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Effect of Correcting the Postnatal Age of Preterm-Born Children on Measures of Associations Between Infant Length-for-Age *z* Scores and Mid-Childhood Outcomes

Nandita Perumal*, Daniel E. Roth, Donald C. Cole, Stanley H. Zlotkin, Johnna Perdrizet, Aluisio J. D. Barros, Ina S. Santos, Alicia Matijasevich, and Diego G. Bassani

* Correspondence to Dr. Nandita Perumal, Department of Global Health and Population, Harvard T. H. Chan School of Public Health, 90 Smith Street, 3rd Floor, Boston MA 02215 (e-mail: nperumal@hsph.harvard.edu).

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Child growth standards are commonly used to derive age- and sex-standardized anthropometric indices but are often inappropriately applied to preterm-born children (<37 weeks of gestational age (GA)) in epidemiology studies. Using the 2004 Pelotas Birth Cohort, we examined the impact of correcting for GA in the application of child growth standards on the magnitude and direction of associations in 2 a priori–selected exposure-outcome scenarios: infant length-for-age *z* score (LAZ) and mid-childhood body mass index (scenario A), and infant LAZ and mid-childhood intelligence quotient (scenario B). GA was a confounder that had a strong (scenario A) or weak (scenario B) association with the outcome. Compared with uncorrected postnatal age, using GA-corrected postnatal age attenuated the magnitude of associations, particularly in early infancy, and changed inferences for associations at birth. Although differences in the magnitude of associations were small when GA was weakly associated with the outcome, model fit was meaningfully improved using corrected postnatal age. When estimating population-averaged associations with early childhood growth in studies where preterm- and term-born children are included, incorporating heterogeneity in GA at birth in the age scale used to standardize anthropometric indices postnatally provides a useful strategy to reduce standardization errors.

corrected age; gestational age; growth standards; infants; preterm birth

Abbreviations: BMI, body mass index; GA, gestational age; IQ, intelligence quotient; LAZ, length-for-age *z* score; LMP, last menstrual period; SD, standard deviation; WHO-GS, World Health Organization Child Growth Standards.

Early childhood growth is a sensitive marker of a wide range of health outcomes later in life, including cardiometabolic health and cognitive development (1–3). Life-course epidemiologic studies, particularly those examining the "developmental origins of health and disease" hypothesis, are therefore often interested in assessing fetal and early childhood growth. A common method to express growth in early childhood is through the application of newborn size or child growth standards to derive age- and sex-standardized anthropometric indices (or *z* scores) relative to a reference population, which are generalizable across populations and over time (4).

The 2006 World Health Organization Child Growth Standards (WHO-GS) are the most widely used normative growth standards to monitor within- and between-child variations in growth (4, 5). These standards, however, are based on a reference population of children born at term, between $37^{0/7}$ and $42^{0/7}$ weeks of gestational age (GA), and therefore are not directly applicable to children born preterm, born prior to $37^{0/7}$ weeks of GA. Several clinical guidelines (6, 7) therefore recommend accounting for variations in GA at birth in the evaluation of postnatal child growth by: 1) using GA-specific neonatal size standards in the assessment of size at birth—a conventional practice in perinatal epidemiology—and 2) using GA-corrected postnatal age ("corrected age") for preterm-born children (i.e., subtracting the number of weeks an infant is born preterm from their postnatal age) in the application of the WHO-GS for assessing postnatal anthropometry up to 24–36 months of age.

Corrected postnatal age, however, is rarely employed in population-based epidemiologic research where preterm- and term-born children are included (8). In a scoping review of 80 epidemiologic studies on child growth, investigators often incorrectly used uncorrected postnatal age to standardize and track growth of preterm-born infants using the WHO-GS and then used a variety of analytical methods, including GA restriction, stratification, and regression-based adjustment, to account for variations in anthropometric indices due to heterogeneity in GA at birth (8). These analytical strategies, however, ignore age-standardization errors in anthropometric indices due to discrepancy in the biological age of the sample population relative to the reference population, which might (or might not) be corrected by regression-based adjustment for GA. For studies examining the developmental origins of health and disease hypothesis, standardization error might have a substantial effect on the direction and/or magnitude of associations between early-life exposures and later health outcomes.

Using data from the 2004 Pelotas (Brazil) Birth Cohort study, we examined the extent to which age-standardization errors in anthropometric indices and indicators due to preterm birth might affect measures of association of early childhood growth with postnatal outcomes. Specifically, we estimated and compared the associations between infant length, measured by length-for-age z score (LAZ), derived using a corrected versus uncorrected (conventional) postnatal age, and postnatal outcomes. We further assessed the impact of varied structural roles of GA, the strength of association between GA and outcome in a given scenario, and the prevalence of preterm birth on the direction and magnitude of population-averaged measures of associations.

METHODS

Data source

The 2004 Pelotas Birth cohort design and data collection procedures have been described in detail elsewhere (9–11). Briefly, 99.3% of all live births (n = 4,231) that occurred in the city of Pelotas from January 1st to December 31st, 2004, were enrolled in the cohort. Information on prenatal exposures and perinatal outcomes were collected soon after delivery based on maternal interviews. Anthropometry was collected at birth and at 3 and 12 months' postnatal age. Child length was measured using a foldable wooden length board with 1-mm precision by trained interviewers who underwent standardization sessions every 3 months. At the 3- and 12-month follow-up visits, 95.7% and 93.6% of the participants enrolled at birth remained in the cohort, demonstrating minimal loss to follow-up (12). The cohort study was approved by the Research Ethics Committee of the Medical School of the Federal University of Pelotas and the World Health Organization Ethics Committee (Geneva) for data collected at birth. Ethical approval for this study was obtained from the Hospital for Sick Children and the University of Toronto.

Measurement of variables

Gestational age. We constructed a variable for GA at birth based on first day of the last menstrual period (LMP) or the Dubowitz score, if LMP was unavailable or was implausible (i.e., ≤22 weeks or ≥45 weeks). To ensure validity of the GA estimate, we used the best available GA-specific size at birth reference/standards to flag implausible GA values as previously described (13). Briefly, observations (n = 215) were flagged if birthweight for GA was: 1) outside the range of 2 standard deviations (SD) according to GA-specific newborn size references/standards (14, 15) for infants born between $22^{0/7}$ to $36^{6/7}$ weeks of GA; or 2) outside 3 SD using WHO-GS at age "0" for children born at ≥37 weeks. If LMP-based GA values were flagged, we used Dubowitz-based GA if they were within the range of plausibility based on the criteria above (n = 174) or flagged again (n = 11) to assess whether these values were within 3 SD of birthweight for GA, because values within this range were less likely to be due to measurement error. Flagged observations for which there was only one method of GA assessment (i.e., LMP or Dubowitz) and that therefore could not be corroborated with another method (n = 30), and those that were outside 3 SD birthweight-for-GA based on both LMP and Dubowitz (n = 1), were set to missing.

Age scales and the application of growth standards. Infant length-for-age z scores (LAZ) at birth and at 3- and 12-month follow-up visits were derived using both a GA-corrected postnatal age ("corrected") and an "uncorrected" postnatal-age strategy. For the uncorrected strategy, we applied the WHO-GS using postnatal age for all children irrespective of their GA at birth (as is conventionally done in epidemiologic studies). In primary analyses, we did not use corrected postnatal age for infants born at term because the WHO-GS are meant to be directly applied to all infants who are born at ≥37 weeks of GA. For the corrected strategy, we used the INTERGROWTH-21st very-preterm size at birth references (16) for infants born between $24^{0/7}$ to $32^{6/7}$ weeks of GA and the INTERGROWTH-21st newborn size standards (15) for infants born at $33^{0/7}$ to $43^{0/7}$ weeks of GA. For measurements after birth, the WHO-GS were applied using corrected age for preterm-born infants (i.e., postnatal age − (280 days − GA at birth)) (7) and postnatal age for term-born infants. For infants born at ≥$43^{0/7}$ weeks of GA (i.e., ≥300 days), we truncated GA to 300 days to allow for the application of INTERGROWTH-21st newborn size standards at birth and minimize data loss (n = 127). Of note, although the corrected strategy uses multiple standards, the primary difference from the uncorrected postnatal-age strategy is the ability to incorporate heterogeneity in GA at birth in the age scale used to derive anthropometric indices.

Definition of exposure/outcomes. We purposely selected 2 empirical scenarios that have previously been observed in the epidemiologic literature for illustration (17, 18) (Figure 1; Web Appendix 1, available at https://academic.oup.com/aje). For scenario A, age- and sex-standardized body mass index (BMI) z scores at 6 years of age were derived using the WHO Anthro 2007 package. In scenario B, child intelligence quotient (IQ) at 6 years of age was assessed

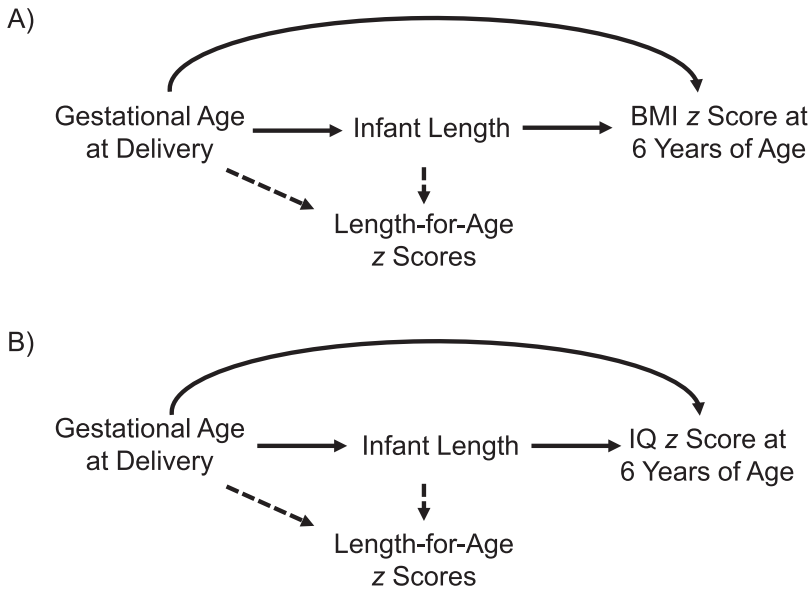

Figure 1. Empirical scenarios in which infant length, as measured by length-for-age z-scores (LAZ), is considered as an exposure. Dashed lines demonstrate the deterministic relationship between measured variables and derived *z* scores. Measures of association of interest are: A) total association between infant LAZ and body mass index (BMI) *z* score at 6 years of age; B) total association between infant LAZ and full-scale intelligence quotient (IQ) *z* score at 6 years of age. In primary analyses, we compared associations when infant LAZ was derived using a gestational age-corrected age versus uncorrected postnatal-age strategy in the application of child growth standards.

using 4 subsets of the Wechsler Intelligence Scale for Children 6–16 years of age—picture completion, block design, arithmetic, and picture concepts—to evaluate global IQ for each child (9). For interpretation, we transformed the IQ measures into z scores by subtracting the group mean from each observation and then dividing by the cohort SD. In sensitivity analyses, we assessed the implications of using corrected versus uncorrected postnatal age for preterm-born children in a scenario where GA is a mediator between maternal high blood pressure during pregnancy (yes/no) and infant LAZ.

Statistical analyses

We used corrected and uncorrected postnatal-age strategies to estimate 3 metrics of infant LAZ: mean LAZ, the proportion of children classified as being stunted (i.e., LAZ < -2), and conditional measures of LAZ. Conditional measures are residuals derived from regressing size at a given follow-up time (i.e., 3-month or 12-month) on size at birth (e.g., $\text{LAZ}_{time\text{`}j\text{'}} = \beta_0 + \beta_1 \text{LAZ}_{\text{Birth}} + \boldsymbol{\varepsilon}$) and interpreted as greater than expected linear growth (positive residual) or lower than expected linear growth (negative residual) within each interval, independent of previous size (19, 20).

For each scenario (Figure 1), linear regressions were used to conduct repeated cross-sectional analyses to estimate and compare associations between mean LAZ and stunting (yes/no) at birth, 3 month, and 12 months, and BMI z score and IQ z scores at 6 years of age. We also estimated and compared measures of association between conditional LAZ within the 2 age intervals (birth to 3 months, and birth to 12 months) and postnatal outcomes. In analyses in which LAZ was derived using uncorrected postnatal age, we further assessed whether the traditional practice of regression-based adjustment of GA (i.e., including GA as a covariate in a model) is likely to produce estimates that are consistent with those obtained from analyses in which LAZ is derived using a corrected postnatal-age strategy. Potential confounders of the association between infant LAZ and postnatal outcomes were identified a priori based on previously published studies (Web Appendix 2) (21–28). Because our aim was to compare the magnitude and direction of associations between methods, as opposed to testing substantive hypotheses, we restricted the analytical sample to complete-case observations in each scenario (Web Figures 1 and 2; Table 1). We assessed differences in the magnitude of associations when using corrected versus uncorrected postnatal-age strategy and used the overall F-statistic from linear models for quantitative comparison of model fit in models adjusting for GA as a covariate versus using corrected age. Because each model within a comparison group (i.e., follow-up visit) contains the same number of covariates (except for how GA at birth is incorporated), the relative values of the F-statistic reflect the predictive values of the models (29). Larger F-statistics indicate improvement to the model; we considered a 5% or greater difference between models as reflective of a meaningful advantage.

In sensitivity analyses, we assessed the robustness of our inferences (i.e., comparing corrected vs. uncorrected postnatal-age strategies) when outliers of infant LAZ were excluded (LAZ < -6 SD or > 6 SD based on uncorrected postnatal age for term-born children, and corrected age

Table 1. Baseline Characteristics of Participants in the Analytical Samples in Each Scenario in the 2004 Pelotas Birth Cohort, Brazil

Characteristics	Scenario A ($n = 961$)[a]			Scenario B ($n = 2,030$)[a]		
	Mean (SD)	No.	%	Mean (SD)	No.	%
Maternal age, years	29 (6.5)			29 (6.4)		
Maternal height, cm	160 (7.2)			161 (7.1)		
Mother living with companion		855	89		1810	89
Maternal education level, years						
<4		162	17		411	20
≥4 and <8		289	30		585	29
≥8		510	53		1,034	51
Parity	2.7 (1.3)			2.8 (1.4)		
Maternal prepregnancy BMI[b]	25 (4.8)			25 (4.7)		
Income quintile						
1 (lowest)		216	22		493	24
2		468	49		951	47
3		208	22		425	21
4		46	4.8		88	4.3
5 (highest)		23	2.4		73	3.6
No. of prenatal visits	8.1 (2.9)			8.0 (3.1)		
Maternal high blood pressure during pregnancy		238	25		484	24
Smoked during pregnancy		281	29		594	29
Female infant		476	50		1,008	50
Gestational age, weeks	39 (2.0)			39 (2.0)		
<37 (preterm birth)		90	9.4		205	10
≥37 (term birth)		871	91		1825	90

Abbreviations: BMI, body mass index; SD, standard deviation.

[a] Scenario A: association between infant length-for-age *z* score (LAZ) and BMI *z* score at 6 years of age. Scenario B: association between infant LAZ and full-scale intelligence quotient (IQ) *z* score at 6 years of age.

[b] Maternal prepregnancy BMI was calculated as prepregnancy weight (kg)/height $(m)^2$.

for preterm-born children at any follow-up visit; $n = 5$), and when corrected postnatal-age strategy was modified by: 1) using the INTERGROWTH-21st postterm standards for preterm-born children based on the Preterm Postnatal Follow-up Study (30) to derive LAZ for preterm-born children at 3 months; 2) using INTERGROWTH-21st very-preterm size at birth references/newborn size standards at birth but uncorrected postnatal age for preterm-born children at 3 and 12 months; or 3) using corrected postnatal age to derive LAZ for all children (including term births) in the application of WHO-GS postnatally. In addition, to estimate the influence of preterm birth prevalence on measures of association when using corrected compared with uncorrected postnatal-age strategy, we empirically simulated the effect of increasing prevalence of preterm birth from 5% to 25% (observable variation in preterm-birth prevalence at the national/regional level (31, 32)) by randomly undersampling preterm or term-born children from the overall data. Measures of association were estimated for each simulated cohort of a given preterm-birth prevalence and averaged over 100 samples. Simulations for each empirical example were conducted using a unique set of 100 random samples. All analyses were performed using Stata, version 14.2 (StataCorp, LP, College Station, Texas).

RESULTS

Of the 4,231 live births in the Pelotas Birth Cohort study, 9.4% ($n = 90/961$) and 10.1% ($n = 205/2,030$) of infants were preterm in the scenarios A and B, respectively, based on the analytical sample size in each scenario (Web Figures

1–2). Table 1 summarizes the baseline characteristics of the participants in the analytical samples.

Using corrected compared with uncorrected postnatal age attenuated the association between infant LAZ and BMI *z* score/IQ *z* score at 6 years of age, particularly at birth; however, absolute differences were small and inferences remained unchanged (Figures 2 and 3; Web Tables 1 and 2). Where GA was a weaker confounder (i.e., LAZ-IQ association relative to LAZ-BMI association), differences in measures of associations between the corrected and uncorrected postnatal age were very small, even at birth. As expected, the differences in mean LAZ, prevalence of stunting, and measures of association between LAZ and BMI *z* score/IQ *z* score at age 6 years were greater among preterm-born children when using corrected postnatal age compared with term-born children (Web Tables 3 and 4 for preterm-born children and Web Tables 5 and 6 for term-born children). For linear growth (i.e., conditional LAZ), using corrected versus uncorrected postnatal age attenuated the association between linear growth at 3 months of age and BMI *z* score/IQ *z* score at 6 years of age; however, absolute differences were very small at 3 months and negligible for conditional LAZ-BMI *z* score/IQ *z* score associations at 12 months of age (Web Tables 7 and 8). Nonetheless, in all scenarios and within a comparison group (i.e., follow-up visit), the *F*-statistic was higher in models in which LAZ was derived using corrected postnatal age compared with using uncorrected postnatal age with conventional regression-based adjustment for GA. Differences in the *F*-statistics were >5% in scenario B and in stratified analyses among term- and preterm-born children (Web Tables 1–6).

In sensitivity analyses, excluding outliers of LAZ ($n = 5$) did not change estimates or inferences from primary analyses (data not shown). Similarly, using INTERGROWTH-21st postterm standards for preterm-born children or using corrected age for all children postnatally did not change inferences from corrected postnatal-age strategy used in primary analyses (Web Figures 3 and 4). There was considerably greater attenuation when using corrected age for all children postnatally; however, this is likely due to overadjustment given that associations were attenuated beyond what would be expected when adjusting for GA in analyses limited to term-born children (see comparisons for 3- and 12-month follow-up visits in Web Tables 5 and 6). Among preterm-born children, associations with conditional LAZ estimated using corrected postnatal age were nearly identical to those obtained from using INTERGROWTH-21st postterm standards for preterm-born children (Web Figure 5). In simulation analyses, differences in associations between infant LAZ-postnatal outcomes, when using corrected versus uncorrected postnatal-age strategy, increased as the prevalence of preterm birth in the sample increased from 5% to 25%. This effect, however, was observed primarily for estimates at birth and in scenarios where GA was a stronger confounder (Web Figures 6–7). However, in a scenario where GA is on the causal pathway, for example, as a mediator between maternal high blood pressure during pregnancy and postnatal infant LAZ at 3 and 12 months, the direction and magnitude of effect measure attenuation, for cross-sectional associations when using corrected versus uncorrected postnatal age, were larger and not consistently in one direction (Web Figures 8 and 9).

DISCUSSION

We have demonstrated the effect of correcting for GA of preterm-born children in the application of child growth standards on population-averaged measures of associations between infant size and linear growth and mid-childhood outcomes using empirical scenarios in a birth cohort in Brazil. The use of GA-specific neonatal size standards and corrected age for preterm-born children in the application of WHO-GS postnatally attenuated the population-averaged magnitude of associations, particularly in early infancy. Using uncorrected postnatal age for all children irrespective of their GA at birth overestimated the effect on infant size (i.e., mean LAZ and risk of stunting). Adjusting for GA in regression-based analyses using postnatal age had a similar effect as using corrected postnatal age; however, it did not fully correct the age standardization errors in anthropometric metrics. Using a corrected postnatal-age strategy improved the predictive ability of the model when compared with regression-based adjustment for GA, with the additional advantage of not assuming linearity of association with GA (an implicit assumption in regression-based adjustment for GA). This suggests that even in scenarios where GA might reasonably be included as a covariate in regression models, there are conceptual and empirical advantages to using GA-specific neonatal size standards in conjunction with corrected age for preterm-born children in the application of WHO-GS postnatally. As anticipated, differences in measures of association between corrected compared with uncorrected postnatal-age strategies increased as the prevalence of preterm birth increased; however, this effect was observed primarily for measures in early infancy and when GA was more strongly associated with the outcome.

Collectively, these findings suggest that for measures of association where infant size and growth are exposures or outcomes of interest, disregarding GA in the application of child growth standards and using uncorrected postnatal age for all children might alter measures of associations meaningfully depending on: 1) the strength of association between GA and an exposure/outcome of interest, 2) children's age at the anthropometric assessment, and 3) the prevalence of preterm birth in the sample population. These findings extend previous work, which showed that using uncorrected postnatal age in the application of child growth standards overestimates the prevalence of early childhood undernutrition, might alter inferences regarding the pattern of undernutrition in early life, and might inflate the fraction of undernutrition attributable to preterm birth (13).

Although the application of fetal and newborn size standards in high-income settings has been questioned with respect to predictive ability for later health outcomes (33), newborn size and postnatal child growth standards continue to be widely used tools to derive metrics of child nutritional status that are comparable across populations and over time, particularly in low- and middle-income countries.

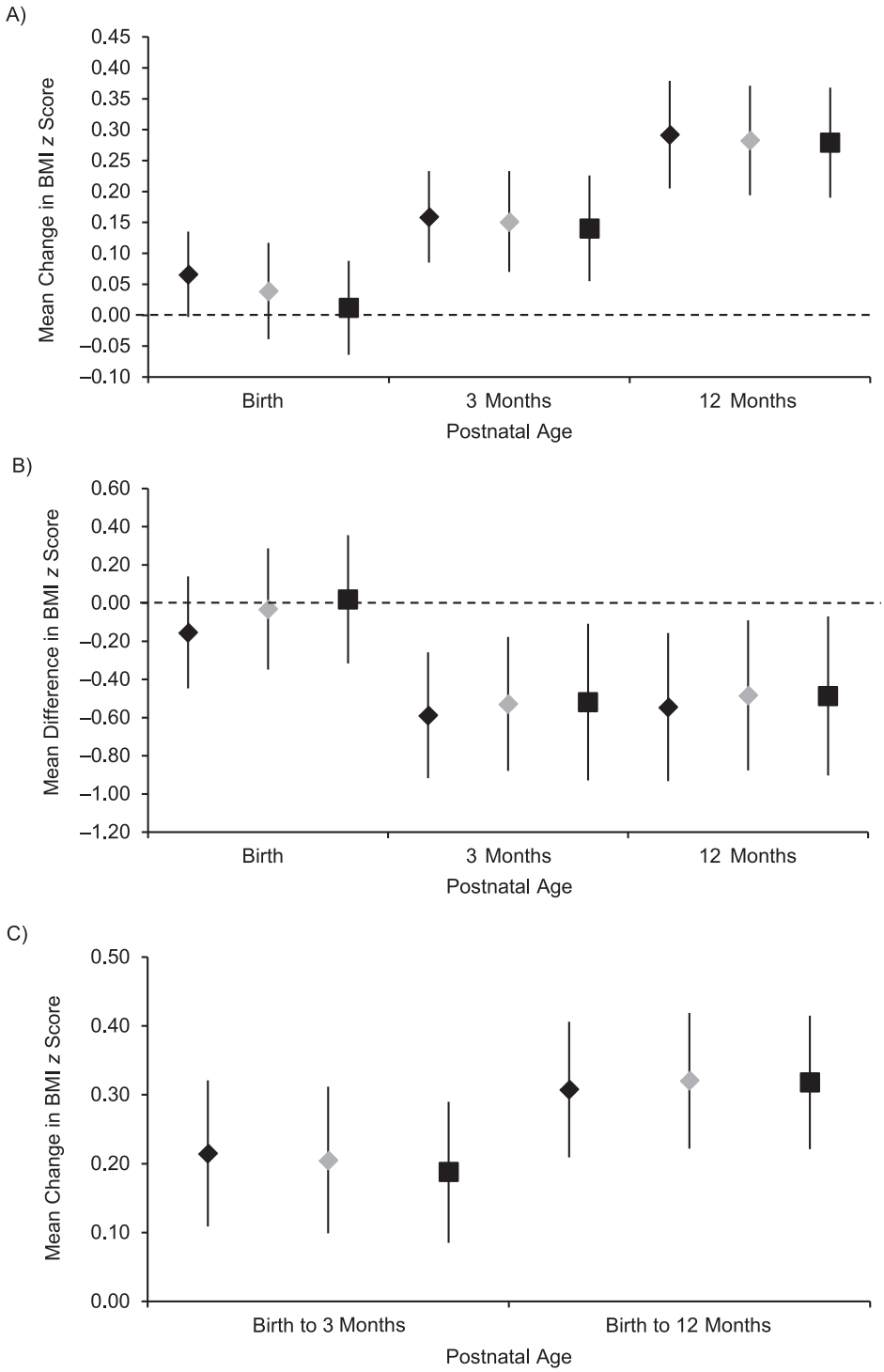

Figure 2. Adjusted associations between mean length-for-age *z* score (LAZ) (A), stunting (LAZ < -2 standard deviations) (B), and conditional LAZ during infancy (C), derived using gestational-age corrected age (black square) versus uncorrected postnatal age (black diamond), on body-mass-index (BMI) *z* scores at 6 years of age in the 2004 Pelotas Birth Cohort, Brazil. Repeated cross-sectional measures of associations at birth (n = 961), 3 months (n = 940), and 12 months (n = 931) were estimated using linear regressions adjusted for maternal prepregnancy BMI, maternal age, maternal education level, family income, maternal height, and parity. Conditional LAZs are residuals derived from linear regressions in which current size is regressed on size at birth. To compare corrected-age strategy with conventional analytical methods, we also estimated measures of association between infant LAZ and BMI *z* score at 6 years when using postnatal age to derive LAZ and adjusting for gestational age at birth as a covariate (gray diamond).

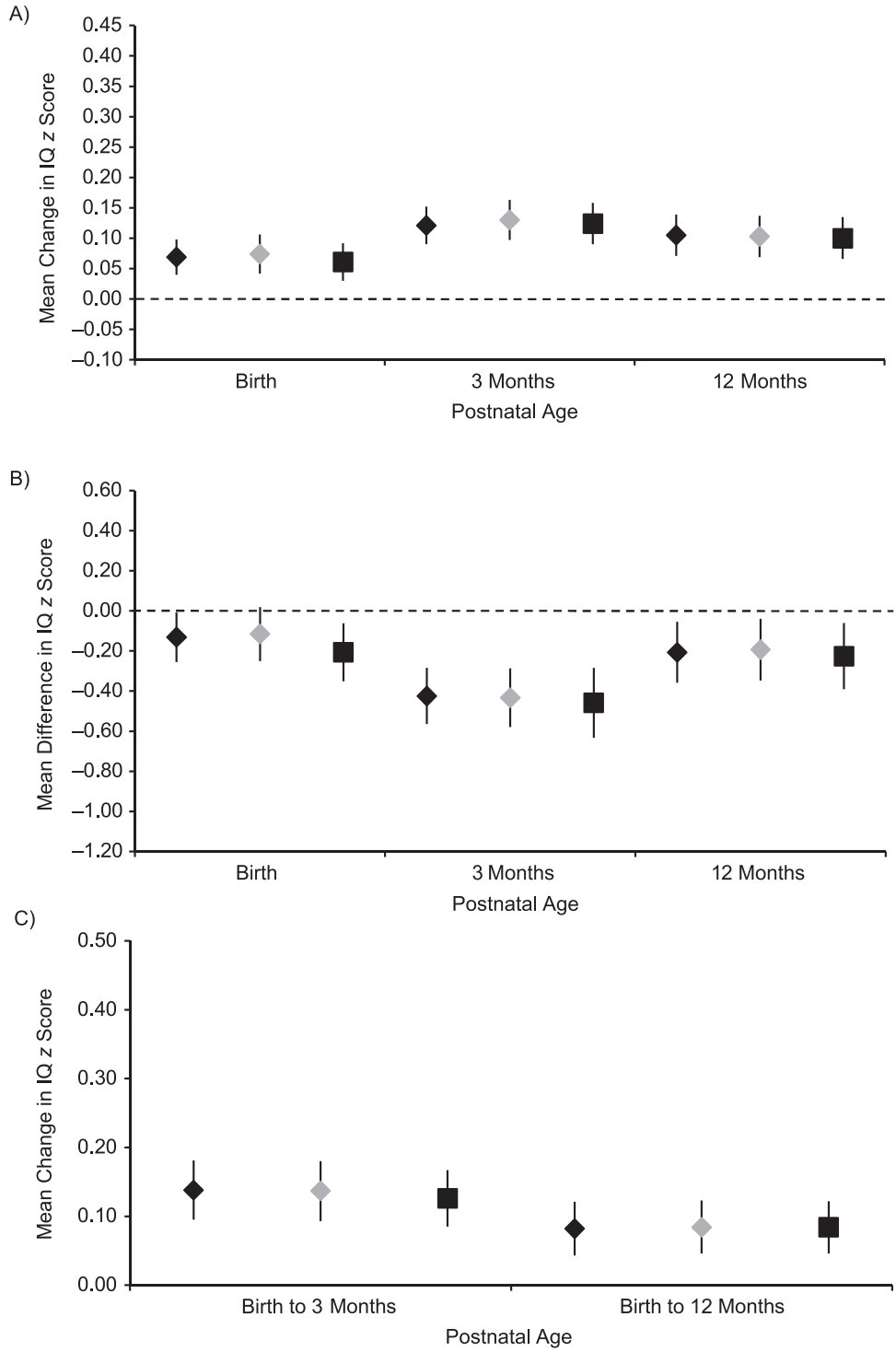

Figure 3. Adjusted associations between mean length-for-age *z* score (LAZ) (A), stunting (LAZ < -2 standard deviations) (B), and conditional LAZ (C) during infancy, derived using gestational-age corrected age (black square) versus uncorrected postnatal age (black diamond), on intelligence quotient (IQ) *z* scores at 6 years of age in the 2004 Pelotas Birth Cohort, Brazil. Repeated cross-sectional measures of associations at birth (n = 2,030), 3 months (n = 1,981), and 12 months (n = 1,972) were estimated using linear regressions adjusted for maternal age, education level, family income, parity, and mother living with a partner. Conditional LAZ are residuals derived from linear regressions in which current size is regressed on size at birth. To compare corrected-age strategy with conventional analytical methods, we also estimated measures of association between infant LAZ and IQ *z* scores at 6 years when using postnatal age to derive LAZ and adjusting for gestational age at birth as a covariate (gray diamond).

In contrast to perinatal and neonatal epidemiology, where GA-specific neonatal size standards are well-accepted and corrected postnatal age is commonly used (34–37), in nutrition and pediatric studies of child growth, variability in GA at birth is often disregarded immediately after birth when deriving standardized measures of postnatal size. Irrespective of the reason for earlier birth, size of infants postnatally should continue to be evaluated based on time since conception (i.e., postmenstrual age) rather than time since birth (i.e., postnatal age). For term-born children, these time scales are equivalent because the WHO-GS are based on a reference population of term births; however, the postmenstrual age of preterm-born children might vary drastically from the postmenstrual age of the reference population depending on when birth occurs.

Disregarding these differences on the postmenstrual age scales means that preterm-born children in the sample population are compared with biologically older children in the reference population, thereby conflating smallness due to preterm birth (i.e., timing of birth) with growth restriction due to all other causes. Because a given anthropometric index (such as low LAZ) could be derived through multiple pathways (e.g., preterm birth or intrauterine growth restriction), addressing age-standardization errors is particularly important for causal inference and to better understand the complex relationships between infant size/linear growth and BMI and IQ in mid-childhood (38–40). The expectation of change in a later health outcome as a function of infant size/growth might vary depending on the relative contributions of preterm birth and intrauterine growth restriction to observed deficits in nutritional status (41).

A limitation of this study was the lack of an ultrasound-based assessment of GA. However, we used a systematic approach to derive GA at birth based on LMP and Dubowitz score to minimize the risk of measurement error, and the measure of GA at birth was consistently used across the 2 strategies compared. A second limitation was the use of complete-case analyses for each scenario, such that a relatively large number of observations were excluded. However, given that the analytical sample was the same when comparing associations across methods (i.e., corrected versus uncorrected postnatal-age strategy) in each scenario, our inferences from methodological comparisons between the 2 strategies were unaffected. In addition, we observed only small absolute differences in measures of associations, in part due to the relatively weak associations between infant size/linear growth and mid-childhood outcomes. The magnitudes of the associations observed in this study are typical of other life-course studies; nonetheless, the differences in associations when using an uncorrected postnatal strategy might be greater in settings where the prevalence of preterm birth and undernutrition are concurrently high. Using corrected age in the application of WHO-GS assumes that preterm- and term-born children have similar growth trajectories; however, using INTERGROWTH-21st postterm standards for preterm-born children did not change the magnitude of the associations compared with corrected age. Finally, it is important to note that while using a GA-corrected postnatal-age strategy allows for standardization of anthropometric indices on the biological scale, it does not circumvent the challenge of collider-stratification bias when GA is on the causal pathway. In such contexts, alternative analytical strategies should be considered to estimate direct effect in the presence of colliders (42–44).

The use of child growth standards in epidemiologic research is common and widely recommended (45). Accommodating heterogeneity in GA at birth in the application of child growth standards postnatally reduces standardization errors in anthropometric indices and indicators and might improve model fit compared with regression-based adjustment for GA. Differences in the magnitude and direction of associations with infant size/growth will depend on the distribution of GA at birth across levels of the exposure, the strength of the association between GA and exposure/outcome of interest, the prevalence of preterm birth in the population, and the timing of size/growth assessment. These findings have important implications for population-based epidemiologic investigations in which children are born across a range of GAs and where child growth standards are used, particularly in early infancy and in settings where the prevalence of preterm birth is high.

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Author affiliations: Department of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Toronto, Canada (Nandita Perumal, Daniel E. Roth, Donald C. Cole, Stanley H. Zlotkin, Johnna Perdrizet, Diego G. Bassani); Centre for Global Child Health, Hospital for Sick Children, Toronto, Canada (Nandita Perumal, Daniel E. Roth, Stanley H. Zlotkin, Diego G. Bassani); Department of Global Health and Population, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Nandita Perumal); Division of Paediatric Medicine, Hospital for Sick Children, Toronto, Canada (Daniel E. Roth); Department of Paediatrics, University of Toronto, Toronto, Canada (Daniel E. Roth, Stanley H. Zlotkin); Department of Nutritional Sciences, University of Toronto, Toronto, Canada (Daniel E. Roth, Stanley H. Zlotkin); Institute for Health Policy Management and Evaluation, University of Toronto, Toronto, Canada (Daniel E. Roth); Division of Gastroenterology, Hepatology, and Nutrition, Hospital for Sick Children, Toronto, Canada (Stanley H. Zlotkin); Munk School of Global Affairs and Public Policy, University of Toronto, Toronto, Canada (Stanley H. Zlotkin); Postgraduate Program in Epidemiology, Federal University of Pelotas, Pelotas, Brazil (Aluisio J. D. Barros, Ina S. Santos, Alicia Matijasevich); and Faculty of Medicine, University of Sao Paulo, Sao Paulo, Brazil (Alicia Matijasevich).

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