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Age at menarche and blood pressure in pregnancy

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ABSTRACT

Objectives: To investigate whether age at menarche is related to maternal blood pressure in pregnancy and, if so, whether obesity and insulin resistance can modify the associations.
Study design: Analysis of data collected from 438 pregnant women from the longitudinal and prospective Cambridge Baby Growth Study.
Main outcome: Testing associations between questionnaire-derived age at menarche and blood pressure measurements in pregnancy collected from hospital notes, and investigating whether any associations were altered by maternal pre-pregnancy body mass index (BMI) and insulin resistance.
Measures: Mean arterial blood pressure at four time points across pregnancy, age at menarche, (Homeostasis Model Assessment) insulin resistance around week 28 of pregnancy.
Results: For each increased year in age at menarche there was a drop in mean arterial blood pressure (mmHg) of 0.6 at 11.9 weeks, 0.9 at 31.4 and 37.0 weeks, and 0.4 at 38.8 weeks (a maximal difference of over 7 mmHg across extremes of AAM). Each association was attenuated by both maternal pre-pregnancy BMI and insulin resistance.
Conclusions: Age at menarche is negatively associated with future blood pressure in pregnancy, so those with the earliest age at menarche have the highest blood pressures. Either these associations may be mediated by links between age at menarche and obesity/insulin resistance, or there may be a confounder (e.g. systemic inflammation) that links age at menarche to each of them.

1. Introduction

Age at menarche (AAM) is influenced by a wide range of genetic [1] and non-genetic determinants [2]. Given that some of the genetic variants associated with AAM are also associated with body mass index (BMI) it is perhaps not surprising that AAM is also associated with some BMI-related pathological conditions such as cardiovascular disease [3] and type 2 diabetes [4]. Early AAM, which accompanies most of the increased risk for these conditions, appears to result from increased follicle-stimulating hormone (FSH) and oestradiol concentrations [5], the latter appearing to be continually raised above expected levels into puberty and beyond possibly because of a reduced sensitivity of the hypothalamic-pituitary axis to the negative feedback of circulating steroid hormones.

The fact that AAM is also related to the risk of developing another BMI-linked condition in pregnancy, gestational diabetes [6], raises the possibility that the hormonal changes involved in altering AAM may also affect pregnancy hormone concentrations. Indeed, there is *in vitro* evidence from cultured bovine granulosa cells that FSH is able to alter expression of pregnancy-associated plasma protein A (PAPP-A) [7]. We recently found non-linear associations between AAM and serum PAPP-A concentrations [8], which could be important because of the potential role of PAPP-A in regulating pregnancy insulin sensitivity [9]. In our study AAM was negatively associated with insulin resistance in pregnancy [8]. Given the links between AAM and cardiovascular disease [3], pre-eclampsia and cardiovascular disease [10] and pre-eclampsia with insulin resistance [11], it is not surprising that AAM has been found to be negatively associated with pre-eclampsia in most [12–15] although not all [16] studies. The first sign of pre-eclampsia is often raised blood pressure. Although AAM is associated with various cardiovascular traits outside of pregnancy its association with blood pressure in pregnancy has not been thoroughly investigated. This study was therefore implemented to investigate potential associations between AAM and blood pressure across pregnancy.

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2. Materials and methods

2.1. Cohort

Between 2001 and 2009 the prospective and longitudinal Cambridge Baby Growth Study recruited 2229 mothers (and their and offspring) attending ultrasound clinics during early pregnancy at the Rosie Maternity Hospital, Cambridge, United Kingdom [9]. The study participants, all of whom were over 16 years of age and none of whom reported suffering from chronic hypertension or were treated with antihypertensives prior to conception, received routine care during pregnancy including the monitoring of their blood pressure. In addition fasting blood samples were collected from 1239 participants (55.6%) for the measurement of plasma glucose and insulin concentrations around week 28 of pregnancy for the evaluation of insulin resistance by the Homeostasis Model Assessment (HOMA) [17]. In this cohort, 96.9% of the offspring were of white ethnicity, 0.9% were Indo-Asian, 0.8% were East-Asian, 0.6% were black (African or Caribbean) and a further 0.8% were of mixed race.

2.2. Age at menarche

Each of the study participants was given a printed questionnaire at recruitment to complete during the rest of the pregnancy [8], of which a total of 1273 women (57.1%) did so. One of the questions asked "What age were you when you had your first period?" The mean (95% confidence interval) AAM of those women was 12.9 (12.9, 13.0) years.

2.3. Blood pressure during pregnancy

Records of routine blood pressure measurements made during pregnancy were collected from the hospital notes from 968 women in the Cambridge Baby Growth Study (hospital notes for the other study participants either not being available or not containing record of these blood pressures) [18]. Of all the readings four times in pregnancy emerged as points when blood pressure was routinely measured in the majority of subjects. According to the gestational week at which the measurements were taken, the first three time points were: (1) at 11.8 (11.5, 12.0) weeks, (2) at 31.4 (31.3, 31.5) weeks and (3) at 37.0 (36.9, 37.0) weeks. The fourth readings were taken specifically during the final 2 weeks prior to parturition (mean 38.8 (38.7, 38.9) weeks). The present analysis was restricted to data from 438 pregnancies where all four blood pressure measurements and the AAM were available.

2.4. Gestational hypertension & hypotension

When hospital notes were investigated additional evidence of hypertensive disorders of pregnancy (HDP) was also sought (defined using the inclusion of a diagnosis of the following terms: "pre-eclampsia", "gestational hypertension" or "pregnancy-induced hypertension"). In addition further women were categorised as having HDP using the National Institute for Health and Care Excellence criteria for gestational hypertension (blood pressure measurements in the second half of pregnancy that are $>=$ 140 mmHg systolic or 90 mmHg diastolic blood pressure in women without chronic hypertension) [19], with the exception that for our study evidence of HDP was accepted if the blood pressure cut offs were exceeded at one reading rather than at least two [18]. Evidence of gestational hypotension was defined in this study as any one of the blood pressure recordings for a study participant being $<=$ 110/60 mmHg.

2.5. Ethics

The Cambridge Baby Growth Study was approved by the local ethics committee, Addenbrooke's Hospital, Cambridge, United Kingdom. All procedures followed were in accordance with the institutional guidelines. Written informed consent was obtained from all the study participants.

2.6. Assays

PAPP-A was measured by time-resolved fluoroimmunoassay (autoDELFIA, Perkin Elmer Ltd., Seer Green, U.K.). The minimum detection limit of this assay was 5 mIU/L. The intra- and inter-assay coefficients of variation (CV) was less than 8% and 10% throughout. Insulin concentrations were measured by enzyme-linked immunosorbent assay using a commercial kit (DSL, London, U.K.). The minimum detection limit of this assay was 1.6 pmol/L. Intra-assay CVs were 4.4 and 5.1% at 62 pmol/L and 215 pmol/L, and equivalent inter-assay CVs were 8.7 and 2.9%; this assay has no cross-reactivity with proinsulin at levels up to 1,000 pmol/L. Blood glucose concentrations were measured using a routine glucose oxidase-based method.

2.7. Calculations

The BMI before pregnancy was calculated as the pre-pregnancy body weight divided by the height squared. The reproductive age was determined as the maternal age at the time of the birth of her baby in the index pregnancy minus the AAM. Mean arterial blood pressure in pregnancy was calculated as the sum of twice the diastolic plus the systolic blood pressure, divided by three. HOMA IR was estimated from the fasting glucose and insulin concentrations using the HOMA calculator available at https://www.dtu.ox.ac.uk/homacalculator/ [17]. The index of multiple deprivation was derived from residential post codes as described [20].

2.8. Statistical analysis

Associations between (mean arterial, systolic or diastolic) blood pressure and AAM were assessed by linear regression (adjusted only for the exact stage of pregnancy or both that and either maternal pre-pregnancy BMI or week 28 HOMA IR). Associations with serial blood pressure measurements were analysed by general estimation equation modelling, adjusting for weeks of gestation (± BMI or HOMA IR) when the blood pressure readings were taken. Associations between other continuous variables (adjusted for confounders where appropriate) were also assessed by linear regression whereas associations with HDP or gestational hypotension were assessed using logistic regression. Associations between categorical variables were tested using the $\chi 2$-test. Unless otherwise stated all other data are presented as means (95% confidence intervals). Statistical analyses were performed using Stata 13 (StataCorp LP, College Station, Texas, U.S.A.). $P < 0.05$ was considered statistically significant throughout.

3. Results

3.1. Study participants

There were no differences between those from the Cambridge Baby Growth Study that were included in the present analysis and those that were not in terms of maternal age, pre-pregnancy BMI, blood pressures in the second half of pregnancy, week 15 PAPP-A concentrations, week 28 glucose and insulin concentrations and HOMA IR, and the baby's birth weight adjusted for known confounders (Table 1). However fewer of those included in the present analysis smoked in pregnancy and they had lower blood pressures at booking clinic, higher gestational ages at the birth of their babies (of an average of around 4 days) and higher unadjusted baby birth weights as well as lower indexes of multiple deprivation. A higher proportion were also nulliparous and developed HDP, although there was no difference in the proportion that developed pre-eclampsia. Mean arterial blood pressure at booking clinic was negatively associated with AAM (see below) in the women included in the

Table 1
Characteristics of those Cambridge Baby Growth Study participants who were part of this analysis (from whom we had self-reported AAM and at least 4 blood pressures in pregnancy recorded from hospital notes) and comparison with those participants that were not included in the analysis.

Characteristic	Included women	Excluded women	p-value
Maternal age (years)	33.4 (33.0, 33.8) (n = 427)	33.6 (33.3, 33.8) (n = 908)	0.5
Pre-pregnancy BMI (kg/m^2)	23.9 (23.4, 24.3) (n = 402)	24.2 (23.9, 24.5) (n = 785)	0.3
Parity (n nulliparous)	214 out of 438 (48.9%)	503 out of 1208 (41.6%)	0.01
Smoked during pregnancy (n)	14 out of 437 (3.2%)	72 out of 1218 (5.9%)	0.03
Index of multiple deprivation	9.0 (8.5, 9.5) (n = 321)	11.1 (9.7, 12.6) (n = 40)	6.6×10^{-3}
Mean arterial blood pressure (mmHg) at 11.7 weeks	80.1 (79.2, 80.9) (n = 438)	81.7 (80.7, 82.8) (n = 260)	0.02
Mean arterial blood pressure (mmHg) at 31.4 weeks	81.4 (80.6, 82.2) (n = 438)	82.0 (81.0, 83.1) (n = 265)	0.3
Mean arterial blood pressure (mmHg) at 37.0 weeks	85.0 (83.9, 85.7) (n = 438)	85.2 (84.0, 86.4) (n = 247)	0.6
Mean arterial blood pressure (mmHg) at 38.8 weeks	87.0 (86.0, 88.0) (n = 438)	86.6 (84.3, 88.9) (n = 90)	0.8
HDP (n)	32 out of 438 (7.3%)	19 out of 530 (3.6%)	0.01
Pre-eclampsia (n)	7 out of 438 (1.6%)	12 out of 530 (2.3%)	0.5
Week 15 serum PAPP-A concentration (mIU/L)	6999 (6143, 7854) (n = 239)	6879 (6331, 7427) (n = 582)	0.3
Week 28 fasting glucose concentration (mmol/L)	4.3 (4.3, 4.4) (n = 313)	4.3 (4.3, 4.4) (n = 770)	0.7
Week 28 fasting insulin concentration (pmol/L)	52 (48, 56) (n = 330)	53 (50, 56) (n = 806)	0.3
Week 28 HOMA IR (%)	90 (85, 96) (n = 310)	93 (89, 96) (n = 749)	0.5
Gestational age of baby at birth (weeks)	40.2 (40.0, 40.3) (n = 438)	39.6 (39.5, 39.7) (n = 1,219)	3.6×10^{-10}
Baby's unadjusted birth weight (kg)	3.563 (3.513, 3.614) (n = 436)	3.448 (3.417, 3.478) (n = 1,213)	5.1×10^{-5}
Baby's adjusted birth weight (kg)*	3.494 (3.451, 3.538) (n = 401)	3.469 (3.438, 3.500) (n = 779)	0.4

Data are means (95% confidence intervals). *adjusted for gestational age at birth, sex, parity and maternal pre-pregnancy BMI.

present analysis, but there was no significant association of AAM with smoking in pregnancy (p = 0.2), gestational age at the birth of their babies (p = 1.0), unadjusted birth weights (p = 0.2), index of multiple deprivation (p = 0.2) or parity (p = 0.08).

3.2. Associations between AAM and blood pressure in pregnancy

At booking clinic AAM showed a negative association with mean arterial blood pressure (Table 2). By weeks 31 and 37 the effect sizes of the negative associations were greater in terms of effect size and significance. Just prior to the birth of their baby the effect size of the

Table 2
Associations between AAM and mean arterial blood pressure in pregnancy in the Cambridge Baby Growth Study in women for whom all data were available.

	Model 1			Model 2			Model 3			Model 4			Model 5		
Gestational Age (Weeks)	N	Change in Mean Arterial Blood Pressure (mmHg/year)	p-value	N	Change in Mean Arterial Blood Pressure (mmHg/year)	p-value	N	Change in Mean Arterial Blood Pressure (mmHg/year)	p-value	N	Change in Mean Arterial Blood Pressure (mmHg/year)	p-value	N	Change in Mean Arterial Blood Pressure (mmHg/year)	p-value
11.9 (11.6, 12.1)	438	−0.6 (−1.2, 0)	0.05	402	−0.6 (−1.2, 0)	0.07	402	−0.1 (−0.7, +0.5)	0.7	308	−0.3 (−1.1, +0.4)	0.3	308	−0.1 (−0.8, +0.6)	0.7
31.4 (31.3, 31.5)	438	−0.9 (−1.3, −0.3)	1.7×10^{-3}	402	−1.0 (−1.6, −0.4)	2.0×10^{-3}	402	−0.6 (−1.0, +0.1)	0.1	308	−0.7 (−1.4, 0)	0.07	308	−0.4 (−1.1, +0.3)	0.2
37.0 (36.9, 37.1)	438	−0.9 (−1.5, −0.2)	7.1×10^{-3}	402	−0.9 (−1.6, −0.3)	4.2×10^{-3}	402	−0.5 (−1.1, +0.2)	0.1	308	−1.1 (−1.8, −0.3)	9.6×10^{-3}	308	−0.7 (−1.5, 0)	0.06
38.8 (38.7, 38.9)	438	−0.4 (−1.1, +0.3)	0.2	402	−0.4 (−1.1, +0.3)	0.3	402	−0.1 (−0.6, +0.8)	0.9	308	−0.5 (−1.4, +0.3)	0.2	308	−0.3 (−1.1, +0.6)	0.5

Data are means (95% confidence interval).
Model 1 is adjusted for gestational age when the blood pressures were measured.
Model 2 is adjusted for gestational age when the blood pressures were measured in women with pre-pregnancy BMI recorded.
Model 3 is adjusted for gestational age and pre-pregnancy BMI when the blood pressures were measured in women with BMI recorded.
Model 4 is adjusted for gestational age when the blood pressures were measured in women with week 28 HOMA IR recorded.
Model 5 is adjusted for gestational age and week 28 HOMA IR when the blood pressures were measured in women with HOMA IR recorded.

Table 3
Associations between serial mean arterial blood pressures (4 measurements taken over pregnancy) and AAM as analysed by general estimation equation modelling.

Mean Arterial Blood Pressure Effect Size (mmHg/year)	p-value	n	Confounders in model
−0.7 (−1.2, −0.2)	6.3×10^{-3}	438	Gestational age when blood pressures measured, identity number
−0.6 (−1.0, −0.2)	7.9×10^{-3}	438	Gestational age when blood pressures measured, identity number, HDP, pre-eclampsia
−0.7 (−1.2, −0.2)	7.1×10^{-3}	402	Gestational age when blood pressures measured, identity number (if BMI data available)
−0.2 (−0.7, 0.3)	0.4	402	Gestational age when blood pressures measured, identity number, BMI
−0.6 (−1.2, 0)	0.05	308	Gestational age when blood pressures measured, identity number (if week 28 HOMA IR data available)
−0.4 (−0.9, 0.2)	0.2	308	Gestational age when blood pressures measured, identity number, week 28 HOMA IR

Data are mean (95% confidence interval).

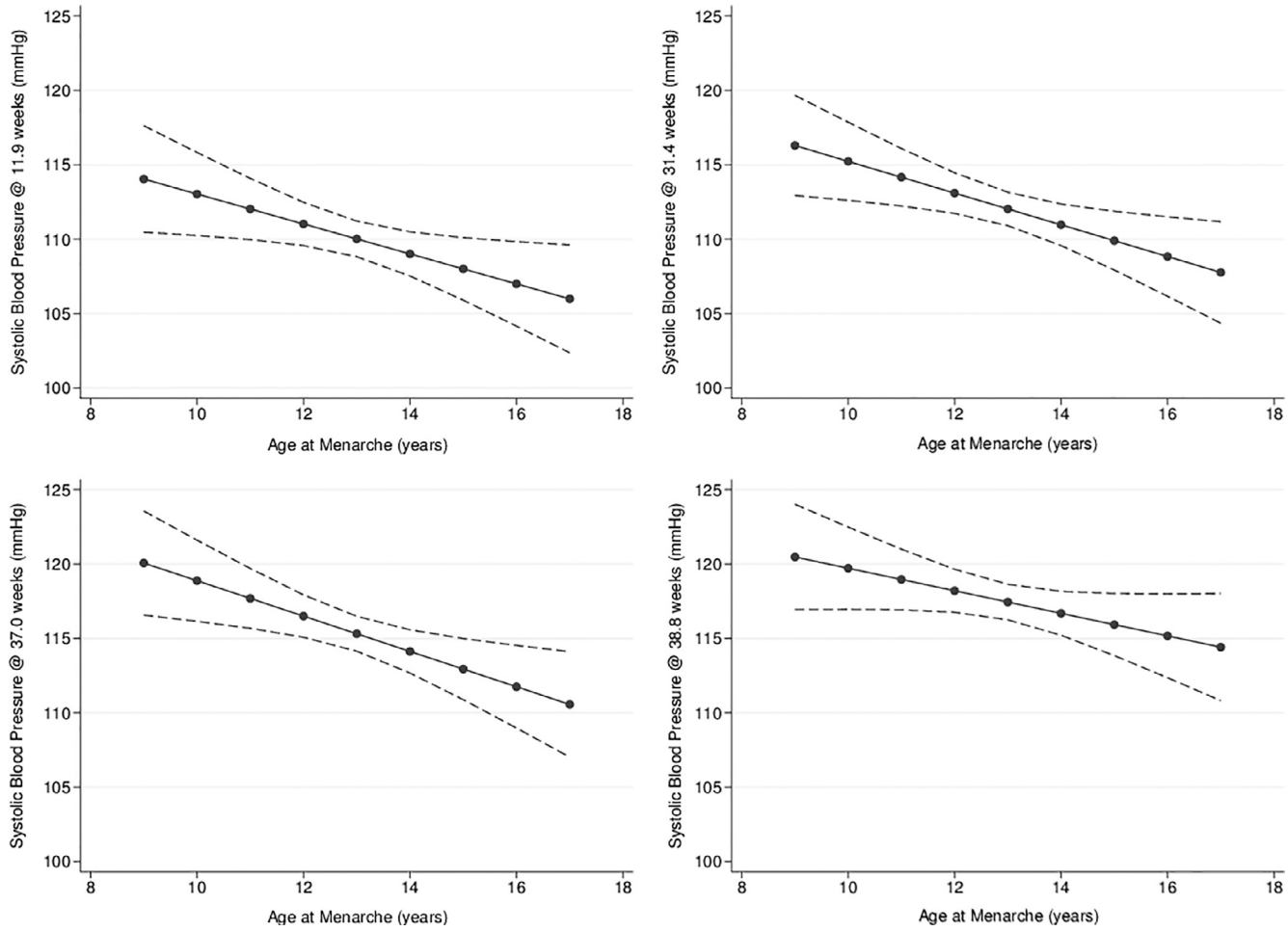

Fig. 1. Predicted systolic blood pressures (after adjustment for gestational age) against AAM in linear regression models from the Cambridge Baby Growth Study: at 11.9 weeks (top left, β = −1.0 (−1.9, −0.2) mmHg/year, p = 0.02), 31.4 weeks (top right, β = −1.1 (–1.9, –0.3) mmHg/year, p = 9.2×10^{-3}), 37.0 weeks (bottom left, β = −1.2 (−2.0, −0.4) mmHg/year, p = 5.3×10^{-3}) and 38.8 weeks (bottom right, β = −0.8 (−1.6, +0.1) mmHg/year, p = 0.08). N = 438 throughout. Solid lines are the means and the dashed lines are the 95% confidence intervals.

association was smaller (and no longer statistically significant), albeit in the same direction as the earlier associations in pregnancy. Overall using repeat measures there was a significant negative association between AAM and mean arterial blood pressure (Table 3), which was attenuated by both pre-pregnancy BMI and HOMA IR as were the individual associations (Table 2). The relationship between blood pressure and AAM appeared to be stronger with systolic (Fig. 1) rather than diastolic blood pressure (Supplementary Table 1). The reproductive age was not associated with mean arterial blood pressure at any of the four blood pressure readings: 11.9 weeks (β = 0.0 (-0.2, 0.2) mmHg/year, p = 0.9, n = 427), 31.4 weeks (β = -0.1 (-0.3, 0) mmHg/year, p = 0.1, n = 427), 37.0 weeks (β = -0.1 (-0.3, +0.1) mmHg/year, p = 0.3, n = 427), 38.8 weeks (β = -0.2 (-0.4, 0) mmHg/year, p = 0.08, n = 427).

3.3. Associations between AAM, HDP and gestational hypotension

There was no significant association between AAM and HDP (odds ratio (OR) 0.89 (0.67, 1.19) per year, p = 0.5, n = 438), even though they were associated with both HOMA IR (OR 1.6 (1.1, 2.3) per HOMA IR unit, p = 0.03, n = 335) and BMI (OR 1.2 (1.1, 1.3) per kg/m^2, p = 5.4×10^{-5}, n = 414) in these women. There was also no significant difference in AAM between those that had HDP and those that did not: no HDP 13.0 (12.8, 13.1) years (n = 413) v. HDP 12.8 (12.2, 13.3) years (n = 25) (p = 0.5).

There was a significant positive association between AAM and

Table 4
Associations between circulating PAPP-A concentrations from around week 15 of pregnancy and mean arterial blood pressures in those pregnancies.

Gestational Age (Weeks)	Change in Mean Arterial Blood Pressure (SDs/year)	N	p-value
11.9 (11.6, 12.1)	−0.182	261	0.01
31.4 (31.3, 31.5)	−0.188	261	0.01
37.0 (36.9, 37.1)	−0.206	261	4.9×10^{-3}
38.8 (38.7, 38.9)	−0.108	261	0.1

Data are means (with 95% confidence intervals for gestational ages).

unadjusted evidence of gestational hypotension (OR 1.2 (1.1, 1.4) per year, $p = 2.3 \times 10^{-3}$, n = 438). Those women who experienced hypotension in pregnancy had significantly later AAMs than those that did not: no hypotension 12.7 (12.5, 12.9) years (n = 193) v. hypotension 13.2 (13.0, 13.3) years (n = 245) ($p = 2.0 \times 10^{-3}$).

3.4. Associations between PAPP-A concentrations, HOMA IR and blood pressure in pregnancy

Blood pressure in pregnancy was negatively associated with serum PAPP-A concentrations from around week 15 of pregnancy (Table 4), with the first three measurements having statistically significant associations and the association with the late pregnancy measurement having a relatively smaller (not statistically significant) effect size. All the blood pressure measurements were also positively associated with week 28 HOMA IR (Table 5). We previously reported associations between AAM and: (1) pre-pregnancy BMI, (2) week 15 circulating PAPP-A concentrations and (3) week 28 HOMA IR in our population [8].

4. Discussion

In this study we have shown negative associations between AAM and four blood pressure measurements in pregnancy. Whilst only three of the associations reached statistical significance, two were strong and all of them plus the combined association were consistently in the same direction with just the effect size altering. The highest blood pressures were consistently in those women with early AAM. The effect sizes were not large enough to independently change the risk for HDP in our population, although AAM was positively associated with evidence of gestational hypotension. The lack of association with HDP or even pre-eclampsia (data not shown) could help explain why AAM is not associated with pre-eclampsia in every study [16]. However with those women with the earliest AAMs having on average predicted mean arterial blood pressure up to over 7 mmHg higher than those with the latest AAMs in our population, factors related to AAM could clearly be associated with changes in risk in combination with other risk factors. The same does not appear to be true for the time elapsed between the AAM and the mother's age at the time of the birth of her baby.

Associations between AAM and mean arterial blood pressure were slightly weaker in the reduced number of women for whom we had pre-pregnancy BMIs available, presumably due to the accompanying reduction in statistical power. They were attenuated when they were adjusted for either pre-pregnancy BMI or HOMA IR (both pre-pregnancy BMI and HOMA IR [8] themselves being strongly negatively associated with AAM), suggesting a potential mechanism involving increased adiposity and insulin resistance underpinning the link between AAM and blood pressure in pregnancy. Insulin resistance and obesity are well known associates of increased blood pressure both in and outside of pregnancy [21]. Evolutionary biology suggests that the insulin resistance may not be causal in this relationship however. Rather both it and increased blood pressure may result from the low grade systemic inflammation occurring as a result of the increased macrophage infiltration of adipose tissue [22] and other tissues containing ectopically-stored lipids [23] that occurs in obesity [24]. Consistent with this AAM has been reported to be negatively associated with circulating C-reactive protein concentrations suggesting a link between early AAM and inflammation [25]. Such effects appear to arise from the interaction between historically beneficial "thrifty" genotypes (that favour energy storage) and modern diets and lifestyles. In pregnancy placental hormones can be part of these processes. In the Cambridge Baby Growth Study we previously found that low week 15 PAPP-A concentrations were associated with insulin resistance in pregnancy [9] and that women with an early AAM had lower PAPP-A concentrations than women with AAMs closer to the average [8]. In the present analysis week 15 PAPP-A concentrations were negatively associated with all the blood pressure measurements. Further studies are needed to identify whether PAPP-A is causal in these processes or whether the associations observed are confounded, possibly by the insulin resistance resulting from the low grade systemic inflammation described above.

Table 5
Associations between HOMA IR (fasting insulin resistance) from around week 28 of pregnancy and mean arterial blood pressures in those pregnancies.

Gestational Age (Weeks)	Change in Mean Arterial Blood Pressure (SDs/year)	N	p-value
11.9 (11.6, 12.1)	0.221	335	4.8×10^{-5}
31.4 (31.3, 31.5)	0.301	335	1.7×10^{-8}
37.0 (36.9, 37.1)	0.314	335	2.7×10^{-9}
38.8 (38.7, 38.9)	0.235	335	1.6×10^{-5}

Data are means (with 95% confidence intervals for gestational ages).

The associations between early AAM and raised blood pressure in pregnancy observed in this study could be part of a particular female life course trajectory framework that is "high risk" for poor cardiometabolic health. AAM has been related to each of the steps in the following sequence: the combination of low birth weight and subsequent catch-up growth in infancy [26], or alternatively *in utero* exposure to gestational diabetes [27], followed by childhood obesity [28], early AAM and subsequent epiphyseal fusion [29], shorter adult height and adult obesity [8], insulin resistance [8], raised blood pressure (the present study; possibly increasing the risk of pre-eclampsia [12–15]) and increased glucose concentrations [8] in pregnancy, cardiovascular disease [3,30] and type 2 diabetes [4] in later life. Although somewhat speculative there is evidence of links between the other factors [31] even if you remove early AAM from the sequence. However these and the present study suggest that AAM should be considered when deliberating over the developmental origins of health and disease.

Although the present study has found apparently robust negative associations between AAM and blood pressure in pregnancy it does have a number of limitations. The first of these is that the women tested may not be entirely representative of the population from which they were sampled. The Cambridge Baby Growth Study cohort as a whole is representative of the South Cambridgeshire population of pregnant women, albeit on average the mothers being slightly older and more likely to be nulliparous [32]. However the subpopulation from whom the present analysis was drawn included women whose blood pressure at booking clinic was slightly lower than that of the cohort as a whole, with their baby's births occurring on average 4 days later than those not included leading to increased unadjusted birth weights of the babies. A lower proportion of the mothers included in the present analysis smoked (although smoking was uncommon as a whole in this population) and they were less deprived in a population not noted for high levels of deprivation. A higher proportion of them were also nulliparous and developed HDP. However the only one of these that was significantly associated with AAM was the booking clinic blood pressure so any biases may have been limited. Another limitation to the study is that the AAM, at a time when AAMs were thought to be declining in the U.K. at a slow rate [33], was self-reported so some of them may have been inaccurate. However it has previously been reported that in a generally well-qualified population, as is a characteristic of the

Cambridge Baby Growth Study [32], recalled AAM tends to be fairly accurate when compared to AAMs from medical notes [34] (these not being available for this cohort). A third limitation is that missing data meant that numbers of participants varied in the different statistical models, which is not uncommon for cohort studies such as this which was not specifically set up for this particular study. However we overcome potential biases resulting from missing data by only analysing data from women for whom we had at least four blood pressure measurements in pregnancy, and then when using adjustments to check for attenuation we repeated the initial analyses in just those women for whom data relating to the potential confounder was available. Despite this procedure being imperfect, and possibly introducing biases into the population analysed, our data has suggested that blood pressure in pregnancy is robustly related to AAM and that adiposity and insulin resistance may be involved in mediating these associations, which is biologically plausible.

In conclusion this study has found negative associations between AAM and subsequent blood pressure in pregnancy (that were not of sufficient effect sizes to change risk of HDP, although positive associations were found between AAM and risk of subsequent gestational hypotension). The associations with blood pressure were attenuated by both BMI and insulin resistance, suggesting that either they may mediate the associations or that there may be a confounder that links AAM to each of them.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.01.004.

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