Original Investigation

Fish Intake in Pregnancy and Child Growth
A Pooled Analysis of 15 European and US Birth Cohorts

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IMPORTANCE Maternal fish intake in pregnancy has been shown to influence fetal growth. The extent to which fish intake affects childhood growth and obesity remains unclear.

OBJECTIVE To examine whether fish intake in pregnancy is associated with offspring growth and the risk of childhood overweight and obesity.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, population-based birth cohort study of singleton deliveries from 1996 to 2011 in Belgium, France, Greece, Ireland, Italy, the Netherlands, Norway, Poland, Portugal, Spain, and Massachusetts. A total of 26 184 pregnant women and their children were followed up at 2-year intervals until the age of 6 years.

EXPOSURES Consumption of fish during pregnancy.

MAIN OUTCOMES AND MEASURES We estimated offspring body mass index percentile trajectories from 3 months after birth to 6 years of age. We defined rapid infant growth as a weight gain *z* score greater than 0.67 from birth to 2 years and childhood overweight/obesity at 4 and 6 years as body mass index in the 85th percentile or higher for age and sex. We calculated cohort-specific effect estimates and combined them by random-effects meta-analysis.

RESULTS This multicenter, population-based birth cohort study included the 26 184 pregnant women and their children. The median fish intake during pregnancy ranged from 0.5 times/week in Belgium to 4.45 times/week in Spain. Women who ate fish more than 3 times/week during pregnancy gave birth to offspring with higher body mass index values from infancy through middle childhood compared with women with lower fish intake (3 times/week or less). High fish intake during pregnancy (>3 times/week) was associated with increased risk of rapid infant growth, with an adjusted odds ratio (aOR) of 1.22 (95% CI, 1.05-1.42) and increased risk of offspring overweight/obesity at 4 years (aOR, 1.14 [95% CI, 0.99-1.32]) and 6 years (aOR, 1.22 [95% CI, 1.01-1.47]) compared with an intake of once per week or less. Interaction analysis showed that the effect of high fish intake during pregnancy on rapid infant growth was greater among girls (aOR, 1.31 [95% CI, 1.08-1.59]) than among boys (aOR, 1.11 [95% CI, 0.92-1.34]; $P = .02$ for interaction).

CONCLUSIONS AND RELEVANCE High maternal fish intake during pregnancy was associated with increased risk of rapid growth in infancy and childhood obesity. Our findings are in line with the fish intake limit proposed by the US Food and Drug Administration and Environmental Protection Agency.

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Early life is a critical period of developmental plasticity. A nutritional stressor or stimulus applied during critical periods of early development could permanently alter body physiology and metabolism, the consequences of which are often observed much later in life.[1] Fish is the major dietary source of ω-3 long-chain polyunsaturated fatty acids (LC-PUFAs), which are transferred across the placenta and may not only benefit offspring neurodevelopment but also influence adipose tissue development.[2] However, fish is also a common source of human exposure to persistent organic pollutants, which may exert endocrine-disrupting properties and contribute to obesity development.[3,4]

In June 2014, the US Food and Drug Administration and Environmental Protection Agency updated their advice on fish consumption for women of childbearing age,[5] encouraging women who are pregnant, breastfeeding, or likely to become pregnant to consume more fish, but no more than 3 servings/week to limit fetal exposure to methyl-mercury. Fish advisories have focused on neurocognitive harms from methylmercury exposure but, to our knowledge, have not considered other childhood outcomes including growth and childhood obesity, areas where evidence is limited.

In a large, Europe-wide study (151 880 mother-child pairs),[6] we found that moderate fish intake during pregnancy was associated with a lower risk of preterm birth and a small but significant increase in birth weight. Few birth cohort studies have examined the association of fish intake in pregnancy with childhood adiposity and have yielded discrepant findings, with reports of either beneficial (ie, lower obesity)[7] or null[8] associations. Likewise, trials have not found a clear and consistent benefit of prenatal ω-3 LC-PUFAs on obesity-related outcomes later in life.[9] To our knowledge, there is no clear answer about the optimal amount and type of fish intake during pregnancy with regard to child growth and development.

In this study, we harmonized and pooled individual data of follow-ups 2-year intervals, until the age of 6 years, from 26 184 pregnant women and their children participating in 15 European and US cohort studies to assess the strength and consistency of the associations of fish intake during pregnancy with body mass index (BMI) growth trajectories, calculated as weight in kilograms divided by height in meters squared, and the risk of childhood overweight and obesity.

Key Points

Question: What is the optimal amount and type of fish intake during pregnancy with regard to child growth and development?

Findings: In this large, multicenter longitudinal study, we found that high fish intake of more than 3 times/week in pregnancy was associated with greater risk of rapid infant growth and childhood overweight and obesity. The effect of fish intake during pregnancy on rapid infant growth was greater among girls than boys.

Meaning: Fish contains important nutrients for developing fetuses and its consumption should not be avoided; however, pregnant women should adhere to fish consumption advisories.

Methods

Study Population

European birth cohort studies participating in our previous analysis on fish intake in pregnancy and birth outcomes[6] were invited to participate. From the 19 potentially eligible European cohorts, 14 cohorts provided relevant data for this analysis. In addition, the Project Viva cohort from the United States agreed to take part. All participating cohorts targeted the general population and, altogether, covered singleton deliveries from 1996 to 2011. All participating women provided written informed consent for themselves and their children in the original cohort studies, and ethical approval was obtained from the local authorized institutional review boards. The Amsterdam Born Children and Their Development Study was approved by the Central Committee on Research Involving Human Subjects in The Netherlands, the medical ethics review committees of the participating hospitals, and the Registration Committee of the Municipality of Amsterdam. The Étude des Déterminants Pré et Postnatals du Développement et de la Santé de l'Enfant Study was approved by the Ethics Committee of Bicêtre Hospital and the National Commission on Data Processing and Liberties. The Flemish Center of Expertise on Environment and Health Study was approved by the Ethical Committee of the University of Antwerp and the Ghent University. The Genetica e Ambiente: Studio Prospettico dell'Infanzia in Italia Study was approved by the Ethics Committee of the Università Cattolica del Sacro Cuore in Rome. The Generation R Study was approved by by the Medical Ethical Committee of the Erasmus Medical Center in Rotterdam. The Generation XXI Study was approved by the Portuguese Data Protection Authority (Comissão Nacional de Protecção de Dados). The Norwegian Human Milk Study was approved by the Regional Ethics Committee for Medical Research in Norway and the Norwegian Data Inspectorate. The Infancia y Medio Ambiente Study was approved by the hospital ethics committees of each participating Spanish region. The Kind, Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg Study was approved by the medical ethics committee of the Maastricht University/University Hospital of Maastricht. The Lifeways Cross Generation Study was approved by the ethics committees in the National University of Ireland, Galway; The Coombe Women's Hospital, Dublin; University College Hospital, Galway; and The Irish College of General Practitioners. The Nascita e INFanzia: gli Effetti dell'Ambiente Study was approved by the Ethical Committee of the San Giovanni Battista Hospital and CTO/CRF/Maria Adelaide Hospital of Turin. The Prevention and Incidence of Asthma and Mite Allergy Study by the the Medical Ethics Committees of the participating institutes the Dutch Central Committee on Research involving Human Subjects. The Project Viva Study by the human participants committees of Harvard Pilgrim Health Care, Brigham, and Women's Hospital and Beth Israel Deaconess Medical Center. The Polish Mother and Child Cohort Study by the Ethical Committee of the Nofer Institute of Occupational Medicine in Lodz. The Mother Child Cohort Study in Crete by the Ethical Committee of the University Hospital of Heraklion.

A data-transfer agreement document was signed by each cohort study, and anonymized data sets were transferred to

the University of Crete for analysis. Characteristics of the participating cohorts are shown in eTable 1 and eFigure 1 in the Supplement.

Fish Intake During Pregnancy

The exposure of interest was the frequency (times per week) of total fish, fatty fish, lean fish, and seafood (other than fish) intake during pregnancy, derived from cohort-specific food frequency questionnaires or questionnaires specifically designed to assess fish intake during pregnancy (eMethods and eTable 1 in the Supplement).

To align our analysis with the 2014 US Food and Drug Administration and the Environmental Protection Agency advice on fish intake during pregnancy and examine a potential dose-response relationship, we categorized total fish intake into the following groups: low, 1 time/week or less; moderate, greater than 1 but not more than 3 times/week; and high, more than 3 times/week. Seven cohorts (the Polish Mother and Child Cohort Study, Flemish Center of Expertise on Environment and Health, Generation R Study, Generation XXI, Lifeways Cross Generation, Prevention and Incidence of Asthma and Mite Allergy, and the Mother Child Cohort in Crete) had less than 5% or 50 participants in at least 1 category and therefore were not included in the categorical dose-response analysis in an attempt to reduce the likelihood of conducting a type II error.

Child Growth and Adiposity Measures

Cohorts provided information on child weight and height up to a maximum follow-up of 6 years, obtained from clinical examinations, medical records, or parental-completed questionnaires. Permissible intervals around the nominal ages were within 3 months for the first 2 years and within 6 months onwards. The time points of interest in childhood were the ages of 2 years, 4 years, and 6 years to reflect different developmental ages (toddler, preschooler, and school-aged child, respectively). Three cohorts (Infancia y Medio Ambiente, Mother Child Cohort in Crete, and the Polish Mother and Child Cohort Study) did not provide growth data at the age of 6 years owing to their relatively recent recruitment period. For each cohort, we constructed sex- and age-specific weight and height growth curves using mixed-effects linear regression models with fractional polynomials of age, including a random intercept for child and random age slopes (eMethods in the Supplement). Actual and predicted measurements were compared to assess model fit, and high levels of agreement were found (eTable 2 in the Supplement). Predicted values were then used to calculate sex- and age-specific BMI *z* scores and BMI percentile values based on the 2006 World Health Organization child growth standards for children 5 years and younger[10] and 2007 World Health Organization growth references for children and adolescents aged 5 to 19 years (eMethods in the Supplement).[11]

We defined rapid infant growth from birth to 2 years as a *z* score change in weight of greater than 0.67 and used the *z* score change of 0.67 or less as the comparison.[12,13] We analyzed child BMI *z* score as a continuous outcome at 2 years, 4 years, and 6 years of age and in categories of overweight and obese (BMI ≥85th percentile for age and sex) at 4 and 6 years, compared with BMI below the 85th percentile.[14]

Covariates

Potential confounding variables were defined as similarly as possible among the cohorts. Information on maternal prepregnancy BMI (in weight in kilograms divided by height in meters squared), maternal smoking during pregnancy (yes or no), gestational weight gain (in kilograms), maternal age at delivery (in years), birth weight (in grams), and child sex (male or female) was collected by means of interviews or self-administered questionnaires, ad hoc measurements, birth records, or medical registries. Information on breastfeeding duration (in months) and maternal education (cohort-specific definitions of low, medium, or high) was obtained through interviews or self-administered questionnaires.

Statistical Analysis

Cohort-Specific Analyses

We used linear regression models to examine the association of fish intake during pregnancy with BMI *z* scores in childhood and logistic regression models for rapid infant growth and childhood overweight/obesity. To select the confounders for adjustment in multivariable models, we used a directed acyclic graph approach based on prior knowledge about parental and child covariates that may be related to child adiposity and/or fish intake in pregnancy.[15] We constructed the graph using DAGitty version 2.1 (DAGitty)[16] to identify minimally sufficient adjustment sets of covariates and chose the set on which we had the best available information (eFigure 2 in the Supplement). We included the following variables in multivariable models: maternal education, maternal prepregnancy BMI, maternal smoking during pregnancy, maternal age at delivery, and birth weight. For the Lifeways Cross Generation cohort, the adjusted models did not include the full list of confounders owing to missing information on prepregnancy BMI.

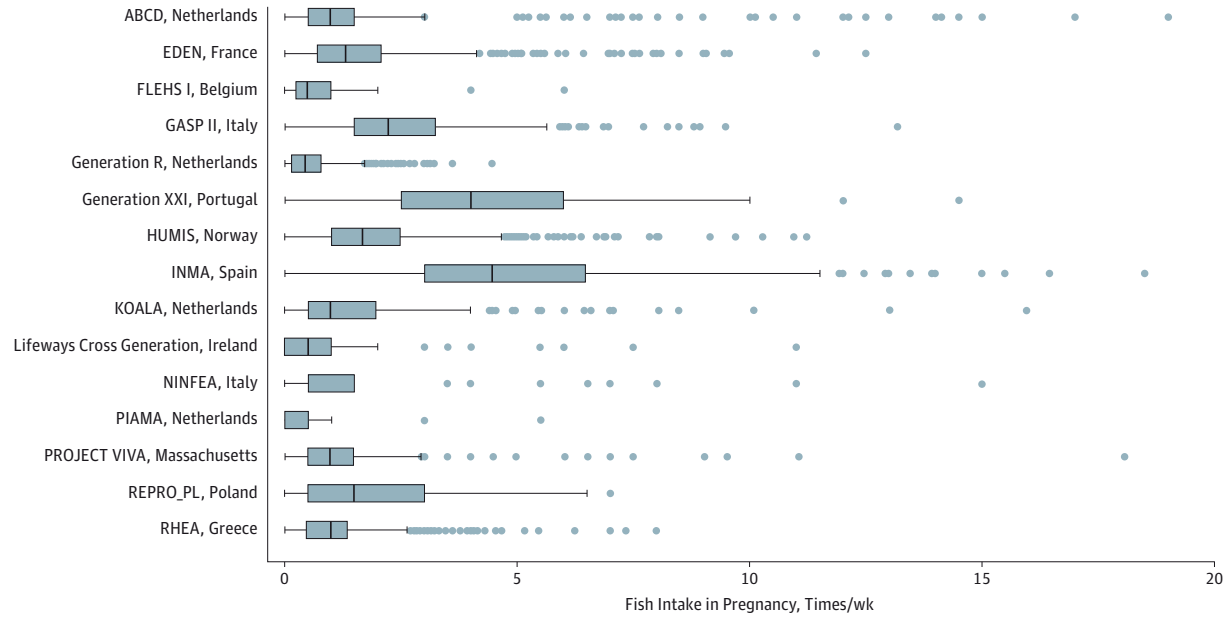
Meta-Analysis and Pooled Analysis

We combined cohort-specific effect estimates for each outcome of interest using random-effects meta-analysis in which the weight assigned to each study was based on both the within- and between-study variability. Heterogeneity among cohort-specific estimates was assessed with the χ^2 test from the Cochran Q and I^2 statistic.[17] To compare growth trajectories based on child BMI percentile values by category of maternal fish intake in pregnancy, we used a mixed-effects linear regression model fitted with random cohort and child intercepts and a random slope for child age. To take into account the potential age-varying effect of maternal fish intake, we added an interaction term for child age and fish intake as a fixed effect.

Sensitivity Analyses

We performed several sensitivity analyses. First, we included all cohorts in the categorical dose-response analysis to examine whether the exclusion of cohorts with less than 5% or 50 participants in at least 1 fish intake category influenced the results. Second, we made further adjustment for gestational

Figure 1. Frequency of Fish Intake in Pregnancy (Times/Week) in Participating Cohorts



The line within the box marks the median; the boundaries of the box indicate the 25th and 75th percentiles; horizontal bars denote the variability outside the upper and lower quartiles (ie, within 1.5 IQR of the lower and upper quartiles); and circles represent outliers. Cohort abbreviations: ABCD, Amsterdam Born Children and their Development; EDEN, Étude des Déterminants Pré et Postnatals du Développement et de la Santé de l'Enfant; FLEHS I, Flemish Center of Expertise on Environment and Health; GASPII, Genetics and Environment Prospective Study on Childhood in Italy; HUMIS, Human Milk Study; INMA, Infancia y Medio Ambiente; KOALA, Kind, Ouders, en Gezondheid: Aandacht voor Leefstijl en Aanleg Birth Cohort Study; NINFEA, Nascita e INFanzia: gli Effetti dell'Ambiente; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; REPRO, Polish Mother and Child Cohort Study; RHEA, Mother Child Cohort in Crete.

weight gain for cohorts with available information. Third, we calculated pooled-effect estimates for child outcomes using mixed-effects regression models with random intercepts for cohort and geographical location according to the United Nations' classification (Eastern Europe, Southern Europe, Western Europe, Northern Europe, and Northern America). Fourth, we calculated pooled-effect estimates using mixed-effects regression models with random intercepts for cohort and recruitment period (recruitment before and after 2004-2005). Fifth, we repeated analyses after removing birth weight from all multivariable models. Sixth, we examined the associations of fish intake variables with childhood obesity (BMI ≥95th percentile for age and sex). Finally, we assessed whether the effect estimates for childhood outcomes varied by child sex (boy vs girl), prepregnancy BMI (≥25 vs <25), maternal smoking during pregnancy (yes vs no), timing of dietary assessment (first, second, or third trimester in pregnancy), low birth weight (<2500 vs ≥2500 g), and breastfeeding duration (>3 vs ≤3 months) by introducing interaction terms (one at a time). We performed analyses with STATA version 13 (StataCorp) and R version R3.1 (R Foundation).

Results

Characteristics of the Participants

The total study population consisted of 26 184 mothers and their offspring with follow-up from birth to 6 years of age. Participants' characteristics are presented in the eTables 3 to 6 in the Supplement. Mothers were predominantly older than 29 years, nonsmokers, had a normal prepregnancy BMI, and breastfed their children for more than 3 months. The ratio of boys to girls was 1.03 (eTable 3 in the Supplement).

The median fish intake during pregnancy varied between study areas and ranged from 0.5 times/week in Belgium (Flemish Center of Expertise on Environment and Health) to 4.45 times/week in Spain (Infancia y Medio Ambiente) (**Figure 1**; eTable 4 in the Supplement). Compared with low and moderate fish consumers (≤3 times/week), women with high fish intake (>3 times/week) during pregnancy had a higher age at delivery in most of the cohorts (6 of 8 cohorts) and were less likely to have smoked during pregnancy. We did not observe any other clear pattern of difference for other sociodemographic characteristics (eTable 5 in the Supplement).

In total, 8215 children (31.0%) were rapid growers from birth to 2 years of age, with the prevalence across cohorts ranging from 17.3% (Norwegian Human Milk Study, Norway) to 56.0% (Mother Child Cohort in Crete, Greece). Four thousand nine hundred eighty-seven (19.4%) and 3476 children (15.2%) were classified as overweight or obese at ages 4 and 6 years, respectively, while the cohort-specific prevalence ranged from 9.5% (Kind, Ouders, en Gezondheid: Aandacht voor Leefstijl en Aanleg Birth Cohort Study, Netherlands) to 55.8% (Lifeways Cross Generation, Ireland) at ages 4 years and from 6.4% (Kind, Ouders, en Gezondheid:

Table 1. Adjusted Combined Associations of Fish Intake in Pregnancy With Offspring BMI *z* Scores During Childhood

Variable	BMI *z* Score[a]											
	2 y				4 y				6 y			
	Cohorts	No. of Participants	Estimate (95% CI)	*P* Value[b]	Cohorts	No. of Participants	Estimate (95% CI)	*P* Value[b]	Cohorts	No. of Participants	Estimate (95% CI)	*P* Value[b]
Fish intake (times/wk)	15	25 625	0.009 (0.003 to 0.016)	.10	14	25 355	0.009 (0.001 to 0.016)	.94	12	22 668	0.010 (0.001 to 0.019)	.84
Fish intake categories[c]												
> 1 but ≤ 3 times/wk	8	7281	−0.005 (−0.038 to 0.028)	.25	8	7281	−0.008 (−0.051 to 0.035)	.09	7	6879	−0.007 (−0.058 to 0.044)	.04
> 3 times/wk	8	2709	0.050 (0.004 to 0.096)	.71	8	2709	0.050 (0.001 to 0.100)	.43	7	1469	0.039 (−0.033 to 0.111)	.13
Types of fish (times/wk)												
Fatty fish	10	11 196	0.003 (−0.014 to 0.020)	.57	9	10 926	0.004 (−0.016 to 0.024)	.59	7	8238	0.015 (−0.010 to 0.040)	.72
Lean fish	9	9615	0.016 (−0.003 to 0.034)	.32	8	9345	0.010 (−0.012 to 0.031)	.30	6	6657	−0.002 (−0.034 to 0.029)	.29
Seafood (other than fish)	12	13 764	0.006 (−0.018 to 0.029)	.62	11	13 494	0.001 (−0.026 to 0.028)	.61	9	10 806	0.010 (−0.031 to 0.051)	.42

Abbreviation: BMI, body mass index.

[a] A BMI *z* score represents the difference from the mean BMI value for the World Health Organization reference population and is expressed in standard deviations. Estimates are beta coefficients (95% CIs) calculated by random-effects meta-analysis by cohort. Linear regression models were adjusted for maternal age, maternal education, prepregnancy BMI, smoking during pregnancy, and birth weight.

[b] *P* value for heterogeneity estimated by the χ^2 test from the Cochran Q.

[c] Reference category: 1 time/week or less. The following numbers of participants were included in this category: 7686 participants for BMI *z* score at ages 2 years and 4 years and 7591 participants for BMI *z* score at age 6 years.

Aandacht voor Leefstijl en Aanleg Birth Cohort Study) to 36.7% (Generation XXI, Portugal) at age 6 years (eTable 6 in the Supplement).

Fish Intake During Pregnancy and Offspring BMI

Women who ate fish more than 3 times/week during pregnancy gave birth to offspring with higher BMI values at 2 years, 4 years, and 6 years of age compared with women who rarely ate fish (≤1 time/week) (**Table 1**). High fish intake during pregnancy was also associated with an increased risk of rapid infant growth from birth to 2 years (adjusted odds ratio [aOR], 1.22 [95% CI, 1.05-1.42]) and increased risk of offspring overweight/obesity at 4 years (aOR, 1.14 [95% CI, 0.99-1.32]) and 6 years of age (aOR, 1.22 [95% CI, 1.01-1.47]) (**Table 2** and **Figure 2**). We did not find evidence for an association of moderate fish intake (>1 but ≤3 times/week) or consumption of different types of fish with child BMI and the risk of rapid infant growth and childhood overweight/obesity (Tables 1 and 2, Figure 2). The effect estimates from the pooled analyses were similar to those from random-effects meta-analyses (data not shown).

Figure 3 depicts the modeled BMI percentile trajectories of children up to 6 years according to different levels of maternal fish consumption in pregnancy. Children of mothers with high fish intake exhibited consistently higher values than did those of mothers with low fish intake, and at 2.5 years onwards, the difference became more pronounced. Children of mothers with moderate fish intake during pregnancy had a similar trajectory to that of children whose mothers had low fish intake, and both followed the typical pattern of BMI growth, that is, a sharp increase in BMI during infancy followed by a decrease later in childhood.

Sensitivity Analyses

Inclusion of all cohorts in the categorical dose-response analysis did not materially change the reported effect estimates (eTables 7 and 8 in the Supplement). The associations of high fish intake with increased risk of childhood overweight and obesity remained significant and of similar magnitude when additional adjustment was made for gestational weight gain when we took into account the geographical location or the recruitment period of each cohort (data not shown). Additionally, exclusion of birth weight from the multivariate models did not materially change the effect estimates (eTables 9 and 10 in the Supplement). When we examined only childhood obesity as an outcome, the association had the same direction as when examining both overweight and obesity, but confidence intervals were wider, possibly because of the small number of obese children (eTable 11 in the Supplement).

The magnitude of the fish intake effect on rapid infant growth and childhood overweight/obesity was greater in girls than in boys (eTable 12 and eFigure 3 in the Supplement). There was no evidence of effect modification by prepregnancy BMI, smoking during pregnancy, timing of dietary assessment, low birth weight, and breastfeeding duration (*P* for interaction >.10 for all).

Table 2. Adjusted Combined Associations of Fish Intake in Pregnancy With Rapid Infant Growth and Childhood Overweight/Obesity

	Rapid Growth[a,b]				Overweight/Obesity[a,c]							
	Birth to 2 y				4 y				6 y			
Variable	Cohorts	No. of Participants	OR (95% CI)	*P* Value[d]	Cohorts	No. of Participants	OR (95% CI)	*P* Value[d]	Cohorts	No. of Participants	OR (95% CI)	*P* Value[d]
Fish intake (times/wk)	15	26 184	1.02 (0.99 to 1.04)	.96	14	25 355	1.02 (0.99 to 1.04)	.99	12	22 668	1.02 (0.99 to 1.05)	.77
Fish intake categories[e]												
> 1 but ≤ 3 times/wk	8	7362	0.96 (0.87 to 1.05)	.75	8	7281	0.95 (0.85 to 1.06)	.24	7	6879	0.93 (0.81 to 1.06)	.19
> 3 times/wk	8	2739	1.22 (1.05 to 1.42)	.86	8	2709	1.14 (0.99 to 1.32)	.44	7	1469	1.22 (1.01 to 1.47)	.29
Types of fish (times/wk)												
Fatty fish	10	11 689	1.01 (0.96 to 1.06)	.96	9	10 926	1.02 (0.97 to 1.07)	.86	7	8238	1.02 (0.95 to 1.09)	.77
Lean fish	9	10 107	1.03 (0.99 to 1.08)	.67	8	9345	1.01 (0.96 to 1.07)	.37	6	6657	0.91 (0.81 to 1.03)	.19
Seafood (other than fish)	12	14 265	0.98 (0.91 to 1.05)	.56	11	13 494	0.96 (0.90 to 1.03)	.75	9	10 806	0.98 (0.86 to 1.10)	.39

Abbreviations: BMI, body mass index; OR, odds ratio.

[a] Odds ratios (95% CIs) were estimated by random-effects meta-analysis by cohort. Logistic regression models were adjusted for maternal age, maternal education, prepregnancy BMI, smoking during pregnancy, and birth weight.

[b] Rapid growth was defined as a weight gain *z* score of more than 0.67 based on World Health Organization curves.

[c] Overweight/obesity was defined as BMI 85th percentile or more for age and sex based on World Health Organization curves.

[d] *P* value for heterogeneity estimated by the χ^2 test from the Cochran Q.

[e] Reference category: 1 time/week or less. The following numbers of participants were included in this category: 7840 participants for rapid growth from birth to age 2 years; 7686 participants for overweight/obesity at age 4 years; and 7591 participants for overweight/obesity at age 6 years.

Discussion

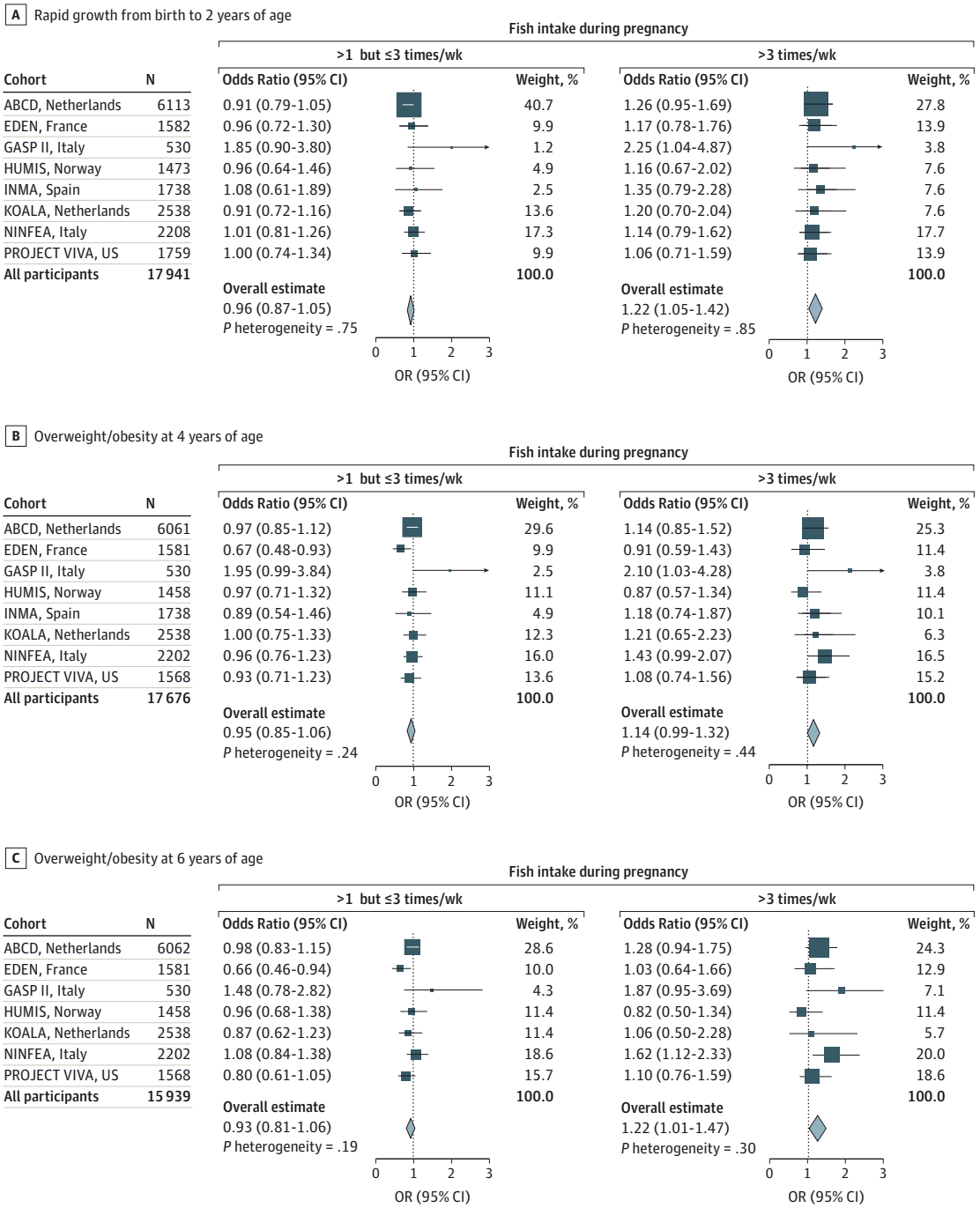
We found that fish intake of more than 3 times/week in pregnancy was associated with higher offspring BMI and greater risk of rapid infant growth and childhood overweight/obesity. To our knowledge, this is the only multicenter study on the long-term effect of maternal fish intake in pregnancy on offspring growth and adiposity. The use of birth cohorts in several locations in Europe and the United States with varying fish intake levels and the absence of heterogeneity between individual cohort effect estimates provide evidence to support the robustness and generalizability of our findings.

Childhood overweight and obesity is considered a major public health issue.[18] Rapid weight gain in infancy has consistently been associated with a subsequent elevated risk of obesity in childhood and later in adulthood.[12,19] Intrauterine life is a sensitive period, during which the capacity for proliferation of mesenchymal precursor cells and their differentiation into adipocytes is very high.[1,2] Fish is the primary dietary source of ω-3 LC-PUFAs. The evidence for a programming effect of ω-3 fatty acids in fetal or early life on later body composition mainly stems from cell culture and animal studies.[20] Reports from human trials have shown limited support for a beneficial effect of ω-3 LC-PUFAs supplementation during early life on body composition later in life.[9,21] Findings from longitudinal birth cohort studies on fish or ω-3 LC-PUFAs during pregnancy and childhood adiposity are also discrepant, with reports of either beneficial (ie, lower adiposity)[7] or null[8,22-25] associations. These inconsistencies may be caused by inadequate sample sizes, exposure profile heterogeneity, or differences in adjustment for confounding variables. Our findings underscore scientific gaps in the experimental evidence, specifically, the lack of studies involving healthy populations and interventions targeting fish intake rather than supplement use, which may exert different effects.

Contamination by environmental pollutants in fish could provide an explanation for the observed association between high fish intake in pregnancy and increased childhood adiposity. In humans, fish consumption is a major source of exposure to endocrine-disrupting chemicals.[26,27] Mixtures of persistent organic pollutants found in fish have been shown to increase fat storage in cultured adipocytes as well as weight gain in animals.[28] It has been proposed that these toxicants may perturb signaling of several nuclear receptors and, through altered gene expression, influence adipocyte differentiation and fat metabolism.[3,4]

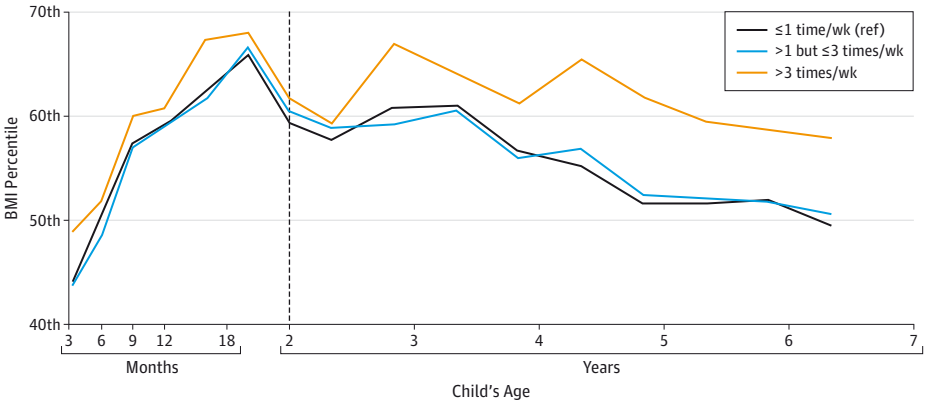
Although we collected information on the consumption of different fish types, we did not have enough data to distinguish between big and small species, cooking procedures, and water source of fish (ie, river or sea), which would be relevant with respect to toxicant exposure. Moreover, in the absence of information regarding levels of persistent organic pollutants across participating cohorts, our hypothesis that fish-associated contaminant exposure may play a role in the observed associations remains speculative. Further analyses

Figure 2. Adjusted Associations of Fish Intake in Pregnancy With Rapid Growth in Infancy and Childhood Overweight/Obesity



Rapid growth was defined as a weight gain *z* score greater than 0.67 based on World Health Organization (WHO) growth curves. Overweight/obesity was defined as body mass index in the 85th percentile or higher for age and sex based on WHO growth curves. Odds ratios (95% CIs) by cohort were obtained by using logistic regression models adjusted for maternal age, maternal education, prepregnancy body mass index, smoking during pregnancy, and birth weight. Reference category was fish intake 1 or more times/week. Combined estimates were obtained by using a random-effects meta-analysis. The names of the cohorts and the cohort-specific ORs (95% CIs) are shown on the left, and weights of each study are shown on the right. The squares represent the point estimate of each study, whereas the size of the square is proportional to the weight assigned to each cohort based on both the within- and between-study variability; horizontal lines denote 95% CIs; and diamonds represent overall estimates. Cohort abbreviations: ABCD, Amsterdam Born Children and their Development; EDEN, Étude des Déterminants Pré et Postnatals du Développement et de la Santé de l'Enfant; FLEHS I, Flemish Center of Expertise on Environment and Health; GASPII, Genetics and Environment Prospective Study on Childhood in Italy; HUMIS, Human Milk Study; INMA, Infancia y Medio Ambiente; KOALA, Kind, Ouders, en Gezondheid: Aandacht voor Leefstijl en Aanleg Birth Cohort Study; NINFEA, Nascita e INFanzia: gli Effetti dell'Ambiente; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; REPRO, Polish Mother and Child Cohort Study; RHEA, Mother Child Cohort in Crete.

Figure 3. Body Mass Index (BMI) Percentile Trajectories From 3 Months to 6 Years According to Different Levels of Fish Intake in Pregnancy



BMI percentile values indicate the place of children in the corresponding growth chart of the World Health Organization reference population (eMethods in the Supplement) and were derived by using mixed-effects linear regression models fitted with: fish intake, an interaction term for fish intake and child age, maternal age, maternal education, prepregnancy BMI, smoking during pregnancy, and birth weight as fixed-effects parameters; random cohort and child intercepts; and a random slope for child age.

incorporating biomarker information on both the amounts of fatty acids and environmental chemicals contained within fish will be helpful for refining estimates of the influence of prenatal fish intake on child growth.

We observed that the effect of fish intake during pregnancy on offspring obesity outcomes was more pronounced in girls than in boys. The placenta tissue carrying the fetal genome and sex appears as a promising candidate to be involved in mediating sex-specific functions and programming effects.[29] Animal studies suggest that maternal diet may induce sexually dimorphic responsiveness in placental gene expression and greater sensitivity of girls to the maternal environment, especially in the biological process of the cell cycle.[30,31]

Although we did not see strong evidence for sociodemographic confounding in this analysis, the possibility of unmeasured residual confounding may still remain. We had no data available to adjust for energy intake or dietary patterns during pregnancy; however, adjustment for gestational weight gain, as a good proxy for total energy intake in pregnancy,[32,33] did not appreciably change the effect estimates. Moreover, although we examined breastfeeding duration as a potential confounder or effect modifier, other differences in child diet or lifestyle factors (eg, physical activity patterns) might have influenced the observed findings. The direction of confounding was differentially distributed across participating cohorts, reflecting that the study design by itself may control to some extent for unmeasured confounding.

Strengths of our study include the large sample size, the centralized data analysis following a consensus protocol, the standardized exposure definition, and the harmonized information about child outcomes and potential confounders.

As in most studies assessing the health effects of diet, we used self-reported dietary information; hence, some information bias might have occurred. However, in most cohorts, fish intake was assessed using detailed food frequency questionnaires that were developed and validated for use in pregnancy, and all data were collected before birth and before growth patterns were known. We used BMI as our main outcome, a measure that incorporates both lean and fat mass; however, a high BMI has been suggested as a sensitive marker for excess adiposity.[34] Further analyses using direct measurements of fat mass and body fat distribution to assess the relationship between fish intake and childhood obesity are an important consideration for future studies.

Conclusions

This large, multicenter study indicates that fish intake of more than 3 times/week in pregnancy is associated with increased risk of rapid growth in infancy and increased adiposity in childhood. Our findings are in line with the fish intake limit for pregnancy proposed by the US Food and Drug Administration and Environmental Protection Agency.

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