Effects of 20-year infancy-onset dietary counselling on cardiometabolic risk factors in the Special Turku Coronary Risk Factor Intervention Project (STRIP): 6-year post-intervention follow-up

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Summary

Background Primordial and primary prevention is the cornerstone for cardiometabolic health. In the randomised, controlled Special Turku Coronary Risk Factor Intervention Project (STRIP; n=1116), a 20-year dietary counselling intervention was given to children biannually from infancy, and cardiometabolic health benefits had been observed among the participants in the intervention group. Here, we report on the key results of the first follow-up done 6 years after the end of the intervention, at age 26 years.

Methods The randomised controlled STRIP study recruited children at age 5 months from well-baby clinics in Turku, Finland, and randomly assigned them to either an intervention or control group; group allocation was unmasked. The intervention introduced participants to a heart-healthy diet, characterised by low proportional intake of saturated fat and cholesterol, by dietary counselling and nutrition education sessions to parents and children from the age of 7 months to 20 years. Children in the control group received only the basic health education given at Finnish well-baby clinics and school health care. We assessed diet, lifestyle, and cardiometabolic risk factor data, including blood pressure, anthropometry, serum biochemistry (lipids, apolipoproteins, glucose, and insulin), and homoeostatic model assessment of insulin resistance (HOMA-IR) in the participants at age 26 years.

Findings 1116 children were included in the original STRIP study, of whom 551 provided data at the age 26 years follow-up, and data for 507 participants were analysed (243 in the intervention group and 264 in the control group). At follow-up, those who had been in the intervention group had slightly lower mean intake of saturated fat as a proportion of total energy intake than the control group (13·0% [SD 3·3] *vs* 13·7% [3·6], p=0·049). A higher proportion of participants in the intervention group achieved the targeted monounsaturated and polyunsaturated fat to saturated fat ratio of more than 2:1 than the control group (78 [39%] of 200 *vs* 70 [30%] of 235; risk ratio [RR] 1·16 [95% CI 1·01–1·33]; p=0·035). A higher proportion of intervention group participants met the ideal total cholesterol concentration of less than 5·17 mmol/L (194 [81%] of 240 *vs* 187 [72%] of 261; RR 1·45 [1·05–2·01], p=0·024) and optimal LDL cholesterol concentration of less than 3·0 mmol/L (166 [69%] of 240 *vs* 158 [61%] of 251; RR 1·30 [1·03–1·66], p=0·031). Those who received the intervention had lower glucose (5·00 mmol/L [SD 0·43] *vs* 5·07 mmol/L [0·46], p=0·040) and HOMA-IR (median 1·44 [IQR 1·09–1·91] *vs* 1·62 [1·22–2·09], p=0·037) than the participants in the control group.

Interpretation Previously observed intervention effects during the 20-year counselling were largely maintained into adulthood 6 years after the withdrawal of the intervention. Dietary counselling introduced in infancy thus provided a sustained benefit to diet quality and cardiometabolic risk factor levels.

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Introduction

Primordial and primary prevention is recognised as the cornerstone for life-long cardiometabolic health. The role of diet in preserving cardiometabolic health is established, with a diet high in saturated fat considered an important contributor to cardiovascular disease morbidity.[1] In Finland, as in other high-income countries, diets have been rich in saturated fat and low in unsaturated fat, and consequently children were exposed to qualitatively poor-fat diets.[2] To address this problem, the Special Turku Coronary Risk Factor Intervention Project (STRIP) was launched in 1989 to introduce a heart-healthy diet to healthy

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Research in context

Evidence before this study

We searched PubMed on Oct 30, 2019, for all manuscripts published in English with the key terms "dietary intervention and fat and children", "dietary intervention and cardiometabolic risk factor", "diet and prevention and cardiometabolic", and "diet and longitudinal and cardiometabolic". We had no specific inclusion or exclusion criteria for the studies searched. Previous studies of dietary advice for reducing cardiometabolic risk in adults and dietary interventions in children have proven successful in enhancing cardiometabolic health, such as lowered serum total cholesterol concentration. However, the interventions have often had short duration and they have not had early childhood perspective. The randomised, controlled Special Turku Coronary Risk Factor Intervention Project (STRIP) has completed a 20-year, intense dietary intervention that introduced a heart-healthy diet to healthy children beginning from infancy. The study has found that the repeated dietary counselling resulted in an improved cardiometabolic risk factor profile in the intervened children—suggesting a reduced risk of later atherosclerotic-related cardiovascular disease and type 2 diabetes.

Added value of this study

Using data from the first follow-up done 6 years after the end of the STRIP intervention, we found that the cardiometabolic health benefits of the intervention were largely preserved at age 26 years. These findings suggest that even after the withdrawal of the intervention, the dietary and cardiometabolic benefits of infancy-onset dietary counselling continued to the age of 20 years and are sustained to young adulthood.

Implications of all the available evidence

Dietary preventive actions can help to promote cardiometabolic health beginning from childhood. Future research will show whether these actions are reflected on reduced cardiometabolic disease morbidity and mortality.

children at a very young age.[3] STRIP is a unique long-term dietary experiment that randomly assigned 1116 healthy babies to either intervention or control and continued the dietary counselling for two decades until age 20 years.

In adults and children, dietary and lifestyle interventions have resulted in reduction of cardiometabolic risk factors.[4–7] During the 20-year intervention period, STRIP has shown that repeated dietary counselling aimed particularly at the replacement of saturated fat with unsaturated fat and low intake of cholesterol results in phenotypic changes in children receiving the intervention, pointing to a reduced risk of atherosclerotic-related cardiovascular diseases and type 2 diabetes[8–12] with no adverse effects on growth, neurological or pubertal development, or psychosocial wellbeing.[13,14] Results of the study have influenced dietary and cardiometabolic risk reduction guidelines aimed at primordial and primary prevention.[15] However, it has not been established whether the observed beneficial effects of the intervention are maintained into adulthood after the intervention ended. Therefore, here, we report whether the cardiometabolic health benefits of the intervention were sustained in young adulthood at age 26 years, 6 years after the dietary counselling intervention ceased.

Methods

Study design and participants

The randomised controlled STRIP study recruited children at age 5 months from well-baby clinics in Turku, Finland, via nurses. Children were randomly assigned by random numbers to either the intervention or control groups at study entry. Study group allocation was unmasked.

The aim of the intervention was to reduce exposure to known environmental cardiometabolic risk factors, particularly through diet. Intervention families met with the counselling team, including nutritionists, nurses, and physicians at 1–3-month intervals until the child was aged 2 years, and twice per year thereafter. The control children were seen twice per year until age 7 years and annually thereafter. Similar measurements, including keeping of food diaries, were performed for both study groups, and they met the same study personnel. The outcomes were assessed by clinic and research staff.

The intervention group received individualised dietary counselling from age 7 months until age 20 years.[3,11] At the early phase of the intervention, breastfeeding was encouraged; breast milk or formula was suggested to be continued until age 12 months. Counselling was given to parents until the child was aged 7 years, and thereafter, gradually more information was given directly to the child. The dietary counselling aimed to increase the parents' and the children's nutrition knowledge and to support the beliefs that the child's diet could be modified and that making favourable dietary changes could improve health. The intervention consisted of 30-min individualised dietary counselling and nutrition education sessions led by a nutritionist. Each session had a specific dietary topic and involved performing tasks. The parents were informed of the sessions' topics and tasks, and encouraged to discuss them at home. Furthermore, parents or children received oral and written feedback about the child's diet (written feedback given for the analysed food diary). The intervention group also received information on their serum cholesterol levels annually. The main target of the counselling was to replace saturated fat with unsaturated fat in the child's diet and concomitantly reduce the intake of cholesterol (reduction in total fat intake was not targeted). The intervention group also received counselling on how to reduce salt intake and to favour wholegrain products, fruit, and vegetables. A fixed diet was never specified; the counselling was individualised and the child's recent food

diary was used as a basis of suggestions for dietary changes (eg, replacement of dairy fat-blend spreads with vegetable oil-based spreads). The dietary recommendations were based on the latest version of the Nordic nutrition recommendations (eg, 30% of energy intake from fat, <10% from saturated fat, 10–15% from protein, and 50–60% from carbohydrates).

Key nutritional targets of the intervention, reflecting nutrition recommendations, were a ratio of polyunsaturated and monounsaturated fat to saturated fat (indicative of dietary fat quality) of more than 2:1, and an intake of saturated fat less than 10% of energy, cholesterol less than 300 mg/day (age ≥18 years), and fibre more than 3 g/MJ or more than 25 g/day (age ≥18 years).[16,17]

As part of the intervention, primary prevention of smoking was introduced at age 8 years.[3] It was based on supporting the self-image of non-smoking children and on understanding the health risks associated with both active and passive smoking. Attitudes towards smoking, avoiding passive smoking, and the development of addiction were also discussed, and suggestions on related topics—eg, how to refuse offered tobacco—were discussed with the child. A physically active lifestyle was encouraged, but it was not a structured, continuous part of the intervention. The children in the control group received only the basic health education given at Finnish well-baby clinics and school health care. Topics related to the intervention were not discussed. To keep the control group participants motivated to stay in the study, they received information on their serum cholesterol levels.

The study was approved by the associated university and hospital district ethical authorities. Written informed consent was obtained from parents at study entry, and from the participants at ages 15, 18, and 26 years.

Procedures

Heights and weights of the participants were measured by physicians or nurses from age 7 months, and waist circumference was measured beginning at age 7 years. Body-mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Sitting blood pressure was measured one to four times at each visit throughout the study using an oscillometric device observing appropriate rest time (15 min) and cuff sizes. In the 26-year follow-up, three blood pressure measurements were taken and the mean was used in the analyses.

Non-fasting venous blood samples were taken before age 5 years. Thereafter, samples were taken after an overnight fast. Established clinical laboratory methods have been used to measure serum total cholesterol, HDL cholesterol, triglycerides, and apolipoproteins APOA1 and APOB from age 7 months until age 20 years,[8] and at follow-up at age 26 years. At follow-up, serum samples were separated, aliquoted, and stored at –70°C (whole blood samples used for glycated haemoglobin measurements were also stored at –70°C). The samples were thawed for the first time for the age 26 years analysis. At follow-up, serum triglyceride concentration was established using the enzymatic glycerol kinase–glycerol phosphate oxidase method (triglyceride reagent, Beckman Coulter, Brea, CA, USA). Serum total cholesterol concentrations were measured by enzymatic cholesterol esterase–cholesterol oxidase method (cholesterol reagent, Beckman Coulter). The same reagent was used for estimating HDL cholesterol concentrations after precipitation of LDL and very low-density lipoprotein with dextran sulfate–Mg^{2+}. APOA1 and APOB were measured immunoturbidimetrically (APOA1 reagent and APOB reagent, Beckman Coulter). All these assays were done on an AU400 instrument (Olympus, Tokyo, Japan). LDL cholesterol was estimated by the Friedewald formula. If triglyceride level was 4·5 mmol/L or greater, LDL cholesterol was set to missing. During the intervention phase, serum glucose and insulin were measured with established clinical laboratory methods.[16] At follow-up, serum glucose concentration was measured by the enzymatic hexokinase method (glucose reagent, Beckman

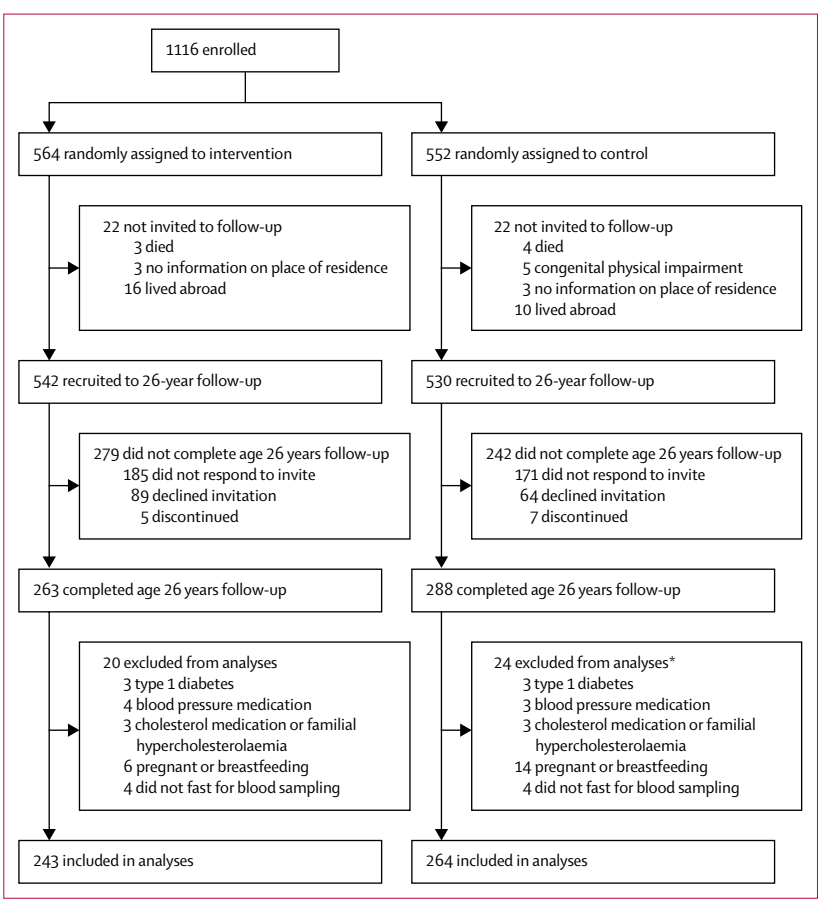

Figure 1: **Trial profile**
During the intervention period (age 7 months to 20 years), reasons for discontinuing in the study were insufficient time, birth of a younger sibling, child's recurrent infections, moving away from the Turku area, and reluctance to blood sampling; these participants were still invited to the follow-up if they met inclusion criteria. *Two control group participants fulfilled two or three exclusion criteria, therefore the number of excluded participants is lower than the number of fulfilled criteria.

	Intervention (n=200)	Control (n=235)	p value
Saturated fatty acids, E%	13·0 (3·3)	13·7 (3·6)	0·049
Monounsaturated fatty acids, E%	13·2 (4·0)	12·9 (3·5)	0·35
Polyunsaturated fatty acids, E%	6·7 (2·3)	6·6 (2·1)	0·55
Polyunsaturated and monounsaturated fat to saturated fat ratio	1·61 (0·53)	1·51 (0·56)	0·070
Polyunsaturated fat to saturated fat ratio	0·55 (0·26)	0·52 (0·26)	0·20
Fat, E%	37·2 (7·3)	37·5 (6·9)	0·66
Dietary cholesterol, mg/day	297 (177)	314 (201)	0·15
Fibre g/day	19·5 (8·2)	19·1 (8·7)	0·57
Fibre, g/MJ	2·4 (0·9)	2·3 (1·0)	0·10
Fibre-rich grains, g/day	73 (43)	68·3 (44·7)	0·30
Vegetables, fruit, and berries, g/day	358 (217)	321 (226)	0·010
Sucrose, E%	5·8 (2·9)	6·2 (3·6)	0·25
Carbohydrates, E%	41·2 (8·4)	40·8 (7·6)	0·45
Protein, E%	19·6 (5·1)	19·2 (5·2)	0·60
Sodium, mg/day	2870 (960)	2930 (1021)	0·20
Energy, kcal	1969 (601)	1996 (563)	0·28

Data are mean (SD). All p values are adjusted for sex and those for dietary cholesterol; fibre-rich grains; vegetables, fruit, and berries; and sodium were adjusted for energy intake; the results remained similar after adjustment. E%=percentage of energy intake.

Table 1: **Dietary measures in the intervention and control groups at the follow-up study aged 26 years**

Coulter) on the AU400 instrument. Serum insulin was measured with a chemiluminescent microparticle immunoassay (Architect insulin assay, Abbott, Chicago, IL, USA) on an Architect ci8200 analyzer (Abbott). To estimate insulin resistance, homoeostatic model assessment of insulin resistance (HOMA-IR; fasting insulin×[fasting glucose/22·5]) was calculated. At follow-up, glycated haemoglobin was measured with HbA1c system reagent (Beckmann Coulter) using an AU400 analyser (Olympus).

Ideal total cholesterol concentration was defined as less than 5·17 mmol/L (<200 mg/dL);[18] ideal blood pressure was systolic blood pressure less than 120 mm Hg and diastolic blood pressure less than 80 mm Hg; ideal serum glucose concentration was less than 5·6 mmol/L (<100 mg/dL); and optimal LDL cholesterol concentration was less than 3·0 mmol/L (<116 mg/dL).[19]

Food diaries, considered the gold-standard method for monitoring diets, were introduced at age 8 months and continued during the intervention period until age 20 years.[3] At first, parents were primarily responsible for completing the food diaries. As the children got older, they were given more responsibility in completing the diaries. Food diaries were also used in the 26-year follow-up. Before the follow-up study visit, a four-day food diary, including one to two weekend days, was filled in on consecutive days. Portion sizes were estimated using household measures or a food picture booklet. During the study visit, the diary was reviewed for completeness and accuracy by a dietary technician. Food and nutrient intakes were analysed with a Micro Nutrica programme developed at the Research and Development Centre of the Social Insurance Institution (Turku, Finland). The programme calculates values of 66 nutrients in more than 4000 foods and dishes. A single dietary technician has analysed all food diaries and updated the data bank throughout the study.

Data on smoking habits have been collected via questionnaires throughout the study, including during follow-up. Regular smoking was defined as smoking at least once per day. Physical activity has been assessed with a questionnaire using the same methods repeatedly from childhood and through the follow-up.[20] The questionnaire covers several physical activity domains allowing the calculation of a metabolic equivalent index.[20]

Throughout the follow-up period, every effort was made to maximise the number of participants with repeated invitations through mail, telephone, and email.

Outcomes

The studied cardiometabolic health markers include diet, smoking, physical activity, BMI, waist circumference, blood pressure, and serum lipids, apolipoproteins, and markers of glucose metabolism.

Statistical analysis

Cross-sectional differences at age 26 years between the intervention and control groups in continuous response variables were studied using analysis of covariance (ANCOVA) or *t* test and log-binomial regression was used for dichotomous responses to report risk ratios (RRs). For insulin, triglycerides, and HOMA-IR, the non-parametric Mann-Whitney U test was used. For the repeated measures analyses covering all available ages, repeated measures ANCOVA was used to assess the association between groups and the continuous response variables. To obtain RRs for dichotomous repeated measurements, log-binomial regression was used. Clustering of measurements within a study participant was accounted for by using generalised estimating equations. In both ANCOVA and log-binomial models, correlation between repeated measurements within a participant was accounted for using a compound symmetry correlation structure. All models included sex as a covariate, except for sex-specific analyses, and repeated-measures models were additionally adjusted for age as a categorical factor. For this 26-year follow-up analysis, we excluded participants who reported using medication for lowering of blood pressure or serum cholesterol, had familial hypercholesterolaemia, were pregnant or breastfeeding, had eaten before blood sampling, or had type 1 diabetes. In the longitudinal analyses, we included all participants who had at least one observation during the 26 years except participants with type 1 diabetes or familial hypercholesterolaemia, following the intention-to-treat approach.

To study differences between those who continued in the STRIP study to the 26-year follow-up compared with those who did not, we conducted a set of loss to follow-up analyses. First, we compared the values of dietary variables,

lifestyle factors, anthropometrics, and serum lipid concentrations in the last available study visit before the follow-up between the participants and non-participants of the age 26 years follow-up study visit using ANCOVA. Because participants who attended the follow-up study were, on average, aged 15 years at their final visit before the follow-up compared with non-participants who were aged 10 years, we adjusted for age at last study visit in addition to sex. Second, for the same variables, we studied whether the STRIP study group modified the association between participation and the variables by adding an interaction term between the STRIP study group and participation to the follow-up study. In case of significant interaction, we calculated the means for each STRIP study group by participation or not in the follow-up (ie, intervention group participants, intervention group dropouts, control group participants, and control group dropouts) adjusted for sex and age at final study visit. Results were considered statistically significant if p<0·05. Adjustment for multiple comparisons was not done because this study is an exploratory long-term follow-up of the STRIP cohort, assessing multiple outcomes. Analyses were performed with SAS, version 9.4. The STRIP study is registered at ClinicalTrials.gov, NCT00223600.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

1116 children (all white; born 1989–1991) were recruited to STRIP, and assigned to either the intervention (n=564) or control (n=552) groups. First study visits (age 7 months) were from November, 1989, to June, 1992. 551 (51%) of the original STRIP participants completed the follow-up study (546 attended the clinic and five provided questionnaire data only), which was done from April 24, 2015, to Jan 2, 2018 (figure 1). The participation rate was similar between the intervention group and control group (p=0·056; figure 1), whereas more women (308 [56%] of 551) attended the follow-up than did men (243 [44%] of 551; p<0·0001). Of the women, 136 (50%) of 270 in the intervention group and 172 (63%) of 274 in the control group participated in the follow-up (p=0·0035). Among the men, 127 (43%) of 294 and 116 (42%) of 278 participated (p=0·72). Of the 517 individuals who participated in the study between ages 18 to 20 years, 370 (72%) completed the follow-up at age 26 years. 44 participants were excluded from the follow-up analysis. No participant had type 2 diabetes. Medication for lowering of blood pressure was used by seven participants (four in the intervention group and three in the control group). Of the five participants with cholesterol-lowering medication, two had familial hypercholesterolaemia and three participants had other indications (two in the intervention and one in the control). The total sample for this age 26 years follow-up was 507 participants, of whom 502 provided clinic visit data (502 provided anthropometrics and blood pressure and 501 provided a blood sample). Data on smoking was available for 479 participants, 476 had completed questions related to physical activity, and 435 completed the food diary.

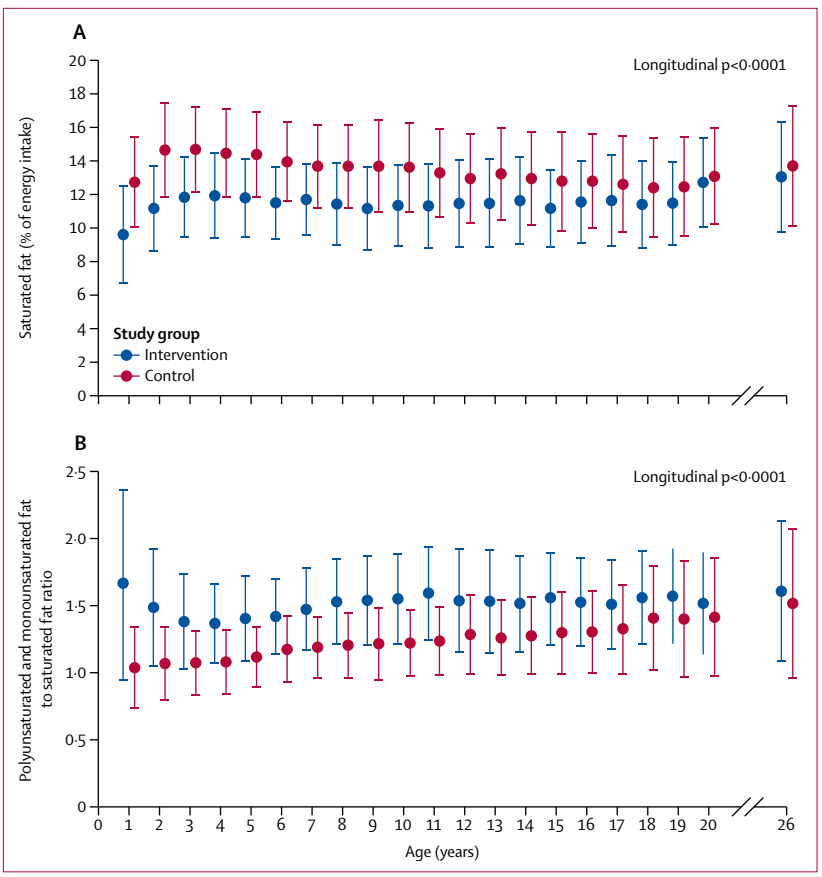

Figure 2: **Dietary fat quality in the STRIP intervention and control groups between ages 13 months and 26 years**

Saturated fat intake as a percentage of total energy intake (A) and polyunsaturated and monounsaturated fat to saturated fat ratio (B). Data points are mean (SD). Longitudinal p value refers to analyses covering the entire study period.

Our previous reports[3,11,21] and the loss to follow-up analyses completed here (appendix pp 1–3) show that during the intervention period, those who have stayed in the study had similar outcomes to those who withdrew. In attrition analyses that examined data from the last study visit before the follow-up at age 26 years, no differences between participants and non-participants of the follow-up were observed (appendix p 4). The follow-up study attrition analyses also indicated that non-participants in the control group had higher intake of energy, total fat and saturated fat as a percentage of energy intake, and cholesterol, and a lower poly-unsaturated and monounsaturated fat to saturated fat ratio than those in the control group who attended the

See Online for appendix

	Intervention	Control	p value
Body-mass index, kg/m²	24·5 (4·1)	24·5 (4·7)	0·81
Waist circumference, cm	81·1 (10·6)	80·8 (12·1)	0·55
Systolic blood pressure, mm Hg	121·9 (10·2)	120·2 (11·2)	0·33
Diastolic blood pressure, mm Hg	71·9 (7·4)	72·0 (7·3)	0·62
Total cholesterol, mmol/L	4·49 (0·84)	4·64 (0·92)	0·065
Non-HDL cholesterol, mmol/L	3·19 (0·80)	3·28 (0·85)	0·18
LDL cholesterol, mmol/L	2·72 (0·72)	2·82 (0·77)	0·079
HDL cholesterol, mmol/L	1·29 (0·32)	1·36 (0·31)	0·064
Triglycerides, mmol/L	0·90 (0·70–1·30)	0·90 (0·70–1·20)	0·35
APOA1, g/L	1·60 (0·27)	1·66 (0·29)	0·10
APOB, g/L	0·73 (0·15)	0·72 (0·16)	0·78
Ratio of APOB to APOA1, g/L	0·47 (0·15)	0·45 (0·13)	0·25
Glucose, mmol/L	5·00 (0·43)	5·07 (0·46)	0·040
Insulin, mU/L	6·50 (5·10–8·50)	7·20 (5·40–9·30)	0·061
HOMA-IR	1·44 (1·09–1·91)	1·62 (1·22–2·09)	0·037

Data are mean (SD) or median (IQR). For body-mass index, waist, and blood pressure, n=240 in the intervention group and n=262 in the control group; and for lipids, apolipoproteins, and glucose metabolism, n=240 in the intervention group and n=261 in the control group. Education level was similar in the intervention and control participants; 71% of those in the intervention group and 68% of those in the control group had higher education level studies (p=0·40). HOMA-IR=homoeostatic model assessment of insulin resistance.

Table 2: **Outcomes at the age 26 years follow-up**

age 26 years follow-up; whereas the opposite was observed for the intervention group non-participants and participants (appendix pp 6–7).

Participants who were in the intervention group had lower saturated fat intake and higher consumption of vegetables, fruit, and berries than those who were in the control group 6 years post-intervention (table 1). Other dietary measures were similar between the groups. In sex-specific analyses, men in the intervention group had higher intake of fibre (g/MJ) and vegetables, fruit, and berries than men in the control group (appendix p 5), but no such difference was seen among women. Longitudinal analyses from age 13 months to age 26 years showed that those who were in the intervention group had lower intake of saturated fat and had a higher polyunsaturated and monounsaturated fat to saturated fat ratio, as well as lower cholesterol and higher fibre intake than those who were in the control group (figure 2; appendix pp 6, 8).

The prevalence of regular smoking was similar between groups at the age 26 years follow-up, and in the longitudinal analyses beginning from age 13 years (appendix pp 6, 9). However, at the end of the intervention period (age 20 years), fewer intervention group participants were regular smokers than the control group participants (16 [10%] of 162 in the intervention group *vs* 37 [17%] of 213 in the control group; RR for control *vs* intervention 1·76 [95% CI 1·02–3·05], p=0·044). No difference in physical activity between the groups was observed at the age 26 years follow-up (p=0·28). For women, the median metabolic equivalent (h/week) was 19·6 (IQR 8·3–32·6) in the intervention group and 19·5 (5·0–32·6) in the control group (p=0·29); for men, it was 31·3 (5·7–32·6) versus 31·3 (8·0–32·6), respectively (p=0·71).

BMI and waist circumference at age 26 years were similar between the groups (table 2). Correspondingly, the prevalence of overweight or obesity (BMI >25 kg/m²) did not differ between groups (82 [34%] of 240 in the intervention group *vs* 93 [35%] of 262 in the control group; p=0·75). Blood pressure of both groups was also similar at age 26 years (table 2). In the longitudinal analyses, no difference in BMI or waist circumference between the groups was noted, whereas the intervention group participants had lower blood pressure than the control group when analysed from age 7 months (appendix pp 6, 10).

At the age 26 years follow-up, serum total cholesterol, LDL cholesterol, and HDL cholesterol concentrations appeared lower in participants who were in the intervention group than in those in the control group, although the differences were not significant (table 2). Serum non-HDL cholesterol, triglycerides, APOA1 and APOB concentrations, and ratio of APOB to APOA1 were similar between the groups (table 2). In sex-specific analyses men had lower total cholesterol, LDL cholesterol, HDL cholesterol, and APOA1 concentrations and higher triglyceride concentrations in the intervention group than in the control group; whereas no group differences were noted among women (appendix p 5).

At the age 26 years follow-up, serum glucose and HOMA-IR were signifcantly lower and insulin was non-significantly lower in those who received the intervention than those in the control group (table 2). Mean HbA1c was similar between the intervention and control groups (for women in the intervention group it was 34·3 mmol/mol [SD 2·6] *vs* the control group 35·0 [3·1], p=0·15; for men in the intervention group it was 34·8 [2·4] *vs* the control group 35·4 [2·5], p=0·43; the p for sexes combined was 0·12).

The longitudinal analyses showed consistently lower levels of total cholesterol, non-HDL cholesterol, LDL cholesterol, and APOB in the participants in the intervention group than those in the control group (figure 3; appendix p 11). In the longitudinal analyses, participants in the intervention group also had lower insulin concentration and lower HOMA-IR than those in the control group (figure 4).

The targeted dietary fat quality defined using polyunsaturated and monounsaturated fat to saturated fat ratio as well as the dietary cholesterol intake were met by more of those who were in the intervention group than the control group at the age 26 years follow-up (table 3). The intervention group participants appeared to more often meet targeted fibre intake, although the difference was not significant.

There was no difference between the groups in the proportions of participants achieving the target of saturated fat less than 10% of energy intake. A greater proportion of participants in the intervention group had ideal total cholesterol and optimal LDL cholesterol and

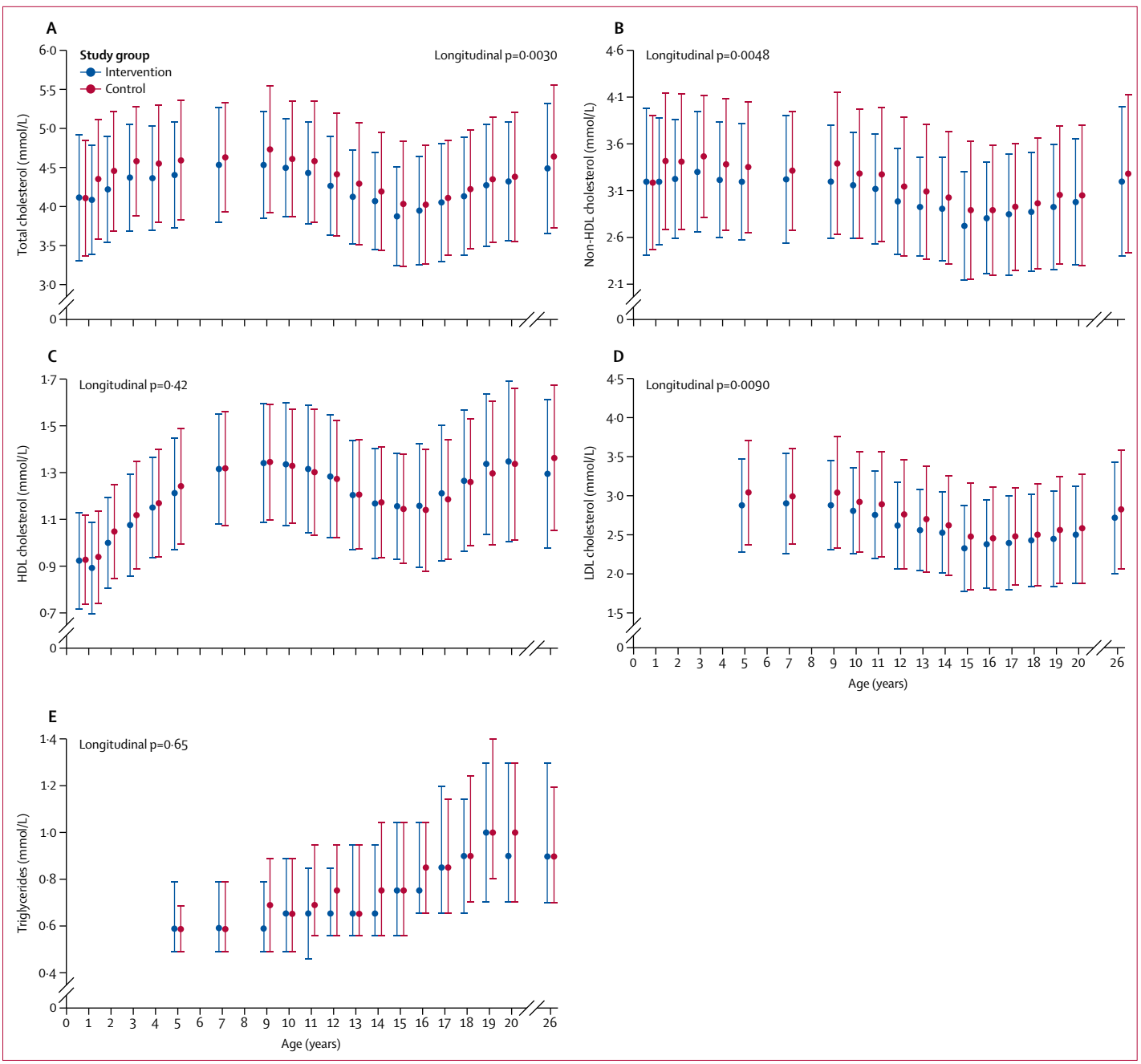

Figure 3: **Serum lipid concentrations in the STRIP intervention and control groups from age 7 months or 5 years to age 26 years**
Total cholesterol (A), non-HDL cholesterol (B), HDL cholesterol (C), LDL cholesterol (D), and triglycerides (E). Data points are mean (SD), except for triglycerides for which median (IQR) is shown. Longitudinal p value refers to analyses covering the entire study period.

more had the combination of the three ideal health factors (total cholesterol <5·17 mmol/L, glucose <5·6 mmol/L, and blood pressure <120/<80 mm Hg) than in the control group.

Discussion

This long-term follow-up of the STRIP study showed that many of the cardiometabolic health benefits observed in children and adolescents after an infant-onset dietary counselling intervention are preserved into young adulthood, 6 years after cessation of the intervention. Reflecting the main intervention target, those who were in the intervention group continued to have better dietary fat quality and furthermore, they consumed more fruit, vegetables, and berries, and the men consumed more fibre. Participants in the intervention group also

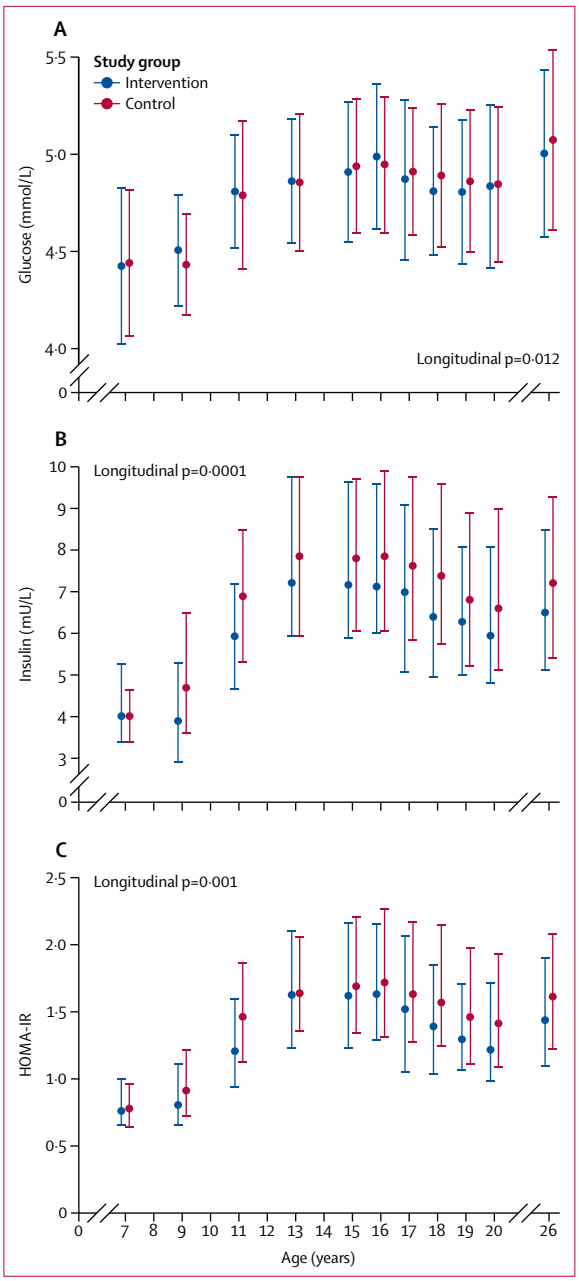

Figure 4: **Serum glucose and insulin concentrations, and HOMA-IR in the STRIP intervention and control groups, ages 7–26 years**
Serum glucose concentrations (A), insulin concentrations (B), and HOMA-IR (C). Data are mean (SD) for glucose and median (IQR) for insulin and HOMA-IR. Longitudinal p value refers to analyses covering the entire study period. HOMA-IR=homoeostatic model assessment of insulin resistance.

continued to have a better cardiometabolic risk profile 6 years after the end of the intervention than those who were in the control group, as indicated by lower serum total cholesterol, LDL cholesterol, and glucose levels as well as better insulin sensitivity (ie, lower HOMA-IR).

A Cochrane review on dietary advice for reducing cardiovascular risk in adults reported a mean reduction of total cholesterol by 0·15 mmol/L (95% CI 0·06–0·23) and LDL cholesterol by 0·16 mmol/L (0·08–0·24) after 3–24 months.[4] The Dietary Intervention Study in Children examining hypercholesterolaemic school-aged children reported that the dietary intervention led to modest lowering of LDL cholesterol over 3 years.[6] In the randomised controlled Dietary Approaches to Stop Hypertension (DASH) trial, an 8-week dietary intervention was done, consisting of a control diet (a diet with increased fruit and vegetables) or the DASH diet (increased intake of fruit, vegetables, and low-fat dairy products, and reduced intake of saturated fat, total fat, and cholesterol).[7] In line with our results, the DASH diet was associated with lower total, LDL, and HDL cholesterol without significant effects on triglycerides.[7] Consistent with our data, the reductions in total and LDL cholesterol were greater in males than females. Similarly, the Cochrane review reported that men, unlike women, achieved cholesterol-lowering effects.[4] In STRIP, the finding that total and LDL cholesterol concentrations were reduced in the intervention group versus the control group in men but not women, despite that lower saturated fat intakes were reported by both men and women, might be related to a higher fibre intake in the men in the intervention group versus the control group, which was not observed in the women.[22] The effect observed in the intake of fibre might thus in part explain the intervention effect on serum cholesterol because we and others have previously reported the inverse association between fibre intake and serum cholesterol levels.[23,24] Overall, there are several plausible mechanisms that might underlie the effects of interventions in which dietary fat quality is modified. For example, the modification of dietary fat quality influences serum LDL cholesterol concentration through regulation of several transcription factors, including LDL-receptor activity and expression.[25] Aside from the effects on total and LDL cholesterol, we have previously reported that the intervention children had lower insulin concentrations and better insulin sensitivity in terms of HOMA-IR compared with control participants.[9] Results of the age 26 years follow-up show that these markers of glucose metabolism continue to be more favourable in the participants who have received the dietary counselling compared with those in the control group. Our results complement previous observations from the Finnish Diabetes Prevention Study, in which individuals in the dietary and lifestyle intervention group had reduced incidence of diabetes.[26] In summary, the STRIP intervention given between ages 7 months and 20 years was able to produce sustained effects on the key targeted dietary and cardiometabolic markers after removal of the intervention. Primordial prevention of cardiometabolic diseases is thus feasible at early age.

At follow-up, the intervention and control group participants had a similar BMI, waist circumference, and blood pressure. These results are in line with our previous data reporting no or marginal intervention

effect when analysed over several ages.[11,27,28] The underlying reason for the absence of an effect on weight status might be that the counselling was not primarily focused on prevention of overweight, and energy intake was not different between the groups at follow-up. In terms of blood pressure, we have been unable to introduce lower sodium intake among the intervention participants than among controls between the ages of 13 months and 20 years,[29] or at the age 26 years follow-up. Absence of intervention effect on weight status might also be related to the absence of effect on blood pressure. Regarding lipids, men in the intervention group had lower HDL cholesterol concentration than those in the control group. Low physical activity and overweight are associated with lower HDL cholesterol concentration;[30,31] however, these characteristics were similar between the men in the intervention and control groups, thus not explaining the observed difference in HDL cholesterol. Replacement of saturated fat with polyunsaturated fat or monounsaturated fat is associated with decreased HDL cholesterol, similar to when fats are replaced with carbohydrates in the diet,[32] suggesting that lower saturated fat intake per se is associated with lower HDL cholesterol. Because intakes of carbohydrate, monounsaturated fat, or polyunsaturated fat were not different between the study groups, these potential dietary mechanisms introducing lower HDL cholesterol concentrations also do not seem to explain the lower HDL cholesterol concentration in the men in the intervention group than those in the control group. Notably, although analyses at follow-up or between ages 13 and 26 years did not reveal an effect for the intervention on regular smoking, we did find that at the end of the intervention period (age 20 years), fewer participants in the intervention group were regular smokers than in the control group. The discrepancy between the intervention effect at age 20 years and 26 years is not due to poorer attendance of the control participants who smoked than the intervention group participants who smoked, as shown by our attrition analyses. The decreased prevalence of tobacco smoking in Finnish young adults (11% of women and men aged 18–29 years in 2017), as observed also in our study, might offer one explanation for the absence of an intervention effect at follow-up. Taken together, our findings suggest that infant-onset dietary counselling over a 20-year period was associated with concomitant and sustained benefits to diet and some, but not all, cardiometabolic risk markers.

We also found that cumulative risk factor levels over the course of the intervention and follow-up tended to be more favourable among those in the intervention group from infancy into young adulthood. These findings are important because prolonged exposure to lower LDL cholesterol beginning early in life has been associated with greater reduction in the risk of coronary heart disease than the contemporary practice of lowering LDL cholesterol with statin use beginning later in life.[33] Also complementing the metabolic memory hypothesis, data from the West of Scotland Coronary Prevention Study have shown that treatment with statins can have an effect on cardiovascular disease mortality even after discontinuation of the drug.[34] Low risk factor levels in childhood might thus have long-lasting effects on atherogenesis and subsequent cardiovascular disease events regardless of their status later in life. A meta-analysis of data from 312 321 individuals showed that long-term exposure to lower LDL cholesterol is associated with a reduction in the risk of coronary heart disease (odds ratio of 0·46 [95% CI 0·41–0·51] for each 1 mmol/L reduction in LDL cholesterol).[33] The observed mean difference of 0·15 mmol/L between the intervention and control group males from age 5 to 26 years would thus translate into a lower coronary heart disease risk among the males in the intervention group. Furthermore, the STRIP intervention effect was not limited to LDL cholesterol. Participants in the intervention group also had lower serum glucose concentration and blood pressure and better insulin sensitivity between early childhood and young adulthood. As hyperglycaemia and insulin resistance were associated with incident type 2 diabetes and the development of atherosclerosis,[35] and increased blood pressure in childhood predisposes individuals to adult hypertension, metabolic syndrome, coronary artery calcification, and increased carotid intima media thickness,[36] the benefits of the intervention might be larger than estimated based on LDL cholesterol alone, and thus, of clinical importance. Future follow-ups of the STRIP study will provide data on whether the intervention

	Target achieved		Risk ratio (95% CI)	p value
	Intervention	Control		
Dietary factors				
Polyunsaturated and monounsaturated fat to saturated fat ratio >2:1	78/200 (39%)	70/235 (30%)	1·16 (1·01–1·33)	0·035
Saturated fat <10% of energy intake	35/200 (18%)	36/235 (15%)	1·03 (0·94–1·12)	0·55
Dietary cholesterol <300 mg/day	131/200 (66%)	137/235 (58%)	1·29 (1·02–1·62)	0·032
Fibre				
>3 g/MJ	48/200 (24%)	42/235 (18%)	1·09 (1·00–1·18)	0·050
>25 g/day	46/200 (23%)	44/235 (19%)	1·05 (0·96–1·16)	0·29
Vegetables, fruit, and berries >500 g/day	41/200 (21%)	41/235 (17%)	1·17 (0·80–1·72)	0·42
Salt <6 g/day	65/200 (33%)	73/235 (31%)	1·06 (0·82–1·38)	0·64
Cardiometabolic health factors				
Ideal total cholesterol <5·17 mmol/L	194/240 (81%)	187/261 (72%)	1·45 (1·05–2·01)	0·024
Ideal glucose <5·6 mmol/L	218/240 (91%)	227/261 (87%)	1·46 (0·88–2·43)	0·14
Ideal blood pressure <120/<80 mm Hg	73/240 (30%)	82/262 (31%)	1·02 (0·92–1·12)	0·77
Meeting all three ideal factors	59/240 (25%)	50/261 (19%)	1·09 (1·00–1·18)	0·045
Optimal LDL cholesterol <3·0 mmol/L	166/240 (69%)	158/261 (61%)	1·30 (1·03–1·66)	0·031

Data are n/N (%) unless otherwise specifed. Risk ratios are for intervention *vs* control group (adjusted for sex).

Table 3: **Effect of the intervention on dietary targets and cardiometabolic health factors at age 26 years follow-up**

effect confers long-term cardiometabolic disease risk reduction.[34]

Limitations of this study include losses to follow-up, which unavoidably occurs in a study as long and involved as STRIP (45 study visits for the intervention group and 28 for the control group). During the first study years, the most common reasons for discontinuation were moving away from the Turku area, recurrent infections, and reluctance to have blood sampled.[3] The number of intervention participants compared with the controls was slightly lower at the end of the intervention period, probably because of the more intense study schedule. The characteristics of those participating in the study and those lost to follow-up have been compared repeatedly, including in this report, and no differences have been found regarding bodyweight, BMI, serum total cholesterol, or saturated fat intake.[3,21] In detailed loss to follow-up analyses regarding components of metabolic syndrome, we found that discontinuation in the study was not affected by these characteristics nor did they modify the discontinuation in the intervention and control groups.[11] Additionally, the participants and non-participants of the follow-up were similar in terms of the analysed dietary components, smoking behaviour, physical activity, BMI, blood pressure, and serum lipids. Furthermore, the parental socioeconomic statuses of the participants and dropouts of the follow-up study were similar. Notably, the intervention and control group participants and dropouts behaved differently in terms of intake of energy, fat, saturated fat, cholesterol, and polyunsaturated and monounsaturated fat to saturated fat ratio. Non-participants in the control group had higher intake of energy, total fat and saturated fat, and cholesterol, as well as a lower polyunsaturated and monounsaturated fat to saturated fat ratio, than those who continued in the control group, whereas the opposite was found for the intervention group non-participants and participants (appendix p 7). These data indicate that the observed intervention effect on dietary fat quality might be an underestimation, and that a more pronounced difference between the groups would have been noted if the control participants were more representative of the group. Furthermore, although the control group children did not receive dietary counselling, they were probably more aware of their health-related factors—ie, diet and serum cholesterol levels—than typical Finnish children through being involved in the study, which might dilute differences between the intervention and control groups. Limitations also include the use of questionnaires to assess data on smoking and physical activity, and although every effort was made to produce high-quality dietary data, food diaries are also subject to misreporting and might introduce social-desirability bias, which could result in over-reporting of healthy foods and under-reporting of unhealthy foods. We also did multiple analyses because of the numerous outcomes, and acknowledge that the longitudinal analyses are driven by the data from the intervention period; additionally, the participants are all white so the results might not be generalisable to other ethnicities. 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, this 6-year post-intervention follow-up showed that the effect of the infancy-onset intervention on diet and cardiometabolic risk factors, continued to the age of 20 years, was largely preserved when those who received the intervention reached adulthood and began life independent of their childhood home. Future follow-ups of the cohort will establish whether the intervention effect continues to persist and how is it reflected in cardiovascular disease markers and events.

Contributors

All authors contributed to the conception and design of the study. KP, HN, SPR, HL, PS, EJ, OS, AJ, TR, JV, and OTR acquired, analysed, or interpreted data. KP and TTL wrote the manuscript. KP is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data. TTL, HN, NK, SPR, HL, B-ML, PS, EJ, CGM, MJ, OS, AJ, TR, and JV contributed to discussion, and reviewed the manuscript critically for important intellectual content. NK contributed to statistical analyses and reporting. OTR revised the manuscript for important intellectual content.

Declaration of interests

We declare no competing interests.

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