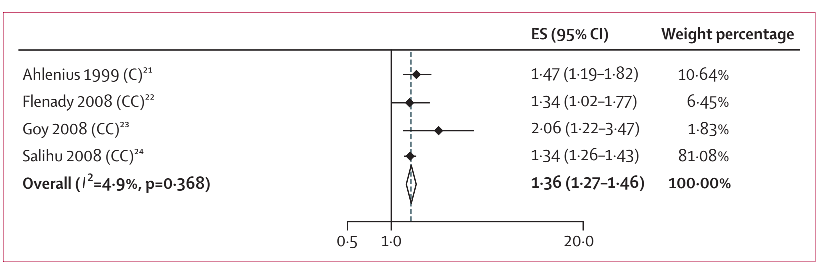

***Figure 3*: Meta-analysis of any smoking and stillbirth risk**
ES=effect size. C=cohort study. CC=case-control study.

excluded higher-order multiples) and deaths of fetuses with congenital abnormalities were excluded from 14.

The 96 included studies were done in 13 high-income countries as follows: USA (n=29), Sweden (n=16), Canada (n=9), Australia (n=12), UK (n=9), Denmark (n=6), Belgium (n=5), Norway (n=3), Italy (n=2), Germany (n=2), and one each from Scotland, New Zealand, and Spain. For a summary of the characteristics of included studies see webappendix p 9.

Meta-analysis revealed that maternal weight, maternal smoking, maternal age, primiparity, small size for gestational age, placental abruption, and pre-existing maternal diabetes or hypertension were the most important and potentially modifiable risk factors from the literature review (table 1).

Combined maternal overweight (BMI 25–30 kg/m²) and obesity (BMI >30 kg/m²) before pregnancy was the top ranking modifiable risk factor for stillbirth in the study countries (table 1). Meta-analysis of five studies that assessed overweight,[13–16,19] and four studies that assessed obesity,[13,15–17] revealed associated increases in the odds of stillbirth of 23% and 60%, respectively (table 1, figure 2). Three studies[17–19] reported on BMI higher than 40 kg/m², which was associated with an increase of two times in the odds of stillbirth (aOR 2·08 [95% CI 1·58–2·73]).

The combined prevalence of overweight and obesity ranged from 28% to 58% across the five study countries, and yielded PARs of around 8–18%. The total number of stillbirths per year associated with this risk factor was 16 822 (table 1).

No association between stillbirth and low maternal weight was shown in two studies that reported on BMI lower than 25 kg/m².[14,16]

A large, well designed, Swedish study by Villamor and Cnattingius[20] reported that the risk of stillbirth increased linearly with weight gain between pregnancies, which supports a causal relation. Women who gained 3 kg/m² or more between the first and second pregnancy, irrespective of whether they were overweight during the first pregnancy, led to a 60% increase in the odds of stillbirth (aOR 1·63 [95% CI 1·20–2·21]). The effect was stronger for term than for preterm births, which suggests a relation between BMI and placental function.

Meta-analysis of four studies[21–24] showed that any smoking during pregnancy (based on maternal reporting in early pregnancy) was associated with a 36% increase in the odds of stillbirth (table 1, figure 3). One high-quality study by Smith and colleagues[16] was assessed as a single study owing to statistical and methodological heterogeneity. This study reported a much stronger association with smoking than all other included studies (aOR 2·48 [95% CI 1·89–3·11]). Salihu and colleagues[25] showed the risk of stillbirth was even greater for women with advancing age. Variation in the population and a different definition of exposure in this study might explain the difference, at least to some extent.

Two studies investigated the association of smoking with unexplained stillbirth. One reported an increase in odds of around 40% (aOR 1·38 [95% CI 1·02–1·87])[22] and the other found no association.[26] Meta-analysis of two studies that investigated a role for heavy smoking (≥10 cigarettes per day)[13,21] showed almost a doubling of the odds (aOR 1·86 [95% CI 1·59–2·17]).

PAR for any smoking was similar across countries, with a range of 4–7%, and represented a total of 1660 stillbirths every year in the five selected countries, and a total of 2852 stillbirths across all high-income countries (table 1). In view of the stronger association found for heavy smoking and the outlying results of the study by Smith and colleagues,[16] the PAR and the number of stillbirths attributable to smoking might be conservative estimates. Assuming the same strength of association, with a much higher prevalence of 50%–60%,[109,110] PAR for Indigenous Australian and Canadian women is estimated to be around 20%.

Meta-analysis of six studies[22,23,27–30] showed that maternal age older than 35 years is associated with an increase of 65% in the odds of stillbirth (figure 4), and the risk increases with increasing age, doubling the odds for women older than 40 years (aOR 2·29 [95% CI 1·54–3·41]).[16,31–35] Salihu and colleagues[31] showed an increased risk of stillbirth with advancing maternal age at 30 years or older. Meta-analysis of two studies that investigated unexplained stillbirths[22,36] showed a non-significant trend towards increased odds of stillbirth (aOR 1·95 [95% CI 0·79–4·86]).

PAR values for maternal age older than 35 years were similar across the five study countries, ranging from 6% to 8%. If all women in these five countries had children before the age of 35 years, around 2460 stillbirths could potentially be averted in 1 year, which is estimated to represent around 4226 stillbirths across all high-income countries (table 1). Compared with women younger than 35 years, the association between age and stillbirth strengthened with increasing maternal age as follows: 35–39 years (aOR 1·46 [95% CI 1·22–1·73]);[16,21,31–33,35] 40–44 years (aOR 1·82 [95% CI 1·43–2·31]);[34,35] older than 45 years (aOR 2·85 [95% CI 1·86–4·36]);[34,35] and in one study,[37] older than 50 years (aOR 2·20 [95% CI 1·01–4·75]) no relation between young maternal age (<20 years) and stillbirth was found in meta-analysis of six studies.[16,29,30,33,35,38] Meta-analysis of two studies on unexplained stillbirth[16,39] also showed no association with young maternal age (aOR 1·31 [95% CI 0·80–2·13]). However, two studies in very young mothers (<15 years) reported significantly increased odds of stillbirth: Salihu and colleagues[40] reported a 57% increase in odds of stillbirth in very young mothers (aOR 1·57, 95% CI 1·49–1·66) and Wilson and colleagues[41] reported an adjusted hazard ratio of 2·6 (95% CI 2·1–3·3) compared with 20–24-year-old mothers.

Primiparity was associated with a 42% increase in the odds of stillbirth in a meta-analysis of three studies (figure 5).[22,29,42] Two studies[22,39] investigated the effect of primiparity on unexplained stillbirth and showed a combined increase in odds of around 60% (aOR 1·57 [95% CI 1·24–1·99]). PARs for stillbirths attributed to primiparity were around 15% for all five selected countries (table 1), which underscores its importance as a contributor to stillbirth.

In high-income countries, the number of women delaying childbearing is rising, which is leading to a growing proportion of primiparous women older than 35 years. Although few studies have rigorously investigated the interaction of these two factors, four high-quality studies[16,43–45] addressed it through subgroup analysis. After controlling for confounders, three studies identified that stillbirth risk in older primiparous women exceeded that in primiparous women younger than 35 years; aORs ranged from 1·68[45] to 3·60.[43] The fourth study by Delbaere and colleagues[44] showed a similar effect but the relation was not significant (aOR 1·69 [95% CI 0·99–2·87]).

Levels of education are an important socioeconomic marker independently associated with stillbirth.[14,28,46–49] Although education systems differ across the world, low education level is generally defined as 10 years or fewer, or 8 years or fewer, and strongly affects stillbirth rates. Meta-analysis of five studies on low education level[14,28,47–49] showed a 70% increase in the odds of stillbirth, with a PAR for stillbirth estimated at around 5% (table 2).

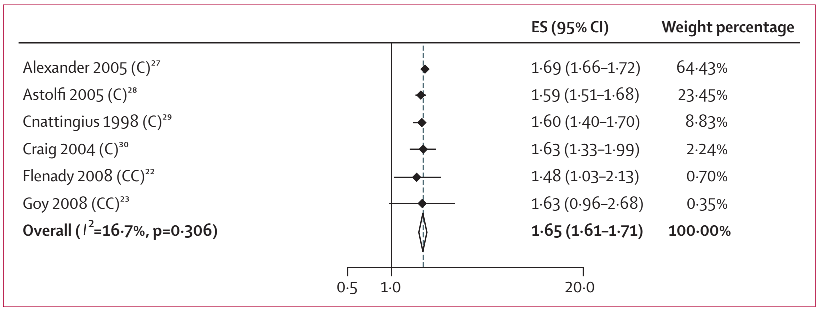

***Figure 4*: Meta-analysis of advanced maternal age (>35 years) and stillbirth risk**
ES=effect size. C=cohort study. CC=case-control study.

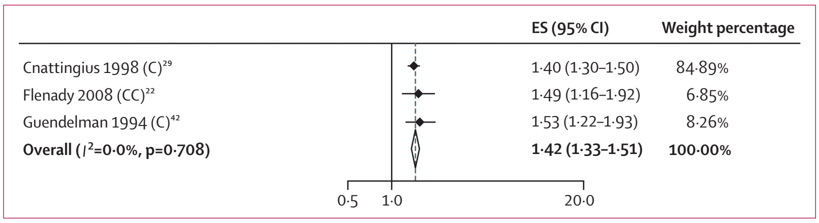

***Figure 5*: Meta-analysis of primiparity and stillbirth risk**
ES=effect size. C=cohort study. CC=case-control study.

Socioeconomic status is measured differently across high-income countries and is strongly inter-related with other socioeconomic factors, such as education, employment, income, and marital status. Thus, comparison of reported study findings is difficult, but two studies from Australia[38] and New Zealand[30] identified relations between stillbirth and low socioeconomic status compared with the highest status groups. The odds of stillbirth were increased by 20% in Australia and by 35%, 32%, and 40% in the three lowest socioeconomic status groups in New Zealand. So-called white collar workers have been estimated to have almost double the odds of stillbirth of so-called blue collar workers (aOR 1·70 [95% CI 1·20–2·30]). A conservative estimate of PAR is 9% (table 2 and webappendix p 29).[38]

We identified one large study[50] that reported the odds of stillbirth more than tripled with no antenatal care (aOR 3·30 [95% CI 3·10–3·60]). A larger proportion of Indigenous compared with non-Indigenous women frequently receive no antenatal care,[109,111] possibly because a large proportion of indigenous populations live in rural and remote areas[109,112] and areas of socioeconomic deprivation. PAR for stillbirth associated with no antenatal care in these populations could be as high as 8%. Nevertheless, the prevalence of women receiving no antenatal care in high-income countries is low, although an important disparity in attendance for antenatal care exists between women from advantaged and disadvantaged backgrounds.

	aOR (95% CI)	Prevalence (%)	PAR (%)
Illicit drug use	1·9 (1·2–3·0)*	2·4	2·1
Low education	1·7 (1·4–2·0)*	6·9	4·9
Low socioeconomic status	1·2 (1·0–1·4)	49·6	9·0
No antenatal care	3·3 (3·1–3·6)	0·3	0·7
Assisted reproductive technology singleton pregnancy	2·7 (1·6–4·7)*	3·1	3·1
Hypertension			
Pregnancy-induced	1·3 (1·1–1·6)*	6·3	1·9
Pre-eclampsia	1·6 (1·1–2·2)*	5·3	3·1
Eclampsia	2·2 (1·5–3·2)	0·1	0·1
Small size for gestational age (<10th centile)	3·9 (3·0–5·1)*	10·0	23·3
Post-term pregnancy (≥42 weeks)	1·3 (1·1–1·7)*	0·9	0·3
Previous stillbirth	2·6 (1·5–4·6)*	0·5	0·8

aOR=adjusted odds ratio. PAR=population-attributable risk. HIC=high-income countries.*aOR results from meta-analysis. The sources used to generate the data of this table are referenced in webappendix p 35–36.

Table 2: PAR for stillbirth in HIC, according to maternal demographic and pregnancy factors

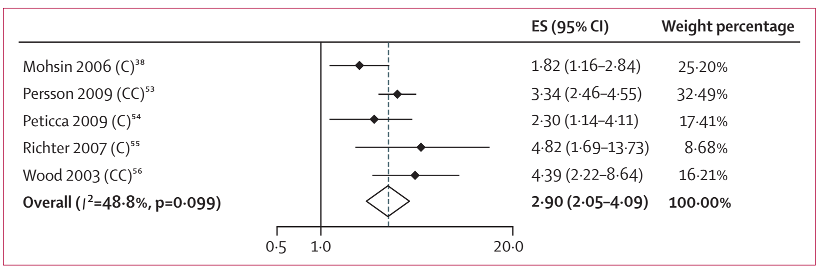

Figure 6: Meta-analysis of pre-existing diabetes and stillbirth risk
ES=effect size. C=cohort study. CC=case-control study.

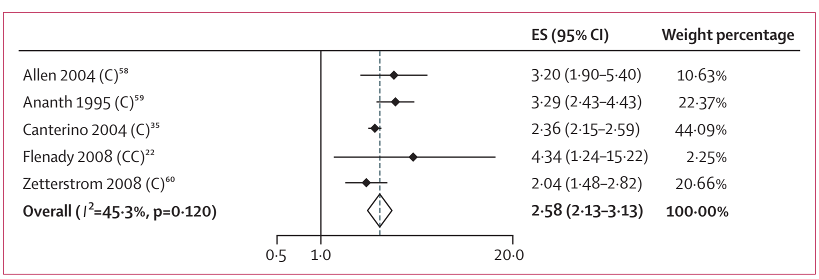

Figure 7: Meta-analysis of pre-existing hypertension and stillbirth risk
ES=effect size. C=cohort study. CC=case-control study.

Inadequate antenatal care has also been associated with stillbirth. Mohsin and colleagues[38] showed that women who had their first antenatal visit after 20 weeks' gestation were slightly more likely to have a stillborn baby than those who had earlier first visits (aOR 1·12 [95% CI 1·01–1·26]). Getahun and colleagues[14] found a 30% increase in the odds of stillbirth for white US women who had no or late antenatal care (adjusted hazard ratio 1·30 [95% CI 1·10–1·50]). In another study,[51] inadequate antenatal care (defined as initiation of antenatal care later than during the first trimester or use of less than half of the recommended visits, or both) was associated with a three-fold increased risk of stillbirth (aOR 3·0 [95% CI 1·71–5·26]).

Suboptimum fetal growth, assessed by the proxy small size for gestational age, is associated with adverse pregnancy outcomes.[113] Meta-analysis of three studies[22,35,52] showed that gestational size of less than 10%, was associated with a four-times higher risk of stillbirth (webappendix p 31). PAR was estimated at 23% (table 2). Meta-analysis of two studies[22,35] showed a similarly strong association between unexplained stillbirth and small size for gestational age (aOR 4·25 [95% CI 1·85–9·75]). With this fetal disorder being primarily related to early stillbirth.[114]

Obesity increases the risk of type 2 and pregnancy-related diabetes, which further increases the risk of adverse outcomes for mothers and babies.[115] The prevalence of obesity and diabetes are increasing and constitute twin epidemics in many high-income countries, posing major challenges in health-care delivery. The contribution of pre-existing diabetes to stillbirths in such countries is small at the population level (PAR 3–5%), but it is one of the maternal medical disorders most strongly associated with stillbirth. We estimated for all high-income countries that around 2194 stillbirths per year can be attributed to pre-existing diabetes (table 1). A meta-analysis of five studies[22,35,58–60] showed that the odds of stillbirth increased nearly three times for women with pre-existing diabetes (table 1, figure 6). Gestational diabetes was not associated with an increased risk of stillbirth in the two studies assessed in this review.[54,57]

Meta-analysis of five studies[22,36,58–60] confirmed that pre-existing hypertension remains an important risk factor for stillbirth in high-income countries, and was associated with a rise in the odds of stillbirth of around 2·6 times (table 1, figure 7) and a PAR of around 7–14% across five countries (table 1). We estimated that around 4242 stillbirths can be attributed to this disorder each year in high-income countries (table 1). Meta-analysis of two studies[22,26] showed an increased risk of unexplained stillbirth associated with pre-existing hypertension (aOR 3·09 [95% CI 1·46–6·57]). Three studies reported on pre-eclampsia.[22,58,61] Meta-analysis showed a 60% increase in the odds of stillbirth, a PAR of around 3%, and 1566 attributable stillbirths (table 1). One study reported a strong association between severe pre-eclampsia and stillbirth (aOR 3·10 [95% CI 2·40–4·00]).[29] Gestational hypertension was associated with a 30% increase in the odds of stillbirth in meta-analysis of four studies (aOR 1·33 [95% CI 1·14–1·58]).[22,36,58,59]

Individual results of two studies showed[62,63] a strong association between placental abruption and stillbirth: McDonald and colleagues[62] in Canada showed an aOR of 11·40 (95% CI 10·60–12·20), and Salihu and colleagues[63] in the USA showed an aOR of 18·90 (95% CI 16·90–20·80). PAR for abruption was estimated to be 15% when the 1% prevalence[116] and effect estimate reported by Salihu and colleagues[63] was used; this was the larger of the two studies. One study showed a non-significant association between placenta praevia with stillbirth (aOR 1·10 [95% CI 0·60–1·90).[14]

We also calculated PAR for several other risk factors (table 2). A discussion of these risk factors is provided online (see webappendix p 1–4).

Discussion

This systematic review shows that a large proportion of stillbirths in high-income countries are attributable to risk factors that are fully or partly avoidable. These findings indicate the possibility for substantial rate reductions.

Obesity is one of the leading factors contributing to the overall burden of disease worldwide.[117] With growing evidence of a causal relation[20] between obesity and various adverse pregnancy outcomes,[115] strategies that increase the proportion of women entering pregnancy within the optimum weight range is a priority for high-income countries.[1] Further research is urgently needed to identify the most useful approaches to weight management before, during, and after pregnancy.[1]

Other important factors that contribute to stillbirth in such countries are maternal age over 35 years, primiparity, and smoking. The risk of stillbirth increases in all women with gestational age[118] but more so in women older than 35 years.[119] Although advanced maternal age is associated with increased risk of obesity, acquired medical disorders, such as diabetes, infertility, the use of reproductive technologies, and multiple gestations,[119] it is an important independent risk factor for stillbirth. Improved community awareness of the associated risks might lower the proportion of women becoming pregnant at older ages. Although, primiparity cannot be removed as a risk factor, early detection of other risk factors and emerging complications (eg, pre-eclampsia and fetal growth restriction) could reduce the risk of stillbirth. Smoking cessation programmes in pregnancy are effective[120] and efforts to increase implementation are needed. This analysis confirmed the increased risk associated with maternal reporting of smoking in early pregnancy. We were unable to assess the effect of quitting in early pregnancy on stillbirth risk, but pregnancy outcomes for these women seem to be similar to those for non-smokers.[121] Therefore, although smoking cessation before becoming pregnant should be the goal, support for quitting should be part of routine antenatal care.

Women from disadvantaged populations in high-income countries continue to have stillbirth rates far in excess of those living without such disadvantage. Programmes that increase the smoking cessation rate in pregnancy and improved access to appropriate antenatal care will assist in closing this gap. As described in the fifth paper of *The Lancet*'s Stillbirths Series,[1] however, poverty could be the overriding factor preventing access to care and obstacles are deeply rooted in the experience of being poor, disadvantaged, and vulnerable.[122] Improvements to the living standards for disadvantaged women, including to education and employment opportunities, are imperative across many high-income countries.[1]

We showed that the risk of stillbirth in such countries remains associated with treatable or preventable disorders and pregnancy complications. Increased clinical and community awareness of the risks associated with common pregestational and gestational medical disorders (eg, diabetes and hypertension) and implementation of best practice guidelines might improve management and lower the associated stillbirth rates.

Small size for gestational age and abruption had the highest PARs of all medical or pregnancy-related disorders and complications studied. This finding indicates the important contribution of placental pathology to stillbirth in high-income countries. A substantial proportion of stillbirths in such countries lack an obvious maternal risk factor and are thought most likely to reflect an incompletely understood abnormality of placental function, which might or might not be associated with impaired growth.

The increasing rates of some important risk factors (eg, advanced maternal age, primiparity, and overweight and obesity), factors, and the interdependent effects of these constitute a major challenge in ensuring optimum pregnancy outcomes for women in high-income countries. These factors are also associated with adverse maternal and infant health outcomes, which frequently have longlasting health implications. Thus, successful prevention strategies are likely to have far reaching effects on the health and wellbeing of the wider population in high-income countries.

Contributions

VF designed the study, oversaw its conduct, and prepared the report with input from all authors. LK coordinated the review, data extraction, and meta-analysis of included studies. VF, LK, PM, AG, and KG collaborated in data extraction and quality assessment. ME oversaw the comparative risk analysis and calculation of PAR values. All authors reviewed the study findings and read and approved the final version before submission.

Conflicts of interest

RF has received payment for providing expert testimony in a court of law. All other authors declare that they have no conflicts of interest.

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