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Arnold, Luke; Hoy, Wendy; Wang, Zhiqiang

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Low birthweight increases risk for cardiovascular disease hospitalisations in a remote Indigenous Australian community – a prospective cohort study

Luke Arnold,[1] Wendy Hoy,[1] Zhiqiang Wang[1]

Abstract

Objectives: To investigate the association between low birthweight (LBW; <2,500 grams) and cardiovascular disease (CVD) hospitalisations in adult life in a remote Indigenous Australian community.

Methods: This was a prospective cohort of 852 participants with recorded birthweight using community-wide health screening examinations conducted between 1992 and 1999 and hospitalisation records up to 2012. Cox proportional hazard models assessed the association between LBW and hypertension, major CVD (heart failure, myocardial infarction and stroke) and any CVD hospitalisations.

Results: There were 236 participants (28%) who had a low birthweight. The LBW group had a higher risk of developing any CVD (HR = 1.43, 95%CI 1.01-2.03), major CVD (HR = 1.51, 95%CI 0.93-2.47) and hypertension (HR = 1.83, 95%CI 1.09-2.96) than the normal birthweight (NBW) group (≥2,500 g). Women with LBW had more than 2.6 times the risk of a hospitalisation associated with hypertension compared to their NBW counterparts (HR = 2.61, 95%CI 1.38-4.93), but this relationship was not seen in men.

Conclusions and implications: LBW increased the risk of cardiovascular disease hospitalisations in adult life in this group. Further CVD prevention initiatives should continue to include LBW as a key predictor of CVD in this community. The mechanisms of gender influence on the hypertension relationship are unknown and require further investigation in indigenous populations worldwide.

Key words: birthweight, hypertension, Indigenous Australians, cardiovascular disease, adult

The fetal origins hypothesis suggests there are intrauterine mechanisms influencing fetal development which have health consequences later in life.[1] The literature supports associating birthweight (BW) with cardiovascular risk factors[2-4] and renal complications[4] throughout childhood years and onwards to adult life. These risk factors lead to some of the major chronic diseases in Australia: cardiovascular disease (CVD), chronic kidney disease (CKD) and type 2 diabetes (T2D). The high prevalence of these chronic diseases largely attributes to the disparity in life expectancy between Indigenous and non-Indigenous Australian men and women.[5]

This connection between birthweight and chronic disease development is a concern for all those interested in improving health equality for Indigenous Australians. Indigenous mothers are more than 2.5 times more likely to give birth to a low birthweight (LBW; less than 2,500 grams) baby than non-Indigenous mothers in Australia.[6] The Northern Territory experiences the worst rates of LBW (16%) compared to overall Indigenous (10.1%) and non-Indigenous (4.6%) Australians. Furthermore, the incidence of LBW infants in some remote Indigenous Australian communities are similar, if not, worse than that of the least developed nations in the world.[7,8] The World Health Organization (WHO) further estimates, using epidemiological evidence, a child born of LBW anywhere in the world is 20 times more likely to die prematurely than normal birthweight babies.[7]

It is widely accepted that LBW increases the risk of developing hypertension in adult life, as proposed by Barker et al.,[9] and an abundant literature supports the importance of LBW for the actual development of cardiovascular diseases.[10] Singh and Hoy[8] identified the inverse association between BW and blood pressure (BP) in an Indigenous Australian remote community. Although the association between BW and CVD risk factors such as albuminuria, lipids and blood pressure has been investigated,[11] the relationship between BW and actual CVD development has not been investigated in any indigenous population worldwide.

This study aimed to quantify the risk of a cardiovascular hospitalisation if a LBW infant is born within a remote Indigenous Australian community.

Methods

This is a prospective cohort study of subjects who participated in baseline examinations conducted between 1992 and 1999, where community-wide health screening

1. Centre for Chronic Disease, School of Medicine, University of Queensland

Correspondence to: Mr Luke Arnold, Centre for Chronic Disease, The University of Queensland School of Medicine, Health Sciences Building – Level 8/Room 828d, Royal Brisbane & Women's Hospital, Herston QLD 4029; e-mail: l.arnold1@uq.edu.au

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exams were conducted with individuals of a remote Northern Territory Indigenous Australian community. The health screening examinations were a part of a broader screen investigating the high rates of chronic disease and premature mortality in a remote Indigenous Australian community. Standardised screening exams were offered to the entire community and were conducted by trained staff. Participants volunteered with written informed consent for clinical examination, biological testing and use of their medical records under NHMRC grant 921134 and approval of the Human Research Ethics Committee, Menzies School of Health Research, Darwin, Northern Territory. The methods of the health screening exams are detailed elsewhere.[12] Information on several chronic disease risk factors was collected, such as: blood pressure, anthropometric measurements, triglycerides, cholesterol, use of tobacco and alcohol, and medical records were reviewed. All participants older than 18 years of age were asked about tobacco and alcohol use at the time of the examination, as a dichotomous yes/no request. The review of medical records enabled identification of diabetes status and birthweight measurements.

Participants were included in the analysis if they fitted the following inclusion criteria: i) were over 18 years old at baseline or became over 18 during the follow-up period; ii) were born to an Aboriginal mother; iii) had birthweight data available; iv) participated in the health screening examination; and v) resided in and was a member of the remote Aboriginal community studied.

Of the 884 participants with birthweight information, 32 participants did not reach adulthood (≥18 years of age) during the 20-year follow-up period and were hence excluded from the analysis. A further three participants were excluded from the hypertension analysis because their hypertension hospitalisation was pregnancy-related, to reduce overrepresentation of women and the risk of a gender bias. A total of 852 participants were included in the cardiovascular hospitalisations analysis and 849 included in the hypertension hospitalisations analysis.

All births occurred in a local mission health clinic or in the regional Royal Darwin Hospital. Deliveries, the tribal or community assignment of the mother, the mother's name and birthweight were recorded in log books. The retrieved birthweights occurred between February 1956 and December 1998. Further details of obtaining and measuring birthweight information are described elsewhere.[13]

Hospitalisation data was matched to health screening examinations using participant identification numbers. We subsequently identified the first event of each outcome (hypertension, any CVD or major CVD) recorded during a hospitalisation in the 20-year follow-up period. These hospitalisation records included any admissions and emergency department visits for all patients who presented to a public hospital in the Northern Territory between 1992 and 2012.

To identify hypertensive cases, we filtered patient hospitalisation records using English Revision International Classification of Diseases (ICD-9 code) codes 401 and International Statistical Classification of Diseases, 10th Revision (ICD-10 code) codes I10. A hypertension event was defined as the first identified ICD code representing essential hypertension after their baseline examination.

Analysis of CVD outcomes were conducted separately for any CVD and major CVD events. The first case of any CVD outcome is defined as the first occurrence of ICD-9 codes between 390-459 and ICD-10 codes I00-99 which did not include codes for hypertension or hypotension (401-405, I10, 458 or I95). Major CVD outcomes were classified as heart failure (HF), myocardial infarction (MI) and stroke, which were identified by patient hospitalisation records using ICD-9 codes 410, 411, 413, 414, 428, 434.91 and ICD-10 codes I21, I24, I25, I50, I60, I61, I63, I64.

Follow-up times were calculated from an adult's health screening examination or from the time a participant became an adult (≥18 years of age) if aged less than 18 years at their health screening exam. For those who were identified by their hospitalisation as a case, their follow-up time was calculated to their first hospitalisation of the cardiovascular outcome. Those who had not reached the endpoint were considered 'censored' at the date of 31 May 2012. Participants who did not have a documented hospitalisation for the cardiovascular outcome, but had died before the end of the follow-up period were censored at the time of death. For participants who died of CVD without a prior CVD hospitalisation the date of their first identified event of CVD was the date of CVD death. For death information, we utilised a comprehensive and maintained mortality database of the study community. The methods of the mortality data have been described in detail elsewhere.[13]

Low birthweight was defined if the recorded weight at time of birth was <2,500 g, as per the recommendations by the World Health Organization.[7] We separated the population into two groups, those with low birthweight (<2,500 g) and those with normal birthweight (≥2,500 g).

We calculated Hazard Ratios (HRs) using the Cox proportional hazard model with adjustment for age and diabetes status (yes/no) at time of health screening examinations, as well as gender and decade of birth. Support for adjusting for these variables was based on the relevant studies in the literature.[2,10,14-19] Ethnicity was not applicable, as participants were all from the same tribal group, and traditional socioeconomic measurements could not be used in this study population. There were insufficient participants with birth length and gestational age information to adjust or categorise the analysis by these variables. Due to the drastic changes in mortality rates by birthweight cohorts and reducing incidence of LBW over the past 40–50 years in this community, the model adjusted for the decade the individual was born.[13]

Much of the information on cardiovascular risk factors collected in health screening examinations was not routinely collected for children under the age of 18. For this reason, we conducted analysis in two ways: the whole population; and those who were adults (≥18 years) at the time of the health screening exam. The subgroup analysis adjusted for age, gender, decade of birth, diabetes status and popular cardiovascular risk factors such as smoking status, alcohol consumption, triglycerides, systolic blood pressure and cholesterol to test their potential confounding influence.

The results of the health screening examinations were compared between <2,500 g and ≥2,500 g groups for men and women, and boys and girls. Continuous variables were compared using a student's two-tail t-test and dichotomous variables were compared using chi-squared (χ^2) tests. Relationships were considered statistically significant if a *p*-value less than 0.05 was achieved. Statistical analysis was conducted using STATA 12.0.[20]

Ethical approval for this study was obtained from the Royal Darwin Hospital and Northern Territory Health Services; the community's Health Board and Land Council; and the Human Research Ethics Committee of the Department of Health and Community Services, NT; the Menzies School of Health Research, NT; and the Behavioural and Social Sciences Ethical Review Committee on behalf of School of Medicine in The University of Queensland.

Results

A total of 852 participants (55% male) were included in the analysis with a total follow-up of 11,113 person-years. The participants represented 100% of the cohort of screened adults and 94% of the children with recorded birthweight information. Six per cent of children did not reach 18 years or age before the end of the follow-up period. There were 236 participants (116 male and 120 female) with recorded low birthweights. Sixty-eight were identified as having a first case of hypertension during the follow-up period, 135 with any CVD and 67 with major CVD outcomes. Forty individuals died from other causes before the follow-up period ended. These deaths were censored and included in the survival analysis, as previously noted.

The health screening characteristics in the low birthweight (LBW) and the normal birthweight (NBW) groups are shown for adults in Supplementary Table 1 (available with the online version of this article). Men in the LBW group were, on average, 4.6 kg lighter in weight (p=0.026) and 1.4 kg/m^2 lower Body Mass Index (BMI) in the LBW group (p=0.032) than the NBW group. Women in the LBW group weighed 5.9 kg (on average) less than their NBW counterparts (p=0.019). There was also a lower rate of tobacco use in the women with LBW (54%) compared to 68% in those with NBW (p=0.050). Rates of tobacco use and alcohol consumption were significantly higher in men than women, irrespective of birthweight. Supplementary Table 2 shows that LBW boys under the age of 18 were, on average, 4.2 kg lighter (p=0.039) and had a BMI 1.2 kg/m^2 less (p=0.037) than their NBW counterparts after adjustment for age. Supplementary Tables 2 and 3 also show that there were no other significant differences between the LBW and NBW groups for boys and girls under the age of 18 in the health screening examinations aside from birthweight.

Table 1 demonstrates the increased risk of the LBW group for all cardiovascular outcomes. Participants of LBW were more than two times at risk of a hypertension hospitalisation than their NBW counterparts. This risk remained consistent when the Cox proportional hazard model was adjusted for age and diabetes status at screening, gender and decade of birth. The LBW group also had an increased risk for any CVD and major CVD outcomes. The adjusted model shows a 43% increased risk of any CVD hospitalisations if born with a low weight (p=0.045) and showed a 51% increased risk in major CVD hospitalisations; however, it failed to achieve statistical significance (p=0.097).

Table 2 demonstrates the sensitivity analysis conducted on participants who were adults at time of the health screening examination. Adjusting for age, smoking status, alcohol consumption and diabetes status at health screening exam, gender and decade of birth in this subgroup produced similar associations seen in the entire population. There was an 83%, 53% and 70% increased risk of hypertension, any CVD and major CVD, respectively, for low birthweight participants. Further adjusting for systolic blood pressure, triglycerides and HDL cholesterol made little difference to the association of BW and hospitalisations associated with hypertension, but reduced the point estimates for any CVD and major CVD and statistical significance.

Table 3 shows that the risk of LBW participants for hypertension was more marked and significant in the female group. The women experienced a crude incidence density nearly three times the amount of the men (women = 15.83 events per 1,000 person-years; men = 5.66 events per 1,000 person-years). A formal test of statistical interaction was conducted on gender with

Table 1: The risk of cardiovascular hospitalisations in adult life if participants were born of low birth weight.

	Participants (n)	Events (n)	Incidence Density (events per 1,000 person-years)	Mean age at hospitalisation, years (95%CI)	Model	HR	95% CI	*p*-value
Hypertension	849	68	10.62	36.5 (34.7–38.3)	Unadjusted	2.29	1.42–3.69	0.001
	849	68			Adjusted[a]	1.83	1.09–2.96	0.014
Any CVD[b]	852	135	16.50	38.5 (37.0–39.9)	Unadjusted	1.46	1.03–2.06	0.032
	852	135			Adjusted[a]	1.43	1.01–2.03	0.045
Major CVD[c]	852	67	8.86	39.5 (37.9–41.1)	Unadjusted	1.71	1.05–2.77	0.031
	852	67			Adjusted[a]	1.51	0.93–2.47	0.097

The corresponding ≥2.5kg group was used as reference for each model

a: Adjusted for age at health screening exam, gender, decade of birth and diabetes status (yes/no) at health screening exam.

b: Any CVD excludes hypertension and hypotension events

c: Major CVD includes Stroke, Myocardial Infarction and Heart Failure

Table 2: Subgroup analysis of participants over 18 years at time of health screening examination and their risk of having a cardiovascular hospitalisation in adult life if born of low birth weight.

	Incidence Density (events per 1,000 person-years)	Model	n	HR	95% CI	*p*-value
Hypertension	15.94	Unadjusted	406	2.01	1.24–3.24	0.004
		Adjusted[a]	393	1.83	1.12–2.99	0.016
		Further adjusted[b]	342	1.84	1.10–3.09	0.021
Any CVD[c]	18.85	Unadjusted	408	1.53	1.03–2.29	0.037
		Adjusted[a]	395	1.53	1.01–2.31	0.045
		Further adjusted[b]	343	1.37	0.87–2.14	0.175
Major CVD[d]	12.12	Unadjusted	408	1.68	1.01–2.81	0.047
		Adjusted[a]	395	1.70	1.01–2.89	0.049
		Further adjusted[b]	343	1.36	0.76–2.45	0.305

The corresponding ≥2.5 kg group was used as reference for each model

a: Adjusted for age at health screening exam, gender, decade of birth, smoking status (yes/no), alcohol consumption (yes/no) and diabetes status at health screening exam (yes/no)

b: Additionally adjusted for other cardiovascular risk factors at health screening examinations, including triglycerides, systolic blood pressure and HDL cholesterol

c: Any CVD excludes hypertension and hypotension events

d: Major CVD includes Stroke, Myocardial Infarction and Heart Failure

Table 3. The gender difference of risk for a hospitalisation in which hypertension was recorded.

	Incidence Density (event per 1,000 person-years)	Model	n	HR	95% CI	*p*-value
Men	5.66	Unadjusted	463	1.38	0.62–3.09	0.426
		Adjusted[a]	463	1.25	0.56–2.80	0.589
Women	15.83	Unadjusted	385	2.91	1.56–5.41	0.001
		Adjusted[a]	385	2.61	1.38–4.93	0.003

The corresponding ≥2.5kg group was used as reference for each model

a: Adjusted for age at baseline screening, gender, smoking status (yes/no), alcohol consumption (yes/no), decade of birth and diabetes status at health screening exam (yes/no)

the adjusted Cox proportional hazard model for hypertension hospitalisations; however, statistical significance was not achieved (p=0.162).

This difference in risk by gender was not apparent in the analyses for any CVD and major CVD (results not shown).

Discussion

There is a significant disparity of risk for cardiovascular outcomes based on birthweight in this remote Indigenous Australian community. Those with LBW have an increased risk of hypertension, any CVD and major CVD hospitalisations in adult life compared to their NBW counterparts. When stratified by gender, LBW women were more than 2.6 times more likely to experience a hospitalisation in which a diagnosis of hypertension was recorded, when compared to women who weighed more than 2,500 g at birth. This association was not statistically significant in men.

These findings support the well-established relationship between LBW and risk of hypertension in adult life, as first hypothesised by Barker et al.[9] They are consistent with the BP and BW relationship first described by Singh and Hoy[8] in this same community. They also show that birthweight is associated with the development of cardiovascular outcomes and precipitating hospitalisations in adult life of remote Indigenous Australians.

These findings are consistent with a comprehensive meta-analysis which determined an inverse association between BW and subsequent development of CVD in non-Indigenous populations.[10] Our findings provide quantifiable evidence for the further extrapolation of this relationship between LBW and CVD development in adult Indigenous Australians, which translate to the burden of hospitalisations and probably premature death.

This study also suggests the effect of LBW on increasing incidence of hypertension hospitalisations in women was greater than that observed in men, although the mechanisms of this gender influence are unknown. This gender difference is contrary to a meta-analysis of studies conducted on general non-Indigenous populations worldwide, which concluded there was no gender dependence for the association between BW and BP.[21] However, the meta-analysis did not include any studies conducted in adult Indigenous Australians. Singh and Hoy[8] encountered an inverse relationship between BW and BP in young adults which was only significant in women. Moreover, Hoy et al. showed a similar inverse relationship in this community between BW and albuminuria.[22] Further studies in remote and urban indigenous populations of the world are needed to investigate this gender difference and provide more insight into the LBW and CVD association.

Through effective improvements in health service delivery and an increased focus on birthweight by health care providers over the past 40–50 years, mean birthweights in this community[13] and across the Northern Territory have been increasing.[23] The continued reduction in LBW rates are encouraging; however, the remaining high incidence of LBW[13] and our observed risk to CVD suggests continued improvements are necessary.

The mortality trend over the similar time period suggests a reduction in natural cause mortality – particularly in women – in this community,[24] and in aboriginal people in the Northern Territory.[25] The increasing mean birthweight may play a significant role in this trend. Increasing birthweight may also further reduce the infant mortality rates as experienced in other Aboriginal populations[26] and risk to natural deaths later in life.[13] The findings of this study provide further evidence to boost health promotion initiatives targeting birthweight due to the large potential benefits to the community.

Several limitations should be considered when interpreting our findings and generalising to other populations. The observed relationships may be caused by an increased total hospitalisation rate in the LBW group. We are unable to exclude the possibility that the relationship observed may have been caused by an increased number of incidental events as a coexisting condition or other factors leading to a higher number of total hospital visits. Secondly, the use of hospitalisation records captures symptomatic and the most serious cases. Therefore, our findings may underestimate the association between birthweight and adulthood development of cardiovascular outcomes.

Thirdly, the missing information of young people at the health screening examinations limited our ability to control for confounding factors in the entire sample. Sensitivity analysis in the adult subgroup of the population showed that age, gender, tobacco use, alcohol consumption, decade of birth and diabetes status only had a small influence over the association. Moreover, information on maternal risk factors such as maternal hypertension, alcohol consumption and tobacco use were unknown for our participants.

Finally, this population-based observational study will understate the association between BW and CVD due to the limited duration of the follow-up period. Another limitation is the assumption that each participant is disease-free at the time of baseline examination; this was due to the fact we were unable to identify cases of CVD through hospital records prior to 1992.

Strengths of this study are that, to our knowledge, these health screening examinations are the most complete for a remote Indigenous Australian community, with the largest sample size, highest community participation rate and the longest follow-up. This study is also the first Indigenous cohort to investigate the association between LBW and long-term CVD development.

Conclusion

Members of this remote Indigenous Australian community are at a significantly higher risk of developing cardiovascular diseases if they were born weighing less

than 2,500 g. Furthermore, LBW women have a more than 2.6 times higher risk of having a hospital admission in which hypertension is recorded. We recognise the vast improvements in mean BW in previous decades within Indigenous Australians; however, birthweight continues to be an important risk factor to ill-health outcomes within this community. The quantifiable association between BW and CVD in adult life suggests continued improvements in LBW rates are essential to continue the reduction in CVD morbidity of this community. We furthermore recommend further studies within indigenous populations (urban and remote) throughout the world to investigate the potential gender influence on the LBW and hypertension relationship.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Supplementary Table 1: Characteristics of adult participants at health screening examinations between 1992 and 1999.

Supplementary Table 2: Characteristics of boys (<18 years old) at health screening examinations between 1992 and 1999.

Supplementary Table 3: Characteristics of girls (<18 years old) at health screening examinations between 1992 and 1999.