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Insufficient Sleep During Infancy Is Correlated with Excessive Weight Gain in Childhood: A Longitudinal Twin Cohort Study

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Abstract

Study Objectives: To examine total sleep duration in infancy and the associations of insufficient sleep duration with later weight gain and the risk of overweight in a longitudinal twin cohort study.

Methods: The data for this study are from the Longitudinal Twin Study (LoTiS), a twin-pregnancy birth cohort study that was carried out in China (n=186 pairs). The sleep data were collected at 6 months using the brief infant sleep questionnaire (BISQ) that was completed by parents with the assistance of a research assistant. Anthropometric data were obtained from the children's health clinic records at 6, 12, 18 and 24 months.

Results: There were no significant differences between infants with insufficient sleep and those with sufficient sleep in terms of height, weight, body mass index, incidence of overweight and body fat mass, while infants with insufficient sleep duration were predisposed to gain excessive weight from 6 to 12 and 6 to 18 months of age (all p <0.05). After adjusting for confounding variables, insufficient sleep duration was found to be correlated with excessive weight gain from 6 to 18 months of age (OR 3.47, 95% CI 1.23-9.78). The relationship was more pronounced in monozygotic (MZ) twins than in dizygotic (DZ) twins.

Conclusions: Insufficient total sleep duration at the age of 6 months is correlated with the risk of excessive weight gain at 18 months of age in twins, particularly in monozygotic twins.

Keywords: sleep duration, child overweight, excessive weight gain, infants, twin study

Trial registration: ChiCTR-OOC-16008203
(http://www.chictr.org.cn/edit.aspx?pid=13839&htm=4).

BRIEF SUMMARY

Current Knowledge/Study Rationale: This study explored the associations of insufficient total sleep duration with later weight gain and the risk of overweight by assessing subjects from a longitudinal twin-pregnancy birth cohort.

Study Impact: Insufficient total sleep duration in early infancy predisposes individuals to excessive weight gain at 18 and 24 months of age, which is considered a risk factor for childhood obesity. Taking this finding into consideration, strategies should be adopted to improve infant sleep duration.

INTRODUCTION

Obesity has been recognized as the product of an imbalance between energy intake and expenditure in adults, but multiple factors have been identified that contribute to the obesity epidemic, and some of these factors, such as high birthweight, parental obesity and catch-up growth, are present before 2 years of age.[1, 2] In addition, evidence from recent decades has suggested that sleep, including sleep duration and sleep quality, may be associated with the development of obesity.[3, 4]

Sleep plays a particularly relevant role during early development when physical, brain and cognitive development is occurring at a rapid rate.[5, 6] Sufficient sleep is not only necessary for the development of the nervous and physiological systems during infancy but also contributes to the regulation of metabolic and hormonal processes in childhood.[7] Fatigue due to sleep restriction may affect body weight by reducing physical activity and increasing energy intake. In addition, lack of sleep may lead to fluctuations in hormone levels, such as a reduction in leptin and an increase in ghrelin, resulting in increased appetite and weight gain.[i]

With respect to sleep duration and obesity, most studies have suggested that sleep duration is inversely associated with the risk of obesity.[8-13] However, these studies were cross-sectional, and most of the studies were conducted in toddlerhood or childhood. Investigations of sleep duration in infancy and its impact on later growth are limited. According to the concept of "the first 1,000 days", comprising the period from conception to age 2 years, infancy is a window for sensing and responding to environmental changes. It is worth exploring the impact of sleep duration in early infancy on later weight development before 2 years of age, which may provide evidence to guide recommendations regarding sleep and improve weight management.

Owing to the distinct genetic and environmental factors affecting individual infants, studies with singleton infants as participants have to address many confounding variables. However, twin offspring provide an invaluable model for investigating the variations in genetics, as birth mother, age and the intrauterine environment are naturally standardized.[14, 15] Twin offspring also share common characteristics related to their growth environment and upbringing, such as their eating behaviors, outdoor activities and screen time. Previous studies have described the sleep behaviors of twins in infancy or adolescence. Several papers have addressed the interactive effect of genes

and the environment on sleep in twins aged 15 and 18 months.[16-18] Two studies explored the relationship between sleep and energy intake in twins aged 21 and 16 months.[19, 20] One paper described the effect of sleep on later emotional regulation in a twin cohort aged 14-18 years.[21] Therefore, the twin model is excellent for investigating the relationship between sleep duration and infant growth, and there are thus far very few studies in this field.

In the present study, we aimed to explore whether insufficient sleep duration in early infancy has an adverse impact on later weight gain and the risk of overweight based on a longitudinal twin birth cohort. The findings may provide a reference that can be used to predict those at risk and develop interventions to promote a healthy sleep pattern.

METHODS

Participants

The Longitudinal Twin Study (LoTiS) (Trial registration Number: ChiCTR-OOC-16008203) is an ongoing prospective longitudinal study established in Chongqing, China, that was launched in January 2016. Women with twin pregnancies achieved by natural conception were recruited at 11-16 weeks of gestation, and their twins were enrolled in pediatric follow-up after birth. The detailed cohort study protocol has been reported previously.[22] Twins in the LoTiS meeting the following criteria were excluded: 1) twin to twin transfusion syndrome; 2) twin anemia-polycythemia sequence syndrome; 3) twin reverse arterial perfusion syndrome; and 4) severe congenital malformations. In total, 186 pairs of twins were involved in the initial investigation conducted at 6 months of age, and the parents were asked to complete a sleep questionnaire for their children. Then, the infants' anthropometric indices were assessed at 12, 18, and 24 months of age. A total of 173 (93.0%) pairs completed the 12-month follow-up, and 165 (88.7%) and 153 (82.3%) pairs were followed-up at 18 months and 24 months of age, respectively.

In this study, 6 months and 12 months of age correspond to the corrected age rather than chronological age since twins are normally born at approximately 37 weeks of gestation. The corrected age at a time point was calculated as the chronological age minus the difference between term birth (40 weeks) and chronological gestational weeks at delivery.

Demographic Data Collection

The demographic information of infants (e.g., sex, birth weight, birth length) was obtained from medical records. Small for gestational age (SGA) was defined as a birth weight less than the 10th centile according to the ROCG Green-top Guideline No. 31, and SGA was diagnosed according to the birthweight centiles for twin-birth neonates by gestational age in China.[23] The zygosity of twins was identified by short tandem repeat polymerase chain reaction (STR-PCR). Parental education level, maternal age at delivery, prepregnancy body mass index (BMI) (calculated as the ratio of prepregnancy weight (kg) to the squared height (m^2)), mode of conception and gestational age at delivery were collected from the LoTiS database (https://www.medscinet.com/Lotis/app).

Assessment of Infant Sleep Duration

Data concerning the infants' sleep characteristics were collected with a questionnaire completed by the parents or other caregivers when the infants were 6 months old. The sleep investigation was based on the brief infant sleep questionnaire (BISQ),[24] which includes 11 questions about the sleep duration and sleep quality of infants. Parents or other caregivers were asked to consider their infants' sleep over the past week. The reliability of the questionnaire for assessing and screening sleep in infants and children has been validated.[25, 26] The total sleep duration was calculated as the sum of nocturnal (7 p.m.-7 a.m.) and daytime (7 a.m.-7 p.m.) sleep. Several studies conducted among different ethnicities have shown that a sufficient sleep duration for infants at 6 months of age is 12 hours per day; thus, we defined an insufficient sleep duration as less than 12 hours per day.[27-29]

Anthropometric Measurements

Infant growth was monitored by assessing weight and length/height at 6, 12, 18 and 24 months. Anthropometric data were obtained at the indicated time (± 3 days) by trained nurses. Weight was measured with the participants unclothed using a digital measuring bed (Beideneng, Shanghai, China) with a weight accuracy within 0.1 kg, and length was measured at the same time, with an accuracy within 0.1 cm. These measurements were obtained at 6 and 12 months of age. At 18 and 24 months of age, weight and height were measured while the participants were standing with a physical examination instrument (Beideneng, Shanghai, China), with the same accuracy as the digital measuring bed. All anthropometric measurements were performed in triplicate. Mean

values of the available measures were used for analysis. Age- and sex-specific weight, height and BMI values were calculated according to the World Health Organization Growth Standards (https://www.who.int/childgrowth/software/en/).

Main Outcome Variables and Confounding Variables

The primary outcome was the incidence of overweight at 6, 12, 18 and 24 months. Overweight at different time points was defined as a BMI-for-age z-score greater than the 85th percentile. The secondary outcome was excessive weight gain during a specific period. Because there was no clear standard for excessive weight, weight changes between 6 to 12, 6 to 18 and 6 to 24 months were dichotomized using the internal 90^{th} percentile as the cutoff point with the statistical method (percentile method) described in a previous study.[30] The cutoff point used for excessive weight gain between 6 and 12 months was 2.1 kg, that between 6 and 18 months was 3.4 kg, and that between 6 and 24 months was 5.0 kg.

The following variables were considered confounding factors: maternal age at delivery (years), maternal prepregnancy BMI (kg/m^2), parental educational level, parity, mode of conception (assisted reproductive technology, natural conception), gestational age at delivery (weeks), zygosity of the twin pair (monozygotic, dizygotic), identify of the primary caregiver, identify of the questionnaire respondent, SGA, sex, birthweight and feeding type at the age of 6 months ("yes" was defined as the infant having been fed with breast milk, while "no" meant the infant was exclusively fed with formula).

Ethics Approval

This study was performed in compliance with the principles of the Declaration of Helsinki. All procedures were approved by the Ethics Committee of Chongqing Medical University (No. 201530). Written informed consent was obtained from all participants.

Statistical Analysis

All data analyses were conducted using SPSS software version 25.0 (IBM, Armonk, NY, USA). Frequencies and percentages are used to describe the distributions of categorical variables, and continuous variables are expressed as the means ± standard deviations. T-tests were performed to

study the difference between the insufficient sleep duration group and the sufficient sleep duration group in terms of z-scores at each time point. A two-way ANOVA was conducted to study the difference in weight gain between the groups adjusted for sex. The chi-square test or Fisher's exact test was used for comparisons between categorical variables. A binary logistic regression model was used to examine the associations between insufficient sleep duration and the later risk of overweight or excessive weight gain, and a linear regression model was used to examine the correlation between sleep duration and later weight gain. Finally, we used generalized estimation equation (GEE) models to conduct multivariable regression with adjustment for the correlation between twins in a set. The potential confounders included in multivariable analyses were maternal prepregnancy BMI, parental education level, mode of conception, parity, maternal age at delivery, gestational age, birth weight, SGA, zygosity, sex, type of feeding at the age of 6 months, identify of the primary caregiver and identify of the questionnaire respondent. $P < 0.05$ was considered statistically significant.

RESULTS

Total sleep duration was dichotomized at 12 hours. There were 212 infants with insufficient sleep and 160 infants with sufficient sleep in this study. We divided all twin pairs into three groups (both sufficient sleep, both insufficient sleep and discordant sleep) according to the consistency of sleep sufficiency between twins. The comparison of baseline information, including demographic and clinical characteristics, between these groups is summarized in Table 1. Overall, the mean maternal age at delivery was 30.5 years, and 60.8% of the mothers conceived naturally. Infants had a mean birthweight of 2.5 kilograms, approximately half (50.5%) were preterm neonates, and the rate of SGA at birth was 12.1%. Compared to the twins with sufficient sleep, the twins with insufficient sleep had lower levels of parental education (31.7% vs. 16.0%, $p<0.05$), a greater proportion of natural conception (68.3% vs. 52.0%, $p<0.05$), a greater than 50% incidence of MZ (53.5% vs. 33.3%, $p<0.05$), a smaller proportion of term birth (57.4% vs. 37.3%, $p<0.001$) and a smaller proportion of breastfeeding (25.7% vs. 43.3%, $p<0.05$).

Table 2 presents the results of the comparisons among infants with insufficient sleep duration and those with sufficient sleep duration. At 6 months of age, a cross-sectional comparison was conducted for sleep duration, anthropometric data and the incidence of overweight, and no

significant difference was found between these two groups at this time point. We further examined the long-term impact of sleep duration on growth development at 12, 18 and 24 months of age and found no significant difference in the incidence of overweight between infants with insufficient sleep and those with sufficient sleep duration at these time points. Moreover, the comparisons were further examined among monozygotic (MZ) and dizygotic (DZ) twins. As shown in Supplementary Table 1, among MZ twins, although weight or height development differed between infants with sufficient sleep or those with insufficient sleep, the incidence of overweight was not significantly different. Similarly, the incidence of overweight was not significantly different among DZ twins in the different groups (Supplementary Table 2).

In addition, we carried out an investigation of the associations of total sleep duration with weight gain and the risk of excessive weight gain. The results presented in Table 3 show that infants with insufficient sleep duration exhibited more weight gain from 6 to 24 months and a higher risk of excessive weight gain from 6 to 12 months and from 6 to 18 months than those with sufficient sleep duration. However, the results of subgroup analyses showed that insufficient sleep duration was correlated with greater weight gain and a higher risk of excessive weight gain at three time points among MZ twins (Supplementary Table 3) but not DZ twins (Supplementary Table 4).

Taking into consideration the fact that maternal factors and neonatal factors could contribute to infant growth development, the longitudinal association of insufficient sleep duration and subsequent weight development was examined by the GEE model. The results of logistic regression showed that insufficient sleep duration was negatively correlated with the risk of excessive weight gain from 6 to 18 months (Table 4, model 1). After adjusting for covariates, the correlation was still significant (Table 4, models 2 and 3). The results of linear regression showed that there were no correlations between sleep duration and weight gain (Table 5). Nevertheless, sleep duration was negatively associated with weight gain from 6 to 18 and from 6 to 24 months among MZ twins with or without adjustments for confounding factors (Supplementary Table 5).

DISCUSSION

Evidence of a negative correlation between sleep duration and obesity has been accumulating in adults, and recent studies have increasingly focused on children.[7, 31, 32] In particular, research on

the relationship between sleep and obesity during early childhood remains controversial.[33] However, very few studies have investigated the relationship between sleep duration within the first 6 months of life and later obesity.[30, 34] Tuohino T et al demonstrated that insufficient sleep duration at the age of 3 months, but not later ages (8, 18, 24 months), is associated with a greater weight-for-length/height z-score at the age of 24 months.[30] The generation R study conducted in the Netherlands suggested that shorter sleep duration at 2 months predicted higher fat mass at 6 years.[35] Taveras EM et al reported that an average daily sleep duration of less than 12 hours from 6 months to 24 months of age was correlated with a greater BMI z-score and appeared to be a risk factor for overweight and adiposity in preschool-aged children.[34] In contrast to our study, all the aforementioned investigations were conducted in singleton offspring.

In general, twins share the same environmental exposure, including nutrition and living environment. Therefore, twins provide an ideal model to evaluate individual exposure factors, such as variations in sleep behavior, on developmental outcomes. The results showed that greater weight gain from 6 to 24 months and a higher incidence of excessive weight gain from 6 to 12 and from 6 to 18 months of age were found in infants with insufficient sleep duration when compared to those with sufficient sleep duration. Only excessive weight gain from 6 to 18 months was significant after adjusting for confounders in the GEE models, and there was no significant association between sleep duration and the incidence of overweight in infancy despite the trend. A large study conducted among Australian children showed no associations between sleep duration at 0-1 years of age and BMI at 2-3 years of age.[36] In a Danish child population, insufficient sleep durations at the ages of 9 and 18 months were not associated with increased adiposity at the age of 3 years.[33] However, a longer period of observation is warranted to ascertain whether insufficient sleep duration in early infancy affects the incidence of overweight in later life.

In the present study, although no significant associations were found between an insufficient sleep duration at 6 months and overweight at 2 years old, a correlation was observed between insufficient sleep duration and excessive weight gain from 6 to 18 months, implying a risk of overgrowth later in life. This finding is consistent with a study reporting that insufficient sleep duration is associated with a heavier weight profile in older children[37] and a systematic review that showed that insufficient sleep duration consistently predicts subsequent weight gain.[38] Among the mechanisms

underlying the association between insufficient sleep and weight gain,[39] the nighttime consumption of energy-rich products, such as milk, may be important.[19, 20, 40, 41] This finding was observed before an association with weight emerged and suggests that a higher energy intake may be a major mechanism by which sleep influences weight gain, while the relationship between energy expenditure and sleep duration is complex in early childhood.[42, 43] Moreover, we further carried out similar analyses in MZ and DZ twins, and the association between sleep deprivation and excess weight gain was more pronounced in MZ twins than in DZ twins. The results suggest that the relationship between sleep duration and weight gain may be more strongly affected by genetic factors than the intrauterine shared environment. In general, there exists a certain correlation between sleep deprivation and weight gain. In addition, sleep is thought to be essential for growth during child development. The pulsatile release of human growth hormone occurs during slow-wave sleep.[44] The existence of this contradictory relationship during early development may contribute to the underestimation and unpredictability of the incidence of overweight. It is necessary to investigate more detailed sleep profiles, with long-term observations of growth indicators.

The strength of our study was the specific study population. Since women who are pregnant with twins are prone to premature delivery and their neonates are prone to low birthweight, more attention should be paid to the growth development of twin offspring. Because sleep duration is a heritable trait,[45] individual differences in genetic make-up influence sleep-wake regulation, and obesity is a comprehensive result of factors related to heredity and the environment, twins provide a natural model to investigate the complex interaction of genetics with the environment. Another strength of our study was that weight, height and BMI were converted to z-scores based on the WHO growth standards, and those standards are commonly referenced in China.

However, limitations also exist, such as the use of parent-reported questionnaires to assess sleep duration, which may have led to the underestimation or overestimation of sleep duration. A meta-analysis reported that the recommended sleep duration for infants is 12.8 hours, and infants in Asian countries had significantly shorter sleep durations.[46] This finding was in agreement with our data, in which the mean sleep duration was 11.7 hours for infants aged 6 months. Further assessment of sleep duration by actigraph recordings may provide more accurate measurements.

Moreover, sleep duration assessments at other time points in early life are critical to fully elucidate the programming role of sleep behavior in children's development; however, such assessments were unfortunately not included in the initial protocol of the LoTiS. Since we observed the correlation between insufficient sleep at 6 months of age and excessive weight gain at 18 and 24 months, the findings indicate that the effect of sleep duration on weight development may continue for a longer period. Therefore, the LoTiS will continue to monitor the growth and development of twins, and more assessments of sleep will be performed to further elucidate the impact of sleeping behavior on growth in twins.

The aforementioned controversial conclusions about the correlation between sleep duration in early infancy and later overweight might be explained by the differences in study populations and survey time points. In our study, we surveyed the sleep of infants at 6 months of age because the sleep rhythm is commonly initially established at this time, which is also the developmental stage in which activity increases and complementary foods are introduced, making it a critical stage of growth and development. Therefore, it was meaningful to explore the impact of sleep duration at 6 months on later growth development.

CONCLUSION

The current study suggests that insufficient sleep duration at 6 months of age increases the risk of excessive weight gain at 18 months. The correlation between sleep in early infancy and growth should receive more attention, as interventions regarding sleep during infancy could affect metabolic health risks later in life. In general, these findings suggest that insufficient sleep duration early in life may contribute to excessive weight gain, suggesting the important effect of sleep duration on child growth.

ABBREVIATIONS

ART, assisted reproductive technology

BAZ, body mass index-for-age z-score

BISQ, brief infant sleep questionnaire

BMI, body mass index

GEE, generalized estimation equation

HAZ, height-for-age z-score
LoTiS, longitudinal twin cohort study
OR, odds ratio
SGA, small for gestational age
STR-PCR, short tandem repeat polymerase chain reaction
WAZ, weight-for-age z-score
WHO, world health organization
MZ, monozygotic
DZ, dizygotic

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DISCLOSURE STATEMENT

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