Response to the Letter to the Editor by Goldberg and Terry

Bianca L. De Stavola, Rachel Denholm, and Isabel dos-Santos-Silva

Correspondence to Professor Isabel dos-Santos-Silva, Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom (email: isabel.silva@lshtm.ac.uk)

Author affiliations: Population, Practice and Policy Programme, University College London Great Ormond Street Institute of Child Health, London, UK (Bianca L. De Stavola); Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK (Rachel Denholm); Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK (Rachel Denholm; Isabel dos-Santos-Silva).

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Goldberg and Terry (G&T) raise several points of interest in their letter (1). These arise from the complexities of modelling – and then interpreting – the relationship between early life longitudinal information and later life outcomes. As such analyses were at the core of our paper (2), we welcome the opportunity to clarify our results.

The first point G&T raise concerns our report of no association between successive increments in standardized height and weight in infancy/early childhood (later referred to as z-scores) and either total breast volume or percent water. G&T point out that the estimates that refer to these successive increments are mutually adjusted, and hence, in their view, can only capture "direct effects" of each of these increments. We disagree with this interpretation as explained below.

This criticism would be correct if we had used absolute z-scores when fitting the models. However, by using consecutive increments in z-scores, we estimated the cumulative effect of increasing each age-specific z-score by one unit. As demonstrated in De Stavola et al. ((3) – equation 5), a model that is specified in terms of absolute values of an exposure measured longitudinally can be reparametrized as a model that includes the first of these measures and its consecutive increments, with the coefficients of the two models having different interpretations. Letting Y denote percent water and Z_j the z-score measured at time j, for $j=1,\dots,J$, with Z_1 indicating birth weight (or birth length), the two model specifications are:

$$E(Y|Z_1, Z_2, \dots, Z_J) = \beta_0 + \beta_1 Z_1 + \beta_2 Z_2 + \cdots + \beta_J Z_J \qquad (1)$$

$$E(Y|Z_1, Z_2, \dots, Z_J)$$
$$= \beta_0 + \left(\sum_{j=1}^{J} \beta_j\right) Z_1 + \left(\sum_{j=2}^{J} \beta_j\right)(Z_2 - Z_1) + \left(\sum_{j=3}^{J} \beta_j\right)(Z_3 - Z_2) + \cdots$$
$$+ \beta_J Z_J \qquad (2)$$

These equations show that the coefficient of each explanatory variable in specification (2) (i.e. of each increment in z-score) is the sum of the coefficients for the corresponding and later z-scores terms in model (1). Hence, each regression coefficient in (2) is to be interpreted as the expected cumulative change in Y per one-unit change in z-score at the end of that spell. They are therefore in a sense "total" effects, in contrast to the individual β_j coefficients that could instead be interpreted as "direct effects". We would however refrain from labelling these coefficients using this terminology, because of the additional assumptions (especially those of no-unmeasured confounding) invoked in mediation analysis (4).

The results presented in our paper (2) are for models specified as in (2) and covering the full range of measurements, i.e. from birth to young adulthood. In response to G&T's comments therefore, we report here alternative versions of (2), where we vary the timing of the final increment when estimating their association with MRI percent water. Moreover, as we only published results from models that included birth weight, birth length and successive increments in both height and weight, we now report coefficients estimated separately for these two dimensions (Table 1). The size and significance of these new sets of estimates show how it is still the later (post-pubertal) measurements that exert the strongest impact, confirming our original interpretation.

The second point G&T raise concerns whether our data provided any evidence of modification by birth size of the effect of weight and length increments at different ages. The last column of Table 1 reports the results of the corresponding interaction tests. Only that between birth weight and weight gain between ages 0-3 months indicates a weak synergism between them.

In conclusion, we hope that these additional considerations will contribute to clarify some of the complexities of studying the relationship between early life growth and MRI breast-tissue composition.

<u>References</u>

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Table 1: Cumulative linear regression models for magnetic resonance imaging (MRI) breast percent water at age 21 years with birth length or weight and additionally standardized height or weight increments between ages 0 to respectively 15 and 21 years, Avon Longitudinal Study of Parents and Children, 1991-2014 (n=480).

Growth variable, units	Model 1		Model 2		Model 3		Model 4		Model 5		p-value for interaction [c]
	RC [a]	95% CI [b]	RC [a]	95% CI [b]	RC [a]	95% CI [b]	RC [a]	95% CI [b]	RC [a]	95% CI [b]	
Height, cm											
Birth length	1.02	0.98, 1.07	0.99	0.93, 1.05	0.99	0.93, 1.06	0.98	0.93, 1.04	0.98	0.93, 1.03	
Height increments between ages, cm [d]											
0 – 3 months	1.02	0.96, 1.08	1.09	0.98, 1.20	1.08	0.98, 1.20	1.07	0.98, 1.16	1.06	0.98, 1.15	0.325
3 – 12 months	1.01	0.96, 1.07	0.93	0.82, 1.05	0.93	0.83, 1.05	0.94	0.85, 1.04	0.95	0.86, 1.04	0.843
1 – 3 years	1.02	0.97, 1.07	1.12	0.99, 1.25	1.12	1.00, 1.25	1.10	1.00, 1.21	1.10	1.00, 1.20	0.737
3 – 7 years	1.00	0.96, 1.05	0.92	0.82, 1.03	0.92	0.82, 1.02	0.94	0.86, 1.03	0.95	0.87, 1.03	0.224
7 – 10 years			1.06	1.00, 1.12	1.07	1.01, 1.13	1.06	1.01, 1.12	1.06	1.01, 1.11	0.052
10 – 12 years					0.97	0.95, 1.00	1.01	0.98, 1.03	1.01	0.99, 1.03	0.101
12 – 15 years [e]							1.07	1.04, 1.10	1.05	1.02, 1.08	0.475
Weight, kg											
Birth weight	1.03	0.99, 1.06	1.03	0.99, 1.06	1.03	1.00, 1.07	1.04	1.01, 1.07	1.07	1.04, 1.10	
Weight increments between ages, kg [d]											
0 – 3 months	0.99	0.97, 1.02	0.99	0.96, 1.01	0.99	0.97, 1.01	1.00	0.98, 1.02	1.01	0.99, 1.03	0.038
3 – 12 months	0.97	0.95, 1.00	0.97	0.95, 1.00	0.97	0.95, 0.99	0.98	0.96, 1.00	1.00	0.98, 1.03	0.104
1 – 3 years	1.00	0.97, 1.03	0.98	0.95, 1.01	0.97	0.94, 1.00	0.99	0.96, 1.01	1.02	1.00, 1.05	0.300
3 – 7 years	0.88	0.85, 0.91	0.97	0.92, 1.02	0.95	0.91, 1.00	0.94	0.90, 0.98	1.03	0.98, 1.09	0.347
7 – 10 years			0.91	0.87, 0.94	0.89	0.86, 0.93	0.94	0.91, 0.97	1.03	0.99, 1.08	0.153
10 – 12 years					0.93	0.91, 0.96	0.95	0.93, 0.97	0.94	0.92, 0.96	0.992
12 – 15 years							0.89	0.87, 0.90	0.89	0.88, 0.91	0.761
15 – 21 years									0.79	0.73, 0.85	0.118

CI: confidence interval; RC: relative change in breast percent water per one standard deviation increment in the exposure of interest

[a] RC estimates were adjusted for all the earlier height and weight measurements, and additionally for age and menstrual phase at magnetic resonance imaging (MRI) examination. MRI breast percent water was log transformed. Exponentiated estimated regression parameters are presented.
[b] 95% CI were calculated by exponentiating the original 95% CIs (as detailed in (2)).
[c] p-values for the interaction between each height increment with birth length, and each weight increment with birth weight in Model 5.
[d] Height and weight growth measures from birth to age 10 years were derived using linear spline multilevel modelling of height and weight (as detailed in (5)). From age 10 years, growth measures were calculated from a piecewise mixed effect model with knots at age 10, 12 and 15 years (as detailed in (2)). All growth measures, and all growth differences, were standardised, with regression coefficients representing expected changes per one standard deviation.
[e] Adult height was attained by age 15 years and therefore height increments between age 15 and 21 years were not included in the model.