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Commentary

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Commentary: Disentangling the contributions of childhood and adult weight to cardiovascular disease risk

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When Abraham *et al.* embarked on the study described in their 1971 paper,[1] it was already known that high adult body weight is a risk factor for cardiovascular disease (CVD) and that childhood and adult weight tend to be positively correlated. They wanted to find out if childhood weight makes an independent contribution to CVD risk over and above its correlation with adult weight. They successfully re-traced ~ 700 men who attended schools in Hagerstown, MD, USA, between 1923 and 1928 and had weight recorded at the age of 9–13 years, and measured adult weight, CVD risk markers (blood pressure, glucose and lipids) and four morbidities ('diabetes', 'hypertensive vascular disease', 'arteriosclerotic heart disease', 'cardiovascular renal disease'). They analysed the data by tabulating these outcomes across categories of childhood and adult weight, and then cross-tabulating them according to both childhood and adult weight simultaneously. This must have been one of the first studies to investigate the relationship of an early life characteristic to adult CVD.

They started out with three possible 'causal pathways' in mind (Figure 1): (i) childhood weight is positively associated with adult weight, but most of the variability in CVD risk is explained by adult weight; (ii) childhood weight is positively associated with risk, and adult weight has no independent additional effect; or (iii) both childhood and adult weight are positively and independently associated with risk, or in other words a component of higher childhood weight that is not encapsulated in adult weight is associated with increased risk. A fourth possibility (iv) was that childhood and adult weight are independently associated with risk but in opposite directions, such that lower child weight, or a component of it, is associated with increased risk.

Abraham's analysis confirmed a strong correlation between childhood and adult weights. Children in the highest or lowest weight categories tended to remain in the same categories as adults. The risk for most of the CVD outcomes increased with increasing adult body weight. Though not so strongly, most of the outcomes also increased with increasing childhood weight. However, in the cross-tabulations, they found something unexpected. The highest morbidity appeared to be among those men who were lightest as children but heaviest as adults.

One problem with their analysis was that, because of the correlation between childhood and adult weight, the lightest child-heaviest adult cell in these tables contained very few men ($N < 10$). They also tried grouping the men according to the degree of change in weight category between childhood and adulthood. Again, small numbers in key cells substantially defeated them, but they concluded that the highest morbidity was in men who had the greatest upward change in body weight. They could not test most

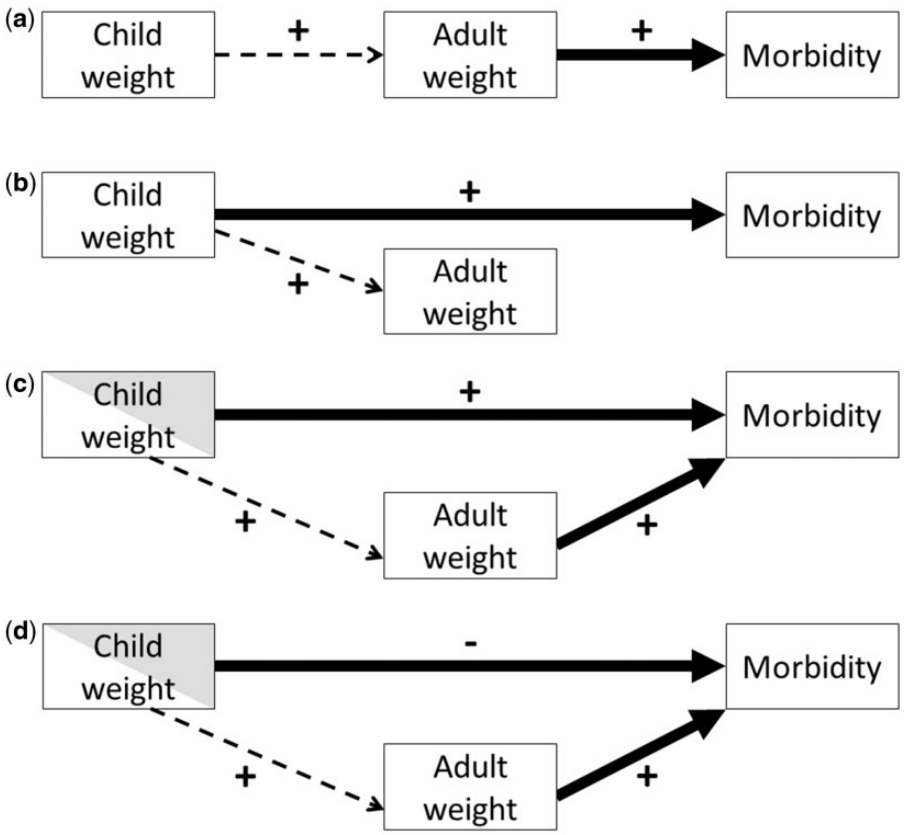

Figure 1 Alternative 'causal pathways' linking child and adult weight to CVD morbidity. Heavy black arrows represent main independent effects; dashed arrows represent correlations, but no/little independent effect on the outcome

of these associations statistically with the tests available at that time, due to small numbers and limited software. However, they concluded that the overweight adult who had been a below average weight child had the highest adult CVD morbidity, and that morbidity was 'a function of adult acquired 'fatness'.' To paraphrase their conclusions: fat 'thin' men, who had been thin children and became fat adults, were at higher risk than fat 'fat' men, who had been fat all their lives.

How would we tackle this question today? Like Abraham *et al.*, we might initially do some cross-tabulations. Despite the problems of low numbers in extreme cells, this is a good way of getting to know such data, but is too often left out nowadays in the rush to construct a regression model. A similar method, that adds further information, is to create contour plots, which can be designed in such a way that contours only appear where there are sufficient data. Figure 2 shows hypothetical contour plots for the scenarios depicted in Figure 1.

We would probably then go on to use multiple regression, and examine associations between childhood weight and adult risk unadjusted and then adjusted for adult weight. These two analyses would answer two separate questions. The unadjusted model is 'forward-looking'. Only childhood weight is known, and we are like a paediatrician with a child standing in front of us, trying to predict its future CVD risk. The association between childhood weight and the outcome is therefore the total or 'net' effect of childhood weight, including any effect acting through its positive association with adult weight and any positive (Figure 1c) or negative (Figure 1d) effect that does not act through adult weight. The second question is 'backward-looking'. We now know adult weight, and are like an adult physician with the person standing in front of us, trying to isolate the contribution made by his or her childhood weight. The effect of childhood weight in a model adjusted for adult weight will reflect its independent contribution.

It sounds simple, but in reality it is not easy to interpret the results. We have been grappling with similar problems over many years, in relation to 'developmental origins of adult health and disease' (DOHaD) concepts, trying to disentangle associations between birthweight, adult body mass index (BMI) and adult CVD. One issue is that when there are only two measurements to predict the outcome (childhood weight and adult weight), it is impossible to separate the effects of childhood weight, adult weight and

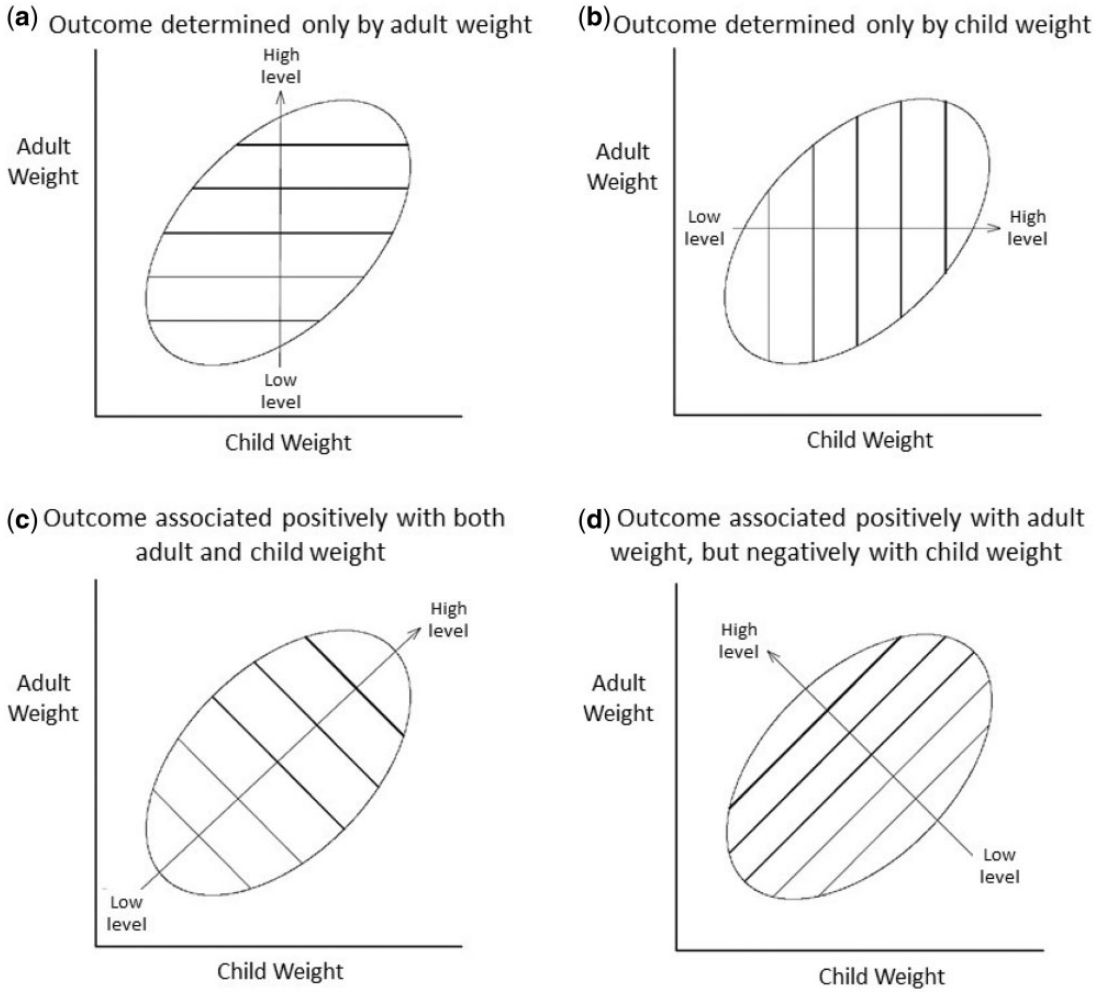

Figure 2 Hypothetical contour plots corresponding to the 'causal pathways' shown in Figure 1. Increasing thickness of the contour lines represents increasing risk

the growth that led from one to the other, which is just the difference between them; a greater difference could result from lower early weight or higher later weight, or both. It also gives no information about the importance of the timing of weight change. When both childhood weight and adult weight are included in the model, an inverse association between childhood weight and morbidity could mean that morbidity is associated either with low childhood weight or with a greater change in weight between childhood and adulthood. This was pointed out by Lucas *et al.* in relation to the inverse association between birthweight and adult blood pressure.[2] They argued that the inverse association between birthweight and adult blood pressure after adjusting for adult BMI indicates that accelerated post-natal growth, rather than programming by fetal undernutrition, could be a cause of hypertension. The truth is that it is impossible to distinguish between these two possibilities when these are the only data available. This is conceptually identical to the 'age, period, cohort' problem in epidemiology, where it is known to be impossible to disentangle the effects of year of birth, age at death and year of death on disease mortality rates.[3]

A helpful step is to examine whether the association between adult weight and morbidity differs at different levels of childhood weight. If so, then there is a statistical interaction, which suggests that childhood weight modifies the effects of adult weight. An example, using risk contours, is shown using data from the 1923–33 Helsinki birth cohort study from Finland (Figure 3). In this example, the earlier measure is ponderal index at birth, and the later measure is BMI at age 11 years. A higher 11-year BMI is associated with an increased risk of adult coronary heart disease in adult life, but the increase in risk is greater among men who were thin (had a low ponderal index) at birth than among men who had a high ponderal index at birth. This gives more confidence that thinness at birth is intrinsically important in relation to later CVD.

Abraham *et al.* would have benefited from having data at intervening time points between childhood and adult life. Statistical methods have been developed to use serial

childhood measurements to isolate associations of size and growth at specific ages with later outcomes. For example, conditional variables are standardized residuals derived from regressing size (e.g. weight) at any age on previous size measurements, producing independent, uncorrelated variables representing greater or lesser size at each age than expected, given earlier size.[5,6] They overcome the problems caused by the strong correlations between serial measures of body size in an individual.

The conditional method can be used to take both 'forward-looking' and 'backward-looking' approaches. Figure 4 shows data from the 1934–44 Helsinki birth cohort study, in which birthweight, weight at 2 years and BMI at 11 years were available. Adult BMI was based on actual measurements, and hypertension was defined by use of medications.[7] In the forward-looking analysis, without adult weight (Figure 4a), lower birthweight and higher conditional BMI at age 11 years were associated with an increased risk of adult hypertension. The data could also be interpreted as showing that lower birthweight and greater weight gain between 2 and 11 years were associated with adult hypertension. Conditional weight at 2 years (or weight gain between birth and 2 years) was unrelated to hypertension. These are the 'net effects' of early size.

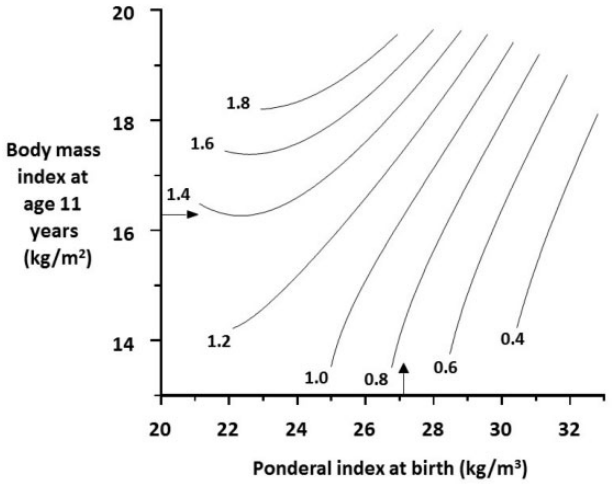

Figure 3 Hazard ratios for death from coronary heart disease for men born in Helsinki 1924–33 according to ponderal index at birth and BMI at age 11 years. Arrows indicate average values.
Source: Eriksson *et al.* 1999[4]

Now, if adult BMI is included in the model (Figure 4b) we get the 'backward-looking view. Knowing adult BMI, conditional BMI at 11 years is no longer positively related to hypertension. This suggests that the positive association of conditional 11-year BMI in the forward-looking analysis was acting on adult hypertension risk mainly through adult BMI. The associations of 2-year conditional weight and 11-year conditional BMI with hypertension have both become, like that of birthweight, negative or inverse. We conclude that a component of 11-year BMI tracks through into adult BMI and is a risk factor for adult hypertension. But there is also a component of weight at 11 years, 2 years and birth whereby a lower body weight is an independent risk factor for later hypertension. These conclusions are substantially similar to those reached by Abraham, but give more information about weight at different ages in

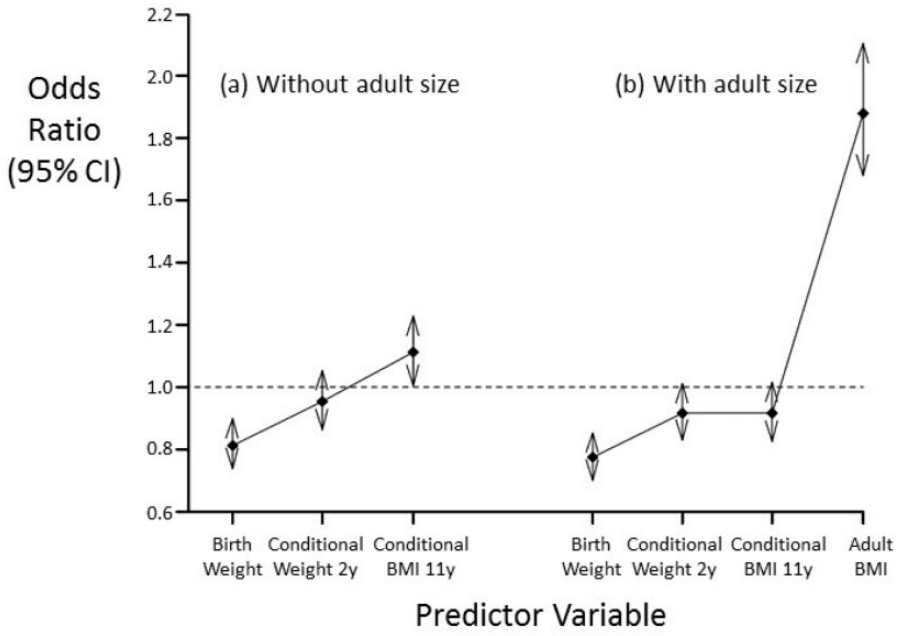

Figure 4 Birthweight and conditional measures of childhood weight and BMI as predictors of adult hypertension in the 1934–44 Helsinki birth cohort; y, years

childhood. The conditional growth approach has been extended to include not only multiple ages, but also multiple measures of body size. For example, Adair *et al.* have investigated independent effects of childhood soft tissue and linear growth on adult human capital and CVD risk markers;[6] And Krishnaveni *et al.* have investigated independent effects of earlier growth in height, adiposity and lean body mass on CVD risk markers in adolescence.[8] The latter study suggested that the positive net effect of childhood weight gain on later blood pressure was mediated by growth in adiposity, and not by linear or lean-tissue growth. Other modelling approaches, in addition to the conditional approach, have been recently reviewed.[9]

Apart from the above considerations, a full interpretation of epidemiological data like that of Abraham *et al.* would also require evaluation of confounding (the possibility that both childhood weight and CVD outcomes are causally related to some other factor, such as: low socioeconomic status); selection bias (the possibility that the association between childhood weight and CVD differed between people who were included in the analysis and those who were not); and the influence of missing data and measurement error. In relation to selection bias, Abraham *et al.* compared childhood weights between those who were and were not re-traced/studied, but could not have answered the more critical question as to whether the association between childhood weight and outcomes differed between these two groups.

Abraham *et al.*, in their discussion, speculated about the biology ('different types of fat') underlying their results. It is worth bringing to bear on this the greater understanding of the biology linking factors in early life to adult disease, that has come from recent research. In the DOHaD world, nobody believes that weight per se (birthweight or childhood weight) 'causes' anything. As Gillman wrote in relation to birthweight, weight is not a 'monolith';[10] weight is made up of multiple components (muscle, bone, fat, different organs and tissues) whose development is influenced by multiple environmental factors. It is the effects of these factors on individual developing tissues, and the end result in terms of their structure and function across the life course, which are thought to cause later disease.

Another effect of the same environmental influences may be, though not invariably, to alter body weight. Hence we can start to see a scenario whereby some mechanisms linking early life weight to adult CVD may differ from the mechanisms linking early life weight to adult weight. One component of early life weight may reflect an exposure that causes an individual to develop later CVD, whereas another may reflect the tracking of weight into adult life, influencing CVD risk in a different way. To flesh this out with an example, adult blood pressure could be high because an individual has reduced numbers of nephrons in the kidneys, resulting from a specific nutritional deficiency in the mother when the fetal kidney was developing.[11] This could also reduce birthweight. However, fetal adiposity may be unaffected by this maternal deficiency, and the newborn has a normal quantity of body fat. The usual relationship between newborn adiposity and adult adiposity pertains, and partly determines adult adiposity and body weight, which are positively associated with blood pressure. One component of birthweight (kidney weight) would be negatively associated with adult blood pressure, but another (body fat) would be positively associated with blood pressure. The persuasive evidence that early life factors are important in the causation of adult CVD rests not so much on the associations with early life body weight as on new observations that these associations stimulated. Animal experiments have shown that adult blood pressure, insulin sensitivity, glucose tolerance and body composition can be influenced by manipulating the mother's diet during pregnancy, and that these effects are matched by changes in individual tissues and metabolic pathways.[12] We are far from understanding early life effects at this level in humans, and Abraham *et al.* were even further from that but their speculations, about 'acquired' fat being different from 'endogenous' fat, highlight the need to delineate underlying mechanisms in order to make sense of the body weight associations.

The article by Abraham *et al.* reminds us how far we have come in terms of the 'tools' of life course epidemiology. They had to trace their study subjects manually from the school records, using telephone directories, service lists and death certificates. They traced an impressive 717 out of 1963 schoolchildren, but paid a price in laboriousness and missing data. The morbidities they studied were not defined, and some of them are all but unrecognizable now. We benefit today from computerized records, growth standards, standardized disease definitions and a far more sophisticated statistical armamentarium. These advances have revolutionized what we can learn from data, but cannot deal with all the limitations of the data themselves.

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