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The Association of Dietary Alpha-Linolenic Acid with Blood Pressure and Subclinical Atherosclerosis in People Born Small for Gestational Age: The Special Turku Coronary Risk Factor Intervention Project Study

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Objective To determine whether dietary alpha-linolenic (omega-3) fatty acid intake is associated with lower blood pressure and aortic intima-media thickness (IMT) in people born small for gestational age (SGA).

Study design Participants were recruited at age 6 months and followed up every 6-12 months until age 19 years. Blood pressure and food records were assessed at each visit. A total of 1009 participants had at least one blood pressure measure and complete birth weight and gestational age data, including 115 (11%) born SGA (birth weight ≤10th percentile). Aortic IMT was assessed by ultrasound at 19 years (n = 413). Analysis was by linear mixed models and multivariable linear regression.

Results Children born SGA had greater systolic and pulse pressure from age 14 years onwards. In those born SGA, systolic blood pressure was 2.1 mm Hg lower ([95% CI 0.8-3.3]; *P* = .001) and pulse pressure 1.4 mm Hg lower ([95% CI 0.3-2.4]; *P* = .01), per exponential increase in alpha-linolenic acid (ALA) intake; weakened by adjustment for anthropometric measures. Long-term ALA intake was inversely associated with aortic IMT at 19 years in those born SGA (−0.30 mm [95% CI −0.52, −0.08] per exponential greater ALA intake; *P* = .008), independent of other dietary and anthropometric factors.

Conclusion Long-term dietary ALA intake during childhood is associated with improved vascular health in people born SGA. *(J Pediatr 2015;166:1252-7)*.

People born small for gestational age (SGA) have an increased risk of adult cardiovascular disease,[1] preceded by a poor cardiovascular risk profile characterized by increased blood pressure and increased arterial intima-media thickness (IMT),[2-4] a marker of subclinical atherosclerosis that is an independent predictor of cardiovascular events.[5]

Currently, there is no widely accepted prevention strategy to reduce cardiovascular risk in people born SGA. Previous evidence suggests that dietary omega-3 fatty acids may improve cardiovascular risk profile specifically in people born SGA.[6-8] Analyses have thus far been restricted to cross-sectional examinations of dietary intake, have not specifically detailed the contribution of plant-derived omega-3 fatty acids, and have focused solely on blood pressure and subclinical atherosclerosis.

Accordingly, we sought to describe the blood pressure from infancy through late adolescence in people born SGA and those with normal birth weight. We then determined whether dietary intake of alpha-linolenic acid (ALA), a predominantly plant-derived omega-3 fatty acid, is associated with lower blood pressure throughout childhood and adolescence, and whether the average intake of ALA during this period is associated with reduced aortic IMT in late adolescence, with a particular focus on those born SGA. We also sought to determine whether similar associations exist between omega-3 fatty acids and other cardiometabolic risk markers in people born SGA.

ALA	Alpha-linolenic acid
BMI	Body mass index
HDL-c	High-density lipoprotein cholesterol
hs-CRP	High-sensitivity C-reactive protein
IMT	Intima-media thickness
PP	Pulse pressure
SBP	Systolic blood pressure
SGA	Small for gestational age
STRIP	Special Turku Coronary Risk Factor Intervention Project

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Methods

Participants in the Special Turku Coronary Risk Factor Intervention Project (STRIP) were recruited at age 5 months of age from the well-baby clinics in Turku, Finland, between February 1990 and June 1992. At 7 months of age, 1062 children were randomized to an intervention group (n = 540) or a control group (n = 522). The intervention group consisted of individualized dietary and lifestyle counseling throughout childhood and adolescence that aimed to reduce environmental risk factors for atherosclerosis.[9] The dietary counseling included, among other things, the addition of 2 or 3 teaspoons of soft margarine or vegetable oil, mainly rapeseed oil, to the child's food from 12 to 24 months of age. In the following years, replacement of saturated fat with unsaturated fat in the child's diet was the main aim of the dietary counseling. Participants attended follow-up study visits every 6-12 months until 19 years of age.

The STRIP study was approved by the joint commission on ethics of the Turku University and the Turku University Central Hospital. Procedures followed were in accordance with the ethical standards of the institutional ethics committee. Written informed consent was obtained from the parents at the beginning of the study and from the adolescents at 15 years of age.

Birth weight and gestational age were recorded from clinical records of the well-baby clinics. Birth weight percentiles based on all participants with valid data in the STRIP study were calculated as previously described,[10-12] and SGA was defined as birth weight ≤10th percentile for gestational age and sex.

A 4-day consecutive food record (3-day food record before 2 years of age) was used to assess dietary intake of ALA, total dietary energy, fiber, sodium, and saturated fatty acids before each study visit, as previously described.[9,13,14] Food records were reviewed for completeness and accuracy by a nutritionist during each study visit. Nutrient intakes were calculated using Micro Nutrica software (Turku, Finland), based on the Food and Nutrient Database of the Social Insurance Institution.[15] The program calculates 66 nutrients of commonly used foods and dishes and permits continuous updating of new single or composite foods.

Weight and height were measured at each visit, to the nearest 0.1 kg and 0.1 cm, respectively. Height was measured as recumbent length until age 2 years, and standing height thereafter. Body mass index (BMI) was calculated as weight/height.[2]

A fasting venous blood sample was drawn at each visit, and concentrations of serum total and high-density lipoprotein cholesterol (HDL-c), triglycerides, and glucose were determined.[14] Low-density lipoprotein cholesterol concentration was calculated with the Friedewald equation.[16] High-sensitivity C-reactive protein (hs-CRP) was assayed by a high-sensitivity turbidimetric immunoassay from samples collected at ages 11, 13, 15, 17, 18, and 19 years; insulin was assayed and homeostatic model assessment of insulin resistance calculated in a subset of participants at ages 7, 9, 11, and 13 years and in all participants annually from 15 to 19 years of age.

Sitting blood pressure was assessed after resting for at least 15 minutes at each study visit with an oscillometric noninvasive blood pressure monitor (Critikon Dinamap 1846 SX until 2001, thereafter Critikon Dinamap Compact T; Critikon, Tampa, Florida), and an appropriate-sized cuff. Blood pressure was measured once at each visit in children aged 7 years and younger, 2-4 times from 8 to 9 years of age, and twice at each visit from then on. The average from each visit was used for analysis.

Aortic and carotid IMT were assessed by noninvasive high-resolution ultrasound when the subject was at 19 years of age by the use of highly reproducible standardized techniques as previously described and used in our laboratory.[17,18]

Statistical Analyses

Systolic blood pressure (SBP) and pulse pressure (PP) were our predefined hemodynamic outcome variables given: (1) their importance to long-term cardiovascular health outcomes;[19-21] and (2) our previous evidence that these may be altered by omega-3 intake in people born SGA.[6,8] Aortic IMT was our predefined structural outcome measure, because it appears to be the most sensitive marker of early vascular risk in children and adolescents.[17,22]

Of those randomized, 1009 had complete birth weight and gestational age data and at least one blood pressure measure. From 7 months to 19 years of age, participants attended an average of 20 study visits at 6- to 12-month intervals, during which blood pressure was measured on average 19 times and dietary ALA intake assessed on average 17 times.

Data for birth weight, gestational age, and carotid or aortic IMT at age 19 years was available for 413 participants, with 403 having complete data for aortic IMT and modeled covariates.

ALA intake was modeled as grams per day in the energy-adjusted mixed models. Results were similar if ALA was formulated as a percentage of energy intake (results not shown). The life-time average ALA intake was calculated from all available measures taken from age 8 months to 19 years, expressed as a percentage of dietary energy intake to avoid potential bias caused by greater absolute consumption of ALA with age. Measures of ALA, triglycerides, insulin, and hs-CRP were log transformed for analysis. The residuals of weight on height were used as a measure of adiposity, independent of height.

Separate linear mixed models were used to determine the associations of SGA and ALA intake, with blood pressure and cardiometabolic risk factors, from 8 months to 19 years of age. Multivariable linear regression was used to determine the association of the average childhood ALA intake with IMT at age 19 years. Both mixed models and multivariable linear regression analyses were adjusted for sex, maternal and paternal age, and STRIP study randomization group. Additional models detailing associations of SGA with blood pressure and arterial IMT were further adjusted for height