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# Characterization of Infant BMI peak in urban China

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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2016-015122 |
| Article Type: | Research |
| Date Submitted by the Author: | 28-Dec-2016 |
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| <b>Primary Subject Heading</b>: | Epidemiology |
| Secondary Subject Heading: | Paediatrics |
| Keywords: | Overweight, Obesity, Body mass index, Longitudinal Study, Infant |
| | |

# Characterization of Infant BMI peak in urban China

Jie Sun[1,2], Bright I Nwaru[3,4], Jing Hua[5], Xiaohong Li[6,7], Zhuochun Wu[1,7]


## Abstract

***Objectives:*** Infant body mass index (BMI) peak, which has been studied in American and European, proves to be a useful indicator for predicting risk of childhood obesity. We aimed to first characterize infant BMI trajectories in a Chinese longitudinal cohort.

***Methods:*** We used serial measurements (n=6-12) of weight and height from healthy term infants (n＝2073) in a birth cohort established in urban Shanghai to estimate BMI growth curves from birth to 13.5 months by a polynomial regression model. The relationship between infant BMI peak and childhood BMI was examined using binary logistic analysis.

***Results:*** Mean BMI peak was 18.33 kg/m$^2$ and occurred at 7.61 months. Boys (n＝1022) had a higher average BMI peak (18.60 vs 18.07 kg/m$^2$, P<0.001) and earlier average timing (7.54 vs 7.67 months, P<0.05) than girls (n＝1051). Higher (OR 3.11; 95% CI 2.64-3.66) and later timing (OR 1.35; 95% CI 1.22-1.50) of infant BMI peak were associated with increased risk of early childhood overweight. Similarly, higher magnitude (OR 2.76; 95% CI 2.05-3.73) and later timing (OR 1.34; 95% CI 1.08-1.67) of infant BMI peak were associated with increased risk of childhood obesity.

***Conclusions:*** Infant BMI peak is valuable for predicting early childhood overweight and obesity in urban China. As this is first Chinese-based study on the topic, further studies are required to evaluate the utilization in other urban settings of China.


**Key words:** Body mass Index, Obesity, Overweight, Longitudinal Study, Infants

**Word Count**：2739 words

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**Strengths and limitations of this study**

This is the first community-based cohort study in China to characterize infant BMI peak.

Association of BMI peak with risk of early childhood overweight and obesity will be evaluated.

It's a longitudinal cohort with careful repeated measurements of child growth parameters.

Only about 69.9% of all children in this age range had health records.

The data of parent's BMI and pregnancy weight gain were not available.

## Introduction

The increasing prevalence of childhood overweight and obesity has become a serious public health crisis worldwide. [1-4] The worldwide prevalence of childhood overweight and obesity increased from 4.2% in 1990 to 6.7% in 2010. [5] In urban areas of China, the prevalence of overweight and obesity among children aged 0-5 years increased from 5.3% in 2005 to 8.5% in 2010. [6] Rapid weight gain in early infancy is related to later obesity and cardiovascular risk factors such as hypertension and impaired glucose tolerance in adulthood.[7-11] Although obesity results from the combined effects of genes, environment and lifestyle, rapid genetic changes could not have occurred to result in the rapid increase in prevalence being observed; consequently, environmental and behavioral factors are believed to be key drivers of the burden of obesity.[12] Therapeutic interventions have low cost-effectiveness and poor long-term effects, so infancy may be the most important period to initiate primary preventive strategies for overweight and obesity. [13-15]

Body mass index (BMI), a useful estimate of adiposity for children aged more than two years, correlates with future health outcomes. [2,7] Based on international literature, few studies have evaluated the associations between infant BMI trajectories and childhood overweight and obesity. [12,16-18] Weight-for-length percentile curves are often used but not with age-based changes that reflect different stages of infancy.[16] BMI increases from birth and reaches a maximum called the 'BMI peak' around age 7-9 months, then, it decreases and reaches a nadir around age 4-6 years before increasing once more. [16-18] From Silverwood et al onwards, both age and BMI at BMI peak were positively associated with later BMI z-scores.[17] So far, several studies have used statistical models of growth trajectories to estimate the magnitude and timing of infant BMI peak. [16-24]

Ancestry-specific differences of Infant BMI peak have been demonstrated between African-American and European populations.[16] However, until date there has been no previous study performed in China to demonstrate the utility of infant BMI peak for predicting the risk of childhood overweight and obesity. Taking advantage of a population-based longitudinal data set that has serial measurements for height and weight from birth into childhood in Shanghai, we aimed to estimate the magnitude, timing of infant BMI peak, and to study the association between infant BMI peak and overweight and obesity by age 2 years.

## Methods

### Study Participants

We obtained data from the Shanghai Jing'an District birth and health records, which is a population-based longitudinal cohort. There are seventeen urban districts and one suburban district in Shanghai, with a population of 19 million in 2009. Jing'an District is located at the city center with a population of 248 thousand in 2009. "Providing free of charge health examination to children aged 0-3 years" was a project funded by Shanghai government for Jing'an children born from September 2009. The community health centers in the Jing'an District provide routine basic medical services to the local community, including well-child routine checks for infants and young children. A District Childcare Database for all local health centers in this project was established and managed by the Jing'an maternal and child health care center. With the information network, data on children's gender, gestational age, birth weight, feeding and sleeping behaviors, amongst others were recorded by the nurses in the health centers when they did the child health examination. All children were followed from one month to two or three years old until they went to kindergarten.

For this study, we used data from the Childcare Database for all children who were born from September 1st 2009 through September 1st 2013 and received care at the health centers of Jing'an district. The children were followed up from birth, with data collected at 1, 2, 4, 6, 9, 12,18 and 24 months of age from all five communities in Jing' an District, representing 69.9% (7456/10674) of all children in this age range in Jing'an District. There were roughly 30% of children moving from Jing'an district to other districts of Shanghai during the study period, which resulted in the missing of the subjects. We gained approval (IRB#2015–TYSQ–03-11) for the current study from the Medical Research Ethics Committee, School of Public Health, Fudan University.

### Inclusion and exclusion criteria

Inclusion criteria for infants included in the study were healthy singleton infants, born between 37 and 42 weeks gestational age without physical problems. Participants were also eligible if they had at least six measurements of height and weight in the first 13.5 months of life. This number and range of measurements were referred to BMI modeling set by the CHOP study in Philadelphia, USA.[16,20] As BMI peak is around age 7-9 months, we included children who had at least one visit in the following age ranged 213-274 days. To test the relationship between infant BMI peak and childhood overweight and obesity, measurements for children at age two years were included when such data were available. There were 21.2% (2268/7456) infants eligible for analysis. Of these, we observed 85.9% (1949/2268) children from birth to age two years till September 1st 2015 (Table 1). Preterm infants (n =195), term infants with congenital defect (n=30) were excluded.

### Anthropometric measures

Weight and length of children were measured using standardized procedures at the community health centers. Weight was measured by an electronic pediatric scale to the nearest 0.005 kg, and length to the nearest 0.1 cm. BMI z-score (BAZ) of children at age two years were calculated according to the 2006 World Health Organization (WHO) Child Growth

Standards using the WHO Anthro 2009 software.[25] The WHO Child Growth Standards was based on a multi-country study involving breastfed children from six geographically distinct sites.[5] Overweight was defined as BAZ > +1 (BMI >85th percentile) while obesity was defined as BAZ>+2 (BMI >95th percentile). Normal weight was defined as −1≤ BAZ ≤ +1.[1,13] Based on reports from previous studies,[11,12,16,18] we extracted factors associated with childhood overweight from the electronic medical records. These factors were birth weight, sex, delivery mode mother's ages, duration of breastfeeding and sleeping data.(Table 2) Because this cohort was set up after birth, some information about pregnancy and parents information was not complete. We classified birth weight as the following categories: 1.5 to less than 2.5 kg, 2.5 to less than 4 kg, and greater than 4 kg.

**BMI trajectory modeling**

BMI peak was identified from subject-specific BMI growth curves established by serial BMI measurements. A polynomial regression model with quadratic terms was fit to the BMI measurements over time. Regression modeling was used for each child to fit the following equation:[16]

$$BMI = \boldsymbol{\beta_0}+[\boldsymbol{\beta_1}* \text{(age in days)}] + [\boldsymbol{\beta_2}*\text{(age in days)}^2]$$

The first inflection point occurred at less than 408 days and identified as BMI peak was derived from the equation. The magnitude and timing of BMI peak and velocity to peak were calculated for each subject from the model. The velocity to the peak was calculated using the following equation, with BMI at 14 days of age as the baseline measurement:[18]

$$(BMI_{Peak}-BMI_{14days}) / (age_{BMIPeak} -14 \text{ days}).$$

The subjects who had a BMI peak within 14–408 days of life were defined as estimable ("fit") BMI trajectories, while those who were not identifiable by the model were called inestimable ("not fit") BMI trajectories.[16]

**Statistical analysis**

SPSS 20.0 statistical software was used for all analyses and metalab2014b for the BMI trajectory modeling. Data were presented as mean with 95% confidence interval. Categorical data were summarized by calculating percentages. The chi-square test and two-sampled t tests were used to examine the differences between participants whose BMI trajectories were estimable or not inestimable for the quadratic regression model and those who did or did not have measurements at age two years. To evaluate the associations between covariates and infant BMI peak characteristics and childhood BMI Z-scores, bivariate analyses were used by one-way ANOVA with post hoc Bonferroni adjustments. Logistic regression was used to assess the associations between infant BMI peak trajectories and childhood BMI Z-scores, adjusting for other background characteristics. Statistical analyses were performed using only the subjects with estimable BMI peak. [16-19] All statistical tests were two-tailed and P values <0.05 were considered statistically significant.

## Results

### Description of the study population

The demographic and independent variables of the study population are presented in Table 3. There were 2268 infants eligible for analysis, 49.6% male and 50.4% female. Most had a normal birth weight of 2.5 to less than 4 kg (n=2073, 91.4%). Eighty-five percent (n =1949) of infants had follow-up data at least through the age of 2 years (Table 3). Evaluated by the WHO Child Growth Standards, 17.0% (n =332) infants were overweight (BAZ > +1) and 2.3% (n =44) obese (BAZ > +2) at age 2 years.

### Results of infant BMI trajectory modeling

Individual BMI trajectories were estimable using the polynomial regression model for 91.4% of the sample, with reasonable fit (mean $R^2$ =0.70±0.23). Mean BMI peak was 18.33 (95% CI 18.26-18.39) kg/$m^2$ and occurred at 7.61 (95% CI 7.55-7.67) months. Those subjects with inestimable BMI peak mostly showed either a BMI peak after 408 days of life or a decrease in BMI after birth. The prevalence of macrosomia (birth weight>4kg) infants with inestimable infancy BMI peak were slightly higher than that with estimable ones (6.7% vs 11.3%, *P* =0.024). Macrosomia born heavier reached their BMI peak much earlier, since some of them attained BMI peak measurements just after birth. There was no significant difference in other factors between subjects with estimable and inestimable peak BMI trajectories (P>0.05).(Table 3)

### *Participants' characteristics in relation to infant BMI trajectories*

Infant BMI trajectories were related to both sex and birth weight (Table 4). BMI peak was greater, and timing of peak BMI was earlier, in boys than in girls and in children of higher birth weight than those of lower birth weight. There was no statistical significant difference in velocity to BMI peak with regards to infant characteristics.

### *General characteristics of children at age two years*

We tested for differences between infants who had BMI data with estimable BMI peak at age two years (n=1790) vs those who did not (n=159). There was no difference between the two groups in sex, birth weight, mother's age, duration of breastfeeding, duration of sleep (*P* >0.05).

### *Association between infant BMI peak and childhood overweight and obesity*

Table 5 shows the results of the association between BMI peak and risk of overweight and obesity at two years of age. When only the infant BMI peak was included in the model, higher magnitude and later timing of infant BMI peak increased the risk of overweight at two years. Furthermore, after adjustment for other infant background factors, higher magnitude (OR 3.11; 95% CI 2.64–3.66) and later timing (OR 1.35; 95% CI 1.22-1.50) of infant BMI peak each increased the risk of overweight at two years. The results were also similar with regards to childhood obesity (Table 5).

## Discussion

Using a longitudinal data from a population-based cohort, we have demonstrated in the current analysis that infant BMI peak is useful for predicting childhood overweight and obesity in urban China. Boys had a higher average BMI peak and earlier average timing than girls. Principally, our results show that higher magnitude and later timing of infant BMI peak were each associated with increased risk of early childhood overweight and obesity.

This is the first community-based cohort study in China to characterize infant BMI peak and evaluate its association with risk of early childhood overweight and obesity. Our findings are therefore generalizable to children of similar age in Shanghai city, and to some degree by extension to other urban areas in China. The used data were routinely collected by the health centers where children are offered routine healthcare, such as immunization and physical examination; thus constitute a valid and reliable data set for addressing the study questions. The longitudinal nature of the cohort and the repeated measurements of height and weight parameters provided us with the opportunity to carefully model the BMI trajectories of infants. One limitation of our investigation was that only about 69.9% (7456/10674) of all children in this age range had health records and 85.9% of eligible children had complete follow-up data up to the age of two years, meaning that those with incomplete data were excluded from analysis and risk of selection bias may not be totally ruled out. Another weakness of the study is that the data of parent's BMI, pregnancy weight gain, gestational diabetes mellitus and income were not available, the reason being that the cohort was set up after birth and not prenatally.

So far, few studies have been conducted on the utility of infant BMI peak for predicting childhood overweight and obesity. [16-18] The principal finding of our study that higher magnitude and later timing of infant BMI peak were each associated with increased risk of early childhood overweight and obesity is similar to previous research from the CHOP study conducted in USA[16] and the Uppsala Family Study in Europe.[17] However, some findings of the current study are not consistent with previous research. A 2010 prospective cohort show that more rapid increases in weight for length in the first six months of life were associated with sharply increased risk of childhood obesity.[26] Most previous studies used weight or BMI at study-dependent fixed ages[26,27] while ours was based on longitudinal and repeated measures of height and weight. Our results also demonstrate that sex and birth weight differences were shown in magnitude and timing of the peak but not in pre-peak velocity.[16,18] In some recent studies, later BMI peak was found for both girls and boys (8-9 months of age).[17,18,20] Furthermore, an earlier and higher BMI peak was found to be positively associated with birth weight.[16,17] In our study, higher birth weight was not associated with a lower velocity, which was found by the CHOP study.[16]

There is no widely accepted method to model infant BMI peak, appropriate peak age range and the number and timing of serial measurements.[20] China is undergoing rapid social and economic developments with consequent improvement in nutritional status. Current estimates indicate that overweight and obesity are rising in China, including among children.[4] However, given the lack of studies evaluating the utility of BMI peak for predicting later childhood overweight and obesity in China, as has been demonstrated in other contexts and shown to be ancestry-specific,[16] it is therefore necessary to undertake such assessment, which will be useful in predicting early onset of obesity and serve as a springboard for planning appropriate interventions targeted at reducing the increasing trend of childhood overweight and obesity in urban China. It is unclear why infants in our study had earlier BMI peaks as (7-8 months) compared to infants from America and Europe (8-9 months),[17,18,20] but as been demonstrated, such differences may reflect possible ancestry-specific BMI peaks across populations; therefore cross-cultrual evaluations are required to ascertain the validity of this assertion. Understanding these differences may help design the protocol of public health interventions to control childhood obesity.[28,29,30]

The principal finding of the current study suggests that infant BMI peak is useful in predicting future risk of overweight and obesity in children in urban China; therefore infancy represents a critical window of opportunity for the prevention of the emerging overweight and obesity epidemic in children.

## Conclusion

Using a community-based longitudinal cohort study with repeated measurements of infant growth parameters, we have for the first time determined that infant BMI peak is valuable for predicting early childhood overweight and obesity in urban China. Further studies are required to evaluate the utilization in other urban settings of China.

## Acknowledgements

We are grateful to the staff in Jing'an maternal and child health care center for data extraction. We also acknowledge all children and their parent's for participating this project.

## Authors' contributions

Jie Sun, Bright I Nwaru, and Zhuochun Wu were responsible for the study design, analysis of the study and approval of the submitted and final version. Jing Hua and Xiaohong Li analyzed the data, interpreted the results and commented on the manuscript.

## Funding

This study was funded by National Natural Science Foundation of China [71573049]..

**Ethics Approval**

All procedures performed in this study were in accordance with the ethical standard. We gained approval (IRB#2015–TYSQ–03-11) for the current study from the Medical Research Ethics Committee, School of Public Health, Fudan University. Informed consent was obtained from all individual participants included in the study.

**Competing interests**

The authors declare that they have no conflict of interest.

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**Table 1 Description of children eligible in the study**

| Year | Eligible children<br>n | Children with data at age 2y<br>n (%) |
|---|---|---|
| 2009 | 190 | 169 (88.9) |
| 2010 | 413 | 369 (89.3) |
| 2011 | 606 | 545 (89.9) |
| 2012 | 660 | 571 (86.5) |
| 2013 | 399 | 295 (73.9) |
| Total number | 2268 | 1949 (85.9) |

**Table 2 Description of dependent and independent variables**

| Variable | Description |
|---|---|
| Dependent Variables | |
| Overweight | 1-if yes at age 2y 0-otherwise |
| Obesity | 1-if yes at age 2y 0-otherwise |
| Independent variables | |
| Sex | 1-male 0-female |
| Delivery Mode | 1-Cesarean Section 0-Vaginal Birth |
| Mother Age | 1-above 35y 0-otherwise |
| Duration of Breastfeeding | Continuous variable |
| Duration of Sleep | Continuous variable |
| Birth Weight | Continuous variable |
| Magnitude of BMI Peak | Continuous variable |
| Timing of BMI Peak | Continuous variable |
| Velocity to BMI Peak | Continuous variable |

**Table 3 Participants' characteristics by subjects with "estimable"* and "inestimable"# BMI peak**

| Characteristics | n | Estimable *, n (%) | Inestimable #, n (%) |
|---|---|---|---|
| Total number | 2268 | 2073 | 195 |
| Sex | | | |
| Male | 1126 | 1022 (49.3) | 104 (53.3) |
| Female | 1142 | 1051 (50.7) | 91 (46.7) |
| Birth weight | | | |
| 1.5 to <2.5kg | 35 | 30 (1.4) | 5 (2.6) |
| 2.5 to <4.0kg | 2073 | 1905 (91.9) | 168 (86.2) |
| **≥4kg** | **160** | **138 (6.7)[a]** | **22 (11.3)** |
| Delivery mode | | | |
| Vaginal birth | 1086 | 989 (47.7) | 97 (49.7) |
| Cesarean section | 1182 | 1084 (52.3) | 98 (50.3) |
| Mother Age | | | |
| >35y | 176 | 159 (7.7) | 17 (8.7) |
| ≤35y | 2092 | 1914 (92.3) | 178 (91.3) |
| Total number with data at age 2y | 1949 | 1790 (86.3) | 159 (81.5) |
| Total number overweight and obese at age 2y | 332 | 313 (17.5) | 19 (11.9) |
| Total number and obese at age | 44 | 43 (2.4) | 1 (0.6) |

a.P<0.05
* Estimable: fit and identifiable BMI peak within 14–408 days of life.
# Inestimable：Not fit and identifiable.
Chi-square tests were used to examine the differences between Estimable or Inestimable group.

**Table 4 Infant characteristics in relation to infant BMI peak trajectories**

| | | infant BMI peak, kg/m2, Mean (95% CI) | Age at Infant BMI peak, mo, Mean (95% CI) | Velocity to Peak, kg/m2, mo. Mean (95% CI) |
|---|---|---|---|---|
| Total | n=2073 | 18.33(18.26-18.39) | 7.61(7.55-7.67) | 0.43(0.42-0.44) |
| Sex | | | | |
| | **male (n=1022)** | **18.60(18.21-18.69)[a]** | **7.54(7.46-7.63)[b]** | 0.42(0.41-0.43) |
| | female (n=1051) | 18.07(17.98-18.16) | 7.67(7.59-7.76) | 0.43(0.42-0.44) |
| Birth Weight | | | | |
| | 1.5 to <2.5kg(n=30) | 17.63(17.13-18.13) | 8.13(7.56-8.70) | 0.44(0.35-0.53) |
| | 2.5 to <4.0kg(n=1905) | 18.27(18.21-18.34) | 7.63(7.57-7.70) | 0.43(0.42-0.44) |
| | **>=4kg(n=138)** | **19.25(18.97-19.52)[b]** | **7.11(6.88-7.34)[a]** | 0.39(0.35-0.42) |
| Delivery Mode | Vaginal birth (n=989) | 18.24(18.14-18.34) | 7.64(7.56-7.73) | 0.43(0.42-0.44) |
| | **Cesarean section (n=1084)** | **18.41(18.32-18.50)[a]** | 7.58(7.49-7.66) | 0.43(0.42-0.44) |
| Mother Age | | | | |
| | >35y(n=159) | 18.42(18.18-18.66) | 7.61(7.49-7.82) | 0.44(0.41-0.48) |
| | <=35y(n=1914) | 18.32(18.25-18.39) | 7.61(7.55-7.67) | 0.42(0.41-0.43) |

a.P<0.001 b.P<0.05

The analysis includes only infants who had BMI peak within 0-408 days and whose BMI trajectories were estimable by the quadratic model.

Bivariate comparison was performed using one-way ANOVA with post hoc Bonferroni multiple comparison test.

**Table 5 Association between infant BMI peak and overweight and obesity at age 2 years**

| | Overweight at 2y (n=1790 ) | | Obesity at 2y (n=1790 ) | |
|---|---|---|---|---|
| | Model containing infant BMI trajectory characteristics alone | Initial model plus all independent variables | Model containing infant BMI trajectory characteristics alone | Initial model plus all independent variables |
| | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Magnitude of BMI peak, kg/m2) | **2.94(2.54-3.40)[a]** | **3.11(2.64-3.66)[a]** | **2.76(2.11-3.60)[a]** | **2.76(2.05-3.73)[a]** |
| Timing of BMI peak, mo | **1.36(1.23-1.51)[b]** | **1.35(1.22-1.50)[a]** | **1.33(1.08-1.65)[b]** | **1.34(1.08-1.67)[b]** |
| Velocity to BMI peak, kg/m2 mo | **0.17(0.07-0.40)[c]** | **0.14(0.06-0.35)[a]** | **0.10(0.02-0.56)[b]** | **0.11(0.02-0.68)[c]** |
| male(vs female) | | **0.66(0.49-0.89)[b]** | | 0.94(0.48-1.85) |
| birth weight,g(continuous) | | 1.00(1.00-1.00) | | 1.00(0.99-1.00) |
| Duration of breastfeeding(continuous) | | 0.97(0.94-1.01) | | 0.92(0.84-1.01) |
| Duration of Sleep(continuous) | | 0.89(0.77-1.02) | | 0.88(0.63-1.23) |
| Cesarean section(vs Vaginal Birth) | | 1.09(0.82-1.45) | | 0.87(0.45-1.65) |
| Mother Age(>35y vs <=35y) | | 0.69(0.39-1.22) | | 0.75(0.21-2.62) |

a.P<0.001 b.P<0.01 c.P<0.05

The analysis includes only infants who had BMI peak within 0-408 days and whose BMI trajectories were estimable by the quadratic model.

**STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology***

**Checklist for cohort, case-control, and cross-sectional studies (combined)**

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 1 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 2 |
| Objectives | 3 | State specific objectives, including any pre-specified hypotheses | 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 3-4,Table-1 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 4 |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | 4 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5,Table-2 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4,5 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 5 |
| Study size | 10 | Explain how the study size was arrived at | 5 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 5,6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 6 |
| | | (*c*) Explain how missing data were addressed | 4 |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed | 4 |

| | | | |
|---|---|---|---|
| | | *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 5 |
| | | (b) Give reasons for non-participation at each stage | 5 |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 3 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Table 3 |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | 4 |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | 7 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 8,Table 5 |
| | | (*b*) Report category boundaries when continuous variables were categorized | Table 3 ,4 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 9 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 9 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 10 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 11 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 12 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Infant BMI Peak as a predictor of overweight and obesity at age 2 years in a Chinese community-based cohort

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2016-015122.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 13-Jun-2017 |
| Complete List of Authors: | Sun, Jie; School of Public Health, Fudan, Department of Social Medicine; Jing'an Maternal and Child Health Care Center, Shanghai, Department of Child Health Care<br>Nwaru, Bright; The University Of Edinburgh, Allergy & Respiratory Research Group, Centre for Population Health Sciences; University of Tampere, School of Health Sciences<br>Hua, Jing; Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, Department of Maternal and Child Health Care<br>Li, Xiaohong; School of Public Health, Fudan University, Department of Health Policy and Management ; Innovation Center for Social Risk Governance in Health<br>Wu, Zhuochun; School of Public Health, Fudan University, Department of Social Medicine;Innovation Center for Social Risk Governance in Health |
| <b>Primary Subject Heading</b>: | Epidemiology |
| Secondary Subject Heading: | Paediatrics |
| Keywords: | Overweight, Obesity, Body mass index, Longitudinal Study, Infant |
| | |

# Infant BMI peak as a predictor of overweight and obesity at age 2 years in a Chinese community-based cohort

Jie Sun[1,2], Bright I Nwaru[3,4], Jing Hua[5], Xiaohong Li[6,7], Zhuochun Wu[1,7]

## Abstract

***Objectives:*** Infant body mass index (BMI) peak, which has been studied in American and European populations and proved to be a useful indicator for predicting risk of childhood obesity, has not been assessed in China. We aimed to characterize infant BMI trajectories in a Chinese longitudinal cohort and to evaluate whether BMI peak can predict overweight and obesity at age 2 years.

***Methods:*** Serial measurements (n=6-12) of weight and length from healthy term infants (n=2073) in a birth cohort established in urban Shanghai were conducted to estimate BMI growth curves from birth to 13.5 months using a polynomial regression model. BMI peak characteristics [age (in months) and magnitude (BMI; in kg/m$^2$) at peak and pre-peak velocities (in kg/m$^2$/month)] were estimated. The relationship between infant BMI peak and childhood BMI at age 2 years was examined using binary logistic analysis.

***Results:*** Mean age at peak BMI was 7.61 months, with a magnitude of 18.33 kg/m2. Boys (n=1022) had a higher average peak BMI (18.60 vs. 18.07 kg/m2, P<0.001) and earlier average timing of achieving peak value (7.54 vs. 7.67 months, P<0.05) than girls (n=1051). With the peak BMI value increasing by 1 kg/m$^2$ or the peak time by 1 month every time, the risk of overweight at age 2 years increased by 2.11 times (OR 3.11; 95% CI 2.64-3.66) and 35% (OR 1.35; 95% CI 1.21-1.50) respectively. Similarly, higher magnitude (OR 2.69; 95% CI 2.00-3.61) and later timing (OR 1.35; 95% CI 1.08-1.68) of infant BMI peak were associated with increased risk of childhood obesity at age 2 years.

***Conclusions:*** Infant BMI peak is proved to be valuable for predicting early childhood overweight and obesity in urban Shanghai. Since this is the first Chinese community-based cohort study on the topic, further studies are required for other infant populations in different areas of China.

**Key words:** Body mass Index, Obesity, Overweight, Longitudinal Study,Infants

**Word Count:** 3694 words

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**Strengths and limitations of this study**

This is the first community-based cohort study in China to characterize infant BMI peak.

Association of BMI peak with risk of early childhood overweight and obesity will be evaluated.

It's a longitudinal cohort with careful repeated measurements of child growth parameters.

Only about 69.9% of all children in this age range had health records.

The data of parent's BMI and pregnancy weight gain were not available.

## Introduction

The worldwide overweight prevalence among children aged under 5 years has risen from 4.8% in 1990 to 6.1% in 2014. The current worldwide obesity epidemic is a serious public health crisis. [1-5] In 2014, almost half (48%) of them lived in Asia.[5] In urban areas of China, the prevalence increased from 5.3% in 2005 to 8.5% in 2010.[6] Rapid weight gain in early infancy is related to later obesity and cardiovascular risk factors such as hypertension and impaired glucose tolerance in adulthood.[7-11] Although obesity results from the combined effects of genes, environment and lifestyle, rapid genetic changes could not have occurred to result in the rapid increase in prevalence being observed; consequently, environmental and behavioral factors are believed to be key drivers of the burden of obesity.[12] Therapeutic interventions have low cost-effectiveness and poor long-term effects, so infancy may be the most important period to initiate primary preventive strategies for overweight and obesity.[13-15]

Body mass index (BMI), a useful estimate of adiposity for children aged more than two years, correlates with future health outcomes.[2, 7] It's reported that even a modest reduction in BMI z-score after one year of obesity intervention was associated with improvement in several cardiovascular risk factors.[16] In young children, waist-to-height-ratio (WHtR) is not superior to BMI in estimating body fat percentage, nor is WHtR better correlated with cardiometabolic risk factors than BMI in overweight/obese children.[17] One study in Singapore suggests an important impact of early BMI development on later metabolic outcomes in Asian populations.[18]

Based on international literature, few studies have evaluated the associations between infant BMI trajectories and childhood overweight and obesity.[12, 19-21] Weight-for-length percentile curves are often used but not with age-based changes that reflect different stages of infancy.[19] BMI increases from birth and reaches a maximum called the 'BMI peak' around age 7-9 months, then, it decreases and reaches a nadir around age 4-6 years before increasing once more.[19-21] From Silverwood et al onwards, both age and magnitude at peak were positively associated with later BMI z-scores.[20] So far, several studies have used statistical models of growth trajectories to estimate the magnitude and timing of infant BMI peak.[18-27]

Ancestry-specific differences of Infant BMI peak have been demonstrated between African-American and European populations.[19] However, until date there has been no previous study performed in China to demonstrate the utility of infant BMI peak for predicting the risk of childhood overweight and obesity. It is possible that different modeling methods (such as natural cubic splines, fractional polynomials) used to derive BMI peak characteristics could account for the observed differences across populations. [18] To make comparison with other populations, we referred to BMI modeling set by the CHOP study in Philadelphia, USA.[19, 23] Taking advantage of a community-based longitudinal data set that has serial measurements for length and weight from birth into childhood in Shanghai, we aimed to estimate the BMI peak characteristics to study the association between infant BMI peak and overweight and obesity at age 2 years.

## Methods

### Study Participants

We obtained data from the Shanghai Jing'an District birth and health records, which is a community-based longitudinal cohort. There are seventeen urban districts and one suburban district in Shanghai, with a population of 19 million in 2009. Jing'an District is located at the city center with a population of 248 thousand in 2009. "Providing free of charge health examination to children aged 0-3 years" was a project funded by Shanghai government for Jing'an children born from September 2009. The community health centers in the Jing'an District provide well-child routine checks for infants and young children. A District Childcare Database for all health centers in this project was established and managed by the Jing'an maternal and child health care center. With the information network, data on children's gender, gestational age, birthweight, feeding and sleeping behaviors, amongst others were recorded by the nurses in the health centers when they did the child health examination. All children were followed from one month to two or three years old until they went to kindergarten.

For this study, we used data from the Childcare Database for all children who were born from September 1st 2009 through September 1st 2013and received care at the health centers of Jing'an district. The children were followed up from birth, with data collected at 1, 2, 4, 6, 9, 12,18 and 24 months of age from all five communities in Jing' an District, representing 69.9% (7456/10674) of all children in this age range in Jing'an District. There were roughly 30% of children moving from Jing'an district to other districts of Shanghai during the study period, which resulted in the loss to follow-up. We gained approval (IRB#2015–TYSQ–03-11) for the current study from the Medical Research Ethics Committee, School of Public Health, Fudan University.

### Inclusion and exclusion criteria

Inclusion criteria for infants included in the study were healthy singleton infants, born between 37 and 42 weeks gestational age without physical problems. Participants were eligible if they had at least six measurements of length and weight in the first 13.5 months of life. This number and range of measurements were referred to BMI modeling set by the CHOP study in Philadelphia, USA.[19, 23] As age of BMI peak is around 7-9 months, we included children who had at least one visit in the following age ranged 213-274 days. To test the relationship between infant BMI peak and childhood overweight and obesity, measurements for children at age 2 years were included when such data were available. Preterm infants (n =289), term twins(n =52), post-term infants(n =11) and term infants with congenital defect (n=30) were excluded. There were 21.2% (2268/7456) infants eligible for analysis. Of these, we observed 85.9% (1949/2268) children from birth to age two years till September 1st 2015 (Figure 1). To assess potential selection bias, we compared demographics and birth characteristics of the analytic sample (n=2268) to the excluded healthy singleton infants (n=4806). There were no substantial differences in sex, birthweight, maternal age or overweight and obese rates at age 2 years of the two samples. (Supplemental Table 1)

### Anthropometric measures

Weight and length of children were measured by the same type of instruments at the community health centers. Weight for infants (0-18months) was measured by an electronic pediatric scale (SECA 376 Weighing Scale) to the nearest 0.005 kg. Weight for toddlers (19-24months) was measured by another type of scale (SECA 704c Weighing Scale) to the nearest 0.05kg. Recumbent length was measured from the top of the head to soles of feet using an infant mat (SECA416 Mobile Measuring Mat) to the nearest 0.1 cm. BMI z-score (BAZ) of children at age two years were calculated according to the 2006 World Health Organization (WHO) Child Growth Standards using the WHO Anthro 2009 software.[28]The

WHO Child Growth Standards was based on a multi-country study involving breastfed children from six geographically distinct sites.[5] Overweight was defined as BAZ > +1 (BMI >85th percentile) while obesity was defined as BAZ>+2 (BMI >97th percentile). Normal weight was defined as −1≤ BAZ ≤ +1.[1, 13] Based on reports from previous studies, [11, 12, 19, 21] we extracted factors associated with childhood overweight from the electronic medical records. These factors were birthweight, sex, delivery mode, maternal ages, duration of breastfeeding and sleeping data. Parents recalled to feeding and sleeping questions in follow-ups. They reported the age in months at which breastfeeding was stopped. Sleep duration in hours was recorded at age 2 years. Because this cohort was set up after birth, some information about pregnancy and parents information was not available.

**BMI trajectory modeling**

BMI peak was identified from subject-specific BMI growth curves established by serial BMI measurements. (Figure 2) A polynomial regression model with quadratic terms was fit to the BMI measurements over time. Regression modeling was used for each child to fit the following equation: [19]

$$\mathrm{BMI} = \beta_0 + \beta_1(age\ in\ days) + \beta_2(age\ in\ days)^2$$

The first inflection point occurred at less than 408 days and identified as BMI peak was derived from the equation. The magnitude and timing of BMI peak could be found by taking derivatives as follows:

$$BMI' = 2\beta_2(\text{age in days}) + \beta_1 = 0$$

Thus,

$$T_{peak} = -\frac{\beta_1}{2\beta_2}$$

$$\mathrm{BMI_{peak}} = \frac{4\beta_0\,\beta_2 - \beta_1^2}{4\,\beta_2}$$

$T_{peak}$ is the timing of BMI peak and $\mathrm{BMI_{peak}}$ is the magnitude of BMI peak.

The pre-peak velocity was calculated using the following equation, with BMI at 14 days of age as the baseline measurement to avoid the period of neonatal weight loss seen in the first two weeks of life:[(21)]

$$(\mathrm{BMI_{Peak}} - \mathrm{BMI_{14days}}) / (\mathrm{T_{peak}} - 14 \text{ days}).$$

The subjects who had a BMI peak within 14–408 days of life were defined as estimable ("fit") BMI trajectories, while those who were not identifiable by the model were called inestimable ("not fit") BMI trajectories.[(19)]

## Statistical analysis

SPSS 20.0 statistical software was used for all analyses and metalab2014b for the BMI trajectory modeling. Data were presented as mean with 95% confidence interval. Categorical data were summarized by calculating percentages. The chi-square test and two-sampled t tests were used to examine the differences between participants whose BMI trajectories were estimable or inestimable for the quadratic regression model and those who did or did not have measurements at age two years. We classified birthweight as the following categories: 1.5 to less than 2.5 kg, 2.5 to less than 4 kg, and greater than 4 kg in the chi-square test. (Table 1)

To evaluate the associations between covariates and infant BMI peak characteristics and childhood BMI Z-scores, bivariate analyses were used by one-way ANOVA with post hoc Bonferroni adjustments.(Table 2) BMI peak characteristics [age (in months) and magnitude (BMI; in kg/m2) at peak and pre-peak velocities (kg/$m^2$/month)] were estimated. The correlations between the estimated BMI peak characteristics were assessed by pearson correlation analysis. (Supplemental Table 2) Logistic regression was used to assess the associations between BMI peak characteristics and childhood overweight (BAZ > +1) or obesity (BAZ > +2), adjusting for other background characteristics. Gender, delivery mode and maternal ages were defined as categorical variables. Birthweight, duration of breastfeeding and sleeping were defined as continuous variable. We derived birthweight-for-gestational-age z-scores using references from International standards for newborn.[29] (Table 3) Statistical analyses were performed using only the subjects with estimable BMI peak.[19-22] All statistical tests were two-tailed and P values <0.05 were considered statistically significant.

## Results

### Description of the study population

The demographic and independent variables of the study population are presented in Table 1. There were 2268 infants eligible for analysis, 49.6% male and 50.4% female. Most had a normal birthweight of 2.5 to less than 4 kg (n=2073, 91.4%). Eighty-five percent (n =1949) of infants had follow-up data at least through the age of 2 years (Table 1). Evaluated by the WHO Child Growth Standards, 17.0% (n =332) infants were overweight (BAZ > +1) and 2.3% (n =44) obese (BAZ > +2) at age 2 years.

### Results of infant BMI trajectory modeling

Individual BMI trajectories were estimable using the polynomial regression model for 91.4% of the sample, with reasonable fit (mean $R^2$=0.70±0.23). Mean magnitude of BMI peak was 18.33 (95% CI 18.26-18.39) kg/$m^2$ and occurred at 7.61 (95% CI 7.55-7.67) months. (Supplemental Figure1) Those subjects with inestimable BMI peak mostly showed either a BMI peak after 408 days of life or a decrease in BMI after birth. The prevalence of macrosomia (birthweight>4kg) infants with inestimable infancy BMI peak were slightly higher than that with estimable ones (6.7% vs 11.3%, *P* =0.024). Macrosomia born heavier reached their BMI peak much earlier, since some of them attained BMI peak measurements just after birth. There was no significant difference in other factors between subjects with estimable and inestimable peak BMI (P>0.05).(Table 1)

### *Participants' characteristics in relation to infant BMI trajectories*

Infant BMI trajectories were related to both sex and birthweight (Table 2). The magnitude of BMI peak was greater, and timing of peak BMI was earlier, in boys than in girls and in children of higher birthweight than those of lower birthweight. There was no statistical significant difference in pre-peak velocities with regards to infant characteristics.

### General characteristics of children at age two years

We tested for differences between infants who had BMI data with estimable BMI peak at age two years (n=1790) vs. those who did not (n=159). There was no difference between the two groups in sex, birthweight, maternal age, duration of breastfeeding, duration of sleep and overweight rates at age 2 years. (*P* >0.05).

### Association between infant BMI peak and childhood overweight and obesity

Table 3 shows the results of the association between BMI peak and risk of overweight and obesity at two years of age. When only the infant BMI peak was included in the model, higher magnitude and later timing of infant BMI peak increased the risk of overweight at two years. Furthermore, after adjustment for other infant background factors, higher magnitude (OR 3.11; 95% CI 2.64–3.66) and later timing (OR 1.35; 95% CI 1.21-1.50) of infant BMI peak each increased the risk of overweight at two years. The results were also similar with regards to childhood obesity (Table 3).

## Discussion

Using a longitudinal data from a community-based cohort, we have demonstrated in the current analysis that infant BMI peak is useful for predicting childhood overweight and obesity in urban China. Boys had a higher average BMI peak and earlier average timing than girls. Principally, our results show that higher magnitude and later timing of infant BMI peak were each associated with increased risk of early childhood overweight and obesity.

This is the first community-based cohort study in China to characterize infant BMI peak and evaluate its association with risk of early childhood overweight and obesity. Overweight and obesity increased remarkably both in rural and urban areas of China.[30] Our findings are therefore generalizable to children of similar age in Shanghai city, and to some degree by extension to other areas in China. The used data were routinely collected by the health centers where children are offered routine healthcare, such as immunization and physical examination; thus constitute a valid and reliable data set for addressing the study questions. The longitudinal nature of the cohort and the repeated measurements of length and weight parameters provided us with the opportunity to carefully model the BMI trajectories of infants. One limitation of our investigation was that only about 69.9% (7456/10674) of all children in this age range had health records and 85.9% of eligible children had complete follow-up data up to the age 2 years, meaning that those with incomplete data were excluded from analysis and risk of selection bias may not be totally ruled out. Another weakness of the study is that the data of parent's BMI, pregnancy weight gain, gestational diabetes mellitus and income were not available, the reason being that the cohort was set up after birth and not prenatally. Thirdly, the BMI peak is estimation and not the true peak. A potential problem of using estimated BMI peak relates to the uncertainty in subsequent regression models. [18]

So far, few studies have been conducted on the utility of infant BMI peak for predicting childhood overweight and obesity.[19-21] The principal finding of our study that higher magnitude and later timing of infant BMI peak were each associated with increased risk of early childhood overweight and obesity is similar to previous research from the CHOP study conducted in USA[19] and the Uppsala Family Study in Europe.[20] However, some findings of the current study are not consistent with previous research. A 2010 prospective cohort show that more rapid increases in weight for length in the first six months of life were associated with sharply increased risk of childhood obesity.[31] Most previous studies used weight or BMI at study-dependent fixed ages[31, 32] while ours was based on longitudinal and repeated measures of length and weight. Our results also demonstrate that sex and birthweight differences were shown in magnitude and timing of the peak but not in pre-peak velocity.[19, 21] In some recent studies, later BMI peak was found for both girls and boys (8-9 months of age) in European or American populations.[20, 21, 23] Girls peaked slightly later than boys in both populations. However, one recent study conducted in Singapore suggests that Asian children peak earlier (6 months) and that sex does not significantly influence age at peak in Asian infants. Different modeling methods could account for the observed differences in BMI peak characteristics across populations. [18] The effect of breastfeeding might also explain the different age of BMI peak across genders and populations. Further research is needed to demonstrate the clinical relevance of the small differences. Furthermore, an earlier and higher BMI peak was found to be positively associated with birthweight.[19, 20] In our study, higher birthweight was not associated with a lower velocity, which was found by the CHOP study.[19]

There is no widely accepted method to model infant BMI peak, appropriate peak age range and the number and timing of serial measurements.[23] China is undergoing rapid social and economic developments with consequent improvement in nutritional status. Current estimates indicate that overweight and obesity are rising in China, including among children.[4] However, given the lack of studies evaluating the utility of BMI peak for predicting later childhood overweight and obesity in China, as has been demonstrated in other contexts and shown to be ancestry-specific,[19] it is therefore necessary to undertake such assessment, which will be useful in predicting early onset of obesity and serve as a springboard for planning appropriate interventions targeted at reducing the increasing trend of childhood overweight and obesity in urban China. It is unclear why infants in our study had earlier BMI peaks as (7-8 months) compared to infants from America and Europe (8-9 months),[20, 21, 23] but as been demonstrated, such differences may reflect possible ancestry-specific BMI peaks across populations; therefore cross-cultural evaluations are required to ascertain the validity of this assertion. Understanding these differences may help design the protocol of public health interventions to control childhood obesity.[33-35]

The principal finding of the current study suggests that infant BMI peak is useful in predicting future risk of overweight and obesity in children in urban China; therefore infancy represents a critical window of opportunity for the prevention of the emerging overweight and obesity epidemic in children.

## Conclusion

Using a community-based longitudinal cohort study with repeated measurements of infant growth parameters, we have for the first time determined that infant BMI peak is valuable for predicting early childhood overweight and obesity in urban China. Further studies are required for other infant populations in different areas of China.

## Acknowledgements

We are grateful to the staff in Jing'an maternal and child health care center for data extraction. We also acknowledge all children and their parent's for participation.

## Authors' contributions

JieSun, Bright I Nwaru, and ZhuochunWuwere responsible for the study design, analysis of the study and approval of the submitted and final version. Jing Hua and Xiaohong Li analyzed the data, interpreted the results and commented on the manuscript.

## Funding

This study was funded by National Natural Science Foundation of China [71573049]..

## Ethics Approval

All procedures performed in this study were in accordance with the ethical standard. We gained approval (IRB#2015–TYSQ–03-11) for the current study from the Medical Research Ethics Committee, School of Public Health, Fudan University. Informed consent was obtained from all individual participants included in the study.

## Competing interests

The authors declare that they have no conflict of interest.

## Data Sharing Statement

No additional data are available.

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**Table 1 Participants' characteristics by subjects with "estimable"* and "inestimable"# BMI peak**

| Characteristics | n | Estimable*, n (%) | Inestimable#, n (%) |
|---|---|---|---|
| Total number | 2268 | 2073 | 195 |
| Gender | | | |
| Male | 1126 | 1022 (49.3) | 104 (53.3) |
| Female | 1142 | 1051 (50.7) | 91 (46.7) |
| Birth weight | | | |
| 1.5 to <2.5kg | 35 | 30 (1.4) | 5 (2.6) |
| 2.5 to <4.0kg | 2073 | 1905 (91.9) | 168 (86.2) |
| **≥4kg** | **160** | **138 (6.7)[a]** | **22 (11.3)** |
| Delivery mode | | | |
| Vaginal birth | 1086 | 989 (47.7) | 97 (49.7) |
| Cesarean section | 1182 | 1084 (52.3) | 98 (50.3) |
| Maternal Age | | | |
| >35y | 176 | 159 (7.7) | 17 (8.7) |
| ≤35y | 2092 | 1914 (92.3) | 178 (91.3) |
| Total number with data at age 2y | 1949 | 1790 (86.3) | 159 (81.5) |
| Total number of overweight and obese at age 2y | 332 | 313 (17.5) | 19 (11.9) |
| Total number of obese at age 2y | 44 | 43 (2.4) | 1 (0.6) |

a.P<0.05
*Estimable: fit and identifiable BMI peak within 14–408 days of life.
# Inestimable：Not fit and identifiable.
Chi-square tests were used to examine the differences between EstimableorInestimable group.

**Table 2 Infant characteristics in relation to infant BMI peak trajectories**

| | | Magnitude(kg/m$^2$), Mean (95% CI) | Age(months), Mean (95% CI) | Pre-peak velocities(kg/m$^2$ /month) Mean (95% CI) |
|---|---|---|---|---|
| Total | n=2073 | 18.33(18.26-18.39) | 7.61(7.55-7.67) | 0.43(0.42-0.44) |
| Gender | | | | |
| | **male (n=1022)** | **18.60(18.21-18.69)[a]** | **7.54(7.46-7.63)[b]** | 0.42(0.41-0.43) |
| | female (n=1051) | 18.07(17.98-18.16) | 7.67(7.59-7.76) | 0.43(0.42-0.44) |
| Birth Weight | | | | |
| | 1.5 to <2.5kg(n=30) | 17.63(17.13-18.13) | 8.13(7.56-8.70) | 0.44(0.35-0.53) |
| | 2.5 to <4.0kg(n=1905) | 18.27(18.21-18.34) | 7.63(7.57-7.70) | 0.43(0.42-0.44) |
| | **>=4kg(n=138)** | **19.25(18.97-19.52)[b]** | **7.11(6.88-7.34)[a]** | 0.39(0.35-0.42) |
| Delivery Mode | Vaginal birth (n=989) | 18.24(18.14-18.34) | 7.64(7.56-7.73) | 0.43(0.42-0.44) |
| | **Cesarean section (n=1084)** | **18.41(18.32-18.50)[a]** | 7.58(7.49-7.66) | 0.43(0.42-0.44) |
| Maternal Age | | | | |
| | >35y(n=159) | 18.42(18.18-18.66) | 7.61(7.49-7.82) | 0.44(0.41-0.48) |
| | <=35y(n=1914) | 18.32(18.25-18.39) | 7.61(7.55-7.67) | 0.42(0.41-0.43) |

a.P<0.001 b.P<0.05

The analysis includes only infants who had BMI peak within 0-408 days and whose BMI trajectories were estimable by the quadratic model.

Bivariate comparison was performed using one-way ANOVA with post hoc Bonferroni multiple comparison test.

Table 3 Association between BMI peak characteristics and overweight and obesity at age 2 years

| | Overweight at 2y (n=1790 ) | | Obesity at 2y (n=1790 ) | |
|---|---|---|---|---|
| | Model containing infant BMI trajectory characteristics alone | Initial model plus all independent variables | Model containing infant BMI trajectory characteristics alone | Initial model plus all independent variables |
| | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Magnitude($kg/m^2$) | **2.94(2.54-3.40)**[a] | **3.11(2.64-3.66)**[a] | **2.76(2.11-3.60)**[a] | **2.69(2.00-3.61)**[a] |
| Age (months) | **1.36(1.23-1.51)**[a] | **1.35(1.21-1.50)**[a] | **1.33(1.08-1.65)**[b] | **1.35(1.08-1.68)**[b] |
| Pre-peak velocities($kg/m^2$ /month) | **0.17(0.07-0.40)**[a] | **0.14(0.06-0.34)**[a] | **0.10(0.02-0.56)**[b] | **0.12(0.02-0.74)**[c] |
| male(vs female) | | **0.67(0.49-0.90)**[b] | | 0.99(0.51-1.96) |
| birth weight z score,(continuous) | | 1.06(0.89-1.26) | | 1.24(0.84-1.82) |
| Duration of breastfeeding(continuous) | | 0.97(0.93-1.01) | | 0.92(0.84-1.01) |
| Duration of Sleep(continuous) | | 0.89(0.77-1.02) | | 0.89(0.63-1.24) |
| Cesarean section(vs Vaginal Birth) | | 1.08(0.81-1.44) | | 0.80(0.42-1.54) |
| Mother Age(>35y vs<=35y) | | 0.68(0.38-1.21) | | 0.74(0.21-2.59) |

a.P<0.001 b.P<0.01 c.P<0.05

The analysis includes only infants who had BMI peak within 0-408 days and whose BMI trajectories were estimable by the quadratic model.

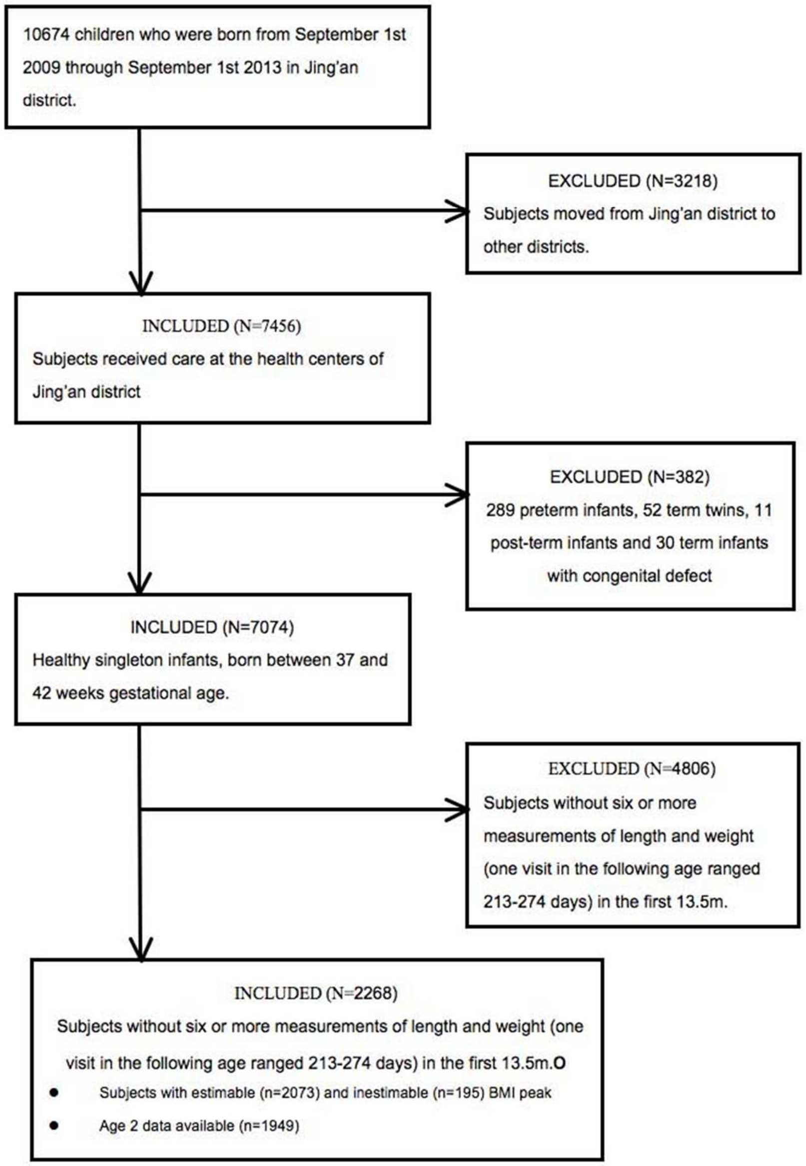



Figure1 Recruitment flow chart and study sample

64x83mm (300 x 300 DPI)

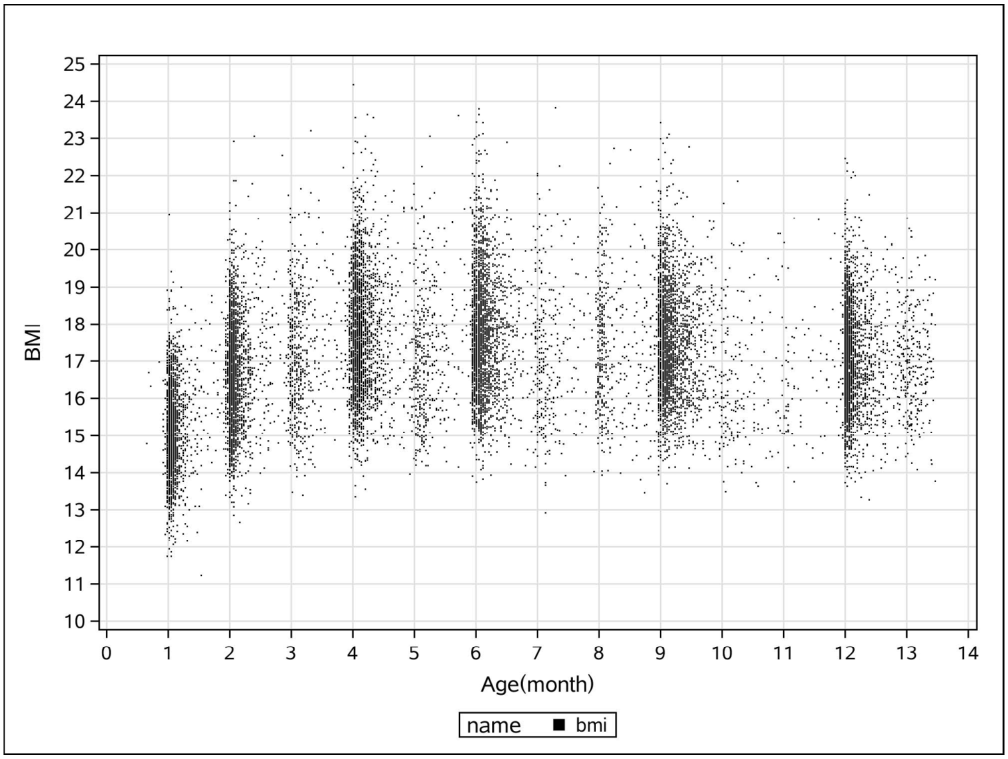



Figure 2 Plot of BMI data by age from birth to 13.5 months

169x127mm (300 x 300 DPI)

**Supplemental Table 1 Characteristics of the analytic and excluded healthy singleton infants**

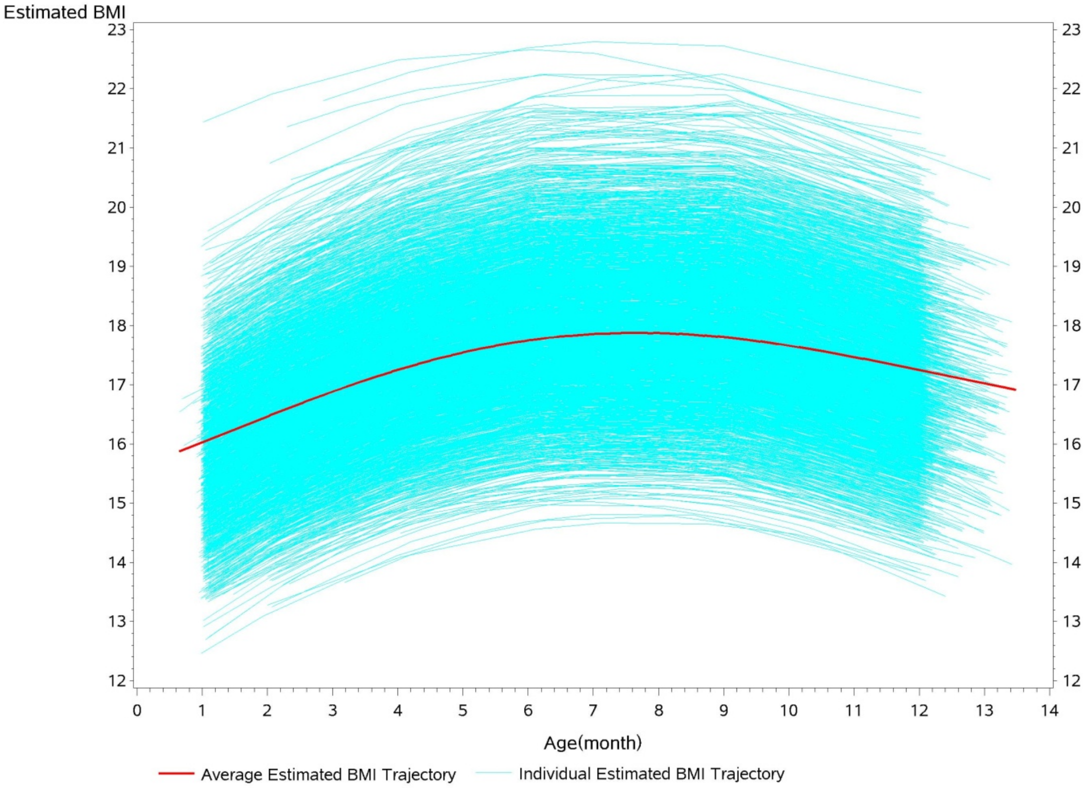
| Characteristics | n | Included, n (%) | Excluded, n (%) |
|---|---|---|---|
| Total number | 7074 | 2268(32.1) | 4806(67.9) |
| Gender | | | |
| Male | 3468 | 1126 (49.6) | 2342 (48.7) |
| Female | 3606 | 1142(50.4) | 2464 (51.3) |
| Birth weight | | | |
| <4.0kg | 6609 | 2108(92.9) | 4501 (93.7) |
| ≥4kg | 465 | 160 (7.1) | 305(6.3) |
| Maternal Age | | | |
| >35y | 570 | 176 (7.8) | 394 (8.2) |
| ≤35y | 6504 | 2092(92.2) | 4412(91.8) |
| Total number with data at age 2y | **1949** | **1949 (85.9)**[a] | **2282 (47.4)** |
| Total number of overweight and obese at age 2y | 751 | 330 (16.9) | 421 (18.4) |
| Total number of obese at age 2y | 99 | 44 (2.3) | 55(2.4) |

a.P<0.05
Chi-square tests were used to examine the differences between includedor excluded group.

**Supplemental Table 2: Correlation matrix of infancy BMI characteristics**

| | Age of BMI Peak, mo | Pre-peak velocities, kg/m2/mo |
|---|---|---|
| Magnitude of BMI peak, kg/m2 | 0.03 | 0.654** |
| Age of BMI Peak, mo | | 0.09** |

Significance is noted as: ** p≤0.01.




**Supplemental Figure1 Infant Estimated BMI trajectory by polynomial regression model**

**STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology***
**Checklist for cohort, case-control, and cross-sectional studies (combined)**

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 1 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 2 |
| Objectives | 3 | State specific objectives, including any pre-specified hypotheses | 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 3-4,Figure1 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 5 |
| | | (*b*)*Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | 5 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5-8 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 6-8 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 6 |
| Study size | 10 | Explain how the study size was arrived at | 6,Figure 1 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 8 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 8-9 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 8 |
| | | (*c*) Explain how missing data were addressed | 6 |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed | 6 |

| | | | |
|---|---|---|---|
| | | *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Figure 1 |
| | | (b) Give reasons for non-participation at each stage | 6 |
| | | (c) Consider use of a flow diagram | Figure 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Table 1,Supplemental Table 1 |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | 5 |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | 8 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Table 3 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 8 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 11 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 11 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 11-12 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 13 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 15 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Infant BMI Peak as a predictor of overweight and obesity at age 2 years in a Chinese community-based cohort

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2016-015122.R2 |
| Article Type: | Research |
| Date Submitted by the Author: | 16-Jul-2017 |
| Complete List of Authors: | Sun, Jie; School of Public Health, Fudan, Department of Social Medicine; Jing'an Maternal and Child Health Care Center, Shanghai, Department of Child Health Care<br>Nwaru, Bright; The University Of Edinburgh, Allergy & Respiratory Research Group, Centre for Population Health Sciences; University of Tampere, School of Health Sciences<br>Hua, Jing; Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, Department of Maternal and Child Health Care<br>Li, Xiaohong; School of Public Health, Fudan University, Department of Health Policy and Management ; Innovation Center for Social Risk Governance in Health<br>Wu, Zhuochun; School of Public Health, Fudan University, Department of Social Medicine;Innovation Center for Social Risk Governance in Health |
| <b>Primary Subject Heading</b>: | Epidemiology |
| Secondary Subject Heading: | Paediatrics |
| Keywords: | Overweight, Obesity, Body mass index, Longitudinal Study, Infant |
| | |

SCHOLARONE™ Manuscripts

# Infant BMI peak as a predictor of overweight and obesity at age 2 years in a Chinese community-based cohort

Jie Sun[1,2], Bright I Nwaru[3,4,5], Jing Hua[6], Xiaohong Li[7,8], Zhuochun Wu[1,8]

## Abstract

***Objectives:*** Infant body mass index (BMI) peak has proven to be a useful indicator for predicting childhood obesity risk in American and European populations. However, it has not been assessed in China. We characterized infant BMI trajectories in a Chinese longitudinal cohort and evaluated whether BMI peak can predict overweight and obesity at age 2 years.

***Methods:*** Serial measurements (n=6-12) of weight and length were taken from healthy term infants (n=2073) in a birth cohort established in urban Shanghai. Measurements were used to estimate BMI growth curves from birth to 13.5 months using a polynomial regression model. BMI peak characteristics, including age (in months) and magnitude (BMI, in $kg/m^2$) at peak and pre-peak velocities (in $kg/m^2$/month), were estimated. The relationship between infant BMI peak and childhood BMI at age 2 years was examined using binary logistic analysis.

***Results:*** Mean age at peak BMI was 7.61 months, with a magnitude of 18.33 $kg/m^2$. Boys (n=1022) had a higher average peak BMI (18.60 vs. 18.07 $kg/m^2$, P<0.001) and earlier average achievement of peak value (7.54 vs. 7.67 months, P<0.05) than girls (n=1051). With 1 $kg/m^2$ increase in peak BMI and one month increase in peak time, the risk of overweight at age 2 years increased by 2.11 times (OR 3.11; 95% CI 2.64-3.66) and 35% (OR 1.35; 95% CI 1.21-1.50), respectively. Similarly, higher BMI magnitude (OR 2.69; 95% CI 2.00-3.61) and later timing of infant BMI peak (OR 1.35; 95% CI 1.08-1.68) were associated with an increased risk of childhood obesity at age 2 years.

***Conclusions:*** We have shown that infant BMI peak is valuable for predicting early childhood overweight and obesity in urban Shanghai. Because this is the first Chinese community-based cohort study of this nature, future research is required to examine infant populations in other areas of China.

**Key words:** Body mass Index, Obesity, Overweight, Longitudinal Study, Infants

**Word Count: 3883 words**

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**Strengths and limitations of this study**

We have demonstrated here for the first time that infant BMI peak is an effective predictor for childhood obesity in Shanghai, an urban city in China.

The longitudinal cohort with careful repeated measurements of child growth parameters provided the opportunity to characterize infant BMI peak over the first year of life.

As we lacked data on parent's BMI and pregnancy weight gain, we could ascertain the influence of these on infant BMI peak and contribution to childhood overweight and obesity.

Selection bias may exist in our study because 14.1% of the infants that were measured did not complete the follow-up at 2 years old.

## Introduction

The worldwide overweight prevalence among children aged under 5 years has risen from 4.8% in 1990 to 6.1% in 2014.[(1)] The current worldwide obesity epidemic is a serious public health crisis. [(1-5)] In 2014, almost half (48%) of obese individuals lived in Asia.[(1)] In urban areas of China, the prevalence of overweight increased from 5.3% in 2005 to 8.5% in 2010.[(6)] Rapid weight gain in early infancy is related to the adult development of obesity and cardiovascular risk factors, including hypertension and impaired glucose tolerance.[(7-11)] Environmental and behavioral factors are believed to be key drivers of obesity because although obesity is genetically influenced, genetic changes cannot explain the rapid increase in the prevalence of obesity.[(12)] Therapeutic interventions in adulthood have poor long-term effects and are not cost effective, therefore the introduction of primary preventive strategies during infancy may be more important to reduce the risk of being overweight and obese.[(13-15)]

Body mass index (BMI), a useful estimate of adiposity for children aged more than two years, correlates with future health outcomes.[(3, 7)] A modest reduction in BMI z-score after one year of obesity intervention may improve several cardiovascular risk factors.[(16)] In young children, waist-to-height-ratio (WHtR) is not superior to BMI in estimating body fat percentage, nor is

WHtR better correlated with cardiometabolic risk factors than BMI in overweight/obese children.[17] One study in Singapore suggested that early BMI may have an important impact on later metabolic outcomes in Asian populations.[18]

Few studies have evaluated the associations between infant BMI trajectory and childhood overweight and obesity.[12, 19-21] Weight-for-length percentile curves are often used but do not account for the age-based changes that reflect different stages of infancy.[19] BMI increases from birth and reaches a maximum called the 'BMI peak' around age 7-9 months old, and then decreases and reaches a nadir around age 4-6 years old before increasing once again.[19-21] According to Silverwood et al, both age and magnitude of BMI peak were positively associated with later BMI z-scores.[20] Additionally, several studies have used statistical models of growth trajectories to estimate the magnitude and timing of infant BMI peak.[18-27]

Ancestry-specific differences in Infant BMI peak are found between African-American and European populations.[19] However, to date there have been no studies performed in China to demonstrate the utility of infant BMI peak for predicting the risk of childhood overweight and obesity. In order to form comparisons with other populations, we referred to a BMI modeling set by a cohort study in Philadelphia, USA [19, 23] Using a community-based longitudinal data set of serial measurements of length and weight from birth to childhood in Shanghai, we aimed to estimate the BMI peak characteristics in order to study the association between the infant BMI peak and overweight and obesity at age 2 years.

## Methods

### Study Participants

We obtained our community-based longitudinal cohort data from the Shanghai Jing'an District birth and health records. Shanghai has a population of 19 million, as of 2009, and is divided into seventeen urban districts and one suburban district. Jing'an District is located at the city center and has a population of 248,000, as of 2009. "Providing free of charge health examination to children aged 0-3 years" was a project funded by the Shanghai government for Jing'an children born from September 2009 onwards. Community health centers in the Jing'an District provide routine well-child checks for infants and young children. A District Childcare Database for all health centers in this project was established and managed by the Jing'an maternal and child health care center. For the Childcare Database, health center nurses record children's gender, gestational age, birthweight, feeding and sleeping behaviors, and other information during the child health examination. All children were followed from the age of one month to two or three years old until they went to kindergarten.

For this study, we used data from the Childcare Database for all children who were born from September 1st 2009 to September 1st 2013 and received care at the Jing'an District health centers. Children were followed from birth, with data collected at 1, 2, 4, 6, 9, 12,18 and 24 months of age from all five communities in Jing'an District, representing 69.9% (7456/10674) of all children in this age range in Jing'an District. Roughly 30% of children moved from Jing'an district to other districts of Shanghai during the study period, which resulted in a loss of follow-up in these cases. We gained approval (IRB#2015–TYSQ–03-11) for the current study from the Medical Research Ethics Committee, School of Public Health, Fudan University.

### Inclusion and exclusion criteria

Inclusion criteria for the infants in this study specified healthy single births, a gestational age between 37 and 42 weeks, and no physical problems. Participants were included if they had at least six measurements of length and weight in the first 13.5 months of life. The number and range of measurements were determined by the BMI modeling set by a cohort study in Philadelphia, USA.[19, 23] Because the BMI peak occurs around 7-9 months old, we included children who had at least one health examination visit between 213-274 days old. To test the relationship between infant BMI peak and childhood overweight and obesity, we included measurements for children at 2 years old when the data was available. Preterm infants (n = 289), term twins (n = 52), post-term infants (n = 11), and term infants with congenital defects (n = 30) were excluded. These children have different curve characteristics than normal term children.[28] We used exclusion criteria similar to the Philadelphia cohort study to compare peak BMI with other populations.[19] There were 21.2% (2268/7456) infants eligible for analysis. Of these, we observed 85.9% (1949/2268) children from birth to age two years, i.e. until September 1st 2015 (Figure 1). To assess potential selection bias, we compared demographics and birth characteristics of the analytic sample (n=2268) to the excluded healthy singleton infants (n=4806). There were no substantial differences in sex, birthweight, maternal age or overweight and obese rates at age 2 years of the two samples. (Supplemental Table 1)

**Anthropometric measures**

Weight and length of children were measured by the same type of instruments at the community health centers. Weight for infants (0-18 months) was measured by an electronic pediatric scale (SECA 376 Weighing Scale) to the nearest 0.005 kg. Weight for toddlers (19-24 months) was measured by another type of scale (SECA 704c Weighing Scale) to the nearest 0.05 kg. Recumbent length was measured from the top of the head to soles of feet using an infant mat (SECA416 Mobile Measuring Mat) to the nearest 0.1 cm. BMI z-score (BAZ) of children at age two years were calculated according to the 2006 World Health Organization (WHO) Child Growth Standards using the WHO Anthro 2009 software.[29]The WHO Child Growth Standards was based on a multi-country study involving breastfed children from six geographically distinct sites.[1] Overweight was defined as BAZ > +1 (BMI >85th percentile) while obesity was defined as BAZ> + 2 (BMI >97th percentile). Normal weight was defined as −1≤ BAZ ≤ +1.[2, 13] Based on reports from previous studies, [11, 12, 19, 21] we extracted factors associated with childhood overweight from the electronic medical records. These factors were birthweight, sex, delivery mode, maternal age, duration of breastfeeding and sleeping data. Parents answered to feeding and sleeping questions in follow-ups. They reported the age in months at which breastfeeding was stopped. Sleep duration in hours was recorded at age 2 years. Because this cohort was set up after birth, some information about pregnancy and parents information was not available.

**BMI trajectory modeling**

BMI peak was identified from subject-specific BMI growth curves established by serial BMI measurements. (Figure 2) A polynomial regression model with quadratic terms was fit to the BMI measurements over time. Regression modeling was used for each child to fit the following equation: [19]

$$\mathrm{BMI} = \beta_0 + \beta_1(age\ in\ days) + \beta_2(age\ in\ days)^2$$

The first inflection point occurred at less than 408 days as derived from the equation and this was identified as BMI peak. The magnitude and timing of BMI peak were found by taking derivatives as follows:

$$BMI' = 2\beta_2(\text{age in days}) + \beta_1 = 0$$

Thus,

$$T_{peak} = -\frac{\beta_1}{2\beta_2}$$

$$\mathrm{BMI_{peak}} = \frac{4\beta_0\beta_2 - \beta_1^2}{4\beta_2}$$

$T_{peak}$ is the timing of BMI peak and $\mathrm{BMI_{peak}}$ is the magnitude of BMI peak.

The pre-peak velocity was calculated using the following equation, with BMI at 14 days of age as the baseline measurement to avoid the period of neonatal weight loss seen in the first two weeks of life:[21]

$$(BMI_{Peak}-BMI_{14days}) / (T_{peak} -14 \text{ days}).$$

The subjects who had a BMI peak within 14 – 408 days of life were defined as estimable ("fit") BMI trajectories, while those who were not identifiable by the model were called inestimable ("not fit") BMI trajectories.[19]

## Statistical analysis

SPSS 20.0 statistical software was used for all analyses and metalab2014b for the BMI trajectory modeling. Data were presented as mean with 95% confidence interval. Categorical data were summarized by calculating percentages. The chi-square test and two-sampled t tests were used to examine the differences between participants whose BMI trajectories were estimable or inestimable for the quadratic regression model and those who did or did not have measurements at age two years. We classified birthweight as the following categories: 1.5 to less than 2.5 kg, 2.5 to less than 4 kg, and equal to or greater than 4 kg in the chi-square test. (Table 1)

To evaluate the associations between covariates and infant BMI peak characteristics and childhood BMI Z-scores, bivariate analyses were used by one-way ANOVA with post hoc Bonferroni adjustments.(Table 2) BMI peak characteristics [age (in months) and magnitude (BMI; in kg/m2) at peak and pre-peak velocities ($kg/m^2$/month)] were estimated. The correlations between the estimated BMI peak characteristics were assessed by pearson correlation analysis. (Supplemental Table 2) Logistic regression was used to assess the associations between BMI peak characteristics and childhood overweight (BAZ > +1) or obesity (BAZ > +2), adjusting for other background characteristics. Gender, delivery mode and maternal ages were defined as categorical variables. Birthweight, duration of breastfeeding and sleeping were defined as continuous variable. We derived birthweight-for-gestational-age z-scores using references from International standards for newborn.[30] (Table 3) The coefficient of determination denoted $R^2$ was used to describe the fit of every subject-specific curve. Statistical analyses were performed using only the subjects with estimable BMI peak.[19-22] All statistical tests were two-tailed and P values <0.05 were considered statistically significant.

## Results

### Description of the study population

The demographic characteristics of the study population are presented in Table 1. There were 2268 infants eligible for analysis, 49.6% male and 50.4% female. Most had a normal birthweight of 2.5 to less than 4 kg (n=2073, 91.4%). Eighty-five percent (n =1949) of infants had follow-up data at least through the age of 2 years (Table 1). Evaluated by the WHO Child Growth Standards, 17.0% (n =332) infants were overweight (BAZ > +1) and 2.3% (n =44) obese (BAZ > +2) at age 2 years.

### Results of infant BMI trajectory modeling

Individual BMI trajectories were estimable using the polynomial regression model for 91.4% of the sample, with reasonable fit (mean $R^2$=0.70±0.23). Mean magnitude of BMI peak was 18.33 (95% CI 18.26-18.39) kg/$m^2$ and occurred at 7.61 (95% CI 7.55-7.67) months. (Supplemental Figure1) Those subjects with inestimable BMI peak mostly showed either a BMI peak after 408 days of life or a decrease in BMI after birth. The prevalence of macrosomia (birthweight>4kg) infants with inestimable infancy BMI peak were higher than that with estimable ones (6.7% vs 11.3%, *P* =0.024). Heavier macrosomia infants reached their BMI peak much earlier than other infants, since some of them attained BMI peak measurements just after birth. There was no significant difference in other factors between subjects with estimable and inestimable peak BMI (P>0.05).(Table 1)

### *Participants' characteristics in relation to infant BMI trajectories*

Infant BMI trajectories were related to both sex and birthweight (Table 2). The magnitude of BMI peak was greater, and timing of peak BMI was earlier, in boys than in girls and in children of higher birthweight than those of lower birthweight. There was no statistical significant difference in pre-peak velocities with regards to infant characteristics.

***General characteristics of children at age two years***

We tested for differences between infants who had BMI data with estimable BMI peak at age two years (n=1790) vs. those who did not (n=159). There was no statistical difference between the two groups in sex, birthweight, maternal age, duration of breastfeeding, duration of sleep and overweight rates at age 2 years. (*P* >0.05).

***Association between infant BMI peak and childhood overweight and obesity***

Table 3 shows the results of the association between BMI peak and risk of overweight and obesity at two years of age. When only the infant BMI peak was included in the model, higher magnitude and later timing of infant BMI peak increased the risk of overweight at two years. Furthermore, after adjustment for other infant background factors, higher magnitude (OR 3.11; 95% CI 2.64–3.66) and later timing (OR 1.35; 95% CI 1.21-1.50) of infant BMI peak each increased the risk of overweight at two years. The results were also similar with regards to childhood obesity (Table 3).

## Discussion

Using a longitudinal set from a community-based cohort, we have demonstrated in the current analysis that infant BMI peak is useful for predicting childhood overweight and obesity in urban China. Boys had a higher average BMI peak and earlier average timing to achieve peak BMI than girls. Principally, our results show that higher BMI magnitude and later timing of infant BMI peak were each associated with increased risk of early childhood overweight and obesity.

This is the first community-based cohort study in China to characterize infant BMI peak and evaluate its association with risk of being overweight and obesity in early childhood. There have been remarkable increases in overweight and obesity in both rural and urban areas of China.[31] Our findings can therefore be generalized to similarly aged children in Shanghai city and, to some degree, be extended to other areas in China. The data used in our analysis were routinely collected by the health centers where children are offered routine healthcare, such as immunizations and physical examination; thus, the collected measurements are a valid and reliable data set for addressing the study questions. The longitudinal nature of the cohort data and the repeated measurements of length and weight parameters provided us with the opportunity to carefully model infant BMI trajectories of infants over the course of the first year of life. A limitation of our investigation was that only about 69.9% (7456/10674) of all children in this age range had health records that only 85.9% of eligible children had complete follow-up data up to 2 years of age. Because children with incomplete data were excluded from the analysis, the risk of selection bias cannot be totally ruled out. Another weakness of the study is that the data concerning parent's BMI, pregnancy weight gain, gestational diabetes mellitus and income were not available, because the cohort was defined after birth and not prenatally. Additionally, the reliability of the anthropometric measurements could not be ascertained due to the retrospective nature of the cohort. Finally, the recorded BMI peak is estimation and not the true peak. Use of estimated BMI peak is potentially related to uncertainty in subsequent regression models. [18]

Few studies have investigated the utility of infant BMI peak in predicting childhood overweight and obesity.[19-21] Principally, we found that higher BMI magnitude and later timing of infant BMI peak were each associated with increased risk of early childhood overweight and obesity. This result is similar to previous research from the cohort study conducted in USA[19] and the Uppsala Family Study in Europe.[20] However, some of our findings are not consistent with previous research. A 2010 prospective cohort study showed that more rapid increases in weight for length in the first six months of life were associated with a sharp increase in childhood obesity risk.[32] Although most previous studies used weight or BMI at study-dependent fixed ages,[32, 33] our work was based on longitudinal and repeated measures of length and weight. Our results also demonstrate the differences in sex and birthweight were associated with BMI magnitude and timing of the BMI peak, but not with pre-peak velocity.[19, 21] In recent studies, later timing of the BMI peak was observed in both girls and boys (8-9 months of age) from European or American populations.[20, 21, 23] Girls peaked slightly later than boys in both populations. However, one recent study conducted in Singapore suggested that Asian children peak earlier (6 months) than European or American children and that sex does not significantly influence age at BMI peak in Asian infants. Notably, that study used natural cubic splines, compared to our analysis that used a polynomial regression model. It is possible that the use of different modeling methods to derive BMI peak characteristics could account for the observed differences across populations. [18] Also, the effect of breastfeeding may also explain the different ages of BMI peak observed across genders and populations. Further research is needed to demonstrate the clinical relevance of these small differences in BMI peak across populations. Furthermore, a previous study found a positive association between an earlier and higher BMI peak and birthweight.[19, 20] In our study, higher birthweight was not associated with a lower velocity, which was found by the Philadelphia cohort study.[19]

There is no widely accepted method to model infant BMI peak, appropriate peak age range and the number and timing of serial measurements.[23] China is undergoing rapid social and economic developments, which is accompanied by an improvement in nutritional status.

Current estimates indicate that overweight and obesity are rising in China, including in children.[5] However, there has been a lack of studies evaluating the utility of BMI peak for predicting risk for being overweight or obese in later childhood in China, although BMI peak has been demonstrated to be ancestry-specific.[19] Therefore, these findings can be used to help predict the early onset of obesity and to serve as a springboard for planning appropriate interventions to reduce the increasing trend of childhood overweightness and obesity in urban China. It is unclear why infants in our study had earlier BMI peaks (7-8 months) than infants from America and Europe (8-9 months),[20, 21, 23] but it has been demonstrated that such differences may reflect ancestry-specific BMI peaks across populations.[19] For this reason, cross-cultural investigations are required to determine the validity of this assertion. Understanding these differences may influence the design of public health intervention protocols to address childhood obesity.[34-36]

## Conclusion

Using a community-based longitudinal cohort study with repeated measurements of infant growth parameters, we have for the first time determined that infant BMI peak is a useful metric to predict early childhood overweight and obesity in urban China. Our findings suggest that higher magnitude and later timing of infant BMI peak increased the risk of early childhood overweight and obesity. Infancy therefore represents a critical window of opportunity to prevent the emerging epidemic of overweight and obesity in children. Further studies from other urban populations in China are required in order to confirm or question our observations.

## Acknowledgements

We are grateful to the staff in Jing'an maternal and child health care center for data extraction. We also acknowledge all children and their parent's for participation.

## Authors' contributions

JieSun, Bright I Nwaru, and ZhuochunWuwere responsible for the study design, analysis of the study and approval of the submitted and final version. Jing Hua and Xiaohong Li analyzed the data, interpreted the results and commented on the manuscript.

## Funding

This study was funded by National Natural Science Foundation of China [71573049].

## Ethics Approval

All procedures performed in this study were in accordance with the ethical standard. We gained approval (IRB#2015–TYSQ–03-11) for the current study from the Medical Research Ethics Committee, School of Public Health, Fudan University. Informed consent was obtained from all individual participants included in the study.

## Competing interests

The authors declare that they have no conflict of interest.

## Data Sharing Statement

No additional data are available.

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**Table 1 Participants' characteristics by subjects with "estimable"* and "inestimable"# BMI peak**

| Characteristics | n | Estimable*, n (%) | Inestimable#, n (%) |
|---|---|---|---|
| Total number | 2268 | 2073 | 195 |
| Gender | | | |
| Male | 1126 | 1022 (49.3) | 104 (53.3) |
| Female | 1142 | 1051 (50.7) | 91 (46.7) |
| Birth weight | | | |
| 1.5 to <2.5kg | 35 | 30 (1.4) | 5 (2.6) |
| 2.5 to <4.0kg | 2073 | 1905 (91.9) | 168 (86.2) |
| **≥4kg** | **160** | **138 (6.7)**[a] | **22 (11.3)** |
| Delivery mode | | | |
| Vaginal birth | 1086 | 989 (47.7) | 97 (49.7) |
| Cesarean section | 1182 | 1084 (52.3) | 98 (50.3) |
| Maternal Age | | | |
| >35y | 176 | 159 (7.7) | 17 (8.7) |
| ≤35y | 2092 | 1914 (92.3) | 178 (91.3) |
| Total number with data at age 2y | 1949 | 1790 (86.3) | 159 (81.5) |
| Total number of overweight and obese at age 2y | 332 | 313 (17.5) | 19 (11.9) |
| Total number of obese at age 2y | 44 | 43 (2.4) | 1 (0.6) |

a.P<0.05
*Estimable: fit and identifiable BMI peak within 14–408 days of life.
# Inestimable：Not fit and identifiable.
Chi-square tests were used to examine the differences between EstimableorInestimable group.

**Table 2 Infant characteristics in relation to infant BMI peak trajectories**

| | | Magnitude(kg/m$^2$), Mean (95% CI) | Age(months), Mean (95% CI) | Pre-peak velocities(kg/m$^2$ /month) Mean (95% CI) |
|---|---|---|---|---|
| Total | n=2073 | 18.33(18.26-18.39) | 7.61(7.55-7.67) | 0.43(0.42-0.44) |
| Gender | | | | |
| | **male (n=1022)** | **18.60(18.21-18.69)[a]** | **7.54(7.46-7.63)[b]** | 0.42(0.41-0.43) |
| | female (n=1051) | 18.07(17.98-18.16) | 7.67(7.59-7.76) | 0.43(0.42-0.44) |
| Birth Weight | | | | |
| | 1.5 to <2.5kg(n=30) | 17.63(17.13-18.13) | 8.13(7.56-8.70) | 0.44(0.35-0.53) |
| | 2.5 to <4.0kg(n=1905) | 18.27(18.21-18.34) | 7.63(7.57-7.70) | 0.43(0.42-0.44) |
| | **>=4kg(n=138)** | **19.25(18.97-19.52)[b]** | **7.11(6.88-7.34)[a]** | 0.39(0.35-0.42) |
| Delivery Mode | Vaginal birth (n=989) | 18.24(18.14-18.34) | 7.64(7.56-7.73) | 0.43(0.42-0.44) |
| | **Cesarean section (n=1084)** | **18.41(18.32-18.50)[a]** | 7.58(7.49-7.66) | 0.43(0.42-0.44) |
| Maternal Age | | | | |
| | >35y(n=159) | 18.42(18.18-18.66) | 7.61(7.49-7.82) | 0.44(0.41-0.48) |
| | <=35y(n=1914) | 18.32(18.25-18.39) | 7.61(7.55-7.67) | 0.42(0.41-0.43) |

a.$P<0.001$ b.$P<0.05$

The analysis includes only infants who had BMI peak within 0-408 days and whose BMI trajectories were estimable by the quadratic model.

Bivariate comparison was performed using one-way ANOVA with post hoc Bonferroni multiple comparison test.

**Table 3 Association between BMI peak characteristics and overweight and obesity at age 2 years**

| | Overweight at 2y (n=1790 ) | | Obesity at 2y (n=1790 ) | |
|---|---|---|---|---|
| | Model containing infant BMI trajectory characteristics alone | Initial model plus all independent variables | Model containing infant BMI trajectory characteristics alone | Initial model plus all independent variables |
| | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Magnitude(kg/m$^2$) | **2.94(2.54-3.40)**[a] | **3.11(2.64-3.66)**[a] | **2.76(2.11-3.60)**[a] | **2.69(2.00-3.61)**[a] |
| Age (months) | **1.36(1.23-1.51)**[a] | **1.35(1.21-1.50)**[a] | **1.33(1.08-1.65)**[b] | **1.35(1.08-1.68)**[b] |
| Pre-peak velocities(kg/m$^2$ /month) | **0.17(0.07-0.40)**[a] | **0.14(0.06-0.34)**[a] | **0.10(0.02-0.56)**[b] | **0.12(0.02-0.74)**[c] |
| male(vs female) | | **0.67(0.49-0.90)**[b] | | 0.99(0.51-1.96) |
| birth weight z score,(continuous) | | 1.06(0.89-1.26) | | 1.24(0.84-1.82) |
| Duration of breastfeeding(continuous) | | 0.97(0.93-1.01) | | 0.92(0.84-1.01) |
| Duration of Sleep(continuous) | | 0.89(0.77-1.02) | | 0.89(0.63-1.24) |
| Cesarean section(vs Vaginal Birth) | | 1.08(0.81-1.44) | | 0.80(0.42-1.54) |
| Mother Age(>35y vs<=35y) | | 0.68(0.38-1.21) | | 0.74(0.21-2.59) |

a.P<0.001 b.P<0.01 c.P<0.05

The analysis includes only infants who had BMI peak within 0-408 days and whose BMI trajectories were estimable by the quadratic model.

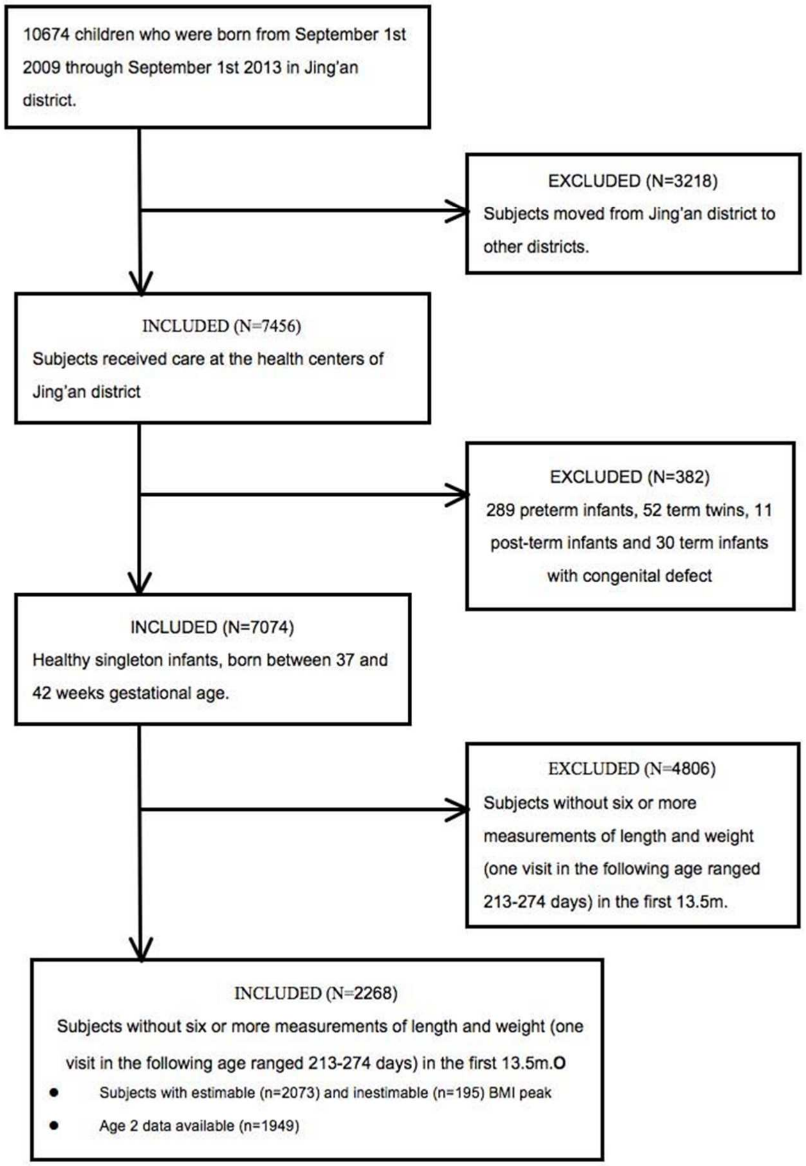



Figure1 Recruitment flow chart and study sample

64x83mm (300 x 300 DPI)

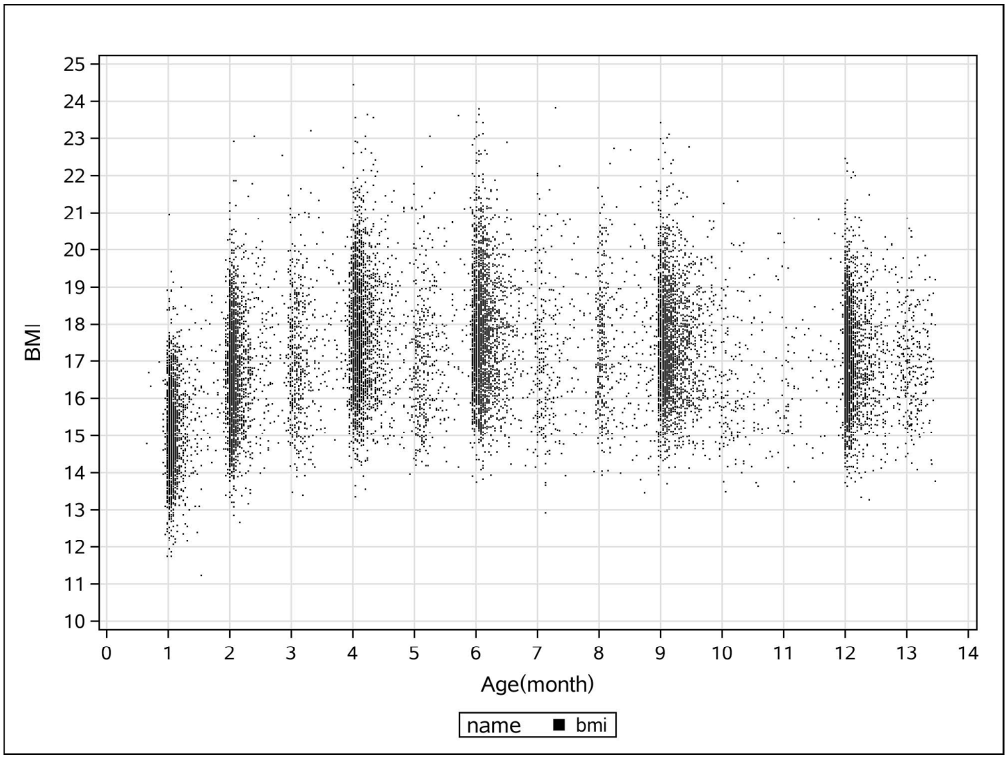



Figure 2 Plot of BMI data by age from birth to 13.5 months

169x127mm (300 x 300 DPI)

**Supplemental Table 1 Characteristics of the analytic and excluded healthy singleton infants**

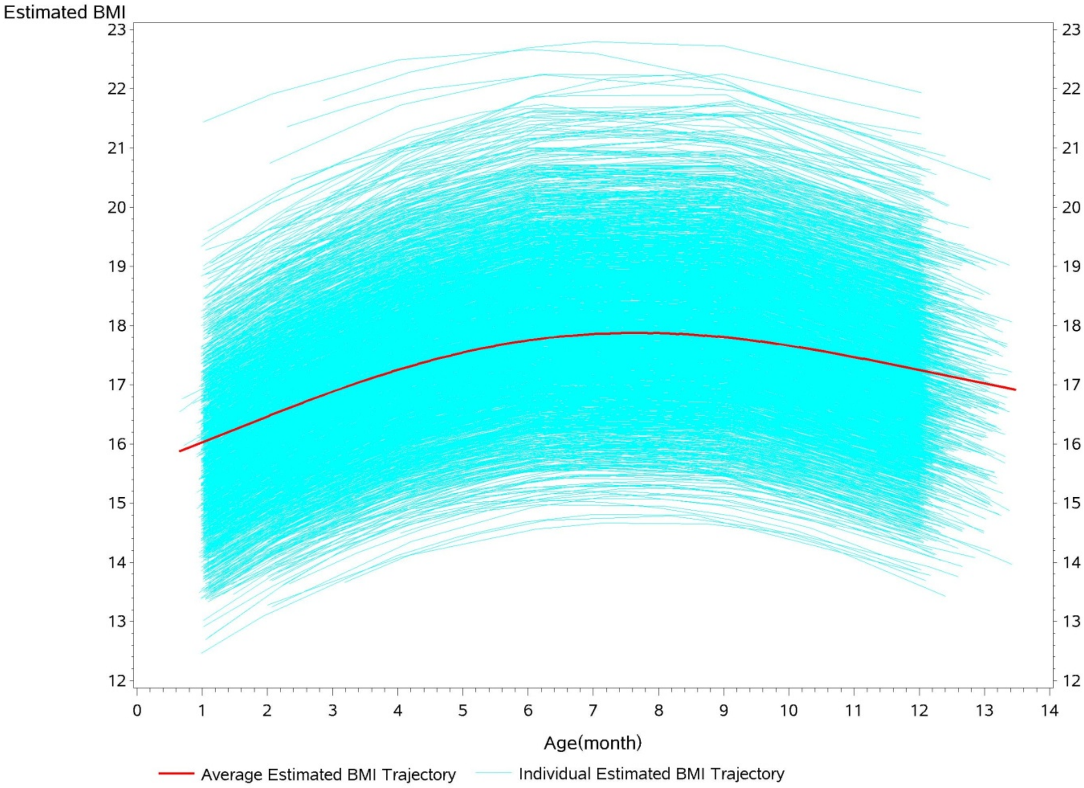
| Characteristics | n | Included, n (%) | Excluded, n (%) |
|---|---|---|---|
| Total number | 7074 | 2268(32.1) | 4806(67.9) |
| Gender | | | |
| Male | 3468 | 1126 (49.6) | 2342 (48.7) |
| Female | 3606 | 1142(50.4) | 2464 (51.3) |
| Birth weight | | | |
| <4.0kg | 6609 | 2108(92.9) | 4501 (93.7) |
| ≥4kg | 465 | 160 (7.1) | 305(6.3) |
| Maternal Age | | | |
| >35y | 570 | 176 (7.8) | 394 (8.2) |
| ≤35y | 6504 | 2092(92.2) | 4412(91.8) |
| Total number with data at age 2y | **1949** | **1949 (85.9)**[a] | **2282 (47.4)** |
| Total number of overweight and obese at age 2y | 751 | 330 (16.9) | 421 (18.4) |
| Total number of obese at age 2y | 99 | 44 (2.3) | 55(2.4) |

a.P<0.05
Chi-square tests were used to examine the differences between includedor excluded group.

**Supplemental Table 2: Correlation matrix of infancy BMI characteristics**

| | Age of BMI Peak, mo | Pre-peak velocities, kg/m2/mo |
|---|---|---|
| Magnitude of BMI peak, kg/m2 | 0.03 | 0.654** |
| Age of BMI Peak, mo | | 0.09** |

Significance is noted as: ** p⩽0.01.




**Supplemental Figure1 Infant Estimated BMI trajectory by polynomial regression model**

**STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology***
**Checklist for cohort, case-control, and cross-sectional studies (combined)**

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 1 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 2 |
| Objectives | 3 | State specific objectives, including any pre-specified hypotheses | 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 3-4,Figure1 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 5 |
| | | (*b*)*Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | 5 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5-8 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 6-8 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 6 |
| Study size | 10 | Explain how the study size was arrived at | 6,Figure 1 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 8 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 8-9 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 8 |
| | | (*c*) Explain how missing data were addressed | 6 |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed | 6 |

| | | | |
|---|---|---|---|
| | | *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Figure 1 |
| | | (b) Give reasons for non-participation at each stage | 6 |
| | | (c) Consider use of a flow diagram | Figure 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Table 1,Supplemental Table 1 |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | 5 |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | 8 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Table 3 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 8 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 11 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 11 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 11-12 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 13 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 15 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2016-015122.R3 |
| Article Type: | Research |
| Date Submitted by the Author: | 06-Aug-2017 |
| Complete List of Authors: | Sun, Jie; School of Public Health, Fudan, Department of Social Medicine; Jing'an Maternal and Child Health Care Center, Shanghai, Department of Child Health Care<br>Nwaru, Bright; The University Of Edinburgh, Allergy & Respiratory Research Group, Centre for Population Health Sciences; University of Tampere, School of Health Sciences<br>Hua, Jing; Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, Department of Maternal and Child Health Care<br>Li, Xiaohong; School of Public Health, Fudan University, Department of Health Policy and Management ; Innovation Center for Social Risk Governance in Health<br>Wu, Zhuochun; School of Public Health, Fudan University, Department of Social Medicine;Innovation Center for Social Risk Governance in Health |
| <b>Primary Subject Heading</b>: | Epidemiology |
| Secondary Subject Heading: | Paediatrics |
| Keywords: | Overweight, Obesity, Body mass index, Longitudinal Study, Infant |
| | |

SCHOLARONE™ Manuscripts

# Infant BMI peak as a predictor of overweight and obesity at age 2 years in a Chinese community-based cohort

Jie Sun[1,2], Bright I Nwaru[3,4,5], Jing Hua[6], Xiaohong Li[7,8], Zhuochun Wu[1,8]

## Abstract

***Objectives:*** Infant body mass index (BMI) peak has proven to be a useful indicator for predicting childhood obesity risk in American and European populations. However, it has not been assessed in China. We characterized infant BMI trajectories in a Chinese longitudinal cohort and evaluated whether BMI peak can predict overweight and obesity at age 2 years.

***Methods:*** Serial measurements (n=6-12) of weight and length were taken from healthy term infants (n=2073) in a birth cohort established in urban Shanghai. Measurements were used to estimate BMI growth curves from birth to 13.5 months using a polynomial regression model. BMI peak characteristics, including age (in months) and magnitude (BMI, in kg/m$^2$) at peak and pre-peak velocities (in kg/m$^2$/month), were estimated. The relationship between infant BMI peak and childhood BMI at age 2 years was examined using binary logistic analysis.

***Results:*** Mean age at peak BMI was 7.61 months, with a magnitude of 18.33 kg/m$^2$. Boys (n=1022) had a higher average peak BMI (18.60 vs. 18.07 kg/m$^2$, P<0.001) and earlier average achievement of peak value (7.54 vs. 7.67 months, P<0.05) than girls (n=1051). With 1 kg/m$^2$ increase in peak BMI and one month increase in peak time, the risk of overweight at age 2 years increased by 2.11 times (OR 3.11; 95% CI 2.64-3.66) and 35% (OR 1.35; 95% CI 1.21-1.50), respectively. Similarly, higher BMI magnitude (OR 2.69; 95% CI 2.00-3.61) and later timing of infant BMI peak (OR 1.35; 95% CI 1.08-1.68) were associated with an increased risk of childhood obesity at age 2 years.

***Conclusions:*** We have shown that infant BMI peak is valuable for predicting early childhood overweight and obesity in urban Shanghai. Because this is the first Chinese community-based cohort study of this nature, future research is required to examine infant populations in other areas of China.

**Key words:** Body mass Index, Obesity, Overweight, Longitudinal Study, Infants

**Word Count: 3883 words**

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**Strengths and limitations of this study**

The longitudinal cohort with careful repeated measurements of child growth parameters provided the opportunity to characterize infant BMI peak over the first year of life.

As we lacked data on parent's BMI and pregnancy weight gain, we could not ascertain the influence of these on infant BMI peak and contribution to childhood overweight and obesity.

Selection bias may exist in our study because 14.1% of the infants that were measured did not complete the follow-up at 2 years old.

## Introduction

The worldwide overweight prevalence among children aged under 5 years has risen from 4.8% in 1990 to 6.1% in 2014.(1) The current worldwide obesity epidemic is a serious public health crisis. (1-5) In 2014, almost half (48%) of obese individuals lived in Asia.(1) In urban areas of China, the prevalence of overweight increased from 5.3% in 2005 to 8.5% in 2010.(6) Rapid weight gain in early infancy is related to the adult development of obesity and cardiovascular risk factors, including hypertension and impaired glucose tolerance.(7-11) Environmental and behavioral factors are believed to be key drivers of obesity because although obesity is genetically influenced, genetic changes cannot explain the rapid increase in the prevalence of obesity.(12) Therapeutic interventions in adulthood have poor long-term effects and are not cost effective, therefore the introduction of primary preventive strategies during infancy may be more important to reduce the risk of being overweight and obese.(13-15)

Body mass index (BMI), a useful estimate of adiposity for children aged more than two years, correlates with future health outcomes.(3, 7) A modest reduction in BMI z-score after one year of obesity intervention may improve several cardiovascular risk factors.(16) In young children, waist-to-height-ratio (WHtR) is not superior to BMI in estimating body fat percentage, nor is WHtR better correlated with cardiometabolic risk factors than BMI in overweight/obese children.[17] One study in Singapore suggested that early BMI may have an important impact on later metabolic outcomes in Asian populations.[18]

Few studies have evaluated the associations between infant BMI trajectory and childhood overweight and obesity.[12, 19-21] Weight-for-length percentile curves are often used but do not account for the age-based changes that reflect different stages of infancy.[19] BMI increases from birth and reaches a maximum called the 'BMI peak' around age 7-9 months old, and then decreases and reaches a nadir around age 4-6 years old before increasing once again.[19-21] According to Silverwood et al, both age and magnitude of BMI peak were positively associated with later BMI z-scores.[20] Additionally, several studies have used statistical models of growth trajectories to estimate the magnitude and timing of infant BMI peak.[18-27]

Ancestry-specific differences in Infant BMI peak are found between African-American and European populations.[19] However, to date there have been no studies performed in China to demonstrate the utility of infant BMI peak for predicting the risk of childhood overweight and obesity. In order to form comparisons with other populations, we referred to a BMI modeling set by a cohort study in Philadelphia, USA [19, 23] Using a community-based longitudinal data set of serial measurements of length and weight from birth to childhood in Shanghai, we aimed to estimate the BMI peak characteristics in order to study the association between the infant BMI peak and overweight and obesity at age 2 years.

## Methods

### Study Participants

We obtained our community-based longitudinal cohort data from the Shanghai Jing'an District birth and health records. Shanghai has a population of 19 million, as of 2009, and is divided into seventeen urban districts and one suburban district. Jing'an District is located at the city center and has a population of 248,000, as of 2009. "Providing free of charge health examination to children aged 0-3 years" was a project funded by the Shanghai government for Jing'an children born from September 2009 onwards. Community health centers in the Jing'an District provide routine well-child checks for infants and young children. A District Childcare Database for all health centers in this project was established and managed by the Jing'an maternal and child health care center. For the Childcare Database, health center nurses record children's gender, gestational age, birthweight, feeding and sleeping behaviors, and other information during the child health examination. All children were followed from the age of one month to two or three years old until they went to kindergarten.

For this study, we used data from the Childcare Database for all children who were born from September 1st 2009 to September 1st 2013 and received care at the Jing'an District health centers. Children were followed from birth, with data collected at 1, 2, 4, 6, 9, 12,18 and 24 months of age from all five communities in Jing'an District, representing 69.9% (7456/10674) of all children in this age range in Jing'an District. Roughly 30% of children moved from Jing'an district to other districts of Shanghai during the study period, which resulted in a loss of follow-up in these cases. We gained approval (IRB#2015–TYSQ–03-11) for the current study from the Medical Research Ethics Committee, School of Public Health, Fudan University.

### Inclusion and exclusion criteria

Inclusion criteria for the infants in this study specified healthy single births, a gestational age between 37 and 42 weeks, and no physical problems. Participants were included if they had at least six measurements of length and weight in the first 13.5 months of life. The number and range of measurements were determined by the BMI modeling set by a cohort study in Philadelphia, USA.[19, 23] Because the BMI peak occurs around 7-9 months old, we included children who had at least one health examination visit between 213-274 days old. To test the relationship between infant BMI peak and childhood overweight and obesity, we included measurements for children at 2 years old when the data was available. Preterm infants (n = 289), term twins (n = 52), post-term infants (n = 11), and term infants with congenital defects (n = 30) were excluded. These children have different curve characteristics than normal term children.[28] We used exclusion criteria similar to the Philadelphia cohort study to compare peak BMI with other populations.[19] There were 21.2% (2268/7456) infants eligible for analysis. Of these, we observed 85.9% (1949/2268) children from birth to age two years, i.e. until September 1st 2015 (Figure 1). To assess potential selection bias, we compared demographics and birth characteristics of the analytic sample (n=2268) to the excluded healthy singleton infants (n=4806). There were no substantial differences in sex, birthweight, maternal age or overweight and obese rates at age 2 years of the two samples. (Supplemental Table 1)

**Anthropometric measures**

Weight and length of children were measured by the same type of instruments at the community health centers. Weight for infants (0-18 months) was measured by an electronic pediatric scale (SECA 376 Weighing Scale) to the nearest 0.005 kg. Weight for toddlers (19-24 months) was measured by another type of scale (SECA 704c Weighing Scale) to the nearest 0.05 kg. Recumbent length was measured from the top of the head to soles of feet using an infant mat (SECA416 Mobile Measuring Mat) to the nearest 0.1 cm. BMI z-score (BAZ) of children at age two years were calculated according to the 2006 World Health Organization (WHO) Child Growth Standards using the WHO Anthro 2009 software.[29]The WHO Child Growth Standards was based on a multi-country study involving breastfed children from six geographically distinct sites.[1] Overweight was defined as BAZ > +1 (BMI >85th percentile) while obesity was defined as BAZ> + 2 (BMI >97th percentile). Normal weight was defined as −1≤ BAZ ≤ +1.[2, 13] Based on reports from previous studies, [11, 12, 19, 21] we extracted factors associated with childhood overweight from the electronic medical records. These factors were birthweight, sex, delivery mode, maternal age, duration of breastfeeding and sleeping data. Parents answered to feeding and sleeping questions in follow-ups. They reported the age in months at which breastfeeding was stopped. Sleep duration in hours was recorded at age 2 years. Because this cohort was set up after birth, some information about pregnancy and parents information was not available.

**BMI trajectory modeling**

BMI peak was identified from subject-specific BMI growth curves established by serial BMI measurements. (Figure 2) A polynomial regression model with quadratic terms was fit to the BMI measurements over time. Regression modeling was used for each child to fit the following equation: [19]

$$\mathrm{BMI} = \beta_0 + \beta_1(age\ in\ days) + \beta_2(age\ in\ days)^2$$

The first inflection point occurred at less than 408 days as derived from the equation and this was identified as BMI peak. The magnitude and timing of BMI peak were found by taking derivatives as follows:

$$BMI' = 2\beta_2(\text{age in days}) + \beta_1 = 0$$

Thus,

$$T_{peak} = -\frac{\beta_1}{2\beta_2}$$

$$\mathrm{BMI_{peak}} = \frac{4\beta_0\beta_2 - \beta_1^2}{4\beta_2}$$

$T_{peak}$ is the timing of BMI peak and $\mathrm{BMI_{peak}}$ is the magnitude of BMI peak.

The pre-peak velocity was calculated using the following equation, with BMI at 14 days of age as the baseline measurement to avoid the period of neonatal weight loss seen in the first two weeks of life:[21]

$$(BMI_{Peak}-BMI_{14days}) / (T_{peak} -14 \text{ days}).$$

The subjects who had a BMI peak within 14 – 408 days of life were defined as estimable ("fit") BMI trajectories, while those who were not identifiable by the model were called inestimable ("not fit") BMI trajectories.[19]

**Statistical analysis**

SPSS 20.0 statistical software was used for all analyses and metalab2014b for the BMI trajectory modeling. Data were presented as mean with 95% confidence interval. Categorical data were summarized by calculating percentages. The chi-square test and two-sampled t tests were used to examine the differences between participants whose BMI trajectories were estimable or inestimable for the quadratic regression model and those who did or did not have measurements at age two years. We classified birthweight as the following categories: 1.5 to less than 2.5 kg, 2.5 to less than 4 kg, and equal to or greater than 4 kg in the chi-square test. (Table 1)

To evaluate the associations between covariates and infant BMI peak characteristics and childhood BMI Z-scores, bivariate analyses were used by one-way ANOVA with post hoc Bonferroni adjustments.(Table 2) BMI peak characteristics [age (in months) and magnitude (BMI; in kg/m2) at peak and pre-peak velocities ($kg/m^2$/month)] were estimated. The correlations between the estimated BMI peak characteristics were assessed by pearson correlation analysis. (Supplemental Table 2) Logistic regression was used to assess the associations between BMI peak characteristics and childhood overweight (BAZ > +1) or obesity (BAZ > +2), adjusting for other background characteristics. Gender, delivery mode and maternal ages were defined as categorical variables. Birthweight, duration of breastfeeding and sleeping were defined as continuous variable. We derived birthweight-for-gestational-age z-scores using references from International standards for newborn.[30] (Table 3) The coefficient of determination denoted $R^2$ was used to describe the fit of every subject-specific curve. Statistical analyses were performed using only the subjects with estimable BMI peak.[19-22] All statistical tests were two-tailed and P values <0.05 were considered statistically significant.

## Results

### Description of the study population

The demographic characteristics of the study population are presented in Table 1. There were 2268 infants eligible for analysis, 49.6% male and 50.4% female. Most had a normal birthweight of 2.5 to less than 4 kg (n=2073, 91.4%). Eighty-five percent (n =1949) of infants had follow-up data at least through the age of 2 years (Table 1). Evaluated by the WHO Child Growth Standards, 17.0% (n =332) infants were overweight (BAZ > +1) and 2.3% (n =44) obese (BAZ > +2) at age 2 years.

### Results of infant BMI trajectory modeling

Individual BMI trajectories were estimable using the polynomial regression model for 91.4% of the sample, with reasonable fit (mean $R^2$=0.70±0.23). Mean magnitude of BMI peak was 18.33 (95% CI 18.26-18.39) kg/$m^2$ and occurred at 7.61 (95% CI 7.55-7.67) months. (Supplemental Figure1) Those subjects with inestimable BMI peak mostly showed either a BMI peak after 408 days of life or a decrease in BMI after birth. The prevalence of macrosomia (birthweight>4kg) infants with inestimable infancy BMI peak were higher than that with estimable ones (6.7% vs 11.3%, $P$ =0.024). Heavier macrosomia infants reached their BMI peak much earlier than other infants, since some of them attained BMI peak measurements just after birth. There was no significant difference in other factors between subjects with estimable and inestimable peak BMI (P>0.05).(Table 1)

### *Participants' characteristics in relation to infant BMI trajectories*

Infant BMI trajectories were related to both sex and birthweight (Table 2). The magnitude of BMI peak was greater, and timing of peak BMI was earlier, in boys than in girls and in children of higher birthweight than those of lower birthweight. There was no statistical significant difference in pre-peak velocities with regards to infant characteristics.

***General characteristics of children at age two years***

We tested for differences between infants who had BMI data with estimable BMI peak at age two years (n=1790) vs. those who did not (n=159). There was no statistical difference between the two groups in sex, birthweight, maternal age, duration of breastfeeding, duration of sleep and overweight rates at age 2 years. (*P* >0.05).

***Association between infant BMI peak and childhood overweight and obesity***

Table 3 shows the results of the association between BMI peak and risk of overweight and obesity at two years of age. When only the infant BMI peak was included in the model, higher magnitude and later timing of infant BMI peak increased the risk of overweight at two years. Furthermore, after adjustment for other infant background factors, higher magnitude (OR 3.11; 95% CI 2.64–3.66) and later timing (OR 1.35; 95% CI 1.21-1.50) of infant BMI peak each increased the risk of overweight at two years. The results were also similar with regards to childhood obesity (Table 3).

## Discussion

Using a longitudinal set from a community-based cohort, we have demonstrated in the current analysis that infant BMI peak is useful for predicting childhood overweight and obesity in urban China. Boys had a higher average BMI peak and earlier average timing to achieve peak BMI than girls. Principally, our results show that higher BMI magnitude and later timing of infant BMI peak were each associated with increased risk of early childhood overweight and obesity.

This is the first community-based cohort study in China to characterize infant BMI peak and evaluate its association with risk of being overweight and obesity in early childhood. There have been remarkable increases in overweight and obesity in both rural and urban areas of China.[(31)] Our findings can therefore be generalized to similarly aged children in Shanghai city and, to some degree, be extended to other areas in China. The longitudinal nature of the cohort data and the repeated measurements of length and weight parameters provided us with the opportunity to carefully model infant BMI trajectories of infants over the course of the first year of life. A limitation of our investigation was that only about 69.9% (7456/10674) of all children in this age range had health records that only 85.9% of eligible children had complete follow-up data up to 2 years of age. Because children with incomplete data were excluded from the analysis, the risk of selection bias cannot be totally ruled out. Another weakness of the study is that the data concerning parent's BMI, pregnancy weight gain, gestational diabetes mellitus and income were not available, because the cohort was defined after birth and not prenatally. Additionally, the reliability of the anthropometric measurements could not be ascertained due to the retrospective nature of the cohort. We acknowledge that the generated from routinely collected data may potentially influence the generalizability of the findings. Finally, the recorded BMI peak is estimation and not the true peak. Use of estimated BMI peak is potentially related to uncertainty in subsequent regression models. [(18)]

Few studies have investigated the utility of infant BMI peak in predicting childhood overweight and obesity.[(19-21)] Principally, we found that higher BMI magnitude and later timing of infant

BMI peak were each associated with increased risk of early childhood overweight and obesity. This result is similar to previous research from the cohort study conducted in USA[19] and the Uppsala Family Study in Europe.[20] However, some of our findings are not consistent with previous research. A 2010 prospective cohort study showed that more rapid increases in weight for length in the first six months of life were associated with a sharp increase in childhood obesity risk.[32] Although most previous studies used weight or BMI at study-dependent fixed ages,[32, 33] our work was based on longitudinal and repeated measures of length and weight. Our results also demonstrate the differences in sex and birthweight were associated with BMI magnitude and timing of the BMI peak, but not with pre-peak velocity.[19, 21] In recent studies, later timing of the BMI peak was observed in both girls and boys (8-9 months of age) from European or American populations.[20, 21, 23] Girls peaked slightly later than boys in both populations. However, one recent study conducted in Singapore suggested that Asian children peak earlier (6 months) than European or American children and that sex does not significantly influence age at BMI peak in Asian infants. Notably, that study used natural cubic splines, compared to our analysis that used a polynomial regression model. It is possible that the use of different modeling methods to derive BMI peak characteristics could account for the observed differences across populations. [18] Also, the effect of breastfeeding may also explain the different ages of BMI peak observed across genders and populations. Further research is needed to demonstrate the clinical relevance of these small differences in BMI peak across populations. Furthermore, a previous study found a positive association between an earlier and higher BMI peak and birthweight.[19, 20] In our study, higher birthweight was not associated with a lower velocity, which was found by the Philadelphia cohort study.[19]

There is no widely accepted method to model infant BMI peak, appropriate peak age range and the number and timing of serial measurements.[23] China is undergoing rapid social and economic developments, which is accompanied by an improvement in nutritional status. Current estimates indicate that overweight and obesity are rising in China, including in children.[5] However, there has been a lack of studies evaluating the utility of BMI peak for predicting risk for being overweight or obese in later childhood in China, although BMI peak has been demonstrated to be ancestry-specific.[19] Therefore, these findings can be used to help predict the early onset of obesity and to serve as a springboard for planning appropriate interventions to reduce the increasing trend of childhood overweightness and obesity in urban China. It is unclear why infants in our study had earlier BMI peaks (7-8 months) than infants from America and Europe (8-9 months),[20, 21, 23] but it has been demonstrated that such differences may reflect ancestry-specific BMI peaks across populations.[19] For this reason, cross-cultural investigations are required to determine the validity of this assertion. Understanding these differences may influence the design of public health intervention protocols to address childhood obesity.[34-36]

## Conclusion

Using a community-based longitudinal cohort study with repeated measurements of infant growth parameters, we have for the first time determined that infant BMI peak is a useful metric to predict early childhood overweight and obesity in urban China. Our findings suggest that higher magnitude and later timing of infant BMI peak increased the risk of early childhood overweight and obesity. Infancy therefore represents a critical window of opportunity to prevent the emerging epidemic of overweight and obesity in children. Further studies from other urban populations in China are required in order to confirm or question our observations.

**Acknowledgements**

We are grateful to the staff in Jing'an maternal and child health care center for data extraction. We also acknowledge all children and their parent's for participation.

**Authors' contributions**

JieSun, Bright I Nwaru, and ZhuochunWuwere responsible for the study design, analysis of the study and approval of the submitted and final version. Jing Hua and Xiaohong Li analyzed the data, interpreted the results and commented on the manuscript.

**Funding**

This study was funded by National Natural Science Foundation of China [71573049].

**Ethics Approval**

All procedures performed in this study were in accordance with the ethical standard. We gained approval (IRB#2015–TYSQ–03-11) for the current study from the Medical Research Ethics Committee, School of Public Health, Fudan University. Informed consent was obtained from all individual participants included in the study.

**Competing interests**

The authors declare that they have no conflict of interest.

**Data Sharing Statement**

No additional data are available.

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**Table 1 Participants' characteristics by subjects with "estimable"* and "inestimable"# BMI peak**

| Characteristics | n | Estimable*, n (%) | Inestimable#, n (%) |
|---|---|---|---|
| Total number | 2268 | 2073 | 195 |
| Gender | | | |
| Male | 1126 | 1022 (49.3) | 104 (53.3) |
| Female | 1142 | 1051 (50.7) | 91 (46.7) |
| Birth weight | | | |
| 1.5 to <2.5kg | 35 | 30 (1.4) | 5 (2.6) |
| 2.5 to <4.0kg | 2073 | 1905 (91.9) | 168 (86.2) |
| **≥4kg** | **160** | **138 (6.7)**[a] | **22 (11.3)** |
| Delivery mode | | | |
| Vaginal birth | 1086 | 989 (47.7) | 97 (49.7) |
| Cesarean section | 1182 | 1084 (52.3) | 98 (50.3) |
| Maternal Age | | | |
| >35y | 176 | 159 (7.7) | 17 (8.7) |
| ≤35y | 2092 | 1914 (92.3) | 178 (91.3) |
| Total number with data at age 2y | 1949 | 1790 (86.3) | 159 (81.5) |
| Total number of overweight and obese at age 2y | 332 | 313 (17.5) | 19 (11.9) |
| Total number of obese at age 2y | 44 | 43 (2.4) | 1 (0.6) |

a.P<0.05
*Estimable: fit and identifiable BMI peak within 14–408 days of life.
# Inestimable：Not fit and identifiable.
Chi-square tests were used to examine the differences between EstimableorInestimable group.

**Table 2 Infant characteristics in relation to infant BMI peak trajectories**

| | | Magnitude(kg/m$^2$), Mean (95% CI) | Age(months), Mean (95% CI) | Pre-peak velocities(kg/m$^2$ /month) Mean (95% CI) |
|---|---|---|---|---|
| Total | n=2073 | 18.33(18.26-18.39) | 7.61(7.55-7.67) | 0.43(0.42-0.44) |
| Gender | | | | |
| | **male (n=1022)** | **18.60(18.21-18.69)[a]** | **7.54(7.46-7.63)[b]** | 0.42(0.41-0.43) |
| | female (n=1051) | 18.07(17.98-18.16) | 7.67(7.59-7.76) | 0.43(0.42-0.44) |
| Birth Weight | | | | |
| | 1.5 to <2.5kg(n=30) | 17.63(17.13-18.13) | 8.13(7.56-8.70) | 0.44(0.35-0.53) |
| | 2.5 to <4.0kg(n=1905) | 18.27(18.21-18.34) | 7.63(7.57-7.70) | 0.43(0.42-0.44) |
| | **>=4kg(n=138)** | **19.25(18.97-19.52)[b]** | **7.11(6.88-7.34)[a]** | 0.39(0.35-0.42) |
| Delivery Mode | Vaginal birth (n=989) | 18.24(18.14-18.34) | 7.64(7.56-7.73) | 0.43(0.42-0.44) |
| | **Cesarean section (n=1084)** | **18.41(18.32-18.50)[a]** | 7.58(7.49-7.66) | 0.43(0.42-0.44) |
| Maternal Age | | | | |
| | >35y(n=159) | 18.42(18.18-18.66) | 7.61(7.49-7.82) | 0.44(0.41-0.48) |
| | <=35y(n=1914) | 18.32(18.25-18.39) | 7.61(7.55-7.67) | 0.42(0.41-0.43) |

a.P<0.001 b.P<0.05

The analysis includes only infants who had BMI peak within 0-408 days and whose BMI trajectories were estimable by the quadratic model.

Bivariate comparison was performed using one-way ANOVA with post hoc Bonferroni multiple comparison test.

Table 3 Association between BMI peak characteristics and overweight and obesity at age 2 years

| | Overweight at 2y (n=1790 ) | | Obesity at 2y (n=1790 ) | |
|---|---|---|---|---|
| | Model containing infant BMI trajectory characteristics alone | Initial model plus all independent variables | Model containing infant BMI trajectory characteristics alone | Initial model plus all independent variables |
| | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Magnitude($kg/m^2$) | **2.94(2.54-3.40)**[a] | **3.11(2.64-3.66)**[a] | **2.76(2.11-3.60)**[a] | **2.69(2.00-3.61)**[a] |
| Age (months) | **1.36(1.23-1.51)**[a] | **1.35(1.21-1.50)**[a] | **1.33(1.08-1.65)**[b] | **1.35(1.08-1.68)**[b] |
| Pre-peak velocities($kg/m^2$ /month) | **0.17(0.07-0.40)**[a] | **0.14(0.06-0.34)**[a] | **0.10(0.02-0.56)**[b] | **0.12(0.02-0.74)**[c] |
| male(vs female) | | **0.67(0.49-0.90)**[b] | | 0.99(0.51-1.96) |
| birth weight z score,(continuous) | | 1.06(0.89-1.26) | | 1.24(0.84-1.82) |
| Duration of breastfeeding(continuous) | | 0.97(0.93-1.01) | | 0.92(0.84-1.01) |
| Duration of Sleep(continuous) | | 0.89(0.77-1.02) | | 0.89(0.63-1.24) |
| Cesarean section(vs Vaginal Birth) | | 1.08(0.81-1.44) | | 0.80(0.42-1.54) |
| Mother Age(>35y vs<=35y) | | 0.68(0.38-1.21) | | 0.74(0.21-2.59) |

a.P<0.001 b.P<0.01 c.P<0.05

The analysis includes only infants who had BMI peak within 0-408 days and whose BMI trajectories were estimable by the quadratic model.

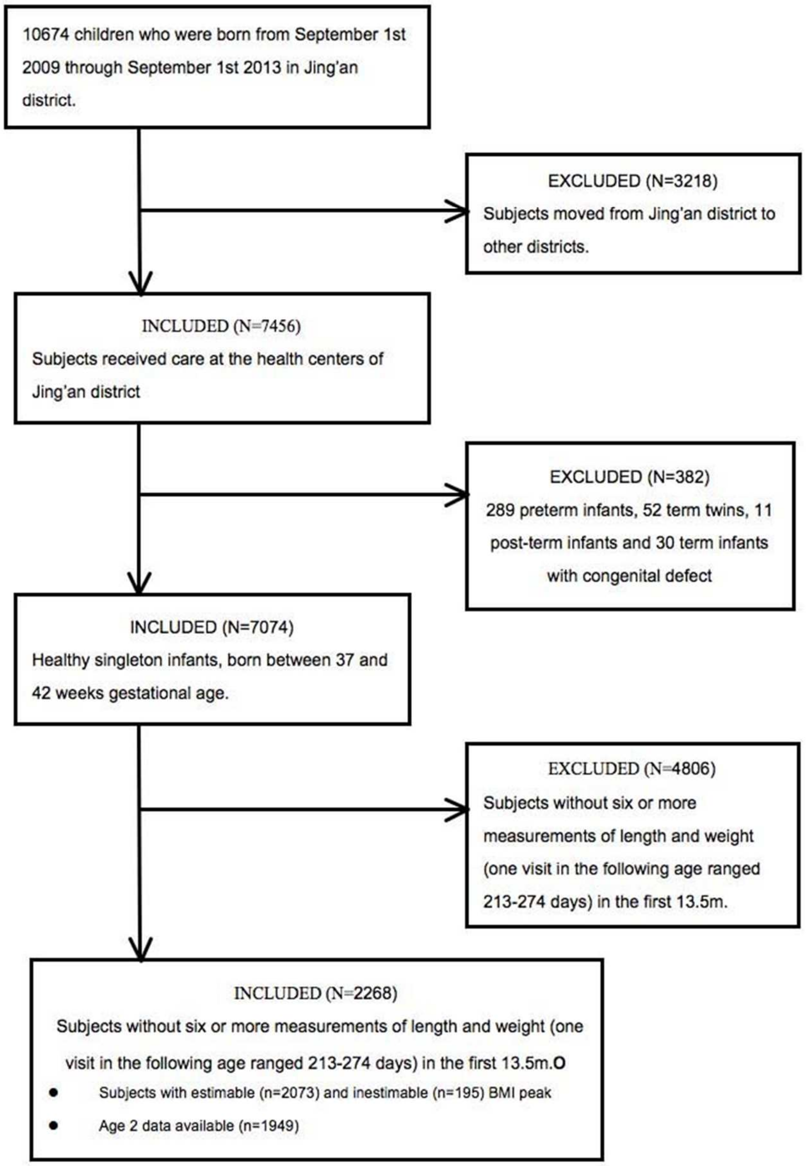



Figure1 Recruitment flow chart and study sample

64x83mm (300 x 300 DPI)

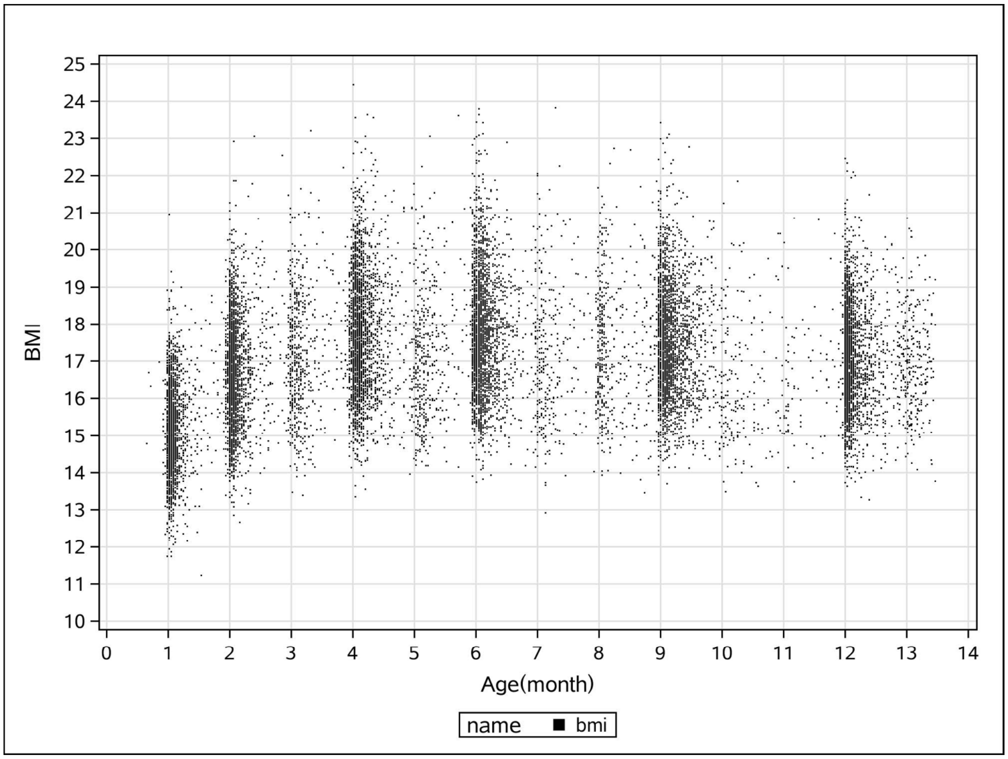



Figure 2 Plot of BMI data by age from birth to 13.5 months

169x127mm (300 x 300 DPI)

**Supplemental Table 1 Characteristics of the analytic and excluded healthy singleton infants**

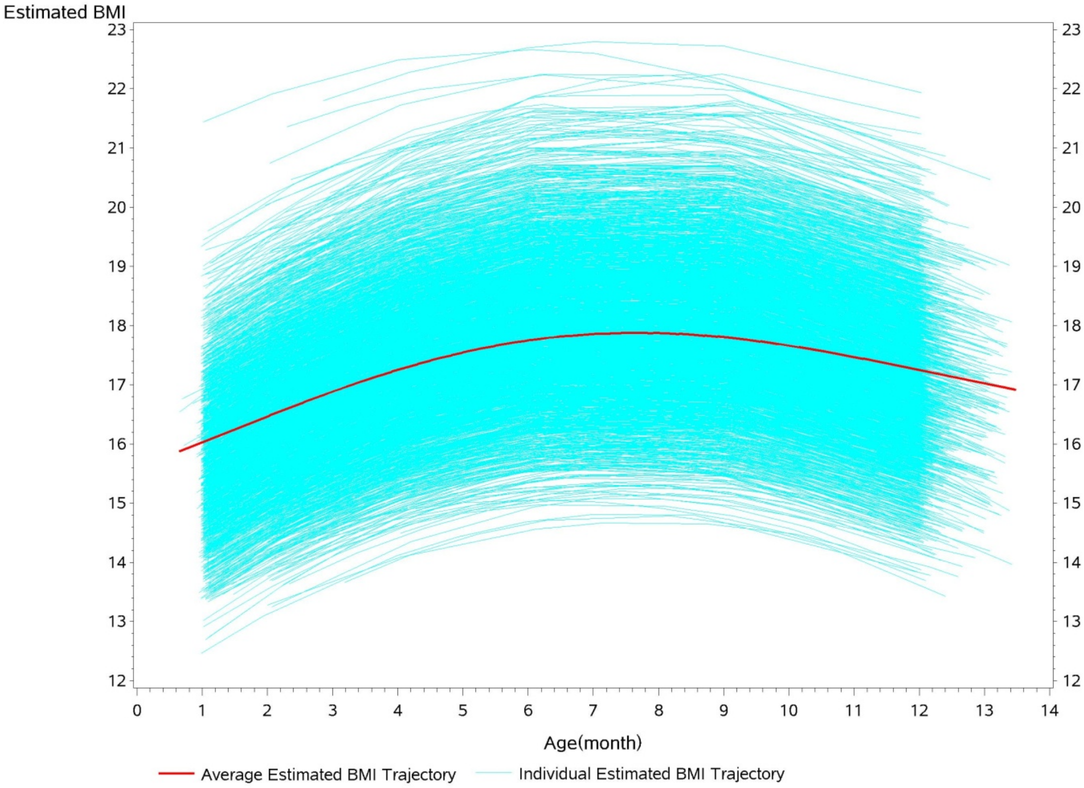
| Characteristics | n | Included, n (%) | Excluded, n (%) |
|---|---|---|---|
| Total number | 7074 | 2268(32.1) | 4806(67.9) |
| Gender | | | |
| Male | 3468 | 1126 (49.6) | 2342 (48.7) |
| Female | 3606 | 1142(50.4) | 2464 (51.3) |
| Birth weight | | | |
| <4.0kg | 6609 | 2108(92.9) | 4501 (93.7) |
| ≥4kg | 465 | 160 (7.1) | 305(6.3) |
| Maternal Age | | | |
| >35y | 570 | 176 (7.8) | 394 (8.2) |
| ≤35y | 6504 | 2092(92.2) | 4412(91.8) |
| Total number with data at age 2y | **1949** | **1949 (85.9)**[a] | **2282 (47.4)** |
| Total number of overweight and obese at age 2y | 751 | 330 (16.9) | 421 (18.4) |
| Total number of obese at age 2y | 99 | 44 (2.3) | 55(2.4) |

a.P<0.05
Chi-square tests were used to examine the differences between includedor excluded group.

**Supplemental Table 2: Correlation matrix of infancy BMI characteristics**

| | Age of BMI Peak, mo | Pre-peak velocities, kg/m2/mo |
|---|---|---|
| Magnitude of BMI peak, kg/m2 | 0.03 | 0.654** |
| Age of BMI Peak, mo | | 0.09** |

Significance is noted as: ** p⩽0.01.




**Supplemental Figure1 Infant Estimated BMI trajectory by polynomial regression model**

**STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology***
**Checklist for cohort, case-control, and cross-sectional studies (combined)**

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 1 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 2 |
| Objectives | 3 | State specific objectives, including any pre-specified hypotheses | 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 3-4,Figure1 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 5 |
| | | (*b*)*Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | 5 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5-8 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 6-8 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 6 |
| Study size | 10 | Explain how the study size was arrived at | 6,Figure 1 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 8 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 8-9 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 8 |
| | | (*c*) Explain how missing data were addressed | 6 |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed | 6 |

| | | | |
|---|---|---|---|
| | | *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Figure 1 |
| | | (b) Give reasons for non-participation at each stage | 6 |
| | | (c) Consider use of a flow diagram | Figure 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Table 1,Supplemental Table 1 |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | 5 |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | 8 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Table 3 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 8 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 11 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 11 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 11-12 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 13 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 15 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.