Risk of recurrent stillbirth: systematic review and meta-analysis

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ABSTRACT

OBJECTIVE
To determine the risk of recurrent stillbirth.

DESIGN
Systematic review and meta-analysis of cohort and case-control studies.

DATA SOURCES
Embase, Medline, Cochrane Library, PubMed, CINAHL, and Scopus searched systematically with no restrictions on date, publication, or language to identify relevant studies. Supplementary efforts included searching relevant internet resources as well as hand searching the reference lists of included studies. Where published information was unclear or inadequate, corresponding authors were contacted for more information.

STUDY SELECTION
Cohort and case-control studies from high income countries were potentially eligible if they investigated the association between stillbirth in an initial pregnancy and risk of stillbirth in a subsequent pregnancy. Stillbirth was defined as fetal death occurring at more than 20 weeks’ gestation or a birth weight of at least 400 g. Two reviewers independently screened titles to identify eligible studies based on inclusion and exclusion criteria agreed a priori, extracted data, and assessed the methodological quality using scoring criteria from the critical appraisal skills programme. Random effects meta-analyses were used to combine the results of the included studies. Subgroup analysis was performed on studies that examined unexplained stillbirth.

RESULTS
13 cohort studies and three case-control studies met the inclusion criteria and were included in the meta-analysis. Data were available on 3 412 079 women with pregnancies beyond 20 weeks duration, of whom 3 387 538 (99.3%) had had a previous live birth and 24 541 (0.7%) a stillbirth. A total of 14 283 stillbirths occurred in subsequent pregnancies, 606/24 541 (2.5%) in women with a history of stillbirth and 13 677/3 387 538 (0.4%) among women with no such history (pooled odds ratio 4.83, 95% confidence interval 3.77 to 6.18). 12 studies specifically assessed the risk of stillbirth in second pregnancies. Compared with women who had a live birth in their first pregnancy, those who experienced a stillbirth were almost five times more likely to experience a stillbirth in their second pregnancy (odds ratio 4.77, 95% confidence interval 3.70 to 6.15). The pooled odds ratio using the adjusted effect measures from the primary studies was 3.38 (95% confidence interval 2.61 to 4.38). Four studies examined the risk of recurrent unexplained stillbirth. Methodological differences between these studies precluded pooling the results.

CONCLUSIONS
The risk of stillbirth in subsequent pregnancies is higher in women who experience a stillbirth in their first pregnancy. This increased risk remained after adjusted analysis. Evidence surrounding the recurrence risk of unexplained stillbirth remains controversial.

Introduction

Over the past two decades many high income countries have achieved substantial reductions in late gestation stillbirths. Norway and the Netherlands show the largest reductions; however, in the United Kingdom the downward trend in stillbirth rates has slowed and become more or less stable. As a result the UK has one of the highest stillbirth rates and is ranked 33rd out of 35 high income countries in Europe, with around one baby in every 200 being stillborn every year. Stillbirth is one of the most common adverse obstetric outcomes and a traumatic experience for parents yet until recently was largely ignored. Couples who have experienced a stillbirth need to understand why it happened and want to know the risk for future pregnancies.

The cause of fetal death is complex as there are many contributing and interacting factors. In addition, certain conditions may be associated with stillbirths without directly causing them—for example, well controlled diabetes mellitus. Thus, for many stillbirths it is difficult to determine the exact cause, and according to classification systems for informing and establishing the likely cause for the loss of the baby these are classified as unexplained. Because of the considerable number of classification systems currently in use, the proportion of stillbirths classified as unexplained varies widely, from 9.5% to 50.2%. Notably, more recent classification systems yield lower proportions of unexplained deaths as they often attribute relatively common conditions such as velamentous insertion of cord as causes of perinatal deaths. At times, stillbirths may be unexplained because of inadequate investigations to determine a cause of death, but even after extensive evaluation many stillbirths remain unexplained.
The increased risk for recurrence of pregnancy complications and outcomes is well recognised. However, the literature on stillbirth recurrence is sparse and inconsistent. Some studies report recurrence risks ranging from twofold to 10-fold, whereas others report no increased risk. Although stillbirth is a common obstetric complication its recurrence is rare and it may be that some primary studies lack the power to detect any increase in risk. Furthermore, many causes of stillbirth (for example, placental abruption) are known to recur in subsequent pregnancies, thus increasing the chances of another stillbirth associated with that cause; but in cases where stillbirth remains unexplained there is no consensus about the risk of stillbirth in the next pregnancy. Because of the uncertainty surrounding the recurrent risk for stillbirth it is difficult for clinicians to counsel couples and to know what level of care to provide in subsequent pregnancies.

We reviewed the evidence on the association between stillbirth in an initial pregnancy and risk of stillbirth in subsequent pregnancies. Specifically, we hypothesised that women whose first pregnancy resulted in a stillbirth or an unexplained stillbirth had an increased risk of stillbirth in any subsequent pregnancy compared with women who had a previous live birth. A priori, we restricted our review to primary studies conducted in high income countries to prevent any distortion of findings from variations in clinical practice and access to healthcare.

Methods

We conducted a systematic review and meta-analysis following the guidelines recommended by the meta-analysis of observational studies. Two people (SB, KL) independently performed the literature search, data extraction, and quality assessment of the included studies. Any disagreement was resolved by discussion between reviewers or referred to a third reviewer (GTJ) if necessary.

Eligibility criteria

Eligible studies were those that were cohort or case-control studies conducted in high income countries (all countries listed with the World Bank as high income members of the Organisation for Economic Co-operation and Development), investigated the association between stillbirth or unexplained stillbirth in an initial pregnancy and risk of stillbirth in a subsequent pregnancy, used a definition of stillbirth as occurring at 20 weeks gestation or more or a birth weight of 400 g or more; and reported estimates of either odds ratio, risk ratio, or hazard ratio, or provided sufficient data for these to be calculated.

Search strategy

With guidance from a librarian we searched a range of electronic bibliographic databases: Medline and Embase through Ovid (1946 to 12 September 2014), the Cochrane Library through Wiley Interscience, Cumulative Index to Nursing and Allied Health Literature (CINAHL) through EBSCO Host, PubMed through the National Center for Biotechnology Information (NCBI), and SCOPUS through Elsevier. During preliminary searches we found that the two concepts of stillbirth and recurrence were more often included in journal abstracts or indexed. Therefore the search strategy stemmed from these two concepts. We used a combination of Medical Subject Headings key words, and text words for “stillbirth”, “recurrence”, “pregnancy”, and “risk factors” that appeared in abstracts and titles. No restrictions were applied to date, publication, or language, although we limited studies to those in human participants. Also, the term “unexplained” was not included in the search strategy. The search strategy was initially developed for use in Medline and was then adapted for searching the other databases (see supplementary file for the search strategies used in each database). In addition, we searched the UK Research Clinical Network Portfolio Database, the MIDIRS website (a broad reference resource available to obstetricians, midwives, and consumers), and the Proquest Dissertations and Theses: UK and Ireland database. We screened the reference lists of all identified studies obtained as full reports, and we also performed searches using Google search engine in an attempt to find pages that might have provided references. If published papers had inadequate or unclear data we contacted the study authors for further information or clarification.

Data extraction and quality assessment

Data extraction was accomplished using two data extraction forms; one that included general study characteristics and one that included sample characteristics, stillbirth rates, and measure of association.

Study quality was assessed using the criteria of the critical appraisal skills programme. The questions assess study validity, risk of bias in recruitment, exposure and outcome measurement, confounding factors, the reporting of results, and the transferability of results. Scores range from 0-11 for case-control studies and from 0-12 for cohort studies, where a higher score indicates higher quality.

Statistical analysis

Meta-analyses were conducted using Revman 5.2 (Cochrane Collaboration 2012). We performed several analyses and present pooled estimated effect sizes using random effects models to incorporate heterogeneity within and between studies. Secondly, we pooled the odds ratios from all studies that provided data adjusted for various potential confounding variables. This was done using the generic inverse weighted method—that is, studies were weighted by the inverse of the standard error of the log transformed odds ratios. We calculated the standard errors of these log odds ratios using published confidence intervals and then used these to weight the studies according to the precision of the odds ratio. To explore the definition of stillbirth as a potential source of heterogeneity we conducted a sensitivity analysis.

Statistical heterogeneity was assessed using the Cochran’s $\chi^2$ test, and the $P$ statistic used to summarise the
degree of variation across studies. As recommended by the Cochrane handbook for systematic reviews,\textsuperscript{30} we considered an I² value of 0-40% to represent low heterogeneity, 30-60% moderate heterogeneity, 50-90%, substantial heterogeneity, and 75-100% considerable heterogeneity.

Assuming there is a causal relation between a risk factor and a disease, the population attributable risk is the proportion of disease or deaths in a population that can be attributed to an exposure. We calculated the population attributable risk (odds ratios were used to estimate the relative risk) using a previously published formula.\textsuperscript{31} The likelihood of publication bias was assessed by visual inspection of a funnel plot.\textsuperscript{32}

Patient involvement
There was no patient involvement in this study.

Results
The database searches returned 6599 potentially relevant unique citations. In addition, one study and a conference abstract were identified through supplementary searches (fig 1). Of these, 38 were selected for further appraisal. Twenty two citations from these did not meet the inclusion criteria and thus were excluded. Thirteen cohort studies\textsuperscript{14 15 17 18 33 34-41} and three case-control studies\textsuperscript{42-44} met the inclusion criteria. All of the included studies except for two reported odds ratios—one reported a hazard ratio\textsuperscript{18} and the other a relative risk.\textsuperscript{43} Because the outcome of interest is rare, the odds ratio, relative risk, and hazard ratio approximate each other.\textsuperscript{29} Fourteen authors were contacted for information.

Eleven responded, with three providing additional data that were included in the analysis.\textsuperscript{35 39 40}

Quality assessment
The quality appraisal scores using the critical appraisal skills programme for all 13 cohort studies were high; median quality score 10.50, with a range of 9.5-11.5 (see supplementary appendix table 1). The median quality score for case-control studies was 8.5, with a range of 7-8.5 (see supplementary appendix table 2). These results showed that the observational studies were of good quality. Twelve studies reported adjusted odds ratios for the association between stillbirth in an initial pregnancy and risk of stillbirth in a subsequent pregnancy. Most studies adjusted for maternal age, smoking, and socioeconomic status. Adjustment for other potential confounders such as living with a partner or marital status, education, race or ethnicity, and interval between pregnancies varied among the studies, with two studies adjusting for body mass index.\textsuperscript{15 17} Six studies that investigated the risk of stillbirth recurrence adjusted for obstetric complications such as pre-eclampsia, placental abruption, or preterm birth medical,\textsuperscript{14 17 18 41} or obstetric risk factors.\textsuperscript{33 37} One of those studies\textsuperscript{43} reported two adjusted odds ratios, one that included gestational age (model 1) and one that excluded gestational age in the logistic regression model (model 2).

Study characteristics
Tables 1 and 2 show the general study characteristics and sample characteristics of included studies. Studies were published between 2001 and 2014 and five were conducted in Australia,\textsuperscript{18 38 40-42} three in Scotland,\textsuperscript{14 17 19} three in the United States,\textsuperscript{15 33 44} and one each in Denmark,\textsuperscript{33} Israel,\textsuperscript{43} the Netherlands,\textsuperscript{37} Norway,\textsuperscript{36} and Sweden.\textsuperscript{34} All articles were in English. Nine of the cohort studies were large population based studies that included data extending over at least 10 years. One of these\textsuperscript{41} included data collected over nearly 40 years, thus the combined data collection period spanned from 1967 to 2009. Eleven of the cohort studies examined the risk of stillbirth recurrence in a second pregnancy. In one of the remaining cohort studies, data were available on a subset of women on their first and second sequential births.\textsuperscript{40} The remaining cohort study examined risk of recurrence of unexplained stillbirth and included women in the exposed group with an unexplained stillbirth that need not necessarily have been their first birth. All case-control studies included women with more than two pregnancies.\textsuperscript{42-44}

Exposure in the included studies
Ascertainment of stillbirth was confirmed through nationwide registers,\textsuperscript{14 34-40 42} hospital databases,\textsuperscript{15 17 18 33 41-44} and hospital records.\textsuperscript{32-44} Seven studies used the World Health Organization international classification of disease codes to classify maternal conditions and obstetric complications.\textsuperscript{14 17 19 33 36 38-41 42-44} Studies used a variety of different definitions of stillbirth, with most of the studies defining stillbirth from an early gestational age (≥20 weeks),\textsuperscript{19 17 18 33 36 38 41-42 44} whereas others used a later gestation (≥22 weeks,\textsuperscript{31 30} ≥24 weeks,\textsuperscript{14 39} and ≥28 weeks).\textsuperscript{36} The remaining study\textsuperscript{40} used
| Reference | Country, study period | Study design and data source | Definition of stillbirth | Confounders taken into account |
|-----------|-----------------------|-----------------------------|-------------------------|-------------------------------|
| Bhattacharya 2010 | Scotland, 1981-2005 | Retrospective population based cohort study using data from Information and Services Division databases of National Health Service, Scotland | Intramural death >20 weeks' gestation and before delivery | Maternal age, smoking status (during and after pregnancy), social class, interpregnancy interval, pre-eclampsia, placental praevia, low birth weight, preterm birth |
| Black 2008 | Scotland, 1976-2006 | Retrospective population based cohort study using data from Aberdeen Maternity and Neonatal Databank | Death of fetus >20 weeks' gestation and before delivery | Maternal age, husband or partner's social class, body mass index, alcohol or illicit drug use, and passive smoking |
| Getahun 2009 | USA, 1991-2008 | Retrospective cohort study using data from three databases: Kaiser Permanente perinatal services system, maternal and infant hospital admissions and outpatient healthcare encounter files | Death of a fetus ≥20 weeks' gestation further categorized as antepartum or intrapartum | Maternal age, ethnicity, education, prenatal care initiation, smoking and alcohol use, interpregnancy interval, sex of fetus, chronic hypertension, diabetes, renal disease, autoimmune disease, cord complications, congenital anomalies, premature rupture of membranes |
| Gordon 2012 | Australia, 2002-06 | Retrospective population based cohort study using data from New South Wales Midwives Data Collection and New South Wales Perinatal Death Database | Examined recurrence, defined as “death of a normally formed fetus before onset of labour where no predisposing factors are considered likely to have caused the death” | Maternal age, pre-existing hypertension, pre-existing diabetes, smoking, ethnicity, pre-eclampsia, gestational diabetes, previous pregnancy outcome—caesarean delivery, small for gestational age, weight at birth |
| Hogberg 2007 | Sweden, 1983-2001 | Population based cohort study using data from Swedish medical birth registry, immigration registry, and education registry | Fetal death after at least 28 completed weeks' gestation | Maternal age, education, living with partner, smoking, ethnicity, interpregnancy interval, previous pregnancy outcome, year of second delivery |
| Lykke 2009 | Denmark, 1978-2007 | Retrospective registry based cohort study using data from national patient registry | Examined stillbirth recurrence in first and second pregnancies | Maternal age, education, height, weight, smoking, parity, interpregnancy interval, previous pregnancy outcome, year of second delivery |
| Measey 2009 | Australia, 1990-99 | Randomly selected unmatched population based case-control study using data from Western Australia Midwives Notification System, Western Australia Death Registration Database, and pathology records from King Edward Memorial Hospital for Women | Antepartum unexplained fetal deaths of at least 400 g or 20 weeks' gestation | Maternal age, indigenous status, previous pregnancy outcome, previous smoking, number of previous caesarean sections, evidence of limiting growth restriction excluded |

**Continued**
## Table 1 | Characteristics of included studies

| Reference          | Country, study period          | Study design and data source                                                                                     | Unexplained stillbirth | Confounders taken into account                                                                 | Definition of stillbirth, and other comments                                                                 |
|--------------------|--------------------------------|------------------------------------------------------------------------------------------------------------------|------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Melve 2010<sup>36</sup> | Norway, 1967-2004            | Retrospective population based cohort study using data from medical birth registry of Norway                          | Not examined           | Maternal age, education, marital status                                                        | Gestational age ≥20 weeks; examined stillbirth recurrence in first and second pregnancies                  |
| Mohsin 2008<sup>41</sup> | Australia, 1994-2004         | Retrospective population based cohort study using linked data from New South Wales Midwife Data Collection           | Not examined           | Maternal age, prenatal care initiation, smoking, birth interval in months<sup>*</sup> (model 2 gestational age excluded from model) | ≥20 completed weeks of gestation or 2400 g; education level and socioeconomic status data not available; examined stillbirth recurrence in first and second pregnancies |
| Nijkamp 2013<sup>37</sup> | Netherlands, 1999-2007       | Retrospective population based cohort study using linked data from national perinatal registry                      | Not examined           | Maternal age, ethnicity, socioeconomic status, and small for gestational age                    | Antepartum or intrapartum fetal death >22 weeks' gestation, fetal deaths associated with major congenital anomaly excluded; examined stillbirth recurrence in first and second pregnancies |
| Ofir 2013<sup>43</sup>   | Israel, 1999-2009            | Case-control study database Sheba Medical Centre                                                                  | Not examined           | Not reported                                                                                   | Antepartum stillbirth >22 weeks’ gestation, detailed medical and obstetric history obtained; postmortem or placental pathology results obtained, when available |
| Patterson 2014<sup>40</sup> | Australia, 2001-09          | Retrospective population based cohort study using linked data from New South Wales Perinatal Data Collection, Admitted Patients Data Collection, and New South Wales Perinatal Death Review Database | Not examined           | Adjued odds ratio not reported for recurrent stillbirth, author supplied data                  | Limited to births of gestational age ≥22 weeks or birth weight ≥500 g (20 weeks' gestation or 400 g if born after 2005); after analyses of risk factors, stillbirths stratified into occurring <26 weeks' gestation, 26-33 weeks, and ≥34 weeks; only used data pertaining to 1st and 2nd sequential births |
| Robson 2001<sup>39</sup> | Australia, 1987-97          | Retrospective population based matched cohort study using data from Pregnancy Outcome Unit and Maternal Perinatal and Infant Mortality Committee | Examined—no rate of postmortem examination reported | Maternal age, parity, antepartum haemorrhage, preterm labour, premature rupture of membranes, gestational diabetes | At least 400 g or 20 completed weeks’ gestation; unexposed group first and second pregnancies but exposed group may have had more than two pregnancies; no data on smoking or body mass index, socioeconomic status |
| Sharma 2006<sup>23</sup> | USA, 1978-97                 | Retrospective population based cohort study using Missouri maternally linked data                                   | Not examined           | Maternal age, parity, marital status, education, smoking, body mass index, adequacy of prenatal care, interpregnancy interval, year of birth | Intrauterine fetal death at ≥22 weeks gestation; examined stillbirth recurrence in first and second pregnancies |
| Smith 2012<sup>39</sup>  | Scotland 1992-2008           | Retrospective population based cohort study using linked data from Scottish registries of pregnancy and perinatal death | Examined               | Reported as maternal characteristics                                                            | ≥24 weeks’ gestation; losses due to congenital anomaly excluded; examined stillbirth recurrence in first and second pregnancies |
| Stillbirth Collaborative Research Network Writing Group 2011<sup>34</sup> | USA, Mar 2006-Sep 2008     | Multisite population based case-control study. Prestudy vital statistics data provided by 59 community and academic hospitals (urban and rural) | Not examined           | Body mass index, blood type, hypertension, diabetes, seizure disorder                           | Fetal deaths occurring at ≥20 weeks’ gestation; fetal deaths at 18 or 19 weeks without good dating included to assure that stillbirths occurring at ≥20 weeks with incorrect dating could be enrolled; cases—only used data for subset of deliveries at ≥24 weeks’ gestation non-anomalous singleton pregnancies |

*<sup>*</sup>= PANZ-PDC= Perinatal Society of Australia and New Zealand-Perinatal Death Classification.  
<sup>1</sup>=<ref>Reference Category</ref>, ≥36.
a combination of at least 22 weeks' gestation or at least 20
weeks if the infant was born after 2005, reflecting a
change in reporting requirements. A birth weight defined
as at least 400 g was also included in two studies\(^\text{38,41}\) and
400 g/500 g in the study that used the combined defini-
tion of at least 20/22 weeks' gestation.\(^\text{40}\)

**Studies that examined risk of recurrence of unexplained stillbirth**

Only three of the cohort\(^\text{38,38,39}\) and one of the case-
control\(^\text{42}\) studies examined risk of recurrence of unex-
plained stillbirth. Two of these\(^\text{38,42}\) identified the causes
of stillbirth using the perinatal death classification sys-
tem of the Perinatal Society of Australia and New Zealand
(PSANZ-PDC).\(^\text{40,41}\) One of the others\(^\text{38}\) used a
modification of Whiffin's.\(^\text{45}\) The remaining study by
Smith\(^\text{39}\) was a conference publication and the author
informed us that the Wigglesworth classification, the most
frequently used classification system in high income
countries, was applied.

**Quantitative data synthesis**

Data were available on 3 412 079 women comprising
3 387 538 (99.3%) who had a live birth and 26 541 (0.7%) who
had a stillbirth in an initial pregnancy. A total of
1 428 283 stillbirths occurred in the subsequent pregnancy,
606/24 541 (2.5%) in women with a history of stillbirth and
14 283 stillbirths in the subsequent pregnancy, 13 677/3 387 538
(0.4%) in women with no such history.

Figure 2 shows the unadjusted risk of stillbirth recur-
rence in women who had experienced a previous still-
birth in any pregnancy compared with those with no
such history. A considerable amount of heterogeneity
between studies was indicated (\(I^2 = 82\%), P < 0.01). Odds
ratios from individual studies ranged from 1.00 to 23.75,
with a clear suggestion of increased odds of subsequent
stillbirth among women who experienced stillbirth in a
previous pregnancy (pooled odds ratio 4.83, 95% confi-
dence interval 3.77 to 6.18). When the analysis was
restricted to only studies that examined risk of stillbirth
recurrence in women with first and second subsequent
pregnancies the risk was slightly less than the
unrestricted pooled odds ratio (4.77-fold, 95% confidence interval 3.70-fold to 6.15-fold) (fig 3).

Using only the adjusted odds ratios reported in primary studies, the increased effect of a previous stillbirth remained (pooled odds ratio 3.38, 95% confidence interval 2.61 to 4.38) (fig 4). The pooled unadjusted odds ratio for these studies was 4.44 (95% confidence interval 3.54 to 5.56).

Subgroup analysis
Because of methodological differences between studies that examined risk of recurrent unexplained stillbirth we were unable to perform the prespecified subgroup analysis. Four studies examined the recurrence risk of unexplained stillbirth. Two of these studies conducted a prospective analysis looking at risk of stillbirth recurrence (explained and unexplained) after a previous unexplained stillbirth. The reported adjusted risks for stillbirth in a subsequent pregnancy after previous unexplained stillbirth in these two studies were 3.11 (95% confidence interval 0.72 to 13.50) and 1.00 (0.23 to 4.30). A retrospective analysis looked at risk of unexplained stillbirth in a subsequent pregnancy after any previous explained or unexplained stillbirth. The reported adjusted risk for unexplained stillbirth after any stillbirth was 3.20 (95% confidence interval 1.59 to 6.45).

Sensitivity analyses
To examine possible sources of heterogeneity across studies, we performed a sensitivity analysis according to the definition of stillbirth, but this did not explain much of the heterogeneity. As data overlapped slightly (as little as 8%) between the studies by Black and colleagues and Bhattacharya and colleagues, we conducted a sensitivity analysis by removing Black and colleagues’ study—the rationale being that Bhattacharya and colleagues’ findings were considered more generalisable because of the population based design. This resulted in a slightly larger overall pooled odds ratio (4.97, 3.87 to 6.38).

As we were interested in potentially modifiable risk factors, we also performed an analysis that included the studies that adjusted only for maternal characteristics. Again there was a clear suggestion of an increased odds of subsequent stillbirth in women who had experienced stillbirth in a previous pregnancy (pooled unadjusted odds ratio 5.48-fold, 95% confidence interval 4.42-fold to 6.79-fold). After adjusting only for maternal factors, the increased risk was slightly attenuated (pooled odds ratio 4.27, 95% confidence interval 3.38 to 5.39). Offir and colleagues reported an exceptionally high odds ratio, of 23.75 (95% confidence interval 8.99 to 62.80). We therefore examined the effect of removing this study from the meta-analysis and found the pooled odds ratio to be reduced slightly, to 4.56 (95% confidence interval 3.77 to 6.18).
3.57 to 5.81). The supplementary file provides details of all sensitivity analyses.

Population attributable risk
We calculated the population attributable risk percentage to assess the proportion of subsequent stillbirth that is attributable to stillbirth in a first pregnancy. Based on unadjusted association measures, the result was 8%.

Publication bias assessment
Although it is difficult to show evidence of asymmetry and therefore publication bias, visual inspection of a funnel plot (fig 5) showed a gap in the middle and bottom right of the plot suggesting that some smaller studies with large effects may be underrepresented.

Discussion
In this systematic review and meta-analysis, women who experienced a stillbirth in an initial pregnancy experienced nearly a fivefold increase in the odds of stillbirth in a subsequent pregnancy. Even when restricting the analysis to first and second pregnancies, the risk of stillbirth in the second pregnancy was increased if the first pregnancy ended in stillbirth. In the meta-analysis using adjusted odds ratios from primary studies the increased odds of recurrence remained, although it was slightly less than the unad-

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**No of events/total**

| Study | Previous stillbirth | Previous live birth | Odds ratio, random (95% CI) | Weight (%) | Odds ratio, random (95% CI) |
|-------|---------------------|---------------------|-----------------------------|------------|-----------------------------|
| Cohort studies |  |  |  |  |  |
| Sharma 2006 | 45/1979 | 1884/402 201 | 10.3 | 4.94 (3.67 to 6.67) |
| Hogberg 2007 | 18/2363 | 1402/524 328 | 8.5 | 2.86 (1.80 to 4.57) |
| Black 2008 | 5/364 | 179/33 715 | 4.8 | 2.61 (1.07 to 6.38) |
| Mohsin 2008 | 72/2168 | 1144/242 672 | 10.8 | 7.25 (5.69 to 9.24) |
| Getahun 2009 | 5/373 | 257/70 942 | 4.9 | 3.74 (1.53 to 9.11) |
| Lykke 2009 | 106/3161 | 1832/533 258 | 11.2 | 10.06 (8.25 to 12.28) |
| Bhattacharya 2010 | 50/2677 | 1399/306 627 | 10.4 | 4.44 (3.34 to 5.90) |
| Melve 2010 | 222/5996 | 3507/568 315 | 11.6 | 6.19 (5.39 to 7.11) |
| Gordon 2012 | 3/348 | 145/51 762 | 3.5 | 3.10 (0.98 to 9.76) |
| Smith 2012 | 21/1323 | 660/242 881 | 8.9 | 5.92 (3.82 to 9.17) |
| Nijkamp 2013 | 12/2058 | 803/250 769 | 7.5 | 1.83 (1.03 to 3.23) |
| Patterson 2014 | 13/872 | 477/144 565 | 7.6 | 4.57 (2.62 to 7.96) |
| Total (95% CI) | 572/23 682 | 13 599/3 372 035 | 100.0 | 4.77 (3.70 to 6.15) |

**Test for heterogeneity:** $\chi^2=0.14$, $I^2=84%$

**Test for overall effect:** $z=12.04$, $P<0.001$

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**Log (odds ratio)**

| Study | Log (odds ratio) | Standard error |
|-------|------------------|----------------|
| Cohort studies |  |  |
| Sharma 2006 | 1.548 | 0.177 |
| Hogberg 2007 | 0.875 | 0.308 |
| Black 2008 | 0.182 | 0.546 |
| Mohsin 2008 | 1.270 | 0.123 |
| Getahun 2009 | 1.253 | 0.329 |
| Bhattacharya 2010 | 0.663 | 0.159 |
| Melve 2010 | 1.504 | 0.228 |
| Gordon 2012 | 0.708 | 0.623 |
| Smith 2012 | 1.758 | 0.227 |
| Nijkamp 2013 | 0.875 | 0.296 |
| Subtotal (95% CI) |  |  |
| Test for heterogeneity: $\chi^2=28.86$, $df=9$, $P<0.001$, $I^2=70%$ |  |  |
| Test for overall effect: $z=8.28$, $P<0.001$ |  |  |

**Case-control studies**

| Study | Log (odds ratio) | Standard error |
|-------|------------------|----------------|
| Measey 2009 | 1.430 | 0.574 |
| SCRNWG 2011 | 1.898 | 0.384 |
| Subtotal (95% CI) |  |  |
| Test for heterogeneity: $\chi^2=0.46$, $df=1$, $P=0.50$, $I^2=0%$ |  |  |
| Test for overall effect: $z=5.49$, $P<0.001$ |  |  |

**Total (95% CI)**

| Test for heterogeneity: $\chi^2=33.20$, $df=11$, $P<0.001$, $I^2=67%$ |  |  |
| Test for overall effect: $z=9.20$, $P<0.001$ |  |  |
| Test for subgroup differences: $\chi^2=2.91$, $df=1$, $P=0.09$, $I^2=65.6%$ |  |  |

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**Fig 3** Random effects model (unadjusted) showing risk of recurrent stillbirth associated with previous stillbirth restricted to women with first and second subsequent pregnancies.

**Fig 4** Random effects model (adjusted for various confounding factors) showing risk of stillbirth associated with previous stillbirth (confounders vary between studies). SCRNWG=Stillbirth Collaborative Research Network Writing Group.
justified analysis. Where the primary studies had specifically looked at unexplained stillbirth, the evidence was less clear cut. Only two studies had looked at unexplained stillbirth in an initial pregnancy and any stillbirth (explained or unexplained) in the subsequent pregnancy and had found no increased risk. However, two other studies had specifically assessed unexplained stillbirth after any stillbirth (explained or unexplained) and reported a greatly increased risk of recurrence.

**Strengths and limitations of this review**

This systematic review and meta-analyses offers the first comprehensive synthesis of the available evidence on the association between stillbirth and unexplained stillbirth in a previous pregnancy and risk of recurrence. Meta-analyses were conducted (unadjusted and adjusted) that included data on a large number of women from high income countries to provide a quantitative summary of the results. The population based design of the included studies is a strength that promotes generalisability within countries as well as transferability of findings to other high income countries. Statistical heterogeneity of studies was substantial as evidenced by the high I² statistic, and therefore as with all reviews of observational studies the findings should be interpreted with caution. Nevertheless, in all comparisons the estimates showed the same direction of effect, which suggests that the association is real.46

Systematic reviews of observational studies typically combine studies that are diverse both clinically and methodologically. As a result, heterogeneity between the results is to be expected.46 In our analyses, primary studies differed in their definition of stillbirth and in their use of classification systems for determining cause of death and consequently in the classification of unexplained stillbirth. Moreover, methodological differences were apparent in their lack of consistency in tackling the effects of confounding. For instance, some studies adjusted for causal factors such as pre-eclampsia and placental abruption or preterm birth, which is not a confounder but rather in the causal path of stillbirth. After adjusting only for maternal characteristics, the estimated risk from these studies was reduced by 22% compared with the unadjusted risk. This suggests that much of the risk of recurrence is not explained by modifiable maternal factors, consistent with the Stillbirth Collaborative Research Network study,44 which showed that apart from the occurrence of previous stillbirth or pregnancy loss, risk factors known at confirmation of pregnancy (a combination of demographic and obstetric maternal characteristics) explained only a small amount of the risk of stillbirth. Nevertheless, the literature on the association between maternal obesity and stillbirth reports an increased risk of stillbirth among women who are obese compared with women of normal weight.47-53

Furthermore, a systematic review of observational studies conducted in high income countries showed that maternal overweight and obesity may have the greatest population attributable risk among modifiable maternal risk factors for stillbirth.54

For studies included in this meta-analysis, collection of important risk factors such as maternal body mass index and smoking was generally inconsistent, and information on alcohol intake was reported in only one study.51 Along with smoking, overweight and obesity are now thought to be causally associated with an increased risk of stillbirth,53 yet only three studies adjusted for body mass index,51 52 53 and although most studies adjusted for smoking for many studies data were incomplete. Residual confounding from poor measurement of these could still explain at least part of the associations reported. Thus our findings might underestimate the risk of recurrence explained by modifiable risk factors.

The evidence surrounding the recurrence risk of unexplained stillbirth remains controversial owing to the few studies looking specifically at unexplained stillbirth, the small number of events in individual studies, and the variation in defining unexplained stillbirth. Although no evidence of publication bias and selective reporting was found these are possible limitations for any systematic review, more so systematic reviews of observational studies. Therefore, despite the best efforts it is possible that not all studies were identified.

**Comparison with previous studies**

Despite a thorough and systematic literature search, no systematic review on this problem was identified. The literature on stillbirth has recently expanded; however, studies that examined the recurrence of stillbirth remain scarce. Primary reports in the literature investigating the risk of stillbirth recurrence yielded inconsistent results, but most published studies suggest an increased risk for women with a history of stillbirth. However, when the previous stillbirth has been unexplained or when the sample size was small, adjustment for confounding factors made confidence intervals cross unity and no increased risk in subsequent stillbirth was found.

Inconsistency in the definition of unexplained stillbirth has also been recognised and it has been pointed out that truly unexplained stillbirths are those in which no cause of death can be found despite thorough post-mortem examination. Gordon and colleagues made the decision a priori to only analyse data from 2002 because from that point all deaths were routinely classified using the perinatal death classification system of the Perinatal Society of Australia and New Zealand. This stillbirth classification system incorporates policy directives that
include recommendations to discuss and offer postmortem examinations to every affected family, and for examination of the placenta. Even so, a postmortem examination was performed in only half of the stillbirths in the cohort. The authors draw attention to the low rate of postmortem examinations undertaken in unexplained stillbirths in New South Wales during the study period (30.8%). Rates of postmortem examination for which parental consent is required are also low in the UK (around 45%), although in Scotland as a result of ongoing commitment to improve procedure, rates of consent are higher.

Nijkamp and colleagues evaluated the subsequent pregnancy outcome after a previous stillbirth. The cause of death in both the index and the subsequent pregnancy was determined and compared using the Tulip classification system, the system developed and currently in use in the Netherlands for classifying cause of death. Of 163 women, 11 had a subsequent stillbirth, and of these at least six showed an association between the cause of death in both events. Stillbirth is a relatively uncommon outcome in high income countries and recurrence even more so. Therefore to provide statistical power to observe the recurrence of unexplained stillbirth, large numbers of births are necessary in primary studies. Systematic reviews and meta-analyses can help overcome this deficiency in primary analyses.

Implications for clinical practice and policy

This research is relevant to public health and clinical practice because it adds to the body of evidence on stillbirth recurrence and can be used to counsel couples who are thinking of conceiving after a previous explained or unexplained pregnancy loss. Smoking and obesity are independently associated with an increased risk of stillbirth, and modification of these lifestyle factors may make a small but important reduction in the risk of recurrence. Current management of pregnancies should take account of pregnancy history and make use of prepregnancy counselling services. Based on the available evidence identified by this review, a stillbirth in an initial pregnancy was associated with an increased risk of a subsequent stillbirth, and pregnancies after a stillbirth should be closely monitored with a view to intervene at the first sign of fetal compromise. Consequently, clinical guidance from the UK Royal College of Obstetricians and Gynaecologists recommends that pregnant women with a previous stillbirth should be managed as high risk, yet many stillbirths result from non-recurrent events such as infection, problems with the umbilical cord, and isolated structural fetal anomalies. There is little evidence that this approach actually prevents stillbirth in the next pregnancy without increasing morbidity from unnecessary interventions.

The demand for international consensus on the use of a universal definition and classification for stillbirth for research purposes has been proposed for some time. To improve understanding of cause related and unexplained risk of stillbirth recurrence, large scale individual patient data meta-analyses are warranted, where uniform definitions and classifications can be applied. This systematic review highlights the scarcity of studies that examined the risk of stillbirth recurrence and shows the need for high quality multicentre studies using standardised definitions of stillbirth and unexplained stillbirth to add to current knowledge. Future research that stratifies women for the key confounding variables of obesity and smoking is needed to assess the impact of lifestyle modification on risk of recurrent stillbirth. In addition, to ascertain cause related recurrence, population based studies that examine the risk of subsequent stillbirth based on the initial cause of death are also needed. A clearly standardised universal definition of stillbirth for research and reporting practices is key issue if the methodological quality of stillbirth research is to be improved, be more comparable, and have more impact. Furthermore, a universal approach for stillbirth classification is fundamental for international comparisons to be meaningful and for progress towards the prevention of stillbirths.

Conclusions and unanswered questions

Stillbirths where no cause of death can be found continue to make a considerable contribution to perinatal mortality in high income countries. Much as stillbirth, and more so unexplained stillbirth, causes high levels of anxiety in future pregnancies for parents and birth attendants, it is a poorly studied complication of pregnancy. If parents are to be accurately informed about future risk, priority must be given to establishing the cause of fetal death.

We have shown that women who experience a stillbirth in their initial pregnancy have a higher risk of stillbirth in a subsequent pregnancy. Even after adjusting for potential confounding factors the increased risk remains. Risk of recurrent unexplained stillbirth is largely unstudied and therefore evidence about this remains controversial. We thank Melanie Bickerton for her guidance on the search strategy.

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Data sharing: No additional data available.

Transparency: The lead author (SB) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Appendix: Updated search strategies

Appendix: Studies excluded on basis of full text

Appendix: Details of sensitivity analyses

Appendix table 1: Number of potentially avoidable deaths in exposed population if babies had same risk as baseline group unadjusted analysis

Appendix tables 2 and 3: Quality assessment of included cohort and case-control studies