

# Modelling the association of blood pressure during pregnancy with gestational age and body mass index

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## Summary

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Improved understanding of the determinants of blood pressure (BP) changes during pregnancy is essential for decreasing the morbidity and mortality borne by women and their families worldwide. While most epidemiological studies consider associations based on categorical risk factor classifications, using measurements on a continuous scale has been advocated as a means of gaining richer insights into biological processes. We modelled the relationship during pregnancy of continuous systolic (S) and diastolic (D) BP distributions with gestational age and pre-pregnancy body mass index (BMI) using fractional polynomials. We used information, including antenatal BP values abstracted from medical records, from a prospective cohort of 1733 women recruited before 20 weeks' gestation.

The percentiles for SBP and DBP changed over pregnancy, with DBP percentiles decreasing initially, followed by an increase starting about mid-second trimester. Modelling the joint impact of BMI and gestational age on mean BP indicated an increase in mean BP with increasing BMI that was attenuated at higher BMI levels, later in pregnancy. This attenuation persisted in a variety of sub-analyses which explored the possibility that it was caused by confounding or by influential groupings of subjects. Estimated longitudinal percentiles that characterise the BP distribution across gestation may facilitate evaluation of BP during pregnancy. BP patterns observed over pregnancy and, in particular, the attenuation of BP increases at high BMI, late in pregnancy, can provide insights towards elucidating the mechanisms that drive BP changes during pregnancy.

**Keywords:** prenatal blood pressure, body mass index, longitudinal, reference range, exposure–response relation, fractional polynomials.

## Introduction

Blood pressure (BP) measurement plays a central role in the screening and management of hypertension during pregnancy.<sup>1,2</sup> Much current knowledge of BP characteristics in pregnancy relates to changes in early pregnancy (around 5–8 weeks' gestation), where profound haemodynamic changes occur, representing maternal adaptive responses necessary for meeting the circulatory needs of the mother and the developing feto-placental unit.<sup>3–7</sup> Pregnancies complicated by intrauterine growth restriction, gestational hypertension and pre-eclampsia

are associated with lower maternal cardiac output and higher total peripheral vascular resistance than uncomplicated pregnancies.<sup>8,9</sup> In pregnant women, increased adiposity has been consistently associated with important medical complications of pregnancy such as pre-eclampsia, gestational diabetes mellitus, abruptio placentae and operative delivery.<sup>10–14</sup> The mechanisms for these associations are, however, incompletely understood.

We have undertaken a series of analytical exercises to better understand what constitutes a 'normal'

sequence of routinely collected BP measurements during pregnancy and to characterise influences upon longitudinal distributions of systolic (S) and diastolic (D) BP throughout pregnancy. As is common practice in epidemiological studies,<sup>15–17</sup> we first completed categorical analyses to document the existence of associations of SBP and DBP with a modifiable characteristic, pre-pregnancy body mass index (BMI), and a non-modifiable characteristic, trimester of pregnancy.<sup>18</sup> Briefly, we noted that mean BP increased across BMI categories (i.e. lean, normal, overweight, obese) within each trimester of pregnancy. We also noted that mean SBP increased across trimesters within BMI category, whereas mean DBP decreased between first and second trimesters and increased in the third trimester.

Given the aforementioned associations, we have initiated a second level of analysis (on the same population studied earlier<sup>18</sup>), which moves the focus from simply documenting associations towards more fully characterising the form of exposure–response relationships. We first sought to estimate reference ranges for both SBP and DBP during pregnancy. Longitudinal reference ranges for a variety of measures during pregnancy have been established, both to characterise the distribution and variability of these variables and to assess their value as screening tools for potential problems in pregnancy.<sup>19–23</sup> Reference ranges for gestational BP may offer insights into the typical pregnancy BP trajectory and the distribution and variability of the trajectory. We note that clinical definitions of BP-related pregnancy conditions such as gestational hypertension are typically based on constant BP thresholds, which ignore changes in the normal trajectory over pregnancy. As a further step towards elucidating the mechanisms underlying BP patterns throughout pregnancy, we modelled the longitudinal relationship between BP and pre-pregnancy BMI across gestation. Our analyses were based on a large sample of pregnant women with an average of 12.2 clinical BP readings recorded during pregnancy.<sup>24</sup>

Because our analyses are based on routinely measured BPs, our results reflect the kind of BP measurements and patterns that occur in routine clinical practice as opposed to measurements that are taken in controlled clinical trial settings. An impressive body of work involving ambulatory BP measurements exists.<sup>25–29</sup> While recognising the superior fidelity of BP measures derived from controlled clinical settings, and the richness of information that may be obtained from

24-hour ambulatory BP profiles, routinely collected BP measures remain the primary tool in clinical evaluations.

## Methods

### *Study design and data collection*

The Omega Study is an ongoing prospective study examining the metabolic and dietary predictors of pre-eclampsia, gestational diabetes and other pregnancy outcomes.<sup>24</sup> The study cohort of 1733 subjects was drawn from women attending prenatal care at clinics affiliated with the Swedish Medical Center and Tacoma General Hospital in Seattle and Tacoma, Washington, USA, respectively. Antepartum characteristics including all recorded BPs and pregnancy outcome information were abstracted from clinic and hospital labour and delivery medical records after the delivery date. When BP from an expected antepartum visit was unavailable, records were augmented by BPs taken upon admission for inpatient observation or to the emergency room. Details of the construction of the database are described elsewhere.<sup>18,24</sup>

### *Statistical analyses*

A range of statistical methodologies exist to facilitate flexible exposure–response modelling, including splines and non-parametric smoothing. We have elected to base our modelling on fractional polynomials (FP).<sup>17,30,31</sup> FPs offer greater flexibility in shape than conventional polynomials and have the advantage over non- or semi-parametric modelling in that they can be expressed concisely and, in consequence, other functions of interest (such as rates of change) may be readily calculated. We emphasise that we do not interpret the individual FP terms, but rather use them as building blocks towards characterising the nature of the exposure–response relationships. In our setting it is the shape associated with the models that is of interest rather than the individual FPs themselves. FPs up to degree 2 based on powers from the set  $P = \{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$  were considered. By a FP of degree 2 in a variable  $X$  (e.g. gestational age), we mean a linear combination of power transformations of the form:  $\beta_0 + \beta_1 X^{p_1} + \beta_2 X^{p_2}$ , where  $X^{p_k} = \ln(X)$  if  $p_k = 0$  and  $X^{p_2} = X^p \ln(X)$  if  $p_1 = p_2 = p$ . It has been found that FPs of degrees higher than 2 are seldom required and may,

to the contrary, introduce an implausible structure into modelled relationships.<sup>30,31</sup> For each degree ( $m = 1$  or  $2$ ), the best FP model (FP1 or FP2) for a particular variable (e.g. gestational age) was based on those elements of  $P$  associated with the smallest residual sum of squares. Comparisons between FP models (FP1 vs. FP2 vs. null) were based on approximate  $\chi^2$  tests with significance level set at 0.1. Sandwich variance estimation was used throughout to accommodate correlation of repeated records for individual women.<sup>32</sup>

Our analysis had two main components. First, we modelled longitudinal BP (SBP or DBP) distributions by maximum pseudo-likelihood estimation using the LMS methodology.<sup>33</sup> This approach assumes that, at any gestational age, the distribution of BP can be transformed to normality by means of a power

transformation. FPs up to degree 1 (L) and 2 (M, S) were used to model the transformation (L), location (M) and spread (S) parameters as smooth functions of gestational age. In particular, the 5th, 10th, 50th, 90th and 95th percentiles of BP were estimated at each gestational age. The fit of these longitudinal reference ranges was evaluated at each gestational age by comparison of the observed and expected frequencies within and beyond the percentile bounds and by examining the distribution of  $z$ -scores, calculated for each observation based on the fitted parameters.

In the second aspect of our analysis of longitudinal features of BP in pregnancy, we considered the three-dimensional association between SBP and DBP, gestational age and pre-pregnancy BMI. The associations were initially explored by means of both

**Table 1.** Percentage characteristics of the study cohort according to categories of maternal pre-pregnancy body mass index (BMI). Seattle and Tacoma, WA, 1996–2002

Characteristics	Lean <20 kg/m <sup>2</sup>	High normal 20–24.9 kg/m <sup>2</sup>	Overweight 25–29.9 kg/m <sup>2</sup>	Obese 30–34.9 kg/m <sup>2</sup>	Obese ≥35 kg/m <sup>2</sup>	Total cohort
	%	%	%	%	%	%
Maternal age (years)						
<20	1.1	0.5	0.8	2.6	3.9	0.9
20–34	74.3	71.7	69.5	68.8	71.2	71.8
35+	24.6	27.8	29.7	28.6	25.0	27.4
Maternal race/ethnicity						
Non-Hispanic white	83.8	87.1	84.6	79.2	75.0	85.3
African American	1.4	0.7	4.9	3.9	5.8	1.7
Asian	10.6	7.0	6.1	5.2	5.8	7.5
Other	4.2	5.2	4.4	11.7	13.5	5.4
Multiparous	31.0	30.9	34.5	39.0	30.8	31.8
<12 Years education	4.6	4.2	4.9	9.2	9.6	4.8
Single	10.6	8.7	11.7	11.7	13.5	9.8
Annual household income (\$)						
70 000+	74.4	72.6	63.2	61.6	50.0	70.5
30 000–69 999	19.8	24.5	29.8	30.1	34.0	24.8
<30 000	5.8	2.9	7.0	8.2	16.0	4.7
Smoked during pregnancy	5.0	6.0	9.2	9.1	7.7	6.5
Physically inactive during pregnancy	16.5	16.4	16.5	18.2	21.1	16.6
Incident pre-eclampsia	3.3	3.2	7.6	5.6	16.0	4.3
Incident gestational diabetes mellitus	1.5	3.7	4.2	12.7	14.0	4.0
Gestational age at delivery (weeks)						
<28 <sup>a</sup>	7.5	3.7	4.0	6.5	9.6	4.9
28–36	7.0	10.4	9.2	9.1	11.5	9.5
37–40	72.4	71.5	71.5	71.4	65.4	71.5
>40	13.1	14.3	15.3	13.0	13.5	14.1
<i>n</i> = 100%	358	997	249	77	52 <sup>b</sup>	1733

<sup>a</sup>Includes pregnancies ending in miscarriage, induced abortion or fetal demise.

<sup>b</sup>33 subjects had BMI values between 35.0 and 39.9 kg/m<sup>2</sup>; 16 subjects had BMI values between 40.0 and 50.0 kg/m<sup>2</sup>; and three subjects had BMI values exceeding 50 kg/m<sup>2</sup>.

categorical analysis and multivariable non-parametric smoothing. Multivariable FPs were then used to model mean BP as a function of (continuous) gestational age, (continuous) pre-pregnancy BMI and interactions between gestational age and BMI. FP models for interaction terms of the form  $XZ$ ,  $X^2Z$  and  $XZ^2$  were considered, where  $X$  represents gestational age and  $Z$  represents BMI. Model fit was assessed by examination of regression residual diagnostics. The multivariable FP analyses were restricted to women with pre-pregnancy BMI  $< 50 \text{ kg/m}^2$ , which excluded three women with higher values that were judged likely to be influential in the model fit.

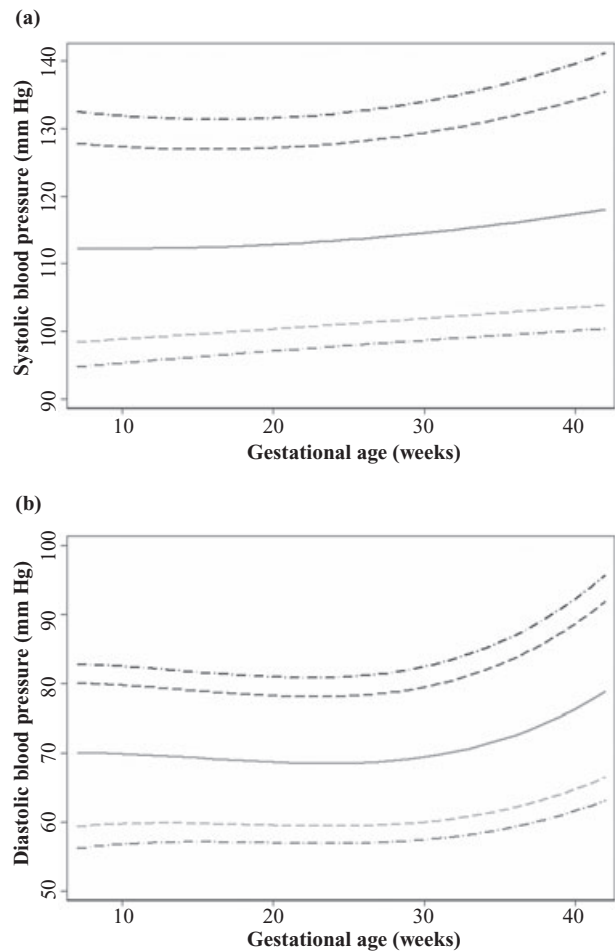
Multivariable FP modelling was repeated with adjustment for possible confounding by maternal race/ethnicity (Non-Hispanic White, African American, Asian, other), maternal age ( $< 20$ ,  $20\text{--}34$ ,  $\geq 35$  years), parity (primipara or multipara), education ( $< 12$  years or  $\geq 12$  years), annual household income ( $< \$30\,000$ ,  $\$30\,000\text{--}\$69\,999$ ,  $\geq \$70\,000$ ), smoking during pregnancy (yes or no), and any participation in leisure time physical activity during pregnancy (yes or no). Adjustment was also carried out for continuous maternal age, years of education and annual household income, modelled using FPs. The robustness of the fitted models was further assessed by comparison with models fitted (i) after excluding certain possibly influential groups of women, (ii) on a random sample of half the subjects, (iii) after excluding the non-routine augmented records and (iv) using random effect modelling rather than sandwich variance estimation. Robustness was also assessed by expanding the range of interactions considered.

Multivariable 'loess' non-parametric smoothing was carried out using RGui, Version 2.1.1.<sup>34</sup> All other analyses were carried out using Stata Software, Version 9.1.<sup>35</sup>

## Results

Characteristics of the study population stratified by five pre-pregnancy BMI categories ( $< 20$ ,  $20\text{--}24.9$ ,  $25\text{--}29.9$ ,  $30\text{--}34.9$  and  $\geq 35 \text{ kg/m}^2$ ) are summarised in Table 1. The fifth category (i.e.  $\geq 35 \text{ kg/m}^2$ ) allows assessment of maternal characteristics for the most obese women in the study cohort.

Longitudinal analyses were based on 12 846 BP records of which 188 records (1.5%) were non-routine measurements from 166 women (referred to as 'aug-

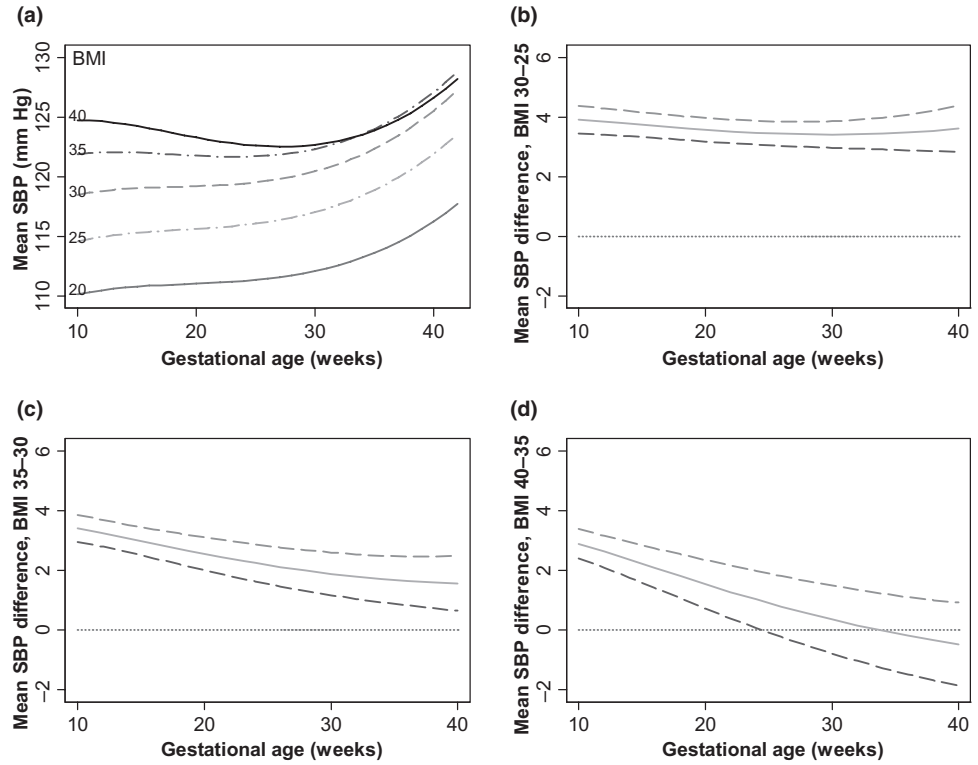


**Figure 1.** Longitudinal 5th, 10th, 50th, 90th and 95th percentiles for (a) systolic and (b) diastolic blood pressure.

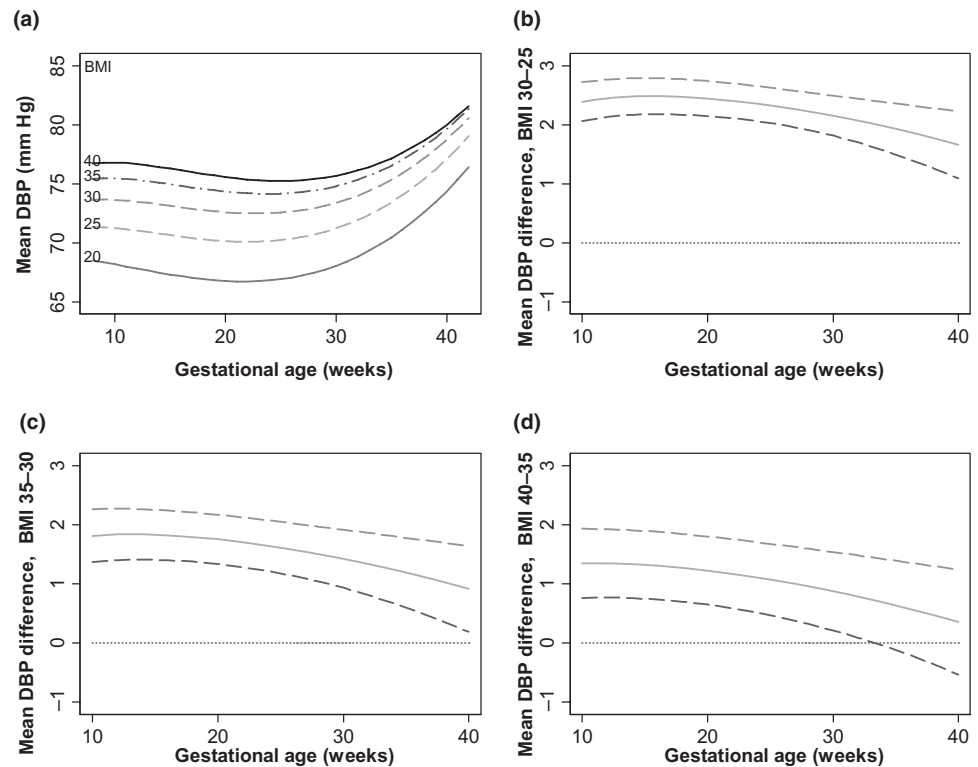
mented records'). Pre-pregnancy BMI was similar in women who did and did not have augmented records ( $23.1 \text{ kg/m}^2$  vs.  $23.8 \text{ kg/m}^2$ ). The average augmented SBP was somewhat higher than the average routine measurement ( $118.9$  vs.  $114.4 \text{ mmHg}$ ), but the average non-routinely and routinely collected DBP were similar ( $70.1$  vs.  $70.2 \text{ mmHg}$ ).

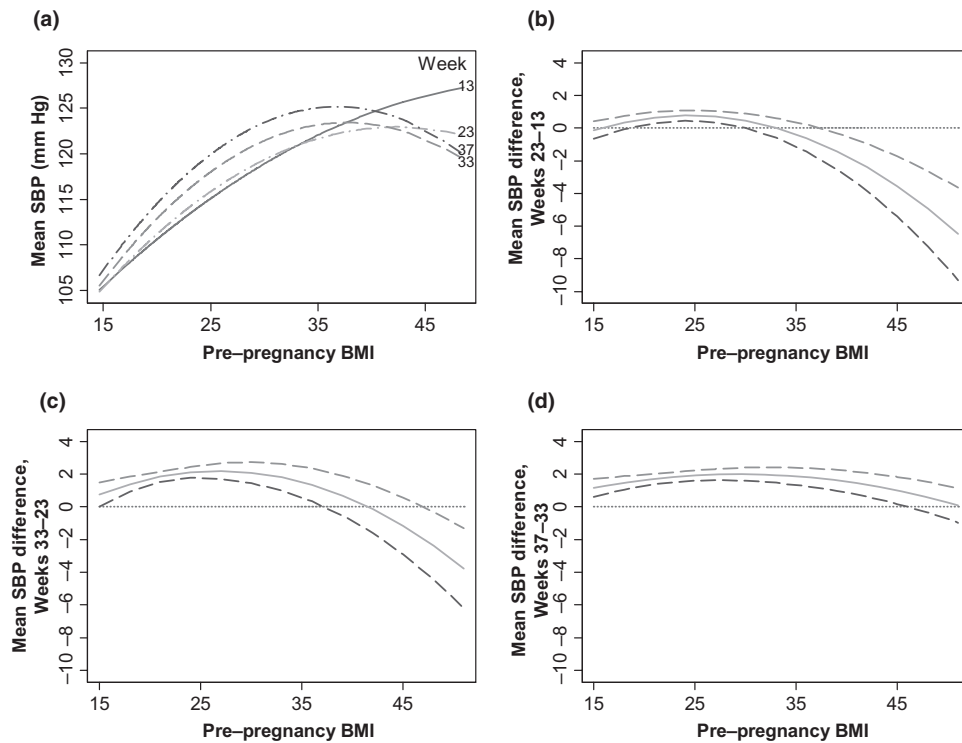
Longitudinal reference ranges for SBP and DBP are shown in Fig. 1a–b and the corresponding equations are provided in Appendix 1. The distribution of SBP was right skewed and SBP percentiles increased gradually throughout pregnancy, with the increase being more pronounced in the third trimester. The percentiles for DBP decreased until about the middle of the second trimester, before increasing again at the end of pregnancy. The cross-sectional variability in both SBP and DBP remained relatively stable over the duration of pregnancy.

**Figure 2.** Mean systolic blood pressure (SBP), at BMI = 20, 25, 30, 35 and 40 kg/m<sup>2</sup> (a), and differences in mean SBP (with 95% point-wise confidence intervals) across body mass index (BMI) levels (b–d), as a function of gestational age.



**Figure 3.** Mean diastolic blood pressure (DBP), at body mass index (BMI) = 20, 25, 30, 35 and 40 kg/m<sup>2</sup> (a), and differences in mean DBP (with 95% point-wise confidence intervals) across BMI levels (b–d), as a function of gestational age.





**Figure 4.** Mean systolic blood pressure (SBP), at gestational ages 13, 23, 33 and 37 weeks (a), and differences in mean SBP (with 95% point-wise confidence intervals) across gestational age (b–d), as a function of pre-pregnancy body mass index (BMI).

The multivariable FP modelling of mean BP (SBP or DBP) as a function of BMI and gestational age results in a fitted three-dimensional surface. For ease of visualisation and interpretation we present slices through these surfaces in Figs 2–5. The corresponding fitted equations are also provided in Appendix 1. Figure 2a (3a) shows estimates of mean SBP (DBP) as a continuous function of gestational age at five different levels of BMI (i.e. 20, 25, 30, 35 and 40 kg/m<sup>2</sup>). At any given gestational age, mean SBP (or DBP) generally increased with increasing BMI. However, the increase was attenuated with increasing BMI, particularly later in pregnancy. Figure 2b–d (3b–d) show estimates and associated point-wise 95% confidence intervals for differences in mean SBP (or DBP) between, respectively, BMI 30 and 25, 35 and 30, and 40 and 35 (kg/m<sup>2</sup>) over gestational age. While the increase in mean SBP between women with BMI 25 and BMI 30 kg/m<sup>2</sup> remained approximately constant throughout pregnancy (average 3.6 mmHg), increases in mean SBP comparing women with BMI 30 and BMI 35 kg/m<sup>2</sup> and women with BMI 35 and BMI 40 kg/m<sup>2</sup> decreased with increasing gestational age. Analogous observations were made for DBP in Fig. 3b–d, although the attenuation was more modest.

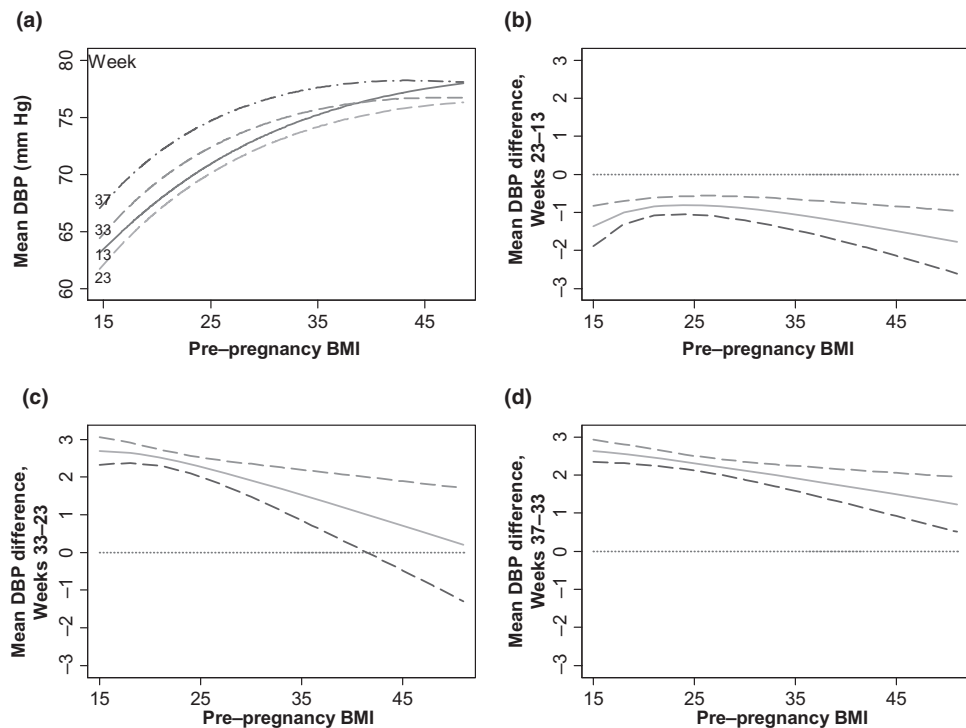
Figure 4a (5a) shows estimates of mean SBP (or DBP) as a continuous function of BMI at gestational ages 13,

23, 33 and 37 weeks. Whereas the overall percentiles for SBP increased with gestational age (Fig. 1a), when the role of BMI is included, we see in Fig. 4a that, for higher BMI levels, mean SBP initially decreased with increasing gestational age, followed by an increase again towards the end of pregnancy. Figure 5a also shows that the increase in mean DBP later in pregnancy (after an initial decrease) was attenuated at higher BMI values. Figure 4b–d (5b–d) show estimates and associated point-wise 95% confidence intervals for differences in mean SBP (DBP) between, respectively, gestational ages 23 and 13, 33 and 23, and 37 and 33 as a function of BMI.

We have explored the robustness of the fitted FP models and of the interaction between gestational age and BMI, in a number of ways. First, the same general features found in our fitted FP models, namely an attenuation in BP later in pregnancy among women with higher BMI, were observed in multivariable non-parametric smoothing of BP as a function of gestational age and BMI (data not shown). This suggests that the observed structure is not an artefact of the choice of FP models.

Our earlier categorical analyses<sup>18</sup> had indicated that the associations between mean BP and gestational age and BMI were not confounded by other demographic and personal characteristics. We refitted the FP models

**Figure 5.** Mean diastolic blood pressure (DBP), at gestational ages 13, 23, 33 and 37 weeks (a), and differences in mean DBP (with 95% point-wise confidence intervals) across gestational age (b–d), as a function of pre-pregnancy body mass index (BMI).



adjusting for potential confounders but, aside from some slight changes in level and very modest reductions in standard errors, the nature of the estimated associations was unchanged. The estimated association, including the attenuation at high BMI, persisted in a variety of sub-analyses which explored the possibility that it was caused by influential groupings of subjects or records.

Finally, we considered the possibility that the observed features were artefacts of our choice of interaction terms [FP models for (a subset of)  $XZ$ ,  $X^2Z$  and  $XZ^2$ , where  $X$  represents gestational age and  $Z$  represents BMI]. In separate analyses we considered all possible interactions of the form  $X^{p_1}Z^{p_2}$  and  $X^{p_3}Z^{p_4}$  where  $p_i \in P$ ,  $i = 1, 2, 3, 4$ , selecting the model with the smallest Akaike Information Criterion.<sup>36</sup> These models were again similar in structure to those described above.

## Discussion

We have estimated longitudinal reference ranges that characterise the BP distribution over pregnancy in our study population. These reference ranges may serve as a resource for evaluation of BP over pregnancy, both cross-sectionally and longitudinally. Consideration of each woman's individual sequence of BP measure-

ments may enable development of a more sensitive and specific obstetric screening instrument for BP-related conditions.

We observed an increase in SBP throughout gestation, with a more rapid increase later in pregnancy. In contrast, other studies have shown a decrease in both SBP and DBP in early pregnancy.<sup>25–29</sup> We believe this discordance may be attributable to the fact that, on average, our BP measurements begin at 8 weeks' gestation, when SBPs are approaching their nadir.

Our previous categorical analysis of the joint impact of BMI and gestational age on BP in pregnancy<sup>18</sup> indicated that mean BP increased across BMI categories (lean, normal, overweight, obese) within each trimester of pregnancy. Our current analyses of continuous variables indicate that, in the later stages of pregnancy, there is a ceiling effect which attenuates this pattern. The characteristics illustrated in Figs 2–5 allow a more nuanced understanding of the BP associations which, if validated in independent studies, may provide useful insights into the factors governing changes in BP throughout pregnancy.

Results from our study should be interpreted in the light of the limitations of the study. We note that modelled associations are data-driven in that we have chosen the FP models that best fit our sample rather

than fitting models that were defined a priori. Validation in an independent dataset will be necessary to confirm these findings.

Second, although BP measurement plays a central role in the screening and management of hypertension during pregnancy, investigators have questioned the validity of conventional (clinic) BP measurements; efforts have been made to improve measurements with ambulatory automated devices that provide a large number of measurements over a period of time.<sup>1</sup> Our analyses are based on routinely collected clinical BP measurements and, as such, reflect characteristics that would emerge in routine follow-up of pregnant women, as opposed to being constrained by trial conditions. Such measurements taken during antepartum visits continue to form the basis upon which clinical diagnoses of pre-eclampsia and other hypertensive diagnoses are made in clinical settings throughout the world.<sup>37</sup> We have attempted to confirm the validity of our clinical BP measurements in a number of ways.<sup>24</sup>

Third, the generalisability of our study may be limited, as our cohort was primarily comprised of non-Hispanic white and well-educated women. However, it seems unlikely that the observed associations are dependent on race or education. Certainly, adjustment for these variables did not alter our key observations.

Fourth, we were not able to evaluate gestational BP changes in relation to direct measures during pregnancy of maternal whole body adiposity or maternal intra-abdominal fat, which may be more strongly related to endothelial dysfunction, hyper-insulinaemia and BP changes across gestation than measures of pre-pregnancy BMI. Future studies should incorporate additional longitudinal measures of maternal adiposity.

We are not aware of other studies that have assessed the continuous longitudinal association between BP and maternal pre-gestational BMI during pregnancy. The pattern of increasing BP with increasing BMI has, however, been noted in non-pregnant women and men.<sup>38–40</sup> Pathophysiological mechanisms for observed increased BPs with increasing BMI remain uncertain, although several biologically plausible hypotheses have been proposed. For instance, investigators have speculated that disturbances in autonomic function such as sympathetic nervous activation may be driven by hyperleptinaemia and hyperinsulinaemia.<sup>41,42</sup> Both conditions are common in obese individuals and in women with hypertensive disorders of pregnancy, including pre-eclampsia.<sup>43–45</sup> Emerging evidence,

however, also suggests that sympathetic hyperactivity may be a cause of hypertension and adult weight gain.<sup>46–48</sup> Alternatively, adiposity-related insulin resistance may indirectly influence BP because hyperinsulinaemia is known to be positively associated with increases in BP, particularly SBP.<sup>48</sup> Future research should focus on elucidating the understanding of what are complex and overlapping relationships, particularly in obese women who represent an increasing fraction of the obstetric population.

We do not yet have an explanation for the observed attenuation of mean BP at high BMI, towards the end of pregnancy. There are, however, other examples of attenuations in biological measures in late gestation. For instance, while birthweight generally increases with increasing gestational age, at the latter stage of pregnancy (beyond 39 weeks), one observes an attenuation of fetal growth.<sup>49</sup> Others have reported attenuations in cardiac output in the latter half of pregnancy.<sup>4</sup>

We have assessed the robustness of our fitted models in a variety of ways and, for this sample, the association appears to be real. Much of modern epidemiological analysis, both as it is taught and practised, is restricted to categorical outcomes and exposures. This paper is an attempt to surmount this barrier in the context of longitudinal studies of BP in pregnancy. We believe that insights are gained that go beyond what would emerge with categorical analyses and the foundations are laid for potential new monitoring tools which offer opportunities for better understanding of complex biological processes.

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## Appendix 1

### Reference ranges

Let  $SBP_{\alpha}$  and  $DBP_{\alpha}$  denote the estimated  $\alpha$ 'th percentiles of SBP and DBP and  $z_{\alpha}$  the  $\alpha$ 'th percentile of the standard normal distribution. Gestational age is denoted by  $g$ .

The estimated percentiles over gestational age are given by:

$$SBP_{\alpha} = (112.18 + 0.0000845g^3)(1 + z_{\alpha}(0.300 - 0.0214g)) * (0.12 - 0.00683g^{0.5} + 0.000000386g^3)^{(1/(0.300 - 0.0214g))}$$

$$DBP_{\alpha} = (70.39 - 0.000506g^3 + 0.000431g^3 \ln(g/10)) * (1 + z_{\alpha}(1.353 - 0.0244g))(0.1128 - 0.00000160g^3 + 0.0000013g^3 \ln(g/10))^{(1/(1.353 - 0.0244g))}$$

### Multivariable modelling

Let  $\mu_{SBP}$  and  $\mu_{DBP}$  denote estimated mean SBP and DBP respectively. Let  $g$  denote gestational age and  $b$  denote pre-pregnancy BMI.

$$\mu_{SBP} = 89.48 - 0.0251g^2 + 0.000373g^3 + 0.495b + 0.251g^{0.5}b - 0.001022gb^2 + 0.000556g^2b$$

$$\mu_{DBP} = -17.73 - 8.510g^{0.5} + 0.000320g^3 - 0.434b + 11669.0g^{-1}b^{-2} + 14.288 \ln(g) + 28.575 \ln(b) - 0.000155g^2b$$