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Impaired Fetal Growth and Arterial Wall Thickening: A Randomized Trial of Omega-3 Supplementation

Michael R. Skilton, Julian G. Ayer, Jason A. Harmer, Karen Webb, Stephen R. Leeder, Guy B. Marks and David S. Celermajer

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Impaired Fetal Growth and Arterial Wall Thickening: A Randomized Trial of Omega-3 Supplementation

WHAT'S KNOWN ON THIS SUBJECT: Impaired fetal growth is an independent risk factor for cardiovascular diseases in adulthood and is associated with arterial wall thickening, a noninvasive measure of subclinical atherosclerosis, in early childhood. No preventive strategy has been identified.

WHAT THIS STUDY ADDS: Dietary omega-3 fatty acid supplementation in early childhood prevented the association of impaired fetal growth with arterial wall thickening, suggesting that this early-life intervention may mitigate the risk of cardiovascular disease in those with impaired fetal growth.

AUTHORS: Michael R. Skilton, PhD,[a] Julian G. Ayer, MBBS, PhD,[b] Jason A. Harmer, BSc,[b] Karen Webb, MPH, PhD,[c] Stephen R. Leeder, MD, PhD,[d] Guy B. Marks, MBBS, PhD,[e] and David S. Celermajer, MBBS, PhD[b]

[a]Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders, [b]Department of Medicine, and [d]Menzies Centre for Health Policy, University of Sydney, Sydney, Australia; [c]Atkins Center for Weight and Health, Department of Nutritional Sciences and Toxicology and School of Public Health, University of California, Berkeley, California; and [e]Woolcock Institute of Medical Research, Glebe, Australia

KEY WORDS

fetal growth, atherosclerosis, omega-3, dietary supplementation

ABBREVIATIONS

CAPS—Childhood Asthma Prevention Study
CI—confidence interval
DHA—docosahexaenoic acid
EPA—eicosapentaenoic acid
IMT—intima-media thickness

Drs Marks, Leeder, and Webb contributed to the design and conduct of the Childhood Asthma Prevention Study; Drs Celermajer, Marks, Ayer, and Mr Harmer designed and conducted the CardioCAPS substudy; Dr Skilton performed the statistical analysis; Drs Skilton and Celermajer wrote the article; and all authors read and approved the final manuscript.

This trial has been registered at www.anzctr.org.au (identifier ACTRN012605000042640).

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Address correspondence to Michael R. Skilton, PhD, Department of Cardiology, Royal Prince Alfred Hospital, Missenden Rd, Camperdown, NSW 2050, Australia. E-mail: michael.skilton@sydney.edu.au

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abstract

OBJECTIVES: Impaired fetal growth is an independent cardiovascular risk factor and is associated with arterial wall thickening in children. No preventive strategy has been identified. We sought to determine whether dietary omega-3 fatty acid supplementation during early childhood prevents the association between impaired fetal growth and carotid arterial wall thickening.

METHODS: The Childhood Asthma Prevention Study was a randomized, controlled single-blind trial in 616 children born at term, recruited antenatally from maternity hospitals in Sydney. Participants were randomized to either a 500-mg-daily fish oil supplement and canola-based margarines and cooking oil (omega-3 group), or a 500-mg-daily sunflower oil supplement and omega-6 fatty acid–rich margarines and cooking oil (control group), from the start of bottle-feeding or 6 months of age until 5 years of age. Carotid intima-media thickness (IMT), a noninvasive measure of subclinical atherosclerosis, was the primary endpoint of a cardiovascular substudy (CardioCAPS) at age 8 years. We examined the association of fetal growth with carotid IMT in children with birth weight <90th percentile (omega-3 group [n = 187], control group [n = 176]).

RESULTS: In the control group, fetal growth was inversely associated with carotid IMT, but this was prevented in the omega-3 group (difference between groups of 0.041 mm [95% confidence interval 0.006, 0.075] per kg birth weight, adjusted for gestational age and gender, $P_{heterogeneity}$ = .02).

CONCLUSIONS: The inverse association of fetal growth with arterial wall thickness in childhood can be prevented by dietary omega-3 fatty acid supplementation over the first 5 years of life. *Pediatrics* 2012;129:e698–e703

Impaired fetal growth is an independent risk factor for cardiovascular diseases in adulthood, such that each 1-kg lower birth weight translates to a 10% to 20% increase in risk of coronary artery disease.[1–3] Consistent with this observation, impaired fetal growth measured by birth weight has been shown to be associated with arterial intima-media thickness (IMT), a noninvasive measure of subclinical atherosclerosis, in adults,[4–6] but we have previously demonstrated that this can be detected as early as in the neonatal period.[7] It has been proposed that interventions implemented during early life, aimed at improving vascular health in those with impaired fetal growth, may be feasible and of clinical relevance.[8,9] Dietary omega-3 fatty acid supplementation may be one such early intervention.[8,10]

The Childhood Asthma Prevention Study (CAPS) was a randomized trial to determine whether the incidence of atopy and asthma could be reduced by dietary omega-3 fatty acid supplementation from age 6 months, or at onset of bottle-feeding, until 5 years of age.[11] A cardiovascular substudy, CardioCAPS, was undertaken at the 8-year visit to assess the effects of an omega-3 fatty acid–enriched diet and body size at birth and during early childhood on markers of vascular health and cardiovascular risk in childhood.[12,13] This article reports on whether dietary omega-3 fatty acid supplementation over the first 5 years of life prevents the previously reported associations of impaired fetal growth with early arterial wall thickening in childhood.

METHODS

Trial Design and Participants

CAPS was a randomized controlled trial of omega-3 fatty acid supplementation and house dust mite reduction (2 × 2 factorial design) for the prevention of asthma and atopy in children at risk for these conditions.[11,14] The study design and protocol, including recruitment methods, and inclusion criteria have been published.[11] Briefly, pregnant women whose unborn children had at least 1 parent or sibling with current asthma or wheezing were randomly assigned to 1 of 4 study groups. Exclusion criteria included babies from a multiple-birth pregnancy and those born before 36 weeks' gestation. Six hundred and sixteen subjects were enrolled from maternity hospitals in western and southwestern Sydney, Australia, between September 1997 and December 1999. The children were assessed at 18 months, 3 years, 5 years, and 8 years. Four hundred and five children without type 1 diabetes participated in CardioCAPS at 8 years. CardioCAPS participants had similar characteristics at baseline to those in the original CAPS trial, with the exception of higher maternal age and education,[12] and their anthropometric and cardiovascular risk characteristics were comparable to those of an unselected community-based population of a similar age from the same geographical area.[13,15] Those with macrosomia (birth weight ≥90th percentile [gender-specific]) were excluded prospectively from this analysis because they were known to be at increased risk of poor vascular health and cardiovascular disease.[16,17] Accordingly, 363 children (control group, n = 176; omega-3 group, n = 187; Table 1) were included in this analysis.

This study was approved by the human research ethics committees of the University of Sydney, the Children's Hospital at Westmead, and Sydney South West Area Health Service. The parent or legal guardian of each participating child provided written informed consent.

Randomization and Blinding

Women were randomized before 36 weeks' gestation by using sequentially numbered sealed envelopes. Block randomization was used, with block sizes of 4 for the first 100 participants and blocks of 12 thereafter. The project coordinator administered the randomization process, and those responsible for recruitment were kept blinded to the randomization methodology until recruitment was closed for the study.

Participants were blinded to the intervention group through the use of oil supplements supplied in capsules of identical appearance and placebo margarines and cooking oils.

Dietary Intervention and Compliance

Participants were randomized to receive diet interventions aimed at achieving a dietary omega-6:omega-3 polyunsaturated fatty acids ratio of 5:1 (omega-3 group) or maintaining a ratio similar to that of the general population (15:1–20:1; control group).[11] The diet interventions consisted of a daily 500-mg oil supplement, margarines, and cooking oil (Table 2).[11] The oil supplement was added to the babies' food from 6 months of age until 5 years of age and added to baby feeding formula before 6 months if formula fed.

TABLE 1 Baseline Demographic and Clinical Characteristics

	Omega-3 Group (n = 187)	Control Group (n = 176)
Maternal age (y)	29.2 (5.0)	29.7 (5.0)
Maternal parity (births)	1.1 (1.3)	1.1 (1.0)
Maternal smoking during pregnancy	44 (24%)	35 (20%)
Hypertension during pregnancy	10 (5%)	12 (7%)
Preeclampsia during pregnancy	5 (3%)	3 (2%)
Gender (male)	95 (51%)	92 (52%)
Gestation (wk)	39.4 (1.2)	39.5 (1.3)
Birth weight (kg)	3.44 (0.41)	3.36 (0.40)
IMT (mm)	0.59 (0.06)	0.59 (0.06)

Data are means (SD) or numbers (%).

TABLE 2 Dietary Supplement Intervention: Design and Adherence

	Omega-3 Group	Control Group
500-mg-daily oil supplement	Tuna fish oil: 37% omega-3; 6% omega-6	Sunflower oil: 0.3% omega-3; 7% omega-6
Margarines and cooking oil	Canola: 6% omega-3; 16% omega-6	High in omega-6 PUFA: 1.2% omega-3; 40% omega-6
Dietary omega-6:omega-3 PUFA ratio (design)	5:1	15:1–20:1
Age 18 mo (background diet measured by weighed food record [g/d])[a]		
Omega-3 PUFA	0.45 (0.31)	0.21 (0.25)[b]
Omega-6 PUFA	3.3 (2.7)	4.2 (3.0)[b]
Age 3 y (background diet measured by food frequency questionnaire [g/d])[a]		
Omega-3 PUFA	1.54 (0.78)	1.24 (0.55)[c]
Omega-6 PUFA	11.5 (5.3)	12.6 (5.5)
Plasma omega-6:omega-3 PUFA ratio		
18 mo	5.2:1 (1.9)	7.6:1 (2.3)[d]
3 y	5.8:1 (1.7)	7.9:1 (1.7)[d]
5 y	6.0:1 (1.6)	7.3:1 (1.5)[d]
8 y[e]	7.2:1 (1.7)	7.3:1 (1.7)
Average oil capsule compliance (%)[f]	54.0	57.5

PUFA, polyunsaturated fatty acids.

[a] Including supplied oils and spreads but not including supplements.

[b] $P < .05$ for comparison of dietary groups.

[c] $P < .001$ for comparison of dietary groups.

[d] $P < .0001$ for comparison of dietary groups.

[e] Postintervention period.

[f] Oil capsule compliance estimated at 6-monthly intervals as the difference in weight of the oil capsules dispensed and returned, divided by capsule weight, then divided by the number of days. Compliance was then averaged over the duration of the study.

Background dietary intake of omega-3 and omega-6 polyunsaturated fatty acids was assessed at 18 months and 3 years by weighed food records and semiquantitative food frequency questionnaire, respectively, as previously described.[18] Compliance to the oil capsule supplements was estimated at 6-monthly intervals based on the difference in weight between the capsules dispensed and those returned.[19] Plasma fatty acids were measured at 18 months, 3 years, 5 years, and 8 years of age, as a percentage of total fatty acids, and used as a measure of adherence to the entire dietary supplement intervention.[20]

Outcome: Carotid IMT

Carotid IMT was the primary outcome measure for CardioCAPS and was assessed by external B-mode ultrasound, as previously described.[13] Briefly, high-resolution longitudinal ultrasound scans of the common carotid arteries were obtained, and the IMT assessed 0 to 1 cm proximal to the carotid bulb. The mean of the IMT from the right and left carotid arteries was used in analysis. The sonographer and IMT reader were blinded to participants' study group.

Terminology

Birth weight is the most commonly used postnatal measure of fetal growth in epidemiologic analyses of the fetal origins hypothesis. Gender and gestation are nonpathologic determinants of birth weight. Accordingly, we have inferred alterations to fetal growth based on birth weight, adjusted for gender and gestational age.

Statistical Analysis

Differences between the two dietary groups were compared by Student's *t* test. Our primary analysis, to determine whether the association of fetal growth with arterial wall thickening was modified by an early-childhood dietary omega-3 fatty acid intervention, was a test of heterogeneity between control and omega-3 groups (by intention to treat) for the association of fetal growth (birth weight, adjusted for gender and gestational age) with carotid IMT derived from multivariable models.[21] A secondary analysis adjusted for age, parental education, breastfeeding at 6 months, maternal smoking during pregnancy, the other randomized treatment arm (house dust mite reduction), and incidence of atopy and/or asthma.

In addition multivariable models were constructed, adjusting for and examining the interaction with childhood BMI, to ascertain whether fetal growth is acting as a proxy for later body size.[22]

Statistical analysis was undertaken by using IBM SPSS Statistics (version 19.0; IBM Corp., Somers, NY). Statistical significance was inferred at $2P \leq .05$.

RESULTS

Participant baseline characteristics are shown in Table 1. The proportion of participants included in this analysis in each diet intervention group did not differ from the proportions for those originally randomized ($P = .51$ by χ^2 analysis). Table 2 shows background dietary intake, oil capsule compliance, and plasma fatty acids stratified by dietary group. The plasma fatty acid levels, used as a measure of adherence to the entire dietary supplement intervention, differed strongly between groups during the dietary intervention period.

Fetal growth was inversely associated with carotid IMT in the control group (Table 3, Fig 1). This significant association was not altered by adjustment for BMI at 8 years (−0.028 [95% confidence interval (CI) −0.054, −0.002] per kg birth weight, adjusted for gestational age and gender, $P = .04$). A birth weight × BMI at 8 years interaction term was not significant ($P_{interaction} = .18$).

In contrast, there was no significant association between fetal growth and carotid IMT in the omega-3 group, indeed, with some evidence for a positive

TABLE 3 Fetal Growth and Carotid IMT Stratified by Dietary Group

	IMT Change Per Unit Increase in Variable (95% CI)	*P*
Control group (*n* = 176)		
Gender (female)	−0.012 (−0.032, 0.008)	.24
Gestational age (wk)	0.008 (−0.000, 0.016)	.06
Birth weight (kg)	−0.027 (−0.052, −0.001)	.04
Omega-3 Group (*n* = 187)		
Gender (female)	−0.002 (−0.021, 0.016)	.82
Gestational age (wk)	0.000 (−0.007, 0.008)	.94
Birth weight (kg)	0.014 (−0.010, 0.038)	.24

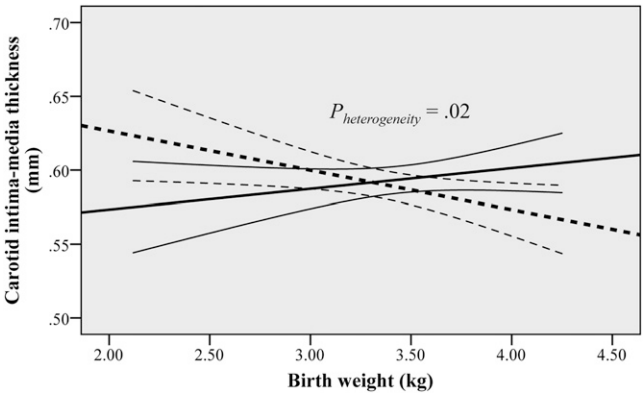

FIGURE 1
Dietary omega-3 fatty acid supplementation and the association of fetal growth with carotid IMT in childhood. Association of birth weight with carotid IMT, adjusted for gestational age and gender, in the control group (dashed line, *P* = .04) and in children who received early-life dietary omega-3 fatty acid supplementation (solid line, *P* = .24), derived by multivariable linear regression modeling. Data presented as regression coefficient and 95% CI.

rather than negative association (Table 3, Fig 1). Furthermore, the association of fetal growth with carotid IMT differed significantly between the two groups (difference between groups of 0.041 mm [95% CI 0.006, 0.075] per kg birth weight, adjusted for gestational age and gender, $P_{heterogeneity}$ = .02). This was the prespecified primary analysis for this examination of fetal growth and the effects of postnatal dietary omega-3 fatty acid supplementation on carotid IMT. Results were similar in a secondary model adjusting for age, parental education, breastfeeding at 6 months, maternal smoking during pregnancy, the other randomized treatment arm, and asthma and/or atopy at 8 years (control group, −0.025 [95% CI −0.050, 0.001], *P* = .06; omega-3 group, 0.014 [95% CI −0.011, 0.040], *P* = .28; difference between groups of 0.039 mm [95% CI 0.003, 0.074] per kg birth weight, adjusted for gestational age and gender, $P_{heterogeneity}$ = .03).

DISCUSSION

A large body of consistent long-term epidemiologic data has linked impaired fetal growth with significant atherosclerotic cardiovascular risk in adult life.[1,3,23–26] Postnatal interventions that might prevent the association of impaired fetal growth with cardiovascular risk markers in humans, however, have not been previously described. We found that dietary omega-3 fatty acid supplementation over the first 5 years of life can prevent the association of impaired fetal growth with early arterial wall thickening during childhood.

We used carotid IMT, considered the best noninvasive measure of atherosclerosis in adults and the best measure of arterial structure in the pediatric population,[27] as a measure of vascular health. Carotid IMT is closely associated with major cardiovascular risk factors in childhood, including diabetes, hyperlipidemia, and obesity.[27] Carotid IMT tracks well over time[28] and is independently associated with incident cardiovascular events in adults.[29] The use of a surrogate measure of cardiovascular disease is necessitated by the long time period between the early-life intervention and the typical age of onset of cardiovascular events many decades later. For birth weights below the point of intersection, the observed effect on carotid IMT is consistent with the omega-3 intervention resulting potentially in a 5% to 7% reduction in risk of future myocardial infarction and a 6% to 8% reduction in risk of future stroke, per kilogram decrease in birth weight (adjusted for gestational age and gender).[29]

Importantly, the early omega-3 fatty acid supplementation did not improve vascular health per se, but rather mitigated the inverse association of fetal growth with arterial wall thickening. Impaired fetal growth results in reductions in serum docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA),[30] possibly via reduced activity of $\Delta 5$ desaturase.[31] The omega-3 fatty acid supplement used in this study was rich in DHA and EPA and resulted in a significant reduction in plasma and dietary omega-6:omega-3 fatty acid ratios, the latter being consistent with increased biosynthesis of DHA and EPA via reduced enzymatic competition with omega-6 fatty acids. Thus, regarding potential mechanisms for the beneficial arterial effect observed, the intervention used in this study could mitigate the adverse effects of reduced $\Delta 5$ desaturase activity. Furthermore, dietary DHA and EPA supplementation appears to have cardioprotective effect in adults,[32] potentially via effects on lipid levels, blood pressure, endothelial function,

and/or antiarrhythmic and antiinflammatory actions,[33,34] and dietary intake of omega-3 fatty acids and supplemental intakes at physiologic doses are generally considered to be safe.[35] Accordingly, a postnatal prevention strategy consisting of dietary omega-3 fatty acid supplementation may be of benefit in reducing the cardiovascular disease burden in individuals with impaired fetal growth.

Studies of the effects of dietary supplementation in pregnant mothers and children living in areas with prevalent maternal and childhood undernutrition on markers of cardiovascular risk assessed later in childhood, adolescence, or adulthood have mostly shown improvements in later blood pressure and measures of metabolic health.[36–39] One maternal and early-childhood caloric supplementation trial examined the central augmentation index in adolescents, as a measure of arterial stiffness, and found improvements in those in the intervention group.[36] However, the algorithms that underlie this marker of vascular health were developed and validated in adults and have not been validated in children.[27] None of these studies have detailed whether there was evidence of heterogeneity between the intervention and control groups for the association of fetal growth with any measure of vascular health or cardiovascular risk.

The benefits of dietary intervention during pregnancy or early childhood are likely to be most pronounced in those with impaired fetal growth, as opposed to those individuals without any putative cardiovascular risk factors. Whereas some degree of impaired fetal growth may be highly prevalent in populations with widespread maternal undernutrition, for those living in developed nations, impaired fetal growth is primarily due to placental insufficiency. In these individuals, prevention strategies specifically targeting those with impaired fetal growth may thus be of greater benefit than population-wide maternal dietary supplementation.

Strengths of this study include the randomized trial design, long-term follow-up into childhood, and documented adherence to the dietary supplement. Although not a prespecified aim of the CAPS study, CardioCAPS was a hypothesis-driven substudy related to our previous findings.[7] Whereas only children considered at risk for developing asthma were recruited, related to the primary outcome of the CAPS study,[11] we have shown that the characteristics of the children in CardioCAPS, including height, weight, blood pressure, and cholesterol, are comparable to an unselected community-based population of a similar age from the same geographical area.[13,15] Furthermore, apart from maternal age and education being higher, CardioCAPS participants had similar characteristics at baseline to those in the original CAPS trial.[12] Accordingly, we believe that the randomization principles hold and that it is unlikely that our findings are due to selection bias. Nevertheless, given this potential limitation, we conducted a secondary analysis adjusting for other variables that may have influenced the observed association, including maternal smoking, parental education, and breastfeeding, in which the observed beneficial effects of the omega-3 intervention in those with impaired fetal growth remained.

Despite the relatively low compliance to the oil capsules, the difference in plasma fatty acid ratios was highly significant between dietary groups at all time points during the intervention period. The true benefits of dietary omega-3 supplementation in those with impaired fetal growth may be greater in highly compliant subjects than that indicated by our results.

In conclusion, we have found that the inverse association between fetal growth and carotid IMT, an early marker of atherosclerosis, can be prevented by dietary omega-3 fatty acid supplementation during early childhood. Further studies might assess whether this intervention reduces the incidence of cardiovascular disease in adulthood in those with impaired fetal growth.

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