Cesarean Delivery and Body Mass Index at 6 Months and Into Childhood

Rebecca Kofod Vinding, MD,[a,b] Tobias Steen Sejersen, MD,[a,b] Bo L. Chawes, MD, DMSc,[a] Klaus Bønnelykke, MD, PhD,[a] Thora Buhl, MD, PhD,[c] Hans Bisgaard, MD, DMSc,[a] Jakob Stokholm, MD, PhD[a,b]

abstract

BACKGROUND AND OBJECTIVES: The prevalence of cesarean delivery (CD) is rising worldwide, and so is childhood obesity. Studies have shown associations between these factors. We examined the development of BMI from birth through childhood to determine whether CDs were associated with differences in growth and obesity.

METHODS: Term children from the birth cohorts Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$ (COPSAC$_{2000}$) and COPSAC$_{2010}$ were included. Height, length, and weight measurements were collected prospectively until 5 years in COPSAC$_{2010}$ and until 13 years in COPSAC$_{2000}$. Dual-energy x-ray absorptiometry (DXA) scans were performed at 3.5 and 7 years. Information on relevant covariates were verified during clinical visits. Analyses were adjusted for covariates associating with CD.

RESULTS: In COPSAC$_{2010}$, 20% (N = 138/673) of the children were delivered by CD; 49% were girls. In COPSAC$_{2000}$, 19% (N = 76/393) were delivered by CD; 51% were girls. Children delivered by CD had a higher mean BMI at 6 months compared with those delivered vaginally: COPSAC$_{2010}$ β-coefficient, .41 (95% confidence interval [CI], .12 to .69), P = .01; COPSAC$_{2000}$ β-coefficient, .16 (95% CI, −.11 to .68), P = .16; and meta-analysis β-coefficient, .37 (95% CI, .14 to .60), P = .002. There were no differences in BMI trajectory between the 2 groups by 5 and 13 years, nor cross-sectional BMI at 5 and 13 years, nor in fat percentages from DXA scans.

CONCLUSIONS: Children delivered by CD had a higher BMI at 6 months of age, but this difference did not track into later childhood. Our study does not support the hypothesis that CD leads to later overweight.

[a]*Copenhagen Prospective Studies on Asthma in Childhood, Faculty of Health and Medical Sciences, University of Copenhagen and Danish Pediatric Asthma Center, Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark;* [b]*Department of Pediatrics, Naestved Hospital, Naestved, Denmark; and* [c]*Department of Clinical Physiology and Nuclear Medicine, Herlev-Gentofte, Copenhagen University Hospital, Copenhagen, Denmark*

We are aware of and comply with recognized codes of good research practice, including the Medical Research Council's Good Research Practice and the Guidelines for Good Scientific Practice by the Danish Committees on Scientific Dishonesty. We comply with national and international rules on the safety and rights of patients and healthy subjects, including Good Clinical Practice as defined in the EU's Directive on Good Clinical Practice, the International Conference on Harmonisation's good clinical practice guidelines, and the Helsinki Declaration. We follow national and international rules on the processing of personal data, including the Danish Act on Processing of Personal Data and the practice of the Danish Data Inspectorate.

Dr Vinding carried out the initial analyses, wrote the first draft of the manuscript, and was responsible for data acquisition, analysis, and interpretation; Drs Sejersen, Chawes, and Bønnelykke contributed substantially to the analysis and interpretation of the data and provided important intellectual input; Dr Buhl examined and validated all data from the DXA scans and critically reviewed the manuscript for important intellectual content; Dr Bisgaard, guarantor of the study from conception and design to conduct of the study, had full access to the data and

WHAT'S KNOWN ON THIS SUBJECT: The rate of cesarean delivery is rising worldwide, and so is obesity. Meta-analyses have found an association between these 2 factors, but the findings are ambiguous, and it is unknown how mode of delivery affects growth throughout childhood.

WHAT THIS STUDY ADDS: Children born by cesarean delivery had a higher mean BMI at 6 months of age, but this difference did not track into later childhood. This window of higher BMI in infancy should be explored.

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The prevalence of overweight and obesity among children has been increasing worldwide for the last 3 decades.[1,2] However, it seems that this increase has reached a plateau in Western countries in recent years.[3] It is known that obesity and extensive weight gain in the first years of life are major risk factors for obesity, type 2 diabetes, and cardiovascular disease in adulthood.[4] Furthermore, the timing and velocity of infancy BMI peak, which is reached at around age 6 to 7 months, have been associated with higher BMI later in childhood and cardiovascular disease and type 2 diabetes in early adulthood.[5,6] The increased prevalence of overweight children cannot be explained by changes in genetic factors, because the great increase has occurred over a short period. The causes must therefore be sought in environmental exposures.[7,8]

Over the same period, an increase in the prevalence of cesarean delivery (CD) has been observed, and as observed for obesity this prevalence has also reached a plateau in Western countries in the last decade.[9] Various aberrations have been linked to CD: short-term effects such as hypoglycemia, breastfeeding problems,[10] altered immune responses,[11] and long-term effects on immune-related conditions such as asthma.[9] Two recent meta-analyses have shown associations between CD and obesity in offspring in both childhood and adulthood.[12,13] However, the included studies were heterogeneous in design, typically including only cross-sectional data measurements.

The study aim was to examine the association between CD and BMI patterns among children and adolescents. We analyzed longitudinal BMI data in combination with data on body composition from dual-energy x-ray absorptiometry (DXA) scans from 2 Danish birth cohorts: the Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$ (COPSAC$_{2000}$) and COPSAC$_{2010}$.

METHODS

Study Population

COPSAC$_{2000}$ is a prospective clinical birth cohort study of 411 children born to asthmatic mothers.[14] The children have been followed prospectively until age 13 years.[15,16]

COPSAC$_{2010}$ was designed from the COPSAC$_{2000}$ cohort and is a study of 738 unselected pregnant women and their 700 children, followed prospectively until age 5 years.[17] The mothers participated in a randomized controlled trial of fish oil supplementation and high-dose vitamin D in the third trimester of pregnancy.[18,19]

Exclusion criteria in both cohorts were maternal chronic cardiac, endocrinologic, nephrologic, or pulmonary disease other than asthma, and for the current study we excluded twins and children with a gestational age <36 weeks. Data validation and quality control followed the guidelines for good clinical practice.

Ethics

The studies were conducted in accordance with the guiding principles of the Declaration of Helsinki and were approved by the Local Ethics Committee (COPSAC$_{2000}$: KF 01-289/96, COPSAC$_{2010}$: H-B-2008-093) and the Danish Data Protection Agency (COPSAC$_{2000}$ and COPSAC$_{2010}$: 2015-41-3696). Both parents gave written informed consent before enrollment.

Primary Outcomes

Anthropometrics were assessed at the COPSAC research facility at age 1 month, 6 months, and every 6 months until age 7 years, and then again at 13 years of age for COPSAC$_{2000}$. For COPSAC$_{2010}$ at age 1 week, 1 month, 3 months, 6 months, and every 6 months until age 2 years, and thereafter every 12 months until age 5 years.

Weight was measured without clothes on calibrated digital scales. Length was measured until 2 years with an infantometer (Kiddimeter; Raven Equipment Ltd, Dunmow, Essex, England). Height at later ages and in parents was measured with a stadiometer (Harpenden; Holtain Ltd, Crymych, Dyfed, Wales), which was calibrated yearly.

We analyzed BMIs at 6 months and 1, 5, and 13 years as outcomes. For each child these BMI values were defined as the BMI measurement closest to 6 months or 1 year ± 3 months, 5 years ± 6 months, and 13 years ± 12 months.

DXA Scans

Whole body scans were performed with a Lunar iDXA densitometer (GE Healthcare, Fairfield, CT) and were used to determine both the total body fat percentage (calculated as total fat mass divided by body weight on the day of scan, except for the head, because many patients moved their heads during the scan), and body compartment–specific fat percentage, based on the compartments predefined by the software.[20–22]

The children were DXA scanned at 3.5 years in COPSAC$_{2010}$ and at 7 years in COPSAC$_{2000}$.[23]

All DXA scan data were scrutinized by an experienced specialist and analyzed with enCore software (GE-Healthcare).

Mode of Delivery and Intrapartum Antibiotics

Information on delivery mode was obtained by personal interview at the child's first visit after birth; furthermore, we asked whether the birth was induced. The information was validated against the Danish Medical Birth Registry for all of the children. CD was subcategorized as emergency or elective CD, and

vaginal delivery was categorized as induced or noninduced.

Information on intrapartum antibiotics was available only in $COPSAC_{2010}$ and was obtained by interview 1 week postpartum and birth journal inspection. All women giving birth by CD were treated with prophylactic intrapartum antibiotics.

Covariates

Information on race, gender, gestational age, maternal age at birth, parity, household income, parents' educational level, older siblings, smoking during pregnancy, preeclampsia, diabetes in pregnancy, passive smoking, and days of hospitalization after birth were obtained by personal interviews and if possible validated with register data.

Birth length and weight were obtained at the first clinical visit after birth by personal interview, and thereafter all data were validated against the Danish Medical Birth Registry. Furthermore, if there was a difference >10 g, data were validated against the length and weight measures at 1 week from the research clinic. Birth weight for gestational age *z* score units were derived from ultrasound-based intrauterine growth curves.[24]

The social circumstances were defined as the first component of a principal component analysis on household income, maternal age, and maternal level of education at 2 years with a mean value of 0 and SD of 1 (which explained 52% of the variance in $COPSAC_{2000}$ and 55% of the variance in $COPSAC_{2010}$) (see Supplemental Tables 8 and 9).

Information on breastfeeding was collected by interviewing the mothers at the clinic on the duration of exclusive and total breastfeeding and the use of infant formula when the children were 1, 3, 6, 12, 18, 24, 30, and 36 months old. As soon as the child's diet was supplemented or replaced by continual use (>7 days) of infant formula or complementary foods, we considered exclusive breastfeeding terminated. If the child had received infant formula for a period of <7 days as a supplement to breastfeeding, we still considered it exclusive breastfeeding.

Information on prepregnancy weight of the mothers was collected from pregnancy records in $COPSAC_{2010}$, and BMI was calculated with the height measured at the clinic.

Statistics

Baseline characteristics were compared between children born by CD and vaginal delivery via a χ^2 test or Student's *t* test. Covariates with $P < .1$ were considered potential confounders. We investigated associations between delivery mode and BMI and total fat percentage by Student's *t* test and multiple linear regressions. Meta-analysis estimates were calculated with a random effects regression model. Heterogeneity between studies was estimated by I^2 values.

BMI tracking over time was analyzed by a mixed model (including repeated measures), based on World Health Organization gender-specific BMI *z* scores[25] at every scheduled visit from 1 to 5 years in $COPSAC_{2010}$ and 13 years in $COPSAC_{2000}$. We used *z* scores because BMI does not have a linear development.

Results with a $P < .05$ were considered significant. Missing data were treated as missing observations. Data processing was conducted in R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

The detectable effect sizes (80% power) were estimated via *t* statistics, and they were 0.367, 0.333, and 0.305 for BMI at 6 months, 1 year, and 5 years, respectively, in $COPSAC_{2010}$ and 0.545, 0.516, 0.538, and 1.191 for BMI at 6 months and 1, 5, and 13 years, respectively, in $COPSAC_{2000}$.

RESULTS

Baseline Characteristics

Table 1 shows baseline characteristics of the children born by CD compared with children born by vaginal delivery in both cohorts separately.

In the $COPSAC_{2010}$ cohort, 21% (N = 138) of the children were born by CD, and 19% (N = 76) were born by CD in the $COPSAC_{2000}$ cohort.

The mothers who delivered by CD were significantly older (in $COPSAC_{2000}$, 30.1 vs 29.5 years, $P = .01$; in $COPSAC_{2010}$, 33.2 vs 32.1 years, $P = .01$).

Children born by CD had a lower gestational age (in $COPSAC_{2000}$, 278 vs 281 days, $P = .03$; in $COPSAC_{2010}$, 278 vs 281 days, $P < .001$).

In $COPSAC_{2010}$ the children delivered by CD had a higher *z* score birth weight for gestational age (0.20 vs −0.05, $P = .01$) and a shorter duration of exclusive breastfeeding (93 vs 106 days, $P = .02$); in $COPSAC_{2000}$ we did not find these differences.

In $COPSAC_{2010}$ the mothers who delivered by CD had a higher prepregnancy BMI (mean BMI, 25.5 vs 24.3, $P = .01$), and they were more likely to be nulliparous (52.9% vs 44.7%, $P = .09$).

We observed no other differences associated with delivery mode in the cohorts.

All results were therefore adjusted for age at BMI measurement, gender, parity, mother's age, birth weight for gestational age, and exclusive breastfeeding duration, and, in $COPSAC_{2010}$, for maternal prepregnancy BMI.

Delivery Mode and BMI Development in the First Year of Life

Children born by CD had a higher peak value of mean BMI in infancy in

TABLE 1 Baseline Characteristics of Children Delivered by CD and Vaginally in $COPSAC_{2010}$ and $COPSAC_{2000}$

	$COPSAC_{2010}$					$COPSAC_{2000}$				
	N	CD	*N*	Vaginal Delivery	*P*	*N*	CD	*N*	Vaginal Delivery	*P*
Mode of delivery, % (*N*)	—	20.4 (138)	—	79.6 (535)	—	—	19.3 (76)	—	80.7 (317)	—
Demographics										
Caucasian, % (*N*)	138	97.8 (135)	535	95.5 (511)	.22	76	96.1 (73)	317	96.5 (306)	.84
Female, % (*N*)	138	44.2 (61)	535	50.1 (268)	.22	76	52.6 (40)	317	50.8 (161)	.77
Gestational age, d, mean (SD)	138	277.5 (10.1)	535	281.1 (8.6)	<.01	76	277.6 (12.8)	317	280.6 (10.1)	.03
Age at 5-y BMI measurement, y, mean (SD)	118	5.0 (0.1)	471	5.0 (0.1)	.04	61	5.2 (0.2)	233	5.2 (0.2)	.8
Age at 13-y BMI measurement, y, mean (SD)	—	—	—	—	—	67	12.9 (0.6)	257	12.9 (0.6)	.96
Social circumstances	138	0.2 (1.2)	535	0.0 (0.9)	.43	72	0.1 (1.2)	292	−0.1 (1.1)	.32
Mother's age at birth, y, mean (SD)	138	33.2 (4.8)	535	32.1 (4.2)	.01	76	31.0 (4.5)	317	29.5 (4.4)	.01
Nulliparity, % (*N*)	138	52.9 (73)	535	44.9 (240)	.09	76	44.7 (34)	317	45.4 (144)	.91
Father's height, cm, mean (SD)	121	180.7 (6.8)	505	180.9 (6.7)	.77	63	181.2 (7.9)	245	180.7 (7.2)	.63
Mother asthmatic, % (*N*)	137	30.7 (42)	534	24.7 (132)	.16	76	100 (76)	317	100 (317)	—
Risk factors										
Smoking in pregnancy, % (*N*)	138	8.1 (12)	534	7.5 (40)	.79	76	19.7 (15)	317	26.5 (84)	.22
Exclusive breastfeeding, d, mean (SD)	136	93.4 (66.6)	529	106.3 (57.1)	.02[a]	72	110.8 (67.8)	281	114.8 (58.7)	.61
Mother's prepregnancy BMI, mean (SD)	121	25.5 (4.8)	488	24.3 (4.2)	.01	—	—	—	—	—
Mother's height, cm, mean (SD)	138	166.6 (6.3)	535	167.7 (6.3)	.07	74	167.4 (7.0)	292	167.0 (6.7)	.73
Gestational diabetes, % (*N*)	138	2.1 (3)	535	2.4 (13)	.86	—	—	—	—	—
Preeclampsia, % (*N*)	138	6.5 (9)	535	3.6 (19)	.12	76	7.9 (6)	317	4.1 (13)	.17
Intrapartum antibiotics, % (*N*)	138	100 (138)	532	12.9 (69)	—	—	—	—	—	—
Hospitalization after birth, % (*N*)	138	4.6 (21)	535	4.7 (47)	.94	—	—	—	—	—
Fish oil supplementation, % (*N*)	137	53.3 (73)	534	48.9 (261)	.38	—	—	—	—	—
High-dose vitamin D supplementation, % (*N*)	118	51.7 (61)	452	50.0 (226)	.74	—	—	—	—	—
Anthropometrics										
Birth weight for gestational age *z* score, units[a], mean (SD)	138	0.2 (1.2)	534	−0.1 (0.9)	.01	76	0.1 (1.2)	317	−0.1 (1.1)	.44
Birth weight, kg, mean (SD)	138	3.6 (0.6)	535	3.6 (0.5)	.82	76	3.5 (0.6)	317	3.6 (0.5)	.72
BMI >85 percentile at 5 y, % (*N*)	118	16.9 (20)	471	14.9 (70)	.57	61	16.4 (10)	234	15.8 (37)	.91
BMI >85 percentile at 13 y, % (*N*)	—	—	—	—	—	67	17.9 (12)	259	13.1 (34)	.32
BMI >90 percentile at 5 y, % (*N*)	118	10.9 (14)	471	9.9 (47)	.72	61	14.8 (9)	234	11.16 (26)	.44
BMI >90 percentile at 13 y, % (*N*)	—	—	—	—	—	67	11.9 (8)	259	9.7 (25)	.58

[a] Calculation was based on Maršál's intrauterine growth curves.

TABLE 2 Relationship Between Mode of Delivery and 6-mo, 1-y, 5-y, and 13-y BMI Measurement

	$COPSAC_{2010}$			$COPSAC_{2000}$			Meta-analysis			
	Crude Estimate (95% CI)	*P*	Adjusted Estimate[a] (95% CI)	*P*	Crude Estimate (95% CI)	*P*	Adjusted Estimate[b] (95% CI)	*P*	I^2 (%)	Heterogeneity *P*	Estimate[c] (95% CI)	*P*
BMI at 6 mo	0.36 (0.10 to 0.61)	.007	0.42 (0.13 to 0.70)	.004	0.29 (−0.10 to 0.66)	.139	0.28 (−0.11 to 0.68)	.156	0.0	.60	0.37 (0.14 to 0.60)	.002
BMI at 1 y	−0.01 (−0.239 to 0.21)	.918	−0.05 (−0.30 to 0.20)	.695	0.46 (0.01 to 0.82)	.013	0.50 (0.14 to 0.87)	.007	73.2	.05	0.18 (−0.35 to 0.72)	.51
BMI at 5 y	0.07 (−0.15 to 0.29)	.544	−0.03 (−0.27 to 0.21)	.811	0.20 (−0.18 to 0.58)	.304	0.18 (−0.20 to 0.56)	.349	0.0	.36	0.03 (−0.17 to 0.24)	.764
BMI at 13 y	—	—	—	—	0.15 (−0.68 to 0.98)	.722	−0.03 (−0.87 to 0.82)	.950	—	—	—	—

[a] Adjusted for $COPSAC_{2010}$: age at BMI measurement, gender, parity, mother's age, mother's prepregnancy BMI, birth weight for gestational age, and duration of exclusive breastfeeding.
[b] Adjusted for $COPSAC_{2000}$: age at BMI measurement, gender, parity, mother's age, birth weight for gestational age, and duration of exclusive breastfeeding.
[c] Random effects.

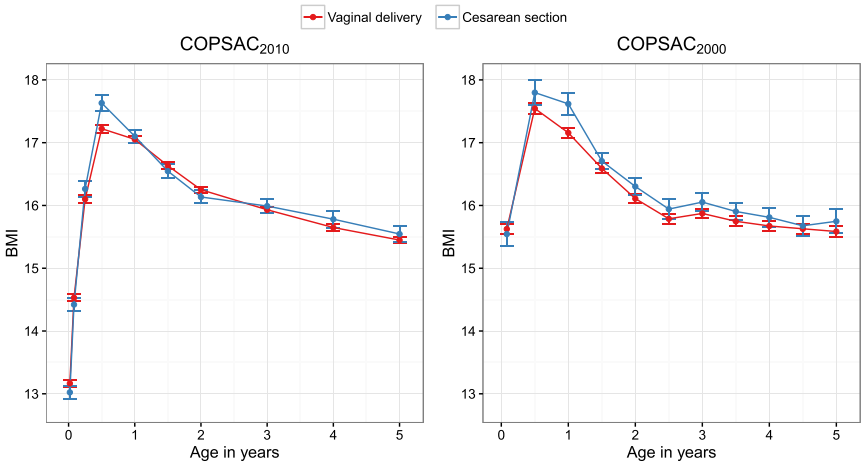

FIGURE 1
BMI in first 5 years of life. Curves showing mean BMI with SEs according to visit age in the first 5 years of life for children delivered by CD and vaginally in $COPSAC_{2010}$ and $COPSAC_{2000}$.

both cohorts compared with children delivered vaginally (Fig 1). In $COPSAC_{2010}$ this difference was most pronounced at age 6 months, 17.6 versus 17.2 (95% confidence interval [CI], 0.10 to 0.61), and subsequently the groups aligned with no difference at age 1 year. In $COPSAC_{2000}$ the BMI values of children born by CD diverged from 6 months compared with children born vaginally, and the difference reached its maximum at age 1 year, 17.6 versus 17.2 (85% CI, 0.01 to 0.82). The differences in BMI at 6 months were significant after adjustment in $COPSAC_{2010}$ (β-coefficient, .41; 95% CI, .12 to .69; $P = .01$) but not in $COPSAC_{2000}$ (β-coefficient, .16; 95% CI, −.11 to .68; $P = .16$). Meta-analysis of BMI at 6 months revealed a significant association with CD in the 2 cohorts (β-coefficient, .37; 95% CI, .14 to .60; $P = .002$) (Table 2) but no difference in the meta-analysis of BMI at 1 year. Adjusting the analyses in $COPSAC_{2010}$ for the pregnancy supplementation trials did not change the results (data not shown).

We subanalyzed the associations between CD and BMI at 6 months of age in the 174 children delivered by asthmatic mothers in $COPSAC_{2010}$ (β-coefficient, .30; 95% CI, −.20 to .80; $P = .22$).

Delivery Mode and BMI Development During Childhood

The BMI curves aligned after the gap in the first year (Fig 1), and we found no difference in mean BMI at 5 years of age with regard to mode of delivery ($COPSAC_{2010}$: $\beta\text{-coefficient}_{adjusted}$, −.03; 95% CI, −.27 to .21; $P = .81$); $COPSAC_{2000}$: $\beta\text{-coefficient}_{adjusted}$, .18; 95% CI, −.20 to .56; $P = .35$) (Table 2). We found no difference in the meta-analysis at this time point.

Figure 2 illustrates the longitudinal BMI development for the children until 13 years of age in the $COPSAC_{2000}$ cohort according to mode of delivery. We found no difference in mean BMI between the 2 groups at age 13 years ($\beta\text{-coefficient}_{adjusted}$, −.03; 95% CI, −.87 to .82; $P = .95$) (Table 2). From 1.5 to 13 years of age the curves are almost coherent, with the CD curve on top, and graphically they reach the time for adiposity rebound (~age 4.5 years) simultaneously and continuing with an identical course into puberty.

Using repeated measurement statistics, we analyzed whether there were a difference in mean BMI from infancy through childhood between children delivered by CD and vaginally. We found no difference in mean *z* score BMI over time:

$COPSAC_{2010}$, 1 to 5 years of age (β-coefficient −.05; SE .07; $P = .95$) and $COPSAC_{2000}$, 1 to 13 years of age (β-coefficient .12; SE .10; $P = .21$).

Furthermore, we compared the ratio of children having a BMI above the 85th and 90th percentiles at 5 and at 13 years of age and found no differences with regard to delivery mode (Table 1).

In $COPSAC_{2010}$ we subanalyzed whether induction of birth in the vaginal delivery group and type of CD could affect the results. We found no differences in BMI at any time in vaginally delivered children with regard to birth induction. Furthermore, we found no differences in BMI with regard to type of CD (Supplemental Tables 5 and 6).

Gender-Specific Growth

Gender-specific growth curves for both cohorts are illustrated in Supplemental Fig 3, showing the mean BMI value in the first year of life. We did not find any gender-specific growth patterns according to mode of delivery.

Delivery Mode and Body Fat Percentage

CD was not associated with significant differences in the body fat percentage of the children measured by DXA scans at age 3.5 years in $COPSAC_{2010}$ and at age 7 years in $COPSAC_{2000}$ (Table 3).

We subanalyzed the DXA scans from $COPSAC_{2010}$ and found no significant regional differences in body fat percentage in legs, arms, trunk, or android region between the 2 delivery groups (Supplemental Table 7).

Intrapartum Antibiotics and Cross-Sectional BMI

Because all women giving birth by CD were treated with intrapartum antibiotics, we wanted to examine whether this treatment could be responsible for some of the effects. In $COPSAC_{2010}$, 13% ($N = 69$) of women with vaginal delivery received intrapartum antibiotics. There were no differences in mean BMI at age 6 months or 5 years in children of these women compared with children whose mothers did not receive antibiotics (Supplemental Table 4).

TABLE 3 Fat Percentage From DXA Scans at 3.5 y in $COPSAC_{2010}$ and at 7 y in $COPSAC_{2000}$

	CD Mean (SD)	Vaginal Mean (SD)	Crude[a] Estimate (95% CI)	*P*	Adjusted[b] Estimate (95% CI)	*P*
$COPSAC_{2010}$						
Fat, %	28.18 (4.79) *N* = 79	28.77 (4.36) *N* = 272	−0.30 (−1.27 to 0.67)	.22	−0.29 (−1.39 to 0.81)	.61
$COPSAC_{2000}$						
Fat, %	27.96 (5.16) *N* = 57	28.28 (5.85) *N* = 233	−0.29 (−1.82 to 1.23)	.70	−0.53 (−0.21 to 1.04)	.51

$COPSAC_{2000}$: age at BMI measurement, gender, parity, mother's age, birth weight for gestational age, and duration of exclusive breastfeeding.

[a] Adjusted for age at DXA scans and gender.

[b] Adjusted for $COPSAC_{2010}$: age at BMI measurement, gender, parity, mother's age, mother's prepregnancy BMI, birth weight for gestational age, and duration of exclusive breastfeeding.

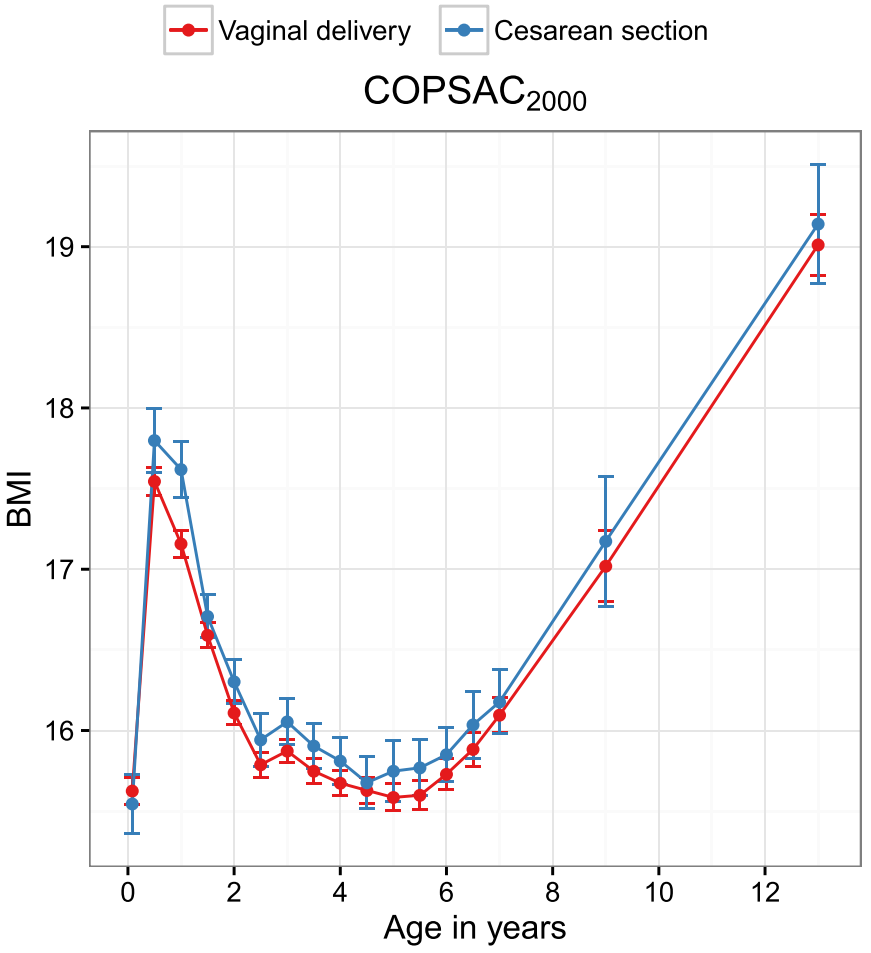

FIGURE 2
BMI in first 13 years of life. Curves showing mean BMI with SEs according to visit age for children delivered by CD and vaginally until 13 years of age in $COPSAC_{2000}$.

DISCUSSION

Primary Findings

We found that children born by CD had a higher BMI peak at 6 months of age compared with children born vaginally. This higher BMI in early childhood did not track into

later childhood and adolescence. Furthermore, we found no association between delivery mode and body fat percentage in children at age 3.5 or 7 years.

Strengths and Limitations

The primary strength of this study was the longitudinal follow-up on growth parameters in 2 comparable cohorts at the same center under a similar design and the subsequent meta-analysis. Each growth measurement was performed with the same equipment by trained COPSAC assistants based on standardized procedures, and the observed growth curves were similar to those of previous reports.[26] The longitudinal follow-up allowed repeated measurement statistics. In addition, we included DXA scans as an objective measure of fat percentage.

Furthermore, we had a broad range of exposures, which were validated by register data and personal interviews with the families. This availability of covariates allowed adjustments for important potential confounders such as gender, parity, birth weight for gestational age, maternal age, prepregnancy BMI, and breastfeeding duration.[27,28] After covariate adjustment, an observed nonsignificant higher BMI at age 13 years disappears completely, which could otherwise have suggested a possible difference not found because of low power at this time point.

It may be a limitation that the $COPSAC_{2000}$ is an asthma high-risk cohort, but in the subanalyzes of children with asthmatic mothers we still observed a difference in BMI at 6 months between the 2 delivery groups, with an estimate comparable to the one we found in $COPSAC_{2000}$.

Another limitation could be the decade between the enrollments of 2 cohorts, leading to different time-related environmental impacts. We saw differences in the duration of breastfeeding and smoking habits (Table 1) between the 2 cohorts; however, the results appear similar, and we believe that we have accounted for the majority of differences through our comprehensive confounder adjustment and meta-analyses of the individual cohort results.

Our post hoc power calculation indicated that the differences we found at 6 months were reliable with >80% power, but we do not have the same power to ensure that the lack of differences we found at 5 and 13 years were true.

Interpretation

We found that children born by CD have higher mean BMI at 6 months of age compared with children born vaginally, leading to a 0.37 difference in mean BMI. We saw no significant association between mode of delivery and BMI or body composition in later childhood or puberty.

These findings suggest that infants delivered by CD have a divergent growth pattern during early infancy but show no risk for overweight in later childhood.

Two recent meta-analyses on this subject have results and conclusions that differ from ours. One study found a greater risk of overweight and obesity in offspring delivered by CD in childhood, youth, and adulthood.[12,13] The other study found that delivery by CD was associated with a greater risk of overweight and obesity and a higher mean BMI in adulthood in unadjusted analyses. However, most of the included studies did not provide information about relevant covariates, such as breastfeeding patterns and mother's BMI, and they used divergent definitions of growth outcomes and age of measurement. In the meta-analyses the main association was found between CD and obesity, according to either BMI >95th percentile for age and gender or the International Obesity Task Force criteria.[29–32] In our birth cohorts the variation in BMI was narrow (Table 2), with only 6 children fulfilling the International Obesity Task Force criteria for risk of obesity at 5 years in each cohort and 7 children at 13 years. Our subanalysis of children with a BMI value above the 85th percentile and 90th percentile at 5 and 13 years of age showed that the distribution according to mode of delivery was the same as in the rest of the children. The prevalence of childhood obesity was ~8.5% in United States[1] and 3.5% in Denmark[2] in 2011. This difference in obesity prevalence could partly account for the ambiguous results.

Other studies have demonstrated findings in line with ours, with increased growth in infancy for children born by CD followed by no long-term effects. One study[33] found a greater likelihood of obesity at age 2 years in children delivered by CD but not later. A study found an increased risk of obesity for 4-year-old boys but no risk for girls and no increased risk at later ages.[34]

Two previous Danish studies showed conflicting results. A register study[35] found that 7-year-old children delivered by CD had a 15% higher risk of being overweight in unadjusted analysis but no difference after adjustment; another study found that men 18 years old delivered by CD had a higher adjusted mean BMI and a higher risk of obesity.[36] However, the latter did not adjust for mother's BMI or breastfeeding pattern.

Both duration of breastfeeding[27] and prepregnancy BMI[28] increase the risk of obesity; we found both of these factors associated with CD. Most children in our cohort were breastfed, and the variation of socioeconomic circumstances was narrow (Table 1) compared with other countries.[30,31,34] We speculate that some of the earlier studies had more diverse populations and that

the lack of sufficient confounder adjustment could partly explain the different associations found between countries.[33,35,36]

Previous studies have indicated that the gut microbiota affects the human metabolism and thereby risk of obesity.[37] It has therefore been hypothesized that differences in gut microbiota caused by CD[38] could explain the differences in BMI. We found a diverging BMI according to delivery mode only in early infancy, which we speculate could be explained partly by differences in the gut microbiota, which in $COPSAC_{2010}$ was apparent only in the first months of life but equalized at 1 year of age.[38]

All children in our study who were delivered by CD had been exposed to intrapartum antibiotics. We analyzed BMI according to antibiotic administration during vaginal delivery but found no relationship between intrapartum antibiotics and BMI in infancy or later in life (Supplemental Table 4). Our data do not support the hypothesis that CD is merely a proxy for intrapartum antibiotics.[29,38]

The mechanism of becoming obese is multifactorial, and increased growth in infancy, especially a high infant BMI peak, has been associated with later risk of overweight and obesity in childhood and adulthood. Our results may have been limited in power when we assessed each cohort separately, which might lead to the lack of difference in BMI at 5 and 13 years. However, our meta-analysis clearly shows no difference at age 5 years, and the nonsignificant higher BMI observed at age 13 years in $COPSAC_{2000}$ disappears after covariate adjustment. It can be hypothesized that CD may be a risk factor only if the child grows up in an environment with other risk factors for obesity. This window of growth should therefore be a focus of interest in future studies, because it could represent a modifiable link in the prevention of obesity in selected children.

CONCLUSIONS

Children delivered by CD had a higher mean BMI at 6 months of age, but this difference did not track into later childhood. At 13 years of age children born by CD had a nonsignificant higher BMI, but after adjustment this difference disappeared. CD did not associate with childhood fat percentage measured by DXA scans. This window of increased BMI in infancy should be explored in populations containing a higher number of obese children.

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ABBREVIATIONS

CD: cesarean delivery
CI: confidence interval
COPSAC: Copenhagen Prospective Studies on Asthma in Childhood
DXA: dual-energy x-ray absorptiometry

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Address correspondence to Hans Bisgaard, MD, DMSc, Copenhagen Prospective Studies on Asthma in Childhood, Faculty of Health and Medical Sciences, University of Copenhagen and Danish Pediatric Asthma Center, Gentofte Hospital, University of Copenhagen, Ledreborg Alle 34, 2820 Gentofte, København, Denmark. E-mail: bisgaard@copsac.com

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