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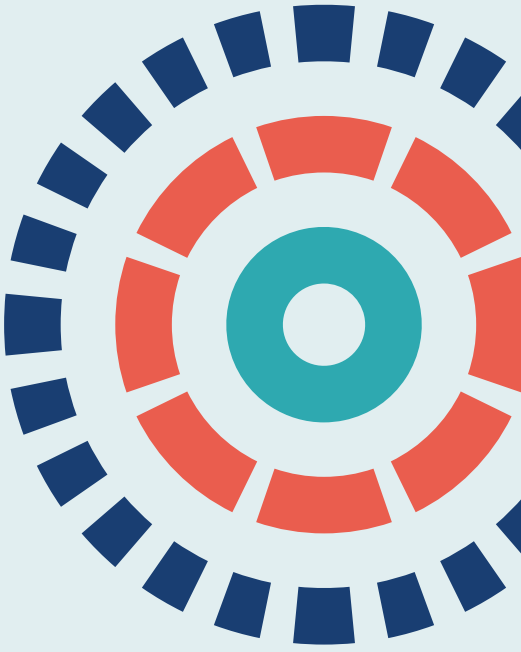

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Validation and development of models using clinical, biochemical and ultrasound markers for predicting pre-eclampsia: an individual participant data meta-analysis

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Abstract

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

John Allotey,[1,2†] Kym IE Snell,[3*†] Melanie Smuk,[2] Richard Hooper,[2] Claire L Chan,[2] Asif Ahmed,[4] Lucy C Chappell,[5] Peter von Dadelszen,[5] Julie Dodds,[1,2] Marcus Green,[6] Louise Kenny,[7] Asma Khalil,[8] Khalid S Khan,[1,2] Ben W Mol,[9] Jenny Myers,[10] Lucilla Poston,[5] Basky Thilaganathan,[8] Anne C Staff,[11,12] Gordon CS Smith[13] Wessel Ganzevoort,[14] *et al.*[‡] on behalf of the IPPIC Collaborative Network[§]

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§The full list of partners in the IPPIC Collaborative Network can be found in *Acknowledgements*.

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 ≥ 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 ≥ 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.

Study registration: This study is registered as PROSPERO CRD42015029349.

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Contents

List of tables

List of figures

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	PlGF	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 ≠ 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.

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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 worldwide[6] 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]

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

We planned to externally validate and update prediction models for (1) early-onset (delivery at < 34 weeks' gestation), (2) late-onset (delivery at ≥ 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

Our IPD meta-analysis followed existing recommendations on prognostic research model development and validation[53–55] and adhered to reporting guidelines for prediction models and IPD meta-analysis.[56,57] We used a prospective protocol[51] 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	***Maternal clinical characteristics at antenatal booking***
	Maternal characteristics: age, BMI, height, weight, ethnicity, smoking, alcohol or substance misuse
	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
	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
	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
	Biochemical markers (first or second trimester): PAPP-A, sFlt-1, PlGF, AFP, human chorionic gonadotropin, sENG, CRP, hypertriglyceridaemia and PAI-1
	Ultrasound markers (first or second trimester)
	CRL, abdominal circumference, expected fetal weight centile, uterine and umbilical artery Doppler (resistance index, pulsatility index, unilateral or bilateral notching)
Outcomes	**Primary outcomes**
	Early-onset (delivery at < 34 weeks' gestation), late-onset (delivery at ≥ 34 weeks' gestation) and any-onset pre-eclampsia
	Secondary outcomes
	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
	Fetal and neonatal complications: birthweight in kg and centile (using the Gestation Network bulk centile calculator[59]), SGA fetus, stillbirth, neonatal death, hypoxic-ischaemic encephalopathy, respiratory distress syndrome, septicaemia, admission to neonatal unit
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; PlGF, placental growth factor; SBP, systolic blood pressure; sENG, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase-1; SGA, small for gestational age.

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-eclampsia[43] (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 groups[74–76] 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/m^2), 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 × DBP)/3. Where BMI was not provided in the data set it was derived using weight (kg)/height (m^2). 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 (PlGF) 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.

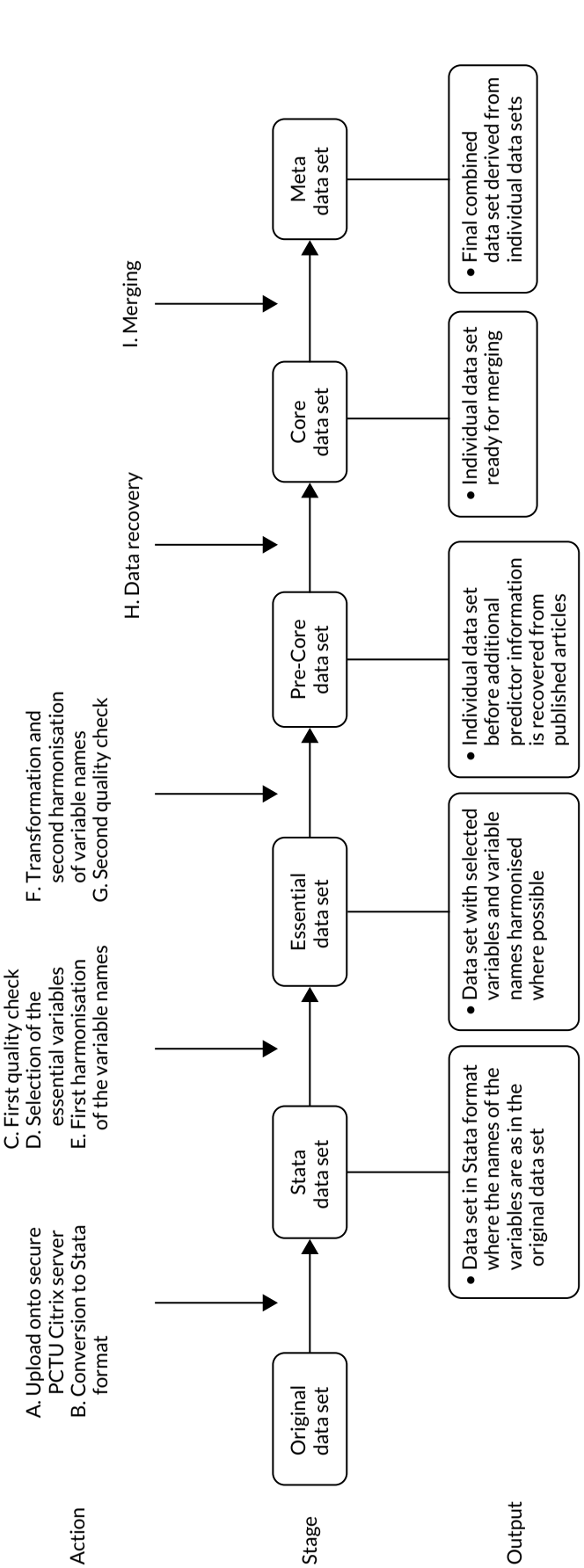


FIGURE 1 Flow diagram of harmonisation of variables in the IPD data sets.

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 ($LP_i = \alpha + \beta_1 \times x_1 + \beta_2 \times x_2 + \ldots$), and the predicted probability of pre-eclampsia,

$$p_i = \frac{e^{LP_i}}{1 + e^{LP_i}}, \tag{1}$$

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:

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

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 PlGF 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 PlGF 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(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 ± 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

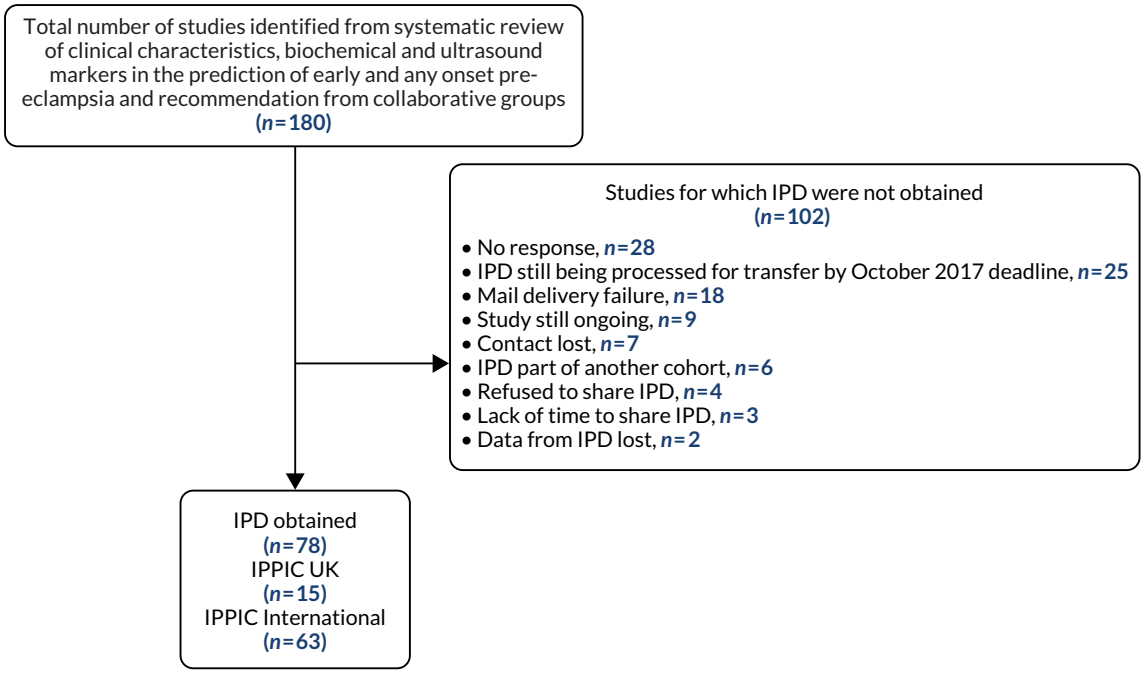


FIGURE 2 Flow diagram of studies included in the IPD meta-analysis, showing reasons why IPD were not obtained.

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	
PlGF	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.

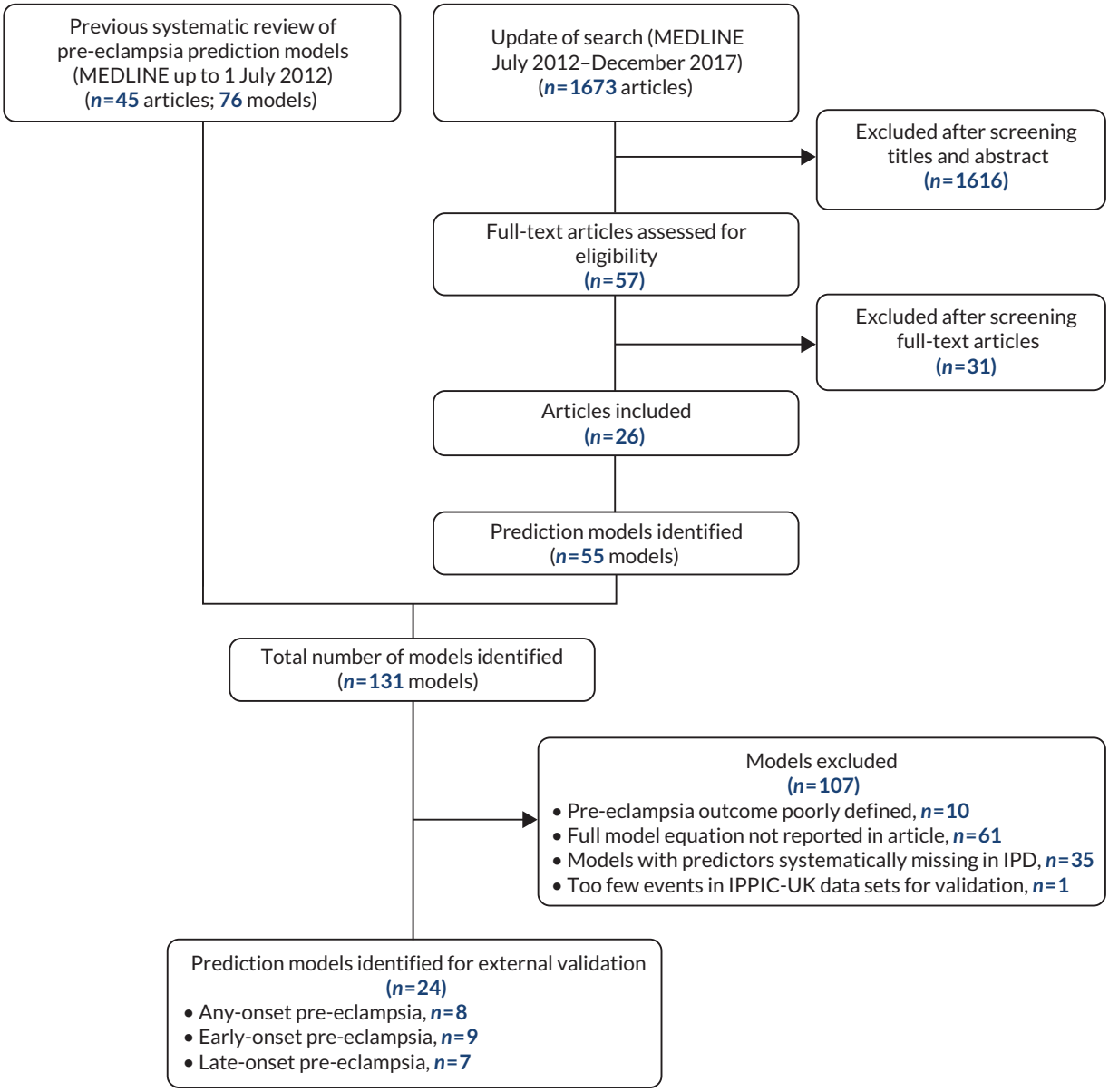


FIGURE 3 Flow chart of pre-eclampsia prediction model selection for external validation in IPPIC-UK data set using IPD meta-analysis. Reproduced from Snell *et al.*[52] Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 2014[115]	Clinical characteristics	LP = −5.803 + 0.302 (if diabetes) + 0.767 (if hypertension) + 0.00948 (MAP)
9	Crovetto *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 2015[236]	Clinical characteristics	Same as model 3
15	Poon *et al.*, 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 *et al.*, 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 *et al.*, 2013[230]	Clinical characteristics	LP = −14.374 + 2.300 (maternal weight, Ln kg) + 1.303 (if nulliparous) + 0.068 (maternal age, years)
18	Plasencia *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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, logit(p) = LP, where the LP = $\alpha + \beta_1 \times x_1 + \beta_2 \times x_2 + \ldots$, 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.

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 conditions[150] and maternal obesity;[122,149] one[42] included only low-risk nulliparous women, and one[161] 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.* 2006[150] and Poston *et al.* 2015[149] 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 UK[42]) 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							
Trimester 1 models							
1	Clinical	Plasencia *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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)
Trimester 2 models							
22	Clinical and ultrasound markers	Yu *et al.*, 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							
Trimester 1 models							
8	Clinical	Baschat *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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)
Trimester 2 models							
23	Clinical and ultrasound markers	Yu *et al.*, 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							
Trimester 1 models							
16	Clinical	Crovetto *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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)
Trimester 2 models							
24	Clinical and ultrasound markers	Yu *et al.*, 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).

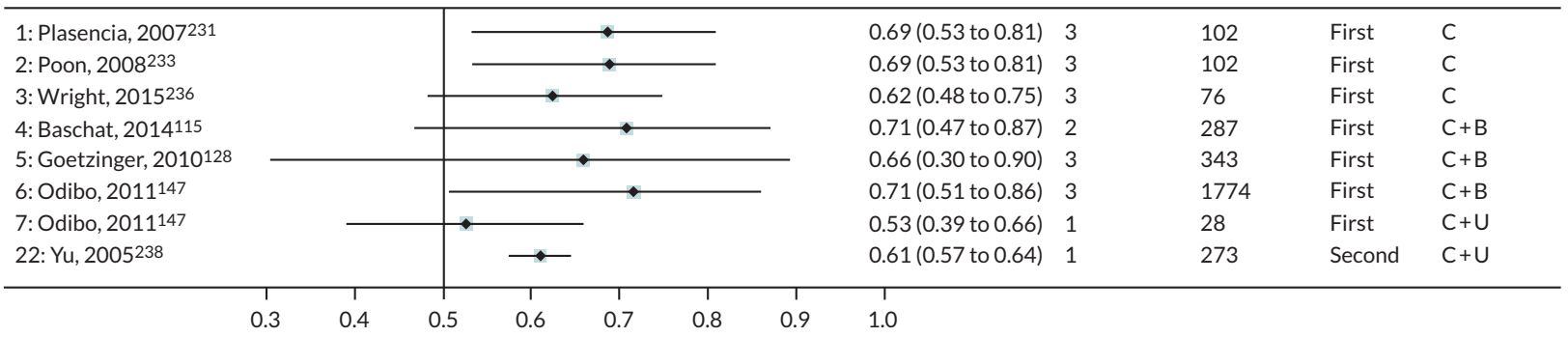
b Number of studies is one fewer for calibration slope of models 9 and 11. The calibration slope could not be estimated reliably in SCOPE UK and was, therefore, excluded from the meta-analysis.

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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 2014[115]	Clinical	Poston *et al.* 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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).

(a)



(b)

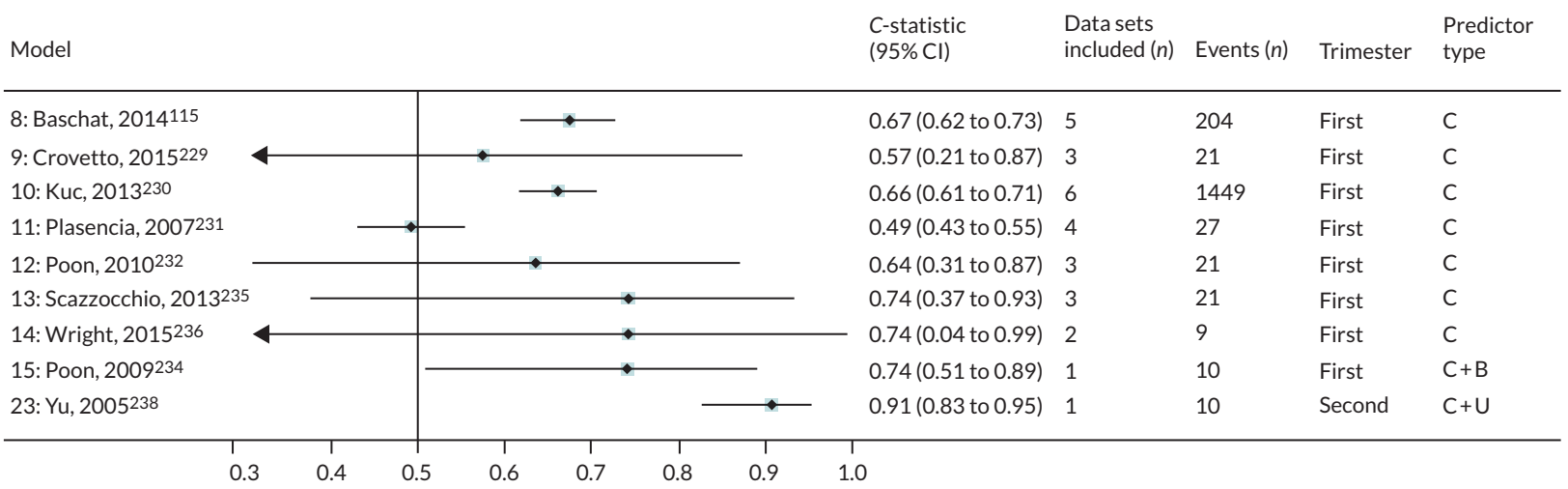


FIGURE 4 Plot of the summary meta-analysis estimates and CIs of the *C*-statistic (pooled across IPPIC-UK validation data sets) for each prediction model. (a) Any-onset pre-eclampsia; (b) early-onset pre-eclampsia; and (c) late-onset pre-eclampsia. This figure contains information from several sources.[115,128,147,229–236,238]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

(c)

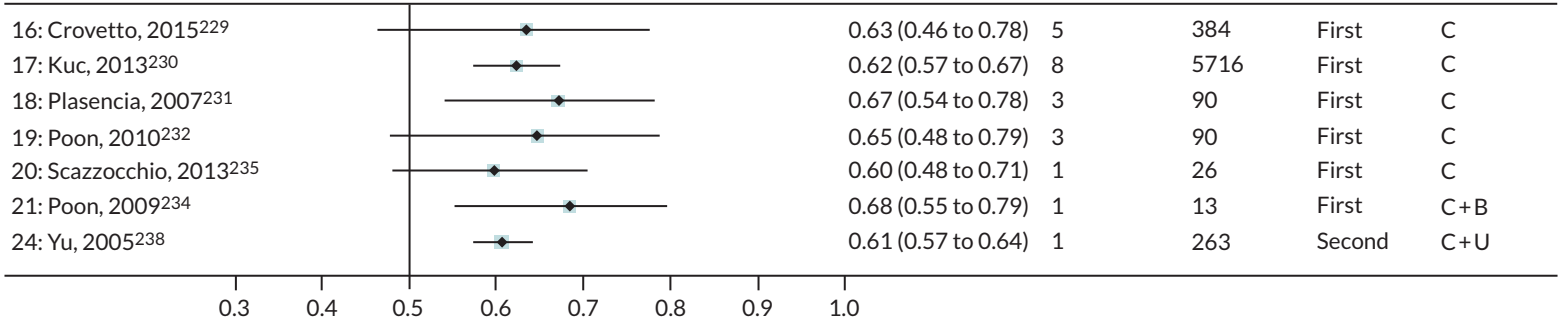


FIGURE 4 Plot of the summary meta-analysis estimates and CIs of the *C*-statistic (pooled across IPPIC-UK validation data sets) for each prediction model. (a) Any-onset pre-eclampsia; (b) early-onset pre-eclampsia; and (c) late-onset pre-eclampsia. This figure contains information from several sources.[115,128,147,229–236,238] 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 2[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 6[147]). Of these, only two models had summary *C*-statistics > 0.7; but only one model's (Odibo *et al.*, model 6[147]) *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 7[147]) 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 4[115]), 0.76 (Goetzinger *et al.*, model 5[128]) and 0.78 (Odibo *et al.*, model 6[147]) in the POP study[161] 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 22[238]), 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 10[230]) 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 10[230]) 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 10[230] 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 15[234]) 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 23[238]) 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 17[230]) 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 21[234]) 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 24[238]) 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*).

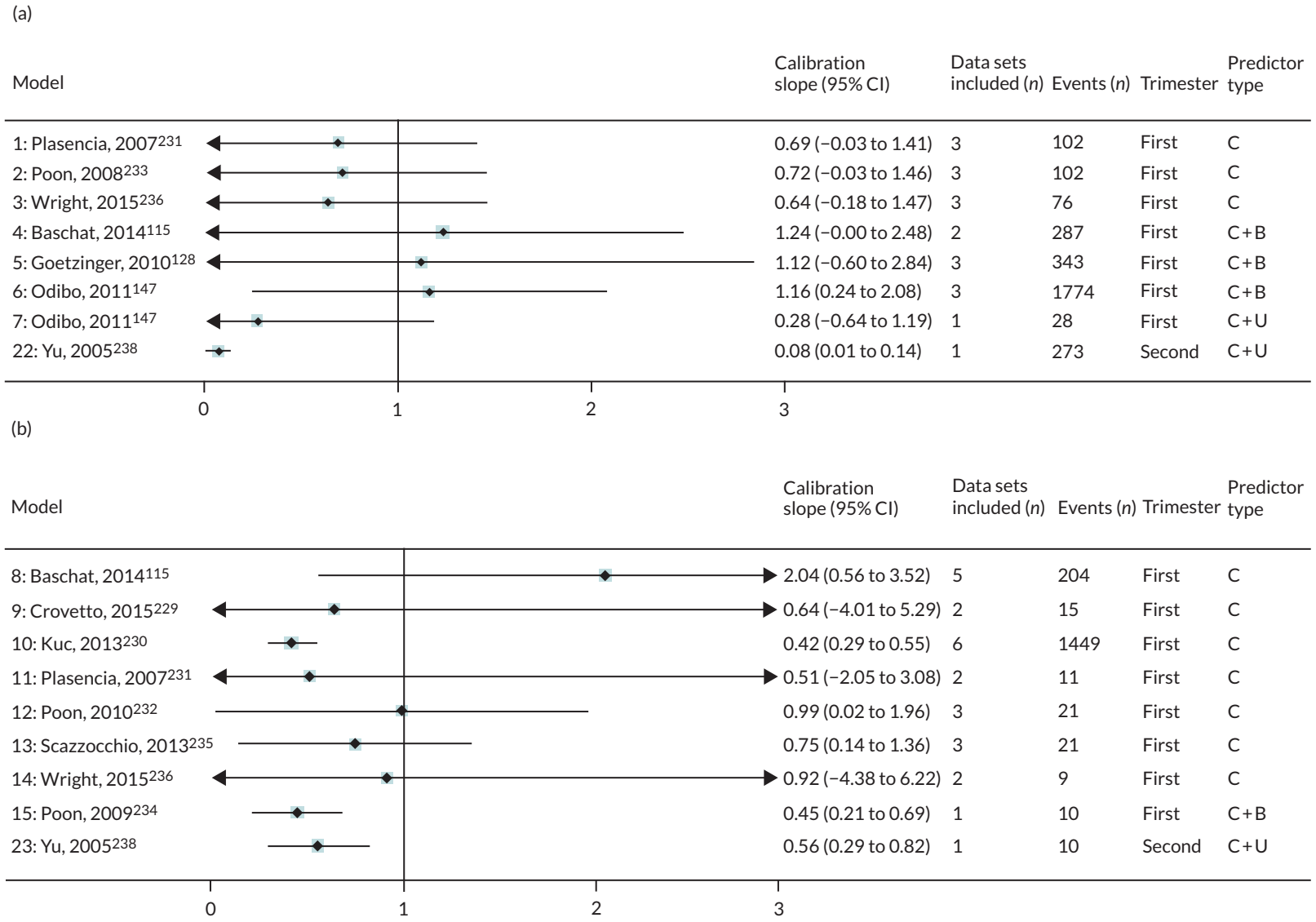


FIGURE 5 Plot of the summary meta-analysis estimates and CIs of calibration (pooled across IPPIC-UK validation data sets) for each prediction model. (a) Any-onset pre-eclampsia; (b) early-onset pre-eclampsia; and (c) late-onset pre-eclampsia. This figure contains information from several sources.[115,128,147,229–236,238]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

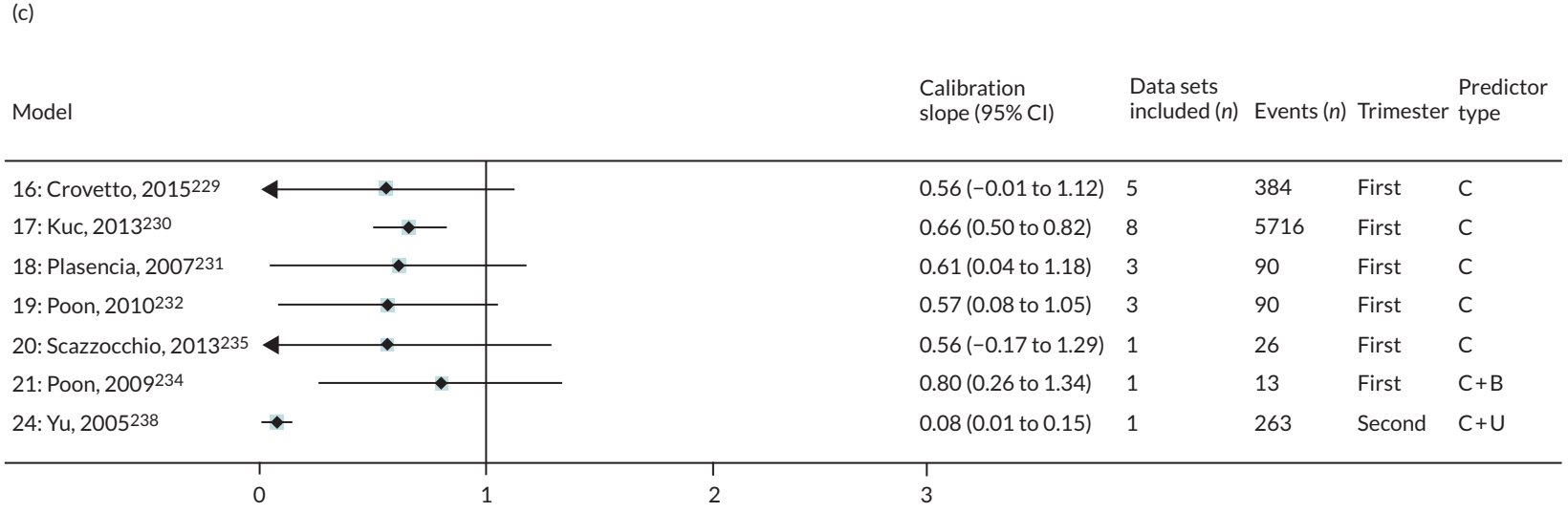


FIGURE 5 Plot of the summary meta-analysis estimates and CIs of calibration (pooled across IPPIC-UK validation data sets) for each prediction model. (a) Any-onset pre-eclampsia; (b) early-onset pre-eclampsia; and (c) late-onset pre-eclampsia. This figure contains information from several sources.[115,128,147,229–236,238]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

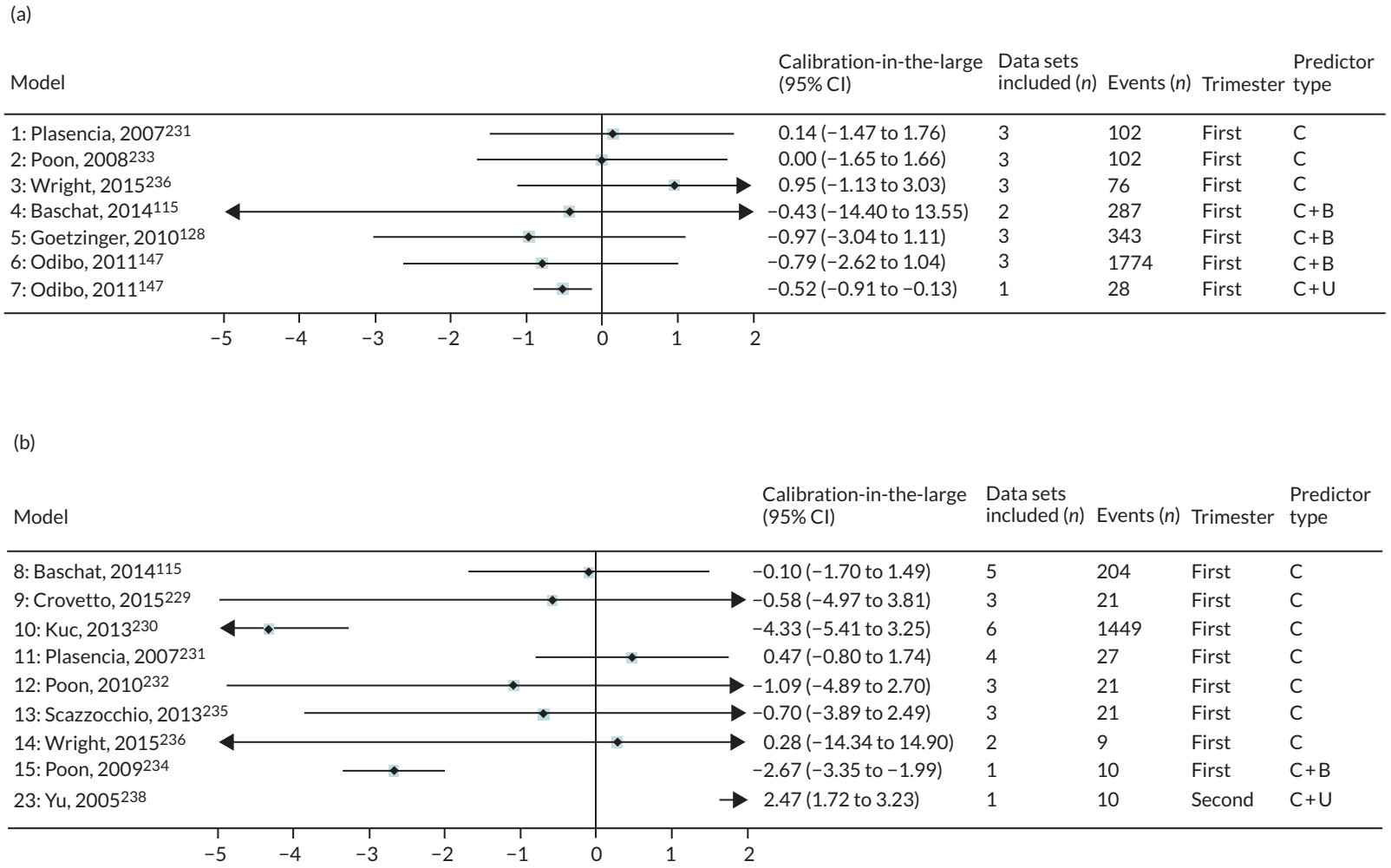


FIGURE 6 Plot of the summary meta-analysis estimates and CIs of calibration-in-the-large (pooled across IPPIC-UK validation datasets) for each prediction model. (a) Any-onset pre-eclampsia; (b) early-onset pre-eclampsia; and (c) late-onset pre-eclampsia. This figure contains information from several 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*)

(c)

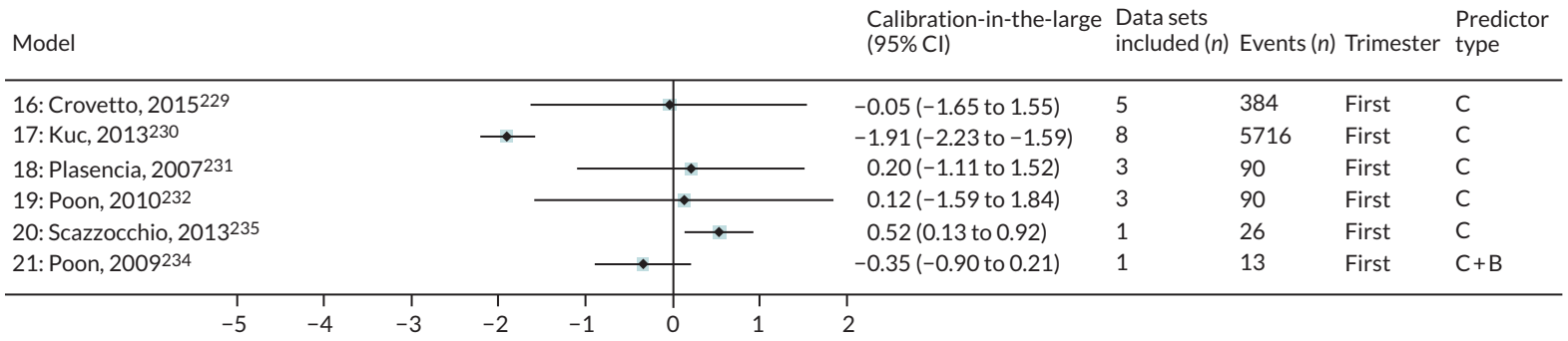


FIGURE 6 Plot of the summary meta-analysis estimates and CIs of calibration-in-the-large (pooled across IPPIC-UK validation datasets) for each prediction model. (a) Any-onset pre-eclampsia; (b) early-onset pre-eclampsia; and (c) late-onset pre-eclampsia. This figure contains information from several 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.*, 2014[115]) and model 5 (Goetzinger *et al.*, 2010[128]), 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.*, 2014[115]), validated in Poston 2006[150] (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.*, 2013[230]), 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.*, 2015[229]) underpredicted risk, particularly in those at highest risk in POP,[161] and model 17 (Kuc *et al.*, 2013[230]) overpredicted risk in both St George's[163] and AMND[114] (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.* 2015[149] and POP[161] 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.

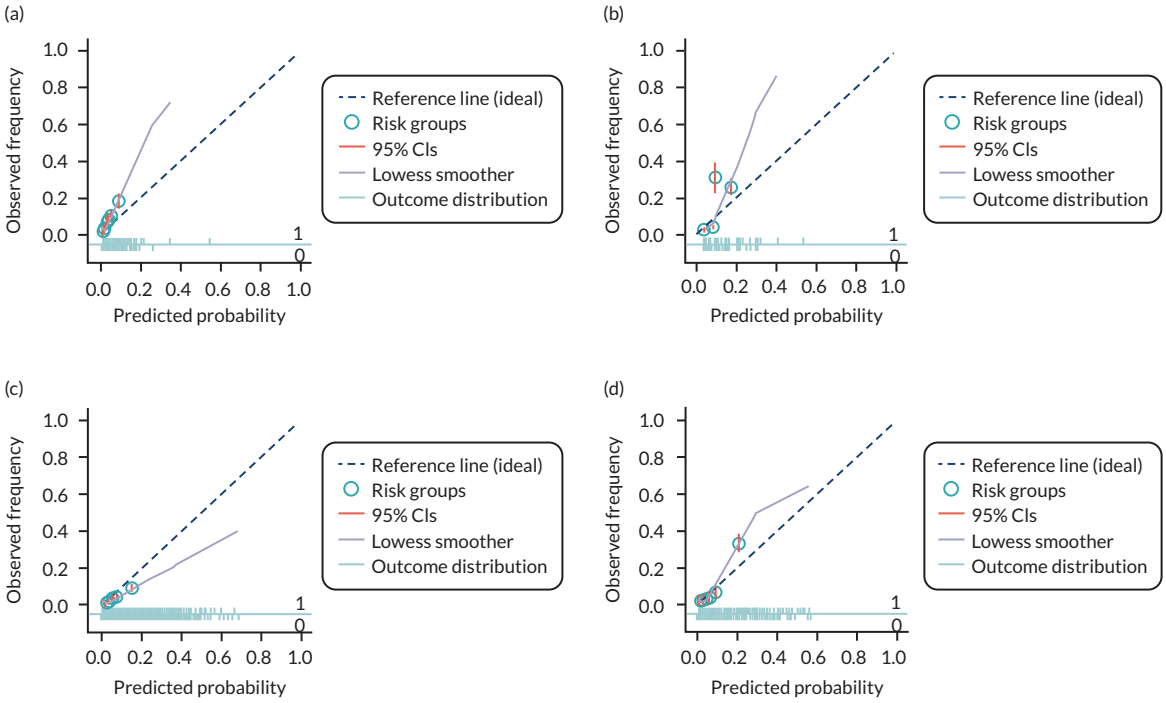


FIGURE 7 Calibration plots for models predicting any-onset pre-eclampsia using first-trimester clinical characteristics and biochemical markers in data sets with > 100 outcome events. (a) Model 4[115] in POP;[161] (b) model 5[128] in POP;[161] (c) model 6[147] in St George's;[163] and (d) model 6[147] 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.

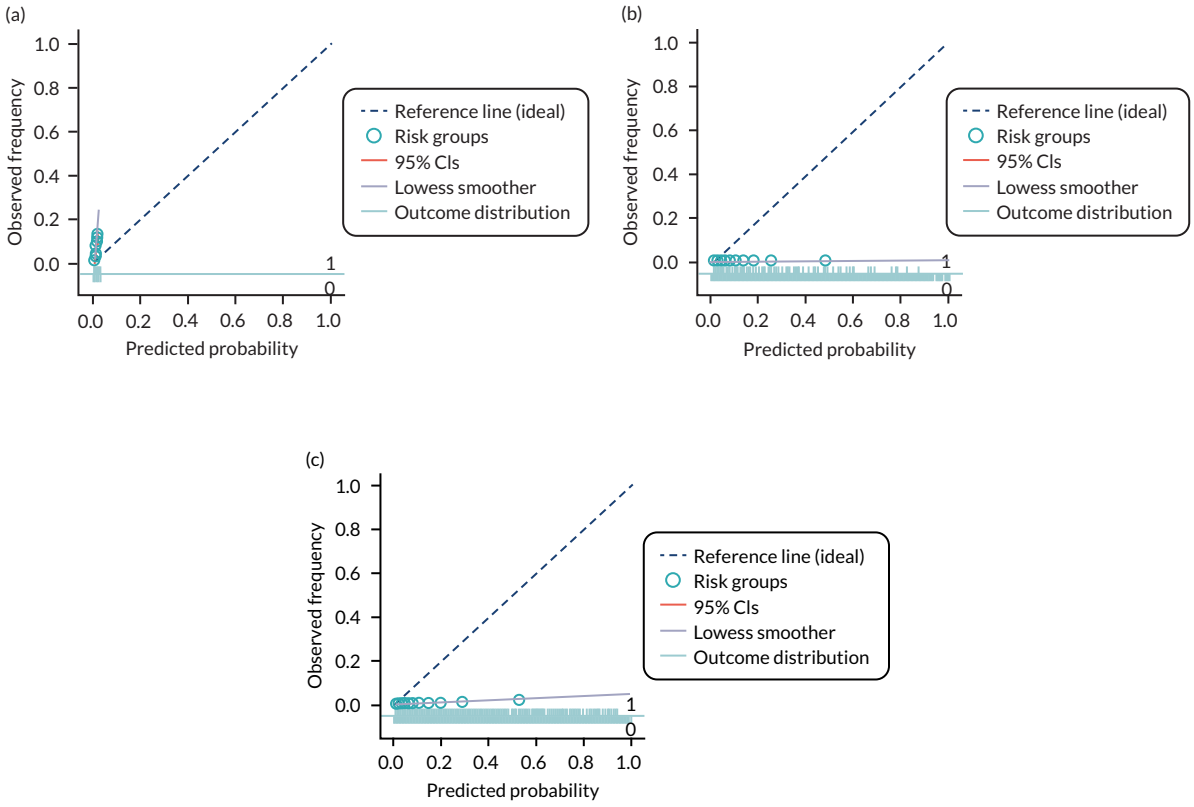


FIGURE 8 Calibration plots for models predicting early-onset pre-eclampsia using first-trimester clinical characteristics marker in data sets with > 100 outcome events. (a) Model 8[115] in Poston 2006;[150] (b) model 10[230] in St George's;[163] and (c) model 10[230] in AMND.[114]

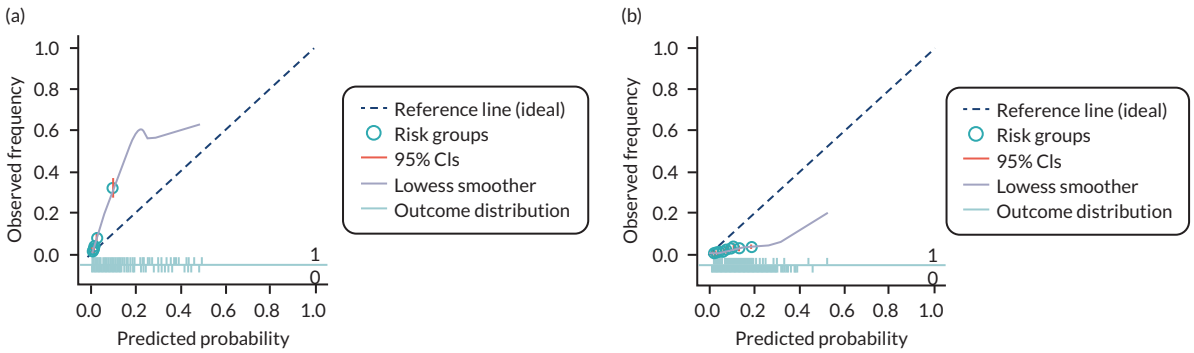


FIGURE 9 Calibration plots for models predicting late-onset pre-eclampsia using first-trimester clinical characteristics marker in data sets with > 100 outcome events. (a) Model 16[229] in POP;[161] (b) model 17[230] in ALSPAC;[103] (c) model 17[230] in St George's;[163] (d) model 17[230] in AMND;[114] and (e) model 17[230] in POP.[161] (*continued*)

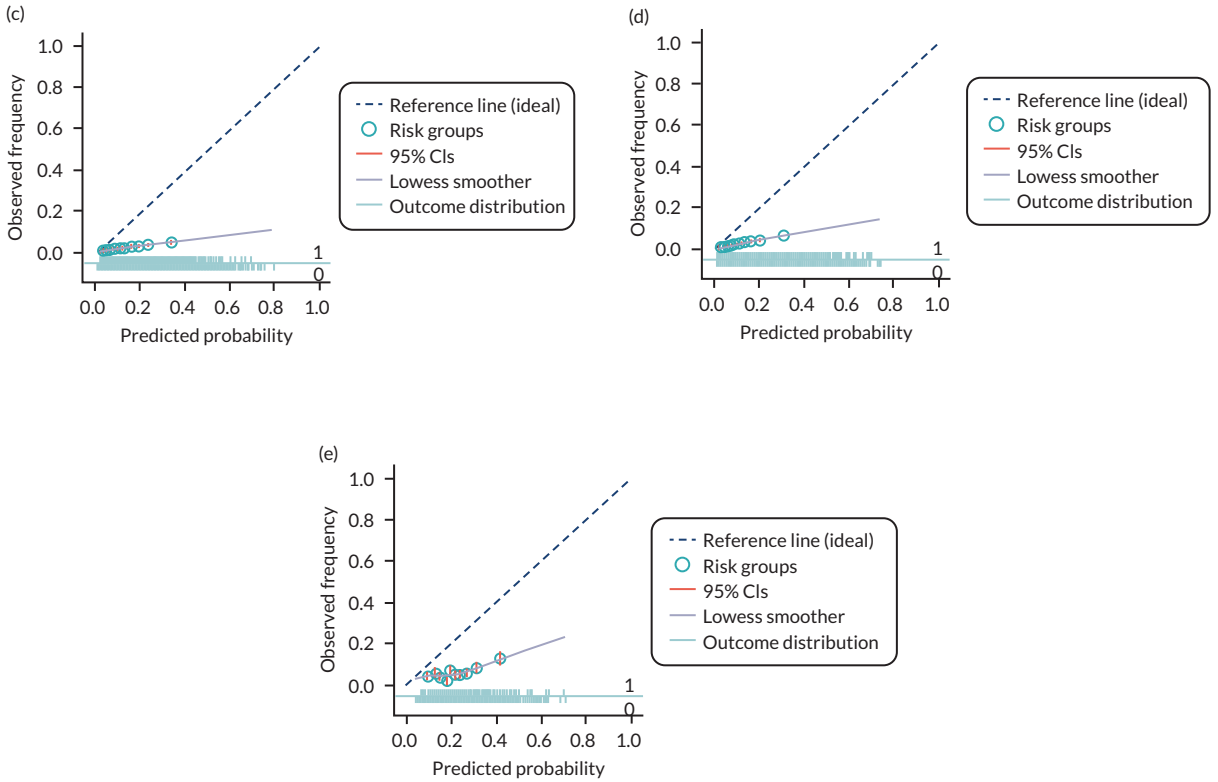


FIGURE 9 Calibration plots for models predicting late-onset pre-eclampsia using first-trimester clinical characteristics marker in data sets with > 100 outcome events. (a) Model 16[229] in POP;[161] (b) model 17[230] in ALSPAC;[103] (c) model 17[230] in St George's;[163] (d) model 17[230] in AMND;[114] and (e) model 17[230] 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 set[161] 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.* 2015[149] 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.* 2013[230] 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*).

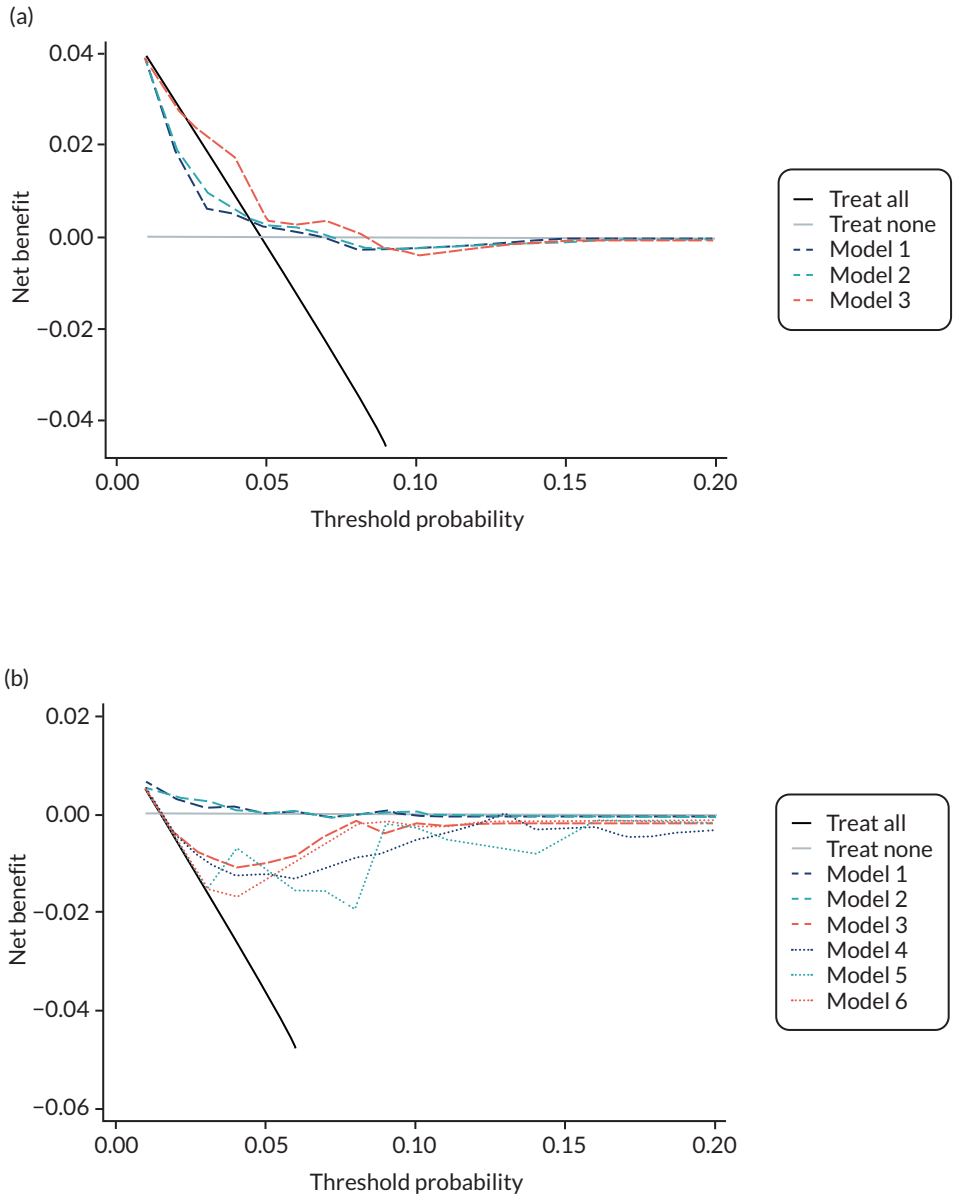


FIGURE 10 Decision curves for prediction models of any-onset pre-eclampsia in the (a) SCOPE UK,[42] (b) Allen *et al.*,[108] (c) Poston *et al.* 2015[149] and (d) POP[161] data sets. Reproduced from Snell *et al.*[52] Open Access This article is licensed under a Creative Commons Attribution 4.0 International 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*)

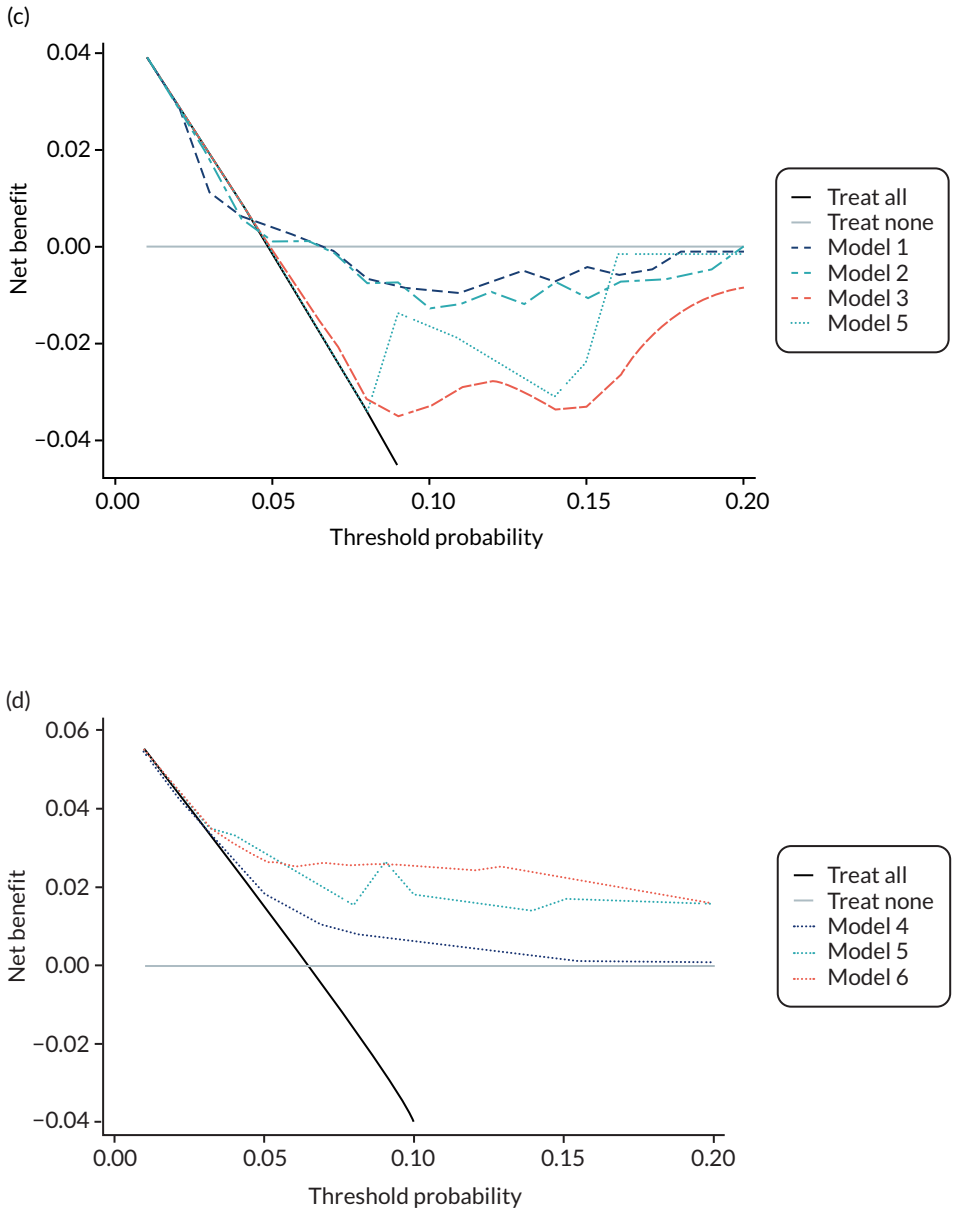


FIGURE 10 Decision curves for prediction models of any-onset pre-eclampsia in the (a) SCOPE UK,[42] (b) Allen *et al.*,[108] (c) Poston *et al.* 2015[149] and (d) POP[161] data sets. Reproduced from Snell *et al.*[52] Open Access This article is licensed under a Creative Commons Attribution 4.0 International 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.

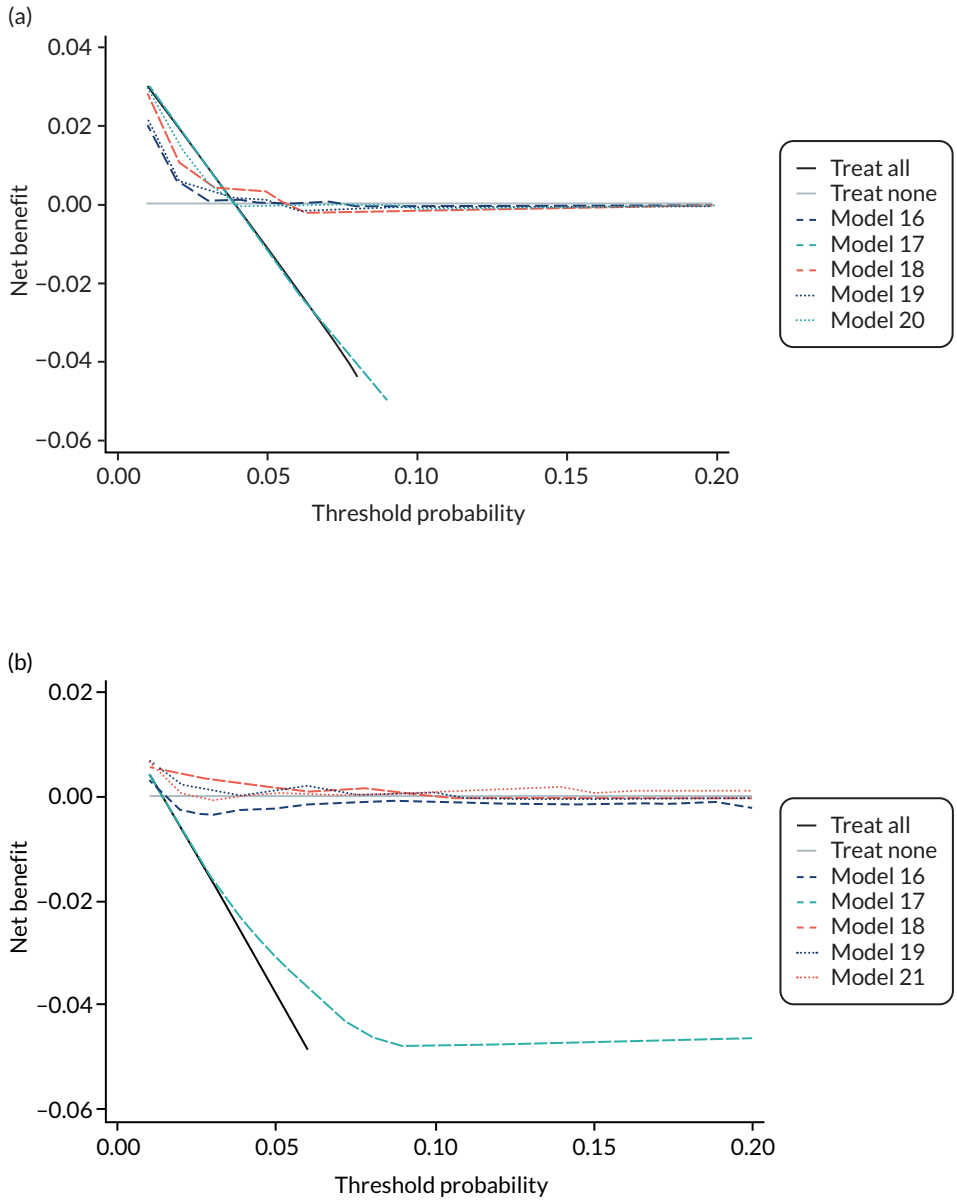


FIGURE 11 Decision curves for prediction models of late-onset pre-eclampsia in (a) SCOPE UK,[42] (b) Allen *et al.*,[108] (c) Poston *et al.* 2015[149] and (d) POP[161] data sets. Net benefit values on the *y*-axis are often best multiplied by 1000 to reveal the extra number of women who would be correctly treated per 1000 women who used the model, with none treated incorrectly. Reproduced from Snell *et al.*[52] (*continued*)

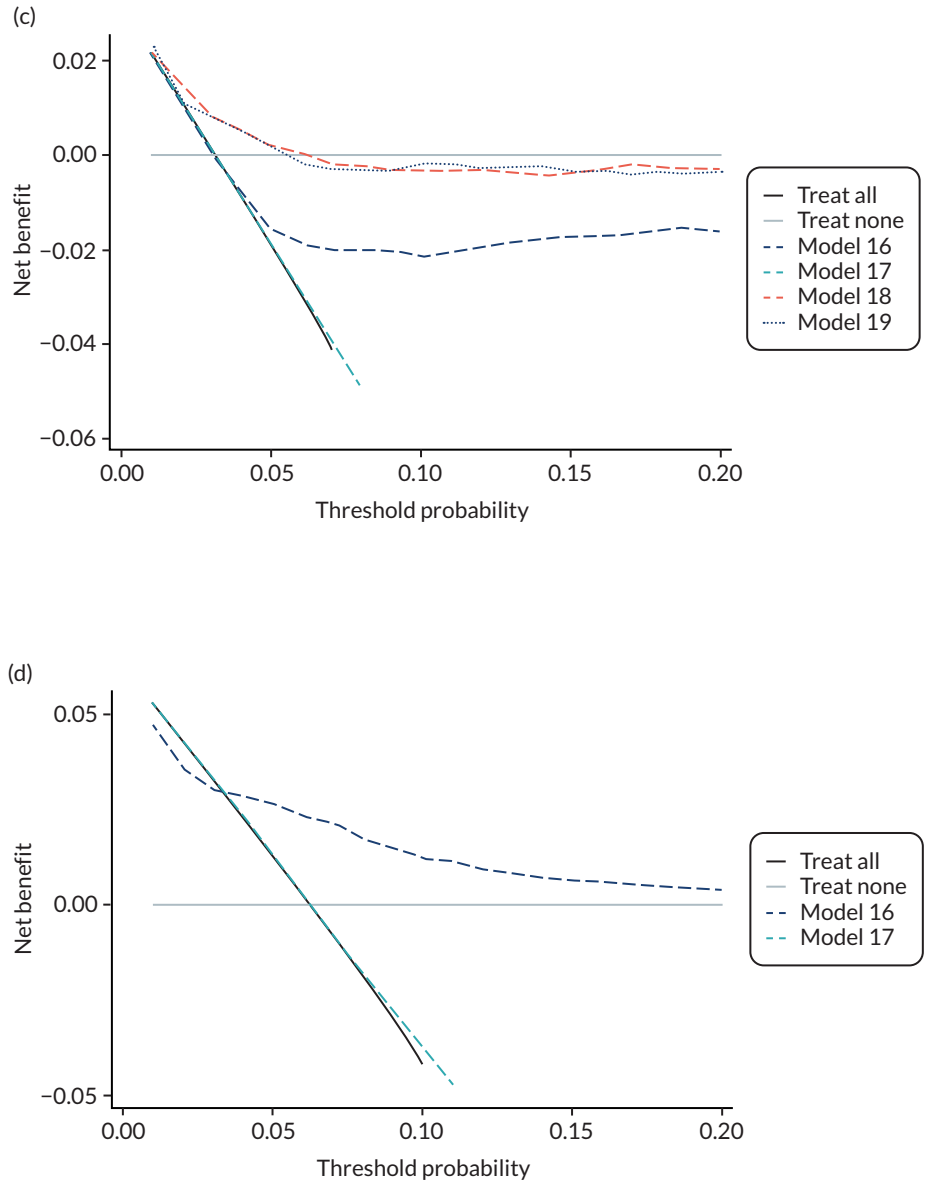


FIGURE 11 Decision curves for prediction models of late-onset pre-eclampsia in (a) SCOPE UK,[42] (b) Allen *et al.*,[108] (c) Poston *et al.* 2015[149] and (d) POP[161] data sets. Net benefit values on the *y*-axis are often best multiplied by 1000 to reveal the extra number of women who would be correctly 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	PlGF (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 POUCH[131] (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 *et al.*[108] (*N* = 1045)	Poston *et al.* 2015[149] (*N* = 1554)	Baschat *et al.*[115] (*N* = 1704)	Antsaklis *et al.*[110] (*N* = 3328)	WHO[175] (*N* = 7273)	NICH LR[159] (*N* = 3097)	POUCH[131] (*N* = 3019)	van Kuijk *et al.* 2014[166] (*N* = 230)	STORK G[135] (*N* = 812)	Vinter *et al.*[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 *et al.*[108] (*N* = 1045)	Poston *et al.* 2015[149] (*N* = 1554)	Baschat *et al.*[115] (*N* = 1704)	Antsaklis *et al.*[110] (*N* = 3328)	WHO[175] (*N* = 7273)	NICH LR[159] (*N* = 3097)	POUCH[131] (*N* = 3019)	van Kuijk *et al.* 2014[166] (*N* = 230)	STORK G[135] (*N* = 812)	Vinter *et al.*[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 PlGF	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 PlGF	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 POUCH[131] 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(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(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 $(BMI/10)^{-2}$. 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.

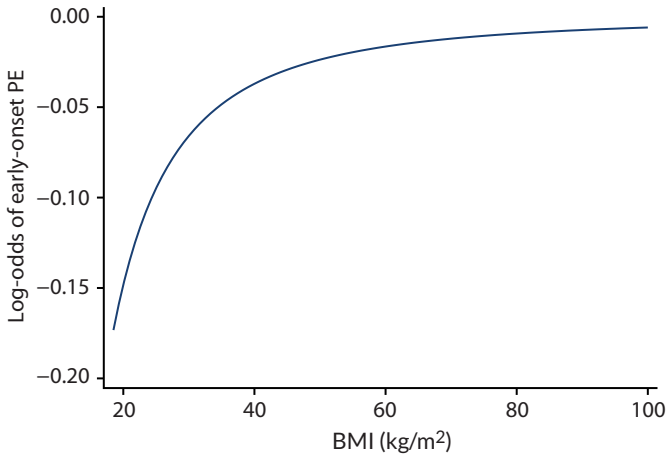


FIGURE 12 Relationship between first-trimester BMI and risk of early-onset pre-eclampsia when using $(BMI/10)^{-2}$ transformation.

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

	Any-onset PE			Early-onset PE			Late-onset PE		
Variable	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

	Any-onset PE			Early-onset PE			Late-onset PE		
Variable	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 $(BMI/10)^{-2}$ 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 $(BMI/10)^{-2}$ 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(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(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											
First-trimester models											
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
Second-trimester models											
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											
First-trimester models											
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
Second-trimester models											
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											
First-trimester models											
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
Second-trimester models											
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

	Prediction from first-trimester predictors			Prediction from second-trimester predictors		
Variable	Any-onset PE	Early-onset PE	Late-onset PE	Any-onset PE	Early-onset PE	Late-onset PE
sFlt-1	✓	✓	✓		✓ (ln)	
PAPP-A						
PlGF	✓		✓	✓	✓ (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

	Any-onset PE			Early-onset PE			Late-onset PE		
Variable	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
PlGF	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

	Any-onset PE			Early-onset PE			Late-onset PE		
Variable	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(sFlt-1 + 0.5)[a]				1.581 (1.100 to 2.271)	0.458	0.013			
PlGF or ln(PlGF + 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(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

	Number of			C-statistic			Calibration slope			Calibration-in-the-large		
Model	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								
First-trimester models								
1	Clinical	Logit(p) = −6.5297 − 0.0151 × age + 0.0156 × SBP + 0.0370 × BMI + 0.9287 × nulliparous + 1.2574 × previous PE + 1.5019 × renal disease + 1.5689 × hypertension + 0.3578 × 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 × age + 0.0142 × SBP + 0.0373 × BMI + 1.0232 × nulliparous + 1.2163 × previous PE + 0.8620 × renal disease + 2.0191 × hypertension + 0.0191 × diabetes − 0.000218 × sFlt-1 − 0.00478 × PlGF	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]
Second-trimester models								
1. 4	Clinical	Logit(p) = −8.0909 − 0.0165 × age + 0.0108 × SBP + 0.0198 × DBP + 0.0614 × BMI + 0.9616 × nulliparous + 1.4068 × previous PE + 0.9700 × renal disease + 1.7763 × 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 × age + 0.0185 × SBP − 0.0083 × DBP + 0.0668 × BMI + 2.0169 × nulliparous + 1.7592 × previous PE + 1.3675 × renal disease + 2.3073 × hypertension − 0.00262 × PlGF	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								
First-trimester models								
2	Clinical	Logit(p) = −7.9161 − 0.0360 × age − 0.0176 × SBP + 0.0753 × DBP − 0.5937 × $(BMI/10)^{-2}$ + 1.7440 × previous PE + 2.2795 × renal disease + 0.5486 × hypertension + 1.7185 × 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 × age + 0.0555 × SBP − 0.0040 × DBP − 0.0069 × BMI + 1.5442 × previous PE + 1.5372 × renal disease + 0.8644 × hypertension − 0.000535 × 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
Second-trimester models								
5	Clinical	Logit(p) = −10.1805 + 0.0647 × DBP + 2.3643 × previous PE + 1.4929 × renal disease + 1.1445 × 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	Logit(p) = −9.7075 + 0.0705 × DBP + 2.5467 × previous PE + 3.3965 × renal disease + 1.2447 × autoimmune disease + 0.4942 × ln(sFlt-1 + 0.5) − 1.0661 × ln(PlGF + 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]
Late-onset pre-eclampsia								
First-trimester models								
3	Clinical	Logit(p) = −6.7280 − 0.0138 × age + 0.0150 × SBP + 0.0355 × BMI + 1.0363 × nulliparous + 1.1159 × previous PE + 1.2487 × renal disease + 1.6863 × 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	Logit(p) = −5.4124 − 0.0210 × age + 0.0076 × SBP + 0.0434 × BMI + 1.2077 × nulliparous + 1.0260 × previous PE + 0.6499 × renal disease + 2.0344 × hypertension − 0.000171 × sFlt-1 − 0.0051 × PlGF	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]
Second-trimester models								
6	Clinical	Logit(p) = −8.0911 − 0.0137 × age + 0.0104 × SBP + 0.0124 × DBP + 0.0647 × BMI + 1.1891 × nulliparous + 1.1650 × previous PE + 0.7569 × renal disease + 1.9032 × 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	Logit(p) = −7.7252 − 0.0189 × age + 0.0171 × SBP − 0.0136 × DBP + 0.0687 × BMI + 2.3770 × nulliparous + 1.6232 × previous PE + 1.2194 × renal disease + 2.2762 × hypertension − 0.00245 × PlGF	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]

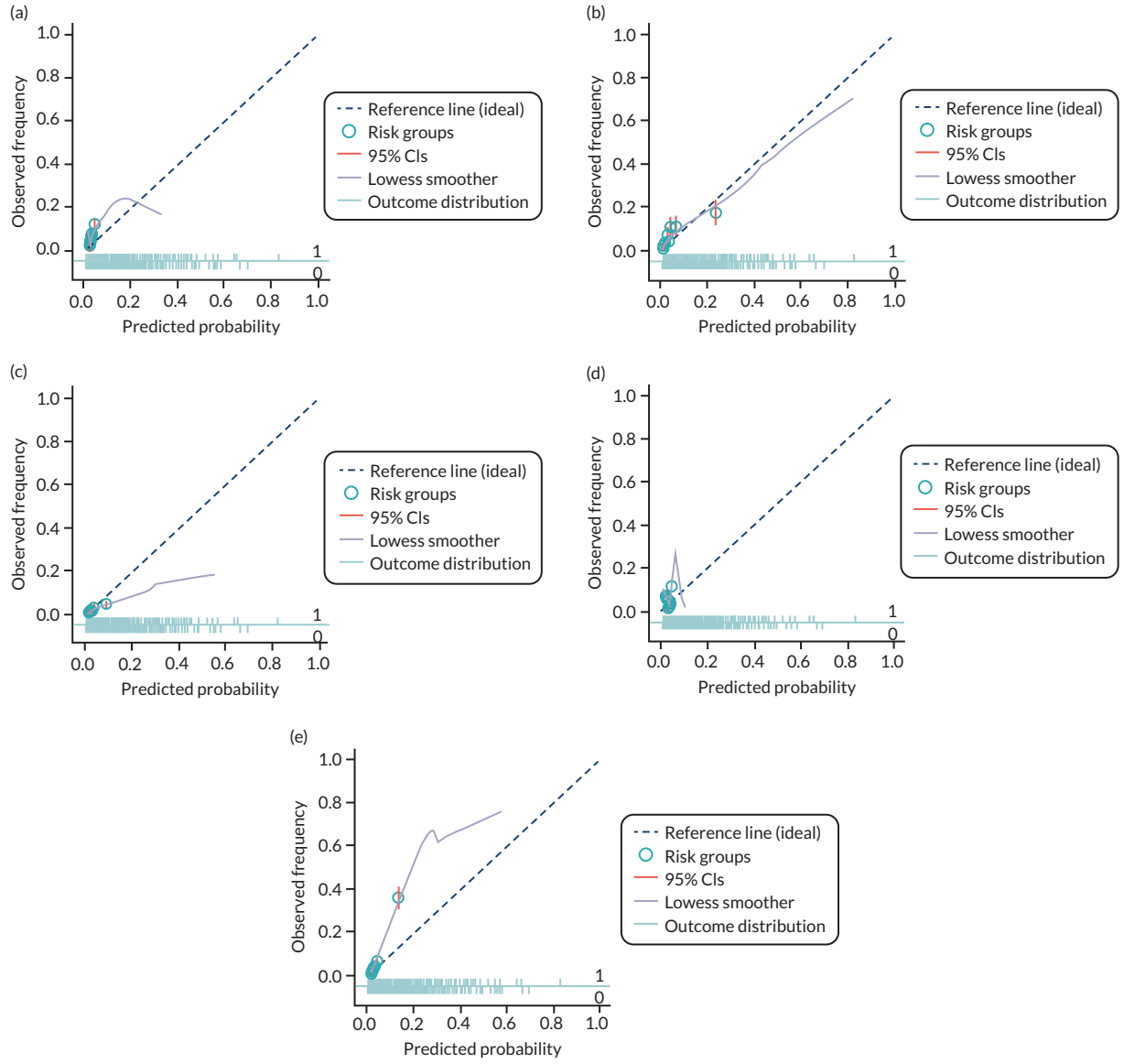


FIGURE 13 Calibration plots for the final (shrunken) model predicting any-onset pre-eclampsia using first-trimester clinical characteristics, in data sets (with > 100 events) used in the development and validation of the model. (a) SCOPE;[42] (b) Baschat;[115] (c) WHO;[175] (d) NICH LR;[159] and (e)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

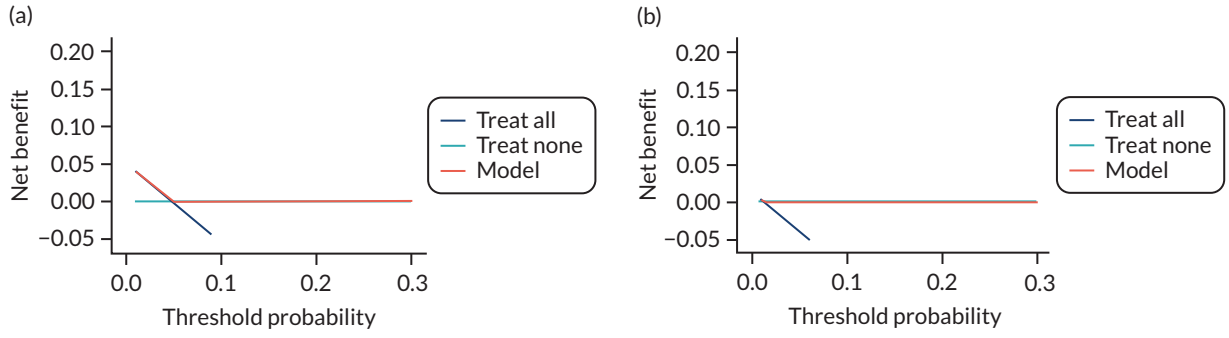


FIGURE 14 Decision curves for the final (shrunken) model predicting any pre-eclampsia using first-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) Allen *et al.*;[108] (c) Poston *et al.* 2015;[149] (d) Baschat *et al.*;[115] (e) 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*)

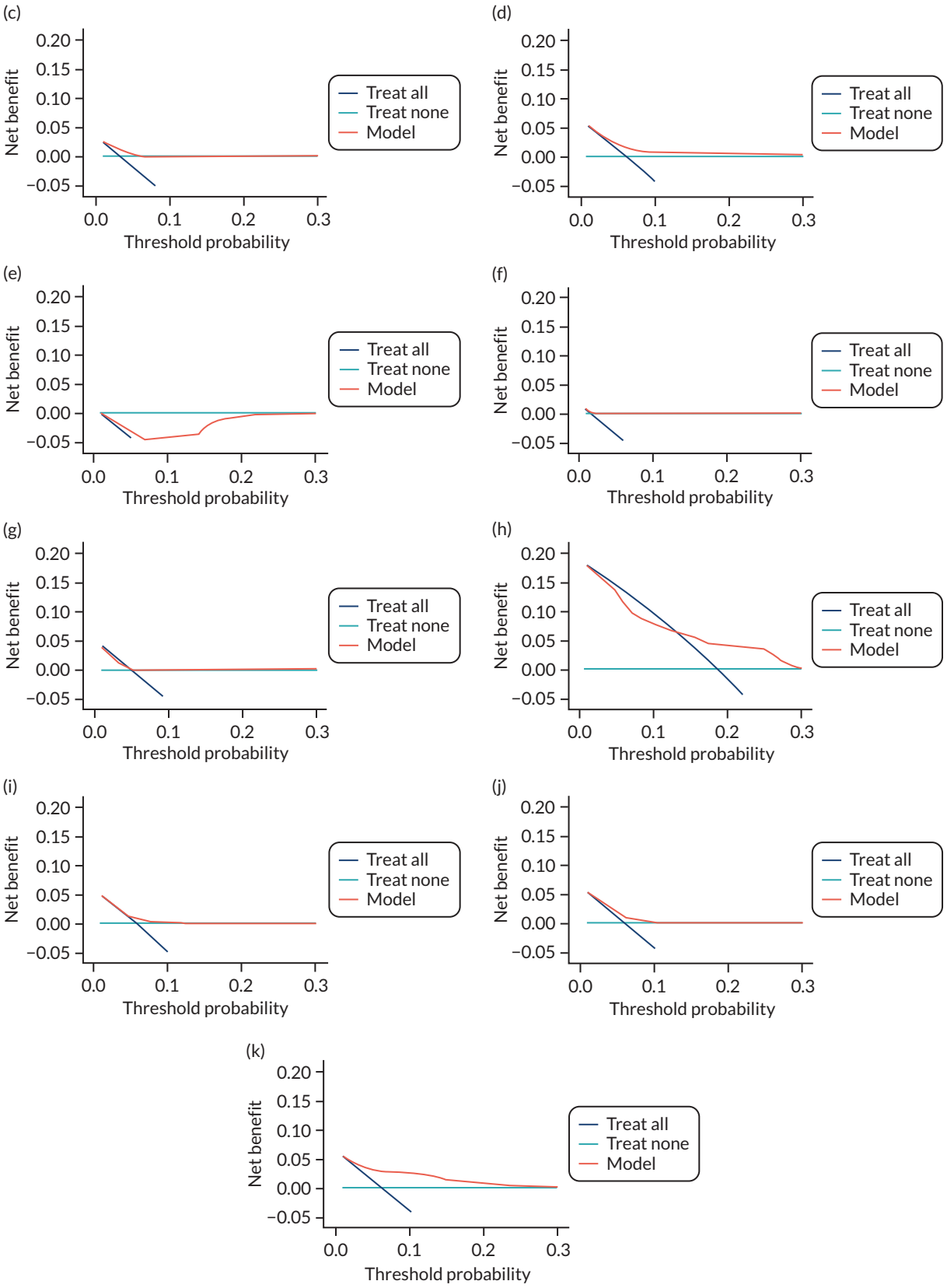


FIGURE 14 Decision curves for the final (shrunken) model predicting any pre-eclampsia using first-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) Allen *et al.*;[108] (c) Poston *et al.* 2015;[149] (d) Baschat *et al.*;[115] (e) 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.

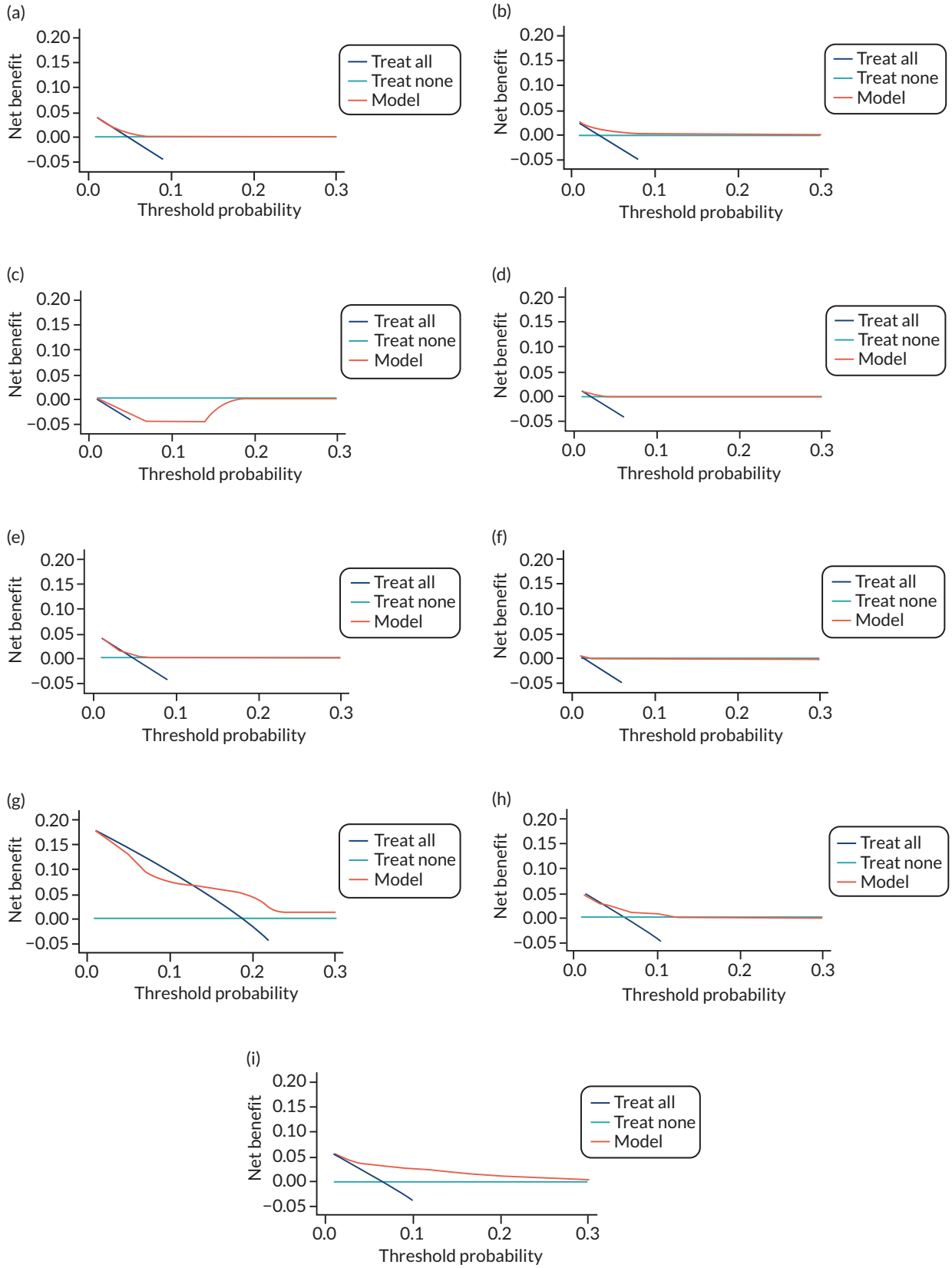


FIGURE 15 Decision curves for the final (shrunken) model predicting any pre-eclampsia using second-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) Poston *et al.* 2015;[149] (c) Antsaklis *et al.*;[110] (d) WHO;[175] (e) NICH LR;[159] (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.

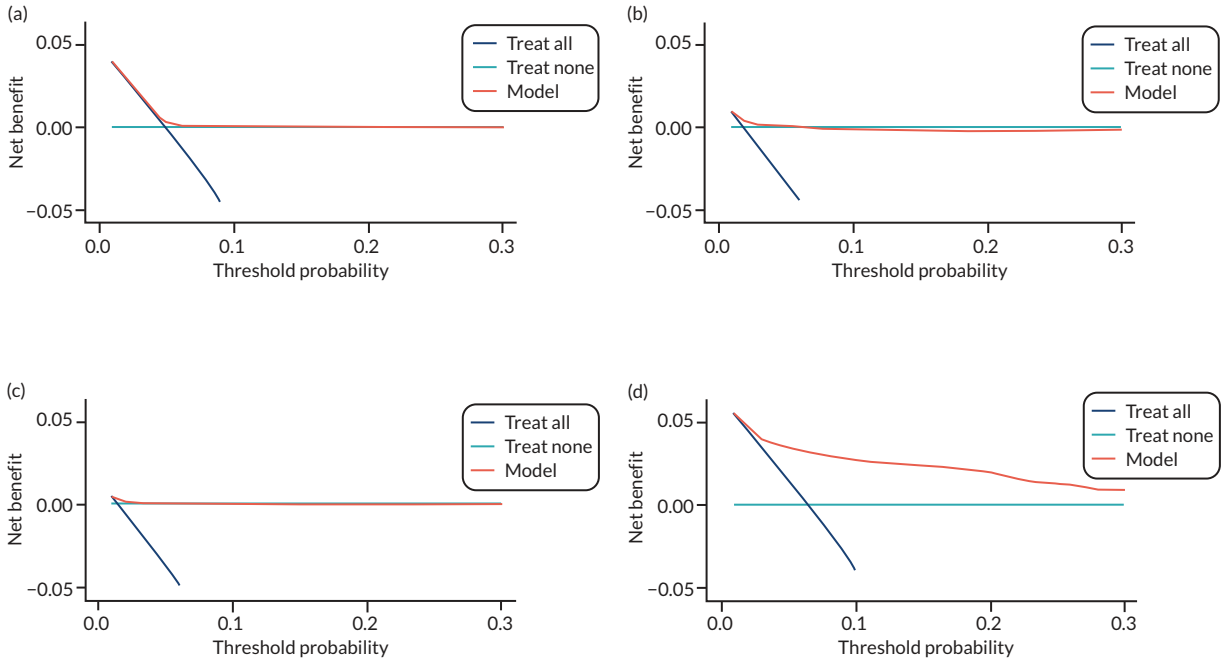


FIGURE 16 Decision curves for the final (shrunken) model predicting any pre-eclampsia using first-trimester clinical characteristics and biochemical markers, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) WHO;[175] (c) POUCH;[131] and (d) POP.[161] Net benefit values 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.

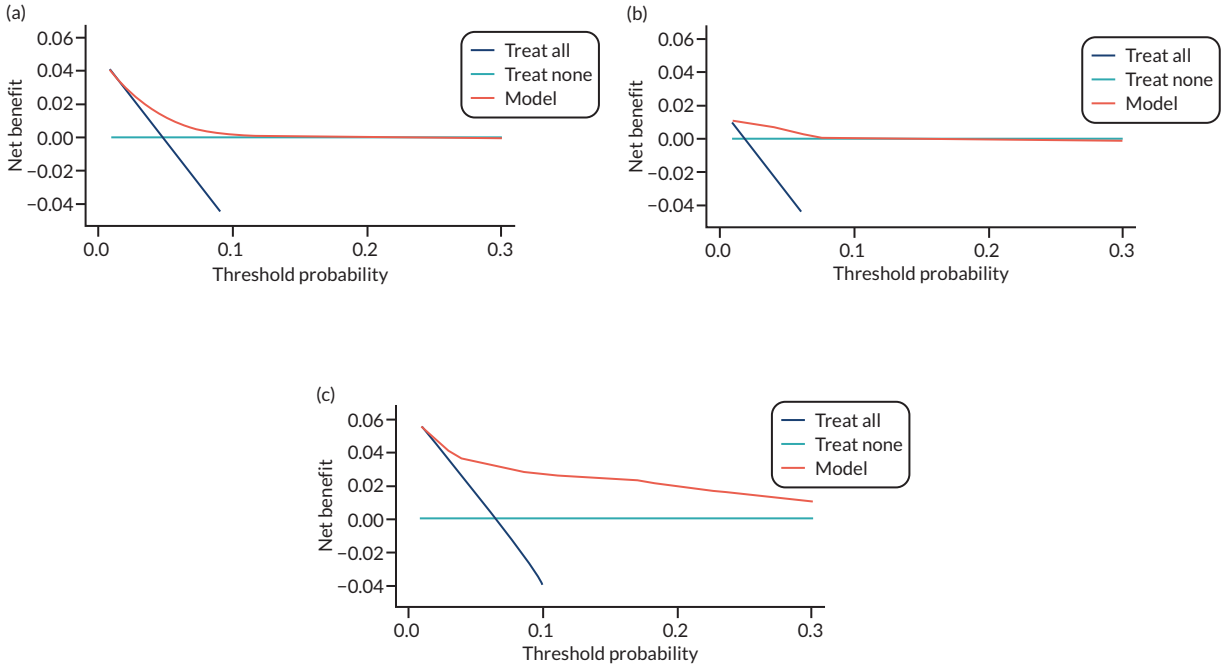


FIGURE 17 Decision curves for the final (shrunken) model predicting any pre-eclampsia using second-trimester clinical characteristics and biochemical markers, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) WHO;[175] and (c) POP.[161] Net benefit values are often 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 POP[161] cohorts. The model shows little benefit or harm in SCOPE,[42] Allen *et al.*,[108] Antsaklis *et al.*,[110] WHO[175] and NICH LR.[159] Using second-trimester clinical characteristics (model 4) shows some improvement in net benefit in SCOPE[161] 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 POP[161] but little improvement in the SCOPE[42] or WHO[175] 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 SCOPE[42] and POP[161] 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, PlGF, 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 (%)
Maternal clinical characteristics					
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 ≥ 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					
PlGF trimester 1	15	0.08	0.02 to 0.35	0.00 to 5.94	55.69
PlGF 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 PlGF, 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, PlGF, sFlt-1 and PAPP-A.[239]

Heterogeneity for predictors varied considerably, and ranged from 0% to 97% for PlGF. 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; $I^2 = 60.11\%$), 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 PlGF 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, PlGF, 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 (%)
Maternal clinical characteristics					
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; $I^2 = 20.77\%$), 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; $I^2 = 95.16\%$), first-trimester (OR 0.33, 95% CI 0.16 to 0.68; $I^2 = 82.67\%$), second-trimester (OR 0.81, 95% CI 0.69 to 0.94; $I^2 = 76.39\%$) or third-trimester (OR 0.68, 95% CI 0.57 to 0.81; $I^2 = 93.60\%$) measurement of PlGF and sFlt-1 measured in the first trimester (OR 0.98, 95% CI 0.97 to 0.99; $I^2 = 37.07\%$), 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 PlGF 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.* model[42] for any-onset pre-eclampsia, the Poon 2009 model[234] for early-onset pre-eclampsia and the Akolekar *et al.* model[241] 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 Excellence[242] in the UK and by the American College of Obstetricians and Gynecologists[73] 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 trial[34] 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.

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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])

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 $\geq$ 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
PlGF	'PlGF (continuous)'	
	'PlGF trimester 1 (continuous)'	
	'PlGF trimester 2 (continuous)'	
	'PlGF 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)'	
PlGF MoM	'PlGF MoM (continuous)'	
	'PlGF MoM trimester 1 (continuous)'	
	'PlGF MoM trimester 2 (continuous)'	
	'PlGF 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)	10388 (19.4)	5 (0)	1528 (2.9)	555 (1)	29318 (53.8)	0 (0)	1492 (2.7)	152 (0.3)	1340 (2.5)
PARIS[112]	35,955	34,609	23.6 (6.1), 11–48	–	–	–	–	–	–	–	19793 (57.5)	6086 (18.5)	2928 (8.8)	498 (1.5)	2403 (7.2)
AMND[114]	138,967	136,635	28.4 (5.6), 13–56	23.9 [5.5], 10–72.1	–	–	–	–	–	–	65206 (47.7)	0 (0)	5194 (3.7)	1329 (1)	3865 (2.8)
Born in Bradford[177]	13,279	13,118	27.5 (5.6), 15–49	25.1 [7.3], 12.9–57	4443 (42.4)	212 (2)	5380 (51.4)	0 (0)	158 (1.5)	278 (2.7)	5034 (39.6)	0 (0)	334 (2.7)	0 (0)	0 (0)
Velauthar[39]	1208	1206	–	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]	4212	4212	29.9 (5.1), 16.1–48.4	24.1 [5.5], 14.7–54.7	3900 (92.6)	25 (0.6)	91 (2.2)	0 (0)	1 (0)	195 (4.6)	4212 (100)	0 (0)	273 (6.5)	10 (0.2)	263 (6.3)
Baschat[115]	1704	1704	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)

	Maternal characteristics and outcomes														
					Ethnicity, *n* (%)								Outcome, *n* (%)		
Study/data set	Total number of pregnancies	Number of singleton pregnancies	Age (years), mean (SD), range	First BMI measured, median [IQR], range	White	Black	Asian	Hispanic	Mixed	Other	Nulliparous, *n* (%)	Previous PE, *n* (%)	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)
Verlohren[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 Ontorio[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[165]	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* (%)						Nulliparous, *n* (%)	Previous PE, *n* (%)	Outcome, *n* (%)		
					White	Black	Asian	Hispanic	Mixed	Other			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)	37738 (100)	4722 (12.6)	321 (0.9)	4085 (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]	1639	1639	22.5 (4), 13–40	21.2 [4.1], 12.1–47.7	1061 (65.5)	502 (31)	0 (0)	0 (0)	0 (0)	57 (3.5)	–	–	8 (0.5)	0 (0)	8 (0.5)
Brown 2007[116]	2785	2702	29.5 (5), 15–46	–	–	–	–	–	–	–	1192 (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 $\geq$ 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 $\geq$ 30 kg/m^2	Women taking vitamin supplements containing doses of vitamin C of 200 mg or more or of vitamin E of $\geq$ 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 $\geq$ 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 Ontorio[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

	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
SCOPE[42]	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[163]	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[161]	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[167]	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)

								Ultrasound markers		Biochemical markers			Outcome		
Multiple pregnancy	History of SGA	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)	15242 (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)

	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)
JSOG[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[136]	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 Ontorio[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)

								Ultrasound markers		Biochemical markers			Outcome		
Multiple pregnancy	History of SGA	BMI	SBP	DBP	MAP	Urine dipstick	PCR	Uterine PI	Umbilical PI	PAPP-A	PlGF	sFlt-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)

	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.

								Ultrasound markers		Biochemical markers			Outcome		
Multiple pregnancy	History of SGA	BMI	SBP	DBP	MAP	Urine dipstick	PCR	Uterine PI	Umbilical PI	PAPP-A	PlGF	sFlt-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	☐	☐	☐	☐	☐
Parity	☐	☐	☐	☐	☐
Previous miscarriage	☐	☐	☐	☐	☐
Previous stillbirth	☐	☐	☐	☐	☐
Previous SGA	☐	☐	☐	☐	☐
Previous any pre-eclampsia	☐	☐	☐	☐	☐
Previous preterm delivery	☐	☐	☐	☐	☐
Previous heritable thrombophilia	☐	☐	☐	☐	☐
Previous autoimmune disease	☐	☐	☐	☐	☐
Family history of pre-eclampsia in first degree relative	☐	☐	☐	☐	☐
Family history of cardiovascular disease	☐	☐	☐	☐	☐
History of renal disease	☐	☐	☐	☐	☐

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

Diet in pregnancy	☐	☐	☐	☐	☐
Physical activity	☐	☐	☐	☐	☐
Ethnicity	☐	☐	☐	☐	☐

2. Examination *

	Very important	Important	Moderately important	Slightly important	Not important
BMI	☐	☐	☐	☐	☐
Height	☐	☐	☐	☐	☐
Weight	☐	☐	☐	☐	☐
Mean arterial pressure	☐	☐	☐	☐	☐
Systolic blood pressure	☐	☐	☐	☐	☐
Diastolic blood pressure	☐	☐	☐	☐	☐
Urine dipstick	☐	☐	☐	☐	☐
24 hour protein	☐	☐	☐	☐	☐
Protein Creatine Ratio (PCR)	☐	☐	☐	☐	☐

3. Ultrasound markers *

	Very important	Important	Moderately important	Slightly important	Not important
Crown-rump length (CRL)	☐	☐	☐	☐	☐
Estimated fetal weight centile	☐	☐	☐	☐	☐
Notching on ultrasound scan	☐	☐	☐	☐	☐
Uterine artery pulsatility index	☐	☐	☐	☐	☐

Umbilical artery pulsatility index	☐	☐	☐	☐	☐
Uterine artery resistance index	☐	☐	☐	☐	☐
Umbilical artery resistance index	☐	☐	☐	☐	☐
Abdominal circumference	☐	☐	☐	☐	☐

4. Biochemical markers *

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

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

Study/data set	Domain: participant selection				
	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				
	Appropriate data sources	Appropriate inclusion and exclusion of participants	Participant selection similar to model development study	Risk	Rationale of rating
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*)

Study/data set	Domain: participant selection				
	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 Ontorio[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*)

Study/data set	Domain: participant selection				
	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

Study/ data set	Domain: predictors					
	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*)

Study/ data set	Domain: predictors					
	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					
	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
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*)

Study/ data set	Domain: predictors					
	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					
	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
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 Ontorio[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
Cameroni[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					
	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
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								
	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
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

Study/data set	Domain: outcome								
	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*)

	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
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

Study/data set	Domain: outcome								
	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*)

	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
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

Study/data set	Domain: outcome								
	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								
	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
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

Study/data set	Domain: outcome								
	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								
	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
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

Study/data set	Domain: outcome								
	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 Ontorio[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								
	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
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

Study/data set	Domain: outcome								
	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*)

	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
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

Study/data set	Domain: outcome								
	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 (PlGF artery RI) + 1.232 (cystatin C/PlGF)	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 × (maternal age) + 6.159 × (maternal weight MoM, log) + 0.027 × (CRL) + (−0.483) × NT + 0.766 × (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 (PlGF, $\log_{10}$) + 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 (PlGF, 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 (PlGF, 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 (PlGF, 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 (PlGF, 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 (PlGF, 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/PlGF); 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 (PlGF 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 (PlGF 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 (PlGF 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
Late-onset pre-eclampsia					
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 (PlGF, $\log_{10}$) + 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 (PlGF, 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 (PlGF, 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 (PlGF, 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 (PlGF, 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 (PlGF, 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 chronic 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, $\text{logit}(p) = \text{LP}$ where the $\text{LP} = \alpha + \beta_1 \times x_1 + \beta_2 \times x_2 + \ldots$, and absolute predicted probabilities (p) can be obtained using the transformation $p = e^{\text{LP}}/(1 + e^{\text{LP}})$. 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 *et al.*[108] (*N* = 1045)	ALSPAC[103] (*N* = 14344)	Chappell *et al.*[121] (*N* = 316)	EMPOWaR[122] (*N* = 449)	Poston *et al.* 2006[150] (*N* = 2422)	Poston *et al.* 2015[149] (*N* = 1554)	St George's[163] (*N* = 54635)	AMND[114] (*N* = 136,635)	Velauthar *et al.*[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 *et al.*[108] (*N* = 1045)	ALSPAC[103] (*N* = 14344)	Chappell *et al.*[121] (*N* = 316)	EMPOWaR[122] (*N* = 449)	Poston *et al.* 2006[150] (*N* = 2422)	Poston *et al.* 2015[149] (*N* = 1554)	St George's[163] (*N* = 54635)	AMND (*N* = 136635)[114]	Velauthar *et al.*[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 *et al.*[108] (*N* = 1045)	ALSPAC[103] (*N* = 14344)	Chappell *et al.*[121] (*N* = 316)	EMPOWaR[122] (*N* = 449)	Poston *et al.* 2006[150] (*N* = 2422)	Poston *et al.* 2015[149] (*N* = 1554)	St George's[163] (*N* = 54635)	AMND (*N* = 136635)[114]	Velauthar *et al.*[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)
First-trimester any-onset pre-eclampsia models											
1	Plasencia *et al.*, 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 *et al.*[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 *et al.* 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 *et al.*, 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 *et al.*[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 *et al.* 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 *et al.*, 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 *et al.*[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 *et al.* 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 *et al.*, 2014[115]	C + B	Allen *et al.*[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 *et al.*, 2010[128]	C + B	Allen *et al.*[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 *et al.* 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 *et al.*, 2011[147]	C + B	Allen *et al.*[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 *et al.*, 2011[147]	C + U	Velauthar *et al.*[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 *et al.*, 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 *et al.* 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 *et al.*[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 *et al.*, 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 *et al.* 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 *et al.*, 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 *et al.* 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 *et al.*, 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 *et al.*[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 *et al.* 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 *et al.*, 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 *et al.* 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 *et al.*, 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 *et al.* 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 *et al.*, 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 *et al.* 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 *et al.*, 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 *et al.*, 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 *et al.*[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 *et al.*[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 *et al.* 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 *et al.*, 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 *et al.*[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 *et al.* 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 *et al.*, 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 *et al.*[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 *et al.* 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 *et al.*, 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 *et al.*[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 *et al.* 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 *et al.*, 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 *et al.*, 2009[234]	C + B	Allen *et al.*[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 *et al.*, 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 *et al.*, 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 *et al.*, 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).

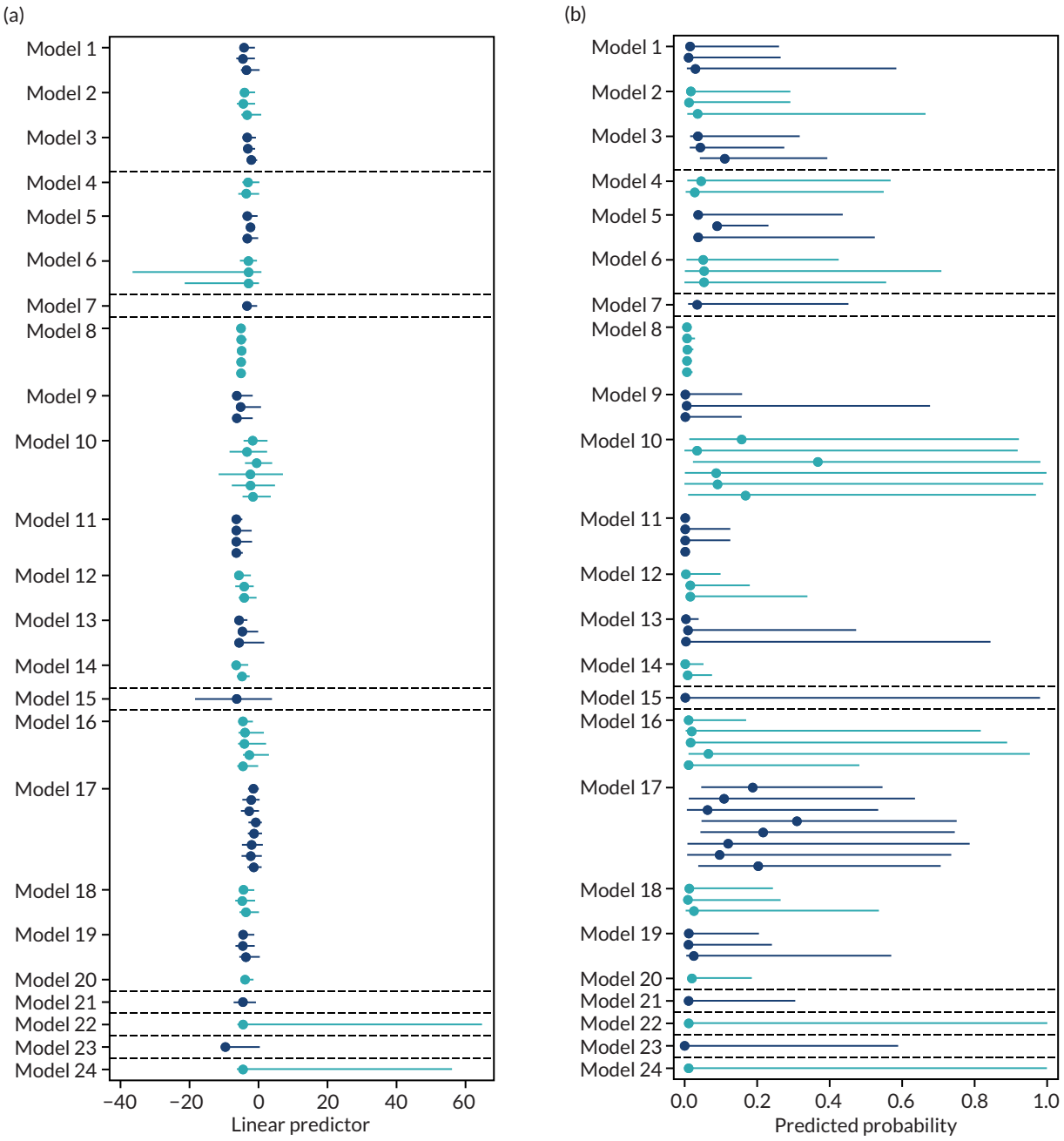


FIGURE 18 Median (dot) and range (bar) of values for (a) LP and (b) predicted probabilities across validation data sets for each model being externally validated. This figure contains information from several sources.[115,128,147,229–236,238] Reproduced from Snell *et al.*[52] Open Access This article 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
First-trimester any-onset pre-eclampsia models								
1	Plasencia *et al.*, 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 *et al.*[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 *et al.* 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 *et al.*, 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 *et al.*[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 *et al.* 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 *et al.*, 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 *et al.*[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 *et al.* 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 *et al.*, 2014[115]	C + B	Allen *et al.*[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 *et al.*, 2010[128]	C + B	Allen *et al.*[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 *et al.* 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 *et al.*, 2011[147]	C + B	Allen *et al.*[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 *et al.*, 2011[147]	C + U	Velauthar *et al.*[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
First-trimester early-onset pre-eclampsia models								
8	Baschat *et al.*, 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 *et al.* 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 *et al.*[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 *et al.*, 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 *et al.* 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 *et al.*, 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 *et al.* 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 *et al.*, 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 *et al.*[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 *et al.* 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)

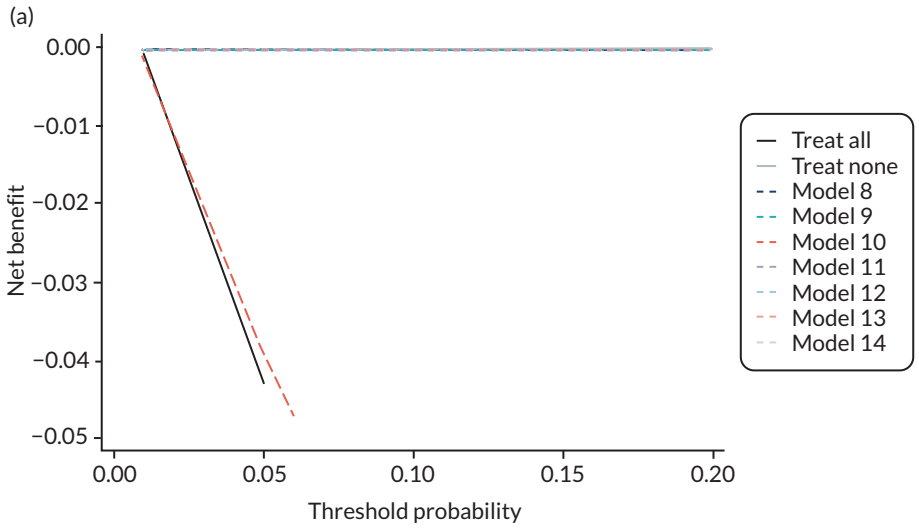
Model number	Authors, year	Type of predictors	Validation cohort	*N*	Events,[a] *n* (%)	Performance statistic (95% CI)		
						C-statistic	Calibration slope	Calibration-in-the-large
12	Poon *et al.*, 2010[232]	C	SCOPE UK[42]	658	6 (0.9)	0.524 (0.355 to 0.687)	0.236 (–1.154 to 1.627)	0.648 (–0.163 to 1.458)
			Poston *et al.* 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 *et al.*, 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 *et al.* 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 *et al.*, 2015[236]	C	Velauthar *et al.*[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 *et al.*, 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 *et al.*, 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 *et al.*[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 *et al.*[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 *et al.* 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 *et al.*, 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 *et al.*[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 *et al.* 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)

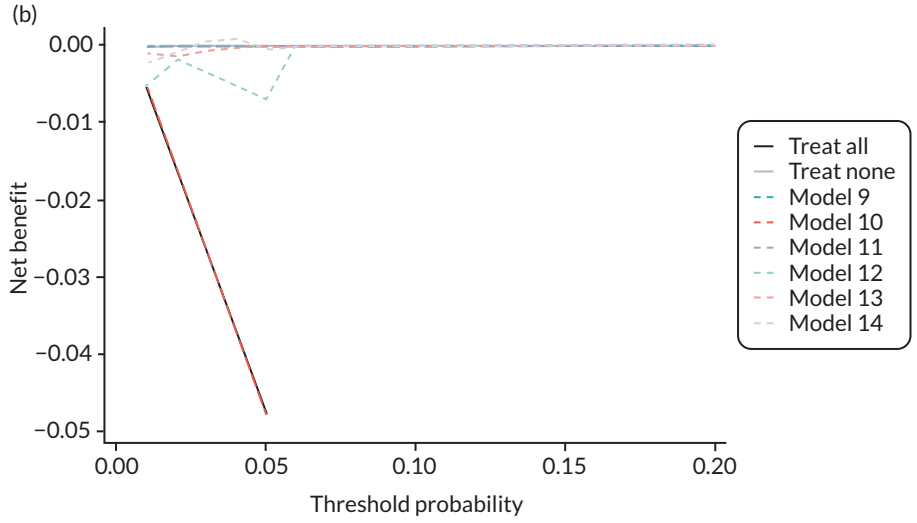
Model number	Authors, year	Type of predictors	Validation cohort	*N*	Events,[a] *n* (%)	Performance statistic (95% CI)		
						C-statistic	Calibration slope	Calibration-in-the-large
			St George's[163]	54,635	1336 (2.4)	0.636 (0.621 to 0.651)	0.632 (0.560 to 0.704)	−1.970 (−2.025 to −1.915)
			AMND[114]	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)
18	Plasencia *et al.*, 2007[231]	C	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 *et al.*[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)
			Poston *et al.* 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)
19	Poon *et al.*, 2010[232]	C	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 *et al.*[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)
			Poston *et al.* 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)
20	Scazzocchio *et al.*, 2013[235]	C	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 *et al.*, 2009[234]	C + B	Allen *et al.*[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 *et al.*, 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 *et al.*, 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 *et al.*, 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

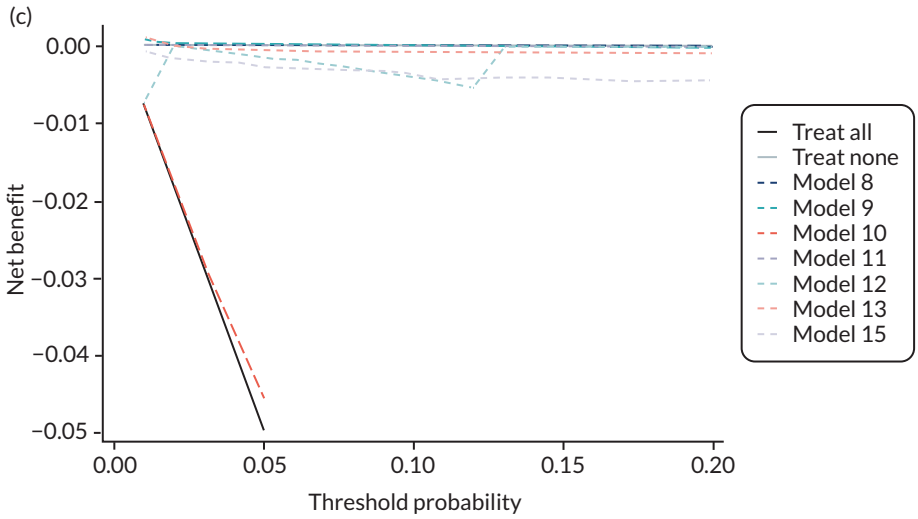
C, clinical characteristics; C + B, clinical and biochemical markers; C + U, clinical characteristics and ultrasound markers; NE, not estimable due to perfect prediction (same predicted probability for all individuals that had the event).

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.* 2015[149] and (c) POP[161]






(c)
0.00
−0.01
−0.02
−0.03
−0.04
−0.05
Net benefit
0.00
0.05
0.10
0.15
0.20
Threshold probability
Treat all
Treat none
Model 8
Model 9
Model 10
Model 11
Model 12
Model 13
Model 15

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.

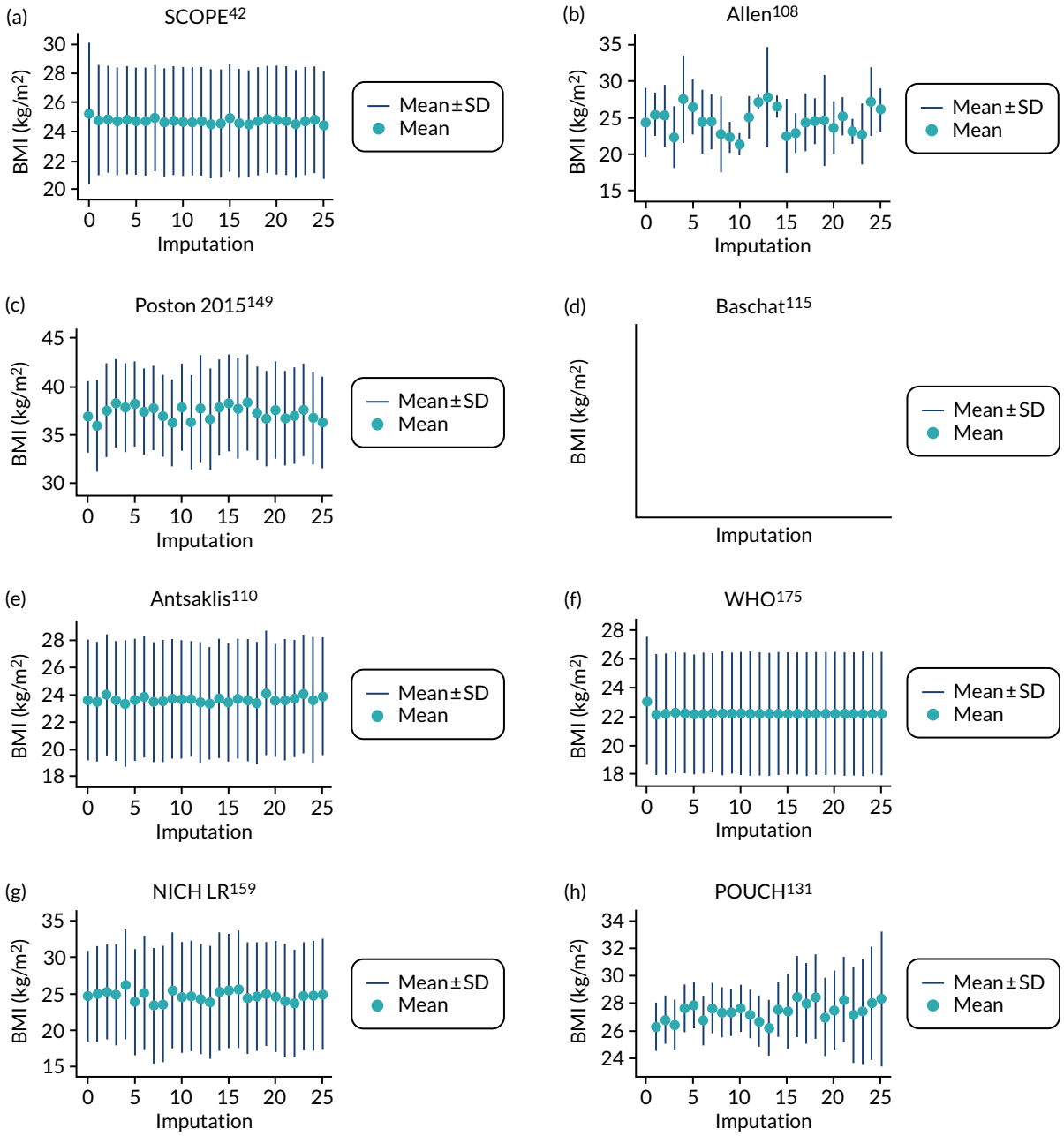


FIGURE 19 Median and range of BMI values in imputed data set for cohorts included in the development of models with trimester 1 clinical characteristics. (*continued*)

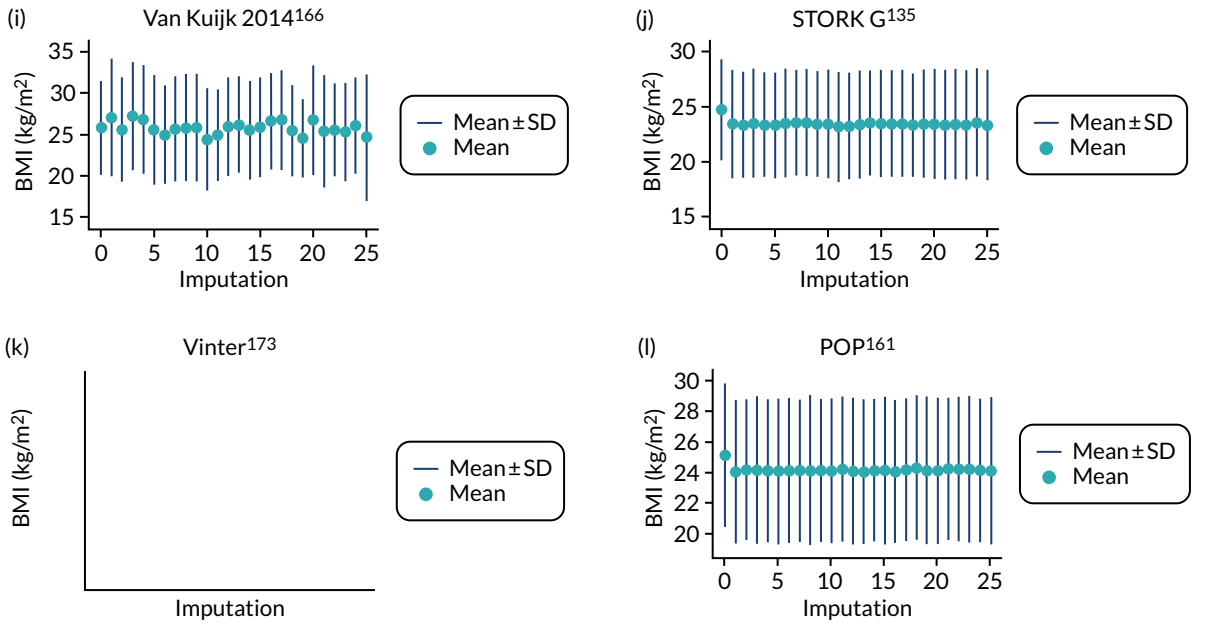


FIGURE 19 Median and range of BMI values in imputed data set for cohorts included in the development of models with trimester 1 clinical characteristics.

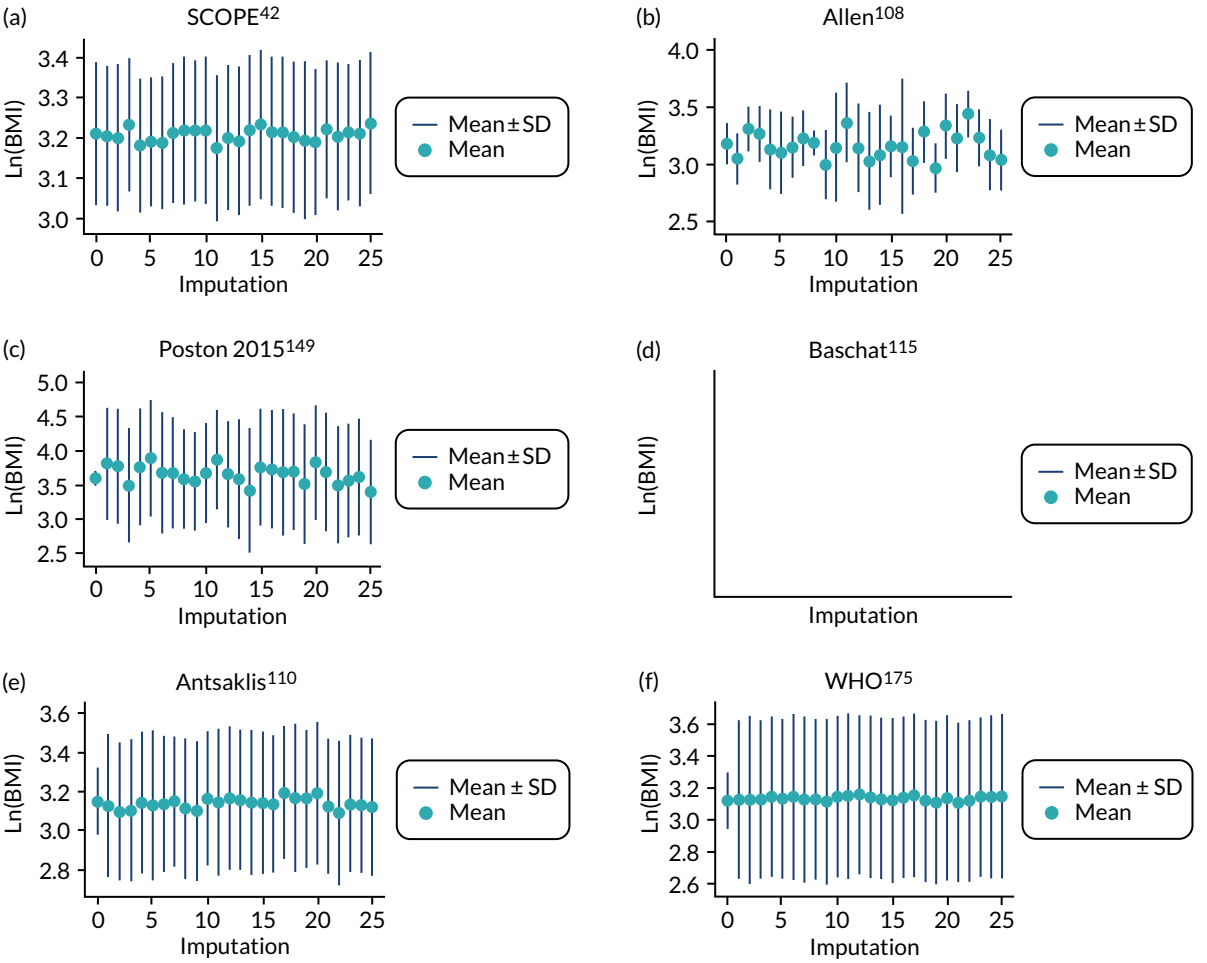


FIGURE 20 Median and range of ln(BMI) values in imputed data set for cohorts included in the development of models with trimester 1 clinical characteristics. (*continued*)

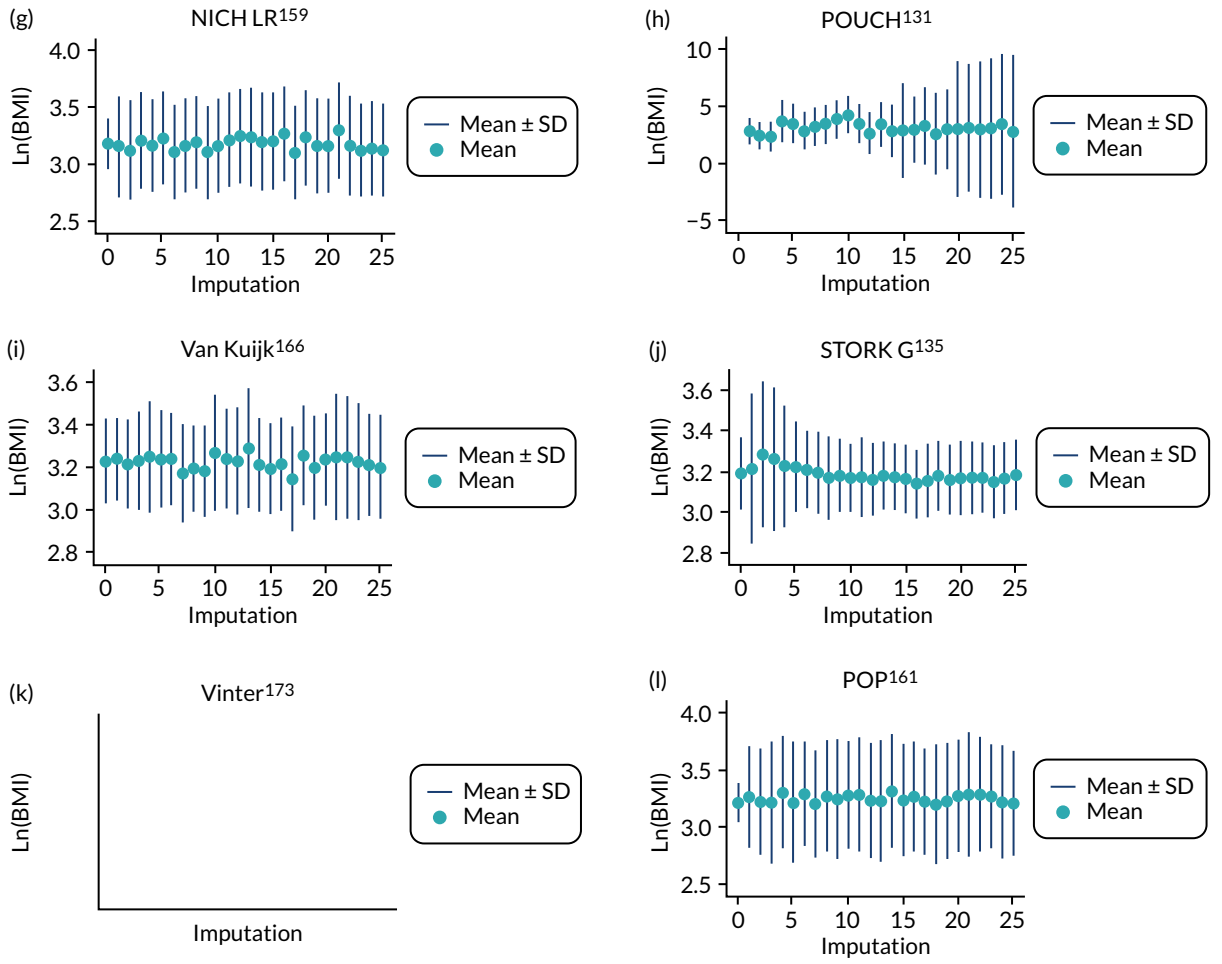


FIGURE 20 Median and range of ln(BMI) values in imputed data set for cohorts included in the development of models with trimester 1 clinical characteristics.

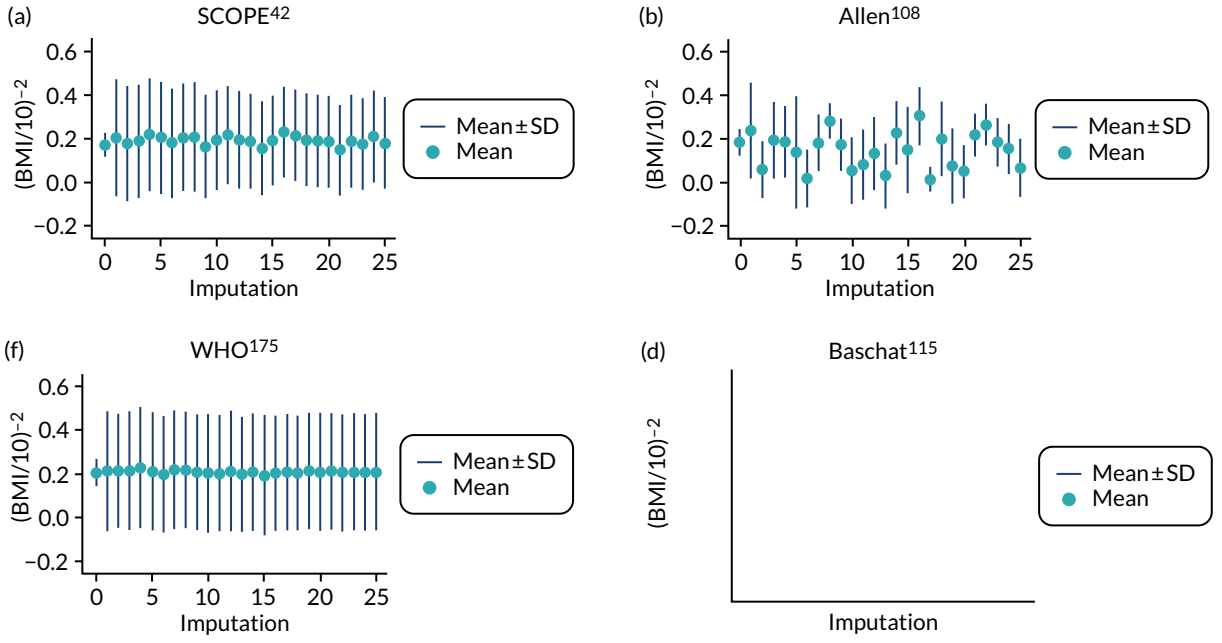


FIGURE 21 Median and range of $(BMI/10)^{-2}$ values in imputed data set for cohorts included in the development of models with trimester 1 clinical characteristics. (*continued*)

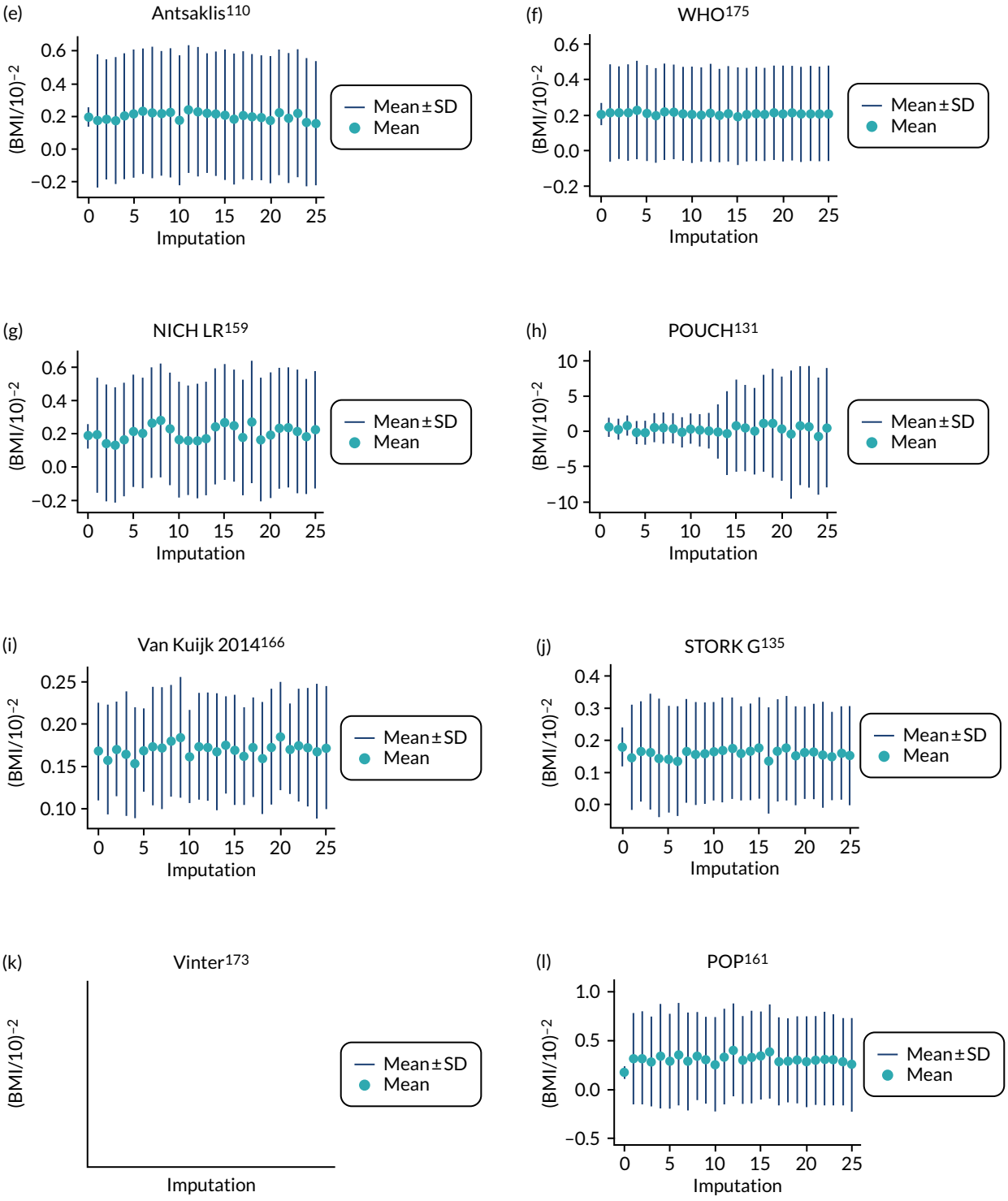


FIGURE 21 Median and range of (BMI/10)$^{-2}$ values in imputed data set for cohorts included in the development of models with trimester 1 clinical characteristics.

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).

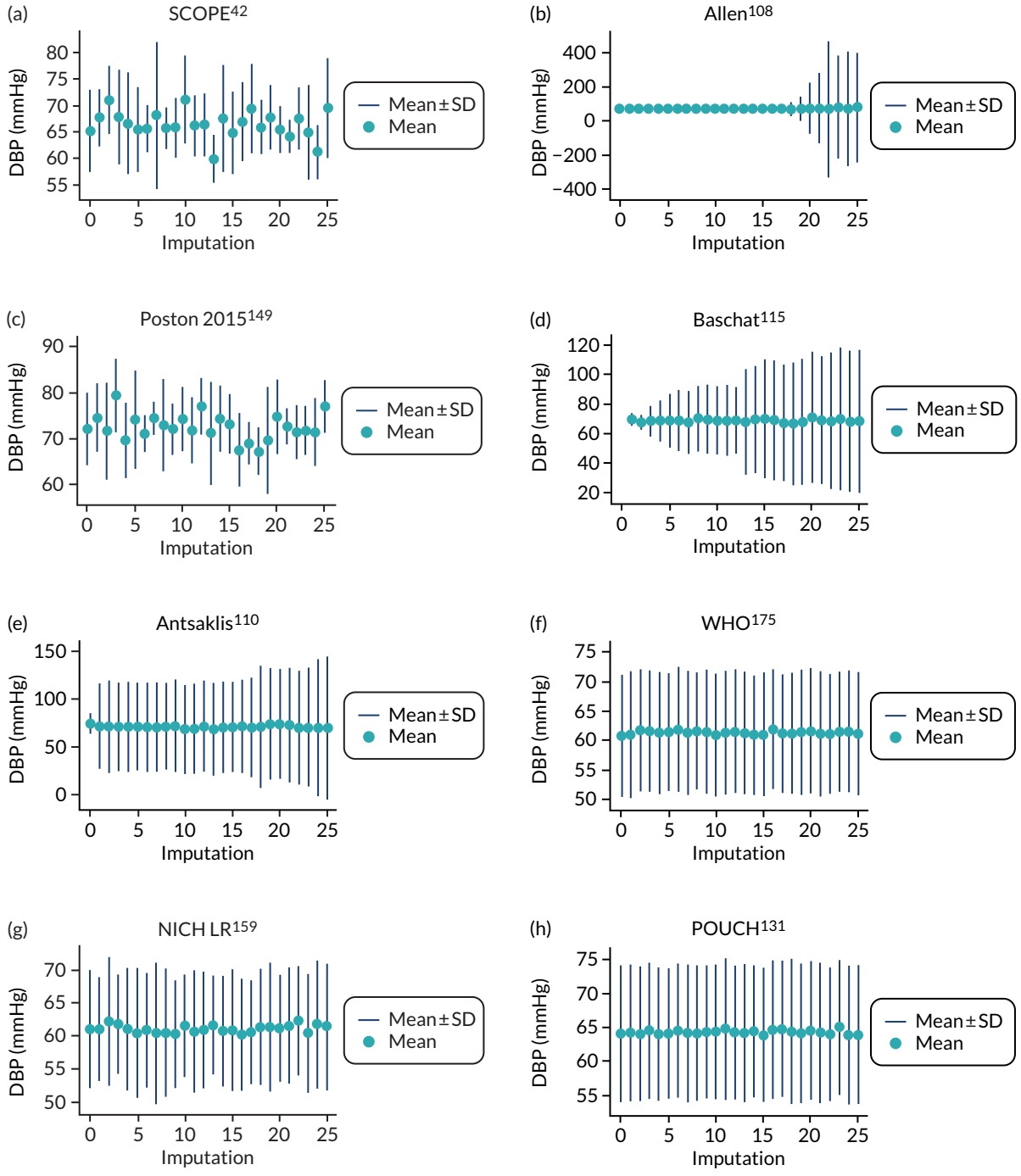


FIGURE 22 Median and range of DBP values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics. (*continued*)

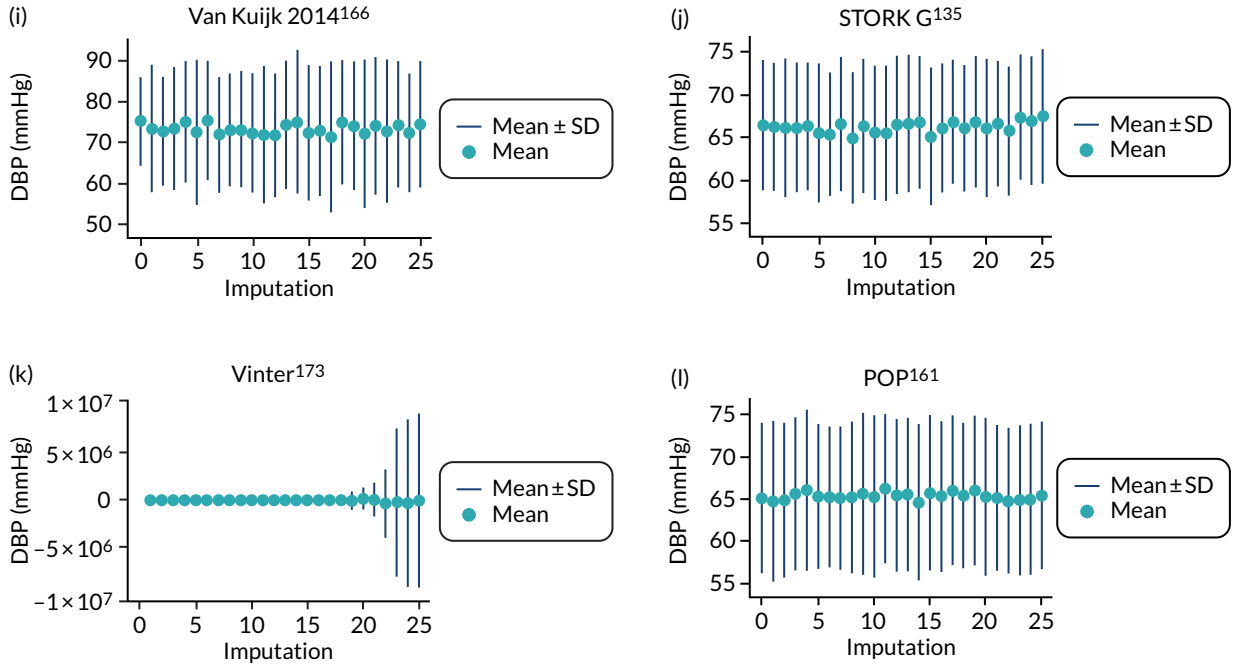


FIGURE 22 Median and range of DBP values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics.

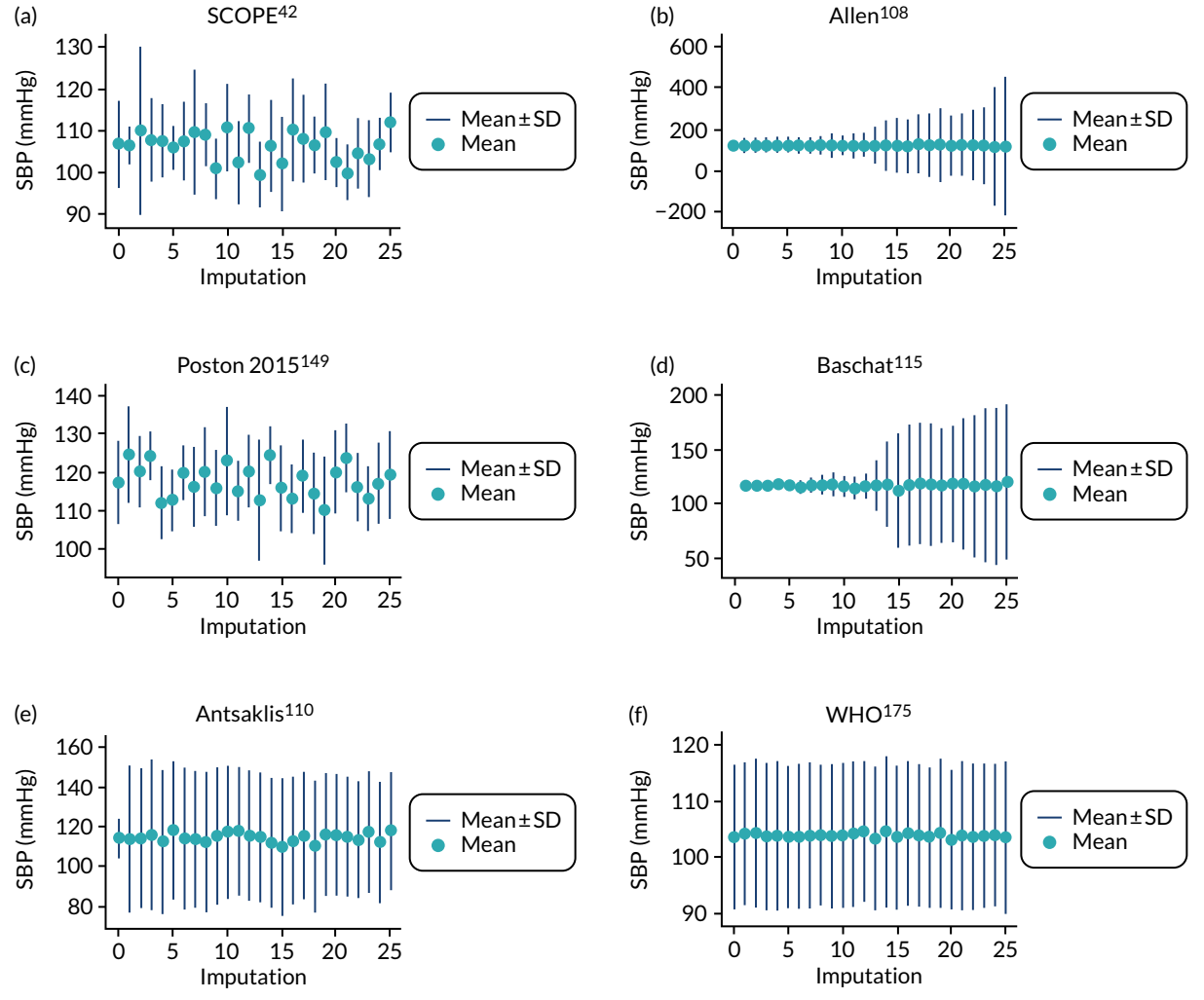


FIGURE 23 Median and range of SBP values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics. (*continued*)

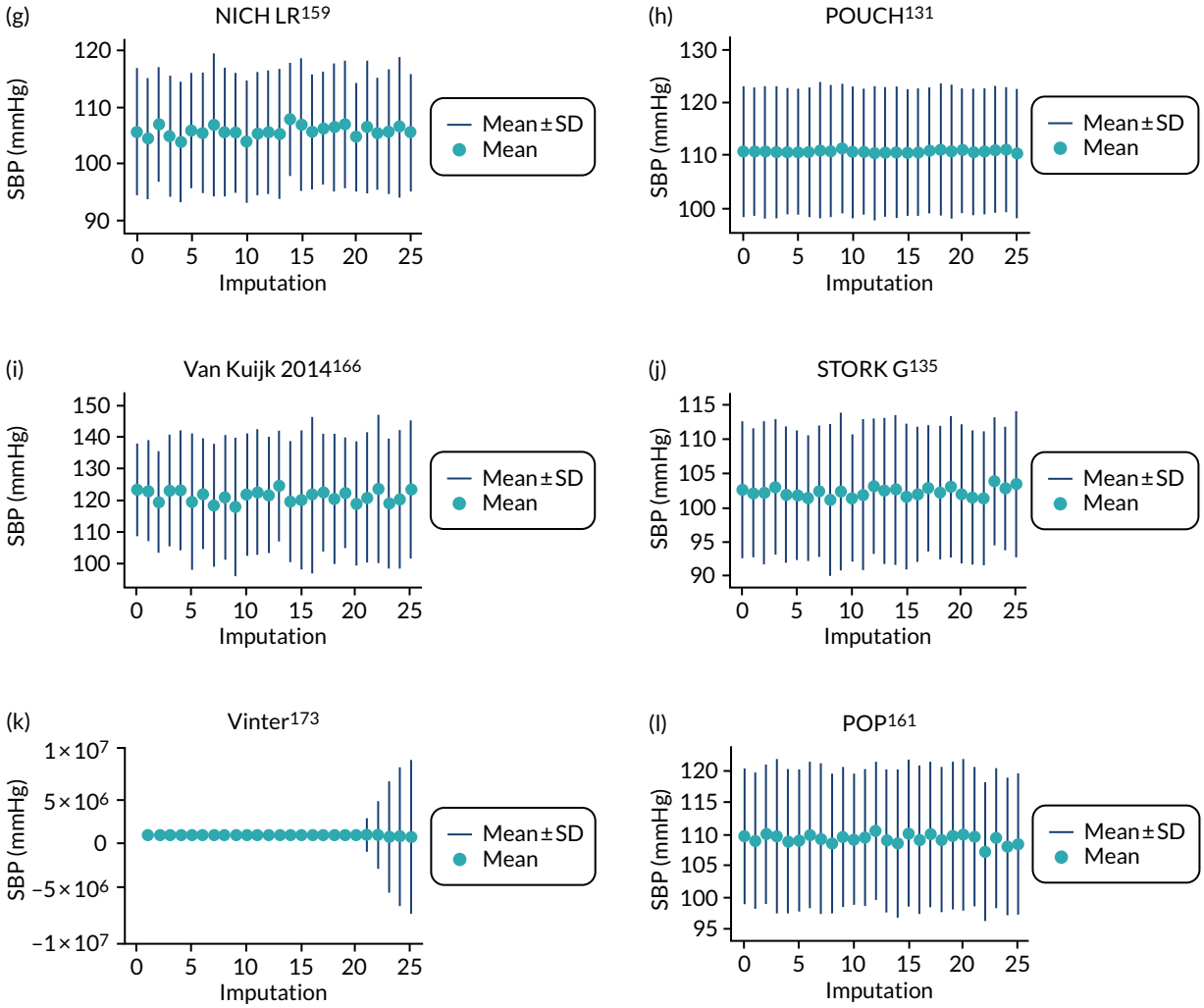


FIGURE 23 Median and range of SBP values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics.

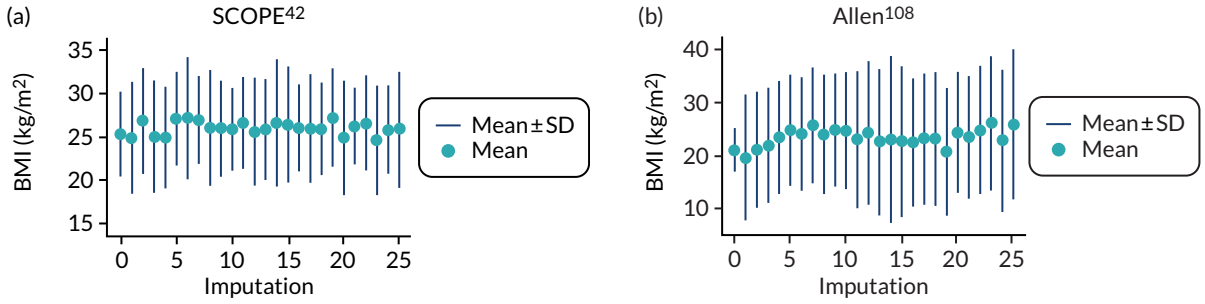


FIGURE 24 Median and range of BMI values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics. (*continued*)

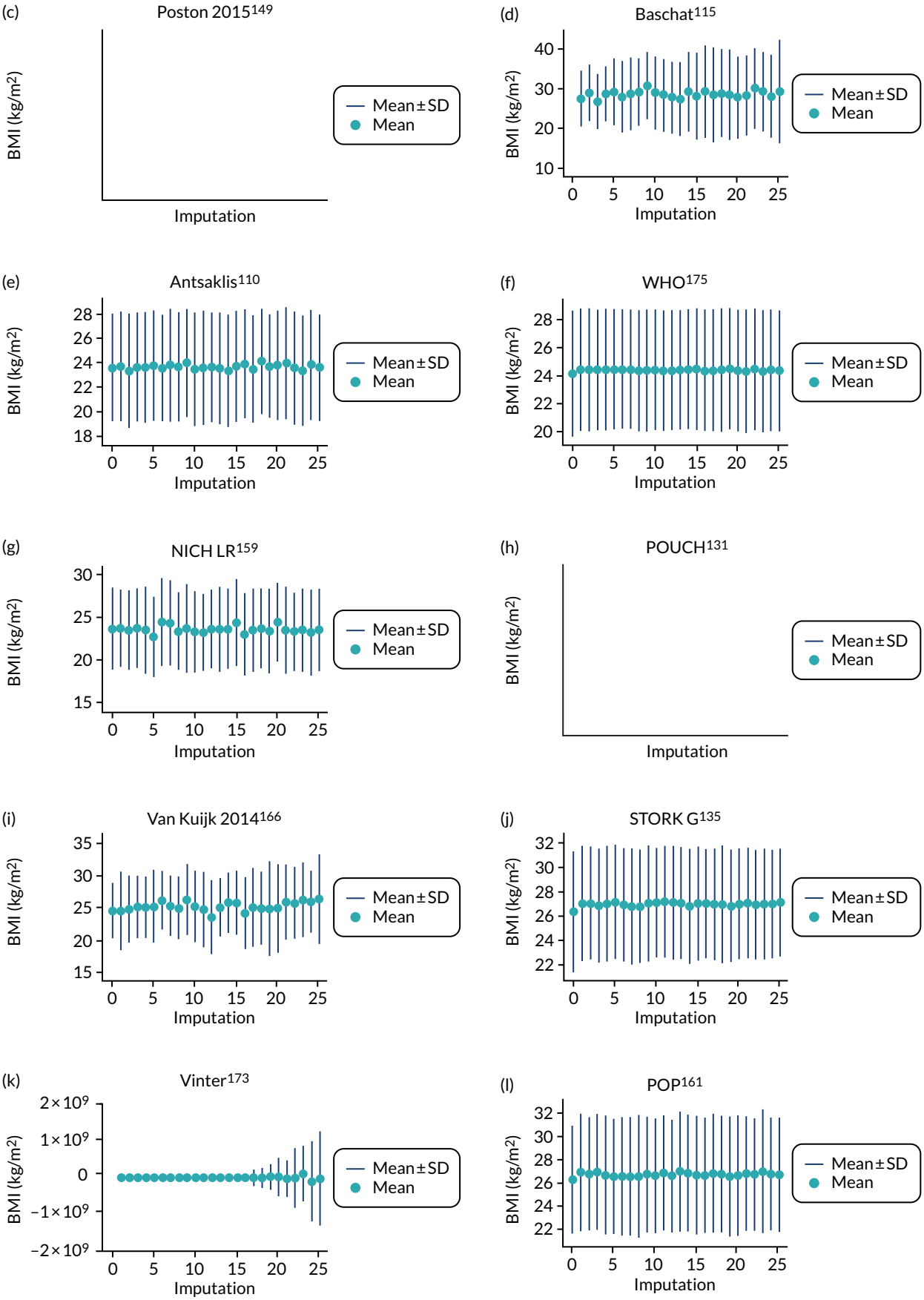


FIGURE 24 Median and range of BMI values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics.

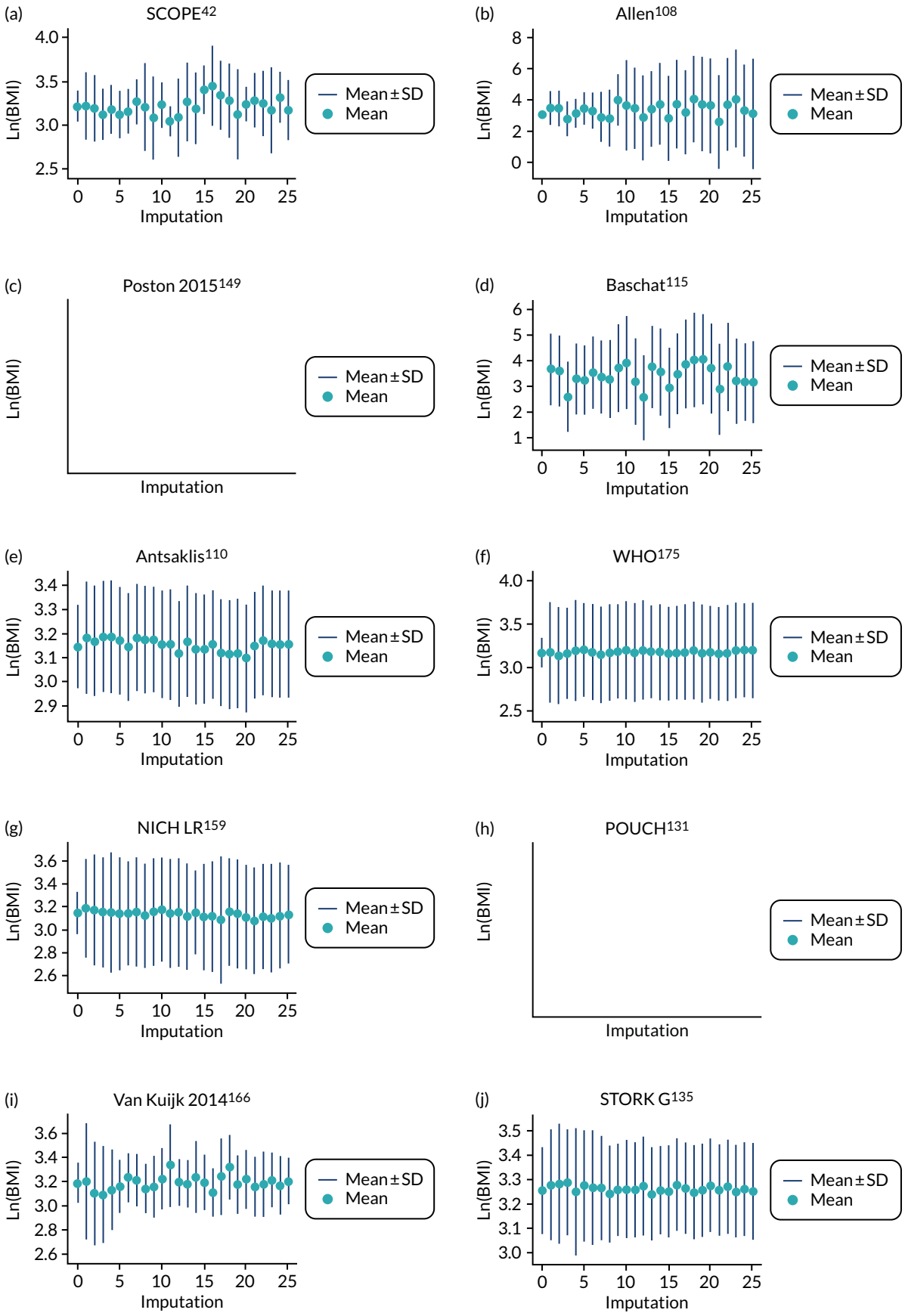


FIGURE 25 Median and range of ln(BMI) values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics. (*continued*)

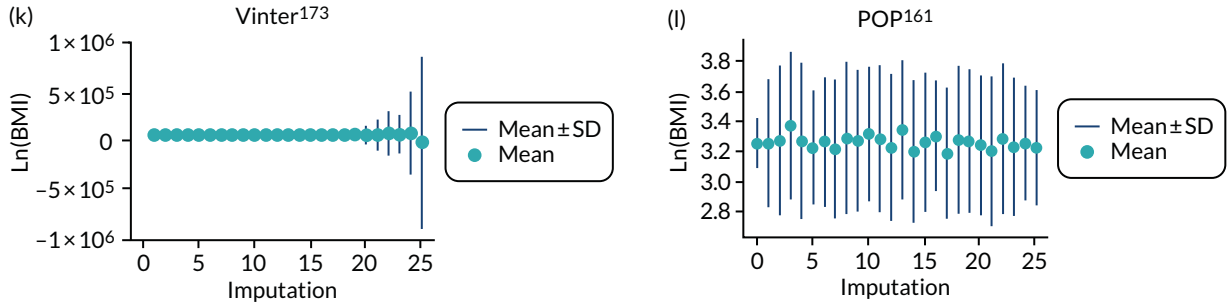


FIGURE 25 Median and range of ln(BMI) values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics.

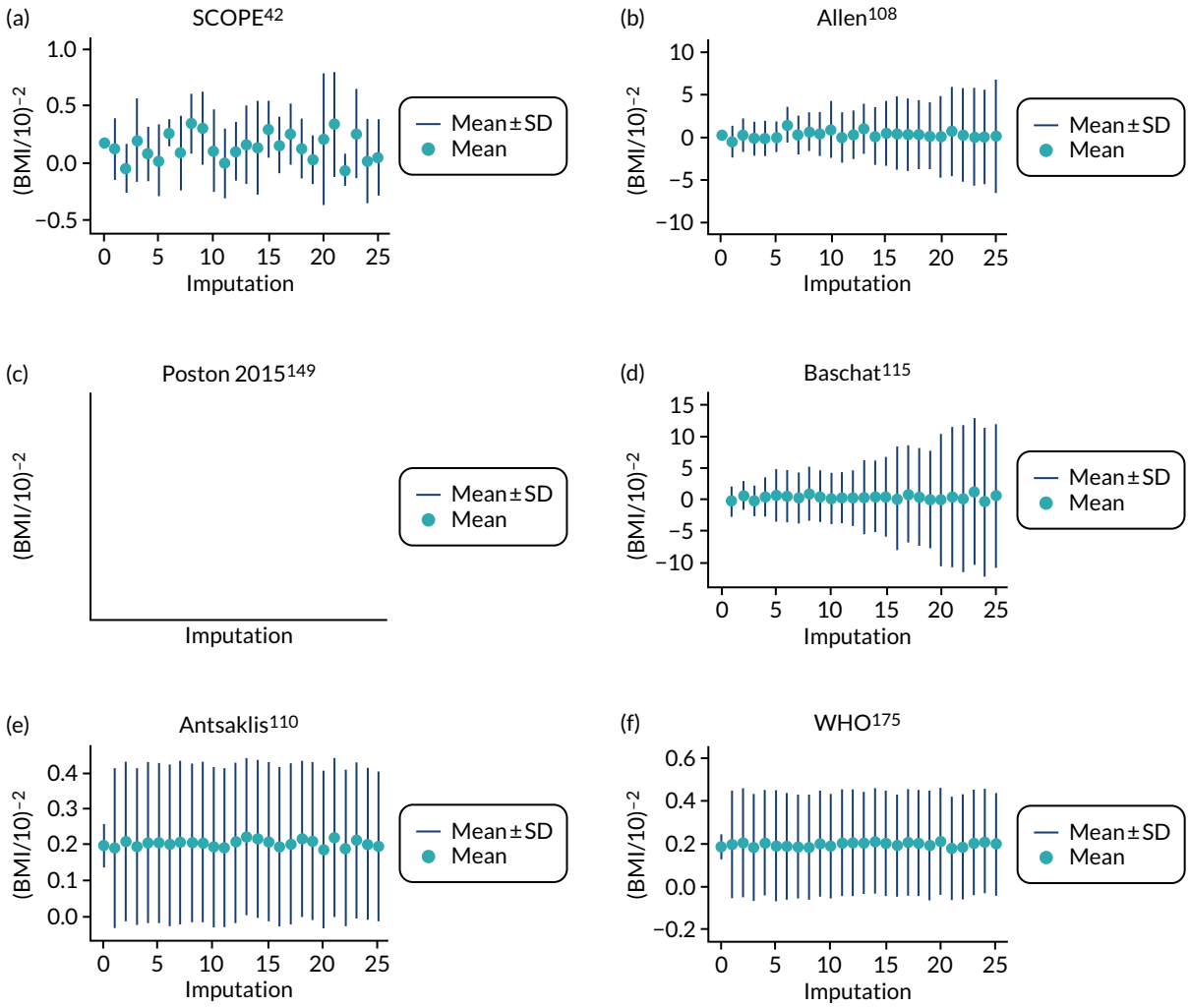


FIGURE 26 Median and range of $(BMI/10)^{-2}$ values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics. (*continued*)

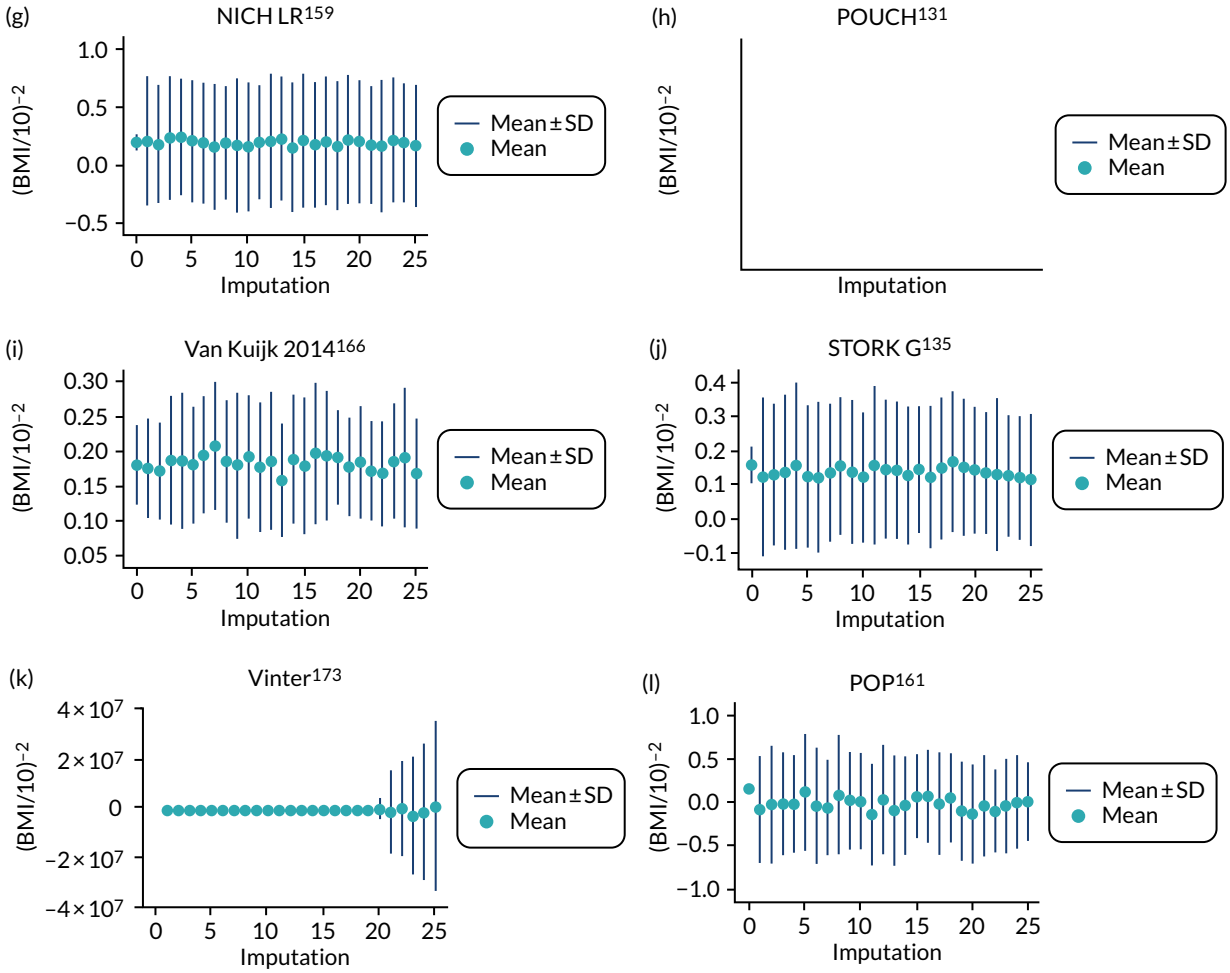


FIGURE 26 Median and range of $(BMI/10)^{-2}$ values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics.

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.

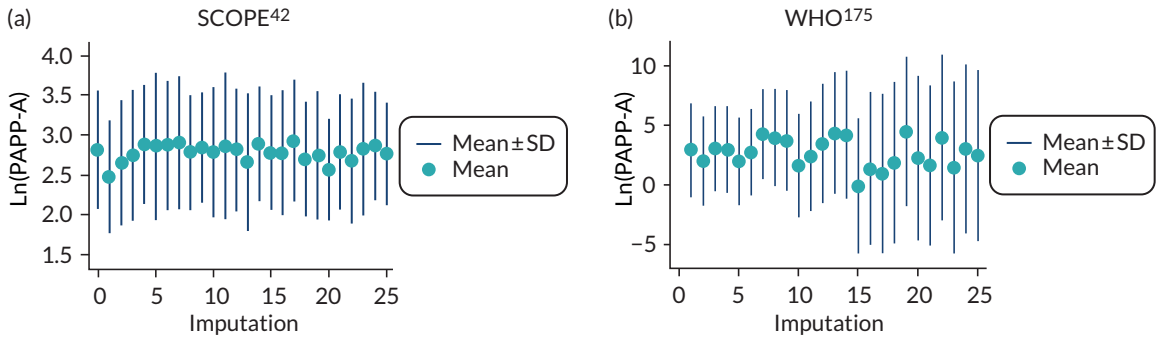


FIGURE 27 Median and range of ln(PAPP-A) values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics. (*continued*)

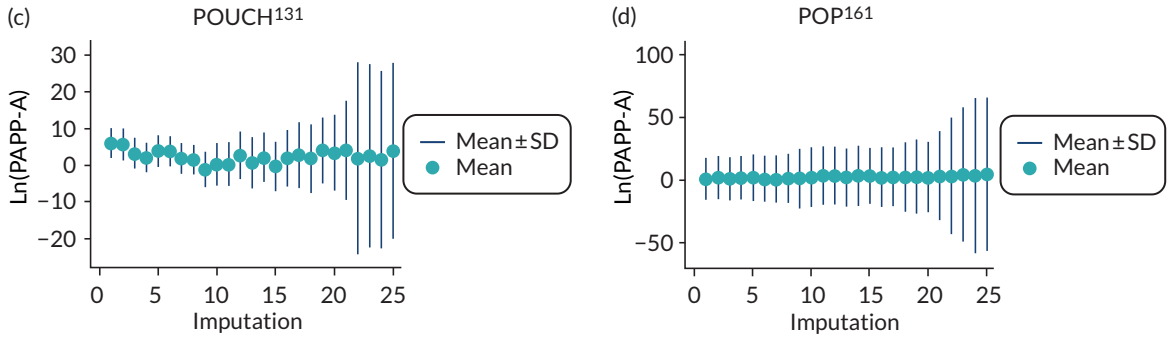


FIGURE 27 Median and range of ln(PAPP-A) values in imputed data set for cohorts included in the development of models with trimester 2 clinical characteristics.

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

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

	BMI			Ln(BMI)			BMI^{-2}		
Variables	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

	C-statistic			Calibration slope			Calibration-in-the-large		
Model	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

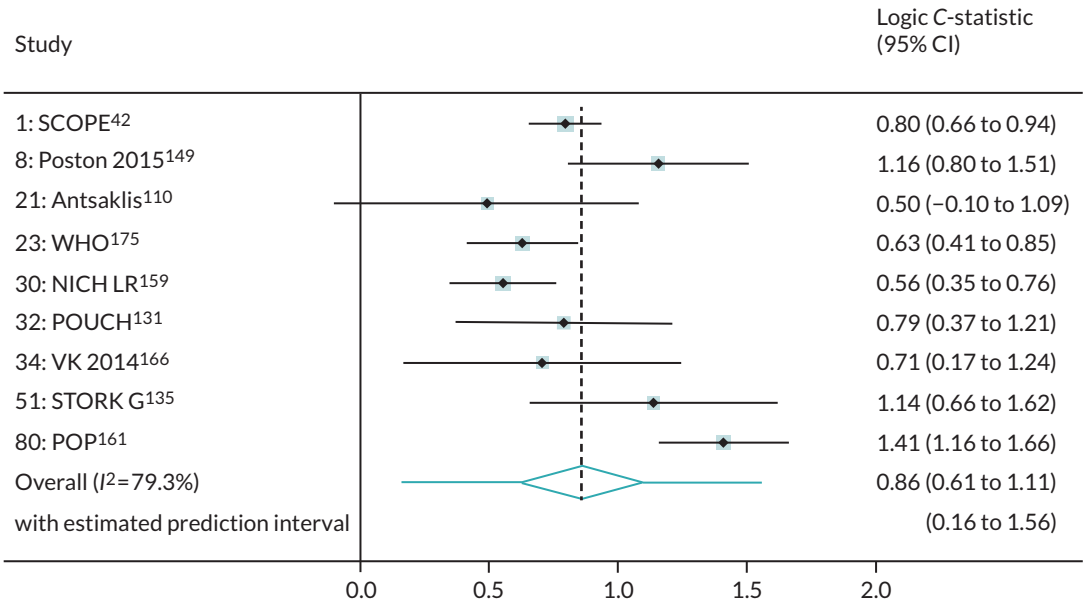


FIGURE 28 Forest plot of logit *C*-statistics for the second-trimester model predicting any-onset pre-eclampsia in data sets used for model development and internal validation. Note: weights are from random-effects model.

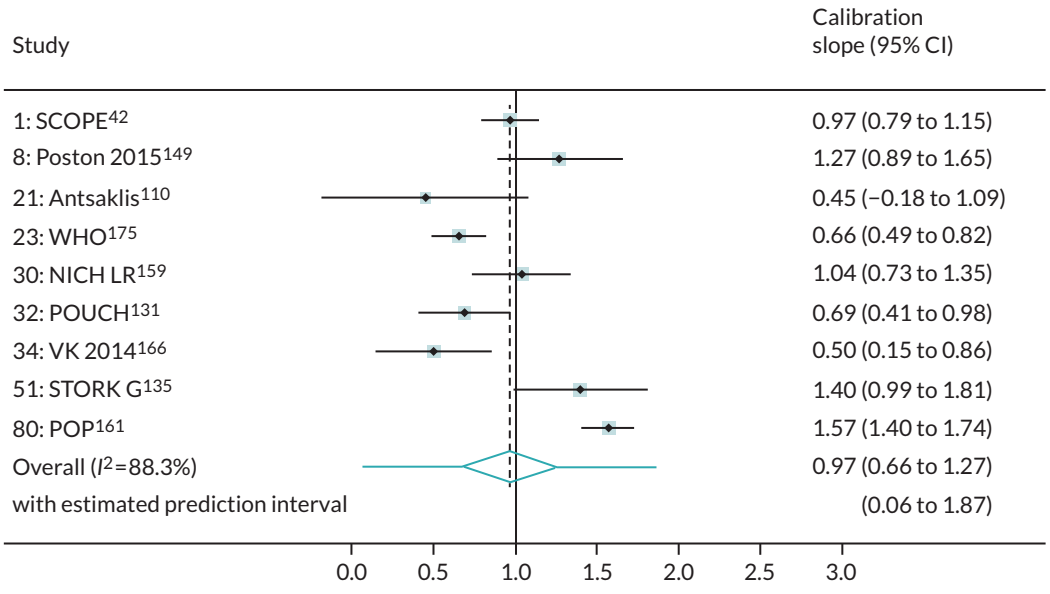


FIGURE 29 Forest plot of calibration slope for the second-trimester model predicting any-onset pre-eclampsia in data sets used for model development and internal validation. Note: weights are from random-effects model.

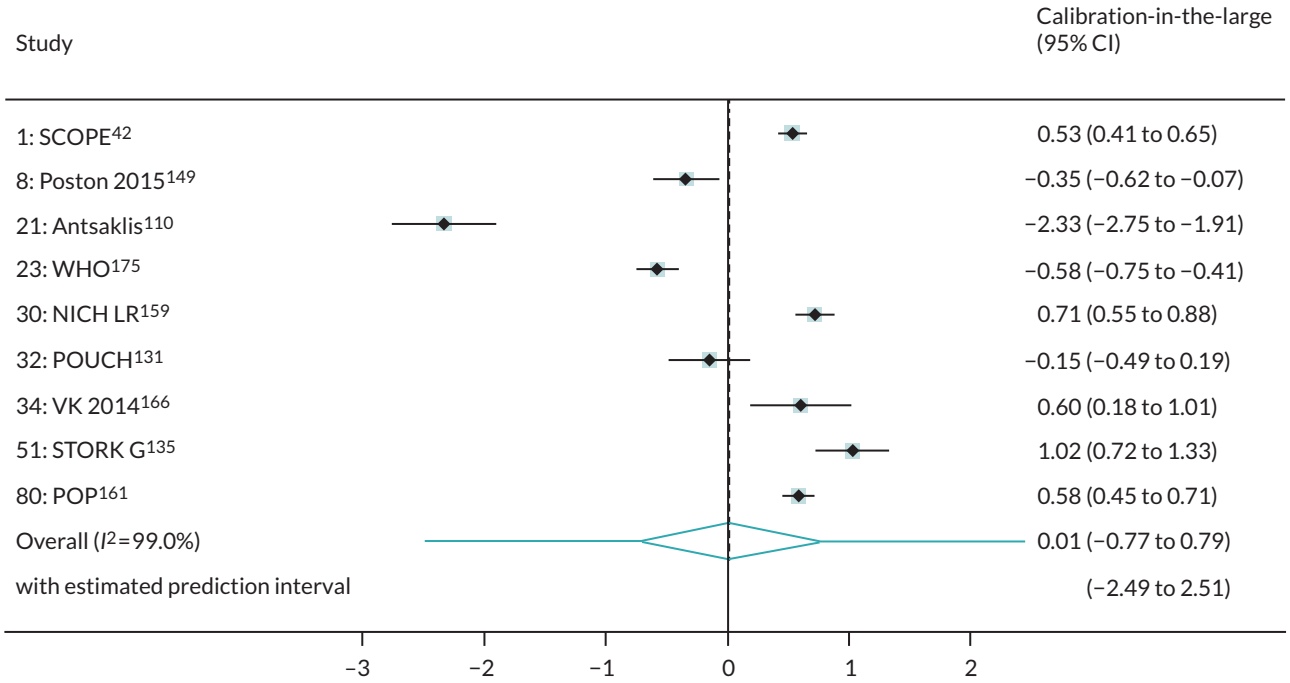


FIGURE 30 Forest plot of calibration-in-the-large for the second-trimester model predicting any-onset pre-eclampsia in data sets used for model development and internal validation. Note: weights are from random-effects model.

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

	Original biochemical markers			Ln(biochemical markers)		
Variable	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
PlGF	−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

	C-statistic			Calibration slope			Calibration-in-the-large		
Model	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	0.696 (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

	Original biochemical markers			Ln(biochemical markers)		
Variable	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

	C-statistic			Calibration slope			Calibration-in-the-large		
Model	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

	Original biochemical markers			Ln(biochemical markers)		
Variable	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
PlGF	−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

	C-statistic			Calibration slope			Calibration-in-the-large		
Model	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	0.688 (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

	Original biochemical markers			Ln(biochemical markers)		
Variable	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
PlGF	−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

	C-statistic			Calibration slope			Calibration-in-the-large		
Model	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

	Original biochemical markers			Ln(biochemical markers)		
Variable	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
PlGF	−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

	C-statistic			Calibration slope			Calibration-in-the-large		
Model	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

	Original biochemical markers			Ln(biochemical markers)		
Variables	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
PlGF	−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

	C-statistic			Calibration slope			Calibration-in-the-large		
Model	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 *et al.*[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 *et al.* 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 *et al.*[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 *et al.*[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 *et al.* 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 *et al.*[173]	304	19	0.679 (0.549 to 0.786)	1.244 (0.260 to 2.227)	0.442 (−0.026 to 0.910)
	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)
First-trimester clinical characteristics and biochemical markers	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)
	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)
Second-trimester clinical characteristics	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 *et al.* 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 *et al.*[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 *et al.* 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 *et al.*[108]	1045	1	NE	0.808 (–0.391 to 2.008)	–1.566 (–3.551 to 0.420)
	Poston *et al.* 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 *et al.*[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 *et al.*[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 *et al.* 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 *et al.*[173]	304	2	0.775 (0.261 to 0.971)	2.114 (–0.318 to 4.547)	–0.033 (–1.425 to 1.359)
	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)
First-trimester clinical characteristics and biochemical markers	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)
	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)
Second-trimester clinical characteristics	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
	van Kuijk *et al.* 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)
Second-trimester clinical characteristics and biochemical markers	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 *et al.*[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 *et al.* 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 *et al.*[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 *et al.*[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 *et al.* 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 *et al.*[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 *et al.* 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 *et al.*[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 *et al.* 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

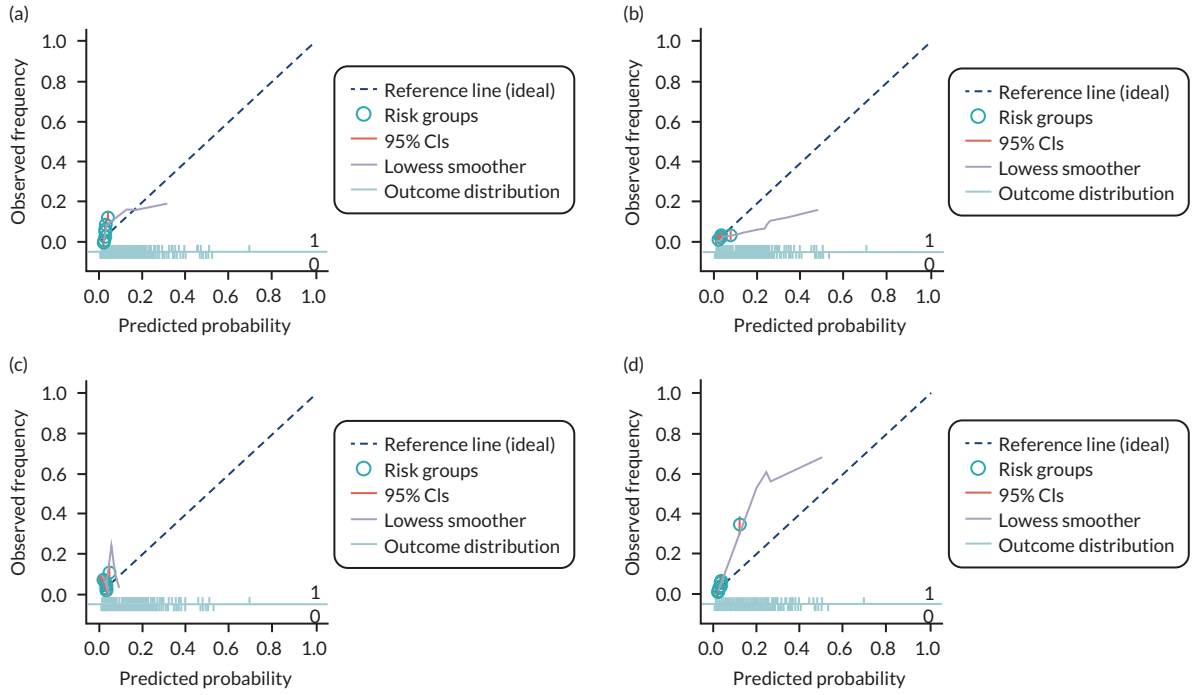


FIGURE 31 Calibration plots for model 3, which includes first-trimester clinical characteristics for predicting late-onset pre-eclampsia. (a) SCOPE;[42] (b) WHO;[175] (c) NICH LR;[159] and (d) POP.[161]

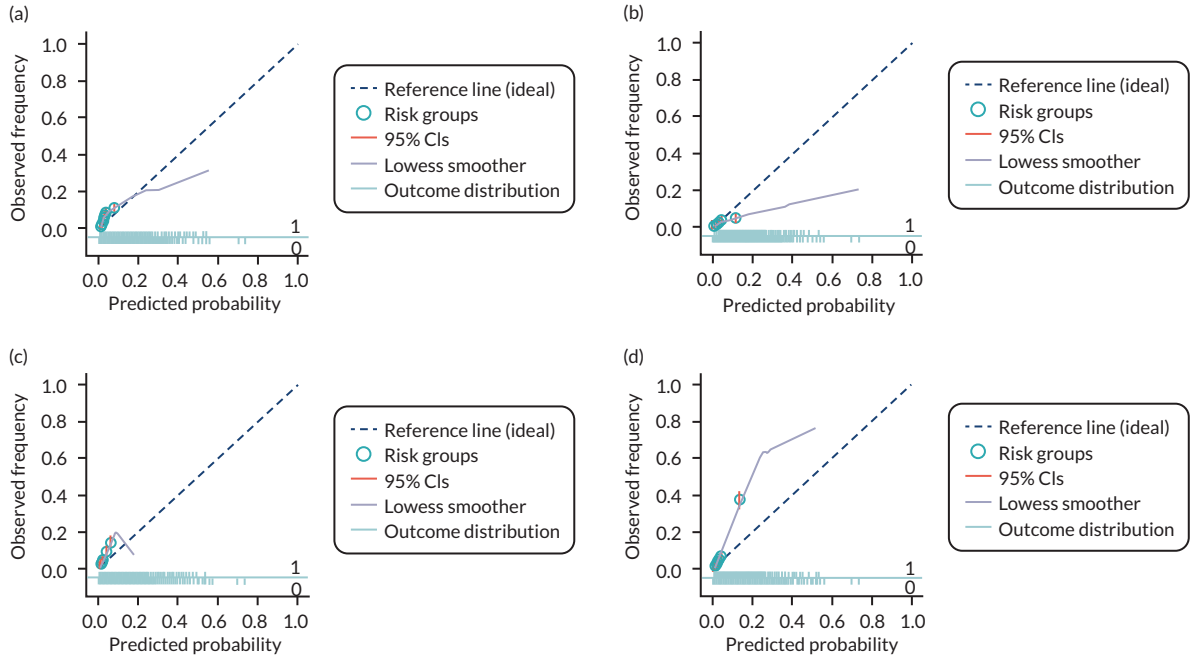


FIGURE 32 Calibration plots for model 4, which includes second-trimester clinical characteristics for predicting any-onset pre-eclampsia. (a) SCOPE;[42] (b) WHO;[175] (c) NICH LR;[159] and (d) POP.[161]

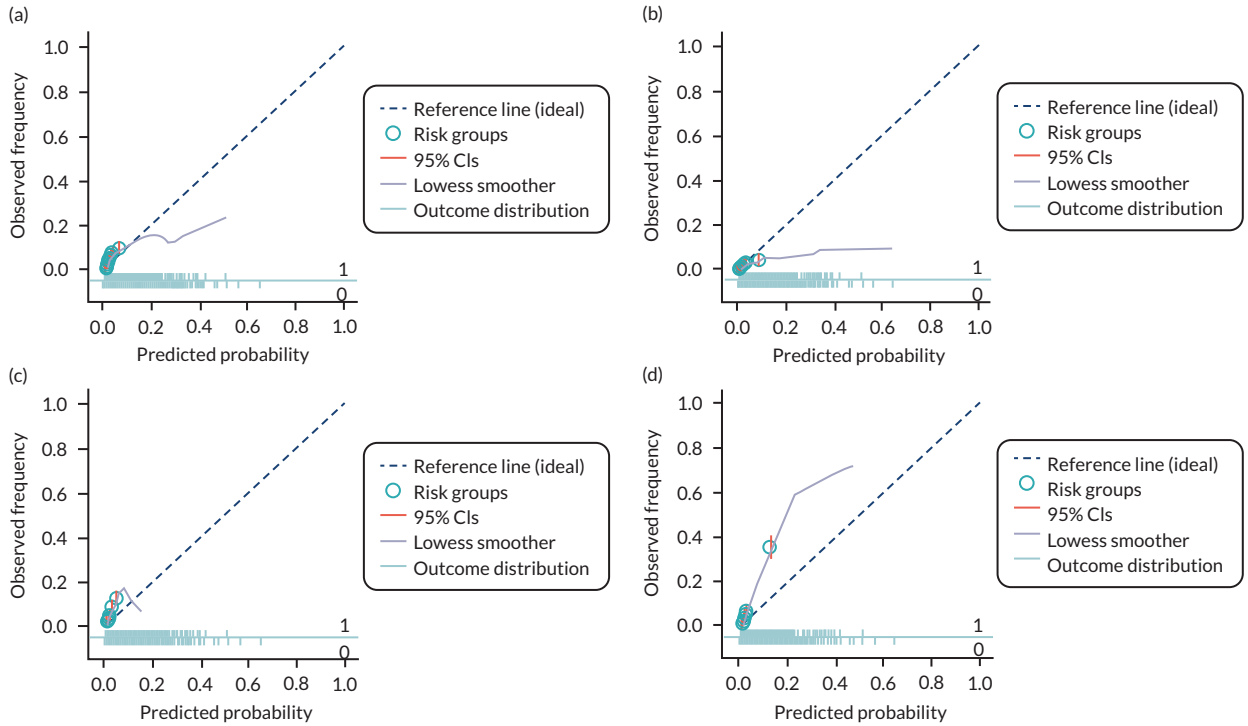


FIGURE 33 Calibration plots for model 6, which includes second-trimester clinical characteristics for predicting late-onset pre-eclampsia. (a) SCOPE;[42] (b) WHO;[175] (c) NICH LR;[159] and (d) POP.[161]

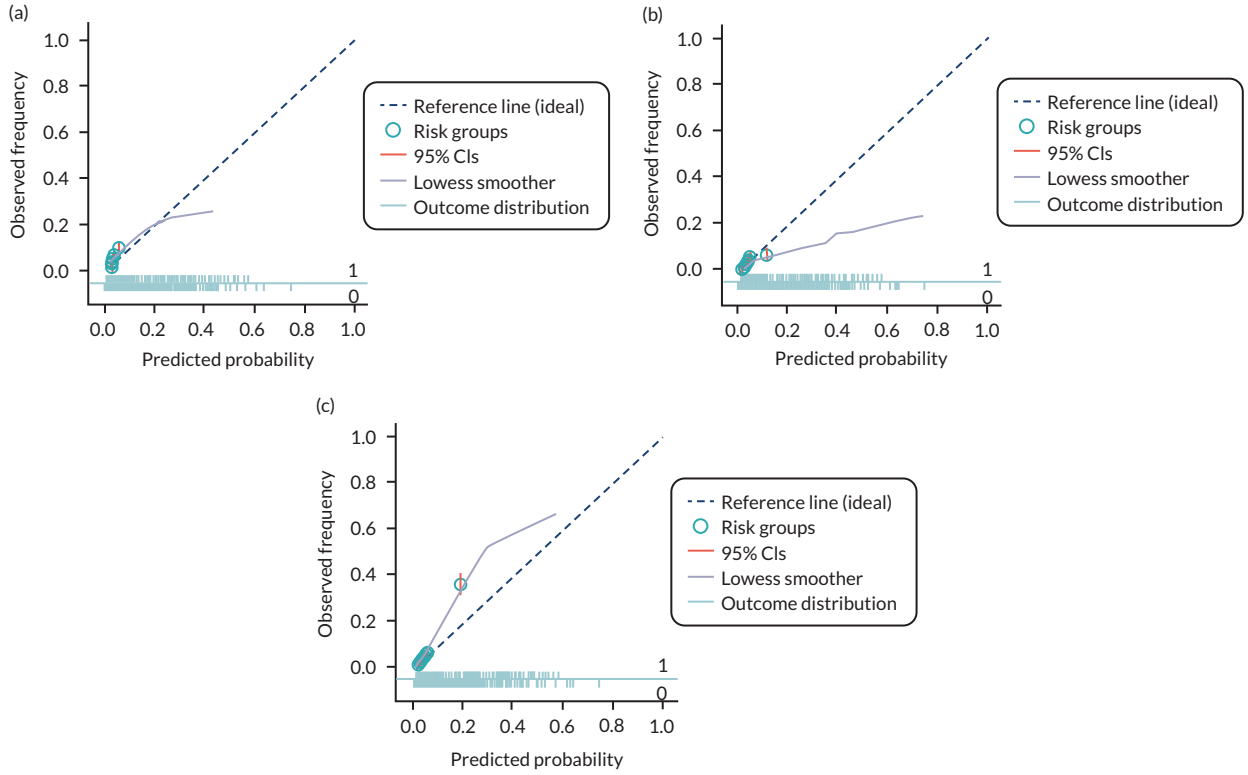


FIGURE 34 Calibration plots for model 7 which includes first-trimester clinical characteristics and biochemical markers for predicting any-onset pre-eclampsia. (a) SCOPE;[42] (b) WHO;[175] and (c) POP.[161]

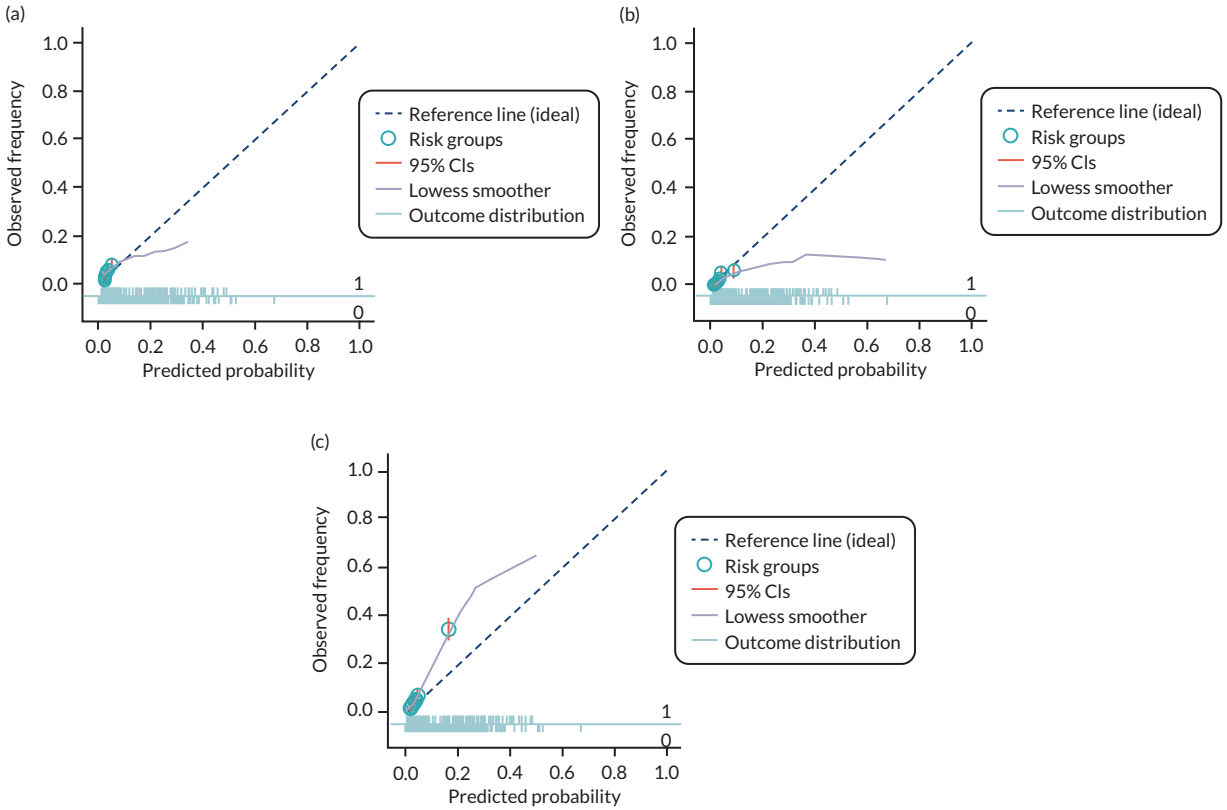


FIGURE 35 Calibration plots for model 9, which includes first-trimester clinical characteristics and biochemical markers for predicting late-onset pre-eclampsia. (a) SCOPE;[42] (b) WHO;[175] and (c) POP.[161]

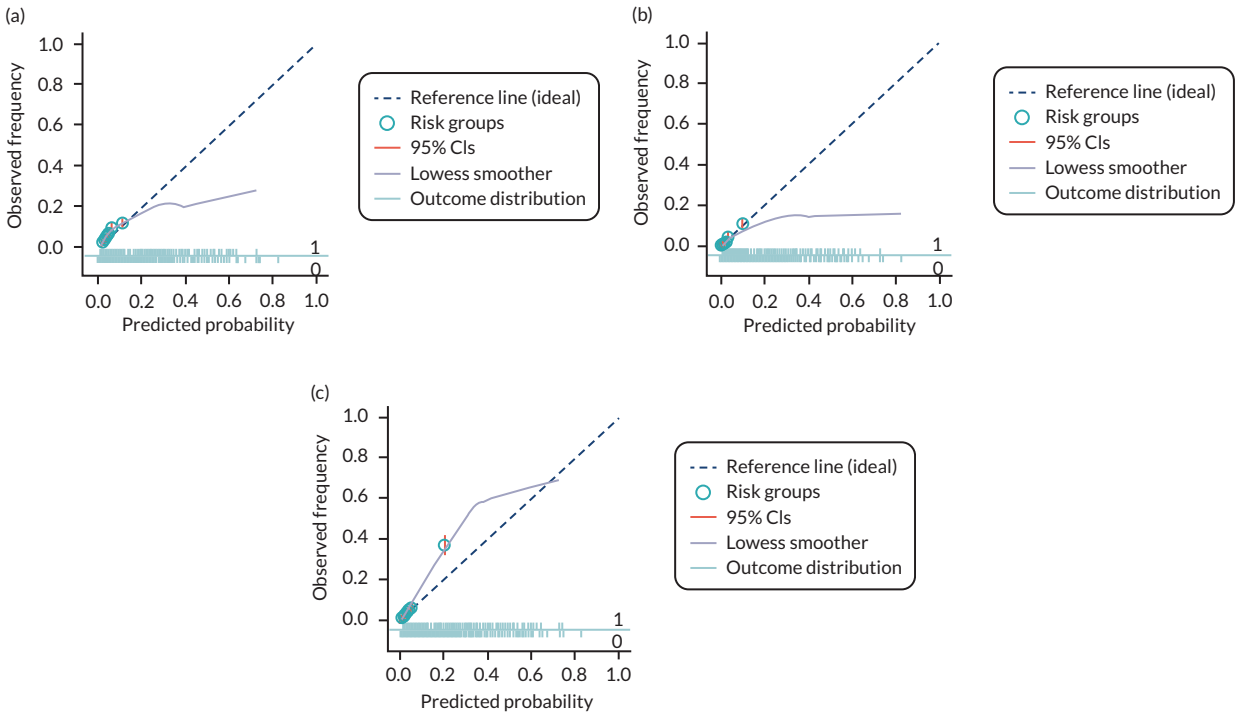


FIGURE 36 Calibration plots for model 10, which includes second-trimester clinical characteristics and biochemical markers for predicting any-onset pre-eclampsia. (a) SCOPE;[42] (b) WHO;[175] and (c) POP.[161]

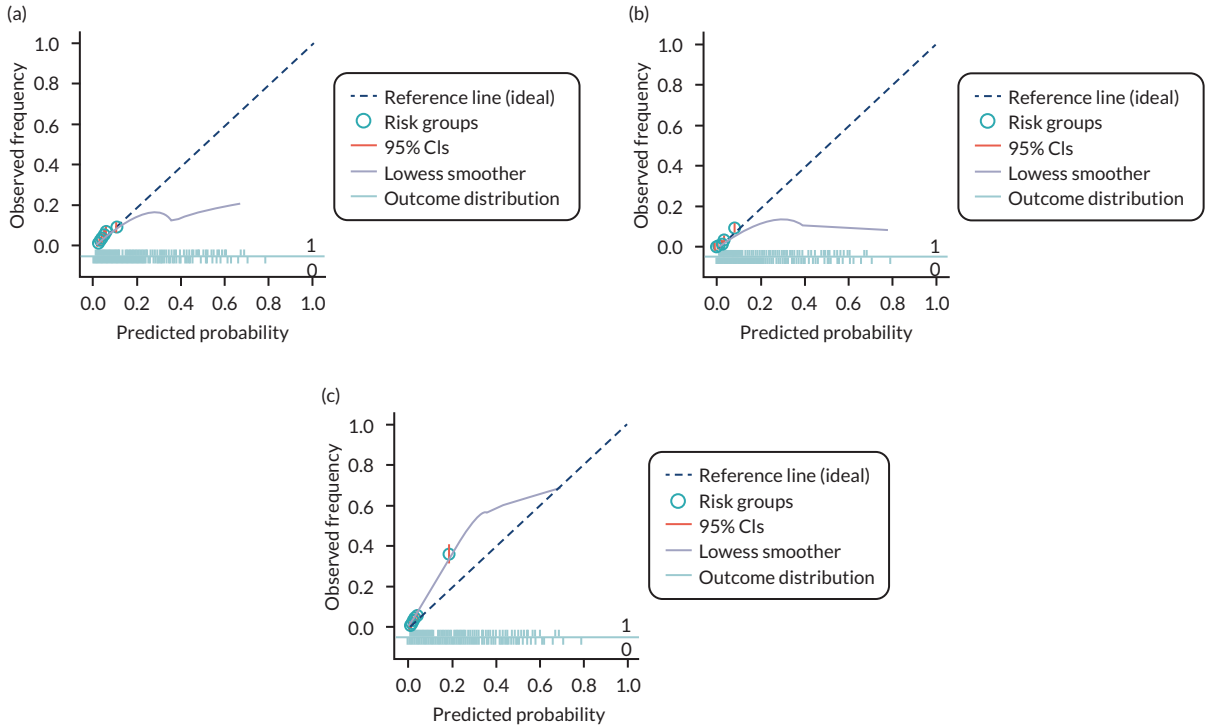


FIGURE 37 Calibration plots for model 12, which includes second-trimester clinical characteristics and biochemical markers for predicting late-onset pre-eclampsia. (a) SCOPE;[42] (b) WHO;[175] and (c) POP.[161]

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

Early-onset pre-eclampsia models

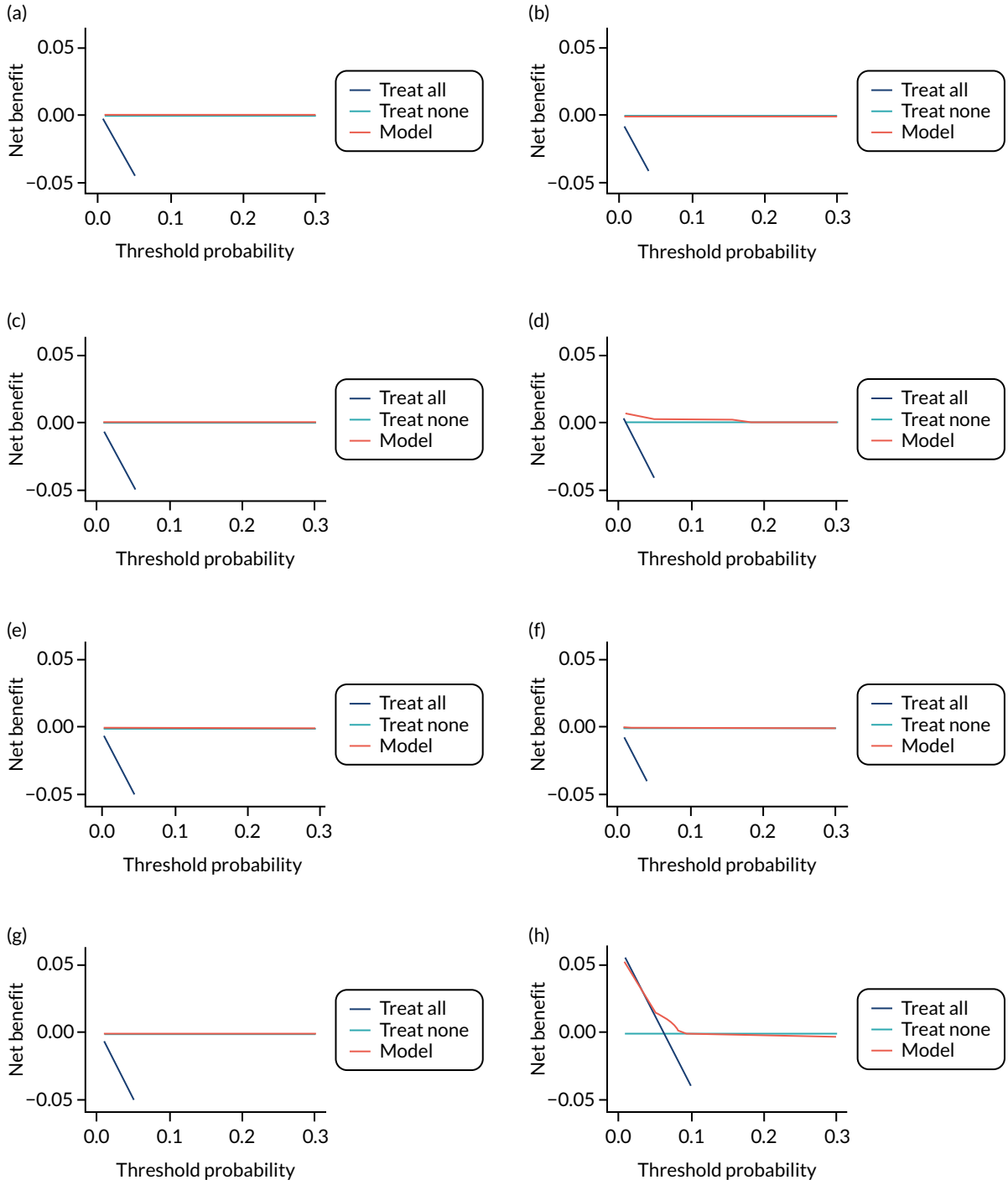


FIGURE 38 Decision curves for the final (shrunken) model predicting early-onset pre-eclampsia using first-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) Allen *et al.*;[108] (c) Poston *et al.* 2015;[149] (d) Baschat *et al.*;[115] (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*)

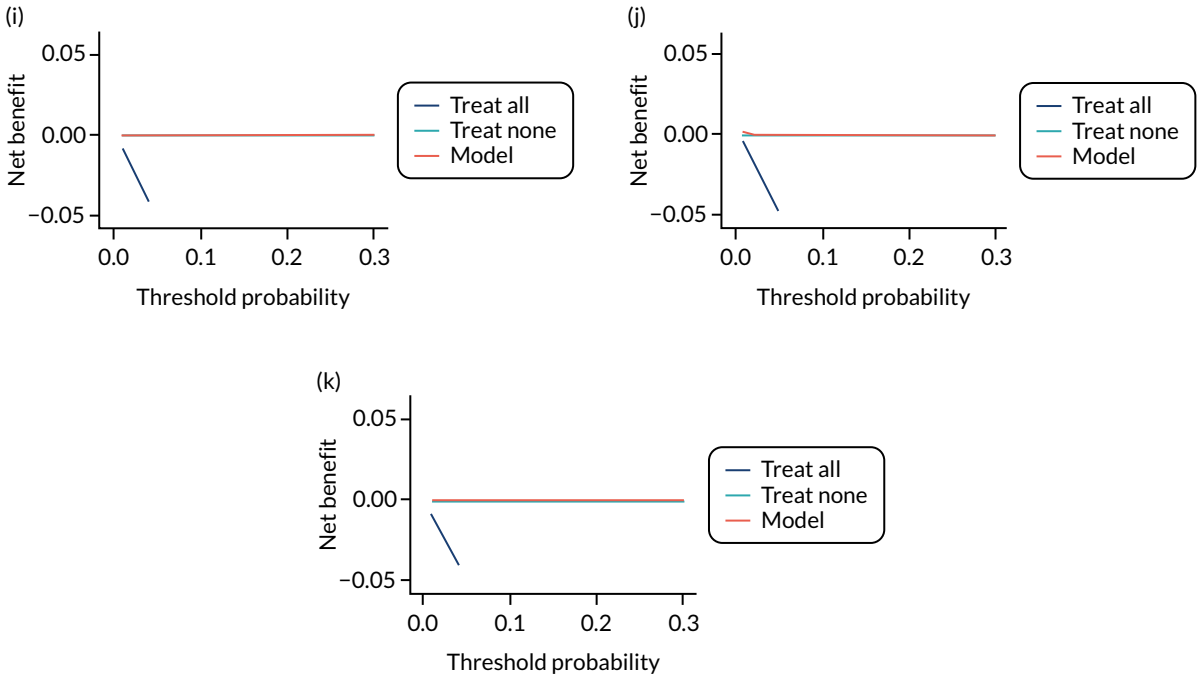


FIGURE 38 Decision curves for the final (shrunken) model predicting early-onset pre-eclampsia using first-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) Allen *et al.*;[108] (c) Poston *et al.* 2015;[149] (d) Baschat *et al.*;[115] (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]

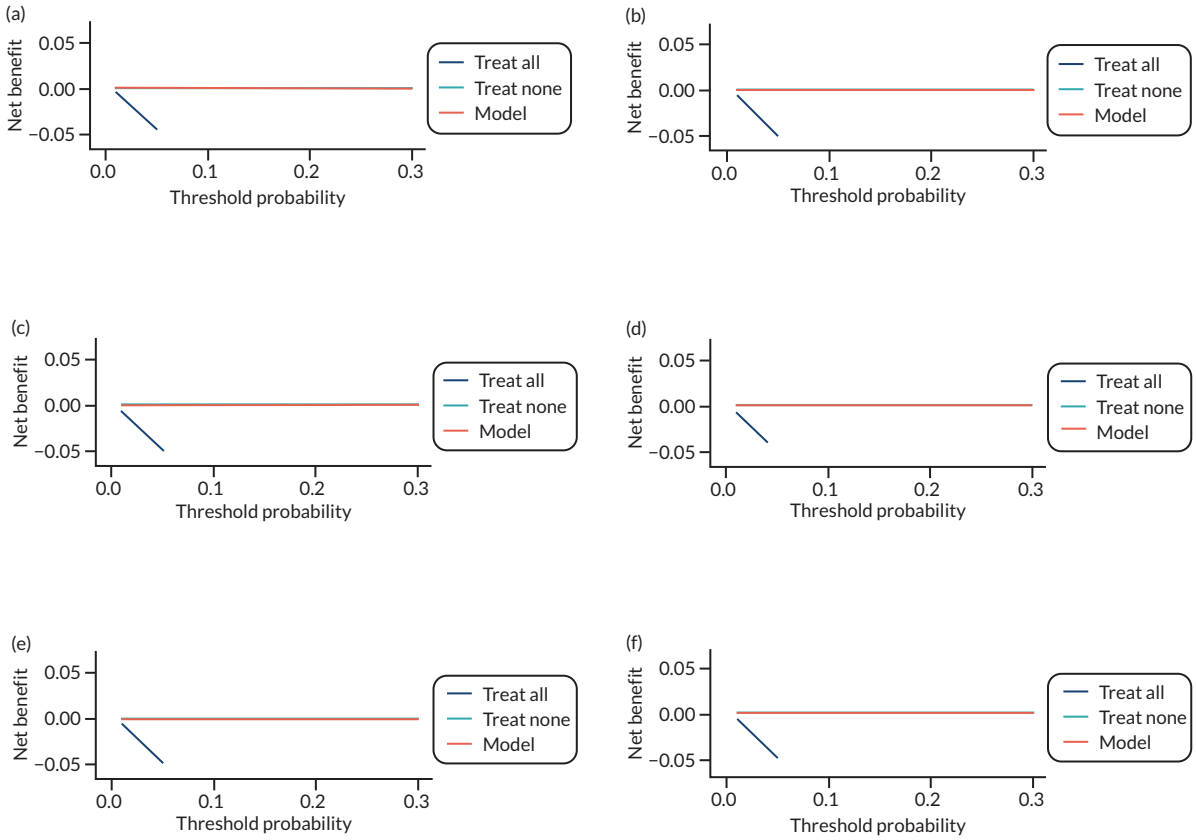


FIGURE 39 Decision curves for the final (shrunken) model predicting early-onset pre-eclampsia using second-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) Poston *et al.* 2015;[149] (c) Antsaklis *et al.*;[110] (d) WHO;[175] (e)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

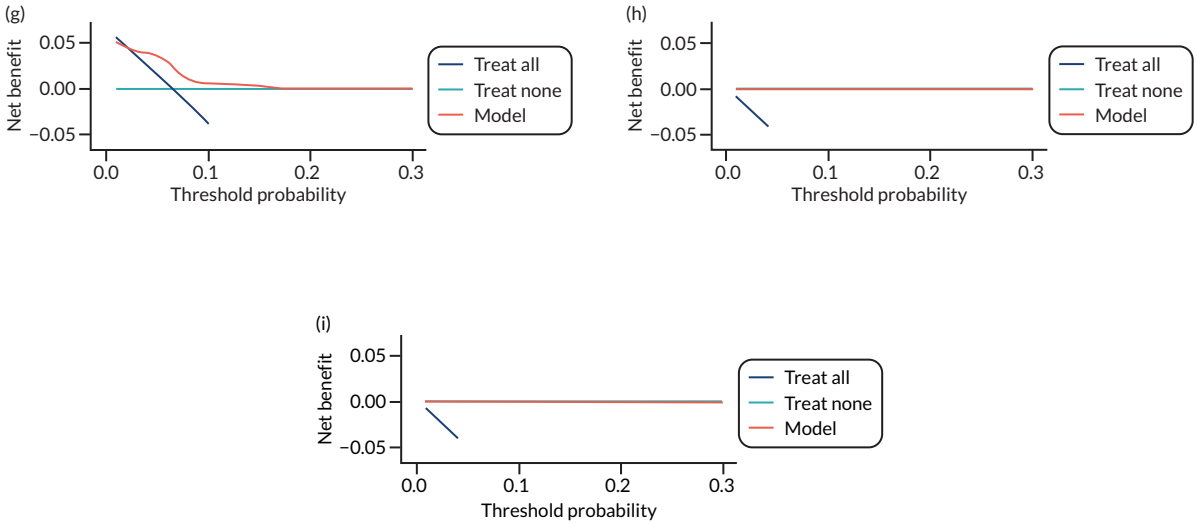


FIGURE 39 Decision curves for the final (shrunken) model predicting early-onset pre-eclampsia using second-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) Poston *et al.* 2015;[149] (c) Antsaklis *et al.*;[110] (d) WHO;[175] (e)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

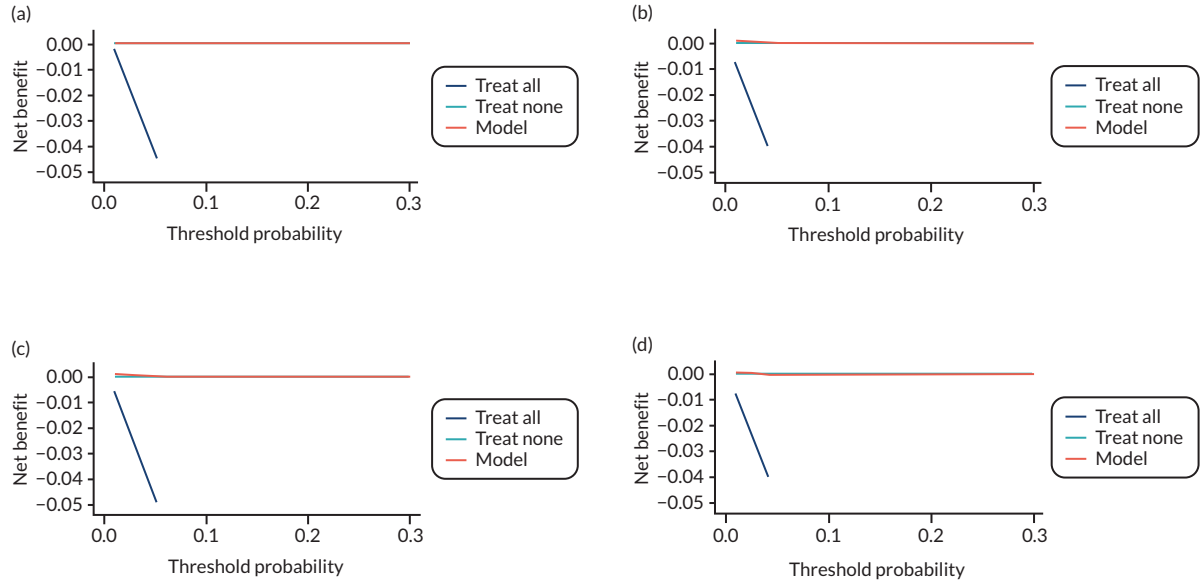


FIGURE 40 Decision curves for the final (shrunken) model predicting early-onset pre-eclampsia using first-trimester clinical characteristics and biochemical markers, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) WHO;[175] (c) POUCH;[131] and (d) POP.[161]

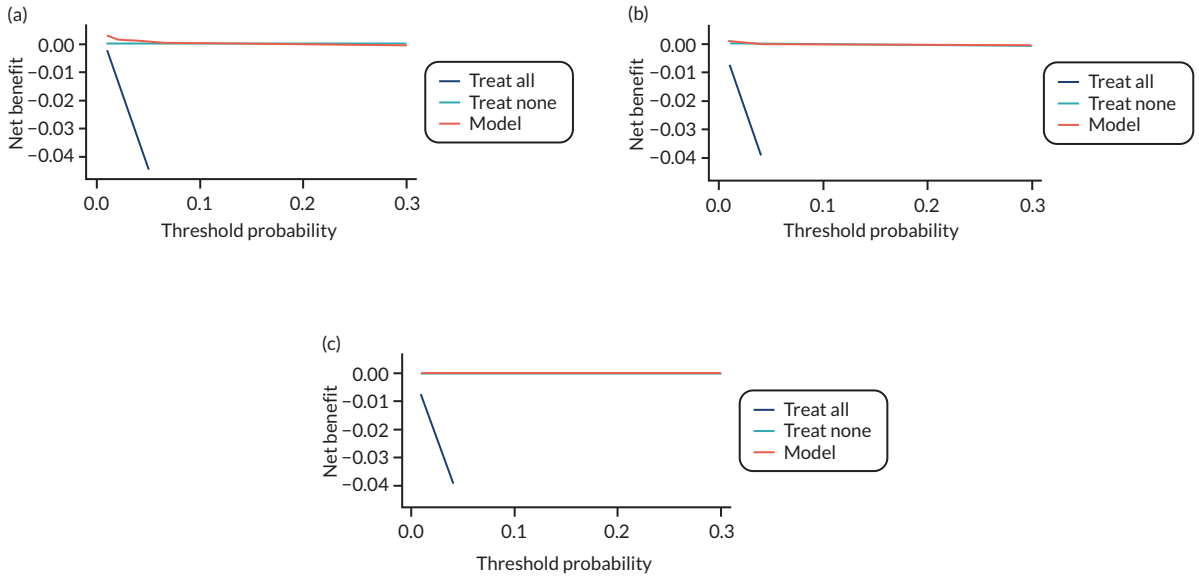


FIGURE 41 Decision curves for the final (shrunken) model predicting early-onset pre-eclampsia using second-trimester clinical characteristics and biochemical markers, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) WHO;[175] and (c) POP.[161]

Late-onset pre-eclampsia models

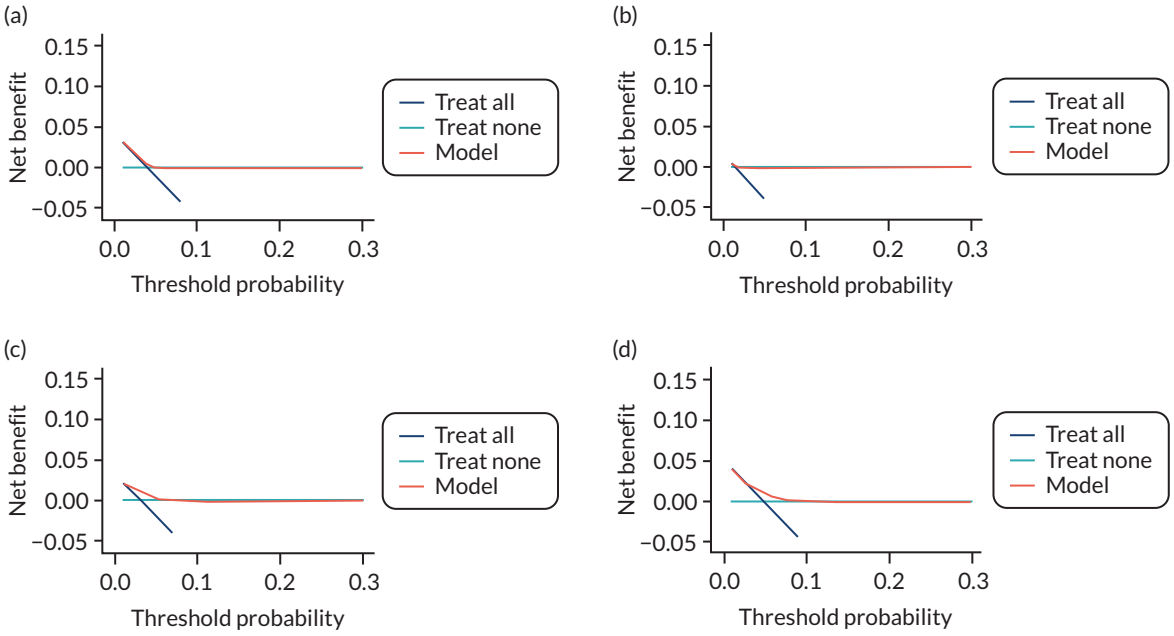


FIGURE 42 Decision curves for the final (shrunken) model predicting late-onset pre-eclampsia using first-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) Allen *et al.*;[108] (c) Poston *et al.* 2015;[149] (d) Baschat *et al.*;[115] (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*)

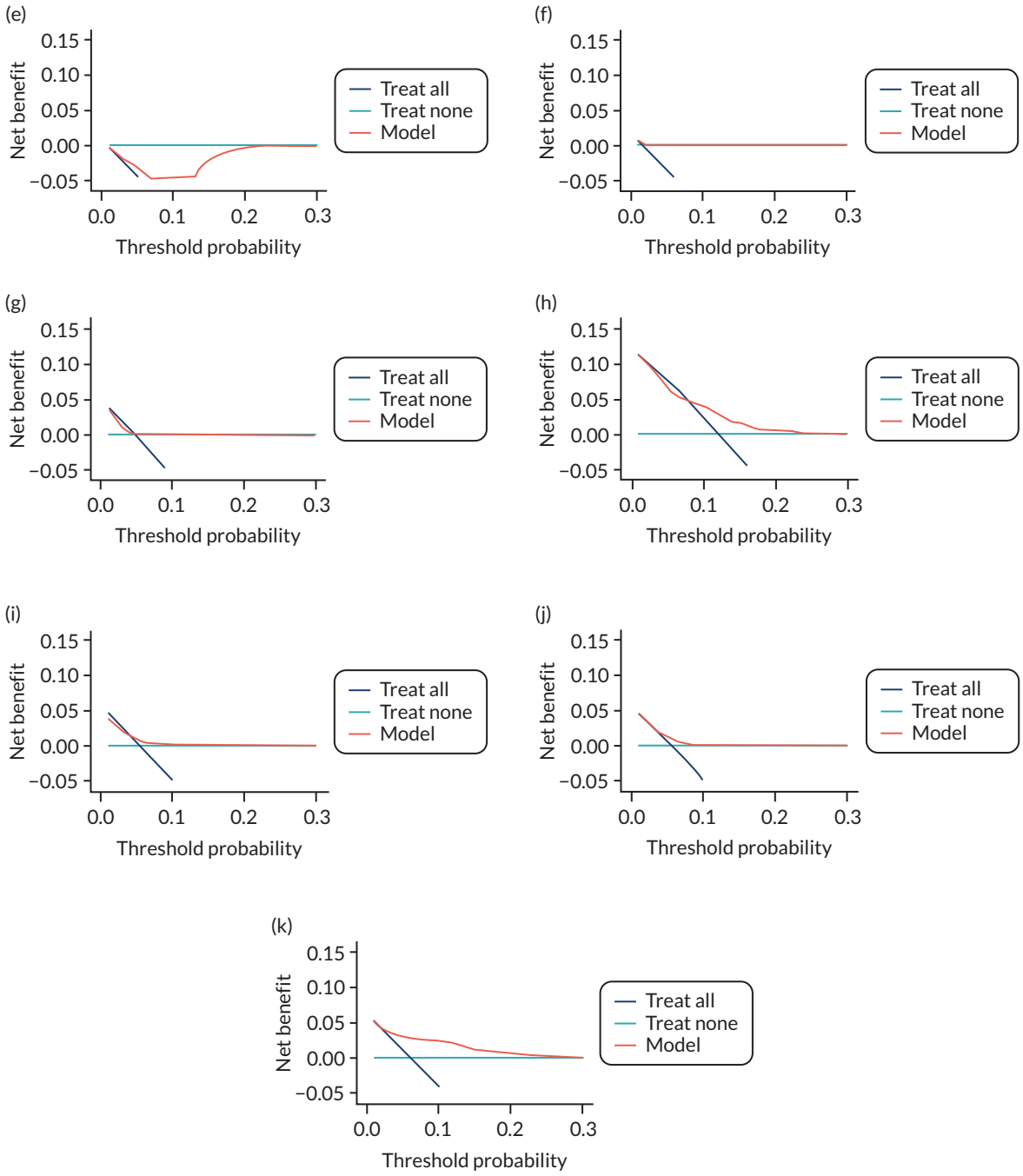


FIGURE 42 Decision curves for the final (shrunken) model predicting late-onset pre-eclampsia using first-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) Allen *et al.*;[108] (c) Poston *et al.* 2015;[149] (d) Baschat *et al.*;[115] (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]

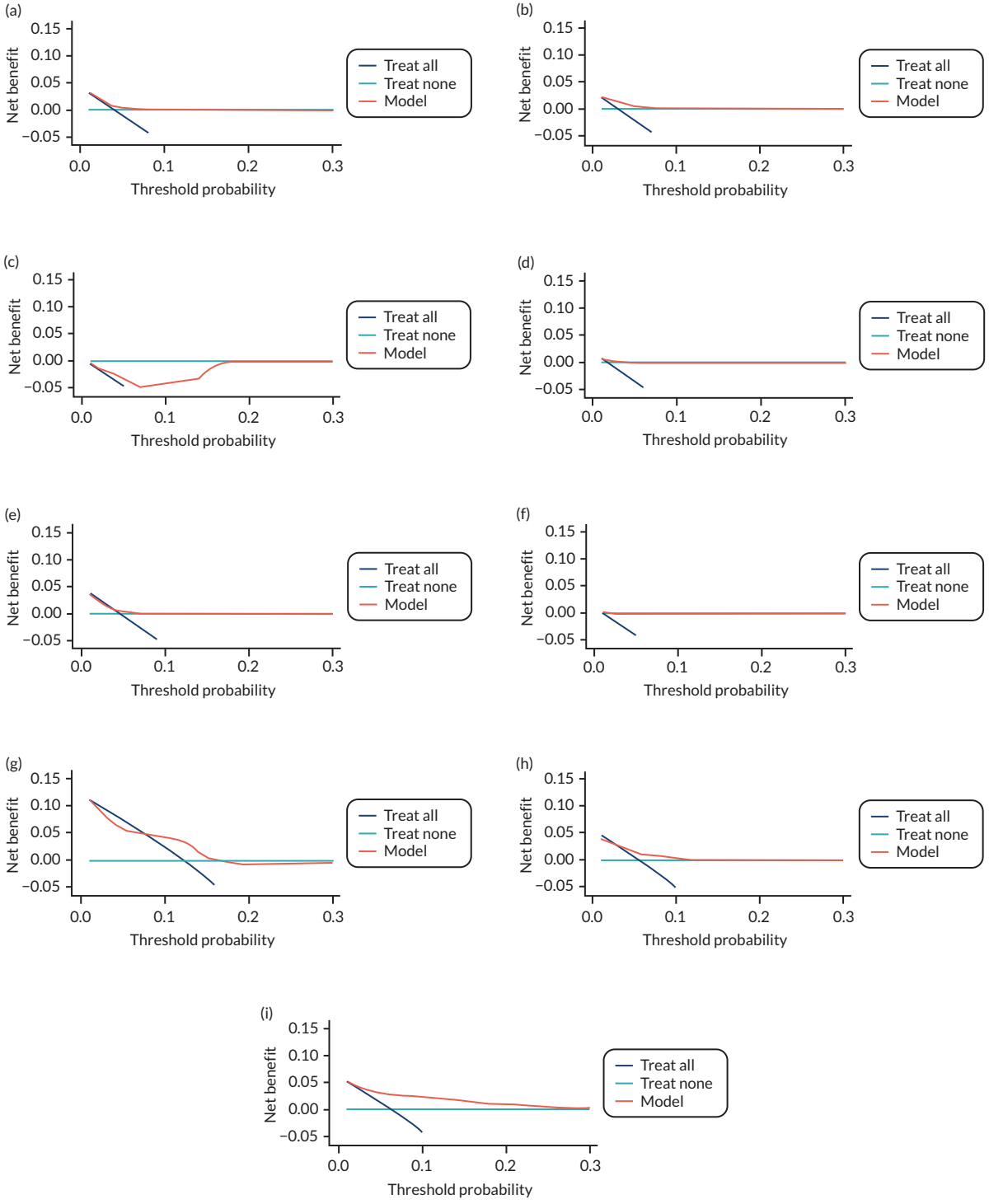


FIGURE 43 Decision curves for the final (shrunken) model predicting late-onset pre-eclampsia using second-trimester clinical characteristics, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) Poston *et al.* 2015;[149] (c) Antsaklis;[110] (d) WHO;[175] (e) NICH LR;[159]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

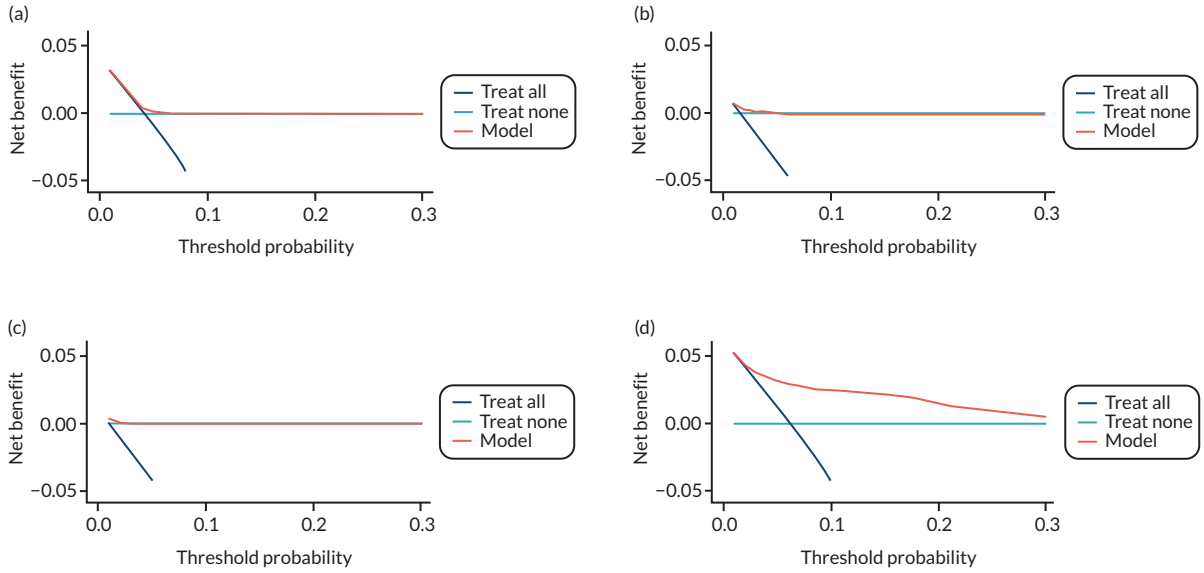


FIGURE 44 Decision curves for the final (shrunken) model predicting late-onset pre-eclampsia using first-trimester clinical characteristics and biochemical markers, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) WHO;[175] (c) POUCH;[131] and (d) POP.[161]

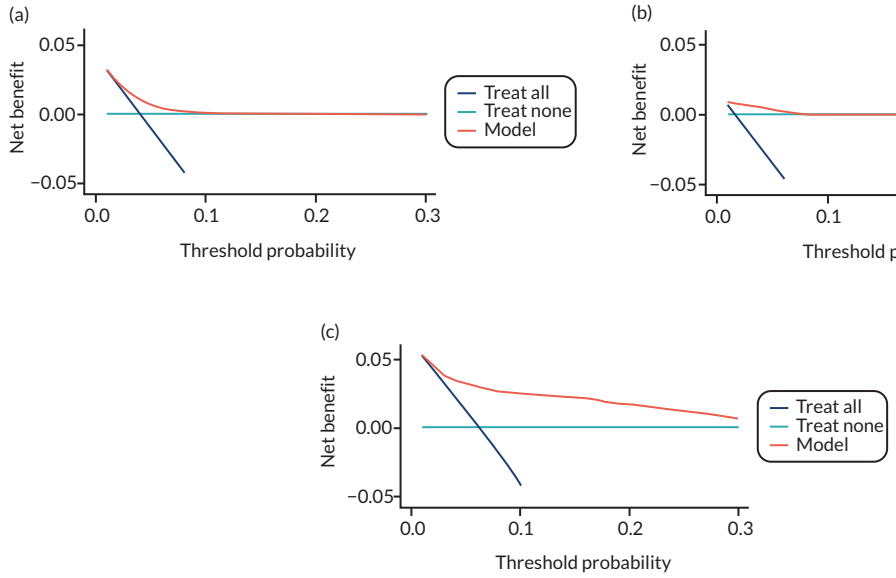


FIGURE 45 Decision curves for the final (shrunken) model predicting late-onset pre-eclampsia using second-trimester clinical characteristics and biochemical markers, in data sets used in the development and validation of the model. (a) SCOPE;[42] (b) WHO;[175] and (c) POP.[161]

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