COHORT PROFILE

Cohort Profile: The STRIP Study (Special Turku Coronary Risk Factor Intervention Project), an Infancy-onset Dietary and Life-style Intervention Trial

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How did the study come about?

It is now clear that atherosclerosis develops as a result of a life-long process often leading to coronary heart disease. 1 Nutritional recommendations have been delivered to the general community to manage this epidemic. Since fat is an important source of energy and cholesterol is required for sex hormone synthesis, fears have emerged that low intake of saturated fat and cholesterol might influence children's growth and development. Infants and young children have therefore been excluded from these nutritional recommendations. 2 However, a number of arguments support the concept that prevention of children's exposure to atherosclerosis risk factors should be started at an early age. Dietary fat intake and quality of fat regulate serum lipoprotein values in childhood in the same way as they do in adults. 3,4 It has also been shown that children with high serum cholesterol and LDL cholesterol values are predisposed to early atherosclerotic changes in aorta and large arteries 5,6 and high LDL cholesterol values in childhood associate with increased atherosclerotic changes in carotid arteries measured decades later. 7 All these changes can be influenced by living habits. A lifestyle with emphasis on avoiding atherosclerosis risk factors might be most easily adopted if introduced in early childhood.

A large cross-sectional coronary risk factor follow-up study, the Cardiovascular Risk in Young Finns (CRYF) has continued in Finland since 1980. In that study, an extensive number of atherosclerosis risk factors have been studied repeatedly in an initial cohort of 3596 individuals from age 3 years onwards. 8 CRYF is a follow-up study without intervention, and a need for an interventional approach to control the coronary risk factors in childhood was evident. Finland is an ideal location to perform an atherosclerosis risk factor intervention study, since serum cholesterol values of Finnish boys have been high in international comparisons 9 and, at the same time, coronary artery disease incidence in Finnish adults has also been very high. Moreover, the participation rate has by tradition been high in Finnish epidemiological trials. Due to these reasons, grant-funded Special Turku Coronary Risk Factor Intervention Project (STRIP) study was launched in 1989 to study whether it is possible to reduce exposure to coronary risk factors effectively and safely from early age on.

What does STRIP cover?

The STRIP study was designed to examine in detail the influences of saturated fat-oriented counselling on dietary intakes, serum lipid and lipoprotein concentrations and growth and development of infants and children.
The STRIP children were recruited into the study at an earlier age than ever before in such a dietary intervention study. Therefore, the main interest has been to investigate the safety of low-saturated fat, low-cholesterol diet in childhood. Despite being an intervention study, STRIP has a large cohort of control children, which has been followed from 7 months of age until early adulthood. Moreover, also the intervention group changes to a cohort when the active dietary intervention stops at 20 years of age. The recent research themes have included measuring vascular endothelial function and structure in study children as well as their family members. The data are also being used to cover questions regarding pubertal development of the study children.

Several substudies, listed in detail in Table 1, have been launched within the STRIP cohort. Among other studies, effects of *Chlamydia pneumoniae* infection on coronary risk factors have been investigated. Psychosocial well being of the STRIP children and families as well as patterns of habitual physical activity and smoking habits have been studied. A plant sterol intervention trial was performed in a STRIP sub-cohort at 6 years of age.10

**Who is the sample?**

The flowchart of STRIP study is shown in Figure 1. Briefly, the study subjects were enrolled at their 5-month visit at Turku City well-baby clinics where the recruitment was performed by nurses. The STRIP children are healthy, i.e. they are not regarded as a ‘risk group’ for atherosclerosis development. Parents and siblings of the study infants and children have been involved in the study as well, and their serum lipoprotein values and blood pressure have been measured at yearly visits at the Research Centre of Applied and Preventive Cardiovascular Medicine at Turku University.

**What kind of counselling is given to STRIP intervention children?**

Dietary counselling of the intervention families has been given by a nutritionist at every visit, i.e. at 3- to 12-month intervals, at the project study site. The child and the family have had an active role in the counselling sessions. The intervention has been individualised and has aimed at child’s fat intake of 30–35% of daily energy (%), saturated to monounsaturated + polyunsaturated fatty acid ratio of 1:2 and cholesterol intake <200 mg/day. Breast feeding or formula was advised during the first year of life and after 12 months of age, 0.5–0.6 l skimmed milk daily has been recommended. To maintain adequate fat intake, the parents were taught to add daily two or three teaspoonfuls (10 g) soft margarine or vegetable oil, mainly low-erucic acid rapeseed oil, to the child’s food from 12 to 24 months of age. Change of the type of milk was the major subject of the intervention during the first month of the trial. The counselling has been individualized and the nutritionist has used the child’s recent food record as a basis for suggestions given. The families have been encouraged to gradually change child’s diet toward better fat composition. A fixed diet was never ordered but suggestions were made to replace high fat and high-saturated fat foods with products containing less fat or unsaturated instead of saturated fat (e.g. cream with modified fat). Use of vegetables, fruits, low salt and whole-grain products were favoured as well. Nutrition recommendations are based on Nordic nutrition recommendations.11

During the first year, the counselling was given primarily to the parents. However, from age 7 years onwards progressively more dietary information and suggestions has been given directly to the child and the child has been met alone by the counselling team. The counselling has been based on the age and cognitive ability of the child at the visits. Most of the material used has been particularly developed for the project because ready-made counselling materials for children are sparse. Early-year counselling sessions included paper-pencil and plastic model type tasks to concretize nutritional concepts. Later the tasks were often computer assisted. The counselling has dealt, for example with salt content of different food items, and how to avoid unnecessary changes towards larger portion sizes. The parents have been carefully informed about the contents of the child’s counselling session and they have been encouraged to further discuss the same food-related topics with the child at home.

In families with smoking parent(s), children’s possibility to be exposed to passive smoking at home was discussed with the parents during the first visits. Child-oriented counselling aiming at prevention of active smoking began at child’s age of 8 years. It covered cardiovascular physiology and (patho)physiological effects of smoking. It was based on supporting the self-image of the non-smoking children and on understanding the risks associated with smoking. At age 16.5 years, passive smoking was also discussed as some teens spent a lot of time with smoking friends. As shown earlier, the intervention is rather complex, directed at parents in the early years of infant’s and child’s life but later directly to the child.

The control children have been seen bi-annually until 7 years of age and annually thereafter. They have received the basic health education routinely given at Finnish well-baby clinics and school health care. At the age of 12 months, cow’s milk with 1.9% (1.5% after May 1995) fat was recommended for daily use. No suggestions on the use of fats have been given to the control families and dietary issues have been discussed only superficially.

**What has been measured?**

The detailed list of studies and substudies in STRIP is given in Table 1. Dietary intakes have been analysed...
using 4-day food records (3-day records before 2 years of age) of the child’s diet every 6–12 months. A nutritionist has checked the food records for accuracy at each occasion. The nutrient intakes have been calculated with Micro-Nutrica software\textsuperscript{12} based on the Food and Nutrient Database of the Social Insurance Institution, Finland. The programme originally calculated 66 nutrients in 1208 foods and 890 dishes commonly used in Finland, and the programme has continuously been updated with new foods and recipes.

Clinical examination of the child has been performed in detail at each visit. Weights of the children were measured to the nearest 0.1 kg and height to the nearest 0.1 cm at each visit. Recumbent length was recorded until 2 years of age and thereafter standing height was measured with a wall-mounted Harpenden stadiometer (Holtain, Crymych, UK). Weights and heights (absolute and relative) were plotted on the Finnish growth charts.\textsuperscript{13} Body mass index (BMI) was calculated as kilogram per square metres. Waist–hip measurements were done after 8 years of age and pubertal stage has been monitored from 9 years of age. Oral health of the participants has been followed. Blood pressure has

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\begin{table}
\centering
\caption{Summary of the data gathered in all STRIP children and substudies performed within the STRIP study.}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Age & Food records & Growth, BP and physical examination & Pubertal stage & Serum lipids\textsuperscript{a} & Ultrasound studies & Other studies \\
\hline
7–8 months\textsuperscript{b} & # & # & # & # & # & Apolipoprotein E-phenotype. Subcohort: \textit{Chlamydia Pneumoniae} (Chl. \textit{pn.})
\hline
13 months & # & # & # & # & # & Psychological studies, SES\textsuperscript{d}. Subcohort: Serum plant sterols, Chl.\textit{pn.}
\hline
18 months & # & # & # & # & # & Psychological studies. Subcohort: leptin, Chl. \textit{pn.}
\hline
2 years & # & # & # & # & # & Psychological studies. Subcohort: Chl. \textit{pn.}, iron and zinc, \textit{trans} fatty acids
\hline
3 years & # & # & # & # & # & Psychological studies. Subcohort: Chl. \textit{pn.}, iron and zinc
\hline
4 years & # & # & # & # & # & Subcohort: Physical activity intervention, Chl. \textit{pn.}, iron and zinc
\hline
5 years & # & # & # & # & # & Psychological studies. Subcohort: Cognitive tests, physical activity intervention, leptin, Chl. \textit{pn.}
\hline
6 years & # & # & # & # & # & Subcohort: Physical activity intervention, plant sterol intervention study
\hline
7 years & # & # & # & # & # & Blood for DNA (refrigerated). Subcohort: Physical activity, LDL and HDL fractions, glucose, insulin, Chl. \textit{pn.}
\hline
8 years & # & #\textsuperscript{c} & # & # & # & Cotinine, self-assessed body image, SES. Subcohort: Bone density, oral health, Chl. \textit{pn.}
\hline
9 years & # & #\textsuperscript{c} & # & # & # & Cotinine, SES. Subcohort: HDL and LDL fractions, Ox-LDL, glucose, insulin, physical activity, bone density, Chl. \textit{pn.}
\hline
10 years & # & #\textsuperscript{c} & # & # & # & Cotinine, Hcy, SES. Subcohort: Chl. \textit{pn.}
\hline
11 years & # & #\textsuperscript{c} & # & # & # & Cotinine, CRP. Subcohort: HDL and LDL fractions, glucose, insulin, bone density, Chl. \textit{pn.}
\hline
12 years & # & #\textsuperscript{c} & # & # & # & Cotinine, Subcohort: HDL and LDL fractions, glucose, insulin, bone density
\hline
13 years & # & #\textsuperscript{c} & # & # & # & Cotinine, CRP, physical activity questionnaire. Subcohort: LDL and HDL fractions
\hline
14 years & # & #\textsuperscript{c} & # & # & # & Cotinine
\hline
15 years & # & #\textsuperscript{c} & # & # & # & Cotinine, CRP, SES, Hcy, physical exercise questionnaire. Subcohort: Glucose, insulin, bone density, bone age
\hline
\end{tabular}
\end{table}

\textit{Chl. \textit{pn.}}, \textit{Chlamydia pneumoniae} antibodies; Ox-LDL, oxidized LDL; CRP, C-reactive protein; Hcy, Homocysteine.\textsuperscript{a}Total and HDL-cholesterol, triglycerides and apolipoproteins A-1 and B annually. \textit{Lp(a)} and cholesterol ester fatty acids annually until 5 years.\textsuperscript{b}Formula-fed infants only at 8 months.\textsuperscript{c}Including waist–hip ratio.\textsuperscript{d}SES, socioeconomic status.\textsuperscript{e}Studied/measured at this visit.
Ultrasound studies were introduced to the study 17 years later. Physical fitness is measured using an indirect shuttle run test. At the age of 9 years, physical fitness was first assessed in a subgroup of 9-year-old children. The heart rate was monitored for 2–3 days and 17 years later. LDL particle sizes and HDL cholesterol have been measured annually until 5 years of age and every 2 years thereafter. Moreover, LDL particle sizes and HDL fractions have been measured repeatedly after 7 years of age. At each time-point, extra two 0.5 ml aliquots of serum have been taken and stored at 70°C. Blood has also been drawn for DNA analyses. Furthermore, serum cholesterol and apolipoprotein values of the parents and siblings have been measured annually.

Patterns of habitual physical activity have been assessed with a self-administered questionnaire at the age of 9 years (n = 195) and at the ages of 13, 15 and 17 years (n = 550). At the age of 9 and 13 years, children’s heart rate was monitored for 2–3 days using electronic detectors (Polar Vantage NV, Polar Electro, Kempele, Finland). The heart rate monitoring data was interfaced with a microcomputer. Physical fitness was first assessed in a subgroup of 9-year-old children using a shuttle run test. At the age of 17 years, physical fitness is measured using an indirect maximal cycle ergometer test.

When children were 11 years of age, non-invasive ultrasound studies were introduced to the study protocol to measure markers of subclinical atherosclerosis. These included carotid and aortic intima-media thickness (IMT), carotid and aortic artery elasticity and brachial artery endothelial-dependent flow-mediated dilation (FMD). This comprehensive assessment of vascular phenotypes has been repeated at 2-year intervals, i.e. at the ages of 13, 15 and 17 years. Cardiac ultrasound to assess myocardial structure and function was added to the protocol at the age of 17 years. Recently, the vascular ultrasound measurements have also been performed for children’s parents and grandparents.

**What is attrition like?**

The required sample size for the STRIP study was predicted to achieve a 1% significance with 80% power, a 0.2 mmol/l true difference in the change of serum cholesterol concentration between the intervention and control groups, with the assumption that the standard deviation of serum cholesterol values is 0.9 mmol/l and the correlation coefficient between the samples at 7 and 13 months of age is 0.5. As a sizeable loss of children during the follow-up time was anticipated already at the recruiting stage of the study, a total of 1062 children was recruited, when only 334 (167 counselling, 167 control) was required to achieve 5% significance and 80% power for repeated measures analysis of variance for the total sequence of 21 measurements (at 7 and 13 months and annually at 2–20 years of age) with the desired effect of 0.2 mmol/l reduction in serum total cholesterol values in the intervention group. Because 532 children participated in the 14-year-visit, the minimum required sample size is still exceeded by 37%.

Approximately half of the initial STRIP cohort still participated in the study at 13 years of age. The most common reasons for discontinuing have been moving away from Turku area, child’s recurrent infections and problems in blood sampling. At 15 years of age, there were slightly more control children than intervention children in the study group, as 53% on the controls still participated in the study, while the number was 47% in the intervention group. Food record return rate of the participants has been above 85%. Depending on age, 0–1% of the growth data and ~5% of pubertal data are missing, whereas blood sampling was successful in 77% of children at 7 months, 89% at 2 years of age and >95% later in childhood.

The characteristics of participants of the study and those lost from the follow-up have been repeatedly compared. Drop-out rate has not been influenced, e.g. by the child’s weight, and comparison of baseline characteristics between children with and without complete ultrasound data revealed no significant differences. Furthermore, those intervention children who had complete ultrasound data did not
What has been found? Main findings and publications

So far the STRIP study has yielded over 100 original peer-reviewed scientific publications. The initial serum cholesterol results until age 13 months were reported by Lapinleimu et al. in 1995 and first growth data by Niinikoski et al. in 1997. These papers showed that the STRIP intervention was effective in decreasing serum cholesterol values during the first 3 years of life without untoward effects on growth. Rask-Nissilä et al. reported the 5-year results, where the cholesterol difference between the intervention and control groups was still significant but no differences were found in neurological and cognitive development between the two study groups. Talvia et al. reported the main dietary results until 10 years of age and Raitakari et al. showed that the endothelial function was better in the intervention than control boys at age 11 years. Moreover, Kallio et al. reported that passive smoking influences endothelial function already at adolescence. The STRIP study’s main dietary intake, lipid, growth and pubertal development results until 14 years of age were recently reported by Niinikoski et al.

Taken together, it seems that low-saturated fat, low-cholesterol diet counselling started in infancy, as given in STRIP, has a significant favourable effect on serum cholesterol values and endothelial function especially in boys, but does not harmfully influence children’s growth of cognitive, neurological or pubertal development.

What are the main strengths and weaknesses of STRIP study?

STRIP study in the foremost prospective infancy-onset coronary risk factor intervention trial. The initial study cohort was large (1062 infants) and at 15 years 50% of the cohort still participated in the project. The subjects were randomly allocated to intervention and control groups, which both included over 250 boys and girls, and the baseline characteristics did not differ between the study groups in any assessable way.

The STRIP study has several dimensions. First, the follow-up period of the intervention and control children and families is long, i.e. from 7 months of age through childhood and adolescence till early adulthood. The coronary risk factor profile exploration has been wide ranging (serum lipids and lipoprotein and apolipoproteins, blood pressure, recurrent infections, oral health, glucose and insulin values, habitual physical activity patterns, smoking, etc.), and many measurable aspects of daily life (nutrition, exercise habits, socioeconomic status (SES), psychosocial well being, etc.) have been explored. The core laboratory examinations have covered the key atherosclerosis risk factors and these values and aspects have been monitored in all STRIP children regularly and frequently, most of them annually. So, the STRIP study produces data in a well-documented manner. Collaboration with national and international studies is welcome.

However, there may have been selection bias in the initial recruitment of the study subjects, when the subjects were enrolled at the age of 7 months. Ideally, they should have been recruited at birth or during pregnancy. Therefore, the 0- to 6-month data are now retrospective. The study may suffer from ~60% participation rate with potential selection. Even though the participants and non-participants did not differ in any quantifiable way from each other, it is alluring to hypothesize that the participating families were initially more interested in health than the non-participants. Further, even though not aimed at, the control families may have been intervened as well as they like the intervention families, have regularly received information about their cholesterol values. The study results have also recently been reported widely in local media, which may also have influenced the dietary habits of the controls. To overcome these potential weaknesses, an effort is being made to recruit a new control group from Finnish young adults who have never been involved in STRIP.

The STRIP study and counselling of the intervention children is planned to continue until the participants are 20-years old. Thereafter, the two groups will be followed up less frequently but active counselling will be discontinued.

Where can I find out more?

List of original publications and other information can be found at http://stripstudy.utu.fi

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