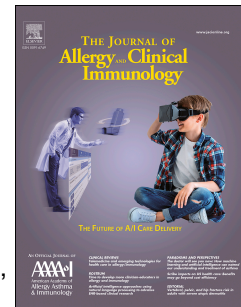


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Title: Infant Body Mass Index Trajectories, and Asthma & Lung Function

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36 writing this manuscript. The study design, results, conclusion and implications reported in
37 this manuscript are those of the authors involved in this study.

38 **Conflicts of Interest:**

39 Current follow-up of MACS study was funded by The National health and Medical Council
40 of Australia. The authors included in this study declare that they have no competing interests.
41 All authors declare: no support from any organization or no financial relationship with any
42 organization that could appear to have influenced the submitted work.

Abstract**Background**

The impact of early rapid body mass index (BMI) increase on asthma risk and subsequent lung function remains contentious, with limited prospective studies during a critical window for lung growth.

Objective:

We investigated the associations between BMI trajectories in the first 2 years of life, and adolescent asthma and lung function.

Methods

Anthropometric data was collected up to 18 times in the first 24 months on 620 infants from the Melbourne Atopy Cohort Study. BMI trajectories were developed using group-based trajectory modelling. Associations between these trajectories and spirometry, fractional exhaled nitric oxide, and current asthma status at 12 and/or 18 years of age were modelled using multiple linear and logistic regression.

Results

Five BMI trajectories were identified. Compared to the “average trajectory”, children belonging to the “early low and catch up” and “persistently high” BMI trajectories were at higher risk of asthma at 18 years (OR=2.2; 95%CI 1.0, 4.8 and 2.4; 1.1, 5.3 respectively). These trajectories were also associated with lower FEV1 by FVC, and higher FeNO levels at 18 years. In addition, children belonging to the “persistently low” trajectory had lower FEV1 (β =-183.9 ml; 95%CI -340.9, -26.9) and FVC (β =-207.8 ml; -393.6, -22.0) at 18 years.

Conclusion

In this cohort, “early low & catch up” and “persistently high” trajectories were associated with asthma and obstructive lung function pattern in adolescence. Having a persistently low BMI at an early age was associated with a restrictive pattern. Thus, maintenance of normal growth patterns may lead to improved adolescent respiratory health.

Word Count: 250

Key Messages

- Five infant BMI trajectories were identified: average, below average, persistently low, early low and catch up, and persistently high.
- Children with high BMI trajectories during the first two years of life are at risk of asthma and obstructive spirometric pattern during adolescence.
- Children with low BMI trajectory during the first two year of life are at risk of restrictive spirometric pattern during adolescence

Capsule Summary

Children in high BMI trajectories in the first two years of life may be at risk of asthma and obstructive lung function deficits while those in the low BMI trajectory may be at risk of restrictive lung function deficits.

Key Words

Infant body mass Index, early rapid growth, Body mass index trajectories, early growth pattern, group-based trajectory modelling, infant growth trajectories, growth developmental trajectories, asthma, and lung function

Abbreviations

BMI: Body mass index

MACS: Melbourne Atopy Cohort Study

ATS: American Thoracic Society

ERS: European Respiratory Society

Pre-BD: Pre-bronchodilator

Post-BD: Post bronchodilator

FeNO: Fractional Exhaled nitric oxide

FEV1: Forced expiratory volume in one second

FVC: Forced vital capacity

FEF25-75: Mid expiratory flow

FEV/FVC: Ratio of Forced expiratory volume in one second and forced vital capacity

GLI: Global Lung Function Initiative

DAG: Directed acyclic causal diagrams

ANU3_2: Australian occupational socioeconomic index

BIC: Bayesian information criterion

TEM: Total effect mediated

Introduction

Childhood asthma and poor lung function lead to disability in children and contribute substantially to subsequent chronic respiratory morbidity and mortality in adults.¹ The prevalence of asthma among children has increased dramatically over the last few decades,² which parallels adoption of a modern “Western” lifestyle.^{3,4} Therefore, obesity, a major characteristic of a modern lifestyle, has been identified as a potential modifiable risk factor for asthma and poor lung function.

While early life adiposity has been recognised as a risk factor for asthma,⁵ there are discrepancies in the recent findings about this association. Some studies reported an increased risk of asthma in children with early life obesity,^{5,6} but other studies were unable to replicate these findings.⁷⁻⁹ One of the major reasons for these inconsistent findings may be that studies that have investigated the link between obesity and asthma are either cross-sectional, or even if longitudinal, only investigated the impact of obesity by measuring body mass index (BMI) at one time point. To determine whether there may be a temporal and causal relationship between obesity and asthma and lung function, it is necessary to incorporate both the age of onset and the persistence of obesity as potential risk factors by developing BMI trajectories. More importantly, early life BMI trajectories could provide a better understanding of these links, given that early life is a critical time for lung growth and development.^{10,11}

Although previous studies have considered childhood obesity as a risk factor for the development of asthma and poor lung function,¹² only a few looked at the impact of early growth on subsequent respiratory health.^{5,13} Previous studies proposed an association between higher childhood BMI trajectories and development of poor respiratory health in adult life.^{5,14} However, these studies did not consider the early life growth, especially during infancy, which could confound this association. These two studies developed BMI trajectories from 1-7+ years, with 2 and 3 BMI data time points in the first year of life. No study to date has investigated the impact of infant BMI trajectories developed using more than 3 data time points on adolescent asthma and lung function, especially using spirometry with inhaled bronchodilator, to fill this critical knowledge gap.

Given the above knowledge gaps, we aimed to investigate the association of early life BMI trajectories (1-24 months) and the development of asthma and lung function during childhood and late adolescence (at 12 and 18 years of age).

Methods

Study Population and Design

We utilised data from the Melbourne Atopy Cohort study (MACS), that started as a randomised controlled trial to evaluate the impact of three different infant formulas (cow's milk, partially hydrolysed whey or standard soy formula) on the incidence of allergic diseases.¹⁵

Data collection

A total of 620 infants with a family history of allergic diseases were enrolled by recruiting pregnant women and their families from 1990 to 1994 from Melbourne, Australia. Eligible infants had at least one first degree family member with a history of any of the allergic diseases (eczema, asthma, allergic rhinitis, or food allergy). Initial approval for the study was given by the Mercy Maternity Hospital Ethics Committee and subsequently by the Royal Children Hospital. Detailed description of the MACS data collection has been published.¹⁵ Briefly, at baseline, information on sociodemographic characteristics, environment and respiratory health of family members was collected. Subsequently, interviewer administered questionnaires collected information on the health of the children including body weight and length/height at 18 time points from birth to 24 months, then at 12 and 18 years. Parents reported asthma status at 12 years, while participants self-reported asthma at 18 years. Spirometry was performed following standardised techniques at 12 years (without inhaled bronchodilator [pre-BD]) and 18 years (pre- and post-BD) (see details of lung function in supplement). Levels of fractional exhaled nitric oxide (FeNO) were measured at 18 years.

Body Mass Index

Body mass index (weight in kilograms divided by height in metres squared) was calculated and converted to z-scores. Data for weight and height was collected at 1-15, 18, 21 and 24 months during early follow-up visits). Age and sex standardized BMI z-scores (British growth chart) were generated using the "zanthro" function in Stata version 14.¹⁶ These z scores were used to develop BMI trajectories using age to define the time variable in trajectory analysis.

Outcomes

Outcomes for this analysis were: 1) current asthma (defined as the number of episodes [one or more] and/or use of asthma medications in the last 12 months), 2) lung function (FEV₁, FVC and FEV₁/FVC) at both 12- and 18-years, 3) lung function growth from 12 to 18 years

(change in FEV₁ and FVC), 4) FeNO at 18 years, and 5) bronchodilator responsiveness at 18 years (see details in supplement)

Covariates

Potential confounders between early life growth trajectories and asthma and lung function outcomes were determined by constructing directed acyclic graphs (DAGs)¹⁷ (supplementary Figures S I and S II). The resultant minimum set of confounders and details of assessment of confounding variables is available in the supplement.

Statistical Analysis

The analysis included all children with anthropometric data for at least 5-18 time points in the first two years of life. We developed trajectories of BMI z-scores measured at up to 18 time points during this period using group-based trajectory modelling, a type of finite mixture modelling using maximum likelihood to identify groups of individuals whose measurements followed a similar pattern over time.¹⁸ We fitted models with increasing numbers of trajectories. Initially, for a specified number of trajectories, different models with different polynomial functions were first compared sequentially to select the model with the highest order polynomial for which all parameters defining the polynomial were significantly different from zero. The most appropriate model with n distinct trajectories was then compared with the most appropriate model with $n+1$ distinct trajectories.¹⁹ Bayesian information criteria (BICs) were used to assess model fit. We selected the final model based on BIC fit along with shape and interpretation of the trajectories.

Associations between BMI trajectories and asthma (at 12 and 18 years) and bronchodilator responsiveness (at 18 years) were assessed using logistic regression models. Associations between BMI trajectories and lung function and FeNO were assessed using linear regression models. The “average trajectory” was used as a reference group for all analyses, as the distribution of this trajectory was around average BMI of the population (Z-score=0). All models (asthma and lung function) were adjusted for the minimum set of potential confounders; sex, breast feeding, mother’s age, parental history of smoking, parental education and socioeconomic status, family history of asthma, respiratory tract infection in the child’s first 2 years of life, age of introduction of first solid food, and number of siblings. There was no evidence for an interaction between BMI trajectories and infant formula allocation (trial intervention) in relation to asthma and lung function outcomes (all p values for interaction > 0.45). Hence, we adjusted the models for trial arms. We tested whether BMI at 18 years mediated the associations between BMI trajectories in early life and asthma and lung function outcomes by assessing total effect mediated (TEM) using the “medeff” package

in Stata. We were unable to consider the potential for BMI at 12 years as a mediator because of insufficient data. All analyses were performed using Stata version 14 (Stata Corp, College Station, TX, USA) with a group-based trajectory modelling plug-in.²⁰

Results

BMI Trajectories and their Characteristics

The numbers of participants with information on asthma status and spirometry at 12 and 18 years are described in Figure I. Five BMI trajectories were identified (Figure II). The ‘average’ trajectory included 154 children (25.3%), the ‘below average’ trajectory 182 (28.8%), the ‘persistently low’ trajectory 84 (13.3%), the ‘early low and catch up’ trajectory 109 (17.9%) and, the ‘persistently high’ trajectory 90 children (14.6%).

Distribution of most baseline variables (sex, parental age, parental education, parental history of smoking, parental history of asthma and age at solid introduction) of participants were similar across all five trajectories (Table I). However, duration of exclusive breast feeding was significantly shorter in participants who belonged to the ‘early low and catch up’ trajectory and the ‘persistently high trajectory’, compared to those who belonged to the average trajectory. Compared to participants in the ‘average’ trajectory, those in the ‘persistently low’ trajectory also had a significantly lower BMI at 18 years (supplementary Table S I & S II). Participants in other early life trajectories were not clearly different from those in the average trajectory in terms of BMI at either 12 years or 18 years.

BMI trajectories, Asthma and FeNO

At 12 years of age, 23.7% (85/359) of participants had current asthma, and at 18 years it was 23.5% (97/417). There was no evidence for any associations between early life BMI trajectories and asthma at 12 years of age (Table II). At 18 years, belonging to both the ‘early low and catch up’ (OR=2.23; 95%CI 1.03, 4.82) and the ‘persistently high’ (OR=2.42; 95%CI 1.11, 5.38) trajectories was associated with an increased risk of asthma. Consistent with this association, belonging to the ‘early low and catch up’ trajectory was associated with increased FeNO levels at 18 years (β =16.7ppb, 95%CI 0.31, 33.0), and there was also some modest evidence for association for belonging to the ‘persistently high’ trajectory (β =13.42ppb, 95%CI -3.33, 30.18) (see Table III). We did not see an interaction with sex at 12 years (p-value; 0.511) or 18 years (p-value: 0.434) in case of BMI trajectories and asthma. Similarly, no interaction was found with current BMI at 12 years (P-value; 0.829) and current BMI at 18 years (p-value; 0.989).

BMI Trajectories and Pre-BD Lung function

There was no evidence that early life BMI trajectories were associated with pre-BD lung function (FEV₁, FVC, FEV₁ by FVC and FEF₂₅₋₇₅) at 12 years of age. However at 18 years, pre-BD FEV₁ by FVC was lower in those belonging to the ‘below average’ ($\beta=-2.0$; 95%CI -4.0, -0.01), the ‘early low and catch up’ ($\beta=-2.4\%$; 95%CI -4.8, -0.1) and the ‘persistently high’ ($\beta=-2.5\%$; 95%CI -4.9, -0.1) trajectories when compared to the “average” trajectory (see Figure III. Similar findings were present for pre-BD FEF₂₅₋₇₅. Details are in supplementary Tables S III. There was no evidence for an association between the trajectories and bronchodilator responsiveness as a categorical variable or a continuous variable (Supplementary Table S IV).

BMI Trajectories and Post-BD Lung function

There was evidence that belonging to the ‘persistently low’ trajectory was associated with a lower post-BD FEV₁ ($\beta=-183.9\text{ml}$; 95%CI -340.9, -26.9) and FVC ($\beta=-207.8\text{ml}$; 95%CI -393.6, -22.0). Belonging to both the ‘below average’ ($\beta=-126.3\text{ml}$; 95%CI -250.4, -2.2) and ‘early low and catch up’ ($\beta=-191.6\text{ml}$; 95%CI -339.6, -43.8) trajectories were associated with a lower post-BD FEV₁. In addition, belonging to the ‘below average’ ($\beta=-1.5\%$; 95%CI -3.1, -0.2), ‘early low and catch up’ ($\beta=-2.1\%$; 95%CI -4.1, -0.2), and ‘persistently high’ ($\beta=-3.1\%$; 95%CI -5.1, -1.2) trajectories were associated with a lower post-BD FEV₁ by FVC, consistent with an obstructive pattern. Belonging to these three trajectories were also related to a lower post-BD FEF₂₅₋₇₅ ($\beta=-436.2\text{ml/s}$ 95%CI -713.6, -158.8, $\beta=-612.5\text{ml/s}$; 95%CI -943.0, -281.9 and $\beta=-440.9\text{ml/s}$; 95%CI -777.5, -104.2, respectively) (Figure III). We found similar and consistent results to adjusted raw values using z-scores of lung function indices for the analysis (Supplementary Table S V).

BMI Trajectories and Lung Function change from 12 years to 18 years

The BMI trajectories were not significantly different with respect to lung function growth from 12 to 18 years. (supplementary Figure SIII).

Mediation by BMI at 18 Years

We found that low BMI at 18 years partially mediated the association between the belonging to “persistently low” BMI trajectory in infancy and low lung function outcomes; by 17% (95%CI= 9, 77%) for post-BD FEV₁ and 28% (95%CI= 16, 110%) for post-BD FVC (supplementary Table S VI). There is no evidence that the associations between belonging to the other early life BMI trajectories and asthma were mediated by BMI at 18 years.

Discussion

This study is the first to investigate the association between BMI trajectories developed using 18 time point BMI data in the first two years of life and subsequent asthma, pre- and post-BD lung function in adolescents. We identified five BMI trajectories. Belonging to both ‘early low and catch up’ and ‘persistently high’ BMI trajectories were associated with current asthma and lower pre-BD and post-BD FEV₁ by FVC (i.e. obstructive physiology) and higher FeNO levels, at the age of 18 years. A novel finding was the link between belonging to the ‘persistently low’ BMI trajectory and low post-BD FEV₁ and FVC with a normal FEV₁ by FVC at the age of 18 years, i.e. a more restrictive spirometric pattern. Associations between BMI trajectories and asthma and lung function at 12 years of age were in similar directions as the 18-year, however there was not enough evidence to support these findings.

While studies have previously reported associations between BMI trajectories through childhood/adolescence and asthma,^{5,10,11,14} none of them had investigated only growth in the first two years of life, a time of rapid and dynamic physiological lung changes and development.²¹ Rzehak et al identified three BMI trajectories from 0 to 6 years of age using data at 7 time points: normal, early rapid growth and persistently rapid growth, and found that belonging to the early rapid growth trajectory was related to a higher risk of asthma at 6 years.⁵ Wadden et al reported three BMI trajectories from 0-10 years using data at 5 time points: stable, decreasing and increasing. They found that the increasing BMI trajectory was associated with asthma at age 10 years in girls.¹¹ Ziyab et al. identified four BMI trajectories, using data from four time points from age 1 to 18 years: normal, early transient overweight, delayed overweight and early persistent obesity.¹⁰ The early persistent obesity group was associated with increased risk of asthma and lower pre-BD FEV₁/FVC at the age of 18 years. Another study in children aged 6-11 years, using data at 6 time points, reported four BMI trajectories: normal growth, rapid growth, persistently overweight and obese and later decline.¹⁴ The persistently overweight trajectory was associated with an increased risk of asthma, while the rapid growth trajectory and persistently overweight trajectories were both associated with a lower pre-BD FEV₁ by FVC at the age of 12 years.¹⁴

None of these previous trajectory studies could be directly compared with our study, given neither the age span of their BMI trajectories nor reference group (the lowest trajectory was used as the reference point in all previous studies) were like our study. Nevertheless, the findings have some consistency. Overall, these studies showed an association of early childhood rapid BMI increase or persistently high BMI trajectories with asthma and obstructive lung function during adolescence. Similarly, we found associations of the

“persistently high” and “early low and catch-up” trajectories with asthma and poor lung function at 18 years.

The richness of anthropometric data collected in early infancy in our study allowed us to identify five BMI trajectories. In contrast, the highest number of BMI trajectories identified in previous studies were four through childhood^{5,10,11,14}. None of the previous studies identified either the persistently low BMI trajectory or investigated the association between BMI trajectories and post-BD lung function. Therefore, our finding of a link between the persistently low BMI trajectory and a restrictive spirometric pattern is novel. The association between the persistently low BMI trajectory and restrictive spirometric pattern was only partially mediated by low BMI at age 18 years, suggesting that the impact of low BMI in early life may potentially be due to under-development of the lung parenchyma.

One of the suggested underlying mechanisms for the association of high adult BMI with subsequent asthma and obstructive lung function is adiposity-related systemic inflammation and reduction in lung volumes.²² We propose that the same mechanism could contribute to poor development of lungs during the first two years of life. Early infancy is a critical period for the development of respiratory system. Adipose tissues release pro-inflammatory cytokines leading to macrophage proliferation in lung tissues with subsequent airway inflammation.^{22,23} Such inflammation in early life may influence asthma and long-term lung function. Other mechanisms may include shared genetic factors, epigenetic effects through prenatal diet; changes in gut microbial flora and maternal smoking during pregnancy.^{24,25} These mechanisms might affect the development of the infant immune system and somatic growth. Given high infant BMI is associated with the development of obesity in later life,²⁶ the impact of later life obesity may be a one of the reasons for the associations observed. Using transverse airway sections from post-mortem lungs, Elliot et al found the accumulation of adipose tissue within the airways itself, in obese participants with asthma, was associated with a greater wall thickness and inflammation in an adult population.²⁷ This possible mechanism of adipose tissue in the airways provides additional biological plausibility for increased asthma in high BMI trajectories and may also be relevant to adverse obesity-related lung function changes during early life. Other possible mechanisms that could affect the airways include the impact of high BMI on hormonal imbalance (lower progesterone production leading to decreased β_2 -receptor function), oxidative stress (associated with increased 8-isoprostane) and release of adipokines (high levels of interleukin-6, tumour necrosis factor- α and leptin).⁷

A possible mechanism of association between persistently lower BMI trajectory and a restrictive spirometric pattern in our study could be reduced skeletal muscle mass in underweight individuals. Loss of abdominal wall, diaphragmatic and intercostal muscle mass could affect respiratory muscle strength and force.²⁸ Another possible reason could be smaller lung size because of poor or under nutrition. We found a low BMI at 18 years for participants with the persistently low trajectory compared to those with the average trajectory, while 18-year BMI was not different for all the other trajectory groups (Table SI). This indicated that those who belong to a persistently low BMI trajectory during first 2 years of life can have lower BMI during adolescence. The mediation analysis suggested lower BMI in late adolescence mediated around a quarter of the association between early life persistently low BMI trajectory and adolescent lung function. Other possible mechanisms would be impaired immunity, other morbidities and physical inactivity related to being underweight.²⁹ This study has a number of important strengths, but also some limitations. The high frequency of BMI (mean =17.5) assessments allowed us to accurately identify BMI patterns using group-based trajectory modelling. Long-term follow-up and repeated lung function assessments were also major strengths. One of the limitations of our study is that small study sample and further loss to follow-ups at 12 and 18 years. However, neither exposure or outcome were related to the loss to follow-up in our study. Therefore, we expect that loss to follow-up may have a minimum influence on the results. Furthermore, we were unable to adjust the full analysis for some potential confounding factors due to missing data e.g. gestational age and birth weight. Another limitation of our study is that we did not measure body composition to investigate the impact of adiposity, however BMI z-scores in children have been found to be closely related to overall adiposity.³⁰ A recent study showed both higher fat mass and BMI trajectories were associated with lung function deficits suggesting that BMI can be used as a surrogate of fat mass.³¹ Similarly, the lung volumes were not measured and therefore we cannot establish the link between trajectories and true lung restriction. Another limitation in this study was that the lung function was not measured earlier than 12 years. Additionally, lung function was measured using different spirometry equipment at 12 and 18 years. This would not affect the age-specific analysis while this could have affected the results for lung function growth. Such misclassification is likely to be non-differential and may have contributed to the null results in the analysis of the lung function growth. We were unable to investigate the lung function growth using post-BD lung function as post-BD was not performed at 12 years. Furthermore, in our mediation analysis, the mediator of the association, BMI at 18 years, was measured at the same time as the outcome.

This is a limitation of this analysis, however, BMI at 18 years is likely to be a proxy the past BMI. Finally, results should be generalised with caution as we studied a high-risk cohort for asthma and allergies. Studies conducted in high risk group can only be applicable to high risk cohorts. These high-risk groups could have high risk of development of the outcome.

In conclusion, the findings are novel given that this is the first study to investigate BMI trajectories in the first two years of life and their association with both pre- and post-BD lung function. Our findings suggest that infants who belonged to a high BMI or an early low and catch-up BMI trajectory from birth to 2 years had an increased risk of asthma and an obstructive spirometric pattern at age 18 years. In contrast, infants who belonged to the persistently low BMI trajectory had an increased risk of a restrictive spirometric pattern at age 18 years, which may be related to global reduction in lung growth or maybe a lower respiratory muscle mass and so power of inspiration/expiration. We found that a shorter duration of exclusive breast feeding, and early introduction of solid food were both associated with high BMI trajectories (Table S II). Our findings highlight that a stable average BMI in early infancy is very important for adolescent respiratory health. Early healthy feeding practices to maintain normal growth patterns in early life may lead to improved respiratory health outcomes later in life. Finally, some of the estimates in our study are imprecise due to small sample size, therefore we do recommend replication of our study findings.

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Authors' contributions

Acquisition of data: SCD, AJL, CL, M.A, and HEW. Analysis and interpretation of data: GBA, SCD, AJL, DSB., HEW, and JLP. Drafting of the manuscript: GBA, SCD, AJL, and DSB. Critical revision of the manuscript for important intellectual content: GBA, SCD, AJL, DSB, CL, JLP, NTW, CS, MJA, and HEW. Statistical analysis: GBA, SCD, AJL, DSB. Obtained funding: SCD, AJL, CL, MJA, NTW, DBS.

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536 **Tables**537 **Table I: Early life characteristics of the BMI trajectory groups**

Baseline Characteristics	Average Trajectory (N=154)	Below average Trajectory (N=182)	Persistently low Trajectory (N=84)	Early Low and catch up Trajectory (N=109)	Persistently high Trajectory (N=90)
Gender N (%)					
Male	76 (49·40)	89 (48·90)	40 (47·62)	64 (58·72)	46 (51·69)
Mother's Age (Years)					
Mean (SD)	31·3 (4·28)	31·0 (4·50)	32·1 (4·39)	31·1 (4·23)	31·0 (4·32)
Father's Age (Years)					
Mean (SD)	33·4 (5·27)	33·5 (5·14)	33·6 (5·64)	33·1 (5·47)	32·8 (4·88)
Mother's Education - N (%)					
Bachelor's degree (>14 years)	100 (64·94)	104 (57·14)	56 (66·67)	59 (54·13)	45 (50·00)
Father's Education - N (%)					
Bachelor's degree (>14 years)	95 (61·69)	112 (61·88)	53 (63·10)	66 (61·11)	52 (58·43)
Mother's Smoking - N (%)					
Ever	32 (20·78)	45 (24·73)	21 (25·00)	34 (31·19)	27 (30·00)
Father's Smoking - N (%)					
Ever	50 (32·47)	59 (32·78)	32 (38·10)	34 (31·48)	30 (34·09)
Mother's Asthma - N (%)					
Asthma	64 (41·56)	75 (41·44)	29 (34·52)	55 (50·46)	44 (48·89)
Father's Asthma - N (%)					
Asthma	46 (29·87)	39 (21·67)	20 (23·81)	19 (17·59)	34 (38·64)
Age at Introduction of Solid Food (Weeks)					
Mean (SD)	19·6 (4·10)	20·4 (4·37)	19·4 (3·85)	19·2 (4·91)	18·5 (4·54)
Exclusive Breast Feeding (Weeks)					
Mean (SD)	14·5 (8·46)	13·6 (9·47)	12·0 (8·84)	9·4 (8·90)	10·2 (8·63)
Total Duration of Breast Feeding (Months)					
Median (IQR)	11·51 (8·28)	10·58 (10·13)	10·13 (9·32)	7·36 (10·82)	6·44 (8·28)

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539 **Table II: Adjusted associations between BMI trajectories and asthma at 12 and 18 years of age.**

	Asthma at 12 Years			Asthma at 18 Years		
	% (n)	Unadjusted OR (95% CI) (N=359)	Adjusted* OR (95% CI) (N=355)	% (n)	Unadjusted OR (95% CI) (N=413)	Adjusted* OR (95% CI) (N=406)
Average (Reference)	20.7 (17/82)	-	-	19.4 (20/103)	-	-
Below average	24.1 (26/108)	1.21 (0.61, 2.42)	1.36 (0.66, 2.83)	26.6 (33/124)	1.50 (0.80, 2.83)	1.81 (0.92, 3.56)
Persistently low	18.8 (9/48)	0.88 (0.35, 2.17)	1.16 (0.45, 2.98)	8.9 (5/56)	0.41 (0.14, 1.15)	0.52 (0.18, 1.54)
Early Low and catch up	30.8 (20/65)	1.69 (0.80, 3.59)	2.01 (0.90, 4.44)	29.9 (20/67)	1.76 (0.86, 3.61)	2.23(1.03, 4.82)
Persistently high	23.2 (13/56)	1.16 (0.51, 2.62)	1.31 (0.54, 3.12)	30.2 (19/63)	1.79 (0.86, 3.71)	2.42(1.11, 5.28)

540 *Adjusted for Sex Mother's age, Father's income and occupation, Mother's asthma, education and smoking, Breast feeding, Bronchitis, Upper
 541 respiratory tract infection, RCT-Treatment arm, Number of siblings, and Age at solid start.

542 The overall 4df test comparing among the 5 trajectories was significant at 18 years with p=0.017

543 **Table III: Adjusted fractions of exhaled nitric oxide (parts per billion) at 18 years of age for different BMI trajectories.**

BMI Trajectories	FeNO (ppb) Coefficient* (95% CI) N=362	544
Average (Reference)	-	545
Below Average	-1.28 (-15.25, 12.68)	546
Persistently Low	1.24 (-16.34, 18.82)	547
Early Low & Catchup	16.7 (0.31, 33.0)	
Persistently High	13.4 (-3.33, 30.2)	548

549 *Adjusted for Sex Mother's age, Father's income and occupation, Mother's asthma, education and smoking, Breast feeding, Bronchitis, Upper
 550 respiratory tract infection, RCT-Treatment arm, Number of siblings, and Age at solid start.

551 The overall 4df test comparing among the 5 trajectories was significant at 18 years with p=0.015

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553

554 **Table. IV: Summary results of lung function indicators at 12 and 18 years of age for different BMI trajectories.**

Lung Function Indicators	BMI Trajectories	At 12 Years	At 18 Years Pre-BD	At 18 Years Post-BD
FEV₁ (mL)	Average (Reference)	-	-	-
	Below Average			↓
	Persistently Low			↓
	Early Low & Catchup			↓
	Persistently High			
FVC (mL)	Average (Reference)	-	-	-
	Below Average			
	Persistently Low			↓
	Early Low & Catchup			
	Persistently High			
FEV₁/FVC	Average (Reference)	-	-	-
	Below Average		↓	↓
	Persistently Low			
	Early Low & Catchup		↓	↓
	Persistently High		↓	↓
FEF₂₅₋₇₅ (mL/s)	Average (Reference)	-	-	-
	Below Average			↓
	Persistently Low			
	Early Low & Catchup		↓	↓
	Persistently High			↓

555 The overall 4df test comparing among the 5 trajectories was significant for Pre-BD lung function at 18 years with p=0.049 and Post-BD lung
 556 function at 18 years with p=0.0198.

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Figures

Figure I: Details of the present study data collection and sample sizes at each follow-up stage.

Figure II: Body Mass Index Z- Score Trajectory Classes Across Ages from 1 to 24 Months.

Figure III : Association* of BMI Trajectories from 0-2 years of age with lung function at 12 and 18 years of age.

* Adjusted for Mother's age, Father's Income and Occupation, Mother's asthma, education and smoking, breast feeding, bronchitis, upper respiratory tract infection, number of siblings, RCT-Treatment arm, age at solids started, current height, age and sex.

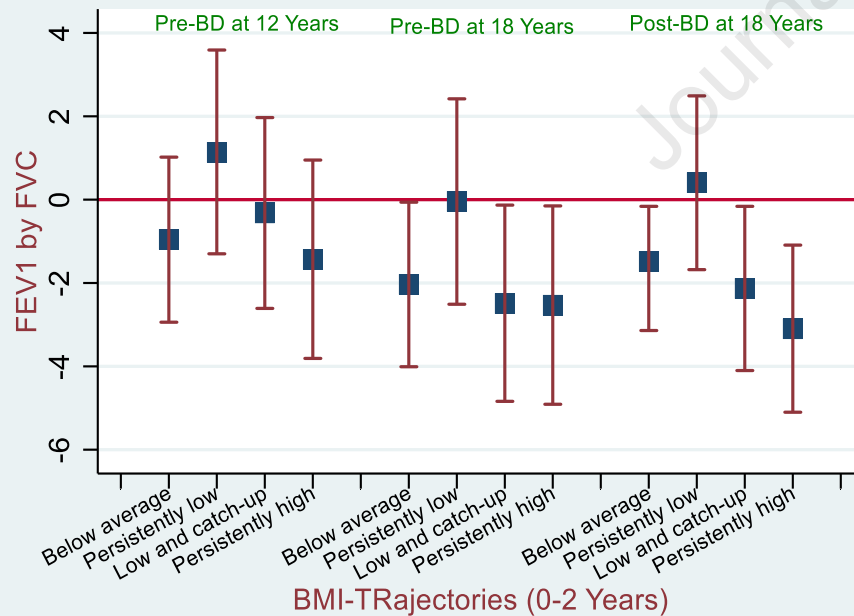
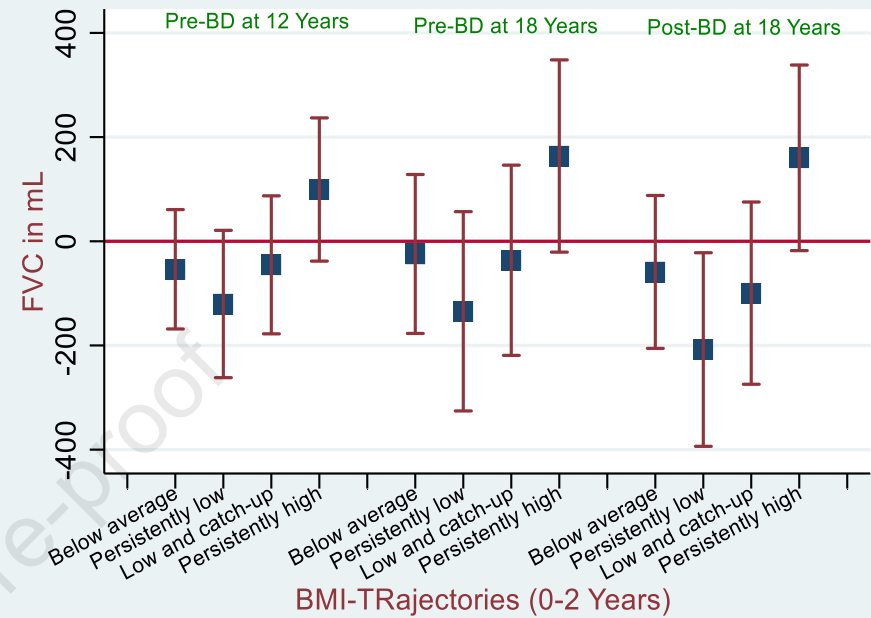
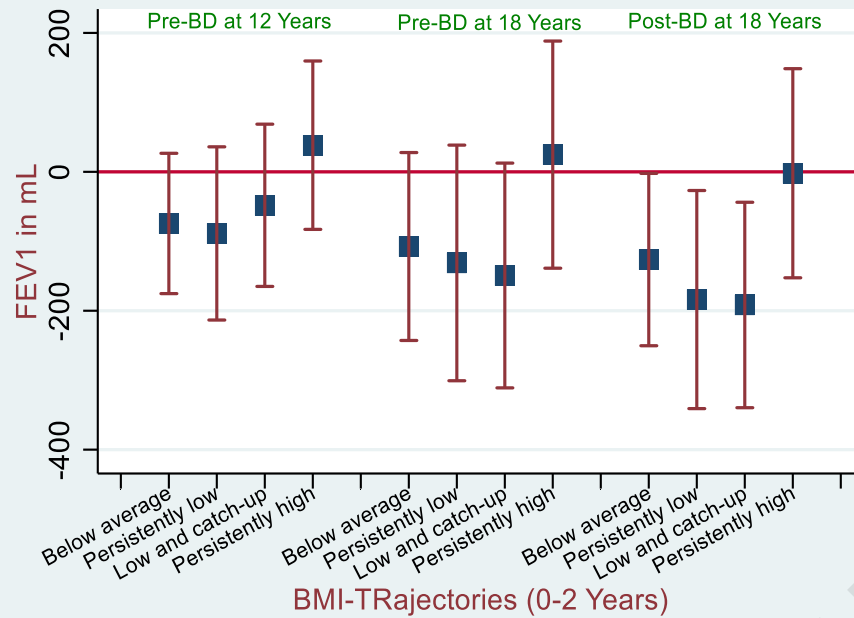


Figure 3: Association of BMI Trajectories from 0-2 years of age with lung function at 12 and 18 years of age

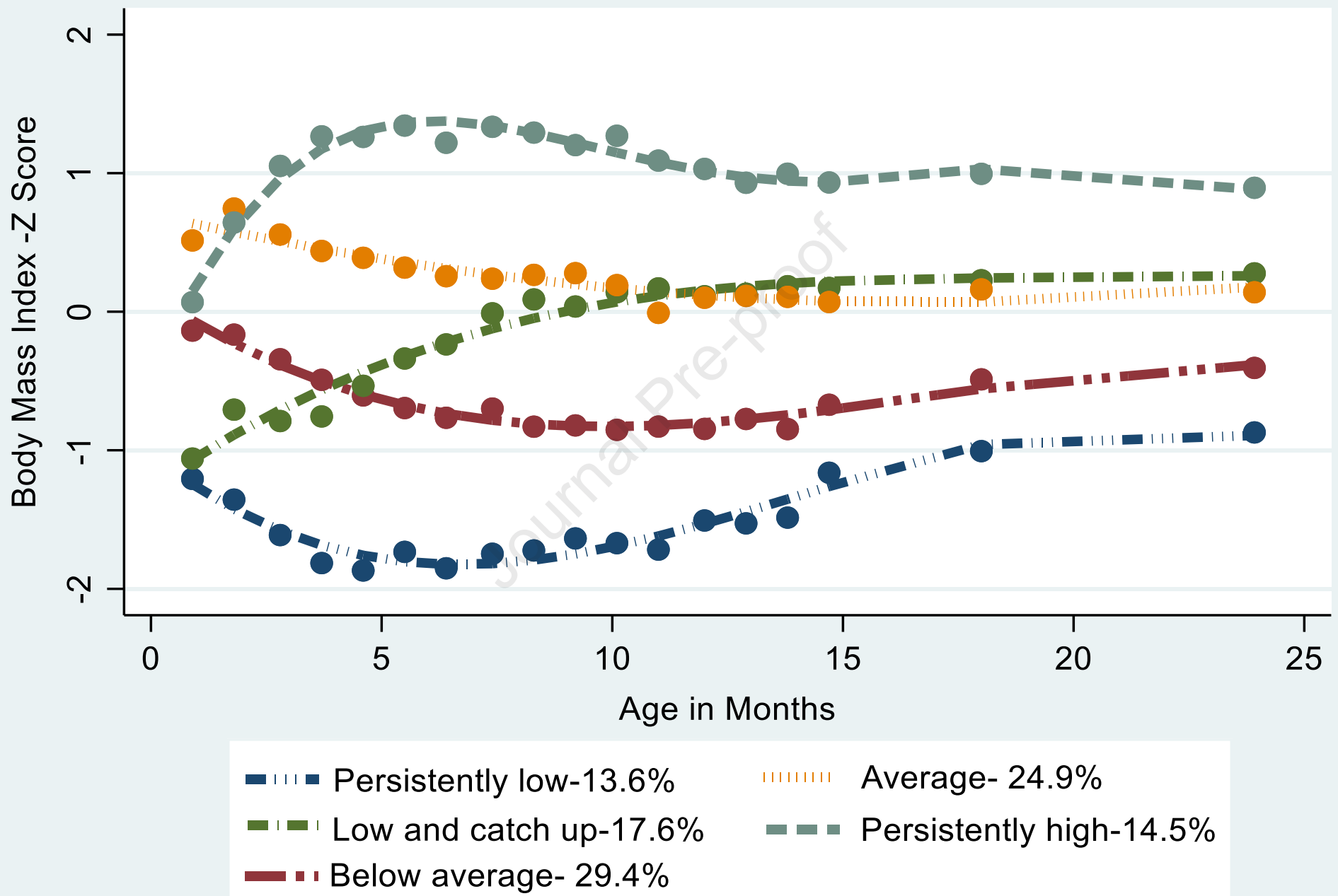


Figure 2: Body Mass Index Z- Score Trajectory Classes Across Ages from 1 to 24 Months

Figure 1: Details of the present study data collection and sample sizes at each follow-up stage.

