



Success in Achieving the Targets of the 20-Year Infancy-Onset Dietary Intervention: Association With Insulin Sensitivity and Serum Lipids

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OBJECTIVE

We examined whether success in achieving the key targets of an infancy-onset 20-year dietary intervention associated with insulin sensitivity and serum lipids from early childhood to young adulthood.

RESEARCH DESIGN AND METHODS

The sample comprised 941 children participating in the prospective, randomized Special Turku Coronary Risk Factor Intervention Project (STRIP). Dietary counseling was given biannually based on the Nordic Nutrition Recommendations with the main aim to improve the quality of dietary fat in children's diets and the secondary aim to promote intake of vegetables, fruits, and whole-grain products. Food records and serum lipid profile were studied annually from 1 to 20 years of age, and HOMA of insulin resistance (HOMA-IR) was assessed between 7 and 20 years of age. Meeting the intervention targets for quality of dietary fat was defined as the ratio of saturated fatty acids (SAFA) to monounsaturated and polyunsaturated fatty acids (MUFA + PUFA) <1:2 and intake of SAFA <10% of total energy intake (E%). Meeting the target for intake of whole-grain products, fruits, and vegetables was indicated by a fiber intake ≥ 3 g/MJ.

RESULTS

Participants in the intervention group had a higher probability of meeting the targets of SAFA/(PUFA + MUFA) <1:2 (risk ratio [RR] 3.91 [95% CI 3.33–4.61]), intake of SAFA <10 E% (RR 3.33 [95% CI 2.99–3.96]), and intake of fiber >3 g/MJ (RR 1.37 [95% CI 1.04–1.80]). Participants who achieved more targets had lower HOMA-IR, lower concentrations of fasting serum glucose, insulin, LDL cholesterol, and non-HDL cholesterol, and a lower ratio of apolipoprotein (Apo) B/ApoA1 (*P* values all ≤ 0.003).

CONCLUSIONS

Achieving the key targets of an infancy-onset 20-year dietary intervention was associated with better insulin sensitivity and serum lipid profile throughout the early life course.

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Dietary composition influences cardio-metabolic diseases such as type 2 diabetes, coronary heart disease, and stroke that together pose substantial health and economic burdens (1). Universally, dietary guidelines emphasize consumption of unsaturated fats and limiting saturated fat and cholesterol intake. In addition, increased consumption of fruits, vegetables, whole grains, and dietary fiber and avoidance of added sugar is encouraged (2,3).

The Special Turku Coronary Risk Factor Intervention Project (STRIP) study is a globally unique human experiment that has conducted a 20-year controlled dietary intervention from infancy to adulthood (4). The personalized dietary counseling was based on Nordic Nutrition Recommendations with the main aim of improving the quality of dietary fat (2). In addition, the counseling promoted intake of vegetables, fruits, and whole-grain products. In our previous reports, we have shown that the repeated dietary counseling provided in STRIP resulted in a number of phenotypic changes among intervention children in line with a reduced risk of atherosclerotic diseases and diabetes (5–11). However, it is not been identified how well study participants met the key intervention targets that reflected the dietary guidelines. Importantly, it has not been explored how meeting these targets associates with markers of cardiometabolic risk.

In order to determine the achievability of the key targets of the infancy-onset dietary intervention, we rank the STRIP study participants according to their success in achieving the main target of the dietary intervention based on quality of dietary fat and the intake of fiber reflecting consumption of whole-grain products, vegetables, and fruit. We then examine the association of achieving these targets, and additionally a low intake of sucrose, on insulin sensitivity and serum lipids from childhood to early adulthood.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The STRIP study, a prospective, randomized, controlled trial to prevent atherosclerosis beginning in infancy, recruited families with 5-month-old infants at well-baby clinics in Turku, Finland from 1990 to 1992 (4). At the age of 7 months, 1,062 infants (56.5% of the eligible age

cohort) were randomly allocated to dietary intervention ($n = 540$) or control ($n = 522$) groups (Supplementary Fig. 1).

The intervention group received individualized dietary counseling at least biannually beginning at 8 months of age until 20 years of age (4,9). The main aim of the intervention has been to replace saturated fat with unsaturated fat. Reduction in total fat intake was not targeted. Breastfeeding or formula was advised during the first year of life. After 12 months of age, 0.5–0.6 L/day of skim milk was recommended. To maintain adequate fat intake, the parents were instructed to add daily two to three teaspoons (10 g) of soft margarine or vegetable oil to the child's food from 12 to 24 months of age. The counseling also promoted the intake of vegetables, fruits, and whole-grain products. In the early years of the intervention, low intake of cholesterol was also discussed with families. The counseling was provided to the parents until the child was 7 years old. After that, more information was gradually given directly to the child. A fixed diet was never ordered; the counseling was individualized, and the child's recent food record was used as a basis of dietary suggestions. The dietary recommendations were based on Nordic Nutrition Recommendations available at the time.

The control group was seen biannually until 7 years of age and annually thereafter until 20 years of age (4). Similar measurements were performed for both study groups, and they met the same study personnel. Children in the control group received only the basic health education given at Finnish well-baby clinics and school health care.

The STRIP study is conducted according to the guidelines of the Declaration of Helsinki, and the study protocol is approved by the local ethics committee. Written informed consent was obtained from parents and from the children at 15 and 18 years of age. The current study comprised participants who provided dietary data between 1 ($N = 941$; 95.6% of those participating in the study visit) and 20 years of age ($N = 300$; 68.5% of those participating in the study visit).

Assessment of Dietary Intake

Food consumption was recorded using a 4-day food record (consecutive days; at

least one weekend day included) (12). A dietitian checked the food records for accuracy, and the food and nutrient intakes were analyzed with a continuously updated Micro-Nutrica program (13).

Targets of the Dietary Intervention and the Success Score

According to the nutritional targets of the dietary intervention given in the study, reflecting dietary guidelines, the targeted quality of dietary fat was defined in the current study as two separate targets: the ratio of saturated fatty acids (SAFA) to monounsaturated and polyunsaturated fatty acids (MUFA + PUFA) $<1:2$ and as the intake of SAFA $<10\%$ of total energy intake (E%). Intake of fiber was chosen to indicate the success of achieving the other key intervention target, favoring whole-grain products, and consumption of fruits and vegetables. The targeted intake of dietary fiber was defined in two ways: 1) ≥ 3 g/MJ (2,3) or 2) being at the top age-specific quintile (≥ 80 th age-specific percentile). In the absence of a consensus recommendation on sucrose intake, we used the lowest age-specific quintile (<20 th age-specific percentile) as the definition of desired sucrose intake in this study. Participants were given one point for meeting each of the four targets: SAFA/(MUFA + PUFA) $<1:2$, SAFA <10 E%, dietary fiber ≥ 80 th age-specific percentile, and sucrose ≤ 20 th age-specific percentile. The range of the score was 0–4 points. Because of the low prevalence of participants meeting all four targets, participants meeting three or four targets were combined for the analyses.

Sensitivity Analyses

The current Nordic Nutrition Recommendation does not set an upper intake level for dietary cholesterol (2). However, low dietary cholesterol was one of the targets of the intervention when the study was launched in 1990 (5). In sensitivity analyses of the current study, we used an additional target of dietary cholesterol <300 mg/day, as recommended in the Dietary Guidelines for Americans in 2010 (14). In the sensitivity analyses, we also used the cutoff point of sucrose <10 E%, mirroring the recommendation for added sugar intake (14).

Anthropometric Measurements

Weight was measured to the nearest 0.1 kg with an electronic scale (S10; Soehnle, Murrhardt, Germany) and height to the nearest 0.1 cm with a Harpenden stadiometer (Holtain, Crymmych, U.K.). BMI was calculated as weight in kilograms divided by height in meters squared.

Laboratory Methods

The blood samples drawn before 5 years of age were nonfasting. From 5 years of age, fasting blood samples were drawn. Serum total cholesterol and triglyceride concentrations were analyzed using a fully enzymatic cholesterol oxidase-p-aminophenazone method (Merck, Darmstadt, Germany) with an automatic Olympus AU400 analyzer (8). Serum HDL cholesterol concentration was measured after precipitation of LDL and very LDL with dextran sulfate 500,000 (8). Non-HDL cholesterol was calculated as total cholesterol – HDL cholesterol concentration. The Friedewald formula was used to calculate the LDL cholesterol concentrations (15). None of the participants had triglycerides >4.52 mmol/L (>400 mg/dL). Apolipoprotein (Apo) A1 and ApoB were determined immunoturbidimetrically (Orion Diagnostica, Espoo, Finland). At 7 years of age, a time-restricted subsample of 200 children equally from both the intervention and control groups was chosen for more detailed laboratory measurements, including determination of serum glucose and insulin concentrations. This cohort comprised those consecutive children who came to their 7-year annual STRIP visit between January 1997 and November 1997. Selection bias did not occur (16). From 15 years of age onwards, annual glucose and insulin concentrations were obtained from all participants. Serum glucose was measured by the glucose dehydrogenase method (Merck Diagnostica) between 7 and 13 years of age and by a hexokinase method (Glucose Olympus System Reagent; Olympus, Ireland) from 15 years of age onwards (10,16). Serum insulin was measured with a microparticle enzyme immunoassay (Insulin IMX system reagent; Abbott, Chicago, IL), or chemiluminescent microparticle immunoassay (ARCHITECT insulin assay; Abbott) between 7 and 13 years of age (16). From 15 years of age onwards, serum insulin was measured by radioimmunoassay (Pharmacia Diagnostics, Uppsala,

Sweden) (10). To correct for differences in analytical level between the methods, a correlation equation obtained by standardized principal component analysis of results of samples analyzed with both methods was used. To estimate insulin resistance, HOMA-IR (fasting insulin mU/mL \times [fasting glucose (mmol/L)/22.5]) was calculated (17).

Statistical Analyses

HOMA-IR, serum insulin, and triglyceride values were log-transformed for the analyses due to right-skewed distributions. Participants with fasting glucose >7 mmol/L (126 mg/dL) and/or fasting insulin >100 mU/L were excluded from analyses concerning fasting glucose, insulin, and HOMA-IR. Differences between participants who had and had not provided dietary data at 20 years of age were examined using the Student *t* test for continuous variables and χ^2 test for categorical variables. Association of the STRIP study group (intervention/control) with the probability of meeting the dietary targets was studied with a modified Poisson regression model with generalized estimating equation for repeated measures (risk ratios calculated for STRIP intervention vs. control group, adjusted for age and sex). Association of the STRIP study group with the score and association of the score with risk factor levels were studied with a linear mixed-effects model for repeated measures using compound symmetry covariance structure. All models included age and sex as covariates. In the repeated measurements model, the compound symmetric covariance structure for each individual was specified. The decision was based on the variance-covariance and correlation matrices, which indicated that correlation was not dependent on the value of lag and that observations from same individual had homogeneous variance and covariance. Sex \times score interactions were studied to investigate if the associations with risk factor levels were similar in males and females. In the case of significant sex interactions, sex-stratified analyses were conducted. Statistical significance was inferred at a two-tailed *P* value <0.05. The statistical analyses were performed with SAS version 9.4.

RESULTS

Characteristics of the study participants are shown in Supplementary Table 1.

Comparisons between participants who provided dietary data and those who did not at 20 years of age are shown in Supplementary Table 2. Males reported dietary data less often than females, and males with dietary data had lower BMIs than males who did not provide dietary data.

Intervention Effect

Participants in the intervention group had a higher probability of meeting the targets of SAFA/(PUFA + MUFA) <1:2, intake of SAFA <10 E%, and intake of dietary fiber >3 g/MJ between 1 and 20 years of age (Fig. 1). The mean proportion of participants who succeeded in achieving an individual dietary target between 1 and 20 years of age in the intervention and control groups was 19.9% vs. 5.0% for SAFA/(PUFA + MUFA) <1:2, 31.8% vs. 9.8% for SAFA <10 E%, and 5.4% vs. 4.0% for dietary fiber >3 g/MJ. Participants in the intervention group also had a higher probability of meeting the additional targets of dietary fiber \geq 80th age-specific percentile, intake of sucrose \leq 20th age-specific percentile, and intake of dietary cholesterol <300 mg/day (Supplementary Fig. 2).

Because of the low proportion of participants meeting the target of dietary fiber \geq 3 g/MJ, we used the criterion of \geq 80th age-specific percentile to define the targeted dietary fiber in the score. Participants were given one point for meeting each of the four targets: SAFA/(MUFA + PUFA) <1:2, SAFA <10 E%, dietary fiber \geq 80th age-specific percentile, and sucrose \leq 20th age-specific percentile. Furthermore, the intervention group had higher score levels (*P* < 0.001, adjusted for age and sex, data not shown).

Association of the Score With BMI, Insulin Sensitivity, and Lipids

The score indicating achievement of the dietary targets was not associated with BMI (Supplementary Fig. 3). As shown in Fig. 2, meeting a higher number of dietary targets was associated with lower concentrations of fasting serum glucose and insulin and lower HOMA-IR. In Table 1, these data are summarized by giving the age- and sex-adjusted means across the entire follow-up. Furthermore, participants with a higher score had, on average, lower concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, and

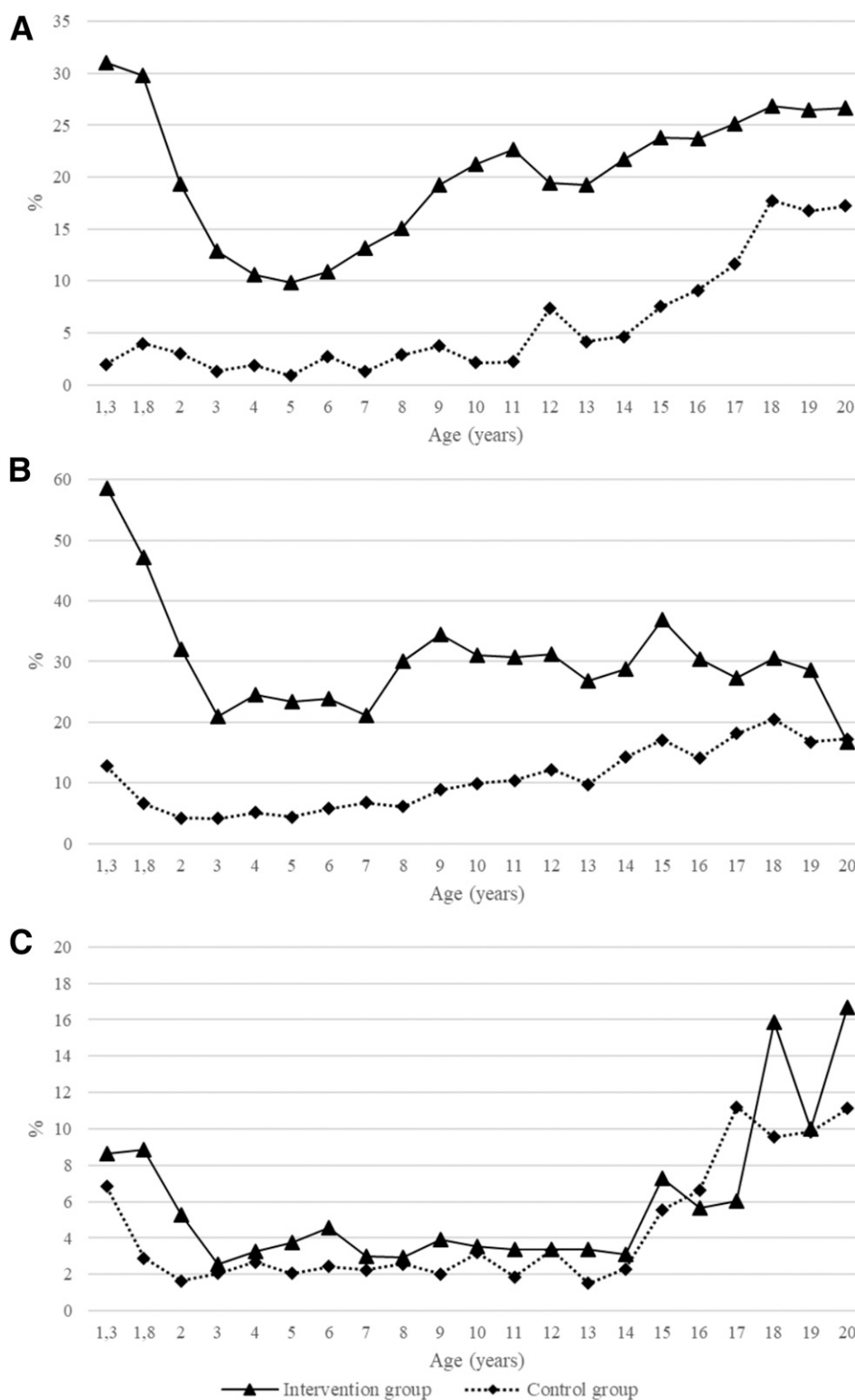


Figure 1—Proportions (%) of participants meeting the dietary target ratios of SAFA to MUFA + PUFA <1:2 (A), intake of saturated fat <10% of total energy (B), and intake of dietary fiber >3 g/MJ (C) in the intervention (solid line) and control (dashed line) groups. Risk ratio indicating the probability of meeting the dietary target in the intervention group in comparison with the control group was 3.91 (95% CI 3.33–4.61; P for difference <0.0001) for ratio of SAFA to MUFA + PUFA <1:2, 3.44 (95% CI 2.99–3.96; P for difference <0.0001) for intake of saturated fat <10% of total energy, and 1.37 (95% CI 1.04–1.80; P for difference 0.03) for intake of dietary fiber >3 g/MJ. P for difference calculated for meeting the dietary targets in the intervention and control groups on average across all of the data points.

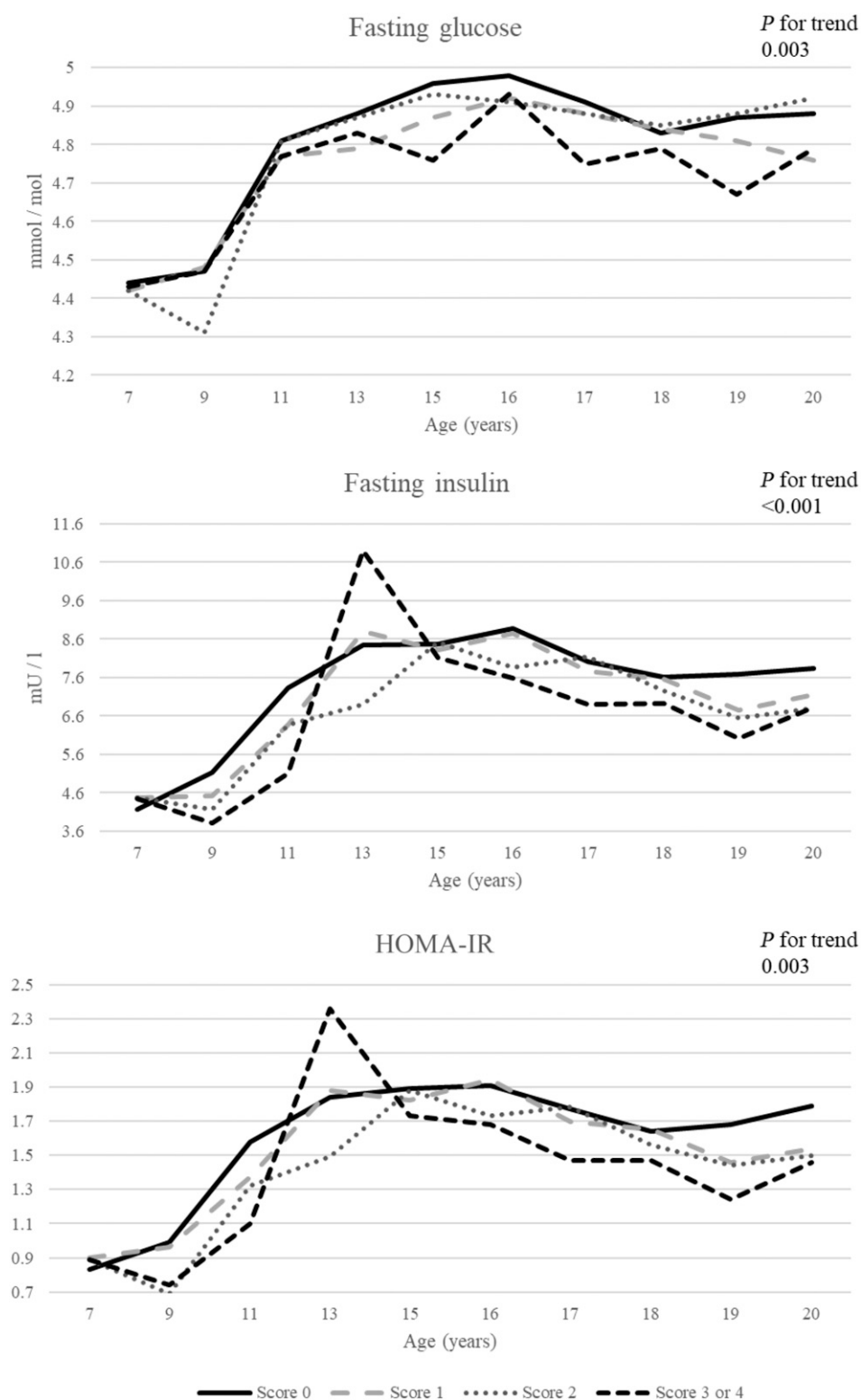


Figure 2—Mean levels of fasting glucose, fasting insulin, and HOMA-IR according to the dietary target score from childhood (7 years) to early adulthood (20 years) in all participants of the STRIP study.

non-HDL cholesterol and lower ApoB/ApoA1 ratio (Fig. 3 and Table 1).

The association of the score with total cholesterol, non-HDL cholesterol, and ApoB/ApoA1 ratio was different between

sexes (sex \times score interaction: $P < 0.10$). In separate analyses, the score was associated with total cholesterol, LDL cholesterol, and non-HDL cholesterol in both sexes, but the association became

nonsignificant in both males and females for ApoB/ApoA1 ratio (Supplementary Table 3).

In sensitivity analyses, a target for dietary cholesterol <300 mg/day was

STRIP study

	Score															
	0				1				2				3			
	Adjusted mean#	SE	95% CI	Adjusted mean#	SE	95% CI	Adjusted mean#	SE	95% CI	Adjusted mean#	SE	95% CI	P for trend			
Fasting glucose (mmol/L)	4.80	0.01	4.78-4.83	4.76	0.01	4.73-4.79	4.79	0.02	4.75-4.82	4.74	0.03	4.69-4.79	0.003			
Fasting insulin (mU/L)	7.16	0.12	6.92-7.40	7.00	0.14	6.72-7.28	6.83	0.18	6.47-7.20	6.47	0.27	5.95-6.99	<0.001*			
HOMA-IR	1.53	0.03	1.48-1.59	1.52	0.03	1.45-1.58	1.47	0.05	1.38-1.56	1.39	0.06	1.27-1.52	0.003*			
Total cholesterol (mmol/L)	4.35	0.02	4.31-4.39	4.31	0.02	4.27-4.35	4.26	0.02	4.22-4.31	4.21	0.03	4.15-4.26	<0.0001			
LDL cholesterol (mmol/L)	2.68	0.02	2.64-2.72	2.65	0.02	2.61-2.69	2.63	0.02	2.59-2.68	2.60	0.03	2.54-2.66	<0.0001			
HDL cholesterol (mmol/L)	1.22	0.01	1.21-1.23	1.21	0.01	1.19-1.22	1.21	0.01	1.20-1.23	1.18	0.01	1.17-1.20	0.0002			
Non-HDL cholesterol (mmol/L)	3.13	0.02	3.09-3.17	3.10	0.02	3.06-3.14	3.05	0.02	3.01-3.09	3.02	0.02	2.97-3.08	<0.0001			
Triglycerides (mmol/L)	0.84	0.01	0.82-0.86	0.85	0.01	0.83-0.88	0.83	0.02	0.81-0.86	0.84	0.02	0.80-0.88	0.64*			
ApoB/ApoA1 ratio	0.60	0.01	0.59-0.61	0.60	0.01	0.60-0.61	0.59	0.01	0.58-0.60	0.60	0.01	0.59-0.61	0.03			

#Age- and sex-adjusted. *Log-transformed.

added to the score in order to reflect the dietary counseling given in the early years of the study. Results remained essentially similar (data not shown). Furthermore, when sucrose <10 E% was used as the definition of desired sucrose intake instead of the lowest age-specific quintile, the results were similar with the exception of fasting glucose and ApoB/ApoA1 ratio, which became nonsignificant ($P = 0.20$ for both; data not shown). In addition, the results remained essentially unchanged when the analyses were adjusted for total energy intake (data not shown). Finally, the association of the score on total cholesterol, LDL cholesterol, non-HDL cholesterol, triglycerides, and ApoB/ApoA1 ratio was essentially similar when the analyses were additionally adjusted for total fat intake. Association of the score and serum HDL cholesterol became marginally nonsignificant after adjusting for total fat intake (Supplementary Table 4).

CONCLUSIONS

This study is the first to report on the success of achieving key dietary aims since infancy and to report the association of achieving the targets on insulin sensitivity and serum lipids. We showed that participants in the intervention group had a higher probability of achieving the key dietary targets between 1 and 20 years of age compared with their peers in the control group. Importantly, we also observed that participants who achieved more dietary targets had better insulin sensitivity and a more favorable serum lipid profile from childhood to early adulthood. These data are unique due to the exceptional dietary data meticulously collected since infancy, the 20-year dietary intervention, and the concurrent assessment of cardiometabolic risk factors. The reported findings are important because hyperglycemia and insulin resistance have been shown to associate with incident type 2 diabetes and the development of atherosclerosis and its complications (18). In addition, meeting the criteria for metabolic syndrome in childhood is independently associated with increased future risk of type 2 diabetes (19).

In STRIP, the main aim of dietary counseling was to improve the quality of dietary fat in children's diets. In this study, we observed that participants in the intervention group had a higher



Our results are in line with the previous observations from the Finnish Diabetes Prevention Study (DPS). In the DPS, individuals in the lifestyle intervention group were more likely to achieve the main goals: weight reduction $>5\%$, fat intake $<30\%$, SFA intake $<10\%$, fiber intake $\geq 15\text{ g}/1,000\text{ kcal}$, and exercise $>4\text{ h}/\text{week}$ after 1 year, with the reduction in the incidence of diabetes directly associated with the number of achieved intervention targets (23). However, in the DPS, participants were middle-aged and overweight with impaired

glucose tolerance, whereas our sample comprised apparently healthy children and adolescents participating in an infancy-onset 20-year intervention. In addition, the intervention targets and outcome measures were different compared with the DPS.

Previously, we have reported a favorable effect of the dietary counseling in STRIP on mean dietary SAFA intake and serum LDL cholesterol concentration through childhood and adolescence (8) and that the intervention group had enhanced insulin sensitivity at 9 years of age (16) and in adolescence (10). Similarly, the Dietary Intervention Study in Children (DISC), a shorter-term intervention study examining hypercholesterolemic school-aged children in the U.S., reported that the dietary intervention led to modest lowering of LDL cholesterol levels over 3 years (24). There are several plausible mechanisms that may underlie the dietary effects of such interventions. The modification of dietary fat intake influences serum LDL cholesterol levels through regulation of several transcription factors, including LDL-receptor activity and expression (25). The association of the target score on total cholesterol, LDL cholesterol, non-HDL cholesterol, triglycerides, and ApoB/ApoA1 ratio was essentially similar when total fat intake was included in the analyses, indicating that other factors may be mediating the effect. However, the inverse association of score and serum HDL cholesterol became marginally nonsignificant when total fat intake was taken into account. Previously, it has been reported that a low-fat diet decreases HDL cholesterol concentrations by decreasing HDL Apo T_m (26). A high triglyceride concentration is independently associated with cardiometabolic outcomes in adults (27). A higher fiber intake is linked with lower concentrations of serum triglycerides (1). In childhood, triglyceride concentrations tend to rise as adiposity increases (28). In this study, there was no association between the dietary score and BMI, which might potentially explain why we did not observe an association between the dietary score and serum triglycerides.

Although previously shown to associate with HOMA-IR, metabolic syndrome, and insulin levels (16,29,30), our measures of fiber intake and quality of dietary fat might not entirely capture the effect

of diet on insulin sensitivity. In addition to diet, overweight and obesity are associated with insulin sensitivity, the metabolic syndrome, and type 2 diabetes. In this study, however, the effect of the score on HOMA-IR and concentrations of insulin and glucose are not explained by these links, because there were no differences in BMI between the score groups. Our results suggest that the observed association of the score with HOMA-IR between early childhood and young adulthood is likely not only due to changes in insulin levels, but also to small reductions within the normoglycemic range in serum glucose.

A potential limitation of the STRIP trial is for selection bias in the initial recruitment of the participants, in which families who took part in the trial might have been more interested in health issues. Moreover, although the control group children did not receive dietary counseling, they were probably more aware of their health-related factors than typical Finnish children. The control families completed food records similar to the intervention peers and received their serum cholesterol values, which could have inadvertently caused them to modify their behavior and diet. Such potential biases may have diluted the observed differences between the intervention and control groups. During an extensive 20 years of follow-up, it is inevitable that loss to follow-up occurred (4). Attrition analyses performed previously have found body weight, BMI, serum total cholesterol, and saturated fat intake did not differ between participants and nonparticipants (4,6,31). At 20 years of age, males less often provided dietary data compared with females, and males who had completed the food records had lower BMI than males who did not complete food records, but no other differences in cardiovascular risk factor levels were observed. Although euglycemic-hyperinsulinemic clamp is considered the gold standard for measurement of insulin resistance, HOMA-IR was used to indicate insulin resistance in this study. An earlier study suggests that an equation including waist circumference, triglycerides, fasting glucose, and HbA_{1c} might perform better than HOMA-IR in estimating insulin resistance (32). Because HbA_{1c} was not measured during follow-up in our study, we were not able to consider other equations to indicate insulin resistance.

As children in the STRIP study are all Caucasian, the results may not be generalizable to other ethnicities. Major strengths of the study are the uniquely long intervention and follow-up period beginning in infancy, the large number of repeatedly studied participants, and the use of well-established methods.

In conclusion, individualized, family-based dietary intervention was associated with better achievement of the key targets of the intervention, reflecting dietary guidelines, between 1 and 20 years of age. Achieving the dietary targets was favorably associated with insulin sensitivity and serum lipids throughout the early life course. The results thus show that dietary and cardiometabolic risk factor changes can be introduced from infancy to young adulthood. Notably, however, many children failed to meet the dietary targets. The findings also further support recent dietary recommendations (2,3) in the prevention of future type 2 diabetes and the promotion of cardiovascular health. Future follow-ups in the STRIP participants will show if the effects of this unique infancy-onset 20-year dietary intervention will persist into later adulthood and if the intervention effect confers long-term cardiometabolic risk reduction (33).

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the conception and the study design, contributed to discussion, and reviewed the manuscript critically for important intellectual content. O.S. substantially contributed to the conception and the study design, acquired data, and reviewed the manuscript critically for important intellectual content. O.T.R. and K.P. substantially contributed to the conception and the design of the study design; acquired, analyzed, and interpreted data; and revised the manuscript for important intellectual content. T.T.L. and J.N. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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