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A critical evaluation of statistical approaches to examining the role of growth trajectories in the developmental origins of health and disease

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The developmental origins of health and disease hypothesis suggests that small birth size in conjunction with rapid compensatory childhood growth might yield a greater risk of developing chronic diseases in later life. For example, there is evidence that people who developed coronary heart disease and diabetes experienced different growth trajectories from those who did not develop these diseases. However, some of the methods used in these articles may have been flawed. We critically evaluate proposed approaches for identifying the growth trajectories distinctive to those developing later disease and identifying critical phases of growth during the early lifecourse. Among the approaches we examined (tracing the z-scores, lifecourse plots and models, lifecourse path analysis, conditional body size analysis, multilevel analysis, latent growth curve models and growth mixture models) conditional body size analysis, multilevel analysis, latent growth curve models and growth mixture models are least prone to collinearity problems caused by repeated measures. Multilevel analysis is more flexible when body size is not measured at the same age for all cohort members. Strengths and weaknesses of each approach are illustrated using real data. Demonstrating the influence of growth trajectories on later disease is complex and challenging; therefore, it is likely that a combination of approaches will be required to unravel the complexity in lifecourse research.

Keywords Developmental origins of health and disease, birthweight, body weight, growth, cohort studies

Introduction

The fetal origins of adult disease hypothesis (FOAD)[1] has attracted considerable attention among medical and epidemiological researchers over the past three decades. It has been shown that birth sizes (usually birthweight) have an inverse relationship with health outcomes in later life, such as cardiovascular diseases,[2] hypertension,[3] diabetes[4] and obesity.[5] An elaboration of the FOAD hypothesis suggests that small birth size in conjunction with compensatory rapid growth in childhood (rather than small birth size

per se) leads to a greater risk of developing chronic adult diseases. As a result, the FOAD hypothesis has been rephrased as 'the developmental origins of health and disease hypothesis' (DOHaD hypothesis).[6]

The DOHaD hypothesis proposes that the risk of chronic disease in adult life is initially induced through predictive adaptive responses that the foetus or infant develops in response to environmental signals from their mothers.[6–8] These responses, including changes in metabolism, hormone production and tissue sensitivity to hormones, may have negative impacts on later health if the postnatal environment experiences substantial changes, leading to a mismatch between prenatal physiological adaption in foetal development and postnatal environment.[9] Furthermore, the predictive adaptive responses are likely to continue into early life and childhood. Consequently, those people with a mismatch may show distinctive growth patterns, and if we can distinguish those patterns, we may be able to use growth data throughout the early lifecourse to identify people at higher risk of developing adverse health outcomes in later life.

Many approaches have been proposed to identify distinctive growth trajectories or critical growth phases in early childhood that may be related to higher risk of chronic diseases in later life. Some aim to model individual growth trajectories, whereas others take a population-average approach.[9–12] The aim of this article is to review the strengths and weaknesses of several proposed strategies and to use real data to compare the results of these approaches.

The illustrative dataset

Throughout this article we use data from a prospective cohort study whose participants were recruited from Metropolitan Cebu, an area of the central Philippines.[13] Data were obtained from the website of the University of North Carolina Population Centre (www.cpc.unc.edu/projects/cebu/datasets); a detailed description of the study can be found on their website and in articles published by Adair and her colleagues.[13,14] In summary, all pregnant residents of 33 randomly selected Metro Cebu communities were invited to participate, and index-child participants include 3080 singletons born during a 1-year period beginning in April 1983. Prenatal data were collected during the 6th to 7th months of pregnancy. We use postnatal data of offspring body weights measured immediately after birth and at ages 1 year, 2 years, 8 years, 15 years and 19 years. The later-life health outcome is systolic blood pressure (*SBP*) measured at age 19 years. We use data from 960 boys with no missing measurements of body weight or blood pressure. Raw body weights are transformed to obtain z-scores by subtracting sample average weights from individual weights and dividing by sample standard deviations at each age. Figure 1 shows observed growth trajectories for raw body weights and for weight z-scores weights from birth to 19 years in 30 randomly selected Cebu boys. Table 1 summarizes means of and correlations between the body size measurements and *SBP*. Note that the first three measurements (at birth, age 1 and age 2 years) were at the same ages for all cohort members, but subsequent body weights (at ages 8, 15 and 19 years) were measured at only roughly the same ages, with 1–2 year differences.[13,14]

Tracing the average z-scores

Following the statistical approach of tracking z-scores over the lifecourse,[7–12] Figure 2a shows average weight z-scores between birth and age 19 years for men who had normal (dashed line) and high (solid line) blood pressure (defined as >115 mmHg) at age 19 years. The mean birthweight z-score of men with high blood pressure was negative: this group achieved above-average body weight at age 1 year. After age 1 year, they gained more weight than those with normal blood pressure. When the mean weight z-score of one subgroup is less than zero, the mean weight z-score of the other group must be greater than zero, as the average weight z-score of the whole group at each age is zero by definition. If the two groups (of men with normal and with high blood pressure) had the same number of subjects, and all subjects were measured at identical ages, the two growth trajectories would be mirror images about zero.

Figure 2a seems to suggest that compensatory growth in body weight during the 1st year of life is associated with an increased risk of developing hypertension in later life.[7–12] However, the correct interpretation is that birthweight has an inverse association with high blood pressure at age 19 years. When the two patterns of growth cross, between birth and 1 year, the average z-score in each group equals zero; so the association of body weight at this age with high blood pressure at age 19 years is zero. After the age of 1 year, the association between body weight and high blood pressure at age 19 years becomes positive, and is greatest at the age of 19 years. The greater the association (positive or negative) between body weight at a particular age and the adult health outcome, the more separation occurs between the mean z-score in the two groups. The correct interpretation is apparent when we compare Figure 2a with Figure 2b, which shows the natural log of the odds ratios for the association of body weight at each age with high blood pressure at age 19 years. Since the difference between the mean z-scores in the two groups at each age reflects the strength of the association at that age, the growth pattern of men with high blood pressure is similar to the trend in the values of the log odds ratio.

Based on tracking z-scores, several studies have concluded that people who develop adult chronic diseases tend to have had a distinctive growth trajectory.[7–12] Figure 2 shows that these patterns are better

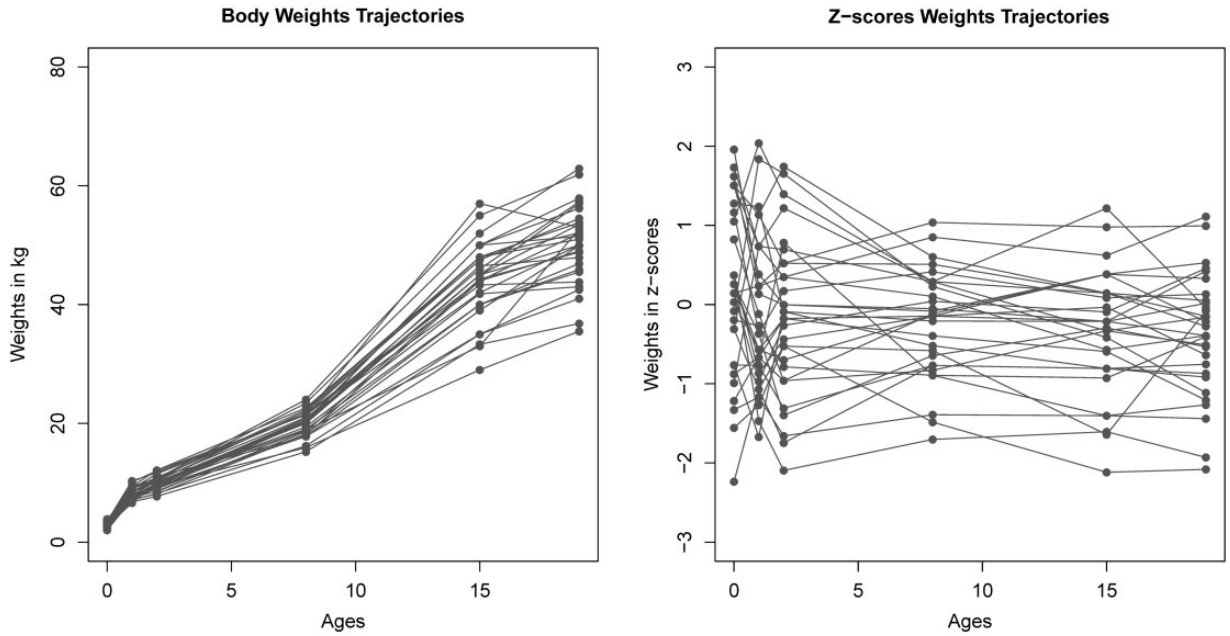

Figure 1 Observed individual weight trajectories of 30 randomly selected Cebu boys during birth to age 19 years

Table 1 Summary statistics of body weight measurements (in kg) and blood pressure (in mmHg) for 960 boys in Cebu cohort

			Pearson correlations						
Variable	Mean	SD	$Weight_0$	$Weight_1$	$Weight_2$	$Weight_8$	$Weight_{15}$	$Weight_{19}$	*SBP*
$Weight_0$	3.04	0.44	1.00						
$Weight_1$	8.27	1.00	0.40	1.00					
$Weight_2$	10.10	1.15	0.36	0.84	1.00				
$Weight_8$	20.67	3.21	0.26	0.61	0.67	1.00			
$Weight_{15}$	46.79	8.40	0.22	0.49	0.54	0.82	1.00		
$Weight_{19}$	53.37	8.58	0.21	0.47	0.53	0.78	0.87	1.00	
SBP	106.37	10.57	0.00	0.08	0.11	0.22	0.27	0.33	1.00

$Weight_n$: n is the age at which body weight is measured; SD, standard deviation.

understood as a connected series of cross-sectional associations of body weight at successive ages with health outcomes in later life. Substantial upward or downward slopes reflect ages during which the magnitude of the association of body size with health outcomes in adulthood is changing rapidly, rather than average growth trajectories.[15] Figure 2 thus confirms, as is well known, that adult body sizes have a positive relationship with later-life adverse health outcomes, but that body sizes at birth or during early childhood have weaker, inverse relationships.

Approaches based on conditioning

In this section, we discuss statistical approaches that estimate the relation between body weight measured at a given age with adjustment for body weights at other ages, i.e. the estimated association is conditional on other body sizes in the same model. For instance, Figure 3 shows a directed acyclic graph, where each body weight may have a direct effect on blood pressure at age 19 years (i.e. the arrow from each weight to blood pressure) but each body weight may also have an indirect impact through its influence on later body weights (i.e. the arrow from each weight to the subsequent weight).

The lifecourse plot

In the lifecourse plot approach,[16,17] the outcome variable is regressed on the body size (or its z-score) measured during the early lifecourse using multiple regression. Suppose that body weight was measured

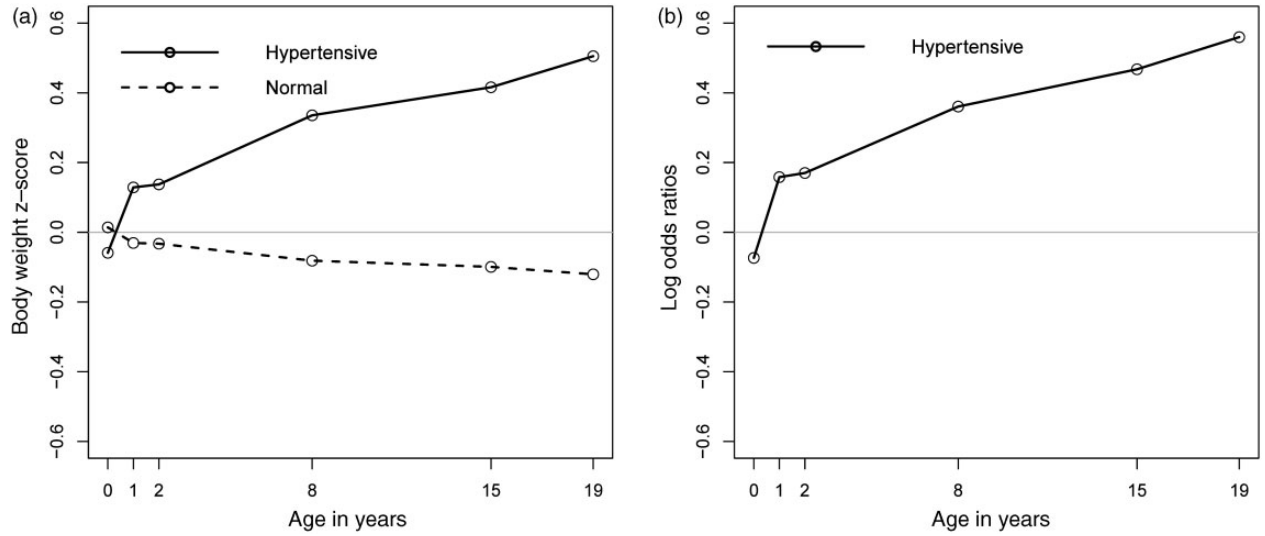

Figure 2 (a) Mean z-scores for body weight from birth to the age of 19 years for men with normal (Normal) or higher blood pressure (Hypertensive) by the age of 19 years; (b) the natural log of Odds Ratio of developing higher blood pressure for 1-unit increase in body weight z-score at each age

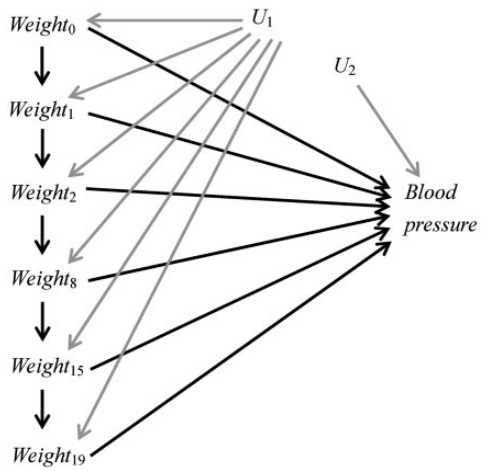

Figure 3 Directed acyclic graph for the relationships among body weights measured at different ages ($Weight_i$) and blood pressure at age 19 years. U_1 represents unmeasured background variables affecting body weights, and U_2 represents background variables affecting blood pressure. This figure shows a simplified scenario, where U_1 and U_2 are not confounders for the relation between body weights and blood pressure

p times at different ages. The lifecourse plot is obtained by regressing the outcome y on these measurements:

$$y = b_0 + \sum_{j=1}^{p} b_j weight_j + e$$

where b_0 is the intercept, b_j the regression coefficient for $weight_j$ and e the residual error term. If sample z-scores for body weight and sample z-scores for blood pressure are used instead, the intercept b_0 will be zero. The partial regression coefficients b_j are typically plotted as a connected line against the ages at which they were measured. A change in the direction of the multiple regression coefficients is interpreted as indicating a critical phase of the relationship between growth and risk of later chronic disease.

Table 2 summarizes results from the multiple linear regression analysis using the Cebu data, and Figure 4 is the lifecourse plot for *SBP* regressed on the six body size z-scores (zwt_0, zwt_1, zwt_2, zwt_8, zwt_{15}, and zwt_{19}) between birth and age 19 years. Regression coefficients in early life and childhood are all small and most of them are negative, whereas the coefficient at age 19 years is large and positive. Each coefficient represents the association between a 1-SD change in weight at that age and later blood pressure, conditional on all other weights. For example, for two individuals with identical weights at birth and all ages after 1 year, a 1-SD higher weight at 1 year would be associated with a difference in SBP in later life of −0.76 (95% CI: −1.95 to +0.44) mmHg. The suggested interpretation of the entire plot is that weight gain from 15 to 19 years of age (i.e. into and through puberty) is associated with high *SBP* at 19 years.

Potential difficulty in the interpretation of the lifecourse plot arises due to collinearity among the series of body size measurements. As growth is a continuous process, successive body size measurements are generally correlated, and the shorter the age interval between two measurements the greater the correlation (Table 1). In Figure 4, when all six body size measurements are included in the multiple regression, zwt_0, zwt_1 and zwt_8 have negative associations with *SBP*, but, zwt_2 and zwt_{19} have positive correlations

Table 2 Results from multiple linear regression for (1) Model for the Lifecourse Plot: *SBP* regressed on birthweight z-scores and five z-score weights at ages 1, 2, 8, 15 and 19 years; (2) Conditional model: *SBP* regressed on birthweight z-scores and five conditional z-score weights at ages 1, 2, 8, 15 and 19 years; (3) Change Score Model 1: *SBP* regressed on birthweight z-scores and changes in consecutive weight z-scores; (4) Change Score Model 2: *SBP* regressed on changes in consecutive changes in weight z-scores and z-score weight at age 19 years

Model for Lifecourse Plot			Conditional Model			Change Scores Model 1			Change Scores Model 2		
	Coef	95% CI		Coef	95% CI		Coef	95% CI		Coef	95% CI
zwt_0	−0.54	−1.23, 0.15	zwt_0	−0.026	(−0.70, 0.64)	zwt_0	2.58	1.73, 3.43	zwt_{1-0}	0.54	−0.15, 1.23
zwt_1	−0.76	−1.95, 0.44	Cond. zwt_1	1.01	(0.28, 1.74)	zwt_{1-0}	3.12	2.31, 3.92	zwt_{2-1}	1.3	0.04, 2.56
zwt_2	0.18	−1.08, 1.45	Cond. zwt_2	1.76	(0.53, 2.99)	zwt_{2-1}	3.87	2.62, 5.13	zwt_{8-2}	1.11	0.13, 2.09
zwt_8	−0.55	−1.83, 0.73	Cond. zwt_8	2.79	(1.90, 3.68)	zwt_{8-2}	3.69	2.80, 4.58	zwt_{15-8}	1.66	0.42, 2.91
zwt_{15}	0.01	−1.41, 1.42	Cond. zwt_{15}	2.9	(1.78, 4.01)	zwt_{15-8}	4.24	3.07, 5.41	zwt_{19-15}	1.66	0.19, 3.12
zwt_{19}	4.24	2.91, 5.56	Cond. zwt_{19}	4.24	(2.91, 5.56)	zwt_{19-15}	4.24	2.91, 5.56	zwt_{19}	2.58	1.73, 3.43

zwt_0: z-scores weight at birth; zwt_{1-0}: change in z-scores between age 1 year and birth; zwt_{2-1}: change in z-scores between ages 2 and 1 year; zwt_{8-2}: change in z-scores between ages 8 and 2 years; zwt_{15-8}: change in z-scores between ages 15 and 8 years; zwt_{19-15}: change in z-scores between ages 19 and age 15 years; zwt_{19}: z-scores weight at age 19 years.

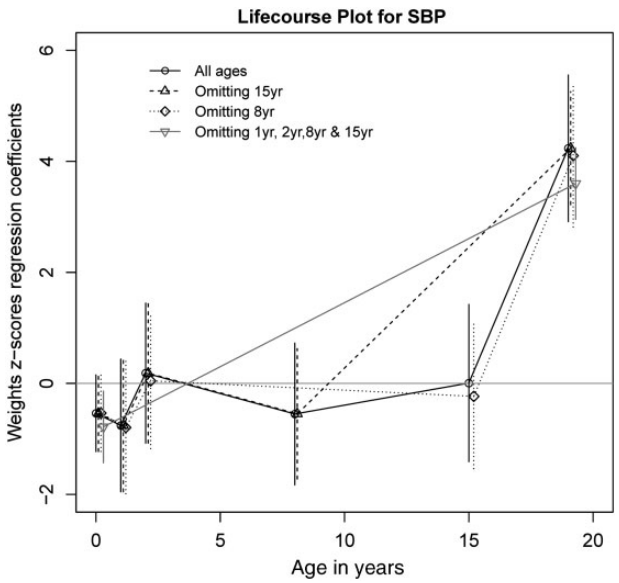

Figure 4 Lifecourse plot for *SBP* on weight z-scores during birth to age 19 years in 960 Cebu boys

with *SBP*(Table 2). Whereas these negative associations in the lifecourse plot can be viewed as adjusted associations, conditional on other weight measurements in the model, change in the direction of association may causes difficulty in the interpretation of individual coefficients. A similar issue arises if one of the six body size measurements is omitted, as the revised plot may look different. In Figure 4, we show lifecourse plots for three alternative scenarios: (i) z-score weight at age 15 years is omitted; (ii) z-score weight at age 8 years is omitted; and (iii) there are only z-score weights at birth and age 19 years. In scenario (i), there is a large change in regression coefficient between ages 8 and 19 years; in scenario (ii), the change is noted between ages 15 and 19 years; and in scenario (iii), the change occurs between birth and age 19 years. These results are not necessarily in conflict with each other, as the body size measurements are sparse and there is no interim measurement between ages 8 and 15 years. However, collinearity causes unstable estimates for regression coefficients and wide confidence intervals, making the interpretation and identification of critical periods difficult.

Path analysis

Lifecourse path analysis[18,19] can be viewed as a modification to the lifecourse plot,[18] and the model depicted in Figure 3 is one example of the lifecourse path analysis. The lifecourse plot only estimates the 'direct' relationships (such as those shown in Figure 3), whereas the path analysis attempts to estimate both direct and indirect paths simultaneously, yielding the overall effect.

Since causal relationships in the path analysis are conditional on other variables in the models, its results are very similar to those from the lifecourse plot: the lifecourse plot can be viewed as one possible lifecourse path model, and the path analysis will yield the same results. Moreover, there are many possible lifecourse path models with slightly modified causal relations among variables, yielding slightly different results. Hence we have not shown the results from the path analysis. Path analysis suffers the same problem of interpretation due to collinearity among repeated measures of the same variables (body size or health outcome).[20,21] For instance, the direct effects of early body sizes on a later health outcome in the path analysis are conditional on later body sizes, and if there are confounders for the relation between later body sizes and the health outcome, the estimated direct effect is biased.

Conditional models

Conditional body size is defined as the difference between observed and predicted body size.[22,23] The predicted body size at age measured on occasion p is obtained by regressing the observed body size on all preceding body sizes ($1 \ldots p$-1) since birth (and, potentially, other covariates), for example:

$$weight_p = b_0 + \sum_{j=1}^{p-1} b_j weight_j + e, \qquad \text{[Equation} - 1\text{]}$$

As the predicted body weight at age on occasion p is $b_0 + \sum_{j=1}^{p-1} b_j weight_j$, the conditional weight is therefore the residual error. As the residual error term is orthogonal (uncorrelated) to covariates in the model, this ensures that conditional body size on occasion p is always orthogonal to all preceding body sizes and all preceding conditional body sizes.

In the conditional body size approach, the health outcome in later life is regressed on all conditional body sizes plus birth size. It has been argued[22,23] that this approach overcomes the problem with collinearity in traditional multiple regression analysis and hence the interpretation of its results is straightforward: the expected change in health outcome given one unit difference between observed and expected body size, conditional on all previous weights.

The conditional body size analysis is equivalent to a series of regression analyses of the outcome (later blood pressure) on each weight, conditional on previous (but not future) weights. For instance, the regression model for *SBP* on p conditional weights is written as:

$$SBP = b_0 + \sum_{j=1}^{p} b_j CWT_j + e$$

where b_0 is the intercept, b_j the regression coefficient for conditional weight (CWT_j) and e the residual error term. The regression coefficients $b_j (j = 1$ to $p)$ can also be obtained by undertaking p multiple regression analyses starting with a simple model with only birthweight as the covariate and then subsequent weight measures are added as covariates one by one:

$$\begin{aligned}
SBP^{(1)} &= a_0^{(1)} + a_1^{(1)} Weight_1 + e^{(1)} \\
SBP^{(2)} &= a_0^{(2)} + a_1^{(2)} Weight_1 + a_2^{(2)} Weight_2 + e^{(2)} \\
&\ldots \\
SBP^{(p)} &= a_0^{(p)} + a_1^{(p)} Weight_1 + a_2^{(p)} Weight_2 \\
&\quad + \ldots + a_p^{(p)} Weight_p + e^{(p)}
\end{aligned}$$

where $a_0^{(k)}$ is the intercept and $e^{(p)}$ the residual error term for the k^{th} ($k = 1$ to p) regression model, and $a_i^{(k)}$ are the regression coefficient for $Weight_j$ in the k^{th} model. It can be shown that the b_j in Equation 1 are equivalent to the $a_k^{(k)}$ in the k^{th} model, i.e. the last regression coefficient in each of the 1 to p models. Therefore, the interpretation of conditional weight is the same as that of raw weight measure with the adjustment for all preceding weights. This method may not completely resolve the collinearity and associated interpretational issues. In general, there are fewer measures per model than in the single lifecourse model, but the size of the standard error is likely to increase with age, since the number of other weight measures included in the model increases.

The conditional weight z-scores analysis (Table 2) shows a similar pattern to that from tracing the z-scores in Figure 2a, i.e. that the association between blood pressure and body size increases with age. As the '‘‘direct' association between blood pressure and body weights increases with age (Table 1) and the correlations between body weights at different ages are positive, the adjustment for preceding weights will diminish the association between blood pressure and the later weight but the general patterns may (and does) remain.

In summary, collinearity among body size measurements and interpretation of coefficients which are conditioned on future measures are potential problems with the lifecourse plot and path analysis. Conditional weight analysis partially resolves the collinearity problem and may seem easier to interpret than the lifecourse plot because each coefficient is explicitly conditioned on past weights only. Consequently, conditional weight analysis may be seen as a compromise between tracing z-scores and lifecourse plot: coefficients in tracing z-scores are simple regression coefficients, and those in lifecourse plot are conditioned on past and future weights. Like tracing body size z-scores, these approaches require that all measures must be taken at the same times/ages for all individuals.

Regression with change scores

If our aim is to identify a critical period of time during the lifecourse in which rapid growth in body size is associated with an increased risk of chronic diseases, an intuitive approach is to regress the outcome on the growth in body size in different periods of time during the lifecourse.[24,25] For p body weight measurements at different ages, there are $p - 1$ variables for incremental changes in body weight, and we can regress the outcome y on $p - 1$ incremental changes in body weight and the first body size or we can regress y on $p - 1$ incremental changes in body size and the last body size. Note that we cannot regress y on $p - 1$ incremental changes in body size, the first and the last body size, as this leads to over-parameterization of the model (due to perfect collinearity).

In our example, there are six body weight z-scores from birth to age 19 years, so we may regress *SBP* on z-score at birth (zwt_0) and five incremental changes in z-scores;the Change Score Model 1 in Table 2 shows

the results from this multiple regression model. The regression coefficients for growth in weight z-scores during adolescence are relatively larger than early growth and birth size, suggesting a greater impact on *SBP,* and (in contrast to the methods discussed so far) z-score weight at birth (zwt_0) has a positive association with *SBP*.

Alternatively, *SBP* can be regressed on the five incremental changes in weight z-scores and weight z-score at age 19 years (zwt_{19}). Change Score Model 2 in Table 2 shows the results from this second multiple regression. Whereas zwt_{19} seems to have the largest effect on *SBP*, the regression coefficients for the five incremental changes in weight z-scores in Change Score Model 2 are much smaller than in Change Score Model 1, but later growth still has a larger effect than early growth. Although the two sets of regression coefficients may look different, there is a simple mathematical relationship between them: for the same variables, regression coefficients in Change Score Model 1 = 2.58 + regression coefficients in Change Score Model 2. Since zwt_{19} can be expressed as:

$$zwt_{19} = zwt_{19-15} + zwt_{15-8} + zwt_{8-2} + zwt_{2-1} + zwt_{1-0} + zwt_0,$$

the regression coefficients for the five incremental changes in body weight z-scores in Change Score Model 1 are those in Change Score Model 2 plus the regression coefficient for zwt_{19} in Change Score Model 2, which is 2.58; and the regression coefficient for zwt_0 in Change Score Model 1 is the same as that for zwt_{19} in Change Score Model 2.

This model is a re-parameterization of the lifecourse plot model,[24] and thus the same advantages and disadvantages apply. However, the weight changes are likely to be less correlated than the actual weights, and thus the problem of collinearity is again at least partially resolved. To include all the incremental changes, birth size and body size in one model requires special statistical methodology, such as partial least squares regression. A detailed explanation of how partial least squares regression may be applied to lifecourse epidemiology is beyond the scope of this review, and we refer readers to our previous studies.[26–28]

Multilevel and latent growth curve modelling

There are two approaches to estimating the effects of growth at different phases on health status in later life. A two-stage approach may be adopted by first estimating changes in body size or growth velocity in different growth phases during the lifecourse; health outcomes in later life are then regressed on these estimated growth variables.[34–36] Alternatively, we can estimate the growth trajectories and their effects on later health outcomes in the same model. Both one-stage and two-stage approaches could use multilevel or latent variable methods to model the growth trajectories.

Multilevel models (MLM), also known as random-effects models or mixed models, can be used to analyse longitudinal data: the repeated measurements are treated as 'level-one' variables clustered within subjects treated as 'level-two' variables.[29–33] Non-linear growth, different phases of growth, and complex level-1 variation or autocorrelation, can be included in such models.[31]

The growth trajectory model can also be estimated under the statistical framework of latent growth curve modelling (LGCM) which is a special type of structural equation model for longitudinal data analysis.[29,30] Similarly to the multivariate MLM, the LGCM can also model jointly the association between the latent growth factors and distal outcome(s), such as SBP. In multilevel models the longitudinal data are in the long format, i.e. the six body weights between birth and age 19 years are treated as repeated measurements and stacked in one column, whereas in LGCM the six body weights are treated as six different variables.

In LGCM, the baseline body weight and change in weights are estimated by two latent variables denoted, for example, as F1 and F2 respectively, whose means are estimated as part of fixed effects and variances as random effects in MLM. The factor loadings for the six body weights on F1 are all unity and, as a result, F1 becomes the estimated baseline body weight. If the factor loadings for the six body weights on F2 are specified by the chronological ages when those weights were measured, F2 is interpreted as the estimated growth in weight per year since birth to age 19 years. One advantage of LGCM is that the first and the last factor loadings can be fixed to be 0 and 19, respectively, whereas the other factor loadings are freely estimated.[29] If the growth is nearly linear, the estimated factor loadings should be close to the chronological ages; otherwise they reflect the different growth velocities throughout the lifecourse.

As Figure 1 clearly indicates, growth in body weight does not follow a linear pattern and we therefore estimate a nonlinear growth model by freeing the factor loadings of the middle four body weights on F2. The four factor loadings estimated by the nonlinear model are 1.962, 2.649, 6.663 and 16.561, for weight at ages 1, 2, 8 and 15 years, respectively. This indicates that the growth velocity between birth and age 1 year is about twice as fast as the overall average, and weight gain then becomes much slower between ages 1 and 8 years, greater between ages 8 and 15 years and slows again after age 15 years. Note that by freeing the factor loadings, the growth curve has been linearized, and the mean of F2 estimates the average weight gain per unit of time. Therefore, the association between F2 and SBP is the association between growth velocity in weight

(or overall weight gain) and *SBP*. The associations between F1 (birthweight) and F2 (growth velocity) with SBP are −4.94 mmHg/kg (95% CI: −7.72 to −2.15) and 8.41 mmHg $kg^{-1}yr^{-1}$(95% CI: 6.63 to 10.19), respectively. However, it should be noted that these associations are mutually adjusted, i.e. both F1 and F2 are included in the model for SBP. Thus, the large negative association between birthweight and later SBP requires careful interpretation as it is conditioned on subsequent growth.

LGCM and MLM can be used to estimate the effects of growth in different periods of the lifecourse on the health outcomes in later life.[24] For instance, to estimate the effect of early (between birth and age 2 years) and later (between ages 2 to 19 years) growth in body weight on *SBP*, we set up three latent variables in the model: the intercept, the growth in body weight between birth and age 2 years, and the growth between age 2 to age 19 years. This model estimates different linear weight gain velocities between birth and age 2 years, and between ages 2 and 19 years. However, as the assumption of linear growth trend is unlikely to be correct, we free the factor loading of $Weight_1$, $Weight_8$ and $Weight_{15}$. The factor loading of *Weight*1 on F2 is 1.48, indicating the growth in weight is greater in the 1st and the 2nd year. The factor loadings of $Weight_8$ and $Weight_{15}$ on F3 are 4.17 and 14.47, respectively, indicating that the growth velocity in weight between ages 8 and 15 years is greater than that between ages 2 and 8 years and between ages 15 and 19 years. Whereas gain in body weight between ages 2 and 19 years has a positive association with *SBP* (8.109, 95% CI: 6.43 to 9.78), the association with weight gain between birth and age 2 years is small and negative (-0.674, 95% CI: −2.20 to 0.85), and birthweight has a negative association with *SBP* (-2.115, 95% CI: −4.50 to −0.18). More details on the results from LGCM can be found in Supplementary data available at *IJE* online.

Although using LGCM to estimate the effects of growth on later outcomes is more flexible than multiple regression, it also has several disadvantages. First, the number of latent variables for growth in the different phases of the lifecourse is limited by the number of body size measurements. How these phases are demarcated needs guidance from biological theory. Second, measurements of body size need to be made at similar ages for the entire cohort in LGCM (although not for the equivalent MLM).When the number of repeated measurements is large, it becomes possible to use complex semi-parametric or non-parametric functions, such as spline functions,[33–35] to model individual growth trajectories within the framework of multilevel modelling, though most commercial software packages have not yet implemented such facilities.

Growth mixture models

Both MLM and LCGM assume that all individuals follow the same basic pattern of growth with random variation about that pattern. However, there may be subgroups within the population showing different patterns of growth. Two methods can identify trajectories for subgroups: group-based modelling[37–39] and growth mixture modelling.[40,41] In group-based modelling, whereas different classes have different growth trajectories, subjects within each class are assumed to have identical intercepts (i.e. baseline values) and slopes (i.e. trajectories).[39,41] In contrast, in growth mixture modelling, within-class variations are allowed in the estimation of class memberships, i.e. within each class there may be variation in growth trajectories.[41] Group-based modelling can be considered a special case of growth mixture modelling, where all within-class variations are constrained to be zero. Different model specifications of the within-class random structure can lead to very different models derived in terms of the 'best' number of growth mixtures, their size and composition.

To illustrate growth mixture modelling, we use the macro PROC TRAJ in the statistical software SAS (version 9.1.3)[38] to analyse the body weight z-scores. We fit a quartic curve for each group and start with a 2-class model and gradually increase the number of classes.

Figure 5 shows the growth curves for each class in different models. There are several statistical indices for selecting the 'best' model,[38–42], e.g. Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC). Both capture model parsimony, though in practice their usefulness is sometimes limited. For instance, Table 3 shows the results of 2- to 5-class models. Both AIC and BIC values reduce with the number of classes, and they are still reducing when the number of classes goes beyond six. However, as the number of subjects in some classes becomes small (less than 5%), we feel it may not be sensible to increase the number of classes.[37–41] Consequently, it is not possible to use either index to determine the most parsimonious model. Furthermore, when the number of classes increases, the interpretation of each class in different models becomes less straightforward; researchers need to draw a balance between model complexity and model interpretability.[42] For our Cebu cohort example, we viewed the 3-class model 'best' in terms of this balance. In this model, class-1 (53%)comprised men who were born small and remained small, and class-2 (44%) comprised men who were born large and remained large; whereas class-3(about 3%) comprised men who were born larger than average and who became even larger after age 8 years. The average *SBP* in class-1, class-2 and class-3 was 105.0, 107.26 and 117.83 mmHg, respectively, and differences between class-2/class-3 and class-1 are: 2.26 mmHg, 95%CI: 0.93 to 3.60; 12.83 mmHg, 95%CI: 8.90 to 16.77.

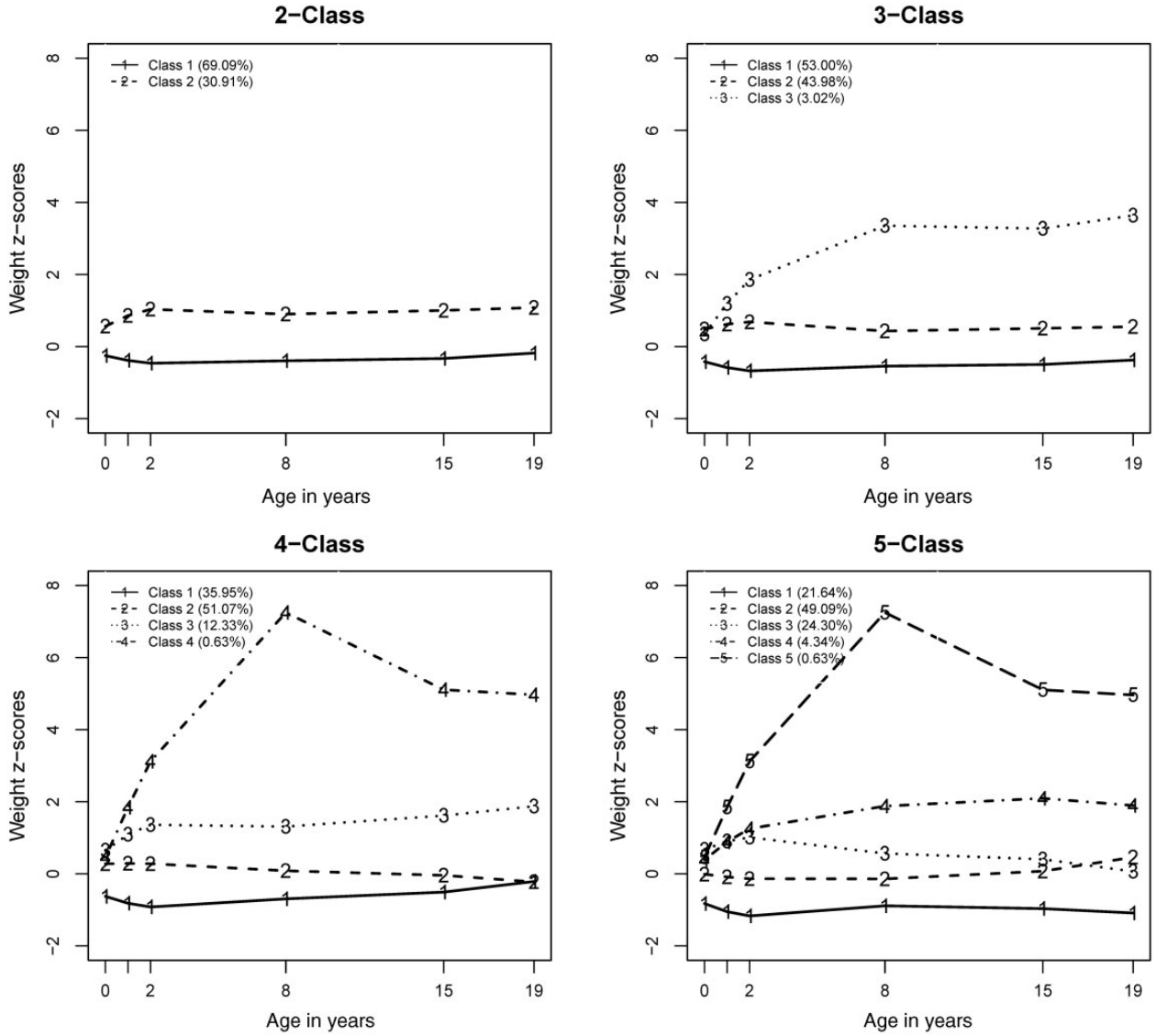

Figure 5 Weight trajectories identified by group-based models with different numbers of classes

Growth mixture modelling also has several disadvantages. As with LGCM, measurements of body size need to be made at similar ages for the entire cohort. Model specifications are also sometimes arbitrary and the selection of the optimal model is not always straightforward, as shown in our example. In the analysis illustrated, there is no within-class variation for the estimated growth curves, but if within-class variation is allowed, the growth trajectories would likely look very different.[42,43] This emphasizes the importance of specifying the underlying random structure in these types of models, and this should be informed, wherever possible, by an understanding of the biological underlying cause of variation.[44] Furthermore, distinctive growth curves such as those in Figure 5 are average patterns from which observed curves may deviate greatly. Finally, the identified trajectories may not always match those hypothesized by researchers; for instance, in our Cebu example we sought to test whether people with an early catch-up growth pattern had a higher risk of developing higher blood pressure in later life, yet no such pattern was identified by GMM. Although we found that men in class-3 (about 3%), who were born larger than average and who also became even larger after age 8 years, had a higher average blood pressure, this does not tell us when or how these differences could have arisen.

Concluding remarks

Our analyses of the Cebu cohort shows that both simple and more sophisticated approaches can yield some similar conclusions, i.e. that weight, or weight gain in late adolescence, has a fairly large, positive

Table 3 Average SBP in each class in different group-based models

	Mean SBP	SD SBP	No. of subjects	Difference in SBP[a]	95% CI for difference in SBP
2-Class Model (BIC = −7464.91, AIC = −7435.71)					
Class-1	105.38	10.45	666		
Class-2	108.60	10.51	294	3.22	(1.78, 4.66)
3-Class Model (BIC = −7038.07, AIC = −6994.27)					
Class-1	105.00	10.48	511		
Class-2	107.27	10.11	421	2.26	(0.93, 3.60)
Class-3	117.83	10.81	28	12.83	(8.90, 16.77)
4-Class Model (BIC = −6807.09, AIC = −6748.68)					
Class-1	104.54	10.06	343		
Class-2	106.22	10.26	495	1.68	(0.27, 3.10)
Class-3	111.55	11.11	116	7.01	(4.85, 9.18)
Class-4	122.89	8.12	6	18.35	(10.04, 26.66)
5-Class Model (BIC = −6663.36, AIC = −6590.36)					
Class-1	104.41	10.35	200		
Class-2	105.91	10.33	485	1.49	(-0.21, 3.20)
Class-3	107.28	9.99	229	2.87	(0.91, 4.84)
Class-4	114.05	12.38	40	9.64	(6.13, 13.15)
Class-5	122.89	8.12	6	18.48	(10.07, 26.88)

[a]The reference class is Class-1 in each model.

association with blood pressure in later life. However, there are also differences in conclusions about the association between early growth and later blood pressure. Table 4 provides a summary of some of the advantages and disadvantages of all approaches evaluated in this study. Choice of approach will depend on the hypothesis to be tested (e.g. whether the hypothesis is about associations between size or changes in size and the future outcome) and study design. Where a study has a small number of measures, at defined time-periods (e.g. weight at birth, 1 year and 5 years), the simple methods (e.g. regressing outcome on each weight measure adjusted for previous weight) are likely to be sufficient. For a study with a larger number of measures, and/or different measurement occasions across individuals, multilevel models would be a more suitable approach. Methods which condition on all periods simultaneously (e.g. lifecourse models and plots and path analysis) require careful interpretation if they are not to lead to erroneous conclusions, and should be avoided. Easier to interpret are models that condition only on earlier changes, though models with multiple change points considered simultaneously still yield overall interpretational difficulties. The latent class models can only be interpreted in terms of differences in the entire trajectory rather than specific periods, and should not be used if there are specific hypotheses about the association between trajectory and outcome, as it is unlikely that the classes identified will correspond exactly to the hypothesis specified.

The lifecourse models (and their associated plots) identified negative associations between some early weight measures and later blood pressure, with wide confidence intervals (including no effect) for all but the last weight measure. In contrast, the inclusion of birthweight and all subsequent weight changes in one model led to the conclusion that birthweight and all subsequent weight changes are positively related to later blood pressure, with the size of the association increasing gradually with age. The latent growth model concluded that birthweight had a large, negative association with SBP, whereas growth velocity had a positive association. For all these methods, care is needed in the interpretation of associations that condition on later (as well as previous) changes. Use of GMM did not identify any classes that demonstrated different initial growth patterns that yielded the same final weight in our chosen 3-class model, and therefore could not be used to examine specific hypotheses about the associations between early growth and later blood pressure. Class-2 and class-3 in the 5-class model did seem to show the same final weight with some differences in earlier life growth trajectories, but their difference in the blood pressure was small (Table 3).

Table 4 Summary of advantages and disadvantages of statistical approaches discussed in this review

	Advantages	Disadvantages
Tracing the z-scores	Simple, straightforward to implement	Just a connection of a series of simple associations at different ages No confidence intervals for the observed trajectories Continuous outcomes have to be dichotomized Body size needs to be measured more or less at the same age for all cohort members Interpretation could be subject to statistical artefact
Lifecourse plot	Simple	Collinearity amongst body size measurements may cause problems with interpretation due to wide confidence intervals Body size needs to be measured more or less at the same age for all cohort members Interpretation not straightforward as conditioning on later measures.
Lifecourse path analysis	Causal relations explicitly specified Multiple outcomes can be analysed simultaneously	Body size needs to be measured more or less at the same age for all cohort members Correct causal relations and models are not always easy to identify Collinearity can still be a problem
Conditional body size analysis	Conditional body size variables are always statistically independent Simple, straightforward to implement and interpret	Body size needs to be measured more or less at the same age for all cohort members Equivalent to a series of multiple regression models with body size measures included as covariates one by one Though conditional body size variables are always statistically independent, their interpretation is similar to the tracing the z-scores or the lifecourse plot.
Regression with change scores	Simple, straightforward to interpret	More than one model is possible but interpretations are different Body size needs to be measured more or less at the same age for all cohort members Is a re-parameterization of the lifecourse plot model Interpretation not straightforward as conditioning on later measures.
Multilevel modelling	Body size does not need to be measured at the same ages for all cohort members Estimates individual trajectories Can model nonlinear growth curves	A two-stage approach may be required to test the association between growth and binary health outcomes in later life or specialist software packages such as Mplus are required to undertake this in one step Parameterizing the trajectory may be done in many different ways, and may lead to differing interpretations
Latent growth curve modelling	Estimates individual trajectories Can model nonlinear growth curves Straightforward to test the association between growth and health outcomes in later life in one stage Straightforward to incorporate latent variables	Body size needs to be measured more or less at the same age for all cohort members Parameterizing the trajectory may be done in many different ways, and may lead to differing interpretations Correct causal relationships are not always easy to identify as associations with outcome are conditioned on all latent variables
Growth mixture modelling	Estimate individual trajectories Identify distinctive subgroups in the population Can model nonlinear growth curves Straightforward to test the association between growth and health outcomes in later life in one stage Straightforward to incorporate latent variables	Computer-intensive technique Body size needs to be measured more or less at the same age for all cohort members Choosing the correct model (number of classes) is not always straightforward Class composition (hence interpretation) varies with different parameterizations of the random variation in the data The interpretation of the classes may not be straightforward The model is likely to identify subclasses of the population whether or not they exist, and whether or not they are meaningful

Finally, we make a few general comments on the selection and comparisons to be made among the different approaches. First, body size and growth cannot be separated conceptually, because growth is derived from repeated measures of body size. For instance, when weight at age 19 years is related to the outcome and previous weights are not, this does not necessarily mean that weight on the 19th birthday matters, as weight at age 19 years is also the sum of all previous weight gains and birthweight. Second, to identify

critical sensitive phases throughout the lifecourse may require several statistical approaches to identify growth trajectory features related to adverse health outcomes in later life. Third, we used body weight z-scores trajectories for some approaches and raw weight scores for others. As z-scores measure the relative body size or ranking of one individual in the sample population, changes in z-scores have a different interpretation from changes in raw weights. One potential advantage of using z-scores for weight instead of weight is that variance of weight increases rapidly with age in the first two decades of life. If the research question is, however, to investigate the association between weight change in adulthood (where the variance remains reasonably stable) and health outcomes in old age, raw body weight would be more appropriate.

In conclusion, each of the approaches discussed has their limitations and we may need a combination of these approaches to unravel the complexities we observe in lifecourse research. The exact choice of method depends upon the nature of the available data and the specific research question(s) of interest; model parameterization then depends upon both construct and context of the data under evaluation. However, any method which explicitly or implicitly conditions on the future needs very careful interpretation and should be avoided in general.

Supplementary Data

Supplementary data is available at *IJE* online.

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