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Preterm birth is associated with an intergenerational effect on cardio-metabolic risk

Clustering of cardiovascular and metabolic risk factors has been proposed as an appropriate method to assess cardio-metabolic profile in both children and adults, providing a more accurate measure than individual risk components.[1] The clustering of cardio-metabolic risk appears to track from childhood to adulthood, with a stronger association observed for composite than for individual risk parameters.[2]

We have previously shown that preterm birth has possible intergenerational effects, with the term-born children of preterm parents displaying increased abdominal adiposity and higher daytime diastolic blood pressure in comparison with the offspring of term parents.[3,4] Here, we assess the clustered cardio-metabolic risk in this cohort in relation to appropriate normative data, to examine the intergenerational effect of preterm birth.

Adults (F1) born of mothers (F0) from the Auckland Steroid trial were recruited to investigate the long-term effects of preterm birth.[3,5] We studied the children (F2) of all singleton F1 adults living in the Auckland region. Recruited children were born at term (37–41 weeks of gestation) from singleton pregnancies. Exclusion criteria were any clinical signs of puberty or adrenarche, or having a first-degree relative with diabetes/metabolic syndrome.

Body composition was assessed using whole-body dual-energy X-ray absorptiometry scans (Lunar Prodigy™, GE Medical Systems, Wisconsin, USA).[3] Insulin sensitivity was assessed using a modified frequently-sampled intravenous glucose tolerance test and Bergman's minimal model software.[5] Fasting blood samples were used to measure lipid profile. Blood pressure was measured by the same researcher using a standard mercury sphygmomanometer with an appropriately sized cuff on the nondominant arm, while seated and after a 5-min rest. Physical activity levels and nutritional intake were estimated, and laboratory assays performed as previously described.[3]

A clustered cardio-metabolic risk Z score was constructed by the sum of four separate Z scores: insulin sensitivity, total cholesterol to HDL-C ratio, systolic blood pressure and total body fat percentage. These parameters are of significance for long-term cardio-metabolic health and were all individually similar between the children of preterm and term parents.[3–5] Each individual sex-specific Z score was calculated as

$$Z = (x - \text{mean})/\text{standard deviation}$$

Z scores for insulin sensitivity were obtained based on mean and SD of our cohort, as there are no normative data. Z scores for other parameters were calculated based on respective paediatric normative data.[6–8.]

Cardio-metabolic Z scores were compared using linear mixed regression models. Important confounders were adjusted for (sex, ethnicity, parental steroid exposure, age and birth order), and family code was included as a random factor to account for sibling clusters.

We analysed data on a subset of participants from the original cohort with complete data who were matched for ethnicity. Consequently, we studied a total of 35 children (60% boys) aged 8·2 ± 1·5 years (range 5·5–10·7 years), including four sibling pairs.

Children of parents born preterm and at term were of similar age, birthweight, and sex ratio, had similar physical activity levels and caloric intake and had parents of similar BMI (data not shown). However, children of preterm parents were born approximately 0·5 weeks earlier ($P = 0{\cdot}042$). We have previously reported that children of parents born preterm had increased abdominal adiposity[3] and higher daytime diastolic blood pressure,[4] but displayed similar lipid profile[3] and glucose homoeostasis.[5]

Here, we show that children of preterm parents were at increased cardio-metabolic risk, displaying higher clustered Z scores compared to the offspring of term parents (1·35 *vs* 0·09; $P = 0{\cdot}047$) (Fig. 1a). Interestingly, children of mothers born preterm ($n = 9$) had significantly higher clustered cardio-metabolic Z scores than children of term parents ($n = 18$) (1·70 *vs* 0·17; $P = 0{\cdot}046$), with Z scores for the offspring of preterm fathers ($n = 8$) being intermediate between the two groups (0·85) and not statistically different from either (Fig. 1b). Note that there were no differences in birthweight, age, sex ratio, physical activity levels or caloric intake among the groups (data not shown).

This study provides further evidence that the impact of preterm birth appears to extend to the subsequent generation,[3,4] with increased cardio-metabolic risk in the term-born offspring of preterm parents. Notably, the data suggest that the adverse effects are particularly marked in the children of mothers born preterm. In addition, as previously shown for alterations in fat distribution,[3] the cardio-metabolic effects remained even after parental adiposity (mean parental BMI) was accounted for.

Our findings are additional evidence of intergenerational effects, corroborating previous data in humans and animal models. To the best of our knowledge, no previous study has addressed the intergenerational effect of preterm birth on cardio-metabolic risk. We applied a clustered risk score in line with recent evidence showing the usefulness and efficiency of this method in the estimation of individual cardio-metabolic risk.[1,2] Of note, the proposed score has been constructed by selecting specific risk components, all of which are recognized as reliable predictors of cardio-metabolic outcomes in children and adults.

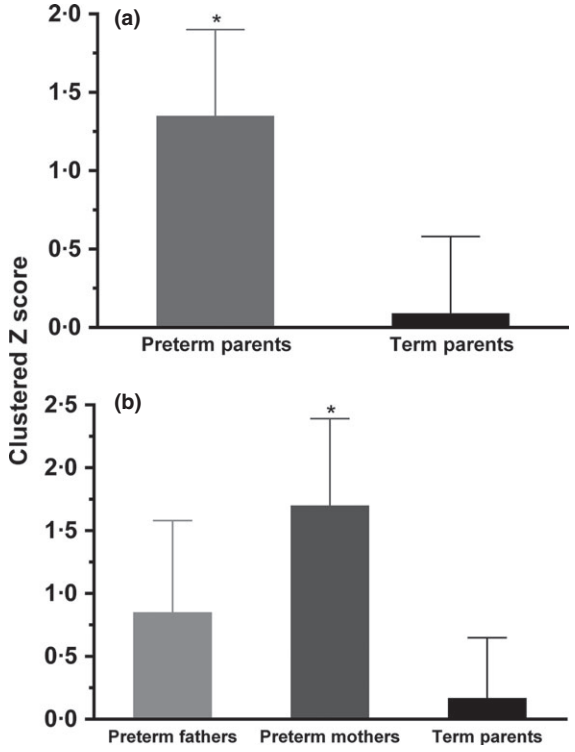

Fig. 1 (a) Clustered cardio-metabolic risk Z scores for children born of preterm parents (grey bars; $n = 17$) or of term parents (black bars; $n = 18$). (b) Clustered cardio-metabolic risk Z scores for children born of preterm fathers ($n = 8$), preterm mothers ($n = 9$) or term parents ($n = 18$). Data are means and standard errors, adjusted for confounders in the multivariate models (i.e. sex, ethnicity, parental steroid exposure, age and birth order). $^*P < 0{\cdot}05$ for comparison with children of term parents.

However, the underpinning mechanisms for these observed effects are still unclear. It has been postulated that adverse conditions *in utero* and early in life can interfere with developmental processes, which may induce epigenetic changes in those born preterm. These changes in gene expression could possibly be involved in the adverse health outcomes observed in preterm children and adults. As epigenetic changes can be inherited, these may modulate unfavourable health effects associated with early life events. Thus, we speculate that epigenetic mechanisms may link preterm birth and an adverse phenotype in the next generation.

Interestingly, children of preterm mothers displayed more marked effects than those of preterm fathers, suggesting a differential contribution of maternal and paternal prematurity on the cardio-metabolic profile of their offspring. The stronger effects of maternal preterm birth may be due to an interaction between heritable maternal factors and environmental influences *in utero*.

With over 10% of all babies worldwide being born less than 37 weeks of gestation, our findings are of relevance. As cardio-metabolic risk tracks from childhood to adulthood, our data suggest long-term implications of preterm birth also for the subsequent generations. Therefore, future studies need to clarify whether the increased cardio-metabolic risk observed in the offspring of preterm parents persists into adulthood.

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