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Prediction of stillbirth: an umbrella review of evaluation of prognostic variables

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Running head: Umbrella review of predictors of stillbirth

ABSTRACT

Background: Stillbirth accounts for over 2 million deaths a year worldwide, and rates remains stubbornly high. Multivariable prediction models may be key to individualised monitoring, intervention or early birth in pregnancy to prevent stillbirth.

Objectives: To collate and evaluate systematic reviews of factors associated with stillbirth in order to identify variables relevant to prediction model development.

Search strategy: Medline, Embase, DARE and Cochrane Library databases and reference lists were searched up to November 2019.

Selection criteria: We included systematic reviews of association of individual variables with stillbirth without language restriction.

Data collection and analysis: Abstract screening and data extraction were conducted in duplicate. Methodological quality was assessed using AMSTAR and QUIPS criteria. The evidence supporting association with each variable was graded.

Results: The search identified 1198 citations. 69 systematic reviews reporting 64 variables were included. The most frequently reported were maternal age (n=5), BMI (n=6) and maternal diabetes (n=5). Uterine artery Doppler appeared to have the best performance of any single test for stillbirth. The strongest evidence of association was for nulliparity and pre-existing hypertension.

Conclusion: We have identified variables relevant to the development of prediction models for stillbirth. Age, parity and prior adverse pregnancy outcomes had a more convincing association than the best performing tests which were PAPP-A, PIGF and

UtAD. The evidence was limited by high heterogeneity and lack of data on intervention bias.

Tweetable abstract: Review shows key predictors for use in developing models predicting stillbirth include age, prior pregnancy outcome and PAPP-A, PLGF and Uterine artery Doppler.

INTRODUCTION

Stillbirth accounts for more global deaths than HIV/AIDS or cancer; [1] although recent years have seen a steady fall in maternal and neonatal mortality, global incidence of stillbirth remains stubbornly high. The majority of the burden occurs in low and middle income settings, but stillbirth reduction is an urgent priority worldwide. The UK incidence of stillbirth fell by a fifth between 1993 and 2015, [2] but remains one of the highest in Europe.[3]

On a global scale, stillbirth prevention includes addressing population level issues including malaria and syphilis treatment and optimising nutrition.[4] In the UK, attention is focused on antenatal identification of high risk pregnancies.[5] Consultation with patients and stakeholders has established that developing new antenatal testing strategies to prevent stillbirth is a key research priority.[6]

Current national guidelines recommend identifying women with any known risk factors for stillbirth as high risk. [7] In most cases, there has been no formal evaluation of these risk factors as clinical tests or consideration that other factors present may modify the risk of stillbirth.

The most important cause of stillbirth is placental dysfunction, but maternal and fetal co-morbidities and environmental and genetic factors also play a significant role.[8] Given this heterogeneity, prediction by single variables is unlikely to be clinically useful.[9] Instead, multivariable prediction models are likely to yield clinically relevant results. [9] Selection of variables for the development of prediction models is often limited by variables commonly available in large datasets[10,11] but optimal model development would take into account all available evidence, including promising new candidate variables.[12]

In order to prioritise variables for inclusion in any model for the prediction of stillbirth we must first critically appraise the available evidence. We undertook an umbrella review to collate and evaluate systematic reviews of risk factors for stillbirth with the aim of

identifying variables that could be relevant to the development of a clinical prediction model for stillbirth.

METHODS

The systematic review was registered with PROSPERO (Registration number: CRD42017074061)(13–15) and reported according to the PRISMA guidelines.[16] Patients were not directly involved in the design of this review.

Literature search

We searched Medline, EMBASE and the Cochrane Library from inception to November 2019 using combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "stillbirth", "stillborn", "meta-analysis" and "review" without language restrictions. (Appendix S1) Reference lists of relevant articles were hand-searched for additional relevant papers.

Study selection and data extraction

Two reviewers (RT and FGS) reviewed all abstracts independently. Any discrepancies were resolved by consensus. We obtained full texts of reviews that met the inclusion criteria. We included reviews that assessed the predictive accuracy or association of single variables with stillbirth. (Table 1, Table S1a) The steering group (AK, ST, RT and FGS) reviewed the list of variables identified at the full text review stage and excluded those deemed by consensus to be unlikely to contribute to a useful clinical prediction model, including rare co-morbidities and environmental exposures. (Table S1b) We excluded reviews evaluating the association of therapeutic drugs with stillbirth. We excluded genetic association studies, but included common thrombophilia mutations as these may be identified during routine care. Variables exclusively related to stillbirth in LMIC settings (eg malaria) were excluded, but reviews from LMIC settings were included where the variables were generalisable. The contributory factors[17] and available variables in LMIC are so different as to mandate a separate approach to prediction of stillbirth.[18,19]

The variables identified were classified as clinical characteristics, biochemical or ultrasound variables. We included reviews of observational and prediction studies evaluating tests in the first, second and third trimester. We accepted and noted the authors' definition of stillbirth. There is no published core outcome set for stillbirth studies and significant variation in outcome reporting was anticipated.

We defined a review as systematic if they included an explicit method for searching the literature, searched >2 databases, and provided clear inclusion and exclusion criteria. Case reports, primary studies, narrative reviews and poster abstracts were excluded. Two reviewers (RT, FGS) independently extracted relevant data. We obtained data on publication year, study funding, databases searched, studies included, number of pregnancies/women and number of stillbirths, definition of stillbirth, inclusion/exclusion criteria, variables evaluated, timing of testing and degree of association.

Quality assessment

Two reviewers (RT, FGS) assessed the methodological quality of the included reviews using the AMSTAR tool (Appendix S2). [20] The tool evaluates whether the reviewers incorporated the following: a prospectively designed study with a clear research question, a comprehensive literature search, relied on the status of publication as an inclusion criterion, duplicated study selection and data extraction, gave details of both included and excluded studies, assessed and documented the risk of bias of the included studies, included information on the funding of primary studies, used appropriate statistical methods to combine the findings of studies and considered the impact of the risk of bias and study heterogeneity in primary studies on the analysis and results, assessed the likelihood of publication bias and reported any conflict of interest.

Because the outcome of interest was the prognostic value of the variables considered, we additionally considered whether the risk of bias in the included studies in each of the key domains identified by the Quality In Prognosis Studies tool (QUIPS) had been assessed. (Appendix S3) The six domains are study participation, attrition, measurement of the predictive variable and the outcome, adjustment for confounders and the quality of analysis and reporting.

Systematic grading of the evidence of association

The purpose of an umbrella review is to provide a broad overview of the field and to assess the strength of the evidence supporting an association or effect.[21] For each variable we identified the meta-analysis with the most component studies reporting sufficient data for comparison. We considered the sample size to be the number of events, not the number of patients. Evidence of association was considered highly convincing with >1000 events, highly statistically significant summary associations ($p<10^{-6}$) with no large heterogeneity ($I^2<50\%$) and no concern about small study effects. Where the sample size was >1000 and $p<10^{-6}$ but there were concerns about heterogeneity or small study effects the grading was reduced to highly suggestive. When the p-value was <0.001 the evidence was graded as suggestive, while meta-analysis supported by <1000 cases but with a p-value <0.05 were considered weak evidence of association. Where the p-value was not reported in the original meta-analysis this was calculated.[22] In some very large studies the number of events was not reported. Assuming a conservative prevalence of stillbirth of 0.5%, we included studies with an overall sample size >200000 as likely to have sufficient events. All calculations were performed in Excel.

RESULTS

The literature search identified 1198 citations. After screening abstracts, 266 full text papers were retrieved for review, of which 197 were excluded. (Figure 1, Table S1a) Sixty-nine systematic reviews were included. [3,9,17,23–88]

Quality assessment using AMSTAR

The methodological quality of the included systematic reviews was assessed using the AMSTAR checklist (Figure 2, Appendix S2). The mean score was 7.4/11 and 76.8% (53/69) of the included studies had an AMSTAR score greater than or equal to 7. Fifty-eight studies (84.0%) declared conflicts of interest. Nineteen studies (27.5%) did not specify funding sources and 13 (18.8%) reported no study funding.

Quality assessment using QUality In Prognosis Studies (QUIPS)

We assessed the risk of bias relating specifically to domains important in prognostic research. (Figure 2) Although most included studies suggested that their findings were relevant to stillbirth prediction, none reported fully on the risk of bias in all QUIPS domains. Most studies (54/69, 78.2%) considered the definition and representativeness of the participants in the primary studies and the adequacy of definition and assessment of exposure (57/69, 82.6%) and outcome (55/69, 79.7%). Only 44/69 (63.7%) noted adjustment for potential confounders or the lack of it in the included studies and just 15/69 (21.7%) considered the impact of loss to follow up on the apparent performance of the predictive variables.

Characteristics of the included studies

The included reviews considered 64 individual variables. (Table 1) The characteristics of the included studies are summarised in Table S2 and Figure 3. The majority of included reviews reported on maternal characteristics such as maternal age, parity, body mass index (BMI), smoking, caffeine and alcohol intake. Medical co-morbidities and past pregnancy outcomes were additionally classified as maternal characteristics. Ultrasound markers reviewed included UtAD, cerebroplacental ratio (CPR), nuchal translucency (NT), echogenic bowel, fetal sex and fetal growth. Biochemical parameters investigated included thrombophilia associated markers (including anticardiolipin antibodies (ACA), lupus anticoagulant (LA) and homocysteine), markers of fetoplacental unit function (human chorionic gonadotrophin (hCG), alpha feto protein (AFP), pregnancy associated plasma protein-A (PAPP-A)) and others including thyroid stimulating hormone (TSH), soluble fms-like tyrosine kinase-1 (sFlt-1), serum uric acid, vitamin D, proteinuria and cell free fetal DNA (cffDNA).

Outcome reporting

The majority of included reviews (n=34) summarised their findings with odds ratios (OR) (Figure 4a) or via narrative synthesis (n=16), while others reported relative risk (RR, n=10) (Figure 4c), likelihood ratios (LR, n=4) (Figure 4b) or sensitivity and specificity (n=3). Other estimates of association included effect size, population attributable risk and

crude incidence. There was also significant variation in outcome reporting both in the reviews and the primary studies. Reported definitions of stillbirth varied in gestational cut offs (range 10-28 weeks) and in the pathology of stillbirth - several excluded congenital anomalies or 'explained' stillbirths.

Maternal characteristics

The majority of identified reviews and the strongest identified evidence related to maternal characteristics. The most frequently reported were maternal age (particularly age >35 years, n=5), BMI or other measures of obesity (n=6) and maternal diabetes (n=5). The association of BMI with stillbirth was supported by highly convincing evidence, and maternal age by highly suggestive evidence. (Table 2) Of the maternal medical conditions reported on, the greatest degree of association was reported with sickle cell disease (1 review, RR 3.99, 95% CI 2.63-6.04), and the supporting evidence was rated as highly suggestive. The value of this variable in a prediction model would relate to the local incidence of sickle cell in the population of intended use. Prior pregnancy history was also strongly associated with stillbirth; a prior stillbirth (2 reviews, OR of 4.83, 95% CI 3.77-6.18),[48] a prior preterm birth (1 review, OR 2.98, 95% CI 2.05-4.34) and a prior birth of a small-for-gestational-age (SGA) baby before 34 weeks (1 review, OR 6.00, 95% CI 3.43-10.49)[49] all supported by highly suggestive or suggestive evidence.

Socioeconomic factors ranging from social deprivation to immigration status and education were associated with stillbirth, chiefly supported by lower quality evidence. Ethnicity was considered in two reviews: in one indigenous or aboriginal status was evaluated[59] and in one stillbirth risk was compared between White, Black and Asian populations.[23] In both cases, non-white women had a higher risk of stillbirth. The degree of association was comparable to maternal age, BMI and prior birth of an SGA baby and supported by highly suggestive evidence.

Maternal smoking was consistently associated with risk of stillbirth. Two studies demonstrated a plausible biological gradient of increasing risk with increasing exposure.[63,64] Caffeine and alcohol use were not consistently associated with stillbirth.

Ultrasound markers

CPR, assessed in three reviews, appeared to have the best performance of any single variable; sensitivity was reported for perinatal death (stillbirth and neonatal death) as 93% (95% CI 71-99%) and specificity 74% (95% CI 60-84%).[74] For stillbirth specifically, the OR was 3.99 (95% CI 1.81-8.8). [73] Second trimester UtAD had a pooled sensitivity of 65% (95%CI 38-85%) and specificity 82% (95% CI 72-88%) for stillbirth, with OR 8.3 (95% CI 3.0-22.4).[71] Similarly, suboptimal fetal growth had a sensitivity of 32% (95% CI 31-34) and specificity 75% (95%CI 75-75%) for stillbirth.[9] Other markers associated with stillbirth included NT, echogenic bowel and male sex.[9] Reviews of ultrasound measures including CPR, UtAD and MCA were limited by variation in the definition of an abnormal result and by small sample sizes. The association was consistent, but the supporting evidence is still weak at best.

Biochemical markers

Key biochemical tests include AFP (two reviews) [AFP>2.0 MoM; Sens 11% (95% CI 9–13%) Spec: 96% (95% CI 96–96%))[9] and PAPP-A (two reviews) [PAPP-A <0.4 MoM; Sens. 15% (95% CI 8-26%) Spec 95% (95%CI 95-96)).[9] Human chorionic gonadotrophin (hCG) (two reviews) had sensitivity of 4% (95% CI 1-14%) and specificity 94% (95% CI 93-94%) in one review, [9] but the other found that hCG added little value to AFP in combination.[84] Placental growth factor (PlGF) is associated with placental function and was reported with a large degree of association, with a diagnostic OR of 49.2 (95% CI 12.7-191) in two reviews.[78,82]

Several thrombophilia markers showed a strong association with stillbirth including LA (two studies, OR 4.3-54.18) (77,89) and ACA (two studies, OR 4.29-15.17).(77) The Factor V Leiden mutation, protein S deficiency and activated protein C resistance (APCR) were all also strongly associated with stillbirth with OR 6.11 (95% CI 2.8-13.2), 16.2 (95% CI 5.1-52.3) and 5.0 (95% CI 2.0-12.4), respectively.[77]

All of these studies were limited by high levels of heterogeneity and small sample sizes.

Grading of evidence

Three variables were supported by highly convincing evidence – nulliparity, pre-existing hypertension and increased maternal BMI. (Table 2) A further seven variables were supported by highly suggestive evidence: maternal age, fetal sex, a history of SGA, ethnicity, sickle cell disease, cigarette smoking and aboriginal or indigenous status. Notably, the strongest evidence available was for elements of maternal medical history and simple physical examination. All biomarker and ultrasound variables were supported by weak evidence at best, (Tables S3 and S4) although the limited evidence available did support significant associations, particularly for PLGF, CPR and uterine artery Doppler.

DISCUSSION

Main findings

This review has identified 69 systematic reviews examining 64 variables potentially associated with stillbirth. No marker had useful screening performance, but several were consistently and strongly associated with stillbirth. Importantly, isolated factors from the obstetric history and examination including age, BMI and prior adverse pregnancy outcomes were better supported by the available evidence than even the most strongly associated tests which were PAPP-A, PlGF, CPR and second trimester UtAD.

Strengths and limitations

Strengths of this review include the comprehensive search and critical evaluation in synthesising a massive quantity of literature. The study was limited by the quality of included reviews, notably in relation to factors important to prediction.

There was substantial missing information relating to measurement of exposures and outcomes and significant variation in outcome reporting was noted. There was variation in the quantities used to assess association – most commonly OR or RR, limiting direct comparisons and lacking information on sensitivity. The variation in the outcomes reported limited comparisons between studies. Abou Nasser et al reported significant associations between anti-phospholipid antibodies and stillbirth,[89] but used the outcome of fetal loss >10 WGA excluding congenital anomaly which may have led to over estimation of the association. In sub-group analysis, the association with fetal loss >20 WGA was less convincing. Similarly, CPR and UtAD performed well as single tests but in

two reviews of CPR sensitivity for perinatal death was reported without the corresponding sensitivity for stillbirth alone,[74,85] limiting direct comparison with UtAD.

The competing risks of stillbirth or livebirth may negatively affect observed predictive accuracy of tests, but were not considered in included reviews. Where a high risk of stillbirth is identified but birth occurs before stillbirth, the case will seem to be a false positive. This is particularly significant for 'late' stillbirths, since it is increasingly likely that birth will supervene and consistent with the observation that tests for predicting early stillbirth are more accurate than those predicting later stillbirth. [9]

Arguably, early birth is most likely to occur in those at highest risk because clinicians act on risk factors for stillbirth. Only three reviews considered this risk of bias and of these, the risk was low in the reviews assessing biochemical markers[84] and Doppler [71] but increased in the review including clinical characteristics.[9]

The strength of evidence is related to the sample size for assessment and when considering a rare event like stillbirth, large sample sizes are required to convincingly support a statistical association. In the case of novel biomarkers or ultrasound testing outwith routine care, the costs of assembling such large samples are restrictive. As work continues on evaluation of promising tests, the future may see better evidence supporting variables such as PLGF, CPR and PAPP-A.

Interpretation
Previous reviews of individual predictors of stillbirth have concluded that multivariable models are likely to be required for meaningful clinical impact.[3,9] In this review we have systematically evaluated factors associated with stillbirth in order to identify variables most relevant to the development of such models. It would not be appropriate to suggest that the strength of association between a single variable and stillbirth would necessarily predict the value of that variable as a predictor in a model. This information is simply presented to inform model developers identifying candidate predictors for model development and should be considered in the light of the intended population and clinical application.

Although clinical characteristics were the variables most convincingly associated with stillbirth in this review, only 19% of stillbirths are associated with established clinical risk factors,[90] and triage based on these alone has a poor PPV. [19] The three variables most consistently associated with stillbirth (nulliparity, pre-existing hypertension and increased maternal BMI) clearly relate to maternal and placental vascular function and are included in national guidelines as recognised risk factors for placental dysfunction,[5] as are maternal age, previous SGA and cigarette smoking. Three promising prognostic tests include PLGF, UtAD and CPR, all of which also primarily relate to placental dysfunction.

A recent systematic review of prediction models in obstetrics found three models for stillbirth.[91] These models included UtAD and ethnicity with history of prior pregnancy loss in one and with BMI in the second, all variables identified as important predictors in this review. [92] Further models have subsequently been developed [18,93,94] but none yet externally validated. Although increasing interest in individualising care has led to increasing numbers of models, transfer to clinical practice has been hampered by a lack of subsequent external validation and clinical evaluation.[95]

Socioeconomic deprivation was consistently associated with stillbirth in both high and low income settings but is measured and defined heterogeneously, limiting the utility of this variable. Similarly, the association of ethnicity with adverse pregnancy outcomes is supported by strong statistical evidence, but problematic as a predictive variable. Self-reported ethnicity varies from clinician perceived ethnicity and rapidly loses specificity in diverse populations with high proportions of 'mixed' ethnicities.[96] Although the observed association is potentially related to biological factors (length of pregnancy and cardiovascular parameters differ with ethnicity and are plausibly associated with stillbirth), it is undoubtedly confounded by factors like higher multiparity in selected groups, structural racism and systemic inequality in access to healthcare. In the light of the consistent findings of the MBRRACE reports that perinatal mortality disproportionately affects Afro-Caribbean babies in the UK, addressing ethnicity based inequity in healthcare is of prime importance, but ethnicity or socioeconomic status as a predictive variable may limit any model developed to only that population in which it is developed.

Nonetheless, these findings reinforce the importance of addressing social inequality as a core strategy for the prevention of stillbirth in any setting.

Conclusion

Clinical and research implications

Informal screening to identify high risk pregnancies is embedded in practice and urgently needs to be improved. Development of robust models remains a challenge because of the rarity of stillbirth as an outcome. The heterogeneous causes of stillbirth may be best addressed by separate models; logically, the initial target should be placental dysfunction, representing the largest and most clearly defined factor contributing to stillbirth. Separate models by gestation could also allow continuous risk assessment through pregnancy, taking into account recently available patient data.

Model development requires a large volume of data with detailed information on a number of candidate predictors and can be optimised by maximising available data and minimising candidate predictors in order to arrive at the best achievable effective sample size.(97) In this review we have identified several key candidate variables which should be considered in model development; maternal age, BMI, parity, essential hypertension, diabetes, history of previous stillbirth, cigarette smoking, uterine artery Doppler, PAPP-A and PlGF.

A large-scale, collaborative approach utilising individual participant data (IPD) meta-analysis offers an innovative approach to addressing the problems of stillbirth prediction. IPD meta-analysis allows the use of all original data and continuous variables with the flexibility to standardise variable and outcome definitions, their combinations and comparisons across datasets.(98) Existing models could be validated and tested against new models,(99) offering the opportunity to build consensus around development and validation of methodologically robust models.

In this era of increasingly personalised medicine, women want individualised recommendations for care and expect clinicians to make the most effective use of available tests. The global loss of millions of lives to stillbirth every year is too significant

a tragedy to waste time generating excessive clinically irrelevant prediction models; the time has come to initiate a collaborative approach in order to definitively answer the question of how to predict, and ultimately prevent, stillbirth.

Contribution to authorship

RT planned and carried out the search, data extraction and analysis and drafted the manuscript. FGS carried out abstract screening, data extraction and reviewed and edited the manuscript. JA contributed to data analysis and reviewed and edited the manuscript. JD, AH, LJ, BK, LM, BWM, JS, GS, BT and PVD all contributed to the design of the study and reviewed and edited the manuscript. ST and AK conceived of and directed the design of the study, chaired the steering group and reviewed and edited the manuscript.

Details of ethics approval

No ethics approval was required for this systematic review in keeping with the National Research Ethics Service assessment.

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Figure and Table Legends

Figure 1. PRISMA flow chart

Figure 2a. Methodological quality of included reviews

Figure 2b. Risk of bias relating to QUIPS domains

Figure 3. Summary of characteristics of included studies

Figure 4. Association of single variables with stillbirth in studies reporting

    a) **Odds ratios**

    b) **Likelihood ratios**

    c) **Risk ratios**

Table 1: List of variables included in this review

Table 2: Variables supported by highly convincing or suggestive evidence

Online Supporting Material

Table S1a: Excluded as did not meet inclusion criteria

Table S1b: Excluded by consensus as not relevant to the development of prediction models

Table S2: Characteristics of included studies

Table S3: Variables supported by weak evidence

Table S4: Variables with no evidence of association

Appendix S1: Literature search strategy

Appendix S2. AMSTAR checklist

Appendix S3. QUIPS checklist

Table 1. **Prognostic variables for stillbirth investigated in the included systematic reviews**.

Parental characteristics and history
Maternal and paternal age
Parity
Body mass index
Pre-existing medical conditions (epilepsy, vitamin D deficiency, hypertension, asthma, chronic kidney disease, sickle cell disease, bipolar disorder, Sjogren's syndrome, psychotic illness, diabetes, sleep disordered breathing, endometriosis,)
Obstetric history (previous Caesarean section, vaginal bleeding in pregnancy, antenatal care attendance, abruption, previous stillbirth, preterm birth, SGA, IVF)
Obstetric cholestasis
Cigarette smoking, smokeless tobacco and second hand smoking exposure
Caffeine and alcohol intake
Aboriginal status
Ethnicity
Perceived reduced fetal movements

Ultrasound markers
Uterine artery Doppler (UtAD)
Cerebroplacental ratio (CPR)
Middle cerebral artery (MCA)
Fetal nuchal translucency (NT)
Any suboptimal fetal growth
Fetal echogenic bowel
Male fetus

Biochemical markers
Prothrombotic markers
Factor V Leiden gene mutation
Anticardiolipin Antibodies (ACA)
Lupus anticoagulant (LA)
AB2G1
Protein S deficiency
Activated Protein C Resistance
Prothrombin G20210A mutation
MTHFR C677T mutation
Protein C deficiency
Markers of fetoplacental unit endocrine dysfunction
Human chorionic gonadotrophin (HCG)
Human placental lactogen (hPL)
Alpha-Fetoprotein (AFP)
Pregnancy-associated plasma protein A (PAPP-A)
Estriol
PLGF
Other markers
Thyroid stimulating hormone (TSH)
Haemoglobin <10
Serum uric acid
Vitamin D
Proteinuria
Bile acids

Combination of markers
Combinations of first trimester biomarkers
(AFP+hCG) (PAPP-A+hCG) (AFP+hCG+uE) (AFP+uE) (hCG+uE)

Table 2. Assessment of the evidence supporting the association of individual variables with stillbirth and perinatal mortality – highly convincing, highly suggestive and suggestive evidence.

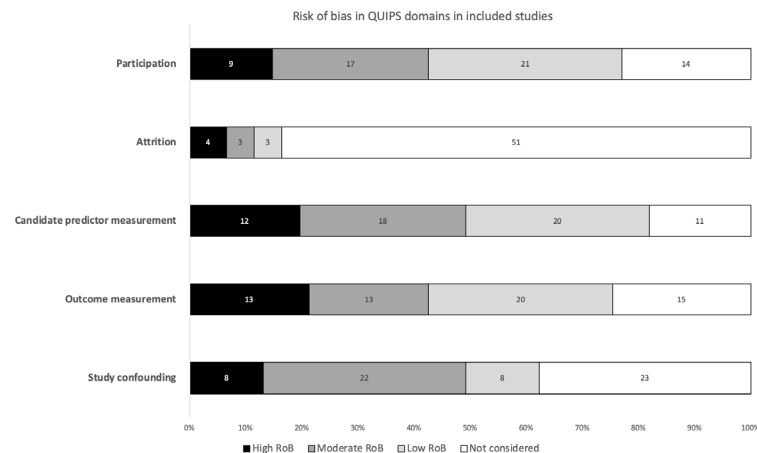| Reference	Variable	Level of comparison	Sample size (cases)	Sample size (events)	Heterogeneity	Small study effect	Effect size measure	Random effects summary effect size	Significance threshold
Highly convincing evidence (>1000 events, <50% heterogeneity, no evidence small study effect, p<0.000001)									
Flenady 2011	Parity	Nulliparity v Multiparity	24977570	74457	0.00%	None	ES	1.42 (1.33-1.51)	<0.000001*
Flenady 2011	Pre-existing hypertension	Affected v unaffected	23002442	66240	45.30%	None	ES	2.58 (2.13-3.13)	<0.000001*
Liu 2016	BMI	>30 v <25	1392799	NR	38.40%	None	OR	1.81 (1.69-1.93)	<0.000001*
Highly suggestive evidence (>1000 cases, p<0.000001)									
Lean 2017	Advanced	>35 v <35 years old	44723207	185384	95.60%	None	OR	1.75 (1.62-1.89)	<0.000001*
Mondal 2014	Fetal sex	Male v female	30840461	183742	71.90%	None	RR	1.1 (1.07-1.13)	<0.000001*
Malacova 2018	Previous SGA	Affected v unaffected	1602682	6782	72.40%	None	OR	1.85 (1.42-2.4)	<0.000001*
Muglu 2019	Ethnicity	Black v White at 37	3081859	1053	(I² 0.13)	None	OR	1.9 (1.66-2.17)	<0.000001*
Oteng-Ntim 2015	Sickle cell disease	Affected v unaffected	26212461	NR	(I² 0.050)	NR	RR	3.99 (2.63-6.04)	<0.000001*
Pineles 2016	Smoking	Any v none	23442770	NR	67%	Present	RR	1.46 (1.38-1.54)	<0.000001*
Shah 2011	Aboriginal women	Aboriginal v non-Aboriginal	5552134	NR	High	Present	OR	1.68 (1.49-1.89)	<0.000001*
Suggestive evidence (>1000 cases, p<0.001)									
Malacova 2018	Previous preterm SGA	Affected v unaffected	1309183	5250	88%	None	OR	3.15 (1.89-5.25)	0.00001*
Keag 2018	Previous CS	Affected v unaffected	703562	2401	34%	None	OR	1.27 (1.15-1.4)	<0.00001
Yu 2017	Diabetes	Pre-gestational v none	24906160	NR	48%	None	OR	3.52 (3.19-3.88)	<0.00001
Oldereid 2018	Paternal age	<35 v >35	5319012	NR	74.70%	None	OR	1.19 (1.1-1.3)	<0.0001
Webb 2005	Psychotic illness	Affected v unaffected	1688137	6012	χ2=6.35, df=5, 0.27	Not assessed	OR	1.89 (1.36-2.62)	0.0002*
Lamont 2015	Previous stillbirth	Affected v unaffected	3412079	14283	82%	Present	OR	4.83 (3.77-6.18)	<0.001
Vos 2014	Social deprivation	Most deprived quintile v least deprived	1857057	NR	0%	NR	OR	1.33 (1.21-1.45)	<0.001

Figure 1. PRISMA flow chart
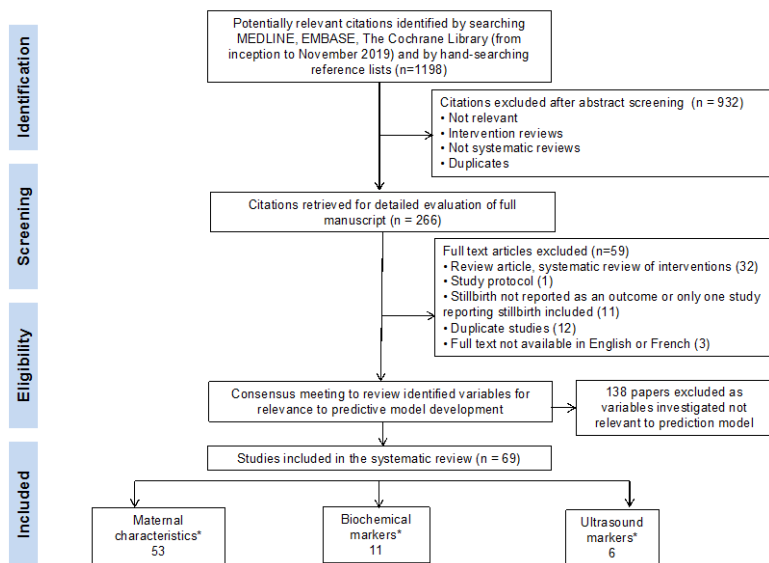
Figure 1 Flow chart illustrating identification of studies included in this systematic review. *some studies reported on markers in more than one category
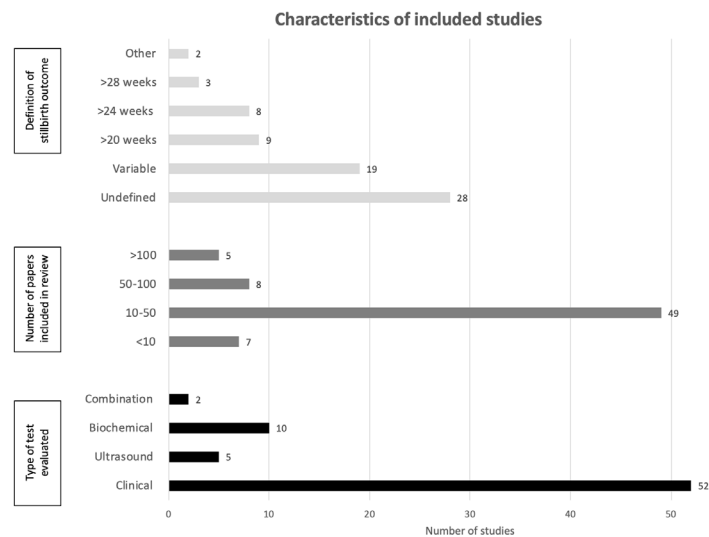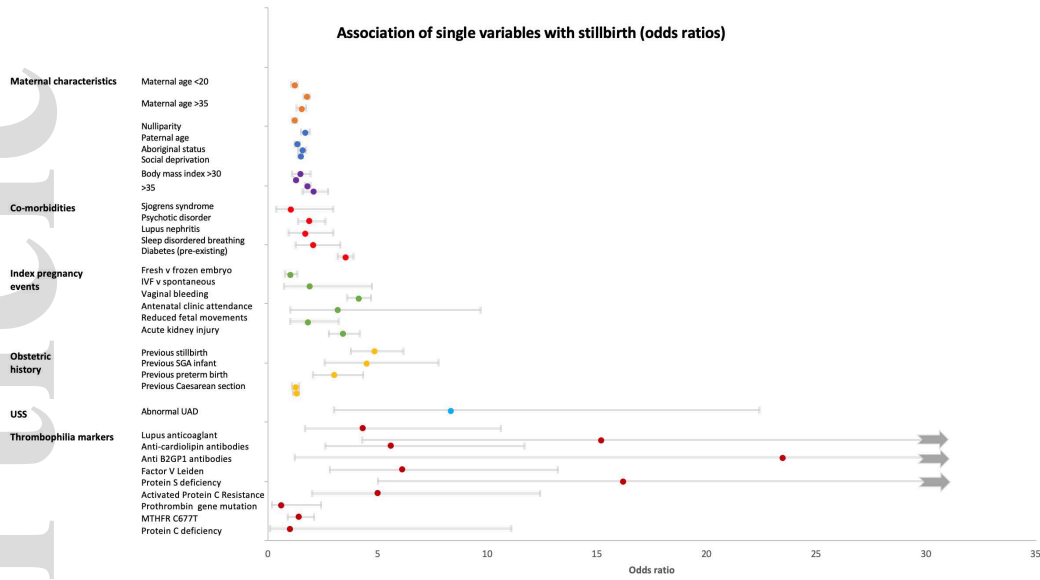
Figure 2a. Methodological quality of included reviews
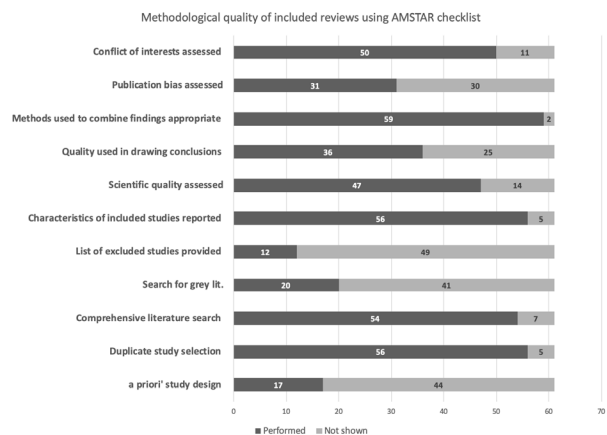
Figure 2b. Risk of bias relating to QUIPS domains in the included studies
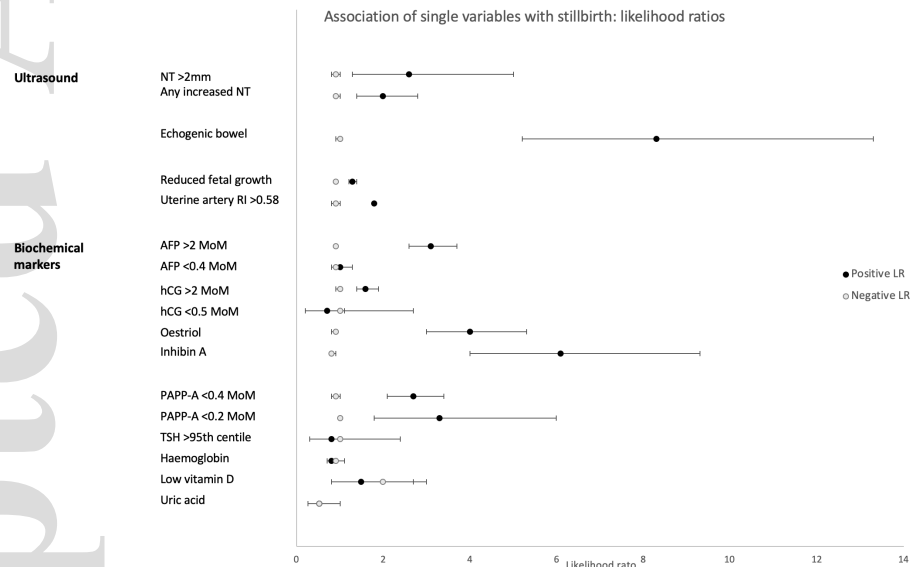

Figure 3. Summary of characteristics of included studies

Figure 4. Association of single variables with stillbirth in studies reporting a) odds ratios

b) likelihood ratios

c) risk ratio