People of shorter height have increased risk of coronary heart disease (CHD). This was suggested by Gertler and White in 1954 and shown in the Whitehall Study\(^1\) and in other populations. The mechanisms remain unclear. Height is determined by genetic and early environmental influences. Prenatal growth, as well as early postnatal growth, which is particularly vulnerable to environmental influences, have both been argued to be important for the association between height and cardiovascular risk factors and disease. People from poor socioeconomic environments are of shorter height; similarly they have increased levels of risk factors and subsequent CHD.\(^2\) It has been suggested that genetic factors that influence growth also have a role in early programming of CHD,\(^3\) and the relative contribution of genetic factors and poor socioeconomic environment is still unknown. A study that sets out to shed light on this question is therefore welcome.

In this issue of the International Journal of Epidemiology, La Batide-Alanore and her co-authors report one of the first studies attempting to disentangle genetic from shared environmental influences on the height—CHD association by examining coronary risk factors.\(^4\) Using data from the STANISLAS study, height in each family member is correlated with cardiovascular risk factors in the other members, and correlations between biological relatives are compared with those between spouses. Their findings are compatible with a weak transmissible component for the association between height and low density lipoprotein (LDL)-cholesterol (correlation among relatives –0.04 and no correlation between spouses), while patterns for high density lipoprotein (HDL)-cholesterol and triglycerides seem to represent environmental, rather than genetic influences. No
familial clustering was observed for the association between height and blood pressure. The authors conclude that a common transmissible factor might explain part of the relationship between short stature and increased LDL-cholesterol.

The STANISLAS study provides a valuable opportunity to study familial influences on the association between growth and cardiovascular risk. It encounters two main limitations.

First, in cohort studies the higher risk of CHD among shorter people is generally not explained by their cholesterol or other risk factors. This implies that elevated lipids do not represent the main underlying pathway of the height—CHD relationship. Therefore, the contribution of genes and environment to the association between height and cholesterol may not elucidate the inverse association between height and CHD. That said, distinguishing the genetic and environmental effects that may link poor growth to cardiovascular risk factors is of interest.

Second, results from familial correlation analysis raise methodological questions. The magnitude of the correlation of two quantitative variables between spouses is compared with the correlation between biological relatives and significant differences taken as evidence for common transmissible factors. This may understate the environmental contribution. If the relevant environmental factors linking height to cardiovascular risk factors are those operating in the early years of life, siblings will share a more similar environment than spouses. Any observed difference may therefore be a combination of a larger degree of similarity between biological relatives compared with spouses, not only in terms of their genes, but also their early life environment.

The authors recommend that the hypothesis of a genetic contribution should more formally be tested by examining polymorphisms of candidate genes, such as those regulating insulin-like growth factors. While familial correlation analysis is rightly interpreted as a preliminary step to determine common transmissible factors, the magnitude of the cross-trait correlations between biological relatives was small and the evidence seems rather weak to call for further research, such as segregation and linkage analysis. After all, strong correlations are found between spouses, underlining effects of assortative mating and shared environment.

Leg length is a marker of early growth of the long bones at specific hormonally controlled phases of development, and recent studies have highlighted the importance of leg length, as opposed to trunk length, for the association between short height and cardiovascular risk. If genes influencing growth through hormonal control were closely linked to those involved in CHD risk, the analysis of components of height may provide further insights. However, increases in height over the last decades have been mainly attributed to increases in leg length and have been more pronounced in children from low socioeconomic strata. This suggests the importance of environmental improvements, rather than genetic influences, for the inverse association between leg length and cardiovascular risk. These secular trends have been largely attributed to changes in social and living conditions and nutrition.

The evidence of a genetically determined association between height and cardiovascular risk factors from this study is weak, and the question arises whether an important effect may have been missed. The analysis of children’s height is blind to growth at later ages, and their final height may not be represented accurately in childhood. This might dilute correlations between the heights of biological relatives. The analysis of total height at one point in time, rather than components of height or repeated measures, does not account for growth at distinct phases of development, which may be of different importance for cardiovascular risk. Moreover, in adults of similar height some will have fulfilled their growth potential, but others will have experienced limited growth due to malnutrition, infections, and psychosocial deprivation. This fundamental difference is likely to be unequally distributed among the different socioeconomic strata. If higher rates of cardiovascular disease were only observed in people who fail to reach their expected height, this would be more consistent with an environmental exposure as the underlying cause.

Twin studies, leaving their own limitations aside, provide a more powerful way of disentangling genetic and environmental effects. For example, if in a twin study differences in height between monozygotic twins were associated with different rates of cardiovascular disease, this would strongly suggest prenatal or postnatal environmental exposures as the cause.

The authors suggest that the inverse association between height and blood pressure seen in adults may be masked by the positive correlation of growth and sexual maturation with blood pressure in children. We have recently shown strong inverse associations between leg length and systolic blood pressure and pulse pressure in adults and hypothesized that early environmental influences may simultaneously affect the growth on the long bones and arterial development, leading to decreased arterial compliance and CHD in adult life.7 The analysis of environmental and genetic influences on the association between growth and subclinical vascular disease in the subset of the STANISLAS cohort with measures of intima-media thickness could provide interesting insights. This equally applies to familial clustering of height with components of the metabolic syndrome, as recent interest has focused on insulin resistance as a potential mediator between early life exposures and adult disease.

Gunnell et al., investigating associations between components of height and cardiovascular risk factors, found that controlling for parental stature had little effect on their findings,8 and this was interpreted as evidence against underlying genetic influences. Now, data from the STANISLAS family study provides further evidence that genetic influences do not seem to explain the association between height and several cardiovascular risk factors. Early socioeconomic circumstances affect growth as well as cardiovascular risk, and people with poor growth may be particularly susceptible to the detrimental effects of low adult social class and associated health behaviours.9 Social mobility may also be selective with respect to body height. Future studies of the association between poor growth and CHD should take account of the evolution of social conditions and health behaviour over the life course.10

References


