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Cardiac and vascular health in late preterm infants

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Abstract

Adults who were born preterm are at increased risk of hypertension and cardiovascular disease in later life. Infants born late preterm are the majority of preterm births; however, the effect of late preterm on risk of cardiovascular disease is unclear. The objective of this study was to assess whether vascular health and cardiac autonomic control differ in a group of late preterm newborn infants compared to a group of term-born infants.

A total of 35 healthy late preterm newborn infants, with normal growth (34–36 completed weeks' gestation) and 139 term-born infants (37–42 weeks' gestation) were compared in this study. Aortic wall thickening, assessed as aortic intima–media thickness (IMT) by high-resolution ultrasound, and cardiac autonomic control, assessed by heart rate variability, were measured during the first week of life. Postnatal age of full-term and late preterm infants at the time of the study was 5 days (standard deviation [SD] 5) and 4 days (SD 3), respectively.

Infants born late preterm show reduced aortic IMT (574 μm [SD 51] vs. 612 μm [SD 73]) and reduced heart rate variability [log total power 622.3 (606.5) ms^2 vs. 1180. 6 (1114.3) ms^2], compared to term infants. These associations remained even after adjustment for sex and birth weight.

Infants born late preterm show selective differences in markers of cardiovascular risk, with potentially beneficial differences in aortic wall thickness in contrast to potentially detrimental differences in autonomic control, when compared with term-born control infants. These findings provide pathophysiologic evidence to support an increased risk of hypertension and sudden cardiac death in individuals born late preterm.

Introduction

Eleven per cent of all births worldwide are preterm.[1] The majority of these infants are born late preterm, after 34 weeks gestation, comprising 6%–8% of all live births.[2,3] People born late preterm are generally believed to have outcomes comparable to those of people born at term, and are managed as such. Despite that, there is evidence that children born late preterm are a group at increased risk of neonatal morbidity and mortality,[2,4,5] as well as poorer childhood neurodevelopmental outcomes.[6,7]

Individuals with impaired growth fetal growth that includes those born small for gestational age or intrauterine growth restricted are at increased risk of cardiovascular disease. People born preterm also have a higher risk of cardiovascular disease in early adulthood, and the limited evidence thus far indicates that this appears to be independent of impaired fetal growth.[8] There is conflicting evidence as to whether this association is apparent in people born late preterm.[9,10] The pathophysiologic pathways that mediate any such increased risk remain uncertain. Young adults born preterm have increased subclinical atherosclerosis, but only when there is concurrent impaired fetal growth.[11] Other studies demonstrate cardiac remodelling, altered systolic and diastolic function and higher prevalence of hypertensive disorders in children and young adults born preterm.[12–14] These changes may limit compensatory adaptions to cardiovascular stress in adulthood. The autonomic nervous system plays an important role in regulating cardiac function both in the short- and longer term. Previous studies have shown that cardiac autonomic activity, particularly parasympathetic activity, is reduced in those born preterm from infancy through to adulthood.[15–19] However, whether those born late preterm are also affected, and whether any such affect is independent of fetal growth is unknown.

Original Article

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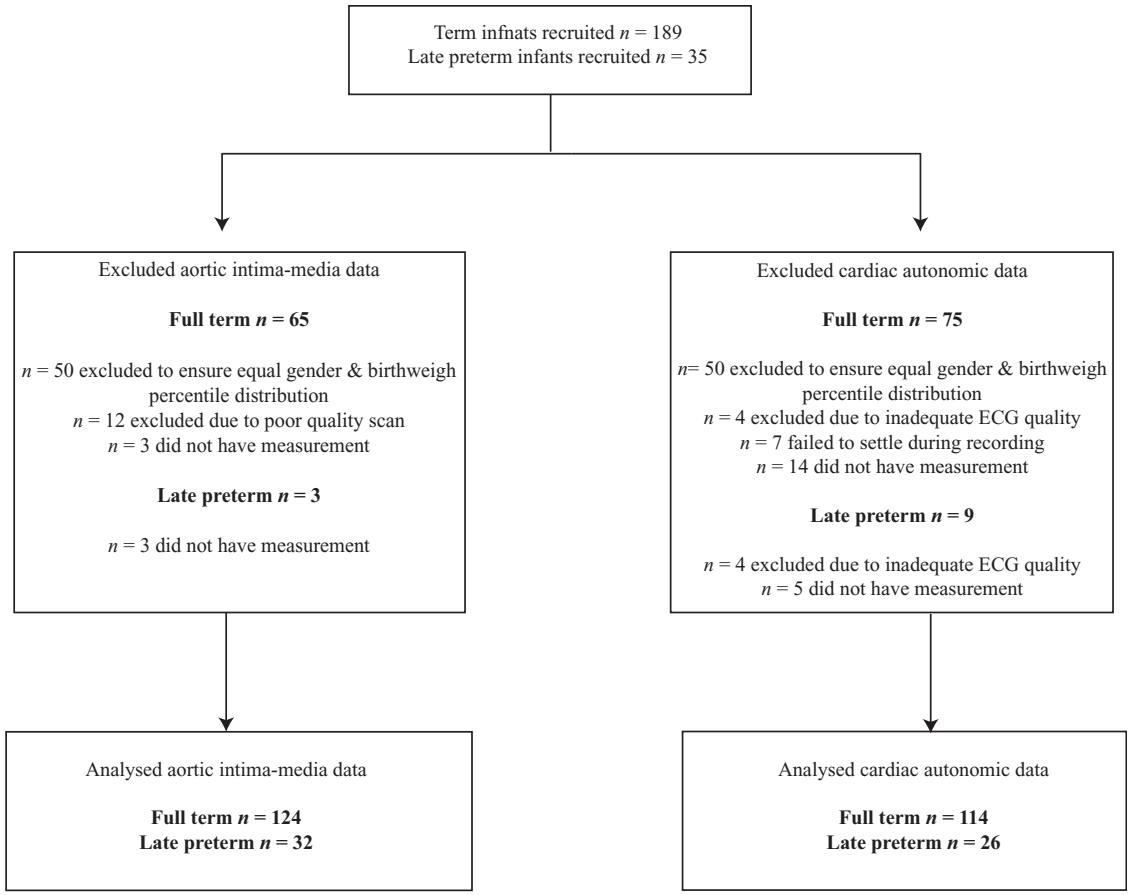

Fig. 1. Study flow.

Accordingly, we sought to describe cardiac autonomic control and subclinical atherosclerosis in a group of healthy late preterm newborn infants with normal growth, and compare these with a group of sex and growth-matched term infants.

Methods

Subjects

We recruited a total of 224 newborns from the postnatal wards and the neonatal unit at the Royal Prince Alfred Hospital, Sydney, a major obstetric tertiary referral centre with approximately 5500 deliveries per year, serving an inner city, multicultural population. This analysis of late preterm was a pre-specified component of a prospective cohort study that examined cardio-metabolic health in newborn infants.[20] Eligible subjects were well singleton newborns between 34 and 42 completed weeks' gestation, as determined by first-trimester ultrasound. Exclusions were major congenital abnormalities and an ongoing need for respiratory support. Infants born late preterm (between 34 and 36 completed weeks' gestation) were oversampled ($n = 35$), with the remaining 189 infants born at term (between 37 and 42 weeks' gestation). None of the late preterm infants had severe fetal growth restriction, and therefore were considered to have normal growth. For this analysis, a subset of the term infants ($n = 139$) were selected matched for sex and distribution of birth weight percentiles. The term group was chosen randomly from within the term (37–42 week's gestation) group, and balanced to ensure equal distribution across gender and body weight percentiles. A study flow diagram is shown in Fig. 1.

This study was approved by the Sydney Local Health District Ethics Committee (protocol X14-0356 & HREC/14/RPAH/478). Participation was voluntary, and informed written consent was obtained from a parent and/or legal guardian of each participating child.

Data collection

Demographic data, smoking and other lifestyle information were collected from mothers using standardised questionnaires. Information on current and previous health status, pregnancy and delivery details, of mothers and infants were collected from medical records.

Body composition and anthropometry

Body composition was measured with air-displacement plethysmography (PEA POD®, COSMED USA Inc., Concord, CA, USA) in the first 24 h after birth as part of routine clinical care of well infants. Air-displacement plethysmography is regarded as the current gold standard for non-invasive assessment of body composition in infants,[21] and has been validated for the term and preterm infants.[22–24] This technique accurately measures body volume by the application of Boyle's law to the displacement of air by the infant in a sealed chamber. Proprietary algorithms are used to calculate fat mass and fat-free mass. Weight is measured with the integrated scales to the nearest gram, and head circumference to

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0.1 cm. Length is measured with an Easy-Glide Bearing Infantometer (Perspective Enterprises, Portage, MI, USA) length board to 0.1 cm. Australian population growth charts were used to calculate birth weight percentiles.[25]

Aortic intima–media thickness (IMT)

The abdominal aorta was imaged by ultrasound using an L18-5 transducer to acquire aortic images for IMT analysis as described previously.[26] Aortic IMT was measured offline using validated semi-automated edge detection (Carotid Analyzer, Medical Imaging Applications, Coralville, IA, USA) software analysis package as described previously.[20]

Heart rate variability

An electrocardiogram (ECG) was recorded continuously for 15 min using standard neonatal 3-lead configuration while the infants were sleeping in a supine position. The ECG analogue output was digitised at 500 Hz, and acquired using commercial hardware (Powerlab, ADInstruments, Sydney, Australia). Infant behaviour was observed closely. Any periods of activity or wakefulness were noted, and these periods were removed from subsequent analysis. Analysis of heart rate and HRV was performed using LabChart (HRV 1 module, version 7, ADInstruments, Sydney, Australia) on up to 3 RR interval epochs of exactly 4 min. Peak detection on ECG was used to create RR sequences. Time-domain measures of HRV included the standard deviation of the normal-to-normal (NN) RR intervals as a measure of overall variability, and two short-term measures: standard deviation of change in successive NN intervals (SDΔNN) and the root mean square of successive differences (RMSSD) in NN interval.[27] Frequency-domain analysis was done by performing a fast Fourier transformation on the RR interval waveform (256 points, Hanning window) with 50% overlap. This provided a resolution (bin width) of 10 Hz. The spectral bands for HRV were investigated in the range of 0–1.1 Hz based on previous studies.[28] Low frequency at 0.04–0.15 Hz, and high frequency at 0.15–1.1 Hz. The high-frequency band was based on respiratory rates in infants at 0.5–1 Hz.[29,30] VLF was not determined due to the short sampling times.

Cardiovascular measurements IMT and HRV were conducted in the first week of life, thereby allowing us to by-and-large exclude postnatal exposures.

Statistical analysis

Statistical analysis was performed using SPSS (IBM Corp., Armonk, NY, USA, version 23). Data were expressed as mean and standard deviation (SD) or number and percentage (%). Data were visually assessed for normality by plotting histograms; log transformations were used for any data that were not normally distributed. Log-transformed data are presented as the median (interquartile range). Between-group comparisons were performed with independent samples *t*-test, chi-squared test or Fisher's exact test, as appropriate. Adjusted analyses were undertaken by multivariable regression modelling. Statistical significance was inferred at $2P < 0.05$.

Results

Participant characteristics

Characteristics of participants, including maternal characteristics, are shown in Table 1. In brief, mothers of preterm infants were more likely to be of Asian ethnicity, in comparison to mothers of the term group, who were more likely to be Caucasian. Maternal characteristics were otherwise similar between groups. Labour was more likely to be spontaneous in the preterm group and birth was more likely to be vaginal in the preterm group. As expected, babies in the preterm group weighed less, were shorter, had lower percentage body fat and smaller head circumference than the term group. Rates of admission to the Neonatal Intensive Care did not differ between groups, consistent with the preterm group being otherwise healthy.

Aortic intima–media thickness (IMT)

Both mean and maximum aortic IMT was greater in full-term infants when compared to late preterm infants (Fig. 2a, Table 2). There was a positive association between aortic IMT and gestational age at birth even after correcting for vessel diameter. These associations remained significant after adjustment for sex and birth weight (Table 3), furthermore, these associations remained similar after adjustment for sex and fat mass.

Heart rate variability

Heart rate was similar between groups (Table 2). Measures of overall HRV both in the time (SDNN) and frequency domain (total power) were lower in late preterm infants, with total power being approximately 39% lower. The short-term time-domain measures SDΔNN and RMSSD were also lower in late preterm infants than in full-term infants. Frequency-domain measures showed no differences in LF power, but a 51% reduction in HF power in the late preterm group (Fig. 2b, Table 2). This was reflected in the LF:HF ratio, which was higher in late preterm infants. In multivariable regression analysis adjusting for sex and birth weight, gestational age was positively associated with overall HRV (SDNN and total power), HF power, mean NN, SDΔNN and RMSSD at birth, and inversely associated with the LF:HF ratio (Table 3), furthermore, these associations remained similar after adjustment for sex and fat mass.

Discussion

Adults who were born preterm are at higher risk of cardiovascular disease in adulthood, although it is unclear whether this includes those born late preterm, and whether any such association is independent of the fetal growth restriction that can contribute to preterm birth. Our findings indicate that infants born late preterm have reduced aortic IMT and poorer cardiac autonomic control, independent of birth weight. Indicating that autonomic control may be an early pathophysiologic marker of cardiovascular risk in individuals born late preterm.

There is some overlap in weight and size between infants born late preterm and those born term. Although this study did not confirm whether the late preterm infants were physiologically and metabolically immature, previous studies indicate infants born late preterm are physiologically and metabolically immature,[31] and maybe at an increased risk of developing medical conditions in the immediate postnatal life. A number of studies have shown previously that individuals born preterm (<35 weeks) and with impaired fetal growth have increased aortic IMT during infancy[32] and increased carotid IMT as children and adults.[11,33] We hypothesised that infants born late preterm (35–37 weeks) may also have increased aortic IMT during infancy. However, we found that aortic IMT was positively associated with gestational age at birth

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Table 1. Maternal and infant characteristics

	Full term	Late preterm	*P*-value (full term vs. late preterm)
Maternal characteristics	$n = 139$	$n = 35$	
Age, years	33 (4)	34 (5)	0.22
Pre-pregnancy BMI, kg/m^2	23 (4)	24 (6)	0.17
Pre-pregnancy weight, kg	63 (12)	65 (18)	0.37
Height, cm	165 (7)	164 (6)	0.21
Weight at first antenatal visit, kg	62 (11)	66 (17)	0.21
Gestational diabetes, *n* (%)	21 (15)	8 (30)	0.27
Preeclampsia, *n* (%)	6 (4)	1 (3)	0.70
Hypertension in pregnancy, *n* (%)	4 (3)	1 (3)	1.00
Histological Chorioamnionitis, *n* (%)	37 (36)	4 (13)	0.01
Maternal smoking, *n* (%)	4 (3)	3 (4)	0.27
Ethnicity, *n* (%)			
Asian	21 (15)	15 (44)	0.01
Caucasian	93 (68)	15 (44)	
Middle Eastern	4 (3)	1 (3)	
Hispanic	1 (1)	0 (0)	
South Asian	11 (8)	3 (9)	
Other	7 (5)	0 (0)	
Mode of birth, *n* (%)			
Vaginal	82 (59)	27 (77)	0.05
Instrumental vaginal	24 (17)	6 (17)	
Caesarean	33 (24)	2 (6)	
Labour			
Spontaneous	75 (54)	27 (77)	0.04
Induced	45 (32)	6 (17)	
No labour	19 (14)	2 (6)	
Infant characteristics			
NICU admissions, *n* (%)	8 (6)	3 (9)	0.56
Postnatal age, days	5 (5)	4 (3)	0.37
Gestational age, weeks	39.2 (1.0)	35.6 (0.4)	<0.001
Sex, female/male	75/64	18/17	0.79
Birth weight, g	3450 (470)	2801 (325)	<0.001
Apgar score at 1 min	8.6 (1.2)	8.8 (0.5)	0.10
Apgar score at 5 min	8.9 (0.4)	8.9 (0.4)	0.59
Length, cm	50 (2)	47 (2)	<0.001
Head circumference, cm	35 (1)	33 (1)	<0.001
Body fat, %	11 (5)	9 (3)	0.01

Data are presented as mean (SD) for continuous variables using independent student *t*-tests and No. (%) for categorical data, using chi-square tests between groups. Full-term group $n = 139$ except for maternal BMI $n = 127$, pre-pregnancy weight $n = 131$, maternal height $n = 128$, weight at antenatal visit $n = 134$, histological Chorioamnionitis $n = 102$. Late preterm group $n = 35$ except for maternal BMI $n = 34$, pre-pregnancy weight $n = 32$, maternal height $n = 34$, histological Chorioamnionitis $n = 30$.

and that these associations were independent of sex and birth weight. Within term infants in this same study, we found that impaired fetal growth is accompanied by increased aortic IMT.[20] For the current analysis, we selected birth weight percentile matched term control infants. Although the late preterm group weighed less, their weight was appropriate for dates and they did not show fetal growth restriction (birth weight range, 2162 – 3305 g). Together, our findings suggest that late preterm birth is not associated with increased aortic IMT in the absence of impaired fetal growth. This supports the finding in young adults

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Table 2. Aortic intima–media thickness and heart rate variability between full-term and late preterm infants

	Full term	Late preterm	*P*-value (full term vs. late preterm)
Aortic IMT	*n* = 124	*n* = 32	
Maximum IMT, μm	612 (73)	574 (51)	0.001
Mean IMT, μm	541 (57)	499 (6)	<0.001
Heart rate variability	*n* = 114	*n* = 26	
Frequency domain			
*Total power (ms^2)	1180. 6 (1114.3)	622.3 (606.5)	0.003
*LF (ms^2)	272.9 (279.7)	258.0 (187.1)	0.43
*HF (ms^2)	128.9 (174.0)	74.5 (93.3)	0.02
*LF: HF	2.2 (2.2)	3.5 (2.7)	0.04
Time domain			
HR (bpm)	127.5 (16.6)	132.9 (12.2)	0.12
Mean NN (ms)	477.6 (55.8)	455.0 (42.1)	0.06
SDNN (ms)	38.0 (12.1)	29.5 (10.4)	0.001
*SDΔNN (ms)	16.0 (13.1)	11.3 (7.5)	0.01
RMSSD (ms)	18.7 (10.2)	13.4 (6.)	0.01

Data are presented as mean (SD) or median (IQR). Log-transformed data are indicated by *. Independent *t*-test between groups.
LF, low frequency; HF, high frequency; LF: HF, low-frequency/high-frequency ratio; HR; heart rate, mean NN; mean of N wave to N wave variation normal; SDNN, the mean of the standard deviation of all normal RR intervals; SDΔNN, SD change in NN; RMSSD, square root of the mean squared differences of successive NN intervals.

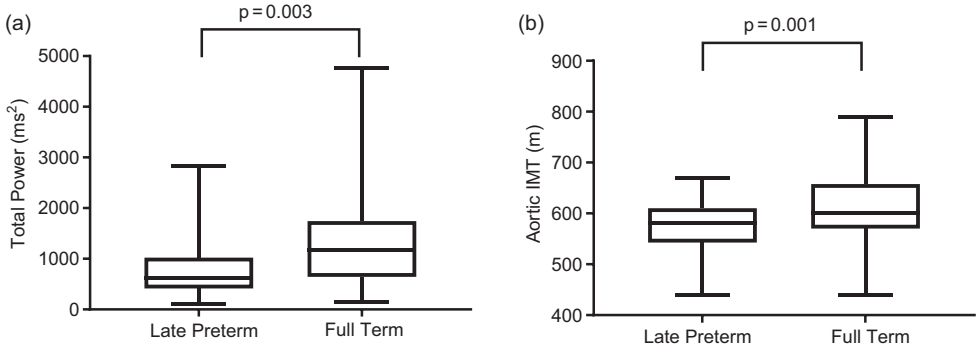

Fig. 2. Effects of late preterm versus full term on markers of cardiovascular risk. (a). Effects of late preterm versus full term on heart rate variability (total power). (b). Effects of late preterm versus full term on maximum aortic intima–media thickness (IMT). Late preterm (between 34 and 36 completed weeks' gestation); full term (between 37 and 42 weeks' gestation). Box, line and error bars are represented as 10th, 25th, 50th (median), 75th and 90th percentiles.

that in those born preterm, only those with concurrent fetal growth restriction have increased severity of subclinical atherosclerosis.[11]

Infants born late preterm had lower overall HRV (total power and SDNN) and lower parasympathetic modulation of the heart, indicated by reduced HF power, RMSSD, and SDΔNN, all markers of parasympathetic modulation of heart rate.[27,34] They also showed an increased low-frequency:high-frequency ratio, although as LF power was not different between groups, this is likely to be a denominator effect, reflecting the reduced HF component.[27] Our findings are consistent with two recent studies in late preterm infants (without overt growth restriction) that showed HRV parameters (RMSSD, HF and SDNN) taken in the first week of life are positively associated with gestational age at birth,[34,35] while the LF:HF ratio is negatively associated with gestational age at birth.[35] Other studies in infants and children born preterm (28–37 weeks' gestation) show reduced HRV, as well as reduced parasympathetic modulation to the heart.[15–19,36] Adults born preterm (34–36 weeks) also show altered autonomic regulation at rest and delayed heart rate recovery after exercise,[37,38] suggesting that these vicissitudes in parasympathetic control in people born late preterm perseverate into adult life and may predispose these individuals to increased cardiovascular risk.

Our data indicate that parasympathetic, but not sympathetic modulation is impaired in late preterm birth, consistent with the ontogenic pattern of autonomic maturation. The sympathetic nervous system develops rapidly during the first trimester, while the parasympathetic branch develops more prominently during the third trimester of pregnancy.[37] Studies show, total myelination of the vagus nerve increases linearly with postconceptional age, resulting in reduced myelination of vagal fibres in those born preterm as infants, which subsequently persists into adulthood.[37] The vagus nerve is the principal mediator of parasympathetic outflow to the heart and central to effecting rapid changes in heart rate responses to a variety of stimuli.[16] The reduced overall HRV and parasympathetic modulation to the heart in these late preterm infants may indicate an impaired ability to adapt to ongoing

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Table 3. Gestational age, aortic intima–media thickness and heart rate variability in infants

	β (95% CI)	*P*-value
	Aortic IMT	
	Maximum aortic IMT, μm	
Gestational age, per week	10 (2, 18)	0.01
	Mean aortic IMT, μm	
Gestational age, per week	9 (2, 15)	0.01
	HRV (frequency domain)	
	Ln total power	
Gestational age, per week	0.12 (0.03, 0.21)	0.01
	Ln LF	
Gestational age, per week	0.03 (−0.07, 0.13)	0.55
	Ln HF	
Gestational age, per week	0.18 (0.05, 0.30)	0.004
	Ln LF: HF	
Gestational age, per week	−0.15 (−0.24, −0.07)	<0.01
	HRV (time domain)	
	HR, bpm	
Gestational age, per week	−1.34 (−3.31, 0.64)	0.18
	Mean NN, ms	
Gestational age, per week	6.09 (−0.57, 12.7)	0.07
	SDNN, ms	
Gestational age, per week	2.20 (0.70, 3.70)	0.004
	Ln SDΔNN	
Gestational age, per week	0.12 (0.04, 0.17)	0.002
	RMSSD	
Gestational age, per week	2.06 (0.88, 3.24)	0.001

Results are unstandardised β-regression coefficients (95% CI) from multivariable models, adjusted for sex and birth weight. Aortic IMT, $n = 156$, HRV, $n = 140$
HF, high frequency; HRV, heart rate variability; LF, low frequency; LF: HF, low-frequency/high-frequency ratio; HR; heart rate, mean NN; IMT, intima–media thickness; mean of N wave to N wave variation normal; RMSSD, square root of the mean squared differences of successive NN interval; and SDNN, the mean of the standard deviation of all normal RR intervals; SDΔNN, SD change in NN

changes in the internal and external environment during the immediate postnatal life, as well as in later life if these autonomic changes are maintained long term.

Our findings suggest a 'two-hit' hypothesis, whereby preterm delivery and fetal growth restriction both contribute to cardiovascular risk, but potentially via distinct mechanisms, with preterm birth being associated with poor cardiac autonomic function and impaired fetal growth with both poor autonomic function and arterial wall thickening. The identified pathways may contribute to both the immediate and later health of individuals born preterm.

We acknowledge the limitations of this study. We were unable to obtain all cardiac autonomic measurements in all of our participants (although similar sample size to that of other work), mainly due to participant compliance, time restrictions prior to leaving the hospital and prioritising our primary outcome, aortic IMT. Future studies may wish to confirm these findings in larger cohorts. The cardiac autonomic changes seen in the late preterm infant may be precipitated by maternal and intrauterine exposures, although we did not seek to elucidate mechanistic pathways linking late prematurity with aortic atherosclerosis or cardiac autonomic control. Although cardiac autonomic measures were taken during sleep, some studies have shown differences in HRV due to sleep state (active vs. quiet sleep).[39] We did not confirm sleep state via polysomnography, which may contribute to increased variability.

Our sample size did not have sufficient statistical power to look at the interplay between ethnicity, preterm birth and types of growth restriction, and remains a topic of potential future research. Future studies should look to include information on paternal data and include infants requiring ongoing respiratory care, which may represent an additional and potentially informing group of patients.

Conclusions

Infants born late preterm are generally considered to be at low risk for immediate and long-term adverse health outcomes, and are clinically treated the same as infants born full term. We find that infants born late preterm present with evidence of autonomic dysfunction, but not subclinical atherosclerosis. Because altered autonomic control may confer an increased risk of raised blood pressure in later life, it may be prudent to consider patients born late preterm at increased risk of cardiovascular disease. Future studies may seek to develop preventative strategies that improve or directly target the identified pathophysiology.

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Conflicts of interest. None.

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

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