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Associations between Body Mass Index Trajectories in the first two years of life and Allergic Rhinitis, Eczema and Food Allergy outcomes up to early adulthood

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(i) Title: Associations between Body Mass Index Trajectories in the first two years of life and Allergic Rhinitis, Eczema and Food Allergy outcomes up to early adulthood

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(i) Conflict of Interests

MJA holds investigator initiated grants from Pfizer, Boehringer-Ingelheim and GSK for unrelated research. He has undertaken an unrelated consultancy for and received assistance with conference attendance from Sanofi. He has also received a speaker's fee from GSK. SCD, AJL and CJL hold an investigator grant from GSK for unrelated research. AJL has received EpiCeram as an interventional product from Primus Pharmaceuticals for unrelated research. MLKT has no conflicts of interest related to this research. MLKT has an unrelated conflict of interest: she is an employee of, and hold share options/interest in, Prota Therapeutics and she has received consultancy fees from Pfizer. She is also inventor on a number of patents. None of these relationships are of relevance to this publication. All authors declare no conflicts of interest in regards to this work.

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(iii) Abstract and keywords

Background

Early life Body Mass Index (BMI) trajectories influence the risk of asthma at 18 years of age. However, it is unclear if these are also associated with other allergic diseases.

Objectives

We investigated the associations between BMI trajectories and subsequent allergic rhinitis, eczema and food sensitisation/allergies.

Methods

Parent-reported anthropometric data were collected 18 times in the first two years of life from a cohort of 620 participants in a high-risk cohort. Group-based trajectory modelling was applied to develop BMI trajectories. Associations between trajectories and allergic rhinitis, eczema and food sensitisation at 6,12, and 18 years of age were assessed using logistic regression models. Potential effect modifications by parental allergic disease, sex and allocated infant formula were assessed.

Results

We identified five BMI trajectories: average, below average, persistently low, early low and catch up, and persistently high. None showed an association with allergic rhinitis. In participants with maternal allergic rhinitis, "early low and catch up" (OR=2.83;95%CI 1.34-5.96, P_{int}=0.05) and "below average" trajectories (OR=2.39; 1.18-7.23, P_{int}=0.02) were associated with allergic rhinitis at 18 years of age compared to the average trajectory. No associations were observed with eczema or food sensitisation.

Conclusion

Infants with early low and catch up, or below average BMI growth, were at increased risk of allergic rhinitis at 18 years if they had a mother with allergic rhinitis. These results require replication, but suggest that interactions between poor intrauterine growth, failure to thrive, and maternal allergies may influence risk of allergic rhinitis.

Keywords: Allergic rhinitis, Body mass index trajectories, Eczema, Food allergies, Group-based trajectory modelling

(iv) Main Text

Introduction

Obesity has been implicated in the aetiology of allergic diseases.[1] While many studies have explored the association between adiposity at a single time point and allergic diseases,[2, 3] few studies have examined longitudinal associations between trajectories of adiposity and allergy disease outcomes.[4-8] Trajectories can reflect the dynamic growth over time, and could elucidate the critical time window that adiposity is associated with allergic diseases.[9]

Recent research suggested early childhood Body Mass Index (BMI) trajectories may influence the risk of asthma.[4, 6] Previously, we identified five distinct BMI trajectories in the first two years of life. The "persistently high" and "early-low and catch-up" trajectories were associated with asthma at 18 years of age.[6] Ziyab et al. reported children in the "early persistently obesity" trajectory from infancy to 18 years of age had a higher odds of adolescent asthma compared to other trajectories.[4]

No prior study has investigated associations between BMI trajectories in the first years of life with allergic rhinitis, eczema or food allergies. The only study explored the association with allergic rhinitis,[8] identified that the "persistently overweight" trajectory from age 6 to 11 was associated with allergic rhinitis at 12 years and incident allergic rhinitis up to early adulthood. This study did not have BMI data prior to aged 6. This is a critical knowledge gap, as the first years of life are associated with rapid and dynamic changes in growth and could be the focus of early prevention measures if likely to be associated with later allergic respiratory diseases.

Our objective was to investigate the association between BMI trajectories within the first 2 years and the risk of allergic diseases, other than asthma, up to 18 years of age using the previously developed trajectories.[6] Our *a priori* primary outcome was allergic rhinitis, which was selected due to its close relationship to asthma and because it is rarely expressed in the first two years of life, when our BMI trajectories were defined. Secondary outcomes were incidence and persistence of eczema and food

allergies from 2 years of age, due to challenges establishing the temporal sequence of the onset of these conditions. We also explored whether sex, parental allergic diseases, and allocated formula received at weaning modified these associations as these factors may impact both growth and risk of allergic diseases.

Methods

Study Population

The Melbourne Atopy Cohort Study (MACS) was initially a randomised controlled trial of the effects of three formulas at weaning on allergic diseases (cow's milk, soy, and partially hydrolysed whey).[10, 11] A total of 620 full-term infants, with a first degree relative with a history of eczema, asthma, allergic rhinitis, or food allergy, were recruited prior to birth. The study was approved by the Mercy Maternity Hospital Ethics Committee (R07/20 and R88/06) and the Royal Children's Hospital Ethics Committee (#28035).

Data Collection

Baseline information was collected at recruitment. A trained nurse surveyed mothers at 18-time points between 0 to 2 years old and annually from aged 3 to 7 years. Parent-reported and self-reported questionnaires were administered at 12 and 18 years respectively.[10] All surveys included questions on the development of allergic diseases and symptoms, and medication use. Anthropometric measurements were collected in all surveys, except 3 to 7 years of age.

Skin prick tests (SPT) to cow's milk, egg white, peanut, dust mite, rye grass and cat dander were performed at 6, 12, 24 months, and 12 years of age according to a standard technique.[12] At the 18 years follow up, SPT to cashew, shellfish, mixed grass pollen, *Alternaria*, *Cladisporium*, *Homodendrum*, and *Penicillium* were also performed. A positive (Histamine 1 mg/mL) control was used for all follow ups.[13, 14]

Exposure Definition

BMI (kg/m^2), was standardised into z-scores using Stata package Zanthro to compare BMI across different age and sex groups.[6] As post birth growth charts for the Australian population are not currently available, the UK 1990 Growth Reference was used, which matched the time frame of recruitment for MACS. BMI trajectories were developed using group-based trajectory modelling with z-scores from up to 18-time points between ages 0-2 years. The final model was selected based on the model fit using the Bayesian Information Criterion, the shape and the interpretability of the trajectories.

Outcome Definitions

Current allergic rhinitis at 6 and 12 years of age: parents reporting one or more episodes of "hay fever" in the past 12 months.

Current allergic rhinitis at 18 years of age: one or more episodes of hay fever in the past 12 months OR a history of hay fever and medication used for the symptoms in the last 12 months.

Non-atopic rhinitis and atopic rhinitis at 12 and 18 years of age: classification of rhinitis was based on the sensitisation and allergic rhinitis status at the measured time point. Sensitisation was assessed using SPT, and atopy was defined as a 3mm or greater wheal to one or more of the aeroallergens. SPT results were only considered valid if participants produced a positive control wheal diameter of 3mm or greater.

Persistence eczema, new onset eczema, current food sensitisation and probable food allergies outcomes: defined in the supplementary. We limited this analysis to current food sensitisation/ probable food allergies because very few food sensitisation cases developed after 2 years of age.

Statistical Analysis

Logistic regression was used and all associations were presented as odds ratios and 95% confidence intervals, estimated using Stata (v15).[15] Multinomial models were used to examine the associations between BMI trajectories and rhinitis, which was a variable with four strata i.e. atopic rhinitis/non-atopic rhinitis/atopy only/no atopic no rhinitis. Exact methods were used if any cell in the tabulation between BMI trajectories and the outcome had five individuals or less, and only unadjusted results were presented. Generalised Estimating Equations (GEE) were used to estimate the overall association between each trajectory and each outcome pooled over the follow up times (6, 12 and 18 years). The GEE model allowed for participants to contribute data at multiple times, while taking into account the correlational structure within an individual.[16] An interaction term with age at follow-up was fitted, and if there was evidence that the associations were dissimilar between timepoints (any P-interaction <0.1), a pooled odds ratio was not presented.

Based on the causal diagram theory (Figure S1),[17] disjunctive cause criterion,[18] and the data available, the analyses were adjusted for the following variables: history of parental allergic diseases, parental education, history of parental smoking, sex, parity, infant formula received at randomisation,[11] socioeconomic status,[19] duration of exclusive breastfeeding, and age at first solid food introduction. Interaction terms were fitted for sex, parental allergic diseases, and allocated formula received at weaning to assess effect modifications using likelihood ratio tests. Stratified associations were reported

168 if the overall P value for the likelihood ratio test was less than 0.1 and the P value for strata-specific
169 interaction terms was less than 0.05.

170 **Results**

171 **Study Population**

172 At baseline, 60.5% of mothers and 45.8% of fathers had a history of allergic rhinitis (Table S1).
173 Almost all (619/620) participants provided at least 5-time points of anthropometric information
174 between 0 and 2 years of age that were used to identify BMI trajectories.[6] Of these, 93% of participants
175 were followed up at 2 years, 78% at 6 years, 58% at 12 years and 68% were followed up at 18 years of
176 age (FigureS2).

177 **BMI Trajectories**

178 Five BMI trajectories were identified in the first 2 years of age (Figure 1).[6] The mean BMI of these five
179 trajectories at 18-time points are described in the supplementary (Figure S3). The "average" trajectory
180 (24.9%) had a mean z-score between zero and one in the first 24 months of life and was used as the
181 reference group. The "persistently high" trajectory had a mean z-score starting at approximately zero,
182 increased rapidly in the first six months of life, then plateaued at a mean z-score of approximately one.
183 The "early low and catch up" trajectory had a mean z-score that started at -1, but gradually increased to
184 be similar to the average trajectory by 1 year of age. The "below average" trajectory was the largest
185 group (29.4%) with a mean z-score between 0 and -1. The "persistently low" trajectory (13.6%) had a
186 mean z-score that started at -1 but decreased to -2 by 5-month of age then slowly increased to -1 at 2
187 years old.

188 None of the BMI trajectories in the first two years of age were associated with ongoing participation at
189 6, 12, and 18 years of age (Table S2 and S3). Outcomes at 6 years of age were not associated with
190 ongoing participation at 12 and 18 years of age (Table S4).

191 **BMI Trajectory and Current Allergic Rhinitis at 6, 12, and 18 years of age**

192 The prevalence of current allergic rhinitis increased from 15.8% (77/489) at 6 years to 37.2%
193 (134/360) at 12 years, and then plateaued at 18 years 36.3% (152/419) (Table S5). While there was no
194 strong evidence of an association between BMI trajectories in the first 2 years of life and current
195 allergic rhinitis at 6, 12, or 18 years of age, the "below average" trajectory had a non-significant trend
196 towards an increased risk of allergic rhinitis at 18 years of age (OR=1.70, 95%CI: 0.97-2.98, Table 1).
197 Moreover, there was a non-significant trend towards the "persistently high" trajectory being associated

with an increased risk of allergic rhinitis across the follow-up period (pooled OR=1.56, 95%CI: 0.96-2.56). The unadjusted and adjusted results were consistent (Table 1).

The association between BMI trajectories and current allergic rhinitis at 18 years of age was modified by maternal allergic rhinitis (P-value for likelihood ratio test = 0.06, Table 2). For those with maternal allergic rhinitis, the "below average" (OR= 2.83; 95%CI:1.34-5.96) and the "early low and catch up" trajectory (OR= 2.92; 95%CI:1.18-7.23) were associated with an increased risk of current allergic rhinitis at 18 years old compared to the "average" trajectory. Effect modifications by maternal allergic rhinitis were not observed at 6 and 12 years of age (Table S6 and S7). Paternal allergic rhinitis, sex, and randomised allocation formula did not modify the associations at 6, 12, and 18 years of age (all P-strata interaction >0.05, data not shown).

The majority of allergic rhinitis was associated with atopy (Table S8). The results were similar between unadjusted and adjusted associations (Table S9 and S10), with evidence for the "persistently high" BMI trajectory being associated with an increased risk of atopic rhinitis at 18 years of age but evidence for non allergic rhinitis was modest. There was also a trend for the "below average" trajectory being associated with an increased risk of atopic rhinitis.

BMI Trajectory and Eczema and Food Sensitisation / Food Allergic Outcomes

While no clear pattern of associations were seen for eczema and food allergy outcomes, there was relatively limited power (Tables S11 to S16).

Discussion

In this cohort of children with a family history of allergic diseases, we did not find evidence that BMI trajectories in the first two years of life were associated with current allergic rhinitis up to early adulthood overall. However, the "below average" trajectory had a non-significant trend towards an increased risk of allergic rhinitis at 18 years of age and the "persistently high" trajectory showed a trend for increased risk over the whole study period. The "persistently high" trajectory was also associated with an increased risk of atopic rhinitis at aged 18. Interestingly, in children with maternal allergic rhinitis, the "early low and catch up" and "below average" trajectories were associated with increased risk of current allergic rhinitis at 18 years.

In this same cohort, we have previously shown children in the "early low and catch up" and "persistently high" group had an increased risk of asthma at aged 18.[6] Moreover, we observed that the

"below average" group had evidence of an airway obstructive pattern (reduced FEV_1/FVC ratio) and a non-significant trend towards an increased risk of asthma at aged 18. Hence, the associations with asthma suggested similarities with our findings in this analysis. We did not observe evidence of associations with the "persistently low" or the "persistently high" trajectory in participants whose mothers had a history of allergic rhinitis, or with any trajectory and eczema and food allergy outcomes. However, our findings were limited by limited sample size, making the estimates of the associations tested imprecise.

This is the first study investigating the association between BMI trajectories in the first two years of life and current allergic rhinitis into early adulthood. The only prior study of BMI trajectories and allergic rhinitis, identified 4 BMI trajectories between 6 and 11 years: declining obesity, persistently overweight, rapid growth, and normal growth.[8] The authors reported the persistently high trajectory was associated with active allergic rhinitis at 12 and incident allergic rhinitis at 18 years of age. Given the different age windows for defining BMI trajectories between this study and our own, these results cannot be directly compared.

While the association between adiposity and allergic rhinitis could be explained by the adiposity-systemic inflammatory effect,[20] reported cross-sectional associations have been inconsistent.[21-24] Interestingly, a cross-sectional study used clinical symptoms with or without at least one positive IgE response to distinguish between allergic rhinitis and non-allergic rhinitis (without evidence of elevated IgE, which is synonymous with our non-atopic rhinitis), found that obesity was associated with an increased risk of non-allergic rhinitis, but a reduced risk of allergic rhinitis in adults.[25] This suggests that the relationship between adiposity and allergic rhinitis may be more complex than simply both being related to systemic inflammation. In this cohort with a family history of allergic diseases based in Melbourne, where there is a high prevalence of allergic sensitisation, most participants with "rhinitis" also had allergic sensitisation. Potentially, these associations may differ across settings where the prevalence of non-allergic rhinitis vary, and in older populations. Of note, we did find that the "persistently high" trajectory was associated with an increased risk of atopic rhinitis, potentially supporting an early life immune programming effect of high BMI in the first two years of life.

We observed belonging to "early low and catch up" or "below average" trajectory was associated with allergic rhinitis at 18 years of age, only in those with a mother with a history of allergic rhinitis. While we do not have a clear biological explanation for the observed findings, children who have maternal allergic rhinitis are likely to be genetically susceptible and at greater risk of developing allergic

diseases.[26] Children in the "early low and catch up" group may have been subjected to intrauterine growth restriction (IUGR), which may have skewed their immune profile towards Th2 even more. IUGR has been hypothesised to be related to impaired thymic function, resulting in an imbalance of cytokines leading to asthma and allergy.[27] While the "persistently low" trajectory may also have been subjected to IUGR, we did not observe clear evidence of associations in this group. However, the "persistently low" group had the smallest number of children, and the lack of associations may be due to limited statistical power.

Interestingly, children in the "below average" trajectory who started life with a normal BMI, also had an increased risk if they had a mother with a history of allergic rhinitis. This group may include most children who experienced "failure to thrive", possibly due to gastro-intestinal allergies,[28] which could result in poor weight gain and be associated with increased risk of allergic rhinitis. Despite this, we did not observe an increased risk of food sensitisation in the first year of life in this group. These interesting interactions require replication to confirm that they were not spurious.

The strengths of the study include: The trajectories were developed using prospective and frequently collected anthropometric data (18-time points) in the first two years of life, modelled using group-based trajectory modelling, which allowed us to capture detailed BMI growth developmental patterns during this period.[6] This mitigated against the potential for recall and observer bias. The temporality was clear for the association between BMI trajectories in the first two years and allergic rhinitis up to 18 years of age.

Several limitations should be noted. Some of our trajectories had only small numbers of participants, and lack of statistical power may explain the absence of some associations. We could not perform adjusted associations for some outcomes because data were sparse. Some potential confounding factors in our causal diagram, such as gestational age, maternal weight, and birth weight were not collected, so we could not adjust for them. Furthermore, parent-reported anthropometric data may have introduced non-differential measurement error given the outcomes were collected long after the exposure data collection, which may have led to an underestimation of these associations. While we found that maternal allergic rhinitis modified these associations, it should be noted these results could be due to chance alone due to multiple hypothesis testing. Finally, MACS is a cohort that was predominately Caucasian, and parents were highly educated and had high socioeconomic status. Hence, the results may not apply to the general population.

In conclusion, we found that among infants with maternal allergic rhinitis, there was evidence that belonging to a BMI trajectory that was low in the first few weeks of life then progressively increasing to normal growth, or a developmental pattern that declined slowly in the first six months of life then remained low was associated with increased risk of allergic rhinitis at aged 18. These results require replication.

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(vi) Key messages

Children with maternal allergic rhinitis and belong to the "early low and catch up" or "below average" Body Mass Index trajectory in the first 2 years of life require close monitoring as they are at higher risk of developing allergic rhinitis at 18 years of age.

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(viii) Tables

Table 1 Associations between current allergic rhinitis at 6, 12, and 18 years of age

	6 Years		12 Years		18 Years		Pooled Associations†	
BMI Trajectories	Unadjusted OR (95% CI) N=489	Adjusted OR§ (95% CI) N =475¶	Unadjusted OR (95% CI) N=360 ‡	Adjusted OR§ (95% CI) N =351¶	Unadjusted OR (95% CI) N=419	Adjusted OR§ (95% CI) N = 411¶	Unadjusted OR (95% CI) Number of participants = 554 Total number of the follow up events =1268	Adjusted OR§ (95% CI) Number of participants = 541 Total number of the follow up events =1243
Average	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Below average	1.43 (0.71, 2.86)	1.35 (0.64, 2.85)	1.12 (0.61, 2.04)	1.13 (0.60, 2.11)	1.64 (0.97, 2.77)	1.70 (0.97, 2.98)	1.38 (0.92, 2.05)	1.39 (0.92, 2.10)
Persistently low	1.14 (0.47, 2.76)	1.11 (0.42, 2.94)	1.16 (0.55, 2.43)	1.18 (0.54, 2.57)	0.90 (0.46, 1.80)	1.00 (0.49, 2.06)	1.05 (0.63, 1.75)	1.09 (0.65, 1.85)
Early low and catch up	1.30 (0.59, 2.86)	1.14 (0.48, 2.68)	1.13 (0.57, 2.23)	1.08 (0.52, 2.22)	1.23 (0.65, 2.30)	1.33 (0.68, 2.60)	1.13 (0.71, 1.80)	1.13 (0.70, 1.84)
Persistently high	1.93 (0.88, 4.23)	1.69 (0.71, 4.00)	1.45 (0.72, 2.91)	1.39 (0.66, 2.92)	1.47 (0.78, 2.77)	1.64 (0.83, 3.23)	1.59 (1.00, 2.55)	1.56 (0.96, 2.56)

† Pooled associations estimated using Generalised Estimation Equations.

‡ Nine participants did not fill out the allergic survey at age 12 years.

§ Adjusted for parental allergic rhinitis, parental education, parental smoking, anu3_2 score (father's occupation), sex, parity, randomised formula allocation, duration of exclusive breastfeeding, and age at first solid food introduction#.

Age at first solid food introduction was treated as a categorical variable (in quintiles) for the 6 years old, due to the nonlinearity association between the outcomes.

¶ N for adjusted OR does not match with the unadjusted ORs because missing data on the confounding variables.

Table 2 Associations between BMI trajectories and current allergic rhinitis at 18 years of age stratified by maternal allergic rhinitis

	Outcomes				
	Current Allergic Rhinitis at 18 Years of Age (N=419)				
	No Maternal Allergic Rhinitis (N=168) †		**Maternal Allergic Rhinitis (N=250)** †		
BMI Trajectories	% with Allergic Rhinitis (n/N)	Adjusted OR ‡ (95% CI) N= 161 §	% with Allergic Rhinitis (n/N)	Adjusted OR ‡ (95% CI) N= 247 §	P for interaction term
Average	41.5% (17/41)	Reference	34.9% (22/63)	Reference	
Below average	36.2% (17/47)	0.73 (0.27, 1.95)	56.6 % (47/83)	**2.83 (1.34, 5.96)**	0.049
Persistently low	29.6% (8/27)	0.38 (0.12, 1.23)	40.7% (11/27)	1.51 (0.56, 4.12)	0.156
Early low and catch up	23.1% (6/26)	0.33 (0.10, 1.11)	55.0% (22/40)	**2.92 (1.18, 7.23)**	0.016
Persistently high	48.1% (13/27)	1.14 (0.37, 3.45)	45.9% (17/37)	1.85 (0.75, 4.59)	0.918

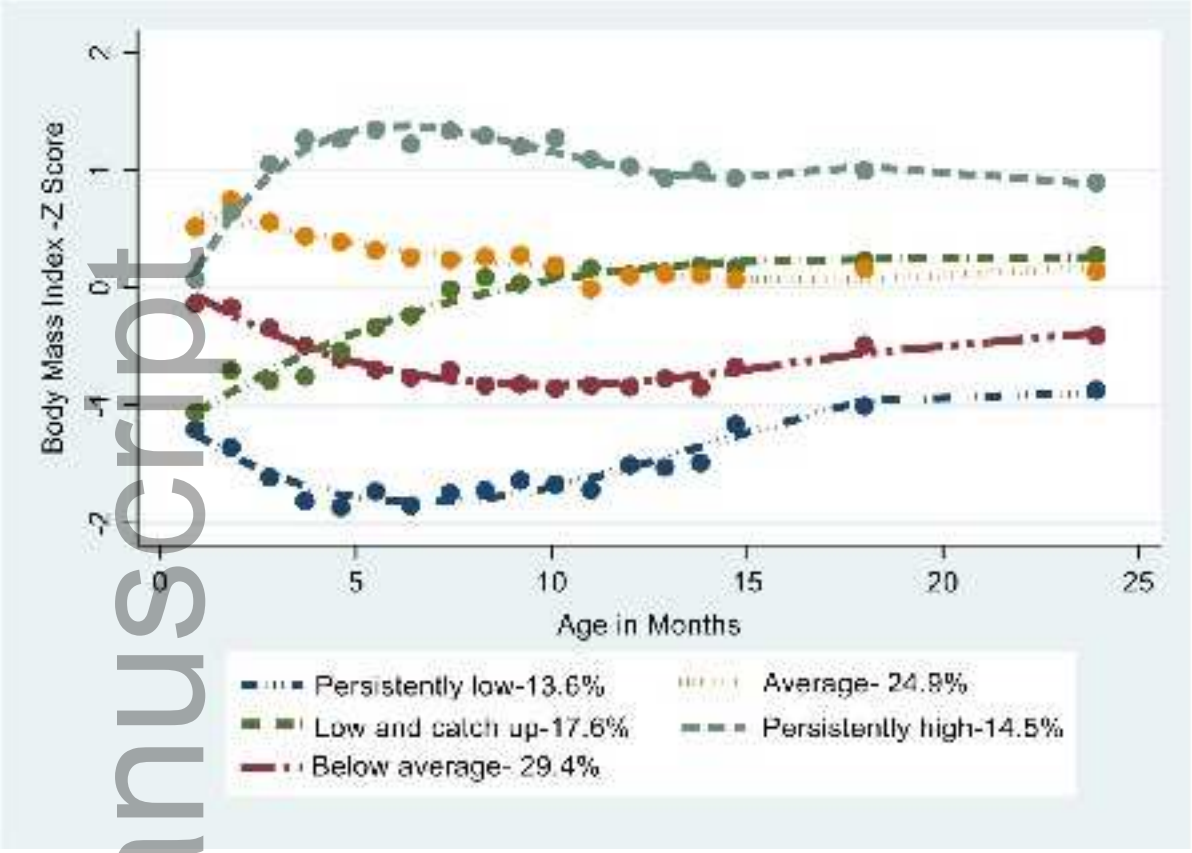
† The numbers do not add up to 419 because one mother did not provide information on maternal allergic rhinitis.

‡ Adjusted for paternal allergic rhinitis, parental education, parental smoking, anu3-2 score (father's occupation), sex, parity, randomised formula allocation, duration of exclusive breastfeeding, and age at first solid food introduction.

§ N for adjusted OR does not match with the total participants with outcomes because missing data on the confounding variables.

(ix) Figure Legends

Figure 1 BMI Z-Score Trajectories from 0-24 months of age



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