Birth weight and adolescent blood pressure measured at age 12 years in the Gateshead Millennium Study.

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Abstract

Birth weight and early growth have been associated with later blood pressure. However, not all studies consistently find a significant reduction in blood pressure with an increase in birth weight. In addition, the relative importance of birth weight and of other lifestyle and environmental factors is often overlooked and the association is rarely studied in adolescents. We investigated early life predictors, including birth weight, of adolescent blood pressure in the Gateshead Millennium Study (GMS).

The GMS is a cohort of 1029 individuals born in 1999-2000 in Gateshead in Northern England. Throughout infancy and early childhood, detailed information was collected including birth weight and measures of height and weight. Assessments of 491 returning participants at age 12 years included measures of body mass and blood pressure. Linear regression and path analysis were used to determine predictors and their relative importance on blood pressure. Birth weight was not directly associated with blood pressure at age 12. However, after adjustment for contemporaneous BMI, an inverse association of standardised birth weight on systolic blood pressure was significant. The relative importance of birth weight on later systolic blood pressure was smaller than other contemporaneous body measures (height and BMI). There was no independent association of birth weight on blood pressure seen in this adolescent population. Contemporaneous body measures have an important role to play. Lifestyle factors that influence body mass or size, such as diet and physical activity, is where interventions directed at early prevention of hypertension should be targeted.

Key words: Blood pressure, birth weight, cohort, obesity

Introduction

Raised blood pressure or hypertension is a modifiable factor that increases the risk of heart attack, stroke and cardiovascular disease. It is estimated that 15% of adults in the UK and around 22% of the adult population worldwide have raised blood pressure (1). Childhood blood pressure strongly predicts adult blood pressure (2). Therefore, investigating factors affecting childhood blood pressure will be important for the prevention of hypertension in later life.

Birth weight and growth in early life have been shown to be directly predictive of blood pressure in childhood, adolescence and adulthood (3-6). Meta-analyses suggest a 1kg increase in birth weight is associated with a 2-4mmHg decrease in systolic blood pressure in adulthood (5, 7). The “fetal origins” hypothesis suggests that restriction or deprivation in utero from poor nutrition, resulting in a small placenta, increases blood pressure in babies in order to maintain blood flow through the placenta (8, 9). It is proposed that these babies who are born with low birth weight have elevated blood pressures throughout life, though not necessarily outside of the normal range.

In contrast, there are other studies that show no association between early life and later blood pressure (10, 11), suggesting such results may be a reflection of random error and inadequate adjustment of confounding factors (12). In addition, the relative importance of birth weight and of other lifestyle and environmental factors is often overlooked. Furthermore, there remains controversy for the adjustment of statistical models for current weight or body mass. It is suggested that controlling for current weight may bias the association of birth weight on blood pressure and thus attenuate or reverse any association (13).

In this study we investigated early life predictors, including birth weight, of adolescent blood pressure in the Gateshead Millennium Study (GMS), a birth cohort from Northern England. Using this cohort we have the opportunity to account for confounding factors such as contemporaneous body size and socio-economic status and to assess the relative importance of factors from across the lifecourse to date.

Methods

The Gateshead Millennium Study

The GMS began as a prospective study of 1029 infants and their families recruited shortly after birth between June 1999 and May 2000 in Gateshead, an urban district in north east England. The cohort has been followed up at regular intervals since recruitment. Full details of recruitment and measures taken since birth are detailed elsewhere (14). For the present study (year 12 follow-up), all families who had not previously opted-out from the cohort were sent a letter and information leaflet inviting them to take part. Ethical approval was granted from Newcastle University Research Ethics Committee.

Sex, birth weight and gestational age were recorded at birth. Those born with a gestational age less than 37 completed weeks were classified as pre-term births. Birth weight was standardised for gestational age and sex, compared to UK 1990 standard (15, 16). Parents received questionnaires at 6 weeks, and 4, 8, and 12 months, which all included questions regarding whether any breast milk was being given at that age. From this, a breast-fed duration variable was derived. Socio-economic status was defined as the ward-level Townsend deprivation score (17) for each study member at the time of their birth. The Townsend deprivation score, derived from 2001 census data (via the link between postcodes and ward identifiers) is a summary measure consisting of the proportion of households in the area without a car, with more than one person per room and that are not owner-occupied and also incorporates the number of men (aged 16-64 years) and women (aged 16-59 years) who were unemployed at the time of the census. The higher the score is, the more socio-economically deprived the area is assumed to be.

Those followed up aged 9 and 12 years had assessments between 2008 – 2010 and 2011 – 2013, respectively, either at school or in the home. Trained research associates recorded height and weight using a portable Leicester height measure and a Tanita TBF300 MA body fat analyser. Individuals were dressed in light indoor clothing, with no shoes or socks. Two measurements were taken and their mean was calculated, from which body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Standard deviation score (z-score) for BMI was calculated using the UK 1990 standard (18). Blood pressure at age 12 was measured on the left arm twice using an Omron 705 CP-II blood pressure cuff monitor. An average of the two measures were used for statistical analysis.

Statistical analysis

Birth weight, birth weight z-score, gestational age, Townsend score, age at follow-up and BMI (absolute BMI and BMI z-score) were treated as continuous. The remaining variables; sex, pre-term birth and breast feeding duration were treated as categorical.

The representativeness of the sample used in this analysis compared to the original GMS cohort was assessed using chi-squared tests for categorical variables (sex, breast feeding duration), t-test for normally distributed continuous variables (birth weight) and Mann-Whitney test for non-normally distributed continuous variables (gestational age and Townsend deprivation score).

Predictors of blood pressure (systolic and diastolic) were investigated using linear regression. Each variable was first tested for significant association with no adjustment (Table 2). Regression coefficients with 95%CI are presented as well as standardised regression coefficients (beta) to allow for comparison of effect sizes from each variable. A standardised coefficient (beta) is the standard deviation increase in blood pressure elicited by a 1 standard deviation increase in the predictor variable. Significant associations found were then adjusted for age, sex and Townsend deprivation score and finally all included in a multivariable regression model (Table 3). Interaction terms were also investigated prior to the final model. A p-value less than 0.05 was considered as significant.

To assess the relative importance of the predictors of blood pressure, the final multivariable regression model was reconstructed as a path diagram and standardised direct effects estimated. The remaining variables (those not independently predictive of blood pressure) were initially added to the path diagram and all paths or correlations with p less than 0.05 modelled. Model fit was assessed using chi-square (using the Bollen-Stine bootstrap modification, over 50000 observations), goodness-of-fix index (GFI), comparative fit index (CFI), and root mean square of error approximation (RMSEA). Adequate fit was defined as a chi-square p-value over 0.05, GFI and CFI over 0.95 and RMSEA under 0.05, all of which were satisfied.

Statistical analyses were performed using the statistical software package Stata, version 13 (StataCorp, College Station, Texas, USA) and path analysis conducted in AMOS 17.0 (SPSS Inc, Chicago, Illinois, USA).

Results

From the original 1029 children recruited to the GMS at birth, 514 (50% of the original cohort) returned for follow-up between 2011 and 2013 (age 12 years). Twins (n=23) were excluded from analysis leaving 491 (47% of the original cohort) singleton study members with valid blood pressure readings. This sample was representative of the original cohort for sex (p=0.328), gestational age (p=0.621) and birth weight (p=0.575). However, this sample were less socio-economically deprived (had lower average Townsend deprivation score, p<0.001) at birth and a higher proportion were breast fed (p<0.001) than those in the original cohort.

Mean systolic blood pressure was 112mmHg (SD 9) and mean diastolic blood pressure was 65mmHg (SD 8) (Table 1). There were no sex differences in blood pressure (Table 2). No significant associations were seen on blood pressure with any of the early life (birth) factors (Table 2). Blood pressure was significantly positively associated with height and BMI (raw and z-score) at age 12 years. These associations remained after adjustment for age, sex and Townsend score at birth (Table 3). For each centimetre increase in height, systolic blood pressure increased by 0.29 mmHg (95%CI 0.17, 0.40) and diastolic blood pressure increased by 0.12mmHg (95%CI 0.02, 0.21). Similarly, for each unit increase in BMI z-score, systolic and diastolic blood pressures increased by 1.36mmHg (95%CI 0.63, 2.08) and 1.61mmHg (95%CI 0.99, 2.23), respectively.

Birth weight and blood pressure after body size adjustment

Birth weight, standardised for sex and gestational age, was not significantly associated with blood pressure at age 12 (Table 2, Table 4). However, after adjustment for contemporaneous BMI or height, an inverse association of standardised birth weight on systolic blood pressure was significant (Table 4). Furthermore, adjusting the association of standardised birth weight on systolic blood pressure for both contemporaneous BMI and height resulted in the magnitude of the standardised regression co-efficient being larger (Table 4). No significant association of standardised birth weight on diastolic blood pressure was seen after adjustment for contemporaneous BMI or height (Table 4). No differences to these findings were seen when removing the small number of pre-term births from the analysis.

Path analysis

The standardised direct effect of birth weight on systolic blood pressure was -0.14 (95%CI -0.24, -0.05) which was mediated through later height and BMI, leaving a relative contribution (standardised total effect) of -0.08 (95%CI -0.18, -0.01) on systolic blood pressure (Figure 1). That is, for a one standard deviation increase in birth weight, systolic blood pressure decreased by

0.08mmHg. The relative contribution of BMI and height at both age 9 and 12 years were of greater importance with standardised total effects on systolic blood pressure of; BMI at age 9 years 0.12 (95%CI 0.03, 0.21), BMI at age 12 years 0.14 (95%CI 0.04, 0.24), height at age 9 years 0.21 (95%CI 0.13, 0.29), height at age 12 years 0.24 (95%CI 0.15, 0.33).

Discussion

Summary of findings

A significant inverse association of birth weight, standardised for sex and gestational age, was seen in the GMS participants at age 12 years. However, this association was significant only after adjustment for current BMI or height and for systolic, but not, diastolic blood pressure. The relative importance of birth weight on later systolic blood pressure was smaller than other body measures (height and BMI) measured at the same time as blood pressure.

We have shown in a simple linear model that birth weight (raw or standardised for sex and gestational age) was not directly predictive of blood pressure at age 12 years. We have, however, seen that, when adjusting for contemporaneous body size, an inverse association of standardised birth weight on systolic blood pressure is significant. These results are similar to that found in children aged 5 to 15 years in the cross-sectional Health Survey for England 1995-2002, where the association between birth weight and blood pressure was strengthened by the adjustment for current weight (19). It was also found, in a subset of those children with data available on paternal characteristics, no association between birth weight and blood pressure, which became significant after adjustment for current weight. Other studies have also shown this change in significance in the association between blood pressure and birth weight after adjustment for current weight (13, 20).

In the previous literature where similar results have been seen and are not attributed to bias or random error, it is hypothesised that those born with low or high birth weight that later become overweight, from excessive fetal growth, over nutrition or growth acceleration, may be associated with the development of later hypertension (3, 19, 21). If true, this could suggest an association whereby individuals at low birth are at an increased risk, but it needs exposure to the later lifestyle or environmental factor for the risk to become apparent, or whereby the avoidance of the later risk factor negates the initial risk. Unfortunately, through lack of statistical power, we are not able to investigate this hypothesis in relation to birth weight extremes within the GMS cohort, since only 5% (n=25, Table 1) of the returning population were born with low birth weight (less than 2.5kg), 2% (n=10) were born with a high birth weight (more than 4.5kg). Further, we could not investigate the impact of pre-term births in this cohort as only 4% of those included were born pre-term. However, we did, mainly, use birth weights standardised for gestational age and sex to account for the associations between fetal growth and gestational age, and no difference to the birth weight findings were seen when restricting the analyses to term births..

Regardless of whether or not we agree that the significant association of birth weight on systolic blood pressure is true, when included in a path model we show that the effect of birth weight on blood pressure is of smaller relative importance to that from height and BMI measured later in the lifecourse. We have previously seen that this cohort reflects the rise in childhood obesity in the UK, (24% of the GMS at age 6-8 years (22) and thus targeting interventions towards maintaining a healthy body size, such as promoting healthy diet and lifestyle, will be more beneficial for blood pressure than interventions aimed at reducing high birth weight. The relative importance of birth weight on blood pressure has not been quantified in children before, however, the authors of a 55-study meta-analysis on birth weight and blood pressure concluded that birth weight is of little relevance to blood pressure in later life (12). Similar conclusions have also been drawn from path analyses on the relative importance of birth weight in the prediction of adult blood pressure (23). In this study the total effect of BMI was found to be over 4 times greater than the total effect from standardised birth weight on adult blood pressure. We report slightly smaller differences in total effects; standardised BMI almost 2 times and height 3 times greater than standardised birth weight on blood pressure. This may suggest that the further through the lifecourse we study, the more important contemporaneous measures become (24).

An interesting result of our analysis is that we find significant associations with birth weight on systolic blood pressure, but not with diastolic blood pressure. Much of the previous literature report similar results on diastolic blood pressure to that with systolic blood pressure and do not report them. It is possible that the present study lacks the statistical power to detect association with diastolic blood pressure since effect sizes are reported to be smaller (5).

In order to assess the relative importance of birth weight on blood pressure, we have used path analysis. Path analysis has some strengths over traditional regression analyses in that it is possible to include variables that co-vary such as BMI and height within one model. This is achieved by modelling co-variation (dashed grey lines, figure 1) and correlation (under linear regression, solid grey lines figure 1) at the same time. Another strength in using path modelling is the illustrative quantification of both direct and indirect pathways of influence on the outcome. Nevertheless, some limitations require consideration. Firstly, the direction of each association must be inferred by the researcher. This is less of an issue in the present study, and in longitudinal studies in general where direction is often determined by clear temporal relationships. As with all forms of statistical modelling, path models are also sensitive to specific features of the underlying data. It is therefore important to consider the characteristics of the cohort studied when comparing to other populations. Finally, path analysis is sensitive to error, since the standard deviation of each estimate strongly contributes to the final effect size. The data used in this study have been collected prospectively and mean values of measures taken, where available (for example blood pressure) are used.

Conclusion

There was no independent association of birth weight on blood pressure seen in this adolescent population. It is more apparent that contemporaneous body measures have an important role to play in determining blood pressure in early adolescence. Regardless of whether an association of birth weight on blood pressure exists, we have shown that the relative importance is small in comparison to other more easily modifiable lifestyle factors. Lifestyle factors that influence body mass or size, such as diet and physical activity, are where intervention should be targeted. Further research into those born at the two ends of the birth weight spectrum (high and low birth weight) and into other modifiable risk factors is needed.

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Conflicts of Interest

The authors declare no conflicts of interest.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines (Gateshead Local Research Ethics Committee) on human experimentation and with the Helsinki Declaration of 1975 as revised in 2008, and has been approved by the institutional committee (Newcastle University Research Ethics Committee).

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Table 1: Summary statistics of the year 12 follow-up sample.

Variable		n	Mean/Median	SD/IQR
Birth weight (kg)		491	3.37	0.53
Birth weight (z-score)		491	-0.15	1.06
Gestational age (weeks)		491	40	39 , 41
Townsend score at birth		485	1.45	-2.26, 3.77
Height at age 9 (cm)		435	135.49	6.20
BMI at age 9 (kg/m^2)		435	17.22	16.04, 19.22
BMI at age 9 (z-score)		435	0.52	1.05
Age at year 12 follow-up (years)		491	12.50	0.29
Height at age 12 (cm)		490	154.67	7.98
BMI at age 12 (kg/m^2)		487	19.78	17.73, 22.44
BMI at age 12 (z-score)		487	0.67	1.18
Systolic blood pressure age 12 (mmHg)		491	112.04	9.37
Diastolic blood pressure age 12 (mmHg)		491	65.42	7.95
		n	***%***	
Sex	Male	242	*49%*	
	Female	249	*51%*	
Pre-term birth <36 weeks	Yes	20	*4%*	
	No	471	*96%*	
Breast feeding duration	>4m	95	*19%*	
	>6wks	57	*12%*	
	<6wks	115	*23%*	
	Formula	205	*42%*	
	Missing	19	*4%*	

SD: standard deviation, IQR: Interquartile range

Table 2: Unadjusted associations with blood pressure at age 12 years

		Systolic blood pressure					Diastolic blood pressure					
Variable		**co-eff**	**95% CI**		**beta**	**p-value**	**co-eff**	**95% CI**		**beta**	**p-value**	**n**
Sex	*Male*	*reference category*				0.182	*reference category*				0.842	491
	Female	-1.13	-2.79	0.53	-0.06		0.14	-1.27	1.56	0.01		
Gestational age (wks)		-0.45	-0.97	0.07	-0.08	0.089	-0.43	-0.87	0.01	-0.09	0.058	491
Pre-term birth	*No*	*reference category*				0.375	*reference category*				0.465	491
	Yes	1.90	-2.30	6.10	0.04		1.32	-2.24	4.89	0.03		
Birth weight (kg)		-1.25	-2.83	0.34	-0.07	0.122	-0.70	-2.04	0.65	-0.05	0.310	491
Birth weight (z-score)		-0.65	-1.43	0.14	-0.07	0.107	-0.35	-1.02	0.32	-0.05	0.306	491
Breast feeding duration	*>4m*	*reference category*				0.890	*reference category*				0.778	472
	>6wks	-1.20	-4.31	1.90	-0.04		-0.11	-2.74	2.51	-0.01		
	<6wks	-0.20	-2.76	2.37	-0.01		0.34	-1.84	2.51	0.02		
	Formula	-0.30	-2.60	2.00	-0.02		0.84	-1.11	2.79	0.05		
Townsend score at birth		0.08	-0.16	0.32	0.08	0.498	0.20	-0.01	0.40	0.09	0.051	485
Height at age 9 (cm)		0.33	0.19	0.47	0.22	<0.001	0.27	0.15	0.39	0.21	<0.001	435
BMI at age 9 (kg/m^2)		0.71	0.39	1.02	0.21	<0.001	0.84	0.57	1.10	0.28	<0.001	435
BMI at age 9 (z-score)		1.69	0.87	2.51	0.19	<0.001	1.85	1.15	2.54	0.24	<0.001	435
Height at age 12 (cm)		0.28	0.18	0.38	0.23	<0.001	0.17	0.09	0.26	0.17	<0.001	490
BMI at age 12 (kg/m^2)		0.58	0.37	0.80	0.24	<0.001	0.66	0.48	0.83	0.32	<0.001	487
BMI at age 12 (z-score)		1.79	1.10	2.49	0.22	<0.001	1.79	1.21	2.37	0.27	<0.001	487
Age at follow-up (yrs)		-0.91	-3.77	1.94	-0.03	0.530	0.91	-1.51	3.34	0.03	0.459	491

co-eff: regression co-efficient, beta: standardised regression co-efficient. 95%CI: 95% Confidence Interval

Table 3: Multivariable linear regression model on blood pressure at age 12 years adjusted for age, sex and Townsend deprivation score.

Variable	Systolic blood pressure					Diastolic blood pressure				
	co-eff	**95% CI**		**beta**	**p-value**	**co-eff**	**95% CI**		**beta**	**p-value**
Birth weight (z-score)	-1.32	-2.12	-0.50	-0.15	0.001	-0.59	-1.27	0.09	-0.08	0.087
BMI at age 12 (z-score)	1.36	0.63	2.08	0.17	<0.001	1.61	0.99	2.23	0.24	<0.001
Height at age 12 (cm)	0.29	0.17	0.40	0.24	<0.001	0.12	0.02	0.21	0.12	0.039

co-eff: regression co-efficient, beta: standardised regression co-efficient. 95%CI: 95% Confidence Interval

Table 4: Linear regression analysis of birth weight, standardised for sex and gestational age, with blood pressure at age 12 years.

	Systolic blood pressure					Diastolic blood pressure					
Birth weight (z-score)	**co-eff**	**95% CI**		**beta**	**p-value**	**co-eff**	**95% CI**		**beta**	**p-value**	**n**
unadjusted	-0.65	-1.43	0.14	-0.07	0.107	-0.35	-1.02	0.32	-0.05	0.306	491
adjusted for Townsend score	-0.64	-1.44	0.16	-0.07	0.119	-0.27	-0.95	0.40	-0.04	0.428	485
adjusted for age at follow-up	-0.63	-1.43	0.14	-0.07	0.107	-0.35	-1.02	0.32	-0.05	0.307	491
adjusted for BMI z-score at age 12	-0.92	-1.71	-0.14	-0.10	0.021	-0.48	-1.13	0.18	-0.06	0.155	487
adjusted for height at age 12	-1.16	-1.95	-0.37	-0.13	0.004	-0.55	-1.23	0.13	-0.07	0.113	490
adjusted for BMI z-score & height at age 12	-1.25	-2.04	-0.47	-0.14	0.002	-0.63	-1.30	0.03	-0.08	0.063	487

co-eff: regression co-efficient, beta: standardised regression co-efficient. 95%CI: 95% Confidence Interval