

# Pathways between birth weight and later body size in predicting blood pressure: Australian Aboriginal Cohort Study 1987–2007

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**Background:** Although a large number of previous studies suggest an association between birth weight and later blood pressure, others do not. Controversy surrounds the relative importance of these associations, in particular in relation to more modifiable factors in later life and whether the association would be seen in a, relatively disadvantaged, Indigenous population. The aim of this study, within the Aboriginal Birth Cohort study, was to examine the relative contributions and mediating pathways of birth weight, and later growth and lifestyle factors to variation in blood pressure at age 16–20 years.

**Methods:** Detailed information was collected prospectively, including maternal smoking, birth weight, childhood BMI. At age 16–20 years, 451 underwent clinical examination, including the measurement of diastolic and systolic blood pressures. These data were analyzed using linear regression and path analyses, incorporating adjustment for potential confounders.

**Results:** Increased BMI at age 18 years was significantly associated with both increasing systolic and diastolic blood pressures. BMI had the highest relative importance and mediated the effects from earlier in life, including birth weight. Being female and living in remote residence were also independently associated with a reduction in systolic blood pressure.

**Conclusion:** Blood pressure in this cohort is primarily influenced by contemporaneous BMI, which in this population at this age is generally lower than that seen in non-Indigenous populations in developed countries. However, other factors, including birth weight, do appear to play a role that is mediated through later BMI.

**Keywords:** aboriginal, birth weight, blood pressure, hypertension

**Abbreviations:** ABC, Aboriginal birth cohort; CFI, comparative fit index; CI, confidence interval; CrI, credible interval; FGR, fetal growth restriction; GFI, goodness-of-fit index; RMSEA, root mean square error of approximation; SD, standard deviation

## INTRODUCTION

Cardiovascular disease is the leading cause of death for Indigenous Australians with a death rate nearly three times that for non-Indigenous Australians [1]. Coronary heart disease, cerebrovascular disease, heart failure and hypertension are the main cardiovascular conditions contributing to this cardiovascular disease burden [2]. Of these conditions, hypertension is the most common cardiovascular disease for both Indigenous males and females, and is a major risk factor for coronary heart disease, stroke, heart failure, peripheral vascular disease and kidney failure [3].

There is substantial literature describing the associations between blood pressure and birth weight. The early literature describes inverse relationships between birth weight and subsequent blood pressure with meta-analyses showing that a 1-kg increase in birth weight was associated with 2–4 mmHg lower systolic blood pressure [4,5]. However, inappropriate adjustment for current weight or BMI [4,6,7], selective publication bias [4] and studies incorporating later life predictors of blood pressure [8–10] suggest, on the contrary, that birth weight may have little relevance to blood pressure measures in adult life.

The early analyses of birth weight, current body size and blood pressure were mostly done using multiple regression analyses [11]. However, path analysis has been shown to have advantages over these regression models. The statistical power is increased, the results are more easily interpreted because of an ability to disentangle indirect and direct effects [8] and comparisons of the relative effect sizes of different risk factors are possible [10].

The vast majority of the studies linking birth weight with blood pressure have been done in developed countries, so it is unclear whether the same findings would be seen in other, less-developed, settings. Although Australia is a

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developed country, it includes a disadvantaged Aboriginal Australian population. In the Australian Aboriginal population, despite recent improvements, low birth weight rates remain twice that for non-Aboriginal Australians, and one Northern Territory study reported fetal growth restriction rates as high as 25% [12]. Recent studies in Aboriginal populations have implicated birth weight with cardiovascular disease mortality [13], adult blood pressure [14] and blood pressure at 11 years of age [15], but have been unable to separate the relative effects of predictors. As factors occurring in later life may be more amenable to interventions, using path analysis and data from the longitudinal prospective Aboriginal birth cohort study [16], at age 16–20 years, we aimed to examine the relative contributions and mediating pathways of birth weight, child and adolescent size and lifestyle factors to explaining variation in systolic and diastolic blood pressure.

## METHODS

Details of recruitment and follow-up of this birth cohort have been previously published [15,16]. In brief, 686 Aboriginal babies out of a possible 1238 born at the Royal Darwin Hospital (1987–1990) were recruited into the study. The babies were recruited consecutively when the principal researcher was available and consent was obtained. There were no significant differences in mean birth weight, birth weight frequencies or sex ratio between those recruited and those not recruited. The Royal Darwin Hospital is not only the routine place of delivery for 98% of Aboriginal mothers within the local health region of 120 000 km<sup>2</sup>, but also functions as the tertiary referral hospital for high-risk deliveries transferred *in utero* from a sparsely populated vast area covering two million km<sup>2</sup> of northern Australia.

At birth, infant birth weight and maternal smoking information were collected from hospital records. Maternal smoking during pregnancy was categorized as follows: 'never', 'light' (up to 10 cigarettes per day) and 'heavy' (>10 cigarettes per day). Within 4 days, the same neonatal paediatrician performed a gestational age assessment according to the Dubowitz Scoring System [17]. Infants were classed as low birth weight (<2.5 kg) or not low birth weight. Fetal growth restriction (FGR) was defined as less than 10th percentile of birth weight for gestational age using an Australian reference standard contemporary with cohort recruitment [16].

At 11 years of age, the participants were measured in light clothing. Height was measured to the nearest millimetre using a portable stadiometer and weight was measured to the last complete 0.1 kg with a digital electronic scale (TBF-521; Tanita Corporation, Arlington Heights, Illinois, USA). These measures were used to calculate BMI (kg/m<sup>2</sup>).

Participants were seen again between December 2005 and January 2008. The participants were measured in light clothing while barefoot with the procedures for height and weight measures and BMI calculation the same as at 11 years of age. Sitting blood pressure was measured using an automatic oscillatory unit (Lifesigns BP Monitor, Welch Allyn, New York, USA). Appropriate cuff sizes were used and three measurements were taken after 5 to 10-min rest with the mean of the three measurements used for analysis.

Residence at the time of blood pressure assessment was defined as remote (residence in defined remote Aboriginal Communities) or other (including the twin cities of Darwin and Palmerston and the greater Darwin area). This is primarily seen as a partial proxy for socioeconomic status for this population. Details on smoking status (current smoker or nonsmoker) were self-reported at the time of follow-up.

## Statistical analysis

The explanatory variables, sex, maternal smoking, smoking at age 16–20 years and residential region, were treated as categorical variables. All other explanatory variables (birth weight, gestational age, BMI at age 11 years and BMI at age 16–20 years) were treated as continuous. Representativeness of the participants in this study compared with those of the original cohort not included was assessed using Student's *t*, Mann-Whitney *U* and  $\chi^2$  tests. Relationships between systolic and diastolic blood pressure and explanatory variables were estimated by linear regression, as were potential interactions between explanatory variables. Unadjusted coefficients, with corresponding 95% confidence intervals, were determined to estimate the total influence (i.e. including both direct and indirect effects) of that variable on blood pressures. Linear regression assumptions were checked and satisfied.

To estimate solely the direct effect of each variable (i.e. not mediated through other factors), an adjusted regression model was generated. To estimate indirect pathways (i.e. nonindependent predictors of blood pressure, which are mediated through other variables), the adjusted model was reconstructed as a path diagram. Variables that were not in the adjusted model (i.e. that were not independently predictive of blood pressure) were then added to the path analysis, and all paths or correlations with  $P < 0.1$  were modelled and included in the path diagram. Variables and paths that did not directly or indirectly predict blood pressure were removed and the final path diagram included all paths with  $P < 0.05$ . Model fit was assessed using model  $\chi^2$  (using the Bollen-Stine bootstrap modification, over 50 000 observations), goodness-of-fit index (GFI), comparative fit index (CFI) and root mean square error of approximation (RMSEA). Adequate fit was defined as a  $\chi^2$  *P* value over 0.05, GFI over 0.95, CFI over 0.95 and RMSEA under 0.05, all of which were satisfied.

To allow comparison between variables, and estimate relative importance, standardized beta coefficients ( $\beta$ ) were derived for each explanatory variable in the path models [where a standardized coefficient is the standard deviation (SD) change in blood pressure elicited by a 1-SD change in the explanatory variable]. Ninety-five percent credible intervals (CrIs), analogous to confidence intervals, are presented.

All analyses were performed using STATA, version 13 (StataCorp, College Station, Texas, USA).

## RESULTS

Valid blood pressure measurements were available for 451 study participants. Ages ranged from 16 to 20 years, mean 18 years, and there was an equal split of males to females,



**TABLE 1. Summary statistics for study participants with blood pressure measures at age 18 years**

Variable	Total	Mean/Median	SD/IQR
Birth weight	451	3.03	0.64
Gestational age	406	39.1	38.3, 39.9
BMI at 11	427	15.72	14.40, 18.02
BMI at 18	450	19.58	17.43, 23.91
Systolic blood pressure at 18	451	109.43	11.83
Diastolic blood pressure at 18	451	68.76	7.81
Age at measurement	451	18	1

	Total	N	%
Sex			
Male	451	224	50
Female		227	50
Maternal smoking	437	207	47
Never		63	15
Light smoker		167	38
Heavy smoker		128	32
Smoking at 18	399	271	68
No		358	79
Yes		93	21
Residential region at 18	451		
Remote			
Other			

IQR, interquartile range; SD, standard deviation.

Table 1. Mean blood pressure was 109 (SD 11.8) and 69 mmHg (SD 7.8) for systolic and diastolic blood pressure respectively, with 99% within the normal range [18], lower than 140/90 mmHg. Using the American Heart Association definition of high-normal or prehypertension (>120/80, but <140/90 [19]), 91 (20%) participants had high-normal or prehypertensive blood pressures.

These participants were representative of the original cohort for early life measures: birth weight ( $P=0.533$ ), gestational age ( $P=0.118$ ), maternal smoking ( $P=0.126$ ) and sex ( $P=0.131$ ). The study participants with complete measures for all explanatory variables used in the path model ( $n=339$ ) were not significantly different from those with blood pressure measurements, but not included in the path model because of missing covariate data.

Few ( $n=28$ ) of the participants were born large-for-gestational age (i.e. birth weight >90th percentile). Of those, the mean systolic blood pressure was 112 mmHg (SD 11.4) and mean diastolic blood pressure was 71 mmHg (SD 8.1). The BMI categories differed in this group

compared with those with a birth weight lower than the 10th percentile ( $n=113$ ) with six (21%) obese, four (14%) overweight and seven (25%) underweight in the large-for-gestational age group and 0 obese, three (8%) overweight and 56 (50%) underweight in the group with fetal growth restriction at birth.

### Regression analysis

Unadjusted associations with systolic blood pressure were seen for sex, birth weight, BMI at age 11 years, BMI at age 16–20 years, smoking and residential region. Increasing birth weight was associated with increased systolic blood pressure by 1.76 mmHg/kg (95% CI 0.04, 3.47) (Table 2).

Increased BMI increased systolic blood pressure by 0.90 mmHg (95% CI 0.06, 1.20) and 0.72 mmHg (95% CI 0.53, 0.91) per unit increase in BMI at age 11 and 16–20 years respectively. Females, smokers and those from the remote residential region had decreased systolic blood pressures compared with males, non smokers and those from other residential regions respectively.

**TABLE 2. Unadjusted associations with blood pressure at age 18 years**

Variable		Systolic blood pressure			Diastolic blood pressure			n
		co-eff	95% CI	P	co-eff	95% CI	P	
Sex	Male	Reference category						
	Female	-6.18	-8.30, -4.10	<0.001	-0.36	-1.81, 1.08	0.622	451
Birth weight		1.76	0.04, 3.47	0.045	0.34	-0.79, 1.48	0.554	451
Gestational age		-0.06	-0.70, 0.58	0.860	-0.15	-0.57, 0.28	0.496	406
Maternal smoking	Never	Reference category						
	Light smoker	0.62	-2.71, 3.95		0.46	-1.76, 2.69	0.899	437
	Heavy smoker	1.83	-0.57, 4.24	0.324	0.27	-1.33, 1.88		
BMI at age 11		0.90	0.60, 1.20	<0.001	0.56	0.36, 0.76	<0.001	427
BMI at age 18		0.72	0.53, 0.91	<0.001	0.43	0.31, 0.56	<0.001	450
Smoking at age 18	No	Reference category						
	Yes	-2.54	-4.95, -0.12	0.039	-2.02	-3.66, -0.39	0.016	399
Residential region at age 18	Remote	-6.18	-8.83, -3.53	<0.001	-2.67	-4.44, -0.90	0.003	451
	Other	Reference category						

CI, confidence interval.



Significant unadjusted associations with diastolic blood pressure were seen for BMI at age 11 years, BMI at age 18 years, smoking and residential region. BMI increased diastolic blood pressure by 0.56 mmHg (95% CI 0.36, 0.76) and 0.43 mmHg (95% CI 0.31, 0.56) per unit increase in BMI at age 11 and 16–20 years respectively. Smokers at age 16–20 years had decreased diastolic blood pressure in comparison with non-smokers. Those living in the remote residential region also had decreased diastolic blood pressure in comparison with those from other residential regions. There were no significant interactions on blood pressure (systolic and diastolic) with sex and birth weight, birth weight and BMI at 11 years and birth weight and BMI at 16–20 years. No association was seen with age and blood pressure.

After adjustment for all other explanatory variables, the associations of sex, BMI at age 16–20 years and residential region with systolic blood pressure and only BMI at 16–20 years with diastolic blood pressure remained significant. Females had systolic blood pressure on average 5.40 mmHg (95%CI –7.48, –3.06) lower than that of males and remote residents had mean systolic blood pressure 3.16 mmHg (95% CI –6.14, –0.018) lower than those from other residential regions (Table 3). Blood pressure was increased by 0.61 mmHg (95% CI 0.27, 0.96) and 0.47 mmHg (95% CI 0.23, 0.71) per unit increase in BMI at age 16–20 years for systolic and diastolic blood pressure respectively.

### Path analysis

The largest standardized total effect on systolic blood pressure came from the association with BMI at age 16–20 years (Fig. 1). Indirect effects on systolic blood pressure were all mediated through BMI at age 16–20 years, including that of birth weight. After BMI, sex had the greatest relative importance on systolic blood pressure, with higher blood pressure in males. The relative importance of birth weight on systolic blood pressure was small (0.09) in comparison with that of sex (0.23), BMI (0.32) and residential region (0.14). All of the effects on diastolic blood pressure at age 18 years were mediated through later body size (Fig. 1).

## DISCUSSION

### Summary of main findings

Contemporaneous BMI had the highest relative importance in terms of explaining variation in both systolic and diastolic blood pressures and was the only independent significant predictor of diastolic blood pressure. Sex and residential area were also significant predictors of systolic blood pressure. Although there was a significant univariate association between birth weight and systolic blood pressure, this was not present in the adjusted model. However, there was an indirect effect of birth weight on systolic blood pressure mediated through later BMI.

### Comparison with previous findings

Although not significant in the adjusted model, the estimated univariate 1-kg increase in birth weight being associated with a 2-mmHg decrease in systolic blood pressure is consistent with the previous meta-analyses of this association [4,5]. Only one previous study of blood pressure, to our knowledge, has taken a similar approach to the pathway methods used in this study [10]. Although that study, part of the Newcastle Thousand Families Study, was in much older participants than in this study, and from a very different population, the findings were similar in that contemporaneous BMI was the strongest predictor of blood pressure. Further, we are unaware of any previous study, other than the Newcastle Thousand Families Study, to assess the relative contribution of birth weight, or any other marker of fetal growth, alongside adult lifestyle risk factors, rather than simply adjusting for such factors.

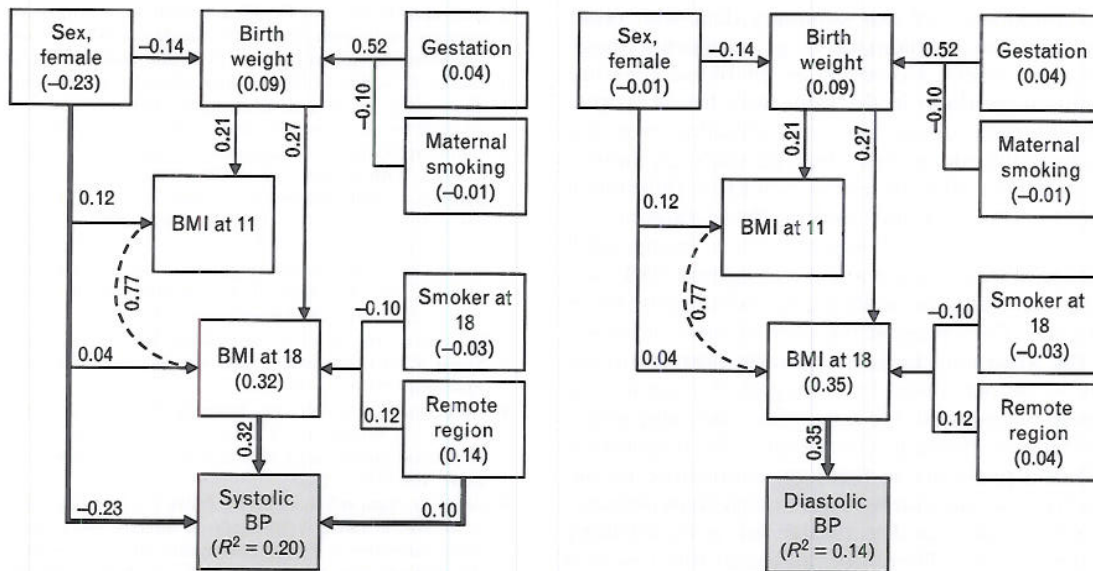
BMI has been consistently found to be associated with blood pressure in many studies [10,20]. However, unlike most other birth cohort studies, the mean BMI z score in this study was nearly half a standard deviation below zero, with low levels of obesity. Our findings, therefore, suggest an association across the BMI range, rather than only at levels of obesity. Within the path analysis, we showed an indirect effect of birth weight mediated through later BMI. It is only by using such models that this can be demonstrated as a way of understanding causal pathways and mediation routes. In this case, the results suggest that although BMI

TABLE 3. Multivariable regression model on blood pressure at age 18 years (n = 339)

Variable	Systolic blood pressure			Diastolic blood pressure			
	co-eff	95% CI	P	co-eff	95% CI	P	
Sex	Male	Reference category					
	Female	–5.40	–7.48, –3.06	<0.001	–0.40	–2.05, 1.25	0.632
Birth weight		0.01	–2.33, 2.35	0.991	–0.72	–2.37, 0.93	0.389
Gestational age		–0.25	–1.11, 0.60	0.561	–0.18	–0.79, 0.42	0.550
Maternal smoking	Never	Reference category					
	Light smoker	–0.06	–3.43, 3.32	0.986	–0.44	–2.82, 1.93	0.693
	Heavy smoker	0.19	–2.40, 2.78		–0.79	–2.60, 1.03	
BMI at age 11		0.12	–0.41, 0.65	0.651	0.07	–0.30, 0.44	0.706
BMI at age 18		0.61	0.27, 0.96	<0.001	0.47	0.23, 0.71	<0.001
Smoking at age 18	No	Reference category					
	Yes	–2.26	–4.76, 0.24	0.077	–1.43	–3.19, 0.33	0.110
Residential region at age 18	Remote	–3.16	–6.14, –0.18	0.038	–1.20	–3.29, 0.88	0.256
	Other	Reference category					

CI, confidence interval.





**FIGURE 1** Path models of systolic and diastolic blood pressure at age 18 years. Significant associations are represented by solid arrows and are labeled with standardized coefficients ( $\beta$ ), with the arrow direction indicating the hypothesized direction of causal flow. Indirect effects are any pathways that are mediated through at least one intermediate (e.g. birth weight  $\rightarrow$  BMI at 18  $\rightarrow$  systolic/diastolic blood pressure). Direct effects are represented by arrows going straight from the independent variable to blood pressure without being mediated through another independent variable. The standardized total effect for each variable on blood pressure is the sum of the direct and indirect effects, and the value is shown underneath the variable name. Co-variation between variables is represented by dashed lines. Error terms are omitted for simplicity.

is the strongest predictor, there is a small contribution of birth weight, as it is one of the predictors of BMI at age 16–20 years.

Socioeconomic environment in childhood has previously been suggested to be important with respect to mortality from cardiovascular disease [21] and in particular associated with adult blood pressure [22,23]. In this study, the measures of socioeconomic status available do not adequately discriminate the cohort population. Region of residence might be a proxy, to some extent, for socioeconomic status, with the presumption of a more disadvantaged status when living in remote area. The higher systolic blood pressure in remote residents remained significant in the adjusted model and likely reflects the more disadvantaged social status of those living in remote areas compared with those living in the more urban areas.

Cigarette smoking was not found to be significantly predictive of blood pressure within this cohort. However, current smoking status had a small indirect relative contribution on blood pressure, mediated through an association with BMI at 16–20 years. Although independent chronic effects of smoking on blood pressure have been previously noted to be small [24], it is possible that within this cohort, the effect of smoking on blood pressure may grow as the study members get older.

**Strengths and limitations**

The main strength of this study is the simultaneous use, within a path analysis, of prospectively collected data relating to blood pressure from different stages of life in an contemporary Australian Aboriginal population wherein the leading cause of death is cardiovascular disease. This analysis is able to disentangle some of the early life course factors. An illustrative quantification of the different

pathways of influence (Fig. 1) is more easily interpreted and shows not only both direct and indirect (i.e. mediating) effects, but also an estimation of their relative impact on the outcome. Importantly, in this study, this analysis demonstrates the lesser importance of birth weight in relation to later, more easily modifiable, predictors of blood pressure, such as contemporaneous BMI. Path analysis has several benefits over standard linear regression. For example, in this study, a regression model would only show the independent significant predictors of blood pressure. The path model goes a step further, showing how completely indirect factors such as birth weight and smoking impact on BMI, and through this have indirect effects on blood pressure.

Nevertheless, some limitations require consideration. The direction of each association has to be inferred by the researcher. This issue can be minimal for longitudinal studies such as this because the direction is often determined by clear temporal relationships. As with all forms of statistical modelling, path models are also sensitive to the specific features of the underlying data. It is therefore important to consider the characteristics of the cohort studied when comparing the model estimates with those seen in other populations. Finally, path analysis is sensitive to error, as the standard deviation of each estimate strongly contributes to the final effect size. Even so, the majority of data for this study were collected prospectively, so sources of error usually associated with retrospective data collection were minimized.

Blood pressure was measured using an automated oscillatory device. Concerns have been raised over the clinical validity of using oscillometric blood pressure devices compared with the ‘gold standard’ auscultatory mercury sphygmomanometers in children [25]. This may, if errors do exist,



mean that comparisons of our summary data with other populations may be problematic (e.g. comparing mean blood pressure values). However, as all blood pressure measurements were done in the same way for all participants, using the same device, any measurement errors are unlikely to have introduced bias into the study, as there is no reason to believe that the errors would be differential with respect to any of the included predictor variables.

These findings of a lesser importance to young adult blood pressure of birth weight relative to current BMI have important public health implications by widening the focus of interventions. They suggest the current rates of hypertension in the Australian Indigenous adult population are more likely to be decreased by strategies to improve life style factors in young adult life rather than focussing solely on prenatal factors affecting birth weight. The importance of higher blood pressures at this age, even those recognized as prehypertensive rather than frankly hypertensive, as risk factors for later cardiovascular risk is increasingly being recognized [26]. Therefore, although this research was based on adolescents, the findings are also relevant to older age groups because of the likely tracking of blood pressure values from adolescence to later adulthood [27–29].

In conclusion, by the application of path analysis to prospectively collected data from an Australian Aboriginal birth cohort, our results show for blood pressure outcomes in young adult life, birth weight is less important than current BMI. These findings have important public health implications and are in contrast to many studies in the literature. If other cohorts analyzing the roles of birth weight and later life style factors in determining blood pressure used path analysis, better insights of the relative importance of early growth in relation to later health may be achieved.

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## Conflicts of interest

There are no conflicts of interest.

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## Reviewer's Summary Evaluation

### Reviewer 1

For programming of cardiovascular disease risk, current evidence emphasizes the relative importance of the prenatal and postnatal periods.

Strengths: In the study performed by Mann *et al.*, the strength is the longitudinal prospective birth cohort of an

Australian Aboriginal population, in which both the impact of prenatal factors affecting birth weight and later growth along with lifestyle factors affecting blood pressure outcomes were assessed at age 16–20 years. The findings will have an impact on public health.

The weakness is that the influence of other relevant factors, such as growth and early-life nutrition, among others, was not considered in the study.

