

The Role of Early Life Food Sensitization in Adolescent Lung Function: Results from 2 Birth Cohort Studies



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What is already known about this topic? The role of food sensitization on lung function outcomes is unclear.

What does this article add to our knowledge? Food sensitization less than 1 year of age was associated with reduced forced expiratory volume in 1 second, partially mediated by the increased risk of asthma.

How does this study impact current management guidelines? Food sensitization is an early biomarker for adolescent lung function impairment.

BACKGROUND: It is unclear whether early life food sensitization (as opposed to aeroallergen sensitization) is associated with subsequent poor lung function. **OBJECTIVES:** We investigated the associations between food sensitization in the first 2 years of life and lung function at 12 to

18 years and whether these observed associations are mediated through aeroallergen sensitization or asthma. **METHODS:** We used data from a high-risk cohort (Melbourne Atopy Cohort Study [MACS]) and a population-based “Influence of life-style—related factors on the development of the

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opinions reported in the paper are those of the authors and are independent from the funding sources. The “influence of Life-style—related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics” (LISApplus) study was mainly supported by grants from the Federal Ministry for Education, Science, Research and Technology and in addition from Helmholtz Zentrum Munich (former GSF), Helmholtz Centre for Environmental Research—UFZ, Leipzig, Research Institute at Marien-Hospital Wesel, Pediatric Practice, Bad Honnef for the first 2 years. The 4-year, 6-year, 10-year, and 15-year follow-up examinations of the LISApplus study were covered from the respective budgets of the involved partners (Helmholtz Zentrum Munich [former GSF], Helmholtz Centre for Environmental Research—UFZ, Leipzig, Research Institute at Marien-Hospital Wesel, Pediatric Practice, Bad Honnef, IUF—Leibniz-Research Institute for Environmental Medicine at the University of Düsseldorf) and in addition by a grant from the Federal Ministry for Environment (IUF Düsseldorf, FKZ 20462296). Furthermore, the 15-year follow-up examination of the LISApplus study was supported by the Commission of the European Communities, the 7th Framework Program: MeDALL project.

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Abbreviations used

ATS- American Thoracic Society

CI- Confidence interval

ERS- European Respiratory Society

FEV₁- Forced expiratory volume in 1 second

FVC- Forced vital capacity

LISAplus- Influence of Life-style—related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics study

MACS- Melbourne Atopy Cohort Study

Post-BD- Postbronchodilator

Pre-BD- Prebronchodilator

RCT- Randomized controlled trial

SPT- Skin prick test

Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics” (LISA-plus) cohort. Food sensitization was assessed at 6, 12, and 24 months in MACS and 24 months in LISAplus. Lung function was evaluated by spirometry at 12 and 18 years in MACS and 15 years in LISAplus. Linear regression models were used to estimate the association with sensitization (food and/or aeroallergen) while adjusting for potential confounders. RESULTS: Sensitization to food without aeroallergen at 6 months was associated with reduced forced expiratory volume in 1 second (FEV₁) at both 12 years (−153 mL; 95% confidence interval [CI] = −256 mL, −51 mL) and 18 years (−206 mL; 95% CI = −347 mL, −65 mL) in MACS. Similar results were observed for sensitization measured at 12 months but not at 24 months. Early-life asthma (but not aeroallergen sensitization) partially mediated these associations. Both cohorts showed that only aeroallergen sensitization at 24 months but not food sensitization was associated with lower adolescent lung function. CONCLUSIONS: This study showed that food sensitization at 6 and 12 months was associated with reduced FEV₁ in adolescence. Our finding that this link is not completely mediated by either subsequent asthma or aeroallergen sensitization is novel and suggests that early food sensitization itself can be used to identify high-risk groups for poor lung health. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1825-34)

Key words: Food sensitization; Atopy; FEV₁; FVC; FEV₁/FVC ratio; Lung function; Spirometry

Lung development commences during the gestational period and continues after birth, with almost 85% of alveoli developing postnatally.¹ Thus, factors that interfere with this process may affect lung function in later life and increase the risk of respiratory disease. It is therefore important to understand potential early life risk factors for lung development.

The mechanisms underlying the relationship between allergen sensitization and lung function remain unclear. It has been shown that sensitization to aeroallergens in early life is associated with reduced lung function during childhood.^{2,3} It has been suggested that persistent environmental exposures in sensitized individuals could induce inflammatory processes that lead to airflow limitation.⁴ Although epidemiological studies have extensively examined

the relationship between aeroallergen sensitization and lung function,^{2,3,5,6} the association between food sensitization and subsequent lung function has received limited attention. This is an important research question in the context of the recently observed rise in food allergies as a potential “second wave epidemic.”⁷ In addition, it is well known that sensitization to food allergens is associated with allergic respiratory diseases such as asthma.⁸⁻¹⁰ Therefore, an analysis that looks at the association between early life food sensitization and subsequent lung function needs to consider the role that concurrent and subsequent asthma may play in this potential association.

A population-based study from Australia has shown that early atopic sensitization, defined as a positive skin prick test (SPT) to at least 1 tested food or aeroallergen in the first year of life, was associated with persistent reduction in lung function from infancy up to 24 years.¹¹ However, it did not assess the role of food sensitization separately. Another recent study¹² has investigated the association between different atopic phenotypes including food sensitization over the first 6 years of life by using a latent class analysis and lung function at the age of 7 years. In this study, it was observed that the “benign atopic phenotype” (which was predominantly related to food sensitization) was not associated with impaired lung function at the age of 7 years.

We aimed to investigate the association between food sensitization in the first 2 years of life and adolescent lung function measures and whether any observed associations were mediated by early life aeroallergen sensitization or asthma status. We investigated these questions using 2 independent cohort studies: the high-risk Melbourne Atopy Cohort Study (MACS) cohort and the population-based “influence of Life-style—related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics” (LISAplus) cohort.

METHODS

Study populations

MACS is an Australian allergy high-risk birth cohort study that recruited 620 neonates with a family history of asthma, food allergy, hay fever, or eczema between 1990 and 1994 from Melbourne. Detailed descriptions of the recruitment and data collection have been previously published.¹³⁻¹⁶ Baseline information was collected during pregnancy. Questionnaires were completed every 4 weeks until 15 months, at 18 months, 2 years, and then annually until age 7, then at 12 and 18 years.

MACS initially started as a randomized controlled trial (RCT) investigating the effect of 3 different infant formulas (cow’s milk, partially hydrolyzed whey, and standard soy formula) implemented at the time of weaning, on the occurrence of allergic disease. Use of an RCT to test additional hypotheses about the association between nonrandomized exposures and outcomes determined during follow-up is well established. It is based on the testable assumption that the randomized intervention will not influence the associations of interest.¹⁷ A previous MACS paper showed that randomization status (infant formula allocation) was not associated with allergic disease outcomes.¹⁸

The study was approved by the Human Research Ethics committees of the Mercy Maternity Hospital, the Royal Children’s Hospital, and the University of Melbourne. Written informed consent was obtained from all mothers and, in the most recent follow-up, all participants.

LISAplus is a German population-based birth cohort study that recruited 3094 Caucasian neonates between 1997 and 1999 from the cities of Munich, Leipzig, Wesel, and Bad Honnef. Details of study design have been published elsewhere.¹⁹ Questionnaires were completed by parents at birth, 0.5, 1, 1.5, 2, 4, 6, 10, and 15 years of age, and physical examinations, including blood sample collection, took place at 2, 6, 10, and 15 years. The study was approved by the local Ethics Committees (Bavarian Board of Physicians, University of Leipzig, and Board of Physicians of North-Rhine-Westphalia) and written parental consent was obtained.

Sensitization assessment

SPTs were performed for MACS participants at 6, 12, and 24 months, according to a standard technique.²⁰ Tested allergens include egg white, cow's milk, peanut, *Dermatophagoides pteronyssinus* (dust mite), *Lolium perenne* (rye grass), and cat dander (Bayer, Spokane, Wash). SPTs were read at 15 to 20 minutes. Wheal size was measured by calculating the mean length of longest wheal diameter and the diameter perpendicular to it.¹⁵ Sensitization was defined as a wheal size of ≥ 2 mm.^{21,22} We used 2 mm as the cutoff as positive SPT reactions are likely to be smaller in children younger than 2 years,²³ presumably because of a lack of antigen-specific IgE and skin reactivity.²⁴

In LISAplus, sensitization was assessed at the age of 2 years using the CAP System FEIA (Pharmacia Diagnostics, Freiburg, Germany) according to the manufacturer's instructions. Food sensitization was measured using a mix of 6 common food allergens (fx5: hen's egg, cow's milk, peanut, wheat flour, soybean, and codfish). Serum-specific IgE (s-IgE) antibodies to aeroallergens of mold (MX1), cat (E1), a mixture of mites and cockroach (HX2), and of pollen (RX1) were all tested separately. Sensitization was defined as an s-IgE antibody level ≥ 0.35 kU_A/L in any of these tests.

Lung function assessment

In MACS, spirometry was conducted at 12 and 18 years following standardized techniques (American Thoracic Society [ATS] Guidelines 1994²⁵ and ATS/European Respiratory Society [ERS] Guidelines 2005²⁶). Lung function assessment (pre-bronchodilator [pre-BD]) was performed at 12 years by trained research nurses using the Spirocard system (SpiroCard PC Spirometer; QRS Diagnostic, Plymouth, Minn). At 18 years, pre- and postbronchodilator (post-BD) (salbutamol) spirometry was conducted by trained respiratory scientists using the EasyOne Spirometer (nidd Medical Technologies Inc., Andover, Mass). Participants were advised not to use short-acting β -agonists and long-acting bronchodilators for 4 and 12 hours before the test, respectively. Height was recorded at the time of testing, without shoes to the nearest 0.1 cm.

In LISAplus, spirometry was performed at the 15-year follow-up before and after bronchodilation (200 μ g salbutamol). A detailed description has been published previously.²⁷ The procedure, all measurements, and the evaluation of the results were in accordance with ATS/ERS recommendations.²⁶ Flow-volume curves were obtained using a pneumotachograph-type spirometer (EasyOne Worldspirometer; NDD, Zurich, Switzerland).

Confounder definitions

Asthma. MACS defined current asthma as one or more episodes of asthma and/or the use of any asthma medications in the last 12 months. LISAplus current asthma was defined based on the Global Allergy and Asthma European Network definition.²⁸ Subjects

providing a positive response to at least 2 of the following 3 questions were considered as currently having asthma: (1) "Has a doctor-diagnosed asthma in your child at age 3 to 15 years?" (2) "Has your child taken asthma medication during the last 12 months?" (3) "Has your child had wheezing or whistling in the chest in the last 12 months?"

Wheeze by the age at which the sensitization was assessed.

In MACS, wheeze by the time of sensitization was defined as present if parents had responded that their child had had more than 5 days in response to the question "How many days of cough and/or chest rattle and/or wheeze has your child had in the past 4 weeks?" by the age that the SPT was performed.²⁹ In LISAplus, wheeze by the age of sensitization was defined as an affirmative response to the question of "In the past 6 months, has your child had whistling or wheezy sound of breathing in the chest?"³⁰

Family history of atopy (in LISAplus). Family history of atopy was defined as being present if the participant had at least 1 first-degree relative with asthma, eczema, or hay fever; asked when the infant was a neonate.

Statistical analysis

All participants from both cohorts who had complete early life sensitization data and lung function outcomes during adolescence were included. Linear regression models were used to assess the association between food sensitization with or without aeroallergen sensitization at 6, 12, or 24 months in MACS or at 24 months in LISAplus. Lung function outcomes included forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), and FEV₁/FVC ratio at 12 and 18 years (in MACS) and at 15 years (in LISAplus). We modeled sensitization as: (1) no sensitization; (2) food sensitization only; (3) aeroallergen sensitization only; and (4) sensitization to both food and aeroallergen, using those who were not sensitized as the reference group. In MACS, the associations were evaluated at each time point separately, irrespective of previous sensitization status. All models were initially adjusted for sex, age, and height. In addition, adjustments were made for formula allocation in MACS and study center in LISAplus. Models were additionally adjusted for other potential confounders including maternal smoking during pregnancy, parental level of education, wheezing by the age of sensitization testing, and exclusive breastfeeding for at least 4 months.³¹ Interactions of atopic sensitization with concurrent asthma, personal smoking (only at 15 or 18 years) and family history of atopy in the LISAplus study, and formula allocation in the MACS study were assessed. Strata-specific associations were reported if interaction *P* values were greater than .1. STATA 13 (StataCorp, College Station, Tex) was used in all analyses in MACS, and R version 3.2.0 was used for all analyses in LISAplus.³² All results are presented as regression coefficients β with the corresponding 95% confidence interval (CI).

Mediation assessment. To assess whether the relationships between food sensitization and lung function were mediated by aeroallergen sensitization or asthma, mediation analysis was conducted. Aeroallergen sensitization at 12 or 24 months and asthma at 6, 12, or 18 years were investigated as potential mediators for the associations between food-only sensitization at 6 and 12 months (exposure) and pre-BD FEV₁ at 12 and 18 years in MACS. The associations between food(s) only sensitization at 6 and 12 months and the possible mediators were first investigated. Then the associations between the potential mediators and pre-BD FEV₁ at 12 and 18 years were examined. Finally, the mediations effects were

TABLE I. Characteristics of participants with both sensitization and lung function data in MACS and LISApplus cohorts

Participants' characteristics	MACS cohort		LISApplus cohort
	At 12 y	At 18 y	At 15 y
Total number (N)	364	399	796
Sex, n (%)			
Male	189 (52)	201 (51)	425 (53)
Female	175 (48)	198 (49)	371 (47)
Age (y), mean (SD)	11.5 (1.9)	17.9 (1.3)	15.1 (0.3)
Height (cm), mean (SD)	149.5 (13)	172.4 (9.4)	171.3 (8.5)
Family history of atopy, n (%)	364 (100)	399 (100)	461 (62)
Current asthma, n (%)	82 (24)	104 (27)	43 (5)
Sensitization, n/N (%)			
Food allergens only			
6 mo	51/342 (15)	59/373 (16)	—
12 mo	47/349 (13)	55/381 (14)	—
24 mo	24/312 (8)	28/326 (9)	62/796 (8)
Aeroallergens only			
6 mo	17/342 (5)	15/373 (4)	—
12 mo	26/349 (7)	27/381 (7)	—
24 mo	53/312 (17)	56/326 (17)	19/796 (2)
Food and aeroallergens			
6 mo	20/342 (6)	23/373 (6)	—
12 mo	40/349 (11)	44/381 (12)	—
24 mo	40/312 (13)	44/326 (14)	19/796 (2)
Lung function parameter, adjusted mean* (SD)			
Pre-BD FEV ₁ (mL)	2366 (651)	3832 (791)	3514 (480)
Post-BD FEV ₁ (mL)	—	4020 (804)	3619 (501)
Pre-BD FVC (mL)	2582 (678)	4543 (975)	4085 (617)
Post-BD FVC (mL)	—	4578 (975)	4075 (611)
Pre-BD FEV ₁ /FVC ratio (%)	92 (7)	85 (8)	86 (2)
Post-BD FEV ₁ /FVC ratio (%)	—	88 (6)	89 (1)

FEV₁, Forced expiratory volume in 1 second; FVC, forced vital capacity; LISApplus, influence of Life-style—related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics study; MACS, Melbourne Atopy Cohort Study; Post-BD, postbronchodilator; Pre-BD, prebronchodilator.

*Adjusted for age, gender, and height.

investigated using *medeff* command in STATA version 13 to estimate the magnitude of the natural direct effect and natural indirect effect (called the “average causal mediation effect”).^{33,34}

RESULTS

Characteristics of participants

The baseline demographic characteristics of the MACS participants have been published previously.³⁵ This analysis was restricted to those who had data on both sensitization and lung function testing (364 participants [59% of original cohort] at 12 years and 399 participants [64% of original cohort] at 18 years). The characteristics of those included participants are presented in Table I. With the exception of a higher proportion of highly educated parents, MACS participants who attended lung function measurement at both 12- and 18-year follow-ups were similar to those who did not attend (see Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

The baseline demographic characteristics of LISApplus participants have been described previously.¹⁹ A total of 796 participants (47% of original cohort) from four study centers (358, 250, 100, and 88 from Munich, Leipzig, Bad Honnef, and Wesel,

respectively) were included in the analysis (Table I). With the exception of a higher proportion of highly educated parents and a lower number of older siblings, LISApplus participants who attended lung function measurement at the 15-year follow-up were similar to those who did not attend (see Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Atopic sensitization in the first 2 years and lung function at 12, 15, and 18 years

Sensitization and pre-BD FEV₁. Sensitization to food only (ie, without aeroallergen sensitization) at 6 months was associated with a reduction in pre-BD FEV₁ at 12 and 18 years (Figure 1). Similar findings were observed for food-only sensitization at 12 months (Figure 1). In addition, sensitization to aeroallergens without coexisting food sensitization at 24 months was associated with a reduction in pre-BD FEV₁ at 15 and at 18 years (Figure 1).

Cosensitization to food and aeroallergens at all 3 time points was not associated with any deficit in pre-BD FEV₁ at 12, 15, or 18 years (Figure 1) (see Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

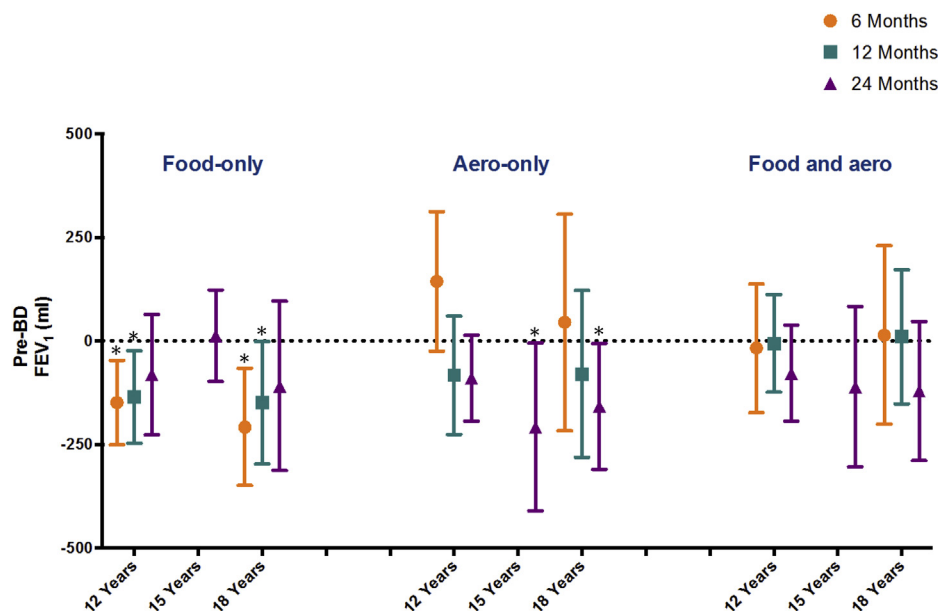


FIGURE 1. The adjusted[†] association between atopic sensitization (food only, aero only, and both food and aero sensitization) in the first 2 years of life and pre-BD FEV₁ at 12, 15, and 18 years. **P* value < .05. [†]Adjusted for gender, age, height, wheezing by the age of testing food sensitization, maternal smoking during pregnancy, parental level of education, and exclusive breast feeding for at least 4 months (formula allocation in MACS and study center in LISApplus). Note: 12- and 18-year data from MACS, 15-year data from LISApplus. FEV₁, Forced expiratory volume in 1 second; LISApplus, influence of Life-style—related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics study; MACS, Melbourne Atopy Cohort Study; Pre-BD, prebronchodilator.

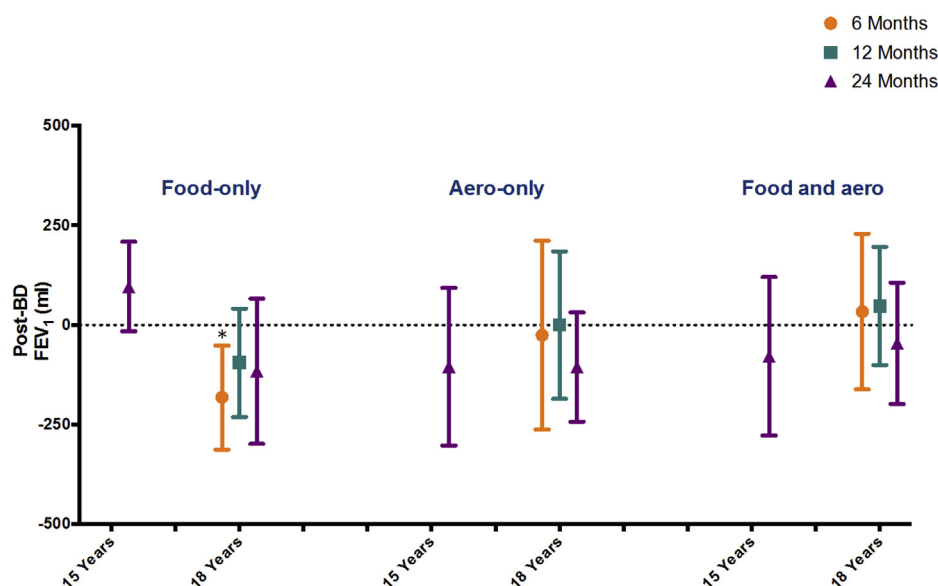


FIGURE 2. The adjusted[†] association between atopic sensitization (food only, aero only, and both food and aero sensitization) in the first 2 years of life and post-BD FEV₁ at 15 and 18 years. **P* value < .05. [†]Adjusted for gender, age, height, wheezing by the age of testing food sensitization, maternal smoking during pregnancy, parental level of education, and exclusive breast feeding for at least 4 months (formula allocation in MACS and study center in LISApplus). Note: 18-year data from MACS, 15-year data from LISApplus; post-BD FEV₁ was not assessed at 12 years. FEV₁, Forced expiratory volume in 1 second; LISApplus, influence of Life-style—related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics study; MACS, Melbourne Atopy Cohort Study; Post-BD, postbronchodilator.

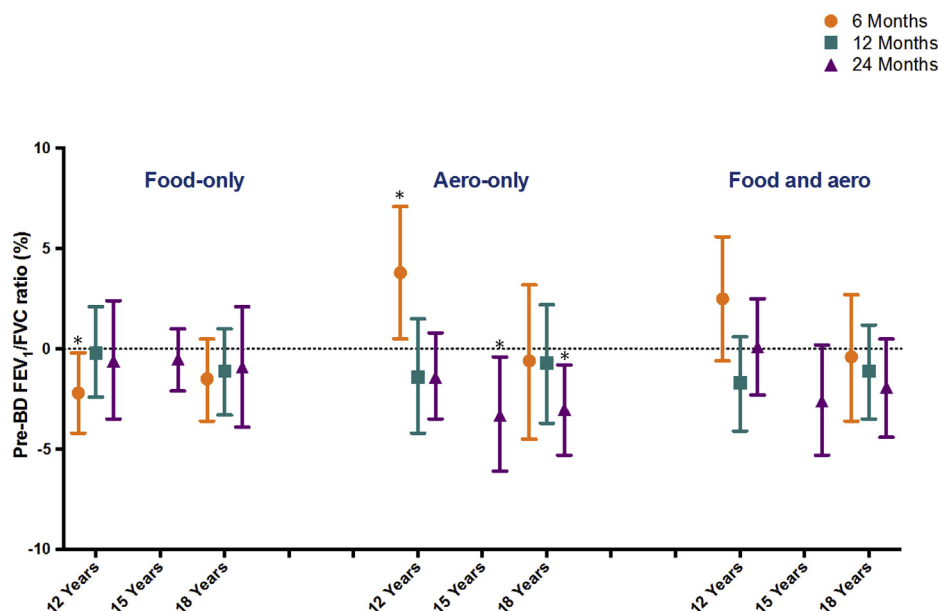


FIGURE 3. The adjusted[†] association between atopic sensitization (food only, aero only, and both food and aero sensitization) in the first 2 years of life and pre-BD FEV₁/FVC ratio at 12, 15, and 18 years. **P* value < .05. [†]Adjusted for gender, age, height, wheezing by the age of testing food sensitization, maternal smoking during pregnancy, parental level of education, and exclusive breast feeding for at least 4 months (formula allocation in MACS and study center in LISApplus). Note: 12- and 18-year data from MACS, 15-year data from LISApplus. FEV₁, Forced expiratory volume in 1 second; FVC, forced vital capacity; LISApplus, influence of Life-style-related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics study; MACS, Melbourne Atopy Cohort Study; Pre-BD, prebronchodilator.

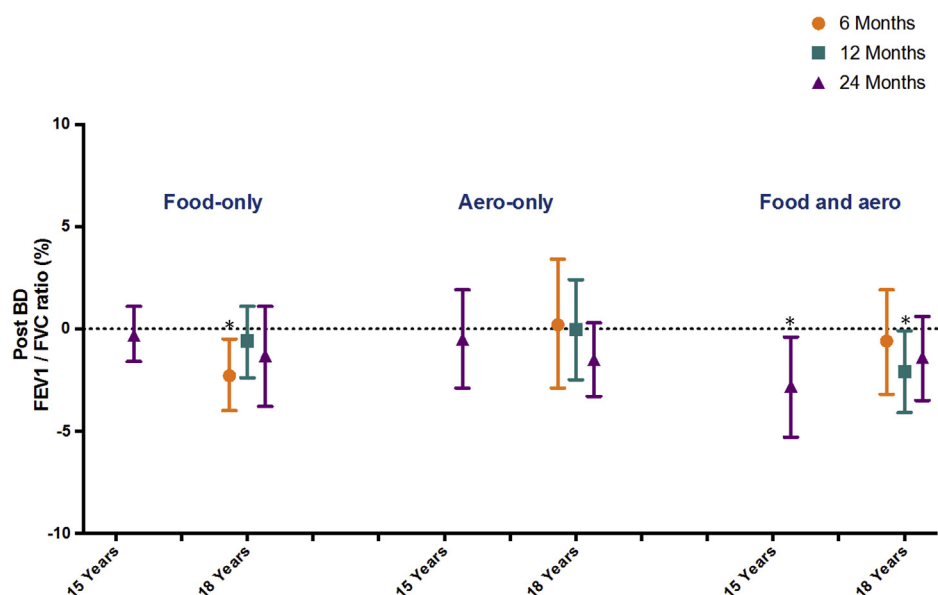


FIGURE 4. The adjusted[†] association between atopic sensitization (food only, aero only, and both food and aero sensitization) in the first 2 years of life and post-BD FEV₁/FVC ratio at 15 and 18 years. **P* value < .05. [†]Adjusted for gender, age, height, wheezing by the age of testing food sensitization, maternal smoking during pregnancy, parental level of education, and exclusive breast feeding for at least 4 months (formula allocation in MACS and study center in LISApplus). Note: 18-year data from MACS, 15-year data from LISApplus; post-BD FEV₁/FVC ratio was not assessed at 12 years. FEV₁, Forced expiratory volume in 1 second; FVC, forced vital capacity; LISApplus, influence of Life-style-related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics study; MACS, Melbourne Atopy Cohort Study; Post-BD, postbronchodilator.

Sensitization and post-BD FEV₁. Sensitization to food without coexisting aeroallergen sensitization at 6 months was associated with a reduction in post-BD FEV₁ at 18 years (Figure 2). However, no other combination of food and/or aeroallergen sensitization at any time point was related to post-BD FEV₁ at 15 or 18 years (Figure 2) (see Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

Sensitization and pre-BD FEV₁/FVC ratio. Sensitization to food only without aeroallergen sensitization at 6 months was associated with a reduction in the pre-BD FEV₁/FVC ratio at 12 years (Figure 3). Furthermore, sensitization to aeroallergens without concurrent food sensitization at 24 months was associated with a reduction in the pre-BD FEV₁/FVC ratio at 15 and 18 years (Figure 3). Surprisingly, sensitization to aeroallergens only at 6 months was associated with an increase in the pre-BD FEV₁/FVC ratio at 12 years. Cosensitization to food and aeroallergens at all 3 time points was not associated with any deficit in the pre-BD FEV₁/FVC ratio at 12, 15, and 18 years (Figure 3) (see Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

Sensitization and post-BD FEV₁/FVC ratio. Sensitization to food only without concurrent aeroallergen sensitization at 6 months was associated with a reduction in the post-BD FEV₁/FVC ratio at 18 years (Figure 4). Also, cosensitization to food and aeroallergen at 12 months was related to the reduced post-BD FEV₁/FVC ratio at 18 years, and cosensitization to food and aeroallergen at 24 months was related to the reduced post-BD FEV₁/FVC ratio at 15 years (Figure 4). In contrast, sensitization to aeroallergen only at any time point was not associated with the post-BD FEV₁/FVC ratio at 15 or 18 years (Figure 4) (see Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

Sensitization and pre- and post-BD FVC. Sensitization to food and/or concurrent aeroallergen at any tested time point was not related to FVC in adolescence, with the exception of food without aeroallergen sensitization at 12 months and pre-BD FVC at 12 years (−144 mL; 95% CI: −271 mL, −16 mL) (see Table E4, available in this article's Online Repository at www.jaci-inpractice.org).

Degree of sensitization and pre- and post-BD FEV₁ and FEV₁/FVC ratio. Given the consistent findings on the link between food sensitization in the first year and FEV₁ and FEV₁/FVC ratio at both 12 and 18 years of age, the associations between degree of food sensitization in the first year and these lung function measures were further explored. We investigated both 6- and 12-months degree to sensitization (eg, numbers of foods meeting criteria for sensitization and size of wheal) and FEV₁/FVC ratio at both 12 and 18 years of age. We observed increasing number of foods sensitization is negatively related to FEV₁ while similar trends are observed with wheal size for all three allergens with some findings being statistically significant (see Tables E5–E8, available in this article's Online Repository at www.jaci-inpractice.org).

Interaction with concurrent asthma, personal smoking, family history of atopy (in LISApplus), and formula allocation (in MACS)

In MACS, there were no significant interactions between food sensitization and concurrent asthma, personal smoking asthma, and formula allocation (all *P* values for interactions >.1). In

LISApplus, however, there was an interaction between asthma and cosensitization to food and aeroallergen for pre-BD FEV₁/FVC ratio and pre- and post-BD FVC. However, the associations remained significant among those without asthma. An interaction between food sensitization and family history of atopy was found only for the post-BD FEV₁/FVC ratio. For this parameter, cosensitization to food and aeroallergens was not significant after stratification for the family history of atopy. Stratification for the family history of atopy showed significant associations for aeroallergen sensitization in subjects with a family history of atopy, but not in those without a family history of atopy. However, there were few individuals who had sensitization without a family history of atopy. In addition, further adjustment for personal smoking did not modify the results.

Assessment of mediators in the MACS study

Results from the causal mediation analysis showed that the association between food-only sensitization at 6 or 12 months on pre-BD FEV₁ at 12 and 18 years was mediated through asthma at 6 years. The proportion of the total causal effect of food sensitization at 12 months mediated by asthma at 6 years was 15.3% (95% CI: 7.9% to 71.4%) for pre-BD FEV₁ at 12 years (direct effect: −114 mL, 95% CI: −230 mL, −2 mL; indirect effect: −20 mL, 95% CI: −48 mL, −2 mL). A similar proportion mediated by asthma at 6 years was observed for food sensitization at 6 months and pre-BD FEV₁ at 18 years 15% (95% CI: 9% to 46%) (direct effect: −184 mL, 95% CI: −334 mL, −39 mL; indirect effect: −32 mL, 95% CI: −77 mL, −4 mL). On the other hand, aeroallergen sensitization at 24 months did not mediate the association between food sensitization at 6 or 12 months and impaired lung function at 12 or 18 years (see Figures E1 and E2, available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

We observed that early life sensitization to food allergens at 6 and 12 months was associated with lower spirometry indices during adolescence. Effects were detected mainly for FEV₁ and FEV₁/FVC ratio. These associations were neither confounded by concurrent wheezing nor modified by subsequent asthma status. Furthermore, these associations were only partially mediated by asthma at 6 years, and not by aeroallergen sensitization at age 2. This is the first study that evaluated the association between early life food sensitization and subsequent lung function and demonstrated that these associations are not completely mediated by the increased risk of aeroallergen sensitization and asthma. It should be noted that sensitization itself may not have any causal effect but may merely be a marker for a more robust Th2 phenotype, leading to subsequent reduced lung function.

The current study investigated the association between early life sensitization and adolescent lung function both in a high allergy risk and an unselected population-based cohort. These cohorts were from different regions of the world, but both were from developed countries with a high prevalence of food sensitization.³⁶ It is often assumed that results from high-risk cohorts may not be applicable to the general population. However, our results were largely consistent between the 2 cohorts (where data were available), despite the geographical differences between cohorts and methods of assessment of sensitization. The associations in the population-based study were only observed among individuals with a family history of atopy. However, this should

be interpreted with caution, as there was little power to show the effect in those without a family history of atopy.

In individuals sensitized to food and/or aeroallergen, a series of cellular and molecular interactions involving B cells, T cells, and antigen presenting cells result in the release of several proinflammatory mediators and cytokines.³⁶ The release of these mediators contributes to the acute symptoms and signs related to allergic reactions, including vasodilatation, increased vascular permeability, and bronchial smooth muscle contraction.^{37,38} After repeated exposure to allergens, persistent inflammation occurs and such inflammation may lead to long-term structural and functional changes of affected tissues.³⁷

Although these inflammatory mechanisms are associated with atopy, and also with loss of lung function, it is not clear whether atopy in early life causes lung function deficits or whether both atopy and reduced lung function are manifestations of a common underlying condition. Turner et al³⁹ reported that infant-onset atopy was associated with a reduction in FEV₁ at 11 years of age. Likewise, our results have shown that food sensitization in the first year of life was related to lower FEV₁ and FEV₁/FVC ratio. On the other hand, Hose et al¹² recently showed that benign atopic phenotype, as determined by latent class analysis over the first 6 years of life, was mainly related to sensitization to food allergens and it was not associated with impaired lung function at the age of 7 years. This discrepancy is most likely due to the differences in the age and/or the type of assessed allergens, as the first assessment of sensitization in this study was performed at the 12 months of life, whereas in the current study, we first assessed sensitization at 6 months.

One possible explanation for the associations observed between early life food sensitization and reduced lung function is that food sensitization is a risk factor for asthma, and the associations with lung function may reflect control of asthma. To address this issue, we have investigated whether the observed associations were modified by current asthma. In MACS, these associations were similar among those with or without current asthma. In LISApplus, although we observed an interaction, we still found an association among those without current asthma. Furthermore, asthma was not found to fully mediate the association. Therefore, we believe that the link between food sensitization and lung function is not entirely related to asthma control.

Childhood asthma, parental smoking, and personal smoking are known to be associated with reduced lung function.^{40,41} Among these, parental smoking is likely to be a confounder of the association between food sensitization and lung function, but asthma is likely to be in the biological pathway given the plausibility of the direction of the association between food sensitization and asthma. As the exposure is early life food sensitization (≤ 2 years) and personal smoking does not occur until much later, it is not a possible confounder but could be an effect modifier. We found maternal smoking during pregnancy to confound the associations between food sensitization and lung function, and therefore adjusted for it in all analyses. Personal history of smoking did not modify the associations observed; these analyses were based on a young age group in which the prevalence of smoking was low ($<7\%$), particularly in the smaller MACS cohort, which may explain the absence of an interaction. A decrease in FEV₁ and FEV₁/FVC ratio that is reversible may be present in individuals with moderate-to-severe asthma.³⁸ Furthermore, childhood asthma has been shown to lead to

airway remodeling, which may result in fixed airflow obstruction.³⁷ Our results showed that the associations between food sensitization and both pre- and post-BD FEV₁ and FEV₁/FVC ratio were partially mediated by asthma. Furthermore, these associations were observed even among nonasthmatics. Together, these findings suggest that food sensitization *per se* may lead to subsequent airway changes and reduced lung function.

The strengths of this study are that it includes longitudinal data from 2 independent cohorts with follow-up that extended from infancy to adolescence. Participants have performed lung function testing according to internationally recognized standards during the adolescent period. In addition, in the current analysis, we were able to examine the relationship between early life food and/or aeroallergen sensitization and adolescent lung function. This is a significant period for lung growth that is associated with changes in the rate of growth of lung volumes, flow, and body dimensions. In MACS, frequent follow-ups, particularly in the first 7 years of life, and early assessments of sensitization allowed exploring the potential pathways for the association between sensitization to food allergens and adolescent lung function.

However, this study also has a number of limitations. Given both MACS and LISApplus are long-term cohort studies, loss to follow-up, which increases with increasing duration of the study, may lead to attrition bias. Attrition bias occurs particularly when it is nonrandom and linked to both study exposures and outcomes. In addition, loss to follow-up may reduce the statistical power of the study, especially in relatively small studies like MACS. However, both MACS and LISApplus studies achieved good follow-up rates (59% and 64% at 12 and 18 years in MACS and 56% at 15 years in LISApplus). It is somewhat reassuring that, with the exception of parental education and the number of older siblings, there were no significant demographic and/or early sensitization differences between attending and nonattending children in either cohort. The second limitation is that we were unable to examine the effect of food sensitization at 6 and 12 months in the population-based LISApplus study, as sensitization was not assessed in the first year of life. As such, we were unable to confirm whether MACS findings on significant deficits in lung function in those who had early life food sensitization are not limited to individuals with a family history of allergic disease. Finally, given the multiple comparisons made in our analysis, there is the potential for some of the associations to be false positive. This limitation should be considered when interpreting our results. However, consistency of the results in relation to 6 months' food sensitization suggests that this association is valid.

In conclusion, food sensitization without coexistent aeroallergen sensitization in the first year of life was associated with decreased FEV₁ and FEV₁/FVC ratio during adolescence in the high allergy risk cohort. Early childhood asthma has only partially mediated the associations between food-only sensitization at 6 and 12 months and pre-BD FEV₁ at 12 and 18 years. As such, there appears to be a direct pathway from food sensitization in infancy to decreased adolescent lung function. Food sensitization in infancy could be a potential risk factor, or early immunological marker, for adolescent lung function impairment. Further research is required to confirm these findings in other settings. It remains to be determined if more appropriate management of asthma

during early childhood can improve lung function in adolescence.

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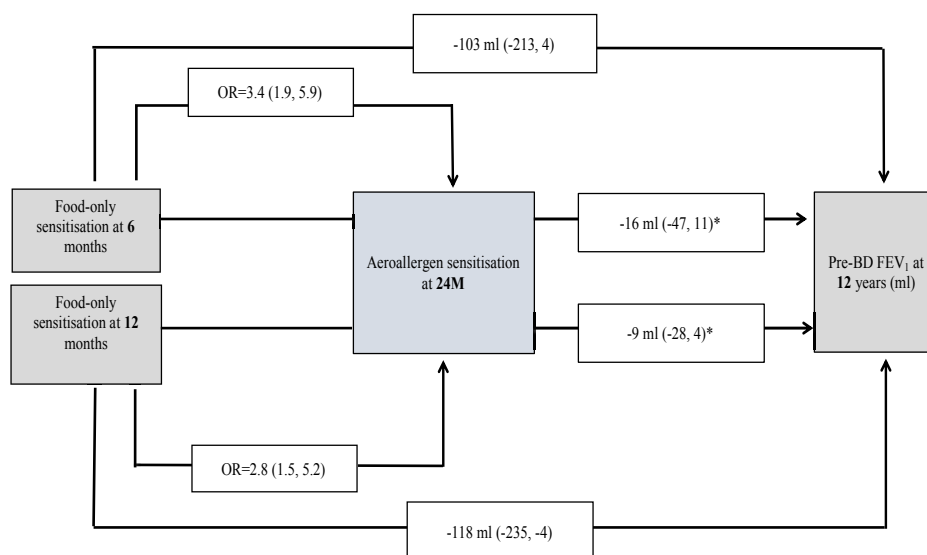


FIGURE E1. Aeroallergens sensitization at 24 months as a potential mediator for the associations between food-only sensitization (ie, without coexisting aeroallergen sensitization) at 6 and 12 months and pre-BD FEV₁ at 12 years in the MACS cohort. FEV₁, Forced expiratory volume in 1 second; MACS, Melbourne Atopy Cohort Study; OR, odds ratio; Pre-BD, prebronchodilator.

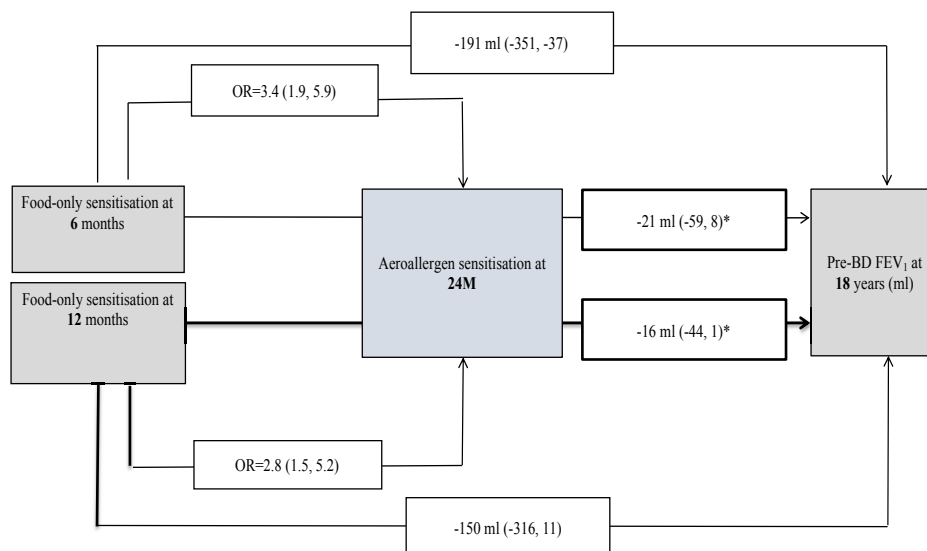


FIGURE E2. Aeroallergens sensitization at 24 months as a potential mediator for the associations between food-only sensitization (ie, without coexisting aeroallergen sensitization) at 6 and 12 months and pre-BD FEV₁ at 18 years in the MACS cohort. FEV₁, Forced expiratory volume in 1 second; MACS, Melbourne Atopy Cohort Study; OR, odds ratio; Pre-BD, prebronchodilator.

TABLE E1. Comparison of baseline characteristics between attendees and nonattendees at 12-year and at 18-year follow-up in MACS and at 15-year follow-up in LISApplus

	MACS						LISApplus		
	At 12 y			At 18 y			At 15 y		
	Attendees N = 366	Nonattendees N = 254	P* value	Attendees N = 404	Nonattendees N = 216	P* value	Attendees N = 991	Nonattendees N = 2103	P* value
Sex									
Male	194 (53)	123 (48)	.26	206 (51)	111 (51)	.91	512 (52)	1072 (51)	.75
Female	172 (47)	131 (52)		198 (49)	105 (49)		479 (48)	1031 (49)	
Parental education									
Maternal higher education	228 (62)	137 (54)	.03	260 (64)	105 (49)	<.01	536 (54)	1015 (49)	<.01
Paternal higher education	225 (62)	153 (60)	.70	265 (66)	113 (52)	<.01	576 (61)	1047 (54)	<.01
No. of older siblings									
No siblings	139 (38)	110 (43)	.18	163 (40)	86 (40)	.89	532 (54)	1207 (58)	.01
1	118 (32)	82 (32)		129 (32)	71 (33)		365 (37)	664 (32)	
≥2	109 (30)	62 (24)		112 (28)	59 (27)		93 (9)	226 (11)	
History of atopic diseases in siblings									
Food allergy	140 (38)	92 (36)	.6	155 (38)	77 (36)	.50	25 (3)	69 (3)	.29
Asthma	135 (37)	84 (33)	.32	141 (35)	78 (36)	.76	5 (1)	23 (1)	.15
Eczema	144 (39)	94 (37)	.55	155 (38)	83 (38)	.98	78 (8)	166 (8)	1.00
Hay fever	84 (23)	51 (20)	.39	90 (22)	45 (21)	.67	17 (2)	47 (2)	.41
History of maternal atopic diseases									
Food allergy	137 (37)	102 (40)	.49	155 (38)	84 (39)	.89	86 (9)	173 (8)	.73
Asthma	159 (43)	109 (43)	.89	169 (42)	99 (46)	.33	64 (7)	131 (6)	.88
Eczema	150 (41)	91 (36)	.19	158 (39)	83 (38)	.86	87 (9)	217 (10)	.19
Hay fever	212 (58)	163 (64)	.11	242 (60)	133 (62)	.60	279 (29)	611 (30)	.50
History of paternal atopic diseases									
Food allergy	79 (22)	52 (21)	.73	78 (19)	53 (25)	.12	63 (7)	111 (6)	.40
Asthma	99 (27)	59 (23)	.28	110 (28)	48 (22)	.17	48 (5)	115 (6)	.40
Eczema	72 (20)	54 (21)	.61	85 (21)	41 (19)	.54	46 (5)	106 (6)	.50
Hay fever	172 (47)	112 (44)	.47	188 (47)	96 (44)	.61	260 (28)	524 (28)	.97
Early food and aeroallergens sensitization									
Food_6M	71 (21)	53 (24)	.32	79 (22)	45 (23)	.66	NA	NA	
Food_12M	84 (24)	61 (30)	.11	97 (26)	48 (27)	.76	NA	NA	
Food_24M	61 (20)	30 (21)	.79	71 (22)	20 (15)	.06	87 (10)	117 (9)	.47
Aero_6M	37 (11)	23 (11)	.92	37 (10)	23 (12)	.52	NA	NA	
Aero_12M	64 (18)	38 (19)	.89	69 (18)	33 (19)	.95	NA	NA	
Aero_24M	93 (30)	38 (26)	.41	96 (30)	35 (26)	.35	40 (5)	63 (5)	.89

LISApplus, Influence of Life-style-related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics study; MACS, Melbourne Atopy Cohort Study.

Bold indicates statistical significance ($P < .05$).

*From Pearson's χ^2 test.

TABLE E2. Associations between atopic sensitization in the first 2 years and FEV₁ (pre- and post-BD) at 12, 15, and 18 years

Atopic sensitization	12 y (MACS)				15 y (LISAplus)				18 y (MACS)			
	N (%)	Adj. mean*	Model 1 [†]	Model 2 [‡]	N (%)	Adj. mean*	Model 1 [†]	Model 2 [‡]	N (%)	Adj. mean*	Model 1 [†]	Model 2 [‡]
FEV ₁ pre-BD (mL)												
6 mo												
No	254 (74)	2371	—	—					276 (74)	3872	—	—
Food only	51 (15)	2222	−149 (−252, −46)	−149 (−251, −47)					59 (16)	3668	−197 (−339, −56)	−208 (−349, −66)
			<.01	<.01							<.01	<.01
Aero only	17 (5)	2513	142 (−27, 310)	144 (−25, 312)					15 (4)	3995	59 (−202, 321)	45 (−217, 306)
			.10	.10							.44	.73
Food and aero	20 (6)	2353	−19 (−174, 137)	−17 (−173, 137)					23 (6)	3866	3 (−212, 218)	14 (−201, 230)
			.81	.82							.97	.89
12 mo												
No	236 (68)	2382	—	—					255 (67)	3872	—	—
Food only	47 (13)	2251	−131 (−241, −21)	−135 (−247, −24)					55 (14)	3716	−158 (−306, −11)	−149 (−297, −1)
			.02	.01							.03	.04
Aero only	26 (7)	2301	−81 (−224, 61)	−83 (−226, 60)					27 (7)	3793	−65 (−266, 137)	−80 (−281, 122)
			.26	.25							.52	.43
Food and aero	40 (12)	2382	−0.3 (−118, 118)	−6 (−124, 112)					44 (12)	3883	6 (−175, 168)	10 (−152, 172)
			.99	.91							.94	.90
24 mo												
No	195 (62)	2346	—	—	681 (88)	3520			198 (61)	3885	—	—
Food only	24 (8)	2277	−70 (−214, 74)	−81 (−227, 64)	61 (8)	3533	17 (−93, 128)	13 (−98, 123)	28 (9)	3805	−99 (−300, 103)	−109 (−313, 96)
			.33	.27			.76	.82			.33	.29
Aero only	53 (17)	2258	−89 (−192, 14)	−90 (−194, 14)	17 (2)	3293	−221 (−424, −18)	−208 (−410, −5)	56 (17)	3714	−151 (−302, −0.3)	−158 (−310, −6)
			.09	.08			.03	.04			.05	.04
Food and aero	40 (13)	2287	−59 (−174, 56)	−78 (−194, 38)	19 (2)	3414	−98 (−292, 95)	−111 (−304, 83)	44 (13)	3734	−120 (−286, 47)	−121 (−289, 47)
			.31	.18			.32	.26			.08	.15
FEV ₁ post-BD (mL)												
6 mo												
No									269 (74)	4054	—	—
Food only									57 (16)	3901	−178 (−308, −47)	−182 (−313, −52)
											<.01	<.01
Aero only									15 (4)	3914	−18 (−256, 219)	−26 (−263, 211)
											.88	.83
Food and aero									23 (6)	4017	26 (−170, 221)	33 (−162, 229)
											.79	.73
12 mo												
No									248 (67)	4027	—	—

(continued)

TABLE E2. (Continued)

Atopic sensitization	12 y (MACS)				15 y (LISAplus)				18 y (MACS)			
	N (%)	Adj. mean*	Model 1†	Model 2‡	N (%)	Adj. mean*	Model 1†	Model 2‡	N (%)	Adj. mean*	Model 1†	Model 2‡
Food only									54 (15)	3950	−105 (−239, 30) .12	−95 (−231, 41) .17
Aero only									26 (7)	4080	8 (−177, 193) .93	−0.2 (−186, 185) .99
Food and aero									43 (11)	4100	42 (−106, 191) .57	47 (−101, 196) .53
24 mo												
No					665 (88)	3616	—	—	193 (61)	4033	—	—
Food only					59 (8)	3714	100 (−12, 213) .08	96 (−16, 209) .09	28 (9)	3917	−103 (−284, 78) .26	−116 (−299, 66) .21
Aero only					18 (2)	3499	−112 (−310, 86) .27	−105 (−303, 93) .30	55 (17)	3949	−103 (−239, 34) .14	−106 (−243, 31) .13
Food and aero					18 (2)	3547	−64 (−263, 135) .53	−79 (−278, 120) .43	43 (13)	4010	−42 (−193, 109) .58	−46 (−199, 106) .55

FEV₁, Forced expiratory volume in 1 second; LISAplus, Influence of Life-style—related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics study; MACS, Melbourne Atopy Cohort Study; Post-BD, postbronchodilator; Pre-BD, prebronchodilator.

Bold indicates statistical significance ($P < .05$).

*Mean adjusted for gender, height, and age.

†Regression coefficients (95% confidence intervals) and P values adjusted for gender, age, and height (study center in LISAplus).

‡Regression coefficients (95% confidence intervals) and P values adjusted for gender, age, height, wheezing by the age of testing food sensitization, maternal smoking during pregnancy, parental level of education, and exclusive breast feeding for at least 4 months (formula allocation in MACS and study center in LISAplus).

TABLE E3. Associations between atopic sensitization in the first 2 years and FEV₁/FVC ratio (pre- and post-BD) at 12, 15, and 18 years

Atopic sensitization	12 y (MACS)				15 y (LISAplus)				18 y (MACS)			
	N (%)	Adj. mean*	Model 1 [†]	Model 2 [‡]	N (%)	Adj. mean*	Model 1 [†]	Model 2 [‡]	N (%)	Adj. mean*	Model 1 [†]	Model 2 [‡]
FEV ₁ /FVC ratio pre-BD (%)												
6 mo												
No	254 (74)	92	—	—					276 (74)	85	—	—
Food only	51 (15)	89	−2.3 (−4.3, −0.3)	−2.2 (−4.2, −0.2)					59 (16)	83	−1.4 (−3.5, 0.6)	−1.5 (−3.6, 0.5)
			.02	.03							.16	.14
Aero only	17 (5)	95	3.7 (0.4, 7.1)	3.8 (0.5, 7.1)					15 (4)	85	−0.5 (−4.4, 3.3)	−0.6 (−4.5, 3.2)
			.03	.02							.78	.74
Food and aero	20 (6)	94	2.6 (−0.5, 5.6)	2.5 (−0.6, 5.6)					23 (6)	85	−0.4 (−3.6, 2.7)	−0.4 (−3.6, 2.7)
			.09	.10							.80	.80
12 mo												
No	236 (68)	92	—	—					255 (67)	85	—	—
Food only	47 (13)	92	−0.4 (−2.5, 1.7)	−0.2 (−2.4, 2.1)					55 (14)	84	−1.1 (−3.2, 1.1)	−1.1 (−3.3, 1.0)
			.72	.88							.32	.29
Aero only	26 (7)	91	−1.4 (−4.3, 1.4)	−1.4 (−4.2, 1.5)					27 (7)	84	−0.7 (−3.6, 2.2)	−0.7 (−3.7, 2.2)
			.31	.34							.63	.61
Food and aero	40 (12)	90	−1.8 (−4.2, 44.1)	−1.7 (−4.1, 0.6)					44 (12)	84	−1.1 (−3.4, 1.3)	−1.1 (−3.5, 1.2)
			.11	.14							.37	.34
24 mo												
No	195 (62)	92	—	—	681 (88)	87	—	—	198 (61)	86	—	—
Food only	24 (8)	91	−0.8 (−3.7, 2.2)	−0.6 (−3.5, 2.4)	61 (8)	86	−0.6 (−2.1, 1)	−0.5 (−2.1, 1.0)	28 (9)	85	−0.8 (−3.8, 2.1)	−0.9 (−3.9, 2.1)
			.61	.70			.49	.50			.57	.54
Aero only	53 (17)	90	−1.4 (−3.5, 0.8)	−1.4 (−3.5, 0.8)	17 (2)	83	−3.3 (−6.2, −0.4)	−3.3 (−6.1, −0.4)	56 (17)	83	−3.0 (−5.2, −0.7)	−3.0 (−5.3, −0.8)
			.20	.20			.03	.03			<.01	<.01
Food and aero	40 (13)	92	−0.2 (−2.6, 2.1)	0.1 (−2.3, 2.5)	19 (2)	84	−2.5 (−5.2, 0.3)	−2.6 (−5.3, 0.2)	44 (13)	83	−1.9 (−4.4, 0.4)	−1.9 (−4.4, 0.5)
			.84	.93			.08	.07			.11	.11
FEV ₁ /FVC ratio post-BD (%)												
6 mo												
No									269 (74)	89	—	—
Food only									57 (16)	86	−2.2 (−4.0, −0.4)	−2.3 (−4.0, −0.5)
											.01	.01
Aero only									15 (4)	90	0.3 (−2.8, 3.5)	0.2 (−2.9, 3.4)
											.82	.86
Food and aero									23 (6)	88	−0.7 (−3.3, 1.9)	−0.6 (−3.2, 1.9)
											.58	.63
12 mo												
No									248 (67)	89	—	—
Food only									54 (15)	88	−0.6 (−2.3, 1.1)	−0.6 (−2.4, 1.1)
											.50	.50

(continued)

TABLE E3. (Continued)

Atopic sensitization	12 y (MACS)				15 y (LISAplus)				18 y (MACS)			
	N (%)	Adj. mean*	Model 1 [†]	Model 2 [‡]	N (%)	Adj. mean*	Model 1 [†]	Model 2 [‡]	N (%)	Adj. mean*	Model 1 [†]	Model 2 [‡]
Aero only									26 (7)	89	0.1 (−2.5, 2.4) .96	−0.04 (−2.5, 2.4) .97
Food and aero									43 (11)	87	−2.0 (−4.0, −0.1) .04	−2.1 (−4.1, −0.1) .03
24 mo												
No					665 (88)	89	—	—	193 (61)	89	—	—
Food only					59 (8)	89	−0.3 (−1.7, 1.1) .66	−0.3 (−1.6, 1.1) .68	28 (9)	87	−1.3 (−3.8, 1.1) .29	−1.3 (−3.8, 1.1) .30
Aero only					18 (2)	89	−0.5 (−2.9, 1.9) .71	−0.5 (−2.9, 1.9) .70	55 (17)	88	−1.5 (−3.3, 0.3) .11	−1.5 (−3.3, 0.3) .11
Food and aero					18 (2)	86	−2.7 (−5.1, −0.3) .03	−2.8 (−5.3, −0.4) .02	43 (13)	88	−1.4 (−3.5, 0.6) .17	−1.4 (−3.5, 0.6) .17

FEV₁, Forced expiratory volume in 1 second; FVC, forced vital capacity; LISAplus, influence of Life-style-related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics study; MACS, Melbourne Atopy Cohort Study; Post-BD, postbronchodilator; Pre-BD, prebronchodilator.

Bold indicates statistical significance ($P < .05$).

*Mean adjusted for gender, height, and age.

†Regression coefficients (95% confidence intervals) and P values adjusted for gender, age, and height (study center in LISAplus).

‡Regression coefficients (95% confidence intervals) and P values adjusted for gender, age, height, wheezing by the age of testing food sensitization, maternal smoking during pregnancy, parental level of education, and exclusive breast feeding for at least 4 months (formula allocation in MACS and study center in LISAplus).

TABLE E4. Associations between atopic sensitization in the first 2 years and FVC (pre- and post-BD) at 12, 15, and 18 years

Atopic sensitization	12 y (MACS)				15 y (LISApplus)				18 y (MACS)			
	N (%)	Adj. mean*	Model 1 [†]	Model 2 [‡]	N (%)	Adj. mean*	Model 1 [†]	Model 2 [‡]	N (%)	Adj. mean*	Model 1 [†]	Model 2 [‡]
FVC pre-BD (mL)												
6 mo												
No	254 (74)	2588	—	—					276 (74)	4582	—	—
Food only	51 (15)	2482	−106 (−225, 14)	−113 (−231, 6)					59 (16)	4437	−137 (−299, 24)	−143 (−305, 19)
			.08	.06							.09	.08
Aero only	17 (5)	2620	32 (−164, 229)	21 (−173, 215)					15 (4)	4701	63 (−237, 363)	59 (−240, 359)
			.74	.83							.67	.69
Food and aero	20 (6)	2505	−83 (−264, 98)	−81 (−261, 98)					23 (6)	4571	3 (−244, 249)	16 (−231, 263)
			.36	.37							.98	.89
12 mo												
No	236 (68)	2591	—	—					255 (67)	4587	—	—
Food only	47 (13)	2458	−134 (−260, −7)	−144 (−271, −16)					55 (14)	4451	−127 (−295, 41)	−115 (−284, 55)
			.03	.02							.13	.18
Aero only	26 (7)	254	−45 (−209, 118)	−57 (−219, 105)					27 (7)	4502	−64 (−293, 165)	−72 (−302, 157)
			.58	.48							.58	.53
Food and aero	40 (12)	2638	47 (−89, 182)	40 (−94, 174)					44 (12)	4637	38 (−147, 223)	48 (−137, 233)
			.49	.56							.68	.61
24 mo												
No	195 (62)	2561	—	—	681 (88)	4085	—	—	198 (61)	4566	—	—
Food only	24 (8)	2492	−69 (−234, 96)	−78 (−243, 86)	61 (8)	4114	39 (−92, 170)	33 (−99, 164)	28 (9)	4524	−71 (−300, 158)	−82 (−314, 149)
			.40	.34			.56	.63			.54	.48
Aero only	53 (17)	2493	−68 (−186, 51)	−70 (−188, 48)	17 (2)	3969	−122 (−362, 119)	−106 (−347, 136)	56 (17)	4508	−31 (−203, 140)	−39 (−212, 134)
			.26	.24			.32	.39			.72	.65
Food and aero	40 (13)	2493	−68 (−200, 64)	−95 (−227, 38)	19 (2)	4121	36 (−193, 266)	29 (−202, 259)	44 (13)	4503	−37 (−227, 152)	−42 (−234, 149)
			.31	.16			.76	.81			.69	.66
FVC post-BD (mL)												
6 mo												
No									269 (74)	4601	—	—
Food only									57 (16)	4544	−87 (−245, 71)	−89 (−247, 70)
											.27	.27
Aero only									15 (4)	4382	−55 (−343, 232)	−59 (−346, 228)
											.70	.68
Food and aero									23 (6)	4603	67 (−169, 304)	70 (−167, 307)
											.57	.56
12 mo												
No									248 (67)	4575	—	—
Food only									54 (15)	4526	−87 (−249, 75)	−77 (−241, 87)
											.29	.35

(continued)

TABLE E4. (Continued)

Atopic sensitization	12 y (MACS)				15 y (LISApplus)				18 y (MACS)			
	N (%)	Adj. mean*	Model 1 [†]	Model 2 [‡]	N (%)	Adj. mean*	Model 1 [†]	Model 2 [‡]	N (%)	Adj. mean*	Model 1 [†]	Model 2 [‡]
Aero only									26 (7)	4607	−9 (−232, 214)	−18 (−242, 206)
											.93	.87
Food and aero									43 (11)	4744	132 (−47, 311)	141 (−38, 320)
											.14	.12
24 mo												
No					665 (88)	4068	—	—	193 (61)	4561	—	—
Food only					59 (8)	4180	120 (−15, 255)	115 (−21, 250)	28 (9)	4552	−27 (−244, 189)	−44 (−263, 175)
							.08	.10			.80	.69
Aero only					18 (2)	3942	−132 (−369, 105)	−123 (−360, 115)	55 (17)	4531	−43 (−207, 120)	−48 (−213, 117)
							.27	.31			.60	.56
Food and aero					18 (2)	4151	83 (−156, 321)	71 (−168, 310)	43 (13)	4596	18 (−163, 199)	13 (−170, 196)
							.50	.56			.84	.89

FVC, Forced vital capacity; LISApplus, influence of Life-style—related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics study; MACS, Melbourne Atopy Cohort Study; *Post-BD*, postbronchodilator; *Pre-BD*, prebronchodilator.

Bold indicates statistical significance ($P < .05$).

*Mean adjusted for gender, height, and age.

†Regression coefficients (95% confidence intervals) and P values adjusted for gender, age, and height (study center in LISApplus).

‡Regression coefficients (95% confidence intervals) and P values adjusted for gender, age, height, wheezing by the age of testing food sensitization, maternal smoking during pregnancy, parental level of education, and exclusive breast feeding for at least 4 months (formula allocation in MACS and study center in LISApplus).

TABLE E5. Associations between degree of sensitization to food allergens (at 6 and 12 months) and pre-BD FEV₁ (at 12 years) in MACS

	12 y (MACS)	
	FEV ₁ pre-BD (mL)	
	Coef. (95% CI)	P value
At 6 mo		
Per 1 mm increase in each SPT		
Milk	−30.34 (−63.15, 2.47)	.07
Egg	−5.95 (−19.70, 7.80)	.40
Peanut	−32.47 (−58.01, −6.94)	.01
Per 1 mm increase in the aggregated SPT to food allergens*	−8.64 (−17.53, 0.25)	.06
Per food allergen sensitization (2 mm+)*	−81.36 (−136.62, −26.09)	<.01
No. of food allergens sensitized (2 mm+)		
0	Ref	—
1	−74.66 (−184.80, 35.48)	.18
2+	−206.98 (−347.60, −66.35)	<.01
At 12 mo		
Per 1 mm increase in each SPT		
Milk	−14.32 (−34.48, 5.84)	.16
Egg	−8.54 (−17.74, 0.67)	.07
Peanut	−18.42 (−34.89, −1.94)	.03
Per 1 mm increase in the aggregated SPT to food allergens*	−6.83 (−12.60, −1.05)	.02
Per food allergen sensitization (2 mm+)*	−63.01 (−110.83, −15.19)	.01
No. of food allergens sensitized (2 mm+)		
0	Ref	—
1	8.97 (−107.12, 125.07)	.88
2+	−188.10 (−305.40, −70.81)	<.01

CI, Confidence interval; FEV₁, forced expiratory volume in 1 second; MACS, Melbourne Atopy Cohort Study; Pre-BD, prebronchodilator; SPT, skin prick test. Bold indicates statistical significance ($P < .05$).

*Includes all 3 food allergens (milk, egg, and peanut).

TABLE E6. Associations between degree of sensitization to food allergens (at 6 and 12 months) and pre- and post-BD FEV₁ (at 18 years) in MACS

	18 y (MACS)			
	FEV ₁ pre-BD (mL)		FEV ₁ post-BD (mL)	
	Coef. (95% CI)	P value	Coef. (95% CI)	P value
At 6 mo				
Per 1 mm increase in each SPT				
Milk	−34.91 (−72.41, 2.59)	.07	−23.39 (−57.51, 10.74)	.18
Egg	−17.26 (−36.97, 2.46)	.09	−12.55 (−30.78, 5.67)	.18
Peanut	−32.14 (70.88, 6.60)	.10	−11.54 (−48.95, 25.87)	.54
Per 1 mm increase in the aggregated SPT to food allergens*	−13.73 (−26.01, −1.45)	.03	−8.56 (−19.94, 2.81)	.14
Per food allergen sensitization (2 mm+)*	−113.99 (−188.64, −39.34)	<.01	−87.45 (−156.39, −18.52)	.01
No. of food allergens sensitized (2 mm+)				
0	Ref	—	Ref	—
1	−62.97 (−209.18, −83.23)	.40	−66.40 (−200.98, 68.16)	.33
2+	−310.94 (−504.81, −117.07)	<.01	−227.20 (−407.49, −46.91)	.01
At 12 mo				
Per 1 mm increase in each SPT				
Milk	−25.39 (−52.45, 1.66)	.07	−22.35 (−46.75, 2.05)	.07
Egg	−7.02 (−19.80, 5.75)	.28	−7.55 (−19.14, 4.05)	.20
Peanut	−20.38 (−43.05, 2.29)	.08	−10.78 (−31.40, 9.85)	.31
Per 1 mm increase in the aggregated SPT to food allergens*	−7.33 (−15.23, 0.56)	.07	−6.12 (−13.28, 1.04)	.09
Per food allergen sensitization (2 mm+)*	−60.89 (−123.57, 1.79)	.06	−34.65 (−91.92, 22.57)	.23
No. of food allergens sensitized (2 mm+)				
0	Ref	—	Ref	—
1	−62.98 (−209.19, 83.23)	.40	−66.41 (−20.99, 68.17)	.33
2+	−310.94 (−504.81, −117.07)	<.01	−227.20 (−407.50, −46.91)	<.01

CI, Confidence interval; FEV₁, forced expiratory volume in 1 second; MACS, Melbourne Atopy Cohort Study; Post-BD, postbronchodilator; Pre-BD, prebronchodilator; SPT, skin prick test.

Bold indicates statistical significance ($P < .05$).

*Includes all 3 food allergens (milk, egg, and peanut).

TABLE E7. Associations between degree of sensitization to food allergens (at 6 and 12 months) and pre-BD FEV₁/FVC ratio (at 12 years) in MACS

	12 y (MACS)	
	FEV ₁ /FVC pre-BD (%)	
	Coef. (95% CI)	P value
At 6 mo		
Per 1 mm increase in each SPT		
Milk	−0.43 (−1.08, 0.22)	.19
Egg	−0.26 (−0.53, 0.01)	.06
Peanut	−0.52 (−1.03, −0.02)	.04
Per 1 mm increase in the aggregated SPT to food allergens*	−0.20 (−0.38, −0.03)	.02
Per food allergen sensitization (2 mm+)*	−0.89 (−1.99, 0.22)	.12
No. of food allergens sensitized (2 mm+)		
0	Ref	—
1	−1.32 (−3.52, 0.89)	.24
2+	−2.24 (−5.05, 0.57)	.12
At 12 mo		
Per 1 mm increase in each SPT		
Milk	−0.22 (−0.62, 0.17)	.27
Egg	−0.12 (−0.30, 0.06)	.20
Peanut	−0.18 (−0.50, 0.15)	.28
Per 1 mm increase in the aggregated SPT to food allergens*	−0.09 (−0.20, 0.03)	.13
Per food allergen sensitization (2 mm+)*	−0.64 (−1.58, 0.31)	.19
No. of food allergens sensitized (2 mm+)		
0	Ref	—
1	0.46 (−1.84, 2.75)	.70
2+	−2.41 (−4.73, −0.09)	.04

CI, Confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; MACS, Melbourne Atopy Cohort Study; Pre-BD, prebronchodilator; SPT, skin prick test.

Bold indicates statistical significance ($P < .05$).

*Includes all 3 food allergens (milk, egg, and peanut).

TABLE E8. Associations between degree of sensitization to food allergens (at 6 and 12 months) and pre- and post-BD FEV₁/FVC ratio (at 18 years) in MACS

	18 y (MACS)			
	FEV ₁ /FVC pre-BD (%)		FEV ₁ /FVC post-BD (%)	
	Coef. (95% CI)	P value	Coef. (95% CI)	P value
At 6 mo				
Per 1 mm increase in each SPT				
Milk	−0.70 (−1.25, −0.16)	.01	−0.65 (−1.10, −0.19)	<.01
Egg	−0.19 (−0.48, 0.10)	.19	−0.24 (−.49, −0.005)	.04
Peanut	−0.21 (−0.78, 0.35)	.46	−0.20 (−0.70, 0.30)	.44
Per 1 mm increase in the aggregated SPT to food allergens*	−0.17 (−0.35, 0.01)	.06	−0.19 (−0.34, −0.04)	.02
Per food allergen sensitization (2 mm+)*	−1.21 (−2.31, −0.10)	.03	−1.34 (−2.26, −0.42)	<.01
No. of food allergens sensitized (2 mm+)				
0	Ref	—	Ref	—
1	−0.29 (−2.46, 1.87)	.79	−1.22 (−3.02, 0.58)	.18
2+	−2.90 (−5.77, −0.03)	.05	−3.06 (−5.47, −0.65)	.01
At 12 mo				
Per 1 mm increase in each SPT				
Milk	−0.53 (−0.92, −0.14)	<.01	−0.52 (−0.83, −0.19)	<.01
Egg	−0.09 (−0.28, 0.09)	.31	−0.18 (−0.33, −0.02)	.02
Peanut	−0.37 (−0.70, −0.04)	.02	−0.24 (−0.51, −0.03)	.08
Per 1 mm increase in the aggregated SPT to food allergens*	−0.13 (−0.24, −0.01)	.03	−0.14 (−0.24, −0.05)	<.01
Per food allergen sensitization (2 mm+)*	−0.71 (−1.63, 0.20)	.13	−0.85 (−1.61, −0.10)	.03
No. of food allergens sensitized (2 mm+)				
0	Ref	—	Ref	—
1	0.21 (−2.02, 2.44)	.86	−0.21 (−2.05, 1.62)	.82
2+	−2.39 (−4.64, −0.14)	.04	−2.37 (−4.23, −0.51)	.01

CI, Confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; MACS, Melbourne Atopy Cohort Study; Post-BD, postbronchodilator; Pre-BD, prebronchodilator; SPT, skin prick test.

Bold indicates statistical significance ($P < .05$).

*Includes all 3 food allergens (milk, egg, and peanut).

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