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Ahmadi Angali, K., Loeloe, M. S., Akhoond, M. R., Daneshkhah, A. & Borazjani, F.

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Early feeding and growth pattern in infants: Using a three-variate longitudinal model derived from Gaussian copula function

Kambiz Ahmadi Angali [1,3], Mohammad Sadegh Loeloe [1],Mohammad Reza Akhoond [2], Alireza Daneshkhah [3], Fatemeh Borazjani [4,5]

(1) Department of Biostatistics, Faculty of Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
(2) Department of Statistics, Mathematical Sciences and Computer Faculty, Shahid Chamran University of Ahvaz, Ahvaz, Iran.
(3) Faculty of Engineering Environment and Computing, Coventry University, Coventry CV1 2JH, UK.
(4) Department of Nutrition, Faculty of Paramedicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
(5) Nutrition and Metabolic Disease Research Center, Ahvaz Jundishapur University of Medical Science, Ahvaz, Iran.

CORRESPONDING AUTHOR: *Fatemeh Borazjani, Ph.D. of Community Nutrition, Assistant professor, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran - E-mail: fa.borazjani@gmail.com, Tel:+98- 6133738269, Fax: +98-6133738282.*

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ABSTRACT

Background: The Gaussian copula model was used to generate joint distributions for continuous longitudinal variables on infant types of feeding and longitudinal measures of height, weight and head circumference
Methods: The study was performed longitudinally in rural areas of southern part of Iran, on children from birth to 9 months of age. Out of 319 infants with serial anthropometric measurements from birth, and 2, 4, 6, 7 and 9 months old, 120 were included. Infants were divided into three groups (breast fed, formula fed and both milk types). A three-variate longitudinal model including Copula function was used to estimate the effect of feeding on growth pattern. All the analyses were performed using SAS version 9.4 (Proc NLmix).
Results: Ninety infants (75%) were breastfed, sixteen (13.3%) were formula fed and fourteen (11.7%) had combined feeding. Copula model showed that, breast fed children had a better weight gain (β=0.627 95% CI 0.217-1.038 P = 0.003), height (β=2.603 95% CI 1.023-4.183 P = 0.001) and head circumference (β=0.8 95% CI 0.069-1.531 P = 0.0) as compared to formula fed children. R2 for Copula model was (wt=0.52, ht=0.96, hc=0.84).
Conclusions: Implication of Copula model was easy to perform. Estimation of the parameters in copula model indicated that, breast milk consumption had a positive effect on the growth of infants.

Key words: Growth; body measures; breast feeding; multivariate longitudinal model; Gaussian Copula model.

INTRODUCTION

Growth of children is considered to be an important component of community health, which evolves as an indicator of overall well-being [1, 2], because it reflects the adequacy of the environment as it influences growth and nutritional status of children, which finally affects health [3, 4]. Normal growth is the regular changes in height, weight and head circumference that are in standard manner for a given population. In most studies, anthropometric indicators such as weight, height and head circumference, and especially regular weighing, are used to monitor children's physical growth and health [5, 6].

Regular monitoring of height, weight and head circumference of children can lead to a timely discovery of growth disturbances and early onset of preventive and therapeutic interventions [7]. Nutrition is the most important factor that affects a child's physical growth process [8]. Infant feeding practice, breast-feeding, has protective role against overweight and delayed introduction of sugar-sweetened beverages feeding approaches may show the metabolic profile of the infant [9].

Breast milk is undoubtedly an ideal food, and in addition to providing all the baby's nutrients, it also has benefits in terms of safety and mental health [10]. In addition, due to the racial disparities and variation of the auxiliary feed in different communities, different information in different countries and regions is essential for comparison of the growth of each child with the conditions of the same region, as well as breastfeeding and formula feeding with their own specific curves [11]. A comparison between the growth curves and the report of National Center for Health Statistics shows a good growth for up to six months, especially in breastfed infants. Some studies have shown a slower growth of breastfed infants in the first months, but finally, reached an optimal growth by the age of 2 years [12]. This may be due to higher protein and energy density of formula than human milk which stimulates the secretion of insulin-like growth factor and then accelerates growth [13].

In most studies that have examined the effects of nutrition on infants' growth, factors such as gender, birth order, household size, maternal health indicators, the economic and cultural status of the family, have also been used to modify their proposed model [12, 14, 15]. In this study, the aim of longitudinal modeling of anthropometric indices is to show height, weight and head circumference of newborns, and the correlation between anthropometric variables is also included in the model. However, most studies similar to cross-sectional analyses at different intervals, have considered usually up to 12 months and have presented different results with several intervals as well as ignored the role of the correlation derived from the longitudinal measurement of observations. With regards to the role of time, in many medical studies, especially that of growth, longitudinal studies play an important role in comparison with cross-sectional studies [16]. Moreover, the benefits of bivariate or multivariate models that consider the dependence of variables on univariate models better control the errors and increase the efficiency in estimating the effects of independent variables [17]. Gaussian copula is used to conveniently manage dependence in regression analysis. The dependence structure identified by the Gaussian copula is a nuisance component [18].

Therefore, the use of three-variate longitudinal model was proposed using the copula function, a powerful statistical framework, for identifying the effect of infant's feeding type on anthropometric indices such as height, weight and head circumference up to nine months.

METHODS

The present study was carried out in some rural areas in the south of Iran, on children brought to the two main health centers from different small villages, for growth monitoring during 2015. In this study, initially, participating mothers (319 participants) were informed and after providing verbal consent, they were included in the study. Data from 120 pair of mother-child with serial anthropometric measures of weight, height and head circumference (n=776) from birth to nine months, as well as maternal type of feeding practice and regularity of supplement use were finally recorded.

The inclusion criteria were birth weight of more than 2,500 g, gestational age at birth between 37 and 42 weeks, absence of congenital complications and having regular growth monitoring. During this period, they were referred six times (at birth, two, four, six, seven and nine months). The anthropometric measures, feeding practice, frequency of breast feeding and neonate's age were obtained from their health record in the health centers. Infants were divided into three groups of feeding practice. The first group is the exclusive breastfeeding, which, according to the World Health Organization (WHO), is using only breast milk and vitamin supplement for the first six months of life [18]. The other two groups consisted of formula feeding and a group that fed with both breast and formula milk. A three-variate longitudinal model of height, weight and head circumference was fitted to the data as a dependent variable using the Gaussian copula function.

Gaussian Copula modeling is the most popular technique for explaining the relationship between two response variables (weight, height and head circumference); this is an alternative method to multivariate analysis, to join response variables. The advantage of this approach is that they connect two response variables based on hidden random effect. This copula approach is a simple tool that provides a better understanding of the influence of a dependence relationship between two random variables which is obscured.

Copula model was adjusted by maternal age (by years), maternal BMI (kg/m^2), infant's gender, type of delivery (normal, cesarean section), birth height (cm), birth weight (kg), birth head circumference (cm), birth order, infant feeding practice, and the frequency of daily lactation and night feeding. Therefore, the effect of independent variables on dependent variables was investigated simultaneously. Easyfit software was used to verify normality of marginal distribution of three anthropometric measures by Kolmogorov-Smirnov test. Shared random effect with normal distribution in marginal models was used to make the correlation of the measurements over time. Statistical analysis was done using the Proc Nlmixed, SAS software version 9.4.

Statistical method

Three variables longitudinal data, Y_{ij1}, Y_{ij2}, Y_{ij3} are realization of birth weight, birth height, and birth head circumference, respectively, where, $i=1,2,...,120$ shows the number of subjects and $j=1,...,5$ is growth monitoring occasions (at birth, two, four, six, seven and nine months).

The linear model for each k = 3 response variable is given as follows.

$$y_{ijk} = X_{ij}^T B_k + Z_{ij}^T B_i + \varepsilon_{ijk}. \qquad k = 1,2,3$$

Where, X_{ij} is a vector of independent variables (auxiliary) and B_k is their corresponding regression coefficients in each linear model; B_i is its corresponding joint effect coefficient for the three models; μ_{ijk} $k=1,2,3$ is the mean response for weight, height and head circumference respectively, as follows:

$$\mu_{ijk}(B_i) = X_{ij}^T B_k + Z_{ij}^T B_i. \qquad k = 1,2,3$$

It is usual to consider that, the conditional distribution of y_{ij1}, y_{ij2}, y_{ij3} given random effect, has normal distribution.

$$y_{ij1}|b_i \sim N(\mu_{ij1}(B_i), \sigma_i^2)$$
$$y_{ij2}|b_i \sim N(\mu_{ij2}(B_i), \sigma_i^2)$$
$$y_{ij3}|b_i \sim N(\mu_{ij3}(B_i), \sigma_i^2)$$

Response variables were used in three-variate Gaussian Copula function, where the conditional distribution function of the responses is defined as follows [19].

$$F_{Y_{ij1},Y_{ij2},Y_{ij3}|B_i}(.|.) = \Phi_3\left[\Phi^{-1}(u_{ij1}(b_i)), \Phi^{-1}(u_{ij2}(b_i)), \Phi^{-1}(u_{ij3}(b_i)); \rho\right].$$

Where, Φ and Φ_3 function are the single and triple cumulative normal distribution functions respectively and are defined as follows:

$$u_{ijk}(b_i) = F_{Y_{ijk}|B_i}(y_{ijk}|b_i). \; k = 1,2,3$$

The variables $\mu_{ijk}(b_i)$ (k=1,2,3) have a uniform distribution in the interval (0 and 1). Furthermore, ρ represents a correlation matrix between the response variables conditional on the random effects, and $\rho=0$ if and only if the responses are independent of each other. It is assumed that $b_i \sim N(0,\sigma_i^2)$ (since each of the three variables: height, weight and head circumference of a baby follows an almost identical growth model over time. The same random effect of was considered identical for all the models). The three-variate density function was obtained using the Gaussian Copula function as follows [20].

$$f_{Y_{ij1}Y_{ij2}Y_{ij3}|B_i}(.|.) = \frac{1}{|R|^{\frac{1}{2}}} \exp\left\{-\frac{1}{2}u'(R^{-1}-I)u\right\} \times f_{Y_{ij1}|B_i}(y_{ij1}|b_i) \times f_{Y_{ij2}|B_i}(y_{ij2}|b_i) \times f_{Y_{ij3}|B_i}(y_{ij3}|b_i). \qquad (1)$$

Where, $u' = \left[u_{ij1}(b_i), u_{ij2}(b_i), u_{ij3}(b_i)\right]$ and it is assumed that $R = \begin{pmatrix} 1 & \rho & \rho \\ \rho & 1 & \rho \\ \rho & \rho & 1 \end{pmatrix}$ is a three-variate Gaussian Copula dependency matrix and I is the same matrix (since, according to Table 3, the mutual correlation coefficients of the three variables are very close. The R matrix is mutual correlation dependency coefficients of Gaussian Copula function which were considered as the same parameter, ρ. The likelihood function and its logarithm are calculated as follows.

$$L_i(\theta) = \int \prod_{i=1}^{n_i} f_{Y_{ij1}Y_{ij2}Y_{ij3}|B_i}(.|.) f_{B_i}(b_i) db_i. \; (2)$$

$$l(\theta) = \log L(\theta) = \sum_{i=1}^{N} \log L_i(\theta) = \sum_{i=1}^{N} l_i(\theta).$$

θ is the vector of all the parameters of the model. Now, by inserting (1) in expression (2), the likelihood function for the Gaussian Copula function can be calculated. The maximum likelihood estimation of parameters θ ($L'(\theta)=0$) was obtained by the Newton-Raphson method, using SAS, PROC NLMIXED software version 9.4.

RESULTS

Of the 120 neonates, 60 (50%) were male and 60 (50%) were female. Sixty-three neonates (52.5%) were born by normal delivery and 57 (47.5%) were born by cesarean delivery. Twenty-nine (24.1%), sixty-seven (55.9%), twenty (16.7%), three (2.5%) and one infant (0.8%) were the first, second, third, fourth and fifth child birth, respectively. The mean age of mothers was 28.6 with a standard deviation of 5.5 years and the mean number of daily breastfeeding was 15 times with a standard deviation of 4.6 times a day and night. Table 1 shows the mean and standard deviation of weight, height and head circumference of newborns from birth to nine months of age. Table 2 shows mother and child information grouped into three types of feeding for children. With Kruskal-Wallis and Chi-square tests, it can be said that the distribution of maternal and infant characteristics such as maternal age (P = 0.36), maternal BMI (P = 0.194), number of breastfeeding per day and night (P =0. 21), the birth order (P = 0.881), delivery type (P = 0.497), birth height (P =0. 611), birth weight (P = 0.929) and birth head circumference (P = 0.788) in each of the three feeding groups are almost identical.

Table 3 shows the correlation matrix between height, weight and head circumference of infants with the Pearson correlation test. As shown in the table, the correlation between the three variables (up to 0.01) is significant and positive. Figure 1 also shows the mutual correlation between the three variables.

Figure 2 shows the mean height, weight and head circumference of infants from birth to 9 months of age in the three feeding groups. According to the graphs, the average growth rate up to 9 months in all the measures: height, weight and head circumference in the breastfed group was better than that of formula-fed and combined feeding groups. Also, the combined feeding showed better growth than formula-feeding.

Table 4 shows the estimation of model parameters for the variables: weight, height and head circumference of infant. The variables for breastfeeding were significantly higher than for formula milk (P = 0.003); in feeding with both milk types as compared to formula milk (P = 0.03), infant gender (P = 0.024) and birth weight (P = 0.0003) were effective in weight gain of the baby. Newborns that are breastfed have a better weight gain than those that are formula fed and had both feeding types. The weight gain of the male baby is greater than that of the female and has a better weight gain pattern.

The variables for breastfeeding were significantly higher than for formula milk (P = 0.002); in feeding with both milk types as compared to formula milk (P = 0.026), infant's gender (P = 0.001) and birth height (P= 0.0001) are effective in height growth of infants. Newborns that are breastfed have a better height growth than those that are formula fed and had combined feeding. The growth of male neonates' height is greater than that of females and has a better height growth pattern.

In breastfeeding as compared to formula milk (P = 0.032), infant's gender (P <0.0001) have effective role in the growth of head circumference of the infant. Newborns that are breastfed have a better head circumference than those that were formula fed and had combined feeding. The growth of head circumference of the male newborns is more than that of the female with a high head circumference at birth and a better head circumference growth pattern (Figure 2).

Considering the dependency coefficient of the Gaussian Copula function (ρ), which is 0.904 (P <0.0001), it can be said that the application of the Gaussian Copula function due to the correlation between height, weight and head circumference, makes the model more efficient.

DISCUSSION AND CONCLUSION

The present study measured statistical dependence between random variables (weight, height and head

FIGURE 1. Scatter plot matrix variables, height, weight and head circumference

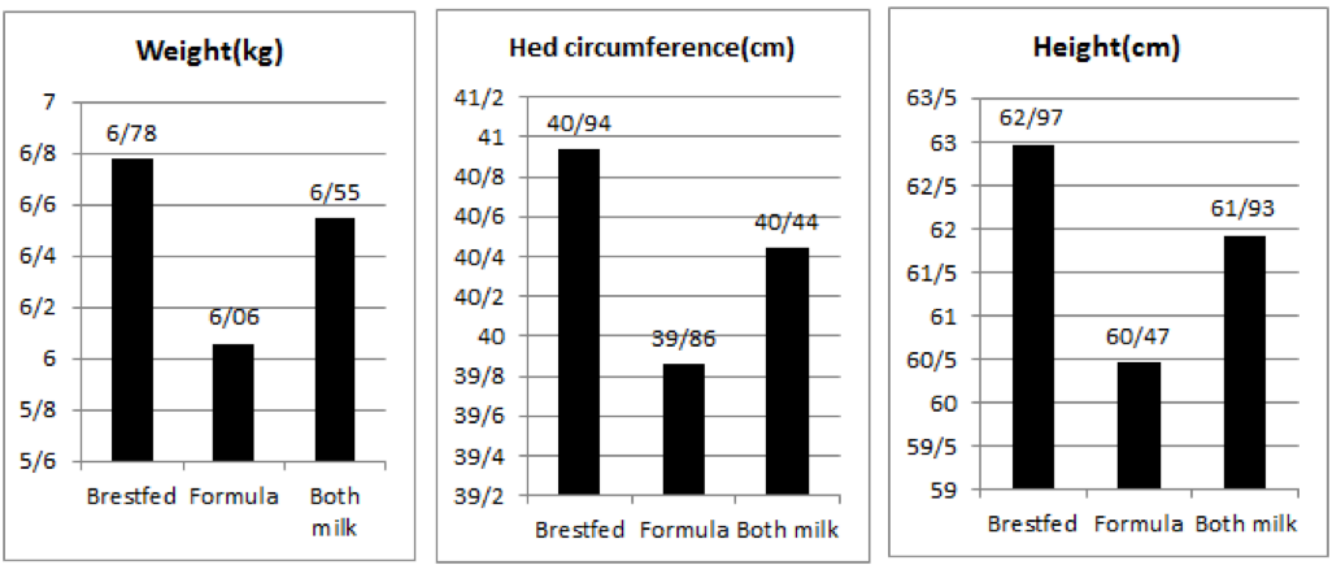

FIGURE 2. Mean height, weight and head circumference of infants from birth to 9 months in each feeding group

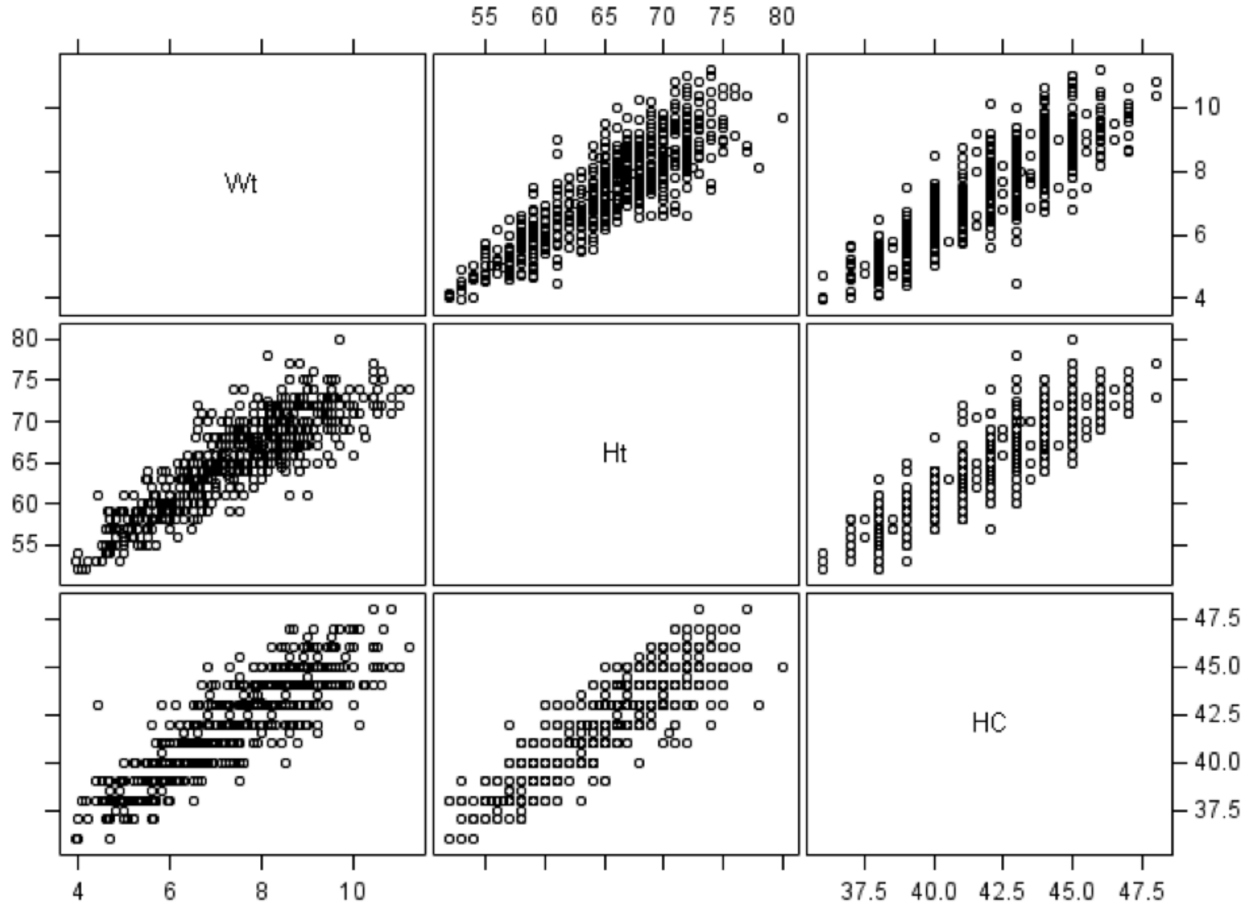

TABLE 1. Mean and Standard Deviation of weight, Height and Head circumference

	TIME OF BIRTH		2 MONTHS		4 MONTHS		6 MONTHS		7 MONTHS		9 MONTHS	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Weight (kg)	3.17	0.48	5.36	0.63	6.8	0.86	7.75	0.95	8.2	1	8.7	1.08
Height (cm)	49.55	2.17	57.52	2.43	62.48	2.61	66.2	2.63	68.36	2.7	71.45	2.91
Head circumference (cm)	34.4	1.7	38.6	1.17	40.94	1.29	42.49	1.32	43.55	1.36	44.6	1.39

circumference), copula densities, and built a mutual (paired) joint distribution of weight, height and head circumference variables based on their marginal distribution. The copula density is the density that filters the marginal information from the joint distribution of the two (paired) response variables. The model showed that infants fed breast milk had a better growth in weight, height and head circumference than infants fed with formula milk and combined feeding. Appropriate feeding practices play a vital role in achieving optimum growth and development. WHO recommends Exclusive Breast Feeding for the first 6 months, followed by the introduction of appropriate complementary feeding at the same time as breastfeeding continues until 2 years of age or beyond [18]. Various studies have been conducted on the effect of feeding practice on the growth of newborns in different regions. In a study in Belarus in 2002, Kramer et al. showed that breastfed infants of up to 9 months of age have a better weight gain, and their height growth is better in 3-6 months, but there was no difference in the growth of the head circumference of infants with breastfeeding as compared to other infants [19]. In another study on Canadian newborns in 2004, they also considered weight indices for age, height for age, weight for height and head circumference of newborns as growth indicators, and

TABLE 2. Mother and child characteristics in Nutrition

	Breastfed	Formula-fed	Both milk types
Number (%) in time of birth	106 (88.3)	5 (4.2)	9 (7.5)
Number (%) in second month	90 (82.6)	9 (8.3)	10 (9.2)
Number (%) in fourth month	96 (80)	18 (15)	6 (5)
Number (%) in sixth month	100 (83.3)	6 (5)	14 (11.7)
Number (%) in seventh month	84 (70)	18 (15)	18 (15)
Number (%) in ninth month	85 (78)	16 (14.7)	8 (7.3)
The mean (SD) maternal age (years)	28.7 (5.5)	27 (5.5)	26.5 (5.6)
The mean (SD) mother's BMI	27.15 (4.5)	27.66 (4.2)	28.13 (3.7)
Number (%) normal delivery	45 (50)	10 (62)	8 (57)
The mean (SD) frequency of milk feeds	15.3 (4.8)	14.06 (5.4)	14.38 (5.5)
The mean (SD) number of children	2 (0.8)	1.98 (0.9)	2.05 (0.8)
The mean (SD) BirthWeight	3.2 (0.4)	3.3 (0.5)	3.51 (0.5)
The mean (SD) Birth height	49.8 (2.1)	49.8 (2.2)	50.1 (1.7)
The mean (SD) Birth head circumference	42.15 (1.8)	41.29 (2.1)	41.87 (1.1)

TABLE 3. Correlation matrix between three variables

		Wt (kg)	Ht (cm)	HC (cm)
Wt(kg)	Corr elation	1	0.863**	0.863**
	P		0.000	0.000
Ht(cm)	Correlation		1	0.879**
	P			0.000
HC(cm)	Correlation			1
	P			

*** Correlation is significant at the 0.01 level (2-tailed).*

examined their effect on the type of nutrition at three-month intervals for twelve months with separate linear models and showed that the growth of infants fed with formula milk, especially at 3-6 months of age is better than that of breast-fed infants [21]. The hormonal differences in feeding practice and appetite regulating hormones (e.g., leptin, adiponectin, and ghrelin) and even insulin-like growth factor 1 are responsible for accelerating growth and increasing muscle mass and adipose tissue. So, the differences between breast- and formula-fed infants provide evidence that feeding type has a metabolic effect on infants. Additionally, formula-fed infants and maternal excess gestational weight gain [22] have a more complex microbiota with greater proportions of Bacteroides, Clostridium and Enterobacteria that support the more weight gain and alter the later life metabolic state [23].

Interestingly, in this study, exclusive breastfed was associated with more rapid growth; it may be related to complementary diet-induced altered metabolic state in infancy.

By introducing infant feeding practices (IFP) based on WHO nutritional recommendations, especially exclusive breastfeeding up to 6 months of age and continuing breastfeeding until 12 months, Kental et al. showed that the index has a positive and significant effect on neonatal growth [24]. By introducing several separate linear models at intervals from the first to the twelfth month of age of infants, Moodie et al. showed that breastfeeding is effective in reducing infants' weight and height growth [14]. Similarly, in another study, Kramer et al. found that breastfeeding had no effect on infant growth as compared to other types of feeding [15]. In a systematic review of 37 studies on the effect of nutritional interventions on children's growth and health from 2010 to 2013, Grantham et al. confirmed the role of nutritional interventions, especially exclusive breastfeeding, in infants' growth and health [25]. Giugliani et al. reviewed 35 studies on the role of nutrition in children from 2004 to 2014 through a systematic review and by meta-analysis, and showed that breastfeeding interventions usually have a positive effect on infants' height and weight gain up to six months of age but from six months, breastfeeding interventions seem to have little effect on the infants' growth. They concluded that the results of studies on the effects of promotion interventions of breastfeeding on the development of children are heterogeneous [26]. Therefore, previous studies have provided different and varied results regarding the effect of breastfeeding on infant growth, some of which are consistent with the current one, but some of them [5]

TABLE 4. Estimation of the Parameters of Multivariate Regression model based on Copula correlation structure

			ESTIMATE	STANDARD ERROR	P	95% CONFIDENCE LIMITS	
weight	Constant		3.736	1.248	0.003	1.263	6.209
	Type of nutrition	Breastfed	0.627	0.207	0.003	0.217	1.038
		Both milk	0.603	0.274	0.030	0.060	1.146
		Formula-fed			**Reference level**		
	Maternal age		-0.021	0.020	0.282	-0.060	0.018
	Maternal BMI		-0.013	0.022	0.560	-0.056	0.031
	Gender	boy	0.435	0.190	0.024	0.058	0.812
		girl			**Reference level**		
	Delivery Type	normal	-0.102	0.183	0.577	-0.464	0.260
		cesarean			**Reference level**		
	Weight birth		0.074	0.020	0.000	0.035	0.113
	frequency of milk feeds		-0.015	0.016	0.325	-0.046	0.015
	Number of children		0.167	0.136	0.221	-0.102	0.436
Height	Constant		60.963	2.474	<.0001	56.060	65.867
	Type of nutrition	Breastfed	2.603	0.797	0.002	1.023	4.183
		Both milk	2.388	1.060	0.026	0.288	4.489
		Formula-fed			**Reference level**		
	Maternal age		-0.054	0.054	0.315	-0.161	0.052
	Maternal BMI		-0.009	0.061	0.877	-0.131	0.112
	Gender	boy	1.867	0.525	0.001	0.826	2.909
		girl			**Reference level**		
	Delivery Type	normal	-0.079	0.499	0.875	-1.068	0.910
		cesarean			**Reference level**		
	Height birth		1.098	0.269	<.0001	0.565	1.631
	frequency of milk feeds		-0.154	0.050	0.003	-0.252	-0.055
	Number of children		0.642	0.382	0.095	-0.114	1.398
Head circumference	Constant		39.774	1.460	<.0001	36.879	42.669
	Type of nutrition	Breastfed	0.800	0.369	0.032	0.069	1.531
		Both milk	0.640	0.485	0.190	-0.322	1.602
		Formula-fed			**Reference level**		
	Maternal age		-0.029	0.028	0.296	-0.084	0.026
	Maternal BMI		-0.001	0.031	0.976	-0.063	0.061
	Gender	boy	1.237	0.270	<.0001	0.703	1.772
		girl			**Reference level**		
	Delivery Type	normal	-0.112	0.258	0.666	-0.622	0.399
		cesarean			**Reference level**		
	Head circumference birth		0.047	0.025	0.066	-0.003	0.097
	frequency of milk feeds		-0.022	0.024	0.363	-0.069	0.025
	Number of children		0.205	0.191	0.288	-0.175	0.584
	ρ		0.904	0.007	<.0001	0.890	0.919

TABLE 5. R^2 and Rmse of Copula model for three variables

Copula model	Weight	height	Head circumference
Rmse	1.2	4.8	2.17
R^2	0.52	.96	.84

did not report the same effects of breastfeeding on infant weight gain but the same linear growth. Another randomized controlled trial of higher- and lower-protein formula, infants fed higher-protein formula gained weight more rapidly during infancy and had a higher obesity risk at 6 years [27, 28]. In contrast, some studies [6, 29] showed no difference in fat mass between predominantly or exclusively breastfed and formula-fed infants from 2 to 4 months of age. While a few prior studies reported either lower [3] or higher [27] fat mass in formula-fed infants, a meta-analysis [30] showed that fat mass is lower in formula-fed infants at 3–4 and 6 months of age.

In most studies on feeding effects on infant growth, cross-sectional analyses were considered at different intervals, usually up to 12 months of age, and the growth indices at any time, regardless of the correlation obtained from the longitudinal measurements were investigated. In most of the studies, growth indices were considered as univariate and there is no significant correlation between them. In the present study, a model that can consider the dependence obtained from longitudinal measurements and anthropometric measurement indices of height, weight and head circumference was used.

Epidemiologic and biological findings over the last decade have shown the well-known benefits of breastfeeding in all countries, both developed and developing, and studies show that exclusive breastfeeding fights infectious diseases, increase intelligence and reduce the risk of ovarian cancer, and also, type 2 diabetes [11, 31, 32]. The increase in breastfeeding to world-wide level terminates about 823,000 deaths annually among children under 5 years of age and 20,000 deaths from breast cancer every year [11]. Therefore, given the great benefits of breast milk in maternal and neonatal health, the results of this study and similar studies on the impact of breastfeeding on the better growth of newborns, encouraging and supporting more mothers in the use of exclusive breastfeeding plays an important role in the health of the baby and mother. Furthermore, study on the factors affecting the birth of newborns with proper growth at the first year of life is very beneficial for later growth. In the current study, majority of the infants are located in the rural area and are breast fed; also, these findings may be relevant in the context of link between early type of feeding and growth pattern which is likely to be explained by differences in patterns of complementary food intake. Moreover, Gaussian copula approach allows variable joint distributions among anthropometric measures to introduce correlation between variables in the resulting joint model. Therefore, it would be useful to have better interpretability of joint modeling as compared to the regular multivariate model. The unavailability of user-friendly software tools led to limited usage by applied researchers. The description of this model is available in statistical literature.

Consequently, these findings are limited to rural areas and cannot be generalized to other areas. Conducting a longitudinal research from pre-pregnancy through lactation in rural and urban health centers, simultaneously, is suggested.

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