Original Article

Reproductive and Developmental Medicine®

# Macrosomia is associated with overweight in childhood: a follow-back of a cohort established in the early years of the obesity epidemic

Temitayo Adebile[1], Amarachukwu F. Orji[1,2], Felix Twum[3], Jian Zhang[1,*]



## Abstract

**Objective:** Interventions currently recommended to control and prevent obesity have not been successful. Recent research has shifted toward the transgenerational cycle of obesity. We assessed the association between fetal macrosomia and early childhood body weight.

**Methods:** We conducted a follow-back study to link birth certificate data to the Third National Health and Nutrition Examination Survey (1988–1994) of 2621 United States-born singletons aged 2–6 years. Birth weight and gestational age data were collected from birth certificates. Fetal macrosomia was defined as ≥90th percentile of gestational age-race-sex-parity specific body weight distribution in 1989 vital statistics.

**Results:** With 12.7% (standard error = 0.85%) of participants born macrosomic, the prevalence of obesity and overweight (BMI percentiles ≥85th in the CDC growth chart) among children was 17.8% (1.17%). When the body weight was measured against age-sex-specific height (BMI percentiles), macrosomia was significantly associated with overweight and obesity (odds ratio [OR] = 1.64, 95% confidence interval = 1.07–2.50) adjusted for family income, maternal age and marital status, race, maternal smoking during pregnancy, and breastfeeding. The association became insignificant after adjusting for postnatal lifestyle and parental body mass index (OR = 1.38 [0.84-2.26]]. When body weight was measured against age, children who were too heavy for their age were more likely to be born macrosomically (OR = 2.64 [1.66-4.22]) than their peers with healthy age-specific body weight.

**Conclusion:** Fetal macrosomia was significantly associated with a doubled risk of heavy body weight in children aged 2–6 years.

**Keywords:** Obesity, Fetal macrosomia, Large for gestational age, NHANES, Birth certificate

## Introduction

The prevalence of obesity is increasing rapidly, especially among children and adolescents in the United States[1] and other countries[2]. Societal strategies implemented to oppose COVID-19 further exacerbated the obesity epidemic and worsened obesity-linked metabolic comorbidities[3], further highlighting the urgent need to curb the obesity epidemic[4–6]. Most interventions currently recommended to control and prevent obesity were unsuccessful, as already concluded before the pandemic[7,8]. Research efforts have recently been directed towards the "first 1000 days" of life[9,10] and the transgenerational cycle of obesity[11–13]. The prevalence of obesity has increased significantly in women of reproductive age in conjunction with an overall soaring trend. Overweight and obesity during pregnancy are causally associated with fetal overnutrition, leading to increased birth weight and macrosomia[14,15]. Macrosomia may persist throughout childhood and be carried into reproductive age, transmitting obesogenic momentum across generations[16]. Breaking the transgenerational cycle, if confirmed as a causal connection, may be the key to curbing or reversing the inexorable upward obesity trend in both developed and developing countries.

Studies have described fetal macrosomia and childhood obesity in Germany[17], the Netherlands[18], other European countries[19], and China[20–22]. However, no relevant studies have been reported on children born in the United States, where childhood obesity has become a major public health challenge. The lack of gestational age-and race/ethnicity-appropriate definitions of macrosomia may be the chief reason. It is increasingly recognized that race/ethnic-specific cutoffs are crucial in obesity-related research to ensure that interventions are targeted equitably from biological and clinical standard points[23,24]. With healthy body weight typically defined by the percentile of age-sex-specific distributions of pediatric reference populations, it is desirable to categorize the fetus/infant as large for gestational age (LGA) or macrosomia according to gestational age among ethnicity-specific reference populations[25,26]. Previous studies defined macrosomia as birth weight equal to or exceeding 4000 g (8 pounds,

[1]Department of Epidemiology, Jiann-Ping Hsu College of Public Health, Georgia Southern University, Statesboro, GA 30460, USA; [2]Department of Global and Community Health, College of Health and Humanities, George Mason University, Fairfax, VA 22030, USA; [3]School of Health Professions, The University of Southern Mississippi, Hattiesburg, MS 39406, USA.

*Corresponding to: Jian Zhang, Jiann-Ping Hsu College of Public Health, Georgia Southern University, PO Box 8015, Statesboro, GA 30460, USA. E-mail: jianzhang@georgiasouthern.edu



Reproductive and Developmental Medicine (2023) 7:4

**Received:** 22 February 2023 **Accepted:** 25 April 2023

http://dx.doi.org/10.1097/RD9.0000000000000067

12 ounces)[20,27,28] or 4500 g (9 pounds, 14 ounces)[29]. These thresholds are useful for medical decision-making regarding operative delivery. However, from a public health perspective, they may not be applicable for identifying preterm fetuses with macrosomia. Thresholds using the 90th percentile of sex-specific distributions[17,21] also fail to consider gestational age and suffer from compromised statistical power for population-wide disease burden assessments[27]. With age-sex-race specifically gestational cutoffs to define fetal macrosomia and a hypothesis generated from previous studies that fetal macrosomia is associated with obesity in early childhood[17–21], we searched for the missing pieces of the puzzle regarding the association in more racially and ethnically diverse populations of US-born children aged 2–6 years.

## Materials and methods

### *Study population*

We retrospectively linked natality data to the 3rd National Health and Nutrition Examination Survey (NHANES III), a cross-sectional survey of US civilians living in households conducted from 1988 to 1994. Because BMI-for-age, the parameter used to define overweight and obesity from the CDC growth chart, is only available for children older than 2 years[30], we excluded children younger than 24 months. Children admitted to neonatal intensive or transitional care facilities for more than 2 weeks were also excluded because they may have received excessive antibiotics, creating unmeasurable confounding effects on the association of interest. After exclusion for several reasons, 2621 children were included in the final analysis (Fig. 1). The NHANES protocol was reviewed and approved by the Institutional Review Board of the National Center for Health Statistics. As the NHANES III data are both publicly available and de-identified, this analysis was exempt from approval by the Institutional Review Boards of the authors' institutions.

### *Race-sex-specific birthweight categories by gestational age*

Variables obtained from birth certificates included birth plurality (singleton or twin), birth order, birth weight (g), and length of gestation (weeks). As in previous studies using the linked file, gestational length from the mother's last menstrual period was examined for completeness and validity[31,32]. To improve race/ethnicity and sex specificity, and comparability with the definition of healthy body weight, which uses percentiles rather than absolute values of the reference population, we calculated birthweight-for-gestational-age against more demographic characteristics, including race (White, Black, and Mexican American), sex (boys *vs.* girls), and maternal parity (primiparas *vs.* multiparas), based on the 1989 vital statistics[33,34]. Small-for-gestational-age, indicating intrauterine growth retardation, was defined as birthweight-for-gestational-age below the race-sex-specific 10$^{th}$ percentile, appropriate-for-gestational age from the race-sex-specific 10$^{th}$ to 89$^{th}$ percentile, and LGA or fetal macrosomia at or above the race-sex specific 90$^{th}$ percentile.

### *Childhood overweight/obesity and growth retardation*

Trained technicians collected the anthropometric data following a standard protocol. Using a computerized formula derived from the 2000 CDC Growth Charts[30], we translated measured weight and height to sex- and age-specific BMI percentiles and

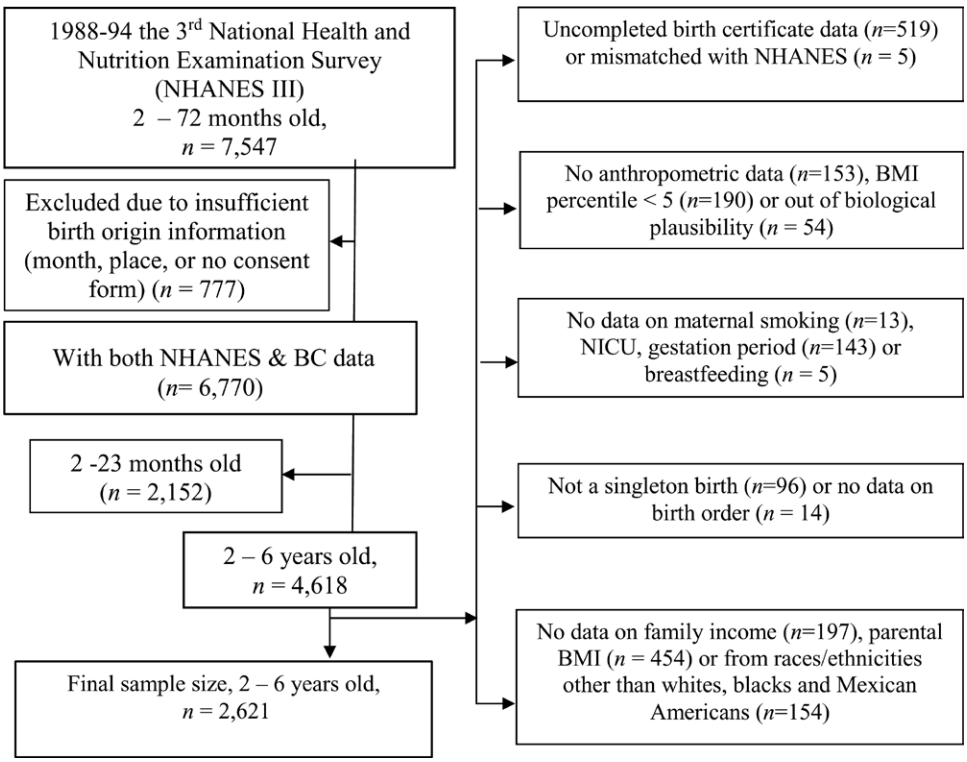


**Fig. 1.** Flow chart of the study population. BC: birth certificate; BMI: body mass index; NHANES: the National Health Examination and Nutrition Survey; NICU: neonatal intensive care unit. Children admitted to NICU or transitional care facilities for more than 2 weeks were excluded in conjunction with other criteria, mainly, due to BMI percentiles out of biological plausibility.

categorized children as obese if they had sex- and age-specific BMI ≥ the 95$^{th}$ percentile, as overweight if the 95$^{th}$ ≥ BMI percentiles > the 85$^{th}$ percentile, and as healthy weight if 85$^{th}$ ≥ BMI percentiles >5$^{th}$. Children with overweight and obesity were combined as overweight to stabilize the estimation and simplify the presentation. Children with BMI <5$^{th}$ were categorized as underweight and excluded from the main analyses because the small number of underweight children precluded the analyses from making meaningful inferences. Corresponding to the age-sex-specific 85$^{th}$ percentile of BMI for defining overweight, we also categorized a child as "too heavy for age" using the age-sex-specific 85$^{th}$ percentile of body weight.

### *Covariates*

Covariates were selected based on the literature review. The data on covariates were obtained from a questionnaire administered to the child's parents or other adult caretakers during the NHANES survey. Maternal smoking status during pregnancy was recorded on birth certificates. However, most mothers declined to respond to smoking-related questions due to the recency effect. Therefore, the smoking status during pregnancy was ascertained in the NHANES. Breastfeeding was classified as yes or no, regardless of breastfeeding duration. The NHANES III classifies participants based on their responses as White, Black, Mexican American, or other. Because the sample size of the "other" category is small, we did not report results for this category. Total family income for the previous 12 months was reported for each category. The poverty-to-income ratio was calculated by comparing the midpoint of the selected income range with the appropriate poverty threshold based on family size and composition. The educational level of the household head represented the highest grade that he or she had completed, regardless of age. Maternal marital status was divided into three categories: never married, currently married with spouses living in the household, and previously married (mothers who were married but their spouses were not living in the household, widowed, divorced, or separated).

Postnatal factors included daily food energy, percentage of kilocalories from total fat, and the pattern of skipping breakfast[35]. Parental body size, measured during NHANES interviews and physical examinations, was used as a proxy for body weight-related genetic predisposition; they are also a good indicator of an obesogenic home environment[36]. Parental BMI was classified as underweight (<18.5 kg/m$^2$), normal weight (18.5–24.9 kg/m$^2$), overweight (25.0–29.9 kg/m$^2$), and obese (≥30.0 kg/m$^2$). Parents with normal weight were used as references and maternal and paternal body size indicators were included separately in the regression models. A single 24-hour diet recall interview was administered to the children's mothers by a trained dietary interviewer using the Dietary Data Collection System. The interviewees were asked to report all foods and beverages consumed during the previous day, spanning 24 hours from midnight to midnight. Data retrieval for daycare and school lunches was carefully planned and executed. The food database was linked to the US Department of Agriculture's Survey Nutrition Database and produced an estimate of the daily total energy intake and the percentage of kilocalories of total fat. Whether a child skipped breakfast was also assessed during a 24-hour diet recall interview[37].

### *Analytical procedures*

With the appropriate weighting and nesting variables accounting for different sample weights and the effects of the complex sample design on variance estimation, we utilized SAS (Version 9.4, Research Triangle Park, NC, USA) to account for the estimates of the weighted study populations and associated standard errors (SE) for each sociodemographic stratum. Using the PROC SURVEYLOGISTIC procedure, we calculated the adjusted odds ratios (ORs) with 95 percent confidence intervals (CIs) of exposure to macrosomia and used the Wald test to determine whether the odds of exposure significantly differed between children with normal weight and those with overweight/obesity. The ORs were hierarchically adjusted in the saturated models to demonstrate the impact of each additional group of variables on the estimations. As there was no significant interaction between macrosomia and the gestational stage, the latter was included as a covariate rather than a stratifying variable. The final multivariable regressions included no other interaction terms to avoid over-specification of the models. Sensitivity analyses were performed to ensure that the main conclusion was not biased by excluding the study participants. All 4618 children aged 2–6 years were included in sensitivity analyses regardless of missing values. Statistical significance was set at $P$ <0.05. We did not use the –2 Log-Likelihood test to simplify regression models. Instead, all the potential confounders were retained in the final adjusted model.

## Results

The prevalence of obesity and overweight combined among children was 17.8% (SE = 1.17%) at age 2–6 years; approximately 14% of parents were with obesity, and more than 40% of mothers were overweight (Table 1) when NHANES was conducted between 1988 and 1994. Less than 10% of the children were born with a small weight for gestational age, and 12.7% (0.85%) were macrosomic. Children with overweight in early childhood were more likely to be born macrosomically than children with healthy body weight, 18.61% *vs.* 11.40%, respectively (Table 2). Children with obese mothers were more likely to be born with macrosomia than children with healthy mothers. The percentages of fetal macrosomia were 10.0% (0.94%) and 17.2% (2.30%) in mothers with healthy weight and obesity, respectively. Mothers aged 35 years or older were twice as likely to give birth to an infant with macrosomia than were mothers younger than 20 years.

Anthropometric measurements collected after the second birthday were associated with more factors than birthweight did. Children of Mexican Americans and Blacks from low-income families, with obese parents, were more likely to have excessive body weight measured by BMI percentiles during early childhood. The percentage of children with overweight or obesity was 26.1% (3.88%) in children who were born with fetal macrosomia, 17.4% (1.19%) in children who were born with normal weight, and 9.81% (3.00%) for infants with small-for-gestational-age (data not shown). Macrosomic infants were more likely than their peers with appropriate birthweight to be classified as "heavy" during early childhood (33.8% [3.53%] *vs.* 15.5% [1.11%]).

When the body weight was measured against body height, expressed as BMI percentile, the association between macrosomia and overweight was suggestive with statistical insignificance after adjusting for postnatal lifestyle and parental BMI; the OR was 1.38 with a 95% CI of (0.84–2.26) (Table 3). Macrosomia, however, was found to be associated with the risk of being "too heavy for age," and the association remained statistically significant after the hierarchical adjustment of a large array of factors. Compared to children with appropriate body weights for age,

**Table 1.**

**Characteristics of the study population sample of 2621 children aged 2–6 years, NHANES 1988–1994.**

| Characteristic* | Level | % (SE)† | *n*† | Weighted population |
|---|---|---|---|---|
| Children's | | | | |
| Child's age (in the month) at survey | 60+ m | 26.2 (1.31) | 615 | 2,348,684 |
| | 48–59 m | 22.6 (1.03) | 613 | 2,021,622 |
| | 36–47 m | 25.8 (1.22) | 674 | 2,308,675 |
| | <36 m | 25.4 (0.96) | 719 | 2,271,989 |
| Child's sex | Girls | 46.7 (1.11) | 1303 | 4,177,214 |
| Body mass index at age 2–6 years | Overweight‡ | 17.8 (1.17) | 529 | 1,589,120 |
| Birth weight | Macrosomia§ | 12.7 (0.85) | 326 | 1,135,034 |
| Race-ethnicity | Whites | 74.8 (1.43) | 958 | 6,696,282 |
| | Blacks | 16.2 (1.36) | 844 | 1,449,638 |
| | Mexican Americans | 8.99 (0.82) | 819 | 805,051 |
| Family and parental characteristics | | | | |
| Mother's body mass index level‖ | Obese | 14.2 (1.21) | 524 | 1,273,581 |
| | Overweight | 18.0 (1.24) | 617 | 1,611,785 |
| Father's body mass index level | Obese | 13.9 (0.95) | 421 | 1,245,570 |
| | Overweight | 43.1 (1.74) | 1134 | 3,854,143 |
| Family income¶ | High | 27.6 (1.52) | 463 | 2,472,087 |
| | Middle | 42.3 (1.49) | 972 | 3,782,825 |
| | Low | 30.1 (1.63) | 1186 | 2,696,059 |
| Family head's marital status | Never | 6.54 (0.67) | 312 | 585,672 |
| | Previously | 13.8 (1.32) | 371 | 1,236,979 |
| | Currently | 79.6 (1.43) | 1938 | 7,128,320 |
| Perinatal parameters | | | | |
| Mothers smoked while pregnant | Yes | 24.4 (1.35) | 530 | 2,183,665 |
| Gestational stage§ | Pre-term | 8.12 (0.69) | 267 | 727,133 |
| Breastfeeding | Yes | 55.5 (1.68) | 1207 | 4,966,212 |
| Received newborn intensive care | Yes | 10.8 (1.15) | 279 | 966,810 |

*The characteristics were assessed between the years 1988 to 1994 unless otherwise indicated.

†Presented as percentages (standard error). *n* is unweighted, but the % and standard error are weighted.

‡Children were classified as obese based on sex-age-specific BMI ≥ the 95th percentile of the reference populations.

§Information was extracted from birth certificates. Small-for-gestational-age was defined as a weight-for-gestational-age below the 10th percentile, appropriate-for-gestational-age from the 10th to the 89th percentile, and large-for-gestational-age or macrosomia at or above the 90th percentile.

‖Parental BMI was classified as underweight (<18.5 kg/m$^2$), normal weight (18.5–24.9 kg/m$^2$), overweight (25.0–29.9 kg/m$^2$), and obese (≥30.0 kg/m$^2$).

¶Based on the Poverty Index Ratio (PIR), respondents were categorized as low-income (PIR < 1.30, the federal cutoff point for eligibility for the Food Stamp Program when the NHANES III was conducted), middle-income (1.30 ≤ PIR < 3.00), and high income.

too-heavy children were twice more likely to be born macrosomic (OR = 95% with CI = 1.66–4.22). No significant interaction was found between birth weight and children's age or gestational stage in relation to body weight or height. Sensitivity analyses, including underweight children and other outliers excluded in the main analyses, did not change the estimates for the association between fetal macrosomia and being too heavy for age; the OR decreased but remained statistically significant, from 2.64 (1.66–4.22) to 1.73 (1.09–2.74).

## Discussion

As the first study using a race/ethnicity-specific definition of fetal macrosomia, we found that fetal macrosomia was significantly associated with a doubled risk of being too heavy for age in children aged 2–6 years. This association was independent of prenatal and postnatal factors, including parental BMI. On the edge of significance, children with fetal macrosomia had an increased risk of overweight and obesity in early childhood.

To the best of our knowledge, this is the first study to examine the association between fetal macrosomia and the risk of obesity in the early life of US-born children. Results from our main effects model are comparable to the results of studies that have been conducted in other countries[17–21,23]. In a study of 1767 Chinese children, the risk of being overweight in children under three years was quadrupled in macrosomic babies compared to children born with appropriate birth weight for gestational age[20]. The risk of obesity (measured by BMI percentile) also failed to reach statistical significance with a risk ratio of 1.64 (0.89–3.00) in Chinese children. In the IDEFICS study examining 10,468 children aged 6.0 ± 1.8 years from eight European countries, Sparano *et al.* found that fetal macrosomia was independently associated with childhood overweight and obesity in the absence of gestational or maternal diabetes[19]. The generalizability of the Chinese study might be questionable because the clinical reliability of anthropometrics has not yet been well established among children aged < 2 years[38] and the interval between birth and the endpoint was too short to extrapolate long-term implications[28]. The major criticism of existing literature testing the "fetal origins hypothesis" is the potential confounding from postnatal factors[39,40], severely clouding the conclusion's validity. Schellong *et al.* performed a meta-analysis to address these limitations, including 643,902 persons aged 1–75 years. The OR of high birthweight (≥4000 g) associated with increased risk of overweight in the meta-analysis was 1.66 (1.55–1.77) in the random-effects model and 1.61 (1.57–1.65) in the fixed-effects model, comparable to the OR estimated in the current report before adjusting for parental BMI and other home obesogenic factors, the limitations shared by most of the previous studies.

Schellong's meta-analysis defined birthweight ≥4000 g as fetal macrosomia; our findings were based on multi-ethnic populations with ethnic-specific cutoffs. The current study had several strengths. Parental BMI explained the largest portion of the variance in child fatness[17,18,41]. Between infancy and ages 3–5 years, food consumption patterns probably have a crucial

**Table 2.**

**Characteristics of the study population by birthweight status, sample of 2 621 children aged 2 - 6 years, NHANES 1988-1994.**

| | | Macrosomia | | Normal | | Small | | |
|---|---|---|---|---|---|---|---|---|
| **Characteristic*** | **Level** | ***n*†** | **Row %(SE)†** | ***n*†** | **Row %(SE)†** | ***n*†** | **Row %(SE)†** | ***P*‡** |
| Body weight | Healthy weight | 245 | 11.40 (0.84) | 1636 | 78.12 (1.09) | 211 | 10.48 (0.99) | 0.003 |
| | Overweight§ | 81 | 18.61 (2.80) | 415 | 76.11 (2.92) | 33 | 5.28 (1.73) | 0.003 |
| Child's sex | Male | 159 | 10.6 (1.11) | 1052 | 80.1 (1.44) | 107 | 9.36 (1.27) | 0.07 |
| | Female | 167 | 15.1 (1.56) | 999 | 75.1 (1.70) | 137 | 9.78 (1.26) | |
| Race-ethnicity | Whites | 120 | 12.7 (1.15) | 743 | 77.3 (1.30) | 95 | 10.1 (1.22) | 0.32 |
| | Blacks | 113 | 13.1 (1.08) | 666 | 79.8 (1.23) | 65 | 7.10 (0.74) | |
| | Mexican Americans | 93 | 12.1 (1.28) | 642 | 78.0 (2.02) | 84 | 9.84 (1.48) | |
| Family income | High | 74 | 15.9 (2.25) | 350 | 77.2 (2.35) | 39 | 6.96 (1.51) | 0.07 |
| | Middle | 108 | 10.0 (1.54) | 780 | 80.3 (1.81) | 84 | 9.62 (1.62) | |
| | Low | 144 | 13.5 (1.40) | 921 | 74.7 (2.13) | 121 | 11.8 (1.80) | |
| Mother's BMI | Normal | 157 | 11.0 (1.10) | 1175 | 78.7 (1.10) | 148 | 10.3 (1.05) | 0.02 |
| | Overweight | 86 | 14.0 (1.94) | 485 | 78.7 (2.82) | 46 | 7.28 (1.81) | |
| | Obese | 83 | 19.2 (2.26) | 391 | 71.9 (3.04) | 50 | 8.85 (2.34) | |
| Father's BMI | Normal | 117 | 10.0 (0.94) | 844 | 80.6 (1.30) | 105 | 9.33 (1.17) | 0.04 |
| | Overweight | 152 | 13.9 (1.52) | 885 | 76.3 (1.67) | 97 | 9.80 (1.30) | |
| | Obese | 57 | 17.2 (2.30) | 322 | 73.3 (2.75) | 42 | 9.52 (2.03) | |
| Mother's age at delivery‖ | 35+ | 34 | 16.7 (4.04) | 131 | 77.1 (3.74) | 16 | 6.18 (2.59) | 0.05 |
| | 20–35 | 254 | 12.9 (1.06) | 1642 | 77.9 (1.10) | 185 | 9.22 (0.90) | |
| | <20 | 38 | 7.78 (2.13) | 278 | 77.2 (2.44) | 43 | 15.0 (2.71) | |
| Gestational stage‖ | Full-term | 252 | 11.7 (1.01) | 1885 | 79.0 (1.06) | 217 | 9.31 (0.89) | 0.003 |
| | Pre-term | 74 | 23.6 (4.68) | 166 | 64.1 (4.72) | 27 | 12.4 (3.25) | |
| Smoke while pregnant | No-smoker | 297 | 15.1 (1.20) | 1626 | 77.3 (1.27) | 168 | 7.55 (0.99) | <0.001 |
| | Smoker | 29 | 5.11 (1.39) | 425 | 79.1 (2.71) | 76 | 15.8 (2.29) | |
| Breastfeeding | Less than 6 months | 84 | 11.6 (1.61) | 558 | 77.7 (1.86) | 68 | 10.6 (2.04) | 0.03 |
| | Never | 169 | 12.0 (1.19) | 1095 | 76.5 (1.85) | 150 | 11.6 (1.66) | |
| | More than 6 months | 73 | 15.3 (2.02) | 398 | 80.1 (2.66) | 26 | 4.53 (1.25) | |

NHANES: the National Health Examination and Nutrition Survey; SE: standard error.

*The characteristics were assessed between the years 1988 and 1994 unless otherwise indicated.

†Presented as percentages (standard error). *n* is unweighted, but the % and standard error are weighted.

‡The test statistics were t-tests (unequal variances) for continuous variables and chi-square for categorical variables.

§Children were classified as obese based on sex-age-specific BMI ≥ the 95th percentile of the reference populations.

‖The information was extracted from birth certificates.

impact on weight status[17,41], maternal smoking during pregnancy, and breastfeeding status, all of which influence growth during early childhood[32]. However, most previous studies have failed to adjust for these covariates simultaneously. Some studies did not consider maternal smoking[17,20], whereas others did not consider parental BMI[42]. The richness of the data collected reliably in the NHANES allowed the current analyses to adjust for major potential confounders for robust estimations.

This study has some limitations. Nationally representative data were collected during the early stages of the obesity epidemic. Although the biological relationship revealed in the current report may be time independent, the population-attributable risk may have changed substantially owing to the rapid evolution of the obesity epidemic. Adjustments are needed when estimating the population-attributable risk of fetal macrosomia towards childhood obesity. The overall prevalence of various prenatal risk factors may have been underestimated since the NHANES did not sample institutionalized children because of the severe medical consequences of pregnancy-related health issues. Women who had experienced spontaneous abortions, ectopic pregnancies, or stillbirths were excluded. These women may be at an elevated risk of giving birth to babies of abnormal weight. Perinatal maternal morbidity was not included and residual confounding effects could not be ruled out. The response rates differed according to sociodemographic status. The children included and those who were excluded differed in mothers' educational attainment, age, and marital status. The number of children ($n$ = 2621) included in this study was much smaller than the total samples ($n$ = 4618). Caution must be exercised when generalizing the conclusions of the current report. Smoking history, breastfeeding, and other key information were assessed retrospectively via self-report interviews and were thus subject to social desirability bias. Approximately 90% of the interviewees were biological mothers in the NHANES 1988–1994[43]; the current study failed to exclude proxies other than biological mothers, such as fathers or other caregivers. No repeated measurements are available to describe the dynamics of related behaviors, including parental BMI and the socioeconomic status of the family, to characterize the timing or relative weight at which adiposity rebounds may occur, and the contribution of these time-dependent patterns to the development of overweight cannot be evaluated. When statistical power is allowed, the analyses should be stratified by race and ethnicity in future studies. Mendelian randomization should be applied when genomic data are available to examine the causal effects in observational studies.

The results of our study, together with others[17–21], indicate that overnutrition manifested by fetal macrosomia persisted and carried obesogenic momentum across generations. Salihu *et al.* recently reported that the rate of fetal macrosomia declined by almost 10% over the previous five decades[44], intuitively contradicting the hypothesis that macrosomia might be pivotal in the transgenerational cycle of obesity. However, Salihu *et al.* used birthweight ≥4000 g to define fetal macrosomia without stratification by gestational age; the unified definition may fail to capture transgenerational momentum in the absence of race-sensitive and gestational age-adjusted definitions, given the high prevalence of preterm births[45]. Underestimation may occur more significantly in populations of color, among which both obesity and preterm birth are inappropriately higher[24,46].

**Table 3.**

**Hierarchically adjusted odds ratio (95% confidence interval) of overweight sample of 2 621 children aged 2 - 6 years, NHANES 1988-1994.**

| | N with valid data and included in regressions | Heavy for height and age (overweight) at age 2–6 years | | | | Heavy for age at age 2–6 years | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Number of | OR (95% CI) of overweight | | | Number of | OR (95% CI) of overweight | | |
| Hierarchical adjustment steps | Used in regression† | Overweight* †(Unweighted sample size) | Large for gestational age (macrosomia) | Appropriate for gestational age | Small for gestational age | Heavy for age (Unweighted sample size) | Large for gestational age (macrosomia) | Appropriate for gestational age | Small for gestational age |
| Crude | 2621 | 529 | 1.68 (1.13–2.48) | 1.00 (reference) | 0.52 (0.26–1.02) | 495 | 2.77 (1.88–4.09) | 1.00 (reference) | 0.21 (0.11–0.40) |
| Age and sex of children‡ | 2621 | 529 | 1.62 (1.09–2.42) | 1.00 (reference) | 0.50 (0.25–1.01) | 495 | 2.76 (1.87–4.09) | 1.00 (reference) | 0.21 (0.11–0.41) |
| Age, sex, and race (ASR) | 2621 | 529 | 1.64 (1.09–2.44) | 1.00 (reference) | 0.50 (0.25–1.01) | 495 | 2.78 (1.87–4.14) | 1.00 (reference) | 0.21 (0.11–0.41) |
| ASR, income, and education (household head) | 2621 | 529 | 1.72 (1.14–2.57) | 1.00 (reference) | 0.49 (0.25–0.96) | 495 | 2.84 (1.90–4.24) | 1.00 (reference) | 0.22 (0.11–0.42) |
| ASR, Income, education, Marital status of household head (ASRIM) | 2621 | 529 | 1.71 (1.14–2.58) | 1.00 (reference) | 0.49 (0.25–0.96) | 495 | 2.84 (1.90–4.24) | 1.00 (reference) | 0.22 (0.11–0.42) |
| ASRIM, mother's age at birth (ASRIMA) | 2621 | 529 | 1.71 (1.13–2.58) | 1.00 (reference) | 0.49 (0.25–0.96) | 495 | 2.78 (1.83–4.24) | 1.00 (reference) | 0.22 (0.12–0.43) |
| ASRIMA, breastfeeding | 2621 | 529 | 1.71 (1.14–2.59) | 1.00 (reference) | 0.47 (0.24–0.94) | 495 | 2.78 (1.83–4.21) | 1.00 (reference) | 0.22 (0.11–0.42) |
| ASRIMA, breastfeeding, maternal smoking during the pregnancy. | 2621 | 529 | 1.68 (1.11–2.54) | 1.00 (reference) | 0.48 (0.24–0.96) | 495 | 2.82 (1.87–4.26) | 1.00 (reference) | 0.22 (0.11–0.42) |
| ASRIM, breastfeeding, maternal smoking, and gestational stage§ | 2621 | 529 | 1.64 (1.07–2.50) | 1.00 (reference) | 0.48 (0.24–0.95) | 495 | 2.84 (1.89–4.28) | 1.00 (reference) | 0.22 (0.11–0.42) |
| ASRIM, breastfeeding, maternal smoking, gestational stage, and lifestyle‖ | 2365 | 469 | 1.56 (0.96–2.53) | 1.00 (reference) | 0.54 (0.27–1.08) | 433 | 2.89 (1.81–4.61) | 1.00 (reference) | 0.24 (0.12–0.47) |
| ASRIM, breastfeeding, maternal smoking, gestational stage, lifestyle, and parental BMI | 2365 | 469 | 1.38 (0.84–2.26) | 1.00 (reference) | 0.54 (0.26–1.10) | 433 | 2.64 (1.66–4.22) | 1.00 (reference) | 0.23 (0.12–0.46) |

ASR: Age, Sex and Race; ARSIM: Age, Sex, Race, Income of family, and Marital status of household head; CI: confidence interval; NHANES: the National Health Examination and Nutrition Survey; OR: odds ratio; SE: standard error.

*Children were classified as overweight or obese based on sex- age-specific BMI ≥ the 95$^{th}$ percentile of the reference populations.

†Children with missing values for variables other than well-established risk factors were included in the analyses to retain statistical power. The regression automatically excluded these children when variables with missing values were introduced on the right side of the regression in the hierarchical steps.

‡Sex was also considered when defining large-for-gestational age (macrosomia), appropriate-for-gestational age, and small-for-gestational age, as race- and sex-specific percentiles were used.

§The gestational stage was dichotomized as pre-term (<37 weeks) or termed (≥37 weeks).

‖The lifestyle indicators included (1) total dietary intake, (2) energy percentage of fat, and (3) skipping breakfast.

The current analysis confirmed the temporality of the causal relationship between macrosomia and obesity using race- and sex-specific percentiles rather than one cutoff value of birth weight for all newborns. Appreciation of the vicious trans-generational cycle is of great implication; preventing *in utero* over-nutrition and weight gain during pregnancy could be a promising strategy to break the vicious cycle and mitigate the risks for subsequent generations, particularly among the population of color.

## Acknowledgments

None.

## Author contributions

J.Z. conceptualized and designed the study. T.A. and A.F.O. carried out the data analysis and drafted the manuscript. T.A., A.F.O., F.T, and J.Z. were involved in writing, revising, and approving the final manuscript as submitted and agreed to be accountable for all aspects of the work. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

## Funding(s)

None.

## Conflict of interest

All authors declare no conflict of interest.

## Data availability statement

The datasets generated during and/or analyzed during the current study are publicly available.

## Informed consent

Consents were obtained from all study participants and kept by the Centers of Disease Control and Prevention, USA.

## Ethics approval

The NHANES protocol used in the study was reviewed and approved by the National Center for Health Statistic's Institutional Review Board (IRB). As the NHANES III data used in this study are both publicly available and de-identified, this analysis was considered by the Georgia Southern University IRB as exempt from approval. The Georgia Southern University IRB committee also exempted this study from receiving informed consent.

## References


[1] Lange SJ, Kompaniyets L, Freedman DS, *et al*.; DNP3. Longitudinal trends in body mass index before and during the COVID-19 pandemic among persons aged 2-19 years - United States, 2018-2020. MMWR Morb Mortal Wkly Rep 2021;70:1278–1283. doi:10.15585/mmwr.mm7037a3.

[2] Gwag SH, Oh YR, Ha JW, *et al*. Weight changes of children in 1 year during COVID-19 pandemic. J Pediatr Endocrinol Metab 2021;35(3):297–302. doi:10.1515/jpem-2021-0554.

[3] Clemmensen C, Petersen MB, Sørensen TIA. Will the COVID-19 pandemic worsen the obesity epidemic? Nat Rev Endocrinol 2020;16:469–470. doi:10.1038/s41574-020-0387-z.

[4] Rodriguez F, Solomon N, de Lemos JA, *et al*. Racial and ethnic differences in presentation and outcomes for patients hospitalized with COVID-19: Findings from the American Heart Association's COVID-19 cardiovascular disease registry. Circulation 2021;143:2332–2342. doi:10.1161/CIRCULATIONAHA.120.052278.

[5] Le Guen CL, King NA, Zhao H, *et al*. COVID-19 patients with obesity at risk for worse outcomes despite younger age and fewer inflammatory derangements. Surg Obes Relat Dis 2021;17:1722–1730. doi:10.1016/j.soard.2021.06.006.

[6] Foulkes AS, Selvaggi C, Shinnick D, *et al*. Understanding the link between obesity and severe COVID-19 outcomes: causal mediation by systemic inflammatory response. J Clin Endocrinol Metab 2021;107(2):e698–e707. doi:10.1210/clinem/dgab629.

[7] Zylke JW, Bauchner H. The unrelenting challenge of obesity. JAMA 2016;315:2277–2278. doi:10.1001/jama.2016.6190.

[8] Frieden TR, Ethier K, Schuchat A. Improving the health of the United States with a "winnable battles" initiative. JAMA 2017;317:903–904. doi:10.1001/jama.2017.0436.

[9] Díaz-Rodríguez M, Pérez-Muñoz C, Carretero-Bravo J, *et al*. Early risk factors for obesity in the first 1000 days-relationship with body fat and BMI at 2 years. Int J Environ Res Public Health 2021;18(15):8179. doi:10.3390/ijerph18158179.

[10] Wallander JL, Berry S, Carr PA, *et al*. Patterns of risk exposure in first 1,000 days of life and health, behavior, and education-related problems at age 4.5: evidence from Growing Up in New Zealand, a longitudinal cohort study. BMC Pediatr 2021;21:285. doi:10.1186/s12887-021-02652-w.

[11] Aiken CE, Ozanne SE. Transgenerational developmental programming. Hum Reprod Update 2014;20:63–75. doi:10.1093/humupd/dmt043.

[12] Vickers MH. Developmental programming and transgenerational transmission of obesity. Ann Nutr Metab 2014;64(Suppl 1):26–34. doi:10.1159/000360506.

[13] Yang H, He B, Yallampalli C, *et al*. Fetal macrosomia in a Hispanic/Latinx predominant cohort and altered expressions of genes related to placental lipid transport and metabolism. Int J Obes 2020;44(8):1743–1752. doi:10.1038/s41366-020-0610-y.

[14] Agudelo-Espitia V, Parra-Sosa BE, Restrepo-Mesa SL. Factors associated with fetal macrosomia. Rev Saude Publica 2019;53:100. doi:10.11606/s1518-8787.2019053001269.

[15] Kaseva N, Vääräsmäki M, Matinolli HM, *et al*. Pre-pregnancy overweight or obesity and gestational diabetes as predictors of body composition in offspring twenty years later: evidence from two birth cohort studies. Int J Obes 2018;42(4):872–879. doi:10.1038/ijo.2017.277.

[16] Yang ST, Liu CH, Wang PH. Minimizing the risk of macrosomia. J Chin Med Assoc 2023;86(5):536–537. doi:10.1097/JCMA.0000000000000901.

[17] Schaefer-Graf UM, Pawliczak J, Passow D, *et al*. Birth weight and parental BMI predict overweight in children from mothers with gestational diabetes. Diabetes Care 2005;28(7):1745–1750. doi:10.2337/diacare.28.7.1745.

[18] Welten M, Wijga AH, Hamoen M, *et al*. Dynamic prediction model to identify young children at high risk of future overweight: development and internal validation in a cohort study. Pediatr Obes 2020;15(9):e12647. doi:10.1111/ijpo.12647.

[19] Sparano S, Ahrens W, De Henauw S, *et al*. Being macrosomic at birth is an independent predictor of overweight in children: results from the IDEFICS study. Matern Child Health J 2012;17(8):1373–1381. doi:10.1007/s10995-012-1136-2.

[20] Pan XF, Tang L, Lee AH, *et al*. Association between fetal macrosomia and risk of obesity in children under 3 years in Western China: a cohort study. World J Pediatr 2019;15(2):153–160. doi:10.1007/s12519-018-0218-7.

[21] Yu Z, Sun JQ, Haas JD, *et al*. Macrosomia is associated with high weight-for-height in children aged 1-3 years in Shanghai, China. Int J Obes 2008;32(1):55–60. doi:10.1038/sj.ijo.0803765.

[22] He X, Shao Z, Jing J, *et al*. Secular trends of birth weight and its associations with obesity and hypertension among Southern Chinese children and adolescents. J Pediatr Endocrinol Metab 2022;35(12):1487–1496. doi:10.1515/jpem-2021-0430.

[23] Ntuk UE, Gill JM, Mackay DF, *et al*. Ethnic-specific obesity cutoffs for diabetes risk: cross-sectional study of 490,288 UK biobank participants. Diabetes Care 2014;37(9):2500–2507. doi:10.2337/dc13-2966.

[24] Harvey L, van Elburg R, van der Beek EM. Macrosomia and large for gestational age in Asia: one size does not fit all. J Obstet Gynaecol Res 2021;47(6):1929–1945. doi:10.1111/jog.14787.

[25] Modzelewski J, Pokropek A, Jakubiak-Proć M, *et al*. Large-for-gestational-age or macrosomia as a classifier for risk of adverse perinatal outcome: a retrospective cross-sectional study. J Matern Fetal Neonatal Med 2022;35(25):5564–5571. doi:10.1080/14767058.2021.1887127.

[26] Duryea EL, Hawkins JS, McIntire DD, *et al*. A revised birth weight reference for the United States. Obstet Gynecol 2014;124(1):16–22. doi:10.1097/AOG.0000000000000345.

[27] Langer O, Berkus MD, Huff RW, *et al*. Shoulder dystocia: should the fetus weighing greater than or equal to 4000 grams be delivered by cesarean section? Am J Obstet Gynecol 1991;165(4 Pt 1):831–837. doi:10.1016/0002-9378(91)90424-p.

[28] Schellong K, Schulz S, Harder T, *et al*. Birth weight and long-term overweight risk: systematic review and a meta-analysis including 643,902 persons from 66 studies and 26 countries globally. PLoS One 2012;7(10):e47776. doi:10.1371/journal.pone.0047776.

[29] Mikulandra F, Perisa M, Stojnić E. When is fetal macrosomia (> or = 4500g) an indication for caesarean section? Zentralbl Gynakol 1996;118(8):441–447.

[30] Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, *et al*. CDC growth charts: United States. Adv Data 2000;8(314):1–27.

[31] Hediger ML, Overpeck MD, Ruan WJ, *et al*. Birthweight and gestational age effects on motor and social development. Paediatr Perinat Epidemiol 2002;16(1):33–46. doi:10.1046/j.1365-3016.2002.00393.x.

[32] Smart SJ, Nikaj AN, Yu L, *et al*. Association between maternal smoking during pregnancy and offspring overweight in U.S.-born children. Pediatr Obes 2021;16(3):e12717. doi:10.1111/ijpo.12717.

[33] Zhang J, Bowes WA, Jr. Birth-weight-for-gestational-age patterns by race, sex, and parity in the United States population. Obstet Gynecol 1995;86(2):200–208. doi:10.1016/0029-7844(95)00142-e.

[34] Overpeck MD, Hediger ML, Zhang J, *et al*. Birth weight for gestational age of Mexican American infants born in the United States. Obstet Gynecol 1999;93(6):943–947. doi:10.1016/s0029-7844(98)00553-5.

[35] Farshchi HR, Taylor MA, Macdonald IA. Deleterious effects of omitting breakfast on insulin sensitivity and fasting lipid profiles in healthy lean women. Am J Clin Nutr 2005;81(2):388–396. doi:10.1093/ajcn.81.2.388.

[36] Johnson R, Welk G, Saint-Maurice PF, *et al*. Parenting styles and home obesogenic environments. Int J Environ Res Public Health 2012;9(4):1411–1426. doi:10.3390/ijerph9041411.

[37] National Center for Health Statistics. Plan and Operation of the Third National Health and Nutrition Examination Survey (NHANES III, 1988-94). Vital and Health Statistics. Hyattsville, MD: US Department of Health and Human Service, Public Health Service, Center for Disease Control and Prevention; 1996.

[38] Nash A, Corey M, Sherwood K, *et al*. Growth assessment in infants and toddlers using three different reference charts. J Pediatr Gastroenterol Nutr 2005;40(3):283–288. doi:10.1097/01.mpg.0000155183.54001.01.

[39] Florath I, Kohler M, Weck MN, *et al*. Association of pre- and post-natal parental smoking with offspring body mass index: an 8-year follow-up of a birth cohort. Pediatr Obes 2014;9(2):121–134. doi:10.1111/j.2047-6310.2012.00146.x.

[40] Hawkins SS, Baum CF, Rifas-Shiman SL, *et al*. Examining Associations between perinatal and postnatal risk factors for childhood obesity using

sibling comparisons. Child Obes 2019;15(4):254–261. doi:10.1089/chi.2018.0335.
[41] Hediger ML, Overpeck MD, Kuczmarski RJ, *et al*. Association between infant breastfeeding and overweight in young children. JAMA 2001;285(19):2453–2460. doi:10.1001/jama.285.19.2453.
[42] Mei Z, Grummer-Strawn LM, Scanlon KS. Does overweight in infancy persist through the preschool years? An analysis of CDC Pediatric Nutrition Surveillance System data. Soz Praventivmed 2003;48(3):161–167. doi:10.1007/s00038-003-2022-x.
[43] Zhang J, Muldoon MF, Mckeown RE, *et al*. Association of serum cholesterol and history of school suspension among school-age children and adolescents in the United States. Am J Epidemiol 2005;161(7):691–699. doi:10.1093/aje/kwi074.
[44] Salihu HM, Dongarwar D, King LM, *et al*. Trends in the incidence of fetal macrosomia and its phenotypes in the United States, 1971-2017. Arch Gynecol Obstet 2020;301(2):415–426. doi:10.1007/s00404-019-05400-9.
[45] Blebu BE, Waters O, Lucas CT, *et al*. Variations in maternal factors and preterm birth risk among non-Hispanic black, white, and mixed-race black/white women in the United States, 2017. Womens Health Issues 2022;32(2):140–146. doi:10.1016/j.whi.2021.10.010.
[46] Green CA, Johnson JD, Vladutiu CJ, *et al*. The association between maternal and paternal race and preterm birth. Am J Obstet Gynecol MFM 2021;3(4):100353. doi:10.1016/j.ajogmf.2021.100353.

Edited by: Yong-Qing Zhu

**How to cite this article:** Adebile T, Orji AF, Twum F, Zhang J. Macrosomia is associated with overweight in childhood: a follow-back of a cohort established in the early years of the obesity epidemic. Reprod Dev Med 2023;7(4):210–217. doi: 10.1097/RD9.0000000000000067