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Gestational age and risk factors for cardiovascular disease: evidence from the 1958 British birth cohort followed to mid-life

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Background Increases in pre-term births and improved survival rates have led to interest in the association between gestational age and health in adulthood. Associations between gestational age and risk factors for cardiovascular disease have not been fully investigated.

Methods Using data from the 1958 British birth cohort (7847 singletons), the associations between gestational age and blood pressure, glycosylated haemoglobin (HbA1c), lipid levels and body mass index (BMI) at age 44–45 years were examined.

Results After adjustment for sex, birthweight standardized for gestational age and sex and current BMI there was a reduction in systolic blood pressure of 0.53 mmHg (95% CI: 0.32, 0.75) for every 1 week increase in gestational age. There was a non-linear association between gestational age and diastolic blood pressure, with those cohort members born at earlier gestational ages found to have higher diastolic blood pressure than those born at term. These associations remained after adjustments. A 'U'-shaped association was found between gestational age and BMI among women ($P = 0.02$ for sex × gestational age interaction) which attenuated after adjustment. There was also a weak inverse association between gestational age and total cholesterol specific to women ($P = 0.01$ for sex × gestational age interaction). No clear associations were found between gestational age and BMI or total cholesterol in men, or between gestational age and HbA1c or other lipid levels in either sex.

Conclusions In the 1958 British birth cohort duration of gestation was associated with blood pressure in mid-life. Understanding this association is necessary to inform policy and preventative interventions.

Keywords Gestational age, lipids, blood pressure, HbA1c, BMI

Introduction

Investigating the relationship between gestational age and long-term health outcomes has become an important research priority due to the increasing proportions of the global population born prematurely (usually defined as gestational age <37 weeks[1]) and, increased survival beyond childhood.[2–4] While the influences of early life factors on cardiovascular disease (CVD) risk are now widely

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acknowledged, the specific influence of gestational age has not been well characterized.

Most research into the effects of gestational age has focused specifically on the association between pre-term birth and educational and neurological outcomes.[5] It is only recently that study populations containing sufficient variation in gestational age have begun to reach adulthood allowing other potential outcomes to be investigated. Nonetheless, some studies suggest that gestational age may, independently of its positive association with birthweight, be inversely associated with risk factors for CVD including: blood pressure (BP);[6–15] insulin resistance[15–17] and lipid levels[18] and with: type 2 diabetes;[19] stroke[20] and cerebrovascular disease mortality.[21] A number of explanations for finding such associations have been proposed. These include the possibility that earlier and more prolonged exposure of babies born at younger gestational ages to the postnatal environment while still developmentally plastic may increase susceptibility to 'programming' effects. Further, variations in gestational age may directly affect organ development. However, associations have not been consistently shown, some outcomes, for example lipids, have only been examined in small samples[7,15,22] and many of the large studies[9,12–14] of BP have included only males but yet where both sexes have been included evidence of sex differences has been found.[8] In addition, follow-up in studies of risk factors for CVD has rarely been beyond early adulthood before CVD usually manifests. Further, many studies are not able to examine variation in outcomes across the full range of gestational age instead comparing a group of individuals born pre-term with a group born at term. It is also notable that, while many studies take some account of other factors, few are able to examine whether associations are explained by birthweight, as a marker of foetal growth rate or later body size. They are also not able to explore whether associations are explained by prenatal factors which influence both gestational age and risk factors for CVD or, investigate the role of potential mediators.

Our objectives were to examine whether gestational age is associated with a range of risk factors for CVD, measured in mid-life, independently of foetal growth rate (as represented by birthweight standardized for gestational age and sex), later body size and prenatal factors. We also aimed to investigate potential mediating factors.

Methods

Study population

The 1958 British birth cohort consists of 17 638 males and females followed-up since their births during one week in March 1958 across England, Scotland and Wales.[23] Subsequently, 920 immigrants with the same birth dates were recruited into the study up to age 16 years. A target of 11 971 cohort members (including 467 immigrants) were invited to participate in a biomedical survey at age 44–45 years, 9377 (78%) responded. Of these, we excluded the 363 immigrant respondents because they lacked perinatal data.

Ethical approval was obtained from the South East Multi-centre Research Ethics Committee; all participants gave written consent.

Measurement of outcomes

All outcome measurements were taken at age 44–45 years by nurses using standardized protocols during home visits. Non-fasting venous blood samples were analysed for total and high density lipoprotein (HDL)-cholesterol and triglyceride levels by an autoanalyser (Olympus AU640, Japan) using enzymatic methods. Low density lipoprotein (LDL)-cholesterol levels were calculated using the Friedewald formula.[24] For participants with a triglyceride level >4.5 mmol/l, LDL-cholesterol levels were not calculated and for those with a triglyceride level >13 mmol/l, HDL-cholesterol levels were not measured. Glycosylated haemoglobin (HbA1c) levels were measured using ion exchange high performance liquid chromatography.

Blood pressure was measured three times after the participant had been seated for five minutes using an Omron 705CP automated digital oscillometric sphygmomanometer (Omron, Tokyo, Japan), a large cuff was used if mid-upper arm circumference >32 cm. Mean diastolic and systolic BP were calculated using those measures attained which nurses reported to be reliable.

We calculated current body mass index (BMI, kg/m^2) using height and weight measurements, taken using Leicester portable stadiometers and Tanita solar scales, respectively, while participants were lightly clothed and unshod. Self-reported weights ($n = 93$) and heights ($n = 78$) were used if measurements were inaccurate or consent for measurement was not provided.

Ascertainment of gestational age

Gestational age measured in days since the start of last menstrual period was recorded at birth and converted into completed weeks. Although included in most analyses as a continuous variable a categorical variable was also created with seven groups: <37, 37, 38, 39, 40, 41 and >41 weeks.

Measures of body size

Birthweight was measured at time of birth in ounces and converted into kilograms. This was then standardized for gestational age and sex. Current (44–45 years) BMI was calculated as described earlier.

Prenatal factors

Maternal age recorded at birth was categorized into six groups: ⩽19, 20–24, 25–29, 30–34, 35–39 and ⩾40 years. Maternal smoking after the 4th month of pregnancy, reported at birth, was categorized as: never smoked; ex-smoker; 1–9, 10–19, ⩾20 cigarettes/day; variable amounts smoked. Pre-eclampsia was defined as albuminurea not attributable to urinary tract infection and diastolic BP >90 mmHg.[25] Father's occupational class at birth (or at 7 years if missing ($n=308$)) was categorized into four groups using the Registrar General's Social Classification: I or II, IIINM, IIIM, IV or V or single mother. The RG classification is a standard method of categorizing occupations in the UK, coded from professional (I) to unskilled manual (V).[26]

Potential mediators (socioeconomic position and adult lifestyle factors)

Own occupational class at age 42 years [or at 33 years if missing ($n=852$)] was categorized into the same four groups as father's occupational class. Educational level attained was recorded at age 42 years and categorized as: degree or higher; advanced secondary; ordinary secondary; below secondary; no qualifications. Smoking status at age 42 years [or at 33 years if missing ($n=168$)], was categorized as: current; never; ex-smoker. A quantity-frequency index of alcohol use at age 44–45 years was derived from the Alcohol Use Disorders Identification Test questionnaire[27] and categorized into five groups of average number of standard drinks consumed: non-drinker; 1–7; 7–14; 14–21; >21 drinks/week.

Statistical analyses

We first used sex-specific linear regression models to test associations between gestational age and each risk factor for CVD. Gestational age was modeled as a continuous variable. Deviation from linearity was tested and where there was evidence of non-linearity, gestational age was modelled as a categorical variable (reference group 40 weeks). Given previous reports of sex differences in the associations between prenatal factors and risk factors for CVD[8,28] we used likelihood ratio tests to investigate gestational age × sex interactions. Because the distribution of triglycerides was positively skewed we used a natural log transformation; geometric means are presented and regression coefficients have been multiplied by 100 and can be interpreted as the percentage difference in mean triglyceride levels.[29] Geometric means are also presented for HbA1c but analyses use untransformed data with robust estimators.

Using multiple regression, adjustments were made first for birthweight standardized for gestational age and sex and then for current BMI. For those outcomes associated with gestational age after these adjustments, additional adjustments were also made for prenatal factors (maternal age and smoking, pre-eclampsia and father's occupational class) and potential mediating factors (own occupational class, educational level, alcohol consumption and smoking) with care taken to ensure that all comparable analyses were performed on the same *N*. Where there was no evidence of interaction between gestational age and sex in earlier models, men and women were included together in this second set of adjusted models with an additional adjustment made for sex.

Multiple births ($n=197$) and women pregnant at the time of the 44–45 years survey ($n=2$) were excluded from all analyses. We repeated analyses after excluding participants with congenital abnormalities ($n=59$) and participants taking medication that may have affected their cardiovascular risk factor levels (i.e. participants were excluded from analyses of lipid levels if taking lipid-regulating medication ($n=187$), from analyses of BP if taking anti-hypertensive medication ($n=339$) and from analyses of HbA1c if taking diabetic medication ($n=117$)). We also examined the effect of adjusting for factors that could affect outcome measurement i.e. delay in the laboratory receiving the blood sample, time of day and month of nurse visit, recent food consumption, air temperature and type of flooring. Neither the exclusions nor additional adjustments greatly altered the magnitude or significance levels of associations described (data not presented).

Results

There were sex differences in the distribution of birthweight and all risk factors for CVD at age 44–45 years ($P<0.001$); men had higher mean birthweight and a less favourable risk factor profile than women (Table 1). As expected, there was a positive linear association between gestational age and birthweight, for every 1-week increase in gestational age there was an increase in birthweight of 0.11 kg (95% CI: 0.10, 0.12) in males and of 0.10 kg (95% CI: 0.09, 0.11) in females. Young maternal age (⩽19 years), smoking during pregnancy, pre-eclampsia and lower paternal occupational class were all associated with increased odds of pre-term birth (results not shown).

Among women there was a non-linear association between gestational age and HbA1c, but no association was found in men (Table 2). Women at either extreme of gestational age had slightly higher mean levels of HbA1c than women born at term. However, this association attenuated after adjustment for current BMI.

There was a linear inverse association between gestational age and total cholesterol in women but no clear association among men (Table 2) ($P=0.01$ for sex × gestational age interaction). After adjustment for birthweight standardized for gestational age and sex, current BMI, prenatal factors and potential mediating factors there remained a reduction of 0.02 mmol/l (95% CI: 0.001, 0.05) in total cholesterol for every 1 week increase in gestational age in women (Table 3).

Table 1 Characteristics of the members of the 1958 British birth cohort who have data on gestational age, were singleton births and participated in the biomedical survey at age 44–45 years

	Men		Women		
	Total *N*	Mean(SD) or *n* (%)	Total *N*	Mean (SD) or *n* (%)	***P*-value[b]**
Gestational age (completed weeks)	3918	39.75 (1.70)	3929	39.81 (1.69)	0.18
<37		143 (3.65)		136 (3.46)	0.33
37		155 (3.96)		152 (3.87)	
38		411 (10.49)		352 (8.96)	
39		858 (21.90)		876 (22.30)	
40		1075 (27.44)		1102 (28.05)	
41		813 (20.75)		809 (20.59)	
>41		463 (11.82)		502 (12.78)	
Birthweight (kg)	3778	3.46 (0.51)	3825	3.31 (0.49)	<0.001
Risk factors for cardiovascular disease at age 44–45 years					
Diastolic blood pressure (mmHg)	3892	82.14 (10.49)	3887	75.60 (10.26)	<0.001
Systolic blood pressure (mmHg)	3892	133.00 (15.12)	3887	120.24 (15.53)	<0.001
HbA1c (%)[a]	3338	5.28 (1.12)	3294	5.15 (1.10)	<0.001
Total cholesterol (mmol/l)	3295	6.09 (1.16)	3247	5.69 (1.00)	<0.001
LDL-cholesterol (mmol/l)	2974	3.58 (0.94)	3189	3.28 (0.87)	<0.001
HDL-cholesterol (mmol/l)	3283	1.44 (0.34)	3245	1.69 (0.40)	<0.001
Triglycerides (mmol/l)[a]	3281	2.08 (1.80)	3239	1.36 (1.70)	<0.001
BMI (kg/m^2)	3904	27.83 (4.34)	3915	27.00 (5.60)	<0.001

[a]Geometric mean.
[b]from *t*-test or χ^2-test of sex difference, as appropriate.

There was no evidence of associations between gestational age and LDL-cholesterol, HDL-cholesterol or triglyceride levels in either sex (Table 2).

In women there was a non-linear association between gestational age and BMI in mid-life but no evidence of an association in men (Table 2) ($P = 0.02$ for sex × gestational age interaction). The association among women was 'U'-shaped whereby those born at either extreme of gestational age had higher mean BMI than women born at term. This association attenuated only slightly after adjustment for birthweight standardized for gestational age and sex (Table 2). However, adjustment for prenatal factors and potential mediating factors attenuated the association (Table 3).

An inverse linear association between gestational age and systolic BP was found in both sexes (Table 2) ($P = 0.11$ for sex × gestational age interaction). In models including men and women, after adjustment for sex, birthweight standardized for gestational age and sex and current BMI there was a reduction in systolic pressure of 0.53 mmHg (95% CI: 0.32, 0.75) for every 1-week increase in gestational age. There was a non-linear association between gestational age and diastolic BP in both sexes (Table 2) ($P = 0.33$ for sex × gestational age interaction). Cohort members with a gestational age <37 weeks were found to have higher diastolic BP than cohort members born at later gestational ages. In models including men and women, adjusted for sex, birthweight standardized for gestational age and sex and current BMI the non-linear association remained ($P = 0.004$ for quadratic term). These associations between gestational age and diastolic and systolic BP were maintained after additional adjustments for prenatal factors and potential mediating factors (Table 4). For example, in fully adjusted models those in the cohort with a gestational age <37 weeks had a mean diastolic BP 2.59 mmHg (95% CI: 1.19, 3.99) higher than those with a gestational age of 40 weeks.

Discussion

In our large British study, encompassing several risk factors for CVD, we found evidence of a robust association between gestational age and blood pressure in mid-life. The increase in systolic blood pressure associated with a decrease in gestational age and, the non-linear association between gestational age and diastolic blood pressure were not fully explained by foetal growth rate (i.e. birthweight standardized for gestational age and sex), current BMI, prenatal factors or potential mediating factors. A 'U'-shaped association between gestational age and BMI found to be specific to women, attenuated after adjustment for prenatal factors and potential mediating factors. Although total cholesterol increased as gestational age decreased among women, this association was weak. There was no clear evidence

Table 2 Differences (95% CIs) in mean levels of risk factors for cardiovascular disease at age 44–45 years by gestational age

	Men		Women	
Risk factors for CVD/ Gestational age (weeks)	Unadjusted	Adjusted for birthweight[a] and BMI at 44–45 years[b]	Unadjusted	Adjusted for birthweight[a] and BMI at 44–45 years[b]
BMI (kg/m^2)		$n = 3764$		$n = 3812$
Per 1 week increase	0.01 (−0.07, 0.09)	0.01 (−0.07, 0.10)	–	–
<37	–	–	1.52 (0.49, 2.55)	1.46 (0.43, 2.49)
37			−0.56 (−1.52, 0.41)	−0.55 (−1.51, 0.42)
38			0.28 (−0.40, 0.96)	0.27 (−0.41, 0.96)
39			−0.08 (−0.59, 0.42)	−0.08 (−0.59, 0.42)
40			0	0
41			0.57 (0.05, 1.08)	0.57 (0.06, 1.08)
>41			0.66 (0.06, 1.26)	0.67 (0.07, 1.27)
P-value*	0.79	0.73	<0.001 (<0.001)	<0.001 (<0.001)
Systolic blood pressure (mmHg)		$n = 3748$		$n = 3778$
Per 1 week increase	−0.34 (−0.62, −0.05)	−0.35 (−0.63, −0.08)	−0.67 (−0.96, −0.37)	−0.72 (−1.00, −0.44)
P-value	0.02[c]	0.01	<0.001	<0.001
Diastolic blood pressure (mmHg)		$n = 3748$		$n = 3778$
<37	1.49 (−0.37, 3.35)	1.50 (−0.30, 3.29)	4.16 (2.28, 6.05)	3.61 (1.81, 5.41)
37	−0.38 (−2.19, 1.42)	−0.54 (−2.28, 1.21)	1.27 (−0.50, 3.04)	1.50 (−0.18, 3.19)
38	0.67 (−0.54, 1.87)	0.40 (−0.76, 1.57)	1.10 (−0.15, 2.34)	0.94 (−0.24, 2.13)
39	−0.47 (−1.42, 0.49)	−0.44 (−1.37, 0.48)	0.35 (−0.57, 1.28)	0.41 (−0.48, 1.29)
40	0	0	0	0
41	−0.45 (−1.42, 0.53)	−0.49 (−1.43, 0.45)	0.70 (−0.25, 1.64)	0.45 (−0.45, 1.35)
>41	−0.35 (−1.51, 0.81)	−0.53 (−1.65, 0.59)	0.13 (−0.97, 1.23)	−0.26 (−1.31, 0.79)
P-value*	0.02 (0.02)	0.02 (0.02)	0.01 (0.01)	0.05 (0.08)
HbA1c (%)		$n = 3215$		$n = 3205$
Per 1 week increase	−0.002 (−0.02, 0.01)	−0.003 (−0.02, 0.01)	–	–
<37	–	–	0.11 (−0.01, 0.23)	0.08 (−0.04, 0.19)
37			0.07 (−0.07, 0.21)	0.08 (−0.05, 0.22)
38			−0.04 (−0.10, 0.01)	−0.05 (−0.10, 0.005)
39			0.002 (−0.06, 0.06)	0.01 (−0.05, 0.06)
40			0	0
41			0.03 (−0.03, 0.09)	0.02 (−0.04, 0.07)
>41			0.04 (−0.04, 0.11)	0.01 (−0.06, 0.08)
P-value*	0.74	0.73	0.04 (0.04)	0.25 (0.25)
Total cholesterol (mmol/l)		$n = 3173$		$n = 3161$
Per 1 week increase	0.02 (−0.004, 0.04)	0.02 (−0.004, 0.04)	−0.02 (−0.04, −0.001)	−0.03 (−0.05,−0.005)
P-value	0.11	0.10	0.04[c]	0.02
LDL-cholesterol (mmol/l)		$n = 2866$		$n = 3104$
Per 1 week increase	0.02 (−0.003, 0.04)	0.02 (−0.003, 0.04)	−0.01 (−0.03, 0.01)	−0.02 (−0.03, 0.003)
P-value	0.09	0.09	0.20[c]	0.11

(continued)

Table 2 Continued

Risk factors for CVD/ Gestational age (weeks)	Men		Women	
	Unadjusted	Adjusted for birthweight[a] and BMI at 44–45 years[b]	Unadjusted	Adjusted for birthweight[a] and BMI at 44–45 years[b]
HDL-cholesterol (mmol/l)		$n = 3161$		$n = 3159$
Per 1 week increase	–0.0004 (–0.01, 0.01)	–0.001 (–0.01, 0.01)	–0.004 (–0.01, 0.004)	–0.001 (–0.01, 0.01)
P-value	0.91	0.85	0.35	0.80
Triglycerides[d]		$n = 3159$		$n = 3154$
Per 1 week increase	0.25 (–0.98, 1.48)	0.31 (–0.85, 1.47)	–0.24 (–1.37, 0.90)	–0.72 (–1.77, 0.33)
P-value	0.69	0.60	0.68	0.18

[*]*P*-values from models including gestational age as a continuous term (*P*-value for quadratic term shown in parentheses if there is evidence of deviation from linearity).
[a]Birthweight standardized for gestational age.
[b]Except where current BMI is the outcome in which case analyses are adjusted for birthweight standardized for gestational age only.
[c]When quadratic term included in model this was of borderline statistical significance ($0.05 < P < 0.08$).
[d]Regression coefficients have been multiplied by 100 and can be interpreted as the percentage difference in mean triglyceride levels.

Table 3 Differences (95% CIs) in mean levels of BMI and total cholesterol at age 44–45 years by gestational age after adjustment for prenatal factors and potential mediators in women

Risk factors for CVD/Gestational age (weeks)	Model 1	Model 2	Model 3
BMI (kg/m^2)			$N = 3317$
<37	1.50 (0.36, 2.63)	1.05 (−0.08, 2.17)	0.89 (−0.23, 2.00)
37	−0.37 (−1.40, 0.66)	−0.55 (−1.57, 0.47)	−0.59 (−1.60, 0.42)
38	0.14 (−0.59, 0.87)	−0.02 (−0.74, 0.70)	0.03 (−0.68, 0.74)
39	0.03 (−0.50, 0.56)	0.07 (−0.45, 0.60)	0.04 (−0.47, 0.56)
40	0	0	0
41	0.59 (0.05, 1.14)	0.53 (−0.01, 1.06)	0.49 (−0.04, 1.02)
>41	0.84 (0.20, 1.48)	0.72 (0.08, 1.35)	0.61 (−0.01, 1.24)
P-value*	0.01 (0.01)	0.05 (0.04)	0.09 (0.08)
Total cholesterol (mmol/l)			$N = 2757$
Per 1 week increase	−0.02 (−0.04, 0.001)	−0.02 (−0.04, 0.002)	−0.02 (−0.05, −0.001)
P-value	0.06	0.07	0.04

**P*-values from models including gestational age as a continuous term (*P*-value for quadratic term shown in parentheses if there is evidence of deviation from linearity).
Model 1: Adjusted for birthweight standardized by gestational age and sex and, in model of total cholesterol also for current BMI.
Model 2: Model 1 plus prenatal factors (maternal age, maternal smoking, pre-eclampsia, father's occupational class).
Model 3: Model 2 plus potential mediators (educational level, own occupational class, smoking and alcohol consumption in adulthood).

of an association between gestational age and BMI or total cholesterol among men or between gestational age and HbA1c or other lipid levels (i.e. LDL-cholesterol, HDL-cholesterol and triglycerides) in either sex.

Methodological considerations

The 1958 cohort has many important strengths. Data on a wide range of factors across life have been collected prospectively. The nationwide sample is large and has been followed-up to an age when CVD is beginning to manifest. Gestational age was measured contemporaneously and variation in CVD risk factor levels can be examined across the full range of gestational age.

Gestational age was calculated using mothers' reports of date of last period. Although some over-estimation may result from this method, different methods of assigning gestational age produce highly correlated estimates.[30,31] As date of last period was reported at the time of birth rather than in the prenatal period women's recall could have been affected by their baby's size with those women who had babies of lower birthweight possibly more likely to falsely recall a shorter gestational age than women

Table 4 Differences (95% CIs) in mean levels of blood pressure (mmHg) at age 44–45 years by gestational age after adjustment for prenatal factors and potential mediators (N=6596)

Risk factors for CVD/Gestational age (weeks)	Model 1	Model 2	Model 3
Systolic blood pressure			
Per 1 week increase	−0.53 (−0.75, −0.32)	−0.52 (−0.73, −0.30)	−0.52 (−0.74, −0.31)
P-value	<0.001	<0.001	<0.001
Diastolic blood pressure			
<37	2.44 (1.04, 3.84)	2.35 (0.94, 3.76)	2.59 (1.19, 3.99)
37	0.44 (−0.86, 1.75)	0.36 (−0.95, 1.67)	0.39 (−0.91, 1.69)
38	0.59 (−0.30, 1.48)	0.56 (−0.33, 1.45)	0.54 (−0.34, 1.43)
39	−0.04 (−0.72, 0.64)	−0.01 (−0.69, 0.67)	0.003 (−0.67, 0.68)
40	0	0	0
41	−0.07 (−0.77, 0.62)	−0.08 (−0.77, 0.62)	−0.06 (−0.76, 0.63)
>41	−0.51 (−1.33, 0.32)	−0.53 (−1.36, 0.30)	−0.46 (−1.28, 0.36)
P-value*	0.01 (0.01)	0.01 (0.02)	0.01 (0.01)

**P*-values from models including gestational age as a continuous term (*P*-value for quadratic term shown in parentheses if there is evidence of deviation from linearity).
Model 1: Adjusted for sex, birthweight standardized by gestational age and sex and current BMI.
Model 2: Model 1 plus prenatal factors (maternal age, maternal smoking, pre-eclampsia, father's occupational class).
Model 3: Model 2 plus potential mediators (educational level, own occupational class, smoking and alcohol consumption in adulthood).

who had babies of normal birthweight. This could have introduced bias. However, foetal growth rate was adjusted for in analyses and misclassification is unlikely to differ by CVD risk factor levels.

Lipids were measured using non-fasted blood samples. While total and HDL cholesterol are not significantly affected by fasting status, triglyceride levels are known to be lower after fasting[32] and to vary by duration of fasting and time of day.[33] However, misclassification of triglyceride levels by gestational age is unlikely and adjusting for time of blood collection and time since consuming food did not alter our findings. Further, fasting and non-fasting levels of triglycerides are positively correlated,[34] a meta-analysis found no significant variation in results from analyses of triglycerides by fasting status[35] and, recent studies have shown that non-fasting levels are themselves a risk factor for cardiovascular disease.[36,37] This suggests that use of non-fasting lipid measures is likely to be acceptable for the purpose of our analyses.

Attrition over time has reduced the original cohort sample and may have introduced bias. Participants not included in analyses were more likely to have lower gestational age and lifetime socioeconomic position, however the cohort followed-up into adulthood remains largely representative of the original sample.[38]

In the 1958 cohort mortality increased with decreasing gestational age[39] (30.9% of those born <37 weeks had died by 7 years compared with 2.4% of those born at 40 weeks) and hence the majority of pre-term births in our analyses were born just under the 37 week cut-off: 70% of our sample with a gestational age <37 weeks were born at 35–36 weeks, although the youngest gestational age was 28 weeks. Survival rates for pre-term births have improved since the 1950s with the consequence that the distribution of gestational age in our sample is likely to differ from that in populations born more recently. Notably, people classified as pre-term in our sample may be a more highly selected, healthy group compared with those born pre-maturely in more recent years. Therefore, associations between pre-term birth and later health may be even stronger in younger cohorts. However, despite babies now surviving at decreasing gestational ages most pre-term births remain close to term[4] and so our findings are likely to be relevant when predicting the impact on subsequent CVD risk of the global increases in pre-term birth.

Due to the lack of variation and small number ($n=279$) with gestational age <37 weeks, our ability to examine associations between gestational age and risk factors for CVD within the pre-term group was limited. Nevertheless, the strength of our study is that we were able to examine the association across the full range of gestational age, and this has revealed variation in levels of some risk factors for CVD across this range.

Comparison with other studies

Our findings in relation to BP are consistent with other studies that also report higher BP in those born at younger gestational ages.[6–10,12–15] However, some of these studies[9,12–14] included only males and others[6,10] only females. Further, our study is one of the first to show that a gestational age/BP association

is found in middle-age when CVD is beginning to manifest, whereas most previous studies measured BP in late adolescence or early adulthood. Our finding of an association between gestational age and BP is also consistent with evidence of an elevated risk of hospital admission for, and death from, stroke (of which hypertension is a contributory factor) among those born at younger gestational ages.[20,21]

All but one study[7,15,18,22,40] examining the association between gestational age and lipid levels found little evidence of an association; the one exception[18] measured lipid levels in umbilical cord blood immediately after birth, thus limiting comparisons.

In contrast to our findings, some other studies have found an association between gestational age and diabetes or markers of increased diabetes risk.[15–17,19] These inconsistencies may be related to variation in the measures of diabetes risk, categorizations of gestational age or the age at which outcome measures were taken.

Explanations

The association between gestational age and BMI among women attenuated after adjustments suggesting that this association was to some extent explained by variation by gestational age in maternal age, maternal smoking, pre-eclampsia, lifetime socioeconomic position and adult lifestyle factors. That the association between gestational age and blood pressure remained after adjustment for these factors suggests that there are other explanations of these associations.

Given the major differences between pre- and postnatal environments, it is possible that earlier and more prolonged exposure of babies born at younger gestational ages to the postnatal environment while still developmentally plastic may increase susceptibility to 'programming' effects. For example, changes in the source and composition of nutrition during critical periods of development may lead to the promotion of fat rather than lean tissue. Further, pre-term birth may result in changes to organ development. Support for these explanations, in relation to BP, is provided by evidence from animal studies[41] suggesting that variation in gestational age is associated with differences in kidney structure.

Differences in the postnatal experiences of children of different gestational ages may also impact on development and subsequent health. For example, the increased time that pre-term babies spend in hospital after birth and the greater attention paid to their subsequent growth may result in exposure to different feeding practices, including nutritional supplements, which may 'program' body composition and metabolism, thereby affecting lifetime weight gain and blood pressure. However, why this would not also affect lipid levels is unclear.

Finally, genetic factors related to both gestational age and BP may explain observed associations. However, a recent study[12] found no evidence to suggest that genetic factors were important in explaining the gestational age–BP association.

That a number of risk factors for CVD were examined but only blood pressure was found to be associated with gestational age in adjusted analyses suggests that gestational age has specific influences, either direct or indirect, on the systems that determine blood pressure rather than having global effects on all aspects of the cardiovascular system. What these specific influences are remains to be elucidated.

Conclusions

We found evidence to suggest that duration of gestation is associated with blood pressure in mid-life in both men and women, with those born at younger gestational ages having higher diastolic and systolic blood pressure compared with those born at term. As these associations were not explained by prenatal factors or potential mediators, further investigation of why there is variation in blood pressure by gestational age is needed to inform policy and preventative interventions.

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Conflicts of interest: None declared.

KEY MESSAGES

- Duration of gestation is associated with blood pressure in mid-life in a British birth cohort.
- Gaining a better understanding of these associations is going to be necessary to inform policy and preventative interventions.
- Duration of gestation is not independently associated with other risk factors for cardiovascular disease in mid-life.

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