SUPPLEMENTAL ONLINE MATERIAL

**Supplemental Methods**

**Prediction of blood pressure at different gestational ages from normograms**

To prevent women who had many measurements of blood pressure during pregnancy from having too high an influence on the models, we randomly selected one blood pressure measurement per woman for any 2-week period where the woman had more than one measurement for inclusion in the models. This led to a median and interquartile range of 10 (9 to 11) blood pressure measurements per woman included in the models.

We included pre-pregnancy BMI in the multilevel models in four categories: underweight (<18.5 kg/m2), normal weight (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2) and obese (≥30 kg/m2) as a covariate and also included an interaction between BMI category and each of the splines to allow the shape of the BP trajectory to differ by BMI category. Smoking (any smoking or never smoked) was also included as a categorical covariate and as an interaction with each of the splines. We fitted separate models for nulliparous and multiparous women.

The equation of the multilevel model for blood pressure change across pregnancy was:



, 

where, *yij* is the value of the *ith* MAP measurement on the *jth* individual, *β0-β24* describe the average trajectory of change, *u0j-u4j* describe how the *jth* individual’s trajectory of MAP deviates from the average and *GAij* is the gestational age in weeks of the *ith* measurement on the *jth* individual. It is centred at 12 weeks in order to set the intercept, β0, to represent blood pressure at 12 weeks. The e0ij and e1ij terms describe the deviation of the *ith* measurement of MAP on the *jth* individual from the individual’s trajectory. These are residual error terms.

The model was fitted separately for nulliparous and multiparous women rather than including parity as additional covariate, to allow for greater flexibility in the shape and variability of the trajectories for nulliparous and multiparous women.

The splines are defined as: (1)

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To calculate predictions conditional on the initial blood pressure measurement we used the multilevel models as above, and applied the method described by Tilling et al(2) and Pan and Goldstein.(3)

The between-individual variance for individual *j* at the initial visit is:

*Vb1j* =

The within-individual variance for individual *j* at the initial visit is:

*Vw1* = .

The covariance between the deviations from the predicted curve at the initial visit (indexed 1) and *g* weeks for the jth individual is: *Vb1,gj*=

From these, the predicted blood pressure at gestational age *g* for individual *j*, conditional on the blood pressure value at the initial visit can be calculated as:



Where y1j is the observed value of the outcome (MAP) at the initial visit. Thus, the deviation of the initial measurement from the average trajectory was combined with the multilevel model information to predict what trajectory would be seen for the rest of gestation.

**Multiple imputation of missing values in ALSPAC and the SWS**

The same variables were included in multiple imputation models in both ALSPAC and SWS. A separate imputation was done for blood pressure at each gestational age: 20, 25, 28, 31, 34 and 36 weeks, imputing only to the number of women who still had not delivered at each gestation. The variables included were either exposures/covariates to include in prediction models, outcomes or predictors of missingness. The variables included and information about how they were included in multiple imputation models are shown in the table below:

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Type of variable** | **Model used to predict missing data in this variable** | **How variable was entered in models to predict missing data in other variables** |
| MAP at initial visit | Continuous | Linear regression | Continuous |
| MAP at X weeks | Continuous | Linear regression | Continuous |
| Preeclampsia | Binary | Logistic regression | Binary |
| Offspring small for gestational age | Binary | Logistic regression | Binary |
| Customised small for gestational age | Binary | Logistic regression | Binary |
| Gestational age at delivery | Continuous | No missing data | Continuous |
| Pre-existing maternal hypertension | Binary | Logistic regression | Binary |
| Previous gestational hypertension | Binary | Logistic regression | Binary |
| Previous gestational diabetes | Binary | Logistic regression | Binary |
| Pre-existing diabetes | Binary | Logistic regression | Binary |
| Maternal age | Continuous | Linear regression | Continuous |
| Parity | Ordered categorical (3 categories) | Ordinal logistic regression | 2 indicator variables |
| Maternal weight | Skewed continuous | Log-linear regression | Continuous |
| Maternal height | Continuous | Linear regression | Continuous |
| Maternal smoking | Binary | Logistic regression | Binary |
| Maternal education | Ordered categorical  (4 categories) | Ordinal logistic regression | 3 indicator variables |
| Household social class | Ordered categorical (5 categories) | Ordinal logistic regression | 4 indicator variables |
| Maternal non-white ethnicity | Binary | Logistic regression | Binary |
| Offspring sex | Binary | Logistic regression | Binary |

**Prediction Models for Preeclampsia:**

The logistic regression models used to predict preeclampsia in ALSPAC are shown below. The risk of preeclampsia is calculated as where ***βX*** is as follows:

map\_1 = MAP at the initial visit matsmok = Maternal smoking in the first trimester

matbmi = Maternal pre-pregnancy BMI esshyp = Essential hypertension

matheight = Maternal height prev\_gesthyp = Gestational hypertension in a previous pregnancy

mat\_over 35 = Maternal age over 35 years prev\_diab = Existing diabetes

par2 = Parity of 1 prev\_gestdiab = Gestational diabetes in a previous pregnancy

par3 = Parity of 2 or more mat\_nonwhite = Maternal non-white ethnicity

**Model 1**

-3.46 + 0.046\*map\_1 + 0.057\*matbmi - 0.024\*matheight + 0.384\*mat\_over35 - 1.590\*par2 - 1.546\*par3 - 0.479\*matsmok + 0.793\*esshyp + 1.346\*prev\_gesthyp + 2.301\*prev\_diab + 0.941\*prev\_gestdiab + 0.429\*mat\_nonwhite

**Model 2**

**20 weeks gestation:** -3.57 + 0.060\*map\_20wks + 0.023\*map\_1 + 0.036\*matbmi - 0.031\*matheight + 0.319\*mat\_over35 - 1.535\*par2 - 1.499\*par3 - 0.446\*matsmok + 0.545\*esshyp + 1.162\*prev\_gesthyp + 2.208\*prev\_diab + 0.896\*prev\_gestdiab + 0.520\*mat\_nonwhite

**25 weeks gestation:** -3.65 + 0.077\*map\_25wks + 0.019\*map\_1 + 0.030\*matbmi - 0.031\*matheight + 0.308\*mat\_over35 - 1.447\*par2 - 1.389\*par3 - 0.411\*matsmok + 0.484\*esshyp + 1.130\*prev\_gesthyp + 2.089\*prev\_diab + 0.870\*prev\_gestdiab + 0.555\*mat\_nonwhite

**28 weeks gestation:** -3.75 + 0.087\*map\_28wks + 0.017\*map\_1 + 0.030\*matbmi - 0.032\*matheight + 0.383\*mat\_over35 - 1.448\*par2 - 1.414\*par3 - 0.398\*matsmok + 0.356\*esshyp + 0.977\*prev\_gesthyp + 2.143\*prev\_diab + 0.948\*prev\_gestdiab + 0.559\*mat\_nonwhite

**31 weeks gestation:** -3.79 + 0.088\*map\_31wks + 0.014\*map\_1 + 0.038\*matbmi - 0.028\*matheight + 0.385\*mat\_over35 - 1.420\*par2 - 1.265\*par3 - 0.523\*matsmok + 0.339\*esshyp + 0.855\*prev\_gesthyp + 1.857\*prev\_diab + 0.773\*prev\_gestdiab + 0.538\*mat\_nonwhite

**34 weeks gestation:** -3.93 + 0.092\*map\_34wks + 0.019\*map\_1 + 0.030\*matbmi - 0.029\*matheight + 0.330\*mat\_over35 - 1.306\*par2 - 1.196\*par3 - 0.590\*matsmok + 0.222\*esshyp + 0.746\*prev\_gesthyp + 1.460\*prev\_diab + 0.533\*prev\_gestdiab + 0.560\*mat\_nonwhite

**36 weeks gestation:** -4.32 + 0.113\*map\_36wks + 0.016\*map\_1 + 0.023\*matbmi - 0.029\*matheight + 0.136\*mat\_over35 - 1.166\*par2 - 1.075\*par3 - 0.411\*matsmok - 0.134\*esshyp + 0.550\*prev\_gesthyp + 1.621\*prev\_diab + 0.854\*prev\_gestdiab + 0.684\*mat\_nonwhite

**Model 3**

**20 weeks gestation:** -3.53 + 0.061\*map\_dev\_20 + 0.043\*map\_1 + 0.054\*matbmi - 0.031\*matheight + 0.321\*mat\_over35 - 1.589\*par2 - 1.553\*par3 - 0.491\*matsmok + 0.541\*esshyp + 1.164\*prev\_gesthyp + 2.196\*prev\_diab + 0.901\*prev\_gestdiab + 0.531\*mat\_nonwhite

**25 weeks gestation:** -3.64 + 0.077\*map\_dev\_25 + 0.043\*map\_1 + 0.049\*matbmi - 0.031\*matheight + 0.309\*mat\_over35 - 1.515\*par2 - 1.456\*par3 - 0.452\*matsmok + 0.479\*esshyp + 1.136\*prev\_gesthyp + 2.080\*prev\_diab + 0.882\*prev\_gestdiab + 0.566\*mat\_nonwhite

**28 weeks gestation:** -3.69 + 0.087\*map\_dev\_28 + 0.042\*map\_1 + 0.049\*matbmi - 0.033\*matheight + 0.384\*mat\_over35 - 1.532\*par2 - 1.496\*par3 - 0.441\*matsmok + 0.351\*esshyp + 0.981\*prev\_gesthyp + 2.139\*prev\_diab + 0.964\*prev\_gestdiab + 0.568\*mat\_nonwhite

**31 weeks gestation:** -3.76 + 0.088\*map\_dev\_31 + 0.039\*map\_1 + 0.059\*matbmi - 0.028\*matheight + 0.385\*mat\_over35 - 1.517\*par2 - 1.361\*par3 - 0.570\*matsmok + 0.338\*esshyp + 0.861\*prev\_gesthyp + 1.852\*prev\_diab + 0.790\*prev\_gestdiab + 0.545\*mat\_nonwhite

**34 weeks gestation:** -3.90 + 0.093\*map\_dev\_34 + 0.046\*map\_1 + 0.060\*matbmi - 0.029\*matheight + 0.333\*mat\_over35 - 1.437\*par2 - 1.330\*par3 - 0.649\*matsmok + 0.214\*esshyp + 0.744\*prev\_gesthyp + 1.441\*prev\_diab + 0.544\*prev\_gestdiab + 0.575\*mat\_nonwhite

**36 weeks gestation:** -4.22 + 0.113\*map\_dev\_36 + 0.050\*map\_1 + 0.073\*matbmi - 0.029\*matheight + 0.133\*mat\_over35 - 1.370\*par2 - 1.294\*par3 - 0.502\*matsmok - 0.127\*esshyp + 0.546\*prev\_gesthyp + 1.609\*prev\_diab + 0.831\*prev\_gestdiab + 0.702\*mat\_nonwhite

**Prediction Models for Preterm Birth:**

The logistic regression models used to predict preterm birth in ALSPAC are shown below. The risk of preterm birth is calculated as where ***βX*** is as follows:

map\_1 = MAP at the initial visit esshyp = Essential hypertension

norm\_wt = normal weight matheight = Maternal height

over\_wt = overweight prev\_gesthyp = Gestational hypertension in a previous pregnancy

obese = obese prev\_diab = Existing diabetes

par2 = Parity of 1 prev\_gestdiab = Gestational diabetes in a previous pregnancy

par3 = Parity of 2 or more mat\_nonwhite = Maternal non-white ethnicity

**Model 1**

-2.39 - 0.003\*map\_1 - 0.439\*norm\_wt - 0.468\*over\_wt - 0.562\*obese - 0.027\*matheight - 0.501\*par2 - 0.229\*par3 + 0.497\*esshyp + 0.403\*prev\_gesthyp + 2.026\*prev\_diab + 1.167\*prev\_gestdiab + 0.746\*mat\_nonwhite

**Model 2**

**20 weeks gestation:** -2.38 + 0.005\*map\_20wks - 0.005\*map\_1 - 0.447\*norm\_wt - 0.487\*over\_wt - 0.592\*obese - 0.028\*matheight - 0.496\*par2 - 0.223\*par3 + 0.474\*esshyp + 0.387\*prev\_gesthyp + 2.016\*prev\_diab + 1.164\*prev\_gestdiab + 0.753\*mat\_nonwhite

**25 weeks gestation:** -2.37 + 0.023\*map\_25wks - 0.011\*map\_1 - 0.477\*norm\_wt - 0.549\*over\_wt - 0.679\*obese - 0.029\*matheight - 0.465\*par2 - 0.191\*par3 + 0.406\*esshyp + 0.343\*prev\_gesthyp + 1.889\*prev\_diab + 1.148\*prev\_gestdiab + 0.776\*mat\_nonwhite

**28 weeks gestation:** -2.46 + 0.030\*map\_28wks - 0.014\*map\_1 - 0.451\*norm\_wt - 0.548\*over\_wt - 0.709\*obese - 0.030\*matheight - 0.447\*par2 - 0.150\*par3 + 0.363\*esshyp + 0.311\*prev\_gesthyp + 1.908\*prev\_diab + 1.045\*prev\_gestdiab + 0.735\*mat\_nonwhite

**31 weeks gestation:** -2.59 + 0.049\*map\_31wks - 0.023\*map\_1 - 0.450\*norm\_wt - 0.542\*over\_wt - 0.748\*obese - 0.031\*matheight - 0.379\*par2 - 0.082\*par3 + 0.247\*esshyp + 0.145\*prev\_gesthyp + 1.702\*prev\_diab + 1.057\*prev\_gestdiab + 0.711\*mat\_nonwhite

**34 weeks gestation:** -2.95 + 0.068\*map\_34wks - 0.024\*map\_1 - 0.422\*norm\_wt - 0.619\*over\_wt - 0.824\*obese - 0.037\*matheight - 0.222\*par2 + 0.029\*par3 + 0.014\*esshyp + 0.038\*prev\_gesthyp + 1.195\*prev\_diab + 1.035\*prev\_gestdiab + 0.743\*mat\_nonwhite

**36 weeks gestation:** -3.86 + 0.076\*map\_36wks - 0.025\*map\_1 - 0.385\*norm\_wt - 0.567\*over\_wt - 0.748\*obese - 0.046\*matheight + 0.146\*par2 + 0.230\*par3 - 0.088\*esshyp - 0.023\*prev\_gesthyp + 1.173\*prev\_diab + 0.723\*prev\_gestdiab + 0.873\*mat\_nonwhite

**Model 3**

**20 weeks gestation:** -2.39 + 0.006\*map\_dev\_20 - 0.003\*map\_1 - 0.441\*norm\_wt - 0.468\*over\_wt - 0.563\*obese - 0.028\*matheight - 0.501\*par2 - 0.228\*par3 + 0.471\*esshyp + 0.385\*prev\_gesthyp + 2.013\*prev\_diab + 1.164\*prev\_gestdiab + 0.754\*mat\_nonwhite

**25 weeks gestation:** -2.42 + 0.024\*map\_dev\_25 - 0.004\*map\_1 - 0.439\*norm\_wt - 0.465\*over\_wt - 0.559\*obese - 0.029\*matheight - 0.488\*par2 - 0.214\*par3 + 0.402\*esshyp + 0.341\*prev\_gesthyp + 1.882\*prev\_diab + 1.148\*prev\_gestdiab + 0.779\*mat\_nonwhite

**28 weeks gestation:** -2.50 + 0.031\*map\_dev\_28 - 0.004\*map\_1 - 0.396\*norm\_wt - 0.437\*over\_wt - 0.552\*obese - 0.030\*matheight - 0.479\*par2 - 0.182\*par3 + 0.358\*esshyp + 0.309\*prev\_gesthyp + 1.901\*prev\_diab + 1.046\*prev\_gestdiab + 0.738\*mat\_nonwhite

**31 weeks gestation:** -2.68 + 0.049\*map\_dev\_31 - 0.008\*map\_1 - 0.369\*norm\_wt - 0.374\*over\_wt - 0.490\*obese - 0.031\*matheight - 0.437\*par2 - 0.141\*par3 + 0.244\*esshyp + 0.144\*prev\_gesthyp + 1.695\*prev\_diab + 1.057\*prev\_gestdiab + 0.714\*mat\_nonwhite

**34 weeks gestation:** -3.06 + 0.068\*map\_dev\_34 - 0.003\*map\_1 - 0.334\*norm\_wt - 0.397\*over\_wt - 0.395\*obese - 0.037\*matheight - 0.319\*par2 - 0.071\*par3 + 0.011\*esshyp + 0.036\*prev\_gesthyp + 1.185\*prev\_diab + 1.031\*prev\_gestdiab + 0.748\*mat\_nonwhite

**36 weeks gestation:** -3.95 + 0.075\*map\_dev\_36 - 0.003\*map\_1 - 0.292\*norm\_wt - 0.322\*over\_wt - 0.135\*obese - 0.046\*matheight + 0.014\*par2 + 0.093\*par3 - 0.089\*esshyp - 0.023\*prev\_gesthyp + 1.165\*prev\_diab + 0.718\*prev\_gestdiab + 0.873\*mat\_nonwhite

**Prediction Models for Small-For-Gestational Age:**

The logistic regression models used to predict small-for-gestational age in ALSPAC are shown below. The risk of small-for-gestational age is calculated as where ***βX*** is as follows:

map\_1 = MAP at the initial visit matsmok = Maternal smoking in the first trimester

norm\_wt = normal weight esshyp = Essential hypertension

over\_wt= overweight matheight = Maternal height

obese = obese prev\_gesthyp = Gestational hypertension in a previous pregnancy

mat\_over 35 = Maternal age over 35 years prev\_gestdiab = Gestational diabetes in a previous pregnancy

par2 = Parity of 1 mat\_nonwhite = Maternal non-white ethnicity

par3 = Parity of 2 or more

**Model 1**

-1.64 + 0.003\*map\_1 - 0.625\*norm\_wt - 0.791\*over\_wt - 1.072\*obese - 0.058\*matheight + 0.182\*mat\_over35 - 0.756\*par2 - 0.824\*par3 + 0.850\*matsmok + 0.447\*esshyp + 0.209\*prev\_gesthyp - 1.445\*prev\_gestdiab + 0.856\*mat\_nonwhite

**Model 2**

**20 weeks gestation:** -1.64 + 0.000\*map\_20wks + 0.003\*map\_1 - 0.626\*norm\_wt - 0.792\* over\_wt - 1.073\*obese - 0.058\*matheight + 0.182\*mat\_over35 - 0.756\*par2 - 0.824\*par3 + 0.851\*matsmok + 0.446\*esshyp + 0.208\*prev\_gesthyp - 1.445\*prev\_gestdiab + 0.857\*mat\_nonwhite

**25 weeks gestation:** -1.64 - 0.004\*map\_25wks + 0.005\*map\_1 - 0.620\*norm\_wt - 0.777\* over\_wt - 1.051\*obese - 0.058\*matheight + 0.186\*mat\_over35 - 0.762\*par2 - 0.831\*par3 + 0.847\*matsmok + 0.463\*esshyp + 0.219\*prev\_gesthyp -1.438\*prev\_gestdiab + 0.852\*mat\_nonwhite

**28 weeks gestation:** -1.63 + 0.003\*map\_28wks + 0.002\*map\_1 - 0.635\*norm\_wt - 0.804\*over\_wt - 1.093\*obese - 0.058\*matheight + 0.183\*mat\_over35 - 0.752\*par2 - 0.821\*par3 + 0.851\*matsmok + 0.428\*esshyp + 0.195\*prev\_gesthyp - 1.411\*prev\_gestdiab + 0.877\*mat\_nonwhite

**31 weeks gestation:** -1.63 + 0.013\*map\_31wks - 0.001\*map\_1 - 0.646\*norm\_wt - 0.829\*over\_wt - 1.127\*obese - 0.059\*matheight + 0.182\*mat\_over35 - 0.732\*par2 - 0.783\*par3 + 0.848\*matsmok + 0.342\*esshyp + 0.122\*prev\_gesthyp - 1.432\*prev\_gestdiab + 0.886\*mat\_nonwhite

**34 weeks gestation:** -1.64 + 0.020\*map\_34wks - 0.003\*map\_1 - 0.648\*norm\_wt - 0.861\*over\_wt - 1.203\*obese - 0.060\*matheight + 0.171\*mat\_over35 - 0.692\*par2 - 0.745\*par3 + 0.857\*matsmok + 0.254\*esshyp + 0.069\*prev\_gesthyp - 1.399\*prev\_gestdiab + 0.921\*mat\_nonwhite

**36 weeks gestation:** -1.67 + 0.011\*map\_36wks - 0.001\*map\_1 - 0.624\*norm\_wt - 0.819\*over\_wt - 1.158\*obese - 0.059\*matheight + 0.170\*mat\_over35 - 0.700\*par2 - 0.754\*par3 + 0.850\*matsmok + 0.256\*esshyp + 0.083\*prev\_gesthyp - 1.360\*prev\_gestdiab + 0.892\*mat\_nonwhite

**Model 3**

**20 weeks gestation:** -1.64 + 0.001\*map\_dev\_20 + 0.003\*map\_1 - 0.625\*norm\_wt - 0.791\*over\_wt - 1.072\*obese - 0.058\*matheight + 0.182\*mat\_over35 - 0.756\*par2 - 0.824\*par3 + 0.850\*matsmok + 0.445\*esshyp + 0.207\*prev\_gesthyp - 1.445\*prev\_gestdiab + 0.857\*mat\_nonwhite

**25 weeks gestation:** -1.64 - 0.004\*map\_dev\_25 + 0.004\*map\_1 - 0.626\*norm\_wt - 0.791\*over\_wt - 1.071\*obese - 0.058\*matheight + 0.186\*mat\_over35 - 0.758\*par2 - 0.826\*par3 + 0.849\*matsmok + 0.462\*esshyp + 0.218\*prev\_gesthyp - 1.438\*prev\_gestdiab + 0.853\*mat\_nonwhite

**28 weeks gestation:** -1.63 + 0.004\*map\_dev\_28 + 0.003\*map\_1 - 0.630\*norm\_wt - 0.792\*over\_wt - 1.076\*obese - 0.058\*matheight + 0.183\*mat\_over35 - 0.756\*par2 - 0.825\*par3 + 0.850\*matsmok + 0.427\*esshyp + 0.194\*prev\_gesthyp - 1.411\*prev\_gestdiab + 0.877\*mat\_nonwhite

**31 weeks gestation:** -1.65 + 0.013\*map\_dev\_31 + 0.003\*map\_1 - 0.626\*norm\_wt - 0.785\*over\_wt - 1.060\*obese - 0.059\*matheight + 0.182\*mat\_over35 - 0.747\*par2 - 0.799\*par3 + 0.841\*matsmok + 0.341\*esshyp + 0.122\*prev\_gesthyp - 1.432\*prev\_gestdiab + 0.887\*mat\_nonwhite

**34 weeks gestation:** -1.67 + 0.020\*map\_dev\_34 + 0.003\*map\_1 - 0.625\*norm\_wt - 0.798\*over\_wt - 1.081\*obese - 0.060\*matheight + 0.172\*mat\_over35 - 0.720\*par2 - 0.774\*par3 + 0.844\*matsmok + 0.254\*esshyp + 0.069\*prev\_gesthyp - 1.400\*prev\_gestdiab + 0.921\*mat\_nonwhite

**36 weeks gestation:** -1.68 + 0.011\*map\_dev\_36 + 0.002\*map\_1 - 0.613\*norm\_wt - 0.786\*over\_wt - 1.072\*obese - 0.059\*matheight + 0.171\*mat\_over35 - 0.719\*par2 - 0.772\*par3 + 0.842\*matsmok + 0.256\*esshyp + 0.082\*prev\_gesthyp - 1.361\*prev\_gestdiab 0.892\*mat\_nonwhite

**Recalibration in SWS**

Prediction models for preeclampsia at each gestational age were recalibrated for use in the SWS using the equation:

Logit(probability of preeclampsia in SWS) = αrecal + βrecal (***βXALSPAC)***

where ***βXALSPAC*** are the parameters from the logistic regression in the ALSPAC cohort as detailed above and αrecal and βrecal represent the extent to which the intercept and the slope respectively of the regression model need to be altered for recalibration to the SWS cohort.

The values of αrecal and βrecal for each of the models at each gestational age are given in the table below.

**Table: Recalibration parameters for each of the prediction models for preeclampsia**

|  |  |  |  |
| --- | --- | --- | --- |
| **Gestational age** | **Model** | **αrecal** | **βrecal** |
| **Initial model** | 1 | -1.55 (-2.29, -0.82) | 0.73 (0.51, 0.95) |
| **20 weeks** | 2 | -1.38 (-2.08, -0.68) | 0.75 (0.54, 0.95) |
| 3 | -1.38 (-2.08, -0.68) | 0.74 (0.54, 0.95) |
| **25 weeks** | 2 | -1.38 (-2.04, -0.72) | 0.73 (0.54, 0.93) |
| 3 | -1.39 (-2.05, -0.73) | 0.73 (0.53, 0.92) |
| **28 weeks** | 2 | -1.03 (-1.78, -0.28) | 0.87 (0.66, 1.09) |
| 3 | -1.03 (-1.79, -0.27) | 0.87 (0.65, 1.09) |
| **31 weeks** | 2 | -0.85 (-1.54, -0.16) | 0.93 (0.72, 1.14) |
| 3 | -0.85 (-1.54, -0.16) | 0.93 (0.72, 1.14) |
| **34 weeks** | 2 | -0.61 (-1.20, -0.01) | 1.00 (0.80, 1.19) |
| 3 | -0.61 (-1.21, -0.01) | 0.99 (0.79, 1.19) |
| **36 weeks** | 2 | -0.53 (-1.29, -0.23) | 0.98 (0.77, 1.18) |
| 3 | -0.54 (-1.28, 0.19) | 0.97 (0.77, 1.17) |

**References**

1. Harrell FE, Jr. *Regression modeling strategies: With applications to linear models, logistic regression and survival analysis.* New York: Springer; 2001.
2. Tilling K, Sterne JAC, Wolfe CDA. Multilevel growth curve models with covariate effects: Application to recovery after stroke. *Stat Med*. 2001;20:685-704.
3. Pan HQ, Goldstein H. Multi-level models for longitudinal growth norms. *Stat Med*. 1997;16:2665-2678

Supplementary Table S1 Comparison of the sources and definitions of outcomes and predictor variables in ALSPAC and SWS

|  |  |  |
| --- | --- | --- |
| **Variable** | **How this was measured/defined in ALSPAC** | **How this was measured/defined in SWS** |
| Preeclampsia | Derived from all blood pressure and urine dipstick measurements taken during pregnancy: SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg along with proteinuria of 1+ or more on 2 occasions after 20 weeks gestation in a previously normotensive woman. | Diagnosis of preeclampsia recorded in and abstracted from obstetric records. |
| Preterm birth | Gestational age at delivery was calculated based on the final clinical estimate of the expected delivery date from obstetric records (mainly based on the last menstrual period date but for a small (unknown) proportion updated following a dating scan).  Preterm birth was defined as delivery at < 37 weeks. | A computerised algorithm was used to derive gestational age using menstrual data (66%) or, when these were uncertain or discrepant with ultrasound assessments, fetal anthropometry in early pregnancy was used.  Preterm birth was defined as delivery at < 37 weeks. |
| Small for gestational age | Birth weight was internally standardised for gestational age at birth and small for gestational age was defined as below the 10th percentile of this measure. | Birth weight was internally standardised for gestational age at birth and small for gestational age was defined as below the 10th percentile of this measure. |
| Initial MAP | The first antenatal measurement of MAP (abstracted from obstetric records), provided that this occurred before 18 weeks gestation | The first antenatal measurement of MAP (abstracted from obstetric records), provided that this occurred before 18 weeks gestation |
| MAP at X weeks gestation | Derived from the closest measure of MAP in the obstetric records occurring within +/- 2 weeks of gestational age X | Derived from the closest measure of MAP in the obstetric records occurring within +/- 2 weeks of gestational age X |
| Maternal BMI | Derived from self-reported maternal height and pre-pregnancy weight from a questionnaire administered in pregnancy | Derived from height measured by research staff prior to pregnancy and self-reported pre-pregnancy weight from an interview at 11 weeks gestation. |
| Maternal height | Self-reported in a questionnaire administered in pregnancy. | Measured by research staff prior to pregnancy. |
| Maternal age | Abstracted from obstetric records. | Abstracted from obstetric records. |
| Maternal parity | Self-reported in a questionnaire administered in pregnancy. | Self-reported at an interview prior to pregnancy. |
| Maternal smoking in pregnancy | Self-reported in a questionnaire at 18 weeks gestation. Women who reported smoking either in the first 3 months of pregnancy or within 2 weeks of the 18 week questionnaire were classed as having smoked during pregnancy. | Self-reported at interviews at 11 and 34 weeks gestation. Women who reported smoking on either occasion were classed as having smoked during pregnancy. An algorithm incorporating information from prior to pregnancy and at 6 months postpartum was used to infer smoking status where one or both measures of smoking were missing. |
| Pre-existing maternal hypertension | Self-reported in a questionnaire administered in pregnancy as having previously had hypertension outside of pregnancy. | Self-reported at an interview at 11 weeks gestation as having previously had high blood pressure outside of pregnancy. |
| Previous gestational hypertension | Self-reported in a questionnaire administered in pregnancy as having previously had hypertension but only in pregnancy. | Self-reported at an interview at 11 weeks gestation as having previously had high blood pressure in pregnancy. |
| Pre-existing diabetes | Self-reported in a questionnaire administered in pregnancy as having previously had diabetes outside of pregnancy. | Self-reported at an interview at 11 weeks gestation as having previously had diabetes outside of pregnancy. |
| Previous gestational diabetes | Self-reported in a questionnaire administered in pregnancy as having previously had diabetes but only in pregnancy. | Self-reported at an interview at 11 weeks gestation as having previously had diabetes in pregnancy. |
| Maternal non-white ethnicity | Self-reported in a questionnaire administered during pregnancy. All ethnicities other than “white” were classed as “non-white”. | Self-reported at an interview prior to pregnancy. All ethnicities other than “white” were classed as “non-white”. |
| Offspring sex | Abstracted from obstetric records. | Abstracted from obstetric records. |

|  |  |  |  |
| --- | --- | --- | --- |
| **Model** | **Preeclampsia** | **Preterm birth** | **Small for gestational age** |
| Model 1 | Initial MAP (continuous)  Maternal BMI (continuous)  Maternal height (continuous)  Maternal age over 35 years (binary)  Maternal parity (3 categories: 0 (ref), 1, 2+)  Maternal smoking in pregnancy (binary)  Pre-existing hypertension (binary)  Previous gestational hypertension (binary)  Pre-existing diabetes (binary)  Previous gestational diabetes (binary)  Maternal non-white ethnicity (binary | Initial MAP (continuous)  Maternal BMI (4 categories: underweight (ref), normal, overweight, obese)  Maternal height (continuous)  Maternal parity (3 categories: 0 (ref), 1, 2+)  Pre-existing hypertension (binary)  Previous gestational hypertension (binary)  Pre-existing diabetes (binary)  Previous gestational diabetes (binary)  Maternal non-white ethnicity (binary) | Initial MAP (continuous)  Maternal BMI (4 categories: underweight (ref), normal, overweight, obese)  Maternal height (continuous)  Maternal age over 35 years (binary)  Maternal parity (3 categories: 0 (ref), 1, 2+)  Maternal smoking in pregnancy (binary)  Pre-existing hypertension (binary)  Previous gestational hypertension (binary)  Previous gestational diabetes (binary)  Maternal non-white ethnicity (binary) |
| Model 2 | As Model 1 plus current MAP (continuous) | As Model 1 plus current MAP (continuous) | As Model 1 plus current MAP (continuous) |
| Model 3 | As Model 1 plus current deviation of MAP from the normative value (continuous) | As Model 1 plus current deviation of MAP from the normative value (continuous) | As Model 1 plus current deviation of MAP from the normative value (continuous) |
| Model 4 | As Model 1 plus both current MAP and current deviation of MAP from the normative value (continuous) | As Model 1 plus both current MAP and current deviation of MAP from the normative value (continuous) | As Model 1 plus both current MAP and current deviation of MAP from the normative value (continuous) |

Supplementary Table S2 Summary of risk factors included in prediction models for preeclampsia, preterm birth and small for gestational age at each stage of gestation

Supplementary Table S3 Cumulative number of women who had delivered and developed preeclampsia at each gestational age

|  |  |  |  |
| --- | --- | --- | --- |
| Gestational age | Number (%) of participants who  **had delivered** | | Number (%) of participants who had developed preeclampsia in ALSPAC |
| ALSPAC | SWS |
| 20 weeks | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 25 weeks | 7 (0.1) | 0 (0.0) | 4 (0.0) |
| 28 weeks | 31 (0.2) | 6 (0.2) | 15 (0.1) |
| 31 weeks | 89 (0.7) | 17 (0.6) | 36 (0.3) |
| 34 weeks | 207 (1.6) | 40 (1.3) | 60 (0.5) |
| 36 weeks | 431 (3.3) | 102 (3.4) | 107 (0.8) |

Supplementary Table S4 Characteristics of pregnancies in the observed and imputed data in ALSPAC and the SWS

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristics** | | | **ALSPAC** | | | | **SWS** | | | |
| N (%) missing | N with data | Observed  Mean (SD)/ % | Imputed  Mean (SD)/ % | N (%) missing | N with data | Observed  Mean (SD)/ % | Imputed  Mean (SD)/ % |
| Preeclampsia | | No | 0  (0.0) | 12679 | 97.6 | 97.6 | 0  (0.0) | 2917 | 97.1 | 97.1 |
| Yes | 317 | 2.4 | 2.4 | 88 | 2.9 | 2.9 |
| Preterm | | No | 0  (0.0) | 12298 | 94.6 | 94.6 | 0  (0.0) | 2837 | 94.4 | 94.4 |
| Yes | 698 | 5.4 | 5.4 | 168 | 5.6 | 5.6 |
| Small-for-gestational age | | No | 152  (1.2) | 11567 | 90.1 | 90.1 | 4  (0.13) | 2701 | 90.0 | 90.0 |
| Yes | 1277 | 9.9 | 9.9 | 300 | 10.0 | 10.0 |
| Maternal BMI | | | 2179 (16.8) | 10817 | 23.0 (3.9) | 23.0 (3.8) | 468 (15.6) | 2537 | 24.9 (4.7) | 24.9 (4.7) |
|  | Underweight | |  | 549 | 5.1 | 5.9 |  | 54 | 2.1 | 2.7 |
| Normal | | 8014 | 74.1 | 72.4 | 1505 | 59.3 | 57.6 |
| Overweight | | 1642 | 15.2 | 16.4 | 646 | 25.5 | 26.6 |
| Obese | | 612 | 5.7 | 5.4 | 332 | 13.1 | 13.1 |
| Maternal height | | | 1536 (11.8) | 11460 | 164.0 (6.7) | 163.9 (6.7) | 15  (0.5) | 2990 | 163.2 (6.4) | 163.2 (6.4) |
| Maternal age | | | 0  (0.0) | 12996 | 27.9 (5.0) | 27.9 (5.0) | 0  (0.0) | 3005 | 30.6 (3.8) | 30.6 (3.8) |
|  | | Up to 34 years |  | 11722 | 90.2 | 90.2 |  | 2590 | 86.2 | 86.2 |
| 35+ years | 1274 | 9.8 | 9.8 | 415 | 13.8 | 13.8 |
| Parity | | Nulliparous | 924  (7.1) | 5509 | 45.6 | 45.9 | 2  (0.1) | 1522 | 50.7 | 50.7 |
| 1 | 4171 | 34.6 | 34.4 | 990 | 33.0 | 33.0 |
| 2+ | 2392 | 19.8 | 19.7 | 491 | 16.4 | 16.3 |
| Maternal smoking in pregnancy | | No | 795  (6.1) | 9101 | 74.6 | 74.1 | 140  (4.7) | 2394 | 83.6 | 83.4 |
| Yes | 3100 | 25.4 | 25.9 | 471 | 16.4 | 16.6 |
| Essential hypertension | | No | 1555 (12.0) | 11011 | 96.2 | 96.3 | 293  (9.8) | 2644 | 97.5 | 97.4 |
| Yes | 430 | 3.8 | 3.7 | 68 | 2.5 | 2.6 |
| Previous gestational hypertension | | No | 1073 (8.3) | 10900 | 91.4 | 91.0 | 1626 (54.1) | 1215 | 88.1 | 62.4 |
| Yes | 1023 | 8.6 | 9.0 | 164 | 11.9 | 37.6 |
| Diabetes | | No | 1380 (10.6) | 11573 | 99.6 | 99.6 | 294  (9.8) | 2699 | 99.6 | 99.4 |
| Yes | 43 | 0.4 | 0.4 | 12 | 0.4 | 0.6 |
| Previous gestational diabetes | | No | 991  (7.6) | 11947 | 99.5 | 99.5 | 1627 (54.1) | 1361 | 98.8 | 91.7 |
| Yes | 58 | 0.5 | 0.5 | 17 | 1.2 | 8.3 |
| Maternal ethnicity | | White | 1426 (11.0) | 11265 | 97.4 | 97.2 | 0  (0.0) | 2868 | 95.4 | 95.4 |
| Non-white | 305 | 2.6 | 2.8 | 137 | 4.6 | 4.6 |

Supplementary Table S5 Mean arterial pressure in the observed and imputed datasets in ALSPAC and the SWS

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Blood pressure**  **(mm Hg)** | **ALSPAC** | | | | | **SWS** | | | | |
| N not yet delivered | N (%) missing | N with data | Observed  Mean (SD) | Imputed  Mean (SD) | N not yet delivered | N (%) missing | N with data | Observed  Mean (SD) | Imputed  Mean (SD) |
| Initial MAP | 12996 | 919 (7.1) | 12077 | 81.3 (8.8) | 81.3 (8.8) | 3005 | 114 (3.8) | 2891 | 81.9 (8.7) | 81.9 (8.7) |
| MAP at 20 weeks | 12996 | 1759 (13.5) | 11237 | 80.3 (8.5) | 80.3 (8.5) | 3005 | 317 (10.5) | 2688 | 80.3 (8.4) | 80.2 (8.4) |
| MAP at 25 weeks | 12989 | 1432 (11.0) | 11557 | 80.9 (8.5) | 80.9 (8.5) | 3005 | 213 (7.1) | 2792 | 81.2 (8.4) | 81.2 (8.4) |
| MAP at 28 weeks | 12965 | 884 (6.8) | 12081 | 81.4 (8.6) | 81.4 (8.6) | 2999 | 81 (2.7) | 2918 | 81.8 (8.5) | 81.7 (8.5) |
| MAP at 31 weeks | 12907 | 657 (5.1) | 12250 | 82.2 (8.7) | 82.1 (8.7) | 2988 | 69 (2.3) | 2919 | 82.7 (8.7) | 82.6 (8.7) |
| MAP at 34 weeks | 12789 | 366 (2.9) | 12423 | 83.0 (9.2) | 83.0 (9.2) | 2965 | 32 (1.1) | 2933 | 83.5 (9.2) | 83.5 (9.2) |
| MAP at 36 weeks | 12565 | 329 (2.6) | 12236 | 84.4 (9.7) | 84.3 (9.7) | 2903 | 19 (0.7) | 2884 | 84.8 (9.3) | 84.8 (9.3) |

Supplementary Table S6 Unadjusted associations of each of the potential predictor variables with preeclampsia, preterm birth and small-for-gestational age in ALSPAC (N=12996) and SWS (N=3005)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **Preeclampsia** | | **Preterm birth** | | **Small-for-gestational age** | |
| **ALSPAC** | **SWS** | **ALSPAC** | **SWS** | **ALSPAC** | **SWS** |
| **Odds ratio (95% CI)** | **Odds ratio**  **(95% CI)** | **Odds ratio**  **(95% CI)** | **Odds ratio**  **(95% CI)** | **Odds ratio**  **(95% CI)** | **Odds ratio**  **(95% CI)** |
| Initial MAP (mmHg) | | 1.07  (1.06, 1.09) | 1.05  (1.02, 1.07) | 1.00  (0.99, 1.01) | 1.02  (1.00, 1.04) | 0.99  (0.99, 1.00) | 0.99  (0.98, 1.00) |
| MAP at 20 weeks (mmHg) | | 1.09  (1.08, 1.11) | 1.07 (1.04, 1.10) | 1.00  (1.00, 1.01) | 1.02  (1.00, 1.04) | 0.99  (0.99, 1.00) | 0.99  (0.98, 1.01) |
| MAP at 25 weeks (mmHg) | | 1.11  (1.10, 1.12) | 1.08  (1.05, 1.10) | 1.02  (1.01, 1.03) | 1.03  (1.01, 1.05) | 0.99  (0.98, 1.00) | 0.99  (0.97, 1.00) |
| MAP at 28 weeks (mmHg) | | 1.11  (1.10, 1.13) | 1.12  (1.09, 1.15) | 1.03  (1.02, 1.04) | 1.04  (1.02, 1.06) | 1.00  (0.99, 1.00) | 1.01  (0.99, 1.02) |
| MAP at 31 weeks (mmHg) | | 1.12  (1.11, 1.13) | 1.13  (1.11, 1.16) | 1.05  (1.04, 1.06) | 1.05  (1.04, 1.07) | 1.01  (1.00, 1.02) | 1.01  (1.00, 1.03) |
| MAP at 34 weeks (mmHg) | | 1.13  (1.12, 1.14) | 1.14  (1.11, 1.16) | 1.07  (1.07, 1.08) | 1.07  (1.06, 1.09) | 1.02  (1.01, 1.02) | 1.01  (1.00, 1.03) |
| MAP at 36 weeks (mmHg) | | 1.14  (1.13, 1.15) | 1.15  (1.13, 1.18) | 1.08  (1.07, 1.09) | 1.07  (1.05, 1.08) | 1.01  (1.01, 1.02) | 1.01  (1.00, 1.02) |
| Maternal BMI (kg/m2) | | 1.10  (1.07, 1.12) | 1.05  (1.01, 1.10) | 0.99  (0.97, 1.01) | 0.99  (0.96, 1.03) | 0.95  (0.93, 0.96) | 0.94  (0.91, 0.97) |
| Maternal height (cm) | | 0.98  (0.96, 1.00) | 1.01  (0.98, 1.04) | 0.97  (0.96, 0.98) | 0.98  (0.95, 1.00) | 0.95  (0.94, 0.96) | 0.93  (0.92, 0.95) |
| Maternal age over 35 years | | 1.42  (1.02, 1.97) | 0.70  (0.35, 1.42) | 0.98  (0.75, 1.26) | 0.84  (0.52, 1.35) | 0.90  (0.74, 1.10) | 1.08  (0.77, 1.51) |
| Maternal parity | 0 (ref) | 1 | 1 | 1 | 1 | 1 | 1 |
| 1 | 0.33  (0.24, 0.45) | 0.16  (0.08, 0.33) | 0.65  (0.54, 0.79) | 0.77  (0.54, 1.10) | 0.48  (0.42, 0.55) | 0.42  (0.31, 0.56) |
| 2 or more | 0.39  (0.27, 0.56) | 0.20  (0.08, 0.49) | 0.88  (0.71, 1.08) | 0.73  (0.46, 1.17) | 0.50  (0.42, 0.60) | 0.51  (0.35, 0.74) |
| Maternal smoking in pregnancy | | 0.53  (0.38, 0.73) | 0.78  (0.41, 1.48) | 1.11  (0.94, 1.33) | 1.64  (1.11, 2.41) | 2.32  (2.04, 2.64) | 2.63  (2.00, 3.46) |
| Pre-existing hypertension | | 3.57  (2.44, 5.24) | 5.39  (2.58, 11.25) | 1.52  (1.06, 2.18) | 2.82  (1.40, 5.66) | 1.34  (1.00, 1.80) | 2.02  (1.05, 3.90) |
| Previous gestational hypertension | | 1.86  (1.35, 2.58) | 8.97  (2.86, 28.14) | 1.20  (0.91, 1.58) | 1.75  (1.13, 2.71) | 0.74  (0.58, 0.94) | 1.85  (0.99, 3.47) |
| Pre-existing diabetes | | 12.12  (5.95, 24.69) | 6.01  (1.34, 27.07) | 7.72  (3.71, 16.08) | 5.88  (1.78, 19.45) | 1.16  (0.45, 2.97) | 1.16  (0.17, 7.91) |
| Previous gestational diabetes | | 2.24  (0.67, 7.48) | 3.37  (0.39, 28.91) | 2.99 (1.40, 6.37) | 2.04  (0.53, 7.95) | 0.17  (0.02, 1.32) | 1.00  (0.13, 7.75) |
| Maternal non-white ethnicity | | 1.55  (0.85, 2.85) | 0.48  (0.12, 1.97) | 2.32  (1.54, 3.49) | 1.67  (0.90, 3.08) | 2.60  (1.96, 3.43) | 2.22  (1.42, 3.46) |

Supplementary Table S7 AUROCs for prediction models for preeclampsia from Models 1-4 at different gestational ages in ALSPAC and the SWS\*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gestational age of prediction (X)** | **Development cohort – ALSPAC** | | | | **Validation cohort – SWS** | | | |
| **AUROC (95% CI)** | | | | **AUROC (95% CI)** | | | |
| **Model 1** | **Model 2** | **Model 3** | **Model 4** | **Model 1** | **Model 2** | **Model 3** | **Model 4** |
| 20 weeks | 0.77  (0.75, 0.80) | 0.79  (0.77, 0.82) | 0.79  (0.77, 0.82) | 0.79  (0.77, 0.82) | 0.79  (0.73, 0.85) | 0.80  (0.74, 0.85) | 0.80  (0.74, 0.85) | 0.80  (0.74, 0.85) |
|  |  | P vs M1 = 0.002 | P vs M1 = 0.001 | P vs M2 = 0.20 |  | P vs M1 = 0.47 | P vs M1 = 0.49 | P vs M2 = 0.63 |
| 25 weeks | 0.77  (0.75, 0.80) | 0.80  (0.77, 0.82) | 0.80  (0.78, 0.83) | 0.80  (0.78, 0.83) | 0.79  (0.73, 0.85) | 0.80  (0.75, 0.86) | 0.80  (0.75, 0.86) | 0.80  (0.75, 0.86) |
|  |  | P vs M1 < 0.001 | P vs M1 < 0.001 | P vs M2 = 0.16 |  | P vs M1 = 0.39 | P vs M1 = 0.38 | P vs M2 = 0.91 |
| 28 weeks | 0.77  (0.75, 0.80) | 0.81  (0.79, 0.84) | 0.81  (0.79, 0.84) | 0.81  (0.79, 0.84) | 0.79  (0.73, 0.85) | 0.84  (0.79, 0.88) | 0.83  (0.78, 0.88) | 0.83  (0.78, 0.88) |
|  |  | P vs M1 < 0.001 | P vs M1 < 0.001 | P vs M2 = 0.42 |  | P vs M1 = 0.003 | P vs M1 = 0.004 | P vs M2 = 0.65 |
| 31 weeks | 0.77  (0.74, 0.79) | 0.82  (0.80, 0.85) | 0.83  (0.80, 0.85) | 0.83  (0.80, 0.85) | 0.79  (0.73, 0.85) | 0.84  (0.79, 0.89) | 0.84  (0.79, 0.89) | 0.84  (0.79, 0.89) |
|  |  | P vs M1 < 0.001 | P vs M1 < 0.001 | P vs M2 = 0.37 |  | P vs M1 = 0.008 | P vs M1 = 0.009 | P vs M2 = 0.83 |
| 34 weeks | 0.77  (0.74, 0.80) | 0.84  (0.82, 0.87) | 0.84  (0.82, 0.87) | 0.84  (0.82, 0.87) | 0.81  (0.75, 0.87) | 0.86  (0.81, 0.90) | 0.86  (0.81, 0.90) | 0.86  (0.81, 0.90) |
|  |  | P vs M1 < 0.001 | P vs M1 < 0.001 | P vs M2 = 0.29 |  | P vs M1 = 0.01 | P vs M1 = 0.01 | P vs M2 = 0.53 |
| 36 weeks | 0.77  (0.74, 0.80) | 0.88  (0.86, 0.90) | 0.88  (0.86, 0.90) | 0.88  (0.86, 0.90) | 0.80  (0.74, 0.87) | 0.88  (0.84, 0.93) | 0.88  (0.84, 0.92) | 0.88  (0.84, 0.92) |
|  |  | P vs M1 < 0.001 | P vs M1 < 0.001 | P vs M2 = 0.15 |  | P vs M1 < 0.001 | P vs M1 < 0.001 | P vs M2 = 0.57 |

\* Model 1 includes maternal covariates and MAP at the first visit; Model 2 is as Model 1 plus the observed value of MAP at X weeks; Model 3 is as Model 1 plus the deviation of the observed value of MAP from the normogram prediction at X weeks; Model 4 is as Model 1 plus both the observed value of MAP at X weeks and the deviation of the observed value of MAP from the normogram prediction at X weeks

Supplementary Table S8 Calibration of the risk score for preeclampsia from Model 2 at 28 weeks gestation in the Southampton Women's Survey (N=2999)\*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Tenth of prediction score** | **Original scale** | | | **Recalibrated** | | |
| **Prediction score values** | | **Proportion who had**  **preeclampsia (95% CI)** | **Prediction score values** | | **Proportion who had preeclampsia (95% CI)** |
| **Mean** | **Range** | **Mean** | **Range** |
| 1 | 0.002 | 0.000 to 0.003 | 0.000 | 0.002 | (0.000, 0.002) | 0.000 |
| 2 | 0.004 | 0.003 to 0.005 | 0.001 | 0.003 | (0.002, 0.003) | 0.001 |
| 3 | 0.006 | 0.005 to 0.008 | 0.000 | 0.004 | (0.003, 0.005) | 0.000 |
| 4 | 0.010 | 0.008 to 0.013 | 0.006 | 0.006 | (0.005, 0.008) | 0.006 |
| 5 | 0.016 | 0.013 to 0.021 | 0.011 | 0.010 | (0.008, 0.012) | 0.011 |
| 6 | 0.027 | 0.021 to 0.033 | 0.018 | 0.015 | (0.012, 0.018) | 0.018 |
| 7 | 0.042 | 0.033 to 0.052 | 0.025 | 0.023 | (0.018, 0.027) | 0.025 |
| 8 | 0.067 | 0.052 to 0.086 | 0.040 | 0.035 | (0.027, 0.043) | 0.040 |
| 9 | 0.117 | 0.086 to 0.158 | 0.057 | 0.057 | (0.043, 0.076) | 0.057 |
| 10 | 0.285 | 0.158 to 0.788 | 0.132 | 0.144 | (0.077, 0.540) | 0.132 |

\* Model 2 includes maternal covariates, MAP at the first visit and MAP at 28 weeks

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Specificity** | **Risk score threshold** | **Sensitivity (95% CI)** | **Positive predictive value**  **(95% CI)** | **Negative predictive value**  **(95% CI)** | **Positive likelihood ratio**  **(95% CI)** | **Negative likelihood ratio**  **(95% CI)** | **N (%) testing positive** | **N (%) true positive** | **N (%) false positive** | **N (%) true negative** | **N (%) false negative** |
| **ALSPAC** | | | | | | | |  |  |  |  |
| 0.75 | 0.027 | 0.71  (0.66, 0.76) | 0.07  (0.06, 0.07) | 0.99  (0.99, 0.99) | 2.84  (2.62, 3.08) | 0.39  (0.32, 0.47) | 3384  (26.1) | 222  (1.7) | 3162  (24.4) | 9490  (73.2) | 91  (0.7) |
| 0.90 | 0.053 | 0.48  (0.42, 0.54) | 0.11  (0.09, 0.12) | 0.99  (0.98, 0.99) | 4.78  (4.19, 5.46) | 0.58  (0.52, 0.65) | 1413  (10.9) | 150  (1.2) | 1264  (9.7) | 11388  (87.8) | 164  (1.3) |
| 0.95 | 0.078 | 0.35  (0.29, 0.40) | 0.15  (0.12, 0.17) | 0.98  (0.98, 0.99) | 6.93  (5.8, 8.27) | 0.69  (0.63, 0.75) | 740  (5.7) | 108  (0.8) | 632  (4.9) | 12020  (92.7) | 205  (1.6) |
| **SWS (without recalibration, using ALSPAC risk score thresholds)** | | | | | | | |  |  |  |  |
| 0.58  (0.49, 0.67) | 0.027 | 0.90  (0.80, 1.00) | 0.06  (0.04, 0.08) | 1.00  (0.99, 1.00) | 2.16  (1.79, 2.61) | 0.16  (0.06, 0.40) | 1298  (43.3) | 78  (2.6) | 1219  (40.6) | 1693  (56.5) | 9  (0.3) |
| 0.73  (0.62, 0.84) | 0.053 | 0.79  (0.64, 0.95) | 0.08  (0.05, 0.11) | 0.99  (0.99, 1.00) | 2.93  (2.18, 3.94) | 0.27  (0.12, 0.60) | 866  (28.9) | 69  (2.3) | 797  (26.6) | 2115  (70.5) | 18  (0.6) |
| 0.80  (0.69, 0.91) | 0.078 | 0.66  (0.47, 0.85) | 0.09  (0.06, 0.13) | 0.99  (0.98, 0.99) | 3.36  (2.36, 4.78) | 0.41  (0.24, 0.72) | 641  (21.4) | 57  (1.9) | 583  (19.4) | 2329  (77.7) | 30  (1.0) |
| **SWS (after recalibration)** | | | | | | | |  |  |  |  |
| 0.75 | 0.034 | 0.76  (0.62, 0.90) | 0.08  (0.06, 0.11) | 0.99  (0.98, 1.00) | 3.03  (2.49, 3.69) | 0.31  (0.16, 0.60) | 794  (26.5) | 66  (2.2) | 728  (24.3) | 2184  (72.8) | 21  (0.7) |
| 0.90 | 0.075 | 0.48  (0.35, 0.62) | 0.13  (0.08, 0.17) | 0.98  (0.98, 0.99) | 4.83  (3.54, 6.58) | 0.57  (0.43, 0.75) | 333  (11.1) | 42  (1.4) | 291  (9.7) | 2621  (87.4) | 45  (1.5) |
| 0.95 | 0.114 | 0.32  (0.20, 0.43) | 0.16  (0.10, 0.22) | 0.98  (0.97, 0.98) | 6.28  (4.22, 9.36) | 0.72  (0.61, 0.85) | 173  (5.8) | 28  (0.9) | 146  (4.9) | 2766  (92.2) | 60  (2.0) |

Supplementary Table S9 Prediction of preeclampsia in ALSPAC and SWS using Model 2 at 28 weeks gestation for fixed specificities\*

\* Model 2 includes maternal covariates, MAP at the first visit and the observed value of MAP at 28 weeks

Supplementary Table S10 AUROCs for prediction models for preterm birth at different gestational ages in ALSPAC and the SWS\*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gestational age of prediction (X)** | **Development cohort – ALSPAC** | | | | **Validation cohort – SWS** | | | |
| **AUROC (95% CI)** | | | | **AUROC (95% CI)** | | | |
| **Model 1** | **Model 2** | **Model 3** | **Model 4** | **Model 1** | **Model 2** | **Model 3** | **Model 4** |
| 20 weeks | 0.61  (0.58, 0.63) | 0.61  (0.58, 0.63) | 0.61  (0.58, 0.63) | 0.61  (0.58, 0.63) | 0.60  (0.55, 0.66) | 0.61  (0.55, 0.66) | 0.61  (0.55, 0.66) | 0.62  (0.56, 0.67) |
|  |  | P vs M1 = 0.99 | P vs M1 = 0.97 | P vs M2 = 0.55 |  | P vs M1 = 0.42 | P vs M1 = 0.28 | P vs M2 = 0.006 |
| 25 weeks | 0.60  (0.58, 0.63) | 0.61  (0.59, 0.63) | 0.61  (0.59, 0.63) | 0.61  (0.59, 0.64) | 0.60  (0.55, 0.66) | 0.61  (0.56, 0.67) | 0.61  (0.56, 0.67) | 0.62  (0.57, 0.68) |
|  |  | P vs M1 = 0.36 | P vs M1 = 0.34 | P vs M2 = 0.44 |  | P vs M1 = 0.26 | P vs M1 = 0.21 | P vs M2 = 0.03 |
| 28 weeks | 0.60  (0.58, 0.63) | 0.61  (0.59, 0.64) | 0.61  (0.59, 0.64) | 0.62  (0.59, 0.64) | 0.61  (0.55, 0.66) | 0.61  (0.56, 0.67) | 0.61  (0.56, 0.67) | 0.62  (0.57, 0.68) |
|  |  | P vs M1 = 0.13 | P vs M1 = 0.12 | P vs M2 = 0.35 |  | P vs M1 = 0.65 | P vs M1 = 0.54 | P vs M2 = 0.02 |
| 31 weeks | 0.60  (0.57, 0.62) | 0.63  (0.60, 0.65) | 0.63  (0.60, 0.65) | 0.63  (0.60, 0.65) | 0.59  (0.54, 0.65) | 0.60  (0.55, 0.66) | 0.60  (0.55, 0.66) | 0.61  (0.56, 0.66) |
|  |  | P vs M1 = 0.005 | P vs M1 = 0.004 | P vs M2 = 0.44 |  | P vs M1 = 0.72 | P vs M1 = 0.62 | P vs M2 = 0.03 |
| 34 weeks | 0.60  (0.57, 0.62) | 0.66  (0.63, 0.69) | 0.66  (0.63, 0.69) | 0.66  (0.63, 0.69) | 0.58  (0.52, 0.64) | 0.65  (0.59, 0.71) | 0.65  (0.59, 0.71) | 0.65  (0.59, 0.71) |
|  |  | P vs M1 < 0.001 | P vs M1 < 0.001 | P vs M2 = 0.71 |  | P vs M1 = 0.01 | P vs M1 = 0.009 | P vs M2 = 0.07 |
| 36 weeks | 0.58  (0.54, 0.62) | 0.69  (0.65, 0.73) | 0.69  (0.65, 0.72) | 0.69  (0.65, 0.73) | 0.53  (0.45, 0.61) | 0.59  (0.51, 0.67) | 0.59  (0.51, 0.67) | 0.58  (0.51, 0.66) |
|  |  | P vs M1 < 0.001 | P vs M1 < 0.001 | P vs M2 = 0.57 |  | P vs M1 = 0.17 | P vs M1 = 0.15 | P vs M2 = 0.12 |

\* Model 1 includes maternal covariates and MAP at the first visit; Model 2 is as Model 1 plus the observed value of MAP at X weeks; Model 3 is as Model 1 plus the deviation of the observed value of MAP from the normogram prediction at X weeks; Model 4 is as Model 1 plus both the observed value of MAP at X weeks and the deviation of the observed value of MAP from the normogram prediction at X weeks

M1: Model 1; M2: Model 2

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gestational age of prediction (X)** | **Development cohort – ALSPAC** | | | | **Validation cohort – SWS** | | | |
| **AUROC (95% CI)** | | | | **AUROC (95% CI)** | | | |
| **Model 1** | **Model 2** | **Model 3** | **Model 4** | **Model 1** | **Model 2** | **Model 3** | **Model 4** |
| 20 weeks | 0.60  (0.57, 0.62) | 0.60  (0.57, 0.62) | 0.60  (0.57, 0.62) | 0.60  (0.57, 0.62) | 0.57  (0.52, 0.63) | 0.57  (0.51, 0.63) | 0.57  (0.52, 0.63) | 0.58  (0.53, 0.64) |
|  |  | P vs M1 = 0.04 | P vs M1 < 0.001 | P vs M2 = 0.59 |  | P vs M1 = 0.36 | P vs M1 = 0.19 | P vs M2 = 0.01 |
| 25 weeks | 0.59  (0.57, 0.62) | 0.60  (0.57, 0.62) | 0.60  (0.57, 0.62) | 0.60  (0.57, 0.62) | 0.57  (0.52, 0.63) | 0.57  (0.52, 0.63) | 0.57  (0.52, 0.63) | 0.59  (0.53, 0.65) |
|  |  | P vs M1 = 0.72 | P vs M1 = 0.69 | P vs M2 = 0.68 |  | P vs M1 = 0.75 | P vs M1 = 0.74 | P vs M2 = 0.02 |
| 28 weeks | 0.59  (0.57, 0.62) | 0.60  (0.57, 0.62) | 0.60  (0.57, 0.62) | 0.60  (0.58, 0.63) | 0.58  (0.52, 0.63) | 0.57  (0.52, 0.63) | 0.57  (0.52, 0.63) | 0.59  (0.53, 0.65) |
|  |  | P vs M1 = 0.24 | P vs M1 = 0.22 | P vs M2 = 0.50 |  | P vs M1 = 0.61 | P vs M1 = 0.75 | P vs M2 = 0.01 |
| 31 weeks | 0.59  (0.57, 0.62) | 0.61  (0.59, 0.64) | 0.62  (0.59, 0.64) | 0.62  (0.59, 0.64) | 0.57  (0.51, 0.62) | 0.57  (0.51, 0.62) | 0.57  (0.51, 0.62) | 0.58  (0.52, 0.64) |
|  |  | P vs M1 = 0.03 | P vs M1 = 0.03 | P vs M2 = 0.47 |  | P vs M1 = 0.92 | P vs M1 = 0.99 | P vs M2 = 0.02 |
| 34 weeks | 0.59  (0.56, 0.62) | 0.64  (0.61, 0.67) | 0.64  (0.61, 0.67) | 0.64  (0.61, 0.67) | 0.56  (0.49, 0.62) | 0.62  (0.55, 0.68) | 0.62  (0.55, 0.68) | 0.62  (0.56, 0.69) |
|  |  | P vs M1 < 0.001 | P vs M1 < 0.001 | P vs M2 = 0.65 |  | P vs M1 = 0.02 | P vs M1 = 0.02 | P vs M2 = 0.11 |
| 36 weeks | 0.57  (0.53, 0.61) | 0.67  (0.63, 0.70) | 0.66  (0.63, 0.70) | 0.67  (0.63, 0.70) | 0.53  (0.45, 0.61) | 0.59  (0.51, 0.67) | 0.59  (0.51, 0.67) | 0.58  (0.50, 0.66) |
|  |  | P vs M1 < 0.001 | P vs M1 < 0.001 | P vs M2 = 0.52 |  | P vs M1 = 0.17 | P vs M1 = 0.15 | P vs M2 = 0.10 |

Supplementary Table S11 AUROCs for prediction models for preterm birth at different gestational ages in ALSPAC and the SWS excluding women who developed preeclampsia\*

\* Model 1 includes maternal covariates and MAP at the first visit; Model 2 is as Model 1 plus the observed value of MAP at X weeks; Model 3 is as Model 1 plus the deviation of the observed value of MAP from the normogram prediction at X weeks; Model 4 is as Model 1 plus both the observed value of MAP at X weeks and the deviation of the observed value of MAP from the normogram prediction at X weeks

M1: Model 1; M2: Model 2

Supplementary Table S12 AUROCs for prediction models for small for gestational age at different gestational ages in ALSPAC and the SWS\*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gestational age of prediction (X)** | **Development cohort – ALSPAC** | | | | **Validation cohort – SWS** | | | |
| **AUROC (95% CI)** | | | | **AUROC (95% CI)** | | | |
| **Model 1** | **Model 2** | **Model 3** | **Model 4** | **Model 1** | **Model 2** | **Model 3** | **Model 4** |
| 20 weeks | 0.70  (0.68, 0.71) | 0.70  (0.68, 0.71) | 0.70  (0.68, 0.71) | 0.70  (0.68, 0.71) | 0.70  (0.61, 0.79) | 0.70  (0.61, 0.79) | 0.70  (0.61, 0.79) | 0.70  (0.61, 0.79) |
|  |  | P vs M1 < 0.001 | P vs M1 < 0.001 | P vs M2 = 0.38 |  | P vs M1 = 0.59 | P vs M1 = 0.76 | P vs M2 = 0.30 |
| 25 weeks | 0.70  (0.68, 0.71) | 0.70  (0.68, 0.71) | 0.70  (0.68, 0.71) | 0.70  (0.68, 0.71) | 0.70  (0.61, 0.79) | 0.70  (0.62, 0.79) | 0.70  (0.61, 0.79) | 0.70  (0.62, 0.79) |
|  |  | P vs M1 = 0.15 | P vs M1 = 0.13 | P vs M2 = 0.51 |  | P vs M1 = 0.55 | P vs M1 = 0.55 | P vs M2 = 0.78 |
| 28 weeks | 0.70  (0.68, 0.71) | 0.70  (0.68, 0.71) | 0.70  (0.68, 0.71) | 0.70  (0.68, 0.71) | 0.71  (0.62, 0.80) | 0.71  (0.62, 0.79) | 0.71  (0.62, 0.79) | 0.71  (0.62, 0.79) |
|  |  | P vs M1 = 0.14 | P vs M1 = 0.14 | P vs M2 = 0.73 |  | P vs M1 = 0.35 | P vs M1 = 0.31 | P vs M2 = 0.95 |
| 31 weeks | 0.70  (0.68, 0.71) | 0.70  (0.68, 0.71) | 0.70  (0.68, 0.71) | 0.70  (0.68, 0.71) | 0.70  (0.61, 0.79) | 0.70  (0.61, 0.79) | 0.70  (0.61, 0.79) | 0.70  (0.61, 0.79) |
|  |  | P vs M1 = 0.14 | P vs M1 = 0.14 | P vs M2 = 0.84 |  | P vs M1 = 0.87 | P vs M1 = 0.85 | P vs M2 = 0.52 |
| 34 weeks | 0.70  (0.68, 0.71) | 0.70  (0.68, 0.72) | 0.70  (0.68, 0.72) | 0.70  (0.68, 0.72) | 0.70  (0.61, 0.79) | 0.70  (0.61, 0.79) | 0.70  (0.61, 0.79) | 0.70  (0.61, 0.78) |
|  |  | P vs M1 = 0.07 | P vs M1 = 0.07 | P vs M2 = 0.76 |  | P vs M1 = 0.93 | P vs M1 = 0.96 | P vs M2 = 0.21 |
| 36 weeks | 0.69  (0.68, 0.71) | 0.70  (0.68, 0.71) | 0.70  (0.68, 0.71) | 0.70  (0.68, 0.71) | 0.71  (0.62, 0.80) | 0.71  (0.62, 0.80) | 0.71  (0.62, 0.80) | 0.71  (0.62, 0.80) |
|  |  | P vs M1 = 0.09 | P vs M1 = 0.09 | P vs M2 = 0.77 |  | P vs M1 = 0.92 | P vs M1 = 0.87 | P vs M2 = 0.11 |

\* Model 1 includes maternal covariates and MAP at the first visit; Model 2 is as Model 1 plus the observed value of MAP at X weeks; Model 3 is as Model 1 plus the deviation of the observed value of MAP from the normogram prediction at X weeks; Model 4 is as Model 1 plus both the observed value of MAP at X weeks and the deviation of the observed value of MAP from the normogram prediction at X weeks

M1: Model 1; M2: Model 2

Supplementary Table S13 Risk factors included in clinical risk prediction model for preeclampsia in the SCOPE study

|  |
| --- |
| **Maternal clinical risk factors model (North et al, 2011)15** |
| Age |
| MAP |
| BMI |
| Family history of preeclampsia |
| Family history of coronary heart disease |
| Woman’s birth weight |
| Vaginal bleeding ≥ 5 days |
| One miscarriage ≤ 10 weeks, same partner |
| ≥ 12 months to conceive |
| High fruit intake (≥ 3/day) |
| Alcohol consumption 1st trimester |
| Number of cigarettes smoked per day |

Supplementary Figure S1 ROC curves at 28 weeks gestation for prediction of preeclampsia in ALSPAC and SWS\*



\* Model 1 includes maternal covariates (pre-pregnancy BMI, height, age over 35, parity, smoking, essential hypertension, previous gestational hypertension, diabetes, previous gestational diabetes, non-white ethnicity) and MAP at the first visit; Model 2 is as Model 1 plus the observed value of MAP at 28 weeks; Model 3 is as Model 1 plus the deviation of the observed value of MAP from the normogram prediction at 28 weeks; Model 4 is as Model 1 plus both the observed value of MAP at 28 weeks and the deviation of the observed value of MAP from the normogram prediction at 28 weeks

Supplementary Figure S2 Expected numbers of women allocated to the low and high risk groups for preeclampsia from a cohort of 1000 women based on testing sequentially using Model 1 at booking followed by Model 2 at subsequent visits with a threshold of 0.013 at each gestational age up to 31 weeks\*

613 women at 31 weeks

(4 will develop preeclampsia)

381 women at 31 weeks

(24 will develop preeclampsia)

41 test negative

574 women at 28 weeks

(3 will develop preeclampsia)

424 women at 28 weeks

(26 will develop preeclampsia)

1 delivered

(0 with preeclampsia)

46 test negative

501 women at 20 weeks

(2 will develop preeclampsia)

499 women at 20 weeks

(27 will develop preeclampsia)

34 test negative

LOW RISK GROUP

HIGH RISK GROUP

1000 women at booking

(29 will develop preeclampsia)

467 women after initial screen

(2 will develop preeclampsia)

533 women after initial screen

(27 will develop preeclampsia)

529 women at 25 weeks

(3 will develop preeclampsia)

471 women at 25 weeks

(26 will develop preeclampsia)

1 delivered

(0 with preeclampsia)

2 delivered

(0 with preeclampsia)

2 delivered

(1 with preeclampsia)

28 test negative

\* After the initial screen, only the high risk group are included in subsequent screening tests. To obtain these numbers we determined the average threshold giving a 95% sensitivity at each stage in the Avon Longitudinal Study of Parents and Children (including the high risk group only after the initial screen), and applied this threshold in the Southampton Women’s Survey.

Model 1 includes maternal covariates and MAP at the first visit; Model 2 additionally includes MAP at the gestational age of testing.