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Associations between birth size and later height from infancy through adulthood: An individual based pooled analysis of 28 twin cohorts participating in the CODATwins project☆

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ABSTRACT

Background: There is evidence that birth size is positively associated with height in later life, but it remains unclear whether this is explained by genetic factors or the intrauterine environment.
Aim: To analyze the associations of birth weight, length and ponderal index with height from infancy through adulthood within mono- and dizygotic twin pairs, which provides insights into the role of genetic and environmental individual-specific factors.
Methods: This study is based on the data from 28 twin cohorts in 17 countries. The pooled data included 41,852 complete twin pairs (55% *monozygotic* and 45% same-sex *dizygotic*) with information on birth weight and a total of 112,409 paired height measurements at ages ranging from 1 to 69 years. Birth length was available for 19,881 complete twin pairs, with a total of 72,692 paired height measurements. The association between birth size and later height was analyzed at both the individual and within-pair level by linear regression analyses.
Results: Within twin pairs, regression coefficients showed that a 1-kg increase in birth weight and a 1-cm increase in birth length were associated with 1.14–4.25 cm and 0.18–0.90 cm taller height, respectively. The magnitude of the associations was generally greater within *dizygotic* than within *monozygotic* twin pairs, and this difference between zygosities was more pronounced for birth length.
Conclusion: Both genetic and individual-specific environmental factors play a role in the association between birth size and later height from infancy to adulthood, with a larger role for genetics in the association with birth length than with birth weight.

1. Introduction

Height is inversely related to all-cause mortality but shows heterogeneous relationships with cause-specific morbidity and mortality [1–3]. For example, there is a well-established association with incidence of cardiovascular diseases (CVD) [1,3]; shorter individuals both in childhood and adulthood have a higher risk of coronary heart disease [4–6]. In contrast, taller people are at a greater risk of death from several specific cancers [3,7]. Epidemiological studies have shown a positive association between size at birth (i.e. birth weight or birth length) and height in childhood [8], adolescence [9,10] and adulthood [11–13]. Similar findings have been observed in studies restricted to children of low birth weight or born small for gestational age [14–16]. The mechanisms underlying this association are, however, still poorly understood. One explanation involves the critical role of intrauterine environment in childhood growth [17,18], but it is unclear to what extent the associations between birth size and later height reflect early developmental factors in the intrauterine environment or whether they are explained by common genetic factors affecting body size already in fetal life.

Twins provide a natural experimental design that offers an opportunity to shed light into the mechanisms underlying the association between birth size and later height [19,20]. Twins come from the same family, share the same maternal environment, have the same gestational age, and in the case of monozygotic (MZ) twins, they share the same genomic sequence, whereas dizygotic (DZ) twins share, on average, 50% of genes identical-by-descent. However, each fetus has its own fetoplacental environmental conditions, such as supply of nutrients and oxygen, which may differ substantially from that of its co-twin [21]. The association between the intra-pair differences in birth size and intra-pair differences in later height cannot be attributed to shared family factors, such as maternal nutrition, smoking during pregnancy, parental education or socio-economic status. Further, differences within MZ pairs cannot be attributed to genetic factors. The comparison of intra-pair associations in MZ and DZ twins is, thus, a strong design to distinguish within-family effects, that is, the non-shared environment and genetic differences between co-twins. Differences in birth size and later height within MZ pairs can only be influenced by environmental factors that are unique to individuals (i.e. the individual-specific intrauterine environment), while differences within DZ pairs can also be