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Abstract

Validation and development of models using clinical, biochemical and ultrasound markers for predicting pre-eclampsia: an individual participant data meta-analysis

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Background: Pre-eclampsia is a leading cause of maternal and perinatal mortality and morbidity. Early identification of women at risk is needed to plan management.

Objectives: To assess the performance of existing pre-eclampsia prediction models and to develop and validate models for pre-eclampsia using individual participant data meta-analysis. We also estimated the prognostic value of individual markers.

Design: This was an individual participant data meta-analysis of cohort studies.

Setting: Source data from secondary and tertiary care.

Predictors: We identified predictors from systematic reviews, and prioritised for importance in an international survey.

Primary outcomes: Early-onset (delivery at < 34 weeks' gestation), late-onset (delivery at \geq 34 weeks' gestation) and any-onset pre-eclampsia.

Analysis: We externally validated existing prediction models in UK cohorts and reported their performance in terms of discrimination and calibration. We developed and validated 12 new models based on clinical characteristics, clinical characteristics and biochemical markers, and clinical characteristics and ultrasound markers in the first and second trimesters. We summarised the data set-specific performance of each model using a random-effects meta-analysis. Discrimination was considered promising for C-statistics of \geq 0.7, and calibration was considered good if the slope was near 1 and calibration-in-the-large was near 0. Heterogeneity was quantified using I^2 and τ^2 . A decision curve analysis was undertaken to determine the clinical utility (net benefit) of the models. We reported the unadjusted prognostic value of individual predictors for pre-eclampsia as odds ratios with 95% confidence and prediction intervals.

Results: The International Prediction of Pregnancy Complications network comprised 78 studies (3,570,993 singleton pregnancies) identified from systematic reviews of tests to predict pre-eclampsia. Twenty-four of the 131 published prediction models could be validated in 11 UK cohorts. Summary C-statistics were between 0.6 and 0.7 for most models, and calibration was generally poor owing to large between-study heterogeneity, suggesting model overfitting. The clinical utility of the models varied between showing net harm to showing minimal or no net benefit. The average discrimination for IPPIC models ranged between 0.68 and 0.83. This was highest for the second-trimester clinical characteristics and biochemical markers model to predict early-onset pre-eclampsia, and lowest for the first-trimester clinical characteristics models to predict any pre-eclampsia. Calibration performance was heterogeneous across studies. Net benefit was observed for International Prediction of Pregnancy Complications first and second-trimester clinical characteristics and clinical characteristics and biochemical markers models predicting any pre-eclampsia, when validated in singleton nulliparous women managed in the UK NHS. History of hypertension, parity, smoking, mode of conception, placental growth factor and uterine artery pulsatility index had the strongest unadjusted associations with pre-eclampsia.

Limitations: Variations in study population characteristics, type of predictors reported, too few events in some validation cohorts and the type of measurements contributed to heterogeneity in performance of the International Prediction of Pregnancy Complications models. Some published models were not validated because model predictors were unavailable in the individual participant data.

Conclusion: For models that could be validated, predictive performance was generally poor across data sets. Although the International Prediction of Pregnancy Complications models show good predictive performance on average, and in the singleton nulliparous population, heterogeneity in calibration performance is likely across settings.

Future work: Recalibration of model parameters within populations may improve calibration performance. Additional strong predictors need to be identified to improve model performance and consistency. Validation, including examination of calibration heterogeneity, is required for the models we could not validate.

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List of supplementary material

Report Supplementary Material 1 Supplementary figures

Supplementary material can be found on the NIHR Journals Library report page (<https://doi.org/10.3310/hta24720>).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AMND	Aberdeen Maternity and Neonatal Databank	OR	odds ratio
BMI	body mass index	PAPP-A	pregnancy-associated plasma protein A
CI	confidence interval	PCR	protein-creatinine ratio
CRP	C-reactive protein	PIGF	placental growth factor
DBP	diastolic blood pressure	POP	Pregnancy Outcome Prediction
HELLP	haemolysis, elevated liver enzymes and low platelet count	PROBAST	Prediction study Risk of Bias Assessment Tool
IPD	individual participant data	SBP	systolic blood pressure
IPPIC	International Prediction of Pregnancy Complications	SCOPE	Screening for Pregnancy Endpoints
IQR	interquartile range	sFlt-1	soluble fms-like tyrosine kinase-1
LP	linear predictor	WHO	World Health Organization
MAP	mean arterial blood pressure		

Plain English summary

What is the problem?

Pre-eclampsia, a condition in pregnancy that results in raised blood pressure and protein in the urine, is a major cause of complications for the mother and baby.

What is needed?

A way of accurately identifying women at high risk of pre-eclampsia to allow clinicians to start preventative interventions such as administering aspirin or frequently monitoring women during pregnancy.

Where are the research gaps?

Although over 100 tools (models) have been reported worldwide to predict pre-eclampsia, to date their performance in women managed in the UK NHS is unknown.

What did we plan to do?

We planned to comprehensively identify all published models that predict the risk of pre-eclampsia occurring at any time during pregnancy and to assess if this prediction is accurate in the UK population. If the existing models did not perform satisfactorily, we aimed to develop new prediction models.

What did we find?

We formed the International Prediction of Pregnancy Complications network, which provided data from a large number of studies (78 studies, 25 countries, 125 researchers, 3,570,993 singleton pregnancies). We were able to assess the performance of 24 out of the 131 models published to predict pre-eclampsia in 11 UK data sets. The models did not accurately predict the risk of pre-eclampsia across all UK data sets, and their performance varied within individual data sets. We developed new prediction models that showed promising performance on average across all data sets, but their ability to correctly identify women who develop pre-eclampsia varied between populations. The models were more clinically useful when used in the care of first-time mothers pregnant with one child, compared to a strategy of treating them all as if they were at high-risk of pre-eclampsia.

What does this mean?

Before using the International Prediction of Pregnancy Complications models in various populations, they need to be adjusted for characteristics of the particular population and the setting of application.

Scientific summary

Background

Pre-eclampsia is a leading cause of maternal and perinatal mortality and morbidity. Current methods of risk assessment for pre-eclampsia are based mainly on clinical history alone and have limited accuracy. Prediction models that incorporate additional information on biochemical and ultrasound markers could improve the predictive performance. Numerous multivariable pre-eclampsia models have been developed to date, but only a few have been externally validated, and none is recommended for use in routine clinical practice. Robust data are needed to externally validate existing models to determine their transportability across new populations and their clinical utility.

Objectives

Primary

The primary objectives were to use individual participant data meta-analysis:

- to validate (across multiple populations and settings) existing models for predicting early-onset, late-onset and any-onset pre-eclampsia based on clinical characteristics only, clinical and biochemical markers, clinical and ultrasound markers, and clinical, biochemical and ultrasound markers
- to develop and validate (across multiple populations and settings) multivariable prediction models for early-onset, late-onset and any-onset pre-eclampsia where existing prediction models have limited performance, or where no such models exist for the relevant pre-eclampsia outcomes
- to estimate the net benefit (clinical utility) of existing and new models to inform clinical decision making based on thresholds of predicted risk
- to estimate the prognostic value of individual clinical, biochemical and ultrasound markers for predicting pre-eclampsia.

Secondary

- To assess the differential performance of the existing models in various predefined subgroups based on population characteristics (unselected; selected) and timing of model use (first trimester; second trimester).
- To study the added accuracy when novel metabolic and microRNA-based biochemical markers are added to the developed model based on clinical, ultrasound and biochemical markers.

Methods

We undertook an individual participant data meta-analysis in line with existing recommendations on prognostic research model development and validation and complied with reporting guidelines for prediction models and individual participant data meta-analysis. We undertook relevant systematic reviews to identify systematic reviews on clinical characteristics, biochemical and ultrasound markers for prediction of pre-eclampsia; prediction models for pre-eclampsia; and relevant studies, birth cohorts or data sets. Primary studies and large birth and population-based cohorts that provided relevant information for assessing the accuracy of clinical, biochemical and ultrasound predictors of pre-eclampsia were included. The primary outcomes were early-onset (delivery at < 34 weeks' gestation), late-onset (delivery at ≥ 34 weeks' gestation) and any-onset pre-eclampsia. We established the International Prediction of Pregnancy Complications collaborative network, and researchers from this group shared their primary data, which required extensive cleaning, standardisation and quality checking.

We externally validated published pre-eclampsia prediction models that reported the full model equation in International Prediction of Pregnancy Complications UK data sets. Partially missing predictors or outcome values missing for < 95% of individuals in a data set were multiply imputed under the missing at random assumption using multiple imputation by chained equations. Imputation was carried out separately in each dataset to account for the clustering of individuals within a data set. The predictive performance of each model was examined using measures of discrimination (C-statistics; no discrimination 0.5 to perfect discrimination 1, with values of ≥ 0.7 deemed most promising) and calibration of predicted to observed risks (calibration slope, with an ideal value of 1; and calibration-in-the-large, with an ideal value of 0) first in the individual participant data for each available data set and then across data sets at the meta-analysis level. We also compared the clinical utility (net benefit) of validated prediction models for each pre-eclampsia outcome using a decision curve analysis.

We then developed and validated new prediction models for early-onset, late-onset and any-onset pre-eclampsia based on clinical characteristic variables alone, clinical characteristics and biochemical markers, and clinical characteristics and ultrasound markers. For each model developed, we summarised the data set-specific performance (C-statistic, calibration slope and calibration-in-the-large), using a random-effects meta-analysis, in terms of the average performance and (to examine potential generalisability across settings) the heterogeneity in performance. We also assessed the clinical utility of developed models using a decision curve analysis.

Outside model development, we also used the full International Prediction of Pregnancy Complications data set to obtain summary-unadjusted estimates of the prognostic effects of prioritised candidate predictors for early-onset, late-onset and any-onset pre-eclampsia, along with 95% confidence intervals and 95% prediction intervals, using a two-stage individual participant data meta-analysis of complete cases of singleton pregnancies. The two-stage approach involves first fitting a logistic regression model for each study and then pooling the log-odds ratios using a conventional random-effects meta-analysis. Clustering of participants within data sets was accounted for by analysing each data set separately in the first stage.

Results

One hundred and twenty-five researchers from 73 teams in 25 countries joined the International Prediction of Pregnancy Complications network (by October 2017) and provided access to anonymised individual data of 3,674,684 pregnancies (78 data sets). More than half of the data sets (58%, 45/78) were prospective cohort studies, 15% (12/78) were randomised controlled trials and 17% (13/78) were large prospective registry data sets or birth cohorts. One data set included individual participant data from 31 randomised controlled trials.

External validation of existing pre-eclampsia prediction models

Of the 131 models identified, 24 could be validated in one or more of the 11 International Prediction of Pregnancy Complications UK data sets. Eight models predicted any-onset pre-eclampsia (three on clinical characteristics only, three with additional biochemical markers and two with additional ultrasound markers), nine predicted early-onset pre-eclampsia (seven included clinical characteristics only, and one each included additional biochemical or ultrasound markers), and seven predicted late-onset pre-eclampsia (five included clinical characteristics only, and one each included additional biochemical and ultrasound markers). Discrimination performance of the models was modest, with summary C-statistics of around 0.6–0.7 for most models. Calibration was generally poor across the data sets, with large heterogeneity in performance across different International Prediction of Pregnancy Complications data sets, with most of the models demonstrating signs of overfitting (summary calibration slope of < 1) and predictions that were systematically too high or too low (calibration-in-the-large $\neq 0$, suggesting poor prediction of overall risk across populations). In most of the data sets, the net benefit of using the models was only slightly greater than the strategy of considering all women to have pre-eclampsia.

Development and validation of International Prediction of Pregnancy Complications pre-eclampsia prediction models

Twelve International Prediction of Pregnancy Complications pre-eclampsia models were developed: four each to predict any-onset, early-onset and late-onset pre-eclampsia (two models each in the first and second trimesters using clinical characteristics, and with additional biochemical markers). We developed each model by meta-analysing 3–11 International Prediction of Pregnancy Complications data sets. The clinical characteristics only models comprised maternal age, body mass index, parity, history of pre-eclampsia, hypertension, diabetes or autoimmune disease and systolic or diastolic blood pressure. In addition to the clinical characteristic predictors, the biochemical marker models included soluble fms-like tyrosine kinase-1, pregnancy-associated plasma protein A and placental growth factor.

For predicting any pre-eclampsia, all second-trimester models (clinical only, clinical and biochemical predictors) showed promising discrimination (average C-statistics of ≥ 0.7); first trimester clinical only, and clinical and biochemical models had summary C-statistics of 0.68 and 0.70, respectively. All models to predict early-onset pre-eclampsia had promising discrimination; the first trimester (clinical only, clinical and biochemical) models had summary C-statistics of 0.72 (95% confidence interval 0.59 to 0.82) and 0.76 (95% confidence interval 0.58 to 0.88) respectively; the corresponding values for second-trimester clinical only and clinical and biochemical models were 0.72 (95% confidence interval 0.60 to 0.82) and 0.83 (95% confidence interval 0.63 to 0.93). For predicting late-onset pre-eclampsia, the second-trimester models (clinical only, clinical and biochemical predictors) showed promising discrimination (average C-statistics ≥ 0.7); the first-trimester models' C-statistics ranged from 0.68 to 0.69. Summary calibration measures often had wide confidence intervals, and there was often large between-study heterogeneity in the calibration performance, particularly for clinical and biochemical marker models. The net benefit of the models varied across individual data sets, ranging from harm to very little benefit to no benefit.

When validated in individual cohorts with over 100 pre-eclampsia events, the first-trimester clinical model for any pre-eclampsia was well calibrated in the Baschat study (any pregnant women in the USA) (Baschat AA, Magder LS, Doyle LE, Atlas RO, Jenkins CB, Blitzer MG. Prediction of preeclampsia utilizing the first trimester screening examination. *Am J Obstet Gynecol* 2014;**211**:514.e1–7); the predictions were too high for individuals in the World Health Organization study (women with risk factors for pre-eclampsia from low-, middle- and high-income countries) (Widmer M, Cuesta C, Khan KS, Conde-Agudelo A, Carroli G, Fusey S, *et al.* Accuracy of angiogenic biomarkers at 20 weeks' gestation in predicting the risk of pre-eclampsia: a WHO multicentre study. *Pregnancy Hypertens* 2015;**5**:330–8) and low for those at high risk in the Pregnancy Outcome Prediction (POP) (nulliparous, singleton pregnancies in the UK) [Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. *Lancet* 2015;**386**:2089–97]. We observed a consistent net benefit for all International Prediction of Pregnancy Complications models when validated in the POP cohort for probability thresholds of $\geq 5\%$. Very little or no net benefit was observed in other data sets.

Summarising the unadjusted prognostic effect of individual predictors of pre-eclampsia

Any-onset pre-eclampsia

We observed a strong unadjusted association between any-onset pre-eclampsia and history of hypertension (odds ratio 4.76, 95% confidence interval 3.56 to 6.35; $I^2 = 98.39\%$), multiparity (odds ratio 0.88, 95% confidence interval 0.79 to 0.99; $I^2 = 96.6\%$), smoking during pregnancy (odds ratio 0.84, 95% confidence interval 0.76 to 0.93; $I^2 = 86.46\%$) and spontaneous mode of conception (odds ratio 0.73, 95% confidence interval 0.64 to 0.84; $I^2 = 58.67\%$), and increasing placental growth factor in the first (odds ratio 0.22, 95% confidence interval 0.09 to 0.50, $I^2 = 85.44$), second (odds ratio 0.66, 95% confidence interval 0.53 to 0.83; $I^2 = 87.27\%$) or third trimester (odds ratio 0.59, 95% confidence interval 0.45 to 0.77; $I^2 = 96.78\%$) showed a reduction in the odds of any-onset pre-eclampsia.

Early-onset pre-eclampsia

Increasing second-trimester measurement of uterine artery pulsatility index values had the strongest association with early-onset pre-eclampsia (odds ratio 14.73, 95% confidence interval 8.12 to 26.72; $I^2 = 60.11\%$). All statistically significant predictors had evidence of an increase in the odds of early-onset pre-eclampsia with increasing values, except placental growth factor measured in the first (odds ratio 0.08, 95% confidence interval 0.02 to 0.35; $I^2 = 55.69\%$) or second trimester (odds ratio 0.07; 95% confidence interval 0.01 to 0.43; $I^2 = 97.18\%$), which showed a decrease in odds with increasing values.

Late-onset pre-eclampsia

The strongest association with late-onset pre-eclampsia was observed for increasing uterine artery pulsatility index values measured in the second trimester (odds ratio 2.95, 95% confidence interval 2.31 to 3.76; $I^2 = 20.77\%$). Multiparity (odds ratio 0.87, 95% confidence interval 0.78 to 0.97; $I^2 = 95.16\%$) and increasing values of first (odds ratio 0.33, 95% confidence interval 0.16 to 0.68; $I^2 = 82.67\%$), second (odds ratio 0.81, 95% confidence interval 0.69 to 0.94; $I^2 = 76.39\%$) or third (odds ratio 0.68, 95% confidence interval 0.57 to 0.81; $I^2 = 93.60\%$) trimester measurement of placental growth factor and first-trimester soluble fms-like tyrosine kinase-1 (odds ratio 0.98, 95% confidence interval 0.97 to 0.99; $I^2 = 37.07\%$) showed a decrease in the odds of late-onset pre-eclampsia.

There was considerable heterogeneity for most prognostic effects, with wide 95% prediction intervals for the potential prognostic effect of factors in new populations.

Conclusions

Among the 24 existing prediction models that could be validated in individual participant data meta-analysis, their predictive performance was generally poor across data sets (both on average and in terms of heterogeneity in calibration of predicted risks with observed risks), with very limited evidence of clinical utility. Some of the heterogeneity in predictive performance of the models is likely due to different methods and timing of measurement, for example in blood pressure and biochemical marker values. Although the International Prediction of Pregnancy Complications models show promising predictive performance on average across data sets, heterogeneity across settings is likely in calibration performance. Ultrasound markers did not improve the predictive performance of the developed International Prediction of Pregnancy Complications clinical characteristic only models. The International Prediction of Pregnancy Complications pre-eclampsia models show consistent net benefit when applied to a cohort of singleton, nulliparous women in the UK. Before application in practice, calibration performance may need to be improved by recalibrating model parameters, such as the intercept, to particular populations and settings.

Recommendations for further research

Going forward, standardisation of measurement methods, for example across laboratories and hospitals, might reduce heterogeneity in calibration performance. A related point is that prediction models in this field need to be clearer with regard to how included predictors should be measured and exactly when this should occur. Validation, including examination of calibration heterogeneity, is still required for the models that we could not validate. The transportability of these and the International Prediction of Pregnancy Complications models needs to be assessed in multiple large data sets across different settings and populations, as does their acceptability to both women and health-care professionals. The impact of using the models in clinical practice needs to be evaluated beyond pre-eclampsia prediction to include the identification of women most at risk of other severe pregnancy complications. Updated models may be needed in local populations, using recalibration of the International Prediction of Pregnancy Complications models in local data sets, to improve calibration performance. Furthermore, additional strong predictors need to be identified to improve model

performance and consistency. New cohorts must standardise the predictors and outcomes measured, including their timing and measurement methods, to enable more homogenous data sets to be combined in individual participant data meta-analyses. In terms of the prognostic ability of particular factors, further analysis of the International Prediction of Pregnancy Complications data using multilevel multiple imputation for missing data and adjusting for confounders would provide a better evaluation of prognostic association.

Study registration

This study is registered as PROSPERO CRD42015029349.

Funding

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Chapter 1 Background

Pre-eclampsia is a pregnancy-specific condition associated with hypertension and multiorgan dysfunction such as proteinuria, renal or hepatic impairment and fetal growth restriction.¹⁻⁵ It is a heterogeneous disorder with a wide spectrum of multiorgan involvement, which reflects its various pathophysiological pathways. Pre-eclampsia affects between 2% and 8% of pregnancies worldwide⁶ and is a leading cause of both maternal and perinatal morbidity and mortality.⁷⁻¹⁰ Each year, 18% of all maternal deaths can be attributed to pre-eclampsia and its complications, with most of these occurring in low- and middle-income countries.^{11,12} In the long term, pre-eclampsia is associated with an increased maternal risk of ischaemic heart disease, chronic hypertension, stroke and end-stage renal disease.^{13,14} Children from pre-eclamptic pregnancies also have higher risks of cardiovascular diseases,^{15,16} mental health disorders and cognitive impairment.^{17,18}

Two subgroups of pre-eclampsia are well recognised: early-onset, requiring delivery before 34 weeks' gestation, and late-onset, with delivery occurring at or after 34 weeks' gestation.¹⁹⁻²¹ Early-onset pre-eclampsia is considered to be a pathophysiologically different disease from late-onset pre-eclampsia in the mechanism leading to placental dysfunction and clinical timing during pregnancy.²² Early-onset pre-eclampsia is associated with a considerably higher increased risk of maternal complications, such as a 20-fold higher rate of mortality, than the late-onset type, and early delivery is the only treatment.²³⁻²⁵ In addition to the prematurity-related complications, the risks of stillbirth and adverse perinatal outcomes are much higher in women with early-onset disease.²⁶

Although the proportion of women with early-onset pre-eclampsia is < 1% of all pregnancies, the complexity of treatment gives rise to high health-care costs.^{27,28} Affected women are often admitted to a tertiary care facility, and 30% experience complications that may necessitate management in an intensive care unit.²⁹ Infants usually need prolonged care for the management of complications, including lifelong disabilities, arising as a result of premature delivery. The additional NHS costs incurred in caring for a baby born at or before 28 weeks and a baby born between 28 and 33 weeks are £94,190 and £61,509, respectively.³⁰ The cost to the NHS of caring for preterm babies, linked to neonatal care, such as incubation, and hospital readmissions, has been estimated at £939M annually.³⁰

Late-onset pre-eclampsia, including pre-eclampsia at term, also poses a significant health burden. It accounts for the majority of pre-eclampsia diagnoses in pregnancy. One-fifth of all women with late-onset disease have maternal complications such as HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome, and more than half of eclamptic seizures occur at term.^{28,31,32}

Pregnant women who are at high risk of pre-eclampsia require close monitoring and are usually started on prophylactic aspirin in early pregnancy to reduce the risk of development of pre-eclampsia and occurrence of adverse outcomes. Early commencement of this has the potential for maximum benefit,³³ which may be limited to early-onset disease.³⁴ It is important to be able to quantify a woman's risk of developing pre-eclampsia during the course of pregnancy to help guide clinical decisions and monitoring strategies. The National Institute for Health and Care Excellence prioritises screening for early-onset pre-eclampsia in its research recommendations on antenatal care of women.³⁵

Currently, the assessment of a woman's risk of developing pre-eclampsia is based mainly on clinical history,³⁶ but such risk-based predictions have been shown to have limited accuracy.³⁷ Risk factors based on clinical characteristics have also been shown to have quantitatively different associations with early- and late-onset pre-eclampsia,²⁶ and, similarly, biochemical and ultrasound markers have variations in their performance in predicting the two types of pre-eclampsia.³⁷⁻³⁹ Prediction models incorporating additional tests for biochemical and ultrasound markers may improve the predictive performance of models.⁴⁰⁻⁴² It is, however, unlikely that a single model will accurately predict both early- and late-onset pre-eclampsia.²⁶

BACKGROUND

There are more than 60 multivariable prediction models developed to predict pre-eclampsia, using various combinations of clinical, biochemical and ultrasound risk factors.⁴³ Such models and tests for predicting pre-eclampsia have been based on findings from aggregate meta-analysis and primary studies, and none is recommended for use in routine clinical practice. This is because there is an absence of information about the reproducibility of the models or their predictive performance in different settings.

Although interventions such as aspirin have been found to significantly reduce the risk of early-onset pre-eclampsia in women predicted to be at 'high risk' of pre-eclampsia using a model, lack of robust information on the accuracy of this model means that we could not rule out potential benefit in women considered to be 'low risk'. Before they can be used in clinical practice, prediction models need to be appropriately validated in multiple data sets external to that used to develop the model. This often takes many years to accomplish in a primary study, and, as a result, very few models have been externally validated to date.⁴³⁻⁴⁶ Individual studies also often have an insufficient sample size to externally validate the relatively rare but serious condition of early-onset pre-eclampsia.²⁶

Meta-analysis of individual participant data (IPD), whereby the raw participant-level information is obtained and synthesised across multiple data sets, overcomes the limitations above.⁴⁷⁻⁵⁰ The availability of the raw data substantially increases the sample size beyond what is achievable in a single study, and offers a unique opportunity to evaluate the generalisability of predictive performance of existing models across a range of clinical settings. Using IPD meta-analysis allows the standardisation of predictors and outcome definitions, takes into account the performance of many candidate prognostic variables, directly handles missing predictors and outcomes data, accounts for heterogeneity in baseline risks, and, most importantly, develops, validates and tailors the use of the most accurate prediction models to the appropriate population.

The unmet need for prediction models for pre-eclampsia, particularly early-onset pre-eclampsia, is mainly a result of lack of information on the generalisability of the models and their performances in external cohorts. Hence, before more resources are spent on developing further models, what is needed is external validation of existing models. If existing models' performances are suboptimal, then further development of new models is warranted with sufficient sample size.

Chapter 2 Objectives

Material in this chapter has been adapted from Allotey *et al.*⁵¹ This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <http://creativecommons.org/licenses/by/4.0/>. The text below includes minor additions and formatting changes to the original text.

We planned to externally validate and update prediction models for (1) early-onset (delivery at < 34 weeks' gestation), (2) late-onset (delivery at \geq 34 weeks' gestation) and (3) any-onset pre-eclampsia, and to further develop new prediction models for the above outcomes, if required, using IPD meta-analysis.

Primary objectives

- To validate and improve or tailor the performance of existing models in relevant population groups for predicting early-onset, late-onset and any-onset pre-eclampsia in our IPD data set based on:
 - clinical characteristics only
 - clinical and biochemical markers
 - clinical and ultrasound markers
 - clinical, biochemical and ultrasound markers.
- Using IPD meta-analysis, to develop and externally validate (using internal–external cross-validation) multivariable prediction models for early, late and any-onset pre-eclampsia in the following circumstances:
 - where existing predictive strategies cannot be adjusted for the target population
 - where no such models exist for the relevant pre-eclampsia outcomes.
- To estimate the prognostic value of individual clinical, biochemical and ultrasound markers for predicting pre-eclampsia by IPD meta-analysis.

Secondary objectives

- To assess the differential performance of the existing models in various predefined subgroups based on population characteristics (unselected; selected) and timing of model use (first trimester; second trimester).
- To study the added accuracy when novel metabolic and microRNA-based biochemical markers are added to the developed model based on clinical, ultrasound and biochemical markers.

Chapter 3 Methods

Material in this chapter has been adapted from Allotey *et al.*⁵¹ This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <http://creativecommons.org/licenses/by/4.0/>. The text below includes minor additions and formatting changes to the original text.

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Our IPD meta-analysis followed existing recommendations on prognostic research model development and validation⁵³⁻⁵⁵ and adhered to reporting guidelines for prediction models and IPD meta-analysis.^{56,57} We used a prospective protocol⁵¹ registered on the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42015029349.⁵⁸

Eligibility criteria

Criteria for including relevant cohorts and studies in the individual participant data

We included primary studies (prospective and retrospective cohort studies, as well as cohorts nested within randomised trials), and large birth and population-based cohorts with information to assess the accuracy of clinical, biochemical and ultrasound predictors in women at low, high or any risk to predict early-, late- or any-onset pre-eclampsia and its associated complications. The process of identifying and selecting studies to invite to form the IPPIC network is described in detail in our published protocol, as well as in the following sections (see *Literature search and study identification*, *The IPPIC pre-eclampsia network* and *Study selection, individual participant data collection and harmonisation*). Studies or cohorts that addressed the structured question in *Table 1* were included in the IPD. The predictors considered for evaluation were chosen a priori and were clearly defined and standardised.^{39,60-72}

The primary outcomes were early-onset (delivery at < 34 weeks' gestation), late-onset (delivery at ≥ 34 weeks' gestation) and any-onset pre-eclampsia. The authors reported the definition of the primary outcome of pre-eclampsia along with gestational age at delivery, which was used to define early- and late-onset disease. Definitions of pre-eclampsia included proteinuric and non-proteinuric pre-eclampsia.^{35,73}

The secondary outcomes were composite adverse maternal or fetal and neonatal outcomes.

Literature search and study identification

We undertook a systematic review of reviews to identify relevant systematic reviews on clinical characteristics, biochemical and ultrasound markers for prediction of pre-eclampsia.³⁷ We adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines on

TABLE 1 Structured question for IPD meta-analysis on prediction of pre-eclampsia

Question components	Definition
Population	Pregnant women
Predictors	<p>Maternal clinical characteristics at antenatal booking</p> <p>Maternal characteristics: age, BMI, height, weight, ethnicity, smoking, alcohol or substance misuse</p> <p>Medical history: pre-existing chronic kidney disease, heritable thrombophilias, autoimmune disease such as systemic lupus erythematosus and antiphospholipid syndrome, type 1 and 2 diabetes and hypertensive diseases</p> <p>Obstetric history: parity, previous pre-eclampsia, gestational diabetes, pregnancy interval of > 10 years, family history of pre-eclampsia, family history of cardiovascular disease, previous miscarriages, preterm birth, stillbirth or SGA fetus</p> <p>Current pregnancy: multiple pregnancy, mode of conception, early pregnancy bleeding, MAP, SBP and DBP, socioeconomic status, new partner, diet or exercise in pregnancy, urine dipstick, PCR, 24-hour protein</p> <p><i>Biochemical markers (first or second trimester):</i> PAPP-A, sFlt-1, PIGF, AFP, human chorionic gonadotropin, sENG, CRP, hypertriglyceridaemia and PAI-1</p> <p>Ultrasound markers (first or second trimester)</p> <p>CRL, abdominal circumference, expected fetal weight centile, uterine and umbilical artery Doppler (resistance index, pulsatility index, unilateral or bilateral notching)</p>
Outcomes	<p>Primary outcomes</p> <p>Early-onset (delivery at < 34 weeks' gestation), late-onset (delivery at ≥ 34 weeks' gestation) and any-onset pre-eclampsia</p> <p>Secondary outcomes</p> <p>Maternal complications: eclampsia, HELLP syndrome, abruption, hepatic and renal failure, cortical blindness, pulmonary oedema, postpartum haemorrhage, disseminated intravascular coagulation, preterm delivery, admission to high-dependency unit/intensive care unit, maternal death, caesarean section, gestational diabetes mellitus</p> <p>Fetal and neonatal complications: birthweight in kg and centile (using the Gestation Network bulk centile calculator⁵⁹), SGA fetus, stillbirth, neonatal death, hypoxic-ischaemic encephalopathy, respiratory distress syndrome, septicaemia, admission to neonatal unit</p>
Study design	Observational studies and cohorts nested within randomised trials

AFP, alpha-fetoprotein; BMI, body mass index; CRL, crown-rump length; CRP, C-reactive protein; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; PAI-1, plasminogen activator inhibitor-1; PAPP-A, pregnancy-associated plasma protein A; PCR, protein-creatinine ratio; PIGF, placental growth factor; SBP, systolic blood pressure; sENG, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase-1; SGA, small for gestational age.

Adapted from Allotey *et al.*⁵¹ This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <http://creativecommons.org/licenses/by/4.0/>. The table includes minor additions and formatting changes to the original table.

reporting, and the review was based on a prospective protocol. The systematic review methods have been published elsewhere, but, briefly, two reviewers independently screened abstracts, extracted data and carried out quality assessment.³⁷ We defined the inclusion and exclusion criteria for the systematic reviews, the outcome of interest (pre-eclampsia) and the predictors. We also updated our previous literature search of prediction models for pre-eclampsia⁴³ (July 2012–December 2017) to identify additional models. We searched the following databases: MEDLINE, EMBASE, Bioscience Information Services (BIOSIS), Latin American and Caribbean Health Sciences Literature (LILACS), PASCAL, Science Citation Index, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled

Trials (CENTRAL), National Institute of Child and Human Development Data and Specimen Hub, Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment database without any language restrictions. Research reported in grey literature was sought by searching a range of relevant databases including the Inside Conferences, Systems for Information in Grey Literature, MotherChild Link Registry (www.linkregistry.org/search.aspx), Dissertation Abstracts and ClinicalTrials.gov. Data extraction following the update of our literature search for prediction models for pre-eclampsia was carried out by two reviewers independently.

We used additional sources such as internet searches using general search engines (e.g. Google; www.google.co.uk/) and meta-search engines (e.g. Copernic; www.copernic.com/), and directly contacted researchers to identify relevant studies, birth cohorts or data sets that may have been missed. Collaborative groups such as the Global Pregnancy Collaboration (CoLab), Pre-eclampsia and Eclampsia Monitoring, Prevention and Treatment (PRE-EMPT) and the Global Obstetrics Network (GONet) were also approached to identify primary studies, unpublished research and birth cohorts.⁷⁴⁻⁷⁶ We did not include studies, birth cohorts or data sets after October 2017, as we needed time to clean and format the data prior to any analysis. The details of the search strategy are provided in *Appendix 2*.

The IPPIC pre-eclampsia network

We established a collaborative network of investigators (IPPIC) from research groups that have undertaken studies on clinical characteristics, biochemical and ultrasound markers in the prediction of early- and any-onset pre-eclampsia. The network is a global effort bringing together 125 researchers, clinicians and epidemiologists from 25 countries and is supported by the World Health Organization (WHO). We invited authors of all primary studies identified from this review and also invited investigators of primary studies and large birth and population-based cohorts that were not included in existing reviews but were identified through our links with other collaborative groups⁷⁴⁻⁷⁶ if these provided relevant information to assess the accuracy of clinical, biochemical and ultrasound predictors of pre-eclampsia.

Study selection, individual participant data collection and harmonisation

The collaborative group agreed the minimum data to be requested for the IPD meta-analysis, and a custom-built database was set up based on these specifications. The minimum data requested were pre-eclampsia outcome with gestational age at delivery, as well as any of the clinical, biochemical and ultrasound predictors of pre-eclampsia listed in *Table 1*. Authors of the primary studies and data sets were contacted to ask if they would share their IPD in any format, along with data dictionaries or descriptions. We identified and invited authors and investigators from 180 data sets to join the project and share their IPD, with at least two further reminders to share data for the project. We continued to contact authors to request that they share their data until the October 2017 deadline for receiving new data sets was reached. When a data set received contained IPD from multiple studies, we checked the identity of each study to avoid duplication.

Original pseudonymised data sets were uploaded to a secure data storage environment (SafeHaven) at the Pragmatic Clinical Trials Unit, Queen Mary University of London, accessible only from a virtual desktop where manipulation of the data along with relevant data checks and documentation took place. The final merged data set, individual formatted files and documentation of all the transformations made were securely transferred to a web-based server at Centro Rosarino de Estudios Perinatales, Rosario, Argentina, a WHO Collaborative Centre in Child and Maternal Health. An independent Data Access Committee and data access process were established to facilitate access to and use of the data for future research.

Data extraction

We considered all recorded variables for inclusion, including those not reported in the published studies. At the study level, we extracted data on the providing collaborator, study design, data source, study period and study inclusion and exclusion criteria. At the participant level, we extracted information on individual participant characteristics and outcome data, as specified in *Table 1*.

Data harmonisation and recovery

Maternal age at baseline was recorded as a continuous variable in years in all data sets except three, in which age was calculated using the date of study or booking visit and the date of birth. Data on parity, defined as the number of pregnancies > 24 weeks' gestation, were mostly recorded in the binary format (nulliparous/multiparous). Any continuous data for parity were therefore also transformed to the binary form. However, we retained the continuous data for any relevant analyses. Assumptions were made when harmonising the ethnicity variable, and this was recoded as white, black, Asian, Hispanic, mixed and other. Pre-gestational diabetes, type 1 diabetes and type 2 diabetes were harmonised as history of diabetes, and history of systemic lupus, multiple sclerosis, idiopathic thrombocytopenia, rheumatoid arthritis or antiphospholipid syndrome were harmonised as history of autoimmune disease. We also harmonised history of glomerulonephritis, nephrotic syndrome, nephritis or nephropathy as history of renal disease.

Maternal characteristic data, such as history of disease and previous pregnancy, were recovered by screening the participant inclusion and exclusion criteria of published articles when this information had not been provided in the original data set. We added data based on existing information contained in the data set and from published articles. For example, we inputted the data as 'no previous history of pre-eclampsia' if all participants in the data set were nulliparous.

Body mass index (BMI) (measured in kg/m²), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) were recorded as continuous measures. Where MAP was not provided but SBP and DBP were, we derived MAP using the formula $MAP = (SBP + 2 \times DBP)/3$. Where BMI was not provided in the data set it was derived using weight (kg)/height (m²). We derived the estimated fetal and birth weight centiles using the Perinatal Institute GROW centile calculator.⁷⁷ Mean values of uterine and umbilical artery pulsatility index were mostly reported in data sets. When these were not available, we derived mean uterine and umbilical artery pulsatility index by averaging the left and right pulsatility index measurements. Data on biochemical marker platform, assay and measurement range were obtained for each relevant recorded biochemical marker in the data sets. Conversion factors were applied where necessary to harmonise the units of measurement. Placental growth factor (PIGF) was mostly reported in the data sets as pg/ml and standardised as such, pregnancy-associated plasma protein A (PAPP-A) was standardised as mIU/l and soluble fms-like tyrosine kinase-1 (sFlt-1) was standardised as pg/ml. The authors' reported definition of the primary outcome of pre-eclampsia along with gestational age at delivery was used to define early- and late-onset disease.

Clinical examinations, biochemical and ultrasound markers were further categorised into the trimester in which they were measured. We defined first-trimester values as ≤ 14 weeks, second-trimester values as > 14 –28 weeks and third-trimester values as > 28 weeks. Where more than one variable measurement was available for a woman in a trimester, we chose the first or the earliest measurement. Harmonisation of the data sets followed the predefined process shown in *Figure 1*. A final list of the variables collected and harmonised for the project is provided in *Appendix 3*.

Data quality

Range and consistency checks were carried out on all data sets received, and summary tables were produced. Missing data > 10% for each variable, range checks for continuous variable measures, obvious errors, and inconsistencies between pre-identified variables or outlying values were queried and rectified with input from the original authors. Two reminders were sent to the original author to respond to queries, and if no response was received, a decision to exclude the variable in question was made by the project team.

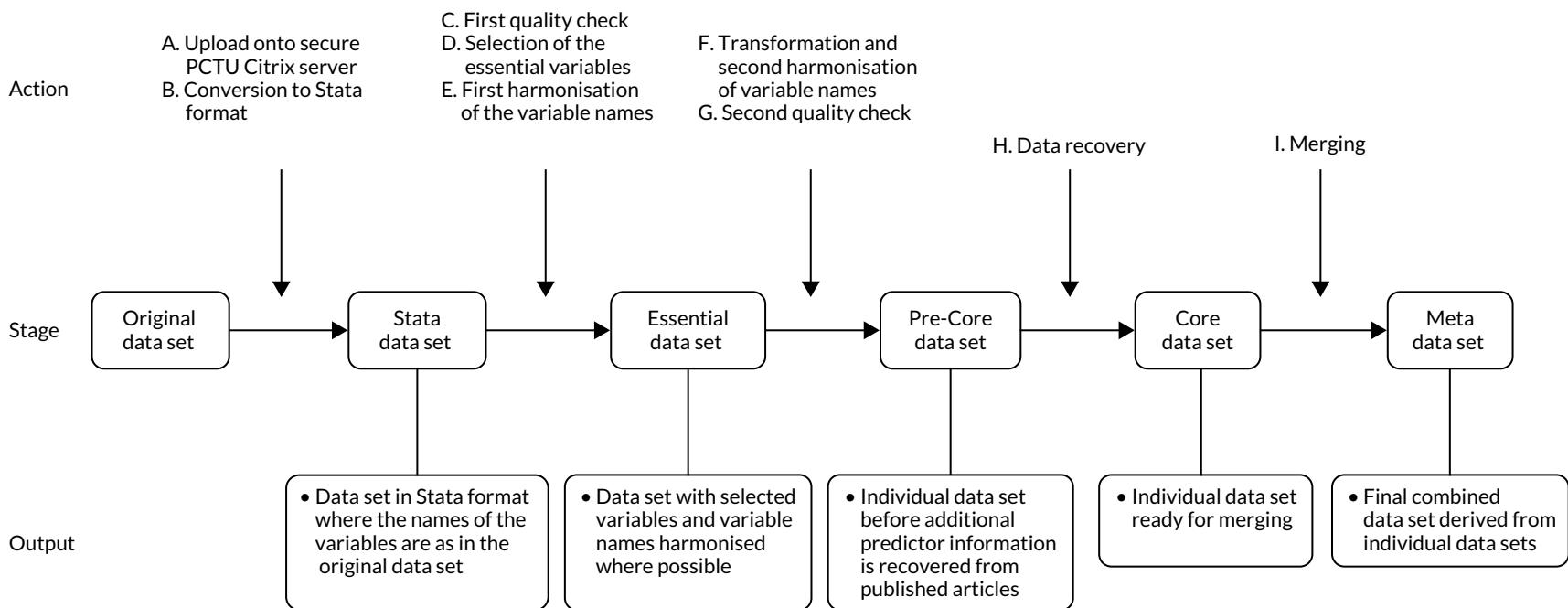


FIGURE 1 Flow diagram of harmonisation of variables in the IPD data sets.

Prioritisation of predictors

We carried out a prospective online prioritisation survey of IPPIC Network collaborators to identify the most clinically relevant predictors of pre-eclampsia for consideration in the development of the prediction models. Collaborators ranked the importance of the predictor variables identified on a scale from one (not important) to five (very important). The results were analysed as mode and interquartile range (IQR) to show variability and consensus in opinions. We a priori identified an IQR of ≤ 1 as indicating consensus between responders. Variables with mode of ≥ 4 and IQR of ≤ 1 were categorised as important, and those with mode of < 4 and IQR > 1 were categorised as unimportant. Variables with mode of 3 and IQR of ≤ 1 were reviewed and recategorised for importance at a consensus meeting.

Quality assessment

We assessed the risk of bias in individual studies and data sets using a modified version of the Prediction study Risk of Bias Assessment Tool (PROBAST).⁷⁸ The tool assessed the quality of data sets and individual studies across three domains: participant selection, predictors and outcomes. We classified the risk of bias to be low, high or unclear for each of the relevant domains. Each domain included signalling questions that were rated as 'yes', 'probably yes', 'probably no', 'no' or 'no information'. Any signalling question rated as 'probably no' or 'no' indicated a potential for bias in the IPD received for that study, which was therefore classed as having a high risk of bias in that domain. The overall risk of bias of an IPD data set was considered low if the data set scored low in all domains, high if any one domain had a high risk of bias, and unclear for any other classifications.

Sample size considerations

No formal sample size requirements were necessary for the meta-analysis. However, to develop a sound prediction model, as a rule of thumb, 10 events are required for each candidate predictor variable. Early-onset pre-eclampsia is uncommon, occurring in only about 0.25–0.50% of all pregnancies. We conservatively estimated that our IPD data set of > 3 million pregnancies would allow us access to about 7500 women with pregnancies complicated by early-onset pre-eclampsia if they all recorded all of the predictors of interest. This would enable us to develop and robustly validate prediction models for the outcomes of any-onset, early-onset and late-onset pre-eclampsia.

Data synthesis

Analysis for prioritisation of pre-eclampsia predictors was carried out using SPSS version 24 (IBM SPSS Statistics for Windows, IBM Corporation, Armonk, NY, USA). IPD meta-analysis to estimate the prognostic value of individual predictors was carried out using Stata[®] version 12.1 (StataCorp LP, College Station, TX, USA) and R version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria). External validation of existing models and model development were carried out using Stata MP version 15 (StataCorp LP, College Station, TX, USA) and R version 3.4.3. The combination of Stata and R was over a single software package to utilise the appropriate packages for each task. For example, multilevel imputation across data sets can be carried out using the 'jomo' package in R, which currently has no equivalent package in Stata.

External validation of existing pre-eclampsia prediction models

We validated each published pre-eclampsia prediction model that reported the full model equation with intercept and predictor effects in IPD from the UK. Analysis was restricted to the IPPIC-UK data sets to allow for the determination of the predictive performance of available models in the context of the UK health-care system and to reduce the heterogeneity in the definition of the outcome, which can vary across IPPIC data sets for different countries.^{4,35} We included UK data sets or subsets of

international data sets with UK participants if country of recruitment was recorded. We validated a prediction model only if at least one IPD data set contained values of all the predictors included in the model. We excluded data sets with no variation in the model predictions across individuals (i.e. every individual had the same predicted probability as a result of strict eligibility criteria). Smaller data sets with no outcome event or a single outcome event were also excluded, as were women with multifetal pregnancies, as the published models were intended to predict the risk of pre-eclampsia in women with singleton pregnancies only.

Missing data

Second-trimester measurements of BMI and MAP were used for model validation if the first-trimester values were missing from the data set.

Any predictors partially missing or outcome values missing for < 95% of individuals in a data set were multiply imputed under the missing at random assumption using multiple imputation by chained equations.^{79,80} Imputation was carried out separately in each UK data set, which acknowledged the clustering of individuals within a data set. We generated 100 imputed data sets for each data set with any missing predictor or outcome values. Linear regression was used to impute for approximately normally distributed continuous variables, predictive mean matching for skewed continuous variables, logistic regression for binary variables, and multinomial logistic regression for categorical variables. Complete predictors were also included in the imputation models as auxiliary variables. To retain congeniality between the imputation and predictive models, the scale used to impute the continuous predictors was chosen to match the prediction models.⁸¹ We undertook imputation checks by looking at histograms, summary statistics and tables of values across imputations, as well as by checking the trace plots for convergence issues.

We summarised the total number of participants, the number of events for each data set, and the overall numbers available for each model validation. We applied the model to each individual i in each (imputed) data set by calculating the linear predictor ($LP_i = \alpha + \beta_1 \times x_1 + \beta_2 \times x_2 + \dots$), and the predicted probability of pre-eclampsia,

$$p_i = \frac{e^{LP_i}}{1 + e^{LP_i}}, \quad (1)$$

for logistic regression equations; others detailed separately). For each prediction model, we summarised the overall distribution of the LP by data set using the median, IQR and full range, averaging statistics across imputations.⁸²

The predictive performance of each model was examined using measures of discrimination and calibration, first in the IPD for each available data set and then across data sets at the meta-analysis level. Discrimination is the ability of the model to separate between women who develop pre-eclampsia and those who do not, and was summarised using the C-statistic (equivalent to the area under the receiver operating characteristic curve for a logistic regression prediction model), with a value of 1 indicating perfect discrimination and a value of 0.5 indicating no discrimination beyond chance. We considered values > 0.7 to be most promising, given previously reported values in the literature, while noting the width of the confidence intervals (CIs).⁸³ Calibration refers to how well the risk predictions from the model agree with the observed outcome risks for individuals in a data set. Calibration was assessed using two measures: calibration slope, which is the slope of the regression line fitted to the relationship between predicted and observed risk probabilities on the logit scale (ideal value of 1); and calibration-in-the-large, which indicates whether risk predictions are systematically too high or too low (ideal value of 0). We produced calibration plots in each data set to visually compare observed and predicted probabilities when there were enough events to categorise participants into risk groups. The predicted probability of pre-eclampsia for each individual was obtained by pooling the imputation-specific estimates of the model's LP and then applying the logit transformation.⁸²

Where data had been imputed in a particular IPD data set, the predictive performance measures were calculated in each of the imputed data sets, and Rubin's rules were then applied to combine statistics (and corresponding standard errors) across imputations.⁸⁴ As the C-statistic is a proportion, it is unlikely to be normally distributed. Hence, we combined C-statistics across imputations on the logit scale,⁸⁵ and standard errors for logit C-statistics were calculated using the delta method, as recommended.⁸⁶

When it was possible to validate a model in multiple data sets, we summarised the performance measures across data sets using a random-effects meta-analysis estimated using restricted maximum likelihood (for each performance measure separately).^{86,87} Summary (average) performance statistics were reported with 95% CI (derived using the Hartung–Knapp–Sidik–Jonkman variance correction).⁸⁸ We also reported the estimate of between-study heterogeneity (τ^2) and the proportion of variability due to between-study heterogeneity (I^2). We generated plots to show and compare the average performance (across data sets) of multiple models, along with CIs.

For each pre-eclampsia outcome (early, late or any onset), we compared prediction models using decision curve analysis in the data sets used most frequently in the external validation of the prediction models, enabling within-data set comparison of the models.^{89,90} Decision curves show the net benefit (i.e. the benefit versus the harm) over a range of threshold probabilities (i.e. for treating women with a predicted risk above the threshold value) and can be compared with treat-all and treat-none strategies. For a probability threshold (p_t), the net benefit is calculated as:

$$\frac{\text{True positives}}{N} - \frac{\text{False positives}}{N} \times \frac{p_t}{1 - p_t}, \quad (2)$$

where 'true positives' and 'false positives' represent the numbers of individuals with a predicted probability $\geq p_t$ who have and do not have the outcome of interest, respectively, and N is the total sample size.^{89,90} Probability thresholds of between 5% and 20% will be clinically meaningful for making decisions about preventative interventions such as aspirin, including commencement of high-dose (150 mg) aspirin in the first trimester. Therefore, the model with the greatest net benefit for a particular threshold is considered to have the greatest clinical value.

Development and validation of pre-eclampsia prediction models

To develop new pre-eclampsia prediction models, non-UK data sets were considered in addition to the UK-only data sets. Prospective cohorts and trials were considered for inclusion in the development set. We excluded case-control studies as they cannot be used to estimate the baseline risk (intercept).

The number and proportion of missing values for each potential predictor and outcome were summarised by data set. Predictors were considered to be systematically missing for a data set if they were not recorded for any individuals or were recorded for very few individuals (< 10%) in that data set. No data sets included all potential predictors of interest; therefore, it was necessary to use a subset of predictors thought to be most predictive and of most interest.

A prioritised list of predictors was drawn up based on consensus among clinical experts in the collaborative group (see *Prioritisation of predictors*). To select data sets for development of a new prediction model (including maternal characteristics and clinical examination variables), it was necessary to compromise between the number of data sets included and the potential predictors that could be considered for inclusion in the models. The aim was to do this in such a way as to maximise both. We undertook the following process:

1. Ranked the prioritised predictors from the most to least relevant based on the scores from the clinical consensus meeting.
2. Excluded predictors that were rarely recorded across data sets (predictors recorded in data sets that total $\leq 5\%$ of all events).

3. Summarised the number of data sets, total sample size and number of events included if all remaining predictors were included.
4. If no data sets or very few data sets included all remaining predictors, the lowest-ranking predictor from the set of predictors was dropped.
5. Repeated steps 3 and 4 until a reasonable number of data sets, sample size and number of events were achieved and, ideally, when excluding further predictors would not mean a significant gain in data sets included.

Subsets of the development data identified for models with clinical and maternal characteristics were used to develop models additionally including biochemical markers or ultrasound markers. These models built on the clinical models, and therefore they required the same clinical variables plus biochemical markers or ultrasound markers. When fitting the biochemical marker models, data sets were included only if both PIGF and sFlt-1 were recorded; however, each biochemical marker could be measured at either trimester 1 or trimester 2. These two biochemical markers were most commonly recorded together, so ensuring that both PIGF and sFlt-1 were recorded in the data sets meant that the relationship between biochemical markers (and trimester of measurement) could be better estimated and used in the imputation models, thereby reducing some uncertainty in the imputed values and reducing the risk of convergence issues.

Missing data

Multiple imputation was implemented using multivariable joint modelling to account for missing data and clustering of participants within data sets. This approach was selected (rather than imputation within data sets, as in *External validation of existing pre-eclampsia models*) to increase the number of data sets used for model development, as many of the potential predictors of interest were systematically missing (i.e. not recorded for anyone) in one or more data sets. The 'jomo'⁹¹ package in R was designed to impute for multilevel (clustered) data and can therefore be used to impute for variables that are systematically missing in some IPPIC data sets, as well as for partially missing variables.⁹² This package uses a Bayesian approach (Markov chain Monte Carlo sampling), so it is necessary to allow a burn-in for the chain to converge before sampling an imputed data set. Rather than repeating the whole process (including the burn-in) for each imputation, imputed data sets are sampled from the same chain by specifying the number of iterations to be left between the samples taken. Prior to running the full imputation, a dummy run was performed to check the chains for signs of non-convergence and to determine a suitable burn-in and sampling interval. Based on these checks, a burn-in of 20,000 was used for imputation of the data used to develop clinical characteristics models and was increased to 30,000 for data used to develop models additionally including biochemical markers or ultrasound markers. After the burn-in, imputations were sampled every 1000 iterations, until 25 imputed data sets had been sampled.

The imputation model included all potential predictors (for trimesters 1 and 2) and outcomes (early- and late-onset pre-eclampsia). Data were imputed separately (using different sets of data sets and predictors) for developing models including only maternal and clinical characteristics, and then for models additionally including biochemical markers or ultrasound markers.

For models with maternal and clinical characteristics, data were imputed for SBP and DBP rather than MAP, as MAP simply combines SBP and DBP and, therefore, imputing them separately would provide more flexibility in how they can be modelled subsequently. A preliminary complete-case analysis was performed to look for potential non-linear relationships between potential predictors and outcomes using multivariable fractional polynomial models. This led to BMI being considered on the original scale, as well as non-linearly using the natural logarithm transformation [$\ln(\text{BMI})$] and BMI^{-2} . Data sets were imputed assuming each of these functions for BMI to enable non-linearity to be considered during model development. Biochemical markers and ultrasound markers were considered on their original scale and on the log-transformed scale (which was decided a priori), and therefore data sets were imputed separately for the transformed and the original biochemical markers or ultrasound markers.

After imputation, the distributions of values for variables were checked by plotting the mean \pm SD for continuous variables against the imputation number (including the original complete data, imputation 0, for reference). For categorical variables, the proportions in each category were compared across imputations and with the original complete data. Methods for imputing for systematically missing predictors are still relatively new and therefore a cautious approach was taken. If the distribution of imputed values for a systematically missing predictor was unusual or extreme, then further examination was done to check the plausibility of the imputation. Alongside this, convergence of the Markov chain Monte Carlo samples was checked. If systematically missing predictor values could not reliably be imputed for a variable in a particular data set (e.g. adequate convergence was not achieved even after a long burn-in), then that data set was excluded from model development when that predictor would be considered (e.g. first-trimester BMI in a first-trimester prediction model).

Model development and validation

Prediction models were developed using random intercept logistic regression with backward elimination for variable selection. The random intercept was used to account for clustering of women within individual data sets. At each stage of the variable selection process, the same model (i.e. including the same predictors) was fitted to all imputations, and pooled Wald tests (using Rubin's rules) were used for backwards elimination, with a p -value of > 0.157 (proxy for Akaike information criterion) for exclusion.^{93,94} Models were developed separately for each pre-eclampsia outcome (any, early and late onset) using predictors recorded at trimester 1 and separately at trimester 2. Furthermore, for each outcome predicted at each trimester, three models were considered: using only clinical characteristics, using clinical characteristics plus biochemical markers, and using clinical characteristics plus ultrasound markers. Therefore, we aimed to develop 18 models in total (one for each combination of the three outcomes, two trimesters and three predictor sets). We were unable to develop models that included clinical characteristics, biochemical and ultrasound markers as no data sets included all relevant predictors of interest.

For each model developed, its predictive performance was assessed in an internal validation using study-specific and overall estimates of discrimination and calibration. After model development, the fitted model (with the average intercept) was applied back into each individual data set to obtain, for each participant, values of the LP and predicted probability of the pre-eclampsia outcome from the developed model. These were then used to calculate the performance statistics described in *External validation of existing pre-eclampsia prediction models*. For each data set, the 'pool last' approach was followed, whereby imputation-specific performance statistics were calculated and then pooled across imputations using Rubin's rules and using a transformed scale where necessary (such as pooling logit C-statistics).⁹⁵ Calibration plots were also produced for data sets that had more than 100 events. The predicted probability of pre-eclampsia for each individual was obtained by pooling the imputation-specific estimates of the model's LP and then applying the logit transformation.⁸²

Summarising study-specific performance after model development is recommended by Royston *et al.*⁹⁶ and Debray *et al.*,⁴⁷ and gives an indication of how the model will perform with new data from populations represented by the included studies. For each model developed, the data set-specific performance statistics were summarised across the data sets using a random-effects meta-analysis, in the same way as described in *External validation of existing pre-eclampsia prediction models*.

The performance statistics of models developed using different functional forms of BMI were compared (in terms of overall predictive performance and homogeneity of performance across data sets) after repeating the model development process in the imputed data sets for each functional form. The model that provided the best overall predictive performance across the different statistics was selected, thereby also selecting the functional form for BMI (if it remained in the model). The same strategy of comparing performance statistics was used for models with biochemical markers and ultrasound markers, to determine whether they should be modelled on their original scale or using a natural logarithm transformation.

For each developed model, to correct for optimism during model development (also known as overfitting), the predictor effects (beta estimates) were shrunk by multiplying each beta estimate by a global shrinkage factor.⁹⁷⁻⁹⁹ The shrinkage factor was taken to be the summary calibration slope from the internal validation process (i.e. the pooled calibration slope from the meta-analysis of data set-specific calibration slope estimates). Bootstrapping was not practical computationally given the need to incorporate both non-linear trend examinations, backwards selection, and multiple imputation (including for systematically missing predictors). Following application of shrinkage, the model's intercept was re-estimated to ensure that predictions were correct on average. This then provided the final model equation.

For each of the final models, decision curves were produced within each data set included in model development and validation. This shows the net benefit across different probability thresholds and compares the use of the model with treat-all and treat-none strategies.

Summarising the prognostic effect of individual predictors of pre-eclampsia

For each outcome (early-onset pre-eclampsia, late-onset pre-eclampsia and any-onset pre-eclampsia) and each candidate predictor (clinical, biochemical, and ultrasound marker) prioritised in *Prioritisation of predictors*, we separately performed an unadjusted two-stage IPD meta-analysis of the prognostic effect to obtain a summary estimate, 95% CI and 95% prediction interval for that predictor. The 95% prediction interval presents the heterogeneity on the same scale as the original outcome and estimates where the true effects are to be expected for similar exchangeable studies.¹⁰⁰ We used the two-stage approach because of the large numbers of studies.

The two-step approach first involves fitting a logistic regression model for each study to obtain the odds ratio (OR) for the prognostic effect, and then pooling the log ORs using a conventional random-effects meta-analysis. The random-effects model allows for heterogeneity between studies, and was estimated using restricted maximum likelihood. The 95% CI of the pooled effect was derived using the Hartung–Knapp approach.^{101,102} Heterogeneity was summarised using the I^2 -statistic (which provides the proportion of total variability due to between-study heterogeneity) and 95% prediction intervals.¹⁰⁰ The trend across multiple categories and continuous variables was considered linear.

A pragmatic decision was made to perform all analyses on complete cases of singleton pregnancies on the IPPIC international data set only, that is, no statistical imputation method was carried out for missing outcome or predictor data. This was because of the length of time it would take to impute and perform pre- and post-imputation checks for the 78 data sets of the IPPIC international IPD, with different combinations of predictors in each data set, with some data sets as large as 600,000 pregnancies. The clustering of participants within data sets was accounted for by analysing each data set separately in the first stage. Clustering of pregnancies by women was not accounted for because of the small number of clusters of women who had been pregnant multiple times. Models were univariable and thus predictors were not adjusted for. Adjustment would have reduced statistical power owing to missing observations and would have distorted the combining of associations in the IPD second stage due to different availability of adjustable variables by data set. The analysis excluded all women with multifetal pregnancies (e.g. twins/triplets); however, we also explored the relationships between multiple birth as a predictor and all pre-eclampsia outcomes.

Chapter 4 Characteristics and quality of data sets included in the individual participant data meta-analysis

Study identification and individual participant data acquisition

One hundred and twenty-five researchers from 73 teams in 25 countries had joined the IPPIC network by October 2017 and provided access to pseudonymised individual data for 3,674,684 pregnancies.^{42,103–178} The most common reason for not obtaining the IPD was not receiving a response from the author to the request to share data (28/180) (Figure 2).

Our search up to September 2014 of reviews that evaluated the performance of single or combined tests for predicting pre-eclampsia identified 73 citations. After evaluation of the abstracts, we included 62 published reviews evaluating one or more tests for predicting pre-eclampsia (Table 2). Clinical characteristics were studied in 32.3% (20/62) of published reviews, biochemical markers were studied in 59.7% (37/62) and ultrasound markers were studied in 8.1% (5/62).

Characteristics of data sets in the IPPIC data repository

Seventy-eight data sets contributed data to the IPPIC data repository.^{42,103–178} More than half of the data sets received (58%, 45/78) were prospective cohort studies; 15% (12/78) were randomised controlled trials and 17% (13/78) were large prospective registry data sets or birth cohorts. One data set

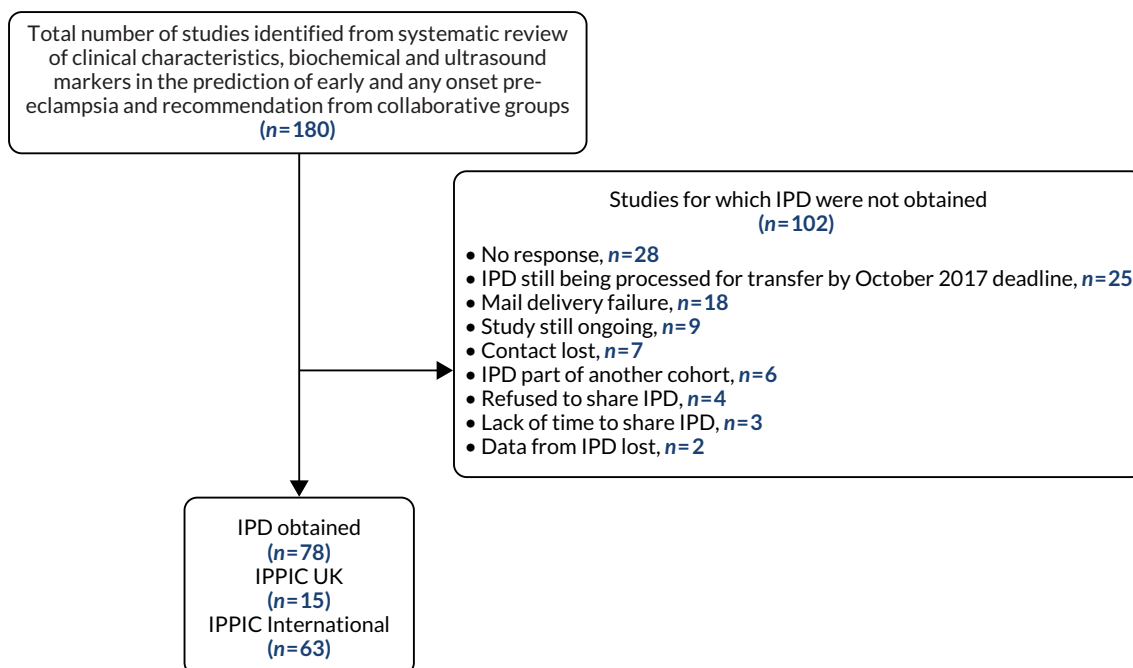


FIGURE 2 Flow diagram of studies included in the IPD meta-analysis, showing reasons why IPD were not obtained.

TABLE 2 Review of reviews on predictors of pre-eclampsia

Systematic review (first author and year)	Number of primary studies	Number of women	Risk factors evaluated	Outcome reported
Maternal clinical characteristics				
Cnossen 2007 ¹⁷⁹	36	1,699,073	BMI	Any-onset pre-eclampsia
O'Brien 2003 ¹⁸⁰	13	1,400,000		Any-onset pre-eclampsia
Wang 2013 ¹⁸¹	29	1,980,761		Any-onset pre-eclampsia
Duckitt 2005 ¹⁸²	2	64,789	Multiple clinical features	Any-onset pre-eclampsia
Alpoim 2013 ¹⁸³	2	1875	ABO blood group status	Early-onset pre-eclampsia
England 2007 ¹⁸⁴	48	N/A	Smoking	Early-onset pre-eclampsia
Rebelo 2013 ¹⁸⁵	23	4265	CRP, BMI	Any-onset pre-eclampsia
Duckitt 2005 ¹⁸²	2	37,988	Parity	Any-onset pre-eclampsia
Luo 2007 ¹⁸⁶	26	N/A		Any-onset pre-eclampsia
Duckitt 2005 ¹⁸²	2	65,314	Age	Any-onset pre-eclampsia
Duckitt 2005 ¹⁸²	2	907	Blood pressure	Any-onset pre-eclampsia
Cnossen 2008 ¹⁸⁷	34	60,599		Any-onset pre-eclampsia
Sgolastra 2013 ¹⁸⁸	15	5023	Periodontal disease	Any-onset pre-eclampsia
Kunnen 2010 ¹⁸⁹	15	N/A		Early-onset pre-eclampsia
Morris 2012 ¹⁹⁰	20	2978	Proteinuria	Any-onset pre-eclampsia
Sanchez-Ramos 2013 ¹⁹¹	24	3186		Early-onset pre-eclampsia
Wolf 2014 ¹⁹²	11	5411	Leisure-time physical activity	Any-onset pre-eclampsia
Palmer 2013 ¹⁹³	11	N/A	Occupational exposures	Any-onset pre-eclampsia
Bonzini 2007 ¹⁹⁴	9	N/A		Any-onset pre-eclampsia
Cnossen 2006 ¹⁹⁵	5	572	Uric acid	Any-onset pre-eclampsia
Uterine artery Doppler ultrasound				
Velauthar 2014 ³⁹	18	55,974	First-trimester Doppler	Early-onset pre-eclampsia
Chien 2000 ¹⁹⁶	27	12,994	Any-trimester Doppler	Any-onset pre-eclampsia
Cnossen 2008 ⁶³	74	79,547		Any-onset pre-eclampsia
Kleinrouweler 2013 ¹⁹⁷	8	6708	Second-trimester Doppler	Early-onset pre-eclampsia
Pedrosa 2011 ¹⁹⁸	N/A	N/A	Doppler combined with other markers	Early-onset pre-eclampsia
Biochemical markers				
Kosmas 2003 ¹⁹⁹	19	5145	Factor V Leiden	Any-onset pre-eclampsia
Dudding 2008 ²⁰⁰	6	6755		Any-onset pre-eclampsia
Rodger 2010 ²⁰¹	10	21,833		Any-onset pre-eclampsia
Xia 2012 ²⁰²	36	9203	MTHFR gene C677T polymorphism	Any-onset pre-eclampsia
Kosmas 2004 ²⁰³	23	6213		Any-onset pre-eclampsia
Zusterzeel 2000 ²⁰⁴	4	579		Any-onset pre-eclampsia
Li 2014 ²⁰⁵	49	18,009		Any-onset pre-eclampsia

TABLE 2 Review of reviews on predictors of pre-eclampsia (continued)

Systematic review (first author and year)	Number of primary studies	Number of women	Risk factors evaluated	Outcome reported
Wang 2013 ²⁰⁶	51	17,749		Any-onset pre-eclampsia
Widmer 2007 ²⁰⁷	10	1173	sFlt-1	Early-onset pre-eclampsia
Jacobs 2011 ²⁰⁸	11	N/A		Early-onset pre-eclampsia
Kleinrouweler 2012 ⁶⁵	19	6708		Early-onset pre-eclampsia
Widmer 2007 ²⁰⁷	14	2045	PIGF	Early-onset pre-eclampsia
Kleinrouweler 2012 ⁶⁵	27	N/A		Any-onset pre-eclampsia
Huppertz 2013 ²⁰⁹	19	16,153	PP13	Early-onset pre-eclampsia
Schneuer 2012 ²¹⁰	7	2989		Early-onset pre-eclampsia
Lau 2013 ²¹¹	41	1940	TNF-alpha, IL-6 and IL-10	Any-onset pre-eclampsia
Tabesh 2013 ²¹²	8	2485	Serum vitamin D	Any-onset pre-eclampsia
Morgan 2013 ²¹³	12	5003	PAI-1 promoter polymorphism	Any-onset pre-eclampsia
Dai 2013 ²¹⁴	29	3228	eNOS polymorphisms	Any-onset pre-eclampsia
Chen 2012 ²¹⁵	18	N/A		Any-onset pre-eclampsia
Qi 2013 ²¹⁶	33	10,671		Any-onset pre-eclampsia
Zhao 2013 ²¹⁷	11	3088	PAI-1 promoter polymorphism	Any-onset pre-eclampsia
Zhao 2012 ²¹⁸	8	1995	AGTR1 +1166A>C polymorphism	Any-onset pre-eclampsia
Zhong 2012 ²¹⁹	11	1749	ACE I/D polymorphism	Any-onset pre-eclampsia
Chen 2012 ²¹⁵	30	8340		Any-onset pre-eclampsia
Ni 2012 ²²⁰	22	7534	AGT M235T polymorphism	Any-onset pre-eclampsia
Kleinrouweler 2012 ⁶⁵	3	N/A	VEGF	Any-onset pre-eclampsia
Hui 2012 ²²¹	37	115,290	Wide range of serum markers	Any-onset pre-eclampsia
Giguere 2011 ²²²	37	N/A	71 different markers	Early-onset pre-eclampsia
Abou-Nassar 2011 ²²³	28	5991	Antiphospholipid antibodies	Any-onset pre-eclampsia
do Prado 2010 ²²⁴	12	7950		Any-onset pre-eclampsia
Gupta 2009 ²²⁵	17	745	Lipid peroxidation	Any-onset pre-eclampsia
Bombell 2008 ²²⁶	16	2374	TNF (-308A) polymorphism	Any-onset pre-eclampsia
Zafarmand 2008 ²²⁷	17	5275	Angiotensinogen gene M235T polymorphism	Any-onset pre-eclampsia
Morris 2008 ⁶⁸	44	169,637	Inhibin A, AFP and three others	Any-onset pre-eclampsia
Wiwanitkit 2006 ²²⁸	6	1690	PAI-1	Any-onset pre-eclampsia
Leeflang 2007 ⁶⁶	5	573	FFN	Any-onset pre-eclampsia

ACE, angiotensin-converting enzyme; AFP, alpha-fetoprotein; CRP, C-reactive protein; FFN, fetal fibronectin; IL-6, interleukin 6; IL-10, interleukin 10; N/A, not applicable; PAI-1, plasminogen activator inhibitor-1; PP13, placental protein 13; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

was IPD made up of 31 RCTs. Most of the data sets were from participants in Europe (60%, 47/78), 18% (14/78) were from North America, 6% (5/78) were from South America, 5% (4/78) were from Asia and Australia, and one (1%) was from Africa. Three of the data sets provided included participants from multiple countries, such as Argentina, Colombia, Kenya, India, Peru, Thailand and New Zealand. Ninety-seven per cent (3,570,993) of the 3,674,684 pregnancies in the IPPIC repository were singleton pregnancies. Individual data set size ranged from 42 to 1,663,167 pregnancies, and the total number of reported pre-eclampsia outcomes in each data set ranged from 0 to 4252 for early-onset pre-eclampsia, from 0 to 38,305 for late-onset pre-eclampsia and from 3 to 42,608 for any-onset pre-eclampsia (see *Appendix 4*). About one-third of the data sets received were on women with high-risk pregnancies only (29%, 23/78), 14% (11/78) of the data sets were on women with low-risk pregnancies and more than half (55%, 43/78) of the data sets included women with pregnancies of any risk. Detailed study characteristics of all IPPIC data sets are provided in *Appendix 5* and a summary of the missing data for prioritised predictors and each pre-eclampsia outcome is provided in *Appendix 6*.

Prioritisation of predictors of pre-eclampsia

In April 2017, the online survey was designed and run using smartsurvey.co.uk (see *Appendix 7*). Ninety-eight members of the IPPIC collaborative network who had agreed to share data by this date were sent an e-mail introducing the survey and explaining the participation requirements and survey objectives. Collaborators had 7 days within which to complete the online survey.

Fifty-four candidate predictor variables were identified (37 clinical characteristics, nine biochemical markers and eight ultrasound markers) and ranked by 33 (34%) IPPIC collaborators. Seventy per cent (23/33) of responders were from Europe, 12% were from both the American (4/33) and Asian (4/33) continents, and 6% (2/33) were from Africa. A consensus group made up of five clinical academics reviewed 13 candidate predictor variables ranked by the online survey participants as being 'moderately important'. This included eight clinical characteristic variables, two biochemical markers and three ultrasound markers. Two each of the clinical characteristic variables and ultrasound markers reviewed by the consensus group (mode of conception, substance misuse in current pregnancy, umbilical artery pulsatility index and estimated fetal weight centile) were included following assessment by the group.

Overall, fewer than half (48%, 26/54) of all assessed predictors were ranked as being important, with 54% (20/37) of clinical characteristics, 33% (3/9) of biochemical markers and 38% (3/8) of ultrasound markers being prioritised as important in predicting pre-eclampsia (*Table 3*).

Quality of the IPPIC data sets

Risk-of-bias assessment using the PROBAST resulted in 77% (60/78) of the included IPD data sets being classified as having an overall low risk of bias, while 22% (17/78) were classified as having an unclear risk of bias. Only one data set (1%, 1/78) received an overall high risk of bias assessment. All of the included data sets had a low risk of bias in the domain of participant selection. For the domain of predictors, 94% (73/78) had a low risk of bias, while 1% (1/78) had a high and 5% (4/78) an unclear risk of bias assessment. The risk of bias in the outcome domain was unclear for 22% (17/78) of the included data sets and low in the rest (78%, 61/78). Detailed assessment of the risk of bias for the IPPIC data sets is presented in *Appendix 8*.

Characteristics of identified prediction models

From our updated literature search (up to December 2017), we identified 131 models developed to predict pre-eclampsia. About half of these (53%, 70/131) reported the model equation in the publication,

TABLE 3 Predictors of pre-eclampsia prioritised by online survey and consensus meeting

Important	Unimportant
Clinical characteristics	
Previous any pre-eclampsia	Previous miscarriage
Chronic or pre-existing hypertension	History of early pregnancy bleeding in current pregnancy
SBP	Alcohol use
BMI	Diet in pregnancy
DBP	Physical activity
Parity	Interval between pregnancies
History of renal disease	Family history of cardiovascular disease
Multiple pregnancy	History of gestational diabetes
History of pre-existing diabetes	Gestational diabetes in current pregnancy
Age	Socioeconomic status
Previous autoimmune disease	Previous stillbirth
Family history of pre-eclampsia in first degree relative	Previous preterm delivery
MAP	Previous heritable thrombophilia
PCR	New partner
Urine dipstick	Height
Previous SGA	Weight
Smoking	24-hour protein
Mode of conception	
Substance misuse in current pregnancy	
Ethnicity	
Ultrasound markers	
Uterine artery pulsatility index	CRL
Umbilical artery pulsatility index	Umbilical artery resistance index
Estimated fetal weight centile	Abdominal circumference
	Notching on ultrasound scan
	Uterine artery resistance index
Biochemical markers	
PIGF	CRP
sFlt-1	Hypertriglyceridaemia
PAPP-A	Human chorionic gonadotropin
	AFP
	PAI-1 polymorphism
	sEng
AFP, alpha-fetoprotein; CRL, crown-rump length; CRP, C-reactive protein; PAI-1, plasminogen activator inhibitor-1; PCR, protein-creatinine ratio; sENG, soluble endoglin; SGA, small for gestational age.	

and only one-fifth of all models (18%, 24/131) from 12 publications met the inclusion criteria for the external validation of their predictive performance in the IPPIC-UK data sets.^{115,128,147,229-237} The primary reasons for not including a model for external validation were the full prediction formula not being reported in the publication (47%, 61/131) and the absence of the predictor information in the IPPIC-UK data sets (27%, 35/131). Other reasons for not validating the models include pre-eclampsia being poorly defined in the study (8%, 10/131) and not enough events in the IPPIC-UK data set to validate the model (1%, 1/131). *Figure 3* is the flow chart of prediction model selection for external validation, and *Appendix 9* shows published pre-eclampsia prediction models reporting a model equation.

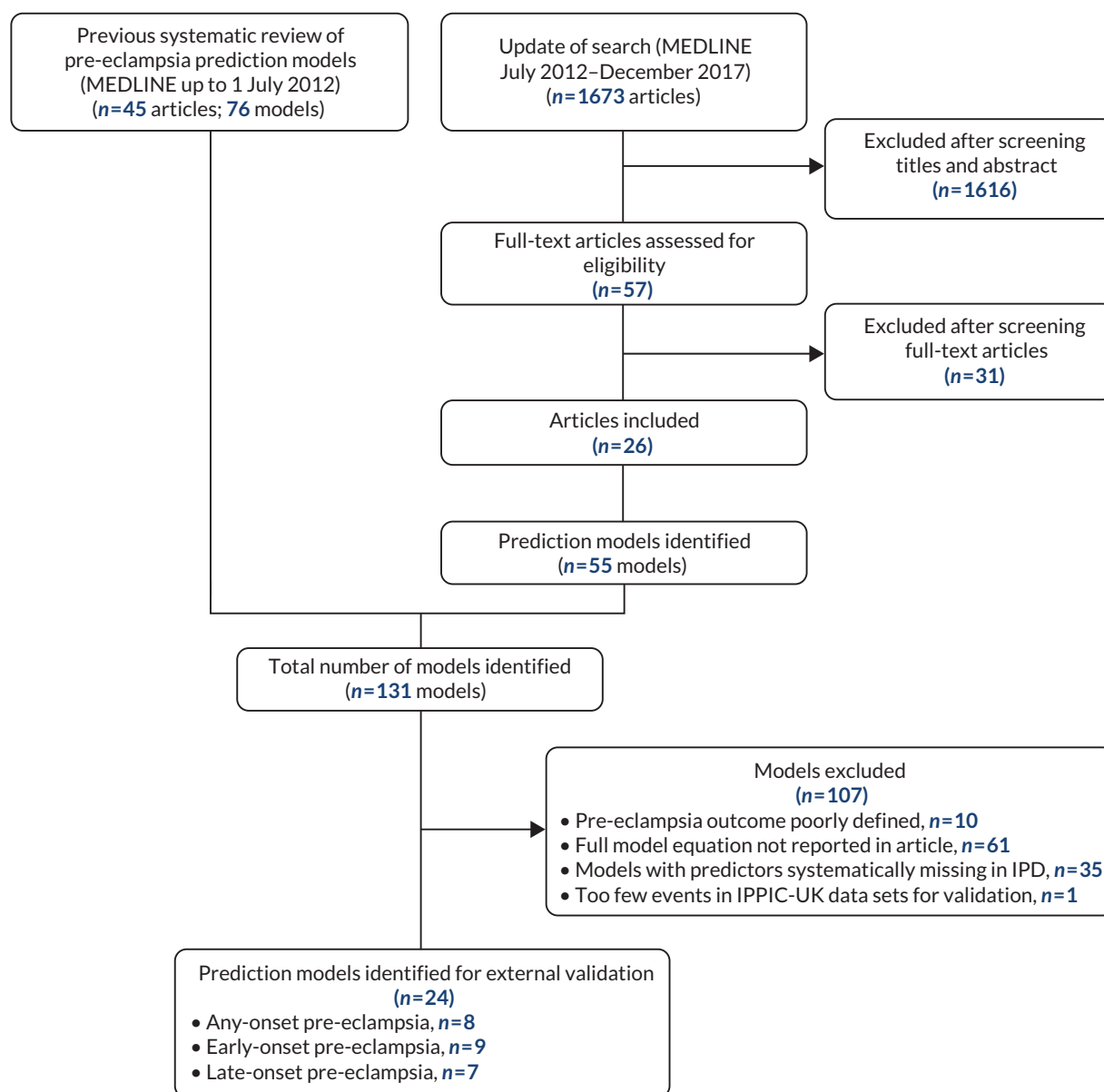


FIGURE 3 Flow chart of pre-eclampsia prediction model selection for external validation in IPPIC-UK data set using IPD meta-analysis. Reproduced from Snell *et al.*⁵² Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Chapter 5 External validation of existing pre-eclampsia prediction models

Characteristics of included prediction models

We identified 24 prediction models that could be externally validated in the IPPIC-UK cohorts. Eight models predicted any-onset pre-eclampsia, nine models predicted early-onset pre-eclampsia and seven models predicted late-onset pre-eclampsia. About half of these models (13/24, 54%) were developed in unselected singleton pregnancies at any risk of pre-eclampsia. Two-thirds of the models included only clinical characteristics as predictors (15/24, 63%), one-fifth (5/24, 21%) included clinical characteristics and biochemical markers, and one-sixth (4/24, 17%) included clinical characteristics and ultrasound markers. It was not possible to validate any of the models that included all three predictor categories (clinical characteristics, biochemical markers and ultrasound markers).

The majority of models (22/24, 92%) were developed using binary logistic regression. The two models by Wright *et al.*²³⁶ modelled the outcome of 'gestational age at delivery with pre-eclampsia' using competing risks models. The models by Wright *et al.*²³⁶ used pre-eclampsia before 34 weeks to define early-onset pre-eclampsia. Over 80% of the models that we validated involved first-trimester predictors (88%, 21/24); only three included second-trimester predictors. Details of the validated models are given in Table 4.

TABLE 4 Pre-eclampsia prediction model equations externally validated in the IPPIC-UK data sets

Model number	Authors, year	Predictor category	Prediction model equation for LP ^a
First-trimester any-onset pre-eclampsia models			
1	Plasencia <i>et al.</i> , 2007 ²³¹	Clinical characteristics	LP = -6.253 + 1.432 (if African Caribbean ethnicity) + 1.465 (if mixed ethnicity) + 0.084 (BMI) + 0.81 (if patient's mother had PE) - 1.539 (if parous without previous PE) + 1.049 (if parous with previous PE)
2	Poon <i>et al.</i> , 2008 ²³³	Clinical characteristics	LP = -6.311 + 1.299 (if African Caribbean ethnicity) + 0.092 (BMI) + 0.855 (if woman's mother had PE) - 1.481 (if parous without previous PE) + 0.933 (if parous with previous PE)
3	Wright <i>et al.</i> , 2015 ²³⁶	Clinical characteristics	Mean gestational age at delivery with PE = 54.3637 - 0.0206886 (age, years - 35, if age ≥ 35) + 0.11711 (height, cm - 164) - 2.6786 (if African Caribbean ethnicity) - 1.129 (if South Asian ethnicity) - 7.2897 (if chronic hypertension) - 3.0519 (if systemic lupus erythematosus or antiphospholipid syndrome) - 1.6327 (if conception by in vitro fertilisation) - 8.1667 (if parous with previous PE) + 0.0271988 (if parous with previous PE, previous gestation in weeks - 24) ² - 4.335 (if parous with no previous PE) - 4.15137651 (if parous with no previous PE, interval between pregnancies in years) ⁻¹ + 9.21473572 (if parous with no previous PE, interval between pregnancies in years) ^{-0.5} - 0.0694096 (if no chronic hypertension, weight in kg - 69) - 1.7154 (if no chronic hypertension and family history of PE) - 3.3899 (if no chronic hypertension and diabetes mellitus type 1 or 2)

continued

TABLE 4 Pre-eclampsia prediction model equations externally validated in the IPPIC-UK data sets (continued)

Model number	Authors, year	Predictor category	Prediction model equation for LP ^a
4	Baschat <i>et al.</i> , 2014 ¹¹⁵	Clinical characteristics and biochemical markers	$LP = -8.72 + 0.157$ (if nulliparous) $+ 0.341$ (if history of hypertension) $+ 0.635$ (if prior PE) $+ 0.064$ (MAP) $- 0.186$ (PAPP-A, Ln MoM)
5	Goetzinger <i>et al.</i> , 2010 ¹²⁸	Clinical characteristics and biochemical markers	$LP = -3.25 + 0.51$ (if PAPP-A < 10th percentile) $+ 0.93$ (if BMI > 25) $+ 0.94$ (if chronic hypertension) $+ 0.97$ (if diabetes) $+ 0.61$ (if African American ethnicity)
6	Odibo <i>et al.</i> , 2011 ¹⁴⁷	Clinical characteristics and biochemical markers	$LP = -3.389 - 0.716$ (PAPP-A, MoM) $+ 0.05$ (BMI) $+ 0.319$ (if black ethnicity) $+ 1.57$ (if history of chronic hypertension)
7	Odibo <i>et al.</i> , 2011 ¹⁴⁷	Clinical characteristics and ultrasound markers	$LP = -3.895 - 0.593$ (mean uterine artery PI) $+ 0.944$ (if pre-gestational diabetes) $+ 0.059$ (BMI) $+ 1.532$ (if history of chronic hypertension)
First-trimester early-onset pre-eclampsia models			
8	Baschat <i>et al.</i> , 2014 ¹¹⁵	Clinical characteristics	$LP = -5.803 + 0.302$ (if diabetes) $+ 0.767$ (if hypertension) $+ 0.00948$ (MAP)
9	Crovetto <i>et al.</i> , 2015 ²²⁹	Clinical characteristics	$LP = -5.177 + 2.383$ (if black ethnicity) $- 1.105$ (if nulliparous) $+ 3.543$ (if parous with previous PE) $+ 2.229$ (if chronic hypertension) $+ 2.201$ (if renal disease)
10	Kuc <i>et al.</i> , 2013 ²³⁰	Clinical characteristics	$LP = -6.790 - 0.119$ (maternal height, cm) $+ 4.8565$ (maternal weight, Ln kg) $+ 1.845$ (if nulliparous) $+ 0.086$ (maternal age, years) $+ 1.353$ (if smoker)
11	Plasencia <i>et al.</i> , 2007 ²³¹	Clinical characteristics	$LP = -6.431 + 1.680$ (if African Caribbean ethnicity) $+ 1.889$ (if mixed ethnicity) $+ 2.822$ (if parous with previous PE)
12	Poon <i>et al.</i> , 2010 ²³²	Clinical characteristics	$LP = -5.674 + 1.267$ (if black ethnicity) $+ 2.193$ (if history of chronic hypertension) $- 1.184$ (if parous without previous PE) $+ 1.362$ (if parous with previous PE) $+ 1.537$ (if conceived with ovulation induction)
13	Scazzocchio <i>et al.</i> , 2013 ²³⁵	Clinical characteristics	$LP = -7.703 + 0.086$ (BMI) $+ 1.708$ (if chronic hypertension) $+ 4.033$ (if renal disease) $+ 1.931$ (if parous with previous PE) $+ 0.005$ (if parous with no previous PE)
14	Wright <i>et al.</i> , 2015 ²³⁶	Clinical characteristics	Same as model 3
15	Poon <i>et al.</i> , 2009 ²³⁴	Clinical characteristics and biochemical markers	$LP = -6.413 - 3.612$ (PAPP-A, Ln MoM) $+ 1.803$ (if history of chronic hypertension) $+ 1.564$ (if black ethnicity) $- 1.005$ (if parous without previous PE) $+ 1.491$ (if parous with previous PE)
First-trimester late-onset pre-eclampsia models			
16	Crovetto <i>et al.</i> , 2015 ²²⁹	Clinical characteristics	$LP = -5.873 - 0.462$ (if white ethnicity) $+ 0.109$ (BMI) $- 0.825$ (if nulliparous) $+ 2.726$ (if parous with previous PE) $+ 1.956$ (if chronic hypertension) $- 0.575$ (if smoker)
17	Kuc <i>et al.</i> , 2013 ²³⁰	Clinical characteristics	$LP = -14.374 + 2.300$ (maternal weight, Ln kg) $+ 1.303$ (if nulliparous) $+ 0.068$ (maternal age, years)
18	Plasencia <i>et al.</i> , 2007 ²³¹	Clinical characteristics	$LP = -6.585 + 1.368$ (if African Caribbean ethnicity) $+ 1.311$ (if mixed ethnicity) $+ 0.091$ (BMI) $+ 0.960$ (if woman's mother had PE) $- 1.663$ (if parous without previous PE)
19	Poon <i>et al.</i> , 2010 ²³²	Clinical characteristics	$LP = -7.860 + 0.034$ (maternal age, years) $+ 0.096$ (BMI) $+ 1.089$ (if black ethnicity) $+ 0.980$ (if Indian or Pakistani ethnicity) $+ 1.196$ (if mixed ethnicity) $+ 1.070$ (if woman's mother had PE) $- 1.413$ (if parous without previous PE) $+ 0.780$ (if parous with previous PE)

TABLE 4 Pre-eclampsia prediction model equations externally validated in the IPPIC-UK data sets (continued)

Model number	Authors, year	Predictor category	Prediction model equation for LP ^a
20	Scazzocchio <i>et al.</i> , 2013 ²³⁵	Clinical characteristics	LP = 6.135 + 2.124 (if previous PE) + 1.571 (if chronic hypertension) + 0.958 (if diabetes) + 1.416 (if thrombophilic condition) - 0.487 (if multiparous) + 0.093 (BMI)
21	Poon <i>et al.</i> , 2009 ²³⁴	Clinical characteristics and biochemical markers	LP = -6.652 - 0.884 (PAPP-A, Ln MoM) + 1.127 (if family history of PE) + 1.222 (if black ethnicity) + 0.936 (if Indian or Pakistani ethnicity) + 1.335 (if mixed ethnicity) + 0.084 (BMI) - 1.255 (if parous without previous PE) + 0.818 (if parous with previous PE)
Second-trimester any-onset pre-eclampsia models			
22	Yu <i>et al.</i> , 2005 ²³⁸	Clinical characteristics and ultrasound markers	LP = 1.8552 + 5.9228 (mean uterine artery PI) ⁻² - 14.4474 (mean uterine artery PI) ⁻¹ - 0.5478 (if smoker) + 0.6719 (bilateral notch) + 0.0372 (age) + 0.4949 (if black ethnicity) + 1.5033 (if history of PE) - 1.2217 (if previous term live birth) + 0.0367 (T2 BMI)
Second-trimester early-onset pre-eclampsia models			
23	Yu <i>et al.</i> , 2005 ²³⁸	Clinical characteristics and ultrasound markers	LP = -9.81223 + 2.10910 (mean uterine artery PI) ³ - 1.79921 (mean uterine artery PI) ³ + 1.059463 (if bilateral notch)
Second-trimester late-onset pre-eclampsia models			
24	Yu <i>et al.</i> , 2005 ²³⁸	Clinical characteristics and ultrasound markers	LP = 0.7901 + 5.1473 (mean uterine artery PI) ⁻² - 12.5152 (mean uterine artery PI) ⁻¹ - 0.5575 (if smoker) + 0.5333 (if bilateral notch) + 0.0328 (age) + 0.4958 (if black ethnicity) + 1.5109 (if history of PE) + 1.1556 (if previous term live birth) + 0.0378 (BMI)

PE, pre-eclampsia; MoM, multiple of the mean; PI, pulsatility index.

a For logistic regression, $\text{logit}(p) = LP$, where the $LP = \alpha + \beta_1 \times x_1 + \beta_2 \times x_2 + \dots$, and absolute predicted probabilities (p) can be obtained using the transformation shown in Equation 1. The model for 'mean gestational age at delivery with PE' assumes a normal distribution with the predicted mean gestational age and SD 6.8833. The risk of delivery with PE is then calculated as the area under the normal curve between 24 weeks and either 42 weeks for any-onset PE (model 3) or 34 weeks for early-onset PE (model 14). For more detail, see Wright *et al.*²³⁶

Ln indicates that a variable was modelled on the natural logarithm scale.

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Characteristics of the IPPIC-UK validation cohorts

Of the 78 data sets in IPPIC repository, 15 (19%, 15/78) were UK data sets. About three-quarters (73%, 11/15) of IPPIC-UK cohorts contained relevant data needed for external validation.^{42,103,108,114,121,122,137,149,150,161,163} Four data sets^{106,112,137,177} did not include the predictor needed to validate the published prediction models.

Four of the included IPPIC-UK studies were prospective cohorts,^{42,108,161} three were prospective registry data sets^{103,114,163} and four were cohorts (control arm) from randomised trials.^{121,122,149,150} All studies reported on early-, late- and any-onset pre-eclampsia. About half of the included IPPIC-UK cohorts consisted of unselected pregnant women (6/11); four included high-risk women such as those with abnormal uterine artery Doppler measurement,^{121,137} history of pre-eclampsia or underlying medical conditions¹⁵⁰ and maternal obesity;^{122,149} one⁴² included only low-risk nulliparous women, and one¹⁶¹ included all nulliparous singleton pregnancies.

All women in the Screening for Pregnancy Endpoints (SCOPE)⁴² and Pregnancy Outcome Prediction (POP)¹⁶¹ studies were nulliparous. The percentage of nulliparous women in the other data sets ranged from 43% to 65%. Among the nine data sets with multiparous women, five recorded previous pre-eclampsia with percentages ranging from 0%¹²² to 27%.¹⁵⁰ The mean age was similar across studies. The median BMI was higher in EMPOWaR,¹²² Poston *et al.* 2006¹⁵⁰ and Poston *et al.* 2015¹⁴⁹ than in other studies. Most data sets that recorded ethnicity predominantly consisted of white women, apart from Allen *et al.*¹⁰⁸ and Velauthar *et al.*³⁹ (47% and 50% Asian women, respectively). All data sets were considered to be at low risk of bias for quality of participant selection (11/11, 100%); 91% (10/11) were considered to be at low risk and 9% (1/11) were considered to be at unclear risk of bias for predictor reporting; and 45% (5/11) were considered to be at low risk and 55% (6/11) were considered to be at unclear risk of bias for outcome reporting (see *Appendix 8*).

Detailed study characteristics (see *Appendix 5*) and summary statistics for the data sets used for external validation, along with a summary of the missing data for each predictor and outcome, are provided in *Appendices 10* and *11*, respectively.

External validation and meta-analysis of predictive performance

We were able to externally validate each of the 24 published models in at least one and in up to eight data sets. Initially, we could use only one data set of nulliparous women (SCOPE UK⁴²) to validate models 3 (Wright *et al.*²³⁶) and 14 (Wright *et al.*²³⁶) owing to a lack of information on 'interval between pregnancies' in data sets. However, to increase the sample size available for validation (and the number of events), we included nulliparous subgroups in other data sets for validating these models if all other predictors were recorded. Models 3 (Wright *et al.*²³⁶) and 14 (Wright *et al.*²³⁶) were 'competing risk' models and did not provide LP values. Therefore, where necessary (e.g. for the assessment of calibration), we used logit probabilities for validation and for comparison with the other models. We were able to validate only models (22–24)²³⁸ with second-trimester predictors (Yu *et al.*²³⁸ for all three models) in the POP study.¹⁶¹ We did not impute second-trimester predictors in the other data sets as these were not recorded or were missing for a large proportion of individuals.

A summary of the LP and predicted probability distributions for each model and validation data set is given in *Appendix 12*. Median predicted probabilities were generally low for models, which is expected for a rare outcome. However, the median predicted probability in validation data sets was higher for model 10 for early-onset pre-eclampsia and for model 17 for late-onset pre-eclampsia (Kuc *et al.*²³⁰ for both). The median predicted probability was 0.034–0.367 across validation data sets for model 10 (Kuc *et al.*²³⁰) and 0.063–0.310 across validation data sets for model 17 (Kuc *et al.*²³⁰).

Performance of the models

The summary (average) performance statistics across all validation data sets for each model are given in *Table 5* and data set-specific performance statistics in data sets with > 100 pre-eclampsia events are provided for each model in *Table 6*. The summary performance statistics are also shown graphically for all models in *Figure 4*. Direct comparison of the prediction models is difficult owing to different data sets (and numbers of individuals and outcomes) contributing to the validation of each prediction model (see *Appendix 13*).

TABLE 5 Summary meta-analysis estimates of predictive performance for each model across validation data sets

Model number	Type of predictor	Authors, year	Number of validation cohorts	Total events	Summary estimate of performance statistic (95% CI); measures of heterogeneity (I^2 , τ^2 where possible to estimate)		
					C-statistic ^a	Calibration slope	Calibration-in-the-large
Any-onset pre-eclampsia							
<i>Trimester 1 models</i>							
1	Clinical	Plasencia <i>et al.</i> , 2007 ²³¹	3	102	0.686 (0.531 to 0.809); $I^2 = 1\%$, $\tau^2 = 0.001$	0.693 (-0.026 to 1.413); $I^2 = 45\%$, $\tau^2 = 0.035$	0.143 (-1.471 to 1.757); $I^2 = 91\%$, $\tau^2 = 0.38$
2		Poon <i>et al.</i> , 2008 ²³³	3	102	0.688 (0.533 to 0.810); $I^2 = 3\%$, $\tau^2 = 0.002$	0.715 (-0.032 to 1.462); $I^2 = 45\%$, $\tau^2 = 0.037$	0.002 (-1.653 to 1.657); $I^2 = 92\%$, $\tau^2 = 0.402$
3		Wright <i>et al.</i> , 2015 ²³⁶	3	76	0.624 (0.481 to 0.748); $I^2 = 0\%$, $\tau^2 = 0$	0.642 (-0.182 to 1.467); $I^2 = 0\%$, $\tau^2 = 0$	0.954 (-1.127 to 3.034); $I^2 = 93\%$, $\tau^2 = 0.640$
4	Clinical and biochemical markers	Baschat <i>et al.</i> , 2014 ¹¹⁵	2	287	0.708 (0.467 to 0.870); $I^2 = 0\%$, $\tau^2 = 0$	1.238 (0.000 to 2.475); $I^2 = 0\%$, $\tau^2 = 0$	-0.427 (-14.405 to 13.551); $I^2 = 98\%$, $\tau^2 = 2.382$
5		Goetzinger <i>et al.</i> , 2010 ¹²⁸	3	343	0.659 (0.303 to 0.896); $I^2 = 93\%$, $\tau^2 = 0.315$	1.124 (-0.595 to 2.843); $I^2 = 76\%$, $\tau^2 = 0.356$	-0.965 (-3.041 to 1.111); $I^2 = 97\%$, $\tau^2 = 0.667$
6		Odibo <i>et al.</i> , 2011 ¹⁴⁷	3	1774	0.715 (0.506 to 0.860); $I^2 = 90\%$, $\tau^2 = 0.101$	1.163 (0.243 to 2.083); $I^2 = 93\%$, $\tau^2 = 0.104$	-0.786 (-2.615 to 1.044); $I^2 = 99\%$, $\tau^2 = 0.511$
7	Clinical and ultrasound markers	Odibo <i>et al.</i> , 2011 ¹⁴⁷	1	28	0.526 (0.390 to 0.658)	0.277 (-0.642 to 1.195)	-0.520 (-0.907 to -0.134)
<i>Trimester 2 models</i>							
22	Clinical and ultrasound markers	Yu <i>et al.</i> , 2005 ²³⁸	1	273	0.610 (0.574 to 0.645)	0.075 (0.007 to 0.144)	NE

continued

TABLE 5 Summary meta-analysis estimates of predictive performance for each model across validation data sets (continued)

Model number	Type of predictor	Authors, year	Number of validation cohorts	Total events	Summary estimate of performance statistic (95% CI); measures of heterogeneity (I^2 , τ^2 where possible to estimate)		
					C-statistic ^a	Calibration slope	Calibration-in-the-large
Early-onset pre-eclampsia							
<i>Trimester 1 models</i>							
8	Clinical	Baschat <i>et al.</i> , 2014 ¹¹⁵	5	204	0.675 (0.617 to 0.728); $I^2 = 0\%$, $\tau^2 = 0$	2.041 (0.560 to 3.522); $I^2 = 69\%$, $\tau^2 = 0.692$	-0.102 (-1.699 to 1.494); $I^2 = 97\%$, $\tau^2 = 1.535$
9		Crovetto <i>et al.</i> , 2015 ²²⁹	3 ^b	21	0.575 (0.208 to 0.875); $I^2 = 69\%$, $\tau^2 = 0.288$	0.642 (-4.006 to 5.291); $I^2 = 81\%$, $\tau^2 = 0.217$	-0.576 (-4.967 to 3.814); $I^2 = 95\%$, $\tau^2 = 2.925$
10		Kuc <i>et al.</i> , 2013 ²³⁰	6	1449	0.661 (0.613 to 0.706); $I^2 = 32\%$, $\tau^2 = 0.011$	0.423 (0.294 to 0.552); $I^2 = 33\%$, $\tau^2 = 0.004$	-4.330 (-5.411 to -3.250); $I^2 = 99\%$, $\tau^2 = 0.946$
11		Plasencia <i>et al.</i> , 2007 ²³¹	4 ^b	27	0.491 (0.429 to 0.553); $I^2 = 38\%$, $\tau^2 = 0.005$	0.513 (-2.050 to 3.076); $I^2 = 0\%$, $\tau^2 = 0$	0.472 (-0.797 to 1.740); $I^2 = 74\%$, $\tau^2 = 0.452$
12		Poon <i>et al.</i> , 2010 ²³²	3	21	0.636 (0.308 to 0.873); $I^2 = 34\%$, $\tau^2 = 0.105$	0.991 (0.022 to 1.959); $I^2 = 0\%$, $\tau^2 = 0$	-1.091 (-4.885 to 2.702); $I^2 = 93\%$, $\tau^2 = 2.175$
13		Scazzocchio <i>et al.</i> , 2013 ²³⁵	3	21	0.743 (0.374 to 0.933); $I^2 = 14\%$, $\tau^2 = 0.057$	0.751 (0.144 to 1.358); $I^2 = 0\%$, $\tau^2 = 0$	-0.699 (-3.885 to 2.486); $I^2 = 90\%$, $\tau^2 = 1.481$
14		Wright <i>et al.</i> , 2015 ²³⁶	2	9	0.742 (0.040 to 0.995); $I^2 = 0\%$, $\tau^2 = 0$	0.919 (-4.378 to 6.216); $I^2 = 0\%$, $\tau^2 = 0$	0.282 (-14.337 to 14.900); $I^2 = 90\%$, $\tau^2 = 2.395$
15	Clinical and biochemical markers	Poon <i>et al.</i> , 2009 ²³⁴	1	10	0.741 (0.507 to 0.888)	0.452 (0.210 to 0.693)	-2.671 (-3.350 to -1.991)
<i>Trimester 2 models</i>							
23	Clinical and ultrasound markers	Yu <i>et al.</i> , 2005 ²³⁸	1	10	0.908 (0.826 to 0.954)	0.557 (0.293 to 0.821)	2.473 (1.716 to 3.229)

Model number	Type of predictor	Authors, year	Number of validation cohorts	Total events	Summary estimate of performance statistic (95% CI); measures of heterogeneity (I^2 , τ^2 where possible to estimate)		
					C-statistic ^a	Calibration slope	Calibration-in-the-large
Late-onset pre-eclampsia							
<i>Trimester 1 models</i>							
16	Clinical	Crovetto <i>et al.</i> , 2015 ²²⁹	5	384	0.634 (0.461 to 0.778); $I^2 = 87\%$, $\tau^2 = 0.264$	0.558 (-0.008 to 1.125); $I^2 = 92\%$, $\tau^2 = 0.179$	-0.048 (-1.647 to 1.551); $I^2 = 98\%$, $\tau^2 = 1.615$
17		Kuc <i>et al.</i> , 2013 ²³⁰	8	5716	0.623 (0.572 to 0.671); $I^2 = 87\%$, $\tau^2 = 0.025$	0.657 (0.496 to 0.818); $I^2 = 60\%$, $\tau^2 = 0.007$	-1.911 (-2.235 to -1.586); $I^2 = 98\%$, $\tau^2 = 0.124$
18		Plasencia <i>et al.</i> , 2007 ²³¹	3	90	0.672 (0.539 to 0.782); $I^2 = 0\%$, $\tau^2 = 0$	0.612 (0.042 to 1.182); $I^2 = 14\%$, $\tau^2 = 0.008$	0.202 (-1.113 to 1.517); $I^2 = 85\%$, $\tau^2 = 0.234$
19		Poon <i>et al.</i> , 2010 ²³²	3	90	0.647 (0.475 to 0.787); $I^2 = 25\%$, $\tau^2 = 0.020$	0.565 (0.081 to 1.050); $I^2 = 0\%$, $\tau^2 = 0$	0.121 (-1.594 to 1.837); $I^2 = 91\%$, $\tau^2 = 0.430$
20		Scazzocchio <i>et al.</i> , 2013 ²³⁵	1	26	0.597 (0.478 to 0.705)	0.562 (-0.168 to 1.291)	0.524 (0.128 to 0.920)
21	Clinical and biochemical markers	Poon <i>et al.</i> , 2009 ²³⁴	1	13	0.684 (0.550 to 0.792)	0.799 (0.257 to 1.341)	-0.349 (-0.902 to 0.205)
<i>Trimester 2 models</i>							
24	Clinical and ultrasound markers	Yu <i>et al.</i> , 2005 ²³⁸	1	263	0.607 (0.570 to 0.642)	0.077 (0.005 to 0.148)	NE

NE, not estimable.

a The C-statistic was pooled on the logit scale; therefore, I^2 and τ^2 are for logit(C-statistic).

b Number of studies is one fewer for calibration slope of models 9 and 11. The calibration slope could not be estimated reliably in SCOPE UK and was, therefore, excluded from the meta-analysis.

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TABLE 6 Predictive performance statistics for models in the individual IPPIC data sets with > 100 events

Model number	Authors, year	Type of predictor	Validation cohort	Number of women	Events ^a (%)	Performance statistic (95% CI)		
						C-statistic	Calibration slope	Calibration-in-the-large
Trimester 1 any-onset pre-eclampsia models								
4	Baschat <i>et al.</i> , 2014 ¹¹⁵	Clinical and biochemical	POP ¹⁶¹	4212	273 (6.5)	0.704 (0.670 to 0.737)	1.237 (1.034 to 1.439)	0.658 (0.533 to 0.782)
5	Goetzinger <i>et al.</i> , 2010 ¹²⁸		POP ¹⁶¹	4212	273 (6.5)	0.764 (0.730 to 0.795)	1.706 (1.499 to 1.913)	-0.070 (-0.195 to 0.054)
6	Odibo <i>et al.</i> , 2011 ¹⁴⁷		St George's ¹⁶³	54,635	1487 (2.7)	0.672 (0.654 to 0.690)	0.962 (0.885 to 1.039)	-0.897 (-0.950 to -0.845)
			POP ¹⁶¹	4212	273 (6.5)	0.779 (0.744 to 0.812)	1.490 (1.329 to 1.651)	-0.033 (-0.159 to 0.094)
Trimester 1 early-onset pre-eclampsia models								
8	Baschat <i>et al.</i> , 2014 ¹¹⁵	Clinical	Poston <i>et al.</i> 2006 ¹⁵⁰	2422	144 (6.0)	0.672 (0.626 to 0.716)	1.281 (0.898 to 1.664)	1.797 (1.628 to 1.967)
10	Kuc <i>et al.</i> , 2013 ²³⁰		St George's ¹⁶³	54,635	151 (0.3)	0.635 (0.587 to 0.679)	0.343 (0.227 to 0.460)	-4.510 (-4.674 to -4.347)
			AMND ¹¹⁴	136,635	1237 (0.9)	0.681 (0.665 to 0.696)	0.470 (0.430 to 0.511)	-3.387 (-3.445 to -3.330)
Trimester 1 late-onset pre-eclampsia models								
16	Crovetto <i>et al.</i> , 2015 ²²⁹	Clinical	POP ¹⁶¹	4212	263 (6.2)	0.781 (0.745 to 0.813)	1.248 (1.120 to 1.376)	1.309 (1.177 to 1.441)
17	Kuc <i>et al.</i> , 2013 ²³⁰		ALSPAC ¹⁰³	14,344	266 (1.9)	0.657 (0.616 to 0.696)	0.761 (0.550 to 0.973)	-1.574 (-1.699 to -1.448)
			St George's ¹⁶³	54,635	1336 (2.4)	0.636 (0.621 to 0.651)	0.632 (0.560 to 0.704)	-1.970 (-2.025 to -1.915)
			AMND ¹¹⁴	136,635	3733 (2.7)	0.844 (0.640 to 0.943)	0.746 (0.449 to 1.042)	-1.439 (-2.092 to -0.787)
			POP ¹⁶¹	4212	263 (6.2)	0.599 (0.561 to 0.636)	0.673 (0.452 to 0.894)	-1.487 (-1.613 to -1.361)
Trimester 2 any-onset pre-eclampsia models								
22	Yu <i>et al.</i> , 2005 ²³⁸	Clinical and ultrasound	POP ¹⁶¹	4212	273 (6.5)	0.610 (0.574 to 0.645)	0.075 (0.007 to 0.144)	NE
Trimester 2 late-onset pre-eclampsia models								
24	Yu <i>et al.</i> , 2005 ²³⁸	Clinical and ultrasound	POP ¹⁶¹	4212	263 (6.2)	0.607 (0.570 to 0.642)	0.077 (0.005 to 0.148)	NE

AMND, Aberdeen Maternity and Neonatal Databank; NE, not estimable owing to perfect prediction (same predicted probability for all individuals who had the event).

^a Estimates are averages across imputations (pooled using Rubin's rules).

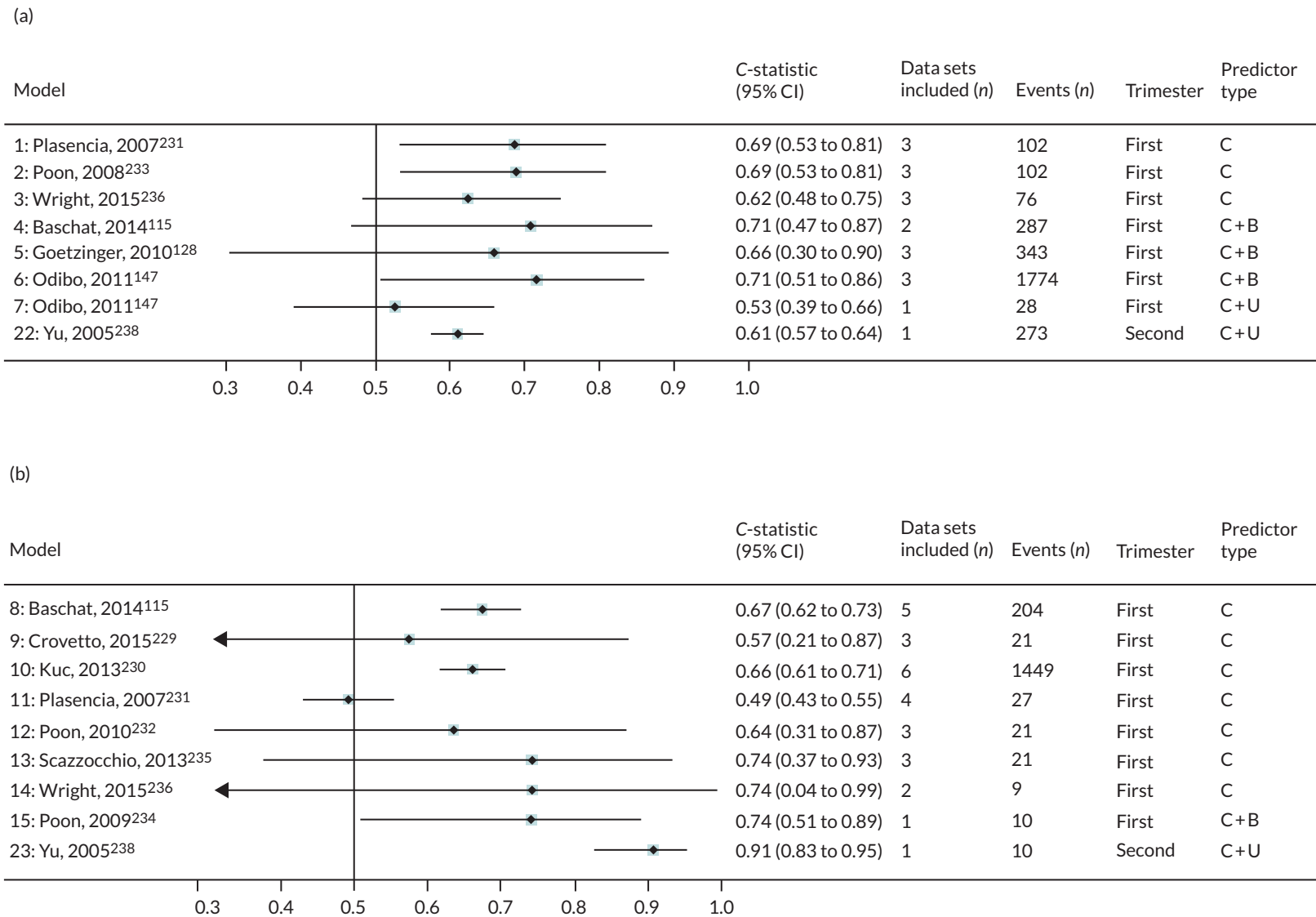


FIGURE 4 Plot of the summary meta-analysis estimates and CIs of the C-statistic (pooled across IPPIC-UK validation data sets) for each prediction model. (a) Any-onset pre-eclampsia; (b) early-onset pre-eclampsia; and (c) late-onset pre-eclampsia. This figure contains information from several sources.^{115,128,147,229–236,238} C, clinical characteristics only; C + B, clinical characteristics and biochemical markers; C + U, clinical characteristics and ultrasound markers. (*continued*)

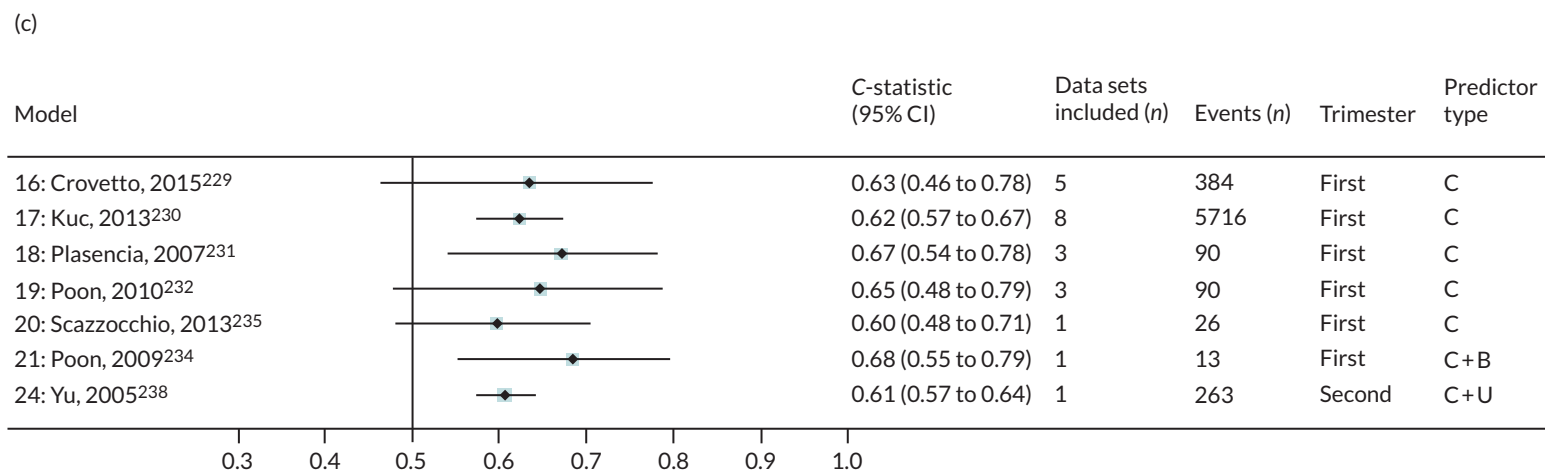


FIGURE 4 Plot of the summary meta-analysis estimates and CIs of the C-statistic (pooled across IPPIC-UK validation data sets) for each prediction model. (a) Any-onset pre-eclampsia; (b) early-onset pre-eclampsia; and (c) late-onset pre-eclampsia. This figure contains information from several sources.^{115,128,147,229-236,238} C, clinical characteristics only; C + B, clinical characteristics and biochemical markers; C + U, clinical characteristics and ultrasound markers.

Any-onset pre-eclampsia

First-trimester clinical characteristics only models

Two (Plasencia *et al.*, model 1;²³¹ Poon *et al.*, model 2³³) of the three first-trimester clinical characteristics models were validated in three cohorts with total pre-eclampsia events > 100. The summary C-statistics were low (< 0.7), and the summary calibration slopes were < 1 for both models.

First-trimester clinical and biochemical models

There was a sufficient number of pre-eclampsia events in total (> 100) for all three clinical and biochemical first-trimester models (Baschat *et al.*, model 4;¹¹⁵ Goetzinger *et al.*, model 5;¹²⁸ Odibo *et al.*, model 6¹⁴⁷). Of these, only two models had summary C-statistics > 0.7; but only one model's (Odibo *et al.*, model 6¹⁴⁷) C-statistic had a lower limit of the 95% CI > 0.50. Their summary calibration slopes were > 1, indicating potential underfitting with predictions that do not span a wide enough range of probabilities compared with what is observed in the validation data sets. One model (Odibo *et al.*, model 7¹⁴⁷) including first-trimester clinical and ultrasound predictors could be validated only in a data set with a very small number of events (i.e. 28 pre-eclampsia outcomes).

When validated in individual cohorts that had at least 100 pre-eclampsia events, promising discrimination was observed for all three models with C-statistics of 0.70 (Baschat *et al.*, model 4¹¹⁵), 0.76 (Goetzinger *et al.*, model 5¹²⁸) and 0.78 (Odibo *et al.*, model 6¹⁴⁷) in the POP study¹⁶¹ cohort of singleton nulliparous women; the corresponding calibration slopes were 1.24, 1.71 and 1.49, indicating underfitting of risks (range of predictions too narrow). Models 5 (Goetzinger *et al.*¹²⁸) and 6 (Odibo *et al.*¹⁴⁷) systematically predicted risks that were too high in all of the validation data sets (calibration-in-the-large < 0).

Second-trimester models

Only one model (Yu *et al.*, model 22²³⁸), which comprised clinical and ultrasound predictors, could be validated. Both discrimination (C-statistic 0.61) and calibration slope were poor (0.075).

Early-onset pre-eclampsia

First-trimester clinical models

Of the seven models, only two (Baschat *et al.*, model 8;¹¹⁵ Kuc *et al.*, model 10²³⁰) could be validated in data sets with adequate total numbers of pre-eclampsia events (> 100). Both had low discrimination, with summary C-statistics < 0.7; the calibration was poor, with calibration slopes of 2.04 and 0.42, respectively.

The performance of the two models (Baschat *et al.*, model 8;¹¹⁵ Kuc *et al.*, model 10²³⁰) in individual cohorts with event size > 100 was low, with C-statistics ranging from 0.63 to 0.68; the calibration slope estimate was either too high (1.28) or too low (0.34, 0.47), respectively. Model 10²³⁰ systematically predicted too high in all their validation data sets (calibration-in-the-large < 0).

First-trimester clinical and biochemical models

The one model (Poon *et al.*, model 15²³⁴) with clinical and biochemical first-trimester predictors had an insufficient number of events ($n = 10$) to provide adequate validation.

Second-trimester models

One model (Yu *et al.*, model 23²³⁸) comprising clinical and ultrasound markers had an insufficient number of events ($n = 10$) to provide adequate validation.

Late-onset pre-eclampsia

First-trimester clinical models

Two of the five models (Crovetto *et al.*, model 16;²²⁹ Kuc *et al.*, model 17²³⁰) were validated across cohorts with total event sizes above 100 and had low summary C-statistics (< 0.7). The summary calibration slope ranged from 0.56 to 0.80 for all five models. CIs were generally wide, with only a few data sets for most model validations and small numbers of pre-eclampsia outcomes per meta-analysis (see Figure 4).

When the performance of the two first-trimester clinical models was assessed within individual cohorts with pre-eclampsia event numbers above 100, model 16 (Crovetto *et al.*²²⁹) showed promising discrimination (C-statistic 0.78) and a calibration slope of 1.25 in the POP study. The other model (Kuc *et al.*,²³⁰ model 17) showed low discrimination and poor calibration (C-statistic 0.60, calibration slope 0.67) in the POP cohort, low discrimination in St George's and ALSPAC cohorts (C-statistic 0.64 and 0.66, respectively), and high discrimination (C-statistic 0.84) with a calibration slope of 0.75 in the Aberdeen Maternity and Neonatal Databank (AMND) cohort.^{103,114,161,163}

First-trimester clinical and biochemical models

The one model (Poon *et al.*, model 21²³⁴) with clinical and biochemical markers had an insufficient number of pre-eclampsia events ($n = 13$) to provide adequate validation.

Second-trimester models

The only model (Yu *et al.*, model 24²³⁸) with second-trimester clinical and ultrasound markers was validated in a single data set (263 events) and showed low C-statistic (0.61) and poor calibration (calibration slope 0.08).

Heterogeneity

Where it was possible to estimate it, heterogeneity across studies varied from small (e.g. models 1, 2 and 3 had $I^2 \leq 3\%$, $\tau^2 \leq 0.002$) to large (e.g. models 5 and 6 had $I^2 \geq 90\%$, $\tau^2 \geq 0.1$) for the C-statistic (on the logit scale), and from moderate to large in the calibration slope for two-thirds of all models (17/24). All models validated in multiple IPD data sets had high levels of heterogeneity in calibration-in-the-large performance, with the I^2 often $> 90\%$ (see Table 5).

For the majority of models (67%, 16/24), the summary calibration slope was ≤ 0.7 . Although this could be a result of chance for some models (95% CIs include 1), it is likely to suggest overfitting in the model development (as the ideal value is 1, and values < 1 indicate predictions that are too extreme) (Figure 5). The exceptions to this were models 4, 5 and 6 (for any-onset pre-eclampsia) and model 8 (for early-onset pre-eclampsia).

Many of the models did not have summary calibration-in-the-large values close to zero, and, even if the average is near zero, this could be due to it performing poorly in the individual validation data sets and averaging out near zero, such as for models 2, 8 and 16.

The predictive performance is likely to be optimistic in small development studies with few pre-eclampsia events, and predictor effects will be too large. If not corrected for (e.g. by penalisation/shrinkage methods), this will result in predictions that are too extreme when validated (hence calibration slope < 1); in other words, the predictor effects will not be as strong as they were thought to be at model development.

By indicating whether predictions are systematically too high or too low, calibration-in-the-large may suggest the need for recalibration of the model intercept. There was very large uncertainty in the summary estimates of calibration-in-the-large for most models, which reflects often small numbers of events and large heterogeneity across the individual data sets contributing towards the validation (Figure 6).

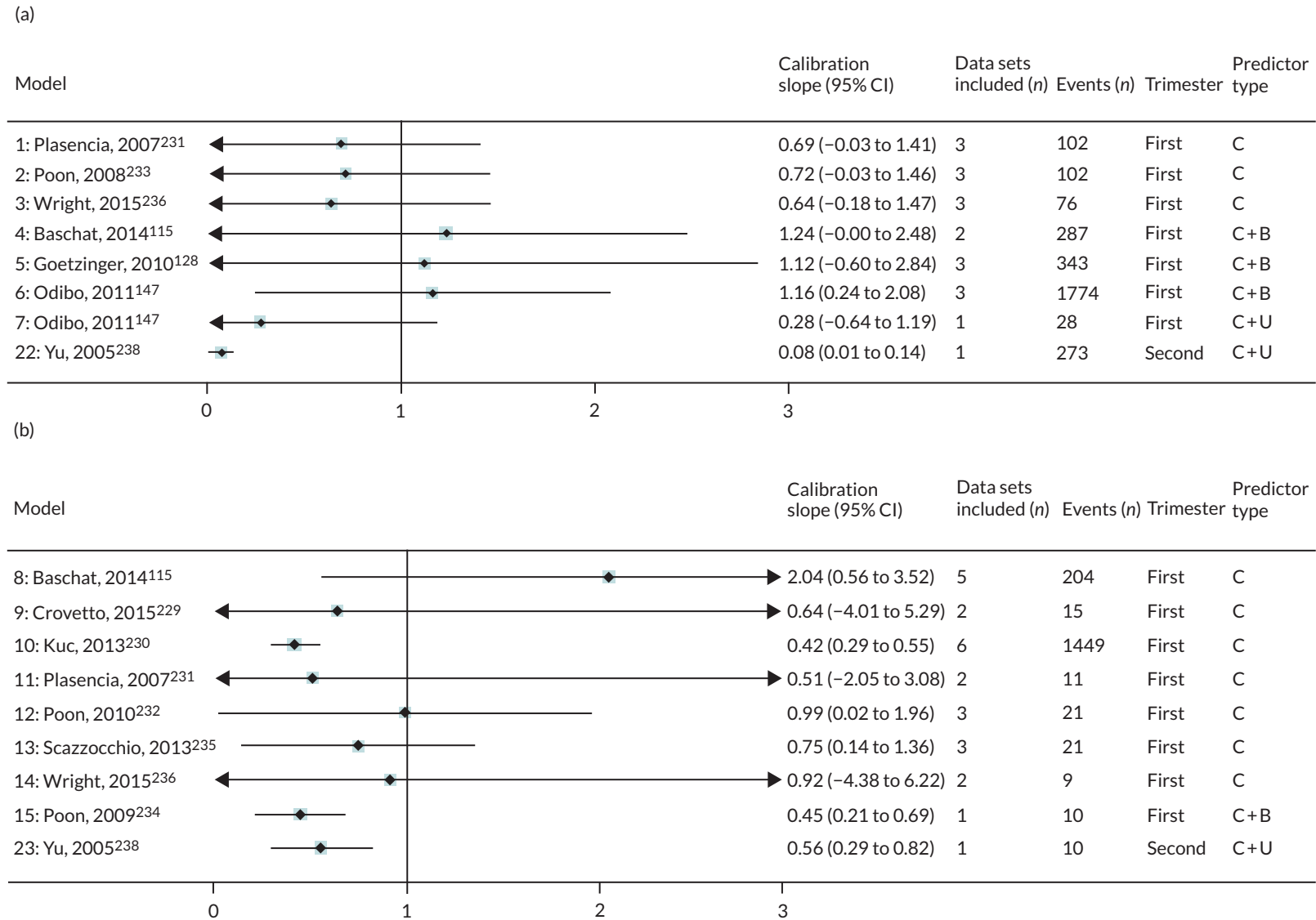


FIGURE 5 Plot of the summary meta-analysis estimates and CIs of calibration (pooled across IPPIC-UK validation data sets) for each prediction model. (a) Any-onset pre-eclampsia; (b) early-onset pre-eclampsia; and (c) late-onset pre-eclampsia. This figure contains information from several sources.^{115,128,147,229-236,238} C, clinical characteristics only; C + B, clinical characteristics and biochemical markers; C + U, clinical characteristics and ultrasound markers. (*continued*)

(c)

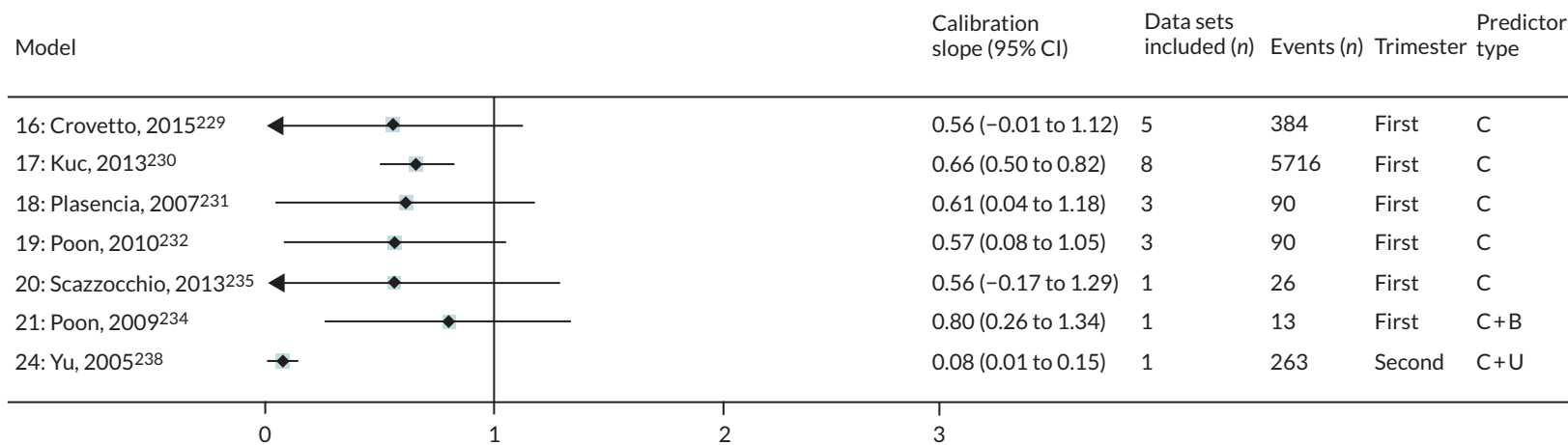


FIGURE 5 Plot of the summary meta-analysis estimates and CIs of calibration (pooled across IPPIC-UK validation data sets) for each prediction model. (a) Any-onset pre-eclampsia; (b) early-onset pre-eclampsia; and (c) late-onset pre-eclampsia. This figure contains information from several sources,^{115,128,147,229-236,238} C, clinical characteristics only; C + B, clinical characteristics and biochemical markers; C + U, clinical characteristics and ultrasound markers.

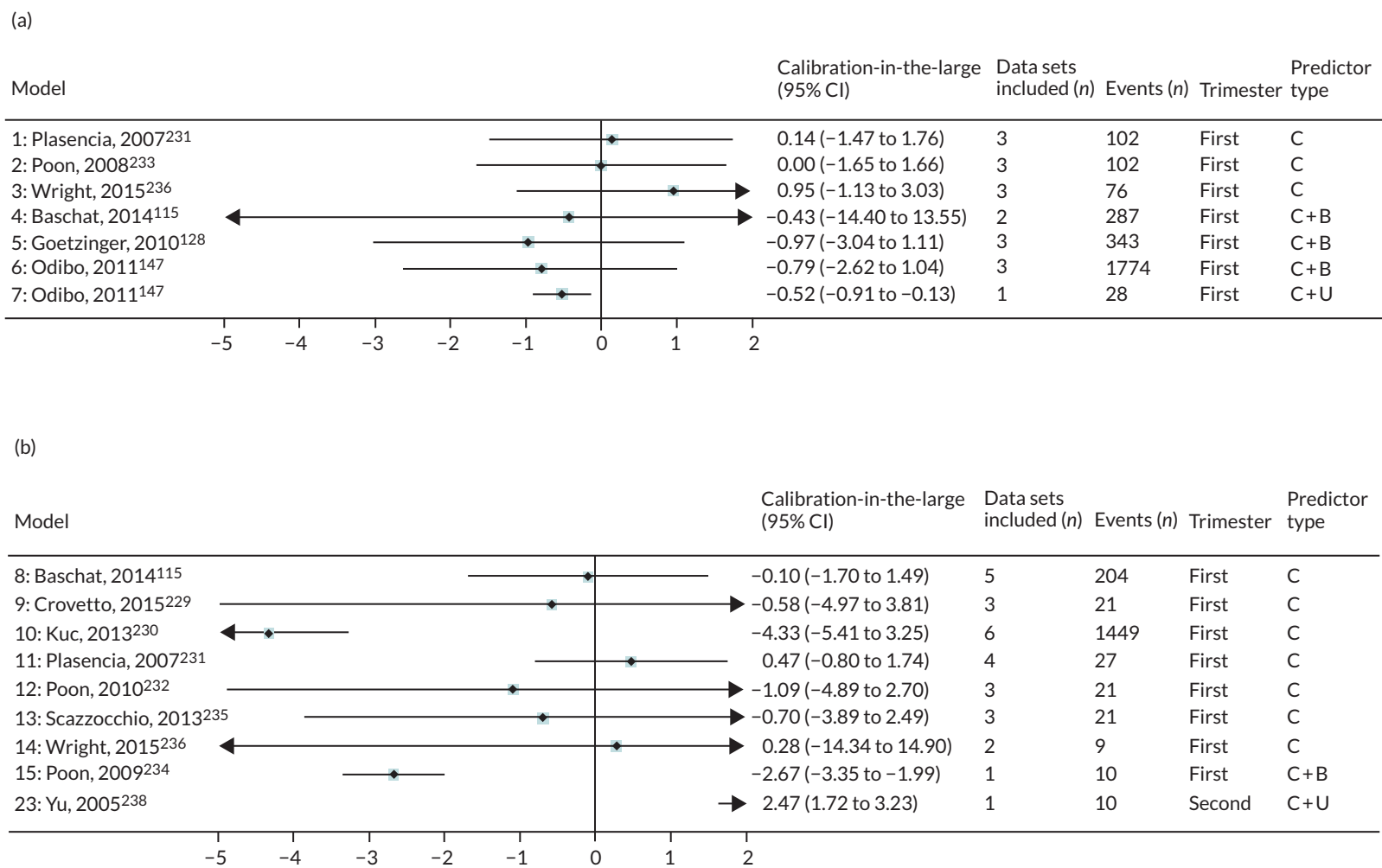


FIGURE 6 Plot of the summary meta-analysis estimates and CIs of calibration-in-the-large (pooled across IPPIC-UK validation datasets) for each prediction model. (a) Any-onset pre-eclampsia; (b) early-onset pre-eclampsia; and (c) late-onset pre-eclampsia. This figure contains information from several sources.^{115,128,147,229-236,238} C, clinical characteristics only; C + B, clinical characteristics and biochemical markers; C + U, clinical characteristics and ultrasound markers. (*continued*)

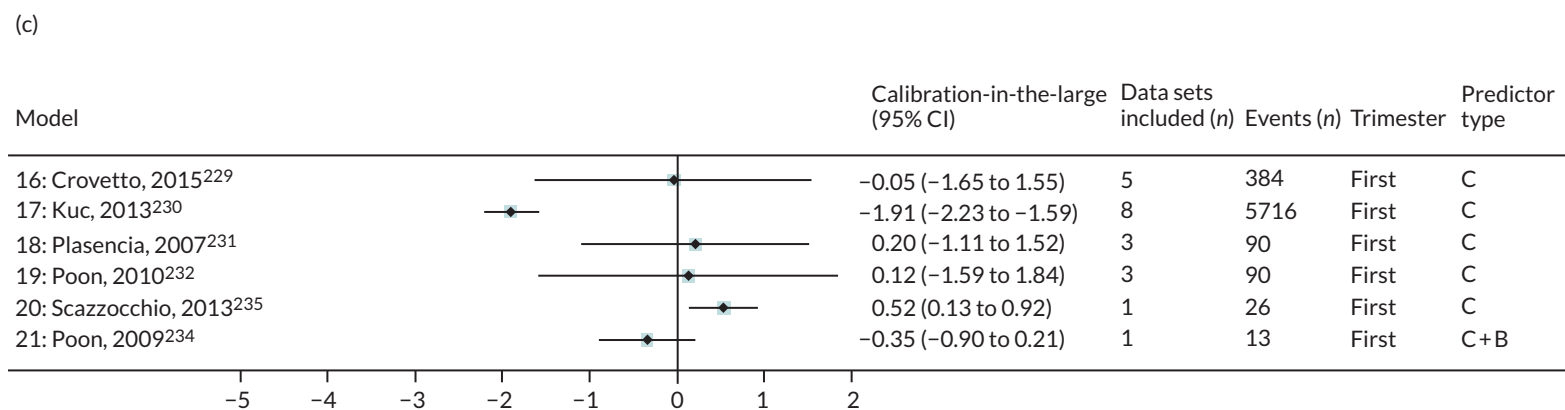


FIGURE 6 Plot of the summary meta-analysis estimates and CIs of calibration-in-the-large (pooled across IPPIC-UK validation datasets) for each prediction model. (a) Any-onset pre-eclampsia; (b) early-onset pre-eclampsia; and (c) late-onset pre-eclampsia. This figure contains information from several sources.^{115,128,147,229-236,238} C, clinical characteristics only; C + B, clinical characteristics and biochemical markers; C + U, clinical characteristics and ultrasound markers.

To illustrate the general concern about poor calibration, calibration plots are presented for models validated in data sets with > 100 events (Figures 7–9). These clearly show the extent of miscalibration, with predicted outcome risk from the models being far greater than the observed probabilities across the entire range of predicted risk in most cases. For any-onset pre-eclampsia, the exceptions to this are model 4 (Baschat *et al.*, 2014¹¹⁵) and model 5 (Goetzinger *et al.*, 2010¹²⁸), when validated in POP (see Figure 7).¹⁶¹ Model 4 and model 5 predictions are too low for those at greatest risk. For early-onset pre-eclampsia, model 8 (Baschat *et al.*, 2014¹¹⁵), validated in Poston 2006¹⁵⁰ (see Figure 8), shows that predictions were all very low (all predicted probabilities < 3%) but the observed frequency of events was higher (up to around 20%). Model 10 (Kuc *et al.*, 2013²³⁰), validated in the St George's cohort,¹⁶³ predicted an average of near 50% for the highest risk group; however, their observed risk was still very close to zero. For late-onset pre-eclampsia, model 16 (Crovetto *et al.*, 2015²²⁹) underpredicted risk, particularly in those at highest risk in POP,¹⁶¹ and model 17 (Kuc *et al.*, 2013²³⁰) overpredicted risk in both St George's¹⁶³ and AMND¹¹⁴ (see Figure 9).

Decision curve analysis

Comparisons of models for any-, early- and late-onset pre-eclampsia using decision curve analysis were carried out in the SCOPE,⁴² Allen *et al.*,¹⁰⁸ Poston *et al.* 2015¹⁴⁹ and POP¹⁶¹ data sets. Net benefit values are often best multiplied by 1000 to reveal the extra number of women who would be correctly treated per 1000 women who used the model, with none treated incorrectly.

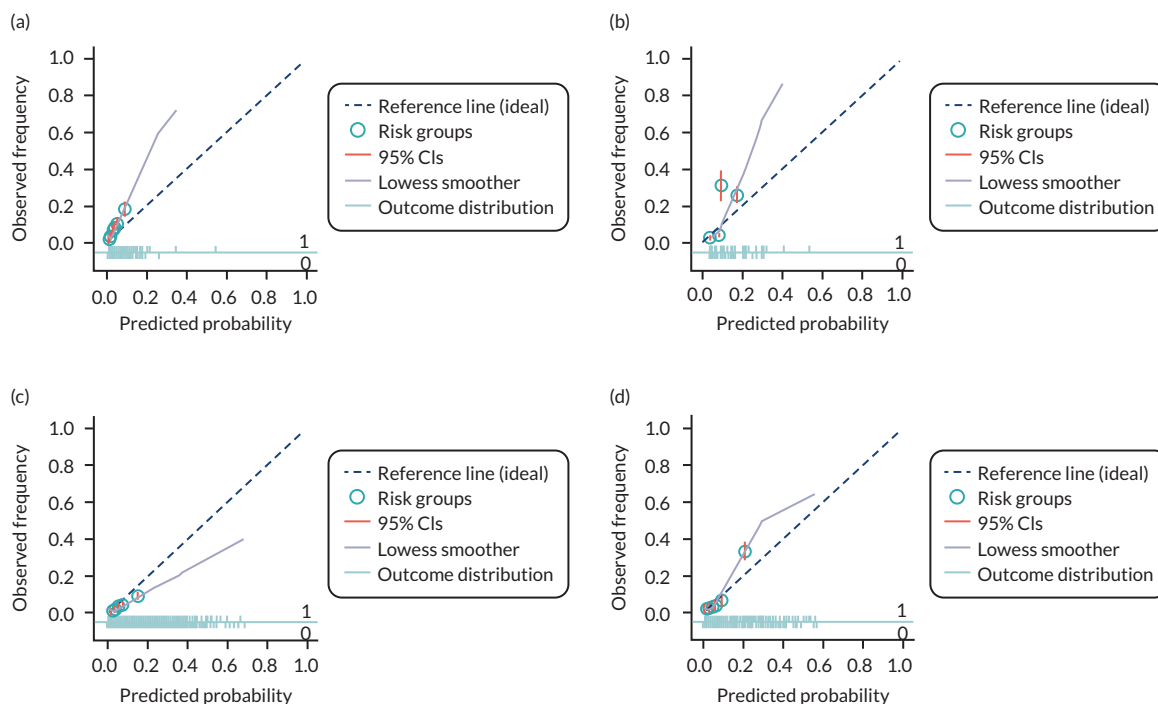


FIGURE 7 Calibration plots for models predicting any-onset pre-eclampsia using first-trimester clinical characteristics and biochemical markers in data sets with > 100 outcome events. (a) Model 4¹¹⁵ in POP;¹⁶¹ (b) model 5¹²⁸ in POP;¹⁶¹ (c) model 6¹⁴⁷ in St George's;¹⁶³ and (d) model 6¹⁴⁷ in POP.¹⁶¹ Reproduced from Snell *et al.*⁵² Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

EXTERNAL VALIDATION OF EXISTING PRE-ECLAMPSIA PREDICTION MODELS

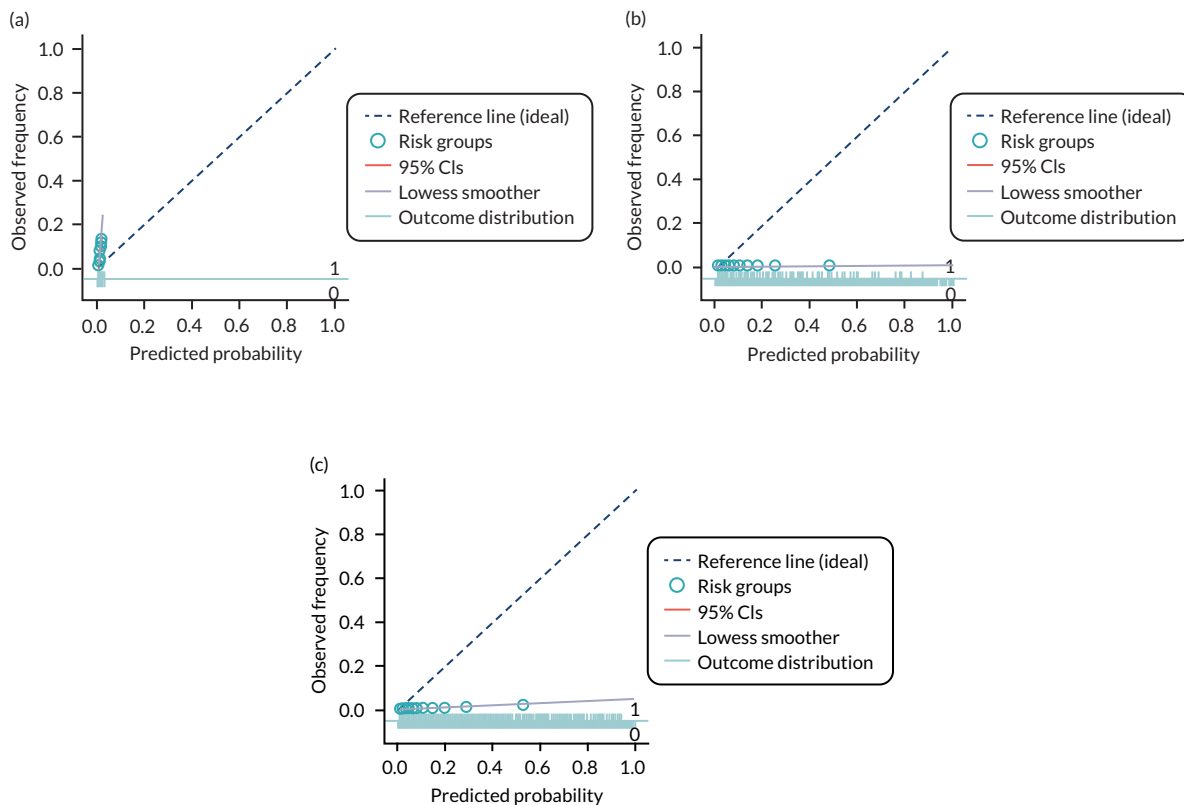


FIGURE 8 Calibration plots for models predicting early-onset pre-eclampsia using first-trimester clinical characteristics marker in data sets with > 100 outcome events. (a) Model 8¹¹⁵ in Poston 2006;¹⁵⁰ (b) model 10²³⁰ in St George's;¹⁶³ and (c) model 10²³⁰ in AMND.¹¹⁴

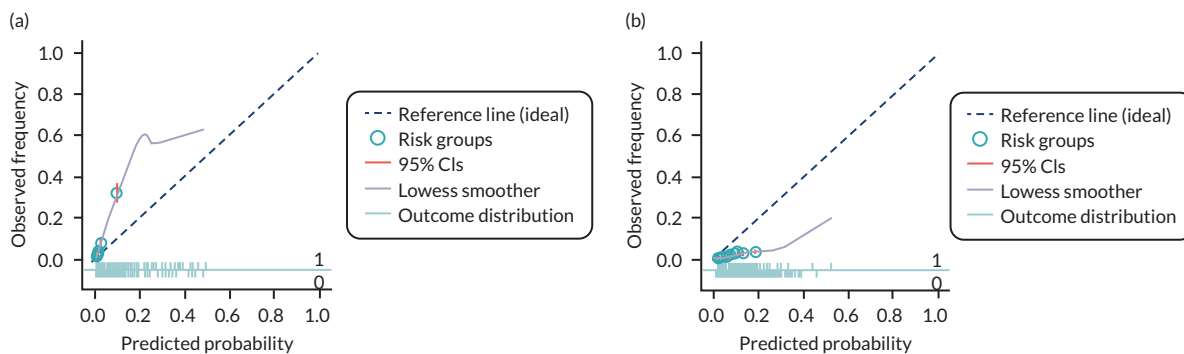


FIGURE 9 Calibration plots for models predicting late-onset pre-eclampsia using first-trimester clinical characteristics marker in data sets with > 100 outcome events. (a) Model 16²²⁹ in POP;¹⁶¹ (b) model 17²³⁰ in ALSPAC;¹⁰³ (c) model 17²³⁰ in St George's;¹⁶³ (d) model 17²³⁰ in AMND;¹¹⁴ and (e) model 17²³⁰ in POP.¹⁶¹ (continued)

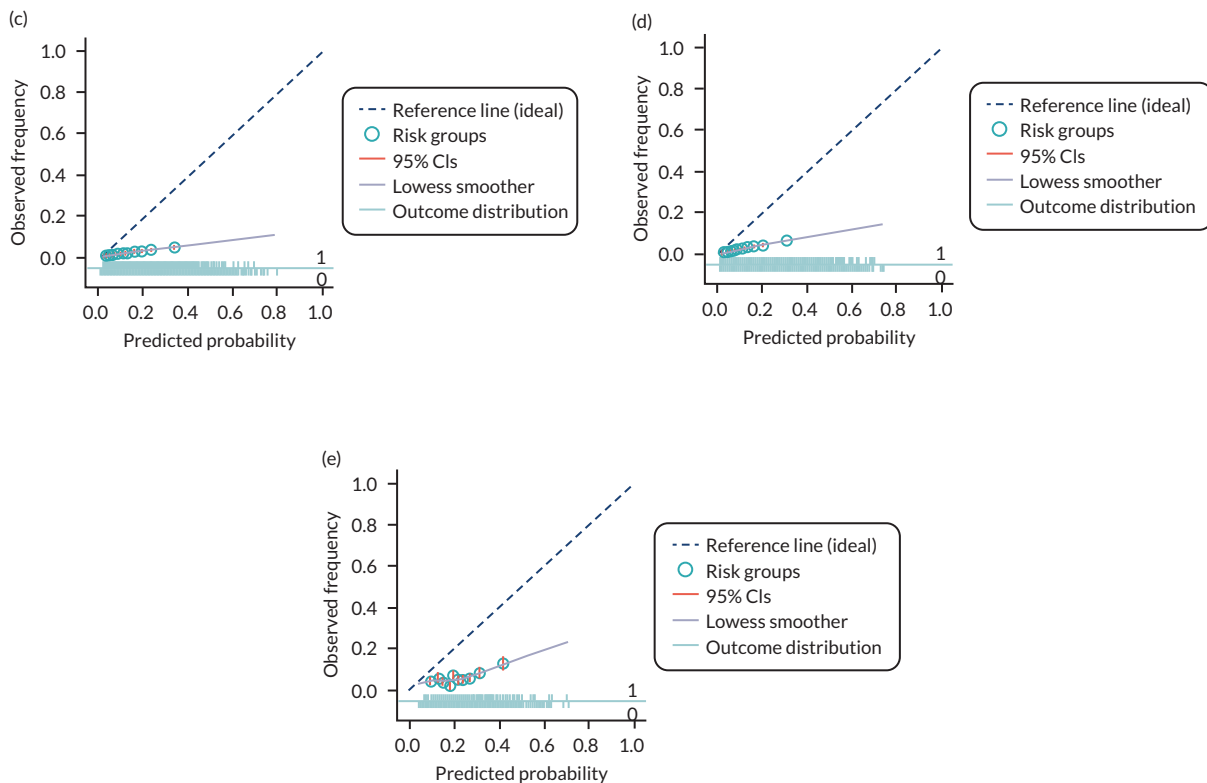


FIGURE 9 Calibration plots for models predicting late-onset pre-eclampsia using first-trimester clinical characteristics marker in data sets with > 100 outcome events. (a) Model 16²²⁹ in POP;¹⁶¹ (b) model 17²³⁰ in ALSPAC;¹⁰³ (c) model 17²³⁰ in St George's;¹⁶³ (d) model 17²³⁰ in AMND;¹¹⁴ and (e) model 17²³⁰ in POP.¹⁶¹

Any-onset pre-eclampsia

Models validated in cohorts with > 100 events

The Goetzinger *et al.*¹²⁸ and Odibo *et al.*¹⁴⁷ models (models 5 and 6) showed a positive net benefit between relevant predicted probability thresholds of 4% to 20% in the POP data set¹⁶¹ comprising any nulliparous women with a singleton pregnancy. The Baschat *et al.*¹¹⁵ model (model 4) also showed a net benefit from 5% to 20% in the POP data set.¹⁶¹ These models, however, showed a net harm across thresholds in the Allen *et al.*¹⁰⁸ and Poston *et al.* 2015¹⁴⁹ data sets (Figure 10).

Early-onset pre-eclampsia

Decision curves for early-onset pre-eclampsia are given in Appendix 14. These did not show any net benefit, with some models showing potential harm compared with a treat-none strategy. This is likely to be because of how rare the outcome is and how few events there were in the data sets used for validation.

Late-onset pre-eclampsia

Models validated in cohorts with > 100 events

For late-onset pre-eclampsia, the Crovetto *et al.*²²⁹ model (model 16) performed better than the Kuc *et al.* 2013²³⁰ model (model 17) in POP,¹⁶¹ with net benefit at thresholds of 4–20%; however, this model did not demonstrate any net benefit over a treat-all or a treat-none strategy in the other three studies (Figure 11).

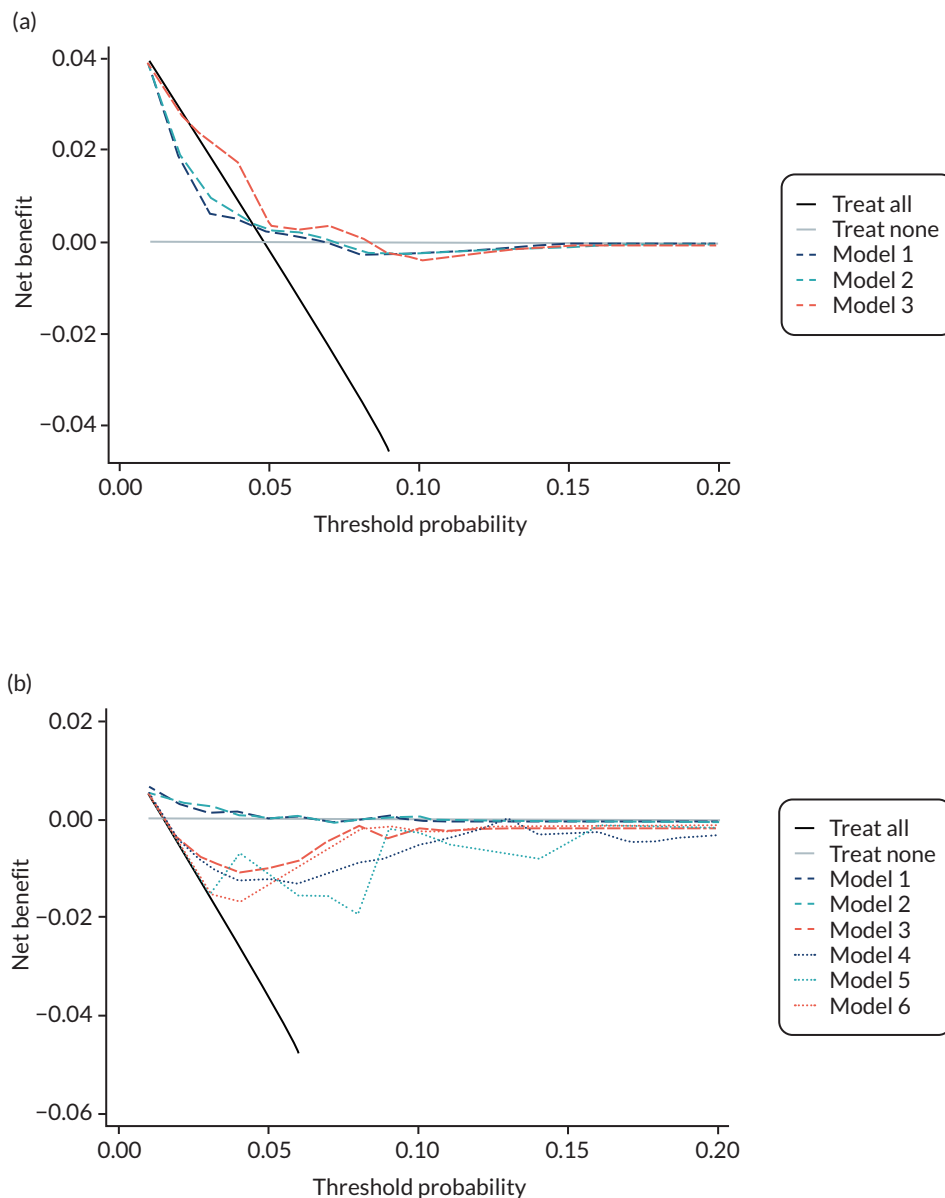


FIGURE 10 Decision curves for prediction models of any-onset pre-eclampsia in the (a) SCOPE UK,⁴² (b) Allen *et al.*,¹⁰⁸ (c) Poston *et al.* 2015¹⁴⁹ and (d) POP¹⁴¹ data sets. Reproduced from Snell *et al.*⁵² Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data. (*continued*)

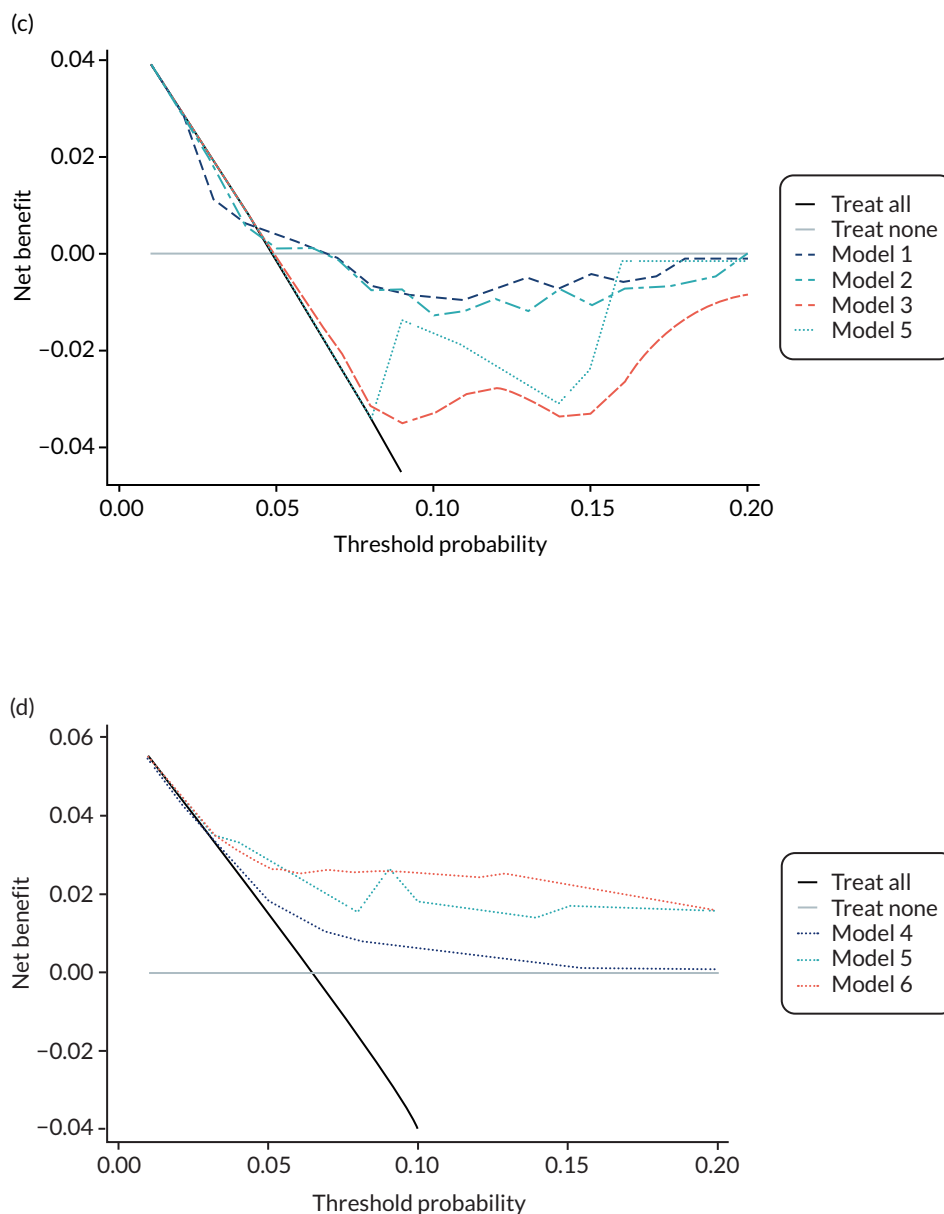


FIGURE 10 Decision curves for prediction models of any-onset pre-eclampsia in the (a) SCOPE UK,⁴² (b) Allen *et al.*,¹⁰⁸ (c) Poston *et al.* 2015¹⁴⁹ and (d) POP¹⁶¹ data sets. Reproduced from Snell *et al.*⁵² Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

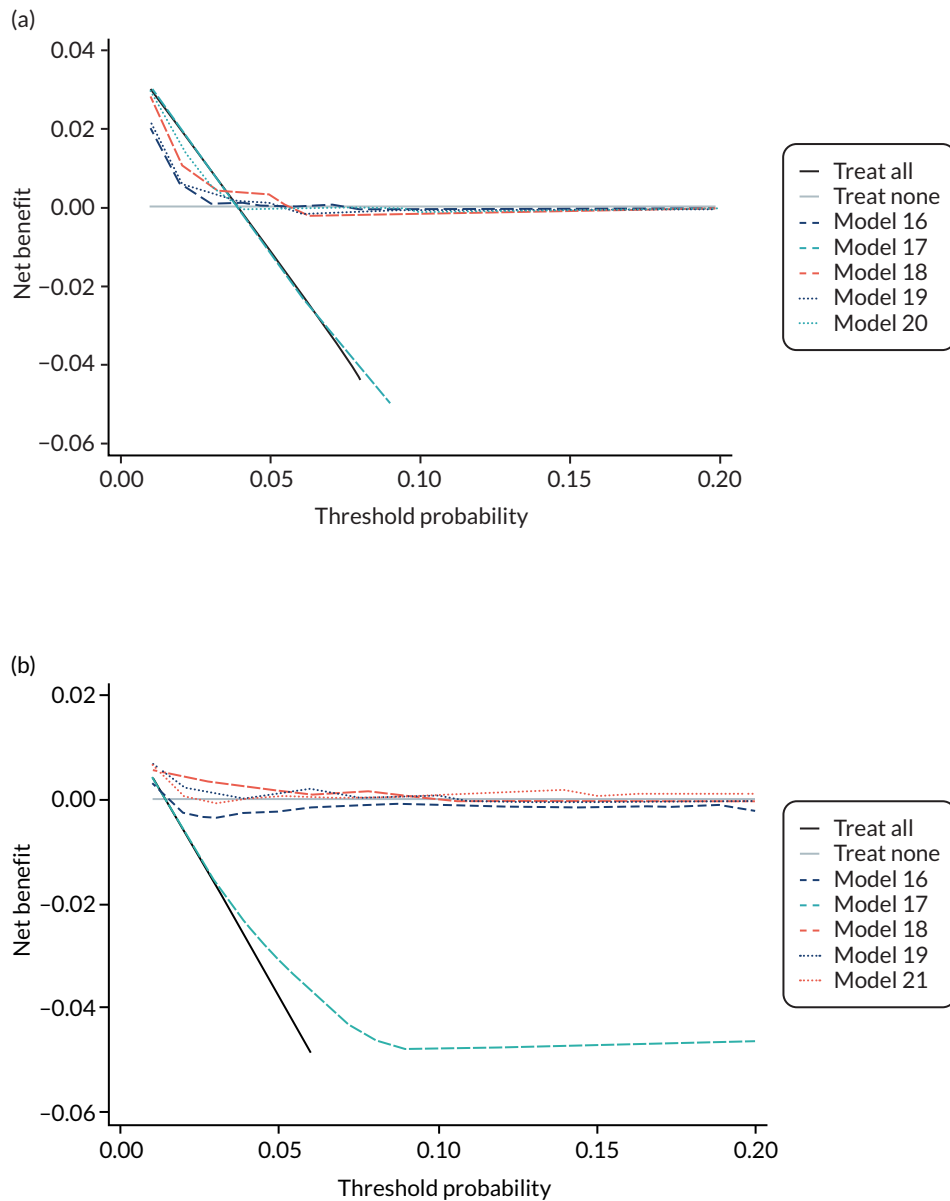


FIGURE 11 Decision curves for prediction models of late-onset pre-eclampsia in (a) SCOPE UK,⁴² (b) Allen *et al.*,¹⁰⁸ (c) Poston *et al.* 2015¹⁴⁹ and (d) POP¹⁶¹ data sets. Net benefit values on the y-axis are often best multiplied by 1000 to reveal the extra number of women who would be correctly treated per 1000 women who used the model, with none treated incorrectly. Reproduced from Snell *et al.*⁵² Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data. (*continued*)

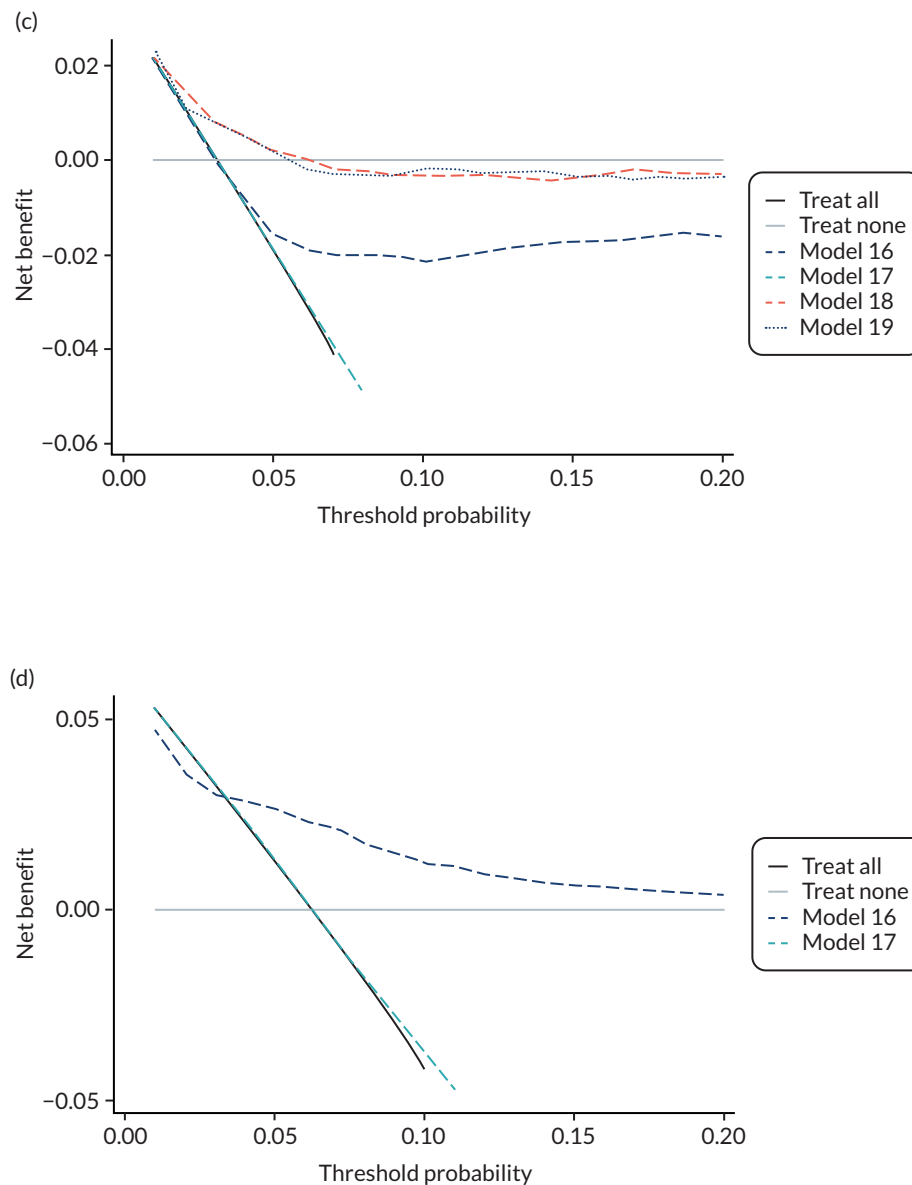


FIGURE 11 Decision curves for prediction models of late-onset pre-eclampsia in (a) SCOPE UK,⁴² (b) Allen *et al.*,¹⁰⁸ (c) Poston *et al.* 2015¹⁴⁹ and (d) POP¹⁶¹ data sets. Net benefit values on the y-axis are often best multiplied by 1000 to reveal the extra number of women who would be correctly treated per 1000 women who used the model, with none treated incorrectly. Reproduced from Snell *et al.*⁵² Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Summary

In summary, although some existing models showed a reasonable ability to discriminate between women who had a pre-eclampsia outcome and those who did not, calibration performance was, overall, poor across the data sets, with large heterogeneity in the calibration performance across different IPPIC data sets. Many of the models demonstrated likely overfitting at model development, with predictions that were too extreme compared with the observed risk in the data sets (calibration slope < 1). A model prediction could also be systematically too low or too high depending on the data set used to validate it (calibration-in-the-large $\neq 0$). The models were validated in a rather heterogeneous group of data sets that had different eligibility criteria. These findings suggest that the differences between women in the data sets are not adequately captured by the set of predictors included in the models. There was also little difference in predictive performance when biochemical markers or ultrasound markers were combined with maternal and clinical characteristics, compared with models with only maternal and clinical characteristics. An important limitation to this work is that it was possible to externally validate only 24 out of the 70 existing models that reported model equations.

None of the existing models validated performed well enough to warrant recalibration. Owing to the large heterogeneity in predictive performance of these existing models across data sets, simple recalibration strategies were unlikely to improve the overall performance or reduce heterogeneity in performance. Therefore, in *Chapter 6* we go on to develop and internally validate new prediction models for pre-eclampsia outcomes using the combined IPPIC data to ascertain whether or not this can address the shortcomings of existing models.

Chapter 6 Development and validation of pre-eclampsia prediction models

In this chapter, we describe the results of developing new prediction models using the IPPIC data sets. The methods for this chapter are detailed in *Chapter 3, Development and validation of pre-eclampsia prediction models*. We aimed to develop 18 models, one for each combination of the three outcomes (any-onset, early-onset and late-onset pre-eclampsia), two trimesters (predictors measured at trimester 1 or at trimester 2) and three predictor sets (clinical characteristics only, clinical characteristics plus biochemical markers, and clinical characteristics plus ultrasound markers).

Summary of international data sets and predictor availability

A total of 78 data sets were included in the IPPIC project. As explained in *Chapter 3*, the available data sets did not record all of the variables of interest, or the same combination of variables as other data sets. The timing of measurements also differed (i.e. trimester 1, trimester 2 or both). Potential predictors deemed 'important' based on the clinical consensus (see *Table 3*) were ranked according to the mean of their scores (ranging from 1, not important, to 5, very important; *Table 7*).

TABLE 7 Ranked clinical characteristics as potential predictors and mean of scores from the clinical consensus group

Rank	Variable	Mean of scores	Data sets with variable, n (%)	Pre-eclampsia, n (% of all)
Maternal clinical characteristics				
1	Previous any PE	4.91	55 (69)	33,583 (33)
2	Chronic or pre-existing hypertension	4.67	70 (86)	90,084 (89)
3	SBP (first or second trimester)	4.48	41 (51)	12,879 (13)
4	BMI (first or second trimester)	4.45	52 (65)	34,453 (34)
5	DBP (first or second trimester)	4.45	41 (51)	12,879 (13)
6	Parity	4.30	52 (65)	41,020 (41)
13	MAP (first or second trimester)	4.27	44 (55)	13,018 (13)
7	History of renal disease	4.24	50 (63)	84,595 (84)
8	Multiple pregnancy	4.12	60 (75)	87,961 (87)
9	History of pre-existing diabetes	4.12	63 (79)	93,588 (93)
10	Age	3.94	73 (91)	97,724 (97)
14	PCR (first or second trimester)	3.91	1 (1)	278 (< 1)
12	Family history of PE in first-degree relative	3.85	14 (18)	995 (1)
11	Previous autoimmune disease	3.82	43 (54)	37,664 (37)
17	Previous SGA	3.79	18 (23)	4064 (4)
15	Urine dipstick (first or second trimester)	3.73	12 (15)	2209 (2)
16	Ethnicity	3.61	57 (71)	72,248 (72)
18	Smoking	3.06	57 (71)	94,252 (94)
19	Mode of conception	2.97	23 (29)	31,096 (31)
20	Substance misuse in current pregnancy	2.48	17 (21)	13,844 (14)

continued

TABLE 7 Ranked clinical characteristics as potential predictors and mean of scores from the clinical consensus group (continued)

Rank	Variable	Mean of scores	Data sets with variable, n (%)	Pre-eclampsia, n (% of all)
Biochemical markers				
1	PIGF (first or second trimester)	4.21	19 (24)	3453 (3)
2	sFlt1 (first or second trimester)	3.94	12 (15)	3175 (3)
3	PAPP-A (first or second trimester)	3.15	9 (11)	871 (< 1)
Ultrasound markers				
1	Uterine artery PI (first or second trimester)	4.03	20 (25)	2999 (3)
2	Estimated fetal weight centile (first or second trimester)	3.33	4 (5)	591 (< 1)
3	Umbilical artery PI (first or second trimester)	3.24	8 (10)	887 (< 1)
PCR, protein-creatinine ratio; PE, pre-eclampsia; PI, pulsatility index; SGA, small for gestational age. Light blue variables were those excluded from model development.				

None of the individual IPPIC data sets had all of the clinical characteristics of interest, and therefore some variables had to be excluded to form the model development sets. We first excluded variables that were not recorded in many data sets or for which few data were available across the data sets with that variable (removed if the proportion of events in data sets with the variable accounted for < 5% of events across all data sets). Protein-creatinine ratio (PCR), urine dipstick, family history of pre-eclampsia and previous small for gestational age fetus were all excluded. We also excluded multiple pregnancy as we aimed to develop models applicable to women with singleton pregnancies. Variables were then removed according to their ranking (lowest-ranking first) until we had a reasonable number of data sets for model development. Substance misuse, mode of conception, smoking and ethnicity were removed. Twelve data sets had all of the remaining clinical variables of interest, and these are summarised in *Table 8*.

Biochemical and ultrasound markers were recorded in very few data sets (see *Table 7*). To develop models including either biochemical or ultrasound markers in addition to clinical characteristics, only subsets of the 12 data sets could be used. Four data sets included biochemical markers and six data sets included ultrasound markers. Estimated fetal weight centile was excluded as a potential predictor as none of the data sets recorded this variable.

Missingness and multiple imputation

Data sets were included if they recorded either first-trimester or second-trimester measurements for the potential predictors of interest; therefore, many variables were systematically missing (not recorded or recorded for < 10% of individuals) in a data set and some were partially missing (missing for some individuals) in a data set. *Table 9* summarises the missingness for variables and outcomes in the development data sets.

When checking convergence following imputation of systematically missing predictors (as described in *Chapter 3, Development and validation of pre-eclampsia prediction models*), values for first-trimester BMI were deemed poorly imputed for POUCH¹³¹ (i.e. convergence was not achieved despite the large burn-in, and extreme values were imputed), so the data set was excluded when developing models using first-trimester clinical characteristics. Three studies^{108,115,173} were excluded from model development using second-trimester clinical characteristics, owing to poor imputation of blood pressures and BMI.

TABLE 8 Patient characteristics in the 12 IPPIC data sets used for model development, using all available data for each variable (excluding missing observations)

Maternal characteristics and outcomes	SCOPE ⁴² (N = 5628)	Allen ¹⁰⁸ (N = 1045)	Poston 2015 ¹⁴⁹ (N = 1554)	Baschat ¹¹⁵ (N = 1704)	Antsaklis ¹¹⁰ (N = 3328)	WHO ¹⁷⁵ (N = 7273)	NICH LR ¹⁵⁹ (N = 3097)	POUCH ¹³¹ (N = 3019)	van Kuijk 2014 ¹⁶⁶ (N = 230)	STORK G ¹³⁵ (N = 812)	Vinter ¹⁷³ (N = 304)	POP ¹⁶¹ (N = 4212)
Maternal age (years), mean (SD), range	28.6 (5.5), 14–45	29.9 (5.1), 15–48	30.5 (5.5), 16–45	30.2 (6.5), 18–50	30.9 (4.8), 14–47	22.5 (5.8), 11–51	20.6 (4.4), 15–39	26.4 (5.8), 15–47	30.8 (4.8), 19–40	29.8 (4.8), 19–45	29.2 (4.2), 19–43	29.9 (5.1), 16–48
BMI (kg/m ²), median [IQR], range	24.2 ^a [21.9–27.5], 15.4 to 58.5	23.6 [21.1–26.8], 14.8 to 51.1	35.1 ^a [32.8–38.5], 30.0 to 66.0	26.7 [23.1–32.2], 15.9 to 72.9	22.7 [20.6–25.7], 14.5 to 50.1	22.2 [20.1–24.9], 13.1 to 50.5	22.7 ^a [20.4–25.7], 13.4 to 51.2	27.7 ^a [24.3–32.9], 15.1 to 66.3	24.1 [21.7–28.4], 18.0 to 38.3	24.2 [21.4–27.0], 16.6 to 43.0	33.6 [31.7–36.7], 28.8 to 46.0	24.1 [21.8–27.3], 14.7 to 54.7
Nulliparous, n (%)	5628 (100)	584 (56)	674 (43)	736 (43)	3328 (100)	6710 (92)	3097 (100)	1293 (43)	0 (0)	377 (46)	160 (53)	4212 (100)
Previous pre-eclampsia, n (%)	0 (0)	17 (2)	69 (4)	95 (6)	0 (0)	460 (6)	0 (0)	106 (4)	209 (92)	0 (0)	1 (< 1)	0 (0)
History of hypertension	24 (< 1)	10 (< 1)	0 (0)	162 (10)	2372 (71)	234 (3)	0 (0)	92 (3)	79 (34)	13 (2)	0 (0)	220 (5)
History of renal disease	0 (0)	3 (< 1)	0 (0)	4 (< 1)	0 (0)	0 (0)	0 (0)	94 (9)	0 (0)	5 (< 1)	0 (0)	41 (< 1)
History of diabetes	0 (0)	11 (1)	0 (0)	81 (5)	28 (< 1)	59 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	16 (< 1)
Outcome, n (%)												
Any-onset pre-eclampsia	278 (5)	14 (1)	54 (4)	106 (6)	32 (1)	141 (2)	156 (5)	44 (3)	43 (20)	46 (6)	19 (6)	273 (6)
Early-onset pre-eclampsia	44 (< 1)	1 (< 1)	5 (< 1)	21 (1)	13 (< 1)	18 (< 1)	12 (< 1)	12 (< 1)	15 (7)	1 (< 1)	2 (< 1)	10 (< 1)
Late-onset pre-eclampsia	234 (4)	13 (1)	49 (3)	85 (5)	19 (< 1)	123 (2)	144 (5)	32 (2)	28 (13)	45 (6)	17 (6)	263 (6)
a Trimester 2 BMI rather than trimester 1.												

TABLE 9 Number and proportion of observations missing values for each variable in each data set included in model development

Variable	Missing or not recorded, n (%)											
	Scope ⁴² (N = 5628)	Allen <i>et al.</i> ¹⁰⁸ (N = 1045)	Poston <i>et al.</i> 2015 ¹⁴⁹ (N = 1554)	Baschat <i>et al.</i> ¹¹⁵ (N = 1704)	Antsaklis <i>et al.</i> ¹¹⁰ (N = 3328)	WHO ¹⁷⁵ (N = 7273)	NICH LR ¹⁵⁹ (N = 3097)	POUCH ¹³¹ (N = 3019)	van Kuijk <i>et al.</i> 2014 ¹⁶⁶ (N = 230)	STORK G ¹³⁵ (N = 812)	Vinter <i>et al.</i> ¹⁷³ (N = 304)	POP ¹⁶¹ (N = 4212)
Maternal clinical characteristics												
Previous PE	0 (0)	0 (0)	8 (1)	0 (0)	0 (0)	1 (0)	0 (0)	1 (0)	2 (1)	0 (0)	0 (0)	0 (0)
History of hypertension	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Trimester 1 SBP	5490 (98)	5 (0)	1536 (99)	0 (0)	2906 (87)	2581 (35)	3020 (98)	2454 (81)	127 (55)	421 (52)	0 (0)	279 (7)
Trimester 2 SBP	7 (0)	1040 (100)	9 (1)	1704 (100)	3321 (100)	1022 (14)	87 (3)	1653 (55)	183 (80)	254 (31)	304 (100)	4076 (97)
Trimester 1 BMI	5490 (98)	5 (0)	1536 (99)	0 (0)	480 (14)	2585 (36)	3024 (98)	3019 (100)	127 (55)	414 (51)	0 (0)	152 (4)
Trimester 2 BMI	7 (0)	1040 (100)	0 (0)	1704 (100)	2966 (89)	1078 (15)	177 (6)	1 (0)	183 (80)	245 (30)	304 (100)	57 (1)
Trimester 1 DBP	5490 (98)	5 (0)	1536 (99)	0 (0)	2913 (88)	2581 (35)	3020 (98)	2454 (81)	127 (55)	421 (52)	0 (0)	279 (7)
Trimester 2 DBP	7 (0)	1040 (100)	9 (1)	1704 (100)	3321 (100)	1023 (14)	87 (3)	1653 (55)	183 (80)	254 (31)	304 (100)	4076 (97)
Nulliparous	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Trimester 1 MAP	5490 (98)	5 (0)	1536 (99)	0 (0)	2913 (88)	2581 (35)	3020 (98)	2454 (81)	127 (55)	421 (52)	0 (0)	280 (7)
Trimester 2 MAP	7 (0)	1040 (100)	9 (1)	1704 (100)	3321 (100)	1023 (14)	87 (3)	1653 (55)	183 (80)	254 (31)	304 (100)	4076 (97)
History of renal disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1921 (64)	0 (0)	0 (0)	0 (0)	0 (0)
Multiple pregnancy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	231 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
History of diabetes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Age	0 (0)	1 (0)	0 (0)	0 (0)	11 (0)	1 (0)	99 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Trimester 1 PCR	5612 (100)	1045 (100)	1554 (100)	1704 (100)	3328 (100)	7273 (100)	3097 (100)	3019 (100)	230 (100)	812 (100)	304 (100)	4212 (100)
Trimester 2 PCR	4464 (79)	1045 (100)	1549 (100)	1704 (100)	3328 (100)	7273 (100)	3097 (100)	3019 (100)	230 (100)	812 (100)	304 (100)	4212 (100)
Family history of PE	0 (0)	6 (1)	61 (4)	1704 (100)	3328 (100)	7273 (100)	3097 (100)	3019 (100)	230 (100)	812 (100)	304 (100)	4212 (100)
History of autoimmune disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	0 (0)	2458 (81)	0 (0)	0 (0)	0 (0)	0 (0)
Previous SGA	5628 (100)	0 (0)	1554 (100)	1704 (100)	3328 (100)	7273 (100)	3097 (100)	3019 (100)	0 (0)	0 (0)	304 (100)	4212 (100)
Trimester 1 urine dipstick	5490 (98)	1045 (100)	1554 (100)	1704 (100)	3328 (100)	2584 (36)	3020 (98)	3019 (100)	230 (100)	812 (100)	304 (100)	4212 (100)
Trimester 2 urine dipstick	7 (0)	1045 (100)	404 (26)	1704 (100)	3328 (100)	1079 (15)	87 (3)	0 (0)	230 (100)	812 (100)	304 (100)	4212 (100)
Ethnicity	0 (0)	2 (0)	0 (0)	0 (0)	7 (0)	6 (0)	0 (0)	0 (0)	230 (100)	0 (0)	0 (0)	0 (0)

Variable	Missing or not recorded, n (%)											
	Scope ⁴² (N = 5628)	Allen <i>et al.</i> ¹⁰⁸ (N = 1045)	Poston <i>et al.</i> ¹⁴⁹ (N = 1554)	Baschat <i>et al.</i> ¹¹⁵ (N = 1704)	Antsaklis <i>et al.</i> ¹¹⁰ (N = 3328)	WHO ¹⁷⁵ (N = 7273)	NICH LR ¹⁵⁹ (N = 3097)	POUCH ¹³¹ (N = 3019)	van Kuijk <i>et al.</i> 2014 ¹⁶⁶ (N = 230)	STORK G ¹³⁵ (N = 812)	Vinter <i>et al.</i> ¹⁷³ (N = 304)	POP ¹⁶¹ (N = 4212)
Smoking	0 (0)	0 (0)	0 (0)	0 (0)	6 (0)	2 (0)	6 (0)	6 (0)	230 (100)	0 (0)	0 (0)	0 (0)
Spontaneous conception	0 (0)	0 (0)	4 (0)	0 (0)	3328 (100)	7273 (100)	3097 (100)	3019 (100)	20 (9)	0 (0)	304 (100)	0 (0)
Substance misuse	0 (0)	0 (0)	1554 (100)	0 (0)	3328 (100)	7273 (100)	3097 (100)	7 (0)	230 (100)	812 (100)	304 (100)	4212 (100)
Biochemical markers												
Trimester 1 PIGF	5628 (100)	5 (0)	1554 (100)	704 (41)	3328 (100)	4842 (67)	3097 (100)	3019 (100)	230 (100)	812 (100)	304 (100)	135 (3)
Trimester 2 PIGF	51 (1)	966 (92)	445 (29)	1704 (100)	3328 (100)	4026 (55)	3097 (100)	1715 (57)	230 (100)	812 (100)	304 (100)	191 (5)
Trimester 1 sFlt-1	5628 (100)	1045 (100)	1554 (100)	1704 (100)	3328 (100)	4989 (69)	3097 (100)	3019 (100)	230 (100)	812 (100)	304 (100)	134 (3)
Trimester 2 sFlt-1	48 (1)	1045 (100)	1554 (100)	1704 (100)	3328 (100)	4125 (57)	3097 (100)	1712 (57)	230 (100)	812 (100)	304 (100)	191 (5)
Trimester 1 PAPP-A	5628 (100)	119 (11)	1554 (100)	704 (41)	3328 (100)	7273 (100)	3097 (100)	3019 (100)	230 (100)	812 (100)	304 (100)	134 (3)
Trimester 2 PAPP-A	48 (1)	1040 (100)	1554 (100)	1704 (100)	3328 (100)	7273 (100)	3097 (100)	3019 (100)	230 (100)	812 (100)	304 (100)	4212 (100)
Ultrasound markers												
Trimester 1 uterine artery PI	5628 (100)	5 (0)	1554 (100)	266 (16)	2895 (87)	7273 (100)	3097 (100)	3019 (100)	230 (100)	812 (100)	304 (100)	4212 (100)
Trimester 2 uterine artery PI	5628 (100)	1040 (100)	1554 (100)	1704 (100)	3204 (96)	7273 (100)	3097 (100)	3019 (100)	230 (100)	812 (100)	304 (100)	133 (3)
Trimester 1 estimated fetal weight	5628 (100)	1045 (100)	1554 (100)	1704 (100)	3328 (100)	7273 (100)	3097 (100)	3019 (100)	230 (100)	812 (100)	304 (100)	4212 (100)
Trimester 2 estimated fetal weight	5628 (100)	1045 (100)	1554 (100)	1704 (100)	3328 (100)	7273 (100)	3097 (100)	3019 (100)	230 (100)	144 (18)	304 (100)	43 (1)
Trimester 1 umbilical artery PI	5628 (100)	1045 (100)	1554 (100)	1704 (100)	3328 (100)	7273 (100)	3097 (100)	3019 (100)	230 (100)	812 (100)	304 (100)	4212 (100)
Trimester 2 umbilical artery PI	3102 (55)	1045 (100)	1554 (100)	1704 (100)	3328 (100)	7273 (100)	3097 (100)	3019 (100)	230 (100)	187 (23)	304 (100)	70 (2)
Outcomes												
Any-onset PE	5 (0)	0 (0)	47 (3)	0 (0)	985 (30)	0 (0)	150 (5)	1648 (55)	13 (6)	0 (0)	0 (0)	5 (0)
Early-onset PE	5 (0)	0 (0)	47 (3)	0 (0)	1007 (30)	0 (0)	150 (5)	1648 (55)	13 (6)	0 (0)	0 (0)	5 (0)
Late-onset PE	5 (0)	0 (0)	47 (3)	0 (0)	1007 (30)	0 (0)	150 (5)	1648 (55)	13 (6)	0 (0)	0 (0)	5 (0)
PE, pre-eclampsia; PI, pulsatility index. Light blue variables were excluded from model development; subsets of the data were used for model development including biochemical or ultrasound markers and therefore data sets that were excluded from development for these models have light blue values.												

For model development including biochemical markers, all four data sets were included for the first-trimester models, and POUCH¹³¹ was excluded for the second-trimester models. For model development including ultrasound markers, two data sets^{135,161} were excluded for first-trimester models, and three data sets^{108,135,149} were excluded for second-trimester models. The relevant imputation checking plots are provided in *Appendix 15* along with an explanation of why these studies were excluded. A summary of the overall sample size and number of events contributing to model development for each combination of trimester of measurement (first or second) and predictor set (clinical characteristics, clinical characteristics plus biochemical markers, clinical characteristics plus ultrasound markers) is given in *Table 10*.

Models including clinical characteristics only

The model development process was performed for data sets imputed with each form of BMI, namely BMI, $\ln(\text{BMI})$ and BMI^{-2} . The resulting models and performance statistics for all clinical characteristic models predicting any-onset, early-onset and late-onset pre-eclampsia are presented in *Appendix 16*. As an example of how the functional form was decided for BMI, let us consider the model including first-trimester clinical characteristics for any-onset pre-eclampsia. The model that included BMI rather than $\ln(\text{BMI})$ or BMI^{-2} had an overall calibration slope closest to 1 (with least heterogeneity across data sets), calibration-in-the-large closest to 0 (with least heterogeneity across data sets), and the C-statistic with least heterogeneity across data sets (C-statistic estimates were very similar across the three models). Therefore, the model with BMI was selected. This process was repeated for models developed using clinical characteristics for all three pre-eclampsia outcomes using first-trimester measurements for potential predictors, and then separately for models using second-trimester measurements.

A summary of the predictors retained for each model after variable selection is given in *Table 11*. For all but one model, BMI was best modelled linearly if it was retained. However, for early-onset pre-eclampsia (for which there are fewer events), first-trimester BMI was modelled non-linearly using $(\text{BMI}/10)^{-2}$. The relationship between BMI and risk (log-odds) of early pre-eclampsia is shown in *Figure 12*. Autoimmune disease was only retained in the model including second-trimester predictors for early-onset pre-eclampsia. Nulliparity was dropped from the models for early-onset pre-eclampsia and diabetes was dropped from the first-trimester model for late-onset pre-eclampsia and all of the second-trimester models. DBP was not retained in the first-trimester models for any-onset or late-onset pre-eclampsia but was retained in the model for early-onset pre-eclampsia and all second-trimester models.

TABLE 10 Summary of sample size and number of events used for model development

Model development including	Number of studies	Total sample size	Any-onset pre-eclampsia	Early-onset pre-eclampsia	Late-onset pre-eclampsia
First-trimester clinical characteristics	11	29,187	1187	149	1039
Second-trimester clinical characteristics	9	29,153	1144	152	993
First-trimester clinical characteristics and biochemical markers	4	20,132	795	103	692
Second-trimester clinical characteristics and biochemical markers	3	17,117	692	72	620
First-trimester clinical characteristics and ultrasound markers	4	11,705	443	84	359
Second-trimester clinical characteristics and ultrasound markers	3	13,168	596	72	524

TABLE 11 Summary of clinical characteristics retained in the models for any-, early- and late-onset pre-eclampsia

Variable	Prediction from first-trimester predictors			Prediction from second-trimester predictors		
	Any-onset PE	Early-onset PE	Late-onset PE	Any-onset PE	Early-onset PE	Late-onset PE
Age	✓	✓	✓	✓		✓
SBP	✓	✓	✓	✓		✓
DBP		✓		✓	✓	✓
BMI	✓ linear	✓ (⁻²)	✓ linear	✓ linear		✓ linear
Nulliparity	✓		✓	✓		✓
Previous PE	✓	✓	✓	✓	✓	✓
Renal disease	✓	✓	✓	✓	✓	✓
Hypertension	✓	✓	✓	✓		✓
Diabetes	✓	✓			Omitted ^a	
Autoimmune disease					✓	

PE, pre-eclampsia.

a Diabetes was omitted from the second-trimester model for early-onset pre-eclampsia because of perfect prediction problems.

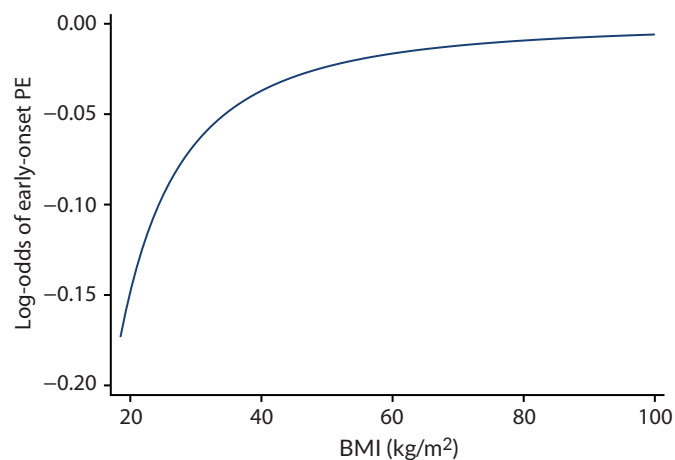


FIGURE 12 Relationship between first-trimester BMI and risk of early-onset pre-eclampsia when using $(\text{BMI}/10)^{-2}$ transformation.

The parameter estimates for models with first-trimester predictors and second-trimester predictors are given in *Tables 12* and *13*, respectively. These are the developed models before adjustment for optimism due to overfitting. Increasing values of BMI, previous pre-eclampsia, history of hypertension, renal disease and diabetes were all associated with an increased risk of the pre-eclampsia outcomes. Increasing age was associated with a decrease in risk of pre-eclampsia. When retained in the models, increasing values of SBP and DBP were associated with an increase in risk for any-onset and late-onset pre-eclampsia, although second-trimester SBP was negatively associated with risk for early-onset pre-eclampsia.

TABLE 12 Parameter estimates for initial prediction models developed using first-trimester clinical characteristics to predict any-, early- or late-onset pre-eclampsia

Variable	Any-onset PE			Early-onset PE			Late-onset PE		
	OR (95% CI)	Beta	p-value	OR (95% CI)	Beta	p-value	OR (95% CI)	Beta	p-value
Age	0.984 (0.972 to 0.995)	-0.016	0.006	0.965 (0.934 to 0.996)	-0.036		0.985 (0.973 to 0.997)	-0.015	0.018
SBP	1.017 (1.010 to 1.025)	0.017	< 0.001	0.983 (0.959 to 1.006)	-0.018	0.089	1.016 (1.008 to 1.025)	0.016	< 0.001
DBP				1.078 (1.032 to 1.126)	0.075				
^a BMI or (BMI/10) ⁻²	1.041 (1.027 to 1.056)	0.040	< 0.001	0.553 (0.270 to 1.133)	-0.593	0.080	1.039 (1.024 to 1.055)	0.039	< 0.001
Nulliparous	2.759 (2.073 to 3.673)	1.015	< 0.001				3.089 (2.268 to 4.206)	1.128	< 0.001
Previous PE	3.952 (2.692 to 5.802)	1.374	< 0.001	5.710 (3.087 to 10.565)	1.742	< 0.001	3.368 (2.204 to 5.145)	1.214	< 0.001
Renal disease	5.163 (2.665 to 10.002)	1.641	< 0.001	9.749 (2.534 to 37.512)	2.277	< 0.001	3.891 (1.919 to 7.892)	1.359	< 0.001
Hypertension	5.555 (4.384 to 7.039)	1.715	< 0.001	1.730 (1.005 to 2.976)	0.548	0.028	6.265 (4.895 to 8.018)	1.835	< 0.001
Diabetes	1.479 (0.883 to 2.477)	0.391	0.137	5.567 (2.449 to 12.653)	1.717	0.003			
Intercept (average)		-6.868			-7.924			-7.052	

PE, pre-eclampsia.

^a BMI modelled non-linearly using (BMI/10)⁻² for early-onset pre-eclampsia.

Note

Results shown are before adjustment for optimism due to overfitting.

TABLE 13 Parameter estimates for initial prediction models developed using second-trimester clinical characteristics to predict any-, early- or late-onset pre-eclampsia

Variable	Any-onset PE			Early-onset PE			Late-onset PE		
	OR (95% CI)	Beta	p-value	OR (95% CI)	Beta	p-value	OR (95% CI)	Beta	p-value
Age	0.983 (0.97 to 0.996)	-0.017	0.013				0.985 (0.972 to 0.999)	-0.015	0.034
SBP	1.011 (1.003 to 1.020)	0.011	0.010				1.011 (1.002 to 1.020)	0.011	0.012
DBP	1.021 (1.007 to 1.034)	0.020	0.003	1.060 (1.018 to 1.104)	0.059	0.006	1.013 (1.001 to 1.026)	0.013	0.035
BMI	1.065 (1.052 to 1.079)	0.063	< 0.001				1.072 (1.059 to 1.086)	0.070	< 0.001
Nulliparous	2.697 (1.905 to 3.820)	0.992	< 0.001				3.592 (2.469 to 5.225)	1.279	< 0.001
Previous PE	4.271 (2.794 to 6.528)	1.452	< 0.001	8.497 (4.579 to 15.767)	2.140	< 0.001	3.500 (2.144 to 5.713)	1.253	< 0.001
Renal disease	2.721 (1.323 to 5.596)	1.001	0.007	3.861 (1.074 to 13.878)	1.351	0.039	2.257 (1.101 to 4.625)	0.814	0.027
Hypertension	6.253 (4.859 to 8.047)	1.833	< 0.001				7.74 (6.020 to 9.953)	2.046	< 0.001
Autoimmune disease				2.817 (0.766 to 10.359)	1.036	0.118			
Intercept (average)		-8.260			-9.641			-8.475	

PE, pre-eclampsia.
Note
Results shown are before adjustment for optimism due to overfitting.

Following internal validation, the predictive performance of the models is summarised in *Table 14*. The average (pooled) C-statistic for the models was close to 0.7, with considerable heterogeneity in the C-statistic across individual data sets. C-statistics were slightly higher for second-trimester models than for first-trimester models. The calibration slope was generally around 0.9 for models of any-onset and late-onset pre-eclampsia but was greater than 1 for early-onset pre-eclampsia (1.001 and 1.105). Again, there was large heterogeneity in the calibration slope across data sets for most models. Average calibration-in-the-large was close to zero but, again, there was large heterogeneity across data sets, suggesting that the baseline risk differs across the individual data sets and is not being fully captured by the predictors included in the models.

To illustrate the heterogeneity in predictive performance across individual data sets, *Appendix 17* provides the forest plots of predictive performance measures for the second-trimester any-onset pre-eclampsia model. It is evident that there is large variability around the average values; for example, the observed calibration slope varies from 0.45 to 1.57 across data sets, and CIs often do not overlap.

Models including clinical characteristics and biochemical markers

Next, we examined whether or not biochemical markers should be included in the prediction models, in addition to the clinical characteristics identified for each outcome in the previous section (see *Models including clinical characteristics only*). Therefore, the clinical characteristics were forced into the models and only the biochemical markers were eligible for removal in the backwards elimination process. First-trimester BMI was previously modelled as $(\text{BMI}/10)^{-2}$ for early pre-eclampsia; however, this transformation was not selected for any of the other clinical characteristic models and therefore may be a result of overfitting in data for which we have the fewest events. Therefore, for comparability and consistency across models, we used BMI rather than $(\text{BMI}/10)^{-2}$ for early pre-eclampsia in the clinical plus biochemical marker models.

In the same way as for BMI in the clinical characteristics models, we considered non-normality for the biochemical markers by developing prediction models with biochemical markers on their original scale and compared this with models developed using natural logarithm-transformed biochemical marker values. Comparisons of biochemical marker and $\ln(\text{biochemical marker})$ models are given in *Appendix 18*. For the first-trimester model for early pre-eclampsia, the model with better predictive performance came from the data with log-transformed biochemical markers; however, all biochemical markers were dropped from the model. Therefore, in this case, we selected the model that retained a biochemical marker in the model (see *Table 16*).

Table 15 shows which biochemical markers were included in each model and if they were log-transformed. PAPP-A was not retained in any of the models, whereas sFlt-1 was retained in all first-trimester prediction models and the second-trimester model for early pre-eclampsia. PlGF was retained in all models except the first-trimester model for early pre-eclampsia. Models included the original biochemical marker values apart from the second-trimester model for early pre-eclampsia, which used $\ln(\text{biochemical marker})$ values. For all but the second-trimester model for early pre-eclampsia, biochemical markers were negatively associated with the pre-eclampsia outcomes, so risk decreased with increasing biochemical marker values (*Tables 16 and 17*).

Table 18 shows the average predictive performance for the models, obtained through internal validation using meta-analysis of the data set-specific performance statistics. Models with the clinical characteristics identified in *Models including clinical characteristics only* were also refitted in the same data so that it was possible to compare the predictive performance of models with and models without the biochemical markers in the same data sets. For all models, the average predictive performance improved with the addition of biochemical markers, and, for most models and performance statistics, heterogeneity across data sets was reduced (lower I^2 and τ^2 values). The average calibration slope was generally < 1 (between 0.857 and 0.961), except for the early-onset pre-eclampsia models, which had calibration slopes of 1.038 and 1.079 for the first- and second-trimester models, respectively.

TABLE 14 Average (pooled) predictive performance statistics for each clinical characteristics model, and estimates of heterogeneity (between-study variance, τ^2 ; proportion of total variability due to between-study variance, I^2) in performance, as obtained from a meta-analysis of data set-specific performance statistics

Number of			C-statistic			Calibration slope			Calibration-in-the-large		
Data sets	Participants	Events	Estimate (95% CI)	τ^2 (for logit C-statistic)	I^2 (for logit C-statistic)	Estimate (95% CI)	τ^2	I^2	Estimate (95% CI)	τ^2	I^2
Any-onset pre-eclampsia											
<i>First-trimester models</i>											
11	29,187	1187	0.677 (0.612 to 0.736)	0.139	83.9	0.915 (0.603 to 1.226)	0.155	86.4	0.012 (-0.630 to 0.654)	0.881	98.7
<i>Second-trimester models</i>											
9	29,153	1144	0.703 (0.648 to 0.753)	0.076	79.3	0.969 (0.664 to 1.273)	0.129	88.3	0.011 (-0.772 to 0.795)	1.003	99.0
Early-onset pre-eclampsia											
<i>First-trimester models</i>											
11	29,187	149	0.719 (0.590 to 0.820)	0.260	49.1	1.001 (0.795 to 1.206)	0.000	0.0	0.090 (-0.377 to 0.557)	0.318	77.9
<i>Second-trimester models</i>											
9	29,153	152	0.723 (0.601 to 0.819)	0.223	56.4	1.105 (0.868 to 1.341)	0.000	0.0	0.037 (-0.465 to 0.539)	0.287	76.4
Late-onset pre-eclampsia											
<i>First-trimester models</i>											
11	29,187	1039	0.677 (0.615 to 0.733)	0.116	79.7	0.919 (0.621 to 1.217)	0.131	82.0	0.016 (-0.705 to 0.736)	1.105	98.8
<i>Second-trimester models</i>											
9	29,153	993	0.705 (0.649 to 0.756)	0.076	78.4	0.930 (0.656 to 1.204)	0.096	84.2	0.014 (-0.897 to 0.925)	1.358	99.1

TABLE 15 Summary of biochemical markers retained in the models (alongside clinical characteristics) for any-, early- and late-onset pre-eclampsia using first- or second-trimester measurements

Variable	Prediction from first-trimester predictors			Prediction from second-trimester predictors		
	Any-onset PE	Early-onset PE	Late-onset PE	Any-onset PE	Early-onset PE	Late-onset PE
sFlt-1	✓	✓	✓		✓ (ln)	
PAPP-A						
PIGF	✓		✓	✓	✓ (ln)	✓
PE, pre-eclampsia.						

Models including clinical characteristics and ultrasound markers

When considered in addition to clinical characteristics, ultrasound markers were not retained in any of the models fitted, whether using the original values or using the logarithm-transformed values. Therefore, the models reverted to the clinical characteristic models, which were reported in more detail and using more data sets in *Models including clinical characteristics only*.

Shrinkage and final models

Following model development and internal validation, shrinkage was applied to the beta coefficients and the final model equations are given in *Table 19*, along with the average performance statistics from meta-analysis across data sets for these models, including 95% CIs for the average performance and 95% prediction intervals for the performance of the model in a new but similar data set. Performance of the models in the individual data sets can be found in *Appendix 19*.

After shrinkage and recalibration of the intercept, each model is, on average, perfectly calibrated across data sets. However, as was observed for existing models in *Chapter 5*, large heterogeneity remains in all of the performance statistics across data sets. The prediction intervals for potential performance in new settings are generally very wide. For example, the prediction interval for the calibration slope of model 4 ranges from 0.07 to 1.93. Therefore, although IPPIC models may predict well on average across populations, they may not be as accurate in particular populations. *Figure 13* presents the calibration plots for model 1 (first-trimester clinical characteristics for the prediction of any pre-eclampsia) by data set. The model is fairly well calibrated for Baschat *et al.*¹¹⁵ however, the predictions are too high for pregnant women in the WHO cohort,¹⁷⁵ but not high enough for those at high risk in the POP cohort.¹⁶¹ Calibration plots for the other models (excluding for early pre-eclampsia, which had too few events in individual data sets) are given in *Appendix 20*. Heterogeneity in calibration performance could be reduced if, when applying the models in practice, model parameters (e.g. intercept) could be recalibrated to each population and setting. This would require local data for recalibration and model updating.

Decision curve analysis

Figures 14–17 are the decision curves in each data set for models predicting any pre-eclampsia. The decision curves show the net benefit or harm across different probability thresholds of the model and compared with the ‘treat-all’ and ‘treat-none’ strategies. Net benefit values are often best multiplied by 1000 to reveal the extra number of women who would be correctly treated per 1000 women who used the model, with none treated incorrectly.

TABLE 16 Parameter estimates for initial prediction models using first-trimester clinical characteristics and biochemical markers to predict any-, early- or late-onset pre-eclampsia

Variable	Any-onset PE			Early-onset PE			Late-onset PE		
	OR (95% CI)	Beta	p-value	OR (95% CI)	Beta	p-value	OR (95% CI)	Beta	p-value
Age	0.977 (0.962 to 0.992)	-0.023	0.003	0.995 (0.954 to 1.039)	-0.005	0.831	0.976 (0.961 to 0.991)	-0.025	0.002
SBP	1.016 (1.004 to 1.028)	0.016	0.011	1.055 (1.026 to 1.085)	0.053	< 0.001	1.009 (0.998 to 1.020)	0.009	0.113
DBP				0.996 (0.960 to 1.033)	-0.004	0.836			
BMI	1.042 (1.009 to 1.077)	0.041	0.015	0.993 (0.933 to 1.057)	-0.007	0.831	1.052 (1.024 to 1.080)	0.051	< 0.001
Nulliparous	3.113 (1.816 to 5.337)	1.136	< 0.001				4.093 (2.258 to 7.418)	1.409	< 0.001
Previous PE	3.857 (2.252 to 6.607)	1.350	< 0.001	4.427 (2.002 to 9.789)	1.488	< 0.001	3.311 (1.745 to 6.283)	1.197	< 0.001
Renal disease	2.603 (1.376 to 4.925)	0.957	0.004	4.397 (1.494 to 12.942)	1.481	0.007	2.135 (1.088 to 4.190)	0.758	0.028
Hypertension	9.403 (7.113 to 12.430)	2.241	< 0.001	2.300 (1.034 to 5.117)	0.833	0.041	10.739 (8.039 to 14.346)	2.374	< 0.001
Diabetes	1.021 (0.401 to 2.605)	0.021	0.965						
sFlt-1	0.9998 (0.9996 to 0.9999)	-2.42 × 10 ⁻⁴	0.012	0.9995 (0.9989 to 1.0001)	-5.15 × 10 ⁻⁴	0.079	0.9998 (0.9996 to 1.0000)	-2 × 10 ⁻⁴	0.026
PIGF	0.995 (0.992 to 0.998)	-0.005	0.001				0.994 (0.991 to 0.997)	-0.006	0.001
Intercept (average)		-5.893			-10.206			-5.787	

PE, pre-eclampsia.

Note

The results shown are before adjustment for optimism due to overfitting.

TABLE 17 Parameter estimates for initial prediction models using second-trimester clinical characteristics and biochemical markers to predict any-, early- or late-onset pre-eclampsia

Variable	Any-onset PE			Early-onset PE			Late-onset PE		
	OR (95% CI)	Beta	p-value	OR (95% CI)	Beta	p-value	OR (95% CI)	Beta	p-value
Age	0.981 (0.966 to 0.996)	-0.019	0.012				0.980 (0.965 to 0.996)	-0.020	0.012
SBP	1.019 (1.009 to 1.030)	0.019	< 0.001				1.018 (1.008 to 1.029)	0.018	0.001
DBP	0.991 (0.979 to 1.004)	-0.009	0.167	1.068 (1.039 to 1.096)	0.065	< 0.001	0.986 (0.973 to 0.999)	-0.014	0.031
BMI	1.072 (1.057 to 1.088)	0.069	< 0.001				1.076 (1.060 to 1.093)	0.073	< 0.001
Nulliparous	8.156 (3.534 to 18.820)	2.099	< 0.001				12.673 (4.777 to 33.622)	2.539	< 0.001
Previous PE	6.237 (2.755 to 14.123)	1.831	< 0.001	10.594 (4.615 to 24.318)	2.360	< 0.001	5.664 (2.223 to 14.431)	1.734	< 0.001
Renal disease	4.150 (1.838 to 9.368)	1.423	0.001	23.285 (2.613 to 207.474)	3.148	0.005	3.680 (1.588 to 8.524)	1.303	0.002
Hypertension	11.034 (8.334 to 14.608)	2.401	< 0.001				11.380 (8.531 to 15.180)	2.432	< 0.001
Autoimmune disease				3.169 (0.397 to 25.315)	1.154	0.277			
sFlt-1 or $\ln(\text{sFlt-1} + 0.5)^a$				1.581 (1.100 to 2.271)	0.458	0.013			
PIGF or $\ln(\text{PIGF} + 0.5)^a$	0.997 (0.996 to 0.998)	-0.003	< 0.001	0.372 (0.277 to 0.500)	-0.988	< 0.001	0.997 (0.996 to 0.998)	-0.003	< 0.001
Intercept (average)		-7.895			-9.343			-8.054	

PE, pre-eclampsia.

a Biochemical markers modelled non-linearly using $\ln(\text{biochemical marker} + 0.5)$ for early-onset pre-eclampsia.**Note**

The results shown are before adjustment for optimism due to overfitting.

TABLE 18 Average (pooled) predictive performance statistics for clinical characteristics and clinical and biochemical marker models, and estimates of heterogeneity in performance (between-study variance, τ^2 ; proportion of total variability due to between-study variance, I^2), as derived from a meta-analysis of data set-specific performance estimates

Model	Number of			C-statistic			Calibration slope			Calibration-in-the-large		
	Data sets	Participants	Events	Estimate (95% CI)	τ^2 (for logit C-statistic)	I^2 (for logit C-statistic)	Estimate (95% CI)	τ^2	I^2	Estimate (95% CI)	τ^2	I^2
First-trimester predictors for any pre-eclampsia (C)	4	20,132	795	0.675 (0.488 to 0.819)	0.212	92.1	0.870 (0.258 to 1.481)	0.123	89.3	-0.009 (-0.924 to 0.907)	0.318	97.8
First-trimester predictors for any pre-eclampsia (C + B)				0.696 (0.516 to 0.832)	0.205	90.7	0.901 (0.355 to 1.447)	0.094	86.7	-0.004 (-0.939 to 0.931)	0.333	97.9
First-trimester predictors for early pre-eclampsia (C)	4	20,132	103	0.749 (0.582 to 0.865)	0.066	28.6	1.047 (0.694 to 1.401)	0	0	0.025 (-1.175 to 1.226)	0.507	90.2
First-trimester predictors for early pre-eclampsia (C + B)				0.762 (0.576 to 0.883)	0.107	37.0	1.038 (0.666 to 1.410)	0	0	0.036 (-1.269 to 1.342)	0.610	91.7
First-trimester predictors for late pre-eclampsia (C)	4	20,132	692	0.665 (0.476 to 0.814)	0.222	93.1	0.809 (0.213 to 1.404)	0.117	87.7	-0.010 (-0.901 to 0.881)	0.295	97.3
First-trimester predictors for late pre-eclampsia (C + B)				0.688 (0.505 to 0.827)	0.212	91.9	0.857 (0.338 to 1.376)	0.085	84.4	-0.005 (-0.932 to 0.922)	0.322	97.5
Second-trimester predictors for any pre-eclampsia (C)	3	17,117	692	0.715 (0.488 to 0.868)	0.141	93.9	0.917 (0.194 to 1.641)	0.079	93.0	0.002 (-1.573 to 1.577)	0.395	98.7
Second-trimester predictors for any pre-eclampsia (C + B)				0.754 (0.526 to 0.894)	0.151	92.4	0.961 (0.358 to 1.564)	0.052	88.7	0.004 (-1.284 to 1.293)	0.262	98.0
Second-trimester predictors for early pre-eclampsia (C)	3	17,117	72	0.709 (0.392 to 0.902)	0.111	40.1	1.045 (0.508 to 1.582)	0	0	0.007 (-2.158 to 2.173)	0.700	93.0
Second-trimester predictors for early pre-eclampsia (C + B)				0.830 (0.629 to 0.934)	0.041	17.4	1.079 (0.567 to 1.591)	0.011	26.0	0.099 (-0.972 to 1.169)	0.107	66.4
Second-trimester predictors for late pre-eclampsia (C)	3	17,117	620	0.706 (0.437 to 0.881)	0.194	95.0	0.884 (0.152 to 1.615)	0.079	91.8	0.002 (-1.509 to 1.513)	0.363	98.4
Second-trimester predictors for late pre-eclampsia (C + B)				0.746 (0.493 to 0.898)	0.181	93.2	0.936 (0.355 to 1.517)	0.047	86.5	0.004 (-1.295 to 1.303)	0.266	97.8

C, clinical characteristics; C + B, clinical characteristics and biochemical markers.
Clinical models were refitted to the same data used for development of the clinical and biochemical marker models to compare predictive performance.

TABLE 19 Final model equations for each outcome, predictor type and trimester of measurement after shrinkage to adjust for optimism (overfitting)

Model number	Predictors	Model equation	Number of			Average statistic (95% CI) [95% prediction interval]		
			Data sets	Participants	Events	C-statistic	Calibration slope	Calibration-in-the-large
Any-onset pre-eclampsia								
<i>First-trimester models</i>								
1	Clinical	Logit(p) = $-6.5297 - 0.0151 \times \text{age} + 0.0156 \times \text{SBP} + 0.0370 \times \text{BMI} + 0.9287 \times \text{nulliparous} + 1.2574 \times \text{previous PE} + 1.5019 \times \text{renal disease} + 1.5689 \times \text{hypertension} + 0.3578 \times \text{diabetes}$	11	29,187	1187	0.677 (0.612 to 0.736) [0.462 to 0.836]	1.000 (0.659 to 1.34) [-0.033 to 2.032]	0.012 (-0.613 to 0.637) [-2.149 to 2.172]
7	Clinical and biochemical markers	Logit(p) = $-5.6061 - 0.0208 \times \text{age} + 0.0142 \times \text{SBP} + 0.0373 \times \text{BMI} + 1.0232 \times \text{nulliparous} + 1.2163 \times \text{previous PE} + 0.8620 \times \text{renal disease} + 2.0191 \times \text{hypertension} + 0.0191 \times \text{diabetes} - 0.000218 \times \text{sFlt-1} - 0.00478 \times \text{PIGF}$	4	20,132	795	0.696 (0.516 to 0.832) [0.202 to 0.954]	1.000 (0.394 to 1.606) [-0.676 to 2.677]	-0.001 (-0.903 to 0.902) [-2.691 to 2.689]
<i>Second-trimester models</i>								
1. 4	Clinical	Logit(p) = $-8.0909 - 0.0165 \times \text{age} + 0.0108 \times \text{SBP} + 0.0198 \times \text{DBP} + 0.0614 \times \text{BMI} + 0.9616 \times \text{nulliparous} + 1.4068 \times \text{previous PE} + 0.9700 \times \text{renal disease} + 1.7763 \times \text{hypertension}$	9	29,153	1144	0.703 (0.648 to 0.753) [0.541 to 0.827]	0.999 (0.685 to 1.314) [0.065 to 1.934]	0.011 (-0.762 to 0.784) [-2.456 to 2.478]
10	Clinical and biochemical markers	Logit(p) = $-7.6942 - 0.0186 \times \text{age} + 0.0185 \times \text{SBP} - 0.0083 \times \text{DBP} + 0.0668 \times \text{BMI} + 2.0169 \times \text{nulliparous} + 1.7592 \times \text{previous PE} + 1.3675 \times \text{renal disease} + 2.3073 \times \text{hypertension} - 0.00262 \times \text{PIGF}$	3	17,117	692	0.754 (0.526 to 0.894) [0.009 to 0.999]	1.000 (0.373 to 1.628) [-2.537 to 4.537]	0.001 (-1.284 to 1.287) [-7.520 to 7.522]
Early-onset pre-eclampsia								
<i>First-trimester models</i>								
2	Clinical	Logit(p) = $-7.9161 - 0.0360 \times \text{age} - 0.0176 \times \text{SBP} + 0.0753 \times \text{DBP} - 0.5937 \times (\text{BMI}/10)^{-2} + 1.7440 \times \text{previous PE} + 2.2795 \times \text{renal disease} + 0.5486 \times \text{hypertension} + 1.7185 \times \text{diabetes}$	11	29,187	149	0.719 (0.590 to 0.820) [0.400 to 0.907]	1.000 (0.795 to 1.205) [0.792 to 1.208]	0.079 (-0.388 to 0.545) [-1.283 to 1.440]
8	Clinical and biochemical markers	Logit(p) = $-10.3842 - 0.0048 \times \text{age} + 0.0555 \times \text{SBP} - 0.0040 \times \text{DBP} - 0.0069 \times \text{BMI} + 1.5442 \times \text{previous PE} + 1.5372 \times \text{renal disease} + 0.8644 \times \text{hypertension} - 0.000535 \times \text{sFlt-1}$	4	20,132	103	0.762 (0.576 to 0.883) [0.341 to 0.952]	1.000 (0.642 to 1.359) [0.516 to 1.485]	0.009 (-1.319 to 1.338) [-3.858 to 3.877]

Model number	Predictors	Model equation	Number of			Average statistic (95% CI) [95% prediction interval]		
			Data sets	Participants	Events	C-statistic	Calibration slope	Calibration-in-the-large
<i>Second-trimester models</i>								
5	Clinical	$\text{Logit}(p) = -10.1805 + 0.0647 \times \text{DBP} + 2.3643 \times \text{previous PE} + 1.4929 \times \text{renal disease} + 1.1445 \times \text{autoimmune disease}$	9	29,153	152	0.723 (0.601 to 0.819) [0.418 to 0.905]	1.000 (0.785 to 1.214) [0.780 to 1.219]	0.058 (-0.464 to 0.580) [-1.369 to 1.485]
11	Clinical and biochemical markers	$\text{Logit}(p) = -9.7075 + 0.0705 \times \text{DBP} + 2.5467 \times \text{previous PE} + 3.3965 \times \text{renal disease} + 1.2447 \times \text{autoimmune disease} + 0.4942 \times \ln(\text{sFlt-1} + 0.5) - 1.0661 \times \ln(\text{PIGF} + 0.5)$	3	17,117	72	0.830 (0.629 to 0.934) [0.078 to 0.996]	1.000 (0.526 to 1.475) [-0.879 to 2.879]	0.119 (-1.176 to 1.414) [-6.600 to 6.838]
<i>Late-onset pre-eclampsia</i>								
<i>First-trimester models</i>								
3	Clinical	$\text{Logit}(p) = -6.7280 - 0.0138 \times \text{age} + 0.0150 \times \text{SBP} + 0.0355 \times \text{BMI} + 1.0363 \times \text{nulliparous} + 1.1159 \times \text{previous PE} + 1.2487 \times \text{renal disease} + 1.6863 \times \text{hypertension}$	11	29,187	1039	0.677 (0.615 to 0.733) [0.480 to 0.826]	1.000 (0.675 to 1.324) [0.051 to 1.949]	0.015 (-0.685 to 0.715) [-2.397 to 2.427]
9	Clinical and biochemical markers	$\text{Logit}(p) = -5.4124 - 0.0210 \times \text{age} + 0.0076 \times \text{SBP} + 0.0434 \times \text{BMI} + 1.2077 \times \text{nulliparous} + 1.0260 \times \text{previous PE} + 0.6499 \times \text{renal disease} + 2.0344 \times \text{hypertension} - 0.000171 \times \text{sFlt-1} - 0.0051 \times \text{PIGF}$	4	20,132	692	0.689 (0.505 to 0.827) [0.190 to 0.954]	1.000 (0.394 to 1.606) [-0.674 to 2.674]	0.000 (-0.895 to 0.896) [-2.655 to 2.656]
<i>Second-trimester models</i>								
6	Clinical	$\text{Logit}(p) = -8.0911 - 0.0137 \times \text{age} + 0.0104 \times \text{SBP} + 0.0124 \times \text{DBP} + 0.0647 \times \text{BMI} + 1.1891 \times \text{nulliparous} + 1.1650 \times \text{previous PE} + 0.7569 \times \text{renal disease} + 1.9032 \times \text{hypertension}$	9	29,153	993	0.705 (0.649 to 0.756) [0.542 to 0.829]	1.000 (0.706 to 1.294) [0.156 to 1.843]	0.012 (-0.872 to 0.896) [-2.809 to 2.833]
12	Clinical and biochemical markers	$\text{Logit}(p) = -7.7252 - 0.0189 \times \text{age} + 0.0171 \times \text{SBP} - 0.0136 \times \text{DBP} + 0.0687 \times \text{BMI} + 2.3770 \times \text{nulliparous} + 1.6232 \times \text{previous PE} + 1.2194 \times \text{renal disease} + 2.2762 \times \text{hypertension} - 0.00245 \times \text{PIGF}$	3	17,117	620	0.745 (0.493 to 0.898) [0.005 to 0.999]	1.000 (0.379 to 1.621) [-2.464 to 4.464]	0.001 (-1.307 to 1.309) [-7.651 to 7.654]

DEVELOPMENT AND VALIDATION OF PRE-ECLAMPSIA PREDICTION MODELS

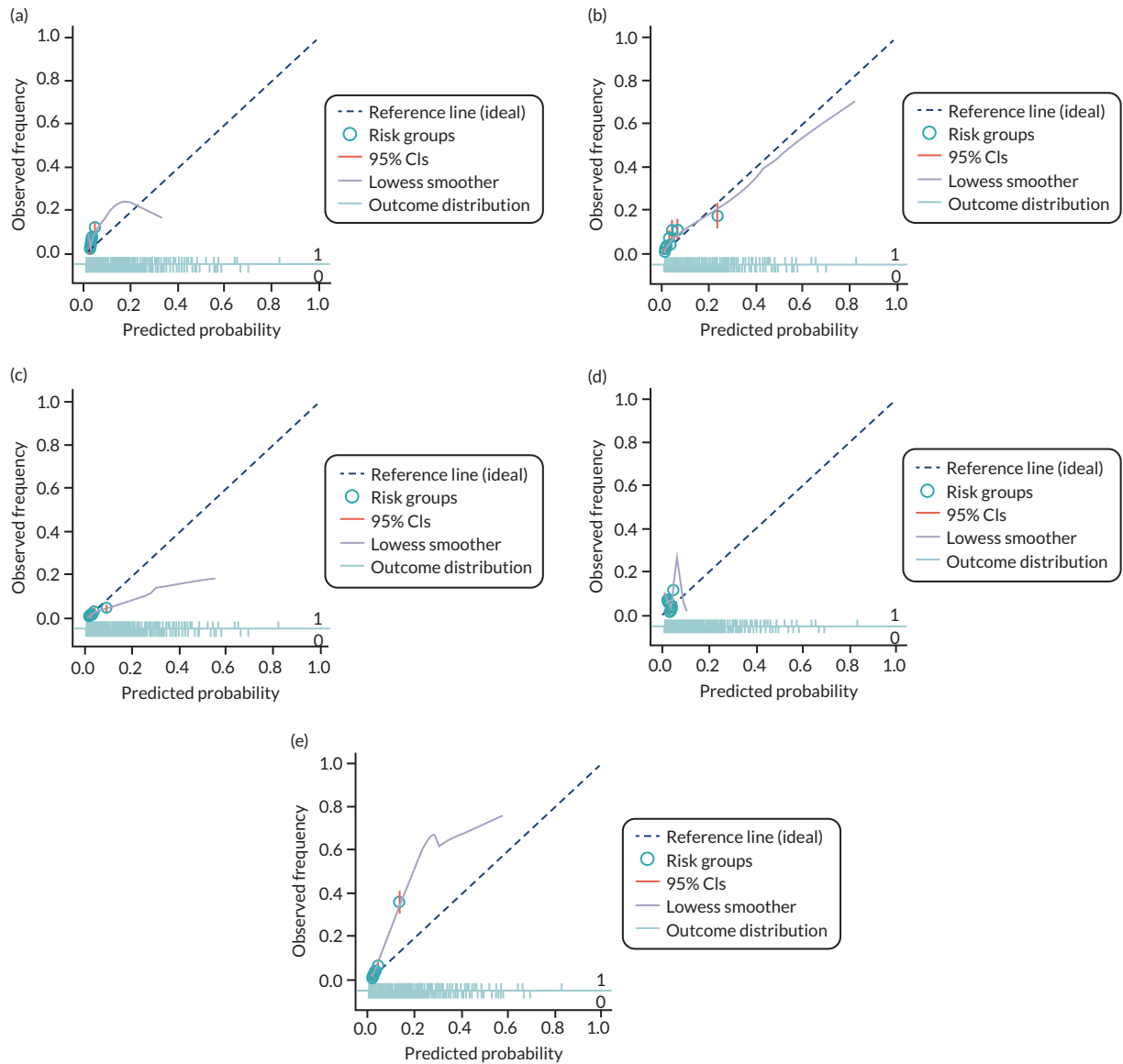


FIGURE 13 Calibration plots for the final (shrunk) model predicting any-onset pre-eclampsia using first-trimester clinical characteristics, in data sets (with > 100 events) used in the development and validation of the model. (a) SCOPE;⁴² (b) Baschat;¹¹⁵ (c) WHO;¹⁷⁵ (d) NICH LR;¹⁵⁹ and (e) POP.¹⁶¹

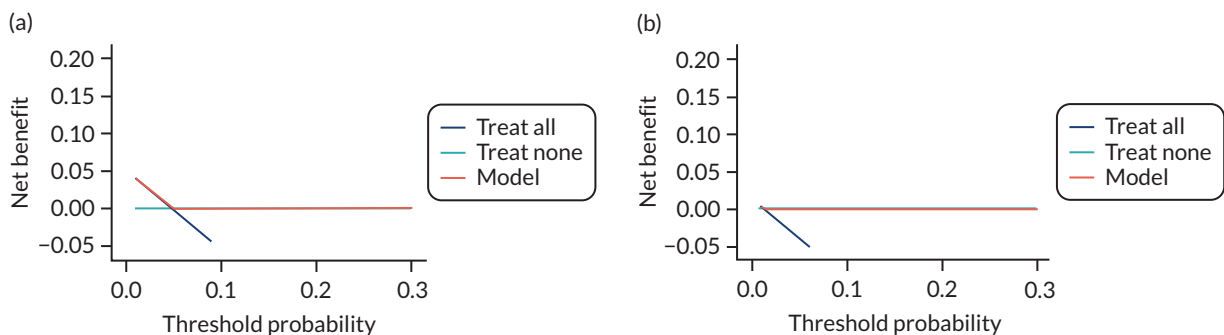


FIGURE 14 Decision curves for the final (shrunk) model predicting any pre-eclampsia using first-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) Allen *et al.*;¹⁰⁸ (c) Poston *et al.* 2015;¹⁴⁹ (d) Baschat *et al.*;¹¹⁵ (e) Antsaklis *et al.*;¹¹⁰ (f) WHO;¹⁷⁵ (g) NICH LR;¹⁵⁹ (h) van Kuijk *et al.* 2014;¹⁶⁶ (i) STORK G;¹³⁵ (j) Vinter *et al.*;¹⁷³ and (k) POP.¹⁶¹ Net benefit values are often best multiplied by 1000 to reveal the extra number of women who would be correctly treated per 1000 women who used the model, with none treated incorrectly. (continued)

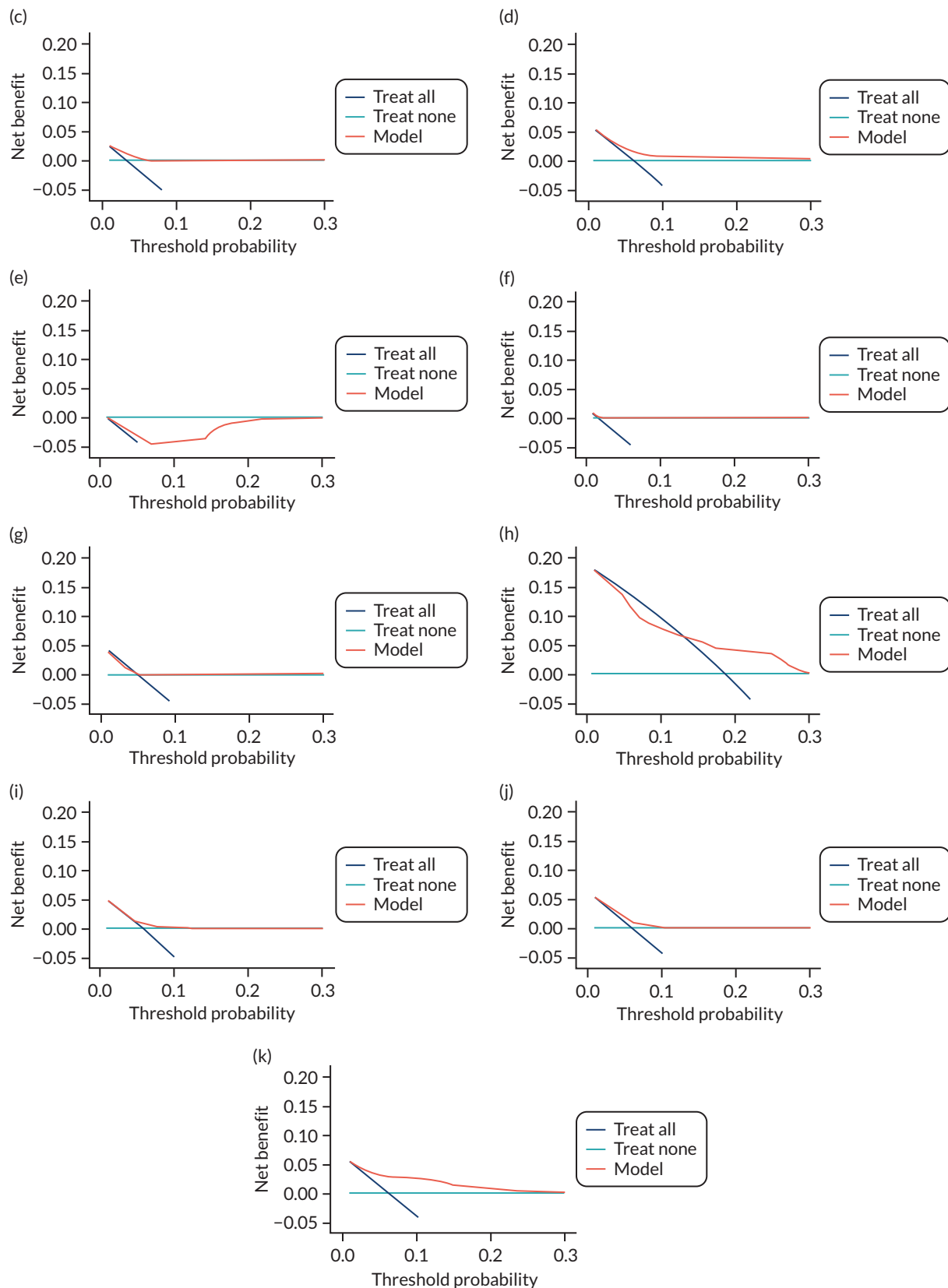


FIGURE 14 Decision curves for the final (shrunk) model predicting any pre-eclampsia using first-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) Allen *et al.*;¹⁰⁸ (c) Poston *et al.* 2015;¹⁴⁹ (d) Baschat *et al.*;¹¹⁵ (e) Antsaklis *et al.*;¹¹⁰ (f) WHO;¹⁷⁵ (g) NICH LR;¹⁵⁹ (h) van Kuijk *et al.* 2014;¹⁶⁶ (i) STORK G;¹³⁵ (j) Vinter *et al.*;¹⁷³ and (k) POP.¹⁶¹ Net benefit values are often best multiplied by 1000 to reveal the extra number of women who would be correctly treated per 1000 women who used the model, with none treated incorrectly.

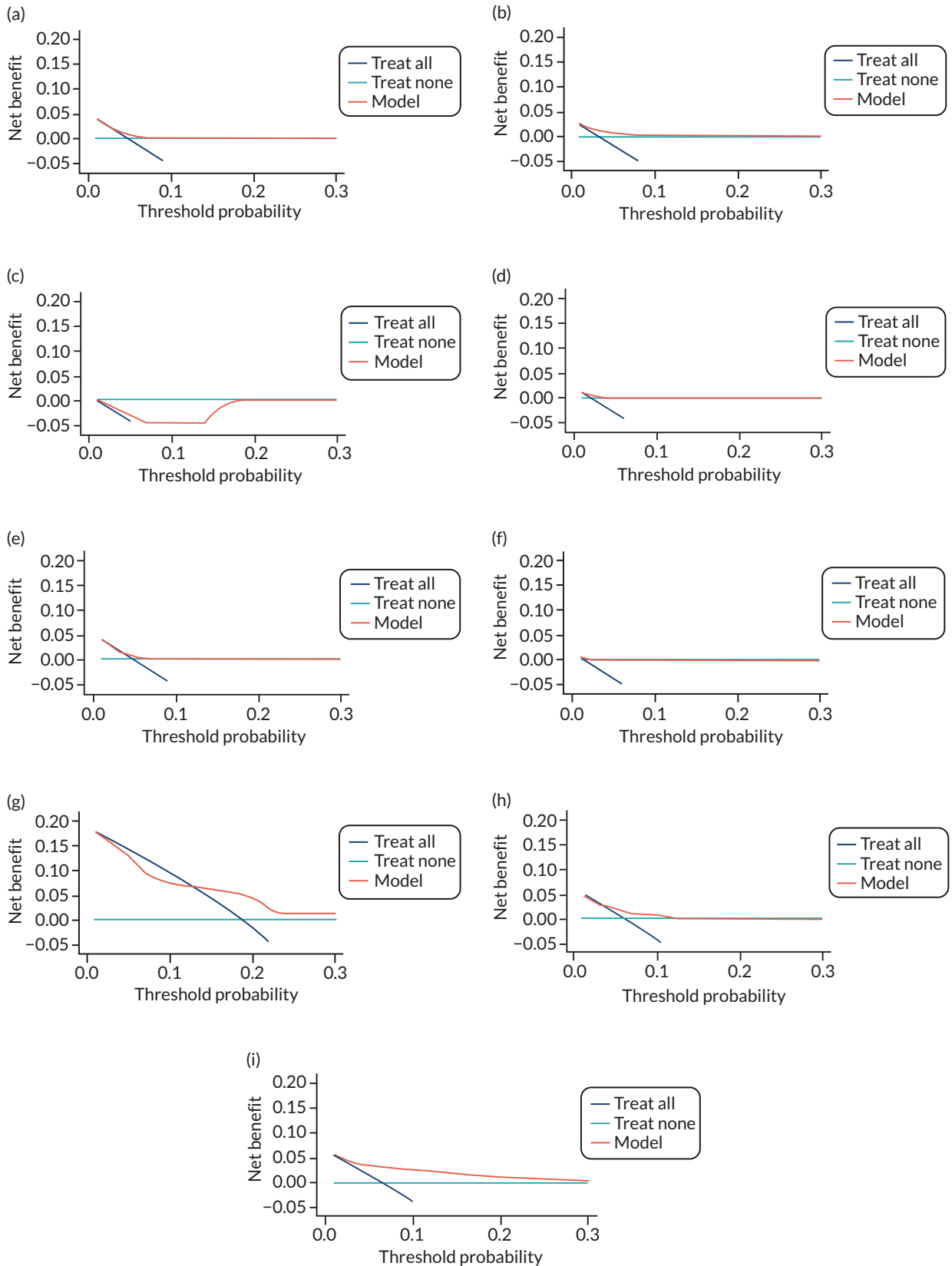


FIGURE 15 Decision curves for the final (shrunk) model predicting any pre-eclampsia using second-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) Poston *et al.* 2015;¹⁴⁹ (c) Antsaklis *et al.*;¹¹⁰ (d) WHO;¹⁷⁵ (e) NICH LR;¹⁵⁹ (f) POUCH;¹³¹ (g) van Kuijk *et al.* 2014;¹⁶⁶ (h) STORK G;¹³⁵ and (i) POP.¹⁶¹ Net benefit values are often best multiplied by 1000 to reveal the extra number of women who would be correctly treated per 1000 women who used the model, with none treated incorrectly.

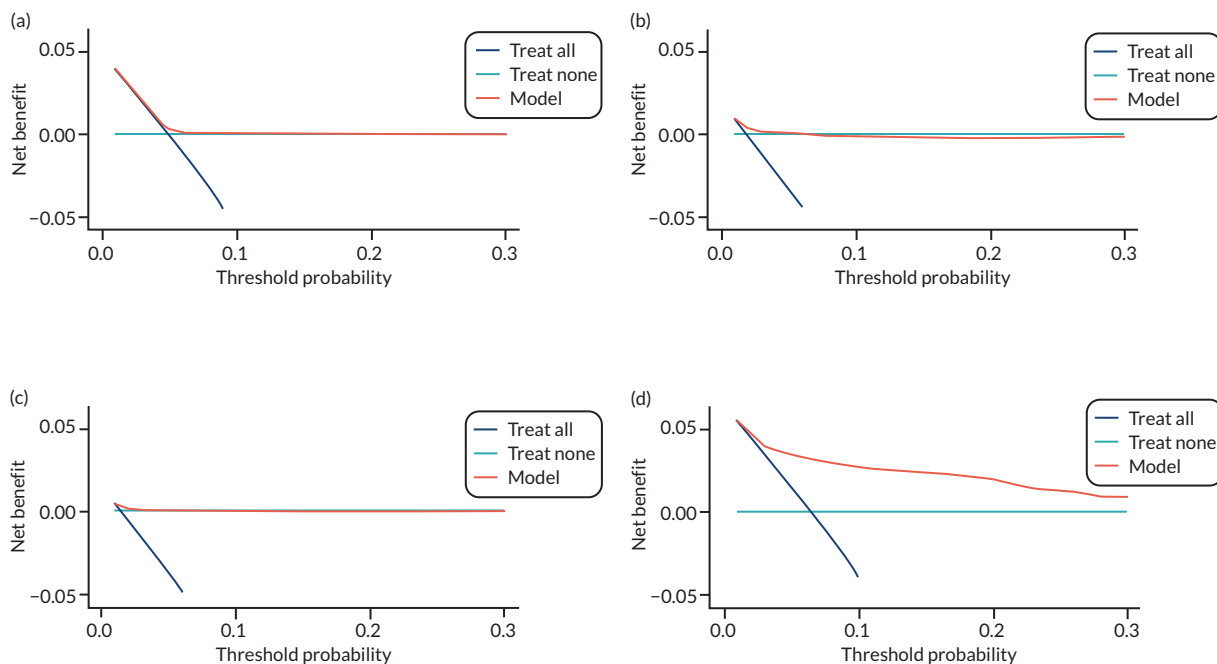


FIGURE 16 Decision curves for the final (shrunk) model predicting any pre-eclampsia using first-trimester clinical characteristics and biochemical markers, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) WHO;¹⁷⁵ (c) POUCH;¹³¹ and (d) POP.¹⁶¹ Net benefit values are often best multiplied by 1000 to reveal the extra number of women who would be correctly treated per 1000 women who used the model, with none treated incorrectly.

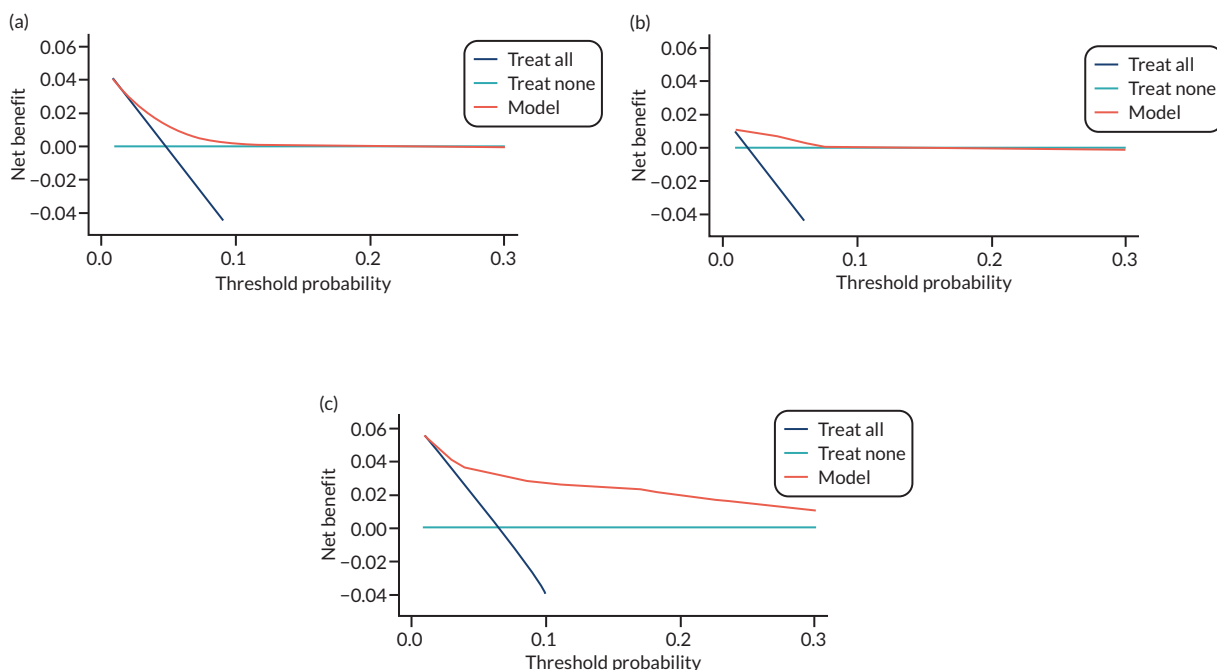


FIGURE 17 Decision curves for the final (shrunk) model predicting any pre-eclampsia using second-trimester clinical characteristics and biochemical markers, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) WHO;¹⁷⁵ and (c) POP.¹⁶¹ Net benefit values are often best multiplied by 1000 to reveal the extra number of women who would be correctly treated per 1000 women who used the model, with none treated incorrectly.

Using first-trimester clinical characteristics (model 1; see *Figure 14*) shows some net benefit at thresholds around 0.05 in the Poston *et al.* 2015,¹⁴⁹ Baschat *et al.*,¹¹⁵ STORK G,¹³⁵ Vinter *et al.*¹⁷³ and POP¹⁶¹ cohorts. The model shows little benefit or harm in SCOPE,⁴² Allen *et al.*,¹⁰⁸ Antsaklis *et al.*,¹¹⁰ WHO¹⁷⁵ and NICH LR.¹⁵⁹ Using second-trimester clinical characteristics (model 4) shows some improvement in net benefit in SCOPE¹⁶¹ but little improvement in the other data sets (see *Figure 15*). In the data sets used for developing and validating models with first-trimester clinical characteristics and biochemical markers (model 7), there may be greater net benefit in POP¹⁶¹ but little improvement in the SCOPE⁴² or WHO¹⁷⁵ cohorts (see *Figure 16*) compared with using clinical characteristics alone. Using second-trimester clinical characteristics and biochemical markers (model 10) shows a slight improvement in the SCOPE⁴² and POP¹⁶¹ cohorts (compared with first-trimester predictors), and the addition of second-trimester biochemical markers has slightly greater net benefit than in models including only second-trimester clinical characteristics (see *Figure 17*).

Decision curves for models predicting early-onset pre-eclampsia show no net benefit in most of the data sets, and decision curves for models predicting late-onset pre-eclampsia are similar to those for any-onset pre-eclampsia (see *Appendix 21, Figures 38–45*).

Summary

We used IPD from the IPPIC data sets to develop and validate new prediction models for early-onset, late-onset and any-onset pre-eclampsia using clinical characteristics alone or with the addition of biochemical markers. The IPPIC data sets used for model development and validation are heterogeneous, with different case mix in different data sets (e.g. owing to different inclusion and exclusion criteria). When the models were validated using an average intercept across data sets, the model performed better in some IPPIC data sets than in others even if the average performance was good. The same was observed in terms of net benefit in the individual data sets. In some data sets, there was potential for net benefit at certain thresholds, whereas there was very little or no net benefit when the models were applied in other data sets.

In summary, these prediction models have the potential to be useful in predicting pre-eclampsia in some populations; however, additional predictors may be needed, or the models may need to be tailored to improve the predictive performance across different settings and populations.

Chapter 7 Predictive performance of individual risk factors for pre-eclampsia

An unadjusted two-stage IPD meta-analysis of the prognostic effect of each candidate predictor prioritised in *Chapter 4, Prioritisation of predictors of pre-eclampsia*, was performed for each outcome of early-onset, late-onset and any-onset pre-eclampsia, using complete cases of singleton pregnancies in the IPPIC international data set. All analyses were carried out on raw values for ultrasound and biochemical markers.

Any-onset pre-eclampsia

We investigated the prognostic value of individual clinical, biochemical and ultrasound markers for predicting pre-eclampsia using a two-stage IPD meta-analysis. The analysis could not be performed for the candidate factors PAPP-A, PIGF, sFlt-1, PCR and umbilical artery pulsatility index because the first-stage logistic regression models could not be fitted owing to complete or quasi-complete separation.²³⁹ This happens when the outcome separates the predictor variable completely or partially, stopping the model from fitting. The results of the two-stage IPD meta-analysis for any-onset pre-eclampsia and each predictor variable are shown in *Table 20*.

TABLE 20 Two-stage IPD meta-analysis for any-onset pre-eclampsia

Predictor	Number of studies	OR	95% CI	95% prediction interval	I ² (%)
<i>Maternal clinical characteristics</i>					
Age	71	1.06	0.97 to 1.17	0.58 to 1.94	95.96
Multiple current pregnancy	23	2.56	1.86 to 3.51	0.67 to 9.75	98.62
Previous pre-eclampsia	35	3.40	2.55 to 4.53	0.87 to 13.26	90.62
Parity	48	0.88	0.79 to 0.99	0.47 to 1.67	96.60
History of hypertension	49	4.76	3.56 to 6.35	0.69 to 32.93	98.39
History of renal disease	21	3.28	2.15 to 5.01	0.70 to 15.44	93.16
History of diabetes	34	2.89	2.15 to 3.88	0.64 to 12.95	95.62
History of autoimmune disease	16	1.94	1.19 to 3.17	0.49 to 7.69	75.43
Family history of pre-eclampsia	15	1.40	1.00 to 1.95	0.55 to 3.58	53.87
Previous SGA	11	1.22	0.82 to 1.82	0.53 to 2.83	48.18
Smoking during pregnancy	54	0.84	0.76 to 0.93	0.50 to 1.42	86.46
Spontaneous mode of conception	22	0.73	0.64 to 0.84	0.49 to 1.09	58.67
Cocaine, heroin or methamphetamine use	8	1.13	0.70 to 1.81	0.47 to 2.68	54.03
BMI	43	1.07	1.06 to 1.08	1.01 to 1.13	96.75
BMI trimester 1	48	1.08	1.06 to 1.09	1.00 to 1.16	93.33
BMI trimester 2	21	1.07	1.05 to 1.09	1.00 to 1.15	86.36
BMI trimester 3	11	1.09	1.06 to 1.14	0.98 to 1.22	87.89
SBP	19	1.60	1.42 to 1.80	0.99 to 2.58	89.98

continued

TABLE 20 Two-stage IPD meta-analysis for any-onset pre-eclampsia (continued)

Predictor	Number of studies	OR	95% CI	95% prediction interval	I ² (%)
SBP trimester 1	39	1.46	1.39 to 1.53	1.15 to 1.85	76.57
SBP trimester 2	28	1.55	1.46 to 1.64	1.24 to 1.94	73.11
SBP trimester 3	19	2.04	1.76 to 2.36	1.13 to 3.66	92.86
DBP	19	1.78	1.55 to 2.05	0.99 to 3.20	88.45
DBP trimester 1	39	1.70	1.57 to 1.85	1.19 to 2.45	79.61
DBP trimester 2	28	1.80	1.62 to 1.99	1.18 to 2.75	84.16
DBP trimester 3	18	2.59	2.04 to 3.29	1.06 to 6.30	94.44
MAP	25	2.00	1.75 to 2.30	1.08 to 3.71	89.06
MAP trimester 1	41	1.79	1.65 to 1.93	1.24 to 2.58	80.57
MAP trimester 2	29	1.92	1.74 to 2.11	1.27 to 2.89	83.52
MAP trimester 3	19	2.71	2.19 to 3.34	1.17 to 6.24	93.89
PCR	3	1.11	0.72 to 1.73	0.48 to 2.60	99.92
PCR trimester 1	1	0.75	0.34 to 1.67	N/A	N/A
PCR trimester 2	1	0.98	0.93 to 1.03	N/A	N/A
Urine dipstick	7	2.72	0.83 to 8.87	0.10 to 75.23	98.34
Urine dipstick trimester 1	6	2.27	1.52 to 3.38	1.20 to 4.29	27.67
Urine dipstick trimester 2	10	1.82	1.30 to 2.54	0.73 to 4.52	74.77
Urine dipstick trimester 3	6	3.46	1.83 to 6.55	0.74 to 16.18	92.92
Ultrasound markers					
Uterine artery PI	11	3.11	1.86 to 5.18	0.71 to 13.66	74.32
Uterine artery PI trimester 1	12	1.67	1.18 to 2.38	0.64 to 4.37	70.27
Uterine artery PI trimester 2	13	4.18	3.25 to 5.38	2.27 to 7.70	47.16
Uterine artery PI trimester 3	3	3.99	0.02 to 688.38	0.00 to 37,752.95	75.04
Umbilical artery PI	5	1.08	0.44 to 2.65	0.44 to 2.65	0.00
Umbilical artery PI trimester 2	8	1.94	0.89 to 4.23	0.52 to 7.26	33.52
Umbilical artery PI trimester 3	5	1.60	0.48 to 5.38	0.21 to 12.31	37.99
Biochemical markers					
PIGF trimester 1	17	0.22	0.09 to 0.50	0.01 to 4.34	85.44
PIGF trimester 2	16	0.66	0.53 to 0.83	0.34 to 1.29	87.27
PIGF trimester 3	12	0.59	0.45 to 0.77	0.25 to 1.36	96.78
sFlt-1 trimester 1	12	0.98	0.97 to 1.00	0.96 to 1.01	51.24
sFlt-1 trimester 2	13	1.02	0.99 to 1.04	0.96 to 1.08	89.91
sFlt-1 trimester 3	9	1.03	1.02 to 1.04	1.00 to 1.06	85.70
PAPP-A trimester 1	11	0.83	0.54 to 1.29	0.21 to 3.24	99.99
PAPP-A trimester 2	4	1.00	0.99 to 1.02	0.98 to 1.02	65.03
N/A, not applicable (only one study); PI, pulsatility index; SGA, small for gestational age.					
Note					
Continuous variables are 1-unit increments, except maternal age, SBP, DBP and MAP, which are 10-unit increments, and PIGF, sFlt-1 and PAPP-A, which are 100-unit increments.					

The study estimates varied considerably in terms of heterogeneity, with most predictors showing heterogeneity of $\geq 70\%$. Variation between the 95% CI for the mean effect and the 95% prediction interval for the distribution of true effects was great for many predictors, which was expected given the varying level of heterogeneity.

The strongest association with the outcome was observed for history of hypertension (OR 4.76, 95% CI 3.56 to 6.35; $I^2 = 98.39\%$), with a fivefold increase in the odds of pre-eclampsia in women with a history of hypertension compared with women without a history of hypertension. Most predictors had evidence of an association at the 5% level. However, maternal age, family history of pre-eclampsia, PCR (for unspecified trimester estimates and trimester 1 and 2 estimates), urine dipstick (unspecified trimester estimates), previous small for gestational age fetus, cocaine, heroin or methamphetamine use, uterine artery pulsatility index (trimester 3), umbilical artery pulsatility index (for unspecified trimester estimates and trimester 2 and 3 estimates), sFlt-1 (all trimesters estimates) and PAPP-A (all trimester estimates) were not statistically significant at the 5% level (see Table 20).

Most statistically significant predictors had evidence of an increase in odds of pre-eclampsia over the course of pregnancy with increasing values, except multiparity (OR 0.88, 95% CI 0.79 to 0.99; $I^2 = 96.6\%$), smoking during pregnancy (OR 0.84, 95% CI 0.76 to 0.93; $I^2 = 86.46\%$), spontaneous mode of conception (OR 0.73, 95% CI 0.64 to 0.84; $I^2 = 58.67\%$) and increasing levels of PIGF measured in the first (OR 0.22, 95% CI 0.09 to 0.50; $I^2 = 85.44$), second (OR 0.66, 95% CI 0.53 to 0.83; $I^2 = 87.27\%$) and third trimester (OR 0.59, 95% CI 0.45 to 0.77; $I^2 = 96.78\%$), which showed a decrease in the odds of pre-eclampsia, thereby providing a possible protective effect.

Early-onset pre-eclampsia

Table 21 shows the results of the two-stage meta-analysis for early-onset (delivery at < 34 weeks' gestation) pre-eclampsia and each predictor variable. Third-trimester predictors were not explored because they do not predate the outcome. The two-stage IPD meta-analysis could not be performed for the following predictors: previous pre-eclampsia, history of hypertension, history of renal disease,

TABLE 21 Two-stage IPD meta-analysis for early-onset pre-eclampsia

Predictor	Number of studies	OR	95% CI	95% prediction interval	I^2 (%)
Maternal clinical characteristics					
Age	64	1.21	1.01 to 1.44	0.45 to 3.22	89.83
Multiple current pregnancy	18	3.63	2.35 to 5.60	0.66 to 19.82	96.96
Parity	37	0.99	0.87 to 1.12	0.56 to 1.74	86.04
BMI	40	1.06	1.04 to 1.08	0.99 to 1.13	85.89
BMI trimester 1	41	1.07	1.05 to 1.09	0.99 to 1.15	73.36
BMI trimester 2	20	1.05	1.02 to 1.08	0.95 to 1.15	66.81
SBP	18	1.65	1.43 to 1.92	0.98 to 2.80	75.60
SBP trimester 1	31	1.50	1.39 to 1.63	1.11 to 2.05	57.89
SBP trimester 2	23	1.73	1.51 to 1.97	1.15 to 2.60	68.74
DBP	18	1.92	1.53 to 2.42	0.86 to 4.31	80.98
DBP trimester 1	30	1.85	1.61 to 2.12	1.10 to 3.10	71.92

continued

TABLE 21 Two-stage IPD meta-analysis for early-onset pre-eclampsia (continued)

Predictor	Number of studies	OR	95% CI	95% prediction interval	I ² (%)
DBP trimester 2	23	2.15	1.79 to 2.59	1.23 to 3.76	69.28
MAP	24	2.18	1.83 to 2.60	1.11 to 4.30	74.08
MAP trimester 1	33	2.00	1.73 to 2.31	1.13 to 3.55	74.01
MAP trimester 2	24	2.25	1.89 to 2.69	1.28 to 3.97	70.79
PCR	3	1.00	1.00 to 1.01	1.00 to 1.01	0.00
PCR trimester 2	1	1.02	0.90 to 1.14	N/A	N/A
Urine dipstick	5	3.30	0.31 to 35.27	0.01 to 922.24	96.69
Urine dipstick trimester 1	3	3.29	0.28 to 38.31	0.04 to 300.79	86.11
Urine dipstick trimester 2	8	3.20	1.79 to 5.72	0.93 to 10.94	67.54
Ultrasound markers					
Uterine artery PI	11	6.27	2.70 to 14.58	0.82 to 48.23	54.17
Uterine artery PI trimester 1	11	2.14	1.24 to 3.67	0.56 to 8.24	50.70
Uterine artery PI trimester 2	13	14.73	8.12 to 26.72	3.10 to 69.96	60.11
Umbilical artery PI	5	5.44	3.27 to 9.06	3.27 to 9.06	0.00
Umbilical artery PI trimester 2	8	6.29	2.85 to 13.92	2.85 to 13.92	0.00
Biochemical markers					
PIGF trimester 1	15	0.08	0.02 to 0.35	0.00 to 5.94	55.69
PIGF trimester 2	13	0.07	0.01 to 0.43	0.00 to 13.16	97.18
sFlt-1 trimester 1	10	0.99	0.97 to 1.01	0.97 to 1.01	0.21
sFlt-1 trimester 2	12	1.05	1.01 to 1.09	0.96 to 1.15	90.28
PAPP-A trimester 1	9	0.99	0.97 to 1.01	0.97 to 1.01	0.43
PAPP-A trimester 2	3	1.00	1.00 to 1.00	1.00 to 1.00	0.00

N/A, not applicable (only one study); PI, pulsatility index.

Note

Continuous variables are one-unit increments, except maternal age, SBP, DBP and MAP, which are 10-unit increments, and PIGF, sFlt-1 and pregnancy-associated plasma protein A, which are 100-unit increments.

history of diabetes, history of autoimmune disease, family history of pre-eclampsia, PCR measured in the first trimester, previous small for gestational age fetus, smoking during pregnancy, spontaneous mode of conception, cocaine, heroin or methamphetamine use, umbilical artery pulsatility index measured in the first trimester, PIGF, sFlt-1 and PAPP-A.²³⁹

Heterogeneity for predictors varied considerably, and ranged from 0% to 97% for PIGF. The strongest association with the outcome was observed for uterine artery pulsatility index measured in the second trimester (OR 14.73, 95% CI 8.12 to 26.72; I² = 60.11%), which suggests an increase in the odds of early-onset pre-eclampsia of about 15 times, with a unit increase in the mean uterine artery pulsatility index. The confidence and prediction intervals for this were wide (95% prediction interval 3.10 to 69.96), demonstrating the variability within the studies. Most predictors had evidence of an association at the 5% level, but parity, PCR measured in the second trimester, urine dipstick (unspecified trimester estimates and first trimester), sFlt-1 (first-trimester estimates) and PAPP-A (all trimester estimates)

were not statistically significant at the 5% level. All statistically significant predictors had evidence of an increase in the odds of early pre-eclampsia with increasing values, except PIGF measured in the first (OR 0.08, 95% CI 0.02 to 0.35; $I^2 = 55.69\%$) or the second trimester (OR 0.07, 95% CI 0.01 to 0.43; $I^2 = 97.18\%$), which showed a decrease in the odds of pre-eclampsia with increasing levels.

Late-onset pre-eclampsia

The results of the two-stage meta-analysis for late-onset (delivery at ≥ 34 weeks' gestation) pre-eclampsia and each predictor variable are shown in *Table 22*. The two-stage IPD meta-analysis could not be performed for the following predictors: previous pre-eclampsia, history of hypertension, history of renal disease, history of diabetes, history of autoimmune disease, family history of pre-eclampsia, PCR measured in the first trimester, previous small for gestational age fetus, smoking during pregnancy, spontaneous mode of conception, cocaine, heroin or methamphetamine use, umbilical artery pulsatility index measured in the first trimester, PIGF, sFlt-1, PAPP-A and PAPP-A measured in the third trimester.²³⁹

TABLE 22 Two-stage IPD meta-analysis for late-onset pre-eclampsia

Predictor	Number of studies	OR	95% CI	95% prediction interval	I^2 (%)
<i>Maternal clinical characteristics</i>					
Age	68	1.04	0.94 to 1.14	0.60 to 1.81	94.66
Multiple current pregnancy	22	2.18	1.59 to 2.99	0.62 to 7.64	98.07
Parity	46	0.87	0.78 to 0.97	0.48 to 1.58	95.16
BMI	42	1.07	1.06 to 1.08	1.02 to 1.12	94.96
BMI trimester 1	45	1.07	1.06 to 1.09	1.00 to 1.15	92.31
BMI trimester 2	19	1.07	1.06 to 1.09	1.01 to 1.14	82.19
BMI trimester 3	10	1.09	1.06 to 1.13	0.99 to 1.21	82.31
SBP	19	1.44	1.29 to 1.61	0.94 to 2.22	87.60
SBP trimester 1	36	1.39	1.31 to 1.47	1.08 to 1.80	77.48
SBP trimester 2	26	1.43	1.33 to 1.54	1.09 to 1.88	76.58
SBP trimester 3	15	1.83	1.54 to 2.18	0.96 to 3.48	93.60
DBP	19	1.56	1.38 to 1.77	0.93 to 2.62	85.49
DBP trimester 1	36	1.58	1.44 to 1.73	1.09 to 2.30	79.70
DBP trimester 2	26	1.59	1.41 to 1.8	0.97 to 2.61	85.68
DBP trimester 3	15	2.20	1.68 to 2.88	0.84 to 5.78	95.00
MAP	25	1.74	1.51 to 2.01	0.94 to 3.22	88.77
MAP trimester 1	38	1.65	1.51 to 1.80	1.12 to 2.42	81.05
MAP trimester 2	27	1.70	1.51 to 1.92	1.02 to 2.85	86.86
MAP trimester 3	15	2.26	1.77 to 2.89	0.91 to 5.60	94.78
PCR	3	1.01	0.98 to 1.04	0.95 to 1.07	96.67
PCR trimester 1	1	0.75	0.34 to 1.67	N/A	N/A
PCR trimester 2	1	0.97	0.92 to 1.03	N/A	N/A
Urine dipstick	7	2.45	0.79 to 7.65	0.10 to 59.76	98.01

continued

TABLE 22 Two-stage IPD meta-analysis for late-onset pre-eclampsia (continued)

Predictor	Number of studies	OR	95% CI	95% prediction interval	I ² (%)
Urine dipstick trimester 1	5	1.85	1.48 to 2.32	1.48 to 2.32	0.00
Urine dipstick trimester 2	9	1.44	1.04 to 1.99	0.63 to 3.27	59.56
Urine dipstick trimester 3	5	2.73	1.47 to 5.04	0.72 to 10.34	81.85
Ultrasound markers					
Uterine artery PI	11	2.19	1.36 to 3.54	0.59 to 8.12	64.30
Uterine artery PI trimester 1	12	1.61	1.09 to 2.39	0.54 to 4.83	71.53
Uterine artery PI trimester 2	12	2.95	2.31 to 3.76	1.94 to 4.48	20.77
Uterine artery PI trimester 3	3	3.98	0.04 to 403.56	0.00 to 11,096.61	67.65
Umbilical artery PI	5	0.91	0.05 to 15.46	0.00 to 375.27	88.83
Umbilical artery PI trimester 2	8	1.25	0.56 to 2.78	0.48 to 3.25	8.11
Umbilical artery PI trimester 3	5	0.91	0.26 to 3.25	0.11 to 7.36	32.31
Biochemical markers					
PIGF trimester 1	17	0.33	0.16 to 0.68	0.03 to 3.93	82.67
PIGF trimester 2	16	0.81	0.69 to 0.94	0.52 to 1.25	76.39
PIGF trimester 3	12	0.68	0.57 to 0.81	0.38 to 1.20	93.60
sFlt-1 trimester 1	11	0.98	0.97 to 0.99	0.95 to 1.01	37.07
sFlt-1 trimester 2	13	1.00	0.99 to 1.00	0.99 to 1.01	8.29
sFlt-1 trimester 3	9	1.02	1.00 to 1.03	0.99 to 1.04	91.03
PAPP-A trimester 1	10	0.83	0.53 to 1.31	0.22 to 3.18	99.99
PAPP-A trimester 2	4	1.00	0.99 to 1.02	0.98 to 1.02	57.98

N/A, not applicable (only one study); PI, pulsatility index.

Note

Continuous variables are 1-unit increments, except maternal age, SBP, DBP and MAP, which are 10-unit increments, and PIGF, sFlt-1 and PAPP-A, which are 100-unit increments.

There was considerable variation in the heterogeneity for predictors, and the strongest association with the outcome was observed for uterine artery pulsatility index measured in the second trimester (OR 2.95, 95% CI 2.31 to 3.76; I² = 20.77%), which suggests that a 1-unit increase in the uterine artery pulsatility index will lead to an approximate increase of three times in the odds of late-onset pre-eclampsia. Most predictors assessed showed evidence of an association at the 5% level. However, maternal age, PCR (for all trimester estimates), urine dipstick (unspecified trimester), third-trimester uterine artery pulsatility index, umbilical artery pulsatility index (unspecified trimester and third trimester), second-trimester sFlt-1 and PAPP-A (all trimesters estimates) were not statistically significant at the 5% level. All statistically significant predictors had evidence of an increase in odds of late-onset pre-eclampsia except parity (OR 0.87, 95% CI 0.78 to 0.97; I² = 95.16%), first-trimester (OR 0.33, 95% CI 0.16 to 0.68; I² = 82.67%), second-trimester (OR 0.81, 95% CI 0.69 to 0.94; I² = 76.39%) or third-trimester (OR 0.68, 95% CI 0.57 to 0.81; I² = 93.60%) measurement of PIGF and sFlt-1 measured in the first trimester (OR 0.98, 95% CI 0.97 to 0.99; I² = 37.07%), which showed a reduction in the odds of late-onset pre-eclampsia.

Forest plots for each predictor assessed and for each outcome are presented in *Report Supplementary Material 1*.

Summary

This unadjusted two-stage IPD meta-analysis of the prognostic effect of candidate predictors of early-, late- and any-onset pre-eclampsia was limited to complete singleton records only and included all 78 studies in the IPPIC database, with missing data assumed to be missing completely at random.⁸⁴ Most predictors had evidence of an association at the 5% level for each outcome. Increasing the values of second-trimester measurement of uterine artery pulsatility index had the strongest statistically significant association with early-onset (OR 14.73, 95% CI 8.12 to 26.72; $I^2 = 60.11\%$) or late-onset (OR 2.95, 95% CI 2.31 to 3.76; $I^2 = 20.77\%$) pre-eclampsia. The predictor with the strongest statistically significant association with any-onset pre-eclampsia was history of hypertension (OR 4.76, 95% CI 3.56 to 6.35; $I^2 = 98.39\%$). Smoking during pregnancy and spontaneous mode of conception were associated with a reduction in odds of any-onset pre-eclampsia only; however, parity was associated with reduced odds of late-onset and any-onset pre-eclampsia. Increases in PIGF measurements were associated with a reduction in the odds of early-, late- and any-onset pre-eclampsia, whereas sFlt-1 was associated with a reduction in the odds of late-onset pre-eclampsia only. Conclusions drawn about the association of predictors with outcomes should take into account the uncertainty resulting from multiple testing type I errors. Further research should consider imputing for missing data to control for the introduction of bias, and this would also allow associations to be adjusted for potential confounders, giving a better evaluation of associations.

Chapter 8 Discussion

Summary of the findings

Existing prediction models for any-, early- and late-onset pre-eclampsia IPD have poor to average predictive performance when externally validated in the combined IPPIC-UK data sets. All models that could be validated showed suboptimal predictive performance across data sets. The clinical utility of the published models was poor.

Most of the IPPIC pre-eclampsia models showed good to average discrimination across data sets; all had good to average calibration across data sets. The models varied in the predictive performance between data sets. The clinical characteristics only and the clinical and biochemical first- and second-trimester models to predict any pre-eclampsia showed consistent net benefit over a strategy of considering all women to have pre-eclampsia for a wide range of probability thresholds beyond 5% in cohort of nulliparous women with singleton pregnancies in the UK. Very few risk factors were associated with pre-eclampsia, with significance in both the CIs and the prediction intervals including BMI, SBP and DBP and MAP for any-, early- and late-onset pre-eclampsia; and urine dipstick, uterine artery pulsatility index and umbilical artery pulsatility index for any- and early-onset pre-eclampsia.

Strengths and limitations

We used the largest data set to date to validate existing prediction models for pre-eclampsia, and to further develop models when required. The IPPIC data set consists of information on predictor variables at various trimesters. We used raw data to determine the presence or absence of pre-eclampsia and the type of onset, ensuring the reliability of the findings. Our comprehensive search identified all published models. By validating them in UK data sets, we were able to assess the extent of transportability of existing models to women managed in the NHS. We assessed the quality of the data sets and studies using robust tools. Rather than develop further models, we ensured that the performances of the existing models were robustly evaluated. The models were validated not only using evidence synthesis, but also within individual data sets. The large sample size provided us with sufficient events for the rare but important outcome of early-onset pre-eclampsia. In addition to reporting the performances of the models in terms of discrimination and calibration, we determined their clinical utility using decision curve analysis.

Prior to the development of the IPPIC pre-eclampsia models, we prioritised the predictors for importance to clinical practice by consensus to ensure face validity. We used multiple imputation to deal with missing values for both predictors and outcomes to avoid the loss of useful information^{84,240} and explored complex associations such as the non-linearity of predictor effects. We were able to report the association between individual clinical, biochemical and ultrasound predictors, measured in the first, second or third trimester, and rates of early-, late- and any-onset pre-eclampsia with very precise estimates. We pooled data from a very large sample size using IPD meta-analysis, and explored a considerable number of risk factors thought to be predictors of pre-eclampsia. We did not dichotomise any of the continuous predictive factors and we also considered the predictive accuracy of these risk factors along with their association.

Our findings were limited by the variations in population mix, the definitions of the predictors in each study and the outcomes reported. Some studies included only nulliparous women, some strictly included low-risk pregnancies and some included all pregnancies. The prioritisation of predictors of pre-eclampsia by members of the collaborative network who contributed data to the project could also be considered a limitation in the identification of predictors to be considered for model development. It was possible

that participants in the survey would rank predictors as important based on their particular research interest, and this method could potentially hamper the identification of new candidate predictors. However, we had a good representation of responses to the survey, and respondents were able to suggest possible factors not already assessed in the survey to be considered as predictors. There was also good consensus among respondents about the importance of predictors assessed, and no new candidate predictors were identified. The individual UK data sets measured different sets of variables (potential predictors) and measured them at different times (e.g. first, second or third trimester). Our validation was carried out considering only UK data sets to reduce the heterogeneity in the outcome definition and to allow existing models' predictive performance to be assessed in the UK health-care system context. However, this limited our ability to validate many of the existing prediction models and meant that we could validate models across the studies only if all of them reported the same variables. We were, therefore, also unable to validate all existing models in our IPD because of the unavailability of predictors in the models in our UK IPD. It is possible that a significant predictor may not have been evaluated if it was not provided across varied data sets. Some studies used data from the same cohort of women to report various prediction models in multiple combinations. The sources of the data also differed across data sets. Some were collected prospectively with the explicit purpose of predicting pre-eclampsia, whereas others were routine registry data. All of the above accounted for the heterogeneity observed in the performance of the models across the data sets. We validated the performances of published models across only UK data sets, but included all data sets for model development. It is likely that the transportability performances may have differed if all available data had been included. Furthermore, some models, such as the North *et al.* model⁴² for any-onset pre-eclampsia, the Poon 2009 model²³⁴ for early-onset pre-eclampsia and the Akolekar *et al.* model²⁴¹ for late-onset pre-eclampsia, could not be validated as the predictor variables in the models were not available in any of the IPPIC-UK data sets.

To ensure that the relevant data were included in the analysis, we dealt with missing data by imputing both within and between studies. We also made assumptions such as using early second-trimester values of BMI and MAP if the first-trimester values were missing. Our analysis of the association of risk factors and the different pre-eclampsia outcomes was limited to complete records only. Our assumption that data missing were missing completely at random is unlikely to be true. Applying multilevel multiple imputation would reduce this bias, and also allow estimates to be adjusted for potential confounders, giving a better evaluation of associations. However, the complexity of modelling the missing data mechanism would make this demanding (or impossible). We therefore present this as the most robustly available assessment of risk factors for pre-eclampsia.

Comparison with existing evidence

Current guidelines such as those by the National Institute for Health and Care Excellence²⁴² in the UK and by the American College of Obstetricians and Gynecologists⁷³ in the USA provide a list of risk factors rather than a prediction model to determine an individual's risk of pre-eclampsia. The predictive performance of both approaches has been shown to be inferior to that of multivariable prediction models.^{236,243,244} However, these models had not been externally validated in multiple data sets until now, with resulting suboptimal predictive performance.

Until now, only a small fraction of the 131 pre-eclampsia prediction models identified have been externally validated (11%, 15/131), and an even smaller proportion (4%, 5/131) have been evaluated for their clinical utility.^{44,108,160,245,246} Studies reporting on the external validation of these models often have not reported performance measures in terms of calibration, which has more value in assessing the predictive performance of the model than discrimination estimates or detection rates.²⁴⁷ Some existing models also used multiples of the mean to standardise biochemical and ultrasound markers, but this is of limited use in real-world settings as the estimates of adjustment factors used to standardise these

measurements to multiple of the mean values in the models are not always known in the population in which the model is to be used. For some of the models that we could validate, the summary performance measures have a lot of uncertainty (wide CIs), reflecting the small numbers of events and/or the heterogeneity. Even with larger numbers of events, CIs can be wide, especially for calibration, so it is possible that, for some of the models, miscalibration is due to chance. However, we must also look at the broader picture emerging across all of the validations. For most models, the majority of summary results for calibration, and the study-specific results for calibration, are suggestive of overfitting (slopes < 1). This is something that the field needs to address as whole. In our IPPIC models, we have examined overfitting in our model development, and adjusted for it.

Recently, the ASPRE trial³⁴ showed that women at high risk of preterm pre-eclampsia who were started on 150 mg of aspirin early in pregnancy had their risk lowered, and their high-risk status was determined using a prediction model. However, a few questions need to be answered before this approach is implemented. First, the extent to which the model over- or underpredicted women's pre-eclampsia risk is not reported in the study, because women assessed as being at low risk of pre-eclampsia using the model were not followed up further. This is also shown by the significant difference in the incidence of preterm pre-eclampsia between the placebo group and the population used to develop the model. Second, it is likely that some women in the group categorised as 'low risk' using the model may have benefited from the intervention. In the absence of follow-up of this group for pre-eclampsia outcomes, we cannot robustly confirm that they would not have benefited from the intervention. Third, the clinical utility of the prediction model has not been assessed, limiting our ability to recommend its routine use in clinical practice. We were unable to validate the exact model used in the ASPRE trial because the multiple of the mean predictors were unavailable in our IPD data set. The authors who developed this model recently validated it in three data sets with 'appropriately trained staff and quality control of measurement'.²⁴⁸ This showed that the model discriminated well, with a large C-statistic in all three validation data sets. However, further independent validation of this model is needed to evaluate its performance in 'real-world' settings.

Although some of the published models showed a promising ability to discriminate between women who had a pre-eclampsia outcome and those who did not, calibration performance was generally poor across the data sets and there was large heterogeneity in the calibration performance across different IPPIC data sets. Although the CIs (e.g. for calibration slope) were sometimes very wide, a general picture is that most models demonstrated overfitting at model development with predictions that were too extreme compared with the observed risk in the data sets (calibration slope < 1). Model predictions were also systematically too low or too high depending on the data set used to validate the model (calibration-in-the-large \neq 0). The models were validated in a rather heterogeneous group of data sets with different eligibility criteria. These findings suggest that the differences between women in the data sets were not adequately captured by the set of predictors included in the models. There was also little difference in predictive performance when biochemical markers or ultrasound markers were combined with maternal and clinical characteristics, compared with models with only maternal and clinical characteristics. Some of the heterogeneity in predictive performance of the models is likely to be due to different methods and timing of measurement, for example in blood pressure and biochemical marker values. Going forward, standardisation of measurement methods, for example across laboratories and hospitals, might reduce heterogeneity in calibration performance. A related point is that prediction models in this field need to be clearer with regard to how and exactly when included predictors should be measured.

For IPPIC models, summary predictive performance was promising, and net benefit was demonstrated in some data sets across clinically relevant thresholds of predicted risk. However, large heterogeneity remained in all performance statistics across data sets. Heterogeneity in calibration performance could be reduced if, when applying the models in practice, model parameters (e.g. intercept) could be recalibrated to each population and setting. This would require local data for recalibration and model updating.

Relevance to clinical practice

Existing models that were externally validated had poor calibration performance and their utility was limited, with no model identified that can be recommended for clinical use. The IPPIC models showed promising performance for predicting pre-eclampsia, in particular in both low- and middle-income countries where only clinical characteristics may be available, and in high-income countries where there is access to additional biochemical markers. However, on application, the predictive performance of the models needs to be improved by recalibration to particular settings and populations; this would require local data. Ultrasound markers did not add any additional information or improve the performance of the prediction models beyond the clinical characteristic only models. This suggests a lack of need for additional time or resources in carrying out these assessments for screening of women at risk of pre-eclampsia. The thresholds of risk on which decision-making is based are likely to vary with the planned intervention (aspirin or calcium), as well as following shared decision-making through discussions between the clinician and the woman.

Relevance to research

Validation, including examination of calibration heterogeneity, is still required for the models we could not validate. For these and the IPPIC models, we need validation in multiple large data sets across different settings and populations to properly assess their transportability.²⁴⁹ The impact of using the models in clinical practice needs to be evaluated beyond predicting pre-eclampsia, but also in the identification of women with pre-eclampsia who are also most likely to have severe complications such as HELLP syndrome, eclampsia, abruption or renal failure. The acceptability of the models to both women and health-care professionals needs to be assessed, including elucidation of their preferred threshold probability for treatment decisions. A decision-analytic model of resource implications, including the cost utilities of consequences of decisions for various false-positive and false-negative cases, is also needed. Updated models may be needed in local populations, for example using recalibration of the IPPIC models in local data sets, to improve calibration performance. Furthermore, additional strong predictors need to be identified to improve model performance and consistency. New cohorts need to standardise the predictors and outcomes measured, including their timing and measurement methods, to enable more homogenous data sets to be combined in IPD meta-analyses.

Conclusion

Among the 24 existing prediction models that could be validated in the IPD meta-analysis, generally their predictive performance was poor across data sets. To address this, IPPIC models were developed with adjustment for overfitting, which show good predictive performance on average across data sets and may have net benefit in singleton nulliparous populations in the UK. However, heterogeneity across settings is likely in calibration performance, and thus the models need to be recalibrated in local settings and populations of application. Ultrasound markers did not improve the predictive performance of the developed IPPIC clinical characteristic-only models. We did not identify any new predictors for our model development that were not considered previously in existing models. Further work is therefore needed to validate other models, identify new predictors and improve calibration performance in all settings of intended use.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review and appropriate agreements being in place.

References

1. Brown MA, Hague WM, Higgins J, Lowe S, McCowan L, Oats J, *et al.* The detection, investigation and management of hypertension in pregnancy: executive summary. *Aust N Z J Obstet Gynaecol* 2000;**40**:133–8. <https://doi.org/10.1111/j.1479-828x.2000.tb01136.x>
2. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet* 2005;**365**:785–99. [https://doi.org/10.1016/S0140-6736\(05\)17987-2](https://doi.org/10.1016/S0140-6736(05)17987-2)
3. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. *Obstet Gynecol* 2003;**102**:181–92. <https://doi.org/10.1097/00006250-200307000-00033>
4. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, *et al.* The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. *Pregnancy Hypertens* 2014;**4**:97–104. <https://doi.org/10.1016/j.pregphy.2014.02.001>
5. Staff AC, Benton SJ, von Dadelszen P, Roberts JM, Taylor RN, Powers RW, *et al.* Redefining preeclampsia using placenta-derived biomarkers. *Hypertension* 2013;**61**:932–42. <https://doi.org/10.1161/HYPERTENSIONAHA.111.00250>
6. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009;**33**:130–7. <https://doi.org/10.1053/j.semperi.2009.02.010>
7. Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. *BMJ* 2005;**331**:1113–17. <https://doi.org/10.1136/bmj.38629.587639.7C>
8. Iams JD, Goldenberg RL, Mercer BM, Moawad A, Thom E, Meis PJ, *et al.* The Preterm Prediction Study: recurrence risk of spontaneous preterm birth. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol* 1998;**178**:1035–40. [https://doi.org/10.1016/S0002-9378\(98\)70544-7](https://doi.org/10.1016/S0002-9378(98)70544-7)
9. Davies EL, Bell JS, Bhattacharya S. Preeclampsia and preterm delivery: a population-based case-control study. *Hypertens Pregnancy* 2016;**35**:510–19. <https://doi.org/10.1080/10641955.2016.1190846>
10. Tang LC, Kwok AC, Wong AY, Lee YY, Sun KO, So AP. Critical care in obstetrical patients: an eight-year review. *Chin Med J* 1997;**110**:936–41.
11. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006;**367**:1066–74. [https://doi.org/10.1016/S0140-6736\(06\)68397-9](https://doi.org/10.1016/S0140-6736(06)68397-9)
12. World Health Organization. *The World Health Report: 2005 – Make Every Mother and Child Count*. Geneva: WHO; 2005. URL: www.who.int/whr/2005/whr2005_en.pdf (accessed 6 December 2018).
13. Carty DM, Delles C, Dominiczak AF. Preeclampsia and future maternal health. *J Hypertens* 2010;**28**:1349–55. <https://doi.org/10.1097/HJH.0b013e32833a39d0>
14. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* 2007;**335**:974. <https://doi.org/10.1136/bmj.39335.385301.BE>
15. Thoulass JC, Robertson L, Denadai L, Black C, Crilly M, Iversen L, *et al.* Hypertensive disorders of pregnancy and adult offspring cardiometabolic outcomes: a systematic review of the literature and meta-analysis. *J Epidemiol Community Health* 2016;**70**:414–22. <https://doi.org/10.1136/jech-2015-205483>

16. Davis EF, Lazdam M, Lewandowski AJ, Worton SA, Kelly B, Kenworthy Y, *et al.* Cardiovascular risk factors in children and young adults born to preeclamptic pregnancies: a systematic review. *Pediatrics* 2012;**129**:e1552–61. <https://doi.org/10.1542/peds.2011-3093>
17. Tuovinen S, Eriksson JG, Kajantie E, Lahti J, Pesonen AK, Heinonen K, *et al.* Maternal hypertensive disorders in pregnancy and self-reported cognitive impairment of the offspring 70 years later: the Helsinki Birth Cohort Study. *Am J Obstet Gynecol* 2013;**208**:200.e1–9. <https://doi.org/10.1016/j.ajog.2012.12.017>
18. Tuovinen S, Räikkönen K, Kajantie E, Pesonen AK, Heinonen K, Osmond C, *et al.* Depressive symptoms in adulthood and intrauterine exposure to pre-eclampsia: the Helsinki Birth Cohort Study. *BJOG* 2010;**117**:1236–42. <https://doi.org/10.1111/j.1471-0528.2010.02634.x>
19. Crispi F, Domínguez C, Llurba E, Martín-Gallán P, Cabero L, Gratacós E. Placental angiogenic growth factors and uterine artery Doppler findings for characterization of different subsets in preeclampsia and in isolated intrauterine growth restriction. *Am J Obstet Gynecol* 2006;**195**:201–7. <https://doi.org/10.1016/j.ajog.2006.01.014>
20. Crispi F, Llurba E, Domínguez C, Martín-Gallán P, Cabero L, Gratacós E. Predictive value of angiogenic factors and uterine artery Doppler for early- versus late-onset pre-eclampsia and intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2008;**31**:303–9. <https://doi.org/10.1002/uog.5184>
21. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. *Hypertension* 2008;**52**:873–80. <https://doi.org/10.1161/HYPERTENSIONAHA.108.117358>
22. Redman CW, Sargent IL, Staff AC. IFPA Senior Award Lecture: making sense of pre-eclampsia – two placental causes of preeclampsia? *Placenta* 2014;(Suppl.):S20–5. <https://doi.org/10.1016/j.placenta.2013.12.008>
23. MacKay AP, Berg CJ, Atrash HK. Pregnancy-related mortality from preeclampsia and eclampsia. *Obstet Gynecol* 2001;**97**:533–8. <https://doi.org/10.1097/00006250-200104000-00011>
24. von Dadelszen P, Payne B, Li J, Ansermino JM, Broughton Pipkin F, Côté AM, *et al.* Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. *Lancet* 2011;**377**:219–27. [https://doi.org/10.1016/S0140-6736\(10\)61351-7](https://doi.org/10.1016/S0140-6736(10)61351-7)
25. von Dadelszen P, Magee LA, Roberts JM. Subclassification of preeclampsia. *Hypertens Pregnancy* 2003;**22**:143–8. <https://doi.org/10.1081/PRG-120021060>
26. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol* 2013;**209**:544.e1–544.e12. <https://doi.org/10.1016/j.ajog.2013.08.019>
27. Murphy DJ, Stirrat GM. Mortality and morbidity associated with early-onset preeclampsia. *Hypertens Pregnancy* 2000;**19**:221–31. <https://doi.org/10.1081/PRG-100100138>
28. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome) *Am J Obstet Gynecol* 1993;**169**:1000–6. [https://doi.org/10.1016/0002-9378\(93\)90043-I](https://doi.org/10.1016/0002-9378(93)90043-I)
29. Churchill D, Duley L. Interventionist versus expectant care for severe pre-eclampsia before term. *Cochrane Database Syst Rev* 2002;**3**:CD003106. <https://doi.org/10.1002/14651858.CD003106>
30. Mangham LJ, Petrou S, Doyle LW, Draper ES, Marlow N. The cost of preterm birth throughout childhood in England and Wales. *Pediatrics* 2009;**123**:e312–27. <https://doi.org/10.1542/peds.2008-1827>

31. Douglas KA, Redman CW. Eclampsia in the United Kingdom. *BMJ* 1994;**309**:1395–400. <https://doi.org/10.1136/bmj.309.6966.1395>
32. Sibai BM. Management of late preterm and early-term pregnancies complicated by mild gestational hypertension/pre-eclampsia. *Semin Perinatol* 2011;**35**:292–6. <https://doi.org/10.1053/j.semperi.2011.05.010>
33. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, *et al.* Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol* 2010;**116**:402–14. <https://doi.org/10.1097/AOG.0b013e3181e9322a>
34. Rolnik DL, Wright D, Poon LC, O’Gorman N, Syngelaki A, de Paco Matallana C, *et al.* Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017;**377**:613–22. <https://doi.org/10.1056/NEJMoa1704559>
35. National Institute for Health and Care Excellence. *Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy*. Clinical Guideline 107. London: National Institute for Health and Care Excellence; 2010. URL: www.nice.org.uk/guidance/cg107 (accessed 31 March 2016).
36. National Institute for Health and Care Excellence. *Hypertension in Pregnancy: Diagnosis and Management*. NICE Guideline 133. London: National Institute for Health and Care Excellence; 2019. URL: www.nice.org.uk/guidance/cg107
37. Townsend R, Khalil A, Premakumar Y, Allotey J, Snell KIE, Chan C, *et al.* Prediction of pre-eclampsia: review of reviews. *Ultrasound Obstet Gynecol* 2019;**54**:16–27. <https://doi.org/10.1002/uog.20117>
38. Allen RE, Rogozinska E, Cleverly K, Aquilina J, Thangaratnam S. Abnormal blood biomarkers in early pregnancy are associated with preeclampsia: a meta-analysis. *Eur J Obstet Gynecol Reprod Biol* 2014;**182**:194–201. <https://doi.org/10.1016/j.ejogrb.2014.09.027>
39. Velauthar L, Plana MN, Kalidindi M, Zamora J, Thilaganathan B, Illanes SE, *et al.* First-trimester uterine artery Doppler and adverse pregnancy outcome: a meta-analysis involving 55,974 women. *Ultrasound Obstet Gynecol* 2014;**43**:500–7. <https://doi.org/10.1002/uog.13275>
40. Conde-Agudelo A, Villar J, Lindheimer M. World Health Organization systematic review of screening tests for preeclampsia. *Obstet Gynecol* 2004;**104**:1367–91. <https://doi.org/10.1097/01.AOG.0000147599.47713.5d>
41. Giguère Y, Charland M, Bujold E, Bernard N, Grenier S, Rousseau F, *et al.* Combining biochemical and ultrasonographic markers in predicting preeclampsia: a systematic review. *Clin Chem* 2010;**56**:361–75. <https://doi.org/10.1373/clinchem.2009.134080>
42. North RA, McCowan LM, Dekker GA, Poston L, Chan EH, Stewart AW, *et al.* Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. *BMJ* 2011;**342**:d1875. <https://doi.org/10.1136/bmj.d1875>
43. Kleinrouweler CE, Cheong-See FM, Collins GS, Kwee A, Thangaratnam S, Khan KS, *et al.* Prognostic models in obstetrics: available, but far from applicable. *Am J Obstet Gynecol* 2016;**214**:79–90. <https://doi.org/10.1016/j.ajog.2015.06.013>
44. Meertens LJE, Scheepers HCJ, van Kuijk SMJ, Aardenburg R, van Dooren IMA, Langenveld J, *et al.* External validation and clinical usefulness of first trimester prediction models for the risk of preeclampsia: a prospective cohort study. *Fetal Diagn Ther* 2019;**45**:381–93. <https://doi.org/10.1159/000490385>
45. Farina A, Rapacchia G, Freni Sterrantino A, Pula G, Morano D, Rizzo N. Prospective evaluation of ultrasound and biochemical-based multivariable models for the prediction of late pre-eclampsia. *Prenat Diagn* 2011;**31**:1147–52. <https://doi.org/10.1002/pd.2849>

46. Herraiz I, Arbués J, Camaño I, Gómez-Montes E, Grañeras A, Galindo A. Application of a first-trimester prediction model for pre-eclampsia based on uterine arteries and maternal history in high-risk pregnancies. *Prenat Diagn* 2009;**29**:1123–9. <https://doi.org/10.1002/pd.2383>
47. Debray TP, Moons KG, Ahmed I, Koffijberg H, Riley RD. A framework for developing, implementing, and evaluating clinical prediction models in an individual participant data meta-analysis. *Stat Med* 2013;**32**:3158–80. <https://doi.org/10.1002/sim.5732>
48. Riley RD, Ensor J, Snell KI, Debray TP, Altman DG, Moons KG, Collins GS. External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. *BMJ* 2016;**353**:i3140. <https://doi.org/10.1136/bmj.i3140>
49. Debray TP, Riley RD, Rovers MM, Reitsma JB, Moons KG, Cochrane IPD Meta-analysis Methods group. Individual participant data (IPD) meta-analyses of diagnostic and prognostic modelling studies: guidance on their use. *PLOS Med* 2015;**12**:e1001886. <https://doi.org/10.1371/journal.pmed.1001886>
50. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010;**340**:c221. <https://doi.org/10.1136/bmj.c221>
51. Allotey J, Snell KIE, Chan C, Hooper R, Dodds J, Rogozinska E, et al. External validation, update and development of prediction models for pre-eclampsia using an Individual Participant Data (IPD) meta-analysis: the International Prediction of Pregnancy Complication Network (IPPIC pre-eclampsia) protocol. *Diagn Progn Res* 2017;**1**:16. <https://doi.org/10.1186/s41512-017-0016-z>
52. Snell KIE, Allotey J, Smuk M, Hooper R, Chan C, Ahmed A, et al. External validation of prognostic models predicting pre-eclampsia: individual participant data meta-analysis. *BMC Med* 2020;**18**:302. <https://doi.org/10.1186/s12916-020-01766-9>
53. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. *BMJ* 2009;**338**:b605. <https://doi.org/10.1136/bmj.b605>
54. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? *BMJ* 2009;**338**:b375. <https://doi.org/10.1136/bmj.b375>
55. Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: developing a prognostic model. *BMJ* 2009;**338**:b604. <https://doi.org/10.1136/bmj.b604>
56. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 2015;**162**:W1–73. <https://doi.org/10.7326/M14-0698>
57. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF, PRISMA-IPD Development Group. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD statement. *JAMA* 2015;**313**:1657–65. <https://doi.org/10.1001/jama.2015.3656>
58. *Accuracy of Clinical Characteristics, Biochemical and Ultrasound Markers in the Prediction of Pre-eclampsia: an Individual Participant Data (IPD) Meta-analysis*. PROSPERO CRD42015029349. 2015. URL: www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015029349 (accessed 27 March 2017).
59. Gardosi J, Clausson B, Francis A. The value of customised centiles in assessing perinatal mortality risk associated with parity and maternal size. *BJOG* 2009;**116**:1356–63. <https://doi.org/10.1111/j.1471-0528.2009.02245.x>
60. Ahmed A. New insights into the etiology of preeclampsia: identification of key elusive factors for the vascular complications. *Thromb Res* 2011;**127**(Suppl. 3):72–5. [https://doi.org/10.1016/S0049-3848\(11\)70020-2](https://doi.org/10.1016/S0049-3848(11)70020-2)

61. Bloomenthal D, von Dadelszen P, Liston R, Magee L, Tsang P. The effect of factor V Leiden carriage on maternal and fetal health. *CMAJ* 2002;**167**:48–54.
62. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. *BMJ* 2014;**348**:g2301. <https://doi.org/10.1136/bmj.g2301>
63. Cnossen JS, Morris RK, ter Riet G, Mol BW, van der Post JA, Coomarasamy A, *et al.* Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. *CMAJ* 2008;**178**:701–11. <https://doi.org/10.1503/cmaj.070430>
64. Gallos ID, Sivakumar K, Kilby MD, Coomarasamy A, Thangaratinam S, Vatish M. Pre-eclampsia is associated with, and preceded by, hypertriglyceridaemia: a meta-analysis. *BJOG* 2013;**120**:1321–32. <https://doi.org/10.1111/1471-0528.12375>
65. Kleinrouweler CE, Wiegerinck MM, Ris-Stalpers C, Bossuyt PM, van der Post JA, von Dadelszen P, *et al.* Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: a systematic review and meta-analysis. *BJOG* 2012;**119**:778–87. <https://doi.org/10.1111/j.1471-0528.2012.03311.x>
66. Leeftang MM, Cnossen JS, van der Post JA, Mol BW, Khan KS, ter Riet G. Accuracy of fibronectin tests for the prediction of pre-eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol* 2007;**133**:12–19. <https://doi.org/10.1016/j.ejogrb.2007.01.003>
67. Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, *et al.* Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling. *Health Technol Assess* 2008;**12**(6). <https://doi.org/10.3310/hta12060>
68. Morris RK, Cnossen JS, Langejans M, Robson SC, Kleijnen J, Ter Riet G, *et al.* Serum screening with Down's syndrome markers to predict pre-eclampsia and small for gestational age: systematic review and meta-analysis. *BMC Pregnancy Childbirth* 2008;**8**:33. <https://doi.org/10.1186/1471-2393-8-33>
69. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet* 2010;**376**:631–44. [https://doi.org/10.1016/S0140-6736\(10\)60279-6](https://doi.org/10.1016/S0140-6736(10)60279-6)
70. Thangaratinam S, Langenveld J, Mol BW, Khan KS. Prediction and primary prevention of pre-eclampsia. *Best Pract Res Clin Obstet Gynaecol* 2011;**25**:419–33. <https://doi.org/10.1016/j.bpobgyn.2011.02.008>
71. van der Tuuk K, Koopmans CM, Groen H, Aarnoudse JG, van den Berg PP, van Beek JJ, *et al.* Prediction of progression to a high risk situation in women with gestational hypertension or mild pre-eclampsia at term. *Aust N Z J Obstet Gynaecol* 2011;**51**:339–46. <https://doi.org/10.1111/j.1479-828X.2011.01311.x>
72. von Dadelszen P, Firoz T, Donnay F, Gordon R, Justus Hofmeyr G, Lalani S, *et al.* Preeclampsia in low and middle income countries-health services lessons learned from the PRE-EMPT (PRE-Eclampsia-Eclampsia Monitoring, Prevention and Treatment) project. *J Obstet Gynaecol Can* 2012;**34**:917–26. [https://doi.org/10.1016/S1701-2163\(16\)35405-6](https://doi.org/10.1016/S1701-2163(16)35405-6)
73. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013;**122**:1122–31.

74. von Dadelszen P, Sawchuck D, Justus Hofmeyr G, Magee LA, Bracken H, Mathai M, *et al.* PRE-EMPT (PRE-eclampsia-Eclampsia Monitoring, Prevention and Treatment): a low and middle income country initiative to reduce the global burden of maternal, fetal and infant death and disease related to pre-eclampsia. *Pregnancy Hypertens* 2013;**3**:199–202. <https://doi.org/10.1016/j.preghy.2013.06.002>
75. GONet: *The Global Obstetrics Network*. URL: www.globalobstetricsnetwork.org/ (accessed 14 March 2019).
76. Myatt L, Redman CW, Staff AC, Hansson S, Wilson ML, Laivuori H, *et al.* Strategy for standardization of preeclampsia research study design. *Hypertension* 2014;**63**:1293–301. <https://doi.org/10.1161/HYPERTENSIONAHA.113.02664>
77. Gardosi J, Francis A. *Customised Centile Calculator*. GROW version 8.0.4. Gestation Network; 2018. URL: www.gestation.net (accessed 14 February 2018).
78. Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS, *et al.* PROBAST: a tool to assess the risk of bias and applicability of prediction model studies. *Ann Intern Med* 2019;**170**:51–8. <https://doi.org/10.7326/M18-1376>
79. Resche-Rigon M, White IR. Multiple imputation by chained equations for systematically and sporadically missing multilevel data. *Stat Methods Med Res* 2018;**27**:1634–49. <https://doi.org/10.1177/0962280216666564>
80. Jolani S, Debray TP, Koffijberg H, van Buuren S, Moons KG. Imputation of systematically missing predictors in an individual participant data meta-analysis: a generalized approach using MICE. *Stat Med* 2015;**34**:1841–63. <https://doi.org/10.1002/sim.6451>
81. Meng XL. Multiple-imputation inferences with uncongenial sources of input. *Statist Sci* 1994;**9**:538–58. <https://doi.org/10.1214/ss/1177010269>
82. Little RJA, Rubin DB. *Statistical Analysis with Missing Data*. 2nd edn. New York, NY: John Wiley; 2002. <https://doi.org/10.1002/9781119013563>
83. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. 2nd edn. Hoboken, NJ: John Wiley & Sons; 2000. <https://doi.org/10.1002/0471722146>
84. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: Wiley; 1987. <https://doi.org/10.1002/9780470316696>
85. Snell KI, Ensor J, Debray TP, Moons KG, Riley RD. Meta-analysis of prediction model performance across multiple studies: which scale helps ensure between-study normality for the C-statistic and calibration measures? *Stat Methods Med Res* 2018;**27**:3505–22. <https://doi.org/10.1177/0962280217705678>
86. Debray TP, Damen JA, Snell KI, Ensor J, Hooft L, Reitsma JB, *et al.* A guide to systematic review and meta-analysis of prediction model performance. *BMJ* 2017;**356**:i6460. <https://doi.org/10.1136/bmj.i6460>
87. Snell KI, Hua H, Debray TP, Ensor J, Look MP, Moons KG, Riley RD. Multivariate meta-analysis of individual participant data helped externally validate the performance and implementation of a prediction model. *J Clin Epidemiol* 2016;**69**:40–50. <https://doi.org/10.1016/j.jclinepi.2015.05.009>
88. Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. *Stat Med* 2001;**20**:3875–89. <https://doi.org/10.1002/sim.1009>
89. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making* 2006;**26**:565–74. <https://doi.org/10.1177/0272989X06295361>
90. Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. *BMJ* 2016;**352**:i6. <https://doi.org/10.1136/bmj.i6>

91. Quartagno M, Carpenter J. *Multilevel Joint Modelling Multiple Imputation: Package 'jomo', Version 2.6-6, License GPL-2*. URL: <https://cran.r-project.org/web/packages/jomo/jomo.pdf> (accessed 3 May 2018).
92. Quartagno M, Carpenter JR. Multiple imputation for IPD meta-analysis: allowing for heterogeneity and studies with missing covariates. *Stat Med* 2016;**35**:2938–54. <https://doi.org/10.1002/sim.6837>
93. Sauerbrei W. The use of resampling methods to simplify regression models in medical statistics. *J Royal Stat Soc* 1999;**48**:313–29. <https://doi.org/10.1111/1467-9876.00155>
94. Heinze G, Wallisch C, Dunkler D. Variable selection – a review and recommendations for the practicing statistician. *Biom J* 2018;**60**:431–49. <https://doi.org/10.1002/bimj.201700067>
95. Wood AM, Royston P, White IR. The estimation and use of predictions for the assessment of model performance using large samples with multiply imputed data. *Biom J* 2015;**57**:614–32. <https://doi.org/10.1002/bimj.201400004>
96. Royston P, Parmar MK, Sylvester R. Construction and validation of a prognostic model across several studies, with an application in superficial bladder cancer. *Stat Med* 2004;**23**:907–26. <https://doi.org/10.1002/sim.1691>
97. Harrell FE. *Regression Modeling Strategies, with Applications to Linear Models, Logistic Regression, and Survival Analysis*. 2nd edn. New York, NY: Springer; 2015. https://doi.org/10.1007/978-3-319-19425-7_10
98. Steyerberg EW. *Clinical Prediction Models. A Practical Approach to Development, Validation, and Updating*. New York, NY: Springer; 2009.
99. Riley RD, van der Windt D, Croft P, Moons KGM, editors. *Prognosis Research in Healthcare: Concepts, Methods and Impact*. Oxford: Oxford University Press; 2019. <https://doi.org/10.1093/med/9780198796619.001.0001>
100. IntHout J, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open* 2016;**6**:e010247. <https://doi.org/10.1136/bmjopen-2015-010247>
101. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol* 2014;**14**:25. <https://doi.org/10.1186/1471-2288-14-25>
102. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. *Stat Med* 2003;**22**:2693–710. <https://doi.org/10.1002/sim.1482>
103. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, et al. Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol* 2013;**42**:97–110. <https://doi.org/10.1093/ije/dys066>
104. *Better Outcomes Registry & Network (BORN) Ontario*. URL: www.bornontario.ca/en/about-born/ (accessed 14 March 2019).
105. Japan Society of Obstetrics and Gynecology. URL: www.jsog.or.jp/modules/en/index.php?content_id=1 (accessed 14 March 2019).
106. Carter J, Seed PT, Tribe RM, David A, Lachelin G, Shennan AH, et al. Saliva progesterone for prediction of spontaneous preterm birth: the POPPY study. *Pregnancy Outcome Poster Abstracts. BJOG* 2017;**124**:122–54. <https://doi.org/10.1111/1471-0528.14589>
107. Al-Amin A, Rolnik DL, Black C, White A, Stolarek C, Brennecke S, da Silva Costa F. Accuracy of second trimester prediction of preterm preeclampsia by three different screening algorithms. *Aust N Z J Obstet Gynaecol* 2018;**58**:192–6. <https://doi.org/10.1111/ajo.12689>

REFERENCES

108. Allen RE, Zamora J, Arroyo-Manzano D, Velauthar L, Allotey J, Thangaratinam S, Aquilina J. External validation of preexisting first trimester preeclampsia prediction models. *Eur J Obstet Gynecol Reprod Biol* 2017;**217**:119–25. <https://doi.org/10.1016/j.ejogrb.2017.08.031>
109. Andersen LB, Dechend R, Jørgensen JS, Luef BM, Nielsen J, Barington T, Christesen HT. Prediction of preeclampsia with angiogenic biomarkers. Results from the prospective Odense Child Cohort. *Hypertens Pregnancy* 2016;**35**:405–19. <https://doi.org/10.3109/10641955.2016.1167219>
110. Antsaklis A, Daskalakis G, Tzortzis E, Michalas S. The effect of gestational age and placental location on the prediction of pre-eclampsia by uterine artery Doppler velocimetry in low-risk nulliparous women. *Ultrasound Obstet Gynecol* 2000;**16**:635–9. <https://doi.org/10.1046/j.1469-0705.2000.00288.x>
111. Arenas J, Fernández-iñarea J, Rodríguez-mon C, Duplá B, Díez E, González-garcía A. Cribado con doppler de las arterias uterinas para la predicción de complicaciones de la gestación. *Clínicae Investigación en Ginecología y Obstetricia* 2003;**30**:178–84. [https://doi.org/10.1016/S0210-573X\(03\)77255-4](https://doi.org/10.1016/S0210-573X(03)77255-4)
112. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA, PARIS Collaborative Group. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet* 2007;**369**:1791–8. [https://doi.org/10.1016/S0140-6736\(07\)60712-0](https://doi.org/10.1016/S0140-6736(07)60712-0)
113. Audibert F, Boucoiran I, An N, Aleksandrov N, Delvin E, Bujold E, Rey E. Screening for preeclampsia using first-trimester serum markers and uterine artery Doppler in nulliparous women. *Am J Obstet Gynecol* 2010;**203**:383.e1–8. <https://doi.org/10.1016/j.ajog.2010.06.014>
114. Ayorinde AA, Wilde K, Lemon J, Campbell D, Bhattacharya S. Data resource profile: the Aberdeen Maternity and Neonatal Databank (AMND). *Int J Epidemiol* 2016;**45**:389–94. <https://doi.org/10.1093/ije/dyv356>
115. Baschat AA, Magder LS, Doyle LE, Atlas RO, Jenkins CB, Blitzer MG. Prediction of preeclampsia utilizing the first trimester screening examination. *Am J Obstet Gynecol* 2014;**211**:514.e1–7. <https://doi.org/10.1016/j.ajog.2014.04.018>
116. Brown MA, Mackenzie C, Dunsmuir W, Roberts L, Ikin K, Matthews J, et al. Can we predict recurrence of pre-eclampsia or gestational hypertension? *BJOG* 2007;**114**:984–93. <https://doi.org/10.1111/j.1471-0528.2007.01376.x>
117. Cameroni I, Roncaglia N, Crippa I, Orsenigo F, Locatelli A, Vergani P, et al. P32.05: Uterine artery Doppler in a risk population: what's its role in the prediction of severe pregnancy complications? *Ultrasound Obstet Gynecol* 2008;**32**:421–2. <https://doi.org/10.1002/uog.5992>
118. Caradeux J, Serra R, Nien JK, Pérez-Sepulveda A, Schepeler M, Guerra F, et al. First trimester prediction of early onset preeclampsia using demographic, clinical, and sonographic data: a cohort study. *Prenat Diagn* 2013;**33**:732–6. <https://doi.org/10.1002/pd.4113>
119. Carbillon L. The imbalance of circulating angiogenic/antiangiogenic factors is mild or absent in obese women destined to develop preeclampsia. *Hypertens Pregnancy* 2014;**33**:524. <https://doi.org/10.3109/10641955.2013.872252>
120. Caritis S, Sibai B, Hauth J, Lindheimer MD, Klebanoff M, Thom E, et al. Low-dose aspirin to prevent preeclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med* 1998;**338**:701–5. <https://doi.org/10.1056/NEJM199803123381101>
121. Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, Hunt BJ, et al. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. *Lancet* 1999;**354**:810–16. [https://doi.org/10.1016/S0140-6736\(99\)80010-5](https://doi.org/10.1016/S0140-6736(99)80010-5)

122. Chiswick C, Reynolds RM, Denison F, Drake AJ, Forbes S, Newby DE, *et al.* Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2015;**3**:778–86. [https://doi.org/10.1016/S2213-8587\(15\)00219-3](https://doi.org/10.1016/S2213-8587(15)00219-3)
123. Conserva V, Muggiasca M, Arrigoni L, Mantegazza V, Rossi E, Ferrazzi E. Recurrence and severity of abnormal pregnancy outcome in patients treated by low-molecular-weight heparin: a prospective pilot study. *J Matern Fetal Neonatal Med* 2012;**25**:1467–73. <https://doi.org/10.3109/14767058.2011.643326>
124. Facchinetti F, Marozio L, Frusca T, Grandone E, Venturini P, Tiscia GL, *et al.* Maternal thrombophilia and the risk of recurrence of preeclampsia. *Am J Obstet Gynecol* 2009;**200**:46.e1–5. <https://doi.org/10.1016/j.ajog.2008.07.032>
125. Figueiró-Filho EA, Oliveira VMd, Coelho LR, Breda I. Marcadores séricos de trombofilias hereditárias e anticorpos antifosfolípidos em gestantes com antecedentes de pré-eclâmpsia grave. *Revista Brasileira de Ginecologia e Obstetrícia* 2012;**34**:40–6. <https://doi.org/10.1590/S0100-72032012000100008>
126. Giguère Y, Massé J, Thériault S, Bujold E, Lafond J, Rousseau F, Forest JC. Screening for pre-eclampsia early in pregnancy: performance of a multivariable model combining clinical characteristics and biochemical markers. *BJOG* 2015;**122**:402–10. <https://doi.org/10.1111/1471-0528.13050>
127. Girchenko P, Lahti M, Tuovinen S, Savolainen K, Lahti J, Binder EB, *et al.* Cohort profile: prediction and prevention of preeclampsia and intrauterine growth restriction (PREDO) study. *Int J Epidemiol* 2017;**46**:1380–1381g. <https://doi.org/10.1093/ije/dyw154>
128. Goetzinger KR, Singla A, Gerkowicz S, Dicke JM, Gray DL, Odibo AO. Predicting the risk of pre-eclampsia between 11 and 13 weeks' gestation by combining maternal characteristics and serum analytes, PAPP-A and free β -hCG. *Prenat Diagn* 2010;**30**:1138–42. <https://doi.org/10.1002/pd.2627>
129. Goffinet F, Aboulker D, Paris-Llado J, Bucourt M, Uzan M, Papiernik E, Bréart G. Screening with a uterine Doppler in low risk pregnant women followed by low dose aspirin in women with abnormal results: a multicenter randomised controlled trial. *BJOG* 2001;**108**:510–18. <https://doi.org/10.1111/j.1471-0528.2001.00116.x>
130. Gurgel Alves JA, Praciano de Sousa PC, Bezerra Maia e Holanda Moura S, Kane SC, da Silva Costa F. First-trimester maternal ophthalmic artery Doppler analysis for prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2014;**44**:411–18. <https://doi.org/10.1002/uog.13338>
131. Holzman C, Bullen B, Fisher R, Paneth N, Reuss L, Prematurity Study Group. Pregnancy outcomes and community health: the POUCH study of preterm delivery. *Paediatr Perinat Epidemiol* 2001;**15**(Suppl. 2):136–58. <https://doi.org/10.1046/j.1365-3016.2001.00014.x>
132. Huang T, Hoffman B, Meschino W, Kingdom J, Okun N. Prediction of adverse pregnancy outcomes by combinations of first and second trimester biochemistry markers used in the routine prenatal screening of Down syndrome. *Prenat Diagn* 2010;**30**:471–7. <https://doi.org/10.1002/pd.2505>
133. Jääskeläinen T, Heinonen S, Hämäläinen E, Pulkki K, Romppanen J, Laivuori H, FINNPEC. Angiogenic profile in the Finnish Genetics of Pre-Eclampsia Consortium (FINNPEC) cohort. *Pregnancy Hypertens* 2018;**14**:252–9. <https://doi.org/10.1016/j.preghy.2018.03.004>
134. Jaddoe VW, van Duijn CM, Franco OH, van der Heijden AJ, van Iizendoorn MH, de Jongste JC, *et al.* The Generation R Study: design and cohort update 2012. *Eur J Epidemiol* 2012;**27**:739–56. <https://doi.org/10.1007/s10654-012-9735-1>

135. Jenum AK, Sletner L, Voldner N, Vangen S, Mørkrid K, Andersen LF, *et al.* The STORK Groruddalen research programme: a population-based cohort study of gestational diabetes, physical activity, and obesity in pregnancy in a multiethnic population. Rationale, methods, study population, and participation rates. *Scand J Public Health* 2010;**38**(Suppl. 5):60–70. <https://doi.org/10.1177/1403494810378921>
136. Olsen J, Melbye M, Olsen SF, Sørensen TI, Aaby P, Andersen AM, *et al.* The Danish National Birth Cohort – its background, structure and aim. *Scand J Public Health* 2001;**29**:300–7. <https://doi.org/10.1177/14034948010290040201>
137. Khan F, Belch JJ, MacLeod M, Mires G. Changes in endothelial function precede the clinical disease in women in whom preeclampsia develops. *Hypertension* 2005;**46**:1123–8. <https://doi.org/10.1161/01.HYP.0000186328.90667.95>
138. Langenveld J, Buttinger A, van der Post J, Wolf H, Mol BW, Ganzevoort W. Recurrence risk and prediction of a delivery under 34 weeks of gestation after a history of a severe hypertensive disorder. *BJOG* 2011;**118**:589–95. <https://doi.org/10.1111/j.1471-0528.2010.02842.x>
139. Lecarpentier E, Tsatsaris V, Goffinet F, Cabrol D, Sibai B, Haddad B. Risk factors of superimposed preeclampsia in women with essential chronic hypertension treated before pregnancy. *PLOS ONE* 2013;**8**:e62140. <https://doi.org/10.1371/journal.pone.0062140>
140. Llurba E, Carreras E, Gratacós E, Juan M, Astor J, Vives A, *et al.* Maternal history and uterine artery Doppler in the assessment of risk for development of early- and late-onset preeclampsia and intrauterine growth restriction. *Obstet Gynecol Int* 2009;**2009**:275613. <https://doi.org/10.1155/2009/275613>
141. Lykke JA, Paidas MJ, Langhoff-Roos J. Recurring complications in second pregnancy. *Obstet Gynecol* 2009;**113**:1217–24. <https://doi.org/10.1097/AOG.0b013e3181a66f2d>
142. Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C, MoBa Study Group. Cohort profile: the Norwegian Mother and Child cohort study (MoBa). *Int J Epidemiol* 2006;**35**:1146–50. <https://doi.org/10.1093/ije/dyl170>
143. Makrides M, Gibson RA, McPhee AJ, Yelland L, Quinlivan J, Ryan P, DOMInO Investigative Team. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. *JAMA* 2010;**304**:1675–83. <https://doi.org/10.1001/jama.2010.1507>
144. Massé J, Forest JC, Moutquin JM, Marcoux S, Brideau NA, Bélanger M. A prospective study of several potential biologic markers for early prediction of the development of preeclampsia. *Am J Obstet Gynecol* 1993;**169**:501–8. [https://doi.org/10.1016/0002-9378\(93\)90608-L](https://doi.org/10.1016/0002-9378(93)90608-L)
145. Mbah AK, Sharma PP, Alio AP, Fombo DW, Bruder K, Salihu HM. Previous cesarean section, gestational age at first delivery and subsequent risk of pre-eclampsia in obese mothers. *Arch Gynecol Obstet* 2012;**285**:1375–81. <https://doi.org/10.1007/s00404-011-2161-x>
146. Mone F, Mulcahy C, McParland P, Stanton A, Culliton M, Downey P, *et al.* An open-label randomized-controlled trial of low dose aspirin with an early screening test for pre-eclampsia and growth restriction (TEST): trial protocol. *Contemp Clin Trials* 2016;**49**:143–8. <https://doi.org/10.1016/j.cct.2016.07.003>
147. Odibo AO, Zhong Y, Goetzinger KR, Odibo L, Bick JL, Bower CR, Nelson DM. First-trimester placental protein 13, PAPP-A, uterine artery Doppler and maternal characteristics in the prediction of pre-eclampsia. *Placenta* 2011;**32**:598–602. <https://doi.org/10.1016/j.placenta.2011.05.006>

148. Ohkuchi A, Minakami H, Sato I, Mori H, Nakano T, Tateno M. Predicting the risk of pre-eclampsia and a small-for-gestational-age infant by quantitative assessment of the diastolic notch in uterine artery flow velocity waveforms in unselected women. *Ultrasound Obstet Gynecol* 2000;**16**:171–8. <https://doi.org/10.1046/j.1469-0705.2000.00192.x>
149. Poston L, Bell R, Croker H, Flynn AC, Godfrey KM, Goff L, *et al*. Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol* 2015;**3**:767–77. [https://doi.org/10.1016/S2213-8587\(15\)00227-2](https://doi.org/10.1016/S2213-8587(15)00227-2)
150. Poston L, Briley AL, Seed PT, Kelly FJ, Shennan AH, Vitamins in Pre-eclampsia (VIP) Trial Consortium. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. *Lancet* 2006;**367**:1145–54. [https://doi.org/10.1016/S0140-6736\(06\)68433-X](https://doi.org/10.1016/S0140-6736(06)68433-X)
151. Prefumo F, Fratelli N, Ganapathy R, Bhide A, Frusca T, Thilaganathan B. First trimester uterine artery Doppler in women with previous pre-eclampsia. *Acta Obstet Gynecol Scand* 2008;**87**:1271–5. <https://doi.org/10.1080/00016340802460347>
152. Rang S, van Montfrans GA, Wolf H. Serial hemodynamic measurement in normal pregnancy, preeclampsia, and intrauterine growth restriction. *Am J Obstet Gynecol* 2008;**198**:519.e1–9. <https://doi.org/10.1016/j.ajog.2007.11.014>
153. Rocha RS, Gurgel Alves JA, Bezerra Maia e Holanda Moura S, Araujo Júnior E, Peixoto AB, Santana EFM, *et al*. Simple approach based on maternal characteristics and mean arterial pressure for the prediction of preeclampsia in the first trimester of pregnancy. *J Perinat Med* 2017;**45**:843–9. <https://doi.org/10.1515/jpm-2016-0418>
154. Rocha RS, Gurgel Alves JA, Bezerra Maia e Holanda Moura S, Araujo Júnior E, Martins WP, Vasconcelos CTM, *et al*. Comparison of three algorithms for prediction preeclampsia in the first trimester of pregnancy. *Pregnancy Hypertens* 2017;**10**:113–17. <https://doi.org/10.1016/j.preghy.2017.07.146>
155. Rumbold AR, Crowther CA, Haslam RR, Dekker GA, Robinson JS, ACTS Study Group. Vitamins C and E and the risks of preeclampsia and perinatal complications. *N Engl J Med* 2006;**354**:1796–806. <https://doi.org/10.1056/NEJMoa054186>
156. Salim R, Czarnowicki T, Nachum Z, Shalev E. The impact of close surveillance on pregnancy outcome among women with a prior history of antepartum complications attributed to thrombosis: a cohort study. *Reprod Biol Endocrinol* 2008;**6**:55. <https://doi.org/10.1186/1477-7827-6-55>
157. Savitri AI, Zuithoff P, Browne JL, Amelia D, Baharuddin M, Grobbee DE, Uiterwaal CS. Does pre-pregnancy BMI determine blood pressure during pregnancy? A prospective cohort study. *BMJ Open* 2016;**6**:e011626. <https://doi.org/10.1136/bmjopen-2016-011626>
158. Ferrazzani S, D'Alessio MC, Fatigante G, Soreca G, De Carolis S, Paradisi G, *et al*. Prophylaxis of recurrent preeclampsia: low-molecular-weight heparin plus low-dose aspirin versus low-dose aspirin alone. *Hypertens Pregnancy* 2006;**25**:115–27. <https://doi.org/10.1080/10641950600745517>
159. Sibai BM, Caritis SN, Thom E, Klebanoff M, McNellis D, Rocco L, *et al*. Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med* 1993;**329**:1213–8. <https://doi.org/10.1056/NEJM199310213291701>
160. Skråstad RB, Hov GG, Blaas HG, Romundstad PR, Salvesen KÅ. Risk assessment for preeclampsia in nulliparous women at 11–13 weeks gestational age: prospective evaluation of two algorithms. *BJOG* 2015;**122**:1781–8. <https://doi.org/10.1111/1471-0528.13194>

161. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. *Lancet* 2015;**386**:2089–97. [https://doi.org/10.1016/S0140-6736\(15\)00131-2](https://doi.org/10.1016/S0140-6736(15)00131-2)
162. Staff AC, Braekke K, Harsem NK, Lyberg T, Holthe MR. Circulating concentrations of sFlt1 (soluble fms-like tyrosine kinase 1) in fetal and maternal serum during pre-eclampsia. *Eur J Obstet Gynecol Reprod Biol* 2005;**122**:33–9. <https://doi.org/10.1016/j.ejogrb.2004.11.015>
163. Stirrup OT, Khalil A, D'Antonio F, Thilaganathan B, Southwest Thames Obstetric Research Collaborative (STORK). Fetal growth reference ranges in twin pregnancy: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort. *Ultrasound Obstet Gynecol* 2015;**45**:301–7. <https://doi.org/10.1002/uog.14640>
164. Trogstad L, Skrondal A, Stoltenberg C, Magnus P, Nesheim BI, Eskild A. Recurrence risk of preeclampsia in twin and singleton pregnancies. *Am J Med Genet A* 2004;**126A**:41–5. <https://doi.org/10.1002/ajmg.a.20512>
165. Van Der Linden EL, Browne JL, Vissers KM, Antwi E, Agyepong IA, Grobbee DE, Klipstein-Grobusch K. Maternal body mass index and adverse pregnancy outcomes: a Ghanaian cohort study. *Obesity* 2016;**24**:215–22. <https://doi.org/10.1002/oby.21210>
166. van Kuijk SM, Delahaije DH, Dirksen CD, Scheepers HC, Spaanderman ME, Ganzevoort W, *et al.* External validation of a model for periconceptual prediction of recurrent early-onset preeclampsia. *Hypertens Pregnancy* 2014;**33**:265–76. <https://doi.org/10.3109/10641955.2013.872253>
167. van Kuijk SM, Nijdam ME, Janssen KJ, Sep SJ, Peeters LL, Delahaije DH, *et al.* A model for preconceptional prediction of recurrent early-onset preeclampsia: derivation and internal validation. *Reprod Sci* 2011;**18**:1154–9. <https://doi.org/10.1177/1933719111410708>
168. van Oostwaard MF, Langenveld J, Bijloo R, Wong KM, Scholten I, Loix S, *et al.* Prediction of recurrence of hypertensive disorders of pregnancy between 34 and 37 weeks of gestation: a retrospective cohort study. *BJOG* 2012;**119**:840–7. <https://doi.org/10.1111/j.1471-0528.2012.03312.x>
169. van Oostwaard MF, Langenveld J, Schuit E, Wigny K, Van Susante H, Beune I, *et al.* Prediction of recurrence of hypertensive disorders of pregnancy in the term period, a retrospective cohort study. *Pregnancy Hypertens* 2014;**4**:194–202. <https://doi.org/10.1016/j.preghy.2014.04.001>
170. Vatten LJ, Eskild A, Nilsen TI, Jeansson S, Jenum PA, Staff AC. Changes in circulating level of angiogenic factors from the first to second trimester as predictors of preeclampsia. *Am J Obstet Gynecol* 2007;**196**:239.e1–6. <https://doi.org/10.1016/j.ajog.2006.10.909>
171. Verlohren S, Galindo A, Schlembach D, Zeisler H, Herraiz I, Moertl MG, *et al.* An automated method for the determination of the sFlt-1/PIGF ratio in the assessment of preeclampsia. *Am J Obstet Gynecol* 2010;**202**:161.e1–161.e11. <https://doi.org/10.1016/j.ajog.2009.09.016>
172. Verlohren S, Herraiz I, Lapaire O, Schlembach D, Moertl M, Zeisler H, *et al.* The sFlt-1/PIGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. *Am J Obstet Gynecol* 2012;**206**:58.e1–8. <https://doi.org/10.1016/j.ajog.2011.07.037>
173. Vinter CA, Jensen DM, Ovesen P, Beck-Nielsen H, Jørgensen JS. The LiP (Lifestyle in Pregnancy) study: a randomized controlled trial of lifestyle intervention in 360 obese pregnant women. *Diabetes Care* 2011;**34**:2502–7. <https://doi.org/10.2337/dc11-1150>

174. Vollebregt KC, Gisolf J, Guelen I, Boer K, van Montfrans G, Wolf H. Limited accuracy of the hyperbaric index, ambulatory blood pressure and sphygmomanometry measurements in predicting gestational hypertension and preeclampsia. *J Hypertens* 2010;**28**:127–34. <https://doi.org/10.1097/HJH.0b013e32833266fc>
175. Widmer M, Cuesta C, Khan KS, Conde-Agudelo A, Carroli G, Fusey S, et al. Accuracy of angiogenic biomarkers at ≤ 20 weeks' gestation in predicting the risk of pre-eclampsia: a WHO multicentre study. *Pregnancy Hypertens* 2015;**5**:330–8. <https://doi.org/10.1016/j.preghy.2015.09.004>
176. Wright E, Audette MC, Ye XY, Keating S, Hoffman B, Lye SJ, et al. Maternal vascular malperfusion and adverse perinatal outcomes in low-risk nulliparous women. *Obstet Gynecol* 2017;**130**:1112–20. <https://doi.org/10.1097/AOG.0000000000002264>
177. Wright J, Small N, Raynor P, Tuffnell D, Bhopal R, Cameron N, et al. Cohort Profile: the Born in Bradford multi-ethnic family cohort study. *Int J Epidemiol* 2013;**42**:978–91. <https://doi.org/10.1093/ije/dys112>
178. Zhang J, Troendle JF, Levine RJ. Risks of hypertensive disorders in the second pregnancy. *Paediatr Perinat Epidemiol* 2001;**15**:226–31. <https://doi.org/10.1046/j.1365-3016.2001.00347.x>
179. Cnossen JS, Leeflang MM, de Haan EE, Mol BW, van der Post JA, Khan KS, ter Riet G. Accuracy of body mass index in predicting pre-eclampsia: bivariate meta-analysis. *BJOG* 2007;**114**:1477–85. <https://doi.org/10.1111/j.1471-0528.2007.01483.x>
180. O'Brien TE, Ray JG, Chan WS. Maternal body mass index and the risk of preeclampsia: a systematic overview. *Epidemiology* 2003;**14**:368–74. <https://doi.org/10.1097/00001648-200305000-00020>
181. Wang Z, Wang P, Liu H, He X, Zhang J, Yan H, et al. Maternal adiposity as an independent risk factor for pre-eclampsia: a meta-analysis of prospective cohort studies. *Obes Rev* 2013;**14**:508–21. <https://doi.org/10.1111/obr.12025>
182. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ* 2005;**330**:565. <https://doi.org/10.1136/bmj.38380.674340.E0>
183. Alpoim PN, de Barros Pinheiro M, Junqueira DR, Freitas LG, das Graças Carvalho M, Fernandes AP, et al. Preeclampsia and ABO blood groups: a systematic review and meta-analysis. *Mol Biol Rep* 2013;**40**:2253–61. <https://doi.org/10.1007/s11033-012-2288-2>
184. England L, Zhang J. Smoking and risk of preeclampsia: a systematic review. *Front Biosci* 2007;**12**:2471–83. <https://doi.org/10.2741/2248>
185. Rebelo F, Schlüssel MM, Vaz JS, Franco-Sena AB, Pinto TJ, Bastos FI, et al. C-reactive protein and later preeclampsia: systematic review and meta-analysis taking into account the weight status. *J Hypertens* 2013;**31**:16–26. <https://doi.org/10.1097/HJH.0b013e32835b0556>
186. Luo ZC, An N, Xu HR, Larante A, Audibert F, Fraser WD. The effects and mechanisms of primiparity on the risk of pre-eclampsia: a systematic review. *Paediatr Perinat Epidemiol* 2007;**21**(Suppl. 1):36–45. <https://doi.org/10.1111/j.1365-3016.2007.00836.x>
187. Cnossen JS, Vollebregt KC, de Vrieze N, ter Riet G, Mol BW, Franx A, et al. Accuracy of mean arterial pressure and blood pressure measurements in predicting pre-eclampsia: systematic review and meta-analysis. *BMJ* 2008;**336**:1117–20. <https://doi.org/10.1136/bmj.39540.522049.BE>
188. Sgolastra F, Petrucci A, Severino M, Gatto R, Monaco A. Relationship between periodontitis and pre-eclampsia: a meta-analysis. *PLOS ONE* 2013;**8**:e71387. <https://doi.org/10.1371/journal.pone.0071387>
189. Kunnen A, van Doormaal JJ, Abbas F, Aarnoudse JG, van Pampus MG, Faas MM. Periodontal disease and pre-eclampsia: a systematic review. *J Clin Periodontol* 2010;**37**:1075–87. <https://doi.org/10.1111/j.1600-051X.2010.01636.x>

190. Morris RK, Riley RD, Doug M, Deeks JJ, Kilby MD. Diagnostic accuracy of spot urinary protein and albumin to creatinine ratios for detection of significant proteinuria or adverse pregnancy outcome in patients with suspected pre-eclampsia: systematic review and meta-analysis. *BMJ* 2012;**345**:e4342. <https://doi.org/10.1136/bmj.e4342>
191. Sanchez-Ramos L, Gillen G, Zamora J, Stenyakina A, Kaunitz AM. The protein-to-creatinine ratio for the prediction of significant proteinuria in patients at risk for preeclampsia: a meta-analysis. *Ann Clin Lab Sci* 2013;**43**:211–20.
192. Wolf HT, Owe KM, Juhl M, Hegaard HK. Leisure time physical activity and the risk of pre-eclampsia: a systematic review. *Matern Child Health J* 2014;**18**:899–910. <https://doi.org/10.1007/s10995-013-1316-8>
193. Palmer KT, Bonzini M, Harris EC, Linaker C, Bonde JP. Work activities and risk of prematurity, low birth weight and pre-eclampsia: an updated review with meta-analysis. *Occup Environ Med* 2013;**70**:213–22. <https://doi.org/10.1136/oemed-2012-101032>
194. Bonzini M, Coggon D, Palmer KT. Risk of prematurity, low birthweight and pre-eclampsia in relation to working hours and physical activities: a systematic review. *Occup Environ Med* 2007;**64**:228–43. <https://doi.org/10.1136/oem.2006.026872>
195. Cnossen JS, de Ruyter-Hanhijärvi H, van der Post JA, Mol BW, Khan KS, ter Riet G. Accuracy of serum uric acid determination in predicting pre-eclampsia: a systematic review. *Acta Obstet Gynecol Scand* 2006;**85**:519–25. <https://doi.org/10.1080/00016340500342037>
196. Chien PF, Arnott N, Gordon A, Owen P, Khan KS. How useful is uterine artery Doppler flow velocimetry in the prediction of pre-eclampsia, intrauterine growth retardation and perinatal death? An overview. *BJOG* 2000;**107**:196–208. <https://doi.org/10.1111/j.1471-0528.2000.tb11690.x>
197. Kleinrouweler CE, Bossuyt PM, Thilaganathan B, Vollebregt KC, Arenas Ramírez J, Ohkuchi A, et al. Value of adding second-trimester uterine artery Doppler to patient characteristics in identification of nulliparous women at increased risk for pre-eclampsia: an individual patient data meta-analysis. *Ultrasound Obstet Gynecol* 2013;**42**:257–67. <https://doi.org/10.1002/uog.12435>
198. Pedrosa AC, Matias A. Screening for pre-eclampsia: a systematic review of tests combining uterine artery Doppler with other markers. *J Perinat Med* 2011;**39**:619–35. <https://doi.org/10.1515/JPM.2011.077>
199. Kosmas IP, Tatsioni A, Ioannidis JP. Association of Leiden mutation in factor V gene with hypertension in pregnancy and pre-eclampsia: a meta-analysis. *J Hypertens* 2003;**21**:1221–8. <https://doi.org/10.1097/00004872-200307000-00002>
200. Dudding T, Heron J, Thakkestian A, Nurk E, Golding J, Pembrey M, et al. Factor V Leiden is associated with pre-eclampsia but not with fetal growth restriction: a genetic association study and meta-analysis. *J Thromb Haemost* 2008;**6**:1869–75. <https://doi.org/10.1111/j.1538-7836.2008.03134.x>
201. Rodger MA, Betancourt MT, Clark P, Lindqvist PG, Dizon-Townson D, Said J, et al. The association of factor V Leiden and prothrombin gene mutation and placenta-mediated pregnancy complications: a systematic review and meta-analysis of prospective cohort studies. *PLOS Med* 2010;**7**:e1000292. <https://doi.org/10.1371/journal.pmed.1000292>
202. Xia XP, Chang WW, Cao YX. Meta-analysis of the methylenetetrahydrofolate reductase C677T polymorphism and susceptibility to pre-eclampsia. *Hypertens Res* 2012;**35**:1129–34. <https://doi.org/10.1038/hr.2012.117>
203. Kosmas IP, Tatsioni A, Ioannidis JP. Association of C677T polymorphism in the methylenetetrahydrofolate reductase gene with hypertension in pregnancy and pre-eclampsia: a meta-analysis. *J Hypertens* 2004;**22**:1655–62. <https://doi.org/10.1097/00004872-200409000-00004>

204. Zusterzeel PL, Visser W, Blom HJ, Peters WH, Heil SG, Steegers EA. Methylenetetrahydrofolate reductase polymorphisms in preeclampsia and the HELLP syndrome. *Hypertens Pregnancy* 2000;**19**:299–307. <https://doi.org/10.1081/PRG-100101991>
205. Li X, Shen L, Tan H. Polymorphisms and plasma level of transforming growth factor-Beta 1 and risk for preeclampsia: a systematic review. *PLOS ONE* 2014;**9**:e97230. <https://doi.org/10.1371/journal.pone.0097230>
206. Wang XM, Wu HY, Qiu XJ. Methylenetetrahydrofolate reductase (MTHFR) gene C677T polymorphism and risk of preeclampsia: an updated meta-analysis based on 51 studies. *Arch Med Res* 2013;**44**:159–68. <https://doi.org/10.1016/j.arcmed.2013.01.011>
207. Widmer M, Villar J, Benigni A, Conde-Agudelo A, Karumanchi SA, Lindheimer M. Mapping the theories of preeclampsia and the role of angiogenic factors: a systematic review. *Obstet Gynecol* 2007;**109**:168–80. <https://doi.org/10.1097/01.AOG.0000249609.04831.7c>
208. Jacobs M, Nassar N, Roberts CL, Hadfield R, Morris JM, Ashton AW. Levels of soluble fms-like tyrosine kinase one in first trimester and outcomes of pregnancy: a systematic review. *Reprod Biol Endocrinol* 2011;**9**:77. <https://doi.org/10.1186/1477-7827-9-77>
209. Huppertz B, Meiri H, Gizurarson S, Osol G, Sammar M. Placental protein 13 (PP13): a new biological target shifting individualized risk assessment to personalized drug design combating pre-eclampsia. *Hum Reprod Update* 2013;**19**:391–405. <https://doi.org/10.1093/humupd/dmt003>
210. Schneuer FJ, Nassar N, Khambalia AZ, Tasevski V, Guilbert C, Ashton AW, et al. First trimester screening of maternal placental protein 13 for predicting preeclampsia and small for gestational age: in-house study and systematic review. *Placenta* 2012;**33**:735–40. <https://doi.org/10.1016/j.placenta.2012.05.012>
211. Lau SY, Guild SJ, Barrett CJ, Chen Q, McCowan L, Jordan V, Chamley LW. Tumour necrosis factor-alpha, interleukin-6, and interleukin-10 levels are altered in preeclampsia: a systematic review and meta-analysis. *Am J Reprod Immunol* 2013;**70**:412–27. <https://doi.org/10.1111/aji.12138>
212. Tabesh M, Salehi-Abargouei A, Tabesh M, Esmailzadeh A. Maternal vitamin D status and risk of pre-eclampsia: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2013;**98**:3165–73. <https://doi.org/10.1210/jc.2013-1257>
213. Morgan JA, Bombell S, McGuire W. Association of plasminogen activator inhibitor-type 1 (–675 4G/5G) polymorphism with pre-eclampsia: systematic review. *PLOS ONE* 2013;**8**:e56907. <https://doi.org/10.1371/journal.pone.0056907>
214. Dai B, Liu T, Zhang B, Zhang X, Wang Z. The polymorphism for endothelial nitric oxide synthase gene, the level of nitric oxide and the risk for pre-eclampsia: a meta-analysis. *Gene* 2013;**519**:187–93. <https://doi.org/10.1016/j.gene.2013.01.004>
215. Chen Z, Xu F, Wei Y, Liu F, Qi H. Angiotensin-converting enzyme insertion/deletion polymorphism and risk of pregnancy hypertensive disorders: a meta-analysis. *J Renin Angiotensin Aldosterone Syst* 2012;**13**:184–95. <https://doi.org/10.1177/1470320311427755>
216. Qi HP, Fraser WD, Luo ZC, Julien P, Audibert F, Wei SQ. Endothelial nitric oxide synthase gene polymorphisms and risk of preeclampsia. *Am J Perinatol* 2013;**30**:795–804. <https://doi.org/10.1055/s-0032-1333406>
217. Zhao L, Bracken MB, Dewan AT, Chen S. Association between the SERPINE1 (PAI-1) 4G/5G insertion/deletion promoter polymorphism (rs1799889) and pre-eclampsia: a systematic review and meta-analysis. *Mol Hum Reprod* 2013;**19**:136–43. <https://doi.org/10.1093/molehr/gas056>

218. Zhao L, Dewan AT, Bracken MB. Association of maternal AGTR1 polymorphisms and preeclampsia: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2012;**25**:2676–80. <https://doi.org/10.3109/14767058.2012.708370>
219. Zhong WG, Wang Y, Zhu H, Zhao X. Meta analysis of angiotensin-converting enzyme I/D polymorphism as a risk factor for preeclampsia in Chinese women. *Genet Mol Res* 2012;**11**:2268–76. <https://doi.org/10.4238/2012.May.21.1>
220. Ni S, Zhang Y, Deng Y, Gong Y, Huang J, Bai Y, Zhou R. AGT M235T polymorphism contributes to risk of preeclampsia: evidence from a meta-analysis. *J Renin Angiotensin Aldosterone Syst* 2012;**13**:379–86. <https://doi.org/10.1177/1470320312440903>
221. Hui D, Okun N, Murphy K, Kingdom J, Uleryk E, Shah PS. Combinations of maternal serum markers to predict preeclampsia, small for gestational age, and stillbirth: a systematic review. *J Obstet Gynaecol Can* 2012;**34**:142–53. [https://doi.org/10.1016/S1701-2163\(16\)35157-X](https://doi.org/10.1016/S1701-2163(16)35157-X)
222. Giguère Y, Charland M, Bujold E, Bernard N, Grenier S, Rousseau F, et al. [Combining biochemical and ultrasonographic markers in predicting preeclampsia: a systematic review.] *Ann Biol Clin* 2011;**69**:257–71. <https://doi.org/10.1684/abc.2011.0572>
223. Abou-Nassar K, Carrier M, Ramsay T, Rodger MA. The association between antiphospholipid antibodies and placenta mediated complications: a systematic review and meta-analysis. *Thromb Res* 2011;**128**:77–85. <https://doi.org/10.1016/j.thromres.2011.02.006>
224. do Prado AD, Piovesan DM, Staub HL, Horta BL. Association of anticardiolipin antibodies with preeclampsia: a systematic review and meta-analysis. *Obstet Gynecol* 2010;**116**:1433–43. <https://doi.org/10.1097/AOG.0b013e3181fe02ec>
225. Gupta S, Aziz N, Sekhon L, Agarwal R, Mansour G, Li J, Agarwal A. Lipid peroxidation and antioxidant status in preeclampsia: a systematic review. *Obstet Gynecol Surv* 2009;**64**:750–9. <https://doi.org/10.1097/OGX.0b013e3181bea0ac>
226. Bombell S, McGuire W. Tumour necrosis factor (–308A) polymorphism in pre-eclampsia: meta-analysis of 16 case-control studies. *Aust N Z J Obstet Gynaecol* 2008;**48**:547–51. <https://doi.org/10.1111/j.1479-828X.2008.00924.x>
227. Zafarmand MH, Nijdam ME, Franx A, Grobbee DE, Bots ML. The angiotensinogen gene M235T polymorphism and development of preeclampsia/eclampsia: a meta-analysis and meta-regression of observational studies. *J Hypertens* 2008;**26**:1726–34. <https://doi.org/10.1097/HJH.0b013e3283009ca5>
228. Wiwanitkit V. Correlation between plasminogen activator inhibitor-1 4G/5G polymorphism and pre-eclampsia: an appraisal. *Arch Gynecol Obstet* 2006;**273**:322–4. <https://doi.org/10.1007/s00404-005-0117-8>
229. Crovetto F, Figueras F, Triunfo S, Crispi F, Rodriguez-Sureda V, Dominguez C, et al. First trimester screening for early and late preeclampsia based on maternal characteristics, biophysical parameters, and angiogenic factors. *Prenat Diagn* 2015;**35**:183–91. <https://doi.org/10.1002/pd.4519>
230. Kuc S, Koster MP, Franx A, Schielen PC, Visser GH. Maternal characteristics, mean arterial pressure and serum markers in early prediction of preeclampsia. *PLOS ONE* 2013;**8**:e63546. <https://doi.org/10.1371/journal.pone.0063546>
231. Plasencia W, Maiz N, Bonino S, Kaihura C, Nicolaidis KH. Uterine artery Doppler at 11 + 0 to 13 + 6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2007;**30**:742–9. <https://doi.org/10.1002/uog.5157>

232. Poon LC, Kametas NA, Chelemen T, Leal A, Nicolaides KH. Maternal risk factors for hypertensive disorders in pregnancy: a multivariate approach. *J Hum Hypertens* 2010;**24**:104–10. <https://doi.org/10.1038/jhh.2009.45>
233. Poon LC, Kametas NA, Pandeva I, Valencia C, Nicolaides KH. Mean arterial pressure at 11(+0) to 13(+6) weeks in the prediction of preeclampsia. *Hypertension* 2008;**51**:1027–33. <https://doi.org/10.1161/HYPERTENSIONAHA.107.104646>
234. Poon LC, Maiz N, Valencia C, Plasencia W, Nicolaides KH. First-trimester maternal serum pregnancy-associated plasma protein-A and pre-eclampsia. *Ultrasound Obstet Gynecol* 2009;**33**:23–33. <https://doi.org/10.1002/uog.6280>
235. Scazzocchio E, Figueras F, Crispi F, Meler E, Masoller N, Mula R, Gratacos E. Performance of a first-trimester screening of preeclampsia in a routine care low-risk setting. *Am J Obstet Gynecol* 2013;**208**:203.e1–203.e10. <https://doi.org/10.1016/j.ajog.2012.12.016>
236. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. *Am J Obstet Gynecol* 2015;**213**:62.e1–62.e10. <https://doi.org/10.1016/j.ajog.2015.02.018>
237. Yu CK, Smith GC, Papageorghiou AT, Cacho AM, Nicolaides KH, Fetal Medicine Foundation Second Trimester Screening Group. An integrated model for the prediction of pre-eclampsia using maternal factors and uterine artery Doppler velocimetry in unselected low-risk women. *Am J Obstet Gynecol* 2006;**195**:330. <https://doi.org/10.1016/j.ajog.2006.06.010>
238. Yu CK, Smith GC, Papageorghiou AT, Cacho AM, Nicolaides KH, Fetal Medicine Foundation Second Trimester Screening Group. An integrated model for the prediction of preeclampsia using maternal factors and uterine artery Doppler velocimetry in unselected low-risk women. *Am J Obstet Gynecol* 2005;**193**:429–36. <https://doi.org/10.1016/j.ajog.2004.12.014>
239. Albert A, Anderson JA. On the existence of maximum likelihood estimates in logistic regression models. *Biometrika* 1984;**71**:1. <https://doi.org/10.1093/biomet/71.1.1>
240. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;**30**:377–99. <https://doi.org/10.1002/sim.4067>
241. Akolekar R, Zaragoza E, Poon LC, Pepes S, Nicolaides KH. Maternal serum placental growth factor at 11 + 0 to 13 + 6 weeks of gestation in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2008;**32**:732–9. <https://doi.org/10.1002/uog.6244>
242. National Institute for Health and Care Excellence. *Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy*. Clinical Guideline 107. London: National Institute for Health and Care Excellence; 2010. URL: www.nice.org.uk/guidance/cg107 (accessed 12 February 2015).
243. O’Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11–13 weeks gestation. *Am J Obstet Gynecol* 2016;**214**:103.e1–103.e12. <https://doi.org/10.1016/j.ajog.2015.08.034>
244. O’Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, de Alvarado M, *et al*. Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks’ gestation: comparison with NICE guidelines and ACOG recommendations. *Ultrasound Obstet Gynecol* 2017;**49**:756–60. <https://doi.org/10.1002/uog.17455>
245. Oliveira N, Magder LS, Blitzer MG, Baschat AA. First-trimester prediction of pre-eclampsia: external validity of algorithms in a prospectively enrolled cohort. *Ultrasound Obstet Gynecol* 2014;**44**:279–85. <https://doi.org/10.1002/uog.13435>

REFERENCES

246. Park FJ, Leung CH, Poon LC, Williams PF, Rothwell SJ, Hyett JA. Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease of pregnancy. *Aust N Z J Obstet Gynaecol* 2013;**53**:532–9. <https://doi.org/10.1111/ajo.12126>
247. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, *et al.* Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010;**21**:128–38. <https://doi.org/10.1097/EDE.0b013e3181c30fb2>
248. Wright D, Tan MY, O’Gorman N, Poon LC, Syngelaki A, Wright A, Nicolaides KH. Predictive performance of the competing risk model in screening for preeclampsia. *Am J Obstet Gynecol* 2019;**220**:199.e1–199.e13. <https://doi.org/10.1016/j.ajog.2018.11.1087>
249. Debray TP, Vergouwe Y, Koffijberg H, Nieboer D, Steyerberg EW, Moons KG. A new framework to enhance the interpretation of external validation studies of clinical prediction models. *J Clin Epidemiol* 2015;**68**:279–89. <https://doi.org/10.1016/j.jclinepi.2014.06.018>

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Appendix 2 Search strategies

TABLE 23 Search strategies for the review of reviews

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

TABLE 24 Search strategies for pre-eclampsia prediction models

Set#	Searched for
#1	Validat*[tiab] OR Predict*[ti] OR Rule*[tiab]
#2	Predict*[tiab] AND (Outcome*[tiab] OR Risk*[tiab] OR Model*[tiab])
#3	(History[tiab] OR Variable*[tiab] OR Criteria[tiab] OR Scor*[tiab] OR Characteristic*[tiab] OR Finding*[tiab] OR Factor*[tiab]) AND (Predict*[tiab] OR Model*[tiab] OR Decision*[tiab] OR Identif*[tiab] OR Prognos*[tiab])
#4	Decision*[tiab] AND (Model*[tiab] OR Clinical*[tiab] OR Logistic Model*[tiab])
#5	Prognostic[tiab] AND (History[tiab] OR Variable*[tiab] OR Criteria[tiab] OR Scor*[tiab] OR Characteristic*[tiab] OR Finding*[tiab] OR Factor*[tiab] OR Model*[tiab])
#6	"risk score"[All fields] OR "prediction model"[All fields] OR "prediction rule"[All fields] OR "risk assessment"[All fields] OR "algorithm"[All fields]
#7	# 1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	(pregnan*[tiab] OR obstetric*[tiab] OR woman[tiab] OR women[tiab]) AND (preeclampsia[tiab] OR pre-eclampsia [tiab])
#9	#7 AND #8
#10	#9 NOT (Animals[MeSH] NOT Humans[MeSH])

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Appendix 3 Individual participant data extracted on the IPPIC project

Candidate predictors	Brief description	Categories
Maternal clinical characteristics		
Age	'Age in years (continuous)'	
Parity	'Number of times giving birth before this pregnancy (continuous)'	0 'No' 1 'Yes'
	'Nulliparous (binary)'	
Previous miscarriage	'Number of previous miscarriages (continuous)'	
	'Previous miscarriage (binary)'	0 'No' 1 'Yes'
	'Previous miscarriage trimester 1 (binary)'	
	'Previous miscarriage trimester 2 (binary)'	
Previous stillbirth	'Previous stillbirth (binary)'	0 'No' 1 'Yes'
History of SGA birth	'SGA in a previous pregnancy (binary)'	0 'No' 1 'Yes'
Previous pre-eclampsia	'Previous history of any pre-eclampsia (binary)'	0 'No' 1 'Yes'
Previous early pre-eclampsia	'Previous early pre-eclampsia (binary)'	0 'No' 1 'Yes'
Gestational age at previous pre-eclampsia	'Gestational age at previous pre-eclampsia (continuous)'	
Previous any preterm delivery	'Previous any preterm delivery (binary)'	0 'No' 1 'Yes'
Previous early preterm delivery	'Previous early preterm delivery < 34 weeks (binary)'	0 'No' 1 'Yes'
Previous late preterm delivery	'Previous late preterm delivery ≥ 34 weeks (binary)'	0 'No' 1 'Yes'
Gestational age at previous preterm delivery	'Gestational age at previous preterm delivery (continuous)'	
Previous heritable thrombophilia	'History of heritable thrombophilia (binary)'	0 'No' 1 'Yes'
Previous autoimmune disease	'History of systemic lupus, rheumatoid arthritis or antiphospholipid syndrome (binary)'	0 'No' 1 'Yes'
History of pre-eclampsia in mother	'Mother has a history of pre-eclampsia (binary)'	0 'No' 1 'Yes'
Family history of pre-eclampsia	'Mother or sister has a history of pre-eclampsia (binary)'	0 'No' 1 'Yes'
Family history of cardiovascular disease	'Family history of cardiovascular disease (binary)'	0 'No' 1 'Yes'
History of renal disease	'History of renal disease (binary)'	0 'No' 1 'Yes'
History of pre-existing diabetes	'History of type 1, type 2 or gestational diabetes (binary)'	0 'No' 1 'Yes'
History of gestational diabetes mellitus	'Previous gestational diabetes mellitus (binary)'	0 'No' 1 'Yes'
Gestational diabetes in current pregnancy	'Gestational diabetes in current pregnancy trimester 1 (binary)'	0 'No' 1 'Yes'
	'Gestational diabetes in current pregnancy trimester 1 (binary)'	0 'No' 1 'Yes'
	'Gestational diabetes in current pregnancy trimester 2 (binary)'	0 'No' 1 'Yes'
	'Gestational diabetes in current pregnancy trimester 3 (binary)'	0 'No' 1 'Yes'

Candidate predictors	Brief description	Categories
Early pregnancy bleeding	'Early pregnancy bleeding in current pregnancy (binary)'	0 'No' 1 'Yes'
Chronic or pre-existing hypertension	'History of chronic, essential or pre-existing hypertension (binary)'	0 'No' 1 'Yes'
Smoking	'Smoked during current pregnancy (binary)'	0 'No' 1 'Yes'
Number of cigarettes smoked per day	'Number of cigarettes smoked per day (continuous)'	
Alcohol use	'Drank Alcohol (binary)'	0 'No' 1 'Yes'
Substance misuse in current pregnancy	'Cocaine, heroin or methamphetamine use in current pregnancy (binary)'	0 'No' 1 'Yes'
Mode of conception	'Spontaneous mode of conception (binary)'	0 'No' 1 'Yes'
Multiple pregnancy	'Multiple pregnancy in current pregnancy (binary)'	0 'No' 1 'Yes'
Number of years between pregnancies	'Number of years between pregnancies (continuous)'	
Maternal education	'Highest level of maternal education attained (categorical)'	1 'Primary' 2 'Secondary' 3 'Tertiary'
	'Maternal years in education primary school (continuous)'	
New partner	'New partner (binary)'	0 'No' 1 'Yes'
Healthy diet in pregnancy	'On healthy diet in pregnancy (binary)'	0 'No' 1 'Yes'
Planned physical activity	'Planned physical activity (categorical)'	1 'Sedentary' 2 'Moderate' 3 'Severe'
Ethnicity	'Ethnicity (categorical)'	1 'White' 2 'Black' 3 'Asian' 4 'Hispanic' 5 'Mixed' 6 'Other'
BMI	'BMI in kg/m ² (continuous)' 'BMI in kg/m ² trimester 1 (continuous)' 'BMI in kg/m ² trimester 2 (continuous)' 'BMI in kg/m ² trimester 3 (continuous)'	
Height	'Height in cm (continuous)'	
Weight	'Weight in kg (continuous)' 'Weight in kg trimester 1 (continuous)' 'Weight in kg trimester 2 (continuous)' 'Weight in kg trimester 3 (continuous)'	
SBP	'SBP in mmHg (continuous)' 'SBP in mmHg trimester 1 (continuous)' 'SBP in mmHg trimester 2 (continuous)' 'SBP in mmHg trimester 3 (continuous)'	

Candidate predictors	Brief description	Categories
DBP	'DBP in mmHg (continuous)'	
	'DBP in mmHg trimester 1 (continuous)'	
	'DBP in mmHg trimester 2 (continuous)'	
	'DBP in mmHg trimester 3 (continuous)'	
MAP	'MAP in mmHg (continuous)'	
	'MAP in mmHg trimester 1 (continuous)'	
	'MAP in mmHg trimester 2 (continuous)'	
	'MAP in mmHg trimester 3 (continuous)'	
Urine dipstick	'Urine dipstick (categorical)'	0 '0 or trace' 1 '1+' 2 '≥ 2+'
	'Urine dipstick trimester 1 (categorical)'	
	'Urine dipstick trimester 2 (categorical)'	
	'Urine dipstick trimester 3 (categorical)'	
24-hour protein	'24-hour protein in g/24hr (continuous)'	
	'24-hour protein in g/24hr trimester 1 (continuous)'	
	'24-hour protein in g/24hr trimester 2 (continuous)'	
	'24-hour protein in g/24hr trimester 3 (continuous)'	
PCR	'PCR in mg/mmol of creatinine (continuous)'	
	'PCR in mg/mmol of creatinine trimester 1 (continuous)'	
	'PCR in mg/mmol of creatinine trimester 2 (continuous)'	
	'PCR in mg/mmol of creatinine trimester 3 (continuous)'	
Ultrasound markers		
Unilateral notching	'Unilateral notching (binary)'	0 'No' 1 'Yes'
	'Unilateral notching trimester 1 (binary)'	
	'Unilateral notching trimester 2 (binary)'	
	'Unilateral notching trimester 3 (binary)'	
Bilateral notching	'Bilateral notching (binary)'	0 'No' 1 'Yes'
	'Bilateral notching trimester 1 (binary)'	
	'Bilateral notching trimester 2 (binary)'	
	'Bilateral notching trimester 3 (binary)'	
Uterine artery PI	'Uterine artery PI (continuous)'	
	'Uterine artery PI trimester 1 (continuous)'	
	'Uterine artery PI trimester 2 (continuous)'	
	'Uterine artery PI trimester 3 (continuous)'	
Umbilical artery PI	'Umbilical artery PI (continuous)'	
	'Umbilical artery PI trimester 1 (continuous)'	
	'Umbilical artery PI trimester 2 (continuous)'	
	'Umbilical artery PI trimester 3 (continuous)'	
Uterine artery PI MoM	'Uterine artery PI MoM (continuous)'	
	'Uterine artery PI MoM trimester 1 (continuous)'	
	'Uterine artery PI MoM trimester 2 (continuous)'	
	'Uterine artery PI MoM trimester 3 (continuous)'	

Candidate predictors	Brief description	Categories
Umbilical artery PI MoM	'Umbilical artery PI MoM (continuous)'	
	'Umbilical artery PI MoM trimester 1 (continuous)'	
	'Umbilical artery PI MoM trimester 2 (continuous)'	
	'Umbilical artery PI MoM trimester 3 (continuous)'	
Uterine artery RI	'Uterine artery RI (continuous)'	
	'Uterine artery RI trimester 1 (continuous)'	
	'Uterine artery RI trimester 2 (continuous)'	
	'Uterine artery RI trimester 3 (continuous)'	
Umbilical artery RI	'Umbilical artery RI (continuous)'	
	'Umbilical artery RI trimester 1 (continuous)'	
	'Umbilical artery RI trimester 2 (continuous)'	
	'Umbilical artery RI trimester 3 (continuous)'	
Uterine artery RI MoM	'Uterine artery RI MoM (continuous)'	
	'Uterine artery RI MoM trimester 1 (continuous)'	
	'Uterine artery RI MoM trimester 2 (continuous)'	
	'Uterine artery RI MoM trimester 3 (continuous)'	
Umbilical artery RI MoM	'Umbilical artery RI MoM (continuous)'	
	'Umbilical artery RI MoM trimester 1 (continuous)'	
	'Umbilical artery RI MoM trimester 2 (continuous)'	
	'Umbilical artery RI MoM trimester 3 (continuous)'	
Abdominal circumference	'Abdominal circumference (continuous)'	
	'Abdominal circumference trimester 2 (continuous)'	
	'Abdominal circumference trimester 3 (continuous)'	
Abdominal circumference centile	'Abdominal circumference centile (continuous)'	
	'Abdominal circumference centile trimester 2 (continuous)'	
	'Abdominal circumference centile trimester 3 (continuous)'	
CRL	'Crown-rump length in mm (continuous)'	
	'Crown-rump length in mm trimester 1 (continuous)'	
	'Crown-rump length in mm trimester 2 (continuous)'	
Expected fetal weight	'Expected fetal weight in grams (continuous)'	
	'Expected fetal weight in grams trimester 1 (continuous)'	
	'Expected fetal weight in grams trimester 2 (continuous)'	
	'Expected fetal weight in grams trimester 3 (continuous)'	
Expected fetal weight centile	'Expected fetal weight centile (continuous)'	
	'Expected fetal weight centile trimester 1 (continuous)'	
	'Expected fetal weight centile trimester 2 (continuous)'	
	'Expected fetal weight centile trimester 3 (continuous)'	
Biochemical markers		
PAPP-A	'PAPP-A (continuous)'	
	'PAPP-A trimester 1 (continuous)'	
	'PAPP-A trimester 2 (continuous)'	
	'PAPP-A trimester 3 (continuous)'	

Candidate predictors	Brief description	Categories
PIGF	'PIGF (continuous)'	
	'PIGF trimester 1 (continuous)'	
	'PIGF trimester 2 (continuous)'	
	'PIGF trimester 3 (continuous)'	
sFlt-1	'sFlt-1 (continuous)'	
	'sFlt-1 trimester 1 (continuous)'	
	'sFlt-1 trimester 2 (continuous)'	
	'sFlt-1 trimester 3 (continuous)'	
sENG	'sENG (continuous)'	
	'sENG trimester 1 (continuous)'	
	'sENG trimester 2 (continuous)'	
	'sENG trimester 3 (continuous)'	
CRP	'CRP (continuous)'	
	'CRP trimester 1 (continuous)'	
	'CRP trimester 2 (continuous)'	
	'CRP trimester 3 (continuous)'	
Hypertriglyceridaemia	'Hypertriglyceridaemia (continuous)'	
	'Hypertriglyceridaemia trimester 1 (continuous)'	
	'Hypertriglyceridaemia trimester 2 (continuous)'	
	'Hypertriglyceridaemia trimester 3 (continuous)'	
PAI-1 polymorphism	'PAI-1 polymorphism (continuous)'	
	'PAI-1 polymorphism trimester 1 (continuous)'	
	'PAI-1 polymorphism trimester 2 (continuous)'	
	'PAI-1 polymorphism trimester 3 (continuous)'	
Human chorionic gonadotropin	'hCG (continuous)'	
	'hCG trimester 1 (continuous)'	
	'hCG trimester 2 (continuous)'	
	'hCG trimester 3 (continuous)'	
AFP	'AFP (continuous)'	
	'AFP trimester 1 (continuous)'	
	'AFP trimester 2 (continuous)'	
	'AFP trimester 3 (continuous)'	
PAPP-A MoM	'PAPP-A MoM (continuous)'	
	'PAPP-A MoM trimester 1 (continuous)'	
	'PAPP-A MoM trimester 2 (continuous)'	
	'PAPP-A MoM trimester 3 (continuous)'	
PIGF MoM	'PIGF MoM (continuous)'	
	'PIGF MoM trimester 1 (continuous)'	
	'PIGF MoM trimester 2 (continuous)'	
	'PIGF MoM trimester 3 (continuous)'	

Candidate predictors	Brief description	Categories
sFlt-1 MoM	'sFlt-1 MoM (continuous)'	
	'sFlt-1 MoM trimester 1 (continuous)'	
	'sFlt-1 MoM trimester 2 (continuous)'	
	'sFlt-1 MoM trimester 3 (continuous)'	
sENG MoM	'sENG MoM (continuous)'	
	'sENG MoM trimester 1 (continuous)'	
	'sENG MoM trimester 2 (continuous)'	
	'sENG MoM trimester 3 (continuous)'	
CRP MoM	'CRP MoM (continuous)'	
	'CRP MoM trimester 1 (continuous)'	
	'CRP MoM trimester 2 (continuous)'	
	'CRP MoM trimester 3 (continuous)'	
Hypertriglyceridaemia MoM	'Hypertriglyceridaemia MoM (continuous)'	
	'Hypertriglyceridaemia MoM trimester 1 (continuous)'	
	'Hypertriglyceridaemia MoM trimester 2 (continuous)'	
	'Hypertriglyceridaemia MoM trimester 3 (continuous)'	
PAI-1 polymorphism MoM	'PAI-1 polymorphism MoM (continuous)'	
	'PAI-1 polymorphism MoM trimester 1 (continuous)'	
	'PAI-1 polymorphism MoM trimester 2 (continuous)'	
	'PAI-1 polymorphism MoM trimester 3 (continuous)'	
Human chorionic gonadotropin MoM	'hCG MoM (continuous)'	
	'hCG MoM trimester 1 (continuous)'	
	'hCG MoM trimester 2 (continuous)'	
	'hCG MoM trimester 3 (continuous)'	
AFP MoM	'AFP MoM (continuous)'	
	'AFP MoM trimester 1 (continuous)'	
	'AFP MoM trimester 2 (continuous)'	
	'AFP MoM trimester 3 (continuous)'	
Primary outcome		
Any-onset pre-eclampsia	'Any-onset pre-eclampsia (binary)'	0 'No' 1 'Yes'
Early-onset pre-eclampsia	'Early-onset pre-eclampsia < 34 weeks (binary)'	0 'No' 1 'Yes'
Late-onset pre-eclampsia	'Late-onset pre-eclampsia ≥ 34 weeks (binary)'	0 'No' 1 'Yes'
Superimposed pre-eclampsia	'Superimposed pre-eclampsia (binary)'	0 'No' 1 'Yes'
Gestational age at diagnosis	'Gestational age in weeks of diagnosis of pre-eclampsia (continuous)'	
SBP	'SBP in mmHg (continuous)'	
	'SBP in mmHg trimester 2 (continuous)'	
	'SBP in mmHg trimester 3 (continuous)'	
Gestational age of measurement	'Gestational age in weeks of measurement of SBP (continuous)'	
DBP	'DBP in mmHg (continuous)'	
	'DBP in mmHg trimester 2 (continuous)'	
	'DBP in mmHg trimester 3 (continuous)'	

Candidate predictors	Brief description	Categories
Gestational age at measurement	'Gestational age in weeks of measurement of DBP (continuous)'	
PCR	'PCR in mg/mmol of creatinine (continuous)'	
	'PCR in mg/mmol of creatinine trimester 2 (continuous)'	
	'PCR in mg/mmol of creatinine trimester 3 (continuous)'	
24-hour protein	'24-hour protein in g/24hr (continuous)'	
	'24-hour protein in g/24hr trimester 2 (continuous)'	
	'24-hour protein in g/24hr trimester 3 (continuous)'	
Urine dipstick	'Urine dipstick (categorical)'	0 '0 or trace' 1 '1+' 2 '≥ 2+'
	'Urine dipstick trimester 2 (categorical)'	
	'Urine dipstick trimester 3 (categorical)'	
Gestational age of measurement	'Gestational age in weeks of measurement of urine dipstick (continuous)'	
Birthweight	'Birth weight in grams (continuous)'	
	'Birth weight in grams trimester 2 (continuous)'	
	'Birth weight in grams trimester 3 (continuous)'	
Birthweight centile	'Birth weight centile (continuous)'	
	'Birth weight centile trimester 2 (continuous)'	
	'Birth weight centile trimester 3 (continuous)'	
Gestational age at delivery	'Gestational age at delivery in weeks (continuous)'	
	'Gestational age at delivery in weeks (categorical)'	0 '≥ 37' 1 '34-36 + 6' 2 '30-33 + 6' 3 '26-29 + 6' 4 '23-25 + 6' 5 '< 23'
Secondary outcome		
Eclampsia	'Eclampsia (binary)'	0 'No' 1 'Yes'
HELLP syndrome	'HELLP syndrome (binary)'	0 'No' 1 'Yes'
Placental abruption	'Placental abruption (binary)'	0 'No' 1 'Yes'
Hepatic failure	'Hepatic failure (binary)'	0 'No' 1 'Yes'
Renal failure	'Renal failure (binary)'	0 'No' 1 'Yes'
Cortical blindness	'Cortical blindness (binary)'	0 'No' 1 'Yes'
Pulmonary oedema	'Pulmonary oedema (binary)'	0 'No' 1 'Yes'
Postpartum haemorrhage	'Postpartum haemorrhage (binary)'	0 'No' 1 'Yes'
Disseminated intravascular coagulation	'Disseminated intravascular coagulation (binary)'	0 'No' 1 'Yes'
Preterm delivery	'Preterm delivery (binary)'	0 'No' 1 'Yes'
	'Preterm delivery < 34 weeks (binary)'	
	'Preterm delivery ≥ 34 weeks (binary)'	
Admission to high-dependency unit	'Admission to high-dependency unit (binary)'	0 'No' 1 'Yes'
Maternal death	'Maternal death (binary)'	0 'No' 1 'Yes'

Candidate predictors	Brief description	Categories
Caesarean section	'Caesarean section (binary)'	0 'No' 1 'Yes'
Stillbirth	'Stillbirth (binary)'	0 'No' 1 'Yes'
	'Stillbirth trimester 2 (binary)'	
	'Stillbirth trimester 3 (binary)'	
Neonatal death	'Neonatal death (binary)'	0 'No' 1 'Yes'
Hypoxic-ischaemic encephalopathy	'Hypoxic ischaemic encephalopathy (binary)'	0 'No' 1 'Yes'
Respiratory distress syndrome	'Respiratory distress syndrome (binary)'	0 'No' 1 'Yes'
Septicaemia	'Septicaemia (binary)'	0 'No' 1 'Yes'
Admission to neonatal unit	'Admission to neonatal unit (binary)'	0 'No' 1 'Yes'
Treatment		
Aspirin	'Aspirin use (binary)'	0 'No' 1 'Yes'
	'Aspirin dose in mg (continuous)'	
	'Aspirin use in trimester 1 (binary)'	0 'No' 1 'Yes'
	'Aspirin use in mg trimester 1 (continuous)'	
	'Aspirin use in trimester 2 (binary)'	0 'No' 1 'Yes'
	'Aspirin use in mg trimester 2 (continuous)'	
	'Aspirin use in trimester 3 (binary)'	0 'No' 1 'Yes'
	'Aspirin use in mg trimester 3 (continuous)'	
Calcium supplement	'Calcium supplement (binary)'	0 'No' 1 'Yes'
Vitamin supplement	'Vitamin supplement (binary)'	0 'No' 1 'Yes'
AFP, alpha-fetoprotein; CRL, crown-rump length; CRP, C-reactive protein; hCG, human chorionic gonadotropin; MoM, multiple of the mean; PAI-1, plasminogen activator inhibitor-1; PI, pulsatility index; RI, resistance index; sENG, soluble endoglin.		

Appendix 4 Participant summary from data sets contributing to the IPPIC project

Study/data set	Maternal characteristics and outcomes														
	Total number of pregnancies	Number of singleton pregnancies	Age (years), mean (SD), range	First BMI measured, median [IQR], range	Ethnicity, n (%)						Nulliparous, n (%)	Previous PE, n (%)	Outcome, n (%)		
					White	Black	Asian	Hispanic	Mixed	Other			Any-onset PE	Early-onset PE	Late-onset PE
SCOPE ⁴²	5628	5628	28.7 (5.5), 14–45	24.2 [5.6], 15.4–58.5	5061 (89.9)	65 (1.2)	304 (5.4)	24 (0.4)	0 (0)	174 (3.1)	5628 (100)	0 (0)	278 (4.9)	44 (0.8)	234 (4.2)
Allen ¹⁰⁸	1045	1045	29.9 (5.1), 15–48	23.6 [5.7], 14.8–51.1	398 (38.2)	108 (10.4)	495 (47.5)	0 (0)	12 (1.2)	30 (2.9)	584 (55.9)	17 (1.6)	14 (1.3)	1 (0.1)	13 (1.2)
ALSPAC ¹⁰³	15,242	15,038	27.7 (4.9), 13–46	21.5 [4], 11.7–61.3	11,769 (97.4)	127 (1.1)	113 (0.9)	0 (0)	0 (0)	76 (0.6)	5704 (45.3)	0 (0)	297 (2.2)	37 (0.3)	260 (1.9)
Chappell ¹²¹	316	316	29.6 (5.9), 16.3–43	24.2 [5.3], 16.4–56.5	215 (68)	91 (28.8)	6 (1.9)	3 (0.9)	0 (0)	1 (0.3)	202 (63.9)	56 (17.7)	35 (12.4)	6 (2.1)	29 (10.2)
EMPOWaR ¹²²	449	449	28.7 (5.4), 17–43	38 [6.8], 30.6–59.7	449 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	291 (65)	0 (0)	10 (4.9)	0 (0)	10 (4.8)
POPPY ¹⁰⁶	1216	1216	32.1 (5.4), 17–51	24.6 [6.8], 14.5–57.9	881 (72.5)	193 (15.9)	85 (7)	0 (0)	0 (0)	57 (4.7)	206 (16.9)	0 (0)	22 (1.8)	2 (0.2)	20 (1.7)
Poston 2006 ¹⁵⁰	2422	2040	30.8 (5.9), 16–45	31.2 [9.8], 16.6–65.4	-	-	-	-	-	-	-	657 (27.1)	371 (15.3)	144 (5.9)	227 (9.4)
Poston 2015 ¹⁴⁹	1554	1554	30.5 (5.5), 16–45	35.1 [5.8], 30–66	954 (61.4)	395 (25.4)	97 (6.2)	0 (0)	0 (0)	108 (6.9)	674 (43.4)	69 (4.5)	54 (3.6)	5 (0.3)	49 (3.3)
Khan ¹³⁷	222	222	-	25.3 [6.6], 18–46.1	-	-	-	-	-	-	146 (65.8)	0 (0)	27 (12.2)	11 (5)	16 (7.2)
St George's ¹⁶³	54,656	54,635	30.5 (5.6), 13–54	23.5 [5.5], 11.9–79.8	33,257 (62.1)	7820 (14.6)	10,388 (19.4)	5 (0)	1,528 (2.9)	555 (1)	29,318 (53.8)	0 (0)	1,492 (2.7)	152 (0.3)	1,340 (2.5)
PARIS ¹¹²	35,955	34,609	23.6 (6.1), 11–48	-	-	-	-	-	-	-	19,793 (57.5)	6,086 (18.5)	2,928 (8.8)	498 (1.5)	2,403 (7.2)
AMND ¹¹⁴	138,967	136,635	28.4 (5.6), 13–56	23.9 [5.5], 10–72.1	-	-	-	-	-	-	65,206 (47.7)	0 (0)	5,194 (3.7)	1,329 (1)	3,865 (2.8)
Born in Bradford ¹⁷⁷	13,279	13,118	27.5 (5.6), 15–49	25.1 [7.3], 12.9–57	4,443 (42.4)	212 (2)	5,380 (51.4)	0 (0)	158 (1.5)	278 (2.7)	5,034 (39.6)	0 (0)	334 (2.7)	0 (0)	0 (0)
Velauthar ³⁹	1,208	1,206	-	23.9 [6], 13.8–46.6	402 (35.3)	90 (7.9)	565 (49.6)	0 (0)	0 (0)	82 (7.2)	598 (52.2)	0 (0)	26 (2.3)	3 (0.3)	23 (2.1)
POP ¹⁶¹	4,212	4,212	29.9 (5.1), 16.1–48.4	24.1 [5.5], 14.7–54.7	3,900 (92.6)	25 (0.6)	91 (2.2)	0 (0)	1 (0)	195 (4.6)	4,212 (100)	0 (0)	273 (6.5)	10 (0.2)	263 (6.3)
Baschat ¹¹⁵	1,704	1,704	30.2 (6.5), 18–50	26.7 [9.1], 15.9–72.9	775 (45.5)	803 (47.1)	88 (5.2)	27 (1.6)	0 (0)	11 (0.6)	736 (43.2)	92 (5.4)	106 (6.2)	21 (1.2)	85 (5)
Audibert ¹¹³	893	893	29.5 (4.5), 18–43	22.6 [4.4], 16.9–50	720 (80.6)	62 (6.9)	14 (1.6)	26 (2.9)	44 (4.9)	27 (3)	893 (100)	0 (0)	40 (4.5)	9 (1)	31 (3.5)

Study/data set	Maternal characteristics and outcomes														
	Total number of pregnancies	Number of singleton pregnancies	Age (years), mean (SD), range	First BMI measured, median [IQR], range	Ethnicity, n (%)						Nulliparous, n (%)	Previous PE, n (%)	Outcome, n (%)		
					White	Black	Asian	Hispanic	Mixed	Other			Any-onset PE	Early-onset PE	Late-onset PE
Caradeux ¹¹⁸	682	682	29 (6.4), 14–45.6	24.9 [5.4], 15.7–48	-	-	-	-	-	-	322 (48.1)	15 (2.2)	28 (4.1)	3 (0.4)	25 (3.7)
Giguère ¹²⁶	7866	7693	-	23 [5.9], 13.9–58.3	6422 (96.9)	37 (0.6)	23 (0.3)	47 (0.7)	47 (0.7)	49 (0.7)	3631 (47.2)	0 (0)	142 (1.8)	13 (0.2)	129 (1.6)
Goetzinger ¹²⁸	4035	4035	34.8 (4.4), 16–52	24.4 [7], 15.4–62.4	3282 (82.6)	397 (10)	112 (2.8)	65 (1.6)	0 (0)	116 (2.9)	751 (20.1)	0 (0)	271 (12.1)	19 (0.8)	252 (11.3)
Antsaklis ¹¹⁰	3328	3328	30.9 (4.8), 14–47	22.7 [5.2], 14.5–50.1	3229 (97.2)	49 (1.5)	32 (1)	0 (0)	0 (0)	11 (0.3)	3328 (100)	0 (0)	32 (1.4)	13 (0.6)	19 (0.8)
Llurba ¹⁴⁰	11,668	11,668	30.2 (5.9), 14–51	-	10,415 (90.6)	125 (1.1)	4 (0)	794 (6.9)	0 (0)	163 (1.4)	-	51 (0.4)	411 (3.5)	69 (0.6)	218 (1.9)
WHO ¹⁷⁵	7315	7273	22.5 (5.8), 11–51	22.4 [4.8], 13.1–54.8	2222 (30.6)	756 (10.4)	1443 (19.9)	0 (0)	0 (0)	2846 (39.2)	6710 (92.3)	432 (5.9)	142 (1.9)	18 (0.2)	124 (1.7)
Andersen ¹⁰⁹	2161	2120	30.2 (4.5), 17–45	23.4 [5.2], 14.9–50.4	1765 (96.6)	3 (0.2)	31 (1.7)	5 (0.3)	0 (0)	24 (1.3)	1193 (56.3)	0 (0)	159 (7.5)	3 (0.1)	156 (7.4)
Arenas ¹¹¹	319	319	30.5 (4.9), 16–43	24.2 [4.3], 17.3–39.1	-	-	-	-	-	-	193 (60.5)	2 (0.6)	11 (3.4)	1 (0.3)	10 (3.1)
FINNPEC ¹³³	2506	2506	30 (5.4), 18–47	23.6 [6.1], 16–50.8	2498 (99.7)	4 (0.2)	4 (0.2)	0 (0)	0 (0)	0 (0)	1653 (66)	189 (7.5)	1440 (57.5)	260 (10.4)	1180 (47.1)
Verlohren ¹⁷¹	253	235	31.9 (5.5), 16–45	25.1 [7.1], 17.9–48.8	160 (68.4)	17 (7.3)	3 (1.3)	37 (15.8)	0 (0)	17 (7.3)	117 (50.2)	38 (15.3)	103 (41.4)	33 (13.3)	70 (28.1)
Generation R ¹³⁴	8727	8631	29.6 (5.3), 15.3–46.3	23.9 [5.3], 15.2–51.2	4800 (58.8)	2117 (26)	484 (5.9)	0 (0)	0 (0)	756 (9.3)	4745 (55.7)	0 (0)	194 (2.3)	24 (0.3)	170 (2)
NICHD HR ³²	2539	1848	27.1 (6.3), 15–43	28.3 [11.6], 13.4–68.5	612 (33.1)	1079 (58.4)	2 (0.1)	148 (8)	0 (0)	7 (0.4)	430 (23.3)	76 (5.9)	485 (19.4)	108 (4.3)	377 (15.1)
NICHD LR ¹⁵⁹	3134	3097	20.6 (4.4), 15–39	22.7 [5.4], 13.4–51.2	548 (17.7)	1515 (48.9)	2 (0.1)	1010 (32.6)	0 (0)	22 (0.7)	3097 (100)	0 (0)	163 (5.5)	13 (0.4)	150 (5)
Placental Health Study ¹⁷⁶	856	856	32.9 (4.1), 18–45	23.3 [4.9], 16.5–41.9	593 (71.4)	29 (3.5)	66 (7.9)	28 (3.4)	0 (0)	115 (13.8)	856 (100)	0 (0)	69 (8.1)	3 (0.4)	66 (7.7)
POUCH ¹³¹	3019	3019	26.4 (5.8), 15–47.3	27.7 [8.6], 15.1–66.3	2018 (66.8)	743 (24.6)	57 (1.9)	160 (5.3)	0 (0)	41 (1.4)	1293 (42.8)	106 (3.5)	44 (3.2)	12 (0.9)	32 (2.3)
van Kuijk 2011 ¹⁶⁷	407	407	28.8 (3.9), 18.9–40.1	24.8 [6.3], 16–42.2	-	-	-	-	-	-	0 (0)	407 (100)	106 (26)	24 (5.9)	82 (20.1)
Van Kuijk 2014 ¹⁶⁶	230	230	30.8 (4.8), 19.8–40.8	24.7 [6.6], 17.3–48.3	-	-	-	-	-	-	0 (0)	209 (91.7)	43 (19.8)	15 (6.9)	28 (12.9)

Study/data set	Maternal characteristics and outcomes														
	Total number of pregnancies	Number of singleton pregnancies	Age (years), mean (SD), range	First BMI measured, median [IQR], range	Ethnicity, n (%)						Nulliparous, n (%)	Previous PE, n (%)	Outcome, n (%)		
					White	Black	Asian	Hispanic	Mixed	Other			Any-onset PE	Early-onset PE	Late-onset PE
Odibo ¹⁴⁷	1200	1200	31.5 (5.6), 17-49	25.4 [8.4], 13.6-67.8	735 (61.3)	325 (27.1)	94 (7.8)	23 (1.9)	22 (1.8)	1 (0.1)	518 (43.2)	64 (5.3)	102 (8.7)	20 (1.7)	82 (7)
PREDO ¹²⁷	1082	1082	-	25.8 [9.9], 17.2-55	1082 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	247 (22.8)	96 (8.9)	20 (1.9)	75 (6.9)
Prefumo ¹⁵¹	273	273	33.4 (4.2), 21-43	23.3 [4.7], 17.4-37.1	203 (74.4)	41 (15)	29 (10.6)	0 (0)	0 (0)	0 (0)	108 (39.6)	56 (20.5)	12 (4.4)	3 (1.1)	9 (3.3)
Skråstad ¹⁶⁰	599	599	27.5 (4), 18-40	23.6 [5.1], 17.1-48.9	589 (98.3)	0 (0)	1 (0.2)	1 (0.2)	4 (0.7)	4 (0.7)	559 (93.3)	33 (5.5)	27 (4.5)	1 (0.2)	26 (4.3)
Verloren ¹⁷²	566	542	31 (6.2), 15-55	27.6 [8.7], 15.9-57.4	503 (93.3)	15 (2.8)	12 (2.2)	0 (0)	0 (0)	9 (1.7)	267 (49.5)	26 (4.6)	94 (17.2)	20 (3.6)	74 (13.5)
Rumbold ¹⁵⁵	1877	1877	26.4 (5.7), 13-44	24.1 [6.2], 13.7-57.6	1777 (94.9)	3 (0.2)	1 (0.1)	1 (0.1)	4 (0.2)	87 (4.6)	1877 (100)	0 (0)	103 (5.5)	6 (0.3)	97 (5.2)
Vollebregt ¹⁷⁴	308	308	-	22.9 [4.3], 17.7-41.2	264 (85.7)	4 (1.3)	14 (4.5)	20 (6.5)	0 (0)	6 (1.9)	256 (83.1)	38 (12.3)	21 (6.8)	7 (2.3)	14 (4.6)
JSOG ¹⁰⁵	406,286	379,390	32.2 (5.4), 10-59	20.5 [3.6], 10.5-69.8	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	379,390 (100)	195,983 (51.9)	1509 (0.4)	22,880 (5.6)	3548 (0.9)	19,323 (4.8)
DOMInO ¹⁴³	2399	2399	28.9 (5.7), 15-47	26.2 [7.6], 15.4-60.2	2111 (88.1)	24 (1)	191 (8)	4 (0.2)	7 (0.3)	60 (2.5)	-	-	76 (3.2)	8 (0.3)	68 (2.9)
Danish National Birth Cohort ¹³⁶	86,082	84,173	29 (4.4), 15-46	23.9 [4.8], 12.5-65.2	-	-	-	-	-	-	0 (0)	-	2144 (2.5)	196 (0.2)	1948 (2.3)
Indonesian Cohort ¹⁵⁷	2252	2223	28.6 (5.9), 10.2-59	22.4 [5.7], 12.9-47.3	0 (0)	0 (0)	2223 (100)	0 (0)	0 (0)	0 (0)	664 (42.7)	3 (0.1)	97 (6.1)	8 (0.5)	80 (5)
Ohkuchi ¹⁴⁸	288	288	28.7 (4), 18-42	-	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	288 (100)	146 (50.7)	9 (3.2)	9 (3.1)	1 (0.3)	8 (2.8)
Lecarpentier ¹³⁹	244	243	35.9 (4.9), 23-53	27.7 [9.7], 15-47.4	93 (38.3)	123 (50.6)	4 (1.6)	0 (0)	0 (0)	23 (9.5)	46 (18.9)	46 (18.9)	58 (23.8)	32 (13.1)	26 (10.7)
TEST ¹⁴⁶	557	557	32 (4.8), 18.2-43.1	24 [5.5], 17.4-45.2	-	-	-	-	-	-	557 (100)	0 (0)	23 (4.1)	2 (0.4)	18 (3.2)
Massé ¹⁴⁴	1244	1244	26.1 (4.2), 15.4-41.8	21.2 [3.8], 14.8-46.9	539 (96.8)	2 (0.4)	10 (1.8)	0 (0)	6 (1.1)	0 (0)	1244 (100)	0 (0)	109 (8.8)	0 (0)	0 (0)
Staff ¹⁶²	240	240	31.1 (4.8), 18-42	24.1 [6.2], 17-45.4	222 (92.5)	5 (2.1)	13 (5.4)	0 (0)	0 (0)	0 (0)	132 (55)	0 (0)	73 (30.4)	41 (17.1)	32 (13.3)
STORK G ¹³⁵	823	812	29.8 (4.8), 19.3-45.1	24.6 [5.7], 16.2-49.8	375 (46.2)	61 (7.5)	198 (24.4)	12 (1.5)	0 (0)	166 (20.4)	377 (46.4)	0 (0)	46 (5.6)	1 (0.1)	45 (5.5)

Study/data set	Maternal characteristics and outcomes														
	Total number of pregnancies	Number of singleton pregnancies	Age (years), mean (SD), range	First BMI measured, median [IQR], range	Ethnicity, n (%)						Nulliparous, n (%)	Previous PE, n (%)	Outcome, n (%)		
					White	Black	Asian	Hispanic	Mixed	Other			Any-onset PE	Early-onset PE	Late-onset PE
Vatten ¹⁷⁰	736	736	27.9 (5.3), 17–43	-	-	-	-	-	-	-	373 (51)	0 (0)	344 (46.7)	154 (20.9)	190 (25.8)
Vinter ¹⁷³	304	304	29.2 (4.2), 19–43	33.6 [5], 28.8–46	304 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	160 (52.6)	1 (0.3)	19 (6.3)	2 (0.7)	17 (5.6)
BORN Ontario ¹⁰⁴	281,466	276,329	-	23.8 [6.9], 9.8–144	-	-	-	-	-	-	116,602 (43.7)	0 (0)	2903 (1)	336 (0.1)	2379 (0.8)
Ghana Cohort ¹⁴⁵	1016	1010	28 (5.1), 18–49	24.8 [6.4], 15.4–64.5	0 (0)	1010 (100)	0 (0)	0 (0)	0 (0)	0 (0)	-	34 (3.3)	16 (2)	0 (0)	9 (1.1)
MoBa ¹⁴²	112,758	110,771	30.1 (4.7), 14–47	24.2 [5], 11–60.1	-	-	-	-	-	-	48,457 (43.9)	0 (0)	4225 (3.7)	414 (0.4)	3785 (3.4)
Huang ¹³²	141,698	141,698	30.8 (5.1), 13.1–53.3	-	89,350 (66.1)	8708 (6.4)	35,293 (26.1)	0 (0)	0 (0)	1760 (1.3)	57,879 (49.1)	0 (0)	1036 (0.7)	0 (0)	0 (0)
Carbillon ¹¹⁹	42,829	42,036	29.2 (5.8), 13–57	23 [6], 11–68	-	-	-	-	-	-	16,809 (40)	391 (0.9)	359 (0.8)	93 (0.2)	266 (0.6)
Goffinet ¹²⁹	3317	3317	28.8 (5.2), 15.4–47.2	-	-	-	-	-	-	-	1485 (46.3)	0 (0)	33 (1.2)	1 (0)	32 (1.2)
Rang ¹⁵²	42	42	29.6 (3.7), 22–39	-	13,752 (32.7)	19,602 (46.6)	2379 (5.7)	0 (0)	0 (0)	6303 (15)	21 (50)	21 (50)	6 (14.3)	2 (4.8)	4 (9.5)
Cameroni ¹¹⁷	173	173	34.5 (4.5), 21–48	-	152 (87.9)	0 (0)	0 (0)	0 (0)	0 (0)	21 (12.1)	74 (42.8)	22 (12.7)	17 (9.8)	1 (0.6)	16 (9.2)
Conserva ¹²³	53	53	33.2 (6), 24–43	-	53 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	34 (64.2)	5 (9.4)	3 (5.7)	0 (0)	3 (5.7)
Facchinetti ¹²⁴	172	172	33.2 (5.2), 20–58	23.4 [5], 18–49.8	172 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	119 (69.2)	52 (30.4)	58 (33.7)	3 (1.7)	55 (32)
Ferrazzani ¹⁵⁸	54	54	32.5 (5), 21–42	-	54 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	54 (100)	10 (19.6)	5 (9.8)	5 (9.8)
Figueiró-Filho ¹²⁵	81	81	30 (6.2), 18–46	-	59 (72.8)	4 (4.9)	0 (0)	0 (0)	17 (21)	1 (1.2)	0 (0)	81 (100)	30 (44.1)	11 (16.4)	18 (26.9)
Langenveld ¹³⁸	208	205	31.5 (3.9), 22–40	24.2 [5.6], 18.4–44.2	171 (88.6)	11 (5.7)	6 (3.1)	0 (0)	0 (0)	5 (2.6)	205 (100)	0 (0)	54 (26.3)	21 (10.3)	32 (15.7)
Lykke ¹⁴¹	536,414	536,409	29.5 (4.2), 15.9–49.9	23.1 [5.3], 12.8–62.9	-	-	-	-	-	-	-	-	10,159 (1.9)	471 (0.1)	9574 (1.8)
Mbah ¹⁴⁵	1,663,167	1,601,906	25.8 (5.6), 11–53	22 [6], 11.1–95.9	1,301,530 (83.6)	236,479 (15.2)	977 (0.1)	0 (0)	161 (0)	18,611 (1.2)	-	-	42,608 (2.6)	4252 (0.3)	38,305 (2.4)

Study/data set	Maternal characteristics and outcomes														
	Total number of pregnancies	Number of singleton pregnancies	Age (years), mean (SD), range	First BMI measured, median [IQR], range	Ethnicity, n (%)						Outcome, n (%)				
					White	Black	Asian	Hispanic	Mixed	Other	Nulliparous, n (%)	Previous PE, n (%)	Any-onset PE	Early-onset PE	Late-onset PE
Trogstad ¹⁶⁴	37,738	37,738	28.1 (4.5), 17–48	–	37,738 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	37,738 (100)	4,722 (12.6)	321 (0.9)	4,085 (11)
Salim ¹⁵⁶	97	97	30.3 (5.8), 18–45	–	–	–	–	–	–	–	–	–	5 (5.2)	2 (2.1)	3 (3.1)
Van Oostwaard 2012 ¹⁶⁸	425	425	32 (4.1), 23–42	24.3 [6.4], 16.2–41.8	288 (84)	46 (13.4)	4 (1.2)	0 (0)	3 (0.9)	2 (0.6)	0 (0)	208 (48.9)	22 (11.6)	4 (2.1)	18 (9.5)
Van Oostwaard 2014 ¹⁶⁹	639	639	32.1 (4.4), 21–43	25.9 [8.7], 17.7–56.5	360 (71.9)	119 (23.8)	17 (3.4)	0 (0)	3 (0.6)	2 (0.4)	0 (0)	224 (35.1)	30 (9.9)	5 (1.6)	25 (8.2)
Zhang ¹⁷⁸	1,639	1,639	22.5 (4), 13–40	21.2 [4.1], 12.1–47.7	1,061 (65.5)	502 (31)	0 (0)	0 (0)	0 (0)	57 (3.5)	–	–	8 (0.5)	0 (0)	8 (0.5)
Brown 2007 ¹¹⁶	2,785	2,702	29.5 (5), 15–46	–	–	–	–	–	–	–	1,192 (44.1)	0 (0)	781 (28)	79 (2.8)	702 (25.2)
Gurgel Alves 2014 ¹³⁰	500	500	–	–	–	–	–	–	–	–	–	–	31 (12.2)	8 (3.1)	23 (9.1)
Rocha ¹⁵³	733	733	26.1 (6.7), 13–45	25 [6], 16–51	–	–	–	–	–	–	–	45 (6.1)	55 (7.5)	11 (1.5)	44 (6)
Costa 2017 ¹⁰⁷	574	574	34.3 (5.3), 18–50.2	25.3 [6], 17.6–51.3	431 (75.3)	21 (3.7)	96 (16.8)	0 (0)	24 (4.2)	0 (0)	251 (43.7)	40 (7)	29 (5.1)	3 (0.5)	26 (4.5)
Rocha ¹⁵⁴	733	733	26.1 (6.7), 13–45	25 [6], 16–51	128 (18.2)	20 (2.8)	556 (79)	0 (0)	0 (0)	0 (0)	360 (49.1)	39 (5.3)	55 (7.5)	11 (1.5)	44 (6)

JSOG, Japan Society of Obstetrics and Gynecology.

Appendix 5 Detailed study characteristics of IPPIC data sets

Study/data set	Study design (randomised, observational)	Data source (trial, cohort, registry)	Country	Data period	Population type [any pregnancy, high risk (women with complications), low risk]	Inclusion criteria	Exclusion criteria
IPPIC-UK							
SCOPE ⁴²	Observational	Prospective cohort	Multicountry (UK, New Zealand, Australia and Republic of Ireland)	2004–8	Low risk	Healthy nulliparous women with singleton pregnancies	Recognised as high risk of pre-eclampsia, small for gestational age fetus or spontaneous preterm birth owing to underlying medical condition such as chronic hypertension requiring antihypertensive drugs, diabetes, renal disease, systemic lupus erythematosus, antiphospholipid syndrome, sickle cell disease or HIV. Previous cervical knife cone biopsy, three or more abortions or miscarriages, current ruptured membranes, known major fetal anomaly or abnormal karyotype, and interventions that can alter the course of pregnancy such as aspirin or cervical suture
Allen ¹⁰⁸	Observational	Prospective cohort	UK	2010–14	Any pregnancy	All pregnant women attending an inner London hospital between 11 and 14 weeks' gestation	Women with multiple pregnancies and fetal anomalies
ALSPAC ¹⁰³	Observational	Prospective birth cohort	UK	1991–2	Any pregnancy	All pregnant women resident in Avon, UK	None
Chappell ¹²¹	Randomised	Trial	UK	NI	High risk	Pregnant women with an abnormal doppler waveform in either uterine artery at 18–22 weeks' gestation or pre-eclampsia in a previous pregnancy that led to preterm delivery, eclampsia or HELLP syndrome	Heparin or warfarin treatment, abnormal fetal anomaly scan or multiple pregnancy

Study/data set	Study design (randomised, observational)	Data source (trial, cohort, registry)	Country	Data period	Population type [any pregnancy, high risk (women with complications), low risk]	Inclusion criteria	Exclusion criteria
EMPOWaR ¹²²	Randomised	Trial	UK	2011-14	High risk	Women at least 16 years of age at recruitment, between 12 and 16 weeks' gestation and with a BMI of 30 kg/m ²	Non-white women and those with: history of diabetes, systemic disease at the time of enrolment (requiring either regular drugs or systemic corticosteroids treatment in the past 3 months), previous delivery of a baby smaller than the third centile for weight, history of pre-eclampsia with delivery before 32 weeks' gestation, known hypersensitivity to metformin hydrochloride or any of the excipients. Known liver or renal failure, acute disorders at the time of trial entry with the potential to change renal function, such as dehydration sufficient to require intravenous infusion, severe infection, shock, intravascular administration of iodinated contrast agents, or acute or chronic diseases that might cause tissue hypoxia (e.g. cardiac or respiratory failure, recent myocardial infarction, hepatic insufficiency, acute alcohol intoxication or alcoholism); lactating women; and women with multiple pregnancy
POPPY ¹⁰⁶	Observational	Prospective cohort	UK	2011-13	Any pregnancy	Pregnant asymptomatic women with a high risk of spontaneous preterm birth, such as previous history of spontaneous preterm delivery, late miscarriage, invasive cervical surgery or a short cervix	NI

Study/data set	Study design (randomised, observational)	Data source (trial, cohort, registry)	Country	Data period	Population type [any pregnancy, high risk (women with complications), low risk]	Inclusion criteria	Exclusion criteria
Poston 2006 ¹⁵⁰	Randomised	Trial	UK	2003–5	High risk	Gestational age of 14–21 weeks plus one or more of the following risk factors: history of pre-eclampsia necessitating preterm delivery, history of HELLP syndrome, eclampsia, essential hypertension requiring medication, maternal DBP of ≥ 90 mmHg before 20 weeks' gestation in current pregnancy, history of diabetes, antiphospholipid syndrome; chronic renal disease, multiple pregnancy; abnormal uterine artery Doppler waveform, primiparity with BMI at first antenatal appointment of ≥ 30 kg/m ²	Women taking vitamin supplements containing doses of vitamin C of 200 mg or more or of vitamin E of ≥ 40 IU daily. Women treated with warfarin
Poston 2015 ¹⁴⁹	Randomised	Trial	UK	2009–14	High risk	Women aged > 16 years with a BMI of ≥ 30 kg/m ² and a singleton pregnancy	Any underlying disorders, including a pre-pregnancy diagnosis of essential hypertension, diabetes, renal disease, systemic lupus erythematosus, antiphospholipid syndrome, sickle cell disease, thalassaemia, coeliac disease, thyroid disease, and current psychosis; or if on metformin
Khan ¹³⁷	Randomised	Trial	UK	NI	High risk	Women identified to be at high risk of adverse pregnancy outcome by uterine arterial waveform analysis	Women with underlying conditions thought likely to compromise renal function, such as diabetes or renal disease
St George's ¹⁶³	Observational	Prospective registry	UK	2000–15	Any pregnancy	All pregnant women attending an inner-London hospital	None

Study/data set	Study design (randomised, observational)	Data source (trial, cohort, registry)	Country	Data period	Population type [any pregnancy, high risk (women with complications), low risk]	Inclusion criteria	Exclusion criteria
PARIS ¹¹²	IPD MA of 31 randomised trials	Trial	33 countries	1985–2005	Varied	Varied (dependent on individual study)	Varied (dependent on individual study)
AMND ¹¹⁴	Observational	Prospective registry	UK	1986–2015	Any pregnancy	Data from every pregnancy event occurring in Aberdeen Maternity Hospital	None
Born in Bradford ¹⁷⁷	Observational	Prospective birth cohort	UK	2007–11	Any pregnancy	All pregnant women attending Bradford Royal Infirmary	None
Velauthar ³⁹	Observational	Prospective cohort	UK	NI	Any pregnancy	All pregnant women attending an inner-London hospital	None
POP ¹⁶¹	Observational	Prospective cohort	UK	2008–12	Any pregnancy	Nulliparous women with singleton pregnancies	None
IPPIC international							
Baschat ¹¹⁵	Observational	Prospective cohort	USA	2007–10	Any pregnancy	All pregnant women attending any of four Baltimore (USA) hospitals for first-trimester screening	None
Audibert ¹¹³	Observational	Prospective cohort	Canada	2006–8	Low risk	Nulliparous women with singleton pregnancies presenting for Down syndrome screening at 11–13 weeks	Pregnancies with a major fetal chromosomal or structural anomaly
Caradeux ¹¹⁸	Observational	Prospective cohort	Chile	NI	Any pregnancy	All pregnant women attending an 11- to 14-week ultrasound evaluation	None
Giguère ¹²⁶	Observational	Prospective cohort	Canada	2005–10	Any pregnancy	Women at least 18 years old and with a gestational age of at least 10 weeks at their first prenatal visit with no chronic hepatic or renal diseases	Pregnancies with major fetal abnormalities and those ending in termination, miscarriage or fetal death before 24 weeks' gestation
Goetzinger ¹²⁸	Observational	Retrospective cohort	USA	2003–8	Any pregnancy	Women seen for aneuploidy screening	None

Study/data set	Study design (randomised, observational)	Data source (trial, cohort, registry)	Country	Data period	Population type [any pregnancy, high risk (women with complications), low risk]	Inclusion criteria	Exclusion criteria
Antsaklis ¹¹⁰	Observational	Prospective cohort	Greece	1997–8	Low risk	All nulliparous women	Women with multiple pregnancies, renal disease, cardiovascular disease and fetal anomalies
Llurba ¹⁴⁰	Observational	Prospective cohort	Spain	2002–6	Any pregnancy	Singleton women attending routine second-trimester anomaly scans	None
WHO ¹⁷⁵	Observational	Prospective cohort	Multicountry (Argentina, Colombia, India, Italy, Kenya, Peru, Switzerland and Thailand)	2006–9	High risk	Women with risk factors for pre-eclampsia	Women with known renal disease or proteinuria
Andersen ¹⁰⁹	Observational	Prospective cohort	Denmark	2010–12	Any pregnancy	Newly pregnant women	Twin pregnancies and early pregnancy fetal losses
Arenas ¹¹¹	Observational	Prospective cohort	Spain	2000–1	Any pregnancy	Women attending routine ultrasound scan at 20 weeks	Multiple pregnancies or congenital defects
FINNPEC ¹³³	Observational	Prospective/retrospective case-control cohort	Finland	2008–11	Any pregnancy	Nulliparous or multiparous women with a singleton pregnancy with or without pre-eclampsia on admission to hospital	Multiple pregnancy, maternal age of < 18 years
Verlohren ¹⁷¹	Observational	Prospective case-control cohort	Spain	NI	Any pregnancy	Singleton pregnancies	Multigestation, antiphospholipid antibody syndrome, systemic lupus erythematosus or any other autoimmune disease, as well as chronic corticosteroid or nonsteroidal anti-inflammatory drug use, except low-dose aspirin (< 150 mg/day)
Generation R ¹³⁴	Observational	Prospective birth cohort	Netherlands	2002–6	Any pregnancy	Resident mothers delivering during the study period	None

Study/data set	Study design (randomised, observational)	Data source (trial, cohort, registry)	Country	Data period	Population type [any pregnancy, high risk (women with complications), low risk]	Inclusion criteria	Exclusion criteria
NICHD HR ³²	Randomised	Trial	USA	1991-5	High risk	Women with pre-gestational, insulin-treated diabetes mellitus, women with chronic hypertension, women with multifetal gestations, and women who had had preeclampsia in a previous pregnancy	Women with multifetal gestation if they also had chronic hypertension, renal disease, diabetes, history of pre-eclampsia and current proteinuria
NICHD LR ¹⁵⁹	Randomised	Trial	USA	NI (early 1990s)	Low risk	Healthy nulliparous women	Women with chronic hypertension, renal disease, diabetes and other illnesses
Placental Health Study ¹⁷⁶	Observational	Prospective cohort	Canada	2012-13	Low risk	Healthy nulliparous women with singleton pregnancies	Chronic hypertension, use of unfractionated or low molecular-weight heparin, pre-gestational diabetes mellitus, major fetal abnormalities, ruptured membranes, vaginal bleeding from 13 0/7 weeks of gestation for greater than 1 day, or a short cervical length on ultrasonography before 20 weeks of gestation (< 2 cm long)
POUCH ¹³¹	Observational	Prospective cohort	USA	1998-2004	Any pregnancy	Women with a singleton pregnancy at 16-27 weeks' gestation, no known chromosomal abnormality, maternal age of at least 15 years, no pre-pregnancy diabetes mellitus	None
van Kuijk 2011 ¹⁶⁷	Observational	Prospective cohort	Netherlands	1993-2008	High risk	Women with preceding singleton pregnancy complicated by pre-eclampsia or HELLP syndrome	NI

Study/data set	Study design (randomised, observational)	Data source (trial, cohort, registry)	Country	Data period	Population type [any pregnancy, high risk (women with complications), low risk]	Inclusion criteria	Exclusion criteria
van Kuijk 2014 ¹⁶⁶	Observational	Prospective and retrospective cohort	Netherlands	2008–12	High risk	Women with preceding singleton pregnancy complicated by pre-eclampsia or HELLP syndrome	Women who had diabetes, autoimmune disease, heart or kidney disease
Odibo ¹⁴⁷	Observational	Prospective cohort	USA	2009–11	Any pregnancy	Women attending first-trimester screening	None
PREDO ¹²⁷	Observational	Prospective case-control cohort	Finland	2005–9	Any pregnancy	Pregnant women with known risk factor for pre-eclampsia and intrauterine growth restriction and those without, attending clinics for their first ultrasound screening between 12 and 14 weeks' gestation	Asthma diagnosed by a physician, allergy to ASA, tobacco smoking during pregnancy, previous peptic ulcer, previous placental ablation, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), rheumatoid arthritis, haemophilia or thrombophilia (previous venous or pulmonary thrombosis and/or coagulation abnormality), gestational weeks + days < 12 + 0 or > 14 + 0 or multiple pregnancy
Prefumo ¹⁵¹	Observational	Prospective cohort	Italy	2001–5	Any pregnancy	Women attending routine antenatal care	Known medical condition (e.g. diabetes mellitus, connective tissue disease, essential hypertension) or a history of recurrent miscarriage
Skråstad ¹⁶⁰	Observational	Prospective cohort	Norway	2010–12	High risk	Nulliparous and high-risk parous women with one or more previous pre-eclampsia pregnancies	Use of any anticoagulant medication or acetylsalicylic acid in pregnancy
Verlohren ¹⁷²	Observational	Prospective case-control cohort	Germany	NI	Any pregnancy	Singleton pregnancies	Multigestation, antiphospholipid antibody syndrome, systemic lupus erythematosus or any other autoimmune disease, as well as chronic corticosteroid or nonsteroidal anti-inflammatory drug use except low-dose aspirin (< 150 mg/day)

Study/data set	Study design (randomised, observational)	Data source (trial, cohort, registry)	Country	Data period	Population type [any pregnancy, high risk (women with complications), low risk]	Inclusion criteria	Exclusion criteria
Rumbold ¹⁵⁵	Randomised	Trial	Australia	2001–5	Low risk	Nulliparous women with a singleton pregnancy between 14 and 22 weeks' gestation and normal blood pressure	Known multiple pregnancy, known potentially lethal fetal anomaly, known thrombophilia, chronic renal failure, antihypertensive therapy, or specific contraindications to vitamin C or E therapy, such as hemochromatosis or anticoagulant therapy
Vollebregt ¹⁷⁴	Observational	Prospective cohort	Netherlands	2004–6	High risk	Healthy nulliparous women at low risk and women with elevated risk for pre-eclampsia or fetal growth restriction with singleton pregnancies	NI
JSOG ¹⁰⁵	Observational	Prospective registry	Japan	2013–14	Any pregnancy	All women giving birth at participating institutions in Japan	None
DOMInO ¹⁴³	Randomised	Trial	Australia	2005–8	Any pregnancy	Singleton pregnancies at less than 21 weeks' gestation	Already taking a prenatal supplement with DHA, their fetus had a known major abnormality, had a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial
Danish Birth Cohort ¹³⁶	Observational	Prospective registry	Denmark	1996–2002	Any pregnancy	All women in Denmark	None
Indonesian Cohort ¹⁵⁷	Observational	Prospective cohort	Indonesia	2012–15	Any pregnancy	All women attending antenatal care	None
Ohkuchi ¹⁴⁸	Observational	Prospective cohort	Japan	NI	Any pregnancy	Women with singleton pregnancies attending antenatal care	None

Study/data set	Study design (randomised, observational)	Data source (trial, cohort, registry)	Country	Data period	Population type [any pregnancy, high risk (women with complications), low risk]	Inclusion criteria	Exclusion criteria
Lecarpentier ¹³⁹	Observational	Retrospective cohort	France	2004–7	High risk	Women with chronic hypertension	Multiple pregnancies, women with secondary hypertension, women with proteinuria at < 20 weeks' gestation, women considered as having chronic hypertension but without any treatment at first prenatal visit, women transferred from other maternities, pregnancies complicated by fetal malformations
TEST ¹⁴⁶	Randomised	Trial	Ireland	2014–16	Low risk	Nulliparous women between 11–14 weeks' gestation and not already on aspirin	Fetal abnormality or contraindication to aspirin
Massé ¹⁴⁴	Observational	Prospective cohort	Canada	1989–91	Low risk	Nulliparous women attending hospital for routine blood sampling at the start of pregnancy	Diabetes mellitus, cardiovascular disease (including chronic hypertension) or renal disease or women seen after 20 weeks
Staff ¹⁶²	Observational	Prospective case-control cohort	Norway	NI	Low risk	Women with singleton pregnancies	NI
STORK G ¹³⁵	Observational	Prospective cohort	Norway	2008–10	Any pregnancy	Healthy pregnant women	Women with diabetes or diseases require intensive hospital follow-up in pregnancy
Vatten ¹⁷⁰	Observational	Prospective case-control cohort	Norway	1992–4	Any pregnancy	Women attending antenatal care	None
Vinter ¹⁷³	Randomised	Trial	Denmark	2007–10	High risk	Women aged between 18–40 years with a pre-pregnancy weight of between 30 and 45 kg/m ²	Women with chronic medical disorders (hypertension, diabetes, alcohol or drug use) and serious obstetric complication (multiple pregnancy, congenital malformation, miscarriage)

Study/data set	Study design (randomised, observational)	Data source (trial, cohort, registry)	Country	Data period	Population type [any pregnancy, high risk (women with complications), low risk]	Inclusion criteria	Exclusion criteria
BORN Ontario ¹⁰⁴	Observational	Prospective registry	Canada	2012–14	Any pregnancy	Women giving birth during the data period in the Ontario region	None
Ghana Cohort ¹⁶⁵	Observational	Prospective cohort	Ghana	2012–14	Any pregnancy	Women < 17 weeks pregnant, at least 18 years old with no established hypertension at booking	None
MoBa ¹⁴²	Observational	Prospective registry	Norway	1999–2005	Any pregnancy	All women giving birth in Norway	None
Huang ¹³²	Observational	Retrospective cohort	Canada	2000–3	Any pregnancy	All women screened in early pregnancy for Down syndrome	None
Carbillion ¹¹⁹	Observational	Prospective registry	France	1996–2005	Any pregnancy	Women giving birth during the data period in that region	None
Goffinet ¹²⁹	Randomised	Trial	France	1994–7	Low risk	All women attending routine antenatal visit before 24 weeks	Any indications for uterine artery Doppler, such as chronic hypertension, diabetes, previous fetal death, intrauterine growth restriction, hypertensive disorders of pregnancy or contraindication for aspirin
Rang ¹⁵²	Observational	Prospective cohort	Netherlands	NI	High risk	Women with a history of early-onset pre-eclampsia in a previous pregnancy or women who had never been pregnant	None
Cameroni 2011 ¹¹⁷	Observational	Retrospective cohort	Italy	NI	High risk	Singleton pregnancies at risk of pre-eclampsia or intrauterine growth restriction	NI

Study/data set	Study design (randomised, observational)	Data source (trial, cohort, registry)	Country	Data period	Population type [any pregnancy, high risk (women with complications), low risk]	Inclusion criteria	Exclusion criteria
Conserva 2012 ¹²³	Observational	Prospective cohort	Italy	2001–8	High risk	Women with previous adverse pregnancy outcomes	Multiple gestation; a previous uneventful pregnancy; a previous pregnancy treated with low-molecular-weight heparin or unfractionated heparin; patients with clinical immune disease and acquired thrombophilia – lupus-like anticoagulant or APL syndrome; patients with positive antinuclear, antimitochondria, anti-smooth muscle antibodies; postnatal or postmortem diagnosis of congenital fetal anomaly or fetal infection; women of non-Caucasian ethnicity; alcohol or illicit drug use; early pregnancy loss was not considered an abnormal pregnancy outcome
Facchinetti ¹²⁴	Observational	Prospective cohort	Italy	2001–6	High risk	Previous singleton pregnancies complicated by pre-eclampsia and received evaluation for thrombophilia	History of thromboembolic diseases, renal and/or cardiovascular disorder, systemic lupus erythematosus, diabetes and any ethnic group other than white
Ferrazzani ¹⁵⁸	Observational	Prospective cohort	Italy	1990–2001	High risk	Previous severe preterm pre-eclampsia	Previous HELLP syndrome
Figueiró-Filho ¹²⁵	Observational	Prospective case-control cohort	Brazil	2007–10	High risk	Women with severe pre-eclampsia in previous pregnancies	Antiphospholipid antibodies and thrombophilia

Study/data set	Study design (randomised, observational)	Data source (trial, cohort, registry)	Country	Data period	Population type [any pregnancy, high risk (women with complications), low risk]	Inclusion criteria	Exclusion criteria
Langenveld ¹³⁸	Observational	Retrospective cohort	Netherlands	1996–2004	High risk	Women with hypertension (including patients with chronic hypertension), pre-eclampsia or HELLP syndrome, and delivered before 34 weeks of gestation in the study period and primiparous with singleton pregnancy without fetal abnormalities in first pregnancy	NI
Lykke ¹⁴¹	Observational	Prospective registry	Denmark	1978–2007	Any pregnancy	Singleton deliveries of women with first delivery aged > 15 years and second delivery aged < 50 years	Cardiovascular diagnosis and type 1 or type 2 diabetes
Mbah ¹⁴⁵	Observational	Prospective registry	USA	1989–2005	Any pregnancy	Women with first and second singleton pregnancies within the gestational age range of 20–44 weeks	None
Trogstad ¹⁶⁴	Observational	Prospective registry	Norway	1967–98	Any pregnancy	Women with a first and second delivery	None
Salim ¹⁵⁶	Observational	Prospective cohort	Israel	2000–6	High risk	Previous pregnancy with antepartum complications at ≥ 23 weeks' gestation	Women who had a previous pregnancy with antepartum complications that could be attributed to multiple gestations, having fetuses with major congenital anomalies or chromosomal abnormalities, fetal infection, chorioamnionitis, hydrops fetalis and diabetes mellitus
van Oostwaard 2012 ¹⁶⁸	Observational	Prospective cohort	Netherlands	2000–2	High risk	Women with a hypertensive disorder in the index pregnancy and delivery at 34–37 weeks of gestation	Fetal abnormalities

Study/data set	Study design (randomised, observational)	Data source (trial, cohort, registry)	Country	Data period	Population type [any pregnancy, high risk (women with complications), low risk]	Inclusion criteria	Exclusion criteria
van Oostwaard 2014 ¹⁶⁹	Observational	Retrospective cohort	Netherlands	2000–2	High risk	Women with a hypertensive disorder in the index pregnancy and delivery at 34–37 weeks' gestation	Fetal abnormalities
Zhang ¹⁷⁸	Observational	Prospective cohort	USA	1959–65	Any pregnancy	Women attending prenatal care	None
Brown 2007 ¹¹⁶	Observational	Retrospective cohort	Australia	1988–98	Any pregnancy	Women referred for management of hypertensive disorders of pregnancy	None
Gurgel Alves 2014 ¹³⁰	Observational	Prospective cohort	Brazil	2009–11	Any pregnancy	Women attending for first-trimester Down syndrome screening	None
Rocha ¹⁵³	Observational	Prospective cohort	Brazil	2009–14	Any pregnancy	Women with singleton pregnancies attending for first-trimester ultrasound scans	Prior maternal renal disease, major fetal malformations or chromosomal abnormalities, miscarriage
Costa 2017 ¹⁰⁷	Observational	Prospective cohort	Australia	2012–15	Any pregnancy	Women attending for their second-trimester morphology ultrasound between 19 and 22 weeks	None
Rocha ¹⁵⁴	Observational	Prospective cohort	Brazil	2009–14	Any pregnancy	Singleton pregnancies of women attending routine ultrasound screening	Kidney disease diagnosis in their history or on ultrasound examination, major fetal malformations or chromosomal abnormalities, and fetuses with crown–rump length of > 84 mm

ASA, acetylsalicylic acid; JSOG, Japan Society of Obstetrics and Gynecology; NI, no information.

Appendix 6 Summary of missing data for prioritised predictors and each pre-eclampsia outcome for all pregnancies

APPENDIX 6

Study	Variable, n (%)												
	Maternal clinical characteristics												
	Ethnicity	Age	Nulliparous	Previous PE	Previous autoimmune disease	Previous heritable thrombophilia	Family history of PE	History of renal disease	History of diabetes	History of hypertension	Smoker	Substance misuse in current pregnancy	Spontaneous conception
SCOPE ¹²	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Allen ¹⁰⁸	2 (0.2)	1 (0.1)	0 (0)	0 (0)	0 (0)	1045 (100)	6 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ALSPAC ¹⁰³	2999 (19.9)	2078 (13.8)	2473 (16.4)	9476 (63)	15,242 (100)	15,242 (100)	15,242 (100)	2798 (18.4)	2857 (18.7)	3049 (20)	2702 (17.7)	2334 (15.3)	2906 (19.1)
Chappell ¹²¹	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	316 (100)	316 (100)	316 (100)	0 (0)	0 (0)	0 (0)	316 (100)	316 (100)
EMPOWaR ¹²²	0 (0)	0 (0)	1 (0.2)	0 (0)	449 (100)	449 (100)	449 (100)	0 (0)	0 (0)	449 (100)	0 (0)	0 (0)	449 (100)
POPPY ¹⁰⁶	0 (0)	0 (0)	0 (0)	1010 (83.1)	1216 (100)	1216 (100)	1216 (100)	1216 (100)	1216 (100)	1216 (100)	1216 (100)	1216 (100)	1216 (100)
Poston 2006 ¹⁵⁰	2422 (100)	22 (1.1)	2422 (100)	0 (0)	0 (0)	2422 (100)	2422 (100)	0 (0)	0 (0)	0 (0)	2422 (100)	2422 (100)	2422 (100)
Poston 2015 ¹⁴⁹	0 (0)	0 (0)	0 (0)	7 (0.5)	0 (0)	1554 (100)	61 (3.9)	0 (0)	0 (0)	0 (0)	0 (0)	1554 (100)	4 (0.3)
Khan ¹³⁷	222 (100)	222 (100)	0 (0)	76 (34.2)	222 (100)	222 (100)	222 (100)	0 (0)	0 (0)	222 (100)	0 (0)	222 (100)	222 (100)
St George's ¹⁴³	1086 (2)	0 (0)	104 (0.2)	25,326 (46.4)	54,656 (100)	54,656 (100)	54,656 (100)	54,656 (100)	54,656 (100)	0 (0)	4054 (7.4)	54,656 (100)	1427 (2.6)
PARIS Collaborative Group ¹¹²	35,955 (100)	35,955 (100)	190 (0.5)	3073 (8.9)	27,798 (77.3)	35,955 (100)	35,395 (98.4)	10,741 (29.9)	7599 (21.1)	19,304 (53.7)	35,955 (100)	35,955 (100)	35,955 (100)
AMND ¹¹⁴	138,967 (100)	19 (0)	7 (0)	72,684 (53.2)	0 (0)	138,967 (100)	138,967 (100)	0 (0)	138,967 (100)	0 (0)	2961 (2.1)	0 (0)	138,967 (100)
Born in Bradford ¹⁷⁷	2676 (20.4)	405 (3.1)	405 (3.1)	8178 (62.3)	13,279 (100)	13,279 (100)	13,279 (100)	13,279 (100)	925 (7)	936 (7)	2679 (20.2)	4038 (30.4)	13,279 (100)
Velauthar ³⁹	67 (5.6)	1208 (100.2)	61 (5.1)	608 (50.4)	1208 (100)	1208 (100)	1208 (100)	1208 (100)	62 (5.1)	62 (5.1)	62 (5.1)	1208 (100)	1208 (100)
POP ¹⁴¹	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1704 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Baschat ¹¹⁵	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	893 (100)	893 (100)	0 (0)	0 (0)	0 (0)	0 (0)	893 (100)	893 (100)
Audibert ¹¹³	682 (100)	3 (0.4)	12 (1.8)	0 (0)	0 (0)	0 (0)	682 (100)	682 (100)	0 (0)	0 (0)	0 (0)	682 (100)	682 (100)
Caradeux ¹¹⁸	63 (14.7)	7866 (102.2)	12 (0.2)	4149 (53.9)	5553 (70.6)	5515 (70.1)	7866 (100)	426 (5.4)	313 (4)	256 (3.3)	872 (11.1)	6307 (80.2)	7866 (100)
Giguère ¹²⁶	63 (1.6)	72 (1.8)	302 (7.5)	3284 (81.4)	0 (0)	4035 (100)	4035 (100)	0 (0)	3406 (84.4)	281 (7)	244 (6)	281 (7)	92 (2.3)
Goetzinger ¹²⁸	7 (0.2)	11 (0.3)	0 (0)	0 (0)	0 (0)	3328 (100)	3328 (100)	0 (0)	0 (0)	0 (0)	6 (0.2)	3328 (100)	3328 (100)
Antsaklis ¹¹⁰	167 (1.4)	11,668 (100)	11,668 (100)	39 (0.3)	11,668 (100)	61 (0.5)	11,668 (100)	11,668 (100)	61 (0.5)	59 (0.5)	1229 (10.5)	11,668 (100)	11,668 (100)
Llurba ¹⁴⁰	6 (0.1)	1 (0)	0 (0)	0 (0)	2 (0)	2 (0)	7315 (100)	0 (0)	1 (0)	1 (0)	2 (0)	7315 (100)	7315 (100)
WHO ¹⁷⁵	299 (14.1)	0 (0)	0 (0)	939 (44.3)	2161 (100)	2161 (100)	2161 (100)	2161 (100)	198 (9.2)	197 (9.1)	2 (0.1)	2161 (100)	2161 (100)
Andersen ¹⁰⁹	319 (100)	0 (0)	0 (0)	0 (0)	0 (0)	319 (100)	319 (100)	319 (100)	319 (100)	0 (0)	0 (0)	0 (0)	319 (100)
Arenas ¹¹¹	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	2506 (100)	2506 (100)	0 (0)	0 (0)	0 (0)	2506 (100)	2506 (100)	2506 (100)
FINNPEC ¹³³	1 (0.4)	0 (0)	3 (1.3)	5 (2.1)	0 (0)	253 (100)	253 (100)	7 (2.8)	3 (1.2)	8 (3.2)	1 (0.4)	253 (100)	253 (100)
Galindo ¹⁷¹	478 (5.5)	2 (0)	108 (1.3)	3938 (45.6)	2573 (29.5)	8727 (100)	8727 (100)	8727 (100)	1397 (16)	1253 (14.4)	1112 (12.7)	0 (0)	592 (6.8)
Generation R ¹³⁴	0 (0)	19 (1)	0 (0)	1250 (67.6)	2539 (100)	2539 (100)	2539 (100)	2539 (100)	0 (0)	0 (0)	0 (0)	2539 (100)	2539 (100)
NICHD HR ³²	0 (0)	99 (3.2)	0 (0)	0 (0)	0 (0)	3134 (100)	3134 (100)	0 (0)	0 (0)	0 (0)	6 (0.2)	3134 (100)	3134 (100)
NICHD LR ¹⁵⁹	25 (2.9)	0 (0)	0 (0)	0 (0)	0 (0)	36 (4.2)	856 (100)	856 (100)	0 (0)	0 (0)	0 (0)	856 (100)	1 (0.1)
Placental Health Study ¹⁷⁶	0 (0)	0 (0)	1 (0)	1 (0)	2458 (81.4)	1706 (56.5)	3019 (100)	1921 (63.6)	0 (0)	1 (0)	6 (0.2)	7 (0.2)	3019 (100)
POUCH ¹³¹	407 (100)	0 (0)	0 (0)	0 (0)	407 (100)	407 (100)	407 (100)	407 (100)	407 (100)	0 (0)	407 (100)	407 (100)	407 (100)
van Kuijk 2011 ¹⁵⁷	230 (100)	0 (0)	0 (0)	2 (0.9)	0 (0)	230 (100)	230 (100)	0 (0)	0 (0)	0 (0)	230 (100)	230 (100)	20 (8.7)
van Kuijk 2014 ¹⁶⁶	0 (0)	1 (0.1)	1 (0.1)	0 (0)	1200 (100)	1200 (100)	1200 (100)	7 (0.6)	0 (0)	0 (0)	9 (0.8)	11 (0.9)	5 (0.4)

Multiple pregnancy	History of SGA	Ultrasound markers											Biochemical markers			Outcome		
		BMI	SBP	DBP	MAP	Urine dipstick	PCR	Uterine PI	Umbilical PI	PAPP-A	PIGF	sFlt-1	Any-onset PE	Early-onset PE	Late-onset PE			
0 (0)	5628 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4464 (79.3)	5628 (100)	3102 (55.1)	48 (0.9)	51 (0.9)	48 (0.9)	5 (0.1)	5 (0.1)	5 (0.1)			
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1045 (100)	1045 (100)	0 (0)	1045 (100)	114 (10.9)	0 (0)	1045 (100)	0 (0)	0 (0)	0 (0)			
0 (0)	15,242 (100)	3147 (20.6)	2011 (13.2)	2011 (13.2)	2011 (13.2)	2087 (13.7)	15,242 (100)	15,242 (100)	15,242 (100)	15,242 (100)	15,242 (100)	15,242 (100)	1546 (10.1)	1546 (10.1)	1546 (10.1)			
0 (0)	316 (100)	33 (10.4)	33 (10.4)	33 (10.4)	33 (10.4)	92 (29.1)	316 (100)	316 (100)	316 (100)	316 (100)	143 (45.3)	238 (75.3)	33 (10.4)	33 (10.4)	33 (10.4)			
0 (0)	0 (0)	334 (74.4)	0 (0)	0 (0)	0 (0)	449 (100)	449 (100)	449 (100)	449 (100)	449 (100)	449 (100)	449 (100)	246 (54.8)	78 (17.4)	239 (53.2)			
0 (0)	1216 (100)	0 (0)	1216 (100)	1216 (100)	1216 (100)	1216 (100)	1216 (100)	1216 (100)	1216 (100)	1216 (100)	1216 (100)	1216 (100)	12 (1)	12 (1)	12 (1)			
0 (0)	2422 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2214 (91.4)	2249 (92.9)	2422 (100)	2422 (100)	2249 (92.9)	2249 (92.9)	0 (0)	0 (0)	0 (0)			
0 (0)	1554 (100)	0 (0)	8 (0.5)	8 (0.5)	8 (0.5)	357 (23)	1547 (99.5)	1554 (100)	1554 (100)	1554 (100)	395 (25.4)	1554 (100)	47 (3)	47 (3)	47 (3)			
0 (0)	222 (100)	0 (0)	2 (0.9)	2 (0.9)	2 (0.9)	222 (100)	222 (100)	222 (100)	43 (19.4)	222 (100)	222 (100)	222 (100)	0 (0)	0 (0)	0 (0)			
0 (0)	54,656 (100)	9151 (16.7)	54,656 (100)	54,656 (100)	54,656 (100)	54,656 (100)	54,656 (100)	20,069 (36.7)	54,656 (100)	54,656 (100)	54,656 (100)	54,656 (100)	0 (0)	0 (0)	0 (0)			
0 (0)	4814 (13.4)	35,955 (100)	5255 (14.6)	5246 (14.6)	5258 (14.6)	35,955 (100)	35,955 (100)	35,955 (100)	35,955 (100)	35,955 (100)	35,955 (100)	35,955 (100)	2603 (7.2)	2630 (7.3)	2630 (7.3)			
0 (0)	138,967 (100)	26,080 (18.8)	138,967 (100)	138,967 (100)	138,967 (100)	138,967 (100)	138,967 (100)	138,967 (100)	138,967 (100)	138,967 (100)	138,967 (100)	138,967 (100)	0 (0)	0 (0)	0 (0)			
0 (0)	13,279 (100)	3360 (25.3)	2747 (20.7)	2747 (20.7)	2747 (20.7)	6122 (46.1)	13,279 (100)	13,279 (100)	13,279 (100)	13,279 (100)	13,279 (100)	13,279 (100)	955 (7.2)	1289 (9.7)	1289 (9.7)			
0 (0)	1208 (100)	67 (5.5)	69 (5.7)	69 (5.7)	69 (5.7)	1208 (100)	600 (49.7)	63 (5.2)	1208 (100)	1208 (100)	1208 (100)	1208 (100)	93 (7.7)	93 (7.7)	93 (7.7)			
0 (0)	1704 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1704 (100)	1704 (100)	266 (15.6)	1704 (100)	704 (41.3)	704 (41.3)	1704 (100)	0 (0)	0 (0)	0 (0)			
0 (0)	893 (100)	0 (0)	893 (100)	893 (100)	893 (100)	893 (100)	893 (100)	28 (3.1)	893 (100)	4 (0.4)	362 (40.5)	893 (100)	0 (0)	0 (0)	0 (0)			
0 (0)	682 (100)	6 (0.9)	3 (0.4)	2 (0.3)	3 (0.4)	682 (100)	682 (100)	38 (5.6)	370 (54.3)	682 (100)	682 (100)	682 (100)	0 (0)	0 (0)	0 (0)			
0 (0)	7866 (100)	1956 (24.9)	539 (6.9)	540 (6.9)	540 (6.9)	7866 (100)	7866 (100)	7866 (100)	7866 (100)	7212 (91.7)	7866 (100)	7212 (91.7)	0 (0)	0 (0)	0 (0)			
0 (0)	4035 (100)	606 (15)	4035 (100)	4035 (100)	4035 (100)	4035 (100)	4035 (100)	4035 (100)	4035 (100)	2119 (52.5)	4035 (100)	4035 (100)	1798 (44.6)	1798 (44.6)	1798 (44.6)			
0 (0)	3328 (100)	9 (0.3)	2898 (87.1)	2905 (87.3)	2905 (87.3)	3328 (100)	3328 (100)	2770 (83.2)	3328 (100)	3328 (100)	3328 (100)	3328 (100)	985 (29.6)	985 (29.6)	985 (29.6)			
0 (0)	0 (0)	11,668 (100)	11,668 (100)	11,668 (100)	11,668 (100)	11,668 (100)	11,668 (100)	6299 (54)	11,668 (100)	11,668 (100)	11,668 (100)	11,668 (100)	0 (0)	0 (0)	0 (0)			
0 (0)	7315 (100)	9 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	7315 (100)	7315 (100)	7315 (100)	7315 (100)	3180 (43.5)	3428 (46.9)	0 (0)	0 (0)	0 (0)			
0 (0)	2161 (100)	3 (0.1)	2161 (100)	2161 (100)	2161 (100)	2161 (100)	2161 (100)	2161 (100)	2161 (100)	2161 (100)	1028 (47.6)	1028 (47.6)	47 (2.2)	47 (2.2)	47 (2.2)			
0 (0)	319 (100)	0 (0)	319 (100)	319 (100)	319 (100)	319 (100)	319 (100)	2 (0.6)	2 (0.6)	319 (100)	319 (100)	319 (100)	0 (0)	0 (0)	0 (0)			
0 (0)	2506 (100)	5 (0.2)	10 (0.4)	10 (0.4)	10 (0.4)	0 (0)	2506 (100)	2506 (100)	2506 (100)	2506 (100)	1930 (77)	1929 (77)	0 (0)	0 (0)	0 (0)			
0 (0)	253 (100)	15 (5.9)	2 (0.8)	2 (0.8)	2 (0.8)	253 (100)	253 (100)	253 (100)	78 (30.8)	253 (100)	3 (1.2)	3 (1.2)	4 (1.6)	4 (1.6)	4 (1.6)			
0 (0)	8727 (100)	38 (0.4)	18 (0.2)	18 (0.2)	18 (0.2)	8727 (100)	8727 (100)	3549 (40.7)	8727 (100)	8727 (100)	635 (7.3)	635 (7.3)	255 (2.9)	10 (0.1)	245 (2.8)			
0 (0)	2539 (100)	25 (1)	0 (0)	0 (0)	0 (0)	0 (0)	2539 (100)	2539 (100)	2539 (100)	2539 (100)	1571 (61.9)	2539 (100)	36 (1.4)	36 (1.4)	36 (1.4)			
0 (0)	3134 (100)	94 (3)	0 (0)	0 (0)	0 (0)	0 (0)	3134 (100)	3134 (100)	3134 (100)	3134 (100)	3134 (100)	3134 (100)	150 (4.8)	150 (4.8)	150 (4.8)			
0 (0)	856 (100)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	0 (0)	754 (88.1)	1 (0.1)	3 (0.4)	856 (100)	856 (100)	856 (100)	0 (0)	0 (0)	0 (0)			
0 (0)	3019 (100)	1 (0)	1648 (54.6)	1648 (54.6)	1648 (54.6)	0 (0)	3019 (100)	3019 (100)	3019 (100)	3019 (100)	1715 (56.8)	1712 (56.7)	1648 (54.6)	1648 (54.6)	1648 (54.6)			
0 (0)	407 (100)	0 (0)	407 (100)	407 (100)	407 (100)	407 (100)	407 (100)	407 (100)	407 (100)	407 (100)	407 (100)	407 (100)	0 (0)	0 (0)	0 (0)			
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	230 (100)	230 (100)	230 (100)	230 (100)	230 (100)	230 (100)	230 (100)	13 (5.7)	13 (5.7)	13 (5.7)			
0 (0)	6 (0.5)	29 (2.4)	81 (6.8)	81 (6.8)	82 (6.8)	1200 (100)	1200 (100)	10 (0.8)	1200 (100)	1200 (100)	697 (58.1)	889 (74.1)	23 (1.9)	23 (1.9)	23 (1.9)			

APPENDIX 6

Variable, n (%)													
Maternal clinical characteristics													
Study	Ethnicity	Age	Nulliparous	Previous PE	Previous autoimmune disease	Previous heritable thrombophilia	Family history of PE	History of renal disease	History of diabetes	History of hypertension	Smoker	Substance misuse in current pregnancy	Spontaneous conception
Odibo ¹⁴⁷	0 (0)	1082 (100)	0 (0)	0 (0)	0 (0)	1082 (100)	1082 (100)	0 (0)	0 (0)	0 (0)	1082 (100)	1082 (100)	125 (11.6)
PREDO ¹²⁷	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	273 (100)	273 (100)	0 (0)	0 (0)	0 (0)	0 (0)	273 (100)	273 (100)
Prefumo ¹⁵¹	0 (0)	0 (0)	0 (0)	0 (0)	599 (100)	599 (100)	599 (100)	599 (100)	599 (100)	0 (0)	0 (0)	599 (100)	0 (0)
Skråstad ¹⁶⁰	3 (0.6)	0 (0)	3 (0.6)	0 (0)	235 (41.5)	0 (0)	566 (100)	2 (0.4)	2 (0.4)	2 (0.4)	21 (3.7)	566 (100)	566 (100)
Verlohren ¹⁷²	4 (0.2)	0 (0)	0 (0)	0 (0)	1877 (100)	0 (0)	1877 (100)	0 (0)	0 (0)	0 (0)	39 (2.1)	1877 (100)	39 (2.1)
Rumbold ¹⁵⁵	0 (0)	308 (100)	0 (0)	0 (0)	308 (100)	308 (100)	308 (100)	2 (0.6)	2 (0.6)	2 (0.6)	308 (100)	308 (100)	308 (100)
Vollebregt ¹⁷⁴	0 (0)	1147 (0.3)	1586 (0.4)	0 (0)	0 (0)	406,286 (100)	406,286 (100)	0 (0)	0 (0)	0 (0)	84,755 (20.9)	406,286 (100)	0 (0)
JSOC ¹⁰⁵	2 (0.1)	0 (0)	2399 (100)	2399 (100)	2399 (100)	2399 (100)	2399 (100)	2399 (100)	2399 (100)	2399 (100)	3 (0.1)	2399 (100)	3 (0.1)
DOMInO ¹⁴³	86,082 (100)	0 (0)	0 (0)	86,082 (100)	0 (0)	86,082 (100)	86,082 (100)	0 (0)	0 (0)	0 (0)	3164 (3.7)	86,082 (100)	86,082 (100)
Danish Birth Cohort ¹⁵²	0 (0)	75 (3.4)	674 (30.3)	0 (0)	2252 (100)	2252 (100)	2252 (100)	2252 (100)	1 (0)	18 (0.8)	1264 (56.1)	2252 (100)	2252 (100)
Indonesian Cohort ¹⁵⁷	0 (0)	288 (100)	0 (0)	4 (1.4)	288 (100)	288 (100)	288 (100)	288 (100)	288 (100)	288 (100)	288 (100)	288 (100)	288 (100)
Ohkuchi ¹⁴⁸	0 (0)	0 (0)	0 (0)	0 (0)	244 (100)	244 (100)	244 (100)	0 (0)	0 (0)	0 (0)	0 (0)	244 (100)	244 (100)
Lecarpentier ¹³⁹	557 (100)	0 (0)	0 (0)	0 (0)	0 (0)	557 (100)	557 (100)	0 (0)	557 (100)	0 (0)	0 (0)	557 (100)	0 (0)
TEST ¹⁴⁶	1244 (100)	0 (0)	0 (0)	0 (0)	1244 (100)	1244 (100)	1244 (100)	0 (0)	0 (0)	0 (0)	1244 (100)	1244 (100)	1244 (100)
Massé ¹⁴⁴	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	240 (100)	240 (100)	0 (0)	0 (0)	0 (0)	0 (0)	240 (100)	240 (100)
Staff ¹⁶²	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	823 (100)	823 (100)	0 (0)	0 (0)	0 (0)	0 (0)	823 (100)	0 (0)
STORK G ¹³⁵	736 (100)	736 (100)	4 (0.5)	363 (49.3)	736 (100)	736 (100)	736 (100)	736 (100)	736 (100)	736 (100)	736 (100)	736 (100)	736 (100)
Vatten ¹⁷⁰	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	304 (100)	304 (100)	0 (0)	0 (0)	0 (0)	0 (0)	304 (100)	304 (100)
Vinter ¹⁷³	281,466 (100)	281,466 (101.9)	10,027 (3.6)	162,627 (58.9)	15,312 (5.4)	281,466 (100)	281,466 (100)	15,312 (5.4)	0 (0)	15,312 (5.4)	0 (0)	21,145 (7.5)	0 (0)
BORN Ontario ¹⁰⁴	0 (0)	0 (0)	1016 (100)	0 (0)	1016 (100)	1016 (100)	1016 (100)	1016 (100)	1016 (100)	0 (0)	1016 (100)	1016 (100)	1016 (100)
Ghana Cohort ¹⁶⁵	112,758 (100)	496 (0.4)	496 (0.4)	63,352 (57.2)	112,758 (100)	112,758 (100)	112,758 (100)	496 (0.4)	0 (0)	496 (0.4)	18,757 (16.6)	0 (0)	0 (0)
MoBA ¹⁴²	6587 (4.6)	141,698 (100)	23,866 (16.8)	83,819 (59.2)	141,698 (100)	141,698 (100)	141,698 (100)	141,698 (100)	0 (0)	0 (0)	141,698 (100)	141,698 (100)	141,698 (100)
Huang ¹³²	42,829 (100)	0 (0)	53 (0.1)	0 (0)	0 (0)	42,829 (100)	42,829 (100)	42,829 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Carbillion ¹¹⁹	3317 (100)	3317 (100)	112 (3.4)	0 (0)	0 (0)	3317 (100)	3317 (100)	0 (0)	0 (0)	592 (17.8)	3317 (100)	3317 (100)	3317 (100)
Goffinet ¹²⁹	42 (100)	42 (100)	0 (0)	0 (0)	42 (100)	42 (100)	42 (100)	42 (100)	42 (100)	0 (0)	0 (0)	42 (100)	42 (100)
Rang ¹⁵²	0 (0)	173 (100)	0 (0)	0 (0)	173 (100)	173 (100)	173 (100)	173 (100)	173 (100)	0 (0)	173 (100)	173 (100)	173 (100)
Cameroni 2011 ¹¹⁷	0 (0)	53 (100)	0 (0)	0 (0)	0 (0)	0 (0)	53 (100)	0 (0)	0 (0)	0 (0)	53 (100)	53 (100)	53 (100)
Conserva 2012 ¹²³	0 (0)	2 (1.2)	0 (0)	1 (0.6)	0 (0)	0 (0)	172 (100)	0 (0)	0 (0)	0 (0)	23 (13.4)	172 (100)	172 (100)
Facchinetti ¹²⁴	0 (0)	54 (100)	0 (0)	0 (0)	0 (0)	54 (100)	54 (100)	0 (0)	0 (0)	0 (0)	54 (100)	54 (100)	54 (100)
Ferrazzani ¹⁵⁸	0 (0)	81 (100)	0 (0)	0 (0)	0 (0)	0 (0)	81 (100)	81 (100)	0 (0)	0 (0)	81 (100)	81 (100)	81 (100)
Figueiró-Filho ¹²⁵	12 (5.9)	2 (1)	0 (0)	0 (0)	19 (9.1)	19 (9.1)	208 (100)	0 (0)	19 (9.1)	16 (7.7)	23 (11.1)	208 (100)	208 (100)
Langenveld ¹³⁸	536,414 (100)	0 (0)	536,414 (100)	536,414 (100)	536,414 (100)	536,414 (100)	536,414 (100)	536,414 (100)	0 (0)	536,414 (100)	189,726 (35.4)	536,414 (100)	536,414 (100)
Lykke ¹⁴¹	46,177 (2.9)	44,301 (2.8)	1,663,167 (100)	1,663,167 (100)	1,663,167 (100)	1,663,167 (100)	1,663,167 (100)	45,547 (2.7)	45,547 (2.7)	45,547 (2.7)	54,336 (3.3)	1,663,167 (100)	1,663,167 (100)

Multiple pregnancy	History of SGA	BMI	Ultrasound markers					Biochemical markers			Outcome				
			SBP	DBP	MAP	Urine dipstick	PCR	Uterine PI	Umbilical PI	PAPP-A	PIGF	sFit-1	Any-onset PE	Early-onset PE	Late-onset PE
0 (0)	1082 (100)	16 (1.5)	670 (61.9)	670 (61.9)	670 (61.9)	1004 (92.8)	1082 (100)	1082 (100)	1082 (100)	661 (61.1)	976 (90.2)	976 (90.2)	0 (0)	1 (0.1)	1 (0.1)
0 (0)	273 (100)	60 (22)	273 (100)	273 (100)	273 (100)	273 (100)	273 (100)	62 (22.7)	273 (100)	273 (100)	273 (100)	273 (100)	0 (0)	0 (0)	0 (0)
0 (0)	599 (100)	0 (0)	0 (0)	0 (0)	0 (0)	599 (100)	599 (100)	98 (16.4)	599 (100)	0 (0)	0 (0)	599 (100)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	12 (2.1)	3 (0.5)	3 (0.5)	3 (0.5)	28 (4.9)	566 (100)	477 (84.3)	166 (29.3)	566 (100)	103 (18.2)	103 (18.2)	18 (3.2)	18 (3.2)	18 (3.2)
0 (0)	0 (0)	152 (8.1)	26 (1.4)	26 (1.4)	26 (1.4)	357 (19)	1877 (100)	1877 (100)	1877 (100)	1877 (100)	1877 (100)	1877 (100)	0 (0)	0 (0)	0 (0)
0 (0)	308 (100)	0 (0)	308 (100)	308 (100)	308 (100)	308 (100)	308 (100)	26 (8.4)	308 (100)	308 (100)	308 (100)	308 (100)	1 (0.3)	1 (0.3)	1 (0.3)
0 (0)	406,286 (100)	57,224 (14.1)	406,286 (100)	406,286 (100)	406,286 (100)	406,286 (100)	406,286 (100)	406,286 (100)	406,286 (100)	406,286 (100)	406,286 (100)	406,286 (100)	0 (0)	9 (0)	9 (0)
0 (0)	2399 (100)	27 (1.1)	2399 (100)	2399 (100)	2399 (100)	2399 (100)	2399 (100)	2399 (100)	2399 (100)	2399 (100)	2399 (100)	2399 (100)	34 (1.4)	34 (1.4)	32 (1.3)
0 (0)	86,082 (100)	9656 (11.2)	86,082 (100)	86,082 (100)	86,082 (100)	86,082 (100)	86,082 (100)	86,082 (100)	86,082 (100)	86,082 (100)	86,082 (100)	86,082 (100)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	177 (7.9)	470 (20.9)	470 (20.9)	471 (20.9)	2248 (99.8)	2252 (100)	2252 (100)	2252 (100)	2252 (100)	2252 (100)	2252 (100)	655 (29.1)	664 (29.5)	664 (29.5)
0 (0)	288 (100)	288 (100)	288 (100)	288 (100)	288 (100)	288 (100)	288 (100)	288 (100)	288 (100)	288 (100)	288 (100)	288 (100)	0 (0)	0 (0)	0 (0)
0 (0)	244 (100)	20 (8.2)	33 (13.5)	33 (13.5)	33 (13.5)	244 (100)	244 (100)	244 (100)	244 (100)	244 (100)	244 (100)	244 (100)	0 (0)	0 (0)	0 (0)
0 (0)	557 (100)	1 (0.2)	0 (0)	0 (0)	0 (0)	557 (100)	557 (100)	3 (0.5)	557 (100)	0 (0)	0 (0)	557 (100)	0 (0)	0 (0)	0 (0)
0 (0)	1244 (100)	2 (0.2)	724 (58.2)	724 (58.2)	724 (58.2)	1244 (100)	1244 (100)	1244 (100)	1244 (100)	1244 (100)	1244 (100)	1244 (100)	0 (0)	109 (8.8)	109 (8.8)
0 (0)	240 (100)	0 (0)	0 (0)	0 (0)	0 (0)	240 (100)	240 (100)	240 (100)	240 (100)	240 (100)	29 (12.1)	8 (3.3)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	3 (0.4)	15 (1.8)	15 (1.8)	15 (1.8)	823 (100)	823 (100)	823 (100)	71 (8.6)	823 (100)	823 (100)	823 (100)	0 (0)	0 (0)	0 (0)
0 (0)	736 (100)	736 (100)	736 (100)	736 (100)	736 (100)	736 (100)	736 (100)	736 (100)	736 (100)	736 (100)	17 (2.3)	56 (7.6)	0 (0)	0 (0)	0 (0)
0 (0)	304 (100)	0 (0)	0 (0)	0 (0)	0 (0)	304 (100)	304 (100)	304 (100)	304 (100)	304 (100)	304 (100)	304 (100)	0 (0)	0 (0)	0 (0)
0 (0)	281,466 (100)	48,947 (17.4)	281,466 (100)	281,466 (100)	281,466 (100)	281,466 (100)	281,466 (100)	281,466 (100)	281,466 (100)	281,466 (100)	281,466 (100)	281,466 (100)	0 (0)	188 (0.1)	188 (0.1)
0 (0)	1016 (100)	8 (0.8)	526 (51.8)	526 (51.8)	526 (51.8)	532 (52.4)	1016 (100)	1016 (100)	1016 (100)	71 (7)	71 (7)	1016 (100)	221 (21.8)	228 (22.4)	228 (22.4)
0 (0)	112,758 (100)	15,779 (14)	23,192 (20.6)	23,348 (20.7)	23,373 (20.7)	112,758 (100)	112,758 (100)	112,758 (100)	112,758 (100)	112,758 (100)	112,758 (100)	112,758 (100)	0 (0)	26 (0)	26 (0)
0 (0)	141,698 (100)	141,698 (100)	141,698 (100)	141,698 (100)	141,698 (100)	141,698 (100)	141,698 (100)	141,698 (100)	141,698 (100)	134,442 (94.9)	141,698 (100)	141,698 (100)	0 (0)	1036 (0.7)	1036 (0.7)
0 (0)	451 (1.1)	2722 (6.4)	122 (0.3)	118 (0.3)	123 (0.3)	5752 (13.4)	42,829 (100)	42,829 (100)	42,829 (100)	42,829 (100)	42,829 (100)	42,829 (100)	0 (0)	0 (0)	0 (0)
0 (0)	3317 (100)	3317 (100)	3317 (100)	3317 (100)	3317 (100)	3317 (100)	3317 (100)	3317 (100)	3317 (100)	3317 (100)	3317 (100)	3317 (100)	602 (18.1)	602 (18.1)	602 (18.1)
0 (0)	42 (100)	42 (100)	0 (0)	0 (0)	0 (0)	42 (100)	42 (100)	0 (0)	42 (100)	42 (100)	42 (100)	42 (100)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	173 (100)	173 (100)	173 (100)	173 (100)	173 (100)	173 (100)	173 (100)	173 (100)	173 (100)	173 (100)	173 (100)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	53 (100)	53 (100)	53 (100)	53 (100)	53 (100)	53 (100)	53 (100)	53 (100)	53 (100)	53 (100)	53 (100)	0 (0)	0 (0)	0 (0)
0 (0)	172 (100)	90 (52.3)	172 (100)	172 (100)	172 (100)	172 (100)	172 (100)	172 (100)	172 (100)	172 (100)	172 (100)	172 (100)	0 (0)	0 (0)	0 (0)
0 (0)	54 (100)	54 (100)	3 (5.6)	3 (5.6)	3 (5.6)	54 (100)	54 (100)	54 (100)	54 (100)	54 (100)	54 (100)	54 (100)	3 (5.6)	3 (5.6)	3 (5.6)
0 (0)	0 (0)	81 (100)	81 (100)	81 (100)	81 (100)	81 (100)	81 (100)	81 (100)	81 (100)	81 (100)	81 (100)	81 (100)	13 (16)	14 (17.3)	14 (17.3)
0 (0)	208 (100)	111 (53.4)	102 (49)	89 (42.8)	102 (49)	208 (100)	208 (100)	208 (100)	208 (100)	208 (100)	208 (100)	208 (100)	3 (1.4)	4 (1.9)	4 (1.9)
0 (0)	536,414 (100)	467,141 (87.1)	536,414 (100)	536,414 (100)	536,414 (100)	536,414 (100)	536,414 (100)	536,414 (100)	536,414 (100)	536,414 (100)	536,414 (100)	536,414 (100)	0 (0)	114 (0)	114 (0)
0 (0)	1,663,167 (100)	82,947 (5)	1,663,167 (100)	1,663,167 (100)	1,663,167 (100)	1,663,167 (100)	1,663,167 (100)	1,663,167 (100)	1,663,167 (100)	1,663,167 (100)	1,663,167 (100)	1,663,167 (100)	45,547 (2.7)	45,598 (2.7)	45,598 (2.7)

APPENDIX 6

Variable, n (%)													
Maternal clinical characteristics													
Study	Ethnicity	Age	Nulliparous	Previous PE	Previous autoimmune disease	Previous heritable thrombophilia	Family history of PE	History of renal disease	History of diabetes	History of hypertension	Smoker	Substance misuse in current pregnancy	Spontaneous conception
Mbah ¹⁴⁵	0 (0)	37,738 (100)	0 (0)	0 (0)	37,738 (100)	37,738 (100)	37,738 (100)	0 (0)	0 (0)	0 (0)	30,152 (79.9)	37,738 (100)	37,738 (100)
Trogstad ¹⁶⁴	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)
Salim ¹⁵⁶	82 (19.3)	232 (54.6)	0 (0)	0 (0)	278 (65.4)	278 (65.4)	425 (100)	278 (65.4)	278 (65.4)	273 (64.2)	242 (56.9)	425 (100)	425 (100)
van Oostwaard 2012 ¹⁶⁸	138 (21.6)	329 (51.5)	0 (0)	0 (0)	407 (63.7)	407 (63.7)	639 (100)	408 (63.8)	406 (63.5)	404 (63.2)	350 (54.8)	639 (100)	639 (100)
van Oostwaard 2014 ¹⁶⁹	19 (1.2)	19 (1.2)	1639 (100)	1639 (100)	1639 (100)	33 (2)	1639 (100)	30 (1.8)	19 (1.2)	17 (1)	26 (1.6)	1639 (100)	1639 (100)
Zhang ¹⁷⁸	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4212 (100)	4212 (100)	0 (0)	0 (0)	0 (0)	0 (0)	4212 (100)	0 (0)
Brown 2007 ¹¹⁶	2785 (100)	2785 (100)	0 (0)	1551 (57.4)	2785 (100)	2785 (100)	2785 (100)	2785 (100)	0 (0)	0 (0)	1368 (49.1)	2785 (100)	2785 (100)
Gurgel Alves ¹³⁰	500 (100)	500 (100)	500 (100)	500 (100)	500 (100)	500 (100)	500 (100)	500 (100)	500 (100)	0 (0)	500 (100)	500 (100)	500 (100)
Rocha ¹⁵³	733 (100)	0 (0)	733 (100)	0 (0)	733 (100)	733 (100)	733 (100)	0 (0)	733 (100)	733 (100)	733 (100)	733 (100)	733 (100)
Costa 2017 ¹⁰⁷	2 (0.3)	0 (0)	0 (0)	0 (0)	574 (100)	0 (0)	574 (100)	574 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Rocha ¹⁵⁴	29 (4)	0 (0)	0 (0)	0 (0)	733 (100)	733 (100)	733 (100)	0 (0)	0 (0)	0 (0)	0 (0)	733 (100)	733 (100)

JSOG, Japan Society of Obstetrics and Gynecology; PE, pre-eclampsia; PI, pulsatility index; SGA, small for gestational age.

Multiple pregnancy	History of SGA	BMI	SBP	DBP	MAP	Urine dipstick	PCR	Ultrasound markers		Biochemical markers			Outcome		
								Uterine PI	Umbilical PI	PAPP-A	PIGF	sFit-1	Any-onset PE	Early-onset PE	Late-onset PE
0 (0)	37,738 (100)	37,738 (100)	37,738 (100)	37,738 (100)	37,738 (100)	37,738 (100)	37,738 (100)	3,7738 (100)	37,738 (100)	37,738 (100)	37,738 (100)	37,738 (100)	299 (0.8)	615 (1.6)	615 (1.6)
0 (0)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	97 (100)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	265 (62.4)	251 (59.1)	247 (58.1)	251 (59.1)	425 (100)	425 (100)	425 (100)	425 (100)	425 (100)	425 (100)	425 (100)	235 (55.3)	235 (55.3)	235 (55.3)
0 (0)	0 (0)	388 (60.7)	373 (58.4)	373 (58.4)	373 (58.4)	639 (100)	639 (100)	639 (100)	639 (100)	639 (100)	639 (100)	639 (100)	335 (52.4)	335 (52.4)	335 (52.4)
0 (0)	17 (1)	78 (4.8)	1639 (100)	1639 (100)	1639 (100)	1639 (100)	1639 (100)	1639 (100)	1639 (100)	1639 (100)	1639 (100)	1639 (100)	0 (0)	0 (0)	0 (0)
0 (0)	4212 (100)	6 (0.1)	143 (3.4)	143 (3.4)	144 (3.4)	4212 (100)	4212 (100)	133 (3.2)	70 (1.7)	134 (3.2)	8 (0.2)	8 (0.2)	5 (0.1)	5 (0.1)	5 (0.1)
0 (0)	2785 (100)	2785 (100)	165 (5.9)	165 (5.9)	165 (5.9)	2785 (100)	2785 (100)	2785 (100)	2785 (100)	2785 (100)	2785 (100)	2785 (100)	0 (0)	0 (0)	0 (0)
0 (0)	500 (100)	500 (100)	500 (100)	500 (100)	500 (100)	500 (100)	500 (100)	7 (1.4)	500 (100)	500 (100)	500 (100)	500 (100)	246 (49.2)	246 (49.2)	246 (49.2)
0 (0)	733 (100)	0 (0)	733 (100)	733 (100)	0 (0)	733 (100)	733 (100)	733 (100)	733 (100)	733 (100)	733 (100)	733 (100)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	0 (0)	574 (100)	574 (100)	0 (0)	574 (100)	574 (100)	32 (5.6)	574 (100)	574 (100)	574 (100)	574 (100)	0 (0)	0 (0)	0 (0)
0 (0)	733 (100)	0 (0)	733 (100)	733 (100)	0 (0)	733 (100)	733 (100)	733 (100)	733 (100)	733 (100)	733 (100)	733 (100)	0 (0)	0 (0)	0 (0)

Appendix 7 International Prediction of Pregnancy Complications Collaborators pre-eclampsia predictors prioritisation survey

Please rank each variable according to its level of importance as a predictor of pre-eclampsia

1. Maternal characteristics *

	Very important	Important	Moderately important	Slightly important	Not important
Age	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Parity	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Previous miscarriage	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Previous stillbirth	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Previous SGA	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Previous any pre-eclampsia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Previous preterm delivery	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Previous heritable thrombophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Previous autoimmune disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Family history of pre-eclampsia in first degree relative	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Family history of cardiovascular disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
History of renal disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Chronic or pre-existing hypertension	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
History of pre-existing diabetes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Previous history of gestational diabetes (GDM)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Gestational diabetes (GDM) in current pregnancy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
History of early pregnancy bleeding in current pregnancy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Multiple pregnancy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Interval between pregnancies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mode of conception	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Smoking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Alcohol use	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Substance misuse in current pregnancy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Socioeconomic status	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
New partner	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Diet in pregnancy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Physical activity	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ethnicity	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. Examination *

	Very important	Important	Moderately important	Slightly important	Not important
BMI	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Height	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Weight	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mean arterial pressure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Systolic blood pressure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Diastolic blood pressure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Urine dipstick	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24 hour protein	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Protein Creatine Ratio (PCR)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. Ultrasound markers *

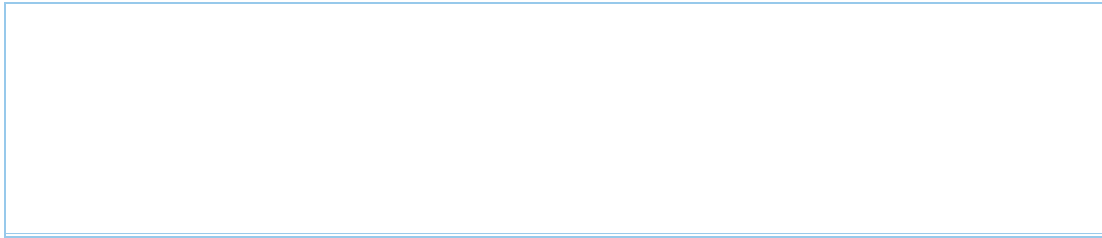
	Very important	Important	Moderately important	Slightly important	Not important
Crown-rump length (CRL)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Estimated fetal weight centile	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Notching on ultrasound scan	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Uterine artery pulsatility index	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Umbilical artery pulsatility index	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Uterine artery resistance index	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Umbilical artery resistance index	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Abdominal circumference	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. Biochemical markers *

	Very important	Important	Moderately important	Slightly important	Not important
Placental growth factor (PlGF)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Soluble fms-like tyrosine kinase one (sFlt1)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Soluble Endoglin (sEng)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C-reactive protein (CRP)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hypertriglyceridaemia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Plasminogen activator inhibitor 1 (PAI-1) polymorphism	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Human chorionic gonadotrophin (HCG)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Alpha-Fetoprotein (AFP)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pregnancy-associated plasma protein A (PAPP-A)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. Please suggest any other predictor not listed which you think might be important to consider.



Appendix 8 Risk-of-bias assessment of data sets on the IPPIC project

TABLE 25 Risk-of-bias assessment for participant selection

Domain: participant selection					
Study/data set	Appropriate data sources	Appropriate inclusion and exclusion of participants	Participant selection similar to model development study	Risk	Rationale of rating
SCOPE ⁴²	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Allen ¹⁰⁸	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
ALSPAC ¹⁰³	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Chappell ¹²¹	Yes	No	N/A	High	Selected high-risk population
EMPOwAR ¹²²	Yes	No	N/A	High	Selected high-risk population
POPPY ¹⁰⁶	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Poston 2006 ¹⁵⁰	Yes	No	N/A	High	Selected high-risk population
Poston 2015 ¹⁴⁹	Yes	No	N/A	High	Selected high-risk population
Khan ¹³⁷	Yes	No	N/A	High	Selected high-risk population
St George's ¹⁶³	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
PARIS Collaborative Group ¹¹²	Yes	Probably no	N/A	High	Likely to be a mix of high- and low-risk population
AMND ¹¹⁴	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Born in Bradford ¹⁷⁷	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Velauthar ³⁹	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
POP ¹⁶¹	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Baschat ¹¹⁵	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Audibert ¹¹³	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Caradeux ¹¹⁸	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Giguère ¹²⁶	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Goetzinger ¹²⁸	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes

continued

TABLE 25 Risk-of-bias assessment for participant selection (continued)

Study/data set	Domain: participant selection			Risk	Rationale of rating
	Appropriate data sources	Appropriate inclusion and exclusion of participants	Participant selection similar to model development study		
Antsaklis ¹¹⁰	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Llurba ¹⁴⁰	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
WHO ¹⁷⁵	Yes	No	N/A	High	Selected high-risk population
Andersen ¹⁰⁹	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Arenas ¹¹¹	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
FINNPEC ¹³³	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Galindo ¹⁷¹	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Generation R ¹³⁴	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
NICHD HR ³²	Yes	No	N/A	High	Selected high-risk population
NICHD LR ¹⁵⁹	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Placental Health Study ¹⁷⁶	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
POUCH ¹³¹	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
van Kuijk 2011 ¹⁶⁷	Yes	No	N/A	High	Selected high-risk population
van Kuijk 2014 ¹⁶⁶	Yes	No	N/A	High	Selected high-risk population
Odibo ¹⁴⁷	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
PREDO ¹²⁷	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Prefumo ¹⁵¹	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Skråstad ¹⁶⁰	Yes	No	N/A	High	Selected high-risk population
Verlohren ¹⁷²	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Rumbold ¹⁵⁵	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Vollebregt ¹⁷⁴	Yes	No	N/A	High	Selected high-risk population
JSOG ¹⁰⁵	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
DOMInO ¹⁴³	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes

TABLE 25 Risk-of-bias assessment for participant selection (continued)

Domain: participant selection					
Study/data set	Appropriate data sources	Appropriate inclusion and exclusion of participants	Participant selection similar to model development study	Risk	Rationale of rating
Danish Birth Cohort ¹³⁶	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Indonesian Cohort ¹⁵⁷	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Ohkuchi ¹⁴⁸	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Lecarpentier ¹³⁹	Yes	No	N/A	High	Selected high-risk population
TEST ¹⁴⁶	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Massé ¹⁴⁴	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Staff ¹⁶²	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
STORK G ¹³⁵	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Vatten ¹⁷⁰	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Vinter ¹⁷³	Yes	No	N/A	High	Selected high-risk population
BORN Ontario ¹⁰⁴	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Ghana Cohort ¹⁶⁵	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
MoBa ¹⁴²	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Huang ¹³²	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Carbillion ¹¹⁹	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Goffinet ¹²⁹	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Rang ¹⁵²	Yes	No	N/A	High	Selected high-risk population
Cameroni ¹¹⁷	Yes	No	N/A	High	Selected high-risk population
Conserva ¹²³	Yes	No	N/A	High	Selected high-risk population
Facchinetti ¹²⁴	Yes	No	N/A	High	Selected high-risk population
Ferrazzani ¹⁵⁸	Yes	No	N/A	High	Selected high-risk population
Figueiro-Filho ¹²⁵	Yes	No	N/A	High	Selected high-risk population
Langenveld ¹³⁸	Yes	No	N/A	High	Selected high-risk population
Lykke ¹⁴¹	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Mbah ¹⁴⁵	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes

continued

TABLE 25 Risk-of-bias assessment for participant selection (continued)

Domain: participant selection					
Study/data set	Appropriate data sources	Appropriate inclusion and exclusion of participants	Participant selection similar to model development study	Risk	Rationale of rating
Trogstad ¹⁶⁴	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Salim ¹⁵⁶	Yes	No	N/A	High	Selected high-risk population
van Oostwaard 2012 ¹⁶⁸	Yes	No	N/A	High	Selected high-risk population
van Oostwaard 2014 ¹⁶⁹	Yes	No	N/A	High	Selected high-risk population
Zhang ¹⁷⁸	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Brown ¹¹⁶	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Gurgel Alves ¹³⁰	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Rocha ¹⁵³	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Costa 2017 ¹⁰⁷	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes
Rocha ¹⁵⁴	Yes	Yes	N/A	Low	Responses to relevant signalling questions are yes

JSOG, Japan Society of Obstetrics and Gynecology; N/A, not applicable.

TABLE 26 Risk-of-bias assessment for predictors

Domain: predictors						
Study/data set	Predictors defined in a similar way for participants	Predictors defined in a similar way to model development study	Predictors assessed without knowledge of outcome data	All predictors available at the time model is to be used	Risk	Rationale of rating
SCOPE ⁴²	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Allen ¹⁰⁸	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
ALSPAC ¹⁰³	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Chappell ¹²¹	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
EMPOWaR ¹²²	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes

TABLE 26 Risk-of-bias assessment for predictors (continued)

Domain: predictors						
Study/ data set	Predictors defined in a similar way for participants	Predictors defined in a similar way to model development study	Predictors assessed without knowledge of outcome data	All predictors available at the time model is to be used	Risk	Rationale of rating
POPPY ¹⁰⁶	NI	N/A	NI	Yes	Unclear	No information to make assessment
Poston 2006 ¹⁵⁰	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Poston 2015 ¹⁴⁹	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Khan ¹³⁷	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
St George's ¹⁶³	Probably yes	N/A	Probably yes	Yes	Low	Responses to relevant signalling questions are yes
PARIS Collaborative Group ¹¹²	Probably no	N/A	Probably yes	Yes	High	Definition of predictor may differ across studies
AMND ¹¹⁴	Probably yes	N/A	Probably yes	Yes	Low	Responses to relevant signalling questions are yes
Born in Bradford ¹⁷⁷	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Velauthar ³⁹	NI	N/A	NI	Yes	Unclear	No information to make assessment
POP ¹⁶¹	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Baschat ¹¹⁵	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Audibert ¹¹³	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Caradeux ¹¹⁸	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Giguère ¹²⁶	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Goetzinger ¹²⁸	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Antsaklis ¹¹⁰	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes

continued

TABLE 26 Risk-of-bias assessment for predictors (continued)

Study/ data set	Domain: predictors				Risk	Rationale of rating
	Predictors defined in a similar way for participants	Predictors defined in a similar way to model development study	Predictors assessed without knowledge of outcome data	All predictors available at the time model is to be used		
Llurba ¹⁴⁰	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
WHO ¹⁷⁵	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Andersen ¹⁰⁹	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Arenas ¹¹¹	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
FINNPEC ¹³³	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Galindo ¹⁷¹	Yes	N/A	Probably yes	Yes	Low	Responses to relevant signalling questions are yes
Generation R ¹³⁴	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
NICHD HR ³²	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
NICHD LR ¹⁵⁹	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Placental Health Study ¹⁷⁶	Yes	N/A	Probably yes	Yes	Low	Responses to relevant signalling questions are yes
POUCH ¹³¹	Yes	N/A	Probably yes	Yes	Low	Responses to relevant signalling questions are yes
van Kuijk 2011 ¹⁶⁷	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
van Kuijk 2014 ¹⁶⁶	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Odibo ¹⁴⁷	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
PREDO ¹²⁷	Yes	N/A	Probably yes	Yes	Low	Responses to relevant signalling questions are yes

TABLE 26 Risk-of-bias assessment for predictors (continued)

Domain: predictors						
Study/ data set	Predictors defined in a similar way for participants	Predictors defined in a similar way to model development study	Predictors assessed without knowledge of outcome data	All predictors available at the time model is to be used	Risk	Rationale of rating
Prefumo ¹⁵¹	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Skråstad ¹⁶⁰	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Verlohren ¹⁷²	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Rumbold ¹⁵⁵	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Vollebregt ¹⁷⁴	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
JSOG ¹⁰⁵	NI	N/A	NI	Yes	Unclear	No information to make assessment
DOMInO ¹⁴³	Yes	N/A	Probably yes	Yes	Low	Responses to relevant signalling questions are yes
Danish Birth Cohort ¹³⁶	Probably yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Indonesian Cohort ¹⁵⁷	Yes	N/A	Probably yes	Yes	Low	Responses to relevant signalling questions are yes
Ohkuchi ¹⁴⁸	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Lecarpentier ¹³⁹	Yes	N/A	Probably yes	Yes	Low	Responses to relevant signalling questions are yes
TEST ¹⁴⁶	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Massé ¹⁴⁴	Probably yes	N/A	Probably yes	Yes	Low	Responses to relevant signalling questions are yes
Staff ¹⁶²	Yes	N/A	Probably yes	Yes	Low	Responses to relevant signalling questions are yes
STORK G ¹³⁵	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes

continued

TABLE 26 Risk-of-bias assessment for predictors (continued)

Study/ data set	Domain: predictors				Risk	Rationale of rating
	Predictors defined in a similar way for participants	Predictors defined in a similar way to model development study	Predictors assessed without knowledge of outcome data	All predictors available at the time model is to be used		
Vatten ¹⁷⁰	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Vinter ¹⁷³	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
BORN Ontario ¹⁰⁴	Yes	N/A	Probably yes	Yes	Low	Responses to relevant signalling questions are yes
Ghana Cohort ¹⁶⁵	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
MoBa ¹⁴²	Probably yes	N/A	Probably yes	Yes	Low	Responses to relevant signalling questions are yes
Huang ¹³²	Probably yes	N/A	Probably yes	Yes	Low	Responses to relevant signalling questions are yes
Carbillion ¹¹⁹	Probably yes	N/A	NI	Yes	Unclear	No information to make assessment
Goffinet ¹²⁹	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Rang ¹⁵²	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Cameron ¹¹⁷	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Conserva ¹²³	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Facchinetti ¹²⁴	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Ferrazzani ¹⁵⁸	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Figueiró-Filho ¹²⁵	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Langenveld ¹³⁸	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes
Lykke ¹⁴¹	Probably yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes

TABLE 26 Risk-of-bias assessment for predictors (continued)

Study/ data set	Domain: predictors					Risk	Rationale of rating
	Predictors defined in a similar way for participants	Predictors defined in a similar way to model development study	Predictors assessed without knowledge of outcome data	All predictors available at the time model is to be used			
Mbah ¹⁴⁵	Probably yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes	
Trogstad ¹⁶⁴	Probably yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes	
Salim ¹⁵⁶	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes	
van Oostwaard 2012 ¹⁶⁸	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes	
van Oostwaard 2014 ¹⁶⁹	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes	
Zhang ¹⁷⁸	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes	
Brown 2007 ¹¹⁶	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes	
Gurgel Alves ¹³⁰	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes	
Rocha ¹⁵³	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes	
Costa 2017 ¹⁰⁷	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes	
Rocha ¹⁵⁴	Yes	N/A	Yes	Yes	Low	Responses to relevant signalling questions are yes	

JSOG, Japan Society of Obstetrics and Gynecology; N/A, not applicable; NI, no information.

TABLE 27 Risk-of-bias assessment for outcome

Study/data set	Domain: outcome							Risk	Rationale of rating
	Outcome appropriately determined	Prespecified or standard definition used	Predictors excluded from outcome definition	Outcome defined and determined in the same way for all participants	Outcome defined and determined in the same way to model development study	Outcome determined without knowledge of predictor information	Time interval between predictor and outcome assessment appropriate		
SCOPE ⁴²	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Allen ¹⁰⁸	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	No information to make assessment
ALSPAC ¹⁰³	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	No information to make assessment
Chappell ¹²¹	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
EMPOWaR ¹²²	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	No information to make assessment
POPPY ¹⁰⁶	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	No information to make assessment
Poston 2006 ¹⁵⁰	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis

Domain: outcome									
Study/data set	Outcome appropriately determined	Prespecified or standard definition used	Predictors excluded from outcome definition	Outcome defined and determined in the same way for all participants	Outcome defined and determined in the same way to model development study	Outcome determined without knowledge of predictor information	Time interval between predictor and outcome assessment appropriate	Risk	Rationale of rating
Poston 2015 ¹⁴⁹	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Khan ¹³⁷	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
St George's ¹⁶³	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	No information to make assessment
PARIS Collaborative Group ¹¹²	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
AMND ¹¹⁴	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	No information to make assessment
Born in Bradford ¹⁷⁷	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	No information to make assessment
Velauthar ³⁹	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	No information to make assessment

continued

TABLE 27 Risk-of-bias assessment for outcome (continued)

Study/data set	Domain: outcome							Risk	Rationale of rating
	Outcome appropriately determined	Prespecified or standard definition used	Predictors excluded from outcome definition	Outcome defined and determined in the same way for all participants	Outcome defined and determined in the same way to model development study	Outcome determined without knowledge of predictor information	Time interval between predictor and outcome assessment appropriate		
POP ¹⁶¹	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Baschat ¹¹⁵	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Audibert ¹¹³	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Caradeux ¹¹⁸	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Giguère ¹²⁶	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis

Domain: outcome									
Study/data set	Outcome appropriately determined	Prespecified or standard definition used	Predictors excluded from outcome definition	Outcome defined and determined in the same way for all participants	Outcome defined and determined in the same way to model development study	Outcome determined without knowledge of predictor information	Time interval between predictor and outcome assessment appropriate	Risk	Rationale of rating
Goetzinger ¹²⁸	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Antsaklis ¹¹⁰	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Llurba ¹⁴⁰	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
WHO ¹⁷⁵	Yes	Yes	No	Probably yes	N/A	Probably no	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Andersen ¹⁰⁹	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis

continued

TABLE 27 Risk-of-bias assessment for outcome (continued)

Study/data set	Domain: outcome							Risk	Rationale of rating
	Outcome appropriately determined	Prespecified or standard definition used	Predictors excluded from outcome definition	Outcome defined and determined in the same way for all participants	Outcome defined and determined in the same way to model development study	Outcome determined without knowledge of predictor information	Time interval between predictor and outcome assessment appropriate		
Arenas ¹¹¹	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
FINNPEC ¹³³	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Galindo ¹⁷¹	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Generation R ¹³⁴	Yes	Probably yes	No	Probably yes	N/A	Probably no	Probably yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
NICHD HR ³²	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis

Domain: outcome									
Study/data set	Outcome appropriately determined	Prespecified or standard definition used	Predictors excluded from outcome definition	Outcome defined and determined in the same way for all participants	Outcome defined and determined in the same way to model development study	Outcome determined without knowledge of predictor information	Time interval between predictor and outcome assessment appropriate	Risk	Rationale of rating
NICHD LR ¹⁵⁹	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Placental Health Study ¹⁷⁶	Yes	Yes	No	Yes	N/A	No	Yes	Unclear	No information to make assessment
POUCH ¹³¹	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	No information to make assessment
van Kuijk 2011 ¹⁶⁷	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
van Kuijk 2014 ¹⁶⁶	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Odibo ¹⁴⁷	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis

continued

TABLE 27 Risk-of-bias assessment for outcome (continued)

Study/data set	Domain: outcome							Risk	Rationale of rating
	Outcome appropriately determined	Prespecified or standard definition used	Predictors excluded from outcome definition	Outcome defined and determined in the same way for all participants	Outcome defined and determined in the same way to model development study	Outcome determined without knowledge of predictor information	Time interval between predictor and outcome assessment appropriate		
PREDO ¹²⁷	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Prefumo ¹⁵¹	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Skråstad ¹⁶⁰	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Verlohren ¹⁷²	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Rumbold ¹⁵⁵	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis

Domain: outcome									
Study/data set	Outcome appropriately determined	Prespecified or standard definition used	Predictors excluded from outcome definition	Outcome defined and determined in the same way for all participants	Outcome defined and determined in the same way to model development study	Outcome determined without knowledge of predictor information	Time interval between predictor and outcome assessment appropriate	Risk	Rationale of rating
Vollebregt ¹⁷⁴	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
JSOG ¹⁰⁵	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	No information to make assessment
DOMInO ¹⁴³	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Danish Birth Cohort ¹³⁶	Yes	Probably yes	No	Probably yes	N/A	Probably no	Probably yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Indonesian cohort ¹⁵⁷	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis

continued

TABLE 27 Risk-of-bias assessment for outcome (continued)

Study/data set	Domain: outcome							Risk	Rationale of rating
	Outcome appropriately determined	Prespecified or standard definition used	Predictors excluded from outcome definition	Outcome defined and determined in the same way for all participants	Outcome defined and determined in the same way to model development study	Outcome determined without knowledge of predictor information	Time interval between predictor and outcome assessment appropriate		
Ohkuchi ¹⁴⁸	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Lecarpentier ¹³⁹	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
TEST ¹⁴⁶	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Massé ¹⁴⁴	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	No information to make assessment
Staff ¹⁶²	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis

Domain: outcome									
Study/data set	Outcome appropriately determined	Prespecified or standard definition used	Predictors excluded from outcome definition	Outcome defined and determined in the same way for all participants	Outcome defined and determined in the same way to model development study	Outcome determined without knowledge of predictor information	Time interval between predictor and outcome assessment appropriate	Risk	Rationale of rating
STORK G ¹³⁵	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	No information to make assessment
Vatten ¹⁷⁰	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Vinter ¹⁷³	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
BORN Ontario ¹⁰⁴	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	Unable to confirm definition of outcome used
Ghana cohort ¹⁶⁵	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
MoBA ¹⁴²	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	No information to make assessment

continued

TABLE 27 Risk-of-bias assessment for outcome (continued)

Study/data set	Domain: outcome								Risk	Rationale of rating
	Outcome appropriately determined	Prespecified or standard definition used	Predictors excluded from outcome definition	Outcome defined and determined in the same way for all participants	Outcome defined and determined in the same way to model development study	Outcome determined without knowledge of predictor information	Time interval between predictor and outcome assessment appropriate			
Huang ¹³²	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	No information to make assessment	
Carbillion ¹¹⁹	NI	NI	Probably no	Probably yes	N/A	Probably no	Probably yes	Unclear	No information to make assessment	
Goffinet ¹²⁹	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis	
Rang ¹⁵²	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis	
Cameroni 2011 ¹¹⁷	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis	

Domain: outcome									
Study/data set	Outcome appropriately determined	Prespecified or standard definition used	Predictors excluded from outcome definition	Outcome defined and determined in the same way for all participants	Outcome defined and determined in the same way to model development study	Outcome determined without knowledge of predictor information	Time interval between predictor and outcome assessment appropriate	Risk	Rationale of rating
Conserva 2012 ¹²³	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Facchinetti ¹²⁴	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Ferrazzani ¹⁵⁸	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Figueiró-Filho ¹²⁵	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Langenveld ¹³⁸	Yes	Yes	No	Probably yes	N/A	Probably no	Probably yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis

continued

TABLE 27 Risk-of-bias assessment for outcome (continued)

Study/data set	Domain: outcome							Risk	Rationale of rating
	Outcome appropriately determined	Prespecified or standard definition used	Predictors excluded from outcome definition	Outcome defined and determined in the same way for all participants	Outcome defined and determined in the same way to model development study	Outcome determined without knowledge of predictor information	Time interval between predictor and outcome assessment appropriate		
Lykke ¹⁴¹	Yes	Yes	No	Probably yes	N/A	Probably no	Probably yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Mbah ¹⁴⁵	Yes	Yes	No	Probably yes	N/A	Probably no	Probably yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Trogstad ¹⁶⁴	Yes	Yes	No	Probably yes	N/A	Probably no	Probably yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Salim ¹⁵⁶	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis

Domain: outcome									
Study/data set	Outcome appropriately determined	Prespecified or standard definition used	Predictors excluded from outcome definition	Outcome defined and determined in the same way for all participants	Outcome defined and determined in the same way to model development study	Outcome determined without knowledge of predictor information	Time interval between predictor and outcome assessment appropriate	Risk	Rationale of rating
van Oostwaard 2012 ¹⁶⁸	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
van Oostwaard 2014 ¹⁶⁹	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Zhang ¹⁷⁸	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Brown 2007 ¹¹⁶	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Gurgel Alves ¹³⁰	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis

continued

TABLE 27 Risk-of-bias assessment for outcome (continued)

Domain: outcome									
Study/data set	Outcome appropriately determined	Prespecified or standard definition used	Predictors excluded from outcome definition	Outcome defined and determined in the same way for all participants	Outcome defined and determined in the same way to model development study	Outcome determined without knowledge of predictor information	Time interval between predictor and outcome assessment appropriate	Risk	Rationale of rating
Rocha ¹⁵³	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Costa 2017 ¹⁰⁷	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis
Rocha ¹⁵⁴	Yes	Yes	No	Yes	N/A	No	Yes	Low	Blood pressure and proteinuria are components of predictor and need to be known for diagnosis

JSOG, Japan Society of Obstetrics and Gynecology; N/A, not applicable; NI, no information.

Appendix 9 Prediction models and equations identified from the literature search

For more information, see published reviews.^{37,42} Model equations were extracted from the original manuscripts, which may not incorporate later corrections to the equation by the authors, if any.

First author, year	Predictor category	Trimester of measurement of variables	Equation(s) ^a	Included in validation	If no, reason for exclusion
Any-onset pre-eclampsia					
Baschat, 2014 ¹¹⁵	C + B	First trimester	LP: $-8.72 + 0.157$ (if nulliparous) $+ 0.341$ (if history of hypertension) $+ 0.635$ (if history of PE) $+ 0.064$ (MAP) $- 0.186$ (PAPP-A, Ln MoM)	Yes	
North, 2011 ⁴²	C	15 weeks' gestation	LP1: $-6.8855 - 0.0393$ (age, years) $+ 0.0659$ (MAP) $+ 0.0483$ (BMI) $+ 0.6861$ (if family history of PE) $+ 0.6232$ (if family history CHD) $- 0.3881$ (woman's birthweight, kg) $+ 0.7129$ (if vaginal bleeding ≥ 5 days) $- 0.8033$ (if one miscarriage ≤ 10 weeks, same partner) $- 0.9070$ (if ≥ 12 months to conceive) $- 0.3733$ (if high fruit intake at 15 weeks) $- 0.508$ (if alcohol consumed in first trimester) $- 0.063$ (number of cigarettes/day at 15 weeks)	No	Predictor not available in IPPIC-UK data set
	C + U		LP2: $-9.1113 + 0.0634$ (MAP) $+ 0.0485$ (BMI) $+ 0.6539$ (if family history of PE) $+ 0.6093$ (if family history of CHD) $- 0.3787$ (participant's birthweight, kg) $+ 0.6493$ (if vaginal bleeding ≥ 5 days) $+ 0.5008$ (if months in sexual relationship ≤ 6 months) $+ 0.5084$ (if bilateral notches) $+ 2.0802$ (mean Ut RI) $- 0.8248$ (one miscarriage ≤ 10 weeks, same partner) $- 0.8983$ (≥ 12 months to conceive) $- 0.4389$ (high fruit intake at 15 weeks) $- 0.5573$ (if alcohol consumed in first trimester)	No	Predictor not available in IPPIC-UK data set
Odibo, 2011 ¹⁴⁷	C + B	First trimester	LP1: $-3.389 - 0.716$ (PAPP-A, MoM) $+ 0.05$ (BMI) $+ 0.319$ (if black ethnicity) $+ 1.57$ (if history of chronic hypertension)	Yes	
	C + B		LP2: $-2.607 - 0.502$ (PP13, MoM) $+ 0.759$ (if pre-gestational diabetic) $+ 0.777$ (if black ethnicity) $+ 1.268$ (if history of chronic hypertension)	No	Predictor not available in IPPIC-UK data set
	C + U		LP3: $-3.895 - 0.593$ (mean uterine artery PI) $+ 0.944$ (if pre-gestational diabetes) $+ 0.059$ (BMI) $+ 1.532$ (if history of chronic hypertension)	Yes	
	C + B + U		LP4: $-1.308 - 0.574$ (PP13, MoM) $- 0.502$ (PAPP-A, MoM) $- 0.643$ (mean uterine artery PI) $+ 0.799$ (if pre-gestational diabetic) $+ 0.664$ (if black ethnicity) $+ 1.340$ (if history of chronic hypertension)	No	Predictor not available in IPPIC-UK data set

First author, year	Predictor category	Trimester of measurement of variables	Equation(s) ^a	Included in validation	If no, reason for exclusion
Seed, 2011	C	Second trimester	LP: $-1.2422 + 0.4061$ (if chronic hypertension) $+ 0.5071$ (if DBP > 70) $- 0.3846$ (if DBP > 90) $+ 0.8890$ (if SBP > 120) $+ 0.7040$ (if previous PE) $- 0.4043$ (if on folates) $+ 0.8311$ (if mother is Indian, Bangladeshi, Pakistani, African or African Caribbean)	No	Predictor not available in IPPIC-UK data set
Goetzinger, 2010 ¹²⁸	C + B	First trimester	LP: $-3.25 + 0.51$ (if PAPP-A < 10th centile) $+ 0.93$ (if BMI > 25) $+ 0.94$ (if chronic hypertension) $+ 0.97$ (if diabetes) $+ 0.61$ (if African American ethnicity)	Yes	
Emonts, 2008	C	Post pregnancy	LP: $-3.72 + 0.030$ (age, years) $- 0.50$ (parity) $+ 0.15$ (gestation) $+ 1.89$ (if chronic hypertension in patient's mother) $+ 0.14$ (BMI) $+ 0.079$ (SBP) $- 0.13$ (DBP)	No	Predictor not available in IPPIC-UK data set
Poon, 2008 ²³³	C	First trimester	LP: $-6.311 + 1.299$ (if African Caribbean ethnicity) $+ 0.092$ (BMI) $+ 0.855$ (if woman's mother had PE) $- 1.481$ (if parous without previous PE) $+ 0.933$ (if parous with previous PE)	Yes	
Plasencia, 2007 ²³¹	C	First trimester	LP: $-6.253 + 1.432$ (if African Caribbean ethnicity) $+ 1.465$ (if mixed ethnicity) $+ 0.084$ (BMI) $+ 0.81$ (if patient's mother had PE) $- 1.539$ (if parous without previous PE) $+ 1.049$ (if parous with previous PE)	Yes	
Yu, 2005 ²³⁸	C + U	Second trimester	LP: $1.8552 + 5.9228$ (mean uterine artery PI) ⁻² $- 14.4474$ (mean uterine artery PI) ⁻¹ $- 0.5478$ (if smoker) $+ 0.6719$ (bilateral notch) $+ 0.0372$ (age) $+ 0.4949$ (if black ethnicity) $+ 1.5033$ (if history of PE) $- 1.2217$ (if previous term live birth) $+ 0.0367$ (BMI)	Yes	
Kenny, 2014	C + B + U	First trimester	LP: $-12.200 - 0.655$ (high fruit intake) $+ 0.054$ (BMI) $+ 0.065$ (MAP) $+ 2.569$ (mean uterine artery RI) $- 0.311$ (PIGF artery RI) $+ 1.232$ (cystatin C/PIGF)	No	Predictor not available in IPPIC-UK data set
Direkvand-Moghadam, 2013	C	First trimester	LP: $0.74 - 1.016$ prior infertility $+ 0.72$ chronic hypertension $+ 1.69$ prior PE	No	Predictor not available in IPPIC-UK data set
Teixeira, 2014	C + B	First trimester	LP: $-5.723 + 0.870$ (if chronic hypertension) $+ 1.428$ (if diabetic) $- 0.787$ (if multiparous) $+ 3.952$ (if history of PE) $+ 0.039 \times$ (maternal age) $+ 6.159 \times$ (maternal weight MoM, log) $+ 0.027 \times$ (CRL) $+ (-0.483) \times$ NT $+ 0.766 \times$ (Free B-HCG MoM, log)	No	Predictor not available in IPPIC-UK data set

First author, year	Predictor category	Trimester of measurement of variables	Equation(s) ^a	Included in validation	If no, reason for exclusion
Early-onset pre-eclampsia					
Crovetto, 2015 ²²⁹	C	First trimester	LP1: $-5.177 + 2.383$ (if black ethnicity) $- 1.105$ (if nulliparous) $+ 3.543$ (if parous with previous PE) $+ 2.229$ (if chronic hypertension) $+ 2.201$ (if renal disease) a priori risk = $\exp(LP1)/(1 + \exp(LP1))$	Yes	
	C + U		LP2: $-21.99 + 12.25$ (a priori risk, \log_{10}) $+ 11.516$ (MAP, MoM) $+ 3.784$ (mean uterine artery PI, MoM)	No	Predictor not available in IPPIC-UK data set
	C + B + U		LP3: $21.515 + 12.884$ (a priori risk, \log_{10}) $+ 11.219$ (MAP, MoM) $+ 3.325$ (mean uterine PI, MoM) $- 7.346$ (PIGF, \log_{10}) $+ 3.559$ (sFlt-1, \log_{10})	No	Predictor not available in IPPIC-UK data set
Baschat, 2014 ¹¹⁵	C	First trimester	LP: $-5.803 + 0.302$ (if history of diabetes) $+ 0.767$ (if history of hypertension) $+ 0.00948$ (MAP)	Yes	
Parra-cordero, 2013	C + B + U	First trimester	LP: $-6.942 + 0.074$ (BMI) $+ 1.878$ (if smoker) $+ 2.1116$ (lowest uterine artery PI, Ln MoM) $- 0.671$ (PIGF, Ln MoM)	No	Predictor not available in IPPIC-UK data set
Scazzocchio, 2013 ²³⁵	C	First trimester	LP1: $-7.703 + 0.086$ (BMI) $+ 1.708$ (if chronic hypertension) $+ 4.033$ (if renal disease) $+ 1.931$ (if parous with previous PE) $+ 0.005$ (if parous with no previous PE) a priori risk = $\exp(LP1)/(1 + \exp(LP1))$	Yes	
	C + U		LP2: $-0.32 + 2.681$ (a priori risk, Ln) $+ 13.12$ (mean uterine artery PI, Ln MoM) $+ 25.733$ (MAP, Ln MoM)	No	Predictor not available in IPPIC-UK data set
Kuc, 2013 ²³⁰	C	First trimester	LP: $-6.790 - 0.119$ (maternal height, cm) $+ 4.8565$ (maternal weight, Ln) $+ 1.845$ (if nulliparous) $+ 0.086$ (maternal age, years) $+ 1.353$ (if smoker)	Yes	
Odibo, 2011	C + B + U	First trimester	LP: $-4.678 - 0.443$ (PP13, MoM) $- 0.009$ (PAPP-A, MoM) $+ 0.347$ (mean uterine artery PI) $+ 3.059$ (if history of chronic hypertension)	No	Predictor not available in IPPIC-UK data set
Seed, 2011	C	Second trimester	LP: $-2.693 + 1.735$ (if SBP > 140) $+ 1.004$ (if on antihypertensive therapy) $- 0.9790$ (if previous PE in most recent pregnancy) $+ 2.121$ (if previous PE with delivery < 34 weeks) $+ 1.285$ (if mother is Indian, Bangladeshi, Pakistani, African)	No	Predictor not available in IPPIC-UK data set
Poon, 2010 (1)	C + B	First trimester	LP1: $3.022 + 2.652$ (maternal factor-derived a priori risk for early-PE, Ln) $- 6.056$ (PIGF, Ln MoM) $+ 3.103$ (inhibin-A, Ln MoM) $+ 9.753$ (TNF-R1, Ln MoM)	No	Predictor not available in IPPIC-UK data set
	C + B		LP2: $2.547 + 2.518$ (combined a priori risk for early-onset PE, Ln) $- 6.012$ (PIGF, Ln MoM)	No	Predictor not available in IPPIC-UK data set

First author, year	Predictor category	Trimester of measurement of variables	Equation(s) ^a	Included in validation	If no, reason for exclusion
Poon, 2010 (2) ²³²	C	First trimester	LP: $-5.674 + 1.267$ (if black ethnicity) + 2.193 (if history of chronic hypertension) - 1.184 (if parous without previous PE) + 1.362 (if parous with previous PE) + 1.537 (if conceived with ovulation induction)	Yes	
Poon, 2009 (1)	C + B	First trimester	LP: $-8.776 + 14.177$ (uterine artery PI, Ln MoM) + 42.960 (MAP, Ln MoM) - 2.249 (PAPP-A, Ln MoM) - 3.529 (PIGF, Ln MoM) + 0.120 (BMI) - 1.472 (if parous with no previous PE)	No	Predictor not available in IPPIC-UK data set
Poon, 2009 (2)	C + U	First trimester	LP: $-3.657 + 1.592$ (maternal factor-derived a priori risk for early PE, Ln) + 31.396 (MAP, Ln MoM) + 13.322 (lowest uterine artery PI, Ln MoM)	No	Predictor not available in IPPIC-UK data set
Poon, 2009 (3) ²³⁴	C + B	First trimester	LP: $-6.413 - 3.612$ (PAPP-A, Ln MoM) + 1.803 (if history of chronic hypertension) + 1.564 (if black ethnicity) - 1.005 (if parous without previous PE) + 1.491 (if parous with previous PE)	Yes	
Akolekar, 2008	C + B + U	First trimester	LP: $-5.620 - 4.717$ (PIGF, Ln MoM) - 1.865 (PAPP-A, Ln MoM) + 14.519 (uterine artery PI, MoM) + 5.471 (if history of chronic hypertension) + 1.159 (if black ethnicity)	No	Predictor not available in IPPIC-UK data set
Onwudiwe, 2008	C + U	First and second trimester	LP: $-11.4487 + 31.2443$ (uterine artery PI, Ln MoM) + 40.1105 (MAP, Ln MoM) + 1.5442 (if African Caribbean ethnicity)	No	Predictor not available in IPPIC-UK data set
Plasencia, 2008	C + U	First trimester	LP: $-6.546 + 3.769$ (if chronic hypertension) + 15.692 (uterine artery PI, Ln MoM)	No	Predictor not available in IPPIC-UK data set
Plasencia, 2007 ²³¹	C	First trimester	LP: $-6.431 + 1.680$ (if African Caribbean ethnicity) + 1.889 (if mixed ethnicity) + 2.822 (if parous with previous PE)	Yes	
Yu, 2005 ²³⁸	U	Second trimester	LP: $-9.81223 + 2.10910$ (mean uterine artery PI) ³ - 1.79921 (mean uterine artery PI) ³ + 1.059463 (if bilateral notch)	Yes	

First author, year	Predictor category	Trimester of measurement of variables	Equation(s) ^a	Included in validation	If no, reason for exclusion
Wright, 2015 ²³⁶	C	First trimester	LP: mean gestational age at delivery with PE = 54.3637 - 0.0206886 (age, years - 35, if age ≥ 35) + 0.11711 (height, cm - 164) - 2.6786 (if Afro-Caribbean ethnicity) - 1.129 (if South Asian ethnicity) - 7.2897 (if chronic hypertension) - 3.0519 (if systemic lupus erythematosus or antiphospholipid syndrome) - 1.6327 (if conception by in vitro fertilisation) - 8.1667 (if parous with previous PE) + 0.0271988 (if parous with previous PE, previous gestation in weeks - 24) ² - 4.335 (if parous with no previous PE) - 4.15137651 (if parous with no previous PE, interval between pregnancies in years) ⁻¹ + 9.21473572 (if parous with no previous PE, interval between pregnancies in years) ^{-0.5} - 0.0694096 (if no chronic hypertension, weight in kg - 69) - 1.7154 (if no chronic hypertension and family history of PE) - 3.3899 (if no chronic hypertension and diabetes mellitus type 1 or 2)	Yes	
Kenny, 2014	C + B + U	First trimester	LP: -14.164 + 0.075 (MAP) + 6.1782 (mean uterine artery RI) + 0.649 (interleukin-1 receptor antagonist/PIGF); early-onset PE: -34.347 + 0.109 (MAP) + 7.679 (mean uterine)	No	Predictor not available in IPPIC-UK data set
Teixeira, 2014	C	First trimester	LP: -4.951 + 1.519 (if chronic hypertension) - 1.201 (if multiparous) + 3.201 (if history of PE) + 7.108 (maternal weight MoM, log)	No	Predictor not available in IPPIC-UK data set
Keikkala, 2013	C + B	First trimester	LP: 1.75 - 3.27 (%hCG-H MoM) - 3.63 (PAPP-AMoM) + 1.49 [parity (1 = nulliparous, 0 = multiparous)] + 0.03 (MAP)	No	Predictor not available in IPPIC-UK data set
Myers, 2013	C	Second trimester	LP1: -8.4093 + 0.9037 (fertility treatment) + 0.7999 (any sister with PE) + 0.1030 (MAP)	No	Predictor not available in IPPIC-UK data set
	C + B		LP2: -7.7769 + 0.7307 (fertility treatment) + 0.1047 (MAP) - 1.7269 (PIGF MoM)	No	Predictor not available in IPPIC-UK data set
	C + U		LP3: -13.5946 + 0.8402 (fertility treatment) + 0.1039 (MAP) + 7.0938 (20-week mean uterine artery RI)	No	Predictor not available in IPPIC-UK data set
	C + B + U		LP4: -12.5382 + 0.1078 (MAP) - 1.5658 (PIGF MoM) + 6.1087 (20-week mean uterine artery RI)	No	Predictor not available in IPPIC-UK data set
	C + B + U		LP5: -10.4272 + 0.0994 (MAP) - 1.1787 (PIGF MoM) + 0.0344 (endoglin 20-week) + 0.5285 (20-week bilateral notches of uterine arteries)	No	Predictor not available in IPPIC-UK data set

First author, year	Predictor category	Trimester of measurement of variables	Equation(s) ^a	Included in validation	If no, reason for exclusion
<i>Late-onset pre-eclampsia</i>					
Crovetto, 2015 ²²⁹	C	First trimester	LP1: $-5.873 - 0.462$ (if white ethnicity) + 0.109 (BMI) - 0.825 (if nulliparous) + 2.726 (if parous with previous PE) + 1.956 (if chronic hypertension) - 0.575 (if smoker) a priori risk = $\exp(LP1) / (1 + \exp(LP1))$	Yes	
	C + U		LP2: $-14.315 + 8.864$ (a priori risk, \log_{10}) + 7.429 (MAP, MoM) + 2.447 (mean uterine artery PI, MoM)	No	Predictor not available in IPPIC-UK data set
	C + B + U		LP3: $25.921 + 9.652$ (a priori risk, \log_{10}) + 6.89 (MAP, MoM) + 2.343 (mean uterine artery PI, MoM) - 5.618 (PIGF, \log_{10}) + 6.579 (sFlt-1, \log_{10})	No	Predictor not available in IPPIC-UK data set
Parra-cordero, 2013	C + B + U	First trimester	LP: $-5.584 + 0.137$ (BMI) + 0.822 (lowest uterine artery PI, Ln MoM) - 0.533671 (PIGF, Ln MoM)	No	Predictor not available in IPPIC-UK data set
Scazzocchio, 2013 ²³⁵	C	First trimester	LP1: $6.135 + 2.124$ (if previous PE) + 1.571 (if chronic hypertension) + 0.958 (if diabetes) + 1.416 (if thrombophilic condition) - 0.487 (if multiparous) + 0.093 (BMI) a priori risk = $\exp(LP1) / (1 + \exp(LP1))$	Yes	
	C + B		LP2: $0.328 + 2.205$ (a priori risk, Ln) - 1.307 (PAPP-A, Ln MoM)	No	Predictor not available in IPPIC-UK data set
Kuc, 2013 ²³⁰	C	First trimester	LP: $-14.374 + 2.300$ (maternal weight, Ln) + 1.303 (if nulliparous) + 0.068 (maternal age, years)	Yes	
Poon, 2010 (1)	C + B	First trimester	LP1: $3.810 + 2.898$ (maternal factor-derived a priori risk for late PE, Ln) - 3.171 (PIGF, Ln MoM) + 3.792 (activin-A, Ln MoM) + 2.013 (MMP-9, Ln MoM) + 5.242 (P-selectin, Ln MoM)	No	Predictor not available in IPPIC-UK data set
			LP2: $3.490 + 2.717$ (combined a priori risk for late PE, Ln) - 2.966 (PIGF, Ln MoM) + 3.937 (activin-A, Ln MoM) + 4.190 (P-selectin, Ln MoM)	No	Predictor not available in IPPIC-UK data set
Poon, 2010 (2) ²³²	C	First trimester	LP: $-7.860 + 0.034$ (age, years) + 0.096 (BMI) + 1.089 (if black ethnicity) + 0.980 (if Indian or Pakistani ethnicity) + 1.196 (if mixed ethnicity) + 1.070 (if woman's mother had PE) - 1.413 (if parous without previous PE) + 0.780 (if parous with previous PE)	Yes	

First author, year	Predictor category	Trimester of measurement of variables	Equation(s) ^a	Included in validation	If no, reason for exclusion
Poon, 2009 (1)	C + B + U	First trimester	LP: $-5.324 + 2.233$ (uterine artery PI, Ln) + 23.134 (MAP, Ln MoM) - 2.408 (PIGF, Ln MoM) + 0.123 (BMI) + 1.019 (if black ethnicity) + 2.028 (if mixed ethnicity) + 1.298 (if family history of PE) - 1.443 (if parous with no previous PE)	No	Predictor not available in IPPIC-UK data set
Poon, 2009 (2)	C + U	First trimester	LP: $-0.468 + 2.272$ (maternal factor-derived a priori risk for late PE, Ln) + 21.147 (MAP, Ln MoM) + 3.537 (lowest uterine artery PI, Ln MoM)	No	Predictor not available in IPPIC-UK data set
Poon, 2009 (3) ²³⁴	C + B	First trimester	LP: $-6.652 - 0.884$ (PAPP-A, Ln MoM) + 1.127 (if family history of PE) + 1.222 (if black ethnicity) + 0.936 (if Indian or Pakistani ethnicity) + 1.335 (if mixed ethnicity) + 0.084 (BMI) - 1.255 (if parous without previous PE) + 0.818 (if parous with previous PE)	Yes	
Akolekar, 2008	C + B + U	First trimester	LP: $-5.136 - 2.400$ (PIGF, Ln MoM) + 2.641 (uterine artery PI, Ln MoM) + 0.108 (BMI) + 1.441 (if patient's mother had PE) + 1.366 (if black ethnicity) + 1.083 (if Indian or Pakistani ethnicity) + 1.549 (if mixed ethnicity) - 1.281 (if parous and no previous PE)	No	Predictor not available in IPPIC-UK data set
Onwudiwe, 2008	C + U	First and second trimester	LP: $-7.4924 + 6.2361$ (uterine artery PI, Ln MoM) + 23.1953 (MAP, Ln MoM) + 0.6003 (if African Caribbean ethnicity) + 0.1197 (BMI) - 1.1058 (if parous without previous PE)	No	Predictor not available in IPPIC-UK data set
Plasencia, 2008	C + U	First trimester	LP: $-6.140 + 0.082$ (BMI) + 0.813 (if African Caribbean ethnicity) - 1.234 (if parous with no previous PE) + 0.922 (if parous with a previous PE) + 1.049 (if patient's mother had PE) + 2.198 (uterine artery PI, Ln MoM)	No	Predictor not available in IPPIC-UK data set
Plasencia, 2007 ²³¹	C	First trimester	LP: $-6.585 + 1.368$ (if African Caribbean ethnicity) + 1.311 (if mixed ethnicity) + 0.091 (BMI) + 0.960 (if patient's mother had PE) - 1.663 (if parous without previous PE)	Yes	
Yu, 2005 ²³⁸	C + U	Second trimester	LP: $0.7901 + 5.1473$ (mean uterine artery PI) ⁻² - 12.5152 (mean uterine artery PI) ⁻¹ - 0.5575 (if smoker) + 0.5333 (if bilateral notch) + 0.0328 (age) + 0.4958 (if black ethnicity) + 1.5109 (if history of PE) + 1.1556 (if previous term live birth) + 0.0378 (BMI)	Yes	
Kenny, 2014	C + B + U	First trimester	LP: $-9.504 - 0.577$ high fruit intake + 0.058 MAP + 0.058 BMI + 0.550 tissue inhibitor of metalloproteinase 1	No	Predictor not available in IPPIC-UK data set

First author, year	Predictor category	Trimester of measurement of variables	Equation(s) ^a	Included in validation	If no, reason for exclusion
Teixeira, 2014	C + B	First trimester	LP: -8.248 + 0.050 (if chronic hypertension) + 1.649 (if diabetic) - 0.623 (if multiparous) + 3.668 (if history of PE) + 5.834 × (maternal weight MoM, log) + 0.036 × (CRL) + (-0.592) × NT + 1.046 × (free B-HCG MoM, log)	No	Predictor not available in IPPIC-UK data set

CHD, coronary heart disease; CRL, crown-rump length; hCG, human chorionic gonadotropin; hCG-H, hyperglycosylated human chorionic gonadotropin; MoM, multiple of the mean; PE, pre-eclampsia; PI, pulsatility index; PP13, placental protein 13; RI, resistance index; SGA, small for gestational age.

a For logistic regression, $\text{logit}(p) = LP$ where the $LP = \alpha + \beta_1 \times x_1 + \beta_2 \times x_2 + \dots$, and absolute predicted probabilities (p) can be obtained using the transformation $p = e^{LP} / (1 + e^{LP})$. The model for 'mean gestational age at delivery with PE' assumes a normal distribution with the predicted mean gestational age and SD 6.8833. The risk of delivery with PE is then calculated as the area under the normal curve between 24 weeks and either 42 weeks for any-onset PE (model 3) or 34 weeks for early-onset PE (model 14). For more detail, see Wright *et al.*²³⁶

Note

Ln and \log_{10} indicate that a variable was modelled on the natural logarithm scale or logarithm with base 10 scale, respectively.

Appendix 10 Patient characteristics of IPPIC-UK individual participant data sets

Maternal characteristics and outcomes	SCOPE UK ⁴² (N = 658)	Allen <i>et al.</i> ¹⁰⁸ (N = 1045)	ALSPAC ¹⁰³ (N = 14344)	Chappell <i>et al.</i> ¹²¹ (N = 316)	EMPOWaR ¹²² (N = 449)	Poston <i>et al.</i> 2006 ¹⁵⁰ (N = 2422)	Poston <i>et al.</i> 2015 ¹⁴⁹ (N = 1554)	St George's ¹⁶³ (N = 54635)	AMND ¹¹⁴ (N = 136,635)	Velauthar <i>et al.</i> ³⁹ (N = 1145)	POP ¹⁶¹ (N = 4212)
Age (years), mean (SD), range	28.5 (5.6), 15–42	29.9 (5.1), 15–48	27.7 (4.9), 13–46	29.6 (5.9), 16–43	28.7 (5.4), 17–43	31.0 (5.8), 16–48	30.5 (5.5), 16–45	30.4 (5.6), 13–54	28.4 (5.6), 13–56	NR	29.9 (5.1), 16–48
BMI (kg/m ²), median [IQR], range	24.1 [21.8–26.8], 16.5–50.0	23.6 [21.1–26.8], 14.8–51.1	21.5 [19.7–23.7], 11.7–61.3	24.2 [21.7–27.0], 16.4–56.5	38.2 [35.2–41.8], 30.8–56.3	30.1 [24.6–34.7], 16.6–65.4	35.1 [32.8–38.5], 30.0–66.0	23.5 [21.3–26.8], 11.9–79.8	28.0 [24.0–32.0], 10.0–72.1	23.9 [21.3–27.3], 13.8–46.6	24.1 [21.8–27.3], 14.7–54.7
Ethnicity, n (%)											
White	554 (84)	398 (38)	11,769 (97)	215 (68)	449 (100)	NR	954 (61)	33,257 (62)	NR	402 (35)	3900 (93)
Black	49 (7)	108 (10)	127 (1)	91 (29)	0 (0)		395 (25)	7820 (15)		90 (8)	25 (< 1)
Asian	47 (7)	495 (47)	113 (< 1)	6 (2)	0 (0)		97 (6)	10,388 (19)		565 (50)	91 (2)
Hispanic	1 (< 1)	0 (0)	0 (0)	3 (< 1)	0 (0)		0 (0)	5 (< 1)		0 (0)	0 (0)
Mixed	0 (0)	12 (1)	0 (0)	0 (0)	0 (0)		0 (0)	1528 (3)		0 (0)	1 (< 1)
Other	7 (1)	30 (3)	76 (< 1)	1 (< 1)	0 (0)		108 (7)	555 (1)		82 (7)	195 (5)
Nulliparous, n (%)	658 (100)	584 (56)	5704 (45)	202 (64)	291 (65)	NR	674 (43)	29,319 (54)	65,206 (48)	598 (52)	4212 (100)
Previous PE, n (%)	0 (0)	17 (2)	NR	56 (18)	0 (0)	657 (27)	69 (4)	NR	NR	NR	0 (0)
Outcome, n (%)											
Any-onset PE	32 (5)	14 (1)	288 (2)	35 (12)	10 (5)	371 (15)	54 (4)	1487 (3)	4970 (4)	26 (2)	273 (6)
Early-onset PE	6 (1)	1 (< 1)	37 (< 1)	6 (2)	0 (0)	144 (6)	5 (< 1)	151 (< 1)	1237 (< 1)	3 (< 1)	10 (< 1)
Late-onset PE	26 (4)	13 (1)	251 (2)	29 (10)	10 (5)	227 (9)	49 (3)	1336 (2)	3733 (3)	23 (2)	263 (6)

NR, not recorded; PE, pre-eclampsia.

Note

Summary of complete data only; therefore, percentages are out of all of those with recorded values rather than out of total individuals.

Appendix 11 Number and proportion missing (or not recorded) for each predictor in each data set used for external validation

Variable	Missing or not recorded, n (%)										
	SCOPE UK ⁴² (N = 658)	Allen <i>et al.</i> ¹⁰⁸ (N = 1045)	ALSPAC ¹⁰³ (N = 14344)	Chappell <i>et al.</i> ¹²¹ (N = 316)	EMPOWaR ¹²² (N = 449)	Poston <i>et al.</i> 2006 ¹⁵⁰ (N = 2422)	Poston <i>et al.</i> 2015 ¹⁴⁹ (N = 1554)	St George's ¹⁶³ (N = 54635)	AMND (N = 136635) ¹¹⁴	Velauthar <i>et al.</i> ³⁹ (N = 1145)	POP ¹⁶¹ (N = 4212)
Predictor											
Maternal age	0 (0)	1 (< 1)	1353 (9)	0 (0)	0 (0)	22 (< 1)	0 (0)	0 (0)	19 (< 1)	1145 (100)	0 (0)
Ethnicity	0 (0)	2 (< 1)	2259 (16)	0 (0)	0 (0)	2422 (100)	0 (0)	1082 (2)	136,635 (100)	6 (< 1)	0 (0)
Nulliparous	0 (0)	0 (0)	1745 (12)	0 (0)	1 (< 1)	2422 (100)	0 (0)	104 (< 1)	6 (< 1)	0 (0)	0 (0)
Parity and previous PE	0 (0)	0 (0)	14,344 (100)	0 (0)	1 (< 1)	2422 (100)	8 (< 1)	54,635 (100)	136,635 (100)	1145 (100)	0 (0)
Family history of PE	0 (0)	6 (< 1)	14,344 (100)	316 (100)	449 (100)	2422 (100)	61 (4)	54,635 (100)	136,635 (100)	1145 (100)	4212 (100)
Family history of PE in mother	0 (0)	6 (< 1)	14,344 (100)	316 (100)	449 (100)	2422 (100)	101 (6)	54,635 (100)	136,635 (100)	1145 (100)	4212 (100)
Spontaneous conception	0 (0)	0 (0)	2167 (15)	316 (100)	449 (100)	2422 (100)	4 (< 1)	1427 (3)	136,635 (100)	1145 (100)	0 (0)
History of hypertension	0 (0)	0 (0)	2307 (16)	0 (0)	449 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (< 1)	0 (0)
History of renal disease	0 (0)	0 (0)	2060 (14)	316 (100)	0 (0)	0 (0)	0 (0)	54,635 (100)	0 (0)	1145 (100)	0 (0)
History of diabetes	0 (0)	0 (0)	2119 (15)	0 (0)	0 (0)	0 (0)	0 (0)	54,635 (100)	136,635 (100)	1 (< 1)	0 (0)
Previous heritable thrombophilia	0 (0)	1045 (100)	14,344 (100)	316 (100)	449 (100)	2422 (100)	1554 (100)	54,635 (100)	136,635 (100)	1145 (100)	4212 (100)
Smoker	0 (0)	0 (0)	1972 (14)	0 (0)	0 (0)	2422 (100)	0 (0)	4053 (7)	2902 (2)	1 (< 1)	0 (0)
Maternal height	0 (0)	0 (0)	8769 (61)	316 (100)	0 (0)	0 (0)	0 (0)	8454 (15)	3867 (3)	5 (< 1)	6 (< 1)
Maternal weight (trimester 1)	0 (0)	5 (< 1)	9190 (64)	316 (100)	152 (34)	0 (0)	0 (0)	7992 (15)	23,926 (18)	6 (< 1)	146 (3)
Trimester 1 BMI	0 (0)	5 (< 1)	2409 (17)	33 (10)	152 (34)	0 (0)	0 (0)	9151 (17)	25,650 (19)	6 (< 1)	152 (4)
Trimester 2 BMI	0 (0)	1040 (100)	14,344 (100)	316 (100)	297 (66)	0 (0)	0 (0)	25,183 (46)	136,635 (100)	1145 (100)	57 (1)

Variable	Missing or not recorded, n (%)										
	SCOPE UK ⁴² (N = 658)	Allen <i>et al.</i> ¹⁰⁸ (N = 1045)	ALSPAC ¹⁰³ (N = 14344)	Chappell <i>et al.</i> ¹²¹ (N = 316)	EMPOWaR ¹²² (N = 449)	Poston <i>et al.</i> 2006 ¹⁵⁰ (N = 2422)	Poston <i>et al.</i> 2015 ¹⁴⁹ (N = 1554)	St George's ¹⁶³ (N = 54635)	AMND (N = 136635) ¹¹⁴	Velauthar <i>et al.</i> ³⁹ (N = 1145)	POP ¹⁶¹ (N = 4212)
Trimester 1 MAP	0 (0)	5 (< 1)	3618 (25)	316 (100)	152 (34)	0 (0)	1536 (99)	54,635 (100)	136,635 (100)	8 (< 1)	280 (7)
Trimester 1 PAPP-A (MoM)	658 (100)	119 (11)	14,344 (100)	316 (100)	449 (100)	2422 (100)	1554 (100)	30,919 (57)	136,635 (100)	1145 (100)	171 (4)
Trimester 1 PAPP-A	658 (100)	119 (11)	14,344 (100)	316 (100)	449 (100)	2422 (100)	526 (34)	54,635 (100)	136,635 (100)	1145 (100)	134 (3)
Trimester 1 UtPI	658 (100)	1045 (100)	14,344 (100)	316 (100)	449 (100)	2422 (100)	1554 (100)	32,595 (60)	136,635 (100)	2 (< 1)	4212 (100)
Trimester 2 UtPI	658 (100)	1045 (100)	14,344 (100)	316 (100)	449 (100)	2257 (93)	1554 (100)	28,109 (51)	136,635 (100)	1145 (100)	133 (3)
Trimester 2 bilateral notching	3 (< 1)	1040 (100)	14,344 (100)	316 (100)	449 (100)	27 (1)	1554 (100)	21,596 (40)	136,635 (100)	1145 (100)	133 (3)
Outcome											
Any-onset PE	4 (< 1)	0 (0)	832 (5)	33 (10)	246 (55)	0 (0)	47 (3)	0 (0)	0 (0)	32 (3)	5 (< 1)
Early-onset PE	4 (< 1)	0 (0)	832 (5)	33 (10)	78 (17)	0 (0)	47 (3)	0 (0)	0 (0)	32 (3)	5 (< 1)
Late-onset PE	4 (< 1)	0 (0)	832 (5)	33 (10)	239 (53)	0 (0)	47 (3)	0 (0)	0 (0)	32 (3)	5 (< 1)
PE, pre-eclampsia; MoM, multiple of the mean; UtPI, uterine artery pulsatility index.											

Appendix 12 Summary of linear predictor and predicted probability values from external validation

TABLE 28 Summary of LP values and predicted probabilities for each model in each data set

Model number	Authors, year	Type of predictors	Study	N	Events, ^a n (%)	LP ^a			Predicted probability ^a			
						Median	IQR	Range (minimum to maximum)	Median	IQR	Range (minimum to maximum)	
<i>First-trimester any-onset pre-eclampsia models</i>												
1	Plasencia <i>et al.</i> , 2007 ²³¹	C	SCOPE UK ⁴²	658	33 (5.0)	-4.186	-4.408 to -3.868	-4.865 to -1.052	0.015	0.012 to 0.020	0.008 to 0.259	
			Allen <i>et al.</i> ¹⁰⁸	1045	14 (1.3)	-4.508	-5.576 to -4.139	-6.464 to -1.023	0.011	0.004 to 0.016	0.002 to 0.264	
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	56 (3.6)	-3.488	-4.531 to -2.943	-5.269 to 0.337	0.03	0.011 to 0.050	0.005 to 0.584	
2	Poon <i>et al.</i> , 2008 ²³³	C	SCOPE UK ⁴²	658	33 (5.0)	-4.047	-4.290 to -3.700	-4.790 to -0.884	0.017	0.014 to 0.024	0.008 to 0.292	
			Allen <i>et al.</i> ¹⁰⁸	1045	14 (1.3)	-4.406	-5.386 to -4.002	-6.337 to -0.885	0.012	0.005 to 0.018	0.002 to 0.292	
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	56 (3.6)	-3.292	-4.220 to -2.700	-5.028 to 0.691	0.036	0.014 to 0.063	0.007 to 0.666	
3	Wright <i>et al.</i> , 2015 ²³⁶	C	SCOPE UK ⁴²	658	33 (5.0)	-3.272	-3.513 to -2.929	-4.179 to -0.758	0.037	0.029 to 0.051	0.015 to 0.319	
			Allen <i>et al.</i> ¹⁰⁸	584	8 (1.4)	-3.093	-3.436 to -2.729	-4.182 to -0.962	0.043	0.031 to 0.061	0.015 to 0.277	
			Poston <i>et al.</i> 2015 ¹⁴⁹	674	36 (5.3)	-2.084	-2.300 to -1.710	-3.090 to -0.437	0.111	0.091 to 0.153	0.044 to 0.393	
4	Baschat <i>et al.</i> , 2014 ¹¹⁵	C + B	Allen <i>et al.</i> ¹⁰⁸	1045	14 (1.3)	-3.041	-3.440 to -2.615	-4.705 to 0.283	0.046	0.031 to 0.068	0.009 to 0.570	
			POP ¹⁶¹	4212	273 (6.5)	-3.549	-3.885 to -3.107	-5.801 to 0.185	0.028	0.020 to 0.043	0.003 to 0.546	
5	Goetzinger <i>et al.</i> , 2010 ¹²⁸	C + B	Allen <i>et al.</i> ¹⁰⁸	1045	14 (1.3)	-3.25	-3.250 to -2.320	-3.250 to -0.260	0.037	0.037 to 0.089	0.037 to 0.435	
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	56 (3.6)	-2.32	-2.320 to -1.710	-2.320 to -1.200	0.089	0.089 to 0.153	0.089 to 0.231	
			POP ¹⁶¹	4212	273 (6.5)	-3.25	-3.250 to -2.320	-3.250 to 0.100	0.037	0.037 to 0.089	0.037 to 0.525	
6	Odibo <i>et al.</i> , 2011 ¹⁴⁷	C + B	Allen <i>et al.</i> ¹⁰⁸	1045	14 (1.3)	-2.92	-3.223 to -2.614	-5.367 to -0.301	0.051	0.038 to 0.068	0.005 to 0.425	
			St George's ¹⁶³	54,635	1487 (2.7)	-2.866	-3.200 to -2.573	-36.527 to 0.882	0.054	0.039 to 0.071	0.000 to 0.707	
			POP ¹⁶¹	4212	273 (6.5)	-2.874	-3.287 to -2.517	-21.418 to 0.230	0.053	0.036 to 0.075	0.000 to 0.557	
7	Odibo <i>et al.</i> , 2011 ¹⁴⁷	C + U	Velauthar <i>et al.</i> ³⁹	1145	28 (2.4)	-3.331	-3.543 to -3.080	-4.586 to -0.194	0.035	0.028 to 0.044	0.010 to 0.452	

Model number	Authors, year	Type of predictors	Study	N	Events, ^a n (%)	LP ^a			Predicted probability ^a			
						Median	IQR	Range (minimum to maximum)	Median	IQR	Range (minimum to maximum)	
First-trimester early-onset pre-eclampsia models												
8	Baschat <i>et al.</i> , 2014 ¹¹⁵	C	SCOPE UK ⁴²	658	6 (0.9)	-5.070	-5.114 to -5.019	-5.234 to -4.069	0.006	0.006 to 0.007	0.005 to 0.017	
			ALSPAC ¹⁰³	14,344	40 (0.3)	-5.013	-5.076 to -4.949	-5.362 to -3.502	0.007	0.006 to 0.007	0.005 to 0.029	
			Poston <i>et al.</i> 2006 ¹⁵⁰	2422	144 (6.0)	-4.891	-5.013 to -4.151	-5.297 to -3.631	0.007	0.007 to 0.016	0.005 to 0.026	
			Velauthar <i>et al.</i> ³⁹	1145	4 (0.3)	-5.029	-5.090 to -4.975	-5.272 to -3.867	0.007	0.006 to 0.007	0.005 to 0.020	
			POP ¹⁶¹	4212	10 (0.2)	-5.059	-5.108 to -4.992	-5.361 to -3.761	0.006	0.006 to 0.007	0.005 to 0.023	
9	Crovetto <i>et al.</i> , 2015 ²²⁹	C	SCOPE UK ⁴²	658	6 (0.9)	-6.282	-6.282 to -6.282	-6.282 to -1.670	0.002	0.002 to 0.002	0.002 to 0.158	
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	6 (0.4)	-5.177	-6.282 to -3.899	-6.282 to 0.749	0.006	0.002 to 0.020	0.002 to 0.679	
			POP ¹⁶¹	4212	10 (0.2)	-6.282	-6.282 to -6.282	-6.282 to -1.670	0.002	0.002 to 0.002	0.002 to 0.158	
10	Kuc <i>et al.</i> , 2013 ²³⁰	C	SCOPE UK ⁴²	658	6 (0.9)	-1.679	-2.24 to -0.955	-4.285 to 2.445	0.157	0.096 to 0.278	0.014 to 0.920	
			ALSPAC ¹⁰³	14,344	40 (0.3)	-3.339	-4.242 to -2.413	-8.414 to 2.483	0.034	0.014 to 0.082	0.000 to 0.919	
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	6 (0.4)	-0.543	-1.413 to 0.373	-3.744 to 3.982	0.367	0.196 to 0.592	0.023 to 0.982	
			St George's ¹⁶³	54,635	151 (0.3)	-2.351	-3.236 to -1.488	-11.455 to 7.092	0.087	0.038 to 0.184	0.000 to 0.999	
			AMND ¹¹⁴	136,635	1237 (0.9)	-2.304	-3.223 to -1.371	-7.660 to 4.857	0.091	0.038 to 0.202	0.000 to 0.992	
			POP ¹⁶¹	4212	10 (0.2)	-1.599	-2.268 to -0.842	-4.585 to 3.497	0.168	0.094 to 0.301	0.010 to 0.970	
11	Plasencia <i>et al.</i> , 2007 ²³¹	C	SCOPE UK ⁴²	658	6 (0.9)	-6.431	-6.431 to -6.431	-6.431 to -4.751	0.002	0.002 to 0.002	0.002 to 0.009	
			Chappell <i>et al.</i> ¹²¹	316	7 (2.1)	-6.431	-6.431 to -4.751	-6.431 to -1.929	0.002	0.002 to 0.009	0.002 to 0.127	
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	6 (0.4)	-6.431	-6.431 to -4.751	-6.431 to -1.929	0.002	0.002 to 0.009	0.002 to 0.127	
			POP ¹⁶¹	4212	10 (0.2)	-6.431	-6.431 to -6.431	-6.431 to -4.542	0.002	0.002 to 0.002	0.002 to 0.011	

continued

TABLE 28 Summary of LP values and predicted probabilities for each model in each data set (continued)

Model number	Authors, year	Type of predictors	Study	N	Events, ^a n (%)	LP ^a			Predicted probability ^a		
						Median	IQR	Range (minimum to maximum)	Median	IQR	Range (minimum to maximum)
12	Poon <i>et al.</i> , 2010 ²³²	C	SCOPE UK ⁴²	658	6 (0.9)	-5.674	-5.674 to -5.674	-5.674 to -2.214	0.003	0.003 to 0.003	0.003 to 0.099
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	6 (0.4)	-4.137	-5.321 to -4.054	-6.858 to -1.508	0.016	0.005 to 0.017	0.001 to 0.181
			POP ¹⁶¹	4212	10 (0.2)	-4.137	-4.137 to -4.137	-5.674 to -0.677	0.016	0.016 to 0.016	0.003 to 0.337
13	Scazzocchio <i>et al.</i> , 2013 ²³⁵	C	SCOPE UK ⁴²	658	6 (0.9)	-5.631	-5.832 to -5.397	-6.282 to -3.145	0.004	0.003 to 0.005	0.002 to 0.041
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	6 (0.4)	-4.662	-4.877 to -4.333	-5.127 to -0.099	0.009	0.008 to 0.013	0.006 to 0.475
			POP ¹⁶¹	4212	10 (0.2)	-5.617	-5.822 to -5.303	-6.448 to 1.688	0.004	0.003 to 0.005	0.002 to 0.844
14	Wright <i>et al.</i> , 2015 ²³⁶	C	SCOPE UK ⁴²	658	6 (0.9)	-6.461	-6.804 to -5.972	-7.744 to -2.932	0.002	0.001 to 0.003	0.000 to 0.051
			Poston <i>et al.</i> 2015 ¹⁴⁹	674	6 (0.4)	-4.761	-5.069 to -4.231	-6.201 to -2.521	0.008	0.006 to 0.014	0.002 to 0.074
15	Poon <i>et al.</i> , 2009 ²³⁴	C + B	POP ¹⁶¹	4212	10 (0.2)	-6.321	-7.824 to -4.693	-18.294 to 3.971	0.002	0.000 to 0.009	0.000 to 0.981
First-trimester late-onset pre-eclampsia models											
16	Crovetto <i>et al.</i> , 2015 ²²⁹	C	SCOPE UK ⁴²	658	26 (4.0)	-4.504	-4.789 to -4.149	-5.703 to -1.592	0.011	0.008 to 0.016	0.003 to 0.169
			Allen <i>et al.</i> ¹⁰⁸	1045	13 (1.2)	-3.914	-4.494 to -3.298	-5.654 to 1.509	0.020	0.011 to 0.036	0.003 to 0.819
			Chappell <i>et al.</i> ¹²¹	316	32 (10.0)	-4.084	-4.648 to -2.645	-5.903 to 2.098	0.017	0.009 to 0.066	0.003 to 0.891
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	51 (3.3)	-2.658	-3.207 to -2.114	-4.468 to 3.007	0.066	0.039 to 0.108	0.011 to 0.953
			POP ¹⁶¹	4212	263 (6.2)	-4.496	-4.775 to -4.109	-6.133 to -0.074	0.011	0.008 to 0.016	0.002 to 0.481

Model number	Authors, year	Type of predictors	Study	N	Events, ^a n (%)	LP ^a			Predicted probability ^a		
						Median	IQR	Range (minimum to maximum)	Median	IQR	Range (minimum to maximum)
17	Kuc <i>et al.</i> , 2013 ²³⁰	C	SCOPE UK ⁴²	658	26 (4.0)	-1.464	-1.871 to -1.062	-3.016 to 0.191	0.188	0.133 to 0.257	0.047 to 0.548
			Allen <i>et al.</i> ¹⁰⁸	1045	13 (1.2)	-2.104	-2.653 to -1.526	-4.520 to 0.558	0.109	0.066 to 0.179	0.011 to 0.636
			ALSPAC ¹⁰³	14,344	266 (1.9)	-2.698	-3.226 to -2.070	-5.045 to 0.134	0.063	0.038 to 0.112	0.006 to 0.533
			EMPOWaR ¹²²	449	28 (6.3)	-0.801	-1.395 to -0.281	-3.032 to 1.118	0.310	0.199 to 0.430	0.047 to 0.751
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	51 (3.3)	-1.286	-1.801 to -0.641	-3.074 to 1.077	0.217	0.142 to 0.345	0.044 to 0.746
			St George's ¹⁶³	54,635	1336 (2.4)	-1.992	-2.562 to -1.437	-4.741 to 1.303	0.120	0.072 to 0.192	0.009 to 0.786
			AMND ¹¹⁴	136,635	3733 (2.7)	-2.238	-2.791 to -1.652	-4.987 to 1.023	0.096	0.058 to 0.161	0.007 to 0.735
POP ¹⁶¹	4212	263 (6.2)	-1.367	-1.723 to -1.011	-3.233 to 0.874	0.203	0.151 to 0.267	0.038 to 0.705			
18	Plasencia <i>et al.</i> , 2007 ²³¹	C	SCOPE UK ⁴²	658	26 (4.0)	-4.346	-4.586 to -4.001	-5.081 to -1.134	0.013	0.010 to 0.018	0.006 to 0.243
			Allen <i>et al.</i> ¹⁰⁸	1045	13 (1.2)	-4.702	-5.848 to -4.318	-6.809 to -1.020	0.009	0.003 to 0.013	0.001 to 0.265
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	51 (3.3)	-3.636	-4.715 to -3.103	-5.514 to 0.141	0.026	0.009 to 0.043	0.004 to 0.535
19	Poon <i>et al.</i> , 2010 ²³²	C	SCOPE UK ⁴²	658	26 (4.0)	-4.460	-4.746 to -3.925	-5.459 to -1.342	0.011	0.009 to 0.019	0.004 to 0.207
			Allen <i>et al.</i> ¹⁰⁸	1045	13 (1.2)	-4.542	-5.007 to -3.860	-6.748 to -1.142	0.011	0.007 to 0.021	0.001 to 0.242
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	51 (3.3)	-3.656	-4.321 to -2.968	-5.612 to 0.285	0.025	0.013 to 0.049	0.004 to 0.571
20	Scazzocchio <i>et al.</i> , 2013 ²³⁵	C	SCOPE UK ⁴²	658	26 (4.0)	-3.894	-4.111 to -3.641	-4.598 to -1.482	0.020	0.016 to 0.026	0.010 to 0.185
21	Poon <i>et al.</i> , 2009 ²³⁴	C + B	Allen <i>et al.</i> ¹⁰⁸	1045	13 (1.2)	-4.505	-5.108 to -3.883	-7.179 to -0.850	0.011	0.006 to 0.020	0.001 to 0.305

continued

TABLE 28 Summary of LP values and predicted probabilities for each model in each data set (continued)

Model number	Authors, year	Type of predictors	Study	N	Events, ^a n (%)	LP ^a			Predicted probability ^a			
						Median	IQR	Range (minimum to maximum)	Median	IQR	Range (minimum to maximum)	
Second-trimester any-onset pre-eclampsia models												
22	Yu <i>et al.</i> , 2005 ²³⁸	C + U	POP ¹⁶¹	4212	273 (6.5)	-4.470	-4.806 to -3.860	-6.206 to 65.058	0.011	0.008 to 0.021	0.002 to 1.000	
Second-trimester early-onset pre-eclampsia models												
23	Yu <i>et al.</i> , 2005 ²³⁸	C + U	POP ¹⁶¹	4212	10 (0.2)	-9.601	-9.694 to -9.412	-9.809 to 0.374	0.000	0.000 to 0.000	0.000 to 0.591	
Second-trimester late-onset pre-eclampsia models												
24	Yu <i>et al.</i> , 2005 ²³⁸	C + U	POP ¹⁶¹	4212	263 (6.2)	-4.488	-4.789 to -3.967	-6.145 to 56.090	0.011	0.008 to 0.019	0.002 to 1.000	

C, clinical characteristics; C + B, clinical and biochemical markers; C + U, clinical characteristics and ultrasound markers.

^a For imputed data, the estimates are the average across imputations (pooled using Rubin's rules).

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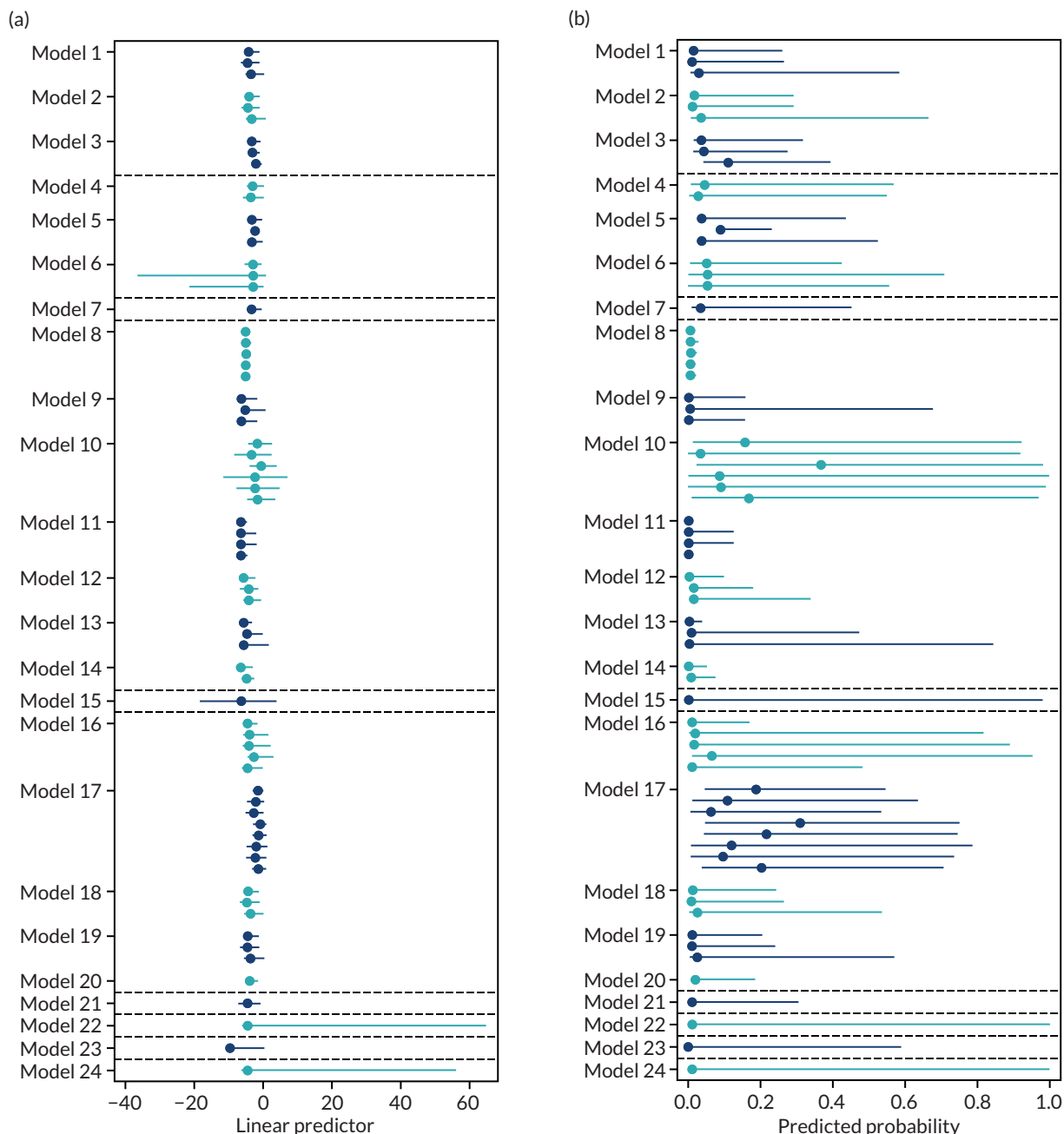


FIGURE 18 Median (dot) and range (bar) of values for (a) LP and (b) predicted probabilities across validation data sets for each model being externally validated. This figure contains information from several sources.^{115,128,147,229-236,238} Reproduced from Snell *et al.*⁵² Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Appendix 13 Predictive performance statistics for models in the individual IPPIC-UK data sets

Model number	Authors, year	Type of predictors	Validation cohort	N	Events, ^a n (%)	Performance statistic (95% CI)		
						C-statistic	Calibration slope	Calibration-in-the-large
<i>First-trimester any-onset pre-eclampsia models</i>								
1	Plasencia <i>et al.</i> , 2007 ²³¹	C	SCOPE UK ⁴²	658	33 (5.0)	0.636 (0.532 to 0.729)	0.521 (0.025 to 1.017)	0.865 (0.502 to 1.228)
			Allen <i>et al.</i> ¹⁰⁸	1045	14 (1.3)	0.782 (0.638 to 0.880)	1.110 (0.600 to 1.619)	-0.117 (-0.651 to 0.417)
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	56 (3.6)	0.692 (0.617 to 0.758)	0.580 (0.346 to 0.813)	-0.326 (-0.610 to -0.042)
2	Poon <i>et al.</i> , 2008 ²³³	C	SCOPE UK ⁴²	658	33 (5.0)	0.637 (0.532 to 0.730)	0.546 (0.051 to 1.040)	0.731 (0.368 to 1.093)
			Allen <i>et al.</i> ¹⁰⁸	1045	14 (1.3)	0.782 (0.638 to 0.880)	1.155 (0.622 to 1.689)	-0.209 (-0.743 to 0.324)
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	56 (3.6)	0.694 (0.620 to 0.759)	0.597 (0.357 to 0.837)	-0.518 (-0.801 to -0.234)
3	Wright <i>et al.</i> , 2015 ²³⁶	C	SCOPE UK ⁴²	658	33 (5.0)	0.647 (0.552 to 0.732)	0.638 (0.097 to 1.179)	1.880 (1.519 to 2.240)
			Allen <i>et al.</i> ¹⁰⁸	584	8 (1.4)	0.680 (0.453 to 0.845)	0.840 (-0.100 to 1.781)	0.367 (-0.334 to 1.069)
			Poston <i>et al.</i> 2015 ¹⁴⁹	674	36 (5.3)	0.592 (0.497 to 0.681)	0.560 (-0.067 to 1.187)	0.544 (0.200 to 0.888)
4	Baschat <i>et al.</i> , 2014 ¹¹⁵	C + B	Allen <i>et al.</i> ¹⁰⁸	1045	14 (1.3)	0.758 (0.620 to 0.857)	1.246 (0.667 to 1.824)	-1.543 (-2.074 to -1.011)
			POP ¹⁶¹	4212	273 (6.5)	0.704 (0.670 to 0.737)	1.237 (1.034 to 1.439)	0.658 (0.533 to 0.782)
5	Goetzinger <i>et al.</i> , 2010 ¹²⁸	C + B	Allen <i>et al.</i> ¹⁰⁸	1045	14 (1.3)	0.670 (0.502 to 0.804)	0.910 (0.092 to 1.729)	-1.691 (-2.221 to -1.162)
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	56 (3.6)	0.521 (0.451 to 0.590)	0.409 (-0.567 to 1.386)	-1.206 (-1.480 to -0.933)
			POP ¹⁶¹	4212	273 (6.5)	0.764 (0.730 to 0.795)	1.706 (1.499 to 1.913)	-0.070 (-0.195 to 0.054)
6	Odibo <i>et al.</i> , 2011 ¹⁴⁷	C + B	Allen <i>et al.</i> ¹⁰⁸	1045	14 (1.3)	0.660 (0.491 to 0.796)	0.847 (-0.022 to 1.716)	-1.512 (-2.041 to -0.982)
			St George's ¹⁶³	54,635	1487 (2.7)	0.672 (0.654 to 0.690)	0.962 (0.885 to 1.039)	-0.897 (-0.950 to -0.845)
			POP ¹⁶¹	4212	273 (6.5)	0.779 (0.744 to 0.812)	1.490 (1.329 to 1.651)	-0.033 (-0.159 to 0.094)
7	Odibo <i>et al.</i> , 2011 ¹⁴⁷	C + U	Velauthar <i>et al.</i> ³⁹	1145	28 (2.4)	0.526 (0.390 to 0.658)	0.277 (-0.642 to 1.195)	-0.520 (-0.907 to -0.134)

Model number	Authors, year	Type of predictors	Validation cohort	N	Events, ^a n (%)	Performance statistic (95% CI)		
						C-statistic	Calibration slope	Calibration-in-the-large
<i>First-trimester early-onset pre-eclampsia models</i>								
8	Baschat <i>et al.</i> , 2014 ¹¹⁵	C	SCOPE UK ⁴²	658	6 (0.9)	0.513 (0.291 to 0.73)	0.212 (-8.468 to 8.892)	0.399 (-0.407 to 1.205)
			ALSPAC ¹⁰³	14,344	40 (0.3)	0.706 (0.600 to 0.794)	2.070 (1.234 to 2.905)	-1.029 (-1.352 to -0.705)
			Poston <i>et al.</i> 2006 ¹⁵⁰	2422	144 (6.0)	0.672 (0.626 to 0.716)	1.281 (0.898 to 1.664)	1.797 (1.628 to 1.967)
			Velauthar <i>et al.</i> ³⁹	1145	4 (0.3)	0.698 (0.434 to 0.876)	1.639 (-4.040 to 7.319)	-0.755 (-1.875 to 0.365)
			POP ¹⁶¹	4212	10 (0.2)	0.739 (0.494 to 0.891)	3.403 (2.017 to 4.789)	-1.054 (-1.674 to -0.433)
9	Crovetto <i>et al.</i> , 2015 ²²⁹	C	SCOPE UK ⁴²	658	6 (0.9)	0.464 (0.428 to 0.500)	NE	1.039 (0.218 to 1.861)
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	6 (0.4)	0.596 (0.278 to 0.850)	0.264 (-0.216 to 0.743)	-2.484 (-3.401 to -1.567)
			POP ¹⁶¹	4212	10 (0.2)	0.721 (0.532 to 0.855)	0.996 (0.596 to 1.395)	-0.317 (-0.943 to 0.309)
10	Kuc <i>et al.</i> , 2013 ²³⁰	C	SCOPE UK ⁴²	658	6 (0.9)	0.762 (0.520 to 0.905)	0.682 (0.050 to 1.314)	-3.709 (-4.530 to -2.889)
			ALSPAC ¹⁰³	14,344	40 (0.3)	0.664 (0.484 to 0.812)	0.442 (-0.025 to 0.909)	-3.458 (-3.786 to -3.130)
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	6 (0.4)	0.519 (0.323 to 0.710)	0.010 (-0.705 to 0.726)	-5.978 (-6.861 to -5.094)
			St George's ¹⁶³	54,635	151 (0.3)	0.635 (0.587 to 0.679)	0.343 (0.227 to 0.460)	-4.510 (-4.674 to -4.347)
			AMND ¹¹⁴	136,635	1237 (0.9)	0.681 (0.665 to 0.696)	0.470 (0.430 to 0.511)	-3.387 (-3.445 to -3.330)
			POP ¹⁶¹	4212	10 (0.2)	0.656 (0.518 to 0.772)	0.450 (-0.069 to 0.969)	-5.191 (-5.815 to -4.567)
11	Plasencia <i>et al.</i> , 2007 ²³¹	C	SCOPE UK ⁴²	658	6 (0.9)	0.465 (0.429 to 0.501)	NE	1.500 (0.691 to 2.309)
			Chappell <i>et al.</i> ¹²¹	316	7 (2.1)	0.706 (0.463 to 0.872)	0.510 (0.013 to 1.007)	0.462 (-0.402 to 1.327)
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	6 (0.4)	0.667 (0.391 to 0.863)	0.517 (-0.135 to 1.170)	-0.478 (-1.367 to 0.411)
			POP ¹⁶¹	4212	10 (0.2)	0.497 (0.496 to 0.498)	NE	0.365 (-0.256 to 0.985)

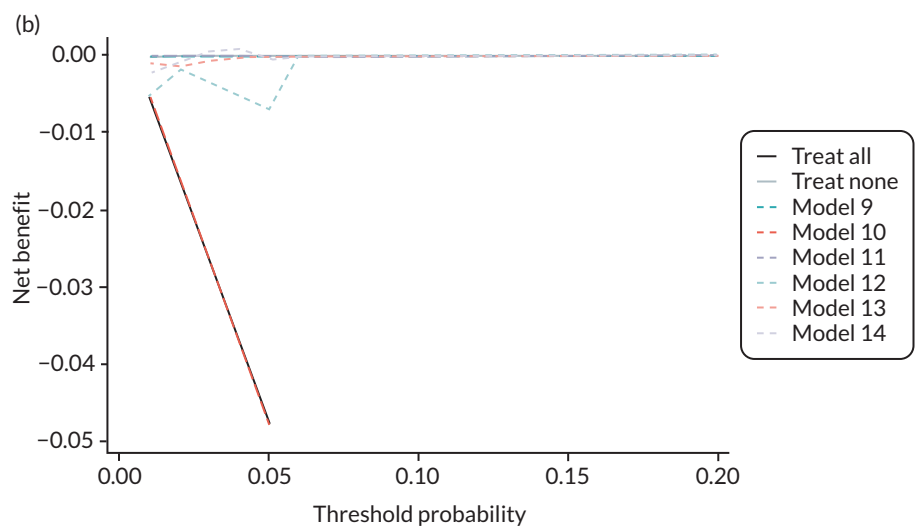
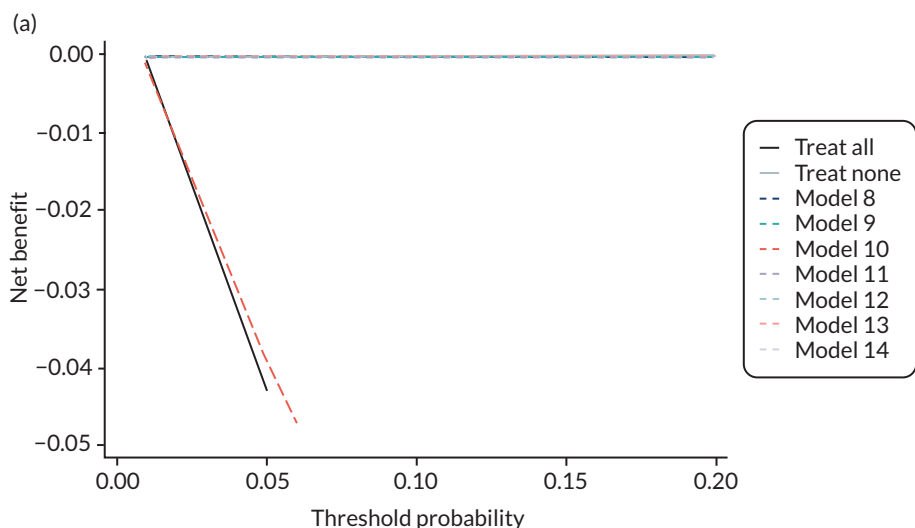
Model number	Authors, year	Type of predictors	Validation cohort	N	Events, ^a n (%)	Performance statistic (95% CI)		
						C-statistic	Calibration slope	Calibration-in-the-large
12	Poon <i>et al.</i> , 2010 ²³²	C	SCOPE UK ⁴²	658	6 (0.9)	0.524 (0.355 to 0.687)	0.236 (-1.154 to 1.627)	0.648 (-0.163 to 1.458)
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	6 (0.4)	0.745 (0.512 to 0.892)	0.846 (0.004 to 1.688)	-1.667 (-2.548 to -0.787)
			POP ¹⁶¹	4212	10 (0.2)	0.687 (0.455 to 0.852)	1.176 (0.617 to 1.734)	-2.228 (-2.849 to -1.606)
13	Scazzocchio <i>et al.</i> , 2013 ²³⁵	C	SCOPE UK ⁴²	658	6 (0.9)	0.728 (0.448 to 0.898)	1.131 (-0.130 to 2.392)	0.788 (-0.020 to 1.596)
			ALSPAC ¹⁰³	1554	6 (0.4)	0.612 (0.333 to 0.834)	0.586 (-0.376 to 1.548)	-1.434 (-2.316 to -0.551)
			Poston <i>et al.</i> 2006 ¹⁵⁰	4212	10 (0.2)	0.844 (0.640 to 0.943)	0.746 (0.449 to 1.042)	-1.439 (-2.092 to -0.787)
14	Wright <i>et al.</i> , 2015 ²³⁶	C	Velauthar <i>et al.</i> ³⁹	658	6 (0.9)	0.763 (0.614 to 0.867)	0.907 (-0.027 to 1.842)	1.396 (0.585 to 2.207)
			POP ¹⁶¹	674	6 (0.4)	0.591 (0.207 to 0.890)	0.958 (-0.727 to 2.642)	-0.906 (-2.048 to 0.236)
15	Poon <i>et al.</i> , 2009 ²³⁴	C + B	SCOPE UK ⁴²	4212	10 (0.2)	0.741 (0.507 to 0.888)	0.452 (0.210 to 0.693)	-2.671 (-3.35 to -1.991)
First-trimester late-onset pre-eclampsia models								
16	Crovetto <i>et al.</i> , 2015 ²²⁹	C	SCOPE UK ⁴²	658	26 (4.0)	0.569 (0.448 to 0.683)	0.379 (-0.231 to 0.988)	1.074 (0.675 to 1.472)
			Allen <i>et al.</i> ¹⁰⁸	1045	13 (1.2)	0.544 (0.352 to 0.723)	0.516 (0.108 to 0.924)	-1.205 (-1.779 to -0.630)
			Chappell <i>et al.</i> ¹²¹	316	32 (10.0)	0.696 (0.586 to 0.788)	0.345 (0.152 to 0.538)	0.037 (-0.451 to 0.525)
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	51 (3.3)	0.504 (0.412 to 0.596)	0.210 (-0.035 to 0.456)	-1.502 (-1.812 to -1.192)
			POP ¹⁶¹	4212	263 (6.2)	0.781 (0.745 to 0.813)	1.248 (1.120 to 1.376)	1.309 (1.177 to 1.441)
17	Kuc <i>et al.</i> , 2013 ²³⁰	C	SCOPE UK ⁴²	658	26 (4.0)	0.544 (0.421 to 0.663)	0.224 (-0.445 to 0.893)	-1.867 (-2.262 to -1.471)
			Allen <i>et al.</i> ¹⁰⁸	1045	13 (1.2)	0.583 (0.425 to 0.726)	0.340 (-0.356 to 1.036)	-2.570 (-3.119 to -2.020)
			ALSPAC ¹⁰³	14,344	266 (1.9)	0.657 (0.616 to 0.696)	0.761 (0.550 to 0.973)	-1.574 (-1.699 to -1.448)
			EMPOWaR ¹²²	449	28 (6.3)	0.337 (0.162 to 0.558)	-0.755 (-1.808 to 0.299)	-2.127 (-2.795 to -1.459)
			Poston <i>et al.</i> 2015 ¹⁴⁹	1554	51 (3.3)	0.592 (0.512 to 0.668)	0.390 (0.019 to 0.762)	-2.435 (-2.724 to -2.147)

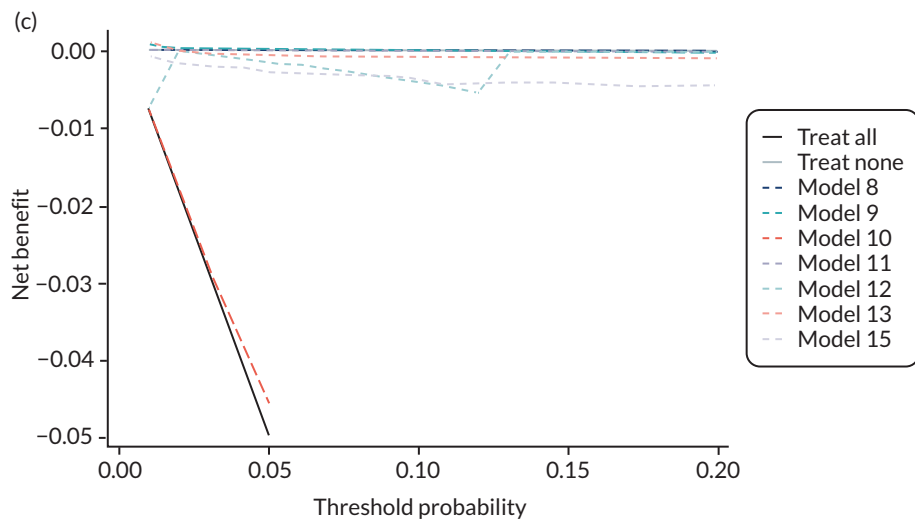
Model number	Authors, year	Type of predictors	Validation cohort	N	Events, ^a n (%)	Performance statistic (95% CI)		
						C-statistic	Calibration slope	Calibration-in-the-large
18	Plasencia <i>et al.</i> , 2007 ²³¹	C	St George's ¹⁶³	54,635	1336 (2.4)	0.636 (0.621 to 0.651)	0.632 (0.560 to 0.704)	-1.970 (-2.025 to -1.915)
			AMND ¹¹⁴	136,635	3733 (2.7)	0.844 (0.640 to 0.943)	0.746 (0.449 to 1.042)	-1.439 (-2.092 to -0.787)
			POP ¹⁶¹	4212	263 (6.2)	0.599 (0.561 to 0.636)	0.673 (0.452 to 0.894)	-1.487 (-1.613 to -1.361)
			SCOPE UK ⁴²	658	26 (4.0)	0.627 (0.509 to 0.732)	0.523 (-0.003 to 1.049)	0.778 (0.377 to 1.178)
			Allen <i>et al.</i> ¹⁰⁸	1045	13 (1.2)	0.751 (0.600 to 0.858)	1.008 (0.459 to 1.556)	0.043 (-0.510 to 0.596)
19	Poon <i>et al.</i> , 2010 ²³²	C	Poston <i>et al.</i> 2015 ¹⁴⁹	1554	51 (3.3)	0.673 (0.596 to 0.742)	0.523 (0.264 to 0.782)	-0.204 (-0.498 to 0.090)
			SCOPE UK ⁴²	658	26 (4.0)	0.570 (0.405 to 0.682)	0.369 (-0.199 to 0.937)	0.909 (0.511 to 1.308)
			Allen <i>et al.</i> ¹⁰⁸	1045	13 (1.2)	0.716 (0.556 to 0.836)	0.913 (0.312 to 1.514)	-0.289 (-0.841 to 0.262)
20	Scazzocchio <i>et al.</i> , 2013 ²³⁵	C	Poston <i>et al.</i> 2015 ¹⁴⁹	1554	51 (3.3)	0.666 (0.591 to 0.734)	0.541 (0.280 to 0.802)	-0.271 (-0.566 to 0.025)
			SCOPE UK ⁴²	658	26 (4.0)	0.597 (0.478 to 0.705)	0.562 (-0.168 to 1.291)	0.524 (0.128 to 0.920)
21	Poon <i>et al.</i> , 2009 ²³⁴	C + B	Allen <i>et al.</i> ¹⁰⁸	1045	13 (1.2)	0.684 (0.550 to 0.792)	0.799 (0.257 to 1.341)	-0.349 (-0.902 to 0.205)
Second-trimester any-onset pre-eclampsia models								
22	Yu <i>et al.</i> , 2005 ²³⁸	C + U	POP ¹⁶¹	4212	273 (6.5)	0.610 (0.574 to 0.645)	0.075 (0.007 to 0.144)	NE
Second-trimester early-onset pre-eclampsia models								
23	Yu <i>et al.</i> , 2005 ²³⁸	C + U	POP ¹⁶¹	4212	10 (0.2)	0.908 (0.826 to 0.954)	0.557 (0.293 to 0.821)	2.473 (1.716 to 3.229)
Second-trimester late-onset pre-eclampsia models								
24	Yu <i>et al.</i> , 2005 ²³⁸	C + U	POP ¹⁶¹	4212	263 (6.2)	0.607 (0.570 to 0.642)	0.077 (0.005 to 0.148)	NE

C, clinical characteristics; C + B, clinical and biochemical markers; C + U, clinical characteristics and ultrasound markers; NE, not estimable due to perfect prediction (same predicted probability for all individuals that had the event).

a For data sets with imputed outcomes, estimates are averages across 100 imputations (pooled using Rubin's rules).

Appendix 14 Decision curves for prediction models of early-onset pre-eclampsia in (a) SCOPE UK,⁴² (b) Poston *et al.* 2015¹⁴⁹ and (c) POP¹⁶¹





Appendix 15 Imputation checking for model development

Imputation checking for clinical characteristics models

Trimester 1 predictors

BMI values were not imputed reliably in POUCH, illustrated by the distribution of imputed values getting wider in later imputations, particularly for transformations of BMI.

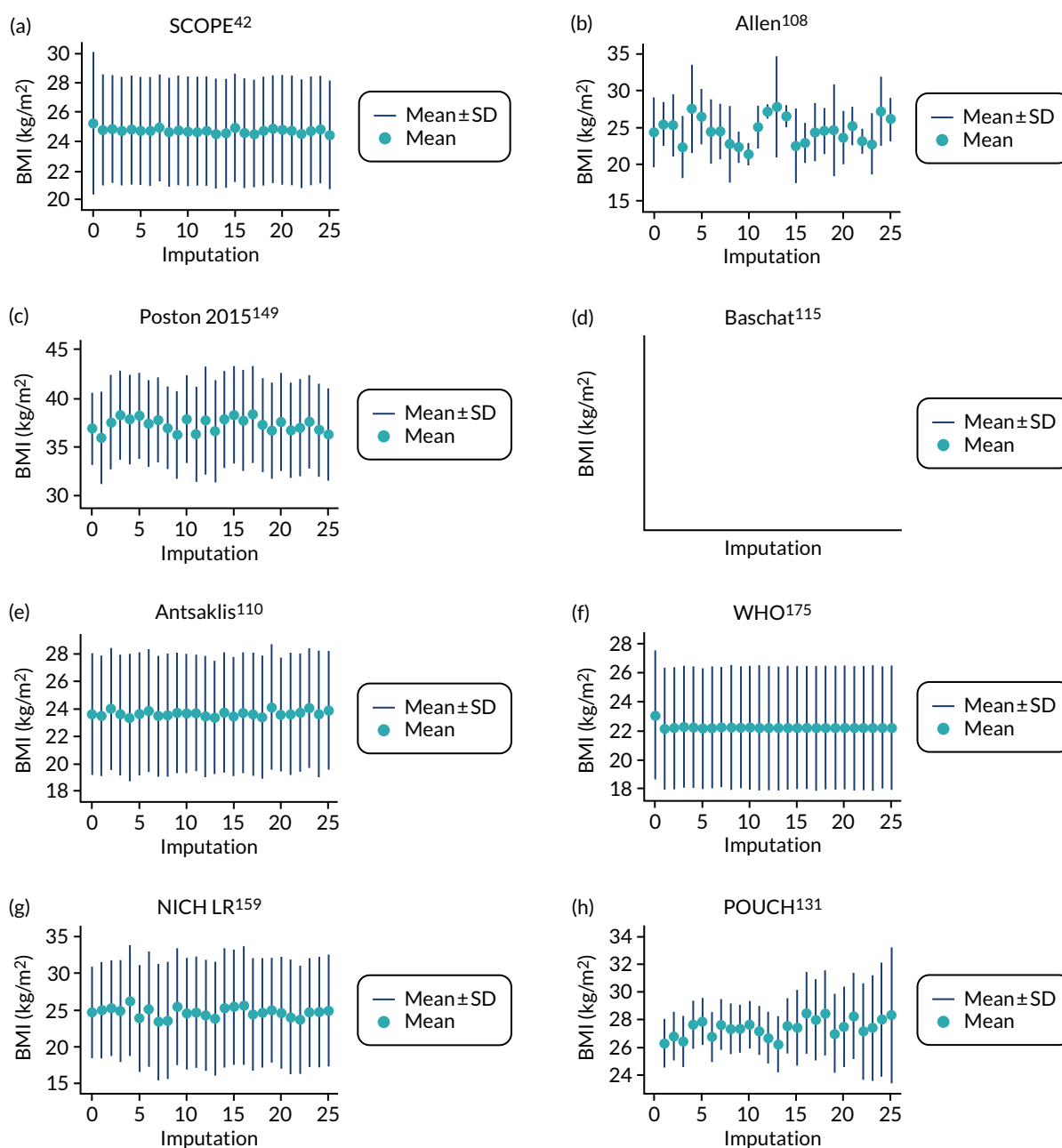


FIGURE 19 Median and range of BMI values in imputed data set for cohorts included in the development of models with trimester 1 clinical characteristics. (continued)

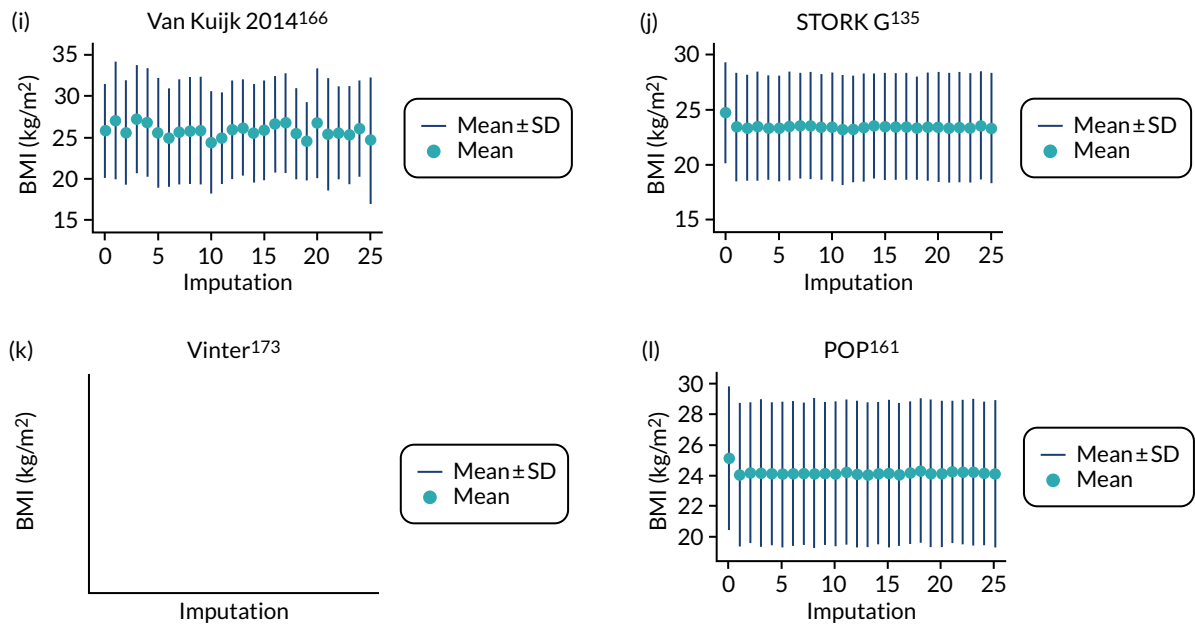


FIGURE 19 Median and range of BMI values in imputed data set for cohorts included in the development of models with trimester 1 clinical characteristics.

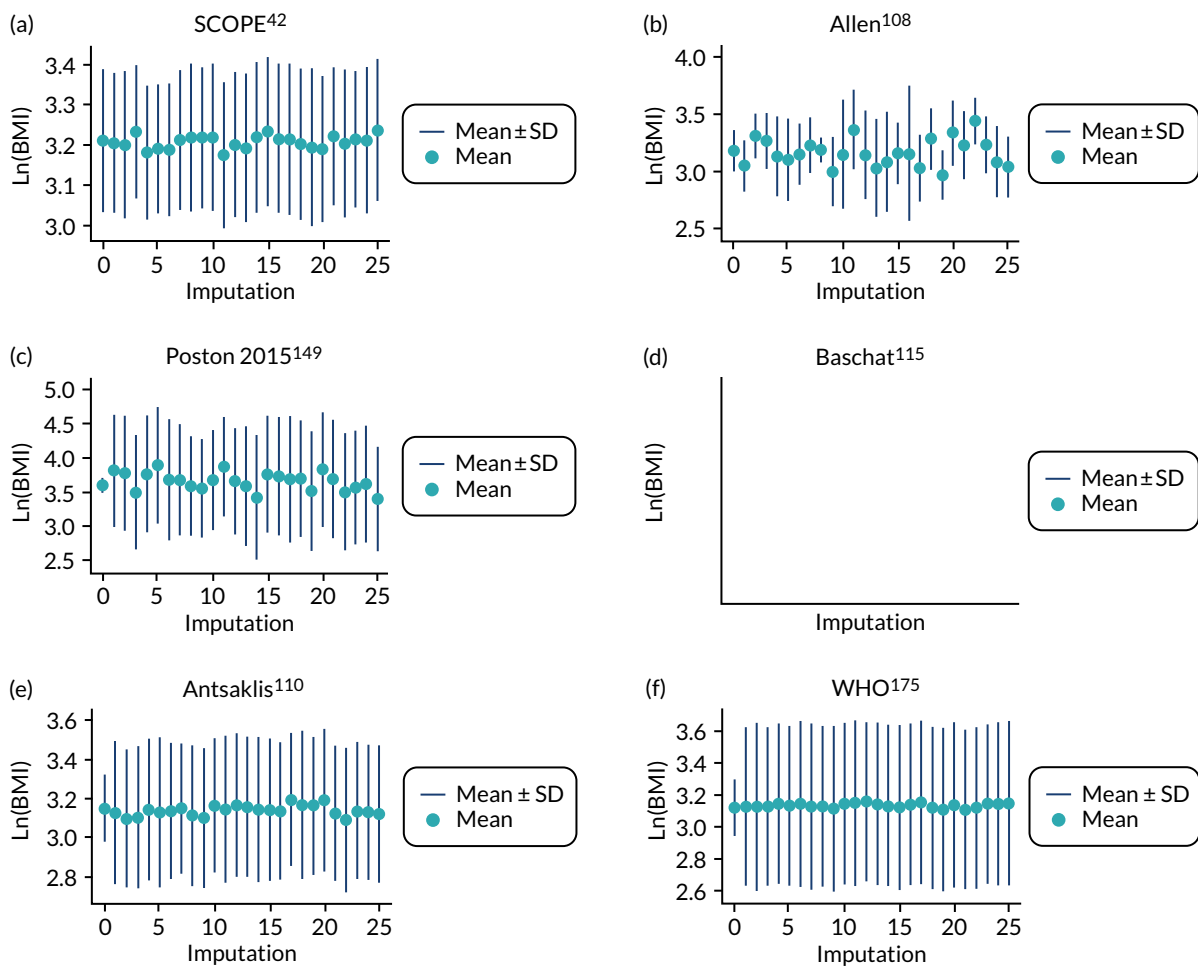


FIGURE 20 Median and range of ln(BMI) values in imputed data set for cohorts included in the development of models with trimester 1 clinical characteristics. (continued)

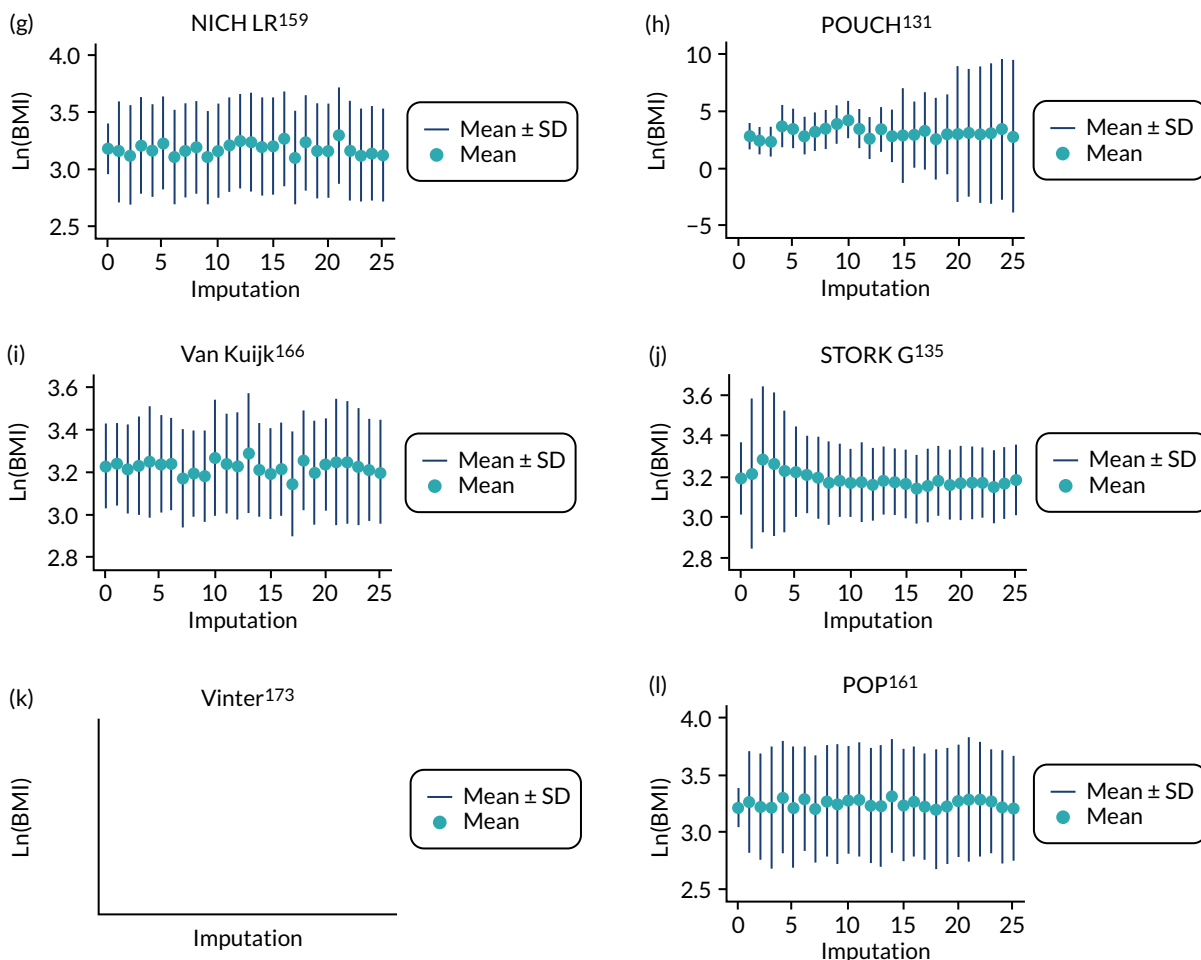


FIGURE 20 Median and range of $\ln(\text{BMI})$ values in imputed data set for cohorts included in the development of models with trimester 1 clinical characteristics.

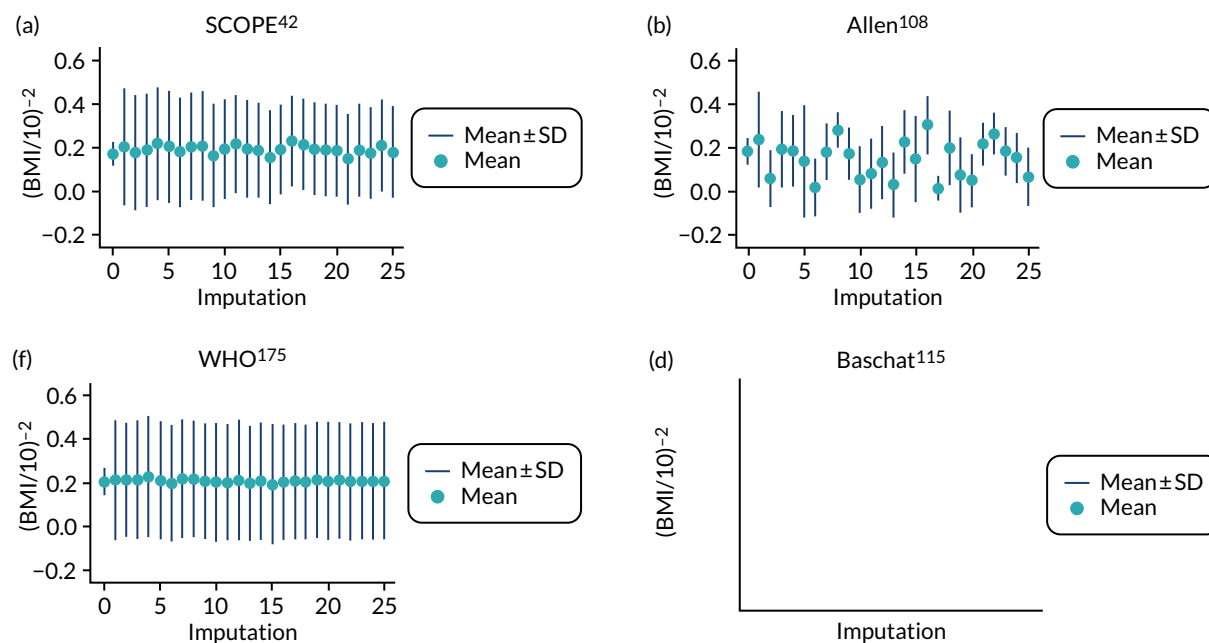


FIGURE 21 Median and range of $(\text{BMI}/10)^{-2}$ values in imputed data set for cohorts included in the development of models with trimester 1 clinical characteristics. (continued)

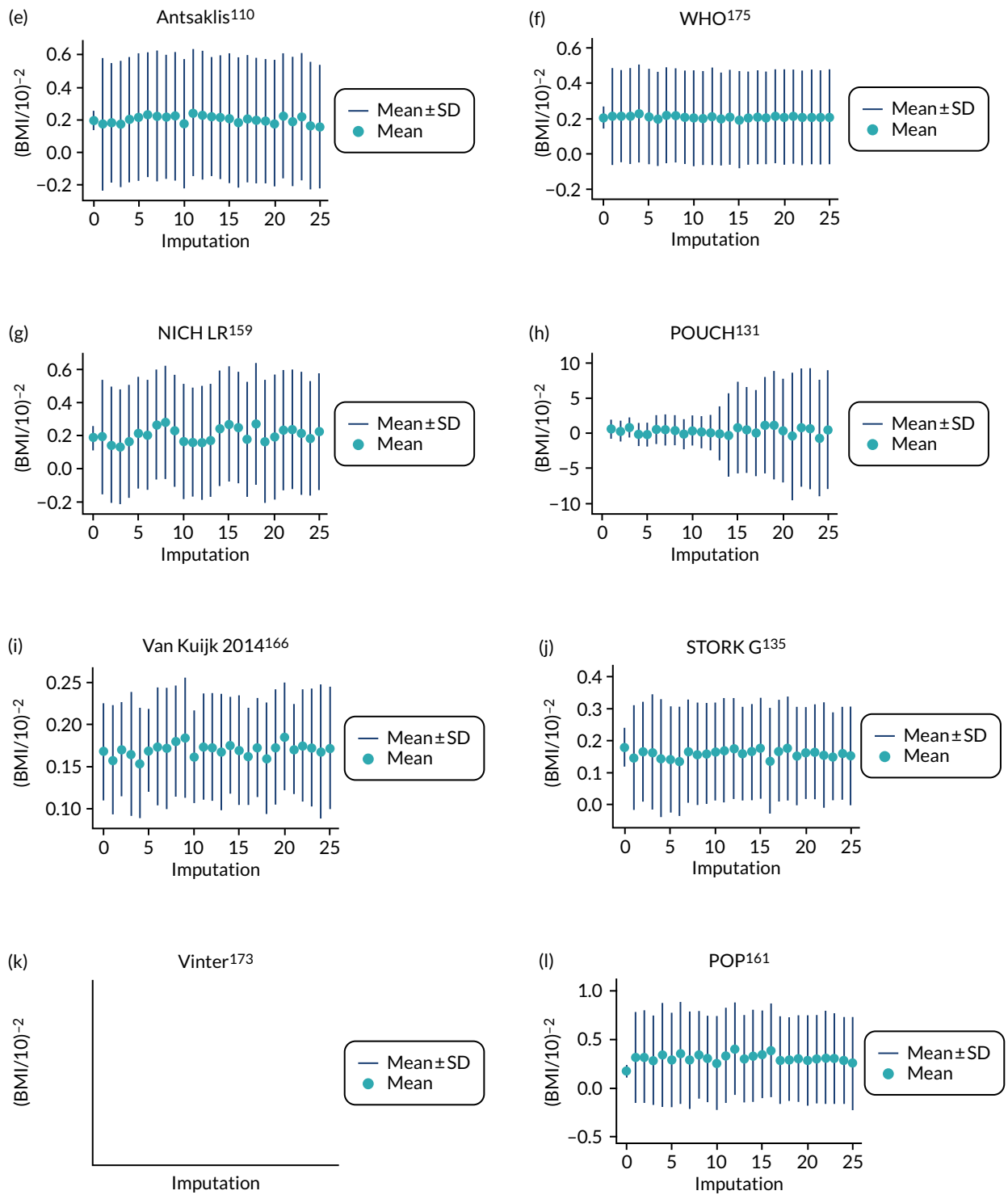


FIGURE 21 Median and range of $(\text{BMI}/10)^{-2}$ values in imputed data set for cohorts included in the development of models with trimester 1 clinical characteristics.

Trimester 2 predictors

SBP, DBP and BMI values were not imputed reliably in Allen, Baschat and Vinter, as illustrated by extreme imputed values for later imputations (particularly for Allen and Vinter).

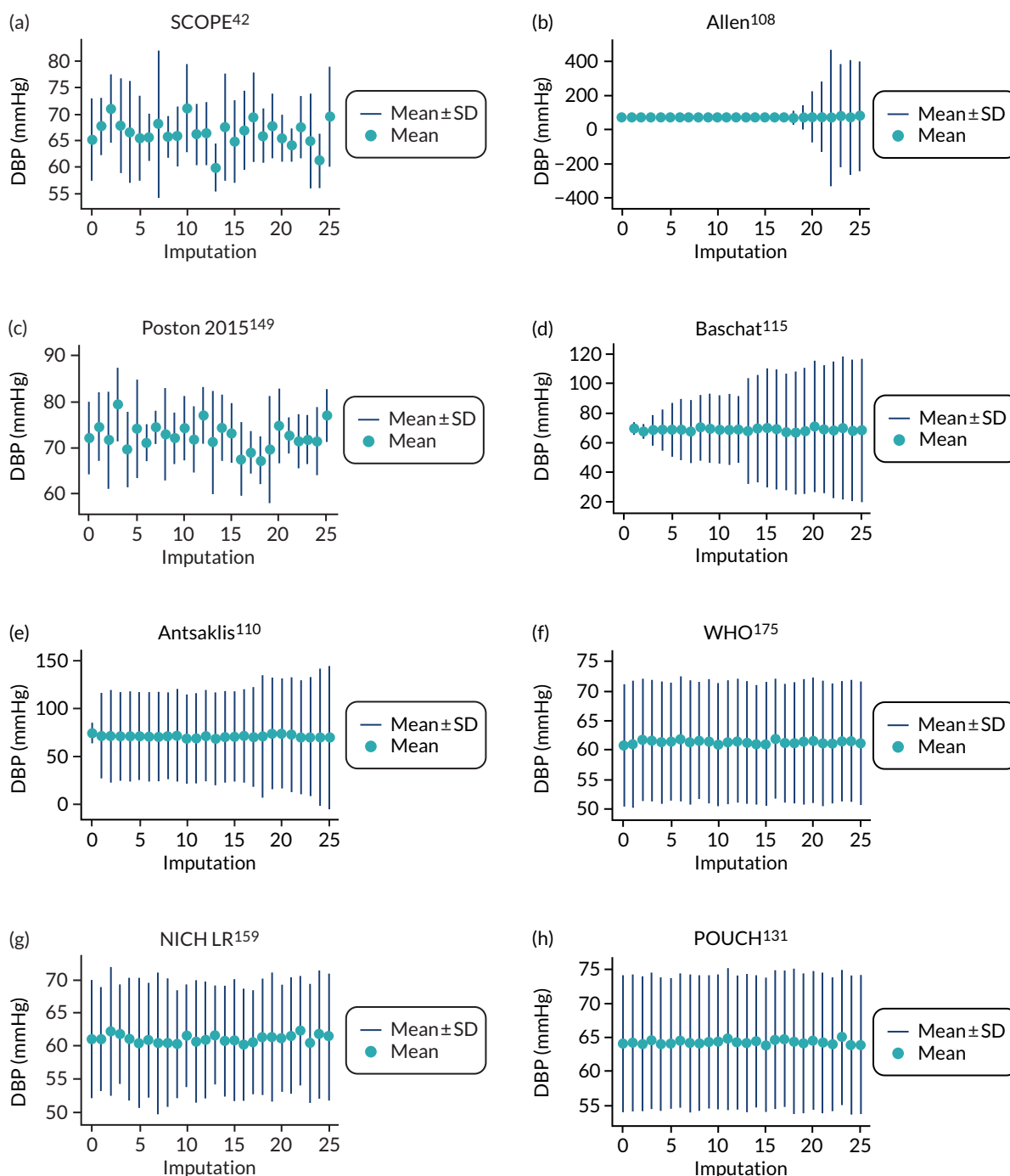


FIGURE 22 Median and range of DBP values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics. (continued)

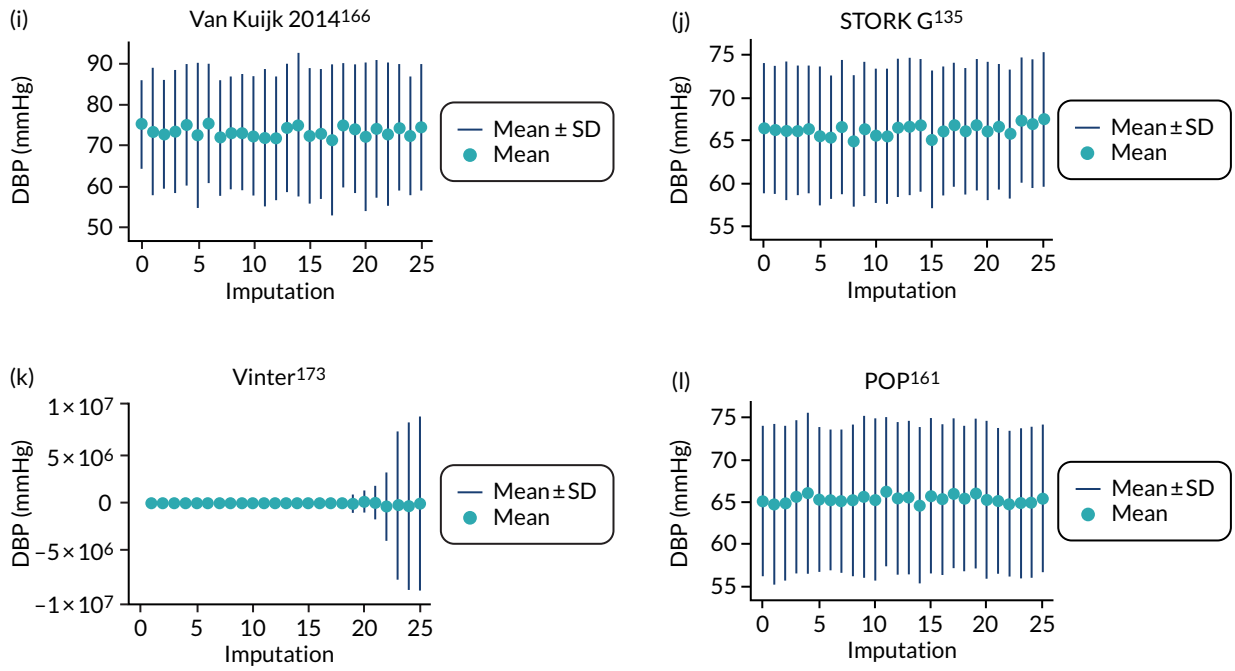


FIGURE 22 Median and range of DBP values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics.

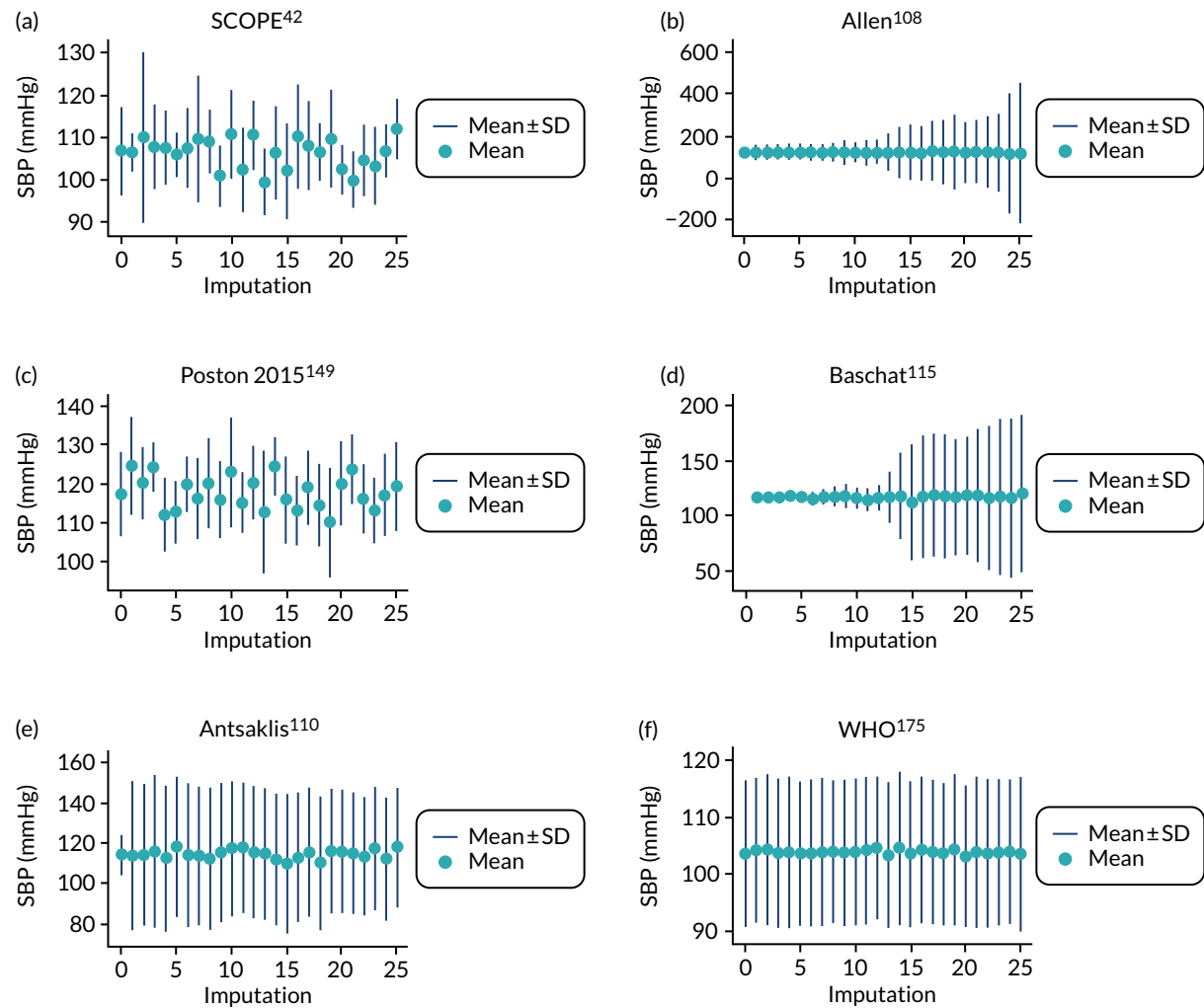


FIGURE 23 Median and range of SBP values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics. (continued)

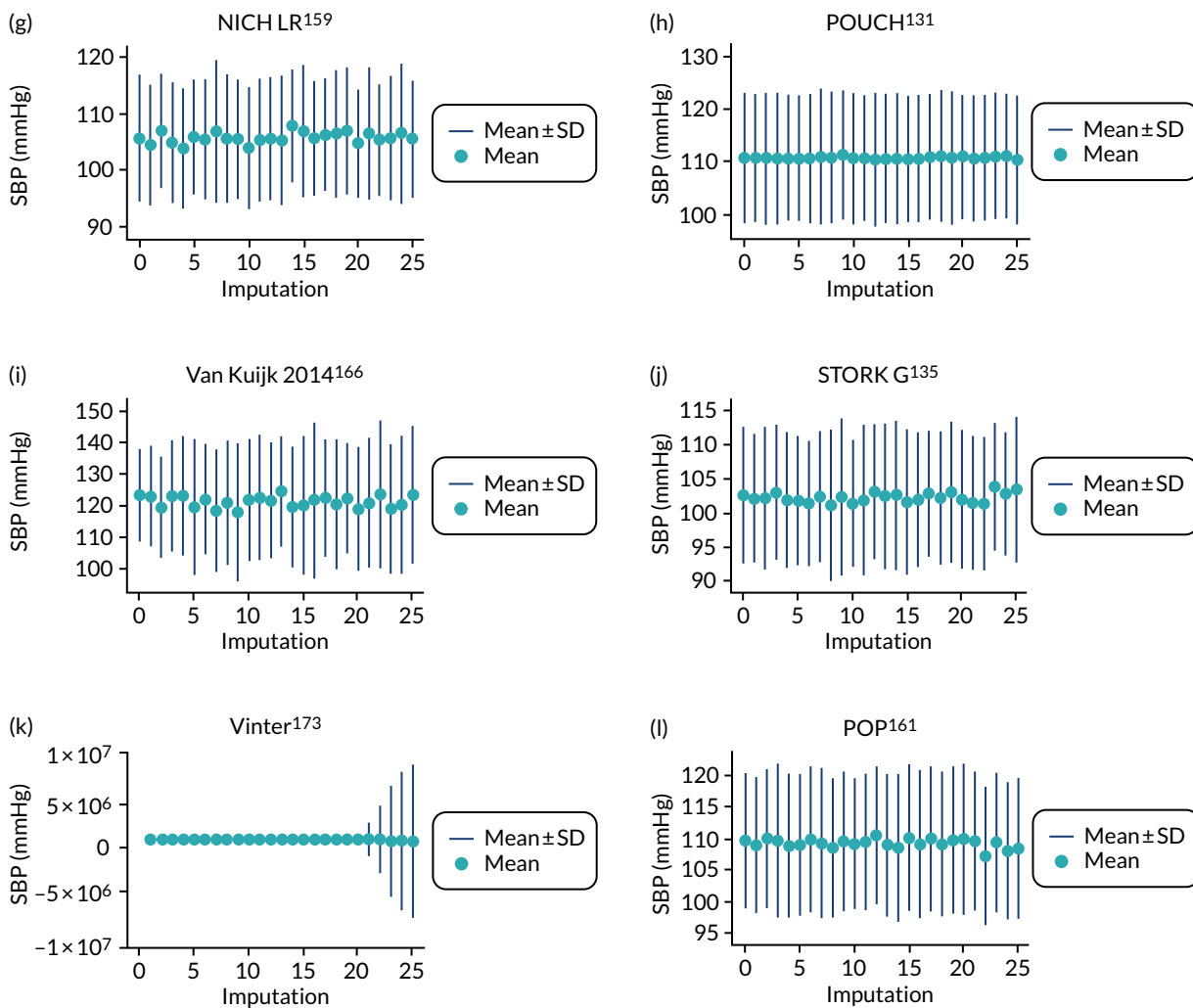


FIGURE 23 Median and range of SBP values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics.

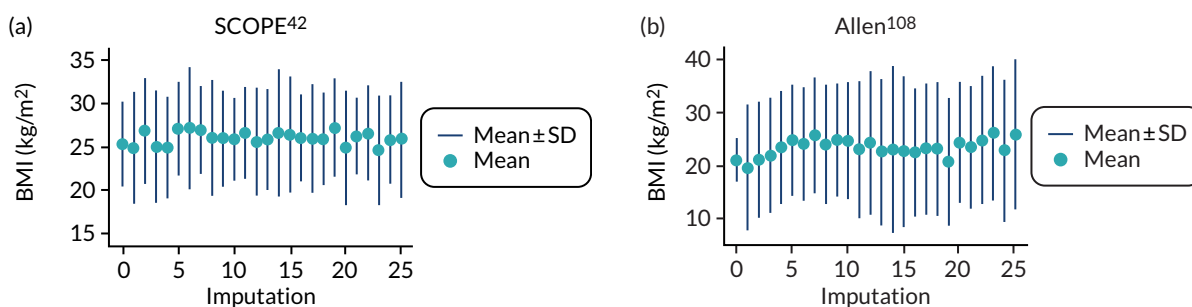


FIGURE 24 Median and range of BMI values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics. (continued)

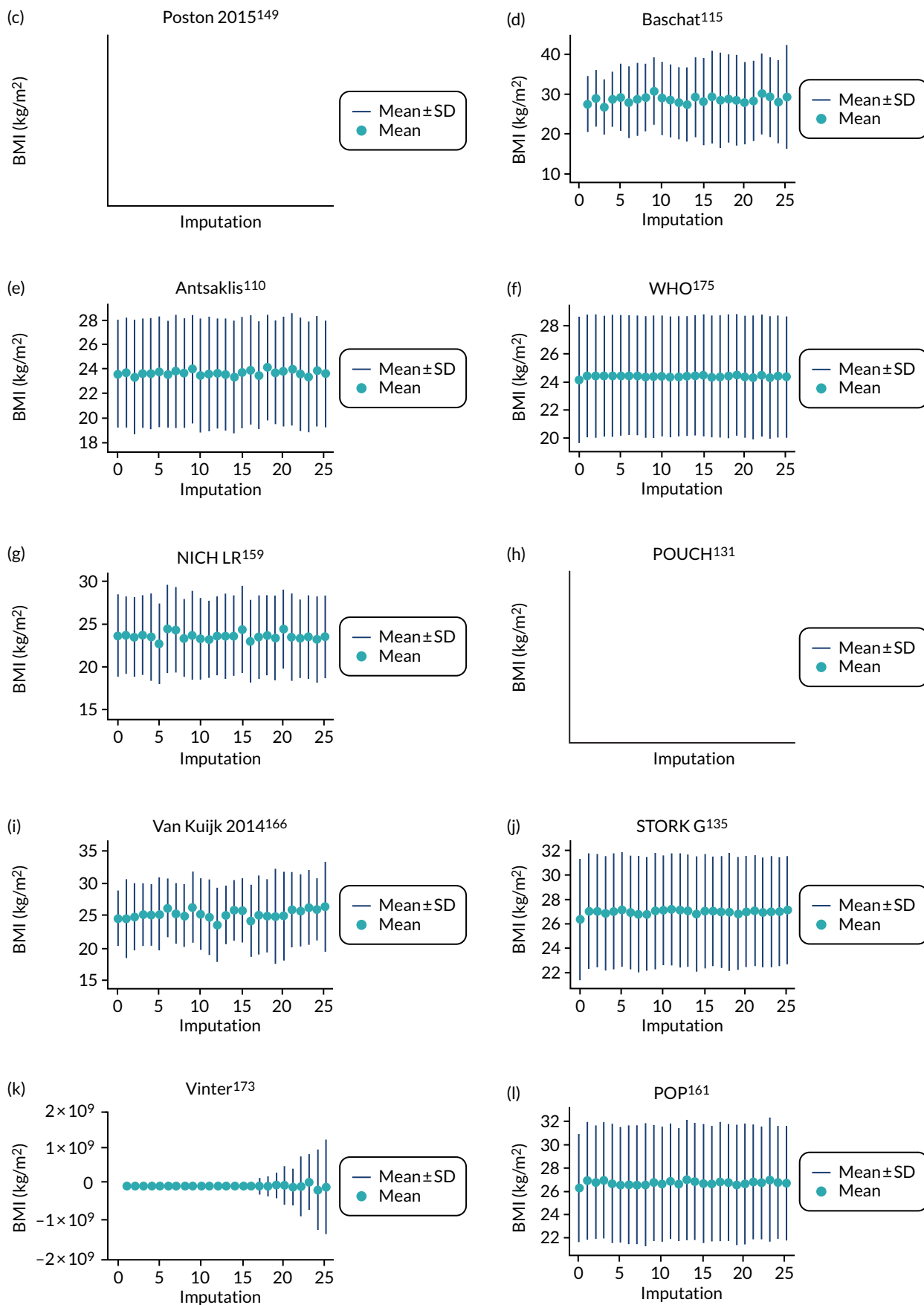


FIGURE 24 Median and range of BMI values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics.

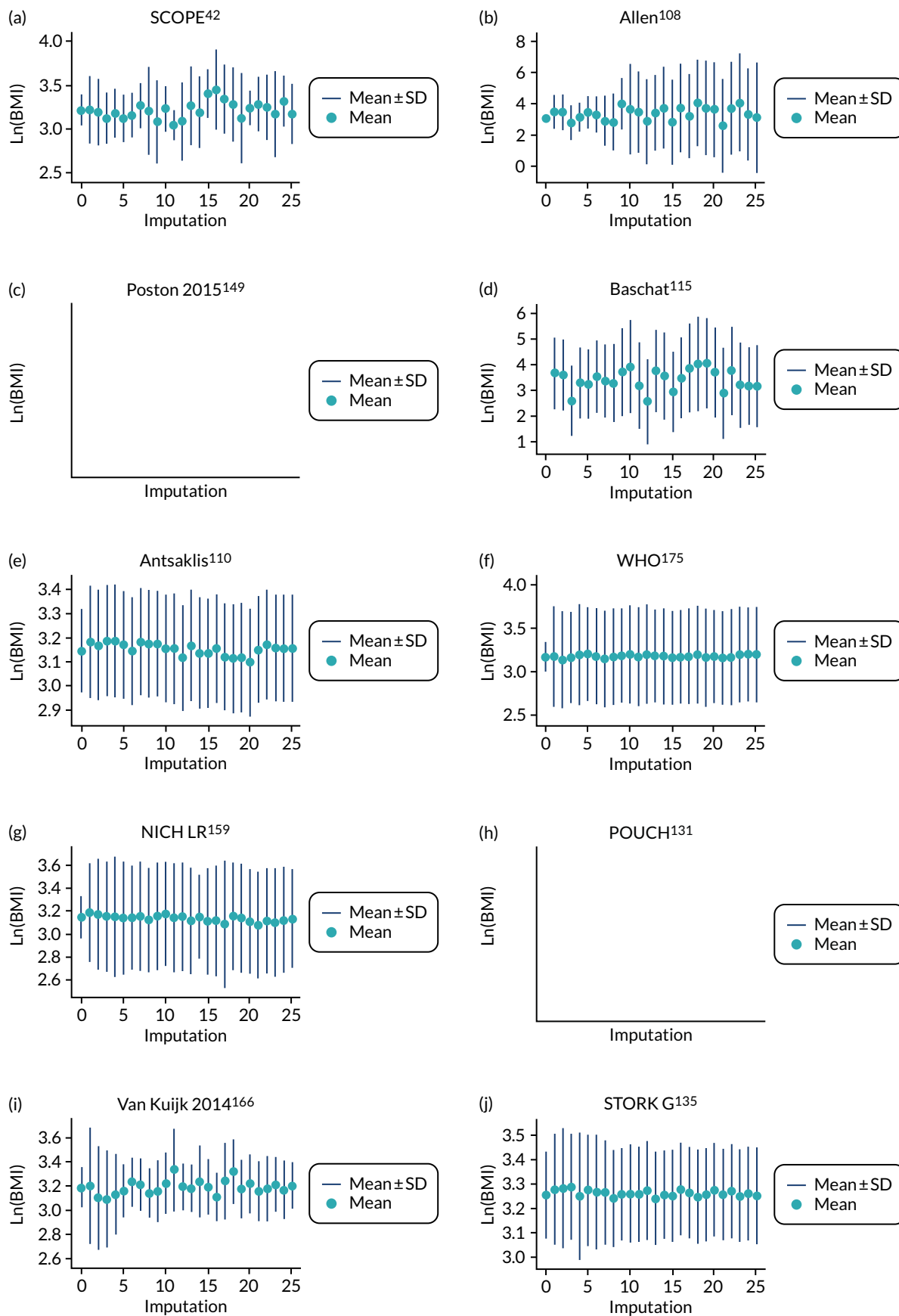


FIGURE 25 Median and range of $\ln(\text{BMI})$ values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics. (continued)

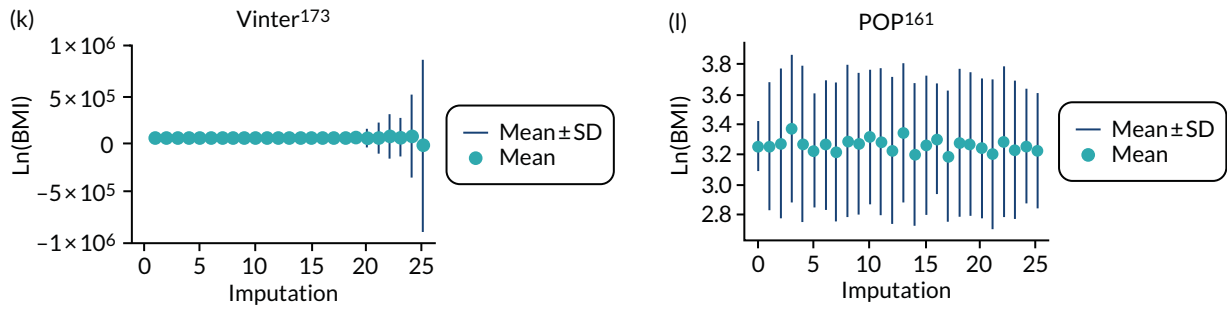


FIGURE 25 Median and range of $\ln(\text{BMI})$ values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics.

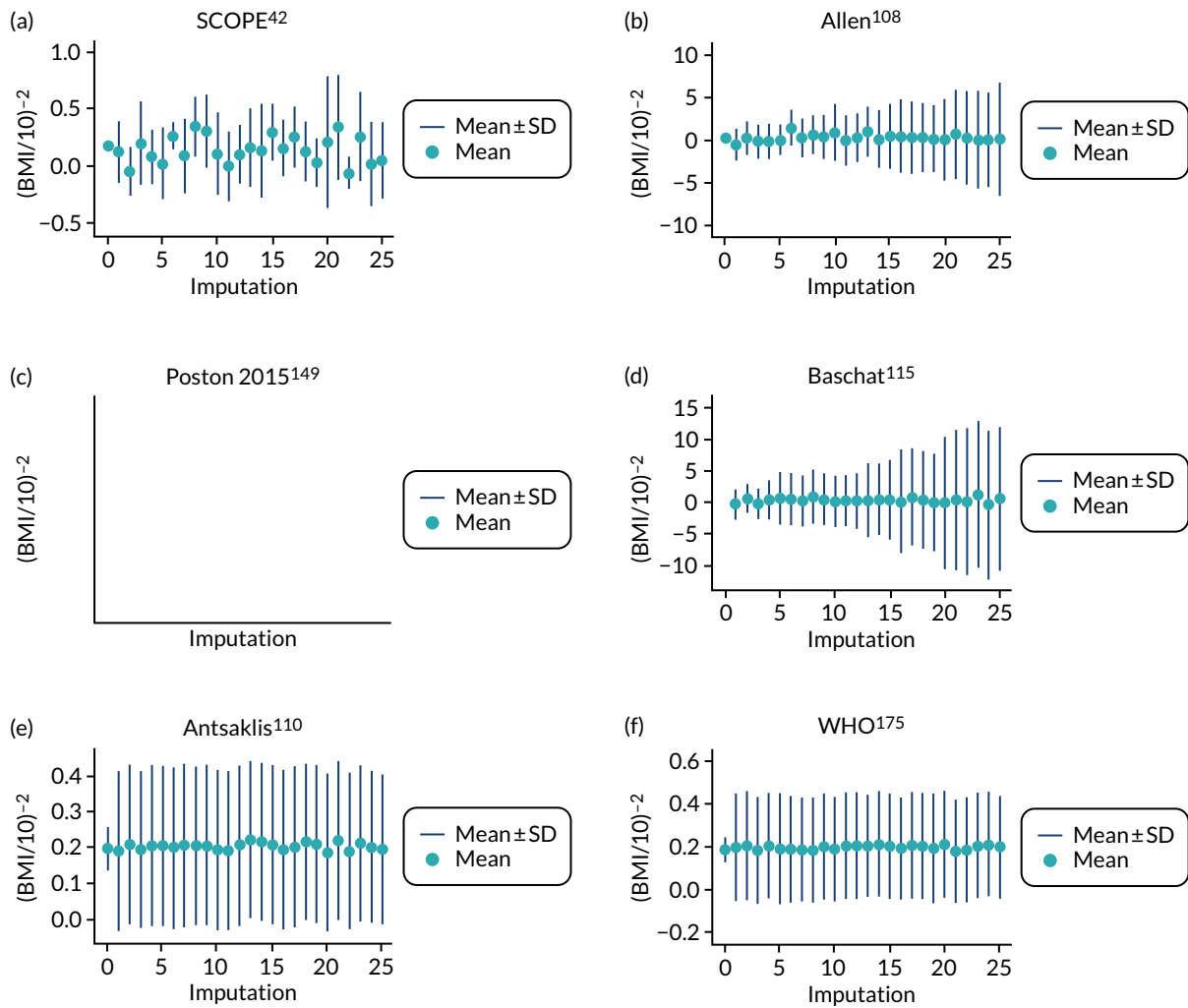


FIGURE 26 Median and range of $(\text{BMI}/10)^{-2}$ values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics. (continued)

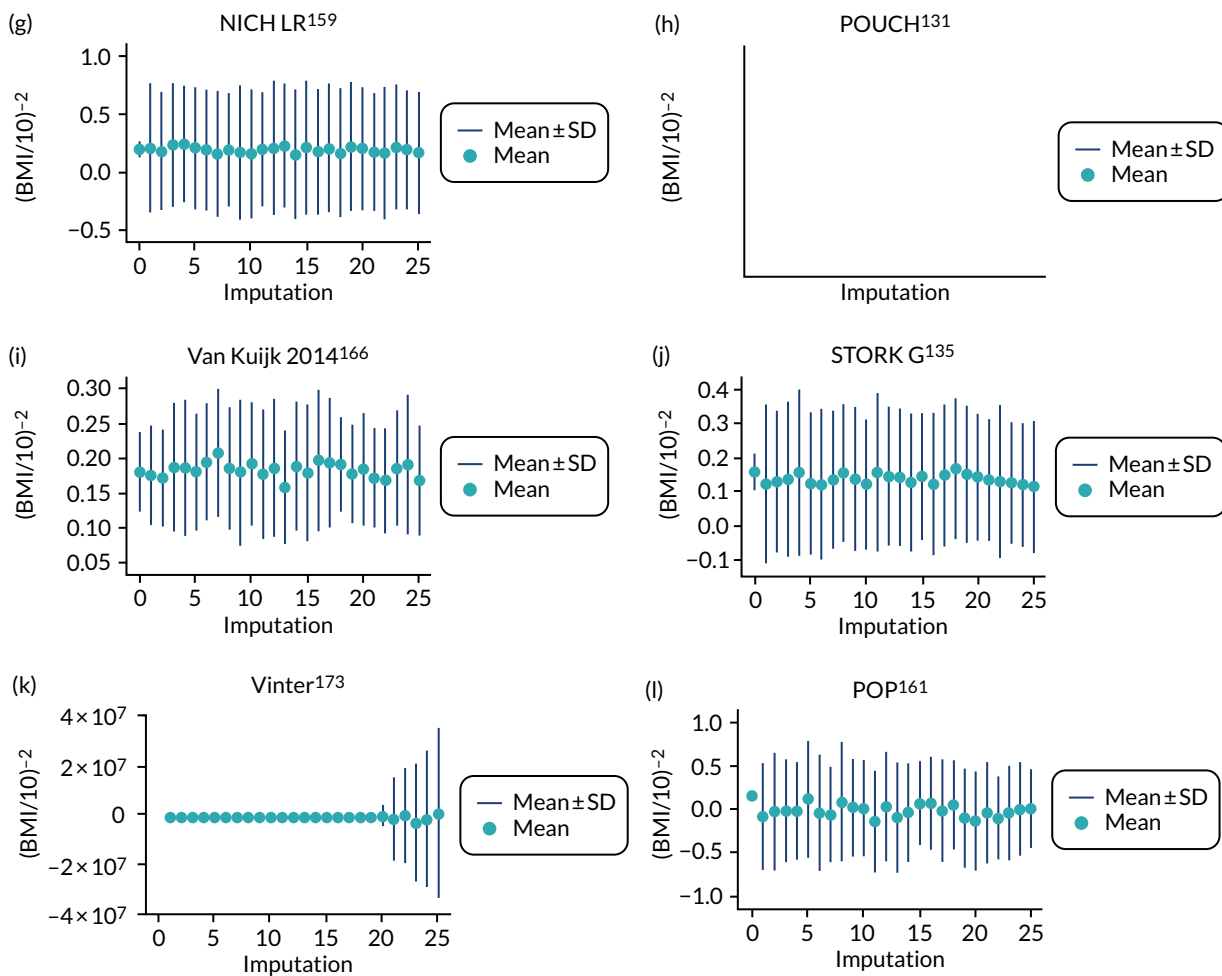


FIGURE 26 Median and range of $(\text{BMI}/10)^{-2}$ values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics.

Imputation checking for clinical characteristics and biochemical markers models

Trimester 2 biomarkers

POUCH was excluded because of the unreliable imputation of PAPP-A, although the range of imputed values in POP was also concerning in later imputations.

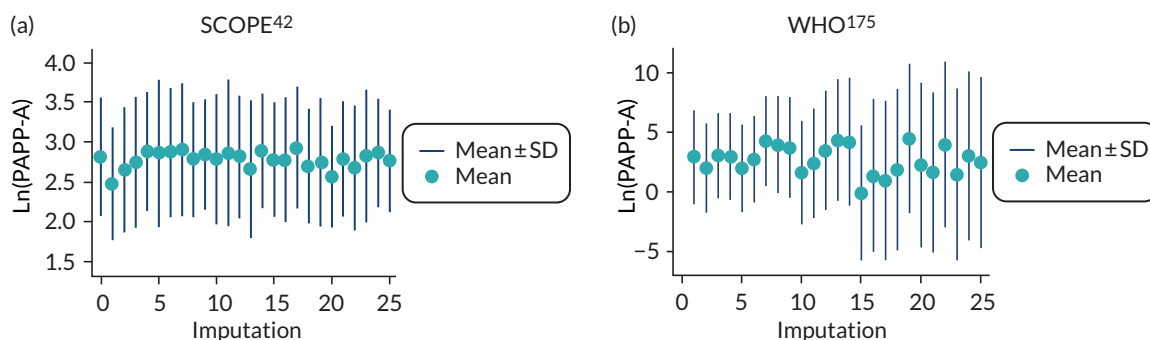


FIGURE 27 Median and range of $\ln(\text{PAPP-A})$ values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics. (continued)

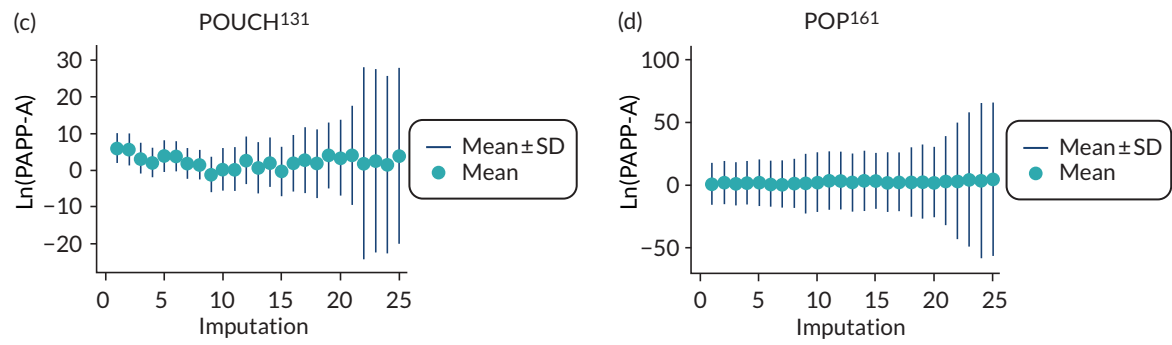


FIGURE 27 Median and range of $\ln(\text{PAPP-A})$ values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics.

Appendix 16 Comparison of clinical characteristics models in data imputed with BMI, $\ln(\text{BMI})$ or BMI^{-2}

TABLE 29 First-trimester models for any-onset pre-eclampsia

Variables	BMI			Ln(BMI)			BMI ⁻²		
	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value
Age (years)	-0.016 (-0.028 to -0.005)	0.984 (0.972 to 0.995)	0.006	-0.020 (-0.032 to -0.008)	0.980 (0.969 to 0.992)	0.001	-0.025 (-0.038 to -0.012)	0.975 (0.963 to 0.988)	< 0.001
SBP	0.017 (0.010 to 0.024)	1.017 (1.010 to 1.025)	< 0.001				-0.012 (-0.027 to 0.002)	0.988 (0.974 to 1.002)	0.100
DBP				0.033 (0.022 to 0.044)	1.034 (1.022 to 1.045)	< 0.001	0.054 (0.033 to 0.075)	1.055 (1.033 to 1.078)	< 0.001
BMI ^a	0.040 (0.027 to 0.054)	1.041 (1.027 to 1.056)	< 0.001	0.510 (0.065 to 0.955)	1.666 (1.068 to 2.599)	0.026	-0.51 (-0.794 to -0.226)	0.601 (0.452 to 0.798)	0.001
Nulliparous	1.015 (0.729 to 1.301)	2.759 (2.073 to 3.673)	< 0.001	0.959 (0.668 to 1.250)	2.609 (1.951 to 3.490)	< 0.001	0.917 (0.632 to 1.202)	2.502 (1.882 to 3.326)	< 0.001
Previous PE	1.374 (0.990 to 1.758)	3.952 (2.692 to 5.802)	< 0.001	1.39 (1.010 to 1.770)	4.015 (2.745 to 5.873)	< 0.001	1.451 (1.067 to 1.835)	4.268 (2.907 to 6.267)	< 0.001
Renal disease	1.641 (0.980 to 2.303)	5.163 (2.665 to 10.002)	< 0.001	1.57 (0.905 to 2.236)	4.809 (2.471 to 9.357)	< 0.001	1.541 (0.866 to 2.216)	4.668 (2.377 to 9.168)	< 0.001
Hypertension	1.715 (1.478 to 1.951)	5.555 (4.384 to 7.039)	< 0.001	1.713 (1.471 to 1.955)	5.545 (4.352 to 7.065)	< 0.001	1.734 (1.485 to 1.983)	5.663 (4.414 to 7.264)	< 0.001
Diabetes	0.391 (-0.125 to 0.907)	1.479 (0.883 to 2.477)	0.137	0.564 (0.058 to 1.069)	1.757 (1.06 to 2.913)	0.029	0.704 (0.196 to 1.213)	2.022 (1.216 to 3.363)	0.007
Intercept	-6.868 (-7.904 to -5.831)			-7.711 (-9.300 to -6.123)			-5.875 (-7.306 to -4.443)		

a BMI modelled on different scales as indicated by column headings.

TABLE 30 Performance statistics for first-trimester models for any-onset pre-eclampsia

Model	C-statistic			Calibration slope			Calibration-in-the-large		
	Estimate (95% CI)	τ^2 (for logit C-statistic)	I^2 (for logit C-statistic)	Estimate (95% CI)	τ^2	I^2	Estimate (95% CI)	τ^2	I^2
Model with BMI	0.677 (0.612 to 0.736)	0.139	83.9	0.915 (0.603 to 1.226)	0.155	86.4	0.012 (-0.630 to 0.654)	0.881	98.7
Model with ln(BMI)	0.670 (0.589 to 0.742)	0.228	88.7	0.874 (0.473 to 1.275)	0.297	92.1	0.015 (-0.627 to 0.656)	0.880	98.6
Model with BMI ⁻²	0.678 (0.597 to 0.750)	0.229	87.3	0.872 (0.436 to 1.308)	0.336	93.1	0.014 (-0.637 to 0.664)	0.910	98.6

TABLE 31 First-trimester models for early-onset pre-eclampsia

Variables	BMI			Ln(BMI)			BMI ⁻²		
	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value
Age (years)				-0.038 (-0.071 to -0.005)	0.963 (0.932 to 0.995)	0.025	-0.036 (-0.068 to -0.004)	0.965 (0.934 to 0.996)	0.029
SBP	0.014 (-0.002 to 0.030)	1.014 (0.998 to 1.031)	0.089				-0.018 (-0.041 to 0.006)	0.983 (0.959 to 1.006)	0.147
DBP				0.059 (0.031 to 0.088)	1.061 (1.031 to 1.092)	< 0.001	0.075 (0.032 to 0.119)	1.078 (1.032 to 1.126)	0.001
BMI ^a	0.033 (-0.004 to 0.070)	1.033 (0.996 to 1.072)	0.080				-0.593 (-1.311 to 0.125)	0.553 (0.27 to 1.133)	0.105
Previous PE	1.593 (0.964 to 2.222)	4.918 (2.623 to 9.222)	< 0.001	1.682 (1.065 to 2.299)	5.377 (2.902 to 9.961)	< 0.001	1.742 (1.127 to 2.358)	5.710 (3.087 to 10.565)	< 0.001
Renal disease	2.538 (1.212 to 3.865)	12.656 (3.360 to 47.681)	< 0.001	2.258 (0.910 to 3.607)	9.567 (2.483 to 36.856)	0.001	2.277 (0.930 to 3.625)	9.749 (2.534 to 37.512)	0.001
Hypertension	0.645 (0.071 to 1.219)	1.906 (1.074 to 3.382)	0.028	0.554 (-0.018 to 1.126)	1.741 (0.982 to 3.085)	0.058	0.548 (0.005 to 1.091)	1.73 (1.005 to 2.976)	0.048
Diabetes	1.298 (0.433 to 2.163)	3.661 (1.541 to 8.695)	0.003	1.603 (0.790 to 2.415)	4.966 (2.204 to 11.190)	< 0.001	1.717 (0.896 to 2.538)	5.567 (2.449 to 12.653)	< 0.001
Intercept	-8.169 (-9.926 to -6.412)			-8.798 (-10.828 to -6.769)			-7.924 (-9.817 to -6.032)		

a BMI modelled on different scales as indicated by column headings.

TABLE 32 Performance statistics for first-trimester models for early-onset pre-eclampsia

Model	C-statistic			Calibration slope			Calibration-in-the-large		
	Estimate (95% CI)	τ^2 (for logit C-statistic)	I^2 (for logit C-statistic)	Estimate (95% CI)	τ^2	I^2	Estimate (95% CI)	τ^2	I^2
Model with BMI	0.663 (0.504 to 0.791)	0.469	71.2	1.032 (0.802 to 1.262)	0.006	4.0	0.085 (-0.407 to 0.576)	0.365	80.6
Model with ln(BMI)	0.711 (0.574 to 0.818)	0.351	62.2	1.054 (0.828 to 1.279)	0.000	0.0	0.089 (-0.374 to 0.552)	0.311	77.7
Model with BMI ⁻²	0.719 (0.590 to 0.820)	0.260	49.1	1.001 (0.795 to 1.206)	0.000	0.0	0.090 (-0.377 to 0.557)	0.318	77.9

TABLE 33 Comparison of first-trimester models for late-onset pre-eclampsia

Variables	BMI			Ln(BMI)			BMI ⁻²		
	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value
Age (years)	-0.015 (-0.028 to -0.003)	0.985 (0.973 to 0.997)	0.018	-0.016 (-0.029 to -0.003)	0.984 (0.972 to 0.997)	0.013	-0.022 (-0.035 to -0.009)	0.978 (0.965 to 0.991)	0.001
SBP	0.016 (0.008 to 0.025)	1.016 (1.008 to 1.025)	< 0.001						
DBP				0.027 (0.016 to 0.038)	0.985 (0.973 to 0.997)	< 0.001	0.039 (0.023 to 0.055)	1.039 (1.023 to 1.056)	< 0.001
BMI ^a	0.039 (0.023 to 0.054)	1.039 (1.024 to 1.055)	< 0.001	0.622 (0.141 to 1.102)	1.863 (1.152 to 3.012)	0.013	-0.471 (-0.784 to -0.157)	0.625 (0.456 to 0.855)	0.004
Nulliparous	1.128 (0.819 to 1.436)	3.089 (2.268 to 4.206)	< 0.001	1.084 (0.771 to 1.397)	2.957 (2.163 to 4.043)	< 0.001	1.030 (0.725 to 1.336)	2.802 (2.065 to 3.803)	< 0.001
Previous PE	1.214 (0.790 to 1.638)	3.368 (2.204 to 5.145)	< 0.001	1.244 (0.824 to 1.663)	3.468 (2.280 to 5.275)	< 0.001	1.278 (0.857 to 1.700)	3.591 (2.356 to 5.474)	< 0.001
Renal disease	1.359 (0.652 to 2.066)	3.891 (1.919 to 7.892)	< 0.001	1.295 (0.585 to 2.006)	3.652 (1.795 to 7.431)	< 0.001	1.267 (0.552 to 1.983)	3.551 (1.736 to 7.263)	0.001
Hypertension	1.835 (1.588 to 2.082)	6.265 (4.895 to 8.018)	< 0.001	1.866 (1.618 to 2.114)	6.460 (5.041 to 8.279)	< 0.001	1.846 (1.595 to 2.097)	6.335 (4.928 to 8.143)	< 0.001
Intercept	-7.052 (-8.173 to -5.931)			-8.042 (-9.834 to -6.250)			-6.552 (-7.824 to -5.280)		

a BMI modelled on different scales as indicated by column headings.

TABLE 34 Performance statistics for first-trimester models for late-onset pre-eclampsia

Model	C-statistic			Calibration slope			Calibration-in-the-large		
	Estimate (95% CI)	τ^2 (for logit C-statistic)	I^2 (for logit C-statistic)	Estimate (95% CI)	τ^2	I^2	Estimate (95% CI)	τ^2	I^2
Model with BMI	0.677 (0.615 to 0.733)	0.116	79.7	0.919 (0.621 to 1.217)	0.131	82.0	0.016 (-0.705 to 0.736)	1.105	98.8
Model with ln(BMI)	0.666 (0.590 to 0.733)	0.181	84.5	0.845 (0.476 to 1.215)	0.237	88.4	0.021 (-0.704 to 0.745)	1.108	98.7
Model with BMI ⁻²	0.677 (0.599 to 0.746)	0.202	85.5	0.856 (0.453 to 1.259)	0.277	90.3	0.016 (-0.732 to 0.765)	1.192	98.9

TABLE 35 Second-trimester models for any-onset pre-eclampsia

Variables	BMI			Ln(BMI)			BMI ⁻²		
	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value
Age (years)	-0.017 (-0.030 to -0.004)	0.983 (0.970 to 0.996)	0.013	-0.011 (-0.025 to 0.002)	0.989 (0.975 to 1.002)	0.102	-0.016 (-0.028 to -0.003)	0.984 (0.972 to 0.997)	0.014
SBP	0.011 (0.003 to 0.020)	1.011 (1.003 to 1.020)	0.010	0.017 (0.005 to 0.030)	1.018 (1.005 to 1.030)	0.008	0.019 (0.012 to 0.025)	1.019 (1.012 to 1.026)	< 0.001
DBP	0.020 (0.007 to 0.033)	1.021 (1.007 to 1.034)	0.003				0.012 (0.004 to 0.021)	1.013 (1.004 to 1.021)	0.004
BMI ^a	0.063 (0.051 to 0.076)	1.065 (1.052 to 1.079)	< 0.001	1.485 (1.119 to 1.851)	4.414 (3.061 to 6.367)	< 0.001	-1.317 (-2.029 to -0.604)	0.268 (0.131 to 0.547)	< 0.001
Nulliparous	0.992 (0.644 to 1.340)	2.697 (1.905 to 3.82)	< 0.001	1.015 (0.664 to 1.365)	2.758 (1.943 to 3.916)	< 0.001	0.970 (0.628 to 1.313)	2.638 (1.873 to 3.716)	< 0.001
Previous PE	1.452 (1.027 to 1.876)	4.271 (2.794 to 6.528)	< 0.001	1.561 (1.112 to 2.010)	4.765 (3.041 to 7.466)	< 0.001	1.575 (1.153 to 1.997)	4.831 (3.167 to 7.368)	< 0.001
Renal disease	1.001 (0.280 to 1.722)	2.721 (1.323 to 5.596)	0.007	0.863 (0.224 to 1.502)	2.371 (1.251 to 4.492)	0.009	0.908 (0.276 to 1.540)	2.480 (1.318 to 4.666)	0.005
Hypertension	1.833 (1.581 to 2.085)	6.253 (4.859 to 8.047)	< 0.001	1.906 (1.659 to 2.152)	6.725 (5.255 to 8.606)	< 0.001	1.868 (1.606 to 2.130)	6.476 (4.984 to 8.415)	< 0.001
Intercept	-8.260 (-9.350 to -7.169)			-10.891 (-12.550 to -9.232)			-6.684 (-7.853 to -5.516)		

a BMI modelled on different scales as indicated by column headings.

TABLE 36 Performance statistics for second-trimester models for any-onset pre-eclampsia

Model	C-statistic			Calibration slope			Calibration-in-the-large		
	Estimate (95% CI)	τ^2 (for logit C-statistic)	I^2 (for logit C-statistic)	Estimate (95% CI)	τ^2	I^2	Estimate (95% CI)	τ^2	I^2
Model with BMI	0.703 (0.648 to 0.753)	0.076	79.3	0.969 (0.664 to 1.273)	0.129	88.3	0.011 (-0.772 to 0.795)	1.003	99.0
Model with ln(BMI)	0.690 (0.636 to 0.739)	0.062	76.2	0.993 (0.625 to 1.361)	0.181	89.9	0.010 (-0.789 to 0.809)	1.044	99.0
Model with BMI ⁻²	0.684 (0.613 to 0.747)	0.131	86.9	0.992 (0.556 to 1.429)	0.291	93.3	0.011 (-0.888 to 0.910)	1.336	99.2

TABLE 37 Second-trimester models for early-onset pre-eclampsia

Variables	BMI			Ln(BMI)			BMI ⁻²		
	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value
Age (years)							-0.025 (-0.060 to 0.009)	0.975 (0.942 to 1.009)	0.151
SBP				0.037 (0.007 to 0.066)	1.037 (1.007 to 1.068)	0.017	0.021 (0.007 to 0.036)	1.022 (1.007 to 1.037)	0.005
DBP	0.059 (0.018 to 0.099)	1.060 (1.018 to 1.104)	0.006				0.018 (0.005 to 0.030)	1.018 (1.005 to 1.031)	0.006
Previous PE	2.140 (1.521 to 2.758)	8.497 (4.579 to 15.767)	< 0.001	2.142 (1.511 to 2.773)	8.516 (4.532 to 16.003)	< 0.001	2.322 (1.718 to 2.926)	10.195 (5.575 to 18.646)	< 0.001
Renal disease	1.351 (0.072 to 2.630)	3.861 (1.074 to 13.878)	0.039	1.444 (0.296 to 2.593)	4.238 (1.344 to 13.363)	0.014	1.422 (0.257 to 2.588)	4.147 (1.293 to 13.300)	0.017
Autoimmune disease	1.036 (-0.266 to 2.338)	2.817 (0.766 to 10.359)	0.118	1.084 (-0.338 to 2.505)	2.955 (0.713 to 12.247)	0.133	1.463 (0.190 to 2.737)	4.321 (1.209 to 15.446)	0.025
Intercept	-9.641 (-12.515 to -6.768)			-9.766 (-13.178 to -6.355)			-8.631 (-10.526 to -6.735)		

TABLE 38 Performance statistics for second-trimester models for early-onset pre-eclampsia

Model	C-statistic			Calibration slope			Calibration-in-the-large		
	Estimate (95% CI)	τ^2 (for logit C-statistic)	I^2 (for logit C-statistic)	Estimate (95% CI)	τ^2	I^2	Estimate (95% CI)	τ^2	I^2
Model with BMI	0.723 (0.601 to 0.819)	0.223	56.4	1.105 (0.868 to 1.341)	0.000	0.0	0.037 (-0.465 to 0.539)	0.287	76.4
Model with ln(BMI)	0.702 (0.631 to 0.764)	0.000	0.0	1.169 (0.835 to 1.503)	0.031	16.9	0.049 (-0.451 to 0.549)	0.285	76.7
Model with BMI ⁻²	0.719 (0.650 to 0.779)	0.006	3.7	1.126 (0.730 to 1.522)	0.093	45.0	0.035 (-0.445 to 0.514)	0.271	77.0

TABLE 39 Second-trimester models for late-onset pre-eclampsia

Variables	BMI			Ln(BMI)			BMI ⁻²		
	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value
Age (years)	-0.015 (-0.028 to -0.001)	0.985 (0.972 to 0.999)	0.034	-0.011 (-0.026 to 0.003)	0.989 (0.975 to 1.003)	0.112	-0.013 (-0.027 to 0.000)	0.987 (0.974 to 1.000)	0.052
SBP	0.011 (0.002 to 0.020)	1.011 (1.002 to 1.020)	0.012	0.009 (-0.003 to 0.021)	1.009 (0.997 to 1.021)	0.130	0.018 (0.010 to 0.026)	1.018 (1.010 to 1.026)	< 0.001
DBP	0.013 (0.001 to 0.026)	1.013 (1.001 to 1.026)	0.035	0.010 (-0.002 to 0.021)	1.010 (0.998 to 1.022)	0.097	0.010 (0.001 to 0.019)	1.010 (1.001 to 1.019)	0.035
BMI ^a	0.070 (0.057 to 0.082)	1.072 (1.059 to 1.086)	< 0.001	1.534 (1.186 to 1.882)	4.636 (3.274 to 6.563)	< 0.001	-1.566 (-2.371 to -0.760)	0.209 (0.093 to 0.468)	< 0.001
Nulliparous	1.279 (0.904 to 1.654)	3.592 (2.469 to 5.225)	< 0.001	1.212 (0.844 to 1.579)	3.359 (2.325 to 4.852)	< 0.001	1.181 (0.798 to 1.563)	3.257 (2.222 to 4.774)	< 0.001
Previous PE	1.253 (0.763 to 1.743)	3.500 (2.144 to 5.713)	< 0.001	1.363 (0.859 to 1.866)	3.906 (2.361 to 6.462)	< 0.001	1.346 (0.864 to 1.829)	3.842 (2.371 to 6.226)	< 0.001
Renal disease	0.814 (0.096 to 1.531)	2.257 (1.101 to 4.625)	0.027	0.548 (-0.110 to 1.206)	1.730 (0.896 to 3.341)	0.102	0.753 (0.104 to 1.401)	2.123 (1.110 to 4.060)	0.023
Hypertension	2.046 (1.795 to 2.298)	7.740 (6.020 to 9.953)	< 0.001	2.066 (1.801 to 2.330)	7.890 (6.056 to 10.279)	< 0.001	2.093 (1.831 to 2.356)	8.112 (6.240 to 10.545)	< 0.001
Intercept	-8.475 (-9.645 to -7.306)			-11.157 (-12.740 to -9.574)			-6.850 (-8.166 to -5.535)		

a BMI modelled on different scales as indicated by column headings.

TABLE 40 Performance statistics for second-trimester models for late-onset pre-eclampsia

Model	C-statistic			Calibration slope			Calibration-in-the-large		
	Estimate (95% CI)	τ^2 (for logit C-statistic)	I^2 (for logit C-statistic)	Estimate (95% CI)	τ^2	I^2	Estimate (95% CI)	τ^2	I^2
Model with BMI	0.705 (0.649 to 0.756)	0.076	78.4	0.930 (0.656 to 1.204)	0.096	84.2	0.014 (-0.897 to 0.925)	1.358	99.1
Model with ln(BMI)	0.683 (0.613 to 0.746)	0.107	83.8	0.888 (0.493 to 1.283)	0.213	90.7	0.015 (-0.899 to 0.929)	1.360	99.2
Model with BMI ⁻²	0.682 (0.613 to 0.743)	0.119	84.7	0.883 (0.507 to 1.259)	0.204	89.9	0.015 (-1.026 to 1.057)	1.784	99.3

Appendix 17 Forest plots of predictive performance estimates in the individual data sets for the second-trimester model for any-onset pre-eclampsia

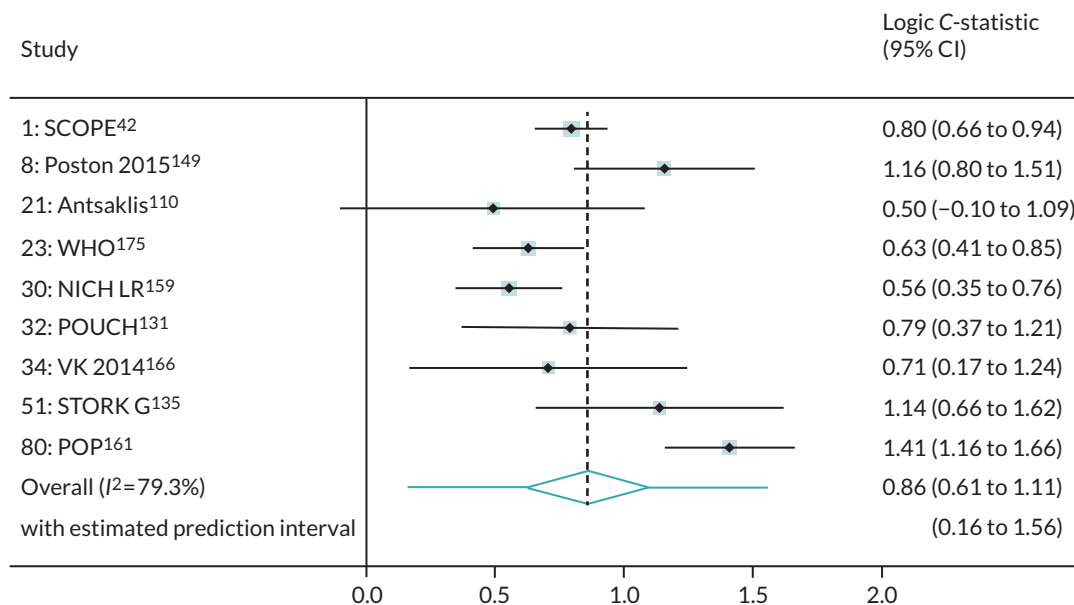


FIGURE 28 Forest plot of logit C-statistics for the second-trimester model predicting any-onset pre-eclampsia in data sets used for model development and internal validation. Note: weights are from random-effects model.

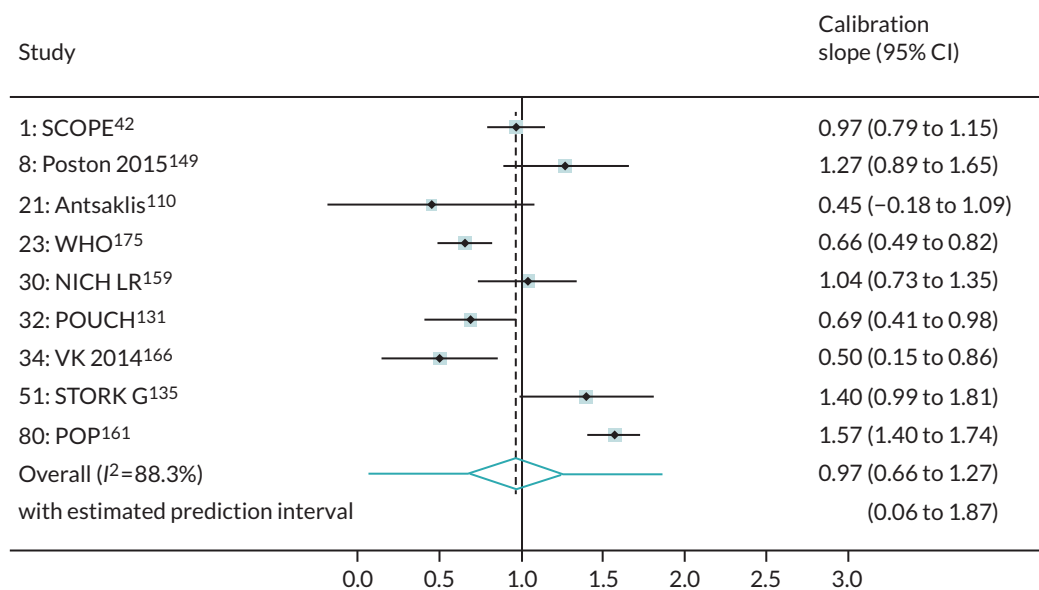


FIGURE 29 Forest plot of calibration slope for the second-trimester model predicting any-onset pre-eclampsia in data sets used for model development and internal validation. Note: weights are from random-effects model.

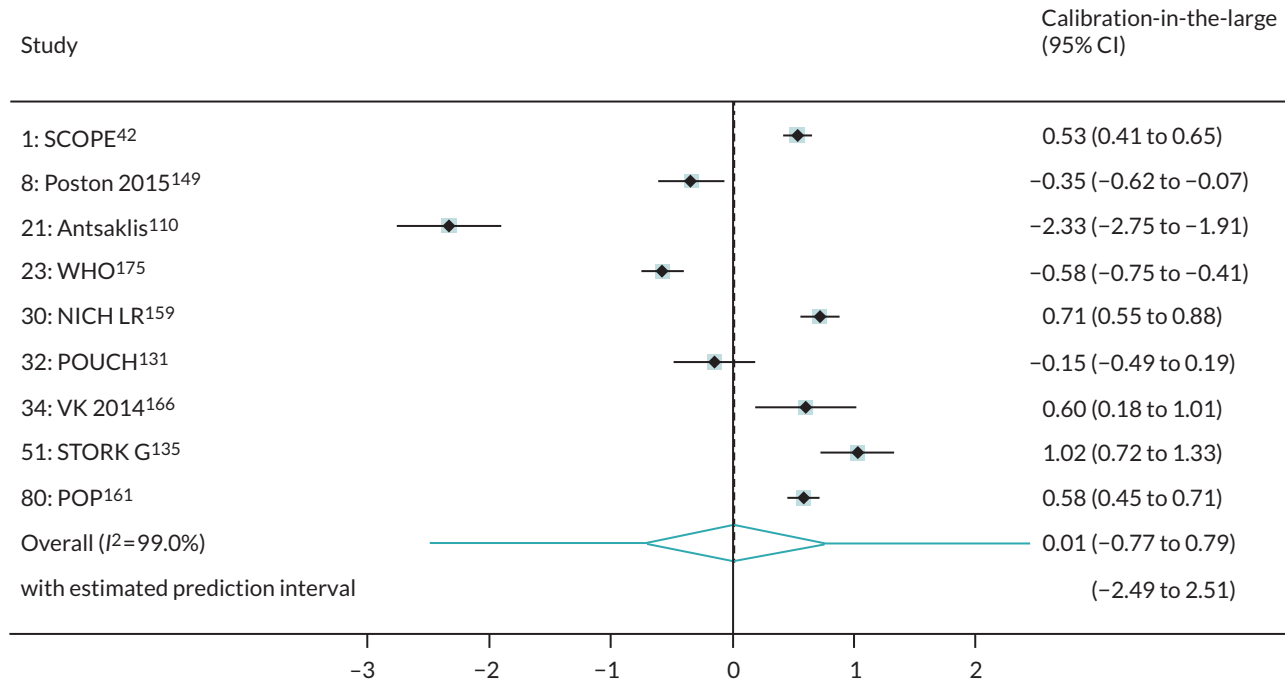


FIGURE 30 Forest plot of calibration-in-the-large for the second-trimester model predicting any-onset pre-eclampsia in data sets used for model development and internal validation. Note: weights are from random-effects model.

Appendix 18 Comparison of clinical characteristic and biochemical marker models in data imputed with original biochemical markers or natural log-transformed biochemical markers

TABLE 41 First-trimester models for any pre-eclampsia

Variable	Original biochemical markers			Ln(biochemical markers)		
	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value
Age (years)	-0.023 (-0.038 to -0.008)	0.977 (0.962 to 0.992)	0.003	-0.023 (-0.039 to -0.007)	0.977 (0.962 to 0.993)	0.006
SBP	0.016 (0.004 to 0.028)	1.016 (1.004 to 1.028)	0.011	0.024 (0.014 to 0.034)	1.024 (1.014 to 1.034)	< 0.001
BMI	0.041 (0.009 to 0.074)	1.042 (1.009 to 1.077)	0.015	0.036 (0.016 to 0.056)	1.037 (1.016 to 1.057)	< 0.001
Nulliparous	1.136 (0.597 to 1.675)	3.113 (1.816 to 5.337)	< 0.001	1.267 (0.703 to 1.831)	3.551 (2.020 to 6.241)	< 0.001
Previous PE	1.350 (0.812 to 1.888)	3.857 (2.252 to 6.607)	< 0.001	1.488 (0.901 to 2.076)	4.430 (2.461 to 7.973)	< 0.001
Renal disease	0.957 (0.319 to 1.594)	2.603 (1.376 to 4.925)	0.004	1.058 (0.449 to 1.667)	2.880 (1.566 to 5.296)	0.001
Hypertension	2.241 (1.962 to 2.520)	9.403 (7.113 to 12.430)	< 0.001	2.215 (1.949 to 2.482)	9.165 (7.024 to 11.960)	< 0.001
Diabetes	0.021 (-0.915 to 0.957)	1.021 (0.401 to 2.605)	0.965	0.178 (-0.737 to 1.094)	1.195 (0.479 to 2.985)	0.702
sFlt-1	-2.42×10^{-4} (-4.3×10^{-4} to -5.5×10^{-5})	0.9998 (0.9996 to 0.9999)	0.012	-0.052 (-0.109 to 0.005)	0.949 (0.897 to 1.005)	0.071
PIGF	-0.005 (-0.008 to -0.002)	0.995 (0.992 to 0.998)	0.001	-0.030 (-0.062 to 0.002)	0.970 (0.940 to 1.002)	0.064
Intercept	-5.893 (-7.478 to -4.309)			-7.022 (-8.515 to -5.530)		

TABLE 42 Performance statistics for first-trimester models for any pre-eclampsia

Model	C-statistic			Calibration slope			Calibration-in-the-large		
	Estimate (95% CI)	τ^2 (for logit C-statistic)	ρ^2 (for logit C-statistic)	Estimate (95% CI)	τ^2	ρ^2	Estimate (95% CI)	τ^2	ρ^2
Original biochemical markers	0.696 (0.516 to 0.832)	0.205	90.7	0.901 (0.355 to 1.447)	0.094	86.7	-0.004 (-0.939 to 0.931)	0.333	97.9
Ln(biochemical markers)	0.693 (0.538 to 0.814)	0.150	88.8	0.896 (0.302 to 1.491)	0.120	90.5	0.008 (-0.874 to 0.889)	0.291	97.1

TABLE 43 First-trimester models for early pre-eclampsia

Variable	Original biochemical markers			Ln(biochemical markers)		
	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value
Age (years)	-0.005 (-0.047 to 0.038)	0.995 (0.954 to 1.039)	0.831	-0.013 (-0.054 to 0.028)	0.987 (0.947 to 1.028)	0.523
SBP	0.053 (0.025 to 0.082)	1.055 (1.026 to 1.085)	< 0.001	0.024 (-0.007 to 0.054)	1.024 (0.993 to 1.055)	0.125
DBP	-0.004 (-0.04 to 0.033)	0.996 (0.960 to 1.033)	0.836	0.042 (0.004 to 0.080)	1.043 (1.004 to 1.083)	0.031
BMI	-0.007 (-0.069 to 0.056)	0.993 (0.933 to 1.057)	0.831	0.006 (-0.049 to 0.061)	1.006 (0.952 to 1.062)	0.837
Previous PE	1.488 (0.694 to 2.281)	4.427 (2.002 to 9.789)	< 0.001	1.689 (0.909 to 2.469)	5.412 (2.481 to 11.805)	< 0.001
Renal disease	1.481 (0.401 to 2.560)	4.397 (1.494 to 12.942)	0.007	1.414 (0.325 to 2.503)	4.112 (1.384 to 12.216)	0.011
Hypertension	0.833 (0.033 to 1.633)	2.300 (1.034 to 5.117)	0.041	0.978 (0.201 to 1.755)	2.659 (1.222 to 5.786)	0.014
sFlt-1	-5.15×10^{-4} (-1.1×10^{-3} to 6.1×10^{-5})	0.9995 (0.9989 to 1.0001)	0.079			
Intercept	-10.206 (-13.561 to -6.851)			-10.929 (-13.875 to -7.983)		

TABLE 44 Performance statistics for first-trimester models for early pre-eclampsia

Model	C-statistic			Calibration slope			Calibration-in-the-large		
	Estimate (95% CI)	τ^2 (for logit C-statistic)	I^2 (for logit C-statistic)	Estimate (95% CI)	τ^2	I^2	Estimate (95% CI)	τ^2	I^2
Original biochemical markers	0.762 (0.576 to 0.883)	0.107	37.0	1.038 (0.666 to 1.410)	0	0	0.036 (-1.269 to 1.342)	0.610	91.7
Ln(biochemical markers)	0.745 (0.591 to 0.855)	0.053	27.2	1.022 (0.695 to 1.350)	0	0	0.014 (-1.240 to 1.268)	0.552	90.2

TABLE 45 First-trimester models for late pre-eclampsia

Variable	Original biochemical markers			Ln(biochemical markers)		
	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value
Age (years)	-0.025 (-0.040 to -0.009)	0.976 (0.961 to 0.991)	0.002	-0.024 (-0.042 to -0.006)	0.976 (0.959 to 0.994)	0.009
SBP	0.009 (-0.002 to 0.020)	1.009 (0.998 to 1.020)	0.113	0.020 (0.010 to 0.030)	1.020 (1.010 to 1.031)	< 0.001
BMI	0.051 (0.024 to 0.077)	1.052 (1.024 to 1.080)	< 0.001	0.040 (0.018 to 0.061)	1.040 (1.019 to 1.063)	< 0.001
Nulliparous	1.409 (0.814 to 2.004)	4.093 (2.258 to 7.418)	< 0.001	1.683 (1.035 to 2.330)	5.379 (2.816 to 10.276)	< 0.001
Previous PE	1.197 (0.557 to 1.838)	3.311 (1.745 to 6.283)	< 0.001	1.456 (0.774 to 2.138)	4.289 (2.168 to 8.486)	< 0.001
Renal disease	0.758 (0.084 to 1.433)	2.135 (1.088 to 4.190)	0.028	0.886 (0.225 to 1.547)	2.426 (1.253 to 4.698)	0.009
Hypertension	2.374 (2.084 to 2.663)	10.739 (8.039 to 14.346)	< 0.001	2.326 (2.049 to 2.604)	10.238 (7.756 to 13.515)	< 0.001
sFlt-1	-2×10^{-4} (-3.8×10^{-4} to -2.4×10^{-5})	0.9998 (0.9996 to 1.0000)	0.026	-0.06 (-0.119 to -0.001)	0.942 (0.888 to 0.999)	0.048
PIGF	-0.006 (-0.009 to -0.003)	0.994 (0.991 to 0.997)	0.001	-0.032 (-0.066 to 0.003)	0.969 (0.936 to 1.003)	0.072
Intercept	-5.787 (-7.28 to -4.293)			-7.168 (-8.776 to -5.559)		

TABLE 46 Performance statistics for first-trimester models for late pre-eclampsia

Model	C-statistic			Calibration slope			Calibration-in-the-large		
	Estimate (95% CI)	τ^2 (for logit C-statistic)	ρ^2 (for logit C-statistic)	Estimate (95% CI)	τ^2	ρ^2	Estimate (95% CI)	τ^2	ρ^2
Original biochemical markers	0.688 (0.505 to 0.827)	0.212	91.9	0.857 (0.338 to 1.376)	0.085	84.4	-0.005 (-0.932 to 0.922)	0.322	97.5
Ln(biochemical markers)	0.685 (0.511 to 0.818)	0.188	90.8	0.849 (0.277 to 1.422)	0.112	88.6	0.010 (-0.856 to 0.876)	0.276	96.5

TABLE 47 Second-trimester models for any pre-eclampsia

Variable	Original biochemical markers			Ln(biochemical markers)		
	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value
Age (years)	-0.019 (-0.034 to -0.004)	0.981 (0.966 to 0.996)	0.012	-0.026 (-0.041 to -0.011)	0.974 (0.960 to 0.989)	0.001
SBP	0.019 (0.009 to 0.029)	1.019 (1.009 to 1.030)	< 0.001	0.005 (-0.005 to 0.015)	1.005 (0.995 to 1.015)	0.357
DBP	-0.009 (-0.021 to 0.004)	0.991 (0.979 to 1.004)	0.167	0.020 (0.006 to 0.033)	1.020 (1.006 to 1.034)	0.004
BMI	0.069 (0.055 to 0.084)	1.072 (1.057 to 1.088)	< 0.001	0.069 (0.055 to 0.084)	1.072 (1.057 to 1.087)	< 0.001
Nulliparous	2.099 (1.263 to 2.935)	8.156 (3.534 to 18.820)	< 0.001	2.144 (1.344 to 2.944)	8.532 (3.833 to 18.993)	< 0.001
Previous PE	1.831 (1.013 to 2.648)	6.237 (2.755 to 14.123)	< 0.001	1.947 (1.172 to 2.722)	7.006 (3.227 to 15.209)	< 0.001
Renal disease	1.423 (0.609 to 2.237)	4.150 (1.838 to 9.368)	0.001	1.467 (0.658 to 2.275)	4.335 (1.931 to 9.732)	< 0.001
Hypertension	2.401 (2.120 to 2.682)	11.034 (8.334 to 14.608)	< 0.001	2.389 (2.112 to 2.666)	10.905 (8.268 to 14.383)	< 0.001
PIGF	-0.003 (-0.004 to -0.002)	0.997 (0.996 to 0.998)	< 0.001	-0.539 (-0.658 to -0.420)	0.583 (0.518 to 0.657)	< 0.001
Intercept	-7.895 (-9.314 to -6.476)			-6.070 (-7.559 to -4.581)		

TABLE 48 Performance statistics for second-trimester models for any pre-eclampsia

Model	C-statistic			Calibration slope			Calibration-in-the-large		
	Estimate (95% CI)	τ^2 (for logit C-statistic)	I^2 (for logit C-statistic)	Estimate (95% CI)	τ^2	I^2	Estimate (95% CI)	τ^2	I^2
Original biochemical markers	0.754 (0.526 to 0.894)	0.151	92.4	0.961 (0.358 to 1.564)	0.052	88.7	0.004 (-1.284 to 1.293)	0.262	98.0
Ln(biochemical markers)	0.746 (0.521 to 0.888)	0.150	93.6	0.945 (0.218 to 1.672)	0.081	94.1	0.001 (-1.859 to 1.862)	0.556	99.0

TABLE 49 Second-trimester models for early pre-eclampsia

Variable	Original biochemical markers			Ln(biochemical markers)		
	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value
DBP	0.071 (0.044 to 0.099)	1.074 (1.045 to 1.104)	< 0.001	0.065 (0.039 to 0.092)	1.068 (1.039 to 1.096)	< 0.001
Previous PE	1.998 (1.046 to 2.949)	7.371 (2.847 to 19.084)	< 0.001	2.360 (1.529 to 3.191)	10.594 (4.615 to 24.318)	< 0.001
Renal disease	2.291 (0.151 to 4.431)	9.883 (1.163 to 83.975)	0.036	3.148 (0.961 to 5.335)	23.285 (2.613 to 207.474)	0.005
Autoimmune disease	1.012 (-1.075 to 3.100)	2.752 (0.341 to 22.193)	0.342	1.154 (-0.924 to 3.231)	3.169 (0.397 to 25.315)	0.277
sFlt-1				0.458 (0.096 to 0.820)	1.581 (1.100 to 2.271)	0.013
PIGF	-0.003 (-0.005 to -0.001)	0.997 (0.995 to 0.999)	0.010	-0.988 (-1.283 to -0.693)	0.372 (0.277 to 0.500)	< 0.001
Intercept	-10.116 (-12.119 to -8.114)			-9.343 (-12.661 to -6.025)		

TABLE 50 Performance statistics for second-trimester models for early pre-eclampsia

Model	C-statistic			Calibration slope			Calibration-in-the-large		
	Estimate (95% CI)	τ^2 (for logit C-statistic)	I^2 (for logit C-statistic)	Estimate (95% CI)	τ^2	I^2	Estimate (95% CI)	τ^2	I^2
Original biochemical markers	0.786 (0.389 to 0.955)	0.304	61.2	1.054 (0.475 to 1.633)	0	0	0.024 (-1.308 to 1.357)	0.229	80.9
Ln(biochemical markers)	0.830 (0.629 to 0.934)	0.041	17.4	1.079 (0.567 to 1.591)	0.011	26.0	0.099 (-0.972 to 1.169)	0.107	66.4

TABLE 51 Second-trimester models for late pre-eclampsia

Variables	Original biochemical markers			Ln(biochemical markers)		
	Beta coefficient (95% CI)	OR (95% CI)	p-value	Beta coefficient (95% CI)	OR (95% CI)	p-value
Age (years)	-0.020 (-0.036 to -0.004)	0.980 (0.965 to 0.996)	0.012	-0.027 (-0.043 to -0.012)	0.973 (0.958 to 0.989)	0.001
SBP	0.018 (0.008 to 0.029)	1.018 (1.008 to 1.029)	0.001	0.002 (-0.009 to 0.014)	1.002 (0.991 to 1.014)	0.697
DBP	-0.014 (-0.028 to -0.001)	0.986 (0.973 to 0.999)	0.031	0.018 (0.002 to 0.033)	1.018 (1.002 to 1.034)	0.026
BMI	0.073 (0.058 to 0.088)	1.076 (1.060 to 1.093)	< 0.001	0.074 (0.059 to 0.089)	1.077 (1.061 to 1.093)	< 0.001
Nulliparous	2.539 (1.564 to 3.515)	12.673 (4.777 to 33.622)	< 0.001	2.567 (1.647 to 3.487)	13.023 (5.190 to 32.681)	< 0.001
Previous PE	1.734 (0.799 to 2.669)	5.664 (2.223 to 14.431)	< 0.001	1.839 (0.962 to 2.716)	6.291 (2.617 to 15.120)	< 0.001
Renal disease	1.303 (0.463 to 2.143)	3.680 (1.588 to 8.524)	0.002	1.318 (0.487 to 2.148)	3.735 (1.628 to 8.572)	0.002
Hypertension	2.432 (2.144 to 2.720)	11.380 (8.531 to 15.180)	< 0.001	2.426 (2.144 to 2.709)	11.317 (8.531 to 15.012)	< 0.001
PIGF	-0.003 (-0.004 to -0.002)	0.997 (0.996 to 0.998)	< 0.001	-0.424 (-0.545 to -0.302)	0.655 (0.580 to 0.739)	< 0.001
Intercept	-8.054 (-9.598 to -6.510)			-6.760 (-8.323 to -5.198)		

TABLE 52 Performance statistics for second-trimester models for late pre-eclampsia

Model	C-statistic			Calibration slope			Calibration-in-the-large		
	Estimate (95% CI)	τ^2 (for logit C-statistic)	I^2 (for logit C-statistic)	Estimate (95% CI)	τ^2	I^2	Estimate (95% CI)	τ^2	I^2
Original biochemical markers	0.746 (0.493 to 0.898)	0.181	93.2	0.936 (0.355 to 1.517)	0.047	86.5	0.004 (-1.295 to 1.303)	0.266	97.8
Ln(biochemical markers)	0.730 (0.477 to 0.889)	0.180	94.4	0.909 (0.186 to 1.632)	0.078	92.8	0.001 (-1.697 to 1.700)	0.461	98.7

Appendix 19 Predictive performance of final shrunken prediction models for any-, early- and late-onset pre-eclampsia in the individual data sets used for model development and validation

Model	Data set	N	Events (n)	Performance statistic (95% CI)		
				C-statistic	Calibration slope	Calibration-in-the-large
Any-onset pre-eclampsia						
First-trimester clinical characteristics	SCOPE ⁴²	5628	278	0.597 (0.547 to 0.645)	1.165 (0.722 to 1.608)	0.458 (0.335 to 0.581)
	Allen <i>et al.</i> ¹⁰⁸	1045	14	0.757 (0.633 to 0.849)	1.253 (0.618 to 1.887)	-0.888 (-1.421 to -0.356)
	Poston <i>et al.</i> 2015 ¹⁴⁹	1554	54	0.694 (0.565 to 0.799)	1.340 (0.491 to 2.189)	-0.175 (-0.458 to 0.107)
	Baschat <i>et al.</i> ¹¹⁵	1704	106	0.738 (0.688 to 0.783)	0.747 (0.585 to 0.909)	0.291 (0.079 to 0.503)
	Antsaklis <i>et al.</i> ¹¹⁰	3328	32	0.585 (0.467 to 0.694)	0.291 (-0.264 to 0.846)	-2.201 (-2.559 to -1.843)
	WHO ¹⁷⁵	7273	141	0.637 (0.577 to 0.693)	0.808 (0.569 to 1.047)	-0.638 (-0.806 to -0.469)
	NICH LR ¹⁵⁹	3097	156	0.506 (0.425 to 0.587)	0.024 (-0.858 to 0.906)	0.411 (0.243 to 0.578)
	van Kuijk <i>et al.</i> 2014 ¹⁶⁶	230	43	0.684 (0.581 to 0.772)	0.705 (0.302 to 1.108)	0.780 (0.413 to 1.147)
	STORK G ¹³⁵	812	46	0.723 (0.624 to 0.805)	1.466 (0.957 to 1.975)	1.064 (0.762 to 1.366)
	Vinter <i>et al.</i> ¹⁷³	304	19	0.679 (0.549 to 0.786)	1.244 (0.260 to 2.227)	0.442 (-0.026 to 0.910)
First-trimester clinical characteristics and biochemical markers	POP ¹⁶¹	4212	273	0.799 (0.765 to 0.829)	1.744 (1.578 to 1.909)	0.515 (0.389 to 0.642)
	SCOPE ⁴²	5628	278	0.583 (0.516 to 0.646)	0.891 (0.423 to 1.359)	0.354 (0.228 to 0.479)
	WHO ¹⁷⁵	7273	141	0.687 (0.624 to 0.744)	0.778 (0.565 to 0.992)	-0.835 (-1.007 to -0.664)
	POUCH ¹³¹	3019	44	0.674 (0.553 to 0.775)	0.737 (0.247 to 1.227)	0.204 (-0.138 to 0.545)
Second-trimester clinical characteristics	POP ¹⁶¹	4212	273	0.807 (0.773 to 0.837)	1.464 (1.328 to 1.600)	0.282 (0.154 to 0.411)
	SCOPE ⁴²	5628	278	0.689 (0.658 to 0.719)	1.004 (0.819 to 1.190)	0.514 (0.391 to 0.636)
	Poston <i>et al.</i> 2015 ¹⁴⁹	1554	54	0.761 (0.691 to 0.819)	1.310 (0.914 to 1.706)	-0.342 (-0.617 to -0.067)
	Antsaklis <i>et al.</i> ¹¹⁰	3328	32	0.621 (0.475 to 0.748)	0.468 (-0.191 to 1.128)	-2.293 (-2.707 to -1.879)
	WHO ¹⁷⁵	7273	141	0.653 (0.602 to 0.700)	0.677 (0.506 to 0.847)	-0.585 (-0.756 to -0.414)
	NICH LR ¹⁵⁹	3097	156	0.635 (0.586 to 0.682)	1.076 (0.755 to 1.396)	0.693 (0.531 to 0.856)
	POUCH ¹³¹	3019	44	0.688 (0.592 to 0.770)	0.714 (0.419 to 1.008)	-0.15 (-0.487 to 0.186)
	van Kuijk <i>et al.</i> 2014 ¹⁶⁶	230	43	0.67 (0.543 to 0.776)	0.519 (0.151 to 0.887)	0.632 (0.222 to 1.041)
STORK G ¹³⁵	812	46	0.757 (0.659 to 0.835)	1.443 (1.019 to 1.867)	0.998 (0.693 to 1.303)	
POP ¹⁶¹	4212	273	0.804 (0.762 to 0.840)	1.621 (1.446 to 1.795)	0.573 (0.444 to 0.703)	

Model	Data set	N	Events (n)	Performance statistic (95% CI)		
				C-statistic	Calibration slope	Calibration-in-the-large
Second-trimester clinical characteristics and biochemical markers	SCOPE ⁴²	5628	278	0.670 (0.637 to 0.701)	0.927 (0.743 to 1.110)	0.063 (-0.060 to 0.185)
	WHO ¹⁷⁵	7273	141	0.768 (0.697 to 0.826)	0.782 (0.580 to 0.984)	-0.549 (-0.726 to -0.371)
	POP ¹⁶¹	4212	273	0.814 (0.781 to 0.844)	1.264 (1.145 to 1.383)	0.482 (0.345 to 0.620)
Early-onset pre-eclampsia						
First-trimester clinical characteristics	SCOPE ⁴²	5628	44	0.783 (0.455 to 0.940)	1.680 (-0.026 to 3.387)	0.986 (0.673 to 1.300)
	Allen <i>et al.</i> ¹⁰⁸	1045	1	NE	0.808 (-0.391 to 2.008)	-1.566 (-3.551 to 0.420)
	Poston <i>et al.</i> 2015 ¹⁴⁹	1554	5	0.736 (0.419 to 0.915)	0.934 (-0.251 to 2.118)	-0.462 (-1.374 to 0.451)
	Baschat <i>et al.</i> ¹¹⁵	1704	21	0.846 (0.716 to 0.923)	1.018 (0.752 to 1.284)	0.681 (0.226 to 1.135)
	Antsaklis <i>et al.</i> ¹¹⁰	3328	13	0.459 (0.272 to 0.659)	-0.233 (-1.342 to 0.876)	-0.019 (-0.539 to 0.500)
	WHO ¹⁷⁵	7273	18	0.811 (0.659 to 0.905)	1.079 (0.728 to 1.430)	-0.646 (-1.112 to -0.181)
	NICH LR ¹⁵⁹	3097	12	0.536 (0.283 to 0.771)	0.189 (-1.446 to 1.824)	0.162 (-0.413 to 0.737)
	van Kuijk <i>et al.</i> 2014 ¹⁶⁶	230	15	0.672 (0.446 to 0.839)	0.620 (-0.301 to 1.541)	0.778 (0.221 to 1.335)
	STORK G ¹³⁵	812	1	NE	-1.513 (-7.175 to 4.150)	-1.125 (-3.088 to 0.837)
	Vinter <i>et al.</i> ¹⁷³	304	2	0.775 (0.261 to 0.971)	2.114 (-0.318 to 4.547)	-0.033 (-1.425 to 1.359)
First-trimester clinical characteristics and biochemical markers	POP ¹⁶¹	4212	10	0.779 (0.568 to 0.904)	1.168 (0.676 to 1.660)	-0.235 (-0.858 to 0.388)
	SCOPE ⁴²	5628	44	0.664 (0.509 to 0.790)	0.934 (0.165 to 1.703)	0.899 (0.591 to 1.207)
	WHO ¹⁷⁵	7273	18	0.879 (0.727 to 0.952)	1.010 (0.687 to 1.333)	-0.714 (-1.188 to -0.241)
	POUCH ¹³¹	3019	12	0.773 (0.620 to 0.877)	0.889 (0.475 to 1.302)	0.479 (-0.049 to 1.008)
Second-trimester clinical characteristics	POP ¹⁶¹	4212	10	0.743 (0.496 to 0.895)	1.195 (0.654 to 1.737)	-0.703 (-1.326 to -0.081)
	SCOPE ⁴²	5628	44	0.674 (0.583 to 0.754)	1.268 (0.748 to 1.789)	0.978 (0.681 to 1.275)
	Poston 2015 ¹⁴⁹	1554	5	0.882 (0.703 to 0.959)	1.155 (0.497 to 1.814)	-0.701 (-1.587 to 0.185)
	Antsaklis ¹¹⁰	3328	13	0.701 (0.331 to 0.917)	0.863 (-0.93 to 2.655)	-0.258 (-1.581 to 1.064)
	WHO ¹⁷⁵	7273	18	0.838 (0.671 to 0.930)	1.036 (0.744 to 1.327)	-0.634 (-1.101 to -0.167)
	NICH LR ¹⁵⁹	3097	12	0.556 (0.379 to 0.720)	0.422 (-0.594 to 1.437)	0.557 (-0.017 to 1.132)
	POUCH ¹³¹	3019	12	0.832 (0.691 to 0.917)	0.965 (0.637 to 1.294)	0.377 (-0.211 to 0.965)

Model	Data set	N	Events (n)	Performance statistic (95% CI)		
				C-statistic	Calibration slope	Calibration-in-the-large
Second-trimester clinical characteristics and biochemical markers	van Kuijk <i>et al.</i> 2014 ¹⁶⁶	230	15	0.672 (0.428 to 0.848)	0.659 (-0.270 to 1.588)	0.293 (-0.308 to 0.894)
	STORK G ¹³⁵	812	1	NE	0.311 (-3.395 to 4.018)	-0.970 (-2.932 to 0.991)
	POP ¹⁶¹	4212	10	0.558 (0.311 to 0.779)	0.404 (-0.806 to 1.613)	-0.286 (-0.911 to 0.339)
	SCOPE ⁴²	5628	44	0.805 (0.728 to 0.865)	1.175 (0.891 to 1.458)	-0.159 (-0.458 to 0.141)
	WHO ¹⁷⁵	7273	18	0.912 (0.778 to 0.968)	0.876 (0.598 to 1.153)	-0.128 (-0.61 to 0.354)
	POP ¹⁶¹	4212	10	0.810 (0.575 to 0.931)	0.905 (0.453 to 1.356)	0.805 (0.156 to 1.455)
Late-onset pre-eclampsia						
First-trimester clinical characteristics	SCOPE ⁴²	5628	234	0.630 (0.578 to 0.679)	1.266 (0.844 to 1.688)	0.432 (0.298 to 0.565)
	Allen <i>et al.</i> ¹⁰⁸	1045	13	0.738 (0.599 to 0.842)	1.258 (0.596 to 1.921)	-0.757 (-1.308 to -0.205)
	Poston <i>et al.</i> 2015 ¹⁴⁹	1554	49	0.682 (0.548 to 0.791)	1.208 (0.388 to 2.027)	-0.048 (-0.342 to 0.246)
	Baschat <i>et al.</i> ¹¹⁵	1704	85	0.701 (0.646 to 0.751)	0.601 (0.417 to 0.785)	0.281 (0.050 to 0.513)
	Antsaklis <i>et al.</i> ¹¹⁰	3328	19	0.676 (0.527 to 0.796)	0.781 (-0.075 to 1.637)	-2.669 (-3.128 to -2.211)
	WHO ¹⁷⁵	7273	123	0.606 (0.541 to 0.668)	0.672 (0.374 to 0.970)	-0.588 (-0.768 to -0.409)
	NICH LR ¹⁵⁹	3097	144	0.506 (0.42 to 0.591)	0.025 (-0.948 to 0.998)	0.495 (0.323 to 0.668)
	van Kuijk <i>et al.</i> 2014 ¹⁶⁶	230	28	0.686 (0.574 to 0.780)	0.674 (0.242 to 1.106)	0.536 (0.110 to 0.961)
	STORK G ¹³⁵	812	45	0.733 (0.634 to 0.813)	1.442 (0.947 to 1.937)	1.226 (0.921 to 1.532)
	Vinter <i>et al.</i> ¹⁷³	304	17	0.659 (0.521 to 0.774)	0.954 (0.026 to 1.883)	0.532 (0.039 to 1.026)
	POP ¹⁶¹	4212	263	0.798 (0.763 to 0.828)	1.667 (1.508 to 1.827)	0.621 (0.493 to 0.750)
First-trimester clinical characteristics and biochemical markers	SCOPE ⁴²	5628	234	0.576 (0.521 to 0.630)	0.854 (0.435 to 1.274)	0.304 (0.169 to 0.438)
	WHO ¹⁷⁵	7273	123	0.679 (0.612 to 0.739)	0.810 (0.540 to 1.08)	-0.804 (-0.985 to -0.622)
	POUCH ¹³¹	3019	32	0.662 (0.555 to 0.755)	0.717 (0.224 to 1.211)	0.109 (-0.314 to 0.531)
	POP ¹⁶¹	4212	263	0.805 (0.771 to 0.835)	1.468 (1.331 to 1.606)	0.396 (0.265 to 0.526)

Model	Data set	N	Events (n)	Performance statistic (95% CI)		
				C-statistic	Calibration slope	Calibration-in-the-large
Second-trimester clinical characteristics	SCOPE ⁴²	5628	234	0.678 (0.644 to 0.711)	0.961 (0.760 to 1.161)	0.473 (0.340 to 0.606)
	Poston <i>et al.</i> 2015 ¹⁴⁹	1554	49	0.737 (0.667 to 0.797)	1.153 (0.746 to 1.560)	-0.182 (-0.468 to 0.105)
	Antsaklis <i>et al.</i> ¹¹⁰	3328	19	0.721 (0.555 to 0.843)	1.023 (0.041 to 2.005)	-2.720 (-3.195 to -2.245)
	WHO ¹⁷⁵	7273	123	0.638 (0.586 to 0.688)	0.624 (0.408 to 0.839)	-0.513 (-0.694 to -0.332)
	NICH LR ¹⁵⁹	3097	144	0.636 (0.584 to 0.685)	1.107 (0.764 to 1.451)	0.752 (0.583 to 0.921)
	POUCH ¹³¹	3019	32	0.701 (0.604 to 0.784)	0.741 (0.422 to 1.060)	-0.235 (-0.624 to 0.155)
	van Kuijk <i>et al.</i> 2014 ¹⁶⁶	230	28	0.655 (0.505 to 0.779)	0.457 (0.050 to 0.865)	0.611 (0.154 to 1.067)
	STORK G ¹³⁵	812	45	0.761 (0.662 to 0.838)	1.346 (0.938 to 1.754)	1.195 (0.886 to 1.503)
	POP ¹⁶¹	4212	263	0.805 (0.765 to 0.840)	1.554 (1.397 to 1.710)	0.648 (0.517 to 0.780)
Second-trimester clinical characteristics and biochemical markers	SCOPE ⁴²	5628	234	0.654 (0.617 to 0.688)	0.887 (0.686 to 1.087)	0.003 (-0.129 to 0.136)
	WHO ¹⁷⁵	7273	123	0.754 (0.681 to 0.815)	0.812 (0.585 to 1.040)	-0.531 (-0.717 to -0.345)
	POP ¹⁶¹	4212	263	0.815 (0.782 to 0.845)	1.262 (1.141 to 1.383)	0.524 (0.384 to 0.663)
NE, not estimable.						

Appendix 20 Calibration plots for final shrunken prediction models for any- and late-onset pre-eclampsia

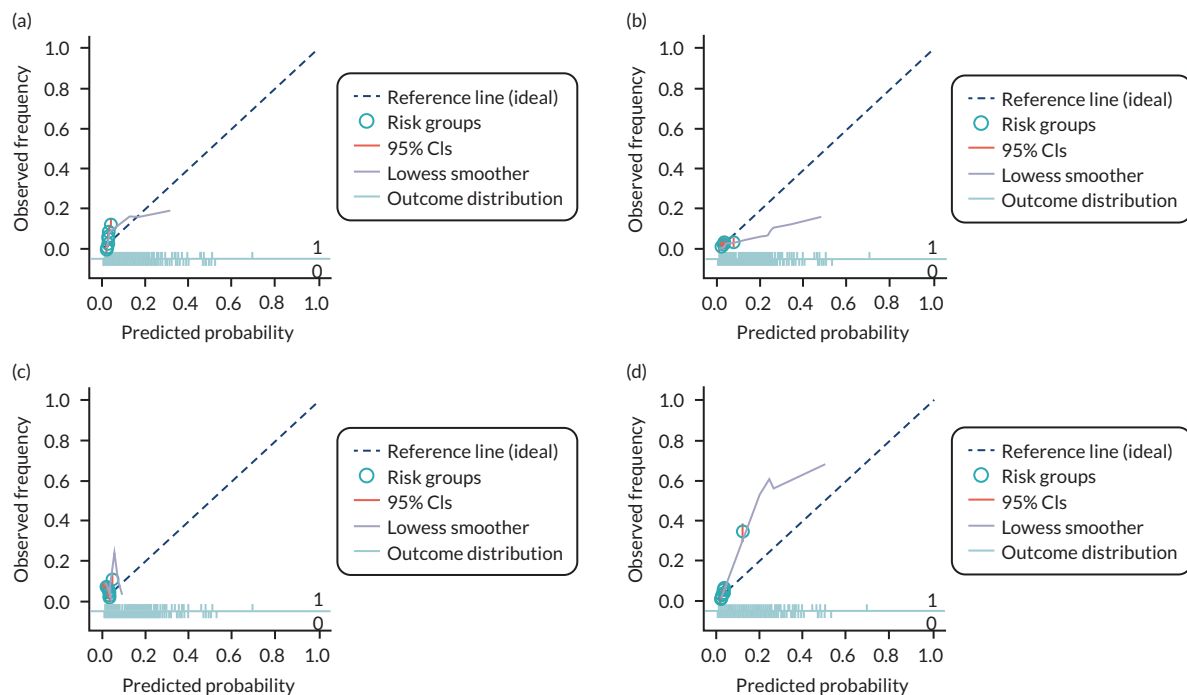


FIGURE 31 Calibration plots for model 3, which includes first-trimester clinical characteristics for predicting late-onset pre-eclampsia. (a) SCOPE;⁴² (b) WHO;¹⁷⁵ (c) NICH LR;¹⁵⁹ and (d) POP.¹⁶¹

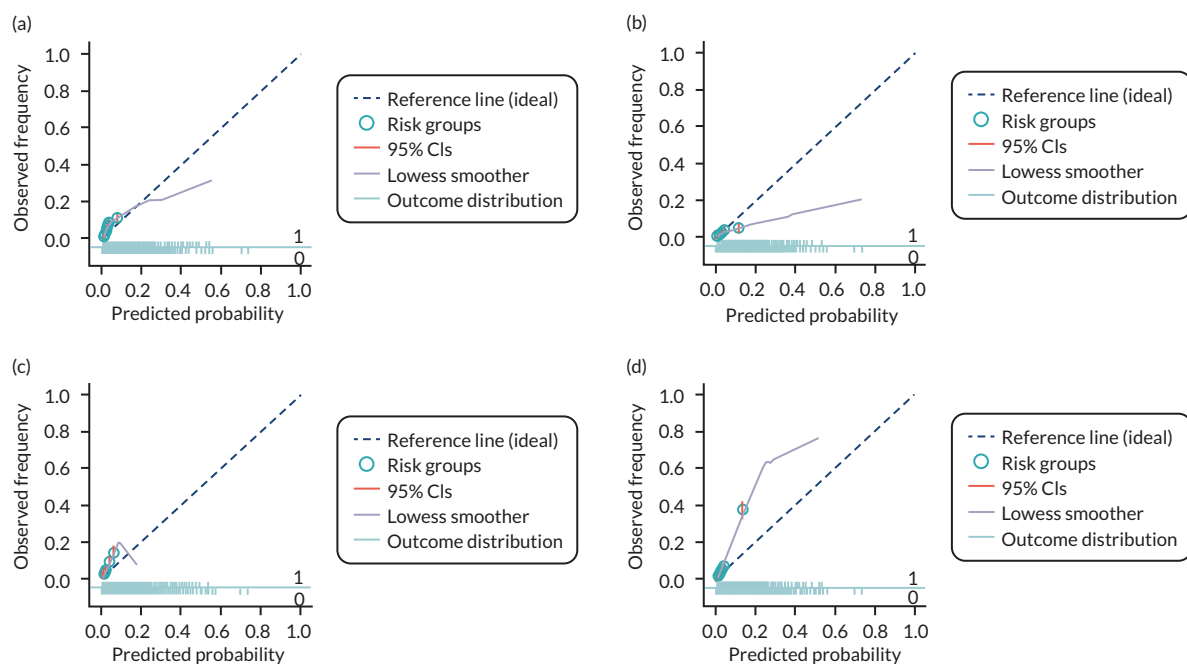


FIGURE 32 Calibration plots for model 4, which includes second-trimester clinical characteristics for predicting any-onset pre-eclampsia. (a) SCOPE;⁴² (b) WHO;¹⁷⁵ (c) NICH LR;¹⁵⁹ and (d) POP.¹⁶¹

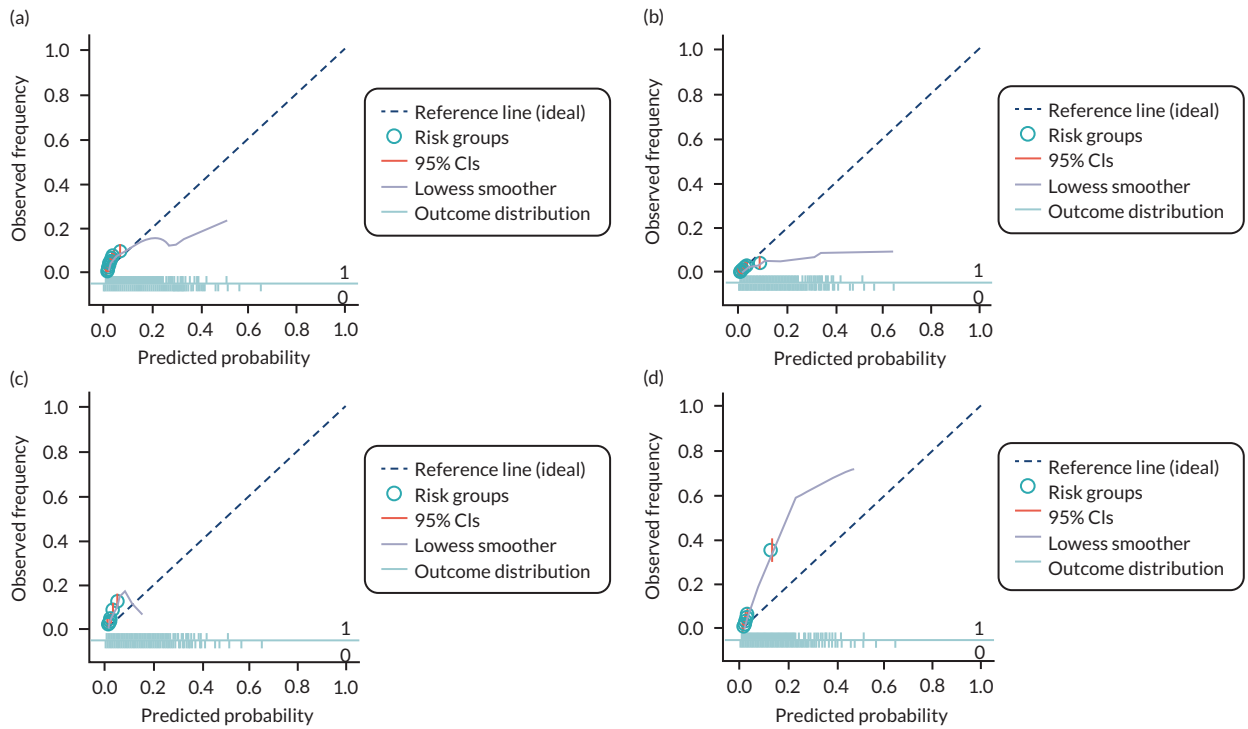


FIGURE 33 Calibration plots for model 6, which includes second-trimester clinical characteristics for predicting late-onset pre-eclampsia. (a) SCOPE;⁴² (b) WHO;¹⁷⁵ (c) NICH LR;¹⁵⁹ and (d) POP.¹⁶¹

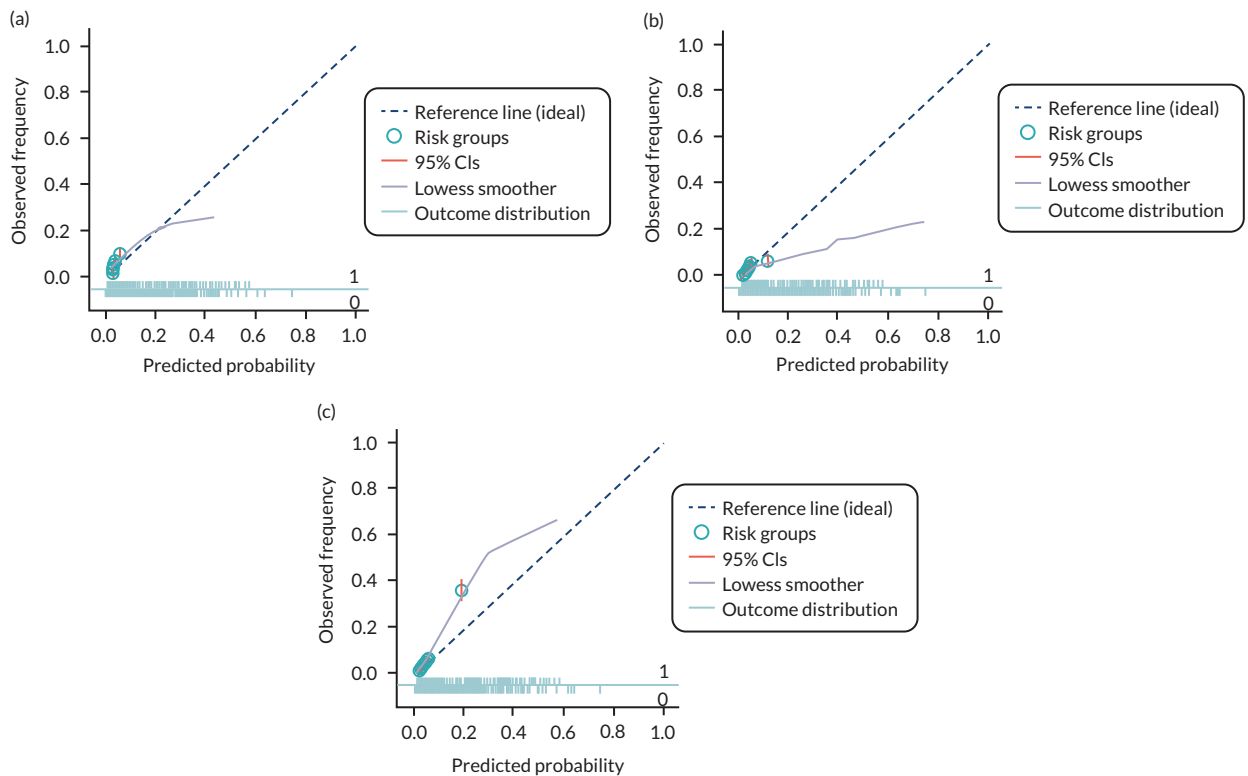


FIGURE 34 Calibration plots for model 7 which includes first-trimester clinical characteristics and biochemical markers for predicting any-onset pre-eclampsia. (a) SCOPE;⁴² (b) WHO;¹⁷⁵ and (c) POP.¹⁶¹

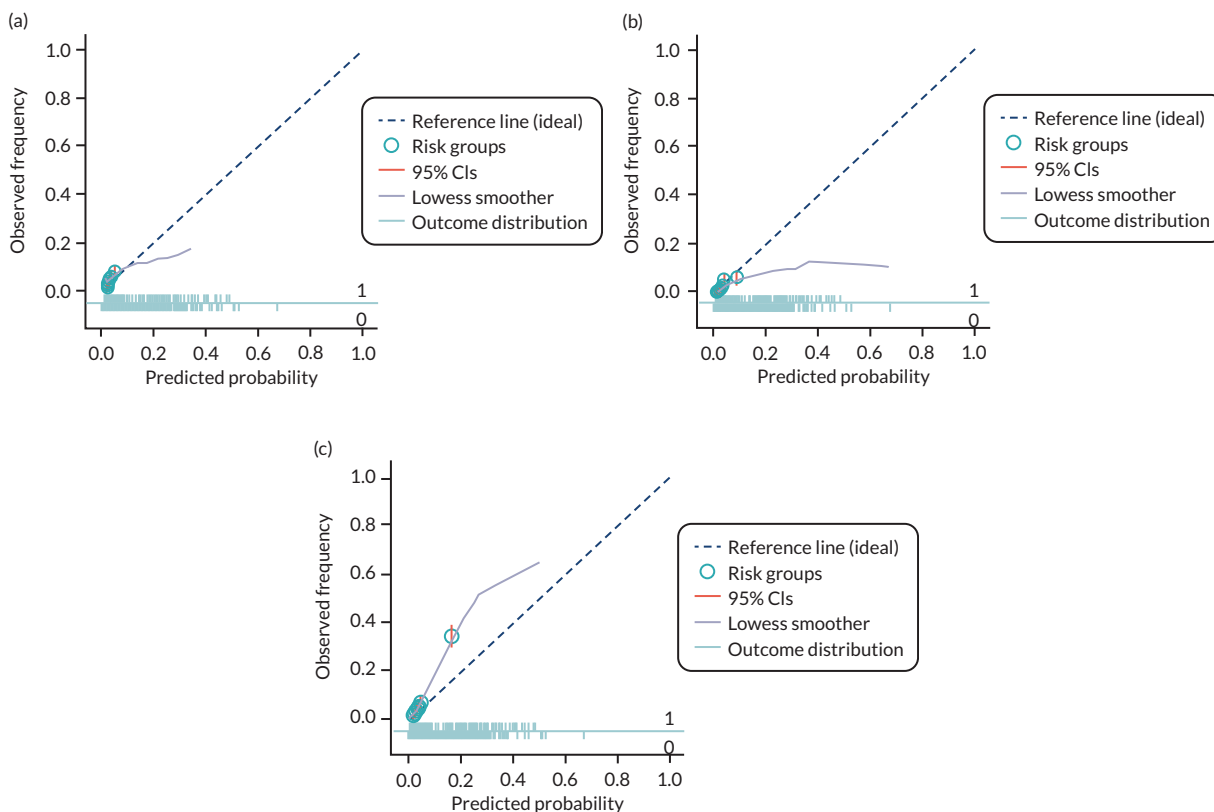


FIGURE 35 Calibration plots for model 9, which includes first-trimester clinical characteristics and biochemical markers for predicting late-onset pre-eclampsia. (a) SCOPE;⁴² (b) WHO;¹⁷⁵ and (c) POP.¹⁶¹

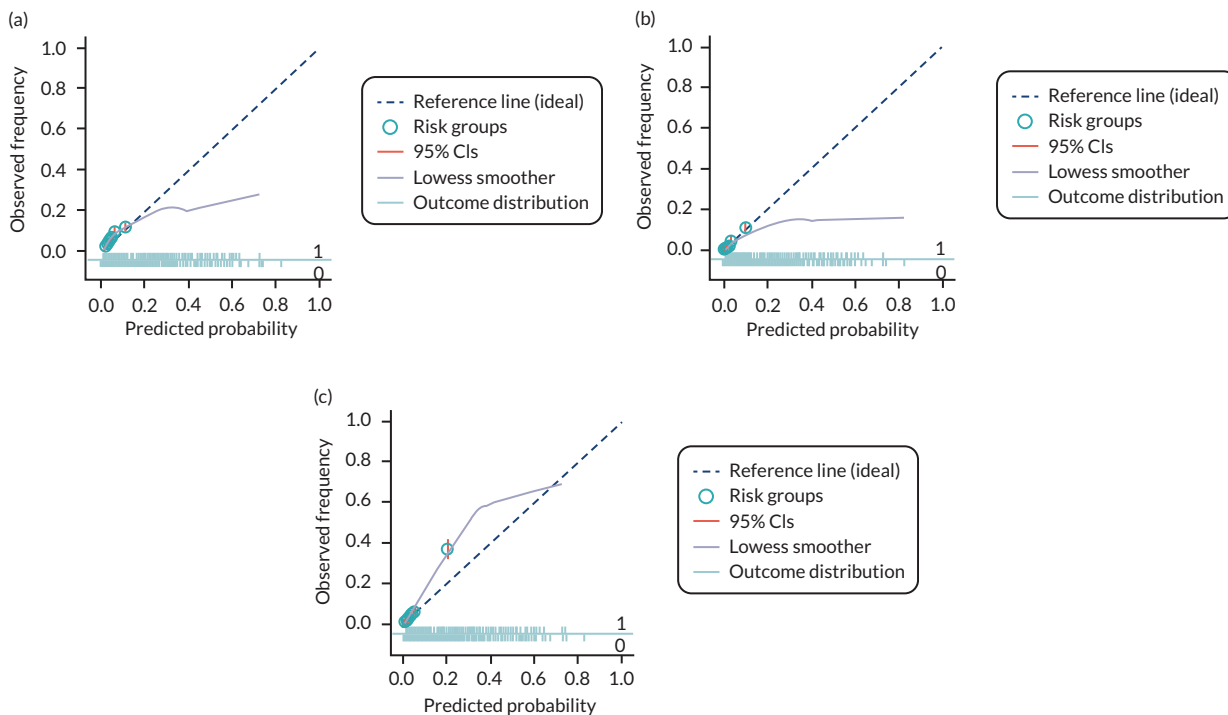


FIGURE 36 Calibration plots for model 10, which includes second-trimester clinical characteristics and biochemical markers for predicting any-onset pre-eclampsia. (a) SCOPE;⁴² (b) WHO;¹⁷⁵ and (c) POP.¹⁶¹

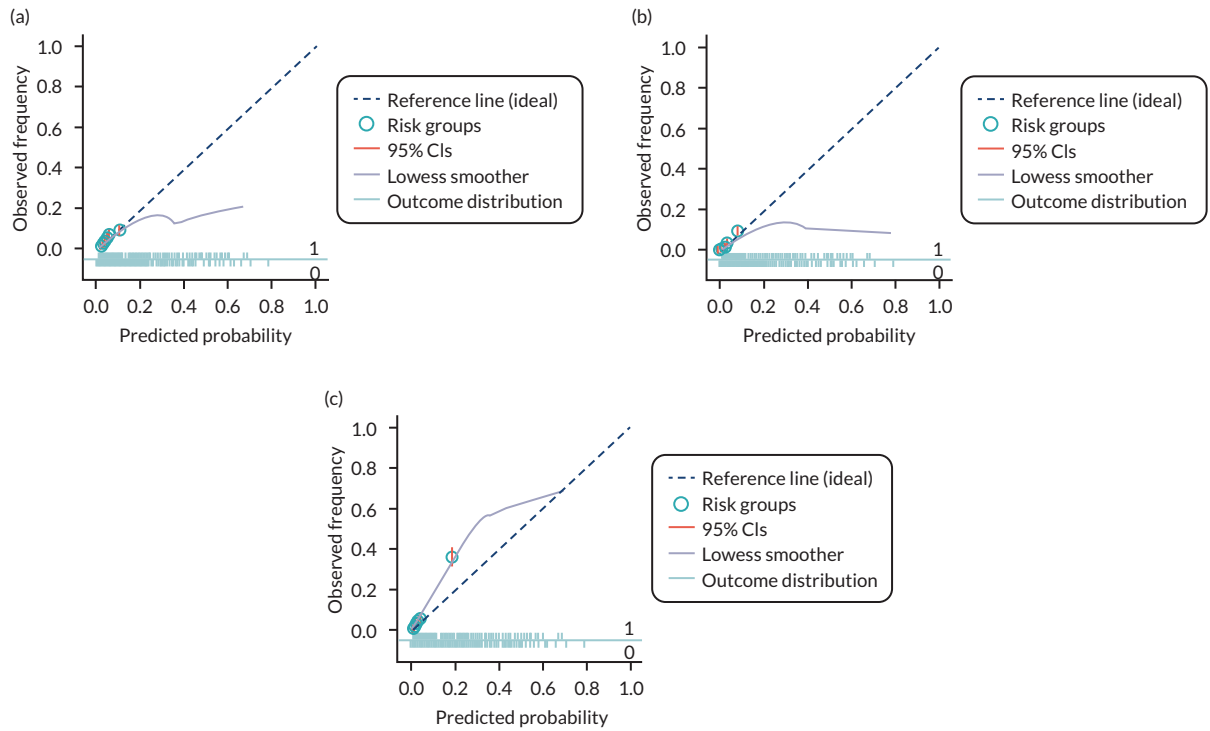


FIGURE 37 Calibration plots for model 12, which includes second-trimester clinical characteristics and biochemical markers for predicting late-onset pre-eclampsia. (a) SCOPE;⁴² (b) WHO;¹⁷⁵ and (c) POP.¹⁶¹

Appendix 21 Decision curve analysis for developed models in each data set

Early-onset pre-eclampsia models

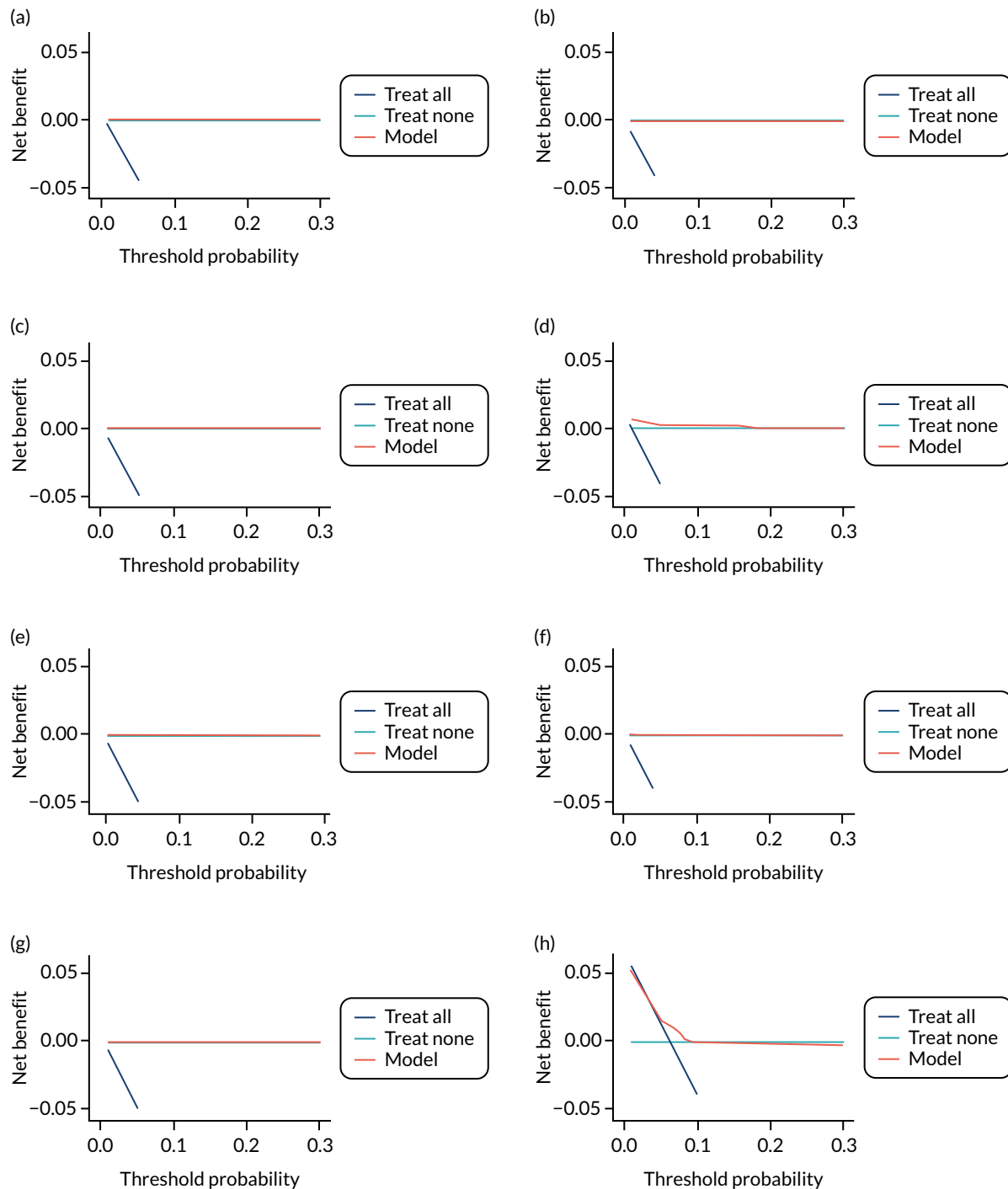


FIGURE 38 Decision curves for the final (shrunken) model predicting early-onset pre-eclampsia using first-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) Allen *et al.*;¹⁰⁸ (c) Poston *et al.* 2015;¹⁴⁹ (d) Baschat *et al.*;¹¹⁵ (e) Antsaklis;¹¹⁰ (f) WHO;¹⁷⁵ (g) NICH LR;¹⁵⁹ (h) Van Kuijk *et al.* 2014;¹⁶⁶ (i) STORK G;¹³⁵ (j) Vinter *et al.*;¹⁷³ and (k) POP.¹⁶¹ (continued)

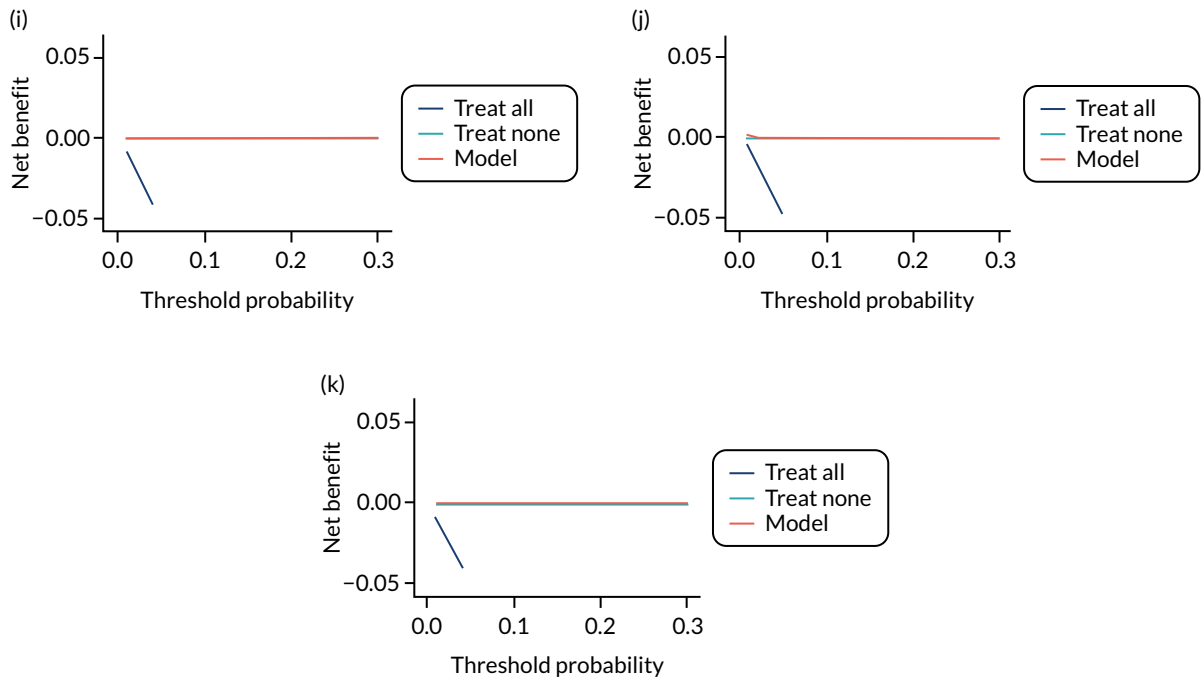


FIGURE 38 Decision curves for the final (shrunk) model predicting early-onset pre-eclampsia using first-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) Allen *et al.*;¹⁰⁸ (c) Poston *et al.* 2015;¹⁴⁹ (d) Baschat *et al.*;¹¹⁵ (e) Antsaklis;¹¹⁰ (f) WHO;¹⁷⁵ (g) NICH LR;¹⁵⁹ (h) Van Kuijk *et al.* 2014;¹⁶⁶ (i) STORK G;¹³⁵ (j) Vinter *et al.*;¹⁷³ and (k) POP.¹⁶¹

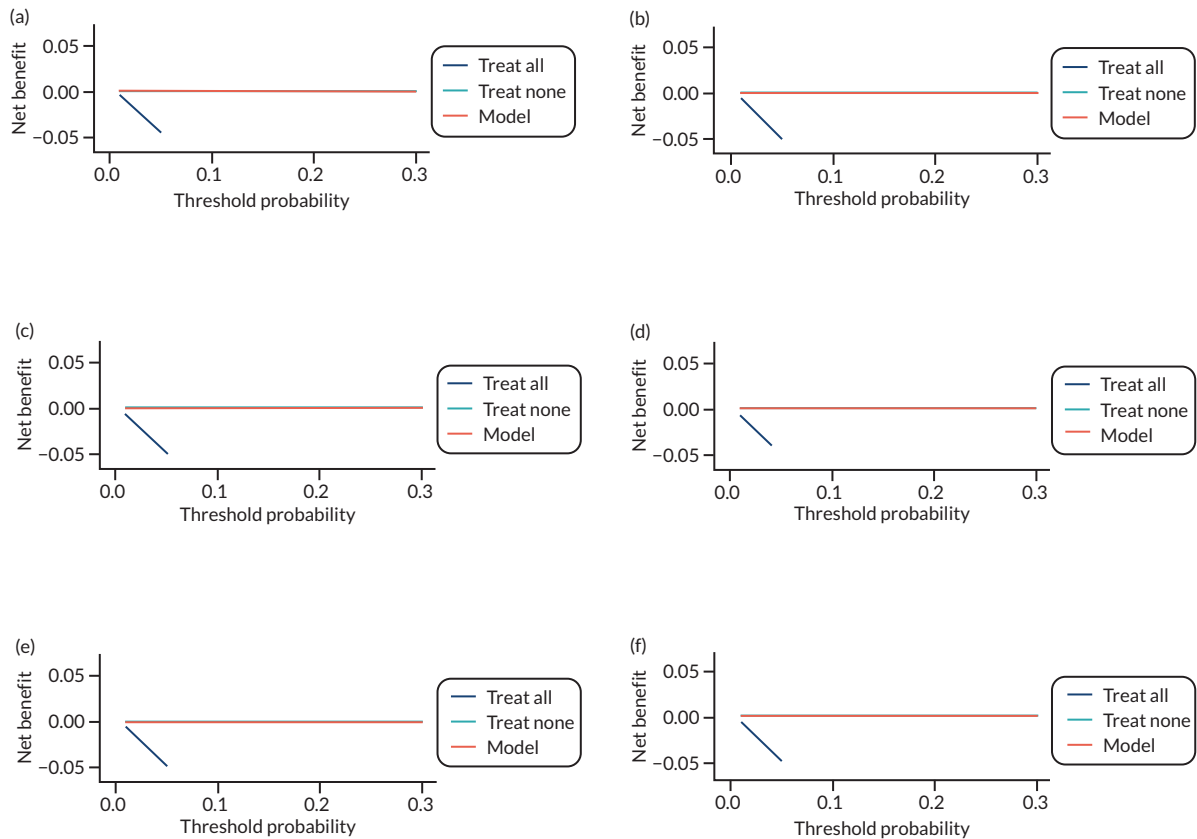


FIGURE 39 Decision curves for the final (shrunk) model predicting early-onset pre-eclampsia using second-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) Poston *et al.* 2015;¹⁴⁹ (c) Antsaklis *et al.*;¹¹⁰ (d) WHO;¹⁷⁵ (e) NICH LR;¹⁵⁹ (f) POUCH;¹³¹ (g) Van Kuijk *et al.* 2014;¹⁶⁶ (h) STORK G;¹³⁵ and (i) POP.¹⁶¹ (continued)

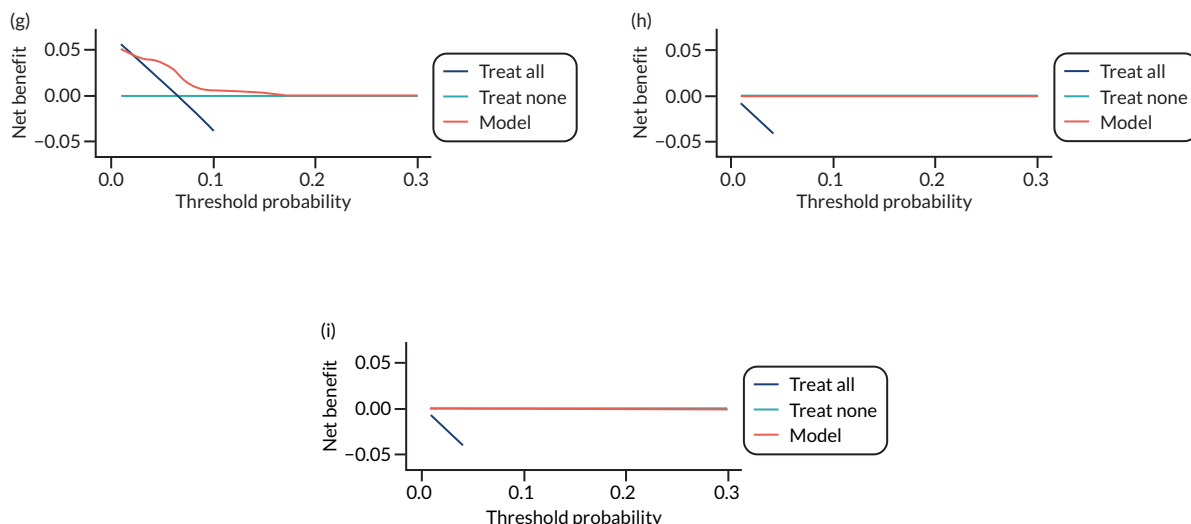


FIGURE 39 Decision curves for the final (shrunk) model predicting early-onset pre-eclampsia using second-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) Poston *et al.* 2015;¹⁴⁹ (c) Antsaklis *et al.*;¹¹⁰ (d) WHO;¹⁷⁵ (e) NICH LR;¹⁵⁹ (f) POUCH;¹³¹ (g) Van Kuijk *et al.* 2014;¹⁶⁶ (h) STORK G;¹³⁵ and (i) POP.¹⁶¹

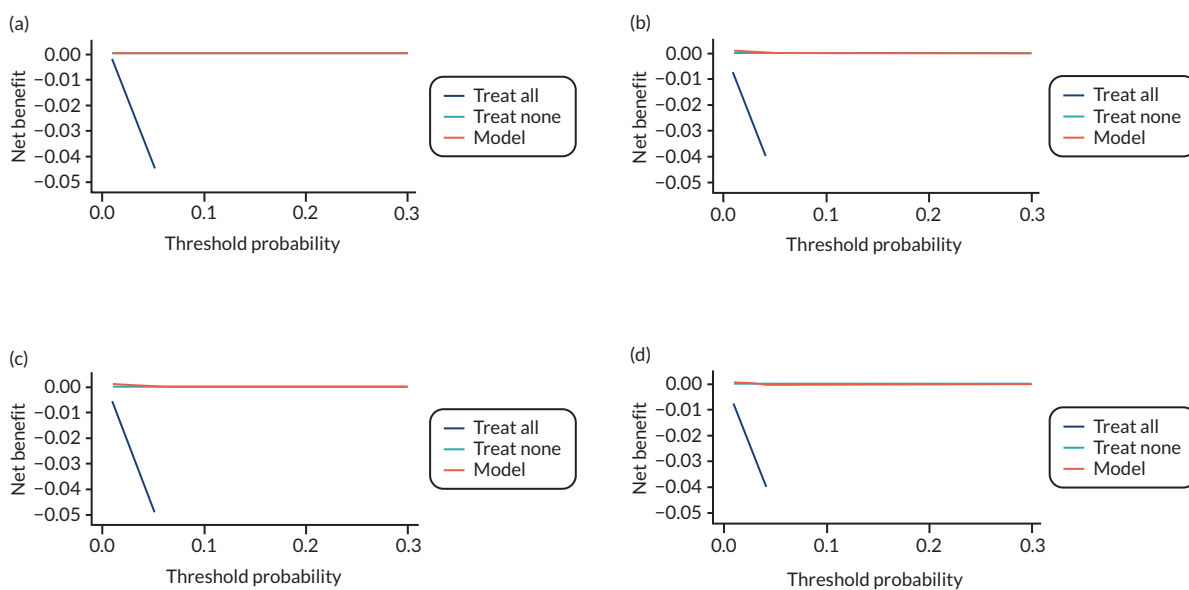


FIGURE 40 Decision curves for the final (shrunk) model predicting early-onset pre-eclampsia using first-trimester clinical characteristics and biochemical markers, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) WHO;¹⁷⁵ (c) POUCH;¹³¹ and (d) POP.¹⁶¹

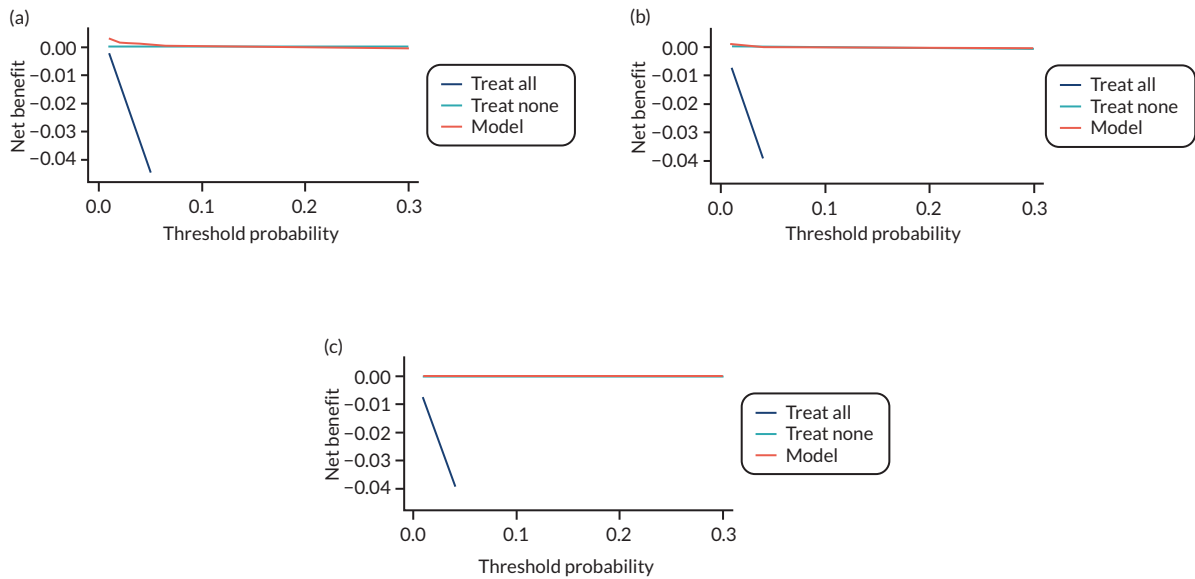


FIGURE 41 Decision curves for the final (shrunk) model predicting early-onset pre-eclampsia using second-trimester clinical characteristics and biochemical markers, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) WHO;¹⁷⁵ and (c) POP.¹⁶¹

Late-onset pre-eclampsia models

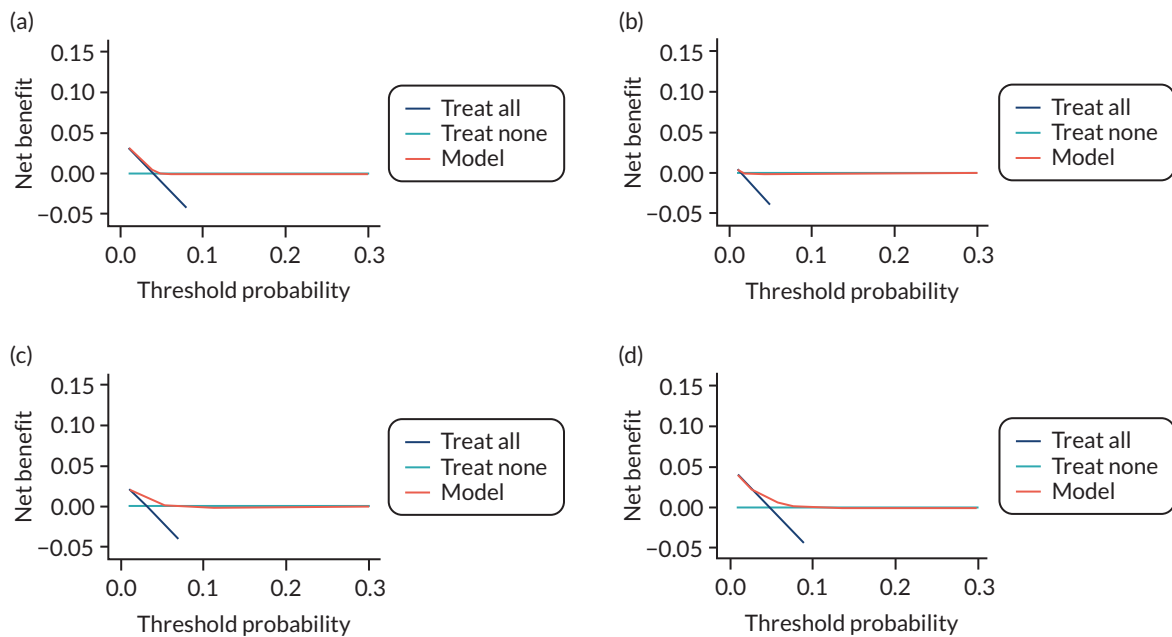


FIGURE 42 Decision curves for the final (shrunk) model predicting late-onset pre-eclampsia using first-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) Allen *et al.*;¹⁰⁸ (c) Poston *et al.* 2015;¹⁴⁹ (d) Baschat *et al.*;¹¹⁵ (e) Antsaklis;¹¹⁰ (f) WHO;¹⁷⁵ (g) NICH LR;¹⁵⁹ (h) Van Kuijk *et al.* 2014;¹⁶⁶ (i) STORK G;¹³⁵ (j) Vinter *et al.*;¹⁷³ and (k) POP.¹⁶¹ (continued)

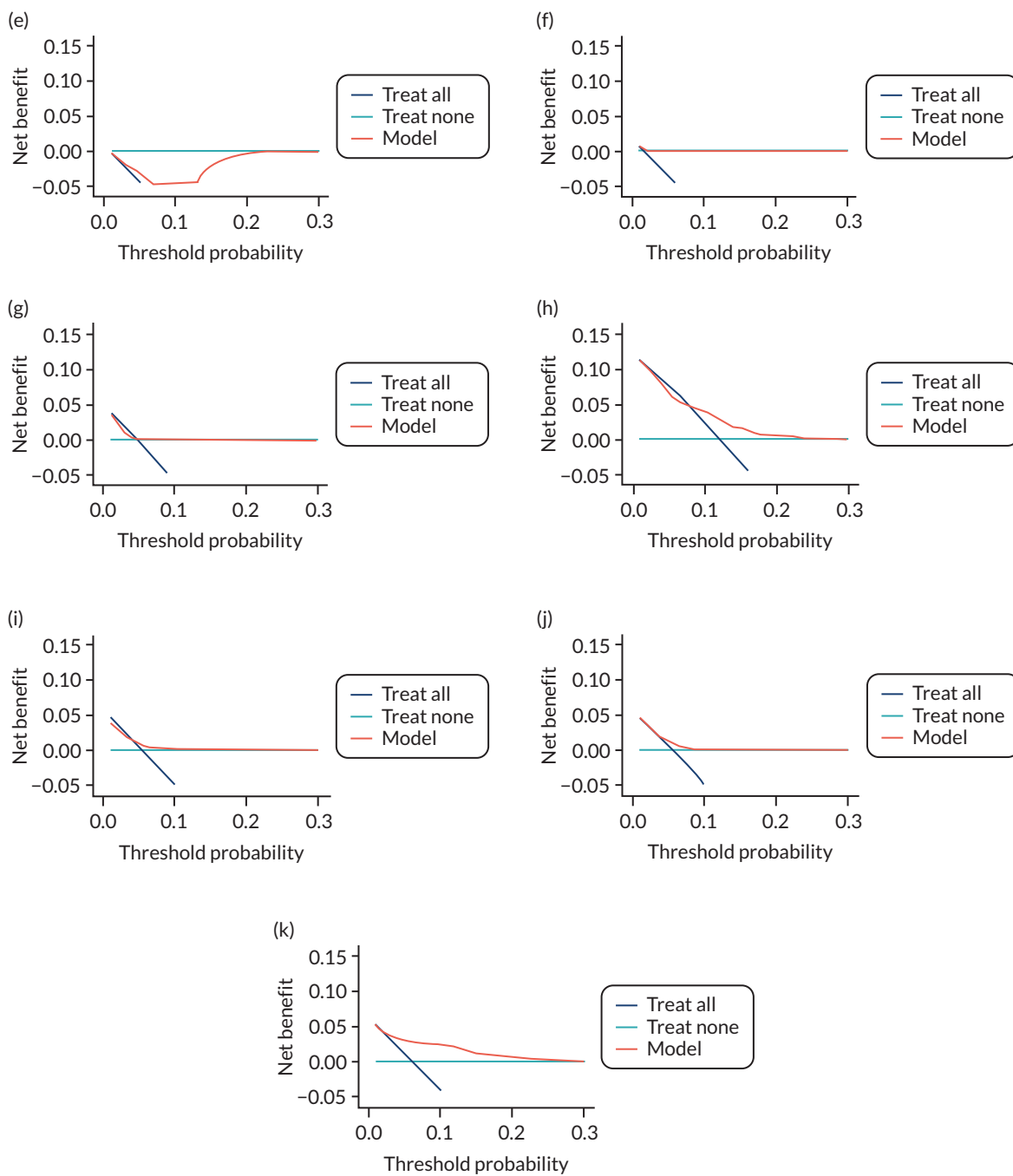


FIGURE 42 Decision curves for the final (shrunk) model predicting late-onset pre-eclampsia using first-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) Allen *et al.*;¹⁰⁸ (c) Poston *et al.* 2015;¹⁴⁹ (d) Baschat *et al.*;¹¹⁵ (e) Antsaklis;¹¹⁰ (f) WHO;¹⁷⁵ (g) NICH LR;¹⁵⁹ (h) Van Kuijk *et al.* 2014;¹⁶⁶ (i) STORK G;¹³⁵ (j) Vinter *et al.*;¹⁷³ and (k) POP.¹⁶¹

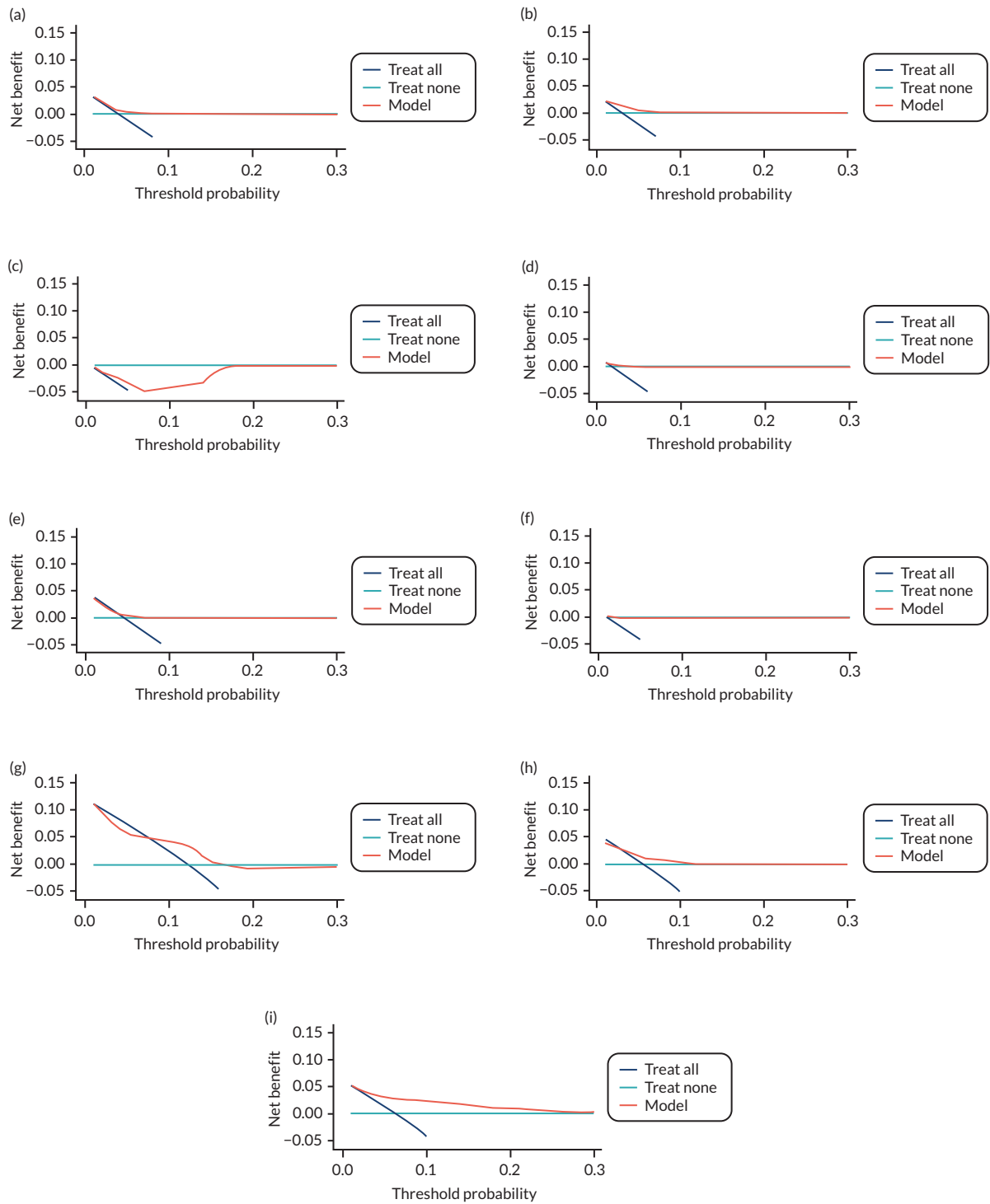


FIGURE 43 Decision curves for the final (shrunk) model predicting late-onset pre-eclampsia using second-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) Poston *et al.* 2015;¹⁴⁹ (c) Antsaklis;¹¹⁰ (d) WHO;¹⁷⁵ (e) NICH LR;¹⁵⁹ (f) POUCH;¹³¹ (g) Van Kuijk *et al.* 2014;¹⁶⁶ (h) STORK G;¹³⁵ and (i) POP.¹⁶¹

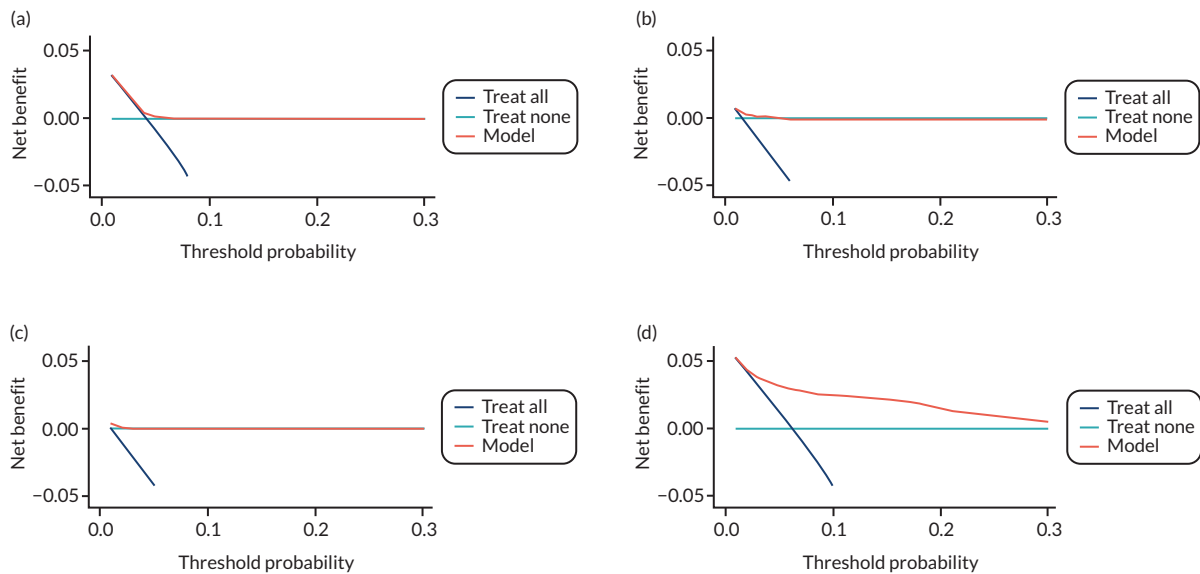


FIGURE 44 Decision curves for the final (shrunken) model predicting late-onset pre-eclampsia using first-trimester clinical characteristics and biochemical markers, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) WHO;¹⁷⁵ (c) POUCH;¹³¹ and (d) POP.¹⁶¹

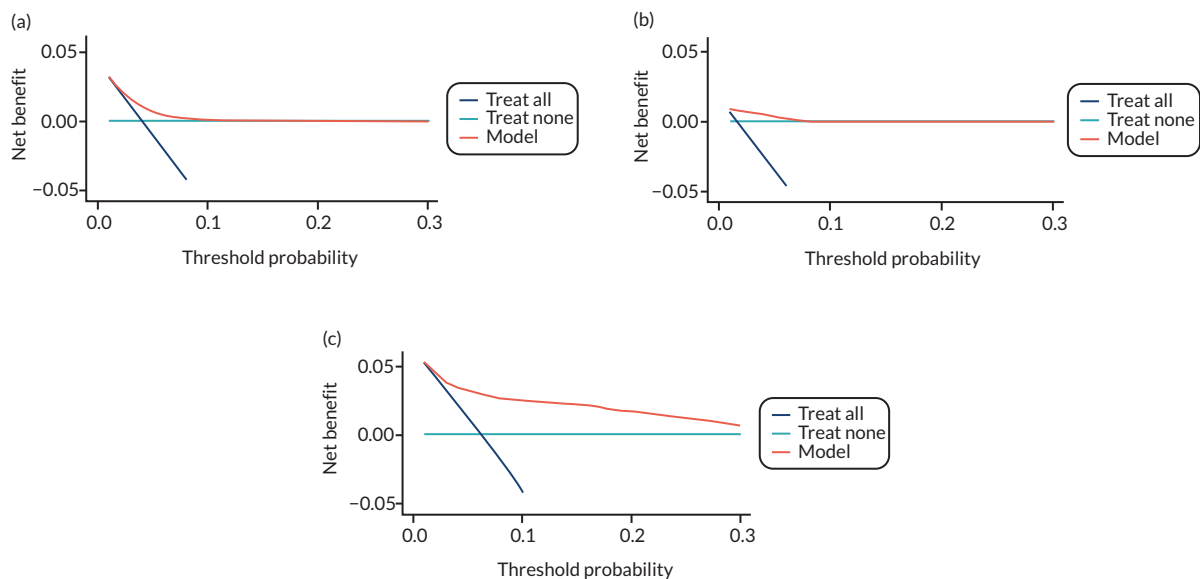


FIGURE 45 Decision curves for the final (shrunken) model predicting late-onset pre-eclampsia using second-trimester clinical characteristics and biochemical markers, in data sets used in the development and validation of the model. (a) SCOPE;⁴² (b) WHO;¹⁷⁵ and (c) POP.¹⁶¹

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