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Prediction of pre-eclampsia: review of reviews

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ABSTRACT

Objective: Primary studies and systematic reviews provide varied accuracy estimates for prediction of pre-eclampsia. We undertook a review of published systematic ~~an umbrella~~ reviews to collate published evidence on the ability of available tests to predict pre-eclampsia, to identify high value avenues for future research and to minimise future research waste in this field.

Methods: We searched Medline, Embase, DARE (Database of Abstracts of Reviews of Effectiveness) and Cochrane Library databases (from database inception to March 2017) and bibliographies for systematic reviews and meta-analyses without language restrictions. We assessed the quality of the included reviews using the AMSTAR tool and a modified QUIPS tool. We evaluated the reviews' comprehensiveness of search, size, tests and outcomes evaluated, data synthesis methods and ~~accuracy~~ predictive ability estimates and risk of bias related to population studied, measurement of predictors and outcomes, study attrition and adjustment for confounding.

Results: From 2444 citations, we included 126~~32~~ reviews, reporting on over 90 predictors and 52 prediction models. ~~More than half~~Around a third of all reviews (29.3~~53.8~~%, 37/126~~71/132~~) investigated biochemical markers for predicting pre-eclampsia; 24.6% (31/126) investigated genetic associations with pre-eclampsia, 36.5~~7.8~~% (46/126~~50/132~~) reported on clinical characteristics; 3.2~~2.3~~% (4/126~~3/132~~) evaluated only ultrasound markers; and 4.8~~5~~% (6/126~~32~~) studied a combination of tests. Reviews included between ~~three~~ two and 26~~574~~

primary studies, including up to 25,356,688 women in the largest review. Only half (67/126~~71/132~~, 53.2~~8~~%) assessed the quality of the included studies. There was a high risk of bias in many of the included reviews, particularly in relation to population representativeness and study attrition. Over 80% (106~~9~~/126~~32~~, 84.1~~2.6~~%) summarised the findings with meta-analysis. Thirty-four studies (324/12~~3~~36~~2~~, 25.4~~7~~%) lacked a formal statement on funding. The predictors with the best test performance were body mass index (BMI>35 specificity 92%, 95% CI 89-95% and sensitivity 21%, 95% CI: 12-31%; BMI >25 specificity 73% , 95% CI: 64-83% and sensitivity 47% , 95%CI: 33-61%), first trimester uterine artery Doppler PI or RI >90th centile (specificity 93%, 95% CI: 90%-96%) and sensitivity 26% (23-31%)), PLGF (specificity 89% , 95% CI: 89-89% and sensitivity 65% , 95% CI: 63-67%~~AUC 0.85, SE 0.068~~) and PP13 (specificity 88% , 95% CI: 87-89% and sensitivity 37% , 95% CI: 33-41%~~AUC 0.88, SE0.0450~~). No single marker had a test performance suitable for routine clinical use. The models combining markers showed promise, but none of the identified models had undergone external validation.

Conclusion: Our review of reviews has questioned the need for further aggregate meta-analysis in this area, given the large number of published reviews subject to the common limitations of primary predictive studies. Prospective, well-designed studies of predictive markers, preferably in randomised intervention studies, and combined through IPD (individual patient data) meta-analysis are needed to develop and validate new prediction models

84 to facilitate the prediction of pre-eclampsia and minimise further research waste
85 in this field.
86

INTRODUCTION

Pre-eclampsia remains a major contributor to maternal and perinatal mortality and morbidity. [1,2] Early treatment with aspirin reduces the risk of pre-eclampsia;[3,4] so accurate screening tests for pre-eclampsia are a clinical priority. Currently, clinical assessment of the risk of pre-eclampsia is based mainly on maternal history[5] with limited predictive ~~accuracy~~ability, [6–8], and is not applicable to nulliparous women. Numerous primary studies have evaluated the ~~accuracy~~ predictive ability of various tests including clinical characteristics, biomarkers, and ultrasound markers, individually or in combination, for predicting early, late, and any onset pre-eclampsia.

Systematic reviews collate evidence and aim to provide meaningful summary estimates of the ~~accuracy~~ predictive ability of tests through meta-analysis. Despite the number of published studies of predictive factors and screening tests for pre-eclampsia, no consensus has been reached; neither clinicians nor national or international guidelines have implemented screening tests in routine clinical practice. This could be because no tests have been identified with adequate performance, but can also be attributed to the variable quality of the reviews. Very few validate existing prediction models [9] or report on test ~~accuracy~~ performance in various combinations, for different thresholds and outcomes.

There is a need to map and critically appraise the available evidence in this field to minimise research waste and prioritise robust investigation of high yield

predictive factors and models. We undertook a review of systematic ~~n umbrella~~ reviews to systematically collate and critically evaluate the published systematic reviews on risk factors identified as predictors for pre-eclampsia and the reported ~~accuracy~~ ability of ~~predictive~~ individual tests ~~in~~ to predict~~ting~~ pre-eclampsia.

METHODS

Our review of reviews was based on a prospective protocol according to current recommendations [10–12] and reported as per the PRISMA guidelines[13]. The study was registered with the PROSPERO database (CRD42015020386, http://www.crd.york.ac.uk/PROSPERO).

Literature search

We searched Medline, Embase and the Cochrane Library including The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), The Cochrane Central Register of Controlled Trials (CENTRAL), Health Technology Assessment Database (HTA) and NHS Economic Evaluation Database (NHS-EED) from inception to March 2017. We used combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "pre-eclampsia", "gestational hypertension", "pregnancy-induced hypertension" and "review" (Supplementary Material ~~1~~). No language restrictions were imposed. Reference lists of relevant articles and reviews were hand searched to identify additional papers.

Study selection and data extraction

Two reviewers (RT, AK) reviewed all abstracts independently. Any discrepancies on the potential relevance of the papers were resolved by consensus. We obtained full text copies of reviews that met the inclusion criteria.

We included reviews that assessed clinical characteristics, biochemical or ultrasound based variables as predictors or predictive tests for pre-eclampsia. We included reviews evaluating predictors in the first, second or third trimester. Case reports, case series, individual observational or randomised studies, narrative reviews, rapid reviews, editorials and poster abstracts were excluded. Two reviewers (RT, AK) independently extracted relevant data. We obtained data on year of publication, number of databases searched, number of studies included, number of pregnancies/women included, screening tests evaluated and the performance of the tests or degree of association reported with the predictors evaluated.

Definitions

We accepted the authors' definition of pre-eclampsia and hypertensive disorders, and further collected data where it was reported discriminating between early onset pre-eclampsia (requiring delivery prior to 34 weeks' gestation), late onset (delivery after 34 weeks' gestation) or delivery at any time.

Clinical characteristics included signs, symptoms, past medical and obstetric history and environmental exposures elicited through maternal history or physical examination by the booking clinician at the first antenatal visit. Biochemical tests included any measurement of molecules in biological fluids (eg serum and urine). Ultrasound tests included any characteristic identified on ultrasound examination of the pregnancy at any gestation.

We defined a predictor as a clinical characteristic, biochemical or ultrasound marker with the potential to predict the outcome of interest (pre-eclampsia). We defined a predictive model as a combination of predictors obtained through logistic regression analysis to discriminate between populations.

We defined a review as systematic if they included an explicit method for searching the literature, searched two or more databases, and if they provided well defined inclusion and exclusion criteria for studies.

Quality assessment of the included reviews

The rigour of the systematic review and risk of bias in the review findings were assessed using the AMSTAR tool and a modified approach to the QUIPS tool by two independent reviewers (RT, YP) [14–16] (Supplementary File 2). For the AMSTAR assessment we considered whether the reviewers undertook the following: 'a priori' study design, a comprehensive literature search, the status of publication (i.e. grey literature) used as an inclusion criterion, duplicate study selection and data extraction, provided details of the included and excluded studies, reported the characteristics of the included studies, assessed and documented the quality of the included studies, appropriately used the scientific quality of the studies in formulating conclusions, used appropriate methods to combine the findings of studies, assessed the likelihood of publication bias and reported any conflict of interest. We assessed the risk of bias reported in the included reviews according to the QUIPS domains that relate to the key methodological concerns of prognostic research. We considered whether the

reviewers had assessed the representativeness of the patient sample, the impact of study attrition, predictor and outcome measurement, important confounders and the quality of the statistical analysis in the primary studies. Where this information was reported we considered whether the authors had made an assessment of the degree of associated risk of bias. For the studies of genetic factors we applied the Venice criteria[17] to assess the epidemiological credibility of the association based on the amount of evidence, replication and protection from bias in each study.

RESULTS

Review identification

Of the 2444 citations identified, 12632 systematic reviews were included in our review. Figure 1 provides details of the review identification and selection process. A list of excluded studies is provided in Supplementary Table 1-3.

Quality Assessment using the AMSTAR tool

Figure 2a provides the findings of the quality assessment of the included reviews using the AMSTAR tool. Less than a quarter of the included reviews followed a prospectively specified protocol (24/126, 19.1%). Most of the reviews did perform a comprehensive literature search (120/126, 95.2%) with the majority of reviewers searching more than 2 databases. (Figure 2a) The majority of reviews undertook duplicate study selection (111/126, 88.1%), provided the characteristics of the included studies (109/126, 86.5%), and assessed the likelihood of publication bias (80/126, 63.5%). However, only a

quarter provided a list of the included and excluded studies (28/126, 22.2%). About half (71/126, 56.3%) of the reviews performed their literature search without language restriction. (Figure 2a)

Just over half assessed the quality of the included studies (67/126, 53.2%), and only a third took into account the quality of the studies in formulating their conclusions (38/126, 30.2%). The most commonly used tools for quality assessment were QUADAS (17/126, 13.5%) and the Newcastle-Ottawa Scale (NOS) (31/126, 24.6%) although neither are designed for predictive research. None of the reviews published since 2013 used the Quality In Prognosis Studies (QUIPS) tool described in that year that is designed for predictive factor study quality assessment.[16]

Although only half of the reviews assessed the quality of the included studies, many of the primary studies were potentially methodologically biased. They were often retrospective or case-control in design and subject to bias. Examples include significant heterogeneity; failure of masking of those managing the pregnancy or the outcome assessors; nested case-control studies including only a subset of pre-eclampsia cases of the original cohort and failure of application of the screening test to all the eligible participants in cohort studies. Furthermore, the included primary studies had numerous limitations including poor reporting of summary statistics, variable cut-offs of continuous variables, variation in outcomes assessed and the adjustment factors used to calculate test performance.[18]

Risk of bias in included reviews assessed using the modified QUIPS tool

Figure 2b shows the findings of the assessment of included studies against the modified QUIPS tool. Only one study reported on all domains. Of the included reviews, 80/126 (63.5%) reported on participants and representativeness of the population and 56/80 (70%) reported a high or moderate risk of bias in this area in the primary studies. Study attrition was considered in 31/126 (24.6%) with 20/31 (64.5%) reporting a high or moderate risk of bias. Measurement of predictors was evaluated in 101/126 (80.2%) reviews, with 63 (62.4%) describing a high or moderate risk of bias. Measurement of the outcome was well reported, considered in 109/126 (86.5%) of reviews, but 67/109 (61.4%) found a high risk of bias, most commonly related to heterogeneity or lack of clarity in the definition of the outcomes in primary studies. Confounding was considered in 84/126 (66.7%) and the review authors reported that 59/84 (70.2%) had a high or moderate risk of bias relating to insufficient or inappropriate adjustment for important covariables.

Characteristics of the included reviews

The included reviews reported on between 3 and 2657~~4~~ primary studies, with the majority including 10-50 primary studies and including up to 25,356,688 pregnancies in the largest review[19]. (Figure 3) ~~96~~ Seventy-nine predictors were evaluated in the included reviews (Table 1). The majority of reviews (53.9~~8~~%, ~~71/132~~68/126) investigated biochemical ~~markers~~ or genetic tests for predicting

pre-eclampsia while 36.57.8% (50/13246/126) related to clinical characteristics. Ultrasound markers were reported in only 3.22.3% (43/12632) and a combination of tests in 4.85% (6/12632) of reviews (Figure 32). We identified two previous ~~umbrella~~ broad systematic reviews of primary studies investigating all screening tests for pre-eclampsia [20,21] from 2004 and 2008.

The most commonly reported clinical characteristics included BMI (n=9 reviews), age (n=2), parity (n=2), blood pressure (n=5) and 6 reviews reported on several clinical characteristics. For the biochemical markers, the following were most commonly studied: PAPP-A (n=44), PlGF (n=5), sFlt-1 (n=3), PP13 (n=4). ~~, VEGF (n=4).~~ Over 30 additional markers were reviewed. The ultrasound tests included uterine artery dopplers (n=8) and placental vascularisation indices (n=1). Only two reviews [22,23] summarised the findings with an individual participant data (IPD) meta-analysis. The details of the included reviews (19–144) and key findings are shown in Table 2. Table 2a describes reviews of maternal characteristics, 2b relates to reviews of ultrasound markers, ~~and~~ 2c to reviews including biomarkers singly or in combination with other factors and 2d to the genetic association studies. ~~The key review findings are highlighted in table 2 (a: maternal characteristics, b: ultrasound markers and c: biochemical markers alone or in combinations) and tests that demonstrated a significant association (defined as AUC>0.8, OR/RR did not cross 1 or specificity >90%) are highlighted.~~

The majority (67/126~~71/132~~, 53.2~~8~~%) of the included reviews reported odds ratio as a single measure of predictor association with pre-eclampsia rather than directly reporting predictive ~~accuracy~~ ability of the predictors investigated. (Table 2). Only 31~~5~~/12632~~2~~ (24.6~~6~~%) studies reported measures of predictive ~~accuracy~~ability, with 19~~9~~ reporting sensitivities and specificities, 6~~7~~ area under the receiver operating curve (AUC) and 6~~9~~ likelihood ratios (LR).

Twenty-~~two~~ one studies declared no funding had been received, while 32~~4~~ studies lacked a formal statement regarding funding of the studies. Of the remaining studies, 14 (19.2~~7.9~~%) declared multiple funding sources. The majority of studies (51/73, 69.8~~5.4~~%) declaring their funding sources had been sponsored by national or regional governmental bodies (e.g. National Institute for Health Research (NIHR), National Institutes of Health (NIH), Canadian Institutes of Health Research (CIHR), Health technology Assessment (HTA), National Health and Medical Research Council (NHMRC)). ~~More than~~Nearly one quarter (21.9~~5.6~~%) were funded through academic institutions, 19.2~~7.9~~% by charitable bodies, 4.1~~3.8~~% received funding from industry and 9.5~~8.9~~% by international bodies, chiefly the World Health Organisation.

There was substantial variation in outcome reporting, including failure to report gestation at delivery and severity of pre-eclampsia. Despite the fact that there has been a transition from a severity-based to a temporal classification of pre-eclampsia [145], only three reviews reported early-onset pre-eclampsia, probably because the outcome was infrequently reported in primary studies (Figure 2).

Some studies combined pre-eclampsia with hypertensive disorders, which limited the comparisons between studies. Considerable heterogeneity was highlighted in many of the included reviews and precluded meta-analysis in 15.1~~7.4~~% (~~23/132~~19/126) reviews.

~~*Quality Assessment using the AMSTAR tool*~~

~~Figure 3 provides the findings of the quality assessment of the included reviews using the AMSTAR tool. Less than a quarter of the included reviews followed a prospectively specified protocol (25/132, 18.9%). Most of the reviews did perform a comprehensive literature search (125/132, 94.7%) with the majority of reviewers searching more than 2 databases (Figure 3). The majority of reviews undertook duplicate study removal (116/132, 87.9%), provided the characteristics of the included studies (115/132, 87.1%), and assessed the likelihood of publication bias (86/132, 65.1%). However, only a quarter provided a list of the included and excluded studies (29/132, 21.9%). About half (71/132, 53.7%) of the reviews performed their literature search without language restriction. (Figure 2)~~

~~Just over half assessed the quality of the included studies (71/132, 53.7%), and only a third took into account the quality of the studies in formulating their conclusions (40/132, 30.3%). The most commonly used tools for quality assessment were QUADAS (17/132, 12.9%) and the Newcastle-Ottawa Scale (NOS) (31/132, 23.5%) although neither are designed for predictive research. None of the reviews published since 2013 used the Quality In Prognosis~~

~~Studies (QUIPS) tool described in that year that is designed for predictive factor study quality assessment.(16)~~

~~Although only half of the reviews assessed the quality of the included studies, many of the primary studies were potentially methodologically biased. They were often retrospective or case-control in design and subject to bias. Examples include significant heterogeneity; failure of masking of those managing the pregnancy or the outcome assessors; nested case-control studies including only a subset of pre-eclampsia cases of the original cohort and failure of application of the screening test to all the eligible participants in cohort studies. Furthermore, the included primary studies had numerous limitations including poor reporting of summary statistics, variable cut-offs of continuous variables, variation in outcomes assessed and the adjustment factors used to calculate test performance.(150)~~

~~*Risk of bias in included reviews assessed using the modified QUIPS tool*~~

~~Figure 4 shows the findings of the assessment of included studies against the modified QUIPS tool. Only one study reported on all domains. Of the included reviews, 81/132 (61.3%) reported on participants and representativeness of the population and 56/81 (69.1%) reported a high or moderate risk of bias in this area in the primary studies. Study attrition was considered in 32/132 (24.2%) with 21/32 (65.6%) reporting a high or moderate risk of bias. Measurement of predictors was evaluated in102/132 (77.3%) reviews, with 64 (62.7%)~~

~~describing a high or moderate risk of bias. Measurement of the outcome was well reported, considered in 114/132 (86.4%) of reviews, but 71/114 (62.2%) found a high risk of bias, most commonly related to heterogeneity or lack of clarity in the definition of the outcomes in primary studies. Confounding was considered in 85/132 (64.4%) and the review authors reported that 60/85 (70.6%) had a high or moderate risk of bias relating to insufficient or inappropriate adjustment for important covariables.~~

Key individual predictors for pre-eclampsia

The included reviews reported on over 90 predictors for pre-eclampsia. The findings of the included reviews are summarised in Table 2. For each predictor we applied the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach to prognostic studies[146] to assess the quality of the evidence supporting the associations found. (Supplementary table 3~~4~~). The most robustly associated clinical, ultrasound and biochemical predictors included BMI, blood pressure, uterine artery Doppler findings and PLGF, sFlt-1 and AFP. (Supplementary Table 4~~5~~)

Clinical characteristics

Maternal BMI was analysed as a continuous, binary or categorical variable, and was consistently considered to be a weak predictor of pre-eclampsia with a number of studies demonstrating a biological gradient, with increasing BMI increasing the risk of pre-eclampsia [98, 106]. Increased maternal blood pressure

(BP), evaluated alone[19,132,136] or in combination with other predictors, [19, 61] in the first or second trimester, was also consistently associated with an increased risk of pre-eclampsia, but the measurement of blood pressure varied between studies.[16, 105, 108] In 2008 Cnossen et al compared the predictive ~~accuracy~~ ability of systolic and diastolic blood pressure (SBP and DBP) and mean arterial pressure (MAP) measured at booking and found that mean arterial pressure had a greater area under the curve (AUC 0.76, 95% CI 0.70-0.82) than either diastolic or systolic blood pressure for all pre-eclampsia.[132]~~.~~

Other clinical characteristics evaluated that demonstrated a consistent association were donor oocyte use in assisted reproduction, sleep disordered breathing, polycystic ovary syndrome, periodontal disease and maternal infections.

Ultrasound markers

First trimester uterine artery Doppler (UtAD) appears to have high specificity (92.1%, 95% CI: 88.6-94.6), but low sensitivity (47.8%, 95% CI: 39.0-56.8%) in predicting early onset pre-eclampsia.[25]~~.~~ The sensitivity of UtAD was even lower for predicting any pre-eclampsia at only 26.4% (95% CI: 22.5-30.8%)(25). One review evaluated placental vascularisation indices (PVIs) measured at 3D ultrasound and found that PVI measured in the first trimester were found to be predictive of later pre-eclampsia with the most sensitive measure being the vascular flow index (VFI).[144] The authors reported an AUC for the prediction of

early pre-eclampsia by the vascular flow index of 0.89 (95% CI: 0.78-1.00) and for any pre-eclampsia of 0.77 (95% CI: 0.69-0.84). [144]

Biochemical markers

The biochemical screening markers were grouped according to their mechanism of action (Table 2). Of markers associated with angiogenesis, both PlGF and sFlt-1 were consistently associated with the risk of pre-eclampsia, with an odds ratio of 9.0 (95% CI 5.6–14.5) for PlGF tested before 30 weeks in one large study[49] and although another reported no significant association between first trimester PlGF and all pre-eclampsia OR 1.94 (95% CI 0.81 to 4.67) there was an association between first trimester PlGF and early onset PE (OR 3.41 ((95% CI 1.61-7.24). [96] For sFlt-1 odds ratios from 1.3 (95% CI 1.02-1.65) to 6.6 (3.1–13.7) were reported, with the association being stronger when tested later in pregnancy. [49,96] For a 5% false positive rate, PlGF and sFlt-1 had sensitivities of 32% and 26%, respectively. [49] Soluble endoglin (sEng) and VEGF were not as consistently found to be associated although at least one study reported that sEng had a sensitivity of 18% to detect PE for a 5% false positive rate. [49] Of the markers routinely tested during aneuploidy screening in the first trimester, alpha feto protein (AFP) had the highest specificity of 96% (95% CI 94 to 98%) with a specificity of only 9% (95% CI 5-16%). [20]

A wide number of gene mutations were considered to be associated with the development of pre-eclampsia, but no single polymorphism was identified with a clinically useful ~~diagnostic~~ predictive performance. (Table 2). The most

frequently investigated genes were methylenetetrahydrofolate reductase (MTHFR) and endothelial nitric oxide synthase (eNOS), and a number of genes relating to elements of the renin-angiotensin-aldosterone system (RAAS) were investigated. The credibility of the association between the MTHFR C677T mutation and pre-eclampsia was generally weak and the association was not large. The credibility of association with mutations of the eNOS gene was moderate, but again this was not a large effect. These patterns do support an association between endothelial and RAAS function and pre-eclampsia, but are not at present useful for prediction of disease.

Multivariable prediction models

No screening marker, whether any of the clinical characteristics, ultrasound or biochemical markers, had both sensitivity and specificity greater than 90%.

Six reviews opted for an approach using combinations of predictive markers (Table 2)[22,85,88,97,99,100] and reported results for 52 individually described models while one group reported on an additional 70 models in groups labelled as 'simple' or 'specialised' based on the inclusion of ultrasound and biochemical tests.[99] Of these studies, only one reported calibration statistics for the model described [22] and one found that of the 14 primary model development papers assessed, only 6 reported model calibration. [99] The remaining prediction modelling papers did not describe calibration of the models presented or assess calibration statistics in the primary studies reviewed. The detection rates (DR) of single markers (ADAM12, beta-hCG, inhibin A, activin A, PP13, PlGF and

PAPP-A) for early-onset pre-eclampsia ranged from 22% to 83% for a fixed false positive rate of 10%. [88] These figures improve to between 38% and 100% when a combination of more than two markers was used. [88] The best results (DR 100%, 95% CI 69-100%) were achieved with the combination of three biochemical markers (Inhibin A, PlGF, PAPP-A), uterine artery Doppler and maternal characteristics. [88] For early-onset pre-eclampsia, a model containing only BMI was significantly improved by the addition of mean resistance index (RI) and bilateral notching, with the AUC increasing from 0.66 to 0.92 (P<0.001). The addition of mean pulsatility index (PI) and bilateral notching improved the AUC from 0.62 to 0.95 (P<0.001). [22] The sensitivity for early-onset pre-eclampsia using uterine artery Doppler PI, with mean arterial pressure was 83%, [85] but only 58.5% for late onset pre-eclampsia with the same markers. The improved performance of models containing Doppler or biomarkers is consistent with the finding of one study that adding ultrasound or biomarkers to models based on maternal characteristics alone led to a median gain of 18% in sensitivity.[99]

DISCUSSION

Our review identified ~~132~~ 126 systematic reviews on over 90 predictors for pre-eclampsia, although only around a quarter directly reported predictive ~~accuracy~~ability. No test was found to have sensitivity and specificity above 90%. A high sensitivity and specificity are necessary to make screening more cost effective than a 'treat-all' policy in clinical practice.[20] BMI >34kg/m^2, AFP and bilateral uterine artery Doppler notching were reported with specificity of >90%

but with low sensitivities, rendering them unsuitable to safely categorise women as 'low risk'. [20] Individual predictors most correlated with pre-eclampsia were uterine artery Doppler indices and angiogenic biomarkers. [22,88,143] Prediction models combining maternal characteristics (particularly BP) with uterine artery Doppler and biomarkers were able to achieve sensitivity and specificity >80%. [22,85,100]

Comparison with ~~published~~ existing evidence

Our search identified one prior 'umbrella' review on this topic [147] and two broad systematic reviews of primary studies for prediction of pre-eclampsia from the HTA in 2008 [20] and the World Health Organisation (WHO) in 2004. [21] All three also identified BMI, uterine artery Doppler and AFP as high performing variables but were also limited by heterogeneity and inconsistent reporting in included primary studies. [20] A subsequently published review of systematic reviews of risk factors for pre-eclampsia, while not examining uterine artery Dopplers, also identified a number of maternal characteristics as important risk factors including obesity, primiparity and smoking status and additionally noted the strong association between assisted reproduction and pre-eclampsia that should be considered in the development of new prediction tools. [148] Several of these studies ~~found that there was~~reported evidence that infrequently studied predictors including kallikreinuria and fibronectin might offer high sensitivity in pre-eclampsia prediction and required further research. No new reviews including these predictors were identified in our search nearly ten years later although new variables, including cell free fetal DNA, can be added to the

selection of variables that require further investigation. Previous reviews have also highlighted the need for development of multi-variable models. ~~While~~ In this review we have ~~we have demonstrated that~~identified over 50 ~~many~~ models that have been reported in the last decade, but we also found none that had undergone external validation and could be recommended for routine practice.

Strengths and weaknesses

The strengths of this review include a thorough search strategy and critically evaluative approach. The analysis collates a wide variety of reviews representing the state of research in this field. The findings of the review are limited by the quality of included studies, compromised by limitations carried over from the primary studies and then the later conduct of the review analysis, especially where investigators did not address risks of bias particular to prediction research.

Clinical and research implications

Maternal characteristics at booking are currently used for screening by most guidelines. [5,149,150] An important characteristic, due to increasing prevalence, is maternal obesity. [151,152] This review confirmed a plausible biological gradient associating maternal obesity with pre-eclampsia and observed that the inclusion of BMI improved the performance of several models. [22,88] It is likely that any clinically useful model would be improved by inclusion of a measurement of maternal obesity.

In seeking to improve on screening by maternal characteristics, many biomarkers were investigated. The angiogenic markers are most promising, particularly PlGF and sFlt-1.[49,61,84,95,96] Of the placental proteins, PP13 and PAPP-A were most consistently associated. [41,61,95,96,101] Large prospective studies using biomarkers are expensive and most data exists for markers routinely obtained during fetal anomaly screening. There is evidence in smaller studies for markers like fibronectin,[20,73] cell free fetal DNA [31,62] and urinary kallikrein[20,21] that requires further investigation.

This review further confirmed the screening performance of uterine artery Doppler in the first and second trimesters. Using a model combining systolic blood pressure, uterine artery PI and bilateral notching with BMI can achieve AUC 0.85 (95% CI: 0.67–1.00).[22] but this model is as yet still undergoing external validation, including in the SPREE study comparing the National Institute for Health and Care Excellence (NICE) and Fetal Medicine Foundation (FMF) screening models.[153]

While in previous years the search has been for a single marker to predict pre-eclampsia, recognition of the heterogeneity of the disease phenotype and complexity of prediction has led to consensus that the best approach to pre-eclampsia screening is likely to be calculating individualised risk based on a combination of markers. [6] In this review we have identified key predictors that could be used in developing such a prediction model and propose a solution to address the problems of inconsistent reporting and heterogeneity that have

consistently affected the ability of prior reviews to make recommendations on screening.[20,21,147] Since information on multiple predictors will be required, model development will optimally utilise individual level data which can facilitate analysis to identify the predictors that explain most of the variance of the full model. The aim of this approach, already established in cardiovascular prediction modelling,[154] is to develop a model well balanced between optimal performance and parsimony of included predictors leading to greatest ease of use in clinical practice.

Using individual patient data meta analysis for model development (IPD-MA) could additionally address poor reporting and heterogeneity in primary studies. While resource intensive and still subject to publication bias, IPD-MA is becoming the gold standard for predictive meta-analysis.[155] The advantages of IPD-MA over conventional meta-analysis include use of all available data; flexibility to combine data uniformly; the use of original data allowing analysis of continuous variables and comparison between datasets.[156] Moreover, it permits comparison of multivariable prediction strategies and the possibility of time-to-event analysis, particularly relevant to pre-eclampsia where gestation is inextricably linked to maternal and fetal outcomes.[157]

Research priorities should include prospectively registered predictive studies of promising markers, with results for each marker alone and in combination with other tests and clear reporting of methods and timing of variable and outcome measurements. A particular focus should be high performance tests in the first

trimester, when the benefits of intervention are greatest. IPD meta-analysis combining the most promising predictors can then be used to develop prediction models for external validation before introduction into clinical practice.

Predictive variables by themselves do not improve outcome; the subsequent preventive interventions do. Since it is not self-evident that a treatment has a stable effect in women with different profiles, predictive markers should be evaluated in studies that evaluate the impact of predictive strategies. [158] The ideal predictor not only predicts pre-eclampsia, but also predicts treatment modification, i.e. whether a treatment improves the outcome in a particular category of patients.

In order to conduct effective primary studies and analyses, consensus on outcomes is needed. Identification of a core outcome set for pre-eclampsia studies [159] is a key priority. Such an approach will enable us to move beyond repeating small, low quality prognostic factor studies to investigating the clinical impact of prediction model use in clinical practice.

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Conflict of interest

BWM reports consultancy for ObsEva, Merck and Guerbet. ST is the CI of the NIHR funded IPD meta-analysis IPPIC to predict pre-eclampsia.

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Figure legends:

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 - AMSTAR assessment of included studies

Figure 2b - QUIPS assessment of included studies

Figure 3. Summary of characteristics of included studies

Table 1. Screening markers for pre-eclampsia investigated in systematic reviews

Maternal characteristics

- Age
- Parity
- Body mass index
- Previous pre-eclampsia
- Family history of pre-eclampsia
- Multiple pregnancy
- Pre-existing medical conditions (such as diabetes, antiphospholipid syndrome)
- Interval between pregnancies
- Common occupational exposures (prolonged working hours, shift work, lifting, standing and heavy physical workload)
- Infection (bacterial/viral/other)
- Periodontal disease
- Mental stress
- Polycystic ovary syndrome
- ABO blood group status
- Ambient air pollution
- Coeliac disease
- Dietary factors (energy, nutrients, foods or overall dietary patterns, alone or in combination with dietary supplements)
- Cigarette smoking
- Donor insemination/donor oocyte use
- Physical activity
- Intra-uterine device (IUD) use
- Meteorological conditions
- Obstructive sleep apnoea
- Chorionic villus sampling
- Past obstetric history (previous pre-eclampsia, stillbirth, growth restriction or abruption)
- Flow mediated dilatation (FMD)
- Blood pressure

Ultrasound markers

- Uterine artery Doppler
- Placental vascularisation indices

Biochemical markers

Angiogenic/antiangiogenic markers

- Placental growth factor (PlGF) (blood and urine)
- Soluble fms-like tyrosine kinase one (sFlt1)
- Soluble endoglin (sEng)
- Vascular endothelial growth factor (VEGF)
- Transforming Growth Factor-Beta 1 (TGFb1)

Inflammatory markers

- Tumour Necrosis Factor alpha (TNF α)
- C-reactive protein (CRP)
- Interleukin-6, -10 and -19

- Interferon (IFN) gamma
- P-selectin
- Pentraxin

Markers of lipid metabolism and oxidative stress

- Serum malondialdehyde (MDA), thiobarbituric acid-reactive substances (TBARS), superoxide dismutase (SOD)
- Hypertriglyceridaemia
- Hyperlipidaemia

Cardiac markers

- B-type natriuretic peptides (BNP)

Markers of renal dysfunction

- Urinary protein to creatinine ratio (PCR)
- Urinary calcium excretion, urinary calcium to creatinine ratio
- Urinary proteinuria (24-hour/spot tests for total proteinuria, albuminuria, microalbuminuria, albumin to creatinine ratio, kallikrein, SDS-PAGE proteins)

Prothrombotic markers

- Factor V Leiden gene mutation
- Prothrombin gene mutation (PGM)
- Anticardiolipin Antibodies (ACA)
- Antiphospholipid antibodies (APLA)
- D-dimer

Markers of fetoplacental unit endocrine dysfunction

- Human chorionic gonadotrophin (HCG)
- Alpha-Fetoprotein (AFP)
- Inhibin A
- Activin A
- Pregnancy-associated plasma protein A (PAPP-A)
- Placental protein 13 (PP13)
- Oestriol
- Metallopeptidase domain 12 (ADAM12)
- Corticotropin releasing hormone
- Serum uric acid
- Vitamin D

Others

- Fibronectin (maternal blood)
- Vitamins and mineral levels (Vitamins C and E, copper, iron and zinc levels)
- Free fetal DNA

Genetic associations

- Methyltetrahydrofolate reductase (MTHFR) polymorphisms
- Glutathione S transferase polymorphisms
- Endothelial nitric oxide synthase polymorphisms
- Plasminogen activator inhibitor 1 (PAI-1) polymorphism
- VEGF polymorphisms
- TGFb1 polymorphisms
- IL-10 polymorphisms
- TNF alpha polymorphisms
- HLA-G 14bp I/D polymorphisms
- AGT II receptor polymorphisms

- ACE I/D polymorphisms
- AGT polymorphisms
- Prothrombin gene polymorphisms

Table 2a. Predictive ability of maternal characteristics for pre to eclampsia

Author Year	No. of primary studies	No. of databases searched	No. of women	Risk factors evaluated	Reported measure of test performance	Review pooled results (95% confidence intervals)	Outcome reported
Maternal characteristics (clinical assessment)							
Cnossen 2007	36	4	1699073	BMI or obesity	Sensitivity and Specificity	BMI >25 Sn 47% (33 to 61) Sp 73% (64 to 83%)	All PE
						BMI >35 Sn 21% (12 to 31) Sp 92% (89 to 95)	
O'Brien 2003	13	2	1390226		RR	0.54% (0.27 to 0.8) increase per 1 kg/m^2 increase in BMI	All PE
Wang 2013*	29	N/A	1980761		RR	Overweight RR 1.58 (1.44 to 1.72)	All PE
						Obese RR 2.68 (2.39 to 3.01)	
						Severely obese RR 3.12 (2.24 to 4.36)	
Salihu 2012	14	2	774366		Narrative		All PE
Poorolajal 2016	23	4	1387599		OR	BMI 25 to 30 OR 1.73 (1.59 to 1.87)	All PE
						BMI> 30 OR 3.15 (2.96 to 3.35)	
Weissgerber 2016	12	3	1103	Flow mediated dilation	SMD	-0.78 (-1.19 to -0.37)	All PE

Alpoim 2013*	2	4	1875	ABO blood group status	OR	AB group OR 2.42 (1.63 to 3.58)	Early-onset PE
						A group OR 0.86 (0.69-1.06)	
						B group OR 1.1 (0.67-1.8)	
						O group OR 0.89 (0.71-1.11)	
Franchini 2016	9	2	697285		OR	O group OR 0.77 (0.67 to 0.88)	All PE
						AB group OR 1.94 (1.2 to 3.13)	
						A group OR 1.78 (1.04 to 3.07)	
Conde Agudelo 2008	5	7	8811336	Maternal infections (UTI, periodontal disease, HIV, malaria, Hepatitis)	OR	UTI OR 1.57 (1.45 to 1.7)	All PE
						Periodontal disease OR 1.76 (1.43 to 2.18)	
						Chlamydia pneumoniae, H. pylori, CMV, HIV, malaria, HSV, BV, *mycoplasma hominis*: not associated	
Rustveld 2008	16	3	20586		OR	Any infection OR 2.08 (1.63 to 2.65)	All PE
Basaran 2016	6	1	47599	Chorionic villus sampling	OR	0.83 (0.42 to 1.67)	All PE
Sgolastra 2013*	15	8	5023	Periodontal disease	OR	2.17 (1.38 to 3.41)	All PE
Kunnen 2010*	15	3	Not specified		Narrative		Early-onset PE
Wei 2013	15	2	9192		OR	2.79 (2.01 to 3.01)	All PE
Ide 2013	5	4	5024		OR	1.61 (1.36 to 1.92)	All PE
Huang 2014	11	2	3916		OR	3.69 (2.58 to 5.27)	All PE
Huang 2016	11	2	11566	Hepatitis B	OR	0.77 (0.65 to 0.90)	All PE
Calvert 2013	9	4	14971	HIV	OR	1.04 (0.60 to 1.79)	All PE
Adams 2016	13	4	21200		Narrative		All PE
Browne 2015	16	3	8817384		OR	1.01 (0.87 to 1.18)	All PE
Zhang 2013	13	5	668005	Mental stress	OR	1.49 (1.27 to 1.74)	All PE
Yu 2016	25	3	Not specified	Polycystic ovarian syndrome	OR	2.79 (2.29 to 3.38)	All PE
Qin 2013	15	3	1198662		OR	2.17 (1.91 to 2.46)	All PE

Pedersen 2014	4 ($PM_{2.5}$)	2	127798 ($PM_{2.5}$)	Ambient air pollution	OR	$PM_{2.5}$ OR 1.31 (1.14 to 1.5)	All PE
	4 (NO_2)		120042 (NO_2)			NO_2 OR 1.07 (1.02 to 1.13)	
	3 (NO_x)		170694 (NO_x)			NO_x OR 1.05 (0.98 to 1.13)	
	3 (PM_{10})		50109 (PM_{10})			PM_{10} OR 1.03 (0.91, 1.17)	
	3 (CO)		95853 (CO)			CO OR 0.95 (0.86 to 1.05)	
	3 (Traffic)		NA (traffic)			Traffic OR 1.03 (1.01 to 1.06)	
	3 (O_3)		115891 (O_3)			O_3 OR 1.09 (0.98 to 1.21)	
Hu 2014	6	5	282117		OR	NO_2 OR 1.1 per 10 ppb (1.03 to 1.17)	All PE
						PM_{10} OR 0.98 per 10 ppb (0.91 to 1.05)	
						$PM_{2.5}$ OR 1.1 (0.96 to 1.26)	
Tersigni 2014	2	2	9436	Celiac disease	OR	1.41 (0.73 to 2.71)	All PE
Wei 2015	17	2	1800000	Cigarette smoking	RR	0.67 (0.6 to 0.75)	All PE
Cnossen 2008	34	4	60599	Blood pressure	AUC	MAP 0.76 (0.70 to 0.82)	All PE
						sBP 0.68 (0.64 to 0.72)	
						dBP 0.66 (0.59 to 0.72)	
Wolf 2014*	11	2	170679	Leisure time physical activity	Narrative		All PE
Aune 2014	15	3	185121		RR	0.65 (0.47 to 0.89)	All PE
Gonzalez-Comadran 2014	7	2	10898	Donor insemination	OR	1.63 (1.36 to 1.95)	All PE
Blazquez 2016	11	3	26302	Donor oocyte use	OR	3.05 (2.48-3.74)	All PE
Masoudian 2016	4	4	16553		OR	4.34 (3.1 to 6.06)	All PE
Jeve 2016	10	7	11539		OR	2.90 (1.98-4.24)	All PE
Thomopoulos 2017	7	2	225279	Assisted reproductive technology use	RR	Ovulation induction RR 1.48 (1.12 to 1.96)	All PE

						IVF/ICSI RR 1.65 (1.53 to 1.77)	
Li 2016	3	4	167680	Intra-uterine device use	RR	0.74 (0.61-0.90)	All PE
Schalekamp-Timmermans 2016	11	n/a	219575	Female fetal gender	OR	1.36 (1.17-1.5)	Early-onset PE
Cormick 2016	2	3	26174	Inter-pregnancy interval	OR	<2 years 1.01 (0.95 to 1.07)	All PE
						>2 years 1.1 (1.02-1.19)	
Kangatharan 2016	5	4	284899		OR	< 6 months 0.95 (0.88 to 1.02)	All PE
Ding 2013	12	3	9962	Sleep disordered breathing	OR	2.19 (1.71 to 2.8)	All PE
Xu 2014	5	5	977		RR	1.96 (1.34 to 2.86)	All PE
Palmer 2013*	11	2	N/A	Occupational exposures	Narrative		All PE
Schoenaker 2014	2	38	271472	Dietary factors	WMD	Kcal/day WMD 46 (-13.8 to 106.23)	All PE
						Mg intake WMD -9.75 mg/day (-21.26 to 1.76)	
						Ca intake WMD -56.32 mg/day (-120.69 to 8.06)	
Beltran 2014	2	24	N/A	Meteorological factors	RR	Birth in Spring v Summer RR 1.05 (0.87 to 1.27)	All PE

Table 2b. Ability of ultrasound markers to predict pre-eclampsia

Author Year	No. of primary studies	No. of databases searched	No. of women	Risk factors evaluated	Reported measure of test performance	Review pooled results (95% confidence intervals)	Outcome reported
Velauthar 2014*	18	3	55974	First trimester uterine artery doppler	Sensitivity and Specificity	Sensitivity 47.8% (39 to 56.8%) Specificity 92.1% (88.6 to 94.6%)	Early-onset PE
						Sensitivity 26.4% (22.5 to 30.8%) Specificity 93.4% (90.4 to 95.5%)	All PE
Cnossen 2008	3	4	4966		Sensitivity and Specificity	PI: Sens 25% (20-31) Spec 95% (95-96%)	All PE
Cnossen 2008	7	4	38230	Second trimester uterine artery doppler	Sensitivity and Specificity	PI: Sens 42% (25-58%) Spec 91% (86-96%),	All PE
	17	4	36969		Sensitivity and Specificity	Bilateral notching: Sens 43% (26-60%), Spec 93% (90-97%)	All PE
Eastwood 2017	3	4	1865	Placental vascularisation indices in first trimester	MD	VI: MD -2.93 (-5.84 to -0.01)	All PE
						FI: MD -2.83 (3.97 to -1.69)	
						VFI: MD -0.93 (-1.6 to -0.25)	
Xu 2016	3	3	65226	Single fetal umbilical artery	OR	0.820 (0.56 to 1.21)	All PE

Table 2c. Ability of biomarkers to predict pre-eclampsia

Author Year	No. of primary studies	No. of databases searched	No. of women	Risk factors evaluated	Reported measure of test performance	Review pooled results (95% confidence intervals)	Outcome reported
Angiogenic and antiogenic markers							
Widmer 2007	10	5	1173	sFlt-1	Narrative		Early-onset PE
Kleinrouweler 2012	19	2	5337		OR	6.6 (3.1 to 13.7)	Early-onset PE
Allen 2014	4	3	1045		OR	1.3 (1.02 to 1.65)	All PE
	3		569		OR	1.2 (0.33 to 4.41)	Early-onset PE
Widmer 2007	14	5	2045	PIGF	Narrative		Early-onset PE
Kleinrouweler 2012	15	2	10612		OR	9.0 (5.6 to 14.5)	All PE
Allen 2014	4	3	987		OR	1.94 (0.81 to 4.67)	All PE
			1590		OR	3.41 (1.61 to 7.24)	Early-onset PE
Wu 2015	8	4	Not specified		Sensitivity and specificity	SN 65% (63-67%), SP 89% (89-89%)	All PE
	3		Not specified		Sensitivity and specificity	SN 37% (27-48%) SP 79% (78-81%)	Early-onset PE
Zhong 2015	2	4	8424		LR	LR+ 4.01 (3.74 to 4.28), LR- 0.67 (0.64 to 0.69)	All PE
	6				LR	LR+ 6.05 (5.55 to 6.55), LR- 0.48 (0.43 to 0.52)	Early-onset PE
Kleinrouweler 2012	4	2	2143	sEng	OR	4.2 (2.4 to 7.2)	All PE
Allen 2014	2	3	854		OR	1.23 (0.79 to 1.94)	All PE

Allen 2014	2		2143		OR	18.54 (8.38 to 41.02)	Early-onset PE
Kleinrouweler 2012*	3	2	265	VEGF	SMD	-1.25 (-2.73 to -0.23)	All PE
Markers of fetal placental unit function							
Schneuer 2012*	4	3	6161	PP13	Sensitivity	All PE: 24% for 5% FPR Early PE: 45% for 5% FPR	Early to onset PE
Allen 2014	4	3	3948		OR	4.42 (2.86 to 6.84)	All PE
	3	3	3984		OR	7.51 (2.5 TO 22.53)	Early-onset PE
Wu 2015	9	4	n/s		Sensitivity and specificity	All PE SN 37% (33-41%) SP 89% (89-89%) Early PE SN 59% (48-69%) SP 92% (91-93%)	All PE
Zhong 2015	6	3	60786		LR	Early PE LR+ 4.2 (3.69 to 4.71) LR- 0.6 (0.53 to 0.66) All PE LR+ 2.69 (2.05 to 3.32) LR- 0.6 (0.53 to 0.66)	All PE
Morris 2017	8	4	132076	PAPP-A	OR	<5th centile OR 1.94 (1.63 to 2.3)	All PE
Allen 2014	12	3	56695		OR	2.05 (1.62 to 2.59)	All PE
	5	3	9713		OR	4.84 (2.49 to 9.41)	Early-onset PE
Wu 2015	14	4	n/s		Sensitivity and specificity	All PE SN 30% (29-32%) SP 92% (92-92%) Early PE SN 26% (19-34%) SP 90% (89-90%) Late PE SN 19% (14024%) SP 89% (89-90%)	All and early PE
Zhong 2015	16	3	385634		LR	Early LR+ 2.98 (2.55 to 3.41) LR- 0.7 (0.65 to 0.74) Late LR+ 1.58 (0.86 to 2.31), LR- 0.87 (0.74 to 1.00)	Early and late PE
Wu 2015	14	4	n/s	Inhibin A	Sensitivity and specificity	SN 32% (25-39%) SP 90% (89-91%)	All PE

Allen 2014	3	3	1152		OR	3.57 (1.68-7.61)	All PE
Liu 2016	12	7	8935	bHCG	SMD	MoMs 2.48 (0.81 to 4.15)	All PE
Zhong 2015	6	4	n/s		LR	Early PE LR+ 1.5 (0.92 to 2.08) LR- 0.95 (0.9 to 1.0) Late PE LR+ 1.41 (0.81 to 2.46) LR- 0.95 (0.88 to 1.03)	All PE
Allen 2014	4	3	11651	bHCG	OR	1.09 (0.86 to 1.39)	All PE
Wu 2015	3	4	n/s	ADAM-12	Sensitivity and specificity	SN 26% (21-32%) SP 84% (82-86%)	All PE
Cnossen 2006	5	4	572	Uric acid	Narrative		All PE
Tabesh 2013*	8	6	2485	Vitamin D	OR	Deficiency 2.78 (1.45 to 5.33)	All PE
Christesen 2012	10	3	28726		Narrative		All PE
Hypponen 2013	6	3	6864		OR	Sufficiency OR 0.52 (0.3 to 0.89)	All PE
Aghajafari 2013	9	5	3191		OR	1.79 (1.25 to 2.58)	All PE
Harvey 2014	11	21	26856		OR	Sufficiency OR 0.78 (0.59 to 1.05) Deficiency OR 0.75 (0.48 to 1.19)	All PE
Inflammatory and immune markers							
Rebelo 2013*	23	3	4265	CRP	WMD	2.3 mg/L (1.27 to 3.34)	All PE
Lau 2013*	41	4	1940	IL6 and IL10	MD	IL-6 7.96 pg/mL (2.65 to 13.28) IL -10 5.54 pg/mL (0.69 to 10.38)	All PE
Xie 2011	43	2	Not specified		WMD	IL-6 OR 1.23 (0.93 to 1.61) WMD 6.58 (5.49 to 7.67) IL-10 OR 1.07 (0.75 to 1.52) WMD 19.3 (8.42 to 30.17)	All PE
Lau 2013*	41	4	1940	TNF alpha	MD	8.11 pg/mL (5.87 to 10.34)	All PE
Xie 2011		2	Not specified		WMD	19.63 pg/ml (18.54-20.72)	All PE
Yang 2014 (AJRI)	16	3	2230	IL-18 and IFN gamma	OR	IL -18 0.07 (-0.40 to 0.53) IFN-gamma 0.93 (0.07 to 1.79)	All PE

Markers of lipid metabolism and oxidative stress							
Gupta 2009*	26	4	1767	Lipid peroxidation	SMD	Malondialdehyde: 1.21 nmol/mL (0.76 to 1.66)	All PE
						Thiobarbituric acid-reactive substances: 1.62 (0.27 to 2.96)	
						Vitamin E -1.12 (-1.77 to -0.48)	
						Vitamin C -0.53 (-1.03 to -0.02)	
						Erythrocyte superoxide dismutase -2.37 (-4.76 to 0.03)	
Gallos 2013	29	7	5867	Hypertriglyceridaemia	MD (mmol/L)	0.78 (0.6 to 0.96)	All PE
Spracklen 2014	74	2	N/S	Hyperlipidaemia	WMD (mg/dL)	Total cholesterol 12.49 (3.44 to 21.54) HDL-C -0.48 (-3.31 – 2.34) LDL-C 3.89 (-0.19 to 7.97) Triglycerides 25.08 (14.39 to 35.77)	All PE
Cardiac and renal markers							
Afshani 2012	12	3	N/S	BNP	Narrative		All PE
Lei 2016	6	3	480	AGT II recepter auto antibodies	OR	32.84 (17.19 to 62.74)	All PE
Thrombotic markers							
Dudding 2008	6	2	6755	Factor V Leiden	OR	1.49 (1.13 to 1.96)	All PE
Kosmas 2003	18	2	4502		OR	(Vv or vv): 2.25 (1.5 to 3.38)	All PE
Rodger 2010*	10	2	21833		OR	1.23 (0.89 to 1.70)	All PE
Wang 2014	23	2	7167		OR	1.6 (1.28 to 2.0)	All PE
do Prado 2010*	12	3	8475	Antiphospholipid antibodies	OR	ACA 2.86 (1.37 to 5.98)	All PE
Abou Nassar 2011*	28	3	22300		OR	LA 2.34 (1.18 to 4.64) ACA 1.52 (1.05 to 2.2) Anti B2GP1 19.14 (6.34 to 57.77)	All PE
Other tests							

Fan 2016	12	2	905	Serum copper levels	SMD	0.69 (0.54 to 0.84)	All PE
Song 2015	26	7	2468	Serum iron	SMD	1.27 (0.76-1.78)	All PE
Zhu 2016	13	2	1013	Serum zinc	SMD	-0.61 (-0.74 to - 0.48)	All PE
Leeflang 2007	5	4	573	FFN	Narrative		All PE
Contro 2016	9	2	1646	cfFDNA	DR	68.8% (57.6 to 77.3) for 10% FPR (17-28 weeks)	All PE
Martin 2014	13	2	N/S		Narrative		All PE
Combinations of markers and models							
Zhu 2015	15	3	N/S	Combination of uterine artery PI, biomarkers and maternal characteristics	Sensitivity alone	*Any PE* All biomarkers 0.584 (0.561 to 0.608) PI+activin A 0.693 (0.592 to 0.779) PI+inhibin A 0.68 (0.59 to 0.757) PI+PAPP-A 0.566 (0.401 to 0.717) PI+PP13 0.69 (0.475 to 0.846) **PI+PIGF 0.88 (0.64 to 0.906)** *Early PE* All biomarkers 0.83 (0.794 to 0.861) **PI+MAP 0.894 (0.852 to 0.925)** PI+PAPP-A 0.729 (0.641 to 0.801) PI+PLGF 0.878 (0.784 to 0.934) PI+PP13 0.774 (0.65 to 0.863) *Late PE* All biomarkers 0.585 (0.525 to 0.642) PI+MAP 0.570 (0.503 to 0.634) PI+PLGF 0.275 (0.047 to 0.746) PI+PP13 0.536 (0.178 to 0.861) **PI+PAPP-A *(1 study only)***	All, early and late onset PE

						0.7 (0.55 to 0.816)	
Al Rubaie 2016	29	3	27958	First trimester predictive models	Narrative		All PE
Hui 2012*	8	3	115290	Combinations of serum markers used in first trimester anomaly screening	LR	AFP+hCG >2.5 MoM LR+ 5.68 (0.73 to 43.97) LR- 0.99 (0.98 to 1.01)	All PE
Kleinrouweler 2013*	8	2	6708	Second trimester uterine artery Doppler + other tests IPD	AUC	sBP+BMI+mean PI+bilateral notching AUC 0.85 (0.67 to 1.0) sBP+BMI AUC 0.65 (0.45 to 0.84) mean PI+bilateral notching AUC 0.75 (0.56 to 0.95)	Early to onset PE
Giguere 2011*	37	2		71 different markers	Narrative		Early to onset PE
Kuc 2011	35	4	138571	Multiple serum and ultrasound markers and maternal characteristics	Narrative		All PE
Multiple tests or markers assessed in single review							
Duckitt 2005	52	2	N/s	Multiple clinical features	Narrative		All PE
Bartsch 2016	2	92	25356688	Multiple maternal clinical features	RR	Previous IUGR 1.4 (0.6 to 3.0) SLE 2.5 (1.0 to 6.3) Nulliparity 2.1 (1.9 to 2.4) Maternal age >35 1.2 (1.1 to 1.3) Maternal age >40 1.5 (1.2 to 2.0) Prior stillbirth 2.4 (1.7 to 3.4) CKD 2.9 (2.6 to 3.1) Multiple preg. 2.9 (2.6 to 3.1) Prior abruption 2.0 (1.4 to 2.7) Diabetes 3.7 (3.1 to 4.3) Prior PE 8.4 (7.1 to 9.9) Chronic HTN 5.1 (4.0 to 6.5)	All PE

						Antiphospholipid syndrome 2.8 (1.8 to 4.3) ART use 1.8 (1.6 to 2.1) BMI >25 2.1 (2.0 to 2.2) BMI >30 2.8 (2.6 to 3.1)	
Morris 2008	44	4	169637	AFP, hCG, estriol, PAPP-A, inhibin A, activin A	LR	AFP LR+ 2.36 (1.46 to 3.83) LR- 0.96 (0.95 to 0.98) hCG LR+ 2.45 (1.57 to 3.84) LR- 0.89 (0.83 to 0.96) Estriol LR+ 1.5 (1.02 to 2.19) LR- 0.99 (0.97 to 1.00) PAPP- A <5th centile LR+ 2.1 (1.57 to 2.81) LR- 0.95 (0.93 to 0.98) Inhibin A LR+ 19.52 (8.33 to 45.79) LR to 0.3 (0.13 to 0.68)	All PE
Zhong 2015	6	4	n/s	PLGF, PAPP-A, hCG, PP13	LR	PLGF: LR+ 4.01 (3.74 to 4.28) PAPP-A: Early PE LR+ 2.98 (2.55 to 3.41) Late PE 1.58 (0.86 to 2.31) hCG Early PE LR+ 1.5 (0.92 to 2.08) Late PE LR+ 1.41 (0.81 to 2.46) PP13: Early PE LR 4.2 (3.69 to 4.71) All PE: LR+ 2.69 (2.05 to 3.32)	All PE
Conde-Agudelo 2004	43	4	42261	Systematic review of all screening tests	LR	Low risk RI LR+ 4.2 (3.6 to 5.1) LR – 0.6 (0.5 to 0.7) Bilateral notching LR+ 6.6 (5.8 to 7.4) LR to 0.8 (0.7 to 0.8) hCG >2.0 MoM LR+ 2.2 (1.7 to 2.9) LR to 0.8 (0.8 to 0.9) Urinary Kallikrein LR+ 4.6 (3.4 to 6.1) LR to 0.3 (0.2 to 0.6) ACA LR+ 6.7 (4.2 to 10.9) LR to 0.8 to 0.9)	All PE
Meads 2008	265	3	not specified	Systematic review of 27 screening tests	Sensitivity and specificity	Bilateral notching: Sn 48% (34 to 62%) Sp 92% (87 to 95%) BMI> 34 Sn 18 (15 to 21) Sp 93 (87 to 97)	All PE

						Kallikreinuria Sn 83% (52 to 98) Sp 98% (98 to 100) Cellular fibronectin Sn 50% (30 to 70) Sp 96% (94 to 98)	

Table 2d. Genetic association studies

Author Year	No. of primary studies	No. of databases searched	No. of women	Genetic factor evaluated	Reported measure of test performance	Review pooled results (95% confidence intervals)	Venice criteria	Outcome reported
Song 2013	10	2	2068	VEGF	OR	1.35 (1.11 to 1.65)	BBB	Any onset PE
Cheng 2013	8	3	1838		OR	+936C/T OR 1.52 (1.08 to 2.12) -634G/C OR 1.24 (1.03 to 1.5) -2578C/A OR 0.98 (0.82 to 1.16) -1154G/A OR 1.30 (0.94 to 1.78)	BBA	Any onset PE
Li 2014	4	3	1084	TGFb1	OR	OR 0.73 (0.56 to 0.95)	BAB	Any onset PE
Yang 2014 (JCMM)	12	3	5493	IL-10 polymorphisms	OR	-819c/T OR 1.28 (1.08 to 1.5) -592c/A OR 1.28 (1.03 to 1.59) -1082A/G 0.93 (0.77 to 1.13)	ACA	Any onset PE
Zhang 2016	13	6	n/s		OR	TvC OR 0.79 (0.58 to 1.07) GvA OR 0.91 (0.75 to 1.11)	ACB	Any onset PE

Lee 2014	2	11	3805		OR	1082 G/A OR 0.89 (0.73 to 1.09) -819 C/T OR 1.3 (1.01 to 1.66) -592 C/A OR 1.22 (0.97 to 1.53)	ACB	Any onset PE
Bombell 2008	16	3	2374	TNF alpha	OR	1.02 (0.86 to 1.2)	ABB	Any onset PE
Pabalan 2015	11	3	1916	HLA-G 14bp I/D polymorphism	OR	Homozygous OR 1.28 (0.93 to 1.75)	BAB	Any onset PE
Anvar 2011	5	11	1217	Glutathione S transferase polymorphisms	OR	GSTM1 OR 0.99 (0.78 to 1.25) GSTT1 OR 0.85 (0.66 to 1.10)	CCC	Any onset PE
Dai 2013*	29	5	3228	eNOS polymorphisms	OR	-786 T>C OR 1.17 (1.02 to 1.35) 4b/a OR 1.46 (1.01 to 2.1) ;	ABB	Any onset PE
Qi 2013*	33	3	10671		OR	G894T OR 1.43 (1.13 to 1.82)	ACA	Any onset PE
Shaik 2011	16	2	4485		OR	0.96 (0.75 to 1.23)	ACB	Any onset PE
Chen 2012*	18	3	N/A		OR	G849T: G allele OR 0.56 (0.33 to 0.97), T allele OR 1.17 (1.01 to 1.36)	ACB	Any onset PE

Zeng 2016	17	5	4729		OR	G894T: 1.46 (1.21 to 1.77) T-786C: 1.3 (1.07 to 1.58)	ABA	Any onset PE
Yu 2006	12	2	3513	eNOS polymorphisms	OR	Asp298 allele homozygous 1.12 (0.84-1.49)	ABA	Any onste PE
Morgan 2013*	12	3	5003	PAI1 polymorphism	OR	1.28 (1.09 to 1.50)	AAB	Any onset PE
Zhao 2012(Mol Hum Rep)	11	3	3088		OR	1.36 (1.13 to 1.64)	BAB	Any onset PE
Xia 2012*	36	4	9203	MTHFR gene C677T polymorphism	OR	1.25 (1.02 to 1.54)	ABB	Any onset PE
Li 2014*	49	4	18009		OR	White OR 1.14 (1.03 to 1.25) Asian OR 1.41 (1.11 to 1.79)	AAA	Any onset PE
Wang 2013*	51	6	17749		OR	1.28 (1.07 to 1.53)	ABB	Any onset PE
Wu 2015	45	4	88628		OR	1.157 (1.057 to 1.266)	ACB	Any onset PE
Kosmas 2004	23	2	6213		OR	1.21 (1.01 to 1.44)	ACB	Any onset PE
Zhang 2016	58	6	36438		OR	1.17 (1.05 to 1.31)	ACB	Any onset PE
Zhao 2012 (JMFNM)	8	4	3990	AGT II receptor polymorphisms	OR	+1166A>C OR 1.19 (0.96 to 1.47)	ABB	Any onset PE
Staines-Urias 2012	192	3	Not specified	AGTR1 rs186	OR	1.22 (0.96 to 1.56)	AAA	Any onset PE
Shaik 2011	17	2	3778	ACE I/D polymorphism	OR	0.987 (0.698 to 1.395)	ACB	Any onset PE
Zhong 2012	11	5	1749		OR	D allele: 1.93 (1.19 to 3.12)	BCB	Any onset PE

Chen 2012*	30	4	8340		OR	DD genotype: 1.44 (1.11 to 1.88)	ACB	Any onset PE
Zhu 2012*	23	6	3551		OR	D allele: 1.31 (1.09 to 1.57)	ACB	Any onset PE
Staines-Urias 2012	192	3	Not specified	ACE rs4646994	OR	1.17 (0.99 to 1.4)	AAA	Any onset PE
Ni 2012*	22	4	7534	AGT polymorphisms	OR	1.33 (1.09 to 1.61)	AAB	Any onset PE
Lin 2012	31	5	8669		OR	1.61 (1.22 to 2.14)	ABA	Any onset PE
Zafarmand 2008	17	3	5275		OR	1.62 (1.12 to 2.33)	ABA	Any onset PE
Staines-Urias 2012	192	3	Not specified	AGT rs699	OR	1.26 (1.00 to 1.59)	AAA	Any onset PE
Rodger 2010	6	2	14254	Prothrombin gene polymorphisms	OR	1.25 (0.79 to 1.99)	BAB	Any onset PE
Wang 2014	16	2	5558		OR	G20210A OR 181 (1.25 to 2.63)	AAB	Any onset PE

OR (Odds Ratio), RR (Relative risk), SMD (summary mean difference), WMD (weighted mean difference), AUC (area under curve), LR (likelihood ratio), Sn (sensitivity), Sp (Specificity)

BMI (body mass index), UTI (urinary tract infection), HIV (human immunodeficiency virus), CMV (cytomegalovirus), HSV to 2 (herpes simplex virus), $PM_{2.5,}$ (Particulate matter) CRP (C reactive protein), PI (pulsatility index), RI (resistance index), ADAM to 12 (a disintegrin and metalloprotease), TNF alpha (tumour necrosis factor alpha), IL 6,10, 18 (Interleukin 6, 10, 18) PAI to 1 (Plasminogen activator inhibitor), PP13 (placental protein 3), PAPP to A (pregnancy associated plasma protein A), hCG (human chorionic gonadotrophin), FFN (fetal fibronectin), cffDNA (cell free fetal DNA), eNOS (endothelial nitric oxide synthase), AGT(Angiontensin), UtA (uterine artery), PLGF (Placental growth factor), MAP (mean arterial pressure), SBP (systolic blood pressure), sEng (soluble endoglin), VEGF (vascular endothelial growth factor), ART (assisted reproductive technologies), TGFb (transforming growth factor beta 1), IFN (interferon), BNP (b naturietic peptide), ACE (angiotensin converting enzyme), HLA (human leukocyte antigen), sFlt to 1 (soluble fms to like tyrosine kinase 1), MTHFR (methyltetrahydrofolate receptor)

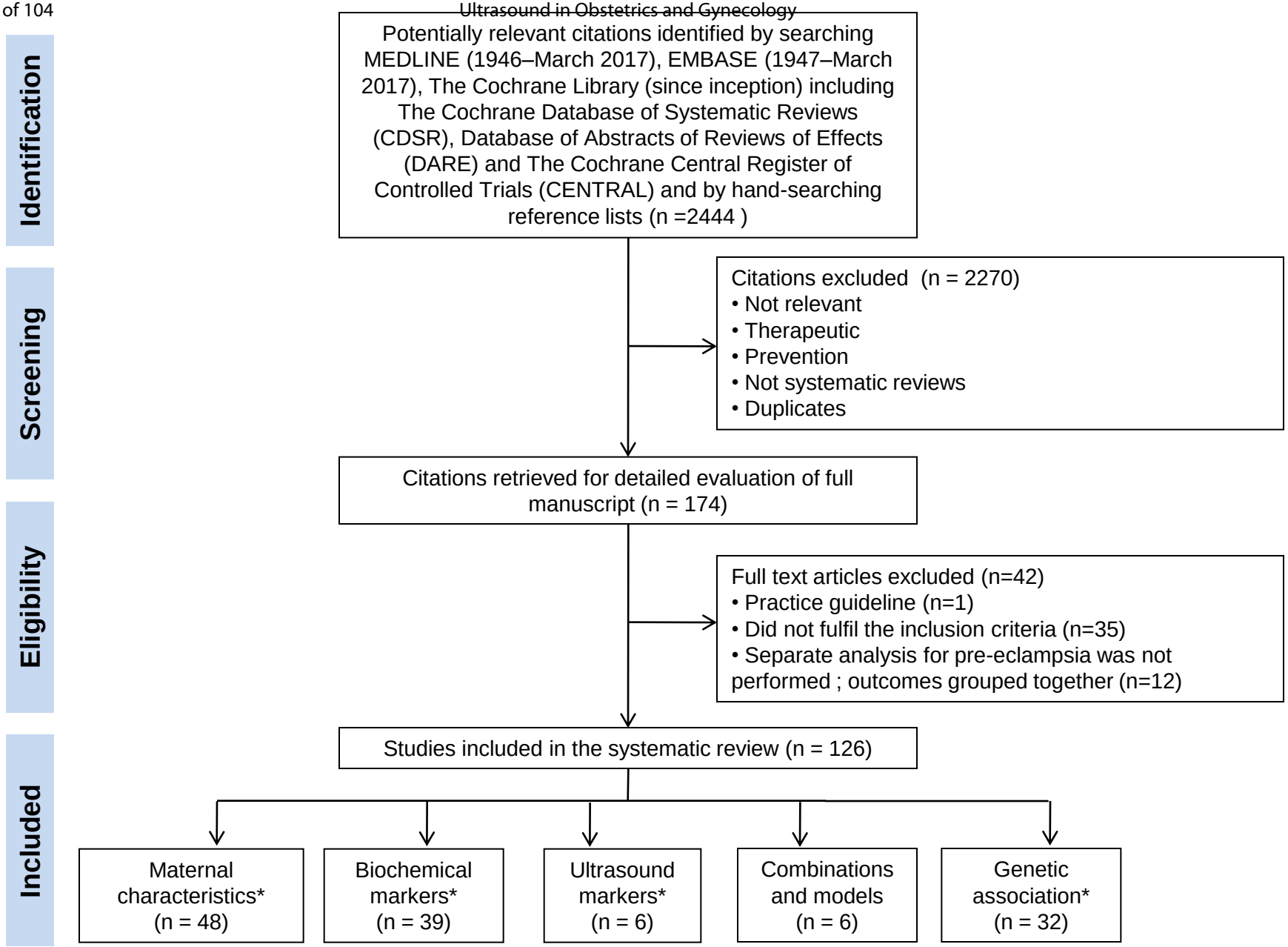


Figure 1 Flow chart illustrating identification of studies included in this systematic review. *some studies reported on markers in more than one category

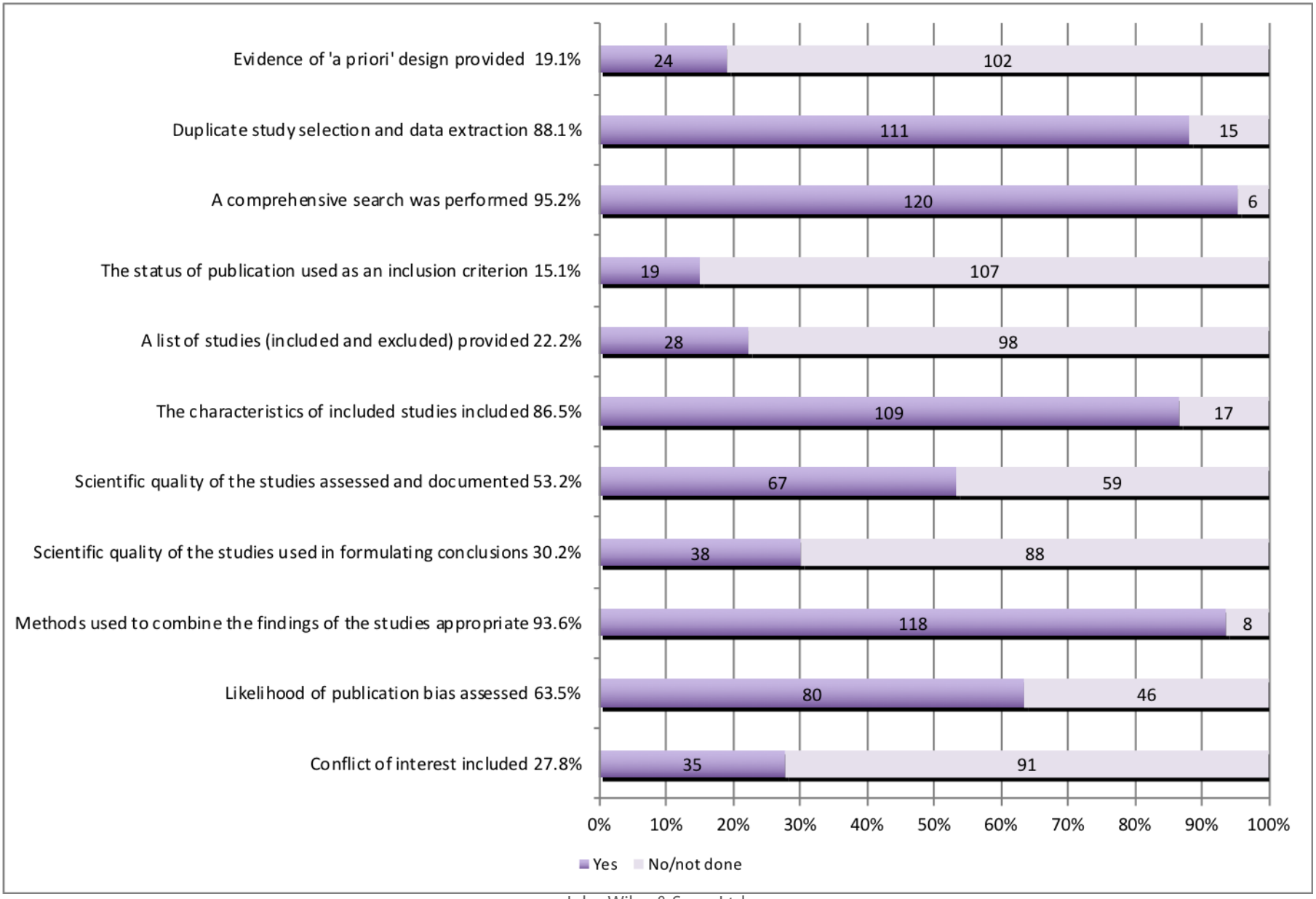


Figure 2a - AMSTAR assessment of included studies

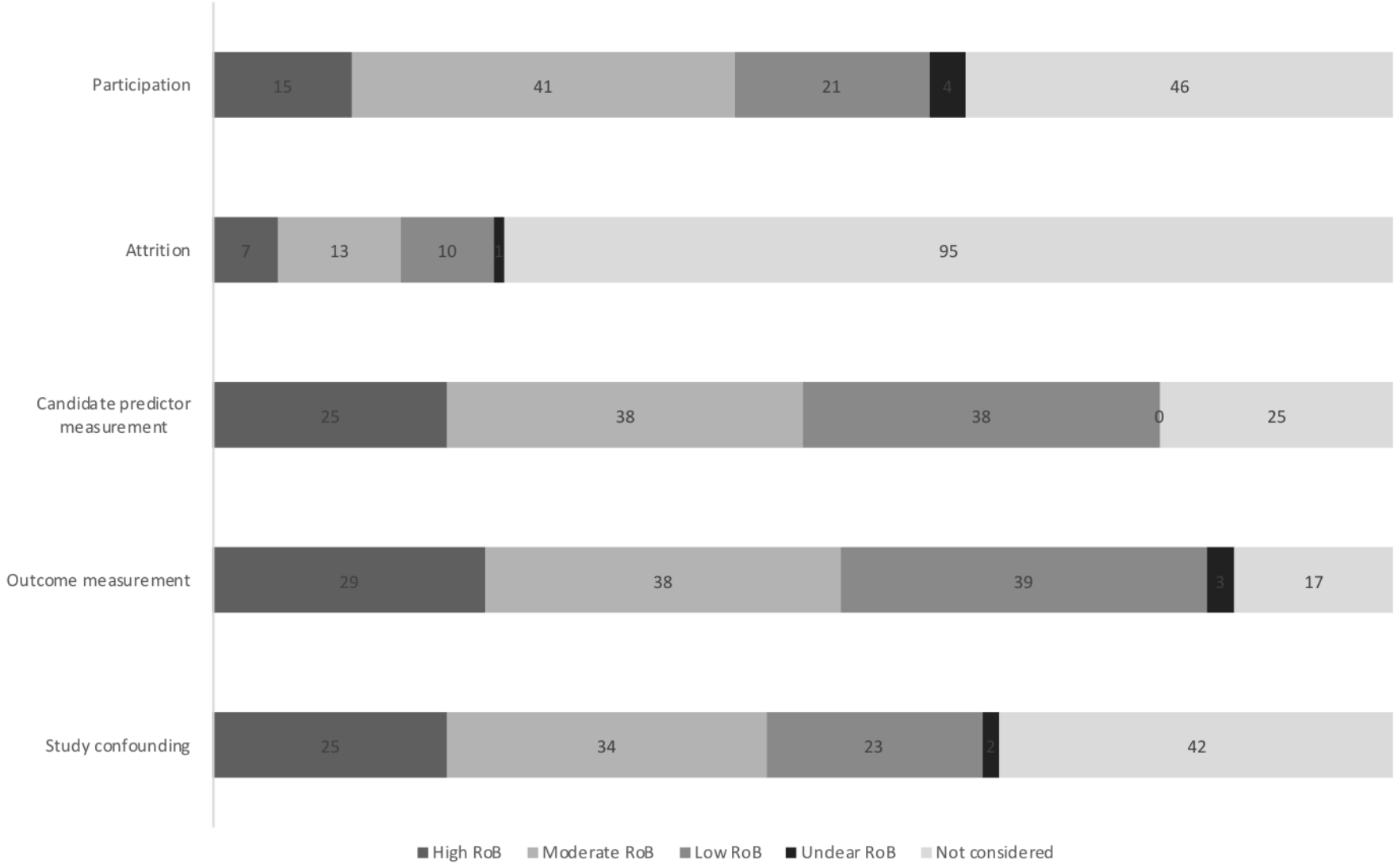
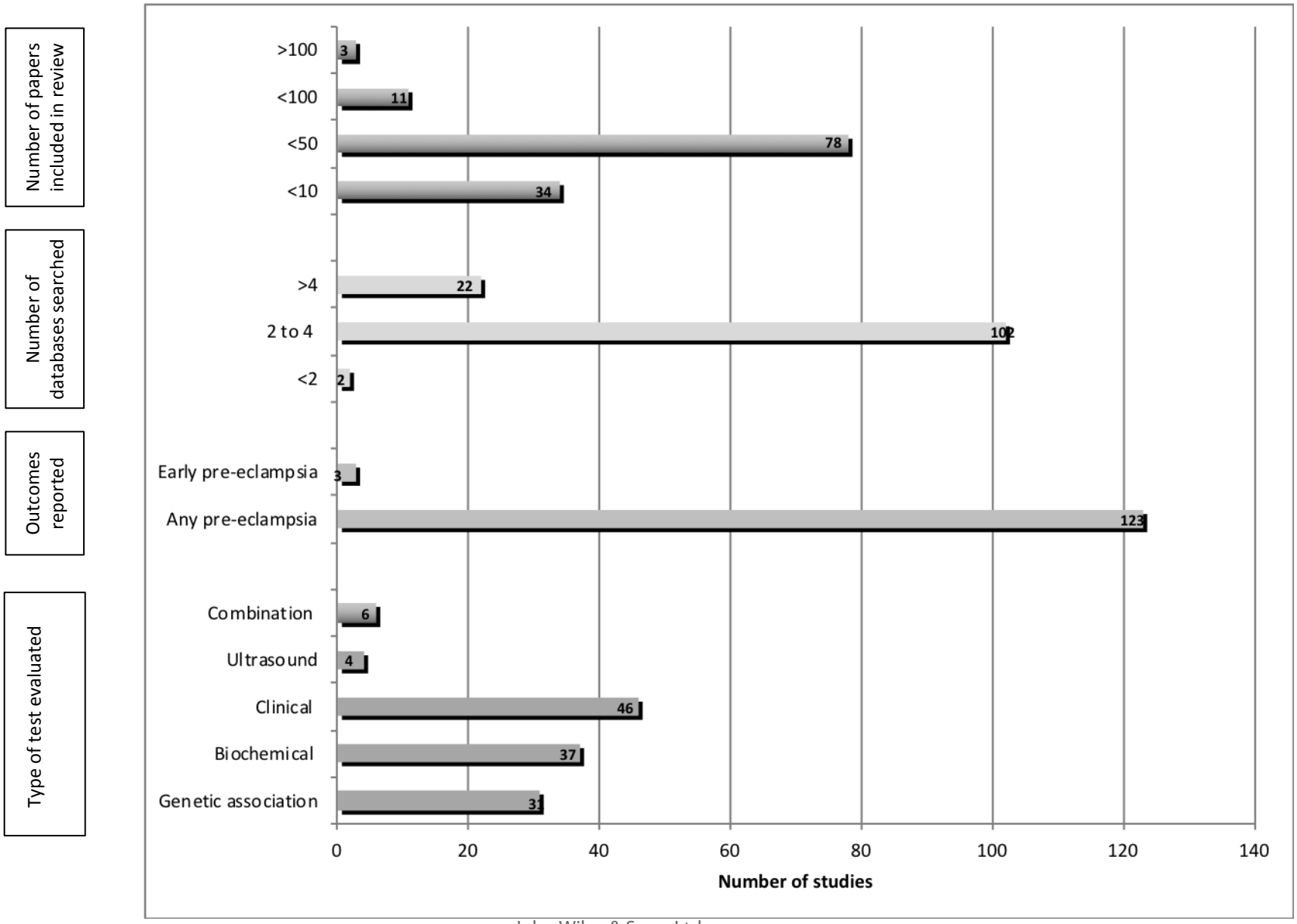


Figure 2b - QUIPS assessment of included studies



Search Strategy

Databases: Embase®, Embase® Alert, MEDLINE®

Set#	Searched for
S1	MESH.EXACT("Pre-Eclampsia") OR MESH.EXACT("Hypertension, Pregnancy-Induced")
S2	(MESH.EXACT.EXPLODE("Pregnancy") OR MESH.EXACT.EXPLODE("Pregnancy Trimesters") OR MESH.EXACT("Pregnancy Complications") OR MESH.EXACT("Pregnancy Complications, Cardiovascular") OR MESH.EXACT("Pregnant Women")) and MESH.EXACT("Hypertension")
S3	(MESH.EXACT.EXPLODE("Pregnancy") OR MESH.EXACT.EXPLODE("Pregnancy Trimesters") OR MESH.EXACT("Pregnancy Complications") OR MESH.EXACT("Pregnancy Complications, Cardiovascular") OR MESH.EXACT("Pregnant Women")) and ti,ab(hypertens[*4])
S4	ti,ab(pregnan*) and MESH.EXACT("Hypertension")
S5	EMB.EXACT("eclampsia and preeclampsia") OR EMB.EXACT("preeclampsia") OR EMB.EXACT("pregnancy toxemia") OR EMB.EXACT("maternal hypertension")
S6	(EMB.EXACT.EXPLODE("pregnancy") OR EMB.EXACT("pregnancy complication") OR EMB.EXACT("pregnancy disorder") OR EMB.EXACT("pregnant woman")) and (EMB.EXACT("essential hypertension") OR EMB.EXACT("hypertension"))
S7	(EMB.EXACT.EXPLODE("pregnancy") OR EMB.EXACT("pregnancy complication") OR EMB.EXACT("pregnancy disorder") OR EMB.EXACT("pregnant woman")) and ti,ab(hypertens[*4])
S8	ti,ab(pregnan*) and (EMB.EXACT("essential hypertension") OR EMB.EXACT("hypertension"))
S9	ti,ab(preeclamp* or preclamp* or "pre eclamp*" or "pre clamp*")
S10	ti,ab((pregnan* or eclamp*) near/3 (toxemi[*2] or toxaemi[*2] or toxicosis))
S11	ti,ab((edema or oedema) near/3 proteinuria near/3 hypertens[*4])
S12	ti,ab("eph gestos[*2]" or "eph toxemi[*2]" or "eph toxaemi[*2]" or "eph complex" or "eph syndrome")
S13	ti,ab(gestation* near/3 (hypertens[*4] or toxemi[*2] or toxaemi[*2] or toxicosis))
S14	ti,ab(maternal near/3 hypertens[*4])
S15	ti,ab(pregnan* near/5 hypertens[*4])
S16	rtype.exact("Meta-Analysis") or MESH.EXACT("Meta-Analysis") or EMB.EXACT("meta analysis") or EMB.EXACT("systematic review")
S17	MESH.EXACT("Meta-Analysis as Topic") or EMB.EXACT("meta analysis (topic)") or EMB.EXACT("systematic review (topic)")
S18	ti,ab("meta analy[*3]" or metaanaly[*3] or "systematic review[*1]")
S19	pub.exact("Cochrane Database of Systematic Reviews" OR "Cochrane Database of Systemic Reviews" OR "Cochrane Library" OR "Cochrane database of systematic reviews (Online)" OR "The Cochrane database of systematic reviews" OR "The Cochrane library")

S20	(s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15) and (s16 or s17 or s18 or s19)
S21	(s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15) and (s16 or s17 or s18 or s19) and human(yes)
S22	((s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15) and (s16 or s17 or s18 or s19)) not (human(yes) or animal(yes) or EMB.EXACT("nonhuman"))
S23	s21 or s22

Databases: The Cochrane Database of Systematic Reviews and Health Technology Assessment

ID	Search
#1	MeSH descriptor: [Pre-Eclampsia] this term only
#2	MeSH descriptor: [Hypertension, Pregnancy-Induced] this term only
#3	MeSH descriptor: [Pregnancy] explode all trees
#4	MeSH descriptor: [Pregnancy Trimesters] explode all trees
#5	MeSH descriptor: [Pregnancy Complications] this term only
#6	MeSH descriptor: [Pregnancy Complications, Cardiovascular] this term only
#7	MeSH descriptor: [Pregnant Women] this term only
#8	MeSH descriptor: [Hypertension] this term only
#9	#3 or #4 or #5 or #6 or #7
#10	#9 and #8
#11	(hypertens*):ti,ab,kw
#12	#9 and #11
#13	(pregnan*):ti,ab,kw
#14	#13 and #8
#15	(preeclamp* or preclamp* or "pre eclamp*" or "pre clamp*"):ti,ab,kw
#16	((pregnan* or eclamp*) near/3 (toxemi* or toxaemi* or toxicosis)):ti,ab,kw
#17	((edema or oedema) near/3 proteinuria near/3 hypertens*):ti,ab,kw
#18	("eph gestos*" or "eph toxemi*" or "eph toxaemi*" or "eph complex" or "eph syndrome"):ti,ab,kw
#19	(gestation* near/3 (hypertens* or toxemi* or toxaemi* or toxicosis)):ti,ab,kw
#20	(maternal near/3 hypertens*):ti,ab,kw
#21	(pregnan* near/5 hypertens*):ti,ab,kw
#22	**#1 or #2 or #10 or #12 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21**

Supplementary Table 1: Excluded studies and reason for the exclusion

Author	Year	Reason for exclusion
Chien	2000	only one database
Luo	2007	only one database
Witwanikit	2006	only one database
England	2007	only one database
Pedrosa	2011	only one database
Jacobs	2011	only one database
Li	2013	all hypertension in pregnancy grouped together
Yang	2014	all hypertension in pregnancy grouped together
Pamidi	2014	all hypertension in pregnancy grouped together
Yin	2015	all hypertension in pregnancy grouped together
Bonzini	2007	all hypertension in pregnancy grouped together
Gong	2015	all hypertension in pregnancy grouped together
Ma	2016	all hypertension in pregnancy grouped together
He	2016	all hypertension in pregnancy grouped together
Mogos	2016	all hypertension in pregnancy grouped together
Hahn	2011	Did not fulfil the criteria of systematic review (AMSTAR 0)
Lashley	2013	does not have analysis for pre-eclampsia, all third trimester complications pooled together
Thomopoulous	2013	all hypertension in pregnancy grouped together
Kleinroweler	2013	Not a review of screening markers for pre-eclampsia; determine common genetic expression signature and identify diagnostic leads in the placentas from pregnancies complicated by pre-eclampsia
Khan	2015	not screening for pre-eclampsia - comparison between biomarkers used for pre-eclampsia and those used for Polycystic ovarian syndrome
Saftlas	2005	only one database
Staff	2011	only one database
Price	2005	Protein-creatinine ratio to predict proteinuria, not specific to pre-eclampsia
Okun	2014	practice guideline
Lee	2014	primary variable was snus use and broad range of health outcomes examined - only one study reported pre-eclampsia
Xie	2017	All hypertensive disorders grouped together (including non pregnancy hypertension)
Ohkuchi	2017	Review article, no new data
Frampton	2016	Testing in symptomatic women
Vaiman	2016	Study of gene expression based on placental biopsies at delivery
Pergiallotis	2016	Testing in symptomatic women
Wilson	2016	Testing at delivery or in puerperium
Castleman	2016	Testing in the puerperium
Sheikh	2016	Chiefly derived from placental samples
Shim	2016	Intervention studies
Pergiallotis	2016	Testing symptomatic women
Acestor	2016	No information about test accuracy or sensitivity or odds ratios

Kandasamy	2015	Testing symptomatic women
Harapan	2015	Narrative review
Ma	2015	All but one study tested in the puerperium
Than	2014	Review article no new data
Giguere	2012	Review article
Matevosyan	2015	Narrative review
Cohen	2015	Testing symptomatic women
Feng	2016	Testing symptomatic women
Cai	2015	Testing at delivery
Morris	2012	Reported accuracy for diagnosis of proteinuria, not PE
Sanchez Ramos	2013	Reported accuracy for diagnosis of proteinuria, not PE
Pinheiro	2012	Testing symptomatic women

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Assessment criteria	Description	Yes/No/Can't answer/Not applicable
Was an 'a priori' design provided?	The research question and inclusion criteria should be established before the conduct of the review.	
Was there duplicate study selection and data extraction?	There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	
Was a comprehensive literature search performed?	At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	
Was a list of studies (included and excluded) provided?		
Were the characteristics of the included studies provided?	In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the tudies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	
Was the scientific quality of the included studies assessed and documented?	'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	
Was the scientific quality of the	The results of the methodological rigor and scientific quality should be considered in the	

included studies used appropriately in formulating conclusions?	analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	
Were the methods used to combine the findings of studies appropriate?	For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).	
Was the likelihood of publication bias assessed?	Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	

Supplementary Table 2a. Assessment of systematic review quality using the AMSTAR tool (14,15)

Assessment criteria	Description	Low/Moderate/High Risk of Bias
Study participants	The study authors have considered how well the primary study samples represent the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.	
Study attrition	The study authors have assessed whether loss to follow-up is associated with key characteristics sufficient to limit potential bias to the reported relationship between candidate predictor and outcome.	
Prognostic Factor Measurement	The study authors have considered if the measurement of the candidate predictor was measured in a reliable and valid way for participants in studies pooled for analysis.	
Outcome measurement	The study authors have considered whether the reference test (outcome) was measured reliably and in a similar fashion across all studies pooled for analysis.	
Study confounding	The study authors have considered whether the primary studies have accounted for important potential confounders and reported the effect of these covariables on their findings.	

Supplementary Table 2b. Assessment of Risk of Bias relating to the domains of the QUIPS tool (16)

Supplementary table 3a. GRADE assessment in Prognostic Research (

GRADE – a body of longitudinal cohort studies initially provides high confidence, and is then rated according to the presence of the following factors.	
Rate down confidence	*Rate up confidence*
Risk of Bias	Large effect
Inconsistency	Dose-response gradient
Imprecision	
Indirectness	
Publication Bias	

Confidence level	Definition
High	We are very confident that the true prognosis (probability of future events) lies close to that of the estimate*
Moderate	We are moderately confident that the true prognosis (probability of future events) is likely to be close to the estimate, but there is a possibility that it is substantially different
Low	Our confidence in the estimate is limited: the true prognosis (probability of future events) may be substantially different from the estimate
Very low	We have very little confidence in the estimate: the true prognosis (probability of future events) is likely to be substantially different from the estimate

Supplementary table 3b. Definitions of GRADE assessment levels

Prognostic marker evaluated	Reviews reporting a significant association (n)/Total number of Reviews reporting this test (N)	GRADE assessment of quality of the supporting evidence for the association
Maternal characteristics		
BMI [19,91,125,130,133]	5/5	High
Nulliparity [19]	1/1	Low
Maternal age >30 [19]	1/1	Low
Maternal age >40 [19]	1/1	Low
Blood pressure [22,132]	2/2	High
Maternal infection (any) [98,129]	2/2	Low
Hepatitis B [141]	0/1	Moderate
HIV [98,103,129,137]	0/4	Very Low
Periodontal disease [33,121,128,135,160]	5/5	Low
Mental stress [122]	1/1	Low
Intrauterine device use [114]	1/1 (negative)	Low
Physical activity levels [116]	1/1 (negative)	Low
Polycystic ovarian syndrome [109,131]	2/2	Low
Group A or AB blood [21 22]	2/2	Moderate
Coeliac disease [104]	0/1	Low
Cigarette smoking [34]	1/1 (negative)	Moderate
Dietary factors [105]	1/1	Very Low
Flow mediated dilatation [124]	1/1	Low
Interpregnancy interval [110,117]	0/2	Moderate
Sleep disordered breathing [92,108]	2/2	Moderate
Previous fetal growth restriction [19]	0/1	Low

Systemic lupus erythematosus[19]	1/1	Low
Chronic kidney disease [19]	1/1	Low
Pre-existing diabetes [19]	1/1	Moderate
Prior abruption [19]	1/1	Low
Previous pre-eclampsia [19]	1/1	Moderate
Chronic hypertension [19]	1/1	Moderate
Antiphospholipid syndrome [19]	1/1	Moderate
Environmental		
Ambient air pollution [50,138]	2/2	Low
Meteorological factors[102]	1/1	Very Low
Pregnancy related		
Donor insemination[106]	1/1	Low
Donor oocyte use [107,115,139]	3/3	Low
Assisted reproductive technology use [19,142]	2/2	Moderate
Fetal sex [23]	0/1	Moderate
Multiple pregnancy [19]	1/1	Low
Chorionic villus sampling [119]	0/1	Very Low
Ultrasound findings		
Uterine artery Doppler[20,21,25,143]	4/4	High
Single umbilical artery[113]	0/1	Low
Placental vascularisation indices[144]	1/1	Low
Biomarkers		
Placental growth factor (PLGF) [49,61,95,96]	3/4	Moderate
Soluble fms-like tyrosine kinase (sFlt1)[49,96]	2/2	Moderate

Soluble endoglin (sEng) [49,96]	1/2	Low
Vascular endothelial growth factor (VEGF)[49,53,60,96]	2/4	Very Low
Transforming growth factor beta-1 (TGFb-1) [89]	1/1	Very Low
Tumour necrosis factor α (TNFα) [46,65,78]	1/3	Very Low
C-reactive protein (CRP) [82]	1/1	Moderate
Interleukin-6 [46,65]	1/2	Low
Interferon-γ (IFN- γ) [55]	0/1	Low
Markers of lipid peroxidation [79]	0/1	Very Low
Hypertriglyceridaemia [83,93]	2/2	Moderate
Cholesterol [93]	1/1	Low
Angiotensin II receptor antibodies [57]	1/1	Moderate
Angiotensin converting enzyme [29,48,63,75,161]	4/5	Moderate
Urinary Kallikrein [20,21]	2/2	Moderate
Factor V Leiden [24,39,51,112]	2/4	Low
Anti-phospholipid antibodies [71,162]	2/2	Low
Human chorionic gonadotrophin (hCG) [21,74,95,134]	4/4	Low
Inhibin A [61]	1/1	Moderate
Pregnancy associated plasma protein-A [41,61,95,96,134]	5/5	Low
Alpha Feto-protein (AFP)[20,134]	2/2	Moderate
A-disintegrin and metalloprotease-12(ADAM-12) (61)	1/1	Very Low
Placental protein-13 (PP-13) [61,95,96,101]	4/4	Moderate

Vitamin D[26,35,58,77]	3/4	Low
Cell free fetal DNA [62]	1/1	Low
Serum zinc[30]	2/2	Very Low
Serum copper[70]	1/1	Low
Serum iron [37]	1/1	Low
Genetic associations		
Prothrombin gene polymorphisms [24,51]	1/2	Low
Methyltetrahydrofolate reductase (MTHFR) [27,40,42,43,87,123]	6/6	Low
Glutathione S Transferase [56]	0/1	Moderate
Endothelial nitric oxide synthase[21,32,38,47,52,63,69]	5/6	Low
Plasminogen activator inhibitor 1 (PAI-1)[45,90]	2/2	Low
Angiotensinogen polymorphisms [28,29,81,86]	3/4	Very Low
Angiotensin II receptor polymorphisms [67,76]	2/2	Low
HLA-G 14bp I/D polymorphism[68]	0/1	Moderate
Interleukin-10 polymorphisms [44,65,66,123]	1/4	Low

Supplementary Table 4. GRADE assessment of reported associations.

Prediction of pre-eclampsia: review of reviews

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Keywords

Pre-eclampsia; screening; prediction; hypertension in pregnancy; systematic review

Short title: Prediction of pre-eclampsia: Review of reviews

ABSTRACT

Objective: Primary studies and systematic reviews provide varied accuracy estimates for prediction of pre-eclampsia. We undertook a review of published systematic reviews to collate published evidence on the ability of available tests to predict pre-eclampsia, to identify high value avenues for future research and to minimise future research waste in this field.

Methods: We searched Medline, Embase, DARE (Database of Abstracts of Reviews of Effectiveness) and Cochrane Library databases (from database inception to March 2017) and bibliographies for systematic reviews and meta-analyses without language restrictions. We assessed the quality of the included reviews using the AMSTAR tool and a modified QUIPS tool. We evaluated the reviews' comprehensiveness of search, size, tests and outcomes evaluated, data synthesis methods and predictive ability estimates and risk of bias related to population studied, measurement of predictors and outcomes, study attrition and adjustment for confounding.

Results: From 2444 citations, we included 126 reviews, reporting on over 90 predictors and 52 prediction models. Around a third of all reviews (29.3%, 37/126) investigated biochemical markers for predicting pre-eclampsia; 24.6% (31/126) investigated genetic associations with pre-eclampsia, 36.5% (46/126) reported on clinical characteristics; 3.2% (4/126) evaluated only ultrasound markers; and 4.8% (6/126) studied a combination of tests. Reviews included between two and 265 primary studies, including up to 25,356,688 women in the

largest review. Only half (67/126, 53.2%) assessed the quality of the included studies. There was a high risk of bias in many of the included reviews, particularly in relation to population representativeness and study attrition. Over 80% (106/126, 84.1%) summarised the findings with meta-analysis. Thirty-four studies (32/126, 25.4%) lacked a formal statement on funding. The predictors with the best test performance were body mass index (BMI>35 specificity 92%, 95% CI 89-95% and sensitivity 21%, 95% CI: 12-31%; BMI >25 specificity 73% , 95% CI: 64-83% and sensitivity 47% , 95%CI: 33-61%), first trimester uterine artery Doppler PI or RI >90th centile (specificity 93%, 95% CI: 90%-96%) and sensitivity 26% (23-31%)), PLGF (specificity 89% , 95% CI: 89-89% and sensitivity 65% , 95% CI: 63-67%) and PP13 (specificity 88% , 95% CI: 87-89% and sensitivity 37% , 95% CI: 33-41%). No single marker had a test performance suitable for routine clinical use. The models combining markers showed promise, but none of the identified models had undergone external validation.

Conclusion: Our review of reviews has questioned the need for further aggregate meta-analysis in this area, given the large number of published reviews subject to the common limitations of primary predictive studies. Prospective, well-designed studies of predictive markers, preferably in randomised intervention studies, and combined through IPD (individual patient data) meta-analysis are needed to develop and validate new prediction models to facilitate the prediction of pre-eclampsia and minimise further research waste in this field.

INTRODUCTION

Pre-eclampsia remains a major contributor to maternal and perinatal mortality and morbidity. [1,2] Early treatment with aspirin reduces the risk of pre-eclampsia;[3,4] so accurate screening tests for pre-eclampsia are a clinical priority. Currently, clinical assessment of the risk of pre-eclampsia is based mainly on maternal history[5] with limited predictive ability, [6–8], and is not applicable to nulliparous women. Numerous primary studies have evaluated the predictive ability of various tests including clinical characteristics, biomarkers, and ultrasound markers, individually or in combination, for predicting early, late, and any onset pre-eclampsia.

Systematic reviews collate evidence and aim to provide meaningful summary estimates of the predictive ability of tests through meta-analysis. Despite the number of published studies of predictive factors and screening tests for pre-eclampsia, no consensus has been reached; neither clinicians nor national or international guidelines have implemented screening tests in routine clinical practice. This could be because no tests have been identified with adequate performance, but can also be attributed to the variable quality of the reviews. Very few validate existing prediction models [9] or report on test performance in various combinations, for different thresholds and outcomes.

There is a need to map and critically appraise the available evidence in this field to minimise research waste and prioritise robust investigation of high yield predictive factors and models. We undertook a review of systematic reviews to

systematically collate and critically evaluate the published systematic reviews on risk factors identified as predictors for pre-eclampsia and the reported ability of individual tests to predict pre-eclampsia.

METHODS

Our review of reviews was based on a prospective protocol according to current recommendations [10–12] and reported as per the PRISMA guidelines[13]. The study was registered with the PROSPERO database (CRD42015020386, http://www.crd.york.ac.uk/PROSPERO).

Literature search

We searched Medline, Embase and the Cochrane Library including The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), The Cochrane Central Register of Controlled Trials (CENTRAL), Health Technology Assessment Database (HTA) and NHS Economic Evaluation Database (NHS-EED) from inception to March 2017. We used combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for “pre-eclampsia”, “gestational hypertension”, “pregnancy-induced hypertension” and “review” (Supplementary Material). No language restrictions were imposed. Reference lists of relevant articles and reviews were hand searched to identify additional papers.

Study selection and data extraction

Two reviewers (RT, AK) reviewed all abstracts independently. Any discrepancies on the potential relevance of the papers were resolved by consensus. We obtained full text copies of reviews that met the inclusion criteria.

We included reviews that assessed clinical characteristics, biochemical or ultrasound based variables as predictors or predictive tests for pre-eclampsia. We included reviews evaluating predictors in the first, second or third trimester. Case reports, case series, individual observational or randomised studies, narrative reviews, rapid reviews, editorials and poster abstracts were excluded. Two reviewers (RT, AK) independently extracted relevant data. We obtained data on year of publication, number of databases searched, number of studies included, number of pregnancies/women included, screening tests evaluated and the performance of the tests or degree of association reported with the predictors evaluated.

Definitions

We accepted the authors' definition of pre-eclampsia and hypertensive disorders, and further collected data where it was reported discriminating between early onset pre-eclampsia (requiring delivery prior to 34 weeks' gestation), late onset (delivery after 34 weeks' gestation) or delivery at any time.

Clinical characteristics included signs, symptoms, past medical and obstetric history and environmental exposures elicited through maternal history or physical examination by the booking clinician at the first antenatal visit. Biochemical tests included any measurement of molecules in biological fluids (eg serum and urine). Ultrasound tests included any characteristic identified on ultrasound examination of the pregnancy at any gestation.

We defined a predictor as a clinical characteristic, biochemical or ultrasound marker with the potential to predict the outcome of interest (pre-eclampsia). We defined a predictive model as a combination of predictors obtained through logistic regression analysis to discriminate between populations.

We defined a review as systematic if they included an explicit method for searching the literature, searched two or more databases, and if they provided well defined inclusion and exclusion criteria for studies.

Quality assessment of the included reviews

The rigour of the systematic review and risk of bias in the review findings were assessed using the AMSTAR tool and a modified approach to the QUIPS tool by two independent reviewers (RT, YP) [14–16] (Supplementary File 2). For the AMSTAR assessment we considered whether the reviewers undertook the following: 'a priori' study design, a comprehensive literature search, the status of publication (i.e. grey literature) used as an inclusion criterion, duplicate study selection and data extraction, provided details of the included and excluded studies, reported the characteristics of the included studies, assessed and documented the quality of the included studies, appropriately used the scientific quality of the studies in formulating conclusions, used appropriate methods to combine the findings of studies, assessed the likelihood of publication bias and reported any conflict of interest. We assessed the risk of bias reported in the included reviews according to the QUIPS domains that relate to the key methodological concerns of prognostic research. We considered whether the

reviewers had assessed the representativeness of the patient sample, the impact of study attrition, predictor and outcome measurement, important confounders and the quality of the statistical analysis in the primary studies. Where this information was reported we considered whether the authors had made an assessment of the degree of associated risk of bias. For the studies of genetic factors we applied the Venice criteria[17] to assess the epidemiological credibility of the association based on the amount of evidence, replication and protection from bias in each study.

RESULTS

Review identification

Of the 2444 citations identified, 126 systematic reviews were included in our review. Figure 1 provides details of the review identification and selection process. A list of excluded studies is provided in Supplementary Table 1.

Quality Assessment using the AMSTAR tool

Figure 2a provides the findings of the quality assessment of the included reviews using the AMSTAR tool. Less than a quarter of the included reviews followed a prospectively specified protocol (24/126, 19.1%). Most of the reviews did perform a comprehensive literature search (120/126, 95.2%) with the majority of reviewers searching more than 2 databases. (Figure 2a) The majority of reviews undertook duplicate study selection (111/126, 88.1%), provided the characteristics of the included studies (109/126, 86.5%), and assessed the likelihood of publication bias (80/126, 63.5%). However, only a

quarter provided a list of the included and excluded studies (28/126, 22.2%). About half (71/126, 56.3%) of the reviews performed their literature search without language restriction. (Figure 2a)

Just over half assessed the quality of the included studies (67/126, 53.2%), and only a third took into account the quality of the studies in formulating their conclusions (38/126, 30.2%). The most commonly used tools for quality assessment were QUADAS (17/126, 13.5%) and the Newcastle-Ottawa Scale (NOS) (31/126, 24.6%) although neither are designed for predictive research. None of the reviews published since 2013 used the Quality In Prognosis Studies (QUIPS) tool described in that year that is designed for predictive factor study quality assessment.[16]

Although only half of the reviews assessed the quality of the included studies, many of the primary studies were potentially methodologically biased. They were often retrospective or case-control in design and subject to bias. Examples include significant heterogeneity; failure of masking of those managing the pregnancy or the outcome assessors; nested case-control studies including only a subset of pre-eclampsia cases of the original cohort and failure of application of the screening test to all the eligible participants in cohort studies. Furthermore, the included primary studies had numerous limitations including poor reporting of summary statistics, variable cut-offs of continuous variables, variation in outcomes assessed and the adjustment factors used to calculate test performance.[18]

Risk of bias in included reviews assessed using the modified QUIPS tool

Figure 2b shows the findings of the assessment of included studies against the modified QUIPS tool. Only one study reported on all domains. Of the included reviews, 80/126 (63.5%) reported on participants and representativeness of the population and 56/80 (70%) reported a high or moderate risk of bias in this area in the primary studies. Study attrition was considered in 31/126 (24.6%) with 20/31 (64.5%) reporting a high or moderate risk of bias. Measurement of predictors was evaluated in 101/126 (80.2%) reviews, with 63 (62.4%) describing a high or moderate risk of bias. Measurement of the outcome was well reported, considered in 109/126 (86.5%) of reviews, but 67/109 (61.4%) found a high risk of bias, most commonly related to heterogeneity or lack of clarity in the definition of the outcomes in primary studies. Confounding was considered in 84/126 (66.7%) and the review authors reported that 59/84 (70.2%) had a high or moderate risk of bias relating to insufficient or inappropriate adjustment for important covariables.

Characteristics of the included reviews

The included reviews reported on between 3 and 265 primary studies, with the majority including 10-50 primary studies and including up to 25,356,688 pregnancies in the largest review[19]. (Figure 3) Seventy-nine predictors were evaluated in the included reviews (Table 1). The majority of reviews (53.9%, 68/126) investigated biochemical or genetic tests for predicting pre-eclampsia

while 36.5% (46/126) related to clinical characteristics. Ultrasound markers were reported in only 3.2% (4/126) and a combination of tests in 4.8% (6/126) of reviews (Figure 3). We identified two previous broad systematic reviews of primary studies investigating all screening tests for pre-eclampsia [20,21] from 2004 and 2008.

The most commonly reported clinical characteristics included BMI (n=9 reviews), age (n=2), parity (n=2), blood pressure (n=5) and 6 reviews reported on several clinical characteristics. For the biochemical markers, the following were most commonly studied: PAPP-A (n=4), PlGF (n=5), sFlt-1 (n=3), PP13 (n=4). Over 30 additional markers were reviewed. The ultrasound tests included uterine artery dopplers (n=8) and placental vascularisation indices (n=1). Only two reviews [22,23] summarised the findings with an individual participant data (IPD) meta-analysis. The details of the included reviews (19–144) and key findings are shown in Table 2. Table 2a describes reviews of maternal characteristics, 2b relates to reviews of ultrasound markers, 2c to reviews including biomarkers singly or in combination with other factors and 2d to the genetic association studies.

The majority (67/126, 53.2%) of the included reviews reported odds ratio as a single measure of predictor association with pre-eclampsia rather than directly reporting predictive ability of the predictors investigated. (Table 2). Only 31/126 (24.6%) studies reported measures of predictive ability, with 19 reporting

sensitivities and specificities, 6 area under the receiver operating curve (AUC) and 6 likelihood ratios (LR).

Twenty-one studies declared no funding had been received, while 32 studies lacked a formal statement regarding funding of the studies. Of the remaining studies, 14 (19.2%) declared multiple funding sources. The majority of studies (51/73, 69.8%) declaring their funding sources had been sponsored by national or regional governmental bodies (e.g. National Institute for Health Research (NIHR), National Institutes of Health (NIH), Canadian Institutes of Health Research (CIHR), Health technology Assessment (HTA), National Health and Medical Research Council (NHMRC)). Nearly one quarter (21.9%) were funded through academic institutions, 19.2% by charitable bodies, 4.1% received funding from industry and 9.5% by international bodies, chiefly the World Health Organisation.

There was substantial variation in outcome reporting, including failure to report gestation at delivery and severity of pre-eclampsia. Despite the fact that there has been a transition from a severity-based to a temporal classification of pre-eclampsia [145], only three reviews reported early-onset pre-eclampsia, probably because the outcome was infrequently reported in primary studies (Figure 2). Some studies combined pre-eclampsia with hypertensive disorders, which limited the comparisons between studies. Considerable heterogeneity was highlighted in many of the included reviews and precluded meta-analysis in 15.1% (19/126) reviews.

Key individual predictors for pre-eclampsia

The included reviews reported on over 90 predictors for pre-eclampsia. The findings of the included reviews are summarised in Table 2. For each predictor we applied the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach to prognostic studies[146] to assess the quality of the evidence supporting the associations found. (Supplementary table 3). The most robustly associated clinical, ultrasound and biochemical predictors included BMI, blood pressure, uterine artery Doppler findings and PLGF, sFlt-1 and AFP. (Supplementary Table 4)

Clinical characteristics

Maternal BMI was analysed as a continuous, binary or categorical variable, and was consistently considered to be a weak predictor of pre-eclampsia with a number of studies demonstrating a biological gradient, with increasing BMI increasing the risk of pre-eclampsia [98, 106]. Increased maternal blood pressure (BP), evaluated alone[19,132,136] or in combination with other predictors, [19, 61] in the first or second trimester, was also consistently associated with an increased risk of pre-eclampsia, but the measurement of blood pressure varied between studies.[16, 105, 108] In 2008 Cnossen et al compared the predictive ability of systolic and diastolic blood pressure (SBP and DBP) and mean arterial pressure (MAP) measured at booking and found that mean arterial pressure had a greater area under the curve (AUC 0.76, 95% CI 0.70-0.82) than either diastolic or systolic blood pressure for all pre-eclampsia.[132]

Other clinical characteristics evaluated that demonstrated a consistent association were donor oocyte use in assisted reproduction, sleep disordered breathing, polycystic ovary syndrome, periodontal disease and maternal infections.

Ultrasound markers

First trimester uterine artery Doppler (UtAD) appears to have high specificity (92.1%, 95% CI: 88.6-94.6), but low sensitivity (47.8%, 95% CI: 39.0-56.8%) in predicting early onset pre-eclampsia.[25] The sensitivity of UtAD was even lower for predicting any pre-eclampsia at only 26.4% (95% CI: 22.5-30.8%)(25). One review evaluated placental vascularisation indices (PVIs) measured at 3D ultrasound and found that PVI measured in the first trimester were found to be predictive of later pre-eclampsia with the most sensitive measure being the vascular flow index (VFI).[144] The authors reported an AUC for the prediction of early pre-eclampsia by the vascular flow index of 0.89 (95% CI: 0.78-1.00) and for any pre-eclampsia of 0.77 (95% CI: 0.69-0.84). [144]

Biochemical markers

The biochemical screening markers were grouped according to their mechanism of action (Table 2). Of markers associated with angiogenesis, both PlGF and sFlt-1 were consistently associated with the risk of pre-eclampsia, with an odds ratio of 9.0 (95% CI 5.6–14.5) for PlGF tested before 30 weeks in one large study[49] and although another reported no significant association

between first trimester PlGF and all pre-eclampsia OR 1.94 (95% CI 0.81 to 4.67) there was an association between first trimester PlGF and early onset PE (OR 3.41 ((95% CI 1.61-7.24). [96] For sFlt-1 odds ratios from 1.3 (95% CI 1.02-1.65) to 6.6 (3.1–13.7) were reported, with the association being stronger when tested later in pregnancy. [49,96] For a 5% false positive rate, PlGF and sFlt-1 had sensitivities of 32% and 26%, respectively. [49] Soluble endoglin (sEng) and VEGF were not as consistently found to be associated although at least one study reported that sEng had a sensitivity of 18% to detect PE for a 5% false positive rate. [49] Of the markers routinely tested during aneuploidy screening in the first trimester, alpha feto protein (AFP) had the highest specificity of 96% (95% CI 94 to 98%) with a specificity of only 9% (95% CI 5-16%). [20]

A wide number of gene mutations were considered to be associated with the development of pre-eclampsia, but no single polymorphism was identified with a clinically useful predictive performance. (Table 2). The most frequently investigated genes were methylenetetrahydrofolate reductase (MTHFR) and endothelial nitric oxide synthase (eNOS), and a number of genes relating to elements of the renin-angiotensin-aldosterone system (RAAS) were investigated. The credibility of the association between the MTHFR C677T mutation and pre-eclampsia was generally weak and the association was not large. The credibility of association with mutations of the eNOS gene was moderate, but again this was not a large effect. These patterns do support an association between endothelial and RAAS function and pre-eclampsia, but are not at present useful for prediction of disease.

Multivariable prediction models

No screening marker, whether any of the clinical characteristics, ultrasound or biochemical markers, had both sensitivity and specificity greater than 90%.

Six reviews opted for an approach using combinations of predictive markers (Table 2)[22,85,88,97,99,100] and reported results for 52 individually described models while one group reported on an additional 70 models in groups labelled as 'simple' or 'specialised' based on the inclusion of ultrasound and biochemical tests. [99] Of these studies, only one reported calibration statistics for the model described [22] and one found that of the 14 primary model development papers assessed, only 6 reported model calibration. [99] The remaining prediction modelling papers did not describe calibration of the models presented or assess calibration statistics in the primary studies reviewed. The detection rates (DR) of single markers (ADAM12, beta-hCG, inhibin A, activin A, PP13, PlGF and PAPP-A) for early-onset pre-eclampsia ranged from 22% to 83% for a fixed false positive rate of 10%. [88] These figures improve to between 38% and 100% when a combination of more than two markers was used. [88] The best results (DR 100%, 95% CI 69-100%) were achieved with the combination of three biochemical markers (Inhibin A, PlGF, PAPP-A), uterine artery Doppler and maternal characteristics. [88] For early-onset pre-eclampsia, a model containing only BMI was significantly improved by the addition of mean resistance index (RI) and bilateral notching, with the AUC increasing from 0.66 to 0.92 ($P<0.001$). The addition of mean pulsatility index (PI) and bilateral notching

improved the AUC from 0.62 to 0.95 (P<0.001). [22] The sensitivity for early-onset pre-eclampsia using uterine artery Doppler PI, with mean arterial pressure was 83%, [85] but only 58.5% for late onset pre-eclampsia with the same markers. The improved performance of models containing Doppler or biomarkers is consistent with the finding of one study that adding ultrasound or biomarkers to models based on maternal characteristics alone led to a median gain of 18% in sensitivity.[99]

DISCUSSION

Our review identified 126 systematic reviews on over 90 predictors for pre-eclampsia, although only around a quarter directly reported predictive ability. No test was found to have sensitivity and specificity above 90%. A high sensitivity and specificity are necessary to make screening more cost effective than a 'treat-all' policy in clinical practice.[20] BMI >34kg/m^2, AFP and bilateral uterine artery Doppler notching were reported with specificity of >90% but with low sensitivities, rendering them unsuitable to safely categorise women as 'low risk'. [20] Individual predictors most correlated with pre-eclampsia were uterine artery Doppler indices and angiogenic biomarkers. [22,88,143] Prediction models combining maternal characteristics (particularly BP) with uterine artery Doppler and biomarkers were able to achieve sensitivity and specificity >80%. [22,85,100]

Comparison with existing evidence

Our search identified one prior 'umbrella' review on this topic [147] and two broad systematic reviews of primary studies for prediction of pre-eclampsia from the

HTA in 2008 [20] and the World Health Organisation (WHO) in 2004.[21] All three also identified BMI, uterine artery Doppler and AFP as high performing variables but were also limited by heterogeneity and inconsistent reporting in included primary studies.[20] A subsequently published review of systematic reviews of risk factors for pre-eclampsia, while not examining uterine artery Dopplers, also identified a number of maternal characteristics as important risk factors including obesity, primiparity and smoking status and additionally noted the strong association between assisted reproduction and pre-eclampsia that should be considered in the development of new prediction tools.[148] Several of these studies reported evidence that infrequently studied predictors including kallikreinuria and fibronectin might offer high sensitivity in pre-eclampsia prediction and required further research. No new reviews including these predictors were identified in our search nearly ten years later although new variables, including cell free fetal DNA, can be added to the selection of variables that require further investigation. Previous reviews have also highlighted the need for development of multi-variable models. In this review we have identified over 50 models that have been reported in the last decade, but we also found none that had undergone external validation and could be recommended for routine practice.

Strengths and weaknesses

The strengths of this review include a thorough search strategy and critically evaluative approach. The analysis collates a wide variety of reviews representing the state of research in this field. The findings of the review are

limited by the quality of included studies, compromised by limitations carried over from the primary studies and then the later conduct of the review analysis, especially where investigators did not address risks of bias particular to prediction research.

Clinical and research implications

Maternal characteristics at booking are currently used for screening by most guidelines. [5,149,150] An important characteristic, due to increasing prevalence, is maternal obesity. [151,152] This review confirmed a plausible biological gradient associating maternal obesity with pre-eclampsia and observed that the inclusion of BMI improved the performance of several models.[22,88] It is likely that any clinically useful model would be improved by inclusion of a measurement of maternal obesity.

In seeking to improve on screening by maternal characteristics, many biomarkers were investigated. The angiogenic markers are most promising, particularly PlGF and sFlt-1.[49,61,84,95,96] Of the placental proteins, PP13 and PAPP-A were most consistently associated. [41,61,95,96,101] Large prospective studies using biomarkers are expensive and most data exists for markers routinely obtained during fetal anomaly screening. There is evidence in smaller studies for markers like fibronectin,[20,73] cell free fetal DNA [31,62] and urinary kallikrein[20,21] that requires further investigation.

473 This review further confirmed the screening performance of uterine artery
474 Doppler in the first and second trimesters. Using a model combining systolic
475 blood pressure, uterine artery PI and bilateral notching with BMI can achieve
476 AUC 0.85 (95% CI: 0.67–1.00).[22] but this model is as yet still undergoing
477 external validation, in the SPREE study comparing the National Institute for
478 Health and Care Excellence (NICE) and Fetal Medicine Foundation (FMF)
479 screening models.[153]
480
481 While in previous years the search has been for a single marker to predict pre-
482 eclampsia, recognition of the heterogeneity of the disease phenotype and
483 complexity of prediction has led to consensus that the best approach to pre-
484 eclampsia screening is likely to be calculating individualised risk based on a
485 combination of markers. [6] In this review we have identified key predictors that
486 could be used in developing such a prediction model and propose a solution to
487 address the problems of inconsistent reporting and heterogeneity that have
488 consistently affected the ability of prior reviews to make recommendations on
489 screening.[20,21,147] Since information on multiple predictors will be required,
490 model development will optimally utilise individual level data which can facilitate
491 analysis to identify the predictors that explain most of the variance of the full
492 model. The aim of this approach, already established in cardiovascular
493 prediction modelling,[154] is to develop a model well balanced between optimal
494 performance and parsimony of included predictors leading to greatest ease of
495 use in clinical practice.
496

Using individual patient data meta analysis for model development (IPD-MA) could additionally address poor reporting and heterogeneity in primary studies. While resource intensive and still subject to publication bias, IPD-MA is becoming the gold standard for predictive meta-analysis. [155] The advantages of IPD-MA over conventional meta-analysis include use of all available data; flexibility to combine data uniformly; the use of original data allowing analysis of continuous variables and comparison between datasets. [156] Moreover, it permits comparison of multivariable prediction strategies and the possibility of time-to-event analysis, particularly relevant to pre-eclampsia where gestation is inextricably linked to maternal and fetal outcomes. [157]

Research priorities should include prospectively registered predictive studies of promising markers, with results for each marker alone and in combination with other tests and clear reporting of methods and timing of variable and outcome measurements. A particular focus should be high performance tests in the first trimester, when the benefits of intervention are greatest. IPD meta-analysis combining the most promising predictors can then be used to develop prediction models for external validation before introduction into clinical practice.

Predictive variables by themselves do not improve outcome; the subsequent preventive interventions do. Since it is not self-evident that a treatment has a stable effect in women with different profiles, predictive markers should be evaluated in studies that evaluate the impact of predictive strategies. [158] The ideal predictor not only predicts pre-eclampsia, but also predicts treatment

modification, i.e. whether a treatment improves the outcome in a particular category of patients.

In order to conduct effective primary studies and analyses, consensus on outcomes is needed. Identification of a core outcome set for pre-eclampsia studies [159] is a key priority. Such an approach will enable us to move beyond repeating small, low quality prognostic factor studies to investigating the clinical impact of prediction model use in clinical practice.

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Conflict of interest

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