Gestational-age-specific reference ranges for blood pressure in pregnancy: findings from a prospective cohort

Short title: Normal blood pressure ranges in pregnancy

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ABSTRACT

Objective: Pregnancy is a period of considerable change in blood pressure, with an early pregnancy decrease followed by a late pregnancy rise. High blood pressure in pregnancy is associated with adverse perinatal outcomes for the mother and offspring. We aimed to define normal ranges of blood pressure across gestation.

Methods: We used repeated antenatal blood pressure measurements (median (interquartile range) 10 (9, 11) per woman) for 10,327 women. Multilevel models were used to derive longitudinal reference ranges for systolic (SBP) and diastolic (DBP) blood pressure from 12-40 weeks gestation for the whole cohort, for women with normal pregnancies (without essential hypertension or preeclampsia who delivered an appropriate-size-for-gestational age infant at term) and for subgroups of normal pregnancies defined by different levels of maternal pre-pregnancy BMI, smoking and parity.

Results: In normal pregnancies the mean (95% reference range) SBP and DBP for nulliparous women at 12 weeks gestation were 112.1 (88.6, 135.5) and 65.4 (48.9, 81.9) mmHg, and at 37 weeks were 116.0 (92.3, 139.7) and 70.0 (52.2, 87.9) mmHg respectively. For every additional 10 mmHg of blood pressure at 12 weeks, normal ranges were 2-3 mmHg higher across gestation. Reference ranges for multiparous women were 1-2 mmHg lower throughout pregnancy. Stratified reference ranges were higher for women in higher pre-pregnancy BMI categories, and lower for smokers than for non-smokers throughout pregnancy.

Conclusion: Normal ranges for blood pressure vary with gestation age and by maternal subgroups. Whole population and stratified normograms could be used as a reference to identify abnormal trajectories.

Keywords: ALSPAC; blood pressure; longitudinal; pregnancy; reference range

Introduction

Around 10% of women experience some form of hypertension during pregnancy,[1, 2] which may be pre-existing or pregnancy-induced. These pregnancies carry a greater risk of a range of adverse perinatal outcomes, including maternal and fetal death,[3-5] intrauterine growth restriction of the infant and preterm birth.[6-8] However, pregnancy is a period of substantial change in blood pressure, with an early pregnancy decrease followed by a steep rise in the latter half of pregnancy.[9, 10] There is evidence that, even among women without pre-existing hypertension or preeclampsia,[11] a greater increase in blood pressure, and the maximum level reached, are also associated with reduced fetal growth.[11, 12]

Furthermore, the early-pregnancy level and the average change in blood pressure have been found to differ by maternal pre-pregnancy BMI, smoking and parity,[10, 13, 14] even among women who then experienced a healthy birth outcome.[10] This would imply that different trajectories of blood pressure may be healthy for different subgroups of women. However, differences in blood pressure trajectories by maternal age and education were much smaller.[10] It is also plausible that the normal trajectory may depend on the initial level of blood pressure, since a greater increase is likely to be tolerable for a woman who begins pregnancy with a relatively low blood pressure. Establishing blood pressure reference ranges across pregnancy for different subgroups of women, who do not experience adverse health outcomes, may provide important information about what is normal at different gestational ages for different women. These normal ranges could be useful for the identification of women whose blood pressure is deviating from a healthy trajectory before they cross the high blood pressure threshold, and thus lead to earlier detection of women at risk. Despite the clear importance of blood pressure in pregnancy, to our knowledge, there are currently no normal

reference ranges to aid clinical interpretation of the repeat antenatal monitoring which is routinely carried out.

Our aim was to develop reference ranges for systolic blood pressure (SBP) and diastolic blood pressure (DBP) across pregnancy, firstly for all women regardless of pregnancy outcome and then for women who have healthy term pregnancies (without essential hypertension or preeclampsia, resulting in a live birth of an appropriate-size-for-gestational-age baby) in a large population-based prospective cohort. We also divided the group of women who had healthy term pregnancies into a low-risk and a high-risk group based on maternal characteristics and fitted reference ranges that were stratified by parity, BMI, smoking and early-pregnancy blood pressure in order to allow for a different normal trajectory of blood pressure change for different subgroups of women.

Methods

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective cohort study investigating the health and development of children. The study has been described in full elsewhere[15] and the study website contains details of available data at http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary. In brief, pregnant women with an expected delivery date between 1st April 1991 and 31st December 1992 living in a defined area of Avon, South West England, were eligible for recruitment. Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and from the National Health Service (NHS) local ethics committee. In total 14,541 women were enrolled and 13,678 had a singleton pregnancy resulting in a live birth. We excluded multiple pregnancies since these would have different patterns of blood pressure change and there

were insufficient numbers to study these in detail. 13,461 of the women had data abstracted from obstetric records and 13,000 had at least one blood pressure measurement during pregnancy. Of these, 10327 had complete data on all maternal characteristics.

Obstetric measurements

All SBP and DBP measurements which were taken as part of routine antenatal care by midwives or obstetricians were abstracted from the women's obstetric records by six trained research midwives. There was no between-midwife variation in mean values of the data abstracted and error rates were consistently <1% in repeated data entry checks. These were single blood pressure measurements taken in the seated position using the appropriate cuff size, using Korotkoff phase V for DBP. The gestational age of measurement was derived from the date of measurement and the expected delivery date. Gestational age at delivery was derived from the expected delivery date and the date of birth. For most women the expected delivery date was based on the last menstrual period date, while for a small proportion this estimate was updated following an ultrasound scan. In the data abstracted from the clinical records it was not recorded which few women had a scan or had their gestational age adjusted.

Birth size

The child's birthweight was obtained from the birth notification. We defined small-for-gestational age (SGA) as below the 10^{th} percentile of birthweight for gestational age and large-for-gestational age (LGA) as above the 90^{th} percentile of birthweight for gestational age

within this cohort by regressing birthweight on gestational age and extracting the residuals.

Hypertension and diabetes before and during pregnancy

Using all available blood pressure measurements, preeclampsia was defined using the International Society for the Study of Hypertension in Pregnancy (ISSHP) definition as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg as well as proteinuria of 1+ or more on urine dipstick testing on two occasions after 20 weeks gestation in a woman who was not known to be hypertensive prior to pregnancy.[16] Women who responded to a questionnaire administered during pregnancy that they had previously had hypertension outside of pregnancy were considered to have essential hypertension. Women who responded that they had previously had diabetes outside of pregnancy were classed as having existing diabetes, and for those without existing diabetes, any diagnosis of gestational diabetes was obtained from obstetric records.

Other maternal characteristics

Maternal pre-pregnancy weight, height, parity and smoking status were obtained from questionnaires administered during pregnancy. Pre-pregnancy BMI was calculated as weight(kg)/ height(m)^2 and classed according to World Health Organisation definitions of underweight (<18.5kg/m^2), normal (18.5-24.9kg/m^2), overweight (25.0-29.9kg/m^2) and obese (≥30.0kg/m^2). A questionnaire at 18 weeks gestation asked about smoking status, which was categorised as: “never during pregnancy”; “pre-pregnancy/first trimester” for women who smoked immediately prior to pregnancy or in the first 3 months and then stopped; or “throughout” for women who continued to smoke after the first 3 months.

Definition of normal pregnancy

To restrict to normal pregnancies we excluded 515 (5.0%) women who delivered preterm (<37 weeks gestation), 937 (9.1%) who had a SGA offspring, 1,040 (10.1%) who had a LGA offspring, 369 (3.6%) with pre-existing hypertension, 213 (2.1%) who developed preeclampsia, 38 (0.4%) with existing diabetes and 46 (0.4%) who developed gestational diabetes (total excluded = 2,823). We did not exclude women who had gestational hypertension, as this would have removed the top end of the blood pressure distribution and biased reference ranges downwards. After these exclusions there remained 7,504 women who had a normal pregnancy.

Statistical Analysis

To develop longitudinal reference ranges for SBP and DBP across gestation we used multilevel models with two levels: measurement occasions (level 1) within women (level 2). These models take into account that the repeated measurements of blood pressure within individuals are not independent, and allow for varying numbers and timings of measurements between women under a missing at random assumption.[17, 18]

Separate multilevel models were fitted with SBP and DBP as the outcome respectively and each had gestational age as the exposure, assuming normal variation in the population at each gestational age. Restricted cubic splines with knots at 11, 18, 30, 36 and 40 weeks gestation were used to describe the shape of the blood pressure trajectory over gestation. Full information is provided in online supplemental material (including the choice of knots). The

baseline gestational age was set at 12 weeks as this was the median time of the first antenatal measurement. In addition to gestational age the models included other explanatory variables as described below, or were fitted separately on certain sub-groups of women to allow for complexity in their trajectories. 95% reference ranges for SBP and DBP from 12 to 40 weeks gestation were then estimated from each fitted model.

We first fitted reference ranges for all women who had complete data on all maternal characteristics, regardless of pregnancy outcome. We then restricted to women who had a normal pregnancy (see definition above). Finally, we divided the women who had a normal pregnancy into subgroups and fitted normal reference ranges for the different subgroups.

The subgroups of interest were defined by the cross-classification of BMI and smoking status. The "low-risk" group comprised those who had normal pre-pregnancy BMI and did not smoke either immediately prior to or during pregnancy. The "high-risk" group included women who were overweight/obese and who smoked either immediately prior to pregnancy or in the first trimester only or who smoked throughout pregnancy. Further reference ranges were produced by pre-pregnancy BMI category (including only those who never smoked) and by smoking status (including only those with a normal pre-pregnancy BMI). In order to predict blood pressure trajectories for the entire duration of pregnancy from a single blood pressure measure at 12 weeks, as would be available in a clinical setting, reference ranges conditional on such possible values were developed for the low-risk group (see supplemental material).[19] In each of these analyses, separate models were fitted for nulliparous and multiparous women. A full list of the subgroups for whom reference ranges have been developed is given in Web-Table 1.

As a sensitivity analysis we re-fitted the reference ranges in the low-risk group as defined when using the customised fetal growth reference of Gardosi et al[20] to define SGA and LGA. Reference ranges were not meaningfully different from those presented here.

We used MLwiN version 2.27 to fit the multilevel models which we ran through Stata using the runmlwin command.[21] Stata version 12.1 was used for all other analyses.

Results

The characteristics of women who had complete data for inclusion in reference ranges and those that were excluded from analysis due to missing maternal characteristic data are shown in Table 1. Women who were included were generally similar to those who were excluded, although they were slightly more likely to be underweight. Women who were included who had normal pregnancies had lower SBP and DBP at 12 and 37 weeks gestation and were less likely to be overweight/obese, less likely to be nulliparous and less likely to smoke throughout pregnancy than women who were considered to have an abnormal pregnancy due to either a medical condition (essential hypertension, preeclampsia, existing or gestational diabetes N=647) or an adverse perinatal outcome (preterm birth, SGA or LGA offspring; N=2404).

Figure 1 shows the reference ranges for SBP and DBP between 12 and 40 weeks gestation for all women and for those women who had a normal pregnancy, by parity. The predicted values and 95% reference ranges at 12, 20 and 37 weeks gestation are shown in Web-Table 2. The reference ranges for SBP and DBP decreased until mid-pregnancy in both nulliparous

and multiparous women before rising until the end of pregnancy, although the decrease was more pronounced in multiparous women than in nulliparous women. The average timing of the nadir varied, occurring at 17 weeks in nulliparous women and 18 weeks in multiparous women in the whole cohort and also when restricting to normal pregnancies. The nadir in DBP occurred at around 19 weeks of gestation in nulliparous women and 20 weeks in multiparous women in the whole cohort and at around 20 weeks for both nulliparous and multiparous women when restricting to normal pregnancies. The 95% reference range for SBP was approximately 45-50 mmHg wide and for DBP was approximately 30-35 mmHg wide in the whole cohort; both widening slightly towards the end of gestation. Upper reference range limits were generally slightly lower across gestation in normal pregnancies than in the whole cohort but, as ranges were also slightly narrower, the lower reference range limits were similar in the whole cohort and in normal pregnancies.

Reference ranges in sub-groups of normal pregnancies

The reference ranges of SBP and DBP across gestation in the low-risk group (normal pre-pregnancy BMI; never smoked) and in the high-risk group (overweight/obese; smoked at any time either immediately prior to or during pregnancy) of women who had normal pregnancies are shown in Figure 2. Web-Table 2 shows the predicted values and 95% reference ranges of SBP and DBP at 12, 20 and 37 weeks gestation. Reference ranges in the high-risk group were generally around 4 mmHg higher than in the low-risk group across pregnancy for both nulliparous and multiparous women. SBP for nulliparous women in the high-risk group did not show a mid-pregnancy dip, but increased throughout pregnancy.

Reference ranges stratified by maternal pre-pregnancy BMI are shown for nulliparous non-smoking women in Figure 3 and for multiparous women in Web-Figure 1. For both nulliparous and multiparous women there was an increasing trend in the limits of the reference ranges with increasing pre-pregnancy BMI category at each gestational age. For example, for nulliparous women, upper and lower reference range limits of SBP were approximately 10 mmHg higher throughout pregnancy for obese compared with normal weight women, and for DBP were approximately 7.5-8 mmHg higher (Web-Table 2). The shape of the blood pressure trajectory also differed by pre-pregnancy BMI category (Web-Figures 2 and 3), with obese women having a more distinct nadir in SBP and DBP than normal weight women in the nulliparous group.

Reference ranges stratified by smoking during pregnancy are shown in Figure 4 for nulliparous normal-weight women and Web-Figure 4 for multiparous women. SBP reference ranges were around 0-1.5 mmHg lower across pregnancy for women who smoked throughout pregnancy than for non-smokers, while DBP reference ranges were around 1-2 mmHg lower (Web-Table 2). Those who smoked only pre-pregnancy/1st trimester had 1-2 mmHg lower SBP and DBP reference ranges in early pregnancy than non-smokers, but this difference attenuated towards the end of gestation. The average SBP and DBP trajectories by smoking status are shown in Web-Figures 5 and 6 respectively.

Figure 5 shows the predicted reference ranges of SBP and DBP across pregnancy, conditional on different possible levels of blood pressure at 12 weeks gestation for nulliparous women. The equivalent reference ranges for multiparous women are shown in Web-Figure 7. For each additional 10 mmHg in SBP at 12 weeks, the reference ranges for SBP were predicted to be

approximately 4 mmHg higher at 20 weeks and around 3 mmHg higher at 37 weeks gestation in both nulliparous and multiparous women (Web-Table 3). For each additional 10 mmHg in DBP at 12 weeks, the reference ranges for DBP were predicted to be around 3 mmHg higher at 20 weeks and around 2.5 mmHg higher at 37 weeks (Web-Table 3).

Discussion

We have derived reference ranges for blood pressure from 12 to 40 weeks gestation in a large population-based pregnancy cohort and compared these with reference ranges for women who had a normal pregnancy, without essential hypertension or preeclampsia, existing or gestational diabetes who delivered an appropriate-sized infant at term. We found that normal pregnancies had generally lower upper reference range limits and narrower reference ranges throughout pregnancy. We also observed differences in reference ranges between different subgroups of women with normal pregnancies based on pre-pregnancy BMI, smoking and parity and found that the expected normal trajectory of blood pressure differed by the blood pressure at the first antenatal visit (in this cohort at around 12 weeks gestation). To our knowledge there are no existing longitudinal reference ranges for blood pressure in normal pregnancy. The shape of the average trajectory of blood pressure in pregnancy as decreasing until mid-pregnancy followed by an increase in late-pregnancy has been well-described,[9, 22, 23] and the addition of normal ranges to these average trajectories allows observed blood pressure measurements at any gestational age to be compared with expected limits.

This study benefits from its large size, repeated measurements of blood pressure and detailed information on maternal characteristics. The blood pressure measurements were collected

during routine clinical practice, and thus will have greater measurement error than standardized measures. However, this means that the reference ranges are applicable to a clinical setting. The pregnancies occurred approximately 20 years ago and levels of obesity in the UK have increased over this period[24] while smoking prevalence has reduced.[25] However, the analyses are stratified by BMI and smoking and these changes are unlikely to have had a large effect on blood pressure levels within strata. The ALSPAC participants also differed slightly from the UK as a whole, being more likely to live in owner-occupied accommodation and to have a car and less likely to be non-white.[15] In the interests of space we have not presented reference ranges for all possible subgroups of women, but have provided examples of low and high-risk groups and demonstrated how reference ranges differ with each of the maternal characteristics. This approach could be extended to develop customised blood pressure charts for all women based on pre-pregnancy BMI, smoking, parity and first blood pressure measurement, however we did not have sufficient power to derive reference ranges for some of the smaller subgroups in the present study. The graphs presented here are illustrative and validation in other cohorts is required before these can be used in clinical practice.

The differences in normal ranges between obese and normal weight women of ~8-10 mmHg in SBP and ~6.5-8 mmHg in DBP at each gestational age are in line with the differences in average trajectories found in our previous study in this cohort with weaker exclusion criteria,[10] in the Generation R study from the Netherlands[13] and in the US-based Omega Study.[26] The two studies in other cohorts, however, included women with preeclampsia, preterm birth and SGA or LGA offspring. The magnitude of the differences between BMI categories may have important implications for risk-related levels of high blood pressure for women of different BMIs and at different gestational ages. For example, for nulliparous

obese women, values of SBP over 140 mmHg were well within the 95% reference range across the whole of pregnancy, whereas for normal weight women the 95% reference range remains below 135 mmHg for much of pregnancy.

Although smaller differences in blood pressure reference ranges were seen between smoking groups (up to 2 mmHg) they suggest that smoking status may be useful to include, along with pre-pregnancy BMI, in prediction models which use deviations from each woman's expected blood pressure trajectory to identify high-risk pregnancies. In our previous study we found strong statistical evidence to support lower average blood pressure trajectories for smokers than for non-smokers,[10] and other cohorts have supported this finding for DBP, although findings relating to SBP have been conflicting.[9, 14, 27] It has been shown that blood pressure tracks moderately across pregnancy, with almost 50% of women remaining in the same third of blood pressure from the 1st trimester to the 3rd trimester,[23] which supports the differences which we found in the expected trajectories of blood pressure across pregnancy by blood pressure levels at 12 weeks.

The diagnostic criteria for hypertensive disorders of pregnancy (HDP) use the same blood pressure thresholds of 140/90 mmHg across the whole gestational period between 20 weeks and delivery and for all women, although nulliparous women, obese women and those with high pre-pregnancy blood pressure are considered to be at high risk for HDP.[28] Our findings suggest that using different blood pressure thresholds for different maternal subgroups to identify women whose blood pressure has deviated from the normal trajectory may provide additional information about risk. Nevertheless, subgroups of women who are known to be at higher risk of adverse perinatal outcomes should be considered as such, even

with blood pressure within the normal range. Our reference ranges also show differences of around 5 mmHg in SBP and DBP between 20 weeks and delivery, suggesting that using different blood pressure thresholds at different gestational ages may improve the identification of women with abnormal trajectories.

There has been much research in the area of fetal growth charts,[29-31] and more recently customised charts which are dependent on maternal characteristics.[20] Routine measurements of symphysis-fundal height and ultrasound scan measurements of fetal size may be compared against these charts and used to identify growth restricted foetuses.[32, 33] There may be potential for blood pressure charts in pregnancy to be used in conjunction with fetal growth charts to aid in the identification of pregnancies at risk of SGA infants, since high blood pressure and greater increases in blood pressure are associated with reduced offspring birthweight.[11, 12] In addition, blood pressure reference ranges may help to identify women who are at risk of preeclampsia and delivering preterm. We have previously shown in this cohort[34] and others elsewhere,[23] that the increase in blood pressure is steeper in preeclamptic compared with normotensive pregnancies. Thus, preeclamptic women would be expected to deviate from the normal pattern of change, although the potential for deviations from the normal trajectory to be used in prediction of adverse outcomes remains to be assessed.

We conclude that the normal pattern of change in blood pressure across gestation, for a healthy term pregnancy resulting in an appropriate sized infant, differs by maternal subgroups. There may be potential to use whole population and stratified normal reference ranges such as these in screening for women with abnormal trajectories, which may be

indicative of potential adverse pregnancy outcomes such as preeclampsia, preterm birth and SGA offspring. However, the value of this will require evaluation through the development and validation of prediction models.

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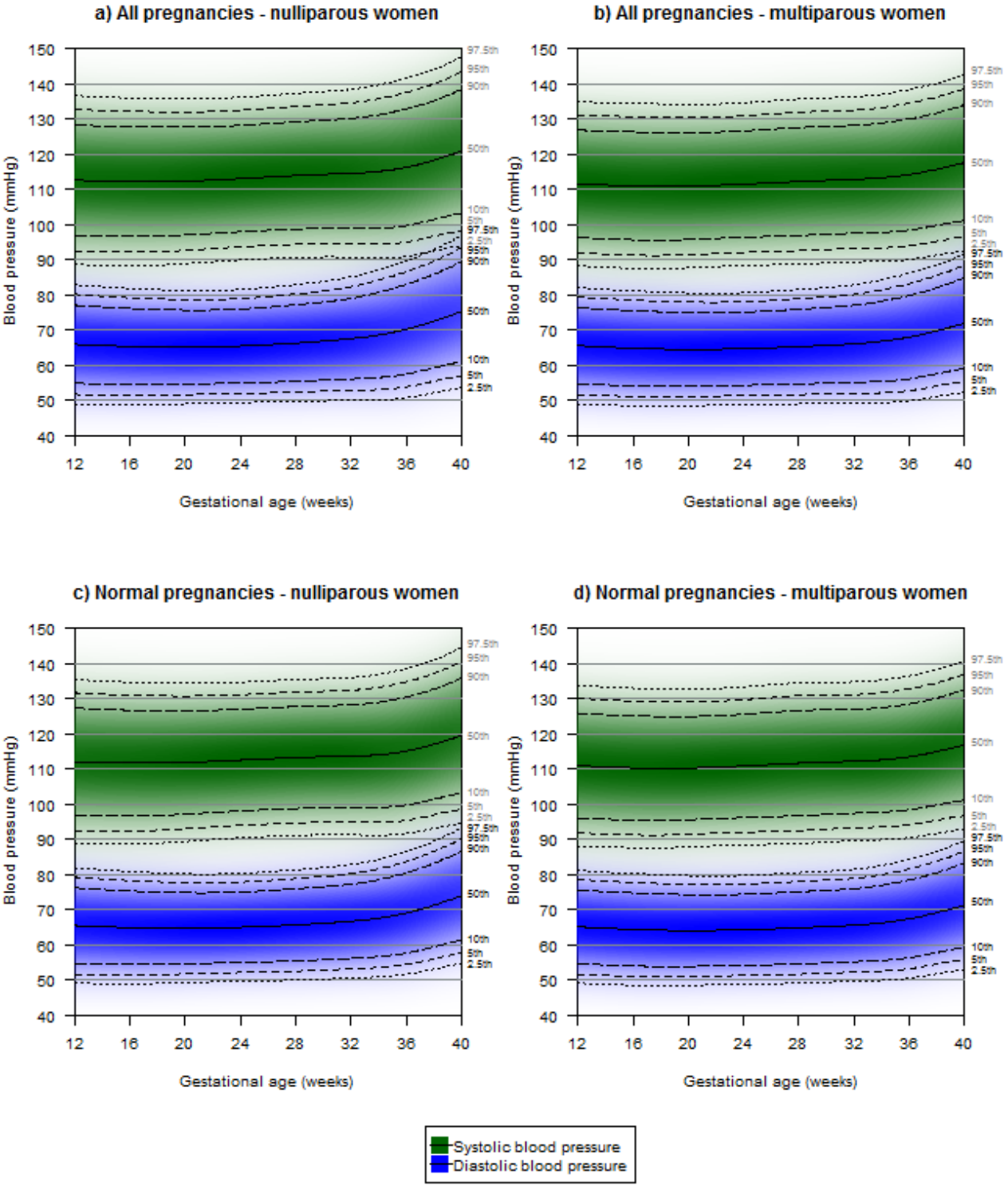
Table 1 Maternal characteristics of women who were excluded from analysis due to incomplete data and of women who were included by pregnancy type

	Pregnancies without complete data (N=2673)		Pregnancies with complete data					
			All (N=10327)		Normal pregnancies (N=7504)		Maternal medical condition or adverse pregnancy outcome (N=2823)	
	N with data	Mean (SD) or %	N	Mean (SD) or %	N	Mean (SD) or %	N	Mean (SD) or %
Blood pressure								
SBP at 12 weeks (mmHg)	2673	112.1 (12.77)	10327	112.1 (12.12)	7504	111.5 (11.83)	2823	113.7 (12.72)
DBP at 12 weeks (mmHg)	2673	65.7 (9.06)	10327	65.7 (8.56)	7504	65.2 (8.30)	2823	66.8 (9.13)
SBP at 37 weeks (mmHg)	2673	116.0 (13.21)	10327	116.0 (12.92)	7504	115.0 (12.22)	2823	118.8 (14.22)
DBP at 37 weeks (mmHg)	2673	70.0 (10.24)	10327	69.9 (9.71)	7504	69.0 (9.06)	2823	72.4 (11.42)
Number of measures* (median (IQR))	2673	10 (8, 11)	10327	10 (9, 11)	7504	10 (9, 12)	2823	10 (8, 11)
Parity								
Nulliparous (%)	794	45.4	4718	45.7	3372	44.9	1346	47.7
Multiparous (%)	954	54.6	5609	54.3	4132	55.1	1477	52.3
Pre-pregnancy BMI								
Underweight (%)	35	7.1	514	5.0	379	5.1	135	4.8
Normal weight (%)	351	71.2	7665	74.2	5703	76.0	1962	69.5
Overweight (%)	77	15.6	1566	15.2	1074	14.3	492	17.4
Obese (%)	30	6.1	582	5.6	348	4.6	234	8.3
Smoking in pregnancy								
Never (%)	1044	55.8	7076	68.5	5176	69.0	1900	67.3
Pre-pregnancy/1st trimester (%)	309	16.5	1373	13.3	1000	13.3	373	13.2
Throughout (%)	518	27.7	1878	18.2	1328	17.7	550	19.5

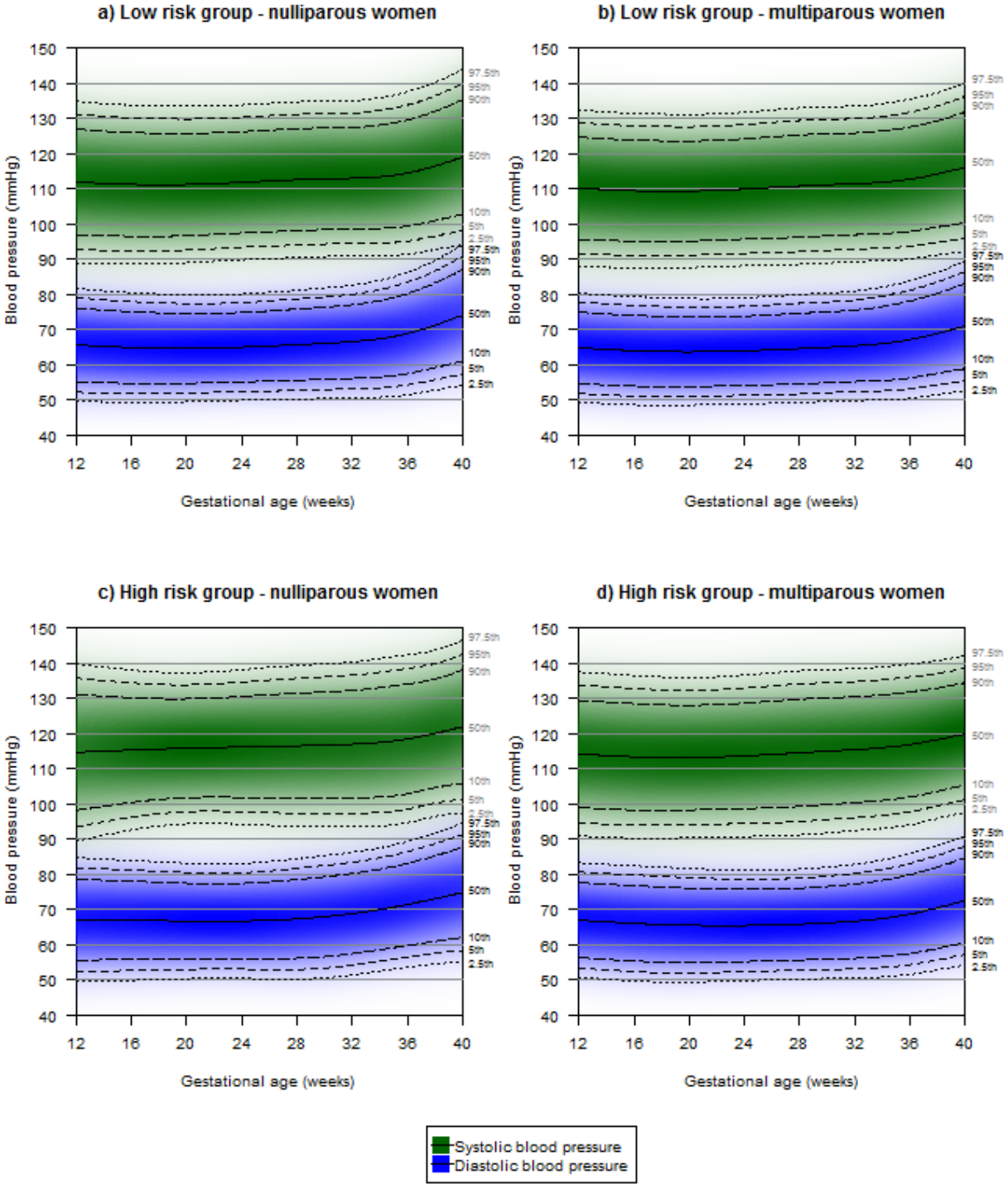
* This is the number of blood pressure measurements per woman after randomly selecting one measure per 2-week period of pregnancy for use in the multilevel models

Figure 1 Reference ranges for systolic and diastolic blood pressure between 12 and 40 weeks gestation in the full cohort with complete data (nulliparous N=4718; multiparous N=5609) and in normal pregnancies only (nulliparous N=3372; multiparous N=4132) [*]



[*] A normal pregnancy was defined as one where the woman did not have essential hypertension, preeclampsia, existing or gestational diabetes and delivered an appropriate-for-gestational-age sized infant at term

Figure 2 Reference ranges for systolic and diastolic blood pressure between 12 and 40 weeks gestation in low-risk (nulliparous N=1832; multiparous N=2193) and high-risk (nulliparous N=205; multiparous N=285) normal pregnancies*



* The low-risk group included women who had a normal pre-pregnancy BMI and did not smoke either immediately prior to or during pregnancy. The high-risk group included overweight or obese women who smoked either immediately prior to pregnancy, in the 1st trimester or throughout pregnancy

Figure 3 Reference ranges for systolic and diastolic blood pressure by maternal pre-pregnancy BMI category for nulliparous non-smokers with normal pregnancies (N=2270)

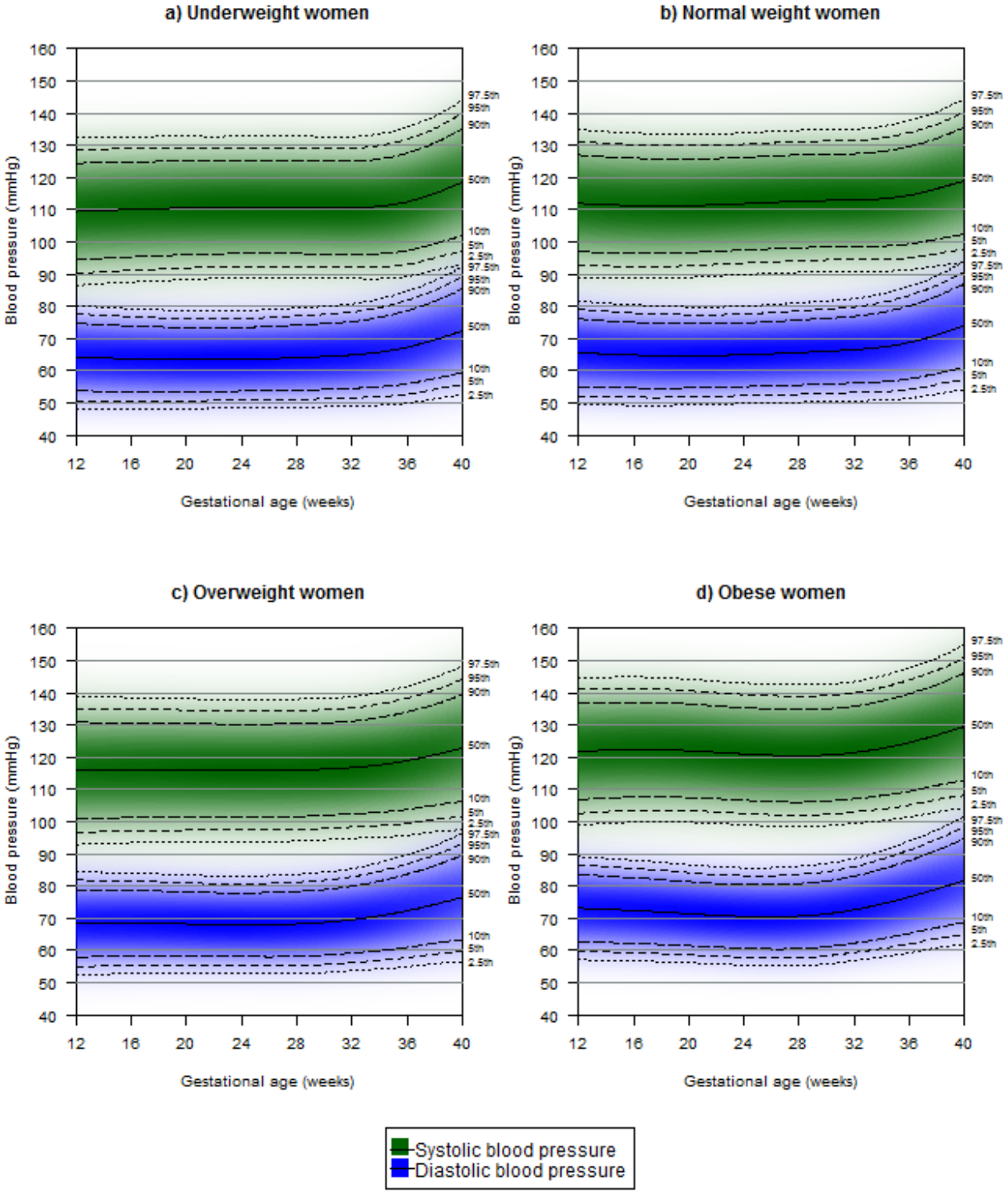


Figure 4 Reference ranges for systolic and diastolic blood pressure by maternal smoking during pregnancy for nulliparous normal-weight women with normal pregnancies (N=2654)

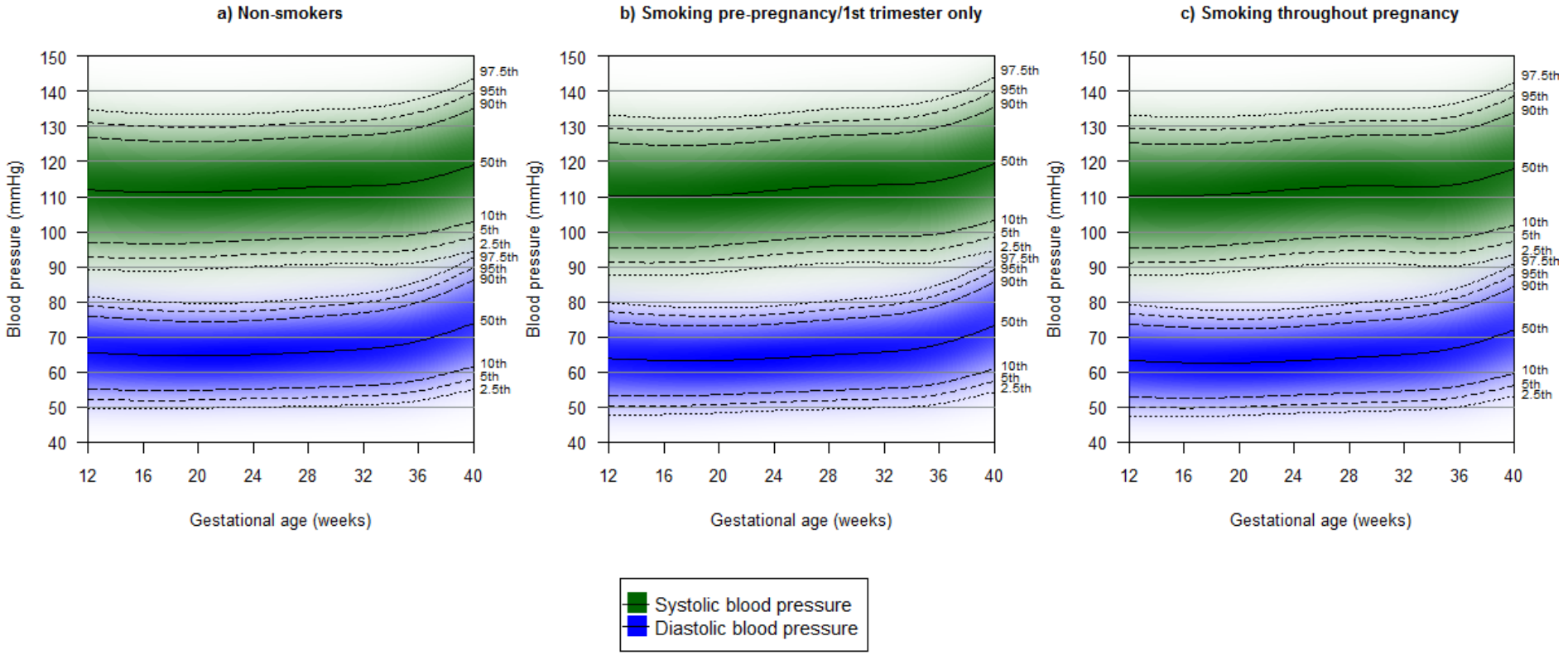
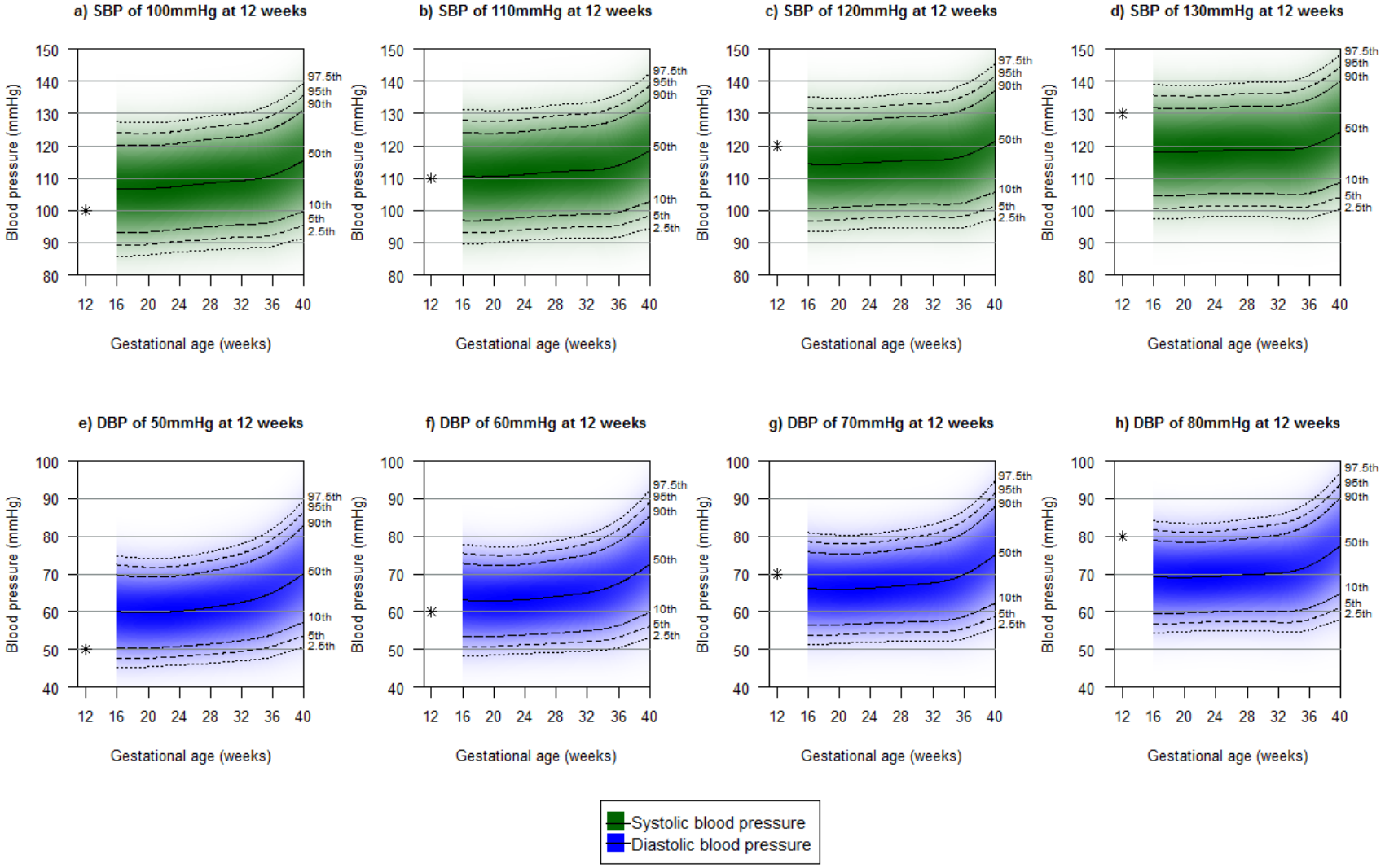


Figure 5 Reference ranges for systolic and diastolic blood pressure in pregnancy conditional on the level of blood pressure at 12 weeks gestation for nulliparous normal-weight non-smoking women with normal pregnancies (N=1832)*



* Note that in each of the plots there is a star that corresponds to the value of SBP/DBP at 12 weeks.

Supplementary Methods

Gestation was initially divided into two-week periods and, for women who had more than one blood pressure measurement available in any two-week period, one blood pressure measurement was selected at random per two-week period for each woman. This was to prevent women who had many measurements during pregnancy, who may represent less-healthy women, having a disproportionately high influence on the multilevel models.

Separate multilevel models with systolic blood pressure (SBP) and diastolic blood pressure (DBP) as outcomes were used to model the trajectory of change in SBP and DBP with gestational age. Several possible parameterisations of the shape of the curve were considered and the fit compared using the BIC and the difference between each individual's predicted values and their actual blood pressure measurements across gestation. These included: fractional polynomial curves with up to two powers of gestational age, using the set of powers (-2, -1, -0.5, 0, 0.5, 1, 2, 3);[1] linear splines with up to 3 knots and restricted cubic splines with up to 5 knots. Linear splines have been fitted previously to these data, and the best-fitting knot point locations were found to be at 18, 30 and 36 weeks gestation.[2] The restricted cubic spline with 5 knots were fitted using knots selected by the percentile method of Harrell[3] and also using the 3 knots found to be optimum for the linear splines (18, 30 and 36 weeks) for the middle 3 knots and the 5^{th} and 95^{th} percentiles of the data for the outer 2 knots (11 and 40 weeks). The fractional polynomial curve had a poorer fit compared with the linear or cubic splines. Linear splines and restricted cubic spline models with knots at 18, 30 and 36, and 11, 18, 30, 36 and 40 weeks respectively had the best fit to the data and fitted similarly. However, due to the smooth nature of the restricted cubic spline, reflecting the

expected smooth change in blood pressure, this was selected and used for the normal reference ranges.

The models had two levels: measurement occasions (level1) within women (level2), reflecting the clustering of the data. Individual-level random effects were fitted for the intercept and for each of the cubic spline parameters, allowing the initial level and shape of the trajectory of change in blood pressure across gestation to vary between women. We allowed the within-individual variation in blood pressure to vary with gestational age as there was evidence of increasing variation in blood pressure as gestational age increased. Thus the model without covariates included took the following form:

$$y_{ij} = \beta_0 + u_{0j} + (\beta_1 + u_{1j})spline1_{ij} + (\beta_2 + u_{2j})spline2_{ij} + (\beta_3 + u_{3j})spline3_{ij} + (\beta_4 + u_{4j})spline4_{ij} + e_{0ij} + e_{1ij}(GA_{ij} - 12)$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \\ u_{3j} \\ u_{4j} \end{bmatrix} \sim N(\mathbf{0}, \Omega_u), \begin{bmatrix} e_{0ij} \\ e_{1ij} \end{bmatrix} \sim N(\mathbf{0}, \Omega_e)$$

where, y_{ij} is the value of the i^{th} SBP or DBP measurement on the j^{th} individual, β_0-β_4 describe the average trajectory of change, u_{0j}-u_{4j} describe how the j^{th} individual's trajectory of SBP or DBP deviates from the average and GA_{ij} is the gestational age in weeks of the i^{th} measurement on the j^{th} individual. It is centred at 12 weeks in order to set the intercept, $\beta_{0,}$ to represent blood pressure at 12 weeks. The e_{0ij} and e_{1ij} terms describe the deviation of the i^{th} measurement of SBP or DBP on the j^{th} individual from the individual's trajectory. These are residual error terms.

The splines are defined as:[3]

$$spline1_{ij} = GA_{ij} - 12$$

$$spline2_{ij} = \frac{(GA_{ij} - 11)_+ - (40-36)^{-1}\{(GA_{ij} - 36)_+^3 (40-11) - (GA_{ij} - 40)_+^3 (36-11)\}}{(40-11)^2}$$

$$spline3_{ij} = \frac{(GA_{ij} - 18)_+ - (40-36)^{-1}\{(GA_{ij} - 36)_+^3 (40-18) - (GA_{ij} - 40)_+^3 (36-18)\}}{(40-11)^2}$$

$$spline4_{ij} = \frac{(GA_{ij} - 30)_+ - (40-36)^{-1}\{(GA_{ij} - 36)_+^3 (40-30) - (GA_{ij} - 40)_+^3 (36-30)\}}{(40-11)^2}$$

where $(x)_+ = \begin{cases} 0 \ if \ \ x \le 0 \\ x \ if \ \ x > 0 \end{cases}$

The variance of the individual blood pressure measurements at each gestational age was calculated as the sum of the between-individual-variance and the within-individual variance.[4]

The between-individual variance at gestational age g, $V_{bg} = \begin{bmatrix} 1 \\ spline1_g \\ spline2_g \\ spline3_g \\ spline4_g \end{bmatrix}^T \Omega_u \begin{bmatrix} 1 \\ spline1_g \\ spline2_g \\ spline3_g \\ spline4_g \end{bmatrix}$,

where, for example, $spline1_g$ represents the value of the first cubic spline at gestational age g.

The within-individual variance at gestational age g, $V_{wg} = \begin{bmatrix} 1 \\ g-12 \end{bmatrix}^T \Omega_e \begin{bmatrix} 1 \\ g-12 \end{bmatrix}$.

Therefore, the value of the 95th percentile for the reference range at gestational age, g, is:

$$\hat{\beta}_0 + \hat{\beta}_1 spline1_g + \hat{\beta}_2 spline2_g + \hat{\beta}_3 spline3_g + \hat{\beta}_4 spline4_g + 1.96 * \sqrt{\hat{V}_{bg} + \hat{V}_{wg}}$$

This gives the reference range for observed measures of blood pressure, rather than for an individual's underlying blood pressure trajectory, as it includes both the between-individual and within-individual variances of blood pressure.

The fit of the model-predicted SBP and DBP across gestation to the observed SBP and DBP values in the nulliparous "low-risk" group (normal pre-pregnancy BMI and non-smoker) is shown in Tables 1 and 2 respectively, and in the multiparous "low-risk" group is shown in Tables 3 and 4. 90% of the predictions for SBP in each gestational period were generally within around 14 mmHg of the observed SBP values and 90% of predictions for DBP in each gestational period were generally within around 11 mmHg of the observed DBP values.

To produce reference ranges by pre-pregnancy BMI category, BMI was entered into the multilevel models as a categorical covariate (underweight, normal weight, overweight, obese) with normal weight as the reference category. A main effect term was included for BMI and also interactions with each of the spline variables. Reference ranges by smoking status were produced similarly, by entering smoking status as a categorical covariate (never smoked, smoked pre-pregnancy/1st trimester, smoked throughout pregnancy), with never smoked as the reference category, as a main effect and also as interactions with each of the splines. The between and within-individual variances were calculated in the same way as for the unadjusted model. Separate multilevel models were fitted for nulliparous and multiparous women.

For the reference ranges which were conditional on SBP or DBP at 12 weeks gestation we used the unadjusted multilevel models as above, fitted only for the low-risk group (normal BMI; non-smokers) of women who had normal pregnancies. We obtained conditional predictions from this using the method described by Tilling et al[4] and Pan and Goldstein.[5]

The covariance between the deviations from the predicted curve at 12 weeks and *g* weeks is

$$V_{b12,g=}\begin{bmatrix} 1 \\ spline1_{12} \\ spline2_{12} \\ spline3_{12} \\ spline4_{12} \end{bmatrix}^T \Omega_u \begin{bmatrix} 1 \\ spline1_{g} \\ spline2_{g} \\ spline3_{g} \\ spline4_{g} \end{bmatrix}$$

Therefore, the predicted SBP or DBP at gestational age *g*, conditional on the value at 12 weeks gestation is:

$$y_g = \frac{\hat{V}_{b12,g}}{\hat{V}_{b12} + \hat{V}_{w12}}(y_{12} - \hat{\beta}_0 + \hat{\beta}_1 spline1_{12} + \hat{\beta}_2 spline2_{12} + \hat{\beta}_3 spline3_{12} + \hat{\beta}_4 spline4_{12}) +$$
$$\hat{\beta}_0 + \hat{\beta}_1 spline1_g + \hat{\beta}_2 spline2g + \hat{\beta}_3 spline3_g + \hat{\beta}_4 spline4_g$$

Where y_{12} is the observed value of the outcome (either SBP or DBP) at 12 weeks gestation, V_{b12} is the between-individual variance in the outcome at 12 weeks and V_{w12} is the within-individual variance. Thus, the deviation of the 12-week measurement from the average trajectory was combined with the multilevel model information to predict what trajectory would be seen for the rest of gestation. Conditional predictions were produced for hypothetical SBP values of 100, 110, 120 and 130 mmHg and DBP values of 50, 60, 70 and 80 mmHg at 12 weeks gestation.

The variance of this prediction is $(V_{bg} + V_{wg}) - \frac{V_{b12,g}^{\ 2}}{(V_{b12} + V_{w12})}$ and is used to calculate the reference ranges.

We tested the fit of the reference ranges conditional on the value of blood pressure at 12 weeks to the measurements in this cohort, by comparing predicted reference ranges conditional on each individual's blood pressure measurement at (or within 3 weeks either side of) 12 weeks gestation against their actual blood pressure measurements from 16 weeks

onwards. The 95% reference ranges for SBP conditional on blood pressure at 12 weeks contained 94.5% of actual blood pressure measurements from 16 weeks gestation onwards for nulliparous women and 94.8% of actual blood pressure measurements for multiparous women. The 95% reference ranges for DBP conditional on blood pressure at 12 weeks contained 95.2% of actual blood pressure measurements for nulliparous women, and 94.6% for multiparous women.

Please note, the following 4 tables are part of the Supplemental Methods and are not referred to in the main text. Thus, they have been labelled as Table X, rather than Web-Table X.

Table 1 Model fit for low-risk SBP model in nulliparous women

Gestational period (weeks)	Number of measurements	Observed SBP Mean (SD)	Predicted SBP Mean (SD)	Observed – Predicted SBP Mean (SD)	90% Limits of Agreement*
Up to 8	192	112.5 (12.83)	113.5 (6.07)	-1.03 (9.21)	(-13.94, 13.91)
9 - 10	420	111.3 (11.52)	112.0 (5.96)	-0.73 (7.97)	(-14.56, 12.20)
11 – 12	739	112.4 (11.37)	112.5 (6.13)	-0.08 (8.33)	(-13.83, 13.95)
13 – 14	817	112.4 (11.96)	111.4 (6.49)	1.04 (8.70)	(-12.76, 15.16)
15 – 16	699	112.4 (11.77)	111.7 (6.61)	0.67 (8.34)	(-13.12, 14.42)
17 – 18	1062	110.9 (12.01)	111.3 (7.01)	-0.46 (8.13)	(-14.42, 13.24)
19 – 20	729	110.8 (11.31)	111.2 (6.93)	-0.38 (7.63)	(-12.68, 13.06)
21 – 22	924	110.9 (11.16)	111.3 (7.04)	-0.35 (7.36)	(-12.48, 11.69)
23 – 24	761	111.9 (11.53)	111.8 (7.30)	0.13 (7.52)	(-11.80, 13.30)
25 – 26	930	112.2 (11.12)	112.0 (7.37)	0.18 (7.01)	(-11.56, 11.37)
27 – 28	962	112.8 (11.27)	112.6 (7.17)	0.20 (7.13)	(-10.89, 12.21)
29 – 30	1343	112.8 (11.31)	112.7 (7.35)	0.05 (7.32)	(-11.30, 11.89)
31 – 32	1452	112.9 (11.35)	112.9 (7.15)	0.02 (7.58)	(-12.02, 12.00)
33 – 34	1588	112.8 (11.14)	113.2 (6.94)	-0.44 (7.76)	(-12.32, 11.92)
35 – 36	1551	114.2 (11.68)	114.1 (7.15)	0.12 (8.10)	(-12.74, 13.09)
37 – 38	1954	115.8 (12.38)	115.5 (7.32)	0.34 (8.27)	(-11.66, 13.87)
39 – 40	1649	117.4 (12.66)	117.5 (7.51)	-0.17 (8.21)	(-13.11, 14.02)
41+	851	119.4 (12.77)	119.5 (7.78)	-0.12 (8.09)	(-13.43, 12.67)

* The range within which 90% of differences between the observed and model predicted values lie.

Table 2 Model fit for low-risk DBP model in nulliparous women

Gestational period (weeks)	Number of measurements	Observed DBP Mean (SD)	Predicted DBP Mean (SD)	Observed – Predicted DBP Mean (SD)	90% Limits of Agreement*
Up to 8	192	66.5 (9.15)	67.0 (3.78)	-0.48 (7.38)	(-12.55, 9.73)
9 - 10	420	65.2 (7.81)	65.8 (3.53)	-0.64 (6.20)	(-10.74, 10.16)
11 – 12	739	66.0 (8.23)	65.8 (3.79)	0.22 (6.46)	(-10.31, 10.66)
13 – 14	817	65.7 (8.13)	65.3 (3.83)	0.42 (6.41)	(-10.19, 11.15)
15 – 16	699	65.3 (7.98)	65.1 (3.95)	0.27 (6.13)	(-9.42, 10.56)
17 – 18	1062	64.5 (8.11)	64.6 (4.02)	-0.12 (6.07)	(-10.07, 10.19)
19 – 20	729	64.5 (7.74)	64.6 (4.09)	-0.18 (5.60)	(-9.74, 9.01)
21 – 22	924	64.2 (7.67)	64.6 (4.23)	-0.33 (5.55)	(-9.05, 8.77)
23 – 24	761	65.2 (7.98)	64.9 (4.20)	0.31 (5.78)	(-9.68, 9.45)
25 – 26	930	65.0 (7.73)	65.0 (4.33)	0.03 (5.61)	(-8.94, 9.39)
27 – 28	962	65.4 (8.07)	65.5 (4.56)	-0.10 (5.47)	(-8.72, 8.82)
29 – 30	1343	66.0 (7.77)	65.8 (4.52)	0.16 (5.46)	(-8.44, 9.20)
31 – 32	1452	66.1 (7.93)	66.2 (4.62)	-0.13 (5.67)	(-9.63, 8.90)
33 – 34	1588	66.7 (8.29)	66.8 (4.66)	-0.12 (6.02)	(-9.29, 9.54)
35 – 36	1551	68.2 (8.64)	68.0 (5.08)	0.16 (6.00)	(-9.47, 10.58)
37 – 38	1954	70.0 (9.17)	69.9 (5.34)	0.13 (6.22)	(-9.99, 10.48)
39 – 40	1649	72.0 (9.89)	72.3 (5.67)	-0.31 (6.41)	(-10.23, 10.56)
41+	851	74.6 (10.11)	74.4 (6.16)	0.25 (6.35)	(-10.04, 10.52)

* The range within which 90% of differences between the observed and model predicted values lie.

Table 3 Model fit for low-risk SBP model in multiparous women

Gestational period (weeks)	Number of measurements	Observed SBP Mean (SD)	Predicted SBP Mean (SD)	Observed – Predicted SBP Mean (SD)	90% Limits of Agreement*
Up to 8	215	110.7 (10.35)	111.9 (5.37)	-1.18 (7.73)	(-14.12, 11.20)
9 - 10	505	110.3 (11.62)	110.5 (5.53)	-0.16 (8.36)	(-13.52, 12.39)
11 – 12	821	110.6 (11.34)	110.5 (6.01)	0.08 (8.12)	(-13.45, 13.66)
13 – 14	985	110.8 (11.58)	109.9 (5.96)	0.89 (8.50)	(-12.79, 15.55)
15 – 16	839	109.5 (11.51)	109.7 (6.24)	-0.19 (7.92)	(-12.98, 13.10)
17 – 18	1257	108.9 (11.32)	109.5 (6.39)	-0.59 (7.95)	(-13.89, 12.92)
19 – 20	858	109.3 (10.78)	109.3 (6.28)	-0.01 (7.66)	(-12.48, 12.39)
21 – 22	1062	109.8 (11.48)	109.6 (6.95)	0.25 (7.49)	(-12.29, 11.77)
23 – 24	916	110.3 (10.55)	110.1 (6.73)	0.22 (7.28)	(-12.30, 11.27)
25 – 26	1080	110.2 (11.62)	110.4 (7.11)	-0.19 (7.53)	(-12.61, 12.55)
27 – 28	1101	110.7 (11.17)	110.6 (7.14)	0.15 (7.23)	(-10.98, 12.20)
29 – 30	1569	111.0 (11.19)	111.1 (7.05)	-0.13 (7.12)	(-11.75, 11.43)
31 – 32	1642	111.4 (11.29)	111.4 (7.05)	0.01 (7.47)	(-11.49, 12.27)
33 – 34	1839	111.7 (11.42)	111.6 (6.98)	0.13 (7.87)	(-12.15, 13.64)
35 – 36	1805	112.3 (11.28)	112.4 (6.91)	-0.05 (7.73)	(-12.48, 12.01)
37 – 38	2213	113.5 (11.39)	113.5 (6.73)	-0.02 (7.68)	(-12.26, 13.20)
39 – 40	2015	115.0 (12.12)	115.1 (7.00)	-0.09 (7.91)	(-12.50, 13.20)
41+	821	116.6 (11.90)	116.5 (6.78)	0.15 (8.01)	(-11.79, 13.85)

* The range within which 90% of differences between the observed and model predicted values lie.

Table 4 Model fit for low-risk DBP model in multiparous women

Gestational period (weeks)	Number of measurements	Observed DBP Mean (SD)	Predicted DBP Mean (SD)	Observed – Predicted DBP Mean (SD)	90% Limits of Agreement*
Up to 8	215	65.8 (7.52)	66.1 (3.19)	-0.30 (6.39)	(-10.05, 11.76)
9 - 10	505	65.0 (8.60)	65.3 (3.43)	-0.25 (6.55)	(-10.65, 10.89)
11 – 12	821	65.2 (7.87)	64.9 (3.61)	0.32 (6.17)	(-9.77, 10.57)
13 – 14	985	64.6 (7.69)	64.4 (3.64)	0.16 (6.12)	(-10.27, 10.30)
15 – 16	839	64.0 (7.95)	64.1 (3.90)	-0.08 (5.96)	(-9.50, 10.30)
17 – 18	1257	63.4 (7.90)	63.7 (4.13)	-0.37 (5.83)	(-10.06, 9.42)
19 – 20	858	63.6 (7.82)	63.6 (4.10)	0.06 (5.63)	(-8.94, 9.41)
21 – 22	1062	63.8 (7.81)	63.7 (4.35)	0.10 (5.48)	(-8.62, 9.34)
23 – 24	916	64.3 (7.64)	63.9 (4.22)	0.33 (5.60)	(-8.88, 9.12)
25 – 26	1080	63.9 (7.84)	64.0 (4.40)	-0.07 (5.54)	(-8.66, 9.30)
27 – 28	1101	64.4 (7.84)	64.3 (4.41)	0.04 (5.33)	(-8.38, 9.33)
29 – 30	1569	64.7 (7.83)	64.7 (4.32)	-0.05 (5.46)	(-8.88, 9.05)
31 – 32	1642	65.1 (7.75)	65.1 (4.42)	-0.04 (5.53)	(-8.99, 8.73)
33 – 34	1839	65.5 (7.89)	65.6 (4.45)	-0.08 (5.69)	(-9.06, 9.50)
35 – 36	1805	66.6 (8.41)	66.5 (4.55)	0.07 (5.98)	(-9.29, 10.39)
37 – 38	2213	68.1 (8.82)	68.0 (4.75)	0.11 (6.14)	(-9.40, 10.47)
39 – 40	2015	69.6 (9.22)	69.7 (4.92)	-0.15 (6.36)	(-10.13, 10.47)
41+	821	71.6 (9.66)	71.5 (5.11)	0.09 (6.47)	(-9.91, 10.90)

* The range within which 90% of differences between the observed and model predicted values lie.

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Web-Table 1 List of all subgroups of women for whom reference ranges have been developed*

	Reference Range Group	Parity	Pre-pregnancy BMI	Smoking during pregnancy	Blood pressure at 12 weeks (mmHg)
All pregnancies (Figure 1)		Nulliparous	-	-	-
		Multiparous	-	-	-
Normal pregnancies	**All normal pregnancies** (Figure 1)	Nulliparous	-	-	-
		Multiparous	-	-	-
	Low-risk women (Figure 2)	Nulliparous	Normal weight	Never smoked	-
		Multiparous	Normal weight	Never smoked	-
	High-risk women (Figure 2)	Nulliparous	Overweight/Obese	Any smoking	-
		Multiparous	Overweight/Obese	Any smoking	-
	Reference ranges by pre-pregnancy BMI category (Figure 3 and Web-Figure 1)	Nulliparous	Underweight	Never smoked	-
		Nulliparous	Normal weight	Never smoked	-
		Nulliparous	Overweight	Never smoked	-
		Nulliparous	Obese	Never smoked	-
		Multiparous	Underweight	Never smoked	-
		Multiparous	Normal weight	Never smoked	-
		Multiparous	Overweight	Never smoked	-
		Multiparous	Obese	Never smoked	-
	Reference ranges by smoking during pregnancy (Figure 4 and Web-Figure 4)	Nulliparous	Normal weight	Never smoked	-
		Nulliparous	Normal weight	Pre-pregnancy/1st trimester only	-
		Nulliparous	Normal weight	Throughout	-
		Multiparous	Normal weight	Never smoked	-
		Multiparous	Normal weight	Pre-pregnancy/1st trimester only	-
		Multiparous	Normal weight	Throughout	-
	Reference ranges conditional on blood pressure at 12 weeks (Figure 5 and Web-Figure 7)	Nulliparous	Normal weight	Never smoked	SBP = 100 at 12 weeks
		Nulliparous	Normal weight	Never smoked	SBP = 110 at 12 weeks
		Nulliparous	Normal weight	Never smoked	SBP = 120 at 12 weeks
		Nulliparous	Normal weight	Never smoked	SBP = 130 at 12 weeks
		Nulliparous	Normal weight	Never smoked	DBP = 50 at 12 weeks
		Nulliparous	Normal weight	Never smoked	DBP = 60 at 12 weeks
		Nulliparous	Normal weight	Never smoked	DBP = 70 at 12 weeks
		Nulliparous	Normal weight	Never smoked	DBP = 80 at 12 weeks
		Multiparous	Normal weight	Never smoked	SBP = 100 at 12 weeks
		Multiparous	Normal weight	Never smoked	SBP = 110 at 12 weeks
		Multiparous	Normal weight	Never smoked	SBP = 120 at 12 weeks
		Multiparous	Normal weight	Never smoked	SBP = 130 at 12 weeks
		Multiparous	Normal weight	Never smoked	DBP = 50 at 12 weeks
		Multiparous	Normal weight	Never smoked	DBP = 60 at 12 weeks
		Multiparous	Normal weight	Never smoked	DBP = 70 at 12 weeks
		Multiparous	Normal weight	Never smoked	DBP = 80 at 12 weeks

* Each row represents a subgroup of women for whom a reference range is presented in this paper. Cells marked with – indicate that this characteristic was not part of the criteria for defining the subgroup for this particular reference range

Web-Table 2 Mean and 95% reference ranges for systolic and diastolic blood pressure at three gestational ages across pregnancy for different subgroups of women from multilevel models

Maternal Subgroup				N	Mean (95% reference range)					
					SBP at 12 weeks	SBP at 20 weeks	SBP at 37 weeks	DBP at 12 weeks	DBP at 20 weeks	DBP at 37 weeks
All women (Figure 1)		Nulliparous		4718	112.7 (88.6, 136.8)	112.4 (88.9, 135.9)	117.2 (91.6, 142.8)	65.9 (48.9, 82.9)	65.1 (48.9, 81.2)	71.2 (51.3, 91.2)
		Multiparous		5609	111.6 (88.2, 135.0)	111.0 (87.7, 134.3)	115.0 (90.6, 139.3)	65.5 (48.9, 82.1)	64.4 (48.4, 80.5)	68.8 (50.3, 87.2)
Normal pregnancies*	**All normal pregnancies** (Figure 1)	Nulliparous		3372	112.1 (88.6, 135.5)	111.9 (89.4, 134.4)	116.0 (92.3, 139.7)	65.4 (48.9, 81.9)	64.6 (49.2, 80.1)	70.0 (52.2, 87.9)
		Multiparous		4132	111.0 (88.1, 133.9)	110.3 (87.8, 132.8)	114.2 (91.0, 137.4)	65.1 (49.0, 81.1)	64.0 (48.4, 79.6)	68.2 (51.0, 85.3)
	Low-risk (normal BMI, non-smokers) (Figure 2)	Nulliparous		1832	112.0 (88.9, 135.0)	111.3 (89.0, 133.5)	115.4 (92.0, 138.8)	65.6 (49.5, 81.7)	64.6 (49.4, 79.8)	69.9 (52.0, 87.8)
		Multiparous		2193	110.2 (88.0, 132.5)	109.4 (87.6, 131.2)	113.5 (90.6, 136.4)	64.7 (49.2, 80.3)	63.6 (48.4, 78.8)	67.9 (50.8, 85.0)
	High-risk (overweight/ obese, any smoking) (Figure 2)	Nulliparous		205	114.7 (89.4, 139.9)	115.9 (94.3, 137.4)	119.2 (95.5, 143.0)	67.0 (49.4, 84.7)	66.7 (50.2, 83.1)	72.2 (54.0, 90.4)
		Multiparous		285	114.3 (91.0, 137.6)	113.2 (90.4, 136.0)	117.6 (94.9, 140.3)	66.9 (50.6, 83.3)	65.4 (49.3, 81.6)	69.5 (52.1, 86.9)
	By BMI (non-smokers only)	Nulliparous (Figure 3)	Underweight	97	109.5 (86.4, 132.5)	110.6 (88.3, 132.8)	113.6 (90.1, 137.2)	64.2 (48.1, 80.3)	63.4 (48.2, 78.6)	68.3 (50.5, 86.2)
			Normal	1832	112.0 (89.0, 135.0)	111.3 (89.0, 133.5)	115.4 (91.9, 138.9)	65.6 (49.5, 81.6)	64.6 (49.4, 79.8)	69.9 (52.1, 87.7)
			Overweight	275	115.9 (92.8, 138.9)	116.0 (93.8, 138.2)	119.8 (96.3, 143.3)	68.4 (52.3, 84.4)	68.2 (53.0, 83.4)	73.2 (55.4, 91.1)
			Obese	66	121.9 (98.8, 144.9)	122.0 (99.8, 144.3)	125.7 (102.2, 149.3)	73.1 (57.0, 89.2)	71.4 (56.2, 86.6)	77.8 (60.0, 95.6)

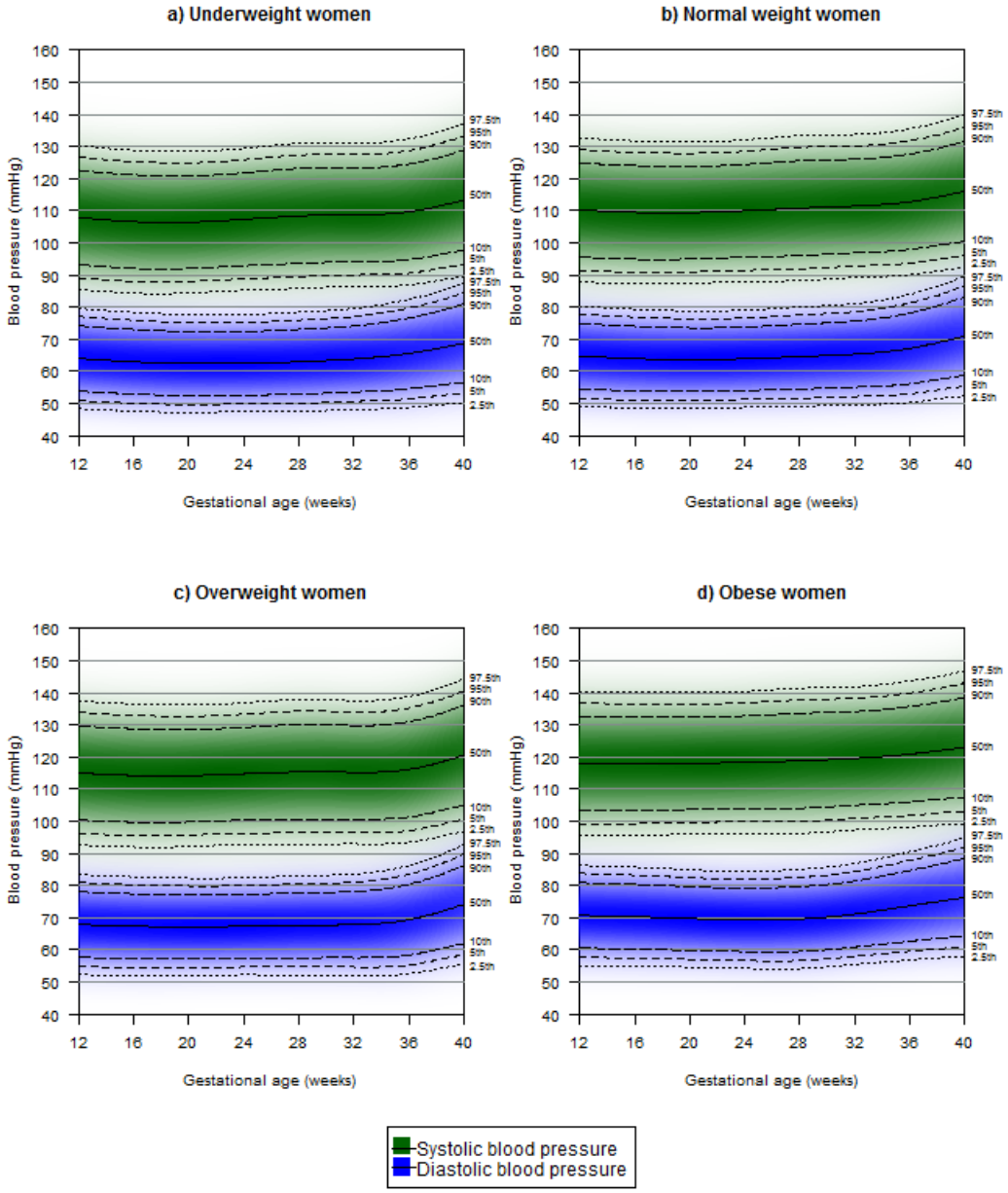
Maternal Subgroup				N	Mean (95% reference range)					
					SBP at 12 weeks	SBP at 20 weeks	SBP at 37 weeks	DBP at 12 weeks	DBP at 20 weeks	DBP at 37 weeks
Normal pregnancies*	By BMI (non-smokers only)	Multiparous (Web-Figure 1)	Underweight	122	107.9 (85.4, 130.4)	106.4 (84.4, 128.5)	110.3 (87.4, 133.2)	64.0 (48.4, 79.6)	62.4 (47.3, 77.6)	66.2 (49.1, 83.4)
			Normal	2193	110.2 (87.7, 132.7)	109.4 (87.4, 131.4)	113.5 (90.6, 136.4)	64.7 (49.1, 80.3)	63.6 (48.5, 78.8)	67.9 (50.8, 85.1)
			Overweight	430	115.1 (92.6, 137.5)	114.2 (92.2, 136.2)	117.0 (94.1, 139.9)	67.8 (52.2, 83.4)	67.1 (52.0, 82.3)	70.3 (53.1, 87.5)
			Obese	161	117.9 (95.4, 140.4)	118.1 (96.0, 140.1)	121.4 (98.5, 144.3)	70.7 (55.1, 86.3)	69.7 (54.6, 84.9)	74.3 (57.2, 91.5)
	By smoking in pregnancy (normal weight women only)	Nulliparous (Figure 4)	Never smoked	1832	112.0 (89.1, 134.9)	111.3 (89.2, 133.3)	115.4 (91.9, 138.9)	65.6 (49.6, 81.5)	64.6 (49.6, 79.6)	69.9 (52.5, 87.2)
			1st trimester	443	110.4 (87.5, 133.3)	110.5 (88.4, 132.6)	115.5 (92.0, 139.0)	63.8 (47.9, 79.8)	63.3 (48.3, 78.3)	69.0 (51.6, 86.3)
			Throughout	379	110.4 (87.5, 133.3)	110.9 (88.8, 133.0)	114.4 (90.9, 137.9)	63.3 (47.3, 79.2)	62.6 (47.6, 77.6)	68.1 (50.7, 85.5)
		Multiparous (Web-Figure 4)	Never smoked	2193	110.2 (88.1, 132.4)	109.4 (87.6, 131.2)	113.5 (90.5, 136.4)	64.7 (49.1, 80.3)	63.6 (48.5, 78.7)	67.9 (51.1, 84.7)
			1st trimester	302	109.0 (86.8, 131.1)	108.6 (86.8, 130.3)	112.6 (89.6, 135.5)	63.4 (47.8, 79.0)	62.7 (47.6, 77.8)	67.1 (50.2, 83.9)
			Throughout	554	109.8 (87.6, 131.9)	109.3 (87.5, 131.1)	113.3 (90.3, 136.2)	63.3 (47.7, 78.9)	62.3 (47.2, 77.4)	66.4 (49.5, 83.2)

* Normal pregnancies are defined as those where the woman did not have essential hypertension or preeclampsia, pre-existing or gestational diabetes and the pregnancy resulted and gave birth to an appropriate-size-for-gestational-age baby at term

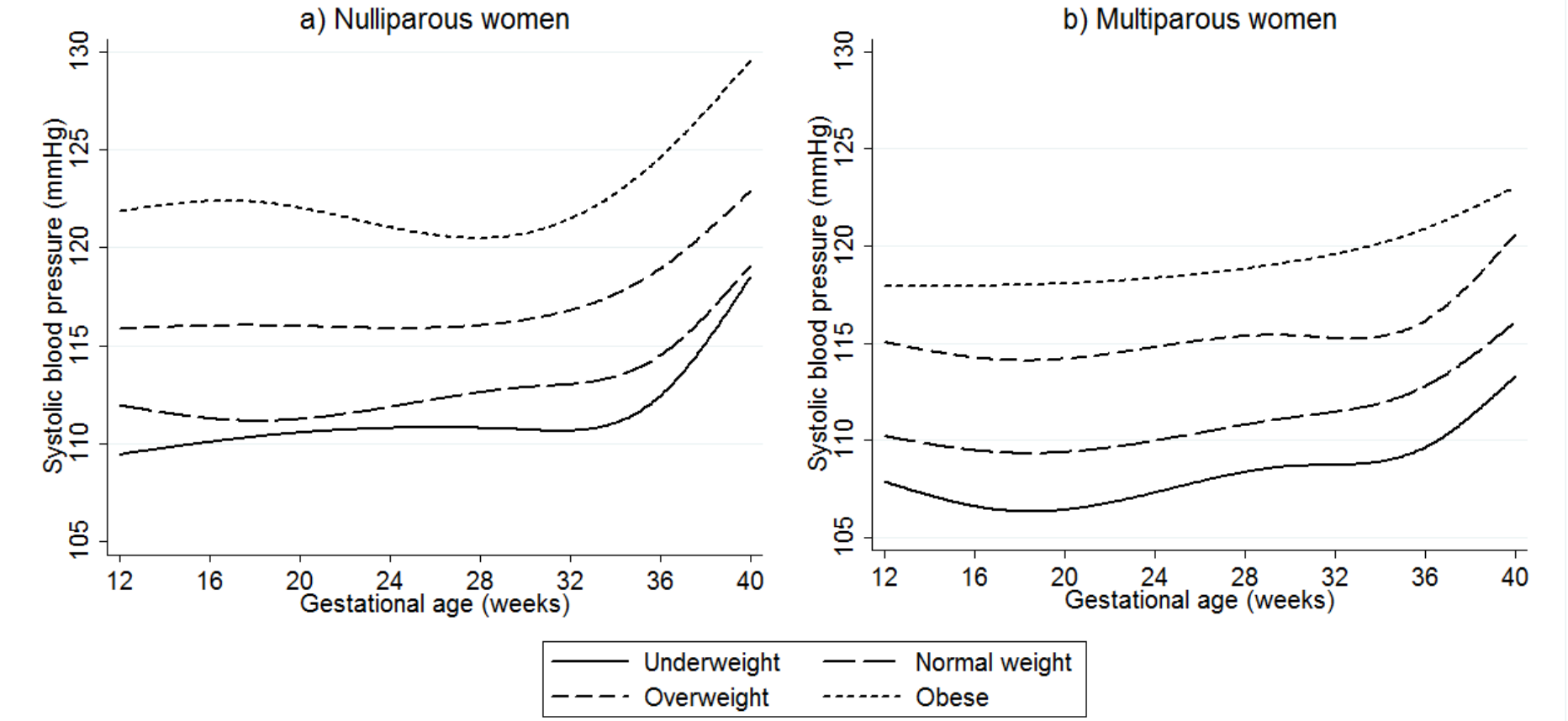
Web-Table 3 Mean and 95% reference ranges for predicted systolic and diastolic blood pressure at 20 weeks and 37 weeks in normal pregnancies for normal weight non-smoking women conditional on hypothetical measurements of SBP and DBP at 12 weeks gestation from multilevel models

	Error prone measurement of SBP at 12 weeks (mmHg)	**Mean (95% reference range) SBP prediction**		**Error prone measurement of DBP at 12 weeks (mmHg)**	**Mean (95% reference range) DBP prediction**	
		20 weeks	**37 weeks**		**20 weeks**	**37 weeks**
Nulliparous women (Figure 5)	100	106.7 (86.2, 127.2)	111.9 (89.5, 134.4)	50	59.7 (45.4, 74.1)	66.2 (48.7, 83.7)
	110	110.5 (90.0, 131.0)	114.8 (92.4, 137.3)	60	62.9 (48.5, 77.2)	68.6 (51.1, 86.0)
	120	114.3 (93.8, 134.8)	117.8 (95.3, 140.2)	70	66.0 (51.6, 80.3)	70.9 (53.5, 88.4)
	130	118.1 (97.6, 138.6)	120.7 (98.2, 143.1)	80	69.1 (54.7, 83.4)	73.3 (55.8, 90.8)
Multiparous women (Web-Figure 7)	100	105.6 (85.4, 125.8)	110.5 (88.5, 132.5)	50	59.0 (44.7, 73.4)	64.1 (47.5, 80.6)
	110	109.3 (89.1, 129.5)	113.4 (91.4, 135.4)	60	62.1 (47.8, 76.5)	66.7 (50.1, 83.3)
	120	113.0 (92.8, 133.2)	116.3 (94.3, 138.3)	70	65.2 (50.9, 79.6)	69.3 (52.7, 85.9)
	130	116.7 (96.5, 136.9)	119.1 (97.1, 141.1)	80	68.4 (54.0, 82.7)	71.9 (55.3, 88.5)

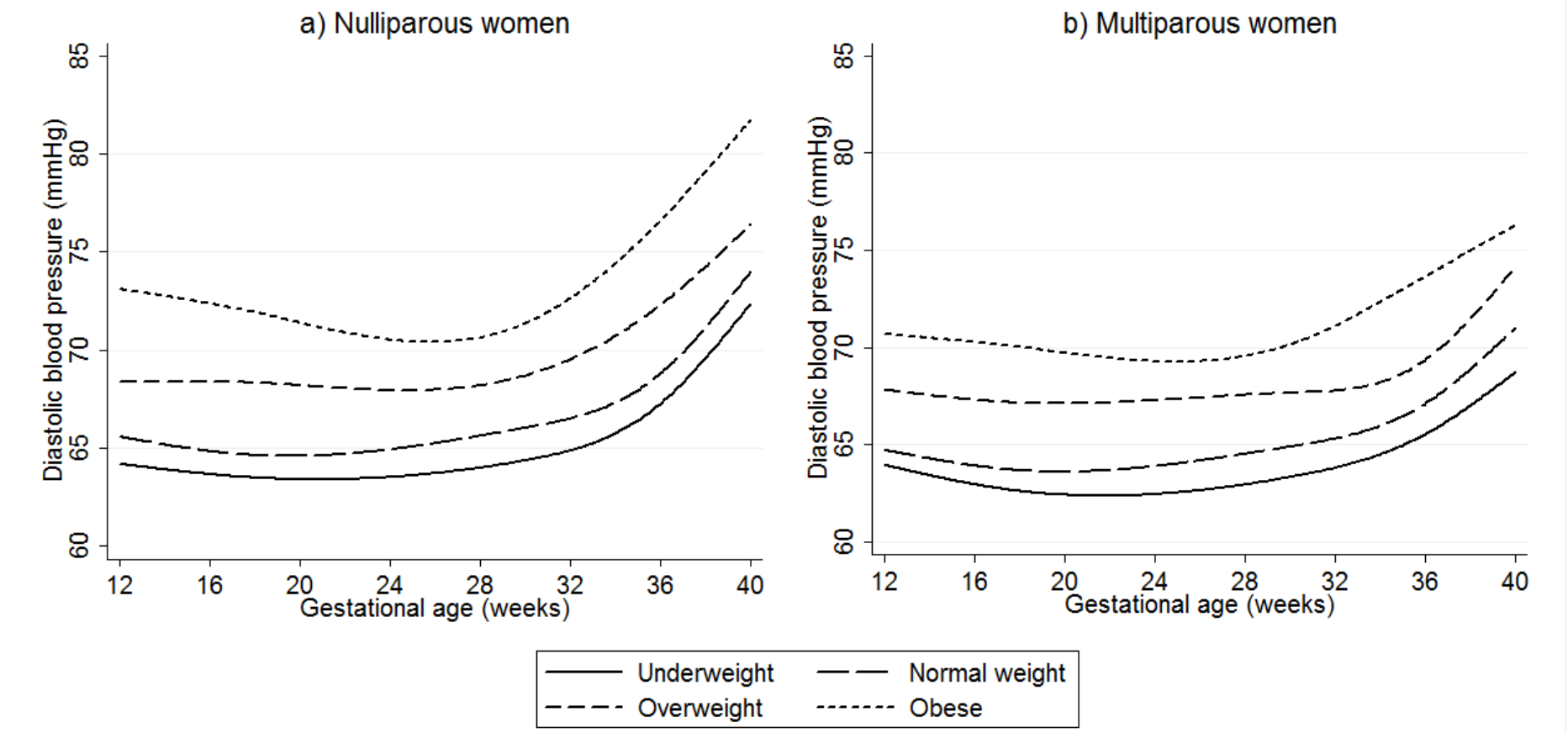
Web-Figure 1 Reference ranges for systolic and diastolic blood pressure by maternal pre-pregnancy BMI category for multiparous non-smokers with normal pregnancies (N=2906)



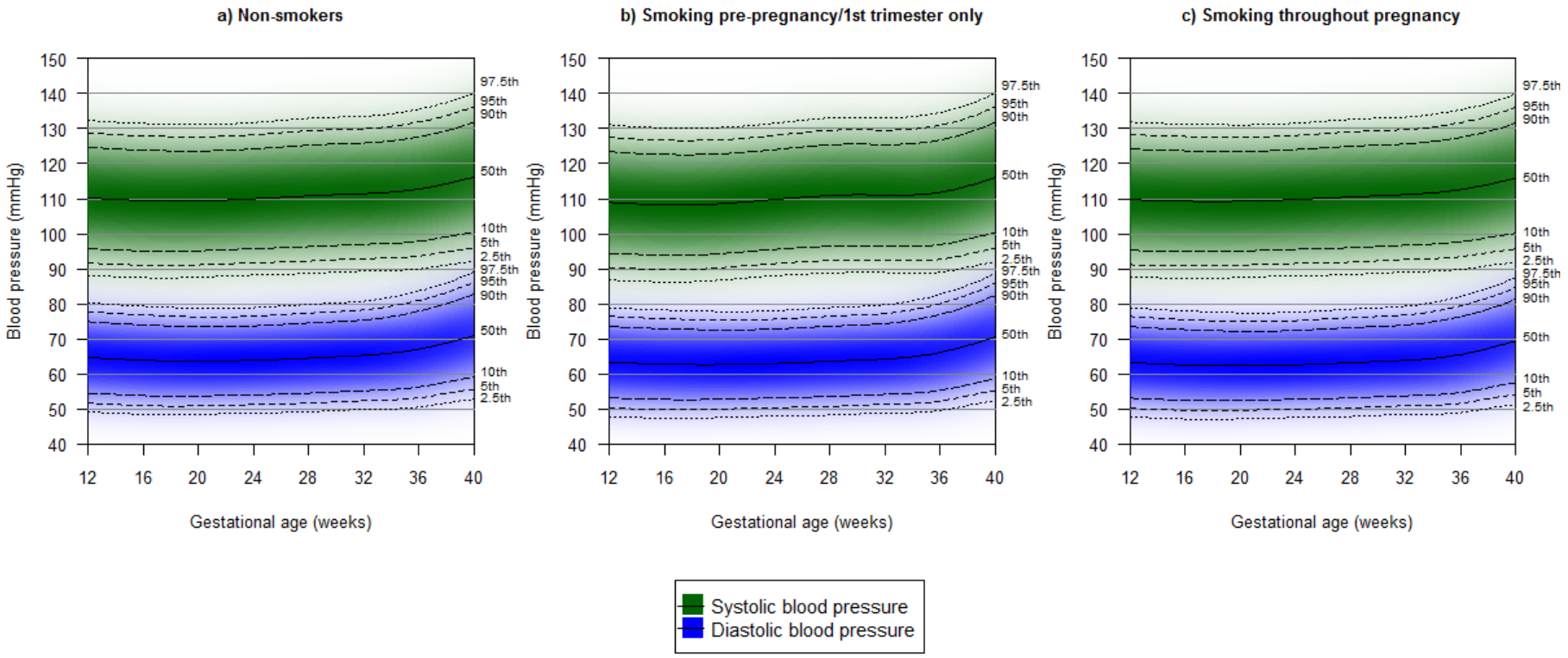
Web-Figure 2 Average trajectories of systolic blood pressure by maternal pre-pregnancy BMI category in a) nulliparous and b) multiparous non-smoking women with normal pregnancies



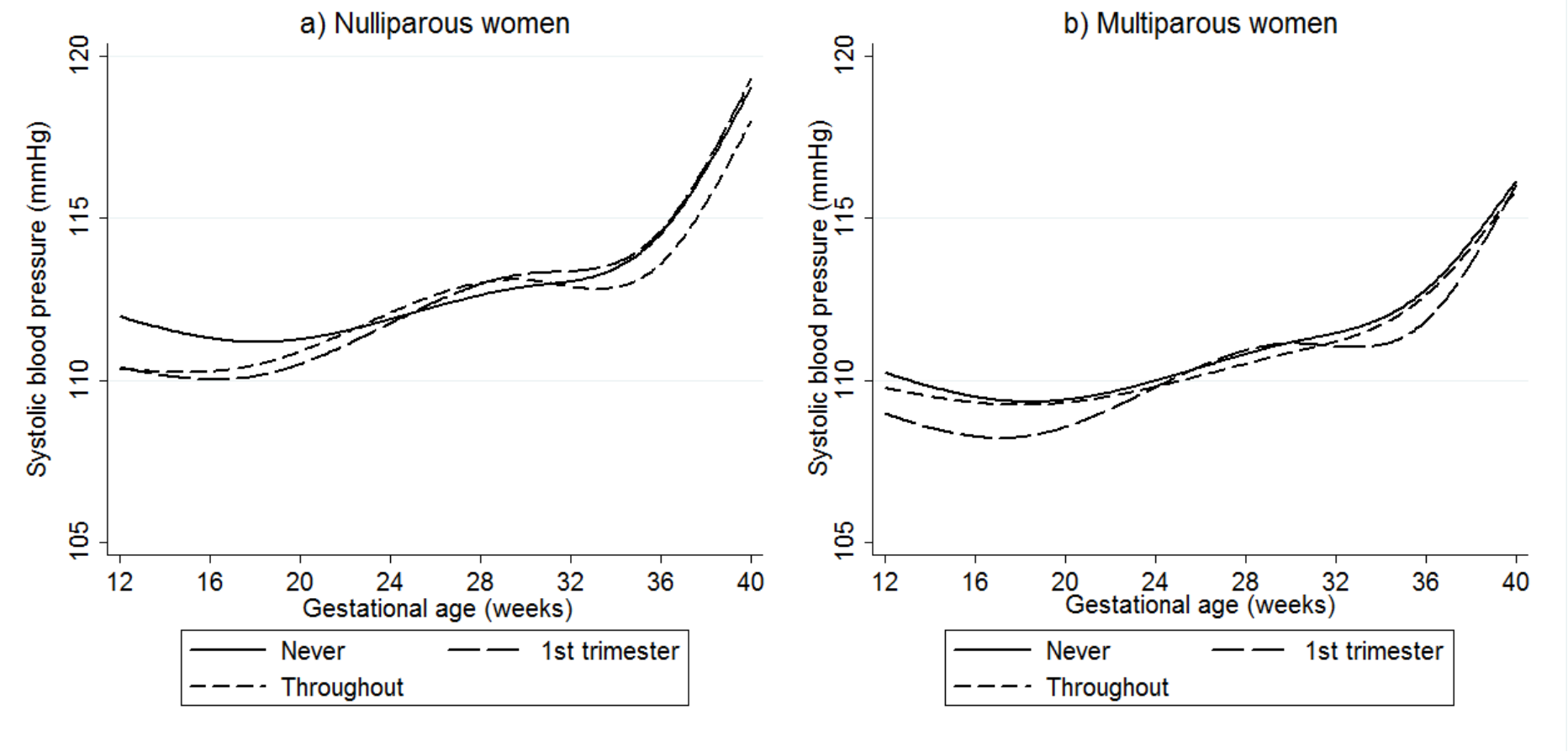
Web-Figure 3 Average trajectories of diastolic blood pressure by maternal pre-pregnancy BMI category in a) nulliparous and b) multiparous non-smoking women with normal pregnancies



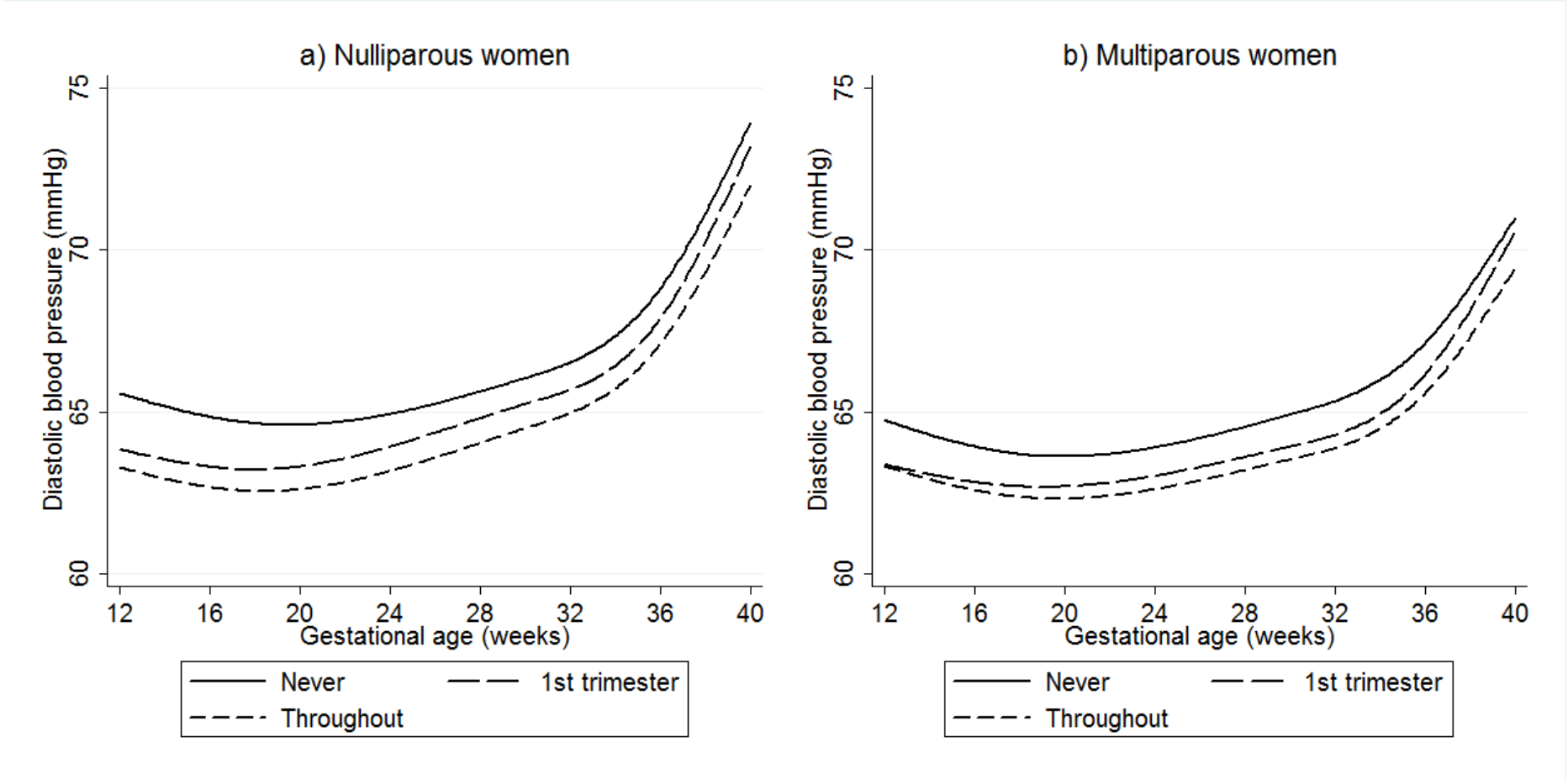
Web-Figure 4 Reference ranges for systolic and diastolic blood pressure by maternal smoking during pregnancy for multiparous normal-weight women with normal pregnancies (N=3049)



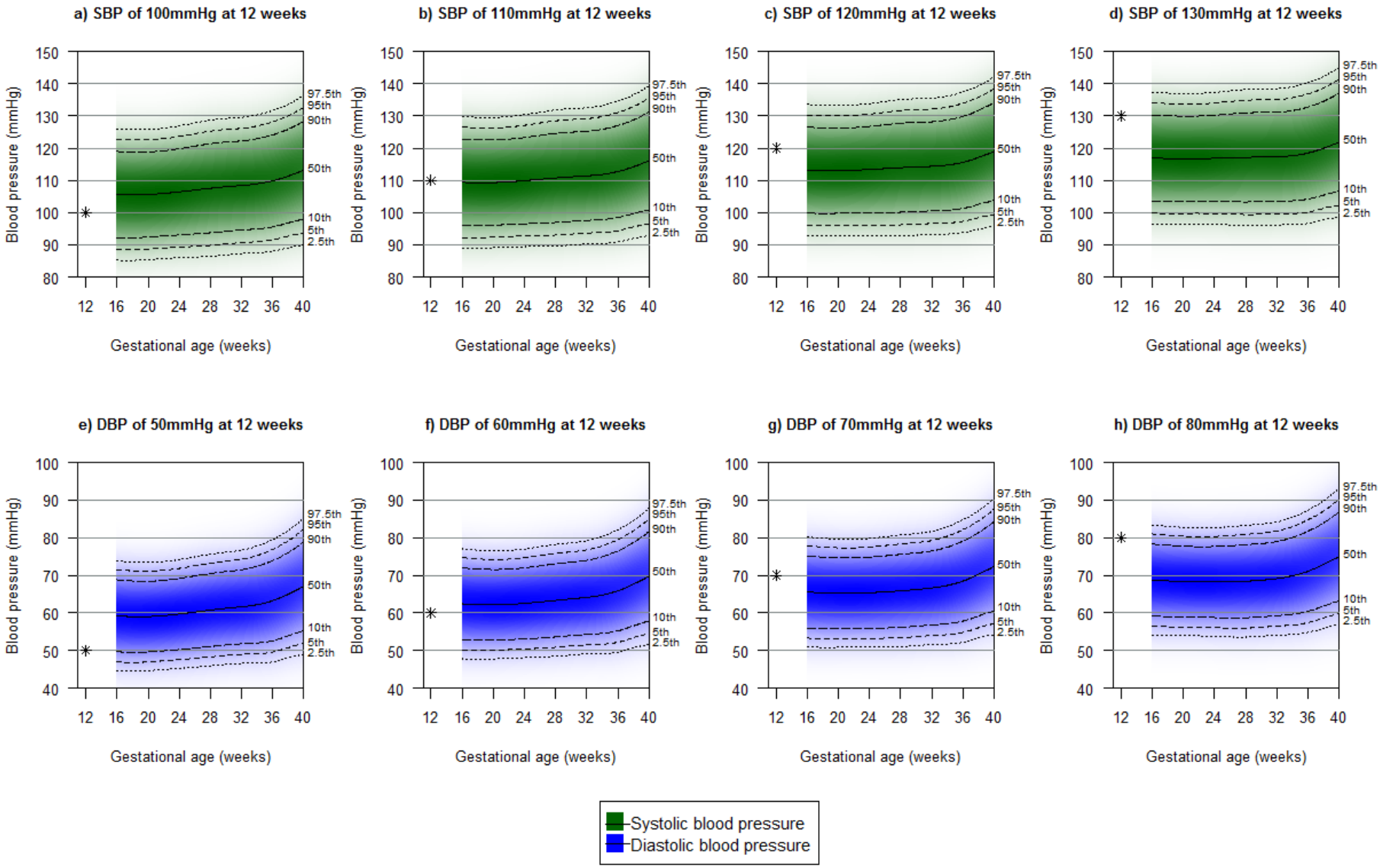
Web-Figure 5 Average trajectories of systolic blood pressure by maternal smoking in pregnancy in a) nulliparous and b) multiparous normal weight women with normal pregnancies



Web-Figure 6 Average trajectories of diastolic blood pressure by maternal smoking in pregnancy in a) nulliparous and b) multiparous normal weight women with normal pregnancies



Web-Figure 7 Reference ranges for systolic and diastolic blood pressure in pregnancy conditional on the level of blood pressure at 12 weeks gestation for multiparous normal-weight non-smoking women with normal pregnancies (N=2193)*



* Note that in each of the plots there is a star that corresponds to the value of SBP/DBP at 12 weeks.