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Letter to the Editor

Blood pressure abnormalities in adults born moderately preterm and their children

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Metabolic abnormalities have been described in subjects born preterm (<37 weeks of gestation) [1,2], including higher blood pressure (BP) that was independent of intrauterine growth restriction [3]. However, very few studies on those born preterm have used 24-hour ambulatory BP monitoring. Further, there is growing evidence from animal and human studies that phenotypic changes resulting from environmental insults can be transmitted to subsequent generations, but to date the impact of parent's preterm birth on their children's BP has not been reported. Thus, we hypothesized that adults born moderately preterm would have higher BP than those born at term. In addition, we hypothesized that their offspring would also display BP abnormalities compared to the offspring of parents born at term.

Ethics approval was obtained from the Multiregion Ethics Committee (Ministry of Health, New Zealand). Written informed consent was obtained from adult participants and verbal assent from their children. Adult participants (F_1) were the offspring of mothers (F_0) from the Auckland Steroid Trial initially recruited in 1969–1974 [4]. At the 30-year follow-up, we recruited all singleton adults (F_1) who had singleton prepubertal children (F_2) born at term (37–41 weeks of gestation) [1].

Body composition was assessed using whole-body dual-energy X-ray absorptiometry (Lunar ProdigyTM, GE Medical Systems, Wisconsin, USA). 24-hour ambulatory BP monitoring was carried out using an oscillometric device (SpaceLabs Monitor 90207; SpaceLabs Medical Inc., Redmond, USA), with BP measured every 30 min during the day and every 45 min at night over 24 h. Readings taken at 08:00–20:00 were classified as daytime BP and those at 24:00–06:00 as nocturnal BP. Participants with insufficient readings (<14 daytime and <7 nighttime systolic and diastolic recordings for adults, and <20 for children) were excluded.

General linear regression models and random effect mixed models were used to assess differences between groups. Important confounding factors were adjusted for, including ethnicity, F_0 steroid exposure, and sex. For children, models also included height as a covariate and family code as a random factor.

A total of 36 adult participants (22 preterm) had sufficient BP readings (Table 1). Adults born preterm had 24-hour mean BP 4.3 mm Hg higher than those born at term ($p = 0.028$; Table 1). Differences in diastolic BP were particularly marked, with adults born preterm having higher diastolic BP in daytime (+5.6 mm Hg; $p = 0.021$) and nighttime (+5.2 mm Hg; $p = 0.042$) (Table 1). Notably, the addition of total body fat percentage into the multivariate models had little effect on differences between groups (data not shown).

Blood pressure load (percentage of ambulatory BP measurements above recommended thresholds [10]) was greater in preterm adults. Mean 24-hour BP loads were greater among adults born preterm than those born at term, for both systolic (16 ± 4% vs 8 ± 5%; $p = 0.036$) and diastolic (26 ± 5% vs 11 ± 6%; $p = 0.002$) BP. Daytime diastolic BP load was also greater in adults born preterm (26 ± 6% vs 12 ± 7%; $p = 0.008$), with a similar trend observed for daytime systolic BP load (12 ± 3% vs 7 ± 5%; $p = 0.073$). There were no significant differences in nocturnal BP load (data not shown).

Data were available from 37 children (26 of parents born preterm) (Table 2). Children of parents born preterm had higher mean 24-hour heart rate (+7.7 bpm; $p = 0.038$) and tended to have higher daytime diastolic BP (+3.8 mm Hg; $p = 0.051$) than the children of parents born at term (Table 2). However, there were no differences between groups in nocturnal or mean 24-hour BP (Table 2).

Adults born preterm had higher BP (particularly diastolic BP) than adults born at term, and more frequently exceeded the thresholds for

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[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Table 1
Parameters from 24-hour ambulatory blood pressure monitoring of adults born preterm or at term. Body composition and blood pressure data are means and 95% confidence intervals adjusted for other confounding factors (including sex) in the multivariate models; other data are means ± SD, where appropriate. Daytime measurements were taken at 08:00–20:00, and nocturnal measurements at 24:00–06:00). BMI, body mass index.

	Adults born preterm	Adults born at term	p-Value
n	22	14	
Demographics			
Age (years)	35.8 ± 1.2	35.6 ± 1.1	0.59
Sex ratio (males)	45%	29%	0.48
Ethnicity (New Zealand European)	64%	62%	0.99
Body composition			
BMI (kg/m^2)	28.6 (26.7–30.5)	26.2 (23.6–28.7)	0.14
Total body fat (%)	35.1 (31.9–38.4)	28.2 (23.9–32.4)	0.01
24-hour blood pressure monitoring			
Number of readings	35.4 ± 9.4	35.3 ± 9.9	0.97
Daytime systolic (mm Hg)	122.8 (117.9–127.8)	118.4 (111.7–125.1)	0.14
Daytime diastolic (mm Hg)	77.0 (72.8–81.5)	71.4 (66.0–77.1)	0.02
Nocturnal systolic (mm Hg)	106.5 (101.4–111.6)	104.9 (98.5–111.3)	0.65
Nocturnal diastolic (mm Hg)	62.4 (58.7–66.3)	57.2 (53.0–61.8)	0.04
Systolic nocturnal dip (%)	13.3 (8.0–18.6)	10.9 (3.3–18.5)	0.43
Diastolic nocturnal dip (%)	18.4 (12.8–24.1)	19.2 (11.2–27.3)	0.86
Mean 24-hour arterial pressure (mm Hg)	87.4 (84.1–90.8)	83.1 (79.3–87.0)	0.03
Mean 24-hour heart rate (bpm)	71.0 (66.3–75.8)	69.0 (63.3–74.7)	0.33

hypertension over the 24-hour assessment period. Importantly, observed differences in BP between groups were independent of adiposity. Further, the prepubertal children born at term to parents born preterm also displayed cardiovascular abnormalities, namely higher mean heart rate and daytime diastolic BP.

The BP parameters of our moderately preterm cohort were similar to those of the Australian and Swedish preterm cohorts [5,6], despite those cohorts being younger and born very preterm. However, the proportion of our preterm cohort displaying BP abnormalities over the 24-hour monitoring was much higher than the Australian cohort and probably related to their older age [5,6].

BP load is considered more predictive of end-organ injury than mean arterial pressure, which provides no information on the blood pressure variability [7]. In fact, it has been proposed that BP load should be included as a criterion along with the mean BP to define the severity of hypertension [8]. Therefore, although the mean arterial pressure profile of our preterm cohort was not in the hypertensive range, the associated abnormalities in BP load suggest a higher risk of later hypertension.

To our knowledge this is the first study reporting ambulatory BP monitoring in the children of parents born preterm. Although we observed higher mean heart rate and daytime diastolic BP in these children, the significance of these isolated findings is unclear. We have reported that these children of parents born preterm have increased abdominal adiposity [2], and obesity is strongly associated with hypertension in children [9]. Thus, long-term follow-up of these children is warranted to determine the extent to which these early findings predict later cardiovascular health risk.

Although the mechanisms underpinning the changes observed in adults born preterm and their children are unclear, subjects born preterm have multiple risk factors for hypertension. These include impaired fetal growth, increased postnatal stress, central arterial line cannulation, and suboptimal postnatal nutrition. In addition, whether as a primary or secondary event, insulin resistance is a well-recognized risk factor for hypertension, and our preterm cohort had a 40% reduction in insulin sensitivity compared to term subjects [1].

In summary, adults born preterm had higher BP and greater BP load than those born at term, suggesting a pre-hypertensive state. As these adults have already been reported to have reduced insulin sensitivity [1] and increased adiposity [2], institution of preventive strategies such as lifestyle modifications in those born preterm would potentially have a positive impact on their later health. Further, children born at term of parents born preterm also have subtle abnormalities in their cardiovascular profiles that warrant ongoing follow-up.

Table 2
Parameters from 24-hour ambulatory blood pressure monitoring among the offspring of parents born preterm or at term. Body composition and blood pressure data are means and 95% confidence intervals adjusted for confounding factors (including sex) in the multivariate models; other data are means ± standard deviation, where appropriate. Daytime measurements were taken between 08:00–20:00, and nocturnal ones at 24:00–06:00). BMI SDS, body mass index standard deviation scores.

	Children of parents born preterm	Children of parents born at term	p-Value
n	26	11	
Demographics			
Age (years)	8.0 ± 1.4	8.8 ± 1.6	0.11
Sex ratio (males)	36%	45%	0.72
Ethnicity (New Zealand European)	40%	45%	0.99
Body composition			
BMI SDS	0.48 (0.00–0.96)	0.75 (0.04–1.45)	0.51
Total body fat (%)	19.1 (16.0–22.7)	16.8 (12.6–22.4)	0.44
24-hour blood pressure monitoring			
Number of readings	32.2 ± 6.9	35.2 ± 9.5	0.28
Daytime systolic (mm Hg)	112.0 (108.7–115.3)	111.7 (106.7–116.7)	0.91
Daytime diastolic (mm Hg)	72.5 (70.4–74.6)	68.7 (65.4–72.0)	0.05
Nocturnal systolic (mm Hg)	99.9 (97.0–102.7)	102.1 (97.6–106.6)	0.39
Nocturnal diastolic (mm Hg)	59.6 (56.8–62.5)	57.5 (53.1–61.9)	0.40
24-hour mean arterial pressure (mm Hg)	80.0 (77.7–82.4)	77.3 (73.6–81.0)	0.21
24-hour mean heart rate (bpm)	85.2 (81.1–89.4)	77.5 (71.2–83.7)	0.04

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Conflict of interest

The authors have no financial or non-financial conflicts of interest to disclose that may be relevant to this work. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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References

[1] S. Mathai, W.S. Cutfield, J.G.B. Derraik, S.R. Dalziel, J.E. Harding, et al., Insulin sensitivity and β-cell function in adults born preterm and their children, Diabetes 61 (2012) 2479–2483.
[2] S. Mathai, J.G.B. Derraik, W.S. Cutfield, S.R. Dalziel, J.E. Harding, et al., Increased adiposity in adults born preterm and their children, PLoS One 8 (2013) e81840.
[3] S.R. Dalziel, V. Parag, A. Rodgers, J.E. Harding, Cardiovascular risk factors at age 30 following pre-term birth, Int. J. Epidemiol. 36 (2007) 907–915.
[4] G.C. Liggins, R.N. Howie, A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants, Pediatrics 50 (1972) 515–525.
[5] A. Kistner, G. Celsi, M. Vanpee, S.H. Jacobson, Increased blood pressure but normal renal function in adult women born preterm, Pediatr. Nephrol. 15 (2000) 215–220.
[6] L.W. Doyle, B. Faber, C. Callanan, R. Morley, Blood pressure in late adolescence and very low birth weight, Pediatrics 111 (2003) 252–257.
[7] W.B. White, H.M. Dey, P. Schulman, Assessment of the daily blood pressure load as a determinant of cardiac function in patients with mild-to-moderate hypertension, Am. Heart J. 118 (1989) 782–795.
[8] E. Lurbe, J.M. Sorof, S.R. Daniels, Clinical and research aspects of ambulatory blood pressure monitoring in children, J. Pediatr. 144 (2004) 7–16.
[9] D.S. Freedman, W.H. Dietz, S.R. Srinivasan, G.S. Berenson, The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study, Pediatrics 103 (1999) 1175–1182.
[10] G. Mancia, G. De Backer, A. Dominiczak, R. Cifkova, R. Fagard, et al., 2007 Guidelines for the Management Of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC), Eur. Heart J. 28 (2007) 1462–1536.