

Effects of Selective Dropout on Infant Growth Standards

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Abstract

Exclusively breastfed (EBF) infants have higher weight gain during the first 2 months, and lower thereafter. The explanation for this phenomenon is not clear. Longitudinal data from the Social Medical Survey of Children Attending Child Health Clinics study with a cohort of 2,151 Dutch children were analyzed according to a pattern mixture model. It appears that higher than average growth of EBF infants during the first 2 months is primarily attributable to selective dropout. Furthermore, between months 2 and 6, light nonEBF infants gain more weight than light EBF infants. Both factors aid in explaining differences in growth between EBF and nonEBF infants. The WHO Child Growth Standards for weight-for-age have been calculated from a subgroup of 903 infants (out of 1,743) that complied with strict feeding criteria. If similar dropout mechanisms operate in the Multicentre Growth Reference Study, then the WHO weight-for-age standards are expected to be systematically different from those for the entire group of 1,743 infants.

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Introduction

In 2006, the World Health Organization (WHO) released growth standards for children 0–5 years [1]. These WHO Child Growth Standards (WHO-CGS) are based in the WHO Multicentre Growth Reference Study (MGRS), a population-based study conducted between 1997 and 2003 in Brazil, Ghana, India, Norway, Oman, and the United States. A novel aspect of the WHO-CGS is the very careful selection of children that are being raised in circumstances that promote optimal, rather than maximal, growth. The WHO-CGS portray the variation in growth of children living in socioeconomic conditions favorable to growth.

The MGRS used three compliance criteria for feeding of infants to be included in the growth standards sample: (1) predominant or exclusive breastfeeding (EBF) for at least 4 months; (2) introduction of complementary foods in the period 4–6 months, and (3) partial breastfeeding to be continued up to at least 12 months. New standards were calculated from the subgroup that complied with these feeding criteria. The standards are ‘recommended for application to all children independently of type of feeding’ [2].

Various studies have shown that growth of EBF infants differs from that of formula-fed or mixed breastfed formula-fed infants (taken together here as ‘nonEBF’). In general, EBF infants gain weight more rapidly during the first 2 months, and grow less rapidly in the period 3–12 months [3, 4]. Haschke and Van t’Hof summarize: ‘Our study confirmed that infants who are fed according to WHO recommendations have higher weight and length during the first 2–3 months of age than infants fed by other modes. Thereafter, they tend to be shorter and lighter, but the differences between feeding groups were small and clinically not relevant’ [5]. Traditional weight-for-age references typically lump together infants with different feeding patterns. The WHO-CGS for weight selected only infant-mother pairs that comply with the WHO feeding regimen. As a result, the WHO-CGS for weight are references that mix feeding modes during the first half year of life, and lower thereafter.

Some have expressed concerns about this finding. Binns and Lee [6] argue that the higher centiles covering the first 6 months of life in the WHO-CGS are the result of sample selection, since only those who grow well are retained. Their fear is that mothers will add ‘top up’ feeds of infant formula or even stop breastfeeding altogether to achieve the higher WHO growth rates. Thus, they argue, the WHO-CGS may turn out to be counterproductive in stimulating breastfeeding. Slow-growing infants who are falling off their growth curve trajectories may be deliberately supplemented or weaned in an effort to reverse those trends [7]. These infants may then show up as bigger than normal after some months.

These concerns relate to the direction of causality. The association between breastfeeding and growth can go either way. Consider the following two causal mechanisms: (a) EBF causes infants to grow differently (faster during months 0–2; slower during months 3–12); (b) growth faltering causes mothers to abandon EBF.

Under mechanism a, we expect that, given 2 infants of the same initial weight, the EBF infant will gain more weight in months 0–2 than the nonEBF infant. Under mechanism b, we expect that, given 2 breastfed infants, the infant with lower weight has an increased chance to switch to complementary foods. As a result, infants that remain to be breastfed will be heavier. Both mechanisms can operate simultaneously.

In this paper, I will attempt to disentangle both mechanisms. I will do so by studying dropout patterns within the group that started EBF. Considerable advances in the statistical literature have been made to address dropout

problems in longitudinal data [8–10]. The paper finishes by addressing some of the implications of the findings.

Data

The Social Medical Survey of Children Attending Child Health Clinics (SMOCC) cohort is a nationally representative cohort of 2,151 children born in the Netherlands in 1988–1989 [11, 12]. During the 1st year of life, data on type of milk feeding and weight were collected at 1, 2, 3, 6, 9, and 12 months of age. Type of feeding (breast, infant formula, cow's milk, or other) was recorded at each visit. EBF at each time point was defined as absence of formula, cow's milk or other foods. Time of dropout was defined as the first occasion at which formula, cow's milk or other foods were introduced.

Statistical Methods

Suppose that $Y = (Y_{ij})$ is an $n \times m$ matrix of planned repeated measures of body-weight Y_{ij} of infant i ($i = 1, \dots, n$) measured at time j ($j = 1, \dots, m$). Without loss of generality, we assume that Y_{ij} has been scaled in standard deviation (SD) units relative to the WHO-CGS. Furthermore, we assume that all infants receive EBF at all occasions, so Y_{ij} is set to missing for occasions where complementary foods were given. Let us define the response indicator $R_{ij} = 1$ if the infant receives EBF at time j , and $R_{ij} = 0$ otherwise. Once infants stop to receive EBF, they seldom, if ever, return to EBF. We may therefore summarize the response indicator R_{ij} for infant i by the dropout indicator $D_i = \sum_j R_{ij}$, which can take values $0, 1, \dots, m$.

The simplest way to analyze these data is to discard all incomplete sequences, known as a complete-case analysis. This is essentially the method by which the WHO has calculated the growth standards. Diggle et al. [8] warn that this approach may introduce bias if the process that created the dropout is related to the measurements, as the complete cases cannot then be assumed to be a random sample with respect to the measurements Y_{ij} . In general, Diggle et al. [8] reject complete case analysis, perhaps with the only exception 'when the scientific questions of interest are genuinely confined to the sub-population of completers, but situations of this kind would seem to be rather specialized'.

In order to move beyond, we need to model both the measurement and the dropout process, i.e. we need to model $P(Y, D)$ instead of $P(Y)$. One general approach is the *pattern mixture model*, which is based on the decomposition $P(Y, D) = P(Y|D)P(D)$. Here, the model part $P(Y|D)$ describes how the measurements Y depend on dropout pattern D . The conditional densities $P(Y|D)$ are subsequently mixed by the intensity of dropout $P(D)$ [13]. For longitudinal data with dropouts, this model is often identified by an extra assumption: the available case missing value (ACMV) restriction [14]. The ACMV assumption implies that, given the past measurements, the distribution of the future (unobserved) measurement in the dropouts is equivalent to the distribution of the measurements of those who do not drop out.

We will study two aspects of the pattern mixture model. First, we will explore $P(Y|D)$ by comparing the mean weight trajectory per dropout pattern until the time of dropout. Second, we will assess how realistic the ACMV restriction is, i.e. we will study

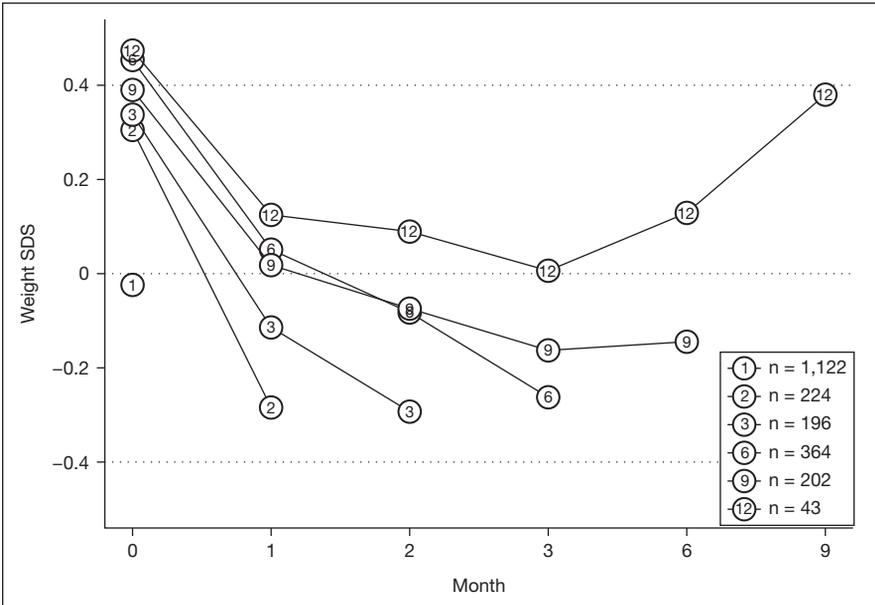


Fig. 1. Trajectory of mean weight SDS per dropout pattern prior to dropout. Trajectories are labeled by month of dropout from EBF. The diagram shows that EBF infants who drop out are lighter before they drop out.

whether EBF and nonEBF groups grow alike. For these data, we are in the fortunate position that we have weight measures available beyond dropout. Both analyses will guide us to evaluate whether modeling the data by a full pattern mixture model would be useful.

Results

Figure 1 portrays the development of the mean weight SDS (WSDS) trajectory by drop out pattern. Only mean WSDS prior to dropout is plotted. The point labeled '1' is the mean WSDS of the group that did not receive EBF at month 1. This group includes three subgroups: (1) infants that never received any breastfeeding, (2) infants with mixed feeding, and (3) infants that initially received EBF but dropped out before month 1. The trajectory labeled '2' is the mean WSDS of 224 infants that received EBF at least up to month 1, but who dropped out at month 2. Likewise, the trajectory labeled '3' is the mean WSDS of 196 infants that received EBF at least up to month 2, but dropped out at month 3, and so on. Except for group 1, all data points apply to infants that actually received EBF. On average, birthweights in the SMOCC are slightly above the

WHO standard. This might be related to longer than average mother's height [15]. Note a striking feature in figure 1: the mean WSDS just one occasion prior to dropout is always lowest among all patterns. For example, average WSDS at month 1 of the 224 infants that dropped out at month 2 is equal to -0.28 SD, which is substantially lower than mean WSDS that receive EBF during at least 2 months. Similar observations apply to the other patterns.

Figure 1 shows that EBF infants who drop out are lighter before they drop out. The consequence is that infants who continue to receive EBF are heavier. If we were to construct standards from these data by taking all children that receive EBF up to – say – month 3, then we single out the data of all 609 infants present in patterns 6, 9 and 12. We implicitly then select infants that thrive well on EBF throughout months 1–3, while excluding data from 420 infants on EBF that have a lower than average weight gain during this period. The effect of this selection is an upward drift. The size of the difference between the included and excluded patterns is about 0.25 – 0.30 SD at any age.

Figure 2 provides another look at the data. The figure allows us to address the question whether the three groups per period (EBF-EBF, nonEBF-non-EBF, EBF-nonEBF = dropout) grow alike. Figure 2a contains the regression lines estimated for the each group separately for months 1–2. The differences in weight gain are small in general. The EBF group grows slightly faster (0.12 SD; table 1) during this month than the nonEBF group. The situation is reversed for the next two periods (2–3 months and 3–6 months), where the nonEBF group gains weight considerably faster than EBF infants (0.20 SD in period 2–3 months, and 0.33 SD in period 3–6 months; fig. 2b, c). Note that the difference varies with initial weight, and is largest for the lightest infants. This suggests that, relative to EBF, lighter infants in the nonEBF group are overfed, presumably due to catch up. Finally, no growth differences occur during period 6–9 months (fig. 2d). Infants with EBF and without EBF grow essentially the same during that period.

When taken together, figures 1 and 2 yield the following picture:

- 1 Infants who receive EBF at month 1 are heavier at birth.
- 2 Higher than average growth of EBF infants during the first 2 months is primarily attributable to selective dropout.
- 3 Between months 2 and 6, light nonEBF infants gain more weight than light EBF infants. In addition, selective dropout continues to operate.
- 4 No differences in weight gain were found between nonEBF and EBF infants between months 6 and 9. Selective dropout continues to operate.

Discussion

Infant growth and dropout are clearly interrelated processes. Our data indicate that the decision to abandon EBF strongly depends on infant weight.

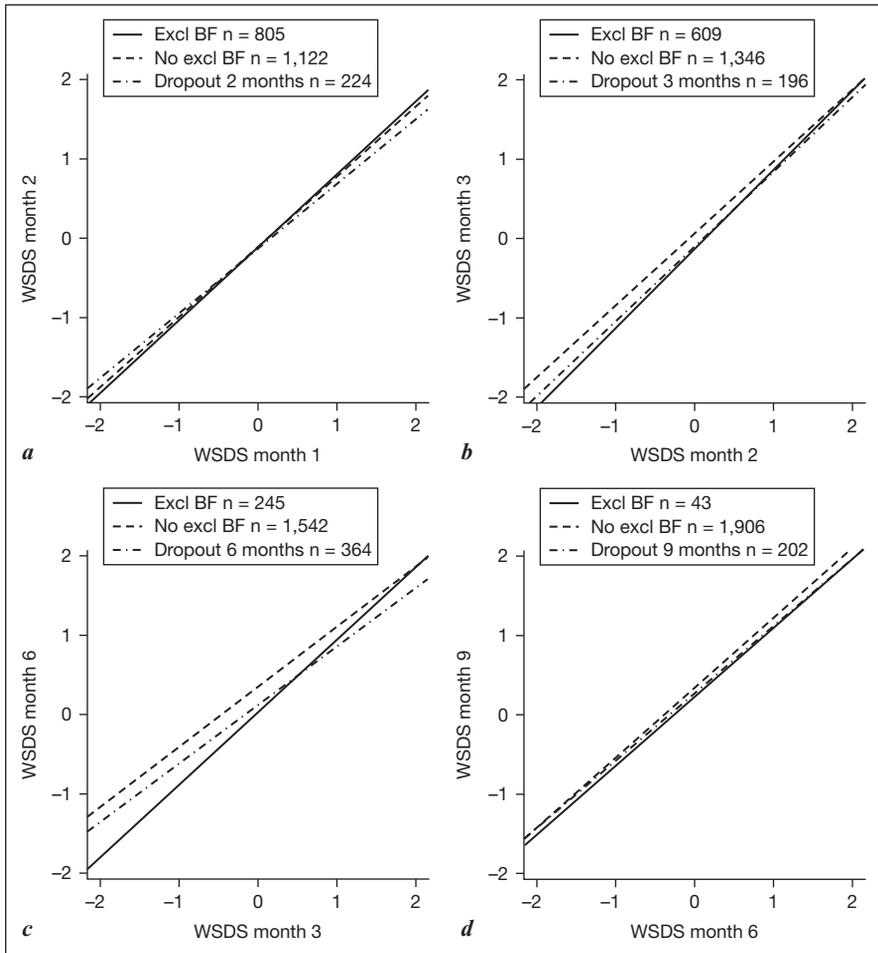


Fig. 2. Regression lines to describe weight gain at four different periods during infancy. Per period, three separate models were fitted corresponding to feeding mode. Differences between feeding modes are small for periods 1–2 months and 6–9 months. In periods 2–3 months and 3–6 months, lighter infants receiving complementary foods gain more weight than lighter infants receiving EBF.

Furthermore, we found that the difference in weight gain between the EBF infants and nonEBF infants depends on initial weight. Both mechanism a and b mentioned in the introduction operate simultaneously, and do so in different ways at different ages.

The WHO standard of weight-for-age is generally higher than other references during the first half year. This cannot be explained as an artifact due to

Table 1. SMOCC data (n = 2,151)

Predictors	WSDS(2)			WSDS(3)			WSDS(6)			WSDS(9)		
	Est	SE	p									
Intercept	-0.12	0.01	<0.001	0.05	0.01	<0.001	0.35	0.02	<0.001	0.33	0.01	<0.001
WSDS(t-1)	0.89	0.01	<0.001	0.90	0.01	<0.001	0.76	0.01	<0.001	0.88	0.01	<0.001
Dropout (0/1)	0.06	0.03	<0.05	-0.16	0.03	<0.001	-0.24	0.03	<0.001	-0.04	0.03	<0.001
EBF-EBF (0/1)	0.12	0.06	<0.05	-0.20	0.01	<0.001	-0.33	0.04	<0.001	-0.11	0.07	<0.001
Slope × drop	-0.01	0.03		0.04	0.03		-0.02	0.03		-0.03	0.03	
Slope × EBF	-0.11	0.08		0.10	0.02	<0.001	0.15	0.04	<0.001	-0.01	0.07	
R ²	0.82			0.85			0.69			0.79		

Parameter estimates from four linear regressions to predict WSDS(*t*) at months 2, 3, 6 and 9 from WSDS of the previous occasion WSDS(*t*-1) and group (EBF-EBF, nonEBF-nonEBF, EBF-nonEBF = dropout). The reference category is nonEBF-nonEBF. R² is the proportion of explained variance.

inadequate modeling. Model fitting and selection has been done very carefully using the best available tools, and is well documented [16, 17]. Diagnostics like the worm plot [18] indicate extremely good model fit. Without doubt, the published standards are a faithful representation of the weight distribution in the selected populations.

However, the findings presented in this paper beg the question whether the selection of infants has been appropriate. The MGRS study enrolled 1,743 newborns into the longitudinal component. The WHO-CGS weight standards were calculated from the compliant subset of $n = 903$ infants (51.8% of 1,743) [2]. Most dropouts occurred because the mothers did not adhere to the strict WHO feeding protocol. If we are willing to assume that the dropout processes in the MGRS are similar to those in SMOCC, then standards calculated on the 903 subset will be different from standards calculated from the full set of 1,743 infants.

One may defend the choice for the compliant subset by arguing that the interest is genuinely confined to the subpopulation of completers. However, that argument is somewhat at variance with the WHO recommendation to use the new standards irrespective of feeding mode, and disregards the selective effect that growth faltering may have on dropout.

A way forward is to calculate references on all 1,743 infants according to the intention to treat principle. In order to do so, we need to know for the dropouts what weights we would have measured had the infant been fed according to the WHO protocol. There are nowadays good methods for making such estimates, e.g. multiple imputation under fully conditional specification [19]. All the relevant data have been collected within the MGRS to enable such analyses. If the findings in this paper hold in the MGRS data, the resulting references are likely to be different from the current standard. A first step to see how large this difference could be is to inspect diagnostic plots like figures 1 and 2 calculated from the MGRS data.

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References

- 1 WHO Multicentre Growth Reference Study Group: WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr* 2006;(suppl)450:76–85.
- 2 WHO Multicentre Growth Reference Study Group: Breastfeeding in the WHO Multicentre Growth Reference Study. *Acta Paediatr* 2006;(suppl)450:16–26.
- 3 Dewey KG, Peerson JM, Brown KH, et al: Growth of breast fed infants deviates from current reference data: a pooled analysis of US, Canadian, and European datasets. *Pediatrics* 1995;96:495–503.

- 4 Frongillo EA: Growth of the breast-fed child; in Martorell R, Haschke F (eds): Nutrition and Growth. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 37–52.
- 5 Haschke F, van't Hof MA: Euro-Growth Study Group. Euro-Growth references for breast-fed boys and girls: influence of breast-feeding and solids on growth until 36 months of age. *J Pediatr Gastroenterol Nutr* 2000;31(suppl 1):S60–S71.
- 6 Binns C, Lee M: New growth standards. *Lancet* 2007;370:1542.
- 7 Kramer MS, Guo T, Platt RW, et al: Breastfeeding and infant growth: biology or bias? *Pediatrics* 2002;100:343–347.
- 8 Diggle PJ, Heagerty P, Liang K-Y, Zeger SL: Analysis of Longitudinal Data, ed 2. Oxford, Clarendon Press, 2002.
- 9 Fitzmaurice G, Davidian M, Verbeke G, Molenberghs G: Longitudinal Data Analysis. Boca Raton, Chapman & Hall/CRC, 2009.
- 10 Daniels MJ, Hogan JW: Missing Data in Longitudinal Studies. Strategies for Bayesian Modeling and Sensitivity Analysis. Boca Raton, Chapman & Hall/CRC, 2008.
- 11 Herrngreen WP, Reerink JD, van Noord-Zaadstra BM, et al: The SMOCC-study: design of a representative cohort of live-born infants in the Netherlands. *Eur J Public Health* 1992;2:117–122.
- 12 Herrngreen WP, van Buuren S, van Wieringen JC, et al: Growth in length and weight from birth to 2 years of a representative sample of Netherlands children (born in 1988–89) related to socioeconomic status and other background characteristics. *Ann Hum Biol* 1994;21:449–463.
- 13 Little RJA: Pattern-mixture models for multivariate incomplete data. *J Am Stat Assoc* 1993;88:125–134.
- 14 Molenberghs G, Michiels B, Kenward MG, Diggle PJ: Monotone missing data and pattern-mixture models. *Stat Neerl* 1998;52:153–161.
- 15 van Buuren S, Van Wouwe JP: WHO Child growth standards in action. *Arch Dis Childhood* 2008;93:549–551.
- 16 WHO Multicentre Growth Reference Study Group: WHO Child Growth Standards. Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva, World Health Organization, 2006.
- 17 Borghi E, de Onis M, Garza C, et al, for the WHO Multicentre Growth Reference Study Group: Construction of the World Health Organization child growth standards: selection of methods for attained growth curves. *Stat Med* 2006;25:247–265.
- 18 van Buuren S, Fredriks M: Worm plot: a simple diagnostic device for modelling growth reference curves. *Stat Med* 2001;20:1259–1277.
- 19 van Buuren S: Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res* 2007;16:219–242.

Discussion

Dr. Sunga: In the Philippines, we have started using the WHO charts. You mentioned that the subjects used in the study were children of breastfeeding mothers from a high socioeconomic class who were also nonsmokers. My question is, would this be the appropriate population considering the differences in the feeding practices between the different socioeconomic groups? Would children from the lower or middle socioeconomic class be more representative of the population?

Dr. van Buuren: This is a very relevant question because it refers to the selection in the first phase, and the selection was created deliberately by the WHO to assess optimal growth in optimal circumstances, i.e. what you can achieve if you are raised in optimal circumstances. That's why this criterion has been applied by the WHO. This is a kind of innovative aspect of the WHO references because this is the first time that the references are made explicitly from a kind of normative spectrum, so 'how should children grow'. This is the kind of WHO philosophy that leads to selection, and whether it applies to mothers of other socioeconomic strata is a point of discussion, but the idea is to have references for optimal growth, for growth in optimal circumstances.

Dr. Lucas: You have reviewed three charts, the Dutch chart, the WHO chart, the CDC chart. They obviously differ according to which people are put in the charts, at different stages, and more philosophy lies behind the selection here, but the real question is which is the best chart in terms of clinical outcome. If we don't know the answer to that, is the choice actually academic?

Dr. van Buuren: I think you cannot say which chart is the best because all charts will be somehow tied to a reference population, so it depends on what your goals are. I can imagine the discussion going on in the UK about which WHO standards one should use. Still, the WHO standards may actually be very useful for countries that do not have their own references. But for countries with their own references, one might discuss the use of WHO references.

Dr. Gillman: My question is about the conclusion that bias might occur, and it really depends on how you interpret your first bullet. The decision to abort exclusive breastfeeding depends on infant weight. If I understand your data correctly, it is shown that aborting exclusive breastfeeding is associated with infant weight, but you really don't have a strong study design where you conclude that infant weight causally is associated with the decision to abort. There could be other reasons why people with children at lower infant weights choose to abort exclusive breastfeeding besides the weight itself. If that's the case, then I am not sure you really have a bias but you have confounding or maybe reverse causation. I think it's really important to get those things straight because we wouldn't want to conclude that infant weight is the cause or the factor and therefore we should change the charts, until we know what the underlying reasons are. Can you respond to that?

Dr. van Buuren: I cannot confirm that weight itself really is a causal factor here. But if you look at the different dropout groups, it's systematically the ones that drop out just before becoming light and much lighter than the ones that stay in. Now, if you only consider the ones left over here, then on average the charts will be higher. So it's not a matter of confounding but simply a matter of selection, i.e. which children do you want to put in the chart.

Dr. Gillman: I understand that if those babies were in the charts it would be lower, you would have a different kind of chart, but I still am not certain as to the reasons why the babies in number 2 and number 3 and possibly number 6 aren't there, and it may not be that they are lighter, it may be something about other decisions based on social circumstances, family circumstances, etc. that may actually drive this, in which case you may actually at the end of the day conclude that the WHO charts got it perfectly right.

Dr. van Buuren: I do not entirely agree with you because the reasons are not that relevant. You see selection from the group that started breastfeeding. I suppose that we want to generalize about that group. At least, that's the assumption that I make. If that assumption is correct, then there is systematic bias.

Dr. Gillman: I think in a statistical sense that's true that you have a cohort and people drop out, and the people who drop out are different from the people who stay in, but the question is why they drop out and if you want to, who is it that you want to conclude is growing the way you want them to grow. It may still be the people who are high SES, nonsmokers and happen to stay in the cohort. That may still be the right group.

Dr. van Buuren: But these are infants and mothers that were already included in the cohort, so I assume that that's the group that you want to base your decision on irrespective of whether they drop out or not and what the reasons were for dropout.

Dr. Haschke: I have two comments. Having worked at the committee which prepared the protocol for the WHO growth study until 1993, it was clear that the WHO growth curves would have the political goal to show that breastfed infants from

different parts of the world show a similar 'healthy' growth pattern. Indeed, the WHO Growth standards indicate that breastfed infants from different parts of the world are growing in a similar way. Unfortunately, the WHO growth charts include no infant cohort 'Asian' genes. The six study sites were in Europe, North and South America, Middle East, West Africa, and India. Therefore, five infant cohorts (including India) have 'Caucasian' genes and one cohort has 'African genes'. More than 50% of the infants of the world have 'Asian' genes. Another issue is the development of the obesity epidemic. In developing countries, infants from higher socioeconomic segments have higher risk to become obese than infants from lower socioeconomic segments.

Dr. van Buuren: I agree with you that it would have been better to include an Asian site because if you look at the world population, the Asians are underrepresented.

Dr. Mobarak: Your cross-sectional studies were conducted in different regions, but you didn't include the Asian sites. Did you see any regional patterns in these cross-sectional studies? I was also wondering why you didn't adopt the intent to treat principle at the beginning because it is obvious that in this kind of large studies there will be dropouts and that could calculate the real effects. Also, if you now adopt the intention-to-treat principle, are you going to change your policies and if so, what will be your new policy?

Dr. van Buuren: Regarding the inclusion of Asian populations, I have already said that it would probably have been better to include more populations. It actually depends on how different growth is among the globe on different continents. As for your second question about the intention to treat principle, the alternative is to use the 'completers only' analysis, which is actually what the WHO did. This takes only the ones that comply with the protocol and makes references from these infants. That's problematic in the sense that you can get bias estimates because of selection. This selection problem is the reason for not doing the complete analysis. The only alternative is then to do the intention-to-treat analysis, which includes all subjects that were admitted in the first place. So it's clear then what the population is to generalize over. It is simply the population that you included in your study. This would not be clear if you took only the completers because that would be a kind of haphazard population.

Dr. Martorell: I was involved in the development of these curves as a member of the Executive Committee that guided the work. We need to understand that WHO intended to create a standard rather than a reference [1]. A reference is representative of a country or a population group. The intent of WHO in creating a standard was quite different and that's why the discussion about 'intent to treat', where you retain all children you enroll initially to derive the curves, doesn't make sense because a priori it was defined that one wanted a population in which there is a very low probability of growth failure due to environmental reasons, for example poverty, poor environmental sanitation or inadequate practices related to breastfeeding and infant feeding. The approach was 'prescriptive' and called for mothers and children to comply with predefined characteristics and practices for data from the child to be included in the development of the standard. We know from quite a lot of data that appropriate breastfeeding and infant feeding practice lead to better mortality and morbidity outcomes, particularly in poor countries [2]. There is a specific pattern of growth that is observed in healthy breastfed babies, as demonstrated in the WHO study and in other samples. Breastfed infants have greater weight for length during the first few months of life but become thinner later; in terms of length, they differ little with respect to references such as the CDC 2000 charts [3]. My final comment is about the lack of a population from Asia. India was one of the countries included, and there was an attempt to include other countries but this did not work out. There are data from

China showing that urban children, in cities like Beijing and Shanghai, have similar growth in length to the WHO curves.

Dr. van Buuren: With respect to the first point, there are only 3 countries or 3 references here. I also made similar plots for the data from France and the UK and it looks the same; there is the same bump at 1.5 years. I think Ekhard Ziegler will show more of this, it's quite a remarkable difference. The second point, there have been studies in China which are more or less similar to the WHO curves. That's reassuring of course, so we need more of those studies to see whether these references hold up against populations in which they were not developed.

Dr. Domellöf: Are you planning to work together with the WHO people on this, do you have a dialogue with them? Also, I would like to comment that our Swedish growth charts are based on formula-fed infants from the 1970s. It is well known among clinicians that breastfed babies have a weight curve bump at about 3 months compared to the reference curves from formula-fed infants, and I don't think that this could be explained by selective dropout, or could it?

Dr. van Buuren: Related to the first one, I sent my manuscript to Mercedes deOnis and she made a comment on it; essentially she is denying that there is a problem in MGRS data. So I quote Mercedes deOnis: 'Unlike what seems to be the case in the Dutch cohort, in the MGRS cohort the decision to abandon exclusive breastfeeding was largely unrelated to infant weight and mainly related to the mother's need to return to work'. Furthermore, she says that when comparing the complying and non-complying babies, there were negligible differences in weight and none in length. She says, we looked at it and we didn't find anything. I would be curious to know if they did the kind of dropout analysis that I just showed; they did an analysis of birthweight. If you look closer at the dropout patterns, my guess would be that what you would see is essentially a flat line with dropouts dropping out from it. Such analysis would have to be done in order to be sure that selection is not a problem in this case. Your second question is about the Swedish data where there is a bump. I am not familiar with the data so I cannot say right at the moment whether selection could be a problem there. It can occur with longitudinal data, so if your data are longitudinal there is the potential of such phenomenon to occur.

Dr. Lucas: I just want to elaborate a bit more on the question that I asked you earlier. Obviously, we can have these charts driven by philosophy, but at the end of the day we want these charts to actually be geared to real clinical outcome data. To illustrate, in developing countries we want to promote growth because that's important for morbidity and mortality risk, whereas in the developed world we would like slow growth because that's best for cardiovascular disease and obesity risk in later life. That would spell out two different sorts of charts, the chart for use in the developing world where what you really want to do is to diagnose growth failure because that has important clinical prognostic significance, whereas in the developed world you might well want charts which justify a lower pattern of growth rate or low rates of early growth and because that would be useful in sort of toning down if you like the more rapid growth that could lead to obesity and cardiovascular disease. But I am worried that the approach is mathematical rather than linked to sort of real outcome. And I agree with your first answer to my question which was that the best chart is a chart that can be used in different circumstances, and those are two circumstances where what you'd want might differ actually.

Dr. van Buuren: If you want to detect failure to thrive or obesity development, you could try to adopt the approach of Tim Cole who constructed thrive lines, which is the lower 5% in a longitudinal sense. You may imagine inverse thrive lines in which you take the 95th percentile, and healthy growth should be between those two. Those could be constructed from the same data and the same chart, so that would tie

together. I cannot help these things being a bit mathematical at times, but they are done for clinical purposes.

Dr. Elmouzan: The WHO standards are, as everybody knows, based on a selective population, and therefore we have the best yardstick to judge the prevalence and to try to improve nutrition and growth, but for a simple pediatrician who is assessing growth of children on a daily basis, especially in developing and transitional countries, do you think it is appropriate to judge these children according to this very high standard of growth.

Dr. van Buuren: It's difficult to answer because the needs for growth charts differ between different people and different countries. I would not be willing to give a general recommendation to always use the WHO charts, but they are of very high quality. If you have mainly a clinical population you may be interested in the outer rather than middle centiles and make provisions for that. So there is not one simple answer to it.

References

- 1 WHO Multicentre Growth Reference Study Group: WHO Child Growth Standards. Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva, World Health Organization, 2006.
- 2 Black RE, Allen LH, Bhutta ZA, et al: Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 2008;371:243–260.
- 3 WHO Multicentre Growth Reference Study Group: WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Suppl* 2006;450:76–85.