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Commentary: Can adult anthropometry be used as a 'biomarker' for prenatal and childhood exposures?

David Gunnell

Life Course Epidemiology

Life course epidemiology is concerned with investigating the effect on health of accumulating and interacting biological, social, and psychosocial processes.[1] Parental health and genetic endowment together with intrauterine, childhood and early adult exposures may all influence an individual's health, but investigating their joint effects presents two important challenges. The first is that many of the exposures studied are socially patterned, therefore identifying the relevant factors using observational studies, which are prone to confounding, is problematic. Randomized controlled trials with long follow-up are the best means of identifying the long-term effects of possible interventions on health.[2] The second challenge is that there are few cohort studies with exposure and health information from before birth until old age. Most of the studies where data have been prospectively recorded at different stages of the life course[3–6] are either of relatively young individuals, or currently limited by insufficient power to examine major clinical end-points.

University of Bristol, Department of Social Medicine, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, UK.

Indirect Measures of Fetal, Infant and Childhood Exposures

When prospectively recorded data on a person's health, diet, health-related behaviours and living conditions at particular ages do not exist, indirect or proxy measures may be used (Table 1). To interpret the association of these measures with later disease requires a fuller understanding of their meaning and shortcomings. The investigation by Wadsworth and colleagues provides information concerning two possible anthropometric 'biomarkers'—leg length and trunk length.[7] Their analysis may provide clues concerning the possible exposures underlying stature-disease associations. Furthermore it suggests that leg length and trunk length may act as markers for exposures operating at different stages during childhood.

Body Shape and Disease

Interest in the association between body shape and health dates back over a century (see Burchard 1936).[8] Early studies of physical illness characterized human body forms into three main classes—endomorphs, ectomorphs and mesomorphs.[9,10] A different form of classification was used in the psychiatric literature—classes include aesthenics, athletics and pyknics.[8] Categorization was based on a number of features including

Table 1 Proxy measures of fetal, infant and childhood exposures

Period of Life course	Measure	Factor(s) the measure may act as a marker for	Limitations
Prenatal	Birthweight/birth length/ birthweight/placental weight[29,30]	Nutrition *in utero*	Also influenced by maternal size, smoking and ill-health (including pre-eclampsia) as well as gestational age and birth order
	Conception and *in utero* development during period of famine[31]	Undernutrition *in utero*	Ecologic marker for famine exposure, mother may not have been affected by famine
	Lung function[32]	Intra-uterine growth retardation/ maternal smoking in pregnancy	Also influenced by adult smoking and other exposures in childhood and adult life. Influences on lung growth not fully understood
	Parental social class[33]	A range of socially patterned exposures	Non-specific
	Season of birth[34]	Exposure *in utero* to infection, food scarcity or particular climatic conditions	Non-specific marker of a range of exposures which show seasonal variation
	Obstetric complications[35]	Anoxia and trauma during delivery	No clear definition of key exposures
Infancy and childhood	Weight at one year[29]	Nutrition and health in the first year of life	Also influenced by birthweight, genetic determinants of growth
	Urban versus rural residence[36]	Exposure to particular infections, diet differences and differences in social conditions	Non-specific marker of a range of possible exposures
	Season of birth[34]	Exposure after birth to seasonal infection, food scarcity or particular climatic conditions	Non-specific marker of a range of possible exposures which show seasonal variation
	Recalled childhood diet[37]	Aspects of childhood diet	Recall bias
	Parental social class[33]	A range of socially patterned exposures	Non-specific
	Education[38]	Socially patterned exposures, later life employment prospects, intellect	Non-specific
	Household crowding[39]	Infection exposure, sleep deprivation and stress	Strongly socially patterned
	Adult height[12]	Diet, health and psychological stress throughout the growing years	Also influenced by birthweight, genetic determinants of growth
	Adult leg length[12]	Pre-pubertal diet, health and psychological stress throughout the growing years	Also influenced by birthweight, genetic determinants of growth (but see text for its advantage over height)
	Body mass index[40]	Balance between energy intake and energy expenditure around the time of measurement	Also influenced by birthweight, genetic determinants of growth
	Lung function[32]	Intra-uterine growth retardation/maternal smoking in pregnancy	Also influenced by adult smoking and other exposures in childhood and adult life. Influences on lung growth not fully understood
	Catch-up growth[41]	Earlier *in utero* or childhood exposure to factors influencing growth	Nature of factor causing earlier growth impairment may be poorly characterized
	Birthorder/sibship size[42]	Exposure to infection	Non-specific marker for exposure to a range on infections and other exposures

height, limb length, weight and fat distribution. More recent investigations have focussed separately on overall stature and adiposity/fat distribution. Adult height is a measure both of genetic endowment and of health and nutrition throughout the growing years.[11] Unlike adiposity measures, height changes little during adulthood. For this reason the association of greater stature with an increased risk of cancer[12] and a decreased risk of cardiovascular disease[13] may reflect the long-term consequences of pre-adult exposures.

Neither the relevant period of growth nor the exposures for which stature may be acting as a 'biomarker' are well characterized. Growth disturbances at several stages of development may contribute to short adult stature.[14] It has been suggested that one way of further investigating height-disease associations may be to study associations between the two components of height—leg length and trunk length—and disease risk. The rationale for such an approach lies in the observation that postnatal linear growth is in greater part due to an increase in leg length than trunk growth and that adversity at this time causes impaired lower limb development.[15] This is demonstrated by changes in the trunk length: height ratio during growth. At birth the ratio is around 0.66, but by puberty it has declined to 0.50 (Figures 1 and 2). From puberty, linear growth occurs equally in trunk and leg length.

It is of interest, therefore, that studies to date indicate that the component of height generating height-cancer and height-cardiovascular disease associations is the leg.[12,16,17] This indicates that the relevant exposures underlying these associations operate pre-pubertally. A better understanding of the nature of these exposures may contribute to understanding the biological mechanisms underlying what at first sight appear to be somewhat peripheral epidemiological observations.

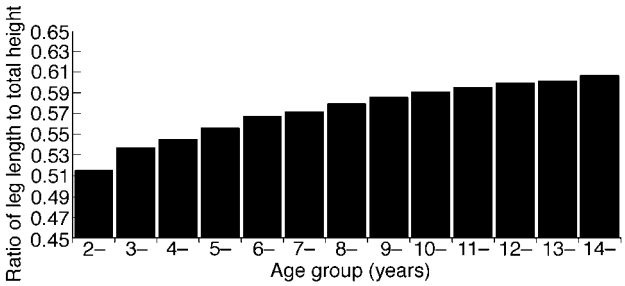

Figure 1 Change in the leg length:height ratio with age. Cross-sectional data from the Carnegie Survey (1937–1939). Source: Family diet and health in pre-war Britain. Carnegie Trust, Dunfermline, 1955

The 1946 Cohort

Previous analyses of the 1946 cohort, the UK's first national birth cohort study, have made important contributions to understanding early life influences on adult health.[4,18–21] Indeed an earlier investigation identified a range of social and pre-natal factors associated with the adult height of cohort members.[22] Relevant factors were: parental height, birthweight, childhood social class, birth order, number of younger siblings, parental education and household crowding.

In this latest analysis, pre-natal, infant and childhood correlates of adult leg length and trunk length are assessed. Most of the factors investigated in the earlier analysis are also examined here. Recent coding of the childhood diet data has also enabled an investigation of diet-stature associations and the influence of infant feeding, parental divorce and death are also assessed. The availability of height measurements at ages 4, 7, 11 and 15 allows the authors to gain insights into the timing of the effects of the exposures, and availability of parental height allows for some control of genetic or inter-generational influences. However, the use of overall parental stature in this way is limited by the possibility that the two components of height may be under separate genetic influence. Information on parental leg length and trunk length was not available.

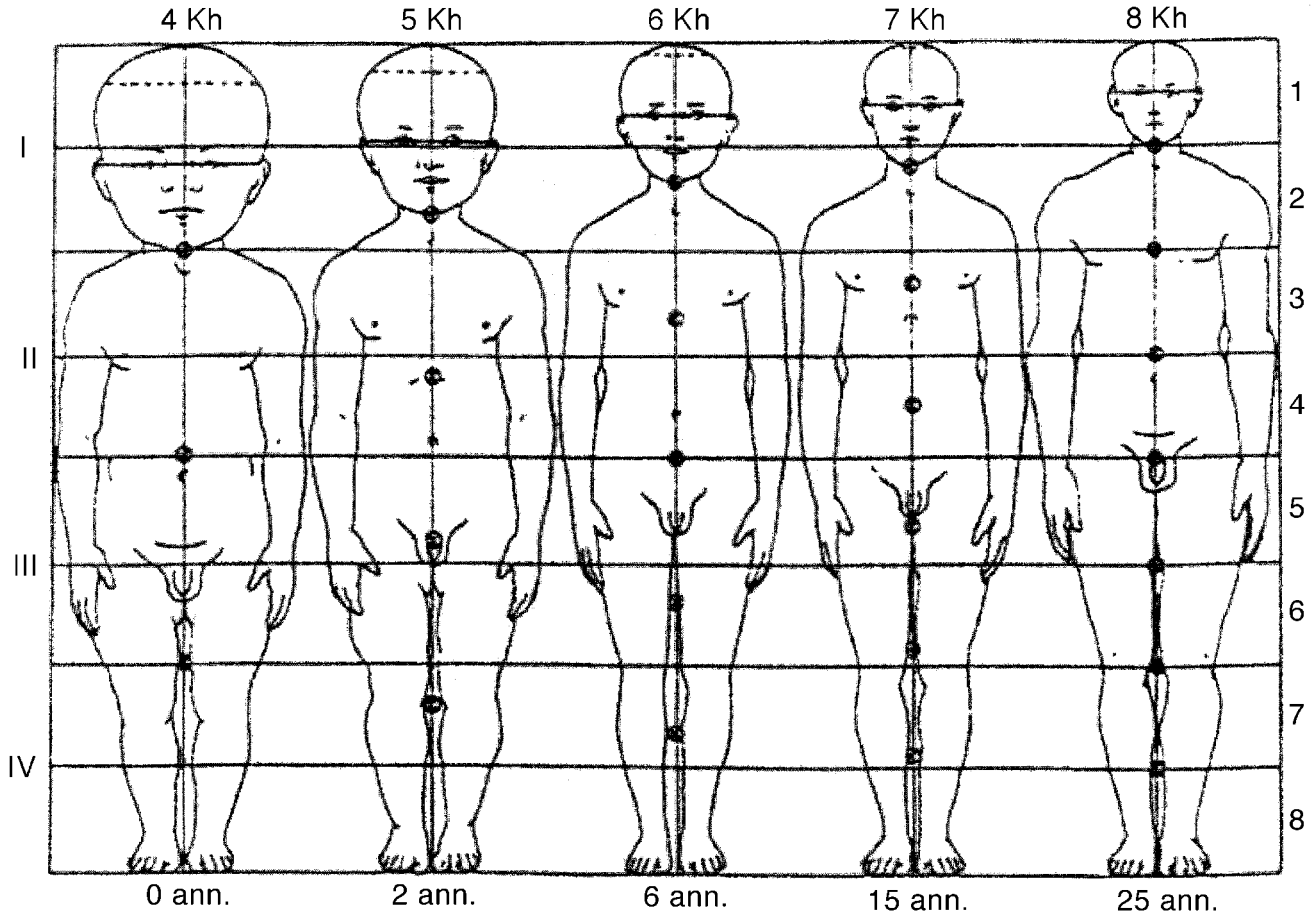

Figure 2 Change in shape of the human body from birth to adulthood

From Stratz CH (1904) Der Korper des Kindes. Fur Eltern, Erzieher, Arzta und Kunstler. Ferdinand Enke. Stuttgart. Reprinted from: Prog Fd Nutr Sci (2) Leitch I. Change in shape of the human body, pp.99–141. Copyright (1976) with permission from Elsevier Science.

The low correlation (0.1) between leg length and trunk length underlines the possibility that the two height components provide relatively independent information on exposures influencing growth. The principle findings are that birthweight and parental height were associated with both components of height, energy intake and breastfeeding were independently associated with leg length, whereas serious illness in childhood and parental divorce were associated with trunk length.

A methodological challenge when examining associations with the components of stature is how to take account of overall body size and whether the biologically relevant measurement is disproportion or absolute length of the leg or trunk. Various approaches have been used previously. Analyses of mortality patterns in the Boyd Orr cohort models examining leg length-mortality associations included a term for trunk length and *vice versa*.[16,23] In assessing the association of leg length and trunk length with cardiovascular disease in Caerphilly men the *ratio* of trunk length to leg length was used.[17] In Wadsworth's analysis the difference between z-scores for leg and trunk length was used. The factors most strongly related to this measure were overcrowding and breastfeeding—overcrowding leading to disproportionately short legs, and breastfeeding to long legs. The authors however make little of this analysis focussing mainly on the multivariable models for leg length and trunk length separately.

How should we interpret these findings? Many factors were examined in the models and the fact that different exposures were associated with each component of height may be a chance finding. The lack of association with most of the nutrients is not surprising in view of the limited nature of the dietary data (mothers recall of the child's diet in the previous 24 hours). This area requires consideration in birth cohorts with more detailed diet information. Whilst the association between leg length and energy intake replicates a finding in univariable analyses of the Boyd Orr cohort, in multivariable analyses in that study energy intake was associated with trunk but not leg length.[24] The association of breastfeeding with leg length replicates findings in the Boyd Orr cohort[25] and suggests this is an area worthy of further study. There is debate concerning the long-term impact of patterns of infant feeding on adult health, but the associations between breastfeeding and leg length suggest this may be a biologically relevant exposure underlying leg length-mortality associations.

Leg Length, Trunk Length and Chronic Disease Risk

This analysis of the 1946 birth cohort provides further evidence of the potential use of leg length as a measure of pre-pubertal exposures. Its independence from birthweight[26] is suggested by the similarity of trunk-birthweight and leg-birthweight associations. Other analyses of the exposures influencing leg and trunk length in childhood and adulthood are now needed to confirm these findings. Similarly further analyses of risk factor and mortality associations with the components of stature are necessary to replicate the findings to date in a limited number of cohorts—Boyd Orr, Caerphilly, NHANES and the Honolulu Heart Programme.[16,17,27,28]

Importantly consensus regarding the relevant 'biomarker' is required—is somatic disproportion or absolute leg the more important. In the Caerphilly study, findings were similar for both measures.

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