Fish intake during pregnancy, fetal growth, and gestational length in 19 European birth cohort studies[1–4]

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ABSTRACT

Background: Fish is a rich source of essential nutrients for fetal development, but in contrast, it is also a well-known route of exposure to environmental pollutants.

Objective: We assessed whether fish intake during pregnancy is associated with fetal growth and the length of gestation in a panel of European birth cohort studies.

Design: The study sample of 151,880 mother-child pairs was derived from 19 population-based European birth cohort studies. Individual data from cohorts were pooled and harmonized. Adjusted cohort-specific effect estimates were combined by using a random- and fixed-effects meta-analysis.

Results: Women who ate fish >1 time/wk during pregnancy had lower risk of preterm birth than did women who rarely ate fish (≤ 1 time/wk); the adjusted RR of fish intake >1 but <3 times/wk was 0.87 (95% CI: 0.82, 0.92), and for intake ≥ 3 times/wk, the adjusted RR was 0.89 (95% CI: 0.84, 0.96). Women with a higher intake of fish during pregnancy gave birth to neonates with a higher birth weight by 8.9 g (95% CI: 3.3, 14.6 g) for >1 but <3 times/wk and 15.2 g (95% CI: 8.9, 21.5 g) for ≥ 3 times/wk independent of gestational age. The association was greater in smokers and in overweight or obese women. Findings were consistent across cohorts.

Conclusion: This large, international study indicates that moderate fish intake during pregnancy is associated with lower risk of preterm birth and a small but significant increase in birth weight. *Am J Clin Nutr* 2014;99:506–16.

INTRODUCTION

The fetal and infant period is a particularly critical developmental period, and there is evidence that has suggested that nutritional perturbations during this period have long-term effects on offspring health (1, 2). Fish is a rich source of nutrients such as polyunsaturated $n-3$ fatty acids, protein, selenium, iodine, and vitamin D, which are considered to be beneficial for fetal growth and development (3) but, in contrast, is also a well-known route of exposure to pollutants such as dioxins, polychlorinated biphenyls, methylmercury, and other heavy metals, which may adversely affect fetal growth and gestational length (4, 5). Findings from prospective birth cohort studies on the relation between fish intake during pregnancy and fetal growth have been discrepant, with reports of either positive or null (6–15) or negative (5, 16–18) effects. These divergent results have been compatible with a hypothesis that there is a differential influence by different types or constituents of fish on fetal growth and birth size. Furthermore, individual studies have not often been

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able to detect small effect sizes. Several recent randomized clinical trials (19–21), and 3 systematic reviews have suggested that maternal $n-3$ supplementation during pregnancy is associated with small but significant increases in the length of gestation and infant birth size (22–24). In contrast, in 2004, the advice jointly issued by 2 US Federal Government agencies for pregnant women or women likely to become pregnant was to restrict their overall consumption of seafood to 340 g/wk (ie, 2 portions/wk) and avoid fetal exposure to trace amounts of several pollutants (25). In this context, pregnant women are faced with conflicting reports on risks and benefits of fish intake, which results in controversy and confusion over the place of fish consumption in a healthy diet in pregnancy. We pooled and harmonized individual data from 151,880 mother-child pairs in

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[2] Study sponsors had no role in study design, data analysis, interpretation of data, or writing of this article.

[3] Research leading to the results presented in this article has received funding from the European Community's Seventh Framework Program (EU- FP7-HEALTH-2009-single-stage-241604). Publication fees were covered by the Special Research Account of University of Crete. Funding per cohort was as follows: Data of the Amsterdam Born Children and their Development cohort study used in this research were in part supported by funds from the Netherlands Organisation for Health Research and Development and Nutricia Research BV. The Danish National Birth Cohort and Danish team were financed by The Danish Council for Strategic Research (09-067124), the March of Dimes Birth Defects Foundation, the Danish Heart Association, the Danish Medical Research Council, the Sygekassernes Helsefond, the Danish National Research Foundation, the Danish Pharmaceutical Association, the Ministry of Health, the National Board of Health, and the Statens Serum Institut. The study on the pre and early postnatal determinants of child health and development was funded by the Fondation pour la Recherche Médicale, the French Ministry of Research: IFR program, the Institut National de la Santé et de la Recherche Médicale Nutrition Research program, the French Ministry of Health Perinatality Program, the French Agency for Environment security, the French National Institute for Population Health Surveillance, the Paris-Sud University, the French National Institute for Health Education, Nestlé, the Mutuelle Genarale de l'Education Nationale, the French speaking association for the study of diabetes and metabolism (Alfediam), and the National Agency for Research; the assessment of exposure to atmospheric pollutants was supported by a grant from the French Agency for Environment Security. Studies of the Flemish Center of Expertise on Environment and Health were commissioned, financed, and steered by the Ministry of the Flemish Community (the Department of Economics, Science and Innovation; the Flemish Agency for Care and Health; and the Department of Environment, Nature and Energy). Genetic and Environment: Prospective Study on Infancy in Italy data used for this research were provided by the Cohort Study, which is supported in part by funds of the Italian Ministry of Health, 2001. The Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam, the Dutch Ministry of Health, Welfare and Sport, and the Netherlands Organisation for Health Research and Development. Generation XXI data used for this research were provided by the Cohort Study, which is supported in part by funds of the Programa Operacional de Saúde-Saúde XXI, Quadro Comunitário de Apoio III; the Northern Regional Administration of Health; the Portuguese Foundation for Science and Technology (PTDC/SAUESA/105033/2008), and the Calouste Gulbenkian Foundation. The Norwegian Human Milk Study data used for this research were provided by the Cohort Study, which is supported in part by funds from the NFR (project 213148), MILPAAHEL growth/obesity and the European Union Seventh Framework project Early Nutrition (grant agreement 289346). Infancia y Medio Ambiente (INMA) data used for this research were provided by the INMA-Environment and Childhood Project, which is supported in part by funds; this study was funded by grants from the Instituto de Salud Carlos III (Red INMA G03/176 and CB06/02/0041), the Spanish Ministry of Health (FIS-PIO41436, PI042018, PI06/0867, PI07/0252, PI081151, and PI09/02311, and FIS-FEDER 03/1615, 04/1112, 04/1931, 05/1079, 05/1052, 06/1213, 07/0314, and 09/02647), the Generalitat de Catalunya-CIRIT 1999SGR00241, the Conselleria de Sanitat Generalitat Valenciana, Department of Health of the Basque Government (2005111093 and 2009111069), the Provincial Government of Gipuzkoa (DFG06/004 and DFG08/001), Obra social Cajastur, Universidad de Oviedo, the European Union Commission (QLK4-1999-01422, QLK4-2002-00603, and CONTAMED FP&-ENV-212502), the Consejeria de Salud de la Junta de Andalucia (grant number 183/07), and the Fundació Roger Tomé. The collection of data from the Kind, Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg (KOALA) Birth Cohort Study used in this analysis was financially supported by the Dutch Board of Health Insurance Companies, the Triodos Foundation, the Phoenix Foundation, the Raphaël Foundation, the Iona Foundation, and the Foundation for the Advancement of Heilpedagogie (all of which are in the Netherlands). Lifeways Cross Generation data used for this research were provided by the Cohort Study, which is supported in part by funds of The Health Research Board, Republic of Ireland. Luchtwegklachten bij Kinderen (LucKi) data used for this research was provided by the Cohort Study, which is supported by Orbis Jeugdgezondheidszorg, GGD Zuid-Limburg, and the Maastricht University. The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health and the Ministry of Education and Research (contract N01-ES-75558), the NIH/NINDS (grants UO1 NS 047537-01 and UO1 NS 047537-06A1), and the Norwegian Research Council/FUGE (grant 151918/S10). Nascita e INFanzia: gli Effetti dell'Ambiente (NINFEA) data used for this research was provided by the Cohort Study, which is supported in part by funds of Compagnia di San Paolo Foundation, Piedmont Region, Italian Ministry of University and Research. The PELAGIE study was supported by grants from the National Institute for Public Health Surveillance, the Ministry of Labor, and the French Agency for Food, Environmental and Occupational Health and Safety. The Prevention and Incidence of Asthma and Mite Allergy birth cohort study has been funded by the Netherlands Organisation for Health Research and Development, the Netherlands Organisation for Scientific Research, the Netherlands Asthma fund, the Netherlands Ministry of Spatial Planning, Housing and the Environment, and the Netherlands Ministry of Health, Welfare and Sport. Polish Mother and Child Cohort Study data used for this research was provided by the Cohort Study, which is supported in part by funds from National Centre for Research and Development, Poland (grant PBZ-MEiN-/8/2/2006; contract K140/P01/2007/1.3.1.1) and grant no. PNRF-218-AI-1/07 from Norway through the Norwegian Financial Mechanism within the Polish-Norwegian Research Fund. The Mother-Child Cohort in Crete project was financially supported by European projects (EU FP6-2003-Food-3-NewGeneris, EU FP6. STREP Hiwate, EU FP7 ENV.2007.1.2.2.2. project 211250 Escape, EU FP7-2008-ENV-1.2.1.4 Envirogenomarkers, EU FP7-HEALTH-2009-single stage CHICOS, and EU FP7 ENV.2008.1.2.1.6. proposal 226285 ENRIECO) and co-financed by the European Union-European Social Fund and the Greek Ministry of Health (Program of Prevention of obesity and neurodevelopmental disorders in preschool children, in Heraklion district, Crete, Greece: 2011–2014, NSRF 2007-2013 project, MIS 349580). The Southampton Women's Survey is supported by grants from the Medical Research Council, the British Heart Foundation, the Food Standards Agency, the British Lung Foundation, Arthritis Research UK, the NIHR Southampton Biomedical Research Centre, the University of Southampton and University Hospital Southampton National Health Service Foundation Trust, and the Commission of the European Community, specific RTD Programme "Quality of Life and Management of Living Resources," within the 7th Framework Programme (research grant FP7/2007-13; EarlyNutrition Project). CM-P was supported by a postdoctoral grant from "Fundación Alfonso Martín Escudero" (Spain).

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Received June 4, 2013. Accepted for publication November 27, 2013.

First published online December 11, 2013; doi: 10.3945/ajcn.113.067421

19 European birth cohort studies to study the association of fish intake during pregnancy with fetal growth and the length of gestation.

SUBJECTS AND METHODS

Subjects

European population-based birth cohorts were able to participate if they included children born from 1990 onward, had information on fish intake during pregnancy, and as a minimum, were at least gestational age and had weight at birth. We identified 29 European birth cohorts from the European inventory of birth cohorts (www.birthcohorts.net) or from cohort's individual websites and published articles (assessed until June 2011). Seven cohorts did not reply to the invitation, and 3 cohorts declined participation for reasons not related to the current hypothesis. Participating cohorts targeted the general population and, altogether, covered births from 1996 to 2011. A data-transfer agreement document was signed by each cohort, and data sets, with personal identifiers removed, were transferred to the University of Crete. Each data set was checked for inconsistencies and completeness, and a total of 151,880 liveborn singleton births were included with available data (nonmissing values) on exposure, outcome, and confounding variables. In total, 27 subjects were excluded from the current analysis because of extreme values on gestational age (<20 or ≥ 45 wk) and birth weight (>7000 g); 79 subjects were excluded because of an implausible combination of gestational age and birth weight (26). Informed consent was obtained from all study participants as part of the original studies, and ethical approval was obtained from the local authorized institutional review boards. Characteristics of cohorts included in the current analysis are shown in **Table 1**.

Exposure assessment: fish intake during pregnancy

Exposure variables were measured as the frequency (times/wk) of total fish, fatty fish, lean fish, and seafood (other than fish) intake during pregnancy derived from cohort-specific food-frequency questionnaires or specially designed questionnaires for fish consumption during pregnancy (Table 1). Salmon, herring, mackerel, trout, sardines, Greenland halibut, anchovy, gurnard, and tuna were classified as fatty fishes, whereas cod, pollack, plaice, flounder, garfish, and similar species were classified as lean fishes. All cohorts assessed fish intake during pregnancy, except in the Endocrine disruptors: longitudinal study on pregnancy abnormalities, infertility, and childhood (France) cohort, where the period of assessment covered the year before pregnancy.

Assessments for standardized categories of fish intake [>1 but <3 times/wk and ≥ 3 times/wk] and birth outcomes compared with a reference category (≤ 1 time/wk) were based on the

TABLE 1
Description of participating cohorts[1]

Cohort	Recruitment period	Provided data on birth outcomes[2]	Provided data on fish intake	Method of dietary assessment	Subjects included[3]
		n	*n*		*n*
ABCD, Amsterdam, NL	2003–2004	7850	7825	Questionnaire	7719
DNBC, nationwide, DK	1996–2002	87,477	63,948	FFQ	57,921
EDEN, Nancy, Poitiers, FR	2003–2005	1905	1838	FFQ	1765
FLEHS I, Flanders, BE	2002–2004	1164	1093	FFQ	1056
GASPII, Rome, IT	2003–2004	606	589	FFQ	536
Generation R, Rotterdam, NL	2001–2006	3366	3366	FFQ	2678
Generation XXI, Porto, PT	2005–2006	357	359	FFQ	276
HUMIS, regional, NO	2003–2009	1734	1696	FFQ	1552
INMA, Asturias, Gipuzkoa, Sabadell, Valencia, ES	2003–2008	2473	2606	FFQ	2295
KOALA, regional, NL	2000–2003	2740	2740	FFQ	2707
Lifeways Cross Generation, Dublin, IR	2001–2003	1068	–1089	FFQ	662
LucKi, regional, NL	2006–current	600	587	FFQ	543
MoBa, nationwide, NO	1999–2008	62,099	62,099	FFQ	58,926
NINFEA, nationwide, IT	2005–current	2553	2268	Questionnaire	2213
PELAGIE, Brittany, FR	2002–2006	3321	3308	Questionnaire	3228
PIAMA, nationwide, NL	1996–1997	3930	3922	Questionnaire	3335
REPRO-PL, nationwide, PL	2007–2011	917	917	FFQ	902
RHEA, Heraklion, GR	2007–2008	1390	1060	FFQ	970
SWS, Southampton, UK	1998–2007	2642	2642	FFQ	2596
Pooled data	—	—	—	—	151,880

[1] ABCD, Amsterdam Born Children and their Development study; BE, Belgium; DK, Denmark; DNBC, Danish National Birth Cohort; EDEN, study on the pre and early postnatal determinants of child health and development; ES, Spain; FFQ, food-frequency questionnaire; FLEHS I, Flemish Center of Expertise on Environment and Health Studies; FR, France; GASPII, Genetic and Environment: Prospective Study on Infancy in Italy; Generation R, The Generation R Study; GR, Greece; HUMIS, Norwegian Human Milk Study; INMA, Infancia y Medio Ambiente–Environment and Childhood Project; IR, Ireland; IT, Italy; KOALA, Kind, Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg Birth Cohort Study; Lifeways, Lifeways Cross Generation Cohort Study; LucKi, Luchtwegklachten bij Kinderen Cohort Study; MoBa, Norwegian Mother and Child Cohort Study; NINFEA, Nascita e INFanzia: gli Effetti dell'Ambiente; NL, Netherlands; NO, Norway; PELAGIE, Endocrine disruptors: Longitudinal study on pregnancy abnormalities, infertility, and childhood; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; PL, Poland; PT, Portugal; REPRO-PL, Polish Mother and Child Cohort Study; RHEA, Mother Child Cohort in Crete; SWS, Southampton Women's Survey; UK, United Kingdom.

[2] Subjects with available information on birth weight or gestational age as provided by cohorts.

[3] Subjects with full information on exposure variables, birth weight, gestational age, and selected confounding variables.

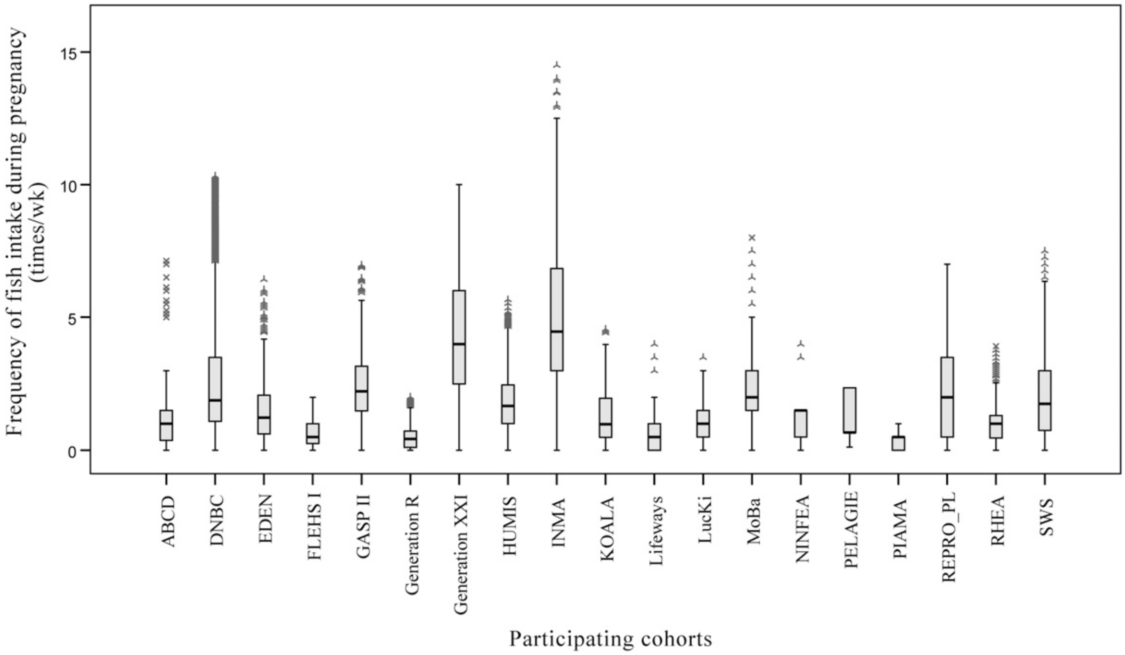

FIGURE 1. Distribution of the frequency of fish intake during pregnancy in participating cohorts. The symbol (⅄) denotes outliers (>1.5 IQRs) of the distribution of fish intake during pregnancy for each cohort; the symbol (×) denotes extreme outliers (>3 IQRs) of the distribution of fish intake during pregnancy for each cohort. ABCD, Amsterdam Born Children and their Development study; DNBC, Danish National Birth Cohort; EDEN, study on the pre and early postnatal determinants of child health and development; FLEHS I, Flemish Center of Expertise on Environment and Health Studies; GASPII, Genetic and Environment: Prospective Study on Infancy in Italy; Generation R, The Generation R Study; HUMIS, Norwegian Human Milk Study; INMA, Infancia y Medio Ambiente–Environment and Childhood Project; KOALA, Kind, Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg Birth Cohort Study; Lifeways, Lifeways Cross Generation Cohort Study; LucKi, Luchtwegklachten bij Kinderen Cohort Study; MoBa, Norwegian Mother and Child Cohort Study; NINFEA, Nascita e Infanzia: gli Effetti dell'Ambiente; PELAGIE, Endocrine disruptors: longitudinal study on pregnancy abnormalities, infertility, and childhood; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; REPRO-PL, Polish Mother and Child Cohort Study; RHEA, Mother Child Cohort in Crete; SWS, Southampton Women's Survey.

calculation of tertiles of total fish intake in the pooled database in an attempt to create a universal categorization in cohorts. However, 6 cohorts [Flemish Center of Expertise on Environment and Health Studies, the Generation R Study, Generation XXI, Endocrine disruptors: longitudinal study on pregnancy abnormalities, infertility, and childhood; Prevention and Incidence of Asthma and Mite Allergy; and Mother-Child Cohort in Crete (RHEA)[5]] had at least one category that contained <5% of participants and, therefore, were excluded from this categorical dose-response analysis.

Birth outcomes

All cohorts provided information on birth weight, gestational age, and infant sex obtained from birth records, medical birth registries, or parental-completed questionnaires. Gestational age was estimated as the interval between the start of the last menstrual period (LMP) and delivery when available and, if this estimation was not inconsistent by ≥7 d, by using an ultrasound- based estimation (72% of births). The ultrasound-based estimation (20.8%) of gestational age was only used if the LMP was unavailable or if the LMP was inconsistent by ≥7 d with the ultrasound-based measurement taken in the first trimester of pregnancy. Finally, an obstetrician estimation (7.2%) was only used if the LMP and ultrasound-based measures were unavailable. Other continuous anthropometric measures provided by cohorts were birth length (available for 15 cohorts) and head circumference (available for 14 cohorts). Neonatal weights were defined as small for gestational age if they were below the 10th percentile of the cohort-specific growth curves stratified by gestational length and sex (available for 17 cohorts). The same method was used to define small-for-gestational-age neonates for length (available for 10 cohorts) and head circumference (available for 8 cohorts). Low birth weight was defined as any newborn with a birth weight <2500 g, whereas high birth weight was defined as a birth weight >4000 g. Preterm birth was defined as being born <37 wk of gestation.

Other variables

Potential confounding variables were defined as similarly as possible in cohorts given the information that was available. In all cohorts, information on maternal age at delivery (continuous in y), maternal prepregnancy BMI [continuous in kg/m^2 and categorized as normal weight (≥18.5 to <25), overweight (≥25 to <30), and obese (≥30)] and maternal height (continuous in cm) were collected by using questionnaires filled in during pregnancy or at birth, medical or national registries, or ad hoc measurements. Maternal educational level (low, medium, or high), maternal country of birth (country of the cohort or foreign country), maternal smoking during pregnancy (yes or no), and parity (multiparous or primiparous) were collected by using questionnaires filled in during pregnancy or at birth or medical birth registries.

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[5] Abbreviations used: HUMIS, Norwegian Human Milk Study; INMA, Infancia y Medio Ambiente; LCPUFA, long-chain PUFA; LMP, last menstrual period; RHEA, Mother-Child Cohort in Crete.

TABLE 2

Crude and adjusted combined associations of fish and seafood intake during pregnancy with birth weight and low-birth-weight neonates[1]

			Birth weight (g)			Low birth weight (<2500 g)		
	Cohorts	Subjects	Crude β (95% CI)	Adjusted β (95% CI)	*P*-heterogeneity	Crude RR (95% CI)	Adjusted RR (95% CI)	*P*-heterogeneity
Fish intake (times/wk)	19	151,880	1.98 (0.59, 3.26)[2]	1.46 (0.45, 2.46)[2]	0.31	1.00 (0.96, 1.04)[3]	1.00 (0.96, 1.04)[3]	0.06
Categories of fish intake[4]								
>1 but <3 times/wk	13	140,337	28.76 (21.59, 35.93)[2]	8.93 (3.31, 14.56)[2]	0.84	0.97 (0.94, 1.14)[3]	0.90 (0.77, 1.20)[3]	0.005
≥3 times/wk	13	140,337	36.79 (28.74, 44.85)[2]	15.20 (8.86, 21.54)[2]	0.67	0.97 (0.95, 1.18)[2]	0.91 (0.81, 1.02)[2]	0.44
Fatty fish (times/wk)	13	131,651	2.24 (−3.46, 7.94)[2]	2.38 (0.51, 4.25)[2]	0.97	0.99 (0.96, 1.01)[2]	0.98 (0.95, 1.02)[2]	0.31
Lean fish (times/wk)	12	129,886	1.02 (−5.09, 7.12)[3]	0.76 (−2.45, 3.98)[3]	0.11	1.03 (0.97, 1.1)[3]	1.05 (0.97, 1.13)[3]	0.004
Seafood (other than fish) (times/wk)	16	138,148	−7.23 (−18.95, 4.49)[3]	−3.92 (−14.31, 6.48)[3]	0.01	1.03 (0.95, 1.1)[2]	1.00 (0.92, 1.10)[2]	0.32

[1] β Coefficients (95% CIs) and RRs (95% CIs) were estimated by using a random- or fixed-effects meta-analysis by cohort. Linear and log-binomial regression models, respectively, were adjusted for maternal age, prepregnancy BMI, maternal height, education level, smoking during pregnancy, parity, infant sex, gestational age, and gestational age squared. *P*-heterogeneity values were estimated by using Cochran's *Q* test.

[2] Fixed-effects meta-analysis: *P*-heterogeneity ≥ 0.05 and $I^2 \leq 25\%$.

[3] Random-effects meta-analysis: *P*-heterogeneity < 0.05 or $I^2 > 25\%$.

[4] Reference category: ≤1 time/wk.

Statistical analysis

We used a 2-stage approach to assess the association of fish intake during pregnancy with birth outcomes. First, associations were analyzed at the cohort level. Second, cohort-specific effect estimates were combined by using a random- and fixed-effects meta-analysis.

Distributions of categorical variables were presented as frequencies and percentages. For continuous data, means ± SDs were used to describe normally distributed variables, and medians and IQRs were used to describe nonnormally distributed variables. Linear and log-binomial regression models were used for continuous and binary outcome measures, respectively. Fish-intake variables were used as continuous variables [effect estimated per 1-unit (times/wk) increments] or categorized in 3 categories [≤1 (reference category), >1 but <3, and ≥3 times/wk]. Adjustment for confounding variables was based on a priori selection of potential risk factors for reduced birth weight or gestational age, including maternal age at delivery (continuous in y), maternal height (continuous in cm), prepregnancy BMI (continuous), maternal education (low, medium, or high), smoking during pregnancy (yes and no), parity (multiparous or primiparous), and infant sex (boy or girl). Gestational age and the square of gestational age were included in models that assessed the association of fish intake during pregnancy with birth weight, birth length, head circumference, and low- and high-birth weight neonates. In 3 cohorts, the adjusted models did not include the full list of confounders because of the unavailability of information [the Luchtwegklachten bij Kinderen (LucKi) cohort provided no information on maternal age and education, the Lifeways Cross Generation cohort provided no information on prepregnancy BMI, and the Norwegian Human Milk Study (HUMIS) cohort provided limited information on parity before index pregnancy in the data set used for this study].

Meta-analyses were performed that combined cohort-specific estimates of the association between fish-intake variables and each birth outcome. Heterogeneity was assessed by using the *Q* test and by I^2 statistic (27, 28), which indicated the proportion of variability in the combined estimate attributable to the heterogeneity across cohorts. If the result of the *Q* test was statistically significant ($P < 0.05$), or I^2 was <25%, we used random-effects analyses (27, 28). Exposure-response slopes derived for each cohort were plotted together with the summary slope from the meta-analysis by using forest plots of β coefficients or RRs with 95% CIs.

Several sensitivity analyses were performed. First, we estimated the effect on birth weight and low-birth-weight neonates after restriction to term deliveries. To determine the influence of any particular cohort effect, we repeated the meta-analyses by leaving out one cohort at a time. In addition, a potential effect modification by maternal smoking and prepregnancy weight status was explored in stratified analyses. Statistical analyses were conducted with SPSS software (version 19; IBM Corp) and R Core Team v2.15.1 software (R Foundation for Statistical Computing).

RESULTS

The mean birth weight across cohorts ranged from 3.201 kg (RHEA cohort; Greece) to 3.595 kg (Danish National Birth Cohort; Denmark), and the mean gestational age ranged from

38.4 wk (RHEA cohort) to 40.1 wk (Danish National Birth Cohort). The proportion of preterm births ranged from 2.8% [Kind, Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg (KOALA) cohort; Netherlands] to 10.5% (RHEA cohort), whereas the proportion of low-birth-weight neonates ranged from 1.7% (Flemish Center of Expertise on Environment and Health Studies cohort; Belgium) to 6.4% (HUMIS cohort; Norway) (*see* Supplemental Table 1 under "Supplemental data" in the online issue). The number of boys in the whole population was higher than the number of girls (overall sex ratio: 1.05). The mean maternal age was ≥29 y in all populations. In the Generation XXI (Portugal), HUMIS (Norway), and Southampton Women's Survey (United Kingdom) cohorts, one-third of pregnant women were overweight or obese (BMI ≥25) before pregnancy. The proportion of women who smoked during pregnancy ranged from 7.7% (KOALA cohort) to 31% Infancia y Medio Ambiente (INMA) cohort; Spain] (*see* Supplemental Table 2 under "Supplemental data" in the online issue). The proportion of nulliparous women exceeded 50% in 9 populations (*see* Supplemental Table 2 under "Supplemental data" in the online issue). The median fish intake in the 19 study populations ranged from 0.4 times/wk (the Generation R study; Netherlands) to 4.5 times/wk (INMA cohort) (**Figure 1**; *see* Supplemental Table 3 under "Supplemental data" in the online issue). The median fatty fish intake in the Genetic and Environment: Prospective Study on Infancy in Italy (Italy), Generation XXI, INMA, and Polish Mother and Child Cohort Study (Poland) cohorts was more than double the overall median intake of 0.5 times/wk. The highest median lean fish (3.5 times/wk) and seafood intake other than fish (0.9 times/wk) was reported in the INMA cohort. Portion sizes of different fish types varied from 100 to 150 g across cohorts with available information on portion-size specification.

Fish intake and fetal growth

Fish intake in pregnancy was positively associated with birth weight and corresponded to a 1.5-g (95% CI: 0.5, 2.5-g) increase per 1-time/wk increase in fish intake (**Table 2**). In a subset of studies with available information on types of fish intake (131,651 participants) the corresponding β coefficient was 2.4 g (95% CI: 0.5, 4.3 g) for fatty fish types and 0.8 g (95% CI: −2.5, 4.0 g) for lean fish types (Table 2). Compared with women who rarely ate fish (≤1 time/wk), women with a higher intake of fish during pregnancy gave birth to neonates with a higher birth weight by 8.9 g (95% CI: 3.3, 14.6 g) for >1 but <3 times/wk and by 15.2 g (95% CI: 8.9, 21.5 g) for ≥3 times/wk (Table 2, **Figure 2**). No significant associations were shown between fish intake and low-birth-weight (Table 2), high-birth-weight, or small-for-gestational age for weight, length, and head circumference neonates (*see* Supplemental Table 4 under "Supplemental data" in the online issue). Findings did not change after the exclusion of extreme values of fish consumption (data not shown).

Fish intake and preterm birth

Fish intake was associated with a higher gestational age of 0.4 d (95% CI: 0.3, 0.6 d) for fish intake >1 but <3 times/wk and of

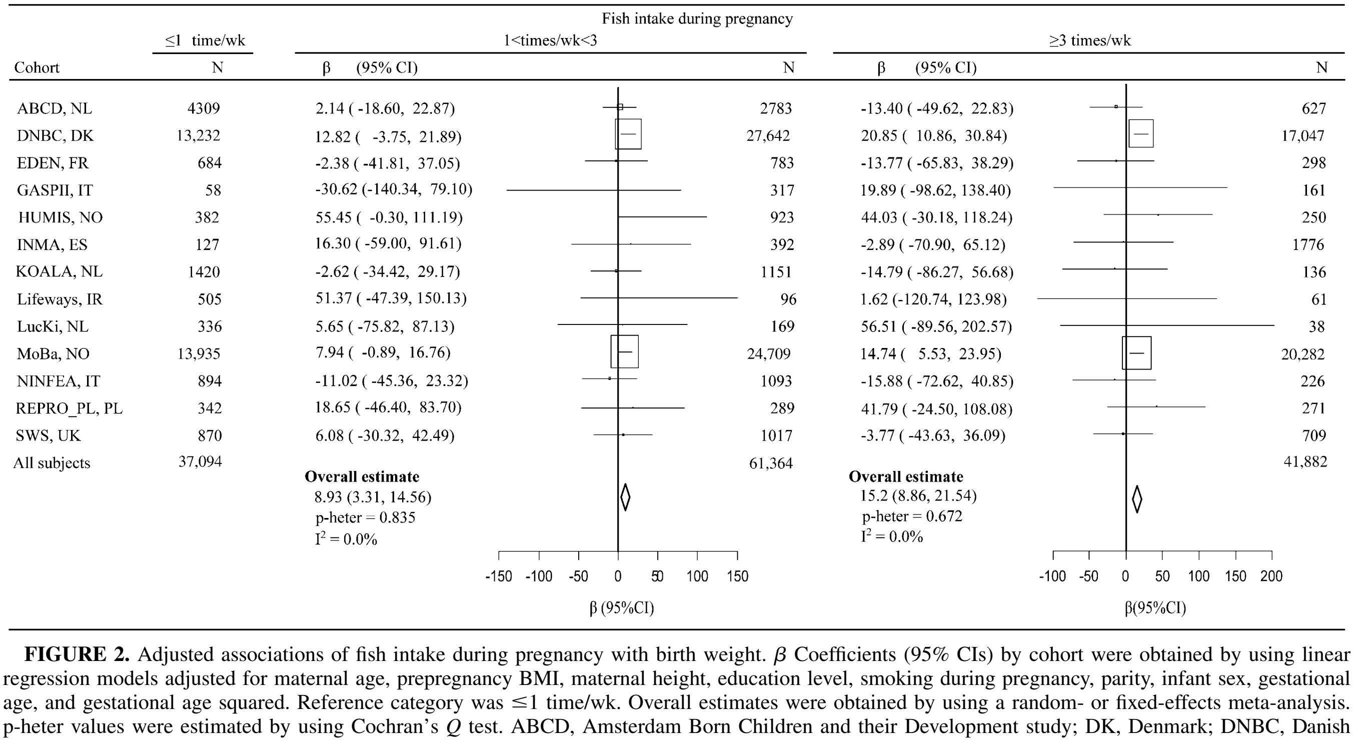


FIGURE 2. Adjusted associations of fish intake during pregnancy with birth weight. β Coefficients (95% CIs) by cohort were obtained by using linear regression models adjusted for maternal age, prepregnancy BMI, maternal height, education level, smoking during pregnancy, parity, infant sex, gestational age, and gestational age squared. Reference category was ≤1 time/wk. Overall estimates were obtained by using a random- or fixed-effects meta-analysis. p-heter values were estimated by using Cochran's *Q* test. ABCD, Amsterdam Born Children and their Development study; DK, Denmark; DNBC, Danish National Birth Cohort; EDEN, study on the pre and early postnatal determinants of child health and development; ES, Spain; FR, France; GASPII, Genetic and Environment: Prospective Study on Infancy in Italy; HUMIS, Norwegian Human Milk Study; INMA, Infancia y Medio Ambiente–Environment and Childhood Project; IR, Ireland; IT, Italy; KOALA, Kind, Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg Birth Cohort Study; Lifeways, Lifeways Cross Generation Cohort Study; LucKi, Luchtwegklachten bij Kinderen Cohort Study; MoBa, Norwegian Mother and Child Cohort Study; NINFEA, Nascita e INFanzia: gli Effetti dell'Ambiente; NL, Netherlands; NO, Norway; p-heter, *P*-heterogeneity; PL, Poland; REPRO-PL, Polish Mother and Child Cohort Study; SWS, Southampton Women's Survey; UK, United Kingdom.

TABLE 3
Crude and adjusted combined associations of fish and seafood intake during pregnancy with gestational age and preterm birth[1]

	Cohorts	Subjects	Gestational age (d) Crude β (95% CI)	Adjusted β (95% CI)	*P*-heterogeneity	Preterm birth (<37 wk gestational age) Crude RR (95% CI)	Adjusted RR (95% CI)	*P*-heterogeneity
Fish intake (times/wk)	19	151,880	−0.02 (−0.09, 0.03)[2]	−0.02 (−0.09, 0.05)[2]	0.06	1.00 (0.97, 1.01)[2]	1.00 (0.97, 1.03)[2]	0.008
Categories of fish intake[3]								
>1 but <3 times/wk	13	140,337	0.47 (0.19, 0.74)[4]	0.41 (0.25, 0.57)[4]	0.24	0.89 (0.81, 0.93)[4]	0.87 (0.82, 0.92)[4]	0.36
≥3 times/wk	13	140,337	0.21 (0.03, 0.45)[4]	0.23 (0.05, 0.41)[4]	0.44	0.87 (0.82, 0.94)[4]	0.89 (0.84, 0.96)[4]	0.55
Fatty fish (times/wk)	13	131,651	0.15 (0.34, 0.03)[2]	0.14 (−0.31, 0.03)[2]	<0.001	1.04 (0.98, 1.10)[2]	1.04 (0.98, 1.09)[2]	0.02
Lean fish (times/wk)	12	129,886	−0.02 (−0.11, 0.07)[2]	−0.02 (−0.12, 0.08)[2]	0.06	0.99 (0.95, 1.04)[2]	1.00 (0.96, 1.05)[2]	0.03
Seafood (other than fish) (times/wk)	16	138,148	−0.02 (−0.17, 0.12)[4]	−0.03 (−0.18, 0.12)[4]	0.32	1.02 (0.96, 1.08)[4]	1.01 (0.96, 1.07)[4]	0.49

[1] β Coefficients (95% CIs) and RRs (95% CIs) were estimated by using a random- or fixed-effects meta-analysis by cohort. Linear and log-binomial regression models, respectively, were adjusted for maternal age, prepregnancy BMI, maternal height, education level, smoking during pregnancy, parity, and infant sex. *P*-heterogeneity values were estimated by using Cochran's *Q* test.

[2] Random-effects meta-analysis: *P*-heterogeneity < 0.05 or $I^2 > 25\%$.

[3] Reference category: ≤1 time/wk.

[4] Fixed-effects meta-analysis: *P*-heterogeneity ≥ 0.05 and $I^2 \leq 25\%$.

0.2 d (95% CI: 0.1, 0.4 d) for fish intake ≥3 times/wk (**Table 3**). Correspondingly, women who ate fish more than 1 time/wk during pregnancy had lower risk of preterm birth than did women who rarely ate fish (≤1 time/wk); the adjusted RR of fish intake >1 but <3 times/wk was 0.87 (95% CI: 0.82, 0.92), and for women who consumed fish ≥3 times/wk, the adjusted RR was 0.89 (95% CI: 0.84, 0.96) (Table 3, **Figure 3**).

Stratified and sensitivity analyses

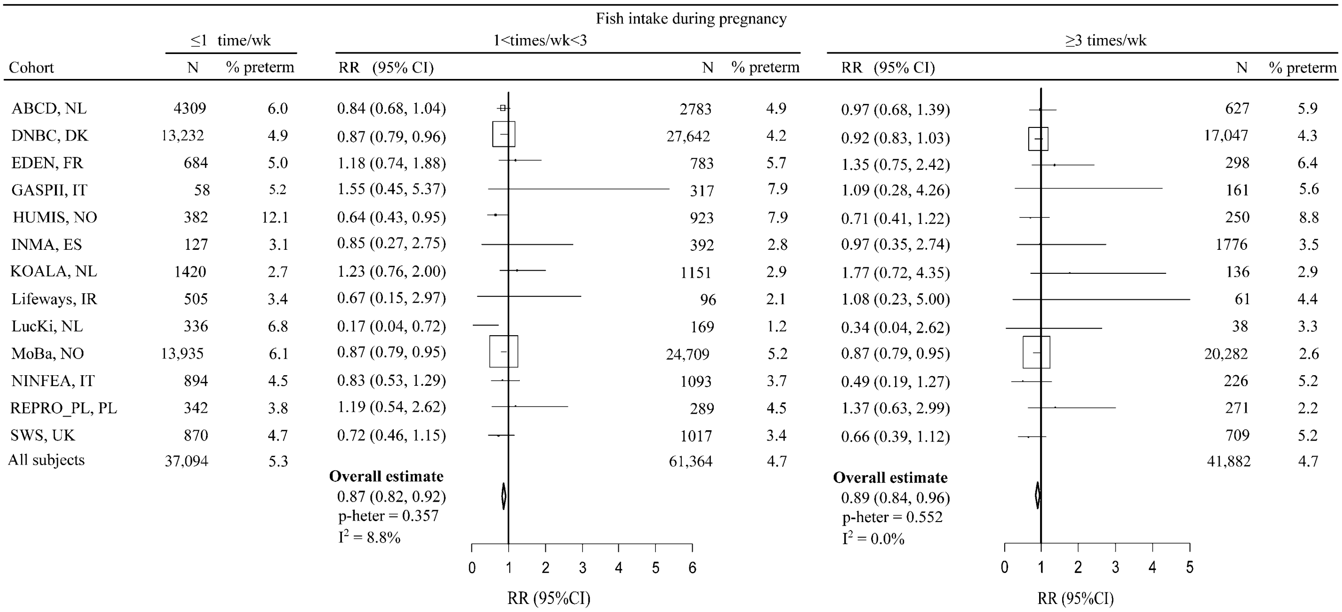
The association of fish intake during pregnancy with birth weight was more pronounced in pregnant women who smoked during pregnancy [β coefficient: 39.5 g (95% CI: 23.5, 55.5 g) for smokers who consumed fish >3 times/wk compared with <1 time/wk; *P*-interaction = 0.01); a significant increase was also observed in nonsmokers but was less pronounced (β coefficient: 10 g (95% CI: 3.2, 17 g) for fish intake ≥3 times/wk) (**Table 4**). A greater association of fish intake with birth weight was also observed in the stratum of women who were overweight or obese prepregnancy than in women with normal BMI prepregnancy (*P*-interaction = 0.03; Table 4).

A sensitivity analysis restricted to infants born at term (gestational age between 37 and 42 wk) showed no material changes in effect estimates for birth weight and low-birth-weight neonates (*see* Supplemental Table 5 under "Supplemental data" in the online issue). We observed similar effect estimates for birth weight and preterm birth, after excluding cohorts one by one, indicating that the overall effects were not produced by any particular population (*see* Supplemental Table 6 under "Supplemental data" in the online issue).

DISCUSSION

To our knowledge, this is the largest study conducted to assess the association of fish intake during pregnancy with birth weight and length of gestation, with the inclusion of >150,000 mother-child pairs. Our findings were consistent between cohorts and supported the evidence for a beneficial role of moderate fish intake during pregnancy in risk of preterm birth and a small but significant increase in birth weight. To what extent this slightly increased fetal growth in the group of women who frequently consumed fish during pregnancy is likely to be associated with future child development is unknown. The ongoing longitudinal follow-up of these population-based birth cohort studies will allow for the study the longer-term consequences of fish intake during pregnancy on child growth and development.

It is possible that the potential benefit of fish consumption could be attributed to its content of n−3 long-chain PUFAs (LCPUFAs). This possibility was supported by the fact that the most-pronounced effect on birth weight was observed for fatty fish types. n−3 LCPUFAs consist primarily of EPA (20:5n−3) and DHA (22:6n−3). Pregnancy is associated with a reduction in the maternal serum DHA percentage and its possible depletion in the maternal store (29). Because the synthesis of n−3 LCPUFAs in the fetus and placenta is low, both the maternal status and placental function are critical for their supply to the fetus (30). It was proposed that n−3 LCPUFAs might also reduce the activity of eicosanoid promoters of the parturition process, particularly prostaglandins F and E and increase the activity of eicosanoids with myometrial relaxant properties, such



	Fish intake during pregnancy							
	≤1 time/wk		1<times/wk<3			≥3 times/wk		
Cohort	N	% preterm	RR (95% CI)	N	% preterm	RR (95% CI)	N	% preterm
ABCD, NL	4309	6.0	0.84 (0.68, 1.04)	2783	4.9	0.97 (0.68, 1.39)	627	5.9
DNBC, DK	13,232	4.9	0.87 (0.79, 0.96)	27,642	4.2	0.92 (0.83, 1.03)	17,047	4.3
EDEN, FR	684	5.0	1.18 (0.74, 1.88)	783	5.7	1.35 (0.75, 2.42)	298	6.4
GASPII, IT	58	5.2	1.55 (0.45, 5.37)	317	7.9	1.09 (0.28, 4.26)	161	5.6
HUMIS, NO	382	12.1	0.64 (0.43, 0.95)	923	7.9	0.71 (0.41, 1.22)	250	8.8
INMA, ES	127	3.1	0.85 (0.27, 2.75)	392	2.8	0.97 (0.35, 2.74)	1776	3.5
KOALA, NL	1420	2.7	1.23 (0.76, 2.00)	1151	2.9	1.77 (0.72, 4.35)	136	2.9
Lifeways, IR	505	3.4	0.67 (0.15, 2.97)	96	2.1	1.08 (0.23, 5.00)	61	4.4
LucKi, NL	336	6.8	0.17 (0.04, 0.72)	169	1.2	0.34 (0.04, 2.62)	38	3.3
MoBa, NO	13,935	6.1	0.87 (0.79, 0.95)	24,709	5.2	0.87 (0.79, 0.95)	20,282	2.6
NINFEA, IT	894	4.5	0.83 (0.53, 1.29)	1093	3.7	0.49 (0.19, 1.27)	226	5.2
REPRO_PL, PL	342	3.8	1.19 (0.54, 2.62)	289	4.5	1.37 (0.63, 2.99)	271	2.2
SWS, UK	870	4.7	0.72 (0.46, 1.15)	1017	3.4	0.66 (0.39, 1.12)	709	5.2
All subjects	37,094	5.3	**Overall estimate** 0.87 (0.82, 0.92) p-heter = 0.357 $I^2 = 8.8\%$	61,364	4.7	**Overall estimate** 0.89 (0.84, 0.96) p-heter = 0.552 $I^2 = 0.0\%$	41,882	4.7

FIGURE 3. Adjusted associations of fish intake during pregnancy with preterm birth. RRs (95% CIs) by cohort were obtained by using log-binomial regression models adjusted for maternal age, prepregnancy BMI, maternal height, education level, smoking during pregnancy, and infant sex. Reference category was ≤1 time/wk. Overall estimates were obtained by using a random- or fixed-effects meta-analysis. p-heter values were estimated by using Cochran's *Q* test. ABCD, Amsterdam Born Children and their Development study; DK, Denmark; DNBC, Danish National Birth Cohort; EDEN, study on the pre and early postnatal determinants of child health and development; ES, Spain; FR, France; GASPII, Genetic and Environment: Prospective Study on Infancy in Italy; HUMIS, Norwegian Human Milk Study; INMA, INMA-Environment and Childhood Project; IR, Ireland; IT, Italy; KOALA, Kind, Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg Birth Cohort Study; Lifeways, Lifeways Cross Generation Cohort Study; LucKi, Luchtwegklachten bij Kinderen Cohort Study; MoBa, Norwegian Mother and Child Cohort Study; NINFEA, Nascita e INFanzia: gli Effetti dell'Ambiente; NL, Netherlands; NO, Norway; p-heter, *P*-heterogeneity; PL, Poland; REPRO-PL, Polish Mother and Child Cohort Study; SWS, Southampton Women's Survey; UK, United Kingdom.

as prostacyclins, resulting in an increase in pregnancy duration (31, 32). A shift of the prostacyclin/thromboxane A balance to a more antiaggregatory and vasodilator state might also increase the placental flow and, as a consequence, fetal growth (33). Several randomized controlled trials showed that maternal intake of $n-3$ LCPUFA during pregnancy resulted in a slightly longer gestation period and somewhat higher birth size, and these results were also confirmed in 3 recent meta-analyses (22–24). Fish are also a good source of vitamin D and B complex and several essential aminoacids and trace elements (eg, selenium, calcium, magnesium, potassium, and iodine), which have been linked to potentially favorable birth outcomes (34–36).

Because the balance between the potential beneficial effect of $n-3$ LCPUFAs and deleterious effect of contaminants in fish intake such as toxins and metals is determined by the relative exposure, results may differ across populations consuming different types of seafood (4, 5, 37). The protective effect of fish intake on preterm birth was shown only in the categorical analysis and not in the continuous analysis. This result could mean that, for very high amounts of fish intake, the protective effect is attenuated and RRs get closer to 1 (a U-shaped association). We were not able to address potential effects at very high amounts of fish consumption through a stratified analysis, as there were only few women with high values of fish intake, and they were not present in all examined cohorts, which made international comparisons difficult. Moreover, we did not have the possibility to collect accurate information on amounts of polychlorinated biphenyls, mercury, and dioxins across all cohorts, which are contaminants that have been negatively associated with birth size and gestational length (38–40). In general, we would expect confounding from pollutants bioaccumulating in fish to bias the association between fish intake and birth weight toward the null. Therefore, any true effect size might be larger than the one reported in this article in the absence of correction for fish pollutants.

We observed a greater association of fish intake with birth weight in the stratum of pregnant women who smoked during pregnancy compared with nonsmokers. Cigarette smoking during pregnancy has been previously shown to cause a 100–300-g reduction in birth weight, whereas other research has indicated even an ∼500-g reduction in populations with certain metabolic gene polymorphisms (41). Numerous studies have shown that smokers generally have poorer-quality diets than do nonsmokers, with lower intakes of fish and antioxidant- rich foods, and the same applies for pregnant women (42). Therefore, the protective effect of regular fish intake during pregnancy in smokers might reflect a high fetal exposure to $n-3$ LCPUFAs and several antioxidant compounds and their property to counter the effect of oxidative stress damage by smoking on fetal tissues. In contrast, in the nonsmokers group, there was also observed a significant increase in birth weight, and the trend over categories was positive (although weaker compared with for smokers). This positive association provides stronger evidence that there is a true association between fish intake and birth weight because any residual confounding by smoking was excluded in this group.

The current study confirmed a more-pronounced association of fish intake during pregnancy with birth weight in overweight and obese women, which is a result that is similar to the findings by Drouillet et al (43) in the study on the pre and early postnatal determinants of child health and development birth cohort. The storage of n−3 LCPUFAs in maternal adipose tissue is of great importance because it represents a pool of fatty acids that can be used via placental transfer to supply the developing fetus (43, 44). Therefore, it might be possible that overweight and obese women with regular fish intake during pregnancy have an enhanced ability to release fatty acids from adipose tissue to sustain fetal growth.

Discrepant findings in earlier birth cohort studies on fish intake and birth outcomes have been puzzling (5–18). Reasons for the inconsistencies may be inadequate sample sizes, exposure misclassification, exposure profile heterogeneity [(ie, consumption frequencies compared with estimated daily intakes (in g)], or differences in adjustment.

Our international study, involving a large number of mother-child pairs, comprehensively recorded a wide range of exposure that allowed us to carry out the most-detailed exploration of potential heterogeneity than, to our knowledge, has been previously reported. In populations included in the current meta-analysis, only 4 populations showed inverse associations between fish intake and birth weight, of which none of the associations was significant. The current findings underscore scientific gaps in the experimental evidence of fish intake during pregnancy, specifically the lack of studies that involve healthy populations and randomized clinical trials that target fish intake rather than using supplements, which may have different mechanistic effects.

Strengths of the current study included the population-based prospective design, large sample size, and centralized statistical analysis after a consensus protocol. We did not rely on published data, which excluded any potential publication bias. The study population included women from the follow-up of several birth cohorts, which provided us with the opportunity to account for the effect of exposures during pregnancy prospectively collected within each cohort. In addition, we adjusted for many socioeconomic and lifestyle variables known to be associated with fish intake during pregnancy and fetal growth, although some residual confounding, mainly related to socioeconomic positions, could not be completely ruled out. After we excluded cohorts one by one, effect estimates did not change importantly, which minimized the effect of single cohorts.

As in most studies on diet and health, we used self-reported dietary information during pregnancy, and therefore, an information bias could have occurred. However, in the majority of cohorts, fish intake was assessed by using a detailed food-frequency questionnaire that was developed and validated for use in pregnancy. Studies of nutrition in pregnancy have suggested that food-frequency methods could present valid and reproducible estimates of dietary intakes in pregnant women (45). Moreover, we collected detailed information on the consumption of different fish types, which enabled us to separate the analyses, although we did not have enough data to distinguish between big and small species that would be relevant in terms of toxicant exposures. Women who consume more fish may have a healthier diet and lifestyle. Although careful adjustment for potential lifestyle confounding variables did not appreciably alter the results, we did not have information on other dietary variables, fish-oil supplementation, and alcohol intake during pregnancy across all cohorts.

TABLE 4

Adjusted combined associations of fish and seafood intake during pregnancy with birth weight (g) stratified by maternal smoking during pregnancy and maternal weight status prepregnancy[1]

	Smoking during pregnancy					Prepregnancy overweight/obesity status				
	Smokers			Nonsmokers		Normal			Overweight or obese	
	Cohorts	Subjects	β (95% CI)	Subjects	β (95% CI)	Cohorts	Subjects	β (95% CI)	Subjects	β (95% CI)
Fish intake (times/wk)	19	25,053	3.02 (0.78, 5.27)[2]	126,827	−0.31 (−2.69, 2.07)[3]	18	108,302	0.69 (−0.48, 1.85)[2]	42,916	1.72 (−1.95;5.39)[3]
Categories of fish intake[4]										
>1 but <3 times/wk	13	22,517	29.25 (14.95, 43.55)[2]	117,820	4.43 (−1.69, 10.55)[2]	12	99,290	2.45 (−4.12, 9.03)[2]	40,385	14.88 (3.84;25.92)[2]
≥ 3 times/wk	13	22,517	39.47 (23.46, 55.49)[2]	117,820	10.08 (3.18, 16.99)[2]	12	99,290	8.15 (0.74, 15.56)[2]	40,385	22.30 (9.88;34.73)[2]
Fatty fish (times/wk)	13	22,433	4.42 (0.20, 8.64)[2]	109,806	1.78 (−0.31, 3.86)[2]	12	56,238	0.74 (−1.42, 2.89)[2]	38,587	4.72 (0.94;8.51)[2]
Lean fish (times/wk)	12	21,966	3.41 (−0.05, 6.88)[2]	108,508	−1.45 (−5.94, 3.04)[3]	11	54,931	−1.04 (−5.27, 3.20)[3]	38,129	1.61 (−1.42;4.65)[2]
Seafood (other than fish) (times/wk)	16	23,096	−3.88 (−15.27, 7.52)[2]	115,052	−2.89 (−12.94, 7.17)[3]	15	97,626	−6.86 (−19.66, 5.95)[3]	39,860	1.77 (−15.72,19.26)[3]

[1] β Coefficients (95% CIs) were estimated by using a random- or fixed-effects meta-analysis by cohort. Linear regression models were adjusted for maternal age, prepregnancy BMI, maternal height, education level, parity, smoking during pregnancy, infant sex, gestational age, and gestational age squared.

[2] Fixed-effects meta-analysis: P-heterogeneity ≥ 0.05 and $I^2 \leq 25\%$.

[3] Random-effects meta-analysis: P-heterogeneity < 0.05 or $I^2 > 25\%$.

[4] Reference category: ≤1 time/wk.

Because preterm birth is a rather heterogeneous entity, we did not have the possibility to distinguish between spontaneous and medically indicated preterm births because this information was not available across all cohorts.

In conclusion, available data from European birth cohort studies indicate that moderate fish intake during pregnancy is associated with lower risk of preterm birth and a small but significant increase in birth weight. Although these findings cannot establish causality, they support the need for public health advice to promote fish consumption in pregnant women in accordance with country-specific restrictions regarding fish species and items known to have high concentrations of pollutants.

The authors' responsibilities were as follows—LC: designed the research; LC, VL, and TR: conducted the research, had full access to all study data, and took responsibility for the integrity of the data and accuracy of the data analysis; TR and DM: analyzed data and performed the statistical analysis; VL and LC: wrote the manuscript: LC, MK, and MV: supervised the study; and all authors: provided essential materials (cohort-specific databases necessary for research), had primary responsibility for the final content of the manuscript, and read and approved the final manuscript. None of the authors had a conflict of interest.

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