

Neonatal size in term children is associated with asthma at age 7, but not with atopic dermatitis or allergic sensitization

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Abstract

Background: We hypothesized that anthropometrics in the newborn is associated with development of asthma later in life.

Methods: The study included a prospective, longitudinal clinical study of a birth cohort of 411 Danish neonates born at term of mothers with a history of asthma. The primary endpoint was physician-diagnosed asthma at age 7 years. Allergic sensitization and atopic dermatitis (AD) were also investigated.

Infant size was measured at the research clinic on four occasions during the first year of life. Risk for asthma, AD, and allergic sensitization at age 6–7 were estimated from logistic regression. Time to first asthma and AD were investigated by Cox regression. Multivariate models were adjusted for gender, gestational age, and mothers smoking during pregnancy.

Results: Neonatal weight, length, body mass index and head circumference (*z*-score) were all significantly associated with asthma at age 7. Adjusted odds ratio for asthma by estimated birth weight *z*-score: 1.87 [1.23–2.84]; *P* = 0.004. Adjusted HR for onset of asthma by neonatal weight *z*-score: 1.46 [1.08–1.96]; *P* = 0.013. Neonatal size did not associate with AD or allergic sensitization.

Conclusions: Increased neonatal size was significantly associated with asthma at age 7 but not AD or allergic sensitization in at-risk children born at term. The findings suggest some common prenatal mechanisms linking body size and asthma.

Childhood obesity (1) and childhood asthma (2, 3) have both increased several fold in recent decades in Westernized cultures, which has led to speculation on a possible associations from changing lifestyle or common genetics (4). Cross-sectional prevalence of childhood asthma and obesity was closely associated analyzed decades apart in children aged

5–6 and 4–11 (5, 6). This however could be an artifact of increasing general prevalence of both in the observed periods (7). Also, longitudinal studies have suggested a temporal relation between an increased body mass index (BMI) and risk of asthma in children from age 7 years to age 18 years by increased BMI with a 1-year lag (8).

High birth weight has been associated with obesity later in childhood (9). Because most asthma cases debut before age 5 (10) and infancy is a growth period known for the development of the adipose tissue, we hypothesized that potential mechanisms linking adiposity and asthma would be found in associations between body size at birth and risk of asthma. We investigated the temporal associations between neonatal size and the development of asthma; atopic dermatitis (AD) and allergic sensitization at age 7 year in the Copenhagen

Abbreviations

AD, atopic dermatitis; BMI, body mass index; CI, confidence interval; COPSAC, Copenhagen Prospective Study on Asthma in Childhood; HC, head circumference; HR, hazard ratio; IgE, immunoglobulin E; MD, missing data; OR, odds ratio; Q25, the 25% quartile value; Q75, the 75% quartile value; SD, standard deviation; sIgE, specific Immunoglobulin E; WHO, World Health Organization.

Prospective Study on Asthma in Childhood (COPSAC) birth cohort of children born at term of mothers with a history of asthma.

Methods

The Copenhagen Prospective Study on Asthma in Childhood is a single-center prospective clinical birth cohort study of 411 infants born at term of mothers with a history of a doctor's diagnosis of asthma. All children were monitored closely at the research clinic at two enrollment visits and at 6 month intervals and at any acute symptoms until the age of 7 years.

See Data S1 for details on study design and ethics, and additional clinical diagnosis and statistical methods.

Clinical diagnoses

Asthma

Asthma was diagnosed based on a predefined algorithm of recurrent episodes of troublesome lung symptoms reported in daily diary cards (further information detailed in Data S1); symptoms judged by the COPSAC doctors to be typical of asthma (e.g., exercise-induced symptoms, prolonged nocturnal cough, recurrent cough outside common cold, symptoms causing wakening at night); the need of intermittent rescue use of inhaled β_2 -agonist; and improvement of symptoms to a 3-month trial of inhaled corticosteroids and relapse after stopping treatment (11, 12).

Eczema

Atopic dermatitis was diagnosed by the COPSAC doctors according to predefined morphology and localization at both scheduled and acute visits. Diagnosis of AD followed the criteria defined by Hanifin–Rajkaas previously detailed (13).

Allergic sensitization

Blood was sampled at the age of 6 years for measurements of eosinophil count (in 10^9 cells/l), total IgE, and specific IgE. The serum level of total IgE was determined by ImmunoCAP (Phadia) with a detection limit of 2 kU/l. Specific IgE was determined by a commercial assay for IgE (Immuno-CAP Phadiatop Infant; Phadia, Uppsala, Sweden) against the most common food and inhalant allergens. Values of Phadiatop Infant of 0.70 kU/l or more were analyzed as a dichotomized variable (sensitized or not sensitized) (12). The conventional cut point of 0.35 kU/l was also investigated.

Growth measures

Neonatal anthropometrics were assessed at the COPSAC clinical research unit at four prescheduled visits during the first year of life (2 and 4 weeks, 6 and 12 months). At every visit, weight was measured using calibrated digital weight scales and length by infantometer, Kiddimetre® (Raven Equipment Limited, Essex, UK) (14).

Weight, length, head circumference (HC), and BMI were converted to age- and gender-specific *z*-scores. *Z*-scores are

standardized numbers with a mean of zero and a normal distribution in an international WHO reference population (15). We hypothesized a linear development of *z*-scores in infancy and summarized postnatal anthropometrics with linear regression of anthropometric *z*-scores in infancy. All infants with at least two measurements minimum 2 months apart were included. This models infant postnatal growth into two parameters – an intercept ('neonatal size') and a slope ('infant growth rate'). A child with intercept = 0 and slope = 0 is following WHO predicted mean growth. Both intercept and slope of the various growth parameters are investigated together as continuous traits to present effects of neonatal size and growth adjusted for one another.

Statistical analysis

Odds ratios (OR) for the three endpoints – allergic sensitization at age 6, AD at age 7, and asthma at age 7 – were modeled by logistic regression. *P*-values correspond to Wald tests.

Co-variables were chosen *a priori* as gender; mothers smoking during pregnancy, and gestational age based on information obtained prospectively at the interviews at the clinic and were included in the analyses. Duration of exclusive breastfeeding (16), mothers' previous deliveries, and mothers' education were also explored as potential confounders.

The overall significance level used was 0.05. Data are presented as mean $\pm$ standard deviation (SD) unless otherwise indicated.

Results

The complete birth cohort included 411 newborns. Thirteen children did not have two measurements at the clinic at least 2 months apart during the first year of life and could not have their infant growth accurately determined, and two children with extreme growth (*z*-scores beyond 5) were excluded as outliers leaving 396 (97% of 411) children eligible for the statistical analysis of time-to-event analysis. Three hundred and eleven of 396 children had complete follow-up data on asthma and AD diagnosis by the age of 7 and were included in logistic regression analyses of these outcomes. Two hundred and ninety-three of 396 children had blood sampled at age of 6 and were included in analysis of allergic sensitization.

Variability of the assessment of length and weight was significantly reduced by only using the standardized measurements at the research clinic at the age of 2 weeks compared to the birth data reported by the midwives. Correlation of measurements from hospital and research clinic (birth and 2 weeks) was weaker than correlation of two measurements at the clinic (2 and 4 weeks) (Fig. S1–S4). Therefore, we did not use midwives measurements of birth weight and length. The 396 children had a mean number of 3.3 growth measurements – only nine (2%) had only two growth measurements and all children had at least one measurement at enrollment visits 2 and 4 weeks.

Characteristics of the study populations are presented in Table 1. Forty-five (14.5%) of 311 had asthma at age 7 and

Table 1 Cohort demographics and neonatal anthropometrics

	Time-to-event asthma/AD N = 396	Asthma/AD at age 7 N = 311	Allergic sensitization at 6 N = 293
Demographics			
Gender, M/F (% male)	196/200 (49.5%)	152/159 (48.9%)	144/149 (49.2%)
Gestational age, median weeks [range]	40 [36–44]	40 [36–44]	40 [36–44]
Mothers smoking during pregnancy, Y/N (% yes)	57/339 (14.4%)	41/270 (13.2%)	39/254 (13.3%)
Exclusive breastfeeding, median days (Q25, Q75)	122 (89, 156)	122 (90, 162)	122 (90, 156)
Mothers previous deliveries, MD/0/1/2 (% 0)	35/214/110/37 (59.3%)	4/192/89/26 (62.5%)	9/173/88/23 (60.9%)
Mothers education, MD/at most college/medium/university (% college)	21/224/99/52 (59.7%)	2/185/83/41 (59.9%)	3/171/83/36 (58.4%)
Endpoints			
Asthma at age 7, Y/N (% yes)		45/266 (14.5%)	
Atopic dermatitis at age 7, Y/N (% yes)		67/244 (21.5%)	
Sensitized at age 6 (>0.35 kU/l sIgE), Y/N (% yes)			105/188 (35.8%)
Sensitized at age 6 (>0.70 kU/l sIgE), Y/N (% yes)			78/215 (26.6%)
Neonatal anthropometrics			
Weight (z-score)			
Size	0.085 ± 1.064 ^{NS}	0.125 ± 1.099*	0.092 ± 1.115 ^{NS}
Growth rate	0.681 ± 1.844***	0.625 ± 1.818***	0.689 ± 1.892***
Length (z-score)			
Size	0.145 ± 1.071**	0.180 ± 1.091**	0.163 ± 1.108*
Growth rate	0.556 ± 1.510***	0.517 ± 1.435***	0.522 ± 1.440***
Head circumference (z-score)			
Size	0.689 ± 1.054***	0.695 ± 1.079***	0.666 ± 1.093***
Growth rate	0.231 ± 1.572**	0.188 ± 1.539*	0.218 ± 1.553*
BMI (z-score)			
Size	0.017 ± 0.998 ^{NS}	0.049 ± 1.022 ^{NS}	0.014 ± 1.035 ^{NS}
Growth rate	0.466 ± 2.060***	0.412 ± 2.002**	0.500 ± 2.125***

AD, atopic dermatitis; MD, missing data; NS, not significant.

P-values correspond to t-test. Null-hypothesis is $z = 0$.

*** $P < 0.0001$;

** $P < 0.01$;

* $P < 0.05$.

67 of 311 (21.5%) had AD at age 7. Seventy-eight of 293 (26.6%) were sensitized to one or more allergens at age 6 using the cut point of 0.70 kU/l, and this prevalence was increased to 105 of 293 (35.8%) by the cut point of 0.35 kU/l. Eleven (24.4%) children of the 45 asthmatic were sensitized at age 6 (cut point of 0.70 kU/l).

Copenhagen Prospective Study on Asthma in Childhood children were larger in length and HC (but not weight nor BMI) compared with the WHO predicted norm. Growth rates of weight, length, HC, and BMI were all significantly above the WHO predicted mean ($P < 0.001$).

Table 2 shows the results for associations between infant growth anthropometrics (size and growth effect are presented independently) and asthma- and atopy-related outcomes adjusted for gender, gestational age, and mothers smoking during pregnancy.

Asthma at age 7 years is significantly associated with the neonatal sizes across anthropometric measures. By each additional neonatal weight z-score (~1 SD), the risk of asthma at age 7 is increased by 87%; OR, 1.87 [1.23–2.84]; $P = 0.004$. Growth rates in infancy show no association on later asthma (Table 2).

Neither allergic sensitization nor AD are associated with neonatal size or growth rates (Table 2). Changing the cut point for allergic sensitization definition to the less restrictive 0.35 kU/l does not change the findings (data not shown).

Additional adjustment for duration of exclusive breastfeeding, mothers' level of education and parity reduced the number of children in the analysis because of children with missing data, but did not change the conclusions of the findings (data not shown).

Time-to-event analysis of first asthma diagnosis and first AD diagnosis are presented in Table S1 confirming that weight, HC, and BMI (but not length) were significantly associated with the development of first asthma diagnosis but not with AD (Table S1).

Discussion

Key findings

We found significant positive associations between not only neonatal BMI but also weight, length, and HC and physician-diagnosed asthma at age 7 (but not AD or allergic

Table 2 Odds ratios for allergic sensitization at age 6, atopic dermatitis at age 7, and asthma at age 7 by estimated birth weight, length, BMI, and infant growth rates. Confounder adjusted results

OR* [95% CI]; <i>P</i> -value	Allergic sensitization at age 6 <i>N</i> = 293	Atopic Dermatitis at age 7 <i>N</i> = 311	Asthma at age 7 <i>N</i> = 311
Neonatal weight			
Size	0.89 [0.64–1.24]; 0.495	0.84 [0.60–1.19]; 0.331	1.87 [1.23–2.84]; 0.004
Growth rate	0.94 [0.78–1.12]; 0.476	0.85 [0.70–1.03]; 0.096	1.15 [0.92–1.44]; 0.214
Neonatal length			
Size	1.03 [0.76–1.40]; 0.857	0.77 [0.54–1.08]; 0.122	1.65 [1.13–2.43]; 0.010
Growth rate	1.20 [0.96–1.49]; 0.109	0.89 [0.70–1.11]; 0.277	0.98 [0.75–1.30]; 0.927
Neonatal head circumference			
Size	1.03 [0.77–1.39]; 0.823	0.81 [0.59–1.11]; 0.193	1.47 [1.03–2.09]; 0.035
Growth rate	0.99 [0.81–1.21]; 0.902	0.86 [0.69–1.07]; 0.173	1.06 [0.85–1.34]; 0.605
Neonatal BMI			
Size	0.81 [0.58–1.14]; 0.228	1.00 [0.71–1.42]; 0.998	1.58 [1.04–2.38]; 0.030
Growth rate	0.87 [0.74–1.03]; 0.097	0.91 [0.76–1.08]; 0.275	1.11 [0.91–1.36]; 0.305

*Risk estimates are adjusted for gender, gestational age, and mothers smoking during pregnancy.
Significant risk estimates are bold.

sensitization) in this prospective study of a birth cohort of young children at-risk for asthma.

Strengths of the study

The main strength of this study is the prospective collection of data in a tightly controlled single-center, clinical birth cohort study, which minimizes the risk of disease misclassification. All children of the cohort were monitored by daily diary cards and visits to the research clinic at 6-month intervals and at every symptomatic episode, where they were assessed by a study physician. Asthma and AD were diagnosed and treated in accordance with predefined algorithms. Allergic sensitization was objectively determined from specific IgE in blood samples minimizing the risk of interobserver variations.

The prospective birth cohort design is a strength because assessing size and growth before onset of disease avoids the risk of reverse causation. Four in five children with persistent asthma debut before the age of 5 (10). Therefore, studies of the association between anthropometrics and asthma later in life may in principle be confounded by early onset asthma affecting subsequent growth rate.

The study is strengthened by the high accuracy of the measurements of weight and length assessed at the research clinic thereby reducing the variability compared to midwives assessments (Fig. S1–S4). Length in particular is difficult to measure in neonates and infants. Therefore, trained assessment with dedicated tools is paramount. The objective assessment at all visits included weighing on a calibrated digital scale and assessment of length using an infantometer. Furthermore, the infancy growth trajectories were summarized by the linear regression of z-scores measured at the repeated visits to the research clinic during the first year of life. We treated z-scores as continuous measures and avoided defining thresholds of obesity as these are not well established in infants (17). This improved accuracy of assessing neonatal size and growth rate in infancy improves the sensitivity of our analysis.

It is a strength of our study that the association between postnatal size and growth rate and risk of asthma is analyzed in a longitudinal birth cohort study, that is, not influenced by underlying concurring lifestyle changes in the population studied cross-sectionally at long intervals.

The study applies two different analysis strategies. For the main analysis of asthma- and atopy-related endpoints at age 6 and 7, we used logistic regression analysis. Additionally, Cox regression was used for time-to-event, which increases the power and patient numbers as shown in our previous studies (13, 16). This leads to two different study populations. While the Cox analysis include all children until first event or dropout of the study, the logistic regression is based on the cross-sectional status at the end of the study period, which leads to a higher loss of subjects but includes children who have returned to the study. It is therefore a strength that both populations reached similar conclusions.

Limitations of the study

For the construction of z-scores we used WHO as reference material. Differences between Danish children and the global cohort used by WHO have previously been reported (18) and is likely the reason for the somewhat skewed distribution of birth measures. However, bias in z-score estimation is not expected to bias the results when children are compared internally within the cohort.

We assume a linear development of z-scores in infancy to predict postnatal growth rate. This is inaccurate but is nondifferential and was chosen to improve precision in the estimation of infancy size and growth from the repeated measurements.

We chose a conservative strategy for covariate adjustment including only a limited choice of co-variables to avoid overfitting of the statistical models. The co-variables (gender, gestational age, and mother's smoking during third trimester of pregnancy) were chosen *a priori* as those we recently reported from the same birth cohort to influence risk of asthma (19). Other potential confounders, such as duration of exclusive

breastfeeding (16), parity, and mothers' level of education, were also investigated but did not alter the conclusions. Still, residual confounding can never fully be ruled out.

The time-to-event analysis is indistinctive to asthma phenotypes and includes transient asthma diagnosis as well as persistent asthma diagnosis equally. Because it is well recognized that different asthma phenotypes exist in childhood also in this cohort (11), the Cox regression results may be somewhat distorted, and this may be a reason for the stronger signals found in the logistic regression analysis despite the lower patient numbers. The limitation of rather small sample sizes for the analyses (311 for asthma and AD analyses, and 293 for the allergic sensitization analysis) may lead to type 2 errors and could be the reason for the insignificant findings for length and growth rates.

Copenhagen Prospective Study on Asthma in Childhood is a selected cohort of high-risk children born to asthmatic mothers. Therefore, the findings from this investigation may not be generalizable to the general Danish background population. Results need replication in a nonselected cohort.

Interpretation

We found a positive and linear association between neonatal size in children born at term and the risk of asthma at age 7; that is, not only weight and BMI but also length and HC showed consistent association with asthma. The association is specific to asthma because no associations were found to AD or allergic sensitization. Our findings suggest that asthma is programmed very early in life probably even prenatally and share some common etiology to neonatal anthropometrics.

Our finding of an association between size and development of asthma finds support in a meta-analysis of 110 402 infants in nine studies showing that high birth weight (>4 kg) is a risk for asthma (20).

A previous birth cohort analysis found no association of birth weight to doctor-diagnosed asthma (21). The main difference is reliance on mailed questionnaires compared with our clinical follow-up with daily diary cards and algorithm-based diagnosis by the research doctors; and more accurate assessment of neonatal anthropometrics at our research clinic vs parents' report of midwives measurements.

In our recent study of a cohort of twins, we found birth weight inversely associated with the development of asthma (22). The observed relation between prevalence and birth weight in our twin cohort suggested that the effect was driven by children with very low birth weight (22), which was in agreement with previous studies (23). It is likely that extreme growth retardation involves other mechanisms that may have an associated risk of asthma. Therefore, understanding an association between the current epidemics of asthma and adiposity may need to be isolated from associations between extreme growth retardation and asthma, that is, may need to focus on studies in children born at term as in our present analysis. Larger HC at birth has previously been found a risk factor for asthma (24). Our results are largely consistent with these findings.

In our previous study of determinants for neonatal lung function, we found high BMI at birth to be associated with reduced lung function (19). Together, these findings suggest

that prenatal growth rate and neonatal size share some common etiology with asthma.

Surprisingly we only found neonatal sizes to be consistently associated with asthma, and not the infant growth rates. This discrepancy could be explained by our construction of infant growth divided based on size and growth rates. Adjusted for each other, size incorporates overall size in infancy, whereas the growth rates incorporate how each child adjust their changing environment from intra- to extra-uterine. Thereby, the general result that overall size in infancy appears to have a larger effect on later asthma than the growth rates indicate that the effect of prenatal growth (size) dominate the effects of infancy growth.

We found no association between neonatal anthropometrics and development of allergic sensitization that contrast another report (25).

Many prenatal factors are known to determine fetal growth and neonatal size. This could be shared genes or possibly these diseases could be linked by the mother's lifestyle creating a prenatal environment including nutrition initiating both an accelerated growth of the child and a disease process related to the development of asthma but not other atopy-related diseases. As infancy is a growth period of fat tissue, it could be speculated whether there is a causal relation between the developing adipose tissue and asthma (26) that work independent of other atopic diseases.

Conclusion

Neonatal size was found to be an independent risk factor for asthma but not for AD or allergic sensitization in Danish high-risk children. Our findings suggest some common etiology between neonatal size and development of asthma.

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Authors contributions

The guarantor of the study is HB who has been responsible for the integrity of the work as a whole, from conception and design to conduct of the study and acquisition of data,

analysis and interpretation of data and writing of the manuscript. AS is responsible for data analysis, interpretation and writing the manuscript. Both co-authors have contributed substantially to the analyses and interpretation of the data and have provided important intellectual input and approval of the final version of the manuscript.

Conflict of interest

The authors have no conflicts of interest relevant to this topic.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Methods.

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Supportive Information

Neonatal Size in Term Children is Associated with Asthma at Age 7, but not Atopic Dermatitis or Allergic Sensitization.

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Methods

DESIGN

The Copenhagen Prospective Study on Asthma in Childhood (COPSAC) is a single-center prospective clinical birth cohort study of 411 infants born at term of mothers with a history of a doctor's diagnosis of asthma. The newborns were enrolled across two visits to the clinic at 2 and 4 weeks; key exclusion criteria were severe congenital abnormality, gestational age <36 weeks, mechanical ventilation, and lung symptoms prior to enrolment as previously described in detail (1). The aim of the study is to identify early life causes of atopic diseases. Children were monitored closely with visits to the clinical research unit every 6 months and at any acute symptom. Data were collected on-line during visits and objective assessments were double checked against source data and the database subsequently locked. The database was monitored by an audit trail. The study is on-going, but for this analysis children are only analyzed until the age of 7.

ETHICS

The study was conducted according to the principles of the Declaration of Helsinki and was approved by The Copenhagen Ethics Committee (KF 01-289/96) and The Danish Data Protection Agency (2008-41-1754). Informed consent was obtained from both parents at enrolment ¹.

CLINICAL DIAGNOSES

Recurrent troublesome lung symptoms

Significant troublesome lung symptoms were recorded by the parents in daily respiratory diaries since the first month of life. The symptoms were explained as symptoms from the lower airways including wheeze, whistling or cough that clearly trouble the well-being of the child, disturbed the sleep or affected its physical activity. The doctors at the research unit reviewed symptom definition and the diary entries with the parents at the 6-monthly clinic visits. Recurrent troublesome lung symptoms were defined from five episodes within a 6 month period, each episode defined as at least three consecutive symptom days recorded in the diary. A 3-month trial of inhaled corticosteroids was initiated at this threshold and effect of this treatment assisted the diagnosis of asthma.

STATISTICAL ANALYSIS

For asthma and atopic dermatitis time-to-event associations were quantified in terms of hazard ratios (HR) by the Cox regression. Asymptotic 95% confidence intervals of HR were calculated on a log-scale

and back-transformed. Controls for functional form and proportional hazards were performed using plots and *P* values based on martingales and Schoenfeld residuals. *P*-values correspond to Wald tests. The analyses were done using PROC LOGISTIC and PROC PHREG in SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

69 of 396 children had been diagnosed with asthma before age 7, and 178 (44.9 %) children diagnosed with atopic dermatitis before age 7. Hazard ratios for first diagnoses of asthma and atopic dermatitis are presented in table E1.

References

1. Bisgaard H. The Copenhagen Prospective Study on Asthma in Childhood (COPSAC): design, rationale, and baseline data from a longitudinal birth cohort study. *Ann Allergy Asthma Immunol.* 2004;93:381–9.

Figure S1: Weight assessed at hospital at birth and at the clinic at 2-weeks shows relatively poor correlation. N=410. Pearson's $r=0.85$.

Y-axis: 0 weeks weight z-score, hospital data

X-axis: 2 weeks weight z-score, clinic data

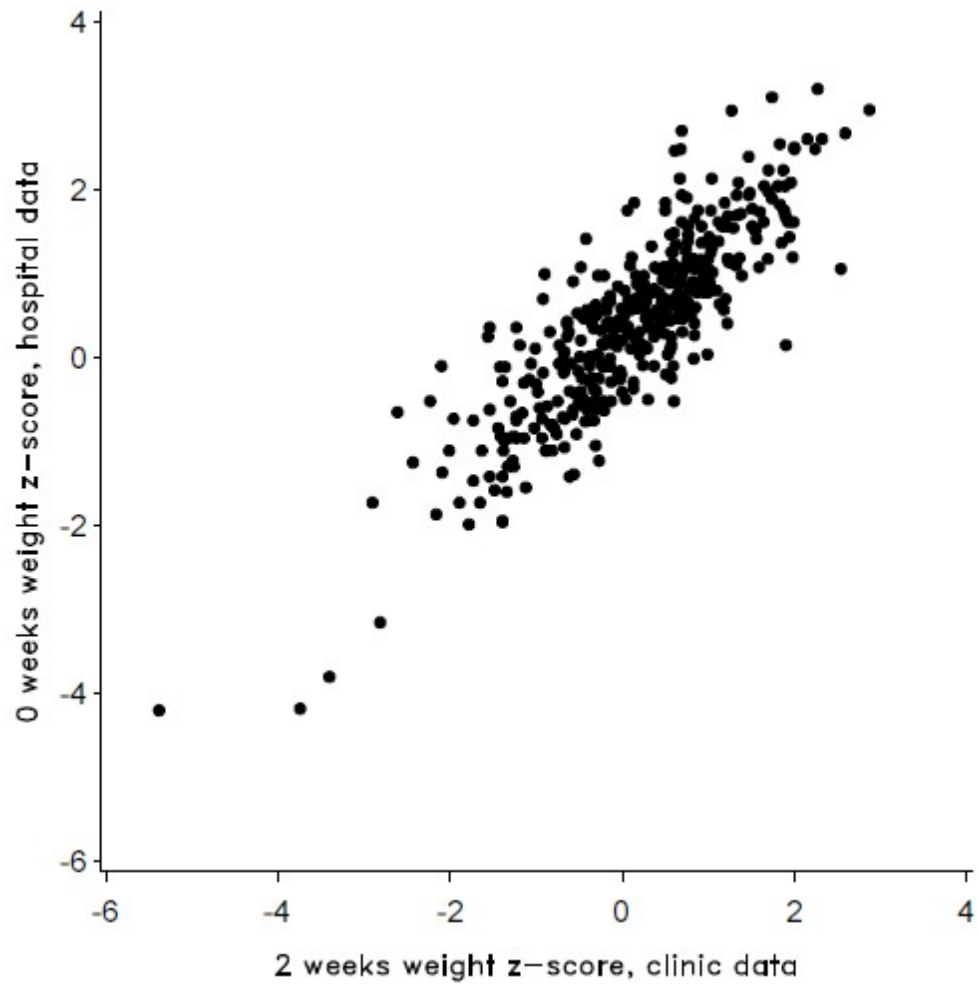


Figure S3: Length assessed at hospital at birth and at the clinic at 2-weeks shows relatively poor correlation. N=408. Pearson's $r=0.77$.

Y-axis: 0 weeks length z-score, hospital data

X-axis: 2 weeks length z-score, clinic data

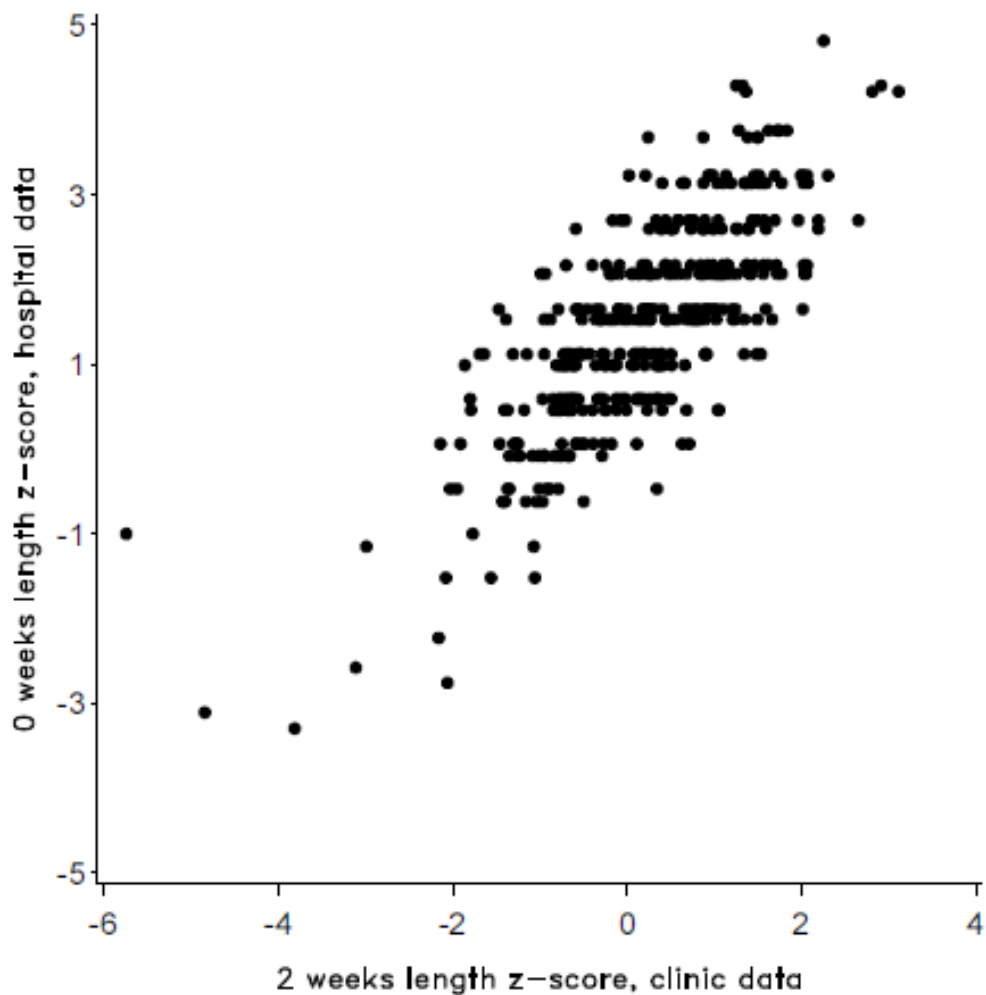
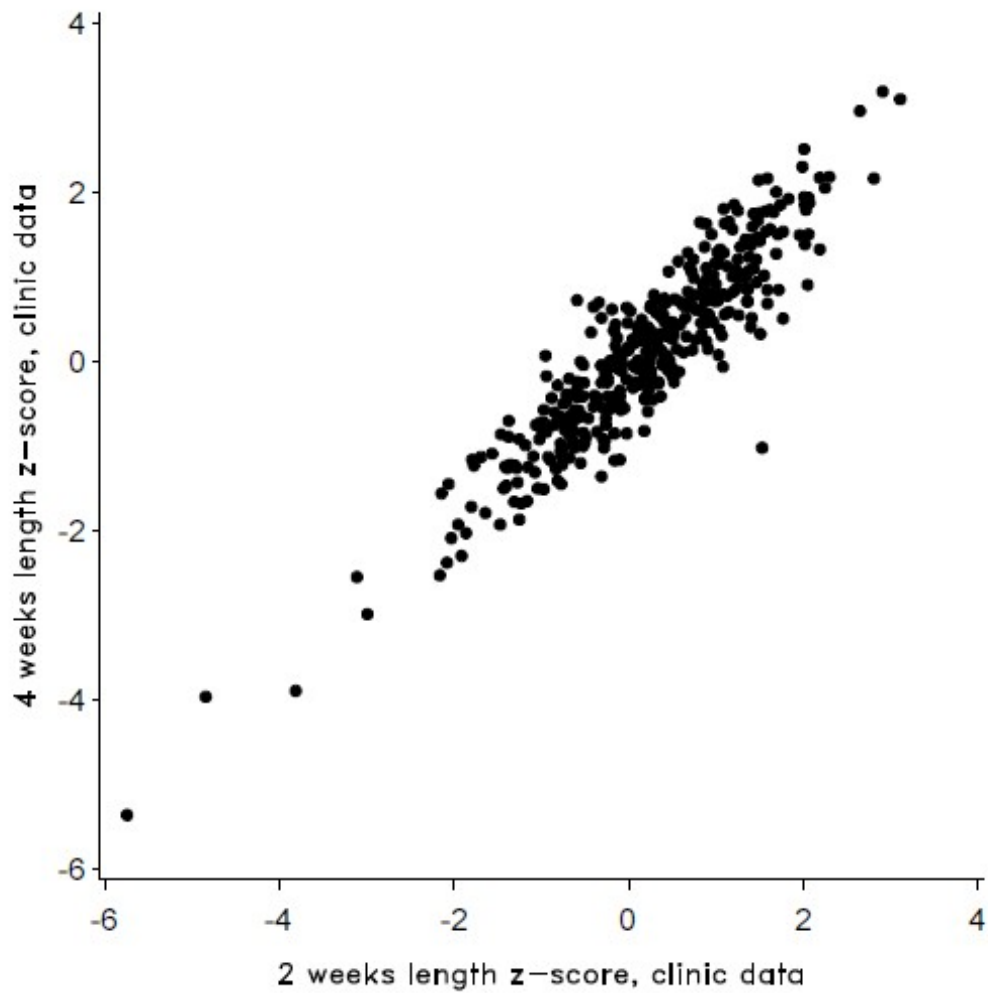


Figure S4: Length assessed at hospital at 2- and 4-week visit to the clinic shows improved correlation. N=398. Pearson's $r=0.92$.

Y-axis: 4 weeks length z-score, clinic data

X-axis: 2 weeks length z-score, clinic data



Tables

Table S1: Hazard ratios for first asthma diagnosis and first AD diagnosis by estimated birth weight, length, head circumference, and BMI. Confounder adjusted results.

HR* [95% CI]; p-value		First AD diagnosis N=396	First asthma diagnosis N=396
Neonatal weight	size	0.96 [0.79-1.16]; p=0.675	1.46 [1.08-1.96]; p=0.013
	growth rate	0.94 [0.85-1.04]; p=0.257	1.17 [1.00-1.36]; p=0.054
Neonatal length	size	0.95 [0.79-1.15]; p=0.592	1.20 [0.91-1.58]; p=0.207
	growth rate	0.94 [0.84-1.05]; p=0.275	1.13 [0.94-1.35]; p=0.192
Neonatal head circumference	size	1.06 [0.89-1.25] p=0.526	1.38 [1.05-1.81]; p=0.021
	growth rate	0.99 [0.89-1.10]; p=0.890	1.09 [0.93-1.29]; p=0.293
Neonatal BMI	size	1.00 [0.82-1.21]; p=0.975	1.44 [1.07-1.95]; p=0.017
	growth rate	0.97 [0.88-1.06]; p=0.509	1.12 [0.97-1.30]; p=0.130

* Risk estimates are adjusted for gender, gestational age, and mothers smoking during pregnancy.