
Peer reviewed version

Link to published version (if available):
10.1093/ajcn/nqy008

Link to publication record in Explore Bristol Research
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via OUP at https://academic.oup.com/ajcn/article/107/4/635/4964654?searchresult=1#115193016. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research
General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
http://www.bristol.ac.uk/pure/about/ebr-terms
INFANT FEEDING AND GROWTH

Putting the Horse Before the Cart

Michael S. Kramer, MD, Neil Davies, PhD, Emily Oken, MD, Richard M. Martin, MB, PhD, Mourad Dahhou, MSc, Xun Zhang, PhD, Seungmi Yang, PhD

Departments of Pediatrics (MSK, MD, XZ), Epidemiology, Biostatistics, and Occupational Health (MSK, SY), McGill University Faculty of Medicine, Montreal, Canada; School of Social and Community Medicine (ND, RMM), University of Bristol, Bristol, U.K.; National Institute for Health Research, Bristol Biomedical Research Centre (RMM), Bristol, UK; and Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute (EO), Boston, USA.

Sources of Support:

The study reported herein was supported by a grant from the Canadian Institutes of Health Research. The 11.5-year follow-up of PROBIT was also supported by grants from the European Union, Early Nutrition Programming Long-term Efficacy and Safety (FOOD-DT-2005-007036) and the USA National Institutes of Health (R01 HD050758). The NIHR Bristol Nutrition Biomedical Research Unit is funded by the National Institute for Health Research (NIHR) and is a partnership between the University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views expressed in this paper are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Clinical Trials Registration website:  http://www.isrctn.org/

Names for PubMed indexing:  Kramer, Davies, Oken, Martin, Dahhou, Zhang, Yang

Short running head:  Infant Feeding and Growth

Contact information:

5252 Blvd de Maisonneuve W., 3F.42
Montreal, Quebec H4A 3S5 Canada
Telephone:  (514) 412-4400 Ext. 22687
Facsimile:  (514) 412-4253
E-mail:  michael.kramer@mcgill.ca
Abbreviations:

Body mass index (BMI)
Intention-to-treat (ITT)
Instrumental variable (IV)
Weight-for-age z-score (WAZ)
Length-for-age z-score (LAZ)
Body mass index z-score (BMIZ)
ABSTRACT

Background: Previous observational studies have consistently shown slower weight and length gains in infants with prolonged breastfeeding than in those who were formula-fed from birth or breastfed for a shorter duration. These studies have inferred that prolonged breastfeeding causes slower growth in infancy.

Objective: We compared infant growth associated with ≥12 months vs a shorter duration of breastfeeding based on three different analytic approaches to the same data from a randomized trial: intention-to-treat (ITT, “as randomized”), observational (“as fed”), and instrumental variable (using randomization as an “instrument” to achieve ≥12 months of breastfeeding).

Design: This is a cluster-randomized trial of a breastfeeding promotion intervention. Anthropometric measurements were obtained at birth and 1, 2, 3, 6, 9, and 12 months.

Results: The three analytic approaches yielded different results. The ITT approach showed more rapid growth in the first 2 months among infants randomized to the breastfeeding promotion intervention vs the control, with a decreasing difference over the ensuing months and nearly identical weight, length, and BMI by 12 months. The observational analysis revealed a different trend: higher weight and length in infants breastfed ≥12 months vs <12 months during the first 3 months, no difference by 6 months, and infants breastfed <12 months with increasingly higher weight and length from 6 to 12 months. The IV analysis showed a temporal
pattern that was similar to that seen in the ITT analysis, but with larger (and less precise) differences among infants breastfed for ≥12 vs <12 months.

**Conclusions:** We observed major differences in experimental (ITT and IV) vs observational approaches to analyzing data obtained from the same children. These approaches lead to opposite causal inferences about the relationship between infant feeding and growth and underline the importance of ensuring that the postulated cause (feeding) temporally precedes its hypothesized effect (growth).

Keywords: breastfeeding; infant growth; reverse causality; randomized controlled trials; instrumental variable
INTRODUCTION

Numerous studies from high-income countries over the last few decades have shown that continued breastfeeding for 12 months or longer is associated with slower growth (in particular, lower weight gains) after the first 2-3 months of life (1). This robust finding was the main basis for a World Health Organization (WHO) expert committee report recommending new infant growth standards based on infants following WHO feeding recommendations (1). The expert committee report led to the WHO’s Multicentre Growth Reference Study and WHO’s current child growth standard (2). More recent publications (3, 4) also report an association between prolonged breastfeeding and slower weight gain during infancy.

Infants who grow more slowly (for genetic or other constitutional reasons) are likely to demand less frequent feeding and to consume smaller volumes. The mother’s milk production is closely titrated to the infant’s demand. The exquisite dyadic interaction between the lactating mother and her infant is universal throughout the mammalian class and has been finely tuned through evolution to maximize infant survival. Despite this well-known interactive system, many researchers investigating infant growth and feeding have used observational associations to infer a causal effect of feeding on growth. In an earlier publication, we demonstrated differences in the analysis of causal effects of breastfeeding (based on intention to treat, i.e., randomized allocation to a breastfeeding promotion intervention) from those derived from an observational analysis (as-fed) within the same randomized trial (5). Faster weight gains were paradoxically observed in the intervention group during the first 2-3 months, but both weight and length had equalized by 12 months of age.
We now extend that previous work to focus on the causal effects of prolonged breastfeeding, i.e., any breastfeeding for 12 months or longer, on growth during infancy. In addition to carrying out ITT and observational analyses, we also add an important new component: instrumental variable (IV) analysis. The IV approach uses randomization as an “instrument” to analyze the effects of prolonged breastfeeding on infant growth in women and infants who comply with (adhere to) the breastfeeding promotion intervention by continuing to breastfeed for at least 12 months (6, 7). Comparing the results of these analyses provides new insight into the possible causal relationship between prolonged breastfeeding and infant growth.

**SUBJECTS AND METHODS**

The Promotion of Breastfeeding Intervention Trial (PROBIT) is a cluster-randomized trial in the Republic of Belarus (8). The clusters that served as units of randomization (intervention) consisted of maternity hospitals and their affiliated polyclinics, i.e., outpatient clinics where children are followed for well child and routine illness care. Cluster randomization was preferred over individual randomization in the trial, because randomizing individual women within the same maternity hospital to different interventions would inevitably lead to “contamination” and consequent dilution of the effect of the intervention. A total of 31 clusters were randomized, and 17,046 mother-infant pairs were recruited between June 1996 and December 1997. Details of the eligibility criteria have been published previously (8), and the study population flow chart is shown in Supplemental Figure 1. The experimental intervention was based on the Baby-Friendly Hospital Initiative developed by the World Health Organization and the United Nations Children’s Fund, which was designed to promote the then current WHO
infant feeding recommendations: exclusive breastfeeding for 4-6 months and continued partial breastfeeding for at least the first year of life (9). The control intervention consisted of the maternity hospital and polyclinic practices that existed at the time of randomization, which were characterized by delayed onset of breastfeeding, routine separation of mother and infant, feeding on a regular schedule, frequent supplementation of breastfeeding with infant formula and other liquids, and early introduction of solid foods.

Follow-up data were obtained at scheduled polyclinic research visits at 1, 2, 3, 6, 9, and 12 months of age. At each of these visits, data were obtained on infant feeding, infections, and rashes, and measurements were obtained of weight, length, and head circumference. Because differences in growth were not major hypotheses of PROBIT (which focused on reduced risks of infection and of atopic eczema), no attempts were made to standardize anthropometric measurements among the study sites.

In this paper, we use three different approaches to analyze weight-for-age z-score (WAZ), length-for-age z-score (LAZ), and BMI-for-age z-score (BMIZ), with z-scores based on the WHO Multicentre Growth Reference (2). The first approach is an intention-to-treat (ITT) analysis, based on randomized allocation to the experimental vs control interventions. The second approach is based on actual breastfeeding; this observational analysis compares growth during the first 12 months of life in infants who were breastfed (to any degree) for at least 12 months and growth in those who were breastfed for less than 12 months; this approach is also referred to as the “as-fed” analysis. The third and final approach is based on instrumental variable (IV) analysis. This is a two-stage statistical procedure in which breastfeeding for 12
months or longer is first modeled as an effect of randomization. In the second step, the predicted probability of breastfeeding ≥12 months from step 1 is used instead of the actual exposure (breastfeeding ≥12 months). The IV procedure estimates the effect of breastfeeding for at least 12 months that is due to randomization (6, 7), in contrast to the effect estimated by the ITT analysis: the effect of being randomized to the breastfeeding promotion intervention. The IV estimates are less precise (have much wider confidence intervals) than the ITT analysis, however, because the IV estimates are based only on the fraction of variation in 12-month breastfeeding rates that was caused by the intervention.

All three approaches included a random effect for polyclinic to account for clustering. To make the three approaches as similar as possible, we present the results both without and with adjustment for potentially confounding covariates: maternal education, infant sex, East vs West region of Belarus and urban vs rural residence, and maternal and paternal height and BMI. The ITT and observational analyses are based on the MIXED procedure in SAS (version 9.2; Cary, NC), while the IV analysis used the ivreg2 procedure in STATA (version 9.4; Seattle, WA).

RESULTS

As previously documented, the randomization resulted in groups (intervention and control) that were very similar in baseline characteristics, including maternal and paternal size, maternal and paternal education, geographic location (East vs West region of Belarus and urban vs rural residence), infant sex, gestational age, birth weight, birth length, and birth head circumference, as well as 5-minute Apgar scores.(8) Rates of any breastfeeding in the intervention and control
groups were 73 vs 60% at 3 months, 50 vs 36% at 6 months, 36 vs 24% at 9 months, and 20 vs 11% at 12 months, respectively (8).

Figure 1 shows the clustered-adjusted WAZ results from all three analytic models. The ITT analysis (Figure 1A) revealed a more rapidly declining WAZ in the control group from birth to 2 months, but a faster rise from 3 to 12 months. By 12 months, the two randomized groups had nearly identical WAZ values.

The observational (“as-fed”) analysis results shown in Figure 1B yielded a very different pattern, with crossover of the two feeding groups at 6 months of age and increasingly higher WAZ values after 6 months in those infants who were breastfed for <12 months relative to those who were breastfed for ≥12 months.

The partial F-statistic was >21.0 (P <0.001) in all of our IV analyses, indicating that randomization provided a strong instrument for breastfeeding ≥12 months. As shown in Figure 1C, the IV results demonstrated a similar temporal pattern as that of the ITT analysis: increasing separation during the first 2 months, followed by a gradually declining separation until 12 months, with similar values achieved by 12 months of age. The absolute differences between infants breastfed ≥12 months vs those breastfed <12 months were much larger than in the ITT analyses, however, and the 95% confidence intervals around the IV estimates for the group breastfed for ≥12 months were very wide.
Supplemental Figures 2 and 3 compare the three approaches for LAZ and BMIZ, respectively. LAZ was well above the WHO reference mean in both feeding groups at birth, fell to near the WHO mean by 2 months, and then continued to rise through 12 months. Conversely, BMIZ values were below the WHO reference mean at birth, rose to the WHO mean by 3-6 months, and continued to rise until 12 months. The temporal patterns of the differences between the two compared feeding groups in LAZ and BMIZ, however, paralleled the pattern observed for WAZ for all three analytic approaches, except for similar LAZ values at 1 month in the IV analysis.

Table 1 shows the complete results for all three anthropometric outcomes from birth to 12 months, along with their 95% confidence intervals. For each of the three analytic approaches, the first column shows the crude, clustered-adjusted results, while the second column shows the very similar results after adjustment for maternal education, infant sex, East vs West and urban vs rural residence, and maternal and paternal height and BMI.

**DISCUSSION**

Our findings demonstrate important differences between experimental (ITT and IV) vs observational approaches to analyzing data obtained from the same children. The causal inferences from these data differ substantially. Causal inference assumes no uncontrolled confounding by unmeasured (or imperfectly measured) covariates. Similar findings in crude and adjusted results from all three analytic approaches (see Table) suggests that confounding due to factors we measured is an unlikely explanation for the differences observed, although we cannot rule out residual confounding due to unmeasured (or imperfectly measured) factors.
Adequate control for confounding is necessary for causal inference, but it is not sufficient. Causality also assumes the temporal precedence of exposure, i.e., that changes in infant feeding occur before the outcome (subsequent infant growth). Thus, for example, breastfeeding for 6-12 months vs breastfeeding for <6 months can cause differences in growth trajectory only for the later period, not the earlier one.

Establishing the temporal sequence between feeding and infant growth is far more difficult than it seems. Mothers and infants are typically studied only at periodic research visits or in the course of routine clinical care. In PROBIT, the research visits occurred at birth and 1, 2, 3, 6, 9, and 12 months. But the infant’s signals of hunger (crying, fussing, and poor sleeping) occur over periods of minutes and hours — not months — and the mother’s feeding responses to those signals are often immediate. Most mothers interpret crying, fussing, and poor sleeping in their infants as hunger. If a mother is unable to satisfy her infant’s needs (e.g., by increasing the frequency of suckling), she will often introduce formula. Formula supplementation reduces the infant’s demand for breast milk, and hence maternal milk output. The reduced maternal milk supply can lead to additional formula supplementation, further reduction in breast milk output, and a vicious cycle terminating in weaning and full formula feeding.

Thus prolonged breastfeeding is a marker for a content (satisfied) infant who does not convey hunger signals that undermine the mother’s confidence in her milk supply. Infants growing along a slower trajectory will have a lower demand for breast milk, but unless the infant’s care provider or family members raise concerns about the infant’s size, breastfeeding continues. We
speculate that the slower growth trajectory is a cause of the continued breastfeeding, mediated by infant contentment and maternal confidence. Continued breastfeeding would then be a consequence of slower prior growth, rather than a cause of slower subsequent growth. Inferring that prolonged breastfeeding slows infant growth therefore reverses the horse and cart. Indeed, slower growth has been reported to predict later weaning in a developing country context (Peru) when combined with low complementary food intake and high diarrheal illness (10,11).

Paradoxically, infants who have grown well up until a given age can provide support to the mother (and physician) to continue breastfeeding (12). Larger infants at any age are likely to reduce their growth in the ensuing interval (regression to the mean) (13), creating an association between continued breastfeeding and slower growth during that interval. Conversely, infants who are smaller at the beginning of an interval tend to grow faster during that interval (13) and are also more likely to be supplemented with formula or weaned (12), creating an association between reduced (or discontinued) breastfeeding and faster growth during the interval. In both of these scenarios, the association is between feeding and growth during the ensuing interval, not prior feeding and growth. Given these associations, which are opposite in direction from those usually presumed or hypothesized, any causal effect of breastfeeding on reducing subsequent growth would be virtually impossible to detect.

In our study, the randomized treatment allocation, and its observed impact on breastfeeding exclusivity and duration, ensure that differences in infant feeding temporally preceded differences in growth in the two randomized groups. The ITT analysis therefore yields a bone fide causal effect. But that causal effect is not of breastfeeding for 12 months or more vs
breastfeeding for a shorter duration. Instead, it is the causal effect of randomization to the breastfeeding promotion intervention. That causal effect was limited to the first 2-3 months of life, after which dilution (“catch-down” growth) led to a gradual disappearance of differences between the two randomized groups by 12 months.

Our observational results are similar to those reported from previous observational studies, at least in direction. By 6 months of age, weight and length among PROBIT infants who were breastfed for at least 12 months were lower than those breastfed for shorter durations. The small magnitude of the observed differences almost certainly reflects the fact that all PROBIT infants were breastfed at birth and that many in the <12 months (comparison) group were breastfed for an appreciable duration. Most previous studies have contrasted growth in infants with prolonged breastfeeding and growth in a formula-fed comparison group, or by using a growth reference based on primarily formula-fed infants (1, 4).

The IV analysis uses randomization as an instrument. The goal is to estimate the causal effect of breastfeeding for 12 months or longer on infant growth, based on the effect observed in women who complied with the intervention, i.e., those randomized to the breastfeeding promotion intervention who breastfed for ≥12 months vs those in the control group who did not (6, 7). Actual breastfeeding behaviour by PROBIT mothers and infants, including the duration and degree of breastfeeding, was influenced by many factors other than randomization and therefore overlapped considerably in the two randomized groups. The IV approach uses randomization to remove the dilution caused by this overlap.
As expected, the IV approach resulted in higher point estimates (for the effect of breastfeeding for ≥12 months on infant growth) than the point estimates obtained from the ITT approach, because they are based on mothers and infants who “complied” with the randomized intervention by breastfeeding for ≥12 months. They are upwardly biased even further, however, because compliance is itself likely to be affected by the infant’s growth, thereby violating an important assumption of IV analysis: that compliance depends only on the treatment, not on the outcome. Moreover, the “cost” of the IV analysis is far lower precision, as reflected by the wide confidence intervals around the point estimates.

Nonetheless, the overall temporal pattern of differences in weight, length, and BMI throughout the first year of follow-up was similar in the ITT and IV analysis: faster growth in the intervention group and the group breastfed ≥12 months vs the control and <12 months groups, respectively, during the first 2-3 months of life, with decreasing differences thereafter and near equivalence by 12 months of age. Our major finding, however, is that the observational analysis yields results that differ in direction from those of both the ITT and IV analyses in the second half of infancy.

We suspect that our results are generalizable to other populations, since the results of our observational analysis mimic those reported in previous studies. Our findings demonstrate the potential for reverse causality (putting the cart before the horse) in observational studies and the superiority of randomized trials for making causal inferences. This is particularly true in areas where the exposure, the outcome, or both are human behaviours or are heavily influenced by
human behaviours (14). The complex interactive behaviour of infant feeding is obviously one
important example of such an area.

ACKNOWLEDGMENT

MSK contributed to the overall conception of the study and drafts and revisions of the
manuscript. ND contributed to the advice on the technical aspects and interpretation of the
instrumental variable analyses, as well as, revisions of the manuscript. EO and RMM
contributed to the overall conception of the project and revisions of the manuscript. MD
contributed to the analyses using all three statistical approaches. XZ contributed advice on the
statistical analyses and revisions of the manuscript. SY contributed to the supervision of all
analyses and revisions of the manuscript.

All the authors have seen and approved the final version, and none of the authors has any conflict
of interest concerning the topic or contents of this manuscript, nor any competing financial
interests.
REFERENCES


<table>
<thead>
<tr>
<th></th>
<th>Intention-to-Treat&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Observation&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Instrumental Variable&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cluster-adjusted</td>
<td>Fully Adjusted</td>
<td>Cluster-adjusted</td>
</tr>
<tr>
<td></td>
<td>(n=16,089-17,046)</td>
<td>(n=13,567-13,889)</td>
<td>(n=16,086-16,602)</td>
</tr>
<tr>
<td><strong>WAZ</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth</td>
<td>0.09 (0.06, 0.13)</td>
<td>0.09 (0.06, 0.13)</td>
<td>0.79 (0.34, 1.24)</td>
</tr>
<tr>
<td>1 month</td>
<td>0.09 (0.06, 0.13)</td>
<td>0.09 (0.06, 0.13)</td>
<td>0.12 (0.20, 0.26)</td>
</tr>
<tr>
<td>2 months</td>
<td>0.11 (0.08, 0.14)</td>
<td>0.21 (0.18, 0.24)</td>
<td>0.22 (0.18, 0.25)</td>
</tr>
<tr>
<td>3 months</td>
<td>0.08 (0.05, 0.10)</td>
<td>0.07 (0.04, 0.10)</td>
<td>0.03 (0.01, 0.07)</td>
</tr>
<tr>
<td>6 months</td>
<td>0.04 (0.01, 0.06)</td>
<td>-0.06 (-0.09, -0.03)</td>
<td>-0.05 (-0.08, -0.01)</td>
</tr>
<tr>
<td>9 months</td>
<td>-0.01 (-0.03, 0.02)</td>
<td>-0.04 (-0.07, -0.01)</td>
<td>-0.07 (-0.10, -0.04)</td>
</tr>
<tr>
<td><strong>LAZ</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth</td>
<td>-0.08 (-0.11, -0.04)</td>
<td>-0.01 (-0.05, 0.03)</td>
<td>0.10 (0.06, 0.15)</td>
</tr>
<tr>
<td>1 month</td>
<td>0.01 (-0.02, 0.04)</td>
<td>0.05 (0.01, 0.09)</td>
<td>0.15 (0.01, 0.19)</td>
</tr>
<tr>
<td>2 months</td>
<td>0.09 (0.05, 0.12)</td>
<td>0.09 (0.05, 0.13)</td>
<td>0.11 (0.07, 0.15)</td>
</tr>
<tr>
<td>3 months</td>
<td>0.13 (0.10, 0.16)</td>
<td>0.12 (0.08, 0.16)</td>
<td>0.09 (0.05, 0.14)</td>
</tr>
<tr>
<td>6 months</td>
<td>0.13 (0.09, 0.16)</td>
<td>0.08 (0.04, 0.12)</td>
<td>-0.06 (-0.10, -0.01)</td>
</tr>
<tr>
<td>9 months</td>
<td>0.06 (0.02, 0.09)</td>
<td>-0.02 (-0.06, 0.00)</td>
<td>-0.05 (-0.14, -0.05)</td>
</tr>
<tr>
<td>12 months</td>
<td>0.03 (-0.005, 0.06)</td>
<td>-0.01 (-0.05, 0.02)</td>
<td>-0.07 (-0.12, -0.03)</td>
</tr>
<tr>
<td><strong>BMIZ</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth</td>
<td>0.06 (0.03, 0.09)</td>
<td>0.02 (-0.01, 0.06)</td>
<td>0.06 (0.02, 0.10)</td>
</tr>
<tr>
<td>1 month</td>
<td>0.10 (0.09, 0.15)</td>
<td>0.10 (0.06, 0.13)</td>
<td>0.21 (0.17, 0.24)</td>
</tr>
<tr>
<td>2 months</td>
<td>0.10 (0.07, 0.13)</td>
<td>0.10 (0.07, 0.14)</td>
<td>0.24 (0.20, 0.27)</td>
</tr>
<tr>
<td>3 months</td>
<td>0.04 (0.01, 0.07)</td>
<td>0.06 (0.02, 0.09)</td>
<td>0.22 (0.18, 0.25)</td>
</tr>
<tr>
<td>6 months</td>
<td>0.001 (-0.03, 0.03)</td>
<td>0.03 (-0.01, 0.06)</td>
<td>0.07 (0.03, 0.11)</td>
</tr>
<tr>
<td>9 months</td>
<td>0.01 (-0.02, 0.04)</td>
<td>0.01 (-0.03, 0.04)</td>
<td>0.002 (-0.04, 0.04)</td>
</tr>
<tr>
<td>12 months</td>
<td>-0.03 (-0.06, -0.004)</td>
<td>-0.01 (-0.04, 0.02)</td>
<td>-0.04 (-0.08, -0.01)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Cluster-adjusted differences in intervention vs control group for intention-to-treat analysis, and between any breastfeeding ≥12 months vs <12 months for observational and instrumental variable analysis.

<sup>2</sup> Intention-to-treat and observational analyses are based on cluster-adjusted MIXED models in SAS (version 9.2; Cary, NC), while instrumental variable analyses used the ivreg2 procedure in STATA (version 9.4; Seattle, WA).
WAZ = weight-for-age z-score; LAZ = length-for-age z-score; BMIZ = BMI-for-age z-score
**Figure 1.** WAZ from birth to 12 months in groups according to the three analytic approaches.

Figure 1A: intention-to-treat analysis comparing intervention (red) vs control (blue) groups (n=16,089-17,046). Figure 1B: observational analysis comparing infants breastfed for ≥12 months (red) vs <12 months (blue) (n=16,086-16,602). Figure 1C: instrumental variable analysis comparing infants breastfed for ≥12 months (red) vs <12 months (blue) (n=16,086-16,602). In all three panels, the vertical error bars denote 95% confidence intervals. Intention-to-treat and observational analyses are based on cluster-adjusted MIXED models in SAS (version 9.2; Cary, NC), while instrumental variable analyses used the ivreg2 procedure in STATA (version 9.4; Seattle, WA).