

ORIGINAL RESEARCH ARTICLE

Effects of intergenerational feeding on the growth and development of infants aged 6-36 months: A cross sectional study

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Abstract

This was an original article, mainly investigated the status and effects of intergenerational feeding of infants aged 6-36 months on their growth and development. The nutrition and development status of infants and toddlers were investigated by questionnaire. Logistic regression was employed to analyze whether intergenerational feeding was an independent factor for infant stunting and malnutrition. Three hundred and ninety-seven infants were chosen to participate in this study. The skip-generation feeding rate of infants aged 6-36 months was 29.6%. There were no significant differences in developmental quotient, low weight, emaciation, growth retardation, age-specific weight, length-specific weight, and age-specific length between the intergenerational feeding group and parental feeding group. The incidence of stunting in the skip-generation feeding group was 9.26% (10/108), higher than the parental feeding group (2.86%, 8/280) ($\chi^2=6.172$, $P=0.013$). Multivariate logistic regression analysis showed that maternal education level ($P=0.034$) along with skip-generation feeding ($P=0.005$) were the main affecting factors of developmental delay in infants aged 6~36 months. We conclude that the rate of intergenerational feeding of infants aged 6 to 36 months is about 30%, and maternal education level along with skip-generation feeding were the main affecting factors of developmental delay in infants aged 6~36 months. (*Afr J Reprod Health* 2025; 29 [2]: 69-77).

Keywords: Development; Infants; Intergenerational feeding; Nutrition; Parental feeding

Résumé

Il s'agissait d'un article original, qui étudiait principalement le statut et les effets de l'alimentation intergénérationnelle des nourrissons âgés de 6 à 36 mois sur leur croissance et leur développement. L'état nutritionnel et de développement des nourrissons et des tout-petits a été étudié au moyen d'un questionnaire. La régression logistique a été utilisée pour analyser si l'alimentation intergénérationnelle était un facteur indépendant de retard de croissance et de malnutrition chez les nourrissons. Trois cent quatre-vingt-dix-sept nourrissons ont été choisis pour participer à cette étude. Le taux d'alimentation par saut de génération des nourrissons âgés de 6 à 36 mois était de 29,6 %. Il n'y avait aucune différence significative en termes de quotient de développement, de faible poids, d'émaciation, de retard de croissance, de poids spécifique à l'âge, de poids spécifique à la longueur et de longueur spécifique à l'âge entre le groupe d'alimentation intergénérationnelle et le groupe d'alimentation parentale. L'incidence du retard de croissance dans le groupe d'alimentation avec saut de génération était de 9,26 % (10/108), supérieure à celle du groupe d'alimentation parentale (2,86 %, 8/280) ($\chi^2 = 6,172$, $P = 0,013$). L'analyse de régression logistique multivariée a montré que le niveau d'éducation de la mère ($P = 0,034$) ainsi que l'alimentation par sauts de génération ($P = 0,005$) étaient les principaux facteurs affectant le retard de développement chez les nourrissons âgés de 6 à 36 mois. Nous concluons que le taux d'alimentation intergénérationnelle des nourrissons âgés de 6 à 36 mois est d'environ 30 % et que le niveau d'éducation de la mère ainsi que l'alimentation intergénérationnelle étaient les principaux facteurs affectant le retard de développement chez les nourrissons âgés de 6 à 36 mois. (*Afr J Reprod Health* 2024; 29 [2]: 69-77).

Mots-clés: Développement; Nourrissons; Alimentation intergénérationnelle; Nutrition; Alimentation parentale

Introduction

Intergenerational feeding means that children whose parents are absent are raised by grandparents. With the rapid change of times, grandparents are having an increasingly crucial role in the upbringing of children, and the proportion of intergenerational feeding is increasing. Available

statistics indicate that the number of children living in grandparents' homes in the United States has risen dramatically over the past few decades, from 2.2 million in 1970 to 3.9 million in 1997, which has nearly doubled in the short 27-year period¹, and reached nearly 7.5 million in 2010. It is reported that in Britain that grandparents are the main providers of childcare². Across Europe, about half

of grandparents had cared for their grandchildren in the preceding year³, and one in five children aged 0 to 12 years is cared for by a grandparent⁴. According to the China Health and Nutrition Survey, more than 50% of grandparents help parents raise their offspring⁵, especially with the release of China's two-child policy, more grandparents have to take the responsibility of caring for a second child. The increasing reliance on grandparents as primary feeders of children means that children's dietary intake, childhood obesity and child health may be increasingly influenced by grandparents' food supply⁶, so it is necessary to study the influence of grandparents on children's health.

The early 1000 days of life refers to the window of opportunity from the fetal period to 2 years after birth, which is an important period in the growth of children⁷. In this window period, if good nutrition and healthy growth of children can be ensured, it is conducive to the development of children's later life continuously, particularly when in combination with good social psychological stimulation, it will further ensure the development of children's cognitive and developmental potential⁸. Therefore, it's even more important to study the effects of generational separation on children early in life. In terms of the impact of generational separation on early childhood nutrition, many studies have shown a correlation between grandparents' feeding and children's weight. Children whose grandparents are the main feeders are more likely to be overweight and obese than those whose parents feed them, with a ratio of over two times. Nevertheless, few studies have analyzed the correlation between generational separation and early childhood malnutrition, and malnutrition in early life does affect children's development and potential development⁹. Currently, there is relatively few domestic research on the effect of generational separation on early childhood development, and there is also few foreign research on early life development. In view of this research gap, the objective of this study was to determine the current situation of intergenerational feeding of infants aged 6-36 months, and to explore the influence of intergenerational feeding on the growth and development of infants aged 6-36 months.

Methods

Study participants

From October 2019 to February 2020, infants aged 6-36 months who received physical examination at the Dongying People's Hospital Dongying, Shandong, China were recruited. Infants and toddlers whose parents agreed to participate in the study were selected for the study. Three hundred and ninety-seven infants and toddlers were included in this study.

Inclusion criteria

(1) Infants 6 to 36 months old. (2) Infants and young children whose parents were willing to take part in the survey.

Exclusion criteria

(1) Preterm infants, low birth weight infants, hearing disorders, birth asphyxia history and other high-risk infants. (2) Infants and young children had a history of diarrhea and infection within the last 1 month. (3) Infants and young children had a family history of developmental disorders. (4) Children whose parents did not agree to participate in the survey or whose information were incomplete.

Research content and index

Questionnaire survey

Parents of infants and young children were surveyed using self-developed questionnaires. The contents of the survey were mainly demographic information, including the sex of the infant, date of birth, the main feeders, the educational level of the parents and feeders, the number of siblings in the family, birth weight, birth length, family type, conception history and whether the history of childbearing. The interviewers underwent training before the commencement of the study. After the parents completed the questionnaire, the investigators re-checked the information with parents to ensure accuracy and completeness of the questionnaire information.

Based on the definition of primary feeders in international studies¹⁰, primary feeders were those who take care of the daily life of infants and toddlers for at least 6 months. There is no clear name for grandparents' care of their grandchildren in China, including intergenerational feeding, intergenerational raising, intergenerational breeding, intergenerational care. All these names are included in the intergenerational care, so our definition of intergenerational feeding is continuous care of infants' daily life for at least 6 months of grandparents or maternal grandparents, and taking care of over 80 percent of their daily lives.

Physical measurement

The height, weight, head circumference, height, and weight of parents of infants and children were measured by trained professionals using uniformly calibrated measuring instruments.

Developmental assessment

Outpatient professional child health care doctors adopted the Neuropsychological Development Scale for children aged 0-6 years, which was developed by the Capital Institute of Pediatrics¹¹.

The scale included gross motor, fine motor, language, adaptive ability along with social behavior five areas. The great movement zone referred to body posture, head balance, and the capacity to sit, climb, stand, walk, run, as well as jump. Fine motor area referred to the capacity to use the fingers. Linguistic competence referred to the ability to understand and express language. Adaptive area referred to a child's ability to respond to and adapt to the requirements of his or her natural environment and society. Social behavior area referred to the ability to communicate with people around and the ability to take care of themselves.

The scale measured a child's mental age and developmental quotient (DQ). Do is one of the core indicators used to measure the level of children's psychological development. It is a measure of children's development in the aspects of gross motor, fine motor, cognitive, emotional and social development.

Evaluation criteria

According to the reference values provided by World Health Organization (WHO)¹², weight for

age is defined as low body weight (underweight), which is a common indicator to judge malnutrition in children. Two standard deviations below average height for age is growth retardation, which usually reflects chronic malnutrition in children. A height-to-weight ratio of less than two standard deviations from the mean is wasting, usually reflecting recent acute malnutrition.

Based on the Neuropsychological Development Scale for children aged 0-6 years old, the developmental quotient DQ score of less than 70 points was considered as developmental delay.

Statistical analysis

SPSS 19.0 statistical software was implemented for statistical analysis. Statistical data were exhibited by component ratio, and analyzed by χ^2 test. Measurement data of normal distribution were described by $\bar{x} \pm s$, and independent sample t test was selected for comparison between 2 groups. Logistic regression analysis was implemented to determine whether intergenerational feeding was a risk factor for developmental delay. Univariate Logistic analysis was implemented on the affecting factors of growth and development indicators, with the independent variable of intergenerational feeding and other influencing factors as covariables. The growth retardation (yes=1, no=0), emaciation (yes=1, no=0), malnutrition (yes=1, no=0), and growth retardation (yes=1, no=0) of infants were used as dependent variables for multivariate Logistic regression analysis to determine whether intergenerational feeding was an influential factor for infant growth and development.

Ethical considerations

Our study was approved by the Ethics Committee of Dongying People's Hospital, the approval number was DYYX-2016-76, and the approval date was September 2, 2016

Results

General data

There were 397 infants, including 222 males (55.9%) and 175 females (44.1%). The rate of intergenerational feeding was 29.5% (117/397).

Table 1: General data of infants

Items	Number	Percentage (%)
Gender		
Male	222	55.9
Female	175	44.1
Feeding pattern		
Intergenerational feeding	117	29.5
Parental feeding	280	70.5
Age		
6 to 12 months	247	62.2
12 to 24 months	111	28.0
24 to 36 months	39	9.8

There were 4 cases (1%) of father feeders, 276 cases (69.5%) of mother feeders, 112 cases (28.1%) of grandmother feeders and 5 cases (1.3%) of grandfather feeders. There were 247 patients (62.2%) aged 6 to 12 months, 111 patients (28%) aged 12 to 24 months, and 39 patients (9.8%) aged 24 to 36 months.

Comparison of general data between intergenerational feeding group and parental feeding group

No significant differences were seen in age, sex, birth weight, birth length, fetal protection history, conception history, number of siblings, parental height and parental weight between the intergenerational feeding group and the parent feeding group at 6 to 36 months ($P>0.05$). Nevertheless, there were statistical differences in parents' education level and family type ($P<0.05$), the education level of mothers in the intergenerational feeding group were higher than the parent feeding group. In addition, 66.7% (78/117) of families in the intergenerational feeding group were large families (three generations living together), while only 40% (112/280) of families in the parent feeding group were large families (Table 2).

Comparison of nutritional status and development of infants in intergenerational feeding group and parent feeding group

Table 3 show that there are no significant differences in body length, body weight, head circumference, length-for-age, weight-for-age,

weight-for-length, developmental quotient, fine motor, cognition, language, social interaction and gross motor between the intergenerational feeding group and the parent feeding group in nutritional status and development ($P>0.05$). No significant differences were shown in the incidence of malnutrition including low body weight, emaciation, and growth retardation between 2 groups ($P>0.05$). The growth retardation rate of intergenerational feeding group was 8.55% (10/117), was significantly higher than 2.86% (8/280) of parental feeding group ($\chi^2=6.172$, $P=0.013$).

Univariate Logistic regression analysis of developmental delay in infants aged 6-36 months

The univariate logistic regression analysis of 397 infants aged 6-36 months showed that feeding type was a crucial factor affecting the development of infant growth retardation, and the probability of growth retardation of infants in the intergenerational feeding group presented 3.178 times higher than that in the parent feeding group ($P<0.05$, Table 4).

Multivariate Logistic regression analysis of the impact of feeding type on developmental delay in infants aged 6 to 36 months

According to professional knowledge, birth height (cm) (continuous variable), birth weight (kg) (continuous variable), pregnancy protection history (with=1, without=0), pregnancy status (artificial insemination=1, natural insemination=0), father's education level (college or above=1, high school or below=0), mother's education level (college or above=1, High school and below=0), number of babies ($\geq 2=1$, 1=0), family type (large family=1, basic family=0) as covariates, feeding type (intergenerational feeding=1, parent feeding=0) as independent variables, and growth retardation in infants (yes=1, no=0) as dependent variables were adopted for multivariate logistic regression analysis (forward, LR). The results showed that after controlling the influence of covariates, the probability of developmental retardation in infants fed by intergeneration was 4.051 times that of infants fed by parents, and the mother's education level was also an influencing factor.

Table 2: Comparison of general data of 397 cases of intergenerational feeding group and parent feeding group

Observation indicators	Parent feeding group (280 cases)	Intergenerational feeding group (117 cases)	Statistical value	P value
Age of the moon	13.39±6.83	13.44±7.30	-0.083	0.934 ^a
Gender			1.447	0.229 ^b
Male	162	60		
Female	118	57		
Birth weight	3.37±0.47	3.37±0.49	0.121	0.904 ^a
Birth length	50.33±1.44	50.32±1.36	0.102	0.919 ^a
History of preventing miscarriages			0.909	0.340 ^b
No	216	85		
Yes	64	32		
History of conception			0.000	1.000 ^c
Spontaneous conception	269	112		
Artificial impregnation	11	5		
Number of siblings			0.713	0.398 ^b
1	184	82		
≥2	96	35		
Paternal height	175.42±5.31	175.59±4.45	-0.305	0.761 ^a
Maternal height	162.85±4.96	162.80±4.84	0.083	0.934 ^a
Paternal weight	77.97±15.15	77.47±13.53	-0.311	0.756 ^a
Maternal weight	61.15±11.79	61.55±12.28	-0.306	0.760 ^a
Paternal education level			4.655	0.031 ^b
Senior high school and below	120	64		
University or above	160	53		
Maternal education level			13.873	<0.001 ^b
Senior high school and below	115	45		
University or above	165	72		
Family style			23.515	<0.001 ^b
Basic family	168	39		
Big family	112	78		

Note: a was independent sample t test, b was χ^2 test, and c was calibrated χ^2 test.

Relative to infants whose mothers were high school or below, the probability of developmental delay in infants whose mothers were college or above was increased by 2.23 times.

Multivariate Logistic regression analysis of the impact of feeding type on nutritional status of infants aged 6-36 months

Birth height (cm) (continuous variable), birth weight (kg) (continuous variable), fetal preservation history (with=1, none=0), conception status (artificial insemination=1, natural conception=0), father's education level (college

and above=1, high school and below=0), mother's education level (college and above=1, high school and below=0), number of babies ($\geq 2=1$, 1=0), family type (large family=1, basic family=0), parents' height (cm) (continuous variable), parental weight (kg) (continuous variable) as covariates, feeding type (generation-skipping feeding=1, parent feeding=0) as independent variables, and infants and young children with growth retardation (yes=1, no=0), low weight (yes=1, no=0), and wasting (yes=1, no=0) as dependent variables were adopted for multivariate Logistic regression analysis.

Table 3: Comparison of nutritional status and development of 397 infants in the intergenerational feeding group and the parent feeding group

Observation indicators	Parent feeding group (280 cases)	Intergenerational feeding group (117 cases)	Statistical value	P value
Body length	77.52±7.29	77.75±7.88	-0.279	0.781 ^a
Body weight	10.26±4.70	10.14±1.86	0.269	0.788 ^a
Head circumference	45.64±2.03	45.84±2.23	-0.874	0.383 ^a
Length-for-age	70.35±6.53	70.11±6.95	0.327	0.744 ^a
Weight-for-age	7.53±1.24	7.48±1.33	0.408	0.684 ^a
Weight-for-length	8.35±1.37	8.39±1.49	-0.196	0.845 ^a
Development quotient	94.97±9.76	95.05±11.51	-0.071	0.944 ^a
Fine motor	94.76±12.22	95.27±14.15	-0.361	0.719 ^a
Cognition	96.68±12.95	96.21±14.03	0.323	0.747 ^a
Language	92.65±15.07	91.96±15.80	0.414	0.679 ^a
Social interaction	94.41±13.99	92.85±15.61	0.979	0.328 ^a
Gross motor	95.99±13.26	97.87±14.36	-1.260	0.208 ^a
Low body weight			-	1.000 ^d
No	277	116		
Yes	3	1		
Emaciation			0.140	0.502 ^c
No	269	114		
Yes	11	3		
Growth retardation			-	0.186 ^d
No	274	117		
Yes	6	0		
Developmental retardation			6.172	0.013 ^b
No	272	107		
Yes	8	10		

Note: a was an independent sample t test, b was χ^2 test, c was calibrated χ^2 test, and d was Fisher's precise test.

Table 4: Univariate Logistic regression analysis of 397 infants with developmental delay aged 6-36 months

Factors	Normal development group		Developmental retardation group		Wald χ^2 value	P value	Odds ratio (95% confidence interval)
	Cases	%	Cases	%			
Birth weight (Kg)	3.37±0.48		3.28±0.45		0.659	0.417	0.655 (0.236~1.819)
Birth length (cm)	50.34±1.44		50.17±0.38		0.243	0.622	0.901 (0.595~1.364)
History of preventing miscarriages					0.847	0.357	
No	289	96.01	12	3.99			1
Yes	90	93.75	6	6.25			1.606 (0.585~4.400)
History of conception					0.112	0.738	
Spontaneous conception	364	95.54	17	4.46			1
Artificial impregnation	15	93.75	1	6.25			1.427 (0.178~11.447)
Paternal education level					1.254	0.263	
Senior high school and below	178	96.74	6	3.26			1
University or above	201	94.37	12	5.63			1.771 (0.651~4.817)
Maternal education level					2.671	0.102	

Senior high school and below	182	97.33	5	2.67			1
University or above	197	93.81	13	6.19			2.402 (0.840~6.870)
Number of babies					0.231	0.631	
1	253	95.11	13	4.89			1
≥2	126	96.18	5	3.82			0.772 (0.269~2.214)
Family style					0.601	0.438	
Basic family	196	94.69	11	5.31			1
Big family	183	96.32	7	3.68			0.682 (0.259~1.796)
Feeding type					5.615	0.018	
Parental feeding	272	97.14	8	2.86			1
Intergenerational feeding	107	91.45	10	8.55			3.178 (1.221~8.268)

The results showed that after controlling for the influence of covariates, intergenerational feeding could not be an independent influencing factor of malnutrition (OR=0.295, 95% CI: 0.003~27.730, $P=0.598$), wasting (OR=0.489, 95% CI: 0.122~1.966, $P=0.314$), and growth retardation (OR=0.000, $P=0.996$)

Discussion

The results of this study indicate manifested that the rate of intergenerational feeding of infants between 6 months and 36 months of age in Dongying City was 29.6%. This is similar to the intergenerational feeding rate in studies elsewhere¹³. Although it was lower than the 52.3% intergenerational feeding rate in previous research in Japan, it also indicated that intergenerational feeding did have a crucial role in family infant feeding. It is believed that with the increasing mortality rate, increasing divorce rate and relationship breakdown rates, and the relaxation of the two-child policy, the role of grandparents in family life will increase. Additionally, this study showed that the grandmother or maternal grandmother was the main caregiver in intergenerational feeding, which is in accordance with previous reports¹⁴. Therefore, the role of grandmother or maternal grandmother in the current and future infant rearing, requires further attention. The educational level of mothers in the intergenerational feeding group was higher than that of the parent feeding group, which is in accordance with the finding that the educational level of mothers is an important factor for grandparents to participate in child feeding¹⁵.

Previous studies on the impact of intergenerational feeding on children's weight have

been inconsistent. Some studies have pointed out that intergenerational feeding is more likely to cause overweight or obesity in children, and children that such children may have higher BMI values. Other studies have reported that intergenerational feeding is beneficial to children's weight. The results of this study focused on the nutritional status of infants and young children who are fed by grandparents versus those who were fed by parents. Previous studies have noted that grandparents focus more on starch intake during generational feeding while parents focus on protein intake. This difference may lead to malnutrition of left-behind children aged 6-12 years old who are fed by older generations. However, our results, including factor analysis did not reveal any statistical difference in the malnutrition status between the two groups. This result may be attributable to differences in the ages of the children or to the fact that children in our sample were not left-behind children.

This study showed that the developmental lag rate of infants under intergenerational feeding was about 8.5%, which presented higher than that of parental feeding, which was in line with previous findings¹⁶. In the five functional areas of gross motor, fine motor, language, adaptive ability along with social behavior, our study did not demonstrate any difference between the intergenerational feeding group and the parent feeding group. This is different from previous research results¹⁷. The reasons for this inconsistency may be due to either differences in the study populations or differences in the ages of the infants. Additionally, the different assessment tools were adopted by the Pediatric Hospital of Fudan University in Shanghai (DST) (Screening Scale for Intelligent Development of

Children aged 0 to 6 years)¹⁸, which mainly included the motor area, social adjustment area, and intelligence area. The results showed that in the social adjustment and intelligence areas, the intergenerational feeding group lagged behind the parent feeding group. Although the results are inconsistent, they all ultimately show the effect of intergenerational feeding on infant development. This is reflected in a recent study, indicating that intergenerational feeding not only impacts on the early development of infants and toddlers, but also is more likely to cause the generation of hyperactivity and other behaviors after the age of 4¹⁹, and intergenerational feeding is also significantly linked to the development of children aged 6-11¹⁵. Therefore, intergenerational feeding has an important impact on the development of children, which will exist from infancy, and based on the theory of the importance of early life education, it is speculated that this impact may influence the later development of children. As for the internal mechanism of the adverse impact of intergenerational feeding on the development of infants, it cannot be explained at present because there are relatively few relevant studies.

The results of this study indicate that the main feeders in the intergenerational feeding group were grandmothers or maternal grandmothers, while the main feeders in the parental feeding group were mothers. By contrast, the participation rate of fathers or grandfathers was relatively low. Therefore, in our regression study, the influence of the father's education level on infant development was not statistically significant, while the mother's education level was statistically significant, and the effect was negative. This implies that the probability of developmental delay in infants whose mothers had higher education is 3.23 times that of infants whose mothers had lower education. Previous reports have made clear that the educational level of mothers contributes to the development of children. We consider that the reason for this result may be that highly educated mothers will be more likely to enter labour force earlier, resulting in the entry of infants into generational feeding²⁰. The probability of developmental retardation of infants in the

intergenerational feeding group is 4.05 times that of infants in the parental feeding group, which increases the probability of developmental retardation of infants in the intergenerational feeding environment. Therefore, the impact of the mother's education level on the growth and development of infants may be confused by the impact of intergenerational feeding. The development of infants aged 6 to 36 months in the intergenerational feeding group was poor, which suggested that we needed to strengthen the early intervention and support of the intergenerational feeding group in clinical work, so as to reduce the adverse effects of intergenerational feeding on infant development.

In this study, although it was found that intergenerational feeding was not conducive to the neurological development of infants, it had no significant effect on malnutrition of infants aged 6-36 months. However, the study also has some limitations. On the one side, the sample size of this study is relatively small, so future studies with large sample data of multi-centers are needed for further verification. On the other side, the differences in nutrition-related feeding behaviors between the intergenerational feeding group and the parent feeding group have not been deeply explored, so the internal mechanism of nutrition needs to be explored in the future. In addition, the intergenerational feeding group of our study included large families and basic families. Since parents may have some intervention or influence of feeding measures in the intergenerational feeding of large families, which may lead to certain confounding effects, the future research design needs to increase the content of specific parents' role in intergenerational feeding. This is helpful to accurately judge the impact of intergenerational feeding group on infant development. At the same time, previous studies have suggested that factors of intergenerational feeders (grandparents or maternal grandparents) themselves can also affect the results of intergenerational feeding. Therefore, factors of intergenerational feeders themselves, such as age and education level, should be added to the impact of subsequent intergenerational feeding on the growth and development of infants.

Study strengths and limitations

Strengths of the study were that it was a cross sectional study, and included Univariate Logistic analysis and Multivariate Logistic regression analysis to study the effect of intergenerational feeding on the growth and development of infants aged from 6-36 months. Limitations were limited study cohort. Our study indicated that maternal education level along with skip-generation feeding were the main affecting factors of developmental delay in infants aged 6~36 months, which may provide feeding reference for infants aged 6 to 36 months.

Conclusion

The rate of intergenerational feeding of infants aged 6 to 36 months is about 30%, and maternal education level along with skip-generation feeding were the main affecting factors of developmental delay in infants aged 6~36 months.

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Contribution of authors

Chen LM and Tian JZ: conceived and designed the study as well as collected and analysed the data. Xu XY, Liu HH, and Zhang YB: prepared the manuscript. All authors mentioned in the article approved the manuscript.

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