**Title:**

The role of early life food sensitization in adolescent lung function: Results from two birth cohort studies

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**Declaration of all source of funding**

Initial funding for the MACS in the first 6 years of the study was from Nestec (a subsidiary of Nestlé Australia). The 12-year follow-up was supported by the Asthma Foundation of Victoria. The 18-year follow-up was supported by grants from the NHMRC of Australia (MACS grant # APP454856). The funding bodies had no role in the study design, collection, analysis or interpretation of data, nor in writing this paper or the decision to publish. The results, conclusions and opinions reported in the manuscript are those of the authors and are independent from the funding sources.

The LISAplus 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-ups examinations of the LISAplus 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). Further, the 15-year follow-up examination of the LISAplus study was supported by the Commission of the European Communities, the 7th Framework Program: MeDALL project.

**Conflict of interest**

No conflict of interest to declare.

**Words count:** abstract 250, text 3750.

**Abstract**

**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 association between food sensitization in the first two years of life and lung function at 12 to 18 years and examined if these associations are mediated through aeroallergen sensitization or asthma.

**Methods:**

We used data from a high-risk cohort (MACS) and a population-based (LISAplus) 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).

**Results:**

Sensitization to food without aeroallergen at 6 months was associated with reduced FEV1 at both 12 years (-153 ml; 95%CI=-256ml, -51ml) and 18 years (-206 ml; 95%CI=-347ml, -65ml) in MACS with similar results for sensitization measured at 12 months but not at 24 months. Early life asthma (but not aeroallergen sensitization) only partially mediated these associations. Both cohorts confirmed that only aeroallergen sensitization at 24 months but not food sensitization was associated with lower adolescent lung function.

**Conclusion:**

This study showed that food sensitization in the first 6 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.

**Highlight box**

* The role of food-sensitization on lung-function outcomes is unclear
* Food-sensitization <1-year was associated with reduced FEV1, partially mediated by increased risk of asthma.
* Food-sensitization is an early biomarker for adolescent lung-function impairment.

**Key words**

Food sensitization; Atopy; FEV1; FVC; FEV1/FVC ratio; Lung function; Spirometry.

**Abbreviations:**

**APCs**: Antigen presenting cells

**ATS**: American Thoracic Society

**CI:** Confidence Interval

**ERS:** European Respiratory Society

**FEV1:** Forced expiratory volume in 1 second

**FVC:** Forced vital capacity

**GA2LEN**: Global Allergy and Asthma European Network

**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 (LISAplus) study

**MACS:** Melbourne Atopy Cohort Study

**Post-BD**: Post-bronchodilator

**Pre-BD**: Pre-bronchodilator

**RCT**: Randomized control trial

**SPT**: Skin prick test

**Introduction**

Lung development and growth 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 risk factors during this critical period of lung development.

It has been shown that sensitization to aeroallergens in early life is associated with loss of lung function during childhood (2, 3). The mechanisms underlying the relationship between allergen sensitization and lung function remain unclear. It has been suggested that persistent environmental exposures 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 not been well evaluated. This is an important research question in the context of the recently observed rise in food allergies as a potential “second wave epidemic” (7). Additionally, 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 of early life food sensitization on lung growth needs to consider the role (direct or indirect) that concurrent asthma may play in altered lung growth.

A population-based study from Australia has shown that early atopic sensitization (defined as a positive skin prick test to at least one 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, they did not assess the role of food sensitization separately. Another recent study (12) 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 explore the association between food sensitization in the first two years of life and adolescent lung function measures and to examine if these associations were mediated by early life aeroallergen sensitization or asthma status in early childhood. We conducted a prospective analysis of two independent cohorts: the high-risk Melbourne Atopic 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 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 from then annually up to the age of 7 then at 12 and 18 years.

MACS initially started as a randomized controlled trial (RCT) investigating the effect of three different infant formulas (cow’s milk, partially hydrolysed whey and standard soy formula) implemented at the time of weaning, on the occurrence of allergic disease. Use of a randomized controlled trial to test additional hypotheses about the association between non-randomized 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 rzecent follow-up, all participants.

LISAplus is a German population-based birth cohort study that recruited 3,094 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**

Skin Prick Tests (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, WA, USA*).* SPTs were read at 15-20 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 ≥2mm (21). We used 2 mm as the cut off given the evidence that positive SPT reactions are likely to be smaller in children younger than 2 years (22), presumably because of a lack of antigen-specific IgE and skin reactivity (23).

Sensitization was assessed in LISAplus 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 Immunoglobulin E antibodies (s-IgE) to aeroallergens of mould (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 kUA/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 1994 (24) and ATS / European Respiratory Society (ERS) Guidelines 2005 (25)). Lung function assessment (pre-bronchodilator) was performed at 12 years by trained research nurses using the Spirocard system (SpiroCard **TM** PC Spirometer, QRS Diagnostic, Plymouth, MN, USA). At 18 years, pre- and post-bronchodilator (salbutamol) spirometry was conducted by trained respiratory scientists using the EasyOneTM Spirometer (ndd Medical Technologies Inc, Andover MA). Participants were advised not to use short-acting beta agonists (by MDI) and long acting bronchodilators for 4 and 12 hours prior to the test respectively. Height was recorded at the time of testing, without shoes to the nearest 0.1cm.

In LISAplus, spirometry was performed at the 15-years follow-up pre- and post- bronchodilation (200µg salbutamol). A detailed description has been published previously (26). The procedure, all measurements as well as the evaluation of the results were in accordance with ATS/ERS recommendations (25). Flow-volume curves were obtained using a pneumotachograph-type (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 (GA2LEN) definition (27). Subjects providing a positive response to at least two of the following three 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*

Wheeze by the time of sensitization was defined as present using the survey administered at the time of SPT. These definitions included: a response of >5 days to the question of “How many days of cough and/or chest rattle and/or wheeze has your child had in the past 4 weeks?” in MACS (28), and 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?” in LISAplus.

*Family history of atopy (in LISAplus)*

Defined if the participant had at least one first degree relative with asthma, eczema or hay fever; asked at birth.

**Statistical analysis**

All participants from both cohorts who had completed early life sensitization data and lung function outcomes during adolescence were included in our analyses. Linear regression models were used to assess the association between food with or without aeroallergen sensitization at 6, 12 or 24 months in MACS or at 24 months in LISAplus. Lung function outcomes included FEV1, FVC and FEV1/FVC ratio at 12 and 18 years (in MACS) and at 15 years (in LISAplus). We modelled 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, formula allocation in MACS and study centre in LISAplus were adjusted. All models were then 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 (29). Interactions of atopic sensitization with concurrent asthma, personal smoking (only at 15 or 18 years) and family history of atopy in LISAplus study and formula allocation in MACS study were assessed. Interaction terms were not included in final models if *p* values were >0.1. STATA 13 (StataCorp, College Station TX) was used in all analyses in MACS and R version 3.2.0 was used for all analyses in LISAplus (30). All results are presented as regression coefficients β with 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 foods 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 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” or ACME in the output from the “*medeff*” command) as the two additive components of the total causal effect (31, 32). If there was an association between the exposure and the potential mediator and between the potential mediator and the outcome and there was a significant indirect effect from “*medeff*” model output, then this variable would be considered as a mediator for the association between foods only sensitization and pre-BD FEV1.

**Results**

**Characteristics of Participants**

The baseline demographic characteristics of the MACS participants have been published previously (33). This analysis was restricted to who had data on both sensitization and lung function testing and included 364 participants (59% of original cohort) at 12 years and 399 participants (64% of original cohort). The characteristics of the included participants are presented in **Table 1**. 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 in the Online Repository”.

The baseline demographic characteristics of LISA participants have been described previously (19). 796 participants (47% of original cohort) from four study centres (358, 250, 100 and 88 from Munich, Leipzig, Bad Honnef and Wesel, respectively) were included in the analysis. The characteristics of analyzed participants are summarized in **Table 1**.

With the exception of a higher proportion of highly educated parents and a lower number of older siblings, LISAplus participants who attended lung function measurement at the 15-year follow-up were similar to those who did not attend “see Table E1 in the Online Repository**”**.

**Sensitization in the first two years and lung function at 12, 15 and 18 years**

*Sensitization and pre-BD FEV1*

Sensitization to food only (i.e. without aeroallergen sensitization) and degree of sensitization to food at 6 months were associated with a reduction in pre-BD FEV1 at 12 and 18 years **(****Figure 1 and Tables E5 – E8)**. Similar findings were observed for food only sensitization at 12 months **(Figure 1)**. Additionally, sensitization to aeroallergens without co-existing food sensitization at 24 months was associated with a reduction in pre-BD FEV1 at 15 and at 18 years **(Figure 1)**.

Co-sensitization to food and aeroallergens at all three-time points was not associated with any deficit in pre-BD FEV1 at 12, 15 or 18 years **(Figure 1)** “see Table E2 in the Online Repository”.

*Sensitization and post-BD FEV1*

Sensitization to food without co-existing aeroallergen sensitization and degree of sensitization food at 6 months were associated with a reduction in post-BD FEV1 at 18 years **(****Figure 2 and Tables E6 & E8)**. 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 in the Online Repository”.

*Sensitization and pre-BD FEV1/FVC ratio*

Sensitization to food only without aeroallergen sensitization at 6 months and degree of sensitization food were associated with a reduction in pre-BD FEV1/FVC ratio at 12 years **(Figure 3 and Tables E5 – E8)**. Furthermore, sensitization to aeroallergens without concurrent food sensitization at 24 months was associated with a reduction in 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 of pre-BD FEV1/FVC ratio at 12 years. Co-sensitization to food and aeroallergens at all three-time points was not associated with any deficit in pre-BD FEV1/FVC ratio at 12, 15 and 18 years **(Figure 3)** “see Table E3 in the Online Repository”.

*Sensitization and post-BD FEV1/FVC ratio*

Sensitization to food only without concurrent aeroallergen sensitization at 6 months and degree of sensitization food were associated with a reduction in post-BD FEV1/FVC ratio at 18 years **(Figure 4 and Tables E6 & E8)**. Also, co-sensitization to food and aeroallergen at 12 months was related to reduced post-BD FEV1/FVC ratio at 18 years, and at 24 months was related to 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 post-BD FEV1/FVC ratio at 15 or 18 years **(Figure 4)** “see Table E3 in the Online Repository”.

*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 exception of food without aeroallergen sensitization at 12 months and pre-BD FVC at 12 years (-144ml; 95% CI -271ml, -16 ml) (Table E4 in the Online Repository).

**Interaction with concurrent asthma, personal smoking, family history of atopy (in LISAplus) 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 were >0.1. In LISAplus, however, there was an interaction between asthma and co-sensitization to food and aeroallergen for pre-BD FEV1/FVC ratio and pre- and post-BD FVC, but exclusion of subjects with asthma in models for that spirometric parameter did not alter the observed associations. An interaction between food sensitization and family history of atopy was found only for post-BD FEV1/FVC ratio. For this parameter, co-sensitization to food and aeroallergens was not significant after stratification for family history of atopy. Stratification for family history of atopy showed significant associations for aeroallergen sensitization in subjects with family history of atopy, but not in those without family history of atopy. However, there were few individuals who had sensitization without family history of atopy. Additionally, further adjustment for personal smoking did not modify the results.

**Assessment of mediators in MACS study**

Results from the causal mediation analysis showed evidence of a direct effect of food only sensitization at 6 or 12 months on pre-BD FEV1 at 12 and 18 years pathway, and an indirect effect 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 -114ml, 95%CI= -230ml, -2ml; indirect effect -20ml, 95%CI= -48ml, -2ml). 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 -184ml, 95%CI= -334ml, -39ml; indirect effect -32ml, 95%CI= -77ml, -4ml). On the other hands, 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 in the Online Repository”.

**Discussion**

We observed that early life sensitization to food allergens, up to 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 aeroallergen sensitization at age two and asthma at 6 years. Sensitization to aeroallergens only was also associated with a reduction in FEV1 and FEV1/FVC ratio in adolescence. This is the first study to evaluate and demonstrate that the association between early life food sensitization on subsequent lung function, and to demonstrate that these associations are not completely mediated by increased risk of aeroallergen sensitization and asthma. However, the 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 westernized countries with a high prevalence of food sensitization (34). It is often assumed that results from a high-risk cohort may not be applicable to the general population, but our results were largely consistent across the two cohorts where data were available, despite the geographical differences between cohorts as well as some differences in the methods of sensitization assessment. 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 (APCs) result in the release of several pro-inflammatory mediators and cytokines (35). 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 (35, 36). After repeated exposure to allergens, persistent inflammation occurs that may lead to long term structural and functional changes of affected tissues (35).

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 al*. (37) reported that infant-onset atopy (defined as positive SPT to any tested foods and aeroallergens on at least one occasion during infancy) 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 decrease FEV1 and FEV1/FVC ratio. On the other hand, Hose *et al*. (12) 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. These discrepancies in the results could be due to the age of lung function assessment or the type of assessed allergens. Additionally, the first assessment of sensitization in this study was performed at the 12 months of life, while in the current study, we first assessed sensitization at 6 months.

Asthma in early childhood has been shown to be associated with airway remodelling which may result in fixed airflow obstruction (38) and subsequently a decrease in lung function mainly in individuals with moderate to severe asthma (39). Nevertheless, to what extent asthma influences this decrease, in sensitized individuals, is less obvious. Our results showed that the associations between food sensitization and decreased FEV1 and FEV1/FVC ratio were partially mediated by asthma at 6 years, suggesting that food sensitization per se may lead to subsequent airway changes and reduced lung function.

The changes in spirometry may reflect control of asthma. However, we have asthma medication use in the last 12 months for both MACS and LISAplus, and these data have been used to classify current asthma at the time of the lung function testing. We have investigated whether our associations were modified by this current asthma variable as stated in the methods and results. In MACS our associations were similar among those with and without current asthma. In LISAplus, although we observed an interaction, exclusion of current asthmatics did not change the findings. Furthermore, asthma was not found to fully mediate the association. In addition, the association between food sensitization and post bronchodilator FEV1, and ratio, suggests that the effect may not be related to asthma control.

Childhood asthma, parental smoking and personal smoking are known to be associated with a reduced lung function (39). A study by Hofhuis *et al*. (40) has shown that infants born to smoking mothers have reduced forced expiratory flows compared to those born to non-smoking mothers. We found maternal smoking during pregnancy to confound the associations and therefore adjusted it in all analyses. Interestingly, personal history of smoking neither confounded nor modified the associations observed. However, our analysis was based on a young age group in which the prevalence of smoking was low (<7%). A decrease in FEV1 and FEV1/FVC ratio that is reversible may be present especially in individuals with moderate to severe asthma is (36). Furthermore, childhood asthma has been shown to lead to airway remodeling, which may result in fixed airflow obstruction (35). Our results showed that the associations between food sensitization and decreased both pre and post BD FEV1 and FEV1/FVC ratio were partially mediated by asthma. Furthermore, these associations were observed even among non-asthmatics. 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 two independent cohorts with long period of follow-up that extended from infancy to adolescence. A large number of participants have performed lung function testing according to internationally recognized standards during the adolescent period. Additionally, 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 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 seven years of life, and early ages for sensitization assessment to a standard battery of allergens allowed exploring the potential pathways for the association between sensitization to food allergens only and adolescent lung function through aeroallergen sensitization at two years and asthma at 6 years.

However, this study also has a number of limitations. Loss to follow-up is a common issue in longitudinal studies and its rate increases with increasing duration of the study. Loss to follow-up is inevitable in most cohort studies and may leads to selection bias, particularly when it is non-random and linked to the study outcomes. Additionally, as a result of loss to follow-up, the statistical power of the study to address specific research questions may reduce, especially in relatively small studies like MACS. However, both MACS and LISAplus studies achieved good follow-up rates, with 59% and 64% attendance at the 12 and 18-year follow-ups, respectively in MACS and approximately 50% at the 15-year follow-ups in LISAplus. However, 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 non-attending children in either cohort. The second limitation is that we were unable to establish the effect of food sensitization at 6 and 12 months in the population-based LISAplus study, as sensitization was not assessed in the first year of life. Since the significant deficit in FEV1 and FEV1/FVC ratio in MACS was demonstrated in those who had early life food sensitization, we were unable to confirm if these findings were limited to individuals at high risk of atopy.

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 suggest that this association is valid.

In conclusion, food sensitization without co-existent aeroallergen sensitization in the first year of life was associated with declines in FEV1 and FEV1/FVC ratio during adolescence in the high allergy risk cohort. Early childhood asthma has only partially mediated these 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 that should be considered when assessing lung function. 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.

**Acknowledgments**

For MACS study, we thank Dr John Thorburn, FRACP, for assistance in patient recruitment and administrative assistance and the Mercy Maternity Hospital Department of Obstetrics for participant recruitment, and Dr Cliff Hosking for study leadership up to the 12-year follow-up. We thank Anne Balloch for assistance with data management. Most importantly, we thank all of the MACS children and parents for their participation and ongoing support for this study.

The authors thank all the families for their participation in the LISAplus study. Furthermore, we thank all members of the LISAplus Study Group for their excellent work.

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Figure legends

**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 <0.05.

*‡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 LISAplus).* ***NB:*** *12 and 18-year data from MACS, 15-year data from LISAplus.*

**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 <0.05.

*‡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 LISAplus).* ***NB:*** *18-year data from MACS, 15-year data from LISAplus, post-BD FEV1 was not assessed at 12 years.*

**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 <0.05. *‡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 LISAplus).* ***NB:*** *12- and 18-year data from MACS, 15-year data from LISAplus.*

**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 <0.05. *‡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 LISAplus).* ***NB:*** *18-year data from MACS, 15-year data from LISAplus, post-BD FEV1/FVC ratio was not assessed at 12 years.*

**Table 1: Characteristics of participants with both sensitization and lung function data in MACS and LISAplus cohorts**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Participants’ characteristics** | **MACS cohort** | | | | **LISAplus cohort** | |
|  | At 12 years | | At 18 years | | At 15 years | |
| **Total Number (N)**  **Sex, n (%)** | 364 | | 399 | | 796 |
| Male | | 189 (52) | | 201 (51) | 425 (53) | | |
| Female | | 175 (48) | | 198 (49) | 371 (47) | | |
| **Age (years), 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 months | 51/342 (15) | | 59/373 (16) | | - | | |
| 12 months | 47/349 (13) | | 55/381 (14) | | - | | |
| 24 months | 24/312 (8) | | 28/326 (9) | | 62/796 (8) | | |
| **Aeroallergens only** |  | |  | |  | | |
| 6 months | 17/342 (5) | | 15/373 (4) | | - | | |
| 12 months | 26/349 (7) | | 27/381 (7) | | - | | |
| 24 months | 53/312 (17) | | 56/326 (17) | | 19/796 (2) | | |
| **Food and aeroallergens** | | |  | |  | | |
| 6 months | 20/342 (6) | | 23/373 (6) | | - | | |
| 12 months | 40/349 (11) | | 44/381 (12) | | - | | |
| 24 months | 40/312 (13) | | 44/326 (14) | | 19/796 (2) | | |
| **Lung Function parameter, adjusted mean\*(SD)** |  | |  | |  | | |
| Pre-BD FEV1 (ml) | 2366 (651) | | 3832 (791) | | 3514 (480) | | |
| Post-BD FEV1 (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 FEV1/FVC ratio (%) | 92 (7) | | 85 (8) | | 86 (2) | | |
| Post-BD FEV1/FVC ratio (%) | - | | 88 (6) | | 89 (1) | | |

\*Adjusted for age, gender and height.