

components of the eye with respect to omalizumab is unclear. A dosing schedule of omalizumab in VKC cases has yet to be established, with reported treatment schedules ranging from 6 months to 2 years, either bi-monthly or monthly.^{1–7} These long, prolonged schedules may both inconvenience patients and increase unnecessary health care costs. In this case report, we describe the first case of VKC to be successfully treated with a single 300-mg dose of omalizumab.

A 54-year-old man with life-long history of seasonal allergic rhinoconjunctivitis with aeroallergen allergies to grass, tree, and ragweed, as determined by positive skin prick testing performed in April 2014, presented with a new symptom of severe ocular allergies during grass allergy season in early May 2017. The patient had no history of perennial alleged sensitivity. On examination, he had large papillae of different shape and size with Trantas' dots and infiltrates on the limbus. He complained of a stringy mucous discharge, photophobia, and painful gritty sensation of both eyes that was worse in the mornings. Superficial keratitis and chemosis was observed bilaterally. No periorbital dermatitis was seen, and he did not wear contact lenses. Because of the cobblestone-like appearance of the upper tarsal, mucus discharge, corneal inflammation, and intense itching criteria make VKC easily distinguishable from other forms of allergic conjunctivitis,⁹ a clinical diagnosis of vernal keratoconjunctivitis was made. The patient was started on treatment of 2 tablets of rupatadine 10 mg once daily and 1 drop of olopatadine hydrochloride ophthalmic solution 0.2% once daily. Despite initial treatment, the patient's ocular symptoms persisted past 4 weeks. Consequently, a decision was made to administer a single 300-mg dose of subcutaneous omalizumab in June 2017.

After treatment with omalizumab, ocular symptoms improved dramatically within a week, with no further symptoms during the remaining 4 weeks of grass allergy season without the use of any ocular therapy, which was discontinued 1 day after omalizumab injection.

Although a number of treatment options exist for VKC, treatment is mainly symptomatic in nature. Topical eye drops are generally preferred as a first choice of treatment, of which topical steroid preparations are most effective.⁶ Accordingly, a great proportion of individuals who develop VKC eventually require topical corticosteroids at some point during the disease process.⁶ However, topical corticosteroids may put patients at risk for acquiring glaucoma and cataracts, an existing risk for patients with VKC.¹⁰

Omalizumab is a safe and effective treatment option for VKC that bypasses the risks associated with topical corticosteroid therapy. However, currently dosage instructions for omalizumab only exist for those affected by asthma or chronic idiopathic urticaria; meanwhile

instructions for a patient with VKC remain unknown. Previous studies have reported high doses and long treatment schedules of omalizumab for treatment of patients with VKC, in accordance with omalizumab dosage guidelines for asthma.^{1–7} Accordingly, longer treatment schedules may lead to reduced patient compliance associated with higher health care costs and the inconvenience of attending multiple medical appointments. This is expected to become a growing problem as omalizumab becomes a more popular treatment option for VKC in the future. By providing a single dose of omalizumab for treatment of VKC, unnecessary costs and inconveniences may be avoided while not compromising on safety and efficacy.

This is the first case to our knowledge of VKC successfully treated using a single 300-mg subcutaneous dose of omalizumab.

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Fatty acids in pregnancy and risk of allergic sensitization and respiratory outcomes in childhood



Some observational studies have suggested associations of higher prenatal fish intake with protection against offspring asthma, attributing associations to greater exposure to marine n-3 long-

chain polyunsaturated fatty acids (LCPUFAs). Two recent randomized clinical trials have tested that hypothesis. Bisgaard and colleagues¹ found that supplementation with n-3 LCPUFAs reduced the risk of persistent wheeze or asthma and lower respiratory tract infections, but not allergic sensitization or eczema, in offspring followed up for the first 3 years of life. Their report, which included a succinct review of the literature, was accompanied by an interactive pro–con debate about the merits of prenatal fatty acid supplementation.² Ramaswami et al² cited an

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essentially negative trial by Best et al,³ suggesting that after 6 years of follow-up, evidence supporting maternal n-3 LCPUFAs supplementation to protect against either allergic disease or asthma in the offspring remained weak. Ramaswami et al² countered that the Bisgaard findings made biologic sense: the n-3 LCPUFAs, mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are substrates for mediators that resolve inflammation and infection (resolvins and protectives), specifically decreasing airway inflammation, mucus metaplasia, and hyperreactivity, while promoting host defense against respiratory infection, acting along pathways that are not directly related to allergic sensitization.

Allergic sensitization evolves throughout childhood, and only some wheeze manifested in infancy persists after age 3 years. In Project Viva, an observational cohort followed up from early pregnancy, we evaluated associations of maternal fish consumption as well as prenatal and cord blood n-3 and n-6 fatty acid (FA) levels with allergic sensitization, eczema/atopic dermatitis, wheeze, and asthma in early childhood (median, 3.3 years) as well as by mid-childhood (median, 7.7 years). Because some n-6 as well as many n-3 FAs have anti-inflammatory properties, we hypothesized that specific n-6 as well as n-3 FAs might protect against sensitization and wheeze in children observed by mid-childhood. This hypothesis was supported by our prior observation in this cohort that higher n-3 EPA and n-6 arachidonic acid (AA) levels were each correlated with lower cord blood lymphocyte proliferation and interferon-gamma levels in response to cockroach and dust mite allergen stimulation, suggesting a dampened response to allergens.⁴ Finally, we evaluated whether greater fish intake in our Massachusetts cohort could account for protective associations of prenatal maternal fatty acids with either allergic sensitization or asthma, knowing that the quantity and type of fish consumption may differ between cultures.

We described details about the analysis cohort ($n = 1,356$), exposures, outcomes, and statistical analysis in the Supplemental File. Main exposures were individual n-3 (α -linolenic acid [ALA], EPA, DHA) and n-6 (linoleic acid [LA], AA) long-chain polyunsaturated FA concentrations in maternal second trimester ($n = 1,201$) and cord ($n = 762$) plasma and prenatal fish and shellfish intake ($n = 1,356$). We calculated multivariable odds ratios for allergic sensitization, atopic dermatitis,⁵ and asthma or wheeze in early and mid-childhood. We categorized all exposures into quartiles and adjusted all models for maternal and paternal history of atopy and child sex and age.

Characteristics of the 1,356 mother-child pairs and exposure distributions are shown in eTables 1 and 2. In early childhood, 40% had allergen sensitization and 21% had parental-reported ever asthma or wheeze diagnosis. In mid-childhood, 53% had allergen sensitization, and 18% had current asthma.

Although cord blood fatty acids were not associated with early childhood allergic sensitization or atopic dermatitis, n-3 and n-6 FAs were inversely associated with early childhood wheeze symptoms (eTable 3). In mid-childhood, but not in early childhood, the odds of allergic sensitization and of current asthma tended to be reduced with higher levels of maternal second trimester n-3 and n-6 FAs (Fig 1). For example, comparing the highest vs. lowest quartile of EPA, the adjusted odds ratio (OR) (95% confidence interval [CI]) was 0.56 (0.32, 0.97) for allergic sensitization and 0.55 (0.31, 0.98) for current asthma.

In contrast, the odds of childhood sensitization were increased with higher maternal consumption of fish or shellfish (eTable 4). Mean (standard deviation [SD]) fish and shellfish consumption was 1.7 (1.4) servings/week. Comparing the highest and the lowest quartiles of fish and shellfish consumption, the adjusted OR (95% CI) for allergen sensitization in mid-childhood was 1.65 (1.07, 2.52). Fish or shellfish consumption had no association with wheeze or asthma; however, shellfish was associated with more atopic dermatitis (36%) in early childhood (OR 1.47; 95% CI 1.02, 2.12).

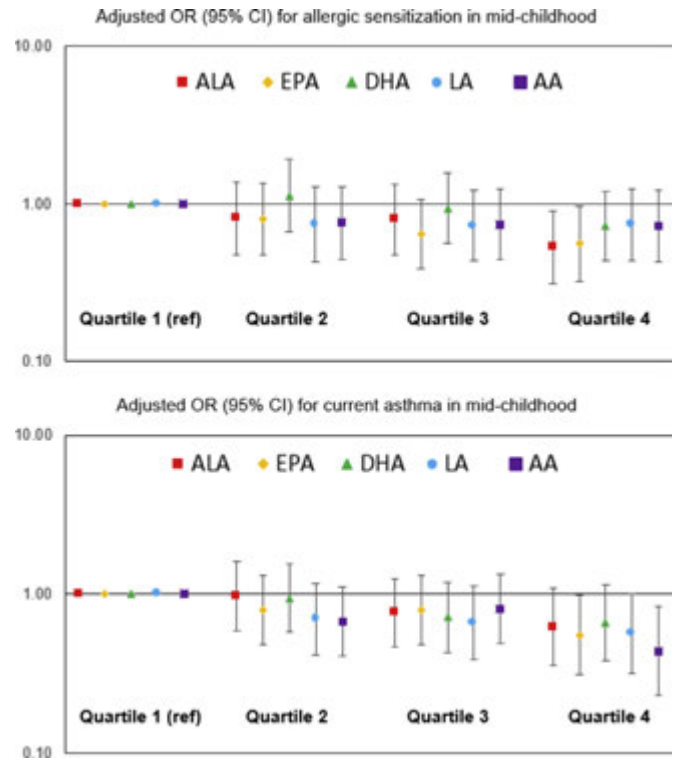


Figure 1. Multivariable associations of fatty acids in second trimester maternal plasma (quartiles 2–4 vs quartile 1) with allergic sensitization and current asthma in mid-childhood. Models were adjusted for maternal and paternal history of atopy and child age and sex. Allergic sensitization was additionally adjusted for parity. Allergen sensitization defined as 1 or more detectable allergen-specific IgE or total IgE of 100 or more IU/mL. Current asthma defined as parental report of ever doctor diagnosis of asthma plus wheeze symptoms or use of asthma medication in the past 12 months. Comparison group includes participants with no asthma, no medication, and no current wheeze.

Thus, our observational data suggest potentially protective effects of prenatal maternal LCPUFAs on long-term allergic sensitization and asthma, but not on atopic dermatitis. Our study limitations include limited allergic sensitization measures in early childhood, the absence of shellfish-specific immunoglobulin E (IgE) measures as well as correlation amongst the n-3 and n-6 FAs, making it difficult to distinguish independent effects. We await the follow-up of the children in the Bisgaard trial to see whether the protective associations of supplementation with n-3 LCPUFAs with asthma endure into mid-childhood, whether new protective associations with allergic sensitization or allergic disease emerge, or whether, as in the Best et al trial, the n-3 LCPUFAs supplements appear to have no long-term protective effects on either allergic disease or asthma.

Our data and some other observational mechanistic studies also suggest that potentially beneficial enduring effects may come from specific n-6 as well as n-3 LCPUFAs.^{6–9} Arachidonic acid, for example, is a precursor to various prostaglandins that have complex relationships with lipoxin, and anti-inflammatory resolvins effects. Protective therapies with specific n-3 and n-6 LCPUFAs may in practice have to be personalized to effect maximal benefits, because maternal, placental, and fetal metabolism and use of supplements may vary by phenotype or genotype.

For optimal brain development, current Food and Drug Administration guidelines recommend that pregnant women consume a minimum of 2 to 3 servings of low-mercury fish every week.¹⁰ Most US women consume less fish, including Project Viva mothers. Further evaluation is warranted to assess whether shellfish, which may be the main source of fish for many pregnant mothers, may contribute

to the risk of allergic sensitization for some offspring. However, given that thinking has come full circle, suggesting potential benefits of higher maternal ingestion of other foods that contain allergens, such studies should be conducted thoughtfully without premature advice that might contradict current policy.

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Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.anai.2018.09.450>.

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Safety of penicillin allergy skin testing in patients with low lung volumes before lung transplant



Penicillin allergy is the most frequently reported drug hypersensitivity reaction, with a prevalence rate of approximately 10% in the United States^{1,2}; however, true reactions exist in only approximately 3% of patients reporting a penicillin allergy.² Penicillin allergy stigma results in higher health care costs and increased prevalence of multi-drug-resistant (MDR) organisms. In the pre-lung transplant population, there are no data on penicillin skin testing in the setting of severely compromised lung function.

The incidence of infections with MDR organisms within patients being evaluated for lung transplantation continues to increase, which is of specific importance in the cystic fibrosis cohort. A recent study examining prevalence of resistance and correlation with recent antibiotic exposure in patients with cystic fibrosis revealed an increased in carbapenem and aztreonam resistance and overall MDR in 2008

when compared with a similar cohort from a decade prior.³ Many of these bacteria, especially *Pseudomonas*, are classically penicillin sensitive species. Patients on a lung transplant list typically undergo quarterly surveillance respiratory cultures; presence of infection or colonization with organisms with certain resistance profiles can be a relative contraindication to transplantation and can compromise a patient's position on a transplant list.⁴ In addition, infection or colonization with MDR organisms can lead to catastrophic posttransplant infections and organ compromise. In patients with *Burkholderia cenocepacia*, colonization, survival rates after transplantation at the 1-year mark are significantly compromised at 30% when compared with the expected 90%.⁵ Despite the relevance, safety of penicillin testing in patients with a low pulmonary reserve before lung transplant remains understudied.

We retrospectively reviewed lung transplant candidates who underwent preoperative penicillin skin testing at Mayo Clinic Hospitals in Rochester, Minnesota, and Jacksonville, Florida, between April

Supplementary Data

Study Population

Project Viva is a prospective pre-birth cohort study in Eastern Massachusetts.¹ We recruited pregnant women from Atrius Harvard Vanguard Medical Associates between 1999 and 2002. We completed in-person visits with the mothers in late first (median, 9.9 weeks' gestation) and second (median, 27.9 weeks) trimesters and with mother-child pairs in the hospital after delivery and in early childhood (median, 3.3 years) and mid-childhood (median, 7.7 years); we sent questionnaires annually between visits. We show the participant flow in [eFigure 1](#). The institutional review boards of participating institutions approved the study, and all mothers provided written informed consent for themselves and their children.

Pregnancy Blood Collection and Fatty Acid Assays

We collected maternal whole blood samples during the routine non-fasting mid-pregnancy clinical blood draw. From these we obtained separate aliquots of plasma, white blood cells, and erythrocytes, which were stored in liquid nitrogen freezers (−80°C) until assay. Cord blood samples were drawn from the umbilical vein in infants delivered on a weekday at 1 of the 2 study hospitals. Plasma samples were stored in liquid nitrogen freezers (−80°C) until assay.

Fatty acids in plasma were extracted and quantified (in micrograms per milliliter), using liquid-gas chromatography. Analytic methods have good within-run precision (coefficient of variance, <5.4%) and have been previously validated.² In this analysis, we included the following fatty acids: individual n-3 FA (ALA, EPA, DHA) and n-6 FA (LA, AA).

Outcome Measurements

Early Childhood Visit

We collected blood via venipuncture, stored plasma at −80°C, and assayed it for IgE specific to mite, cat, dog, cockroach, and *Alternaria*, using the UNICAP System (Pharmacia, Uppsala, Sweden). In samples with low plasma volume, IgE antibodies were measured with the CAP RAST FEIA System (Pharmacia). We defined any *allergen sensitization* as any specific IgE level of 0.35 IU/mL or greater to common indoor (dust mite [*Dermatophagoides farinae*], cat, dog, cockroach), mold (*Alternaria* or *Aspergillus* species); or food (egg white [ovomucoid]) allergen or a total IgE level of 75.6 IU/mL or greater.³

Ever asthma or *wheeze diagnosis* was reported by parents on the early childhood interview as a positive response to whether the child ever received a doctor's diagnosis of asthma, wheeze, or reactive airway disease. We defined *wheezing symptoms in the past 12 months* as parental report of wheezing symptoms in the past 12 months, assessed on the early childhood questionnaire. *Ever atopic dermatitis* was reported by parents on the 6-month, 1-year, 2-year, or early childhood assessments as a positive response to whether the child ever received a doctor's diagnosis of eczema/atopic dermatitis.

Mid-Childhood Visit

We collected blood via venipuncture and stored plasma at −80°C within 48 hours. We measured plasma total IgE and allergen-

specific IgE levels, using ImmunoCAP (Phadia, Uppsala, Sweden). Expanding our allergen panel from that in early life, we measured sensitization to 8 indoor or outdoor inhalant allergens (dust mite, cat, dog, cockroach, *Aspergillus*, *Alternaria*, rye grass, ragweed) and 5 foods (ovomucoid, milk, wheat, peanut, and soybean). We defined *current allergen sensitization* as ≥ 1 detectable allergen-specific IgE or total IgE ≥ 100 .³

We based the asthma outcomes on responses from the mid-childhood questionnaire administered to the mother, asking about symptoms and diagnoses of allergic and airway diseases. Questions were drawn from the International Study of Asthma and Allergies in Childhood (ISAAC).⁴ We defined *current asthma* as a maternal report of ever asthma doctor diagnosis plus wheeze symptoms or use of asthma medication in the past 12 months. The comparison group comprised children reporting no doctor diagnosis and no wheezing symptoms or asthma medication use. We defined *current atopic dermatitis* as parental report of ever doctor diagnosis of eczema/atopic dermatitis on the mid-childhood questionnaire, plus itchy rash in the past 12 months in any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes.

Statistical Analysis

We performed all analyses using SAS 9.4 software (SAS Institute, Cary, North Carolina). We used multiple imputation to account for missing data.

We analyzed associations between exposures and outcomes, using logistic regression models, adjusting for maternal and paternal history of asthma, hay fever, or eczema and child age and sex. We additionally adjusted mid-childhood allergen sensitization for parity. We categorized all exposure into quartiles to examine potential non-monotonic relations.

We also examined maternal fish and shellfish intake (canned tuna, shellfish, dark meat fish, and other fish) during pregnancy (average of first- and second-trimester intake from validated food frequency questionnaires)⁵ in relation to all outcomes, because we considered this exposure relevant to dietary recommendations.

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eTable 1

Characteristics of Participants in the Analysis Sample (N = 1,356)

Characteristics	N = 1,356 %
Maternal age at enrollment, years (mean [SD])	32.2 (5.1)
Maternal education, % ≥ college graduate	69.2
Nulliparous, % yes	47.4
Maternal history of asthma, hay fever, or eczema, % yes	40.3
Paternal history of asthma, hay fever, or eczema, % yes	34.5
Child sex, % male	51.7
Child race/ethnicity, %	
Black	13.8
Hispanic	4.5
White	67.2
Other	14.5
Early childhood	
Age, years (median [IQR])	3.3 (3.1–4.0)
Allergen sensitization, ^a % yes	40.4
Ever asthma or wheeze diagnosis, ^b % yes	21.4
Wheezing symptoms in the past 12 months, ^c % yes	20.9
Ever atopic dermatitis, ^d % yes	36.2
Mid-childhood	
Age, years (median [IQR])	7.7 (7.4–8.3)
Allergen sensitization, ^e % yes	53.0
Current asthma, ^f % yes	17.8
Current atopic dermatitis, ^g % yes	6.4

Abbreviations: SD, standard deviation; IQR, interquartile range.

^aAllergen sensitization defined as ≥ 1 detectable allergen-specific IgE or total IgE ≥ 75.6 IU/mL.^bParental report of ever doctor diagnosis of asthma or wheeze, assessed in the early childhood interview.^cParental report of wheezing symptoms in the past 12 months, assessed in the early childhood questionnaire.^dParental report of ever doctor diagnosis of atopic dermatitis on the 6-month, 1-year, 2-year, or early childhood assessment.^eAllergen sensitization defined as ≥ 1 detectable allergen-specific IgE or total IgE ≥ 100 IU/mL.^fCurrent asthma defined as parental report of ever doctor diagnosis of asthma plus wheeze symptoms or use of asthma medication use in the past 12 months. Comparison group includes participants with no asthma, no medication, and no current wheeze.^gCurrent atopic dermatitis defined as parental report of ever doctor diagnosis of atopic dermatitis on the mid-childhood questionnaire, plus itchy rash in the past 12 months in any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes.**eTable 2**

Distribution of Prenatal Fish and Shellfish Intake (N = 1,356) and Fatty Acid Levels in Second Trimester Maternal Plasma (N = 1,201) and Umbilical Cord Plasma (N = 762)

	Mean	SD	Min	Max
Mean of 1st and 2nd trimester intake, servings/week (N = 1,356)				
Fish ^a and shellfish ^b	1.7	1.4	0.0	19.0
Shellfish ^b	0.4	0.5	0.0	5.0
Fish without shellfish ^a	1.3	1.1	0.0	15.8
Fatty acids, µg/mL				
Second trimester (n = 1,201)				
N-3 FA:				
ALA	24.9	12.9	0.1	89.1
EPA	11.0	8.8	0.4	106.3
DHA	89.3	37.9	13.3	242.3
N-6 FA:				
LA	1,050.9	394.7	132.9	2,821.7
AA	257.9	100.5	42.4	643.7
Cord blood (n = 762)				
N-3 FA:				
ALA	1.3	1.1	0.1	7.7
EPA	1.7	1.7	0.1	16.1
DHA	33.8	20.8	2.8	150.9
N-6 FA:				
LA	91.3	47.2	10.6	339.9
AA	116.2	57.8	14.3	391.2

Abbreviations: FA, fatty acids; ALA, α-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosapentaenoic acid; LA, linoleic acid; AA, arachidonic acid.

^aFish includes canned tuna fish, dark meat fish, and other fish.^bShellfish includes “shrimp, lobster, scallops and clams.”**eTable 3**

Multivariable Associations of Fatty Acids in Cord Plasma with Wheezing Symptoms in Early Childhood

	Cord blood plasma			
	Q1	Q2	Q3	Q4
	Adjusted ^a OR (95% CI)			
Early childhood				
Wheezing symptoms in the past 12 months				
ALA	1.0 (ref)	0.91 (0.58, 1.43)	0.84 (0.52, 1.34)	0.55 (0.33, 0.90)
EPA	1.0 (ref)	0.93 (0.59, 1.46)	0.78 (0.48, 1.25)	0.62 (0.37, 1.03)
DHA	1.0 (ref)	1.15 (0.75, 1.77)	0.88 (0.55, 1.40)	0.58 (0.35, 0.98)
LA	1.0 (ref)	0.86 (0.55, 1.34)	0.84 (0.53, 1.34)	0.58 (0.35, 0.95)
AA	1.0 (ref)	0.94 (0.61, 1.47)	0.81 (0.51, 1.29)	0.65 (0.40, 1.07)

^aModels adjusted for maternal and paternal history of atopy and child age and sex. Abbreviations: FA, fatty acids; ALA, α-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosapentaenoic acid; LA, linoleic acid; AA, arachidonic acid.

eTable 4

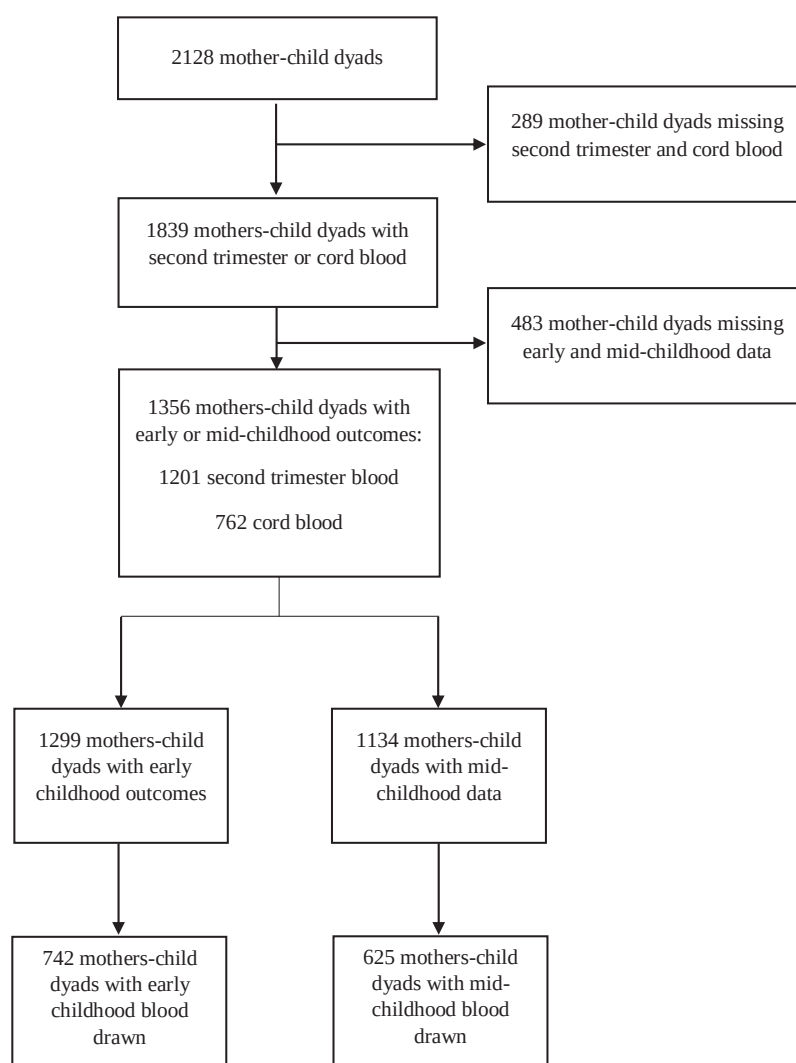
Multivariable Associations of Maternal Fish and Shellfish Intake (Mean of 1st and 2nd Trimester) with Allergy Biomarkers in Early and Mid-childhood Childhood

	Q1	Q2	Q3	Q4
	Adjusted ^a OR (95% CI)			
Early childhood				
Allergen sensitization ^b				
Fish and shellfish	1.0 (ref)	0.94 (0.57, 1.54)	1.23 (0.80, 1.90)	1.65 (1.07, 2.52)
Shellfish	1.0 (ref)	1.06 (0.68, 1.67)	0.99 (0.64, 1.53)	1.55 (0.96, 2.50)
Fish without shellfish	1.0 (ref)	1.14 (0.72, 1.82)	1.45 (0.91, 2.32)	1.51 (0.98, 2.33)
Mid-childhood				
Allergen sensitization ^c				
Fish and shellfish	1.0 (ref)	0.81 (0.47, 1.38)	0.88 (0.54, 1.45)	1.29 (0.80, 2.05)
Shellfish	1.0 (ref)	0.90 (0.55, 1.47)	0.96 (0.60, 1.52)	1.62 (0.95, 2.76)
Fish without shellfish	1.0 (ref)	0.96 (0.56, 1.62)	1.09 (0.64, 1.85)	1.00 (0.63, 1.60)

^aModels adjusted for maternal and paternal history of atopy and child age and sex. Mid-childhood allergen sensitization additionally adjusted for parity.

^bAllergen sensitization defined as ≥ 1 detectable allergen-specific immunoglobulin E or total immunoglobulin E ≥ 75.6 IU/mL.

^cAllergen sensitization defined as ≥ 1 detectable allergen-specific IgE or total IgE ≥ 100 IU/mL.

**eFigure 1.** Flow chart of study population.

Supplementary File

Study Population

Project Viva is a prospective pre-birth cohort study in Eastern Massachusetts.¹ We recruited pregnant women from Atrius Harvard Vanguard Medical Associates between 1999 and 2002. We completed in-person visits with the mothers in late first (median 9.9 weeks gestation) and second (median 27.9 weeks) trimesters and with mother-child pairs in the hospital after delivery and in early childhood (median 3.3 years) and mid-childhood (median 7.7 years); we sent questionnaires annually in-between visits. We show the participant flow in the **Supplementary Figure**. The institutional review boards of participating institutions approved the study and all mothers provided written informed consent for themselves and their children.

Pregnancy blood collection and fatty acid assays

We collected maternal whole blood samples during the routine non-fasting mid-pregnancy clinical blood draw. From these we obtained separate aliquots of plasma, white blood cells, and erythrocytes, which were stored in liquid nitrogen freezers (-80°C) until assay. Cord blood samples were drawn from the umbilical vein in infants delivered on a weekday at one of the two study hospitals. Plasma samples were stored in liquid nitrogen freezers (-80°C) until assay.

Fatty acids in plasma were extracted and quantified (in $\mu\text{g/mL}$) using liquid-gas chromatography. Analytic methods have good within-run precision (coefficient of variance <5.4%) and have been previously validated.² In this analysis, we included the following fatty acids: individual n-3 FA (ALA, EPA, DHA) and n-6 FA (LA, AA).

Outcome Measurements

Early childhood visit

We collected blood via venipuncture, stored plasma at -80°C, and assayed it for IgE specific to mite, cat, dog, cockroach, and *Alternaria*, using the UNICAP System (Pharmacia, Uppsala, Sweden). In samples with low plasma volume, IgE antibodies were measured with the CAP RAST FEIA System (Pharmacia). We defined any *allergen sensitization* as any specific IgE level of 0.35 IU/mL or greater to common indoor [dust mite (*Dermatophagoides farinae*), cat, dog, cockroach], mold (*Alternaria* or *Aspergillus* species); or food [egg white (ovomucoid)] allergen or a total IgE level of 75.6 IU/mL or greater.³

Ever asthma or wheeze diagnosis was reported by parents on the early childhood interview as a positive response to whether the child ever received a doctor's diagnosis of asthma, wheeze, or reactive airway disease. We defined *wheezing symptoms in the past 12 months* as parental report of wheezing symptoms in the past 12 months, assessed on the early childhood questionnaire. *Ever atopic dermatitis* was reported by parents on the 6-month, 1-year, 2-year, or early childhood assessment as a positive response to whether the child ever received a doctor's diagnosis of eczema/atopic dermatitis.

Mid-childhood visit

We collected blood via venipuncture and stored plasma at at -80°C within 48 hours. We measured plasma total IgE and allergen-specific IgE levels using ImmunoCAP (Phadia, Uppsala, Sweden). Expanding our allergen panel from that in early life, we measured sensitization to eight indoor or outdoor inhalant allergens (dust mite, cat, dog, cockroach, *Aspergillus*, *Alternaria*, rye grass, ragweed) and five foods (ovomucoid, milk, wheat, peanut, and soybean). We defined *current allergen sensitization* as ≥ 1 detectable allergen-specific IgE or total IgE ≥ 100 .³

We based the asthma outcomes on responses from the mid-childhood questionnaire administered to the mother, asking about symptoms and diagnoses of allergic and airway

diseases. Questions were drawn from the International Study of Asthma and Allergies in Childhood (ISAAC).⁴ We defined *current asthma* as a maternal report of ever asthma doctor diagnosis plus wheeze symptoms or use of asthma medication in the past 12 months. The comparison group comprised children reporting no doctor diagnosis and no wheezing symptoms/asthma medication use. We defined *current atopic dermatitis* as parental report of ever doctor diagnosis of eczema/atopic dermatitis on the mid-childhood questionnaire, plus itchy rash in the past 12 months in any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes.

Statistical Analysis

We performed all analyses using SAS 9.4 software (SAS Institute, Cary, NC). We used multiple imputation to account for missing data.

We analyzed associations between exposures and outcomes using logistic regression models, adjusting for maternal and paternal history of asthma, hay fever or eczema and child age and sex. We additionally adjusted mid-childhood allergen sensitization for parity. We categorized all exposure into quartiles to examine potential non-monotonic relations.

We also examined maternal fish and shellfish intake (canned tuna, shellfish, dark meat fish, and other fish) during pregnancy (average of first and second trimester intake from validated food frequency questionnaires)⁵ in relation to all outcomes as we considered this exposure relevant to dietary recommendations.

References

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4. Asher MI, Keil U, Anderson HR, *et al.* International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995; 8: 483-491.
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Supplementary Table 1. Characteristics of participants in the analysis sample (N=1356)

Characteristics	N=1356 %
Maternal age at enrollment, years (mean [SD])	32.2 (5.1)
Maternal education, % $\geq$ college graduate	69.2
Nulliparous, % yes	47.4
Maternal history of asthma, hay fever, or eczema, % yes	40.3
Paternal history of asthma, hay fever, or eczema, % yes	34.5
Child sex, % male	51.7
Child race/ethnicity, %	
Black	13.8
Hispanic	4.5
White	67.2
Other	14.5
Early childhood	
Age, years (median [IQR])	3.3 (3.1-4.0)
Allergen sensitization ¹ , % yes	40.4
Ever asthma or wheeze diagnosis ² , % yes	21.4
Wheezing symptoms in the past 12 months ³ , % yes	20.9
Ever atopic dermatitis ⁴ , % yes	36.2
Mid-childhood	
Age, years (median [IQR])	7.7 (7.4-8.3)
Allergen sensitization ⁵ , % yes	53.0
Current asthma ⁶ , % yes	17.8
Current atopic dermatitis ⁷ , % yes	6.4

¹Allergen sensitization defined as ≥ 1 detectable allergen specific IgE or total IgE ≥ 75.6 IU/mL.

²Parental report of ever doctor diagnosis of asthma or wheeze, assessed on the early childhood interview.

³Parental report of wheezing symptoms in the past 12 months, assessed on the early childhood questionnaire.

⁴Parental report of ever doctor diagnosis of atopic dermatitis on the 6-month, 1-year, 2-year, or early childhood assessment.

⁵Allergen sensitization defined as ≥ 1 detectable allergen-specific IgE or total IgE ≥ 100 IU/mL.

⁶Current asthma defined as parental report of ever doctor diagnosis of asthma plus wheeze symptoms or use of asthma medication use in the past 12 months. Comparison group includes participants with no asthma, no medication, and no current wheeze.

⁷Current atopic dermatitis defined as parental report of ever doctor diagnosis of atopic dermatitis on the mid-childhood questionnaire, plus itchy rash in the past 12 months in any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes.

Supplementary Table 2. Distribution of prenatal fish and shellfish intake (N=1356) and fatty acid levels in second trimester maternal plasma (N=1201) and umbilical cord plasma (N=762)

	Mean	SD	Min	Max
Mean of 1st and 2nd trim intake, servings/week (N=1356)				
Fish ¹ and shellfish ²	1.7	1.4	0.0	19.0
Shellfish ²	0.4	0.5	0.0	5.0
Fish without shellfish ¹	1.3	1.1	0.0	15.8
Fatty acids, ug/mL				
Second trimester (N=1201)				
N-3 FA:				
ALA	24.9	12.9	0.1	89.1
EPA	11.0	8.8	0.4	106.3
DHA	89.3	37.9	13.3	242.3
N-6 FA:				
LA	1050.9	394.7	132.9	2821.7
AA	257.9	100.5	42.4	643.7
Cord blood (N=762)				
N-3 FA:				
ALA	1.3	1.1	0.1	7.7
EPA	1.7	1.7	0.1	16.1
DHA	33.8	20.8	2.8	150.9
N-6 FA:				
LA	91.3	47.2	10.6	339.9
AA	116.2	57.8	14.3	391.2

¹Fish includes canned tuna fish, dark meat fish, and other fish

²Shellfish includes "shrimp, lobster, scallops and clams"

Supplementary Table 3. Multivariable associations of fatty acids in cord plasma with wheezing symptoms in early childhood

Cord blood plasma				
Q1	Q2	Q3	Q4	
Adjusted ¹ OR (95% CI)				
Early childhood				
Wheezing symptoms in the past 12 months				
ALA	1.0 (ref)	0.91 (0.58, 1.43)	0.84 (0.52, 1.34)	0.55 (0.33, 0.90)
EPA	1.0 (ref)	0.93 (0.59, 1.46)	0.78 (0.48, 1.25)	0.62 (0.37, 1.03)
DHA	1.0 (ref)	1.15 (0.75, 1.77)	0.88 (0.55, 1.40)	0.58 (0.35, 0.98)
LA	1.0 (ref)	0.86 (0.55, 1.34)	0.84 (0.53, 1.34)	0.58 (0.35, 0.95)
AA	1.0 (ref)	0.94 (0.61, 1.47)	0.81 (0.51, 1.29)	0.65 (0.40, 1.07)

¹Models adjusted for maternal and paternal history of atopy and child age and sex.

Supplementary Table 4. Multivariable associations of maternal fish and shellfish intake (mean of 1st and 2nd trimester) with allergy biomarkers in early and mid-childhood childhood

	Q1	Q2	Q3	Q4
	Adjusted ¹ OR (95% CI)			
Early childhood				
<i>Allergen sensitization</i> ²				
Fish and shellfish	1.0 (ref)	0.94 (0.57, 1.54)	1.23 (0.80, 1.90)	1.65 (1.07, 2.52)
Shellfish	1.0 (ref)	1.06 (0.68, 1.67)	0.99 (0.64, 1.53)	1.55 (0.96, 2.50)
Fish without shellfish	1.0 (ref)	1.14 (0.72, 1.82)	1.45 (0.91, 2.32)	1.51 (0.98, 2.33)
Mid-childhood				
<i>Allergen sensitization</i> ³				
Fish and shellfish	1.0 (ref)	0.81 (0.47, 1.38)	0.88 (0.54, 1.45)	1.29 (0.80, 2.05)
Shellfish	1.0 (ref)	0.90 (0.55, 1.47)	0.96 (0.60, 1.52)	1.62 (0.95, 2.76)
Fish without shellfish	1.0 (ref)	0.96 (0.56, 1.62)	1.09 (0.64, 1.85)	1.00 (0.63, 1.60)

¹Models adjusted for maternal and paternal history of atopy and child age and sex. Mid-childhood allergen sensitization additionally adjusted for parity.

²Allergen sensitization defined as ≥ 1 detectable allergen specific IgE or total IgE ≥ 75.6 IU/mL.

³Allergen sensitization defined as ≥ 1 detectable allergen-specific IgE or total IgE ≥ 100 IU/mL.

Supplementary Figure. Flow chart of study population