

Application of Bayesian Hierarchical Model for Detecting Effective Factors on Growth Failure of Infants Less Than Two Years of Age in a Multicenter Longitudinal Study

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Received 2016 January 28; Accepted 2016 February 01.

Abstract

Background: Nowadays, one of the major public health problems among children is growth failure. It can be characterized in terms of either inadequate growth or the inability to maintain growth.

Objectives: The main objective of this study was to examine the effects of some factors on growth failure among a sample of infants less than two years old.

Materials and Methods: The present longitudinal archival study relied on data gathered from health files from February 2007 to July 2010 for 1,358 children under two years of age, selected from eight health centers in the east and northeast parts of Tehran, Iran. In the present study, growth failure refers to at least a 50 g decrease in an infant's weight as recorded at each attendance in comparison to the previous measurement. The impacts of risk indicators were assessed using the Bayesian hierarchical logistic regression modeling technique.

Results: The highest and lowest percentage of growth failure was 5.8% and 0.1%, respectively, in the eleventh and the first month after birth. The obtained results from the Bayesian hierarchical modeling revealed that diarrhea (95% credible interval (CrI): 0.70 - 3.31), discontinuation of breastfeeding (95% CrI: 0.77 - 5.96), and respiratory infections (95% CrI: 2.07 - 4.61) were significant risk factors for growth failure. The random term at the child level was significant (95% CrI: 0.74 - 7.82), while the variation in centers was extremely small (95% CrI: 0.004 - 4.22).

Conclusions: It was noted that a relatively high prevalence of growth failure was observed in the study sample. For minimizing the impact of significant risk factors on growth failure, the early detection of growth failure and its risk indicators is of great importance. In addition, when the focus of the analysis is on the different nested sources of variability and the data has a hierarchical structure, using a hierarchical modeling approach is recommended to achieve more accurate results.

Keywords: Growth Failure, Risk Factors, Multicenter, Longitudinal Study, Hierarchical Model, Bayesian Method

1. Background

In the primary care setting, assessment of growth and development is the foundation of pediatric care, and various forms of neglect and abuse may have an adverse influence on these factors. If the onset is during infancy, such the condition is referred to as failure to thrive (FTT), which indicates both a deficit in terms of weight for height (wasting) and generally low height (stunting) for a child's age during the first two years of life (1, 2). Stunting is caused by long-term insufficient nutrient intake, and frequent infections and wasting are usually the result of acute significant food shortages and/or disease. FTT is a multidimensional

phenomenon which is influenced by both organic and inorganic factors such as parental education level and employment, chronic disease, insufficient nutrition, and infectious disease (e.g., diarrhea and fever) (1-6). Recent studies have shown that not dealing with this disorder effectively may lead to more serious consequences, such as reduced learning; mental, emotional, or physical disability; an increased death rate; and the appearance of other associated diseases (7). FTT is a serious health issue around the world. In some developing countries, growth failure and malnutrition have been the cause of upwards of half of children's deaths (8). In Iran, there is a relatively high

prevalence of growth failure; based on reports by WHO in 1998, the prevalence of wasting and stunting was 18.5% and 12.8%, respectively (9).

When the outcome variable for each subject under study is measured at different periods of time, this leads to a correlated response which is called longitudinal data. For analyzing longitudinal data, more complex statistical techniques that are able to take into account the dependence of individual observations should be used (10, 11). Generalized linear mixed models (GLMMs) can account for the correlation between observations and heterogeneity by including random effects (12, 13). When the structure of longitudinal data is considered as hierarchical (clustered), the appropriate analytical method is to use a hierarchical model (13). In the past decades, hierarchical modeling has emerged as a highly useful and flexible tool for longitudinal analysis because of the modeling of trends over time at the individual level by incorporating a subject-specific intercept (e.g., slope with time) into a regression model for the response (14). Hierarchical models are sometimes called other things, such as multilevel linear, random coefficients, and mixed effects models. In a hierarchical framework, the random effects and correlation among observations are specified at each level.

According to the findings of some studies, there are several reasons to use hierarchical modeling as a more helpful and powerful application than traditional approaches. Furthermore, it should be noted that in traditional models, the variance of the estimated parameters may be inflated if the correlation between observations that share analogous characteristics in the same cluster is ignored (15). In this research, since a longitudinal dichotomous outcome variable was considerable and the data had a hierarchical structure, a hierarchical logistic regression was used. In logistic longitudinal hierarchical analysis, estimates of the regression coefficients and variance components appear to be very difficult, and different estimation procedures, including Bayesian estimation, may lead to different results based on bias as well as the variance of the parameter estimates themselves (16). However, in this paper, a Bayesian approach was still applied to estimate the fixed and random terms of the model, albeit with caution and awareness of these potential limitations.

Most of the previous reports about the risk factors of FTT and growth failure in Iran and other countries disregard hierarchically structured data in their statistical analyses; the hierarchical modeling approach was therefore implemented in this study in order to take that structure into account in this type of analysis.

2. Objectives

The main goal of this study was to identify some of the most significant factors related to FTT using the Bayesian hierarchical logistic regression model. In addition, the results of this model were compared with those of the usual marginal modeling approach.

3. Materials and Methods

3.1. Study Population

The dataset of this longitudinal archival study contains information on individual infants less than 2 years old who were referred to health centers associated with Shahid Beheshti university of medical science in Tehran (SBUMS) from February 2007 to July 2010. Based on the single-stage cluster sampling technique, eight health centers were randomly selected from 64 health centers of SBUMS. The health files of all of the two-year-old children in these eight centers were gathered. All children who were delivered at term labor, uniparous, with no genetic or congenital diseases, and presented on time at the health center for growth monitoring were included. Among a total of 2,182 infants' health files, 1,358 files were ultimately included in the study after a preliminary assessment (infants with missing or incomplete data for covariates were excluded from the study). The required information in these files was recorded every month in the first year and every other month in the second year for each child (a total of one measurement). The repeated measurements were registered for each child and they were measured in different health centers, hierarchically structuring the data. All children in those centers repeatedly registered during the two years after birth. The mean of repetition of each individual was 9.50. For more details about the total data, the reader can refer to the original article previously published (17).

In our analyses, the binary outcome variable was defined as a weight decrease of a minimum of 50 grams at each attendance as compared to the previous measurement (0 = with growth failure and 1 = without growth failure).

The continuous risk factor of interest at the child level was the time of initiation of complementary foods. The additional categorical variables that were included in the model were fever, teething, diarrhea, respiratory infections, discontinuation of breastfeeding, and urinary tract infections (UTI) (0 = no, 1 = yes).

3.2. Statistical Analysis

3.2.1. A Three-Level Logistic Model for Repeated Measures Data

In the current study, longitudinal (repeated) data was used to determine the growth failure status of each infant.

Because each infant has his/her own characteristics (such as genetic factors, environmental influences, and familial disorders), the probability of growth failure for each infant in each stage of life is different from the others. Hierarchical models as an extension of the GLMMs enabled the incorporation of random effects at more than one level. By using these random terms, it was possible to include the heterogeneity (due to the above mentioned characteristics) among the samples under study (e.g., children) in the modeling process. In addition, to account for clustering in the data, these models permit estimation of the covariate effects on the outcome (13). In this research, three levels of nesting were taken into account: measurements within children, and children within health centers. The random-intercept three-level logistic regression model for repeated measurements can be written as a combination of 2 sub-equations. The difference between the two sub-equations is only in the intercept. The sub-equation 1 (within-subject) is given by:

$$(y_{tij}|p_{tij}) \sim \text{Bernoulli}(p_{tij})$$

$$\begin{aligned} \text{logit}(p_{tij}) &= \ln\left(\frac{p_{tij}}{1-p_{tij}}\right) \\ &= \alpha_{0ij} + \beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_k x_{ki} \end{aligned} \quad (1)$$

Children below the age of two years were evaluated in 17 different points of time. We assumed that the observed response y_{tij} ($i = 1, \dots, 1358$; $t = 1, \dots, 17$; $j = 1, \dots, 8$) was conditionally distributed as Bernoulli, p_{tij} represents the expected probability of growth failure for t^{th} measurement of i^{th} child in the j^{th} health center, conditional on the fixed predictor variables x_{1i}, \dots, x_{ki} and the random effects (variance parameters). In this model, $\beta = (\beta_1, \dots, \beta_k)$ are the regression coefficients that are used to measure the effect of increasing or decreasing x_{ki} by one unit on a log odds ratio. The sub-equation 2 (between-subject) is given by:

$$\alpha_{0ij} = \alpha_{00} + u_{0i} + v_{0ij} \quad (2)$$

Where α_{00} is the expected baseline, the quantities u_{0i} and v_{0ij} are the random effects not related to the lowest level of hierarchy that are generally assumed to follow a normal distribution with a mean of zero and constant variance of $\sigma^2_{u_{0i}}$ and $\sigma^2_{v_{0ij}}$, respectively (18-20). In a multilevel model, the correlation between observations on a certain level can be estimated by an intraclass correlation coefficient (ICC) which indicates the proportion of unexplained outcome variance at the higher level. When the type of outcome variable is categorical, ICC in the three-level model is defined as follows:

$$\frac{\sigma^2_{v_{0ij}}}{(\sigma^2_{v_{0ij}} + \sigma^2_{u_{0i}} + \frac{\pi^2}{3})} \quad (3)$$

Furthermore, in a multilevel logistic regression or logistic random effects model, the errors are assumed to follow a standard logistic distribution with a mean of zero and approximate variance $\pi^2/3 \approx 3.29$ (16).

3.2.2. Estimation Approach

To estimate the parameters in model 1, a Bayesian method was used. Bayesian approaches can define a prior distribution which is independent of the data from which the data is derived. With this approach, the likelihood is combined with prior information to obtain the posterior distribution of the parameters of interest (21). Prior information of some degree can help either in strengthening inferences about the unknown parameters or in reducing sample sizes. The prior knowledge may come from previous but similar situations or experiments, a pilot study, or even the opinions of experts in the field of study. There are two selections of prior distributions for multilevel models: (a) diffuse and (b) informative. With respect to (a), little is known about the quantities of interest a priori, whereas for (b), considerable prior information is available. In this article, (a) is the focus given that it seems natural to seek prior specifications that lead to well-calibrated inferences. In the literature review, it was revealed that Browne and Draper have developed a hybrid Metropolis-Gibbs approach which is useful for the multilevel logistic regression model (22).

Here, prior distributions for the fixed effect parameters α_{00} and β were the multivariate normal distribution, and for the variance parameters, they were a scaled inverse chi-squared, which is equivalent to an inverse gamma. Furthermore, the Markov Chain Monte Carlo (MCMC) methods as one group of Bayesian approaches that generate samples from Markov chains which converge to the posterior distribution (consisting of a mean and standard deviation) were used. It should be noted that the model was fitted by Gibbs sampling, which is one of the MCMC methods. CODA package in R 3.2.0 was used for checking convergence of the MCMC. To be even more specific, using Geweke's diagnostic test, parameters with $|Z| < 2$ designated no differences in the means between the first and the last set of iterations and therefore were indicative of convergence. In addition, the results of the multilevel Bayesian method were compared with a generalized estimating equations (GEE) analysis, which is the most common technique for analyzing longitudinal data (23).

In the present paper, the data were analyzed using descriptive and deductive-statistical methods by SPSS 20.0, and OpenBUGS 3.2.2 software. The relationship between qualitative variables was studied using the chi-square test, and the relations between growth failure and quantitative variables were assessed using the independent samples t-test. In the GEE approach, P values less than 0.05 are

considered as statistically significant, while in a Bayesian sense, a 95% credible interval including zero reveals a non-significant relationship.

4. Results

A total number of 1,358 children were included in this study. Among them, 674 (49.6%) were male and 684 (50.4%) were female. The mean (\pm SD) mothers' age at childbirth and the birth weights were 27.48 (\pm 5.57) years and 3183.62 (\pm 475.63) g, respectively. Furthermore, the range of mothers' age at childbirth in this survey was from 15 to 56 years. The frequency distribution of the two groups of children (with and without growth failure) at 17 measurement time points is summarized in Table 1.

Table 1. Frequency of Distribution of Children Less Than Two Years Old Based on Growth Failure as Measured at 17 Time Points^a

Time of Measurement	With Growth Failure	Without Growth Failure
1	1 (0.1)	795 (58.6)
2	6 (0.4)	815 (60.0)
3	17 (1.3)	874 (64.3)
4	21 (1.5)	881 (64.8)
5	28 (2.1)	891 (65.6)
6	38 (2.8)	884 (65.1)
7	54 (4.0)	879 (64.7)
8	46 (3.4)	866 (63.8)
9	78 (5.7)	855 (63.0)
10	76 (5.6)	829 (61.1)
11	79 (5.8)	825 (60.7)
13	51 (3.8)	854 (62.9)
15	39 (2.9)	839 (61.8)
17	34 (2.5)	824 (60.6)
19	32 (2.4)	829 (61.1)
21	37 (2.7)	775 (57.1)
23	32 (2.4)	749 (55.1)

^aValues are expressed as No. (%).

As shown in this table, the highest and lowest percentage of growth failure was in the eleventh and first months at 5.8% and 0.1%, respectively.

In our analysis, the GEE model with the exchangeable correlation matrix was used for computing odds ratios (OR) as well as their 95% confidence intervals (95% CI), and was performed for the interpretation of the consequences. We included all of the covariates in a single model. Table 2

presents the findings of the parameter estimates using the GEE approach.

The only significant risk factors at a significance level of $\alpha = 0.05$ were teething ($P < 0.001$), presence of diarrhea ($P < 0.001$), respiratory infections ($P < 0.001$), discontinuation of breastfeeding ($P < 0.001$), urinary tract infections ($P < 0.001$) and time of initiation of complementary foods ($P = 0.014$).

Finally, the Bayesian multilevel logistic regression model was used for determining the factors related to the growth failure during the specified time and accounting for the variations among the health centers and the children under study. It should be noted that the parameters attained convergence with a total of 235,000 iterations, excluding the initial 30,000 iterations as the burn-in period. The plots of autocorrelations within a chain were also checked for fixed and random effects. These plots did not show high autocorrelations for all parameters after a specific lag (Figure 1).

Table 3 displays the posterior details, including the means and standard deviations, Monte Carlo error, and the 95% posterior intervals for this model. From the 95% credible intervals (CrI) of fixed effects demonstrated in this table, only the presence of diarrhea (95% CrI: 0.705 - 3.312), discontinuation of breastfeeding (95% CrI: 0.77 - 5.96), and respiratory infections (95% CrI: 2.07 - 4.61) were significantly related to growth failure. In addition, the reported results for random effects reveals that there was a significant random effect (heterogeneity) at the child level (95% CrI: 0.75 - 7.82), but the variation in centers was extremely small (95% CrI: 0.004 - 4.22). The estimate of the proportion of variance (ICC) indicated that 10% of the total variance was attributable to the variation between centers, and 42% was attributable to variation at the children's level.

5. Discussion

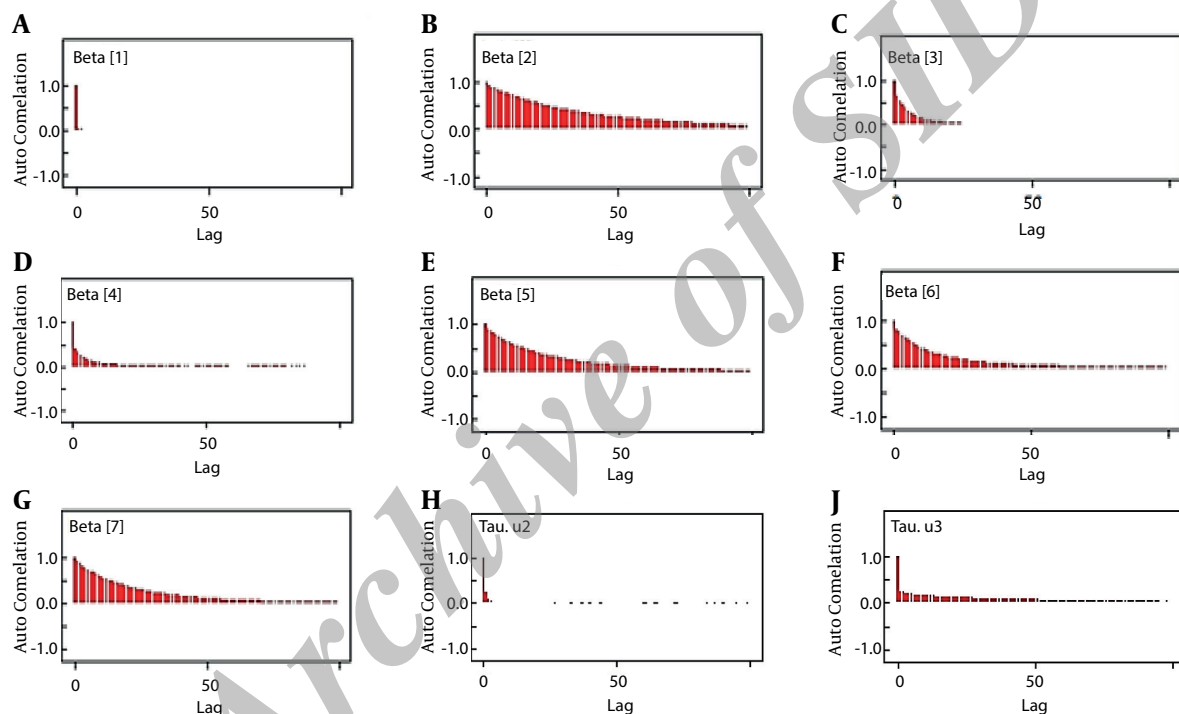
This study attempted to estimate the prevalence of growth failure and investigated the most significant risk factors associated with growth failure in children under two years using a Bayesian multilevel logistic regression model. Diagnosing and treating a child who fails to thrive should focus on identifying any underlying problems that may be causing the condition. Thus, it is important to determine whether FTT results from internal medical problems or factors in the environment. Since, the first two years of a child's life are an essential period of rapid development and growth, detecting and evaluating risk factors which interfere with growth failure is a very important issue during infancy.

The research presented here revealed that the overall prevalence of growth failure in the children under study

Table 2. The GEE Results for Assessing the Concurrent Effects of Risk Factors on Growth Failure

Variables	Estimate	SE	OR (95% CI)	P value
Teething (Ref. = No)	2.59	0.21	13.33 (8.79 - 20.21)	< 0.001
Discontinuation of breastfeeding (Ref. = No)	3.32	0.22	27.60 (17.97 - 42.40)	< 0.001
Diarrhea (Ref.= No)	3.26	0.19	26.18 (17.92 - 38.24)	< 0.001
Respiratory infections (Ref. = No)	3.21	0.15	24.78 (18.48 - 33.21)	< 0.001
Urinary tract infections (Ref. = No)	3.08	0.42	21.87 (9.50 - 50.30)	< 0.001
Fever (Ref. = No)	1.07	1.60	2.92 (0.13 - 67.16)	0.502
Time of initiation of complementary foods	-0.16	0.07	0.85 (0.75 - 0.97)	0.014

Abbreviations: Ref., reference category; SE, standard error.

**Figure 1.** Autocorrelation Plots for all Simulated Parameters of Fixed and Random Effects

was 49.4%. This means that almost half of the children experienced growth failure during their first 24 months of age. Depending on which definition of FIT is used, the prevalence of growth failure is different in various parts of the world (7,17). The prevalence of stunting increases gradually until about 24 months of age, after which the prevalence remains steady. Stunting affects 34% of children under five years of age (almost 195 million, or one in three children) and approximately half of these children live in south Asia. More than 90% of the world's stunted chil-

dren are living in Africa and Asia, which are the countries with the highest stunting rate at 41% and 36%, respectively (24). Likewise, 10 countries account for 60% of the children in the developing world who suffer from wasting, and more than one third of the developing world's children who are wasting live in India. There are similar reports on the prevalence of stunting and wasting in additional countries, such as Abidoye and Sikabofori's (25) study on Nigeria (40.8% and 36.7% of children below two years of age experiencing stunting and wasting, respectively) and the work

Table 3. Results of Point Estimates for Risk Factors in Growth Failure and Variance Components Using the Bayesian Hierarchical Logistic Regression Model

Parameters	Mean ^a	SD ^b	OR	MC Error ^c	2.5% ^d	97.5% ^d
Fixed effects						
Teething (Ref. = No)	-1.91	1.97	0.15	0.031	-6.64	1.08
Discontinuation of Breastfeeding (Ref. = No)	3.40	1.32	29.96	0.014	0.77	5.96
Diarrhea (Ref. = No)	2.06	0.66	7.84	0.004	0.70	3.31
Respiratory infections (Ref. = No)	3.36	0.65	28.80	0.003	2.07	4.61
Urinary tract infections (Ref. = No)	2.22	1.51	9.21	0.018	-0.85	5.05
Fever (Ref. = No)	1.56	1.35	4.76	0.016	-1.24	4.07
Time of initiation of complementary foods (Ref. = No)	0.12	0.21	1.13	0.001	-0.28	0.56
Random effects						
$\sigma^2_{u_{0i}}$ (Between children)	2.89	1.88	-	0.05	0.75	7.82
$\sigma^2_{v_{0ij}}$ (Between centers)	0.70	1.19	-	0.010	0.004	4.22
ICC						
Centers	0.10	-	-	-	-	-
Children	0.42	-	-	-	-	-

Note: Ref., reference category.

^aPosterior mean.

^bposterior standard deviation.

^cMonte Carlo error which measures the variability of each estimate due to the simulation.

^dThe Bayesian central credibility interval is based on the 2.5th and 97.5th percentile points of the posterior distribution.

of Phengxay et al. (8) in Laos (54% and 6% for nutritional stunting and wasting, respectively).

Mahyar et al. in 2010 reported a prevalence rate of 11.5% and 0.7%, respectively, for stunting and wasting in children aged between 0 - 24 months in Qazvin, Iran (7). According to report in 2004, prevalence rates of 20.3% and 4.9% were found for stunting and wasting in children under five years of age in Karaj, Iran (3).

Based on the Bayesian results in Table 3, discontinuation of breastfeeding (OR: 29.96) was determined to be the most significant risk factor for growth failure in these children. Some studies disclosed that this factor is a principle risk indicator for wasting in children (6, 17). Furthermore, discontinuation of breastfeeding may be involved in the relationship between diarrhea infections and growth failure (17, 26-28). Early discontinuation of breastfeeding deprives the child of an ideal food, which includes short and long-term nutritional, immunologic, developmental, and psychological benefits. Therefore, having a higher risk for growth failure may be due to the synergy between infection and malnutrition (29, 30).

In this paper, the present results demonstrated that infectious diseases, such as respiratory and diarrhea infections, were factors associated with growth failure in the children under study. The results revealed that respiratory infections were the second most important risk indicator

for growth failure among these children. Based on some studies, infectious diseases are one of the confirmed factors associated with FTT, which could lead to the deterioration of immune function (31). To our knowledge, there are few studies in the literature that have considered the influence of respiratory infections on FTT (17, 32). Diarrheal disease is the second leading cause of death in children under five years old. Relevant results from similar studies conducted prior to this survey, such as those of Berkman et al. (33) and Kholdi et al. (17), have concluded that in poor areas of developing countries, diarrhea is responsible for weight faltering, especially in children younger than two years of age (3, 5). In 2004, Bloss et al. examined the prevalence and predictors of low weight, stunting, and wasting among children less than five years of age in western Kenya. They found that diarrhea is a related factor for wasting, and upper respiratory infections are significant risk factors for being underweight (32).

Furthermore, the findings of the current study indicated that growth failure was not associated with fever. This is unlike the results provided by Wamani et al. in 2006, where it was reported that fever was associated with failure to thrive (34). Moreover, in children under two years of age, urinary tract infections should also be considered in the differential diagnosis of FTT (35). In contrast to our results, Kholdi et al. (17) found a significant association be-

tween urinary tract infections and growth failure.

In this article, two models for the analysis of longitudinal discrete responses were compared: the multilevel logistic regression model and the marginal model (GEE analysis). The obtained results revealed that respiratory infections, discontinuation of breastfeeding, and diarrhea were common significant factors in both models. However, although the findings of these two models are the same, there are some differences between them. First, the GEE estimates are interpreted as population-averaged, while in a multilevel model, the estimates of the parameters are conditional upon the level of the subject-specific effect. Second, when the data is generated from individuals within a cluster, the results are likely to be correlated. In such circumstances, there are different sources of variability which are ignored by the marginal model. As a result, standard errors will be underestimated, and also the amount of independent information available in the parameter estimation can be erroneously inflated. Indeed, in the marginal model, only the intra-cluster correlation is considered. However, in random effects models (e.g., multilevel models), different sources of variability are accounted for. Furthermore, the marginal models do not distinguish between the different sources of variability, whereas multilevel models explicitly distinguish between the within-subject and between-subject sources of variability by random effects (12, 13).

A principal focus of this analysis was the assessment of the relationship between the different risk factors and growth failure at the child level using a multilevel logistic model and the Bayesian estimation approach. Similar to the results obtained by Browne and Draper (22) and Ferrari et al. (36), it has been shown that an MCMC algorithm for obtaining estimates of the parameters in multilevel logistic regression model is more accurate than the classic approaches, and it has provided narrower confidence intervals. More specifically, in hierarchical logistic regression models, the likelihood function has no closed form. This is due to the fact that it involves a high-dimensional integral for the parameters of the random terms distribution. In this study, it has been revealed that the Bayesian approach of iterative simulation is an appropriate method for solving this problem.

Generally, children diagnosed with FTT are healthy at birth but later fall below the standard measurements for growth. This condition has been broken down into three types: organic FTT (an infant with a medical condition or physical impairment), non-organic FTT (NOFTT), and mixed FTT. This study focused on the first type. Regarding the significant risk factors in the incidence of growth failure in children between birth and two years of age in Tehran, Iran, it seems that promoting knowledge among

parents, improving the child's nutritional status, and increasing the level of health care in health centers may effectively reduce and control this important problem. In addition, the use of multilevel models for the analysis of longitudinal data with more than two levels is suggested, especially when the main focus is on the different nested sources of variability and the data has a hierarchical structure.

One of the main weaknesses of this study was that the results could not be generalized to all Iranian children less than 2 years, because the sample was only selected from health centers in the north and northeast parts of Tehran. In addition, another limitation of our research was the reliance on the available documents in the health centers, which may have included incomplete records or some improper registration. To overcome these limitations, it is suggested that a cohort design be used for studying a complete and generalizable sample in Tehran.

Acknowledgments

This article was a part of a master of science thesis in biostatistics, and it was supported by Hamadan University of Medical Sciences. We are extremely grateful to all of the parents and children who took part in this study. Also, we thank the GP students of Shahed university for gathering the data, and the staff of the health centers of Tehran for their kind cooperation.

Footnote

Authors' Contribution: Nahid Kholdi contributed to the designing data collection of the study. Abbas Moghimbeigi, Maedeh Amini, and Ali Reza Soltanian contributed to the analysis of data. Farid Zayeri and Maedeh Amini contributed to writing and revising the manuscript.

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