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Direct and BMI-mediated effect of birthweight on childhood cardio-metabolic health – a birth cohort study

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Abstract

Background: Different directions of the association of birthweight with cardio-metabolic health have been found, especially in children, which may be explained by the mediating effect of attained adiposity. We aimed to untangle direct and BMI-mediated associations of birthweight with childhood cardio-metabolic indicators.

Methods: Children from Generation XXI birth cohort were included (n=4881). Birthweight was abstracted from clinical files. At age 4 and 7, children were re-evaluated. Glucose, triglycerides, LDL-cholesterol, systolic (SBP) and diastolic blood pressure (DBP) z-scores were the cardio-metabolic traits analyzed. Regression coefficients and respective 95% confidence intervals [β (95%CI)] were computed using path analysis.

Results: Birthweight had inverse total effect on SBP at age 4 [-0.005 (-0.010; -0.001)] and 7 [-0.011 (-0.017; -0.006)] and DBP at 7 [-0.008 (-0.012; -0.004)]. Direct effects were found for SBP at 4 [-0.013 (-0.018; -0.009)] and 7 [-0.014 (-0.019; -0.009)], and DBP at 7 [-0.010 (-0.015; -0.006)], explaining the inverse total effects. Positive BMI-mediated indirect effects were found for all cardio-metabolic traits: higher birthweight was associated with higher childhood BMI, which in turn was associated with higher levels of cardio-metabolic traits.

Conclusions: Positive BMI-mediated effect of birthweight on all cardio-metabolic traits was found. However, direct effects were in the opposite direction, significant for blood pressure, which may explain the diversity of results observed in the literature. Combining the direct and BMI-mediated effects, higher birthweight was associated with lower blood pressure at age 7 and have no effect on other cardio-metabolic traits.

Key words: birthweight; BMI; cardio-metabolic factors; metabolic syndrome.

Introduction

High blood pressure (BP), obesity, impaired glucose levels, and dyslipidaemia are cardio-metabolic indicators that have been found to co-occur in adults and children and to be associated with metabolic and cardiovascular diseases in adults (1, 2). Evidence shows that events occurring during early development, such as nutrition during intrauterine life, may affect the future levels of adiposity and of those cardio-metabolic traits. The association of lower birthweight with worse cardio-metabolic health, firstly described by Barker et al. (3), has been verified in other studies (4-7); though, an association of higher birthweight with worse cardio-metabolic health has also been found, especially in childhood (8, 9).

These effects of intrauterine growth on later health could be mainly dependent on two phenomena: programming and tracking. According to programming, exposures to adverse events, when occurring during critical periods early in life, for instance during intrauterine life, can lead to long lasting modifications in several organs, having impact on later health (5, 10, 11). Tracking refers to the stabilization of a characteristic throughout a person's life (12). So, for example, a higher birthweight child tend to track and have higher weight and adiposity throughout life, which represents higher cardio-metabolic risk than a lower birthweight child that remains with lower weight and adiposity; but, on the other hand, due to programming, it is possible that this higher birth weight child is better adapted to nutritional abundance than the lower birthweight child, which would lower his cardio-metabolic risk when comparing to the lower birthweight child in the same context. Consequently, the mediating role of attained weight/adiposity must be explored.

Our aim was to untangle the direct and body mass index (BMI)-mediated association of birthweight with cardio-metabolic risk during childhood (figure 1).

Subjects and Methods

The study participants are children included in the Generation XXI birth cohort (13) that was assembled between April 2005 and August 2006, at the five public units providing obstetrical and neonatal care to the inhabitants of Porto, Portugal. Follow-up assessments were conducted at 4 years of age, during April 2009 and July 2011, and at 7 years of age, during April 2012 and March 2014.

Initially, the cohort had 8647 members, of which 7459 (86%) and 6889 (80%) were evaluated at the 4 and 7 year' follow-up assessment, respectively. Since the outcomes analysed in this study demand that the child had performed the physical examination (BP and BMI) and the blood sample collection (glucose, triglycerides (TG), and low density lipoprotein cholesterol (LDL-C)), only data regarding participants that were evaluated in person in our department at both follow-ups were used and only singletons were included due to non-independence of observations and different intrauterine growth of multiples. At 4 years follow-up evaluation, only a sub-sample of children collected blood sample (only children that had collected blood from the umbilical cord were eligible), so our sample size for the analysis of glucose, TG, and LDL-C was lower than for the analysis of BP (1031 vs. 4877). More detailed information on the selection criteria are depicted in the supplementary figure, and differences between those included (n=4877 and n=1031) and those not included (n=3470), regarding maternal, pregnancy, delivery and newborn characteristics are presented in the supplementary table 1. Included mothers had higher education and age, lower proportion of smoking during the 3rd trimester of pregnancy and higher proportion of caesarean delivery.

At baseline, a face-to-face interview was conducted by trained interviewers, during the hospital stay, 24 to 72 hours after delivery. During this interview, data on socio-

demographic characteristics, family and personal history of disease, maternal anthropometric parameters before pregnancy, and intra-uterine exposures were gathered. The same interviewers abstracted information regarding the delivery and newborn characteristics (including birthweight), from the clinical files.

At the 4 and 7 year follow-up evaluation, anthropometric and BP measurements were performed by trained researchers and a fasting blood sample was obtained, according to standard procedures. A stadiometer was used to measure height to the nearest 0.1cm, and weight was measured with a digital scale to the nearest 0.1kg, during which children were barefooted and in underwear. Then, BMI was determined as BMI=weight (kg) / height ^{2} (m). After a 10-minute rest, systolic (SBP) and diastolic (DBP) blood pressure were measured two times, 5 minutes apart. The mean of the two measurements was considered when the difference between them was lower than 5 mmHg for SBP and DBP; otherwise, a third measurement was performed and the mean of the 2 closest values was considered. Children collected a venous blood sample, before 11 a.m. and after an overnight fast, after applying a topical analgesic cream (EMLA cream). Samples were centrifuged at 3500 rpm for 10 minutes and then stored at -80ºC. UV enzymatic assay (hexokinase method) was used to measure glucose and enzymatic colorimetric assay was used to measure TG, and total and high density lipoprotein-cholesterol (for posterior estimation of LDL-C through the Friedewald equation) (14). The cardio-metabolic indicators considered were: glucose, TG, LDL-C, SBP and DBP. For glucose, TG and LDL-C, age- and sex-specific z-scores were established based on age- and sex-specific means and standard deviations (SD) derived from the whole Generation XXI cohort. Age-, sex- and height-specific z-scores were calculated for SBP and DBP, following the recommendations of the American Academy of Pediatrics (15).

For BMI, age- and sex-specific z-scores were established according to the World Health Organization (16).

The Ethics Committee of University of Porto Medical School/ S. João Hospital approved the study protocol. The study complies with the Ethical Principles expressed in the Helsinki Declaration. Only children providing oral assent and whose legal guardians provided written informed consent were considered participants.

Statistical analysis

The chi-square test was used to compare proportions, and student's t-test or ANOVA to compare means. Pearson correlations between birthweight, BMI and cardio-metabolic traits z-scores were also estimated. These analysis were performed using SPSS version 21.0.

Path analysis was used to estimate the linear regression coefficients (β) and 95% confidence intervals (95% CI), which represent the increase in the z-scores of the outcomes per each 100g increase in birthweight. Path analysis was conducted according to current knowledge, based on the theoretical model depicted in figure 1. The existence of quadratic associations was tested for all the outcomes and none was present. The presence of multicollinearity was assessed by calculating the Variance Inflation Factor (VIF), which was lower than 5, indicating no multicollinearity (17).

Several confounders were tested, namely, maternal age, education, pre-pregnancy BMI, and parity, diabetes and hypertension during pregnancy, pre-elampsia/eclampsia, tobacco smoke during 3rd pregnancy trimester, gestational weight gain, gestational age, and mode of delivery. On a first stage, confounders were selected based on the literature, on their crude association with birthweight and at least one of the cardio-metabolic traits, and on the change of the adjusted association for more than 10%. Maternal pre-pregnancy BMI, tobacco smoke in the 3rd trimester of pregnancy, and

hypertension during pregnancy fulfill the three criteria. On a second stage, for these three variables, we estimated the modification indices, which showed the need to adjust for maternal pre-pregnancy BMI and tobacco smoke in the 3rd trimester of pregnancy. Path analysis was performed with R software, using lavaan package (18). Considering that we wanted to estimate the 95% CI for the direct and indirect effects, bootstrapping was used.

The Comparative Fit Index (CFI) (19), the Tucker–Lewis Index (TLI) (20), and the Root Mean Square Error of Approximation (RMSEA) were used to assess the general fit of the models (21). A CFI and TLI equal or higher than 0.90 (22) and a RMSEA lower than 0.05 indicate a good model fit (23).

Results

Mean birthweight of the study sample was 3191g (SD 487g) and the mean and standard deviation (or median and interquartile range for TG due to non-normal distribution) of BMI, LDL-C, glucose, TG, SBP and DBP at 4 and 7 years of age are shown in Table 1. All mean (or median) values increased with age, with the exception of TG and LDL-C. The correlations of birthweight, BMI and the z-scores of the cardio-metabolic traits at 4 and 7 years of age can be observed in Table 2. Positive correlations were found between birthweight and BMI at ages 4 and 7, and DBP at age 4 and negative correlations with SBP at ages 4 and 7 and DBP at age 7. No correlation was found between birthweight and glucose, LDL-C and TG. Positive correlations were found between BMI and cardio-metabolic traits z-scores. Several correlations were found between cardio-metabolic traits with each other and also the same cardio-metabolic trait at 4 and 7 years of age. Additionally, the distribution of relevant characteristics by birth weight category are shown in the supplementary table 2, where we can observe significant differences regarding BMI, SBP and DBP, in the same direction as those in Table 2.

The total, direct and indirect (BMI-mediated) effect of birthweight on cardio-metabolic indicators at 4 and 7 years of age are presented in Table 3 and each of the path of the associations are represented in Figure 2. Although the magnitude of the total effects was small, higher birthweight was associated with lower SBP [-0.005 (-0.010; -0.001)] at age 4 and lower SBP [-0.011 (-0.017; -0.006)] and DBP [-0.008 (-0.012; -0.004)] at age 7 (Table 3). These total negative associations of birthweight with SBP at both ages and with DBP at age 7 were explained by the direct effects which were also negative, while the indirect effects were in opposite direction (higher birthweight was associated with higher BMI and higher BMI with higher SBP and DBP levels) (Table 3 and Figure 2). Regarding glucose, TG, and LDL-C at both ages, and DBP at age 4, although no total

effect of birthweight was found (Table 3), an indirect effect was observed - higher birthweight led to higher BMI and higher BMI led to higher glucose, TG, LDL-C and DBP (Table 3 and Figure 2).

In Figure 2, observing the paths between ages 4 and 7, it can be noticed the high tracking effect of BMI and of cardio-metabolic indicators between those ages. Focusing on the particular path that goes from BMI at age 4 to cardio-metabolic indicators at age 7, it is significantly negative for glucose, SBP and DBP. Due to the adjustment for BMI at age 7, this path is in fact representing the hypothetical variation in BMI from ages 4 to 7, i.e. for a given fixed BMI at age 7, a higher BMI at age 4 would represent a higher decrease in BMI between ages 4 and 7.

Discussion

In the present study, it was evaluated the total effect of birthweight on glucose, TG, LDL-C and BP at 4 and 7 years of age and untangled the direct and BMI-mediated effects. It was found that birthweight had an inverse total effect on SBP at ages 4 and 7 and DBP at age 7 - explained by an inverse direct effect. Although no total effect was present for the other cardio-metabolic traits, indirect effects mediated by BMI were present: higher birthweight led to higher childhood BMI, which in turn led to higher cardio-metabolic traits levels.

Harmful levels of cardio-metabolic indicators, such as overweight, impaired glucose metabolism, and high levels of blood lipids and BP, have been a growing problem among children (2, 8). Additionally, the metabolic syndrome, which represents the co-presence of impaired levels of these cardio-metabolic indicators, has already a prevalence of around 3% and a tendency to raise (2, 24). There is a vast literature concerning the association of birthweight with the risk of metabolic syndrome and its individual factors later in life, but the results are not consistent. The first to describe an effect of birthweight on cardio-metabolic health was Barker et al. in 1993, who concluded that low birthweight was associated with a higher risk of developing metabolic syndrome in adulthood (3). In contrast, being overly large at birth has also been associated with higher cardio-metabolic risk, especially in children (8, 9). The opposite directions of the direct and indirect (BMI-mediated) paths of the association between birthweight and cardio-metabolic risk found in the present study may be an explanation to the variety of the results obtained in previous studies, as there are studies that did not consider the attained weight, while others considered different indicators of weight, body size or adiposity. Since intrauterine growth is associated with postnatal growth which is turn is also associated with cardio-metabolic risk, the attained weight

should be considered when exploring the association between birthweight and cardio-metabolic risk (4, 7, 25-27). Additionally, the association of birthweight with later adiposity and cardio-metabolic risk depends on the weight trajectory since birth. So, it is possible that the associations of birthweight with later adiposity and cardio-metabolic risk would differ across the life course, explaining the different results found in adults and children (26).

A positive association between birthweight and childhood BMI was found, which is consistent with most of the recent literature showing positive associations of birthweight and BMI (26-32) and other adiposity parameters (29, 31, 32). Also, BMI at 4 was highly associated with BMI at 7. These results suggest that the tracking effect is strong in respect to weight since birth, and consequently higher birthweight is an adverse event regarding adiposity in childhood, which *per se* could lead to higher cardio-metabolic risk. The direct effect of birthweight on BMI at age 7 is null because a higher weight at birth causes higher weight at 4 and consequently higher weight at 7. This tracking effect on weight is stronger than a possible direct effect of birthweight on BMI at age 7 and so, the relationship between birthweight and BMI at 7, when adjusted for BMI at 4, showing the direct effect, is null.

In regards to BP, many studies in childhood have seen inverse associations with birthweight (33), which also occurred in the present study. Despite the positive effect via BMI (higher birthweight was associated with higher BMI and higher BMI with higher BP levels), the negative direct effect of birthweight on BP seems to be stronger for SBP at both ages and for DBP at 7 years of age. For DBP at 4 years of age, there was no total nor direct effect of birthweight, but only a positive BMI-mediated effect. Comparing the effect of birthweight on BP at 4 and then at 7 years of age, it seems that this effect depends on age of assessment and both for SBP and DBP the inverse

association became stronger at 7, which is in accordance to the literature. A recent systematic review found that with increasing age the association between high birthweight and BP changed from positive to negative, which explained the majority of the variance between studies (34). Another systematic review had previously found that there was a negative association between birthweight and BP, but it was attenuated in the pre-adolescence period when comparing to the adolescence period (33).

Regarding fasting lipids and glucose, studies point to an adverse profile in people who were born with lower birthweight (35-37). In the Helsinki Birth Cohort, lower birthweight was associated with higher odds of taking lipid-lowering medication, with higher TG levels and higher non high density lipoprotein cholesterol in adulthood (36). When we consider the few studies evaluating fasting glucose levels in children, the results are not consistent (37) and some report positive (38), negative (39, 40) and null associations (41). In the present study, no total associations between birthweight and fasting glucose, TG or LDL-C were found, but indirect effects were present, meaning that higher birthweight was associated with higher BMI and higher BMI with higher glucose, TG and LDL-C levels.

From the results of the present study, it can also be inferred that a hypothetical decrease in childhood BMI would be associated with better BP and glucose levels. When the association between BMI at age 4 and cardio-metabolic indicators at age 7 was adjusted for BMI at age 7 (artificially fixing a mean value of BMI at 7), the path that goes from BMI at age 4 to cardio-metabolic traits indicators at age 7 is indicative of the variation in BMI from ages 4 to 7, thus the significant negative association for BP and glucose levels means that a decrease in BMI between age 4 and 7 would be associated with lower BP and glucose levels.

The biological mechanisms by which growth during critical time windows could influence cardio-metabolic risk continue to be unclear. The Developmental Origins of Health and Disease (DOHaD) theory hypothesizes that under- or over- nutrition or other adverse events that occur in certain time windows during early life may lead to long lasting modifications in the organs, which influences cardio-metabolic health (5, 11, 42). Yet, the precise timing of such critical time windows is still a matter of discussion. As, in the present study, it was found both direct and BMI-mediated associations of birthweight and later cardio-metabolic risk, it adds evidence to the importance of intrauterine growth and also post-natal growth.

Strengths and limitations

A population based sample is used in the study. Given that a high proportion of children were not included because of loss to follow-up or because they were not evaluated in person in our department, selection bias may have occurred. Nevertheless, there was few differences between those included in our analyses and those excluded and we do not expect great influence in the estimated associations as previously shown (43).

The lack of statistical power could be the reason for the lack of a direct association between BW and glucose, TG, and LDL-C. Yet, the regression coefficients were very close to the null and the CIs were narrow, which suggests an adequate power to achieve precise estimates. Measurement error could also be present, especially regarding the measurement of the outcomes, which would attenuate the estimates and induce type II errors. However, since we were able to detect associations, we did not expect type II to have occurred.

Nevertheless, as impaired values of cardio-metabolic traits are unusual at these ages (44), possibly the long-term effects of birthweight on cardio-metabolic risk are not yet

completely clear, especially regarding glucose, TG, and LDL-C, and future studies conducted as the population ages may be of interest.

It is also important to mention that residual confounding may be present and other paths not considered in the present study may exist, which would cause the estimates for the direct effects to be biased. Consequently, the causality of the observed associations remains unknown.

Path analysis permits a concurrent estimation of the inter-relations between variables, being considered an extension of regression analysis, yet more advantageous than the traditional approach. It is used to decompose and compare the magnitudes of effects between variables with complex inter-relations or to test mediation effects (45). Yet, beyond the usual assumptions for the traditional approach, to obtain valid inference in mediation analysis of the direct and indirect effects we needed to verify the presence of: a) mediator-outcome confounding; b) exposure-mediator interaction; and c) mediator-outcome confounding affected by the exposure (46). Although several mediator-confounders were tested, it is possible that we missed some unmeasured. This lack of adjustment could induce a spurious association between birthweight and the outcomes, invalidating the direct effects. We also tested the presence of interaction between the exposure and the mediators and we did not identified any, which would make the controlled direct effect and natural direct effect be different.

Conclusions

An effect of birthweight on cardio-metabolic risk, mediated by BMI, was found in childhood, as higher birthweight trigged a higher BMI, which in turn led to impaired levels of cardio-metabolic indicators. Additionally, a BMI decrease during childhood would improve levels of cardio-metabolic indicators. However, the direct effects were

found to be in the opposite direction to the BMI-mediated effect, which could explain the variety of findings observed in the literature. Regarding the total effect, that combines the direct and BMI-mediated effects, a higher birthweight was associated with lower SBP and DBP at age 7 and have no effect on the other cardio-metabolic traits.

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Supplementary information is available at International Journal of Obesity's website.

Supplementary table 1 - Comparison between eligible children included and not included regarding maternal, pregnancy, delivery and newborn characteristics.
Supplementary table 2 - Distribution of relevant characteristics by birth weight category.

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Figure legends

Fig. 1 Hypothesized mechanism linking birthweight with cardio-metabolic health at ages 4 and 7: an overall effect with direct and indirect (BMI-mediated) paths

Fig. 2 Path analysis of the associations of birthweight with cardio-metabolic traits z-scores at ages 4 and 7 (A – Glucose; B – Triglycerides; C - LDL-cholesterol; D – Systolic blood pressure; E – Diastolic blood pressure)