Cohort Profile: The Cardiovascular Risk in Young Finns Study

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How did the study come about?

In Finland, coronary heart disease (CHD) incidence was very high in the 1960s and 1970s.1 In line with this high incidence, the Seven Countries Study showed that the level of serum cholesterol in Finns was also the highest among the investigated countries in the 1960s.2 Because several studies indicated that the atherosclerotic process starts early in life, and in accord with the World Health Organization Recommendation of 19783 which stated that studies assessing atherosclerosis precursors in children should be initiated, a program was launched in Finland in the late 1970s to study cardiovascular risk in the youth.4–6 The Cardiovascular Risk in Young Finns Study was designed as a collaborative effort between five university departments of medical schools (i.e. in Helsinki, Kuopio, Oulu, Tampere and Turku) and several other institutions in Finland. The aim was to study the levels of CHD risk factors and their determinants in children and adolescents of various ages in different parts of the country. Two pilot studies were carried out in 1978 (N = 264, age 8 years) and in 1979 (N = 634, aged 3, 12 and 17 years).6,7 The first main cross-sectional (baseline) study was performed in 1980. The baseline study included 3596 children and adolescents aged 3, 6, 9, 12, 15 and 18 years.8 Between 1980 and 1992, these cohorts were followed up at 3-year intervals. The latest examination of the Cardiovascular Risk in Young Finns Study was performed in 2001, when the participants were young adults, aged 24–39 years. At the time of writing, the 27-year (i.e. 27 years since the start of the study when the participants are aged 30–45 years) follow-up field studies are being conducted, and will be completed in the beginning of 2008.

What does it cover?

The main objectives of the study have been to: (i) study risk factor levels and their possible regional differences, (ii) study the determinants of CHD risk factors and the mechanisms by which risk factor levels change into adult levels, (iii) explore risk factor tracking, i.e. the maintenance of the relative ranking of an individual with respect to his peers, (iv) study possible clustering of risk factors, (v) study the effect of the time of the study and age of subjects on the results, (vi) identify psychological and behavioural risk factors generally, and recognize their age-specificity and (vii) collect background information for future intervention strategies.

In the 21-year follow-up study in 2001, non-invasive ultrasound studies were introduced to the study protocol to measure markers of sub-clinical atherosclerosis. These included carotid artery intima-media...
thickness (IMT), carotid artery elasticity and brachial artery endothelial-dependent flow-mediated dilation (FMD). Therefore, in recent years the main focus has been in vascular epidemiology, including analyses examining the relations between risk factors from childhood to adulthood with the markers of sub-clinical atherosclerosis.

The experience gained in the observational Young Finns Study has set the stage for the Special Turku Coronary Risk Factor Intervention Project for Children (STRIP) Study. STRIP Study is an ongoing mainly on dietary intervention trial to reduce cardiovascular diseases (CVD) risk beginning from infancy.

Who is in the sample?

The study has been carried out in all five Finnish university cities with medical schools and their rural surroundings. The first cross-sectional study was conducted in 1980. Altogether 4320 children and adolescents aged 3, 6, 9, 12, 15 and 18 years were randomly chosen from the population register of these areas to produce a representative sample of Finnish children. In practice, girls and boys of each age cohort in each study community were separately placed in random order on the basis of the unique personal identification number. Every $k$th girl and every $k$th boy in each community was selected so that the sample consisted of the required number of boys and girls. The varying $k$ factors were determined on the basis of sample size and the total number of boys and girls in the different age cohorts in each community. The final sample was designed to apply the following two considerations: (i) children and adolescents from different parts of Finland with varying CHD risk in adults should be studied and (ii) their socioeconomic background and living conditions should vary, so as to represent reasonably well all Finnish children and adolescents and allow comparisons of urban and rural and different socioeconomic groups.

How often have they been followed up?

After the first cross-sectional study in 1980, follow-up studies have been conducted 3 years apart (Table 1). Blood sampling and physical examination were conducted for the whole cohort in 1983 and 1986. In 1989, physical examinations and blood tests were gathered in one centre (Turku). The main aim of this 9-year follow-up was to study long-term tracking of serum lipoproteins in children and adolescents. In addition, background information using questionnaires was gathered from the whole cohort. In 1992, cohorts from Helsinki, Kuopio and Turku areas (~58% of the total cohort) were included for blood sampling. In 1992, physical examinations were performed only in the Turku area. The limitation in the sampling size in 1992 was due to economic constraints and does not imply loss to follow-up due to voluntary non-participation. Psychological data were collected in total cohort also in 1992 and 1997.

What has been measured?

**Cardiovascular risk factors**

The main study variables are shown in Table 2. In the first cross-sectional study in 1980, a comprehensive data collection was performed using questionnaires, physical measurements and blood tests, including general health status, serum lipoproteins, insulin, obesity indices, blood pressure, lifestyle factors, smoking status, alcohol use, food consumption, dietary intakes, food behaviour, physical activity, psychological and behavioural factors and socioeconomic status. In the follow-ups, serial information concerning these risk factors has been gathered. In addition, several novel risk factors, including C-reactive protein (CRP), homocysteine, asymmetric dimethylarginine (ADMA), adiponectin and leptin, were analysed in 2001. In addition, heart rate variability measurements

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*Limitations in the sampling size in 1989 and 1992 do not imply voluntary non-participation. In 1989, physical examinations and blood tests were gathered only in one centre (Turku). In 1992, the limitation in the sampling size was due to economic constraints.
to study autonomic nervous system function were collected in the latest follow-up in 2001.

**Vascular ultrasound studies**

To assess sub-clinical atherosclerosis, carotid artery IMT, carotid elasticity and brachial FMD were measured in the 21-year follow-up at the age of 24–39 years. These non-invasive vascular markers were chosen because they can be measured quickly and with relative ease in large population studies. Increased carotid IMT is a marker of structural atherosclerosis. It correlates with cardiovascular risk factors, coronary atherosclerosis and predicts cardiovascular events. Decreased carotid artery elasticity may reflect early functional changes related to atherosclerosis. It has been implicated as an independent predictor for cardiovascular mortality in high-risk individuals. Brachial FMD responses are thought to reflect systemic vascular endothelial function. Brachial FMD has been shown to predict cardiovascular events, and an improvement in FMD in response to optimized antihypertensive control has been associated with a favourable cardiovascular outcome.

**DNA banking and genotyping**

In 2001, genomic DNA was extracted from peripheral blood leukocytes. DNA samples were genotyped by employing the 5′ nuclease assay and fluorogenic allele-specific TaqMan MGB probes, using the ABI Prism 7900HT Sequence Detection System. The nucleotide sequences of the primers and probes used in the polymerase chain reaction were deduced from published sequences deposited in the GenBank and Celera databases and synthesized by Applied Biosystems.

**What is attrition like?**

The participation rates in follow-up studies have been satisfactory (Table 1). Of those invited (N = 4320), 3596 (83%) participated in the first cross-sectional study in 1980. The main reasons for non-participation included fear of clinical examination (16%), accompanying person was unable to leave from work (12%), child was unwilling to participate (12%) and lack of interest in the study (11%). The follow-up field studies were performed for the whole study population in 1983 and 1986, when 2991 (83.2%) and 2799 (78.3%) subjects participated. In 2001, 2283 subjects (63.5%) of the original cohort participated in clinical examinations and 2620 (72.9%) subjects returned questionnaires. We have examined the representativeness of the participants in 2001 by comparing their baseline (1980) characteristics to those of the participants who dropped out, and found that the participants were more often women and older.
than those who dropped out. Otherwise, comparing those who dropped out and participants using age-adjusted analysis found no significant differences in either men or women in total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, blood pressure, body mass index (BMI) or parents’ study years. In addition, there was no difference in physical activity between participants and dropouts.

What has it found? Key findings and key publications

Results from the Young Finns Study have clearly shown that individual’s biological risk factor profile is significantly modified by early lifestyle-related factors. Important for strategies of primary prevention among children and adolescents is the question of whether risk factors measured at one-time point are predictive of risk factor values years later. Therefore, several analyses into risk factor tracking have been conducted in the Young Finns Study. In the 12-year follow-up between 1980 and 1992, significant tracking was found for each of the serum lipid variables. The range of 12-year correlation was 0.48–0.58, 0.53–0.58, 0.53–0.58 and 0.33–0.37 for serum total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides, respectively.

Common risk factors of CHD such as dyslipidaemia and hypertension often co-exist in adults. This clustering is clinically important, since the harmful effects of multiple risk factors are synergistic. Observations from the 1980 and 1986 studies consistently showed that the clustering of adverse lipids, elevated blood pressure and increased obesity was more prevalent in boys compared with girls. Metabolic deviations related to insulin resistance seem to determine the clustering of biological risk variables in adults. Earlier observations from the Young Finns Study emphasize the role of insulin levels in predicting the clustering of the typical risk factor profile associated with insulin resistance syndrome also in children and adolescents. Fasting insulin concentration is associated with obesity, high triglycerides levels, low HDL cholesterol concentration and elevated blood pressure in children and adolescents, and predicts the development of hypertriglyceridaemia and clustering of these risk variables in young adulthood. In addition to metabolic risk factor clustering, risky behaviours also show significant clustering in the Young Finns population. The data gathered in the follow-up study in 1986 were used to study the clustering of several risk behaviours, such as non-prudent diet, smoking, physical inactivity and frequent inebriation by alcohol. In young adults, the determinants for adverse life-behaviour clustering included male sex, aggressiveness and past unemployment. On the other hand, paying a lot of attention to healthy behaviours, higher education (being a student), good self-perceived health and a high sense of responsibility seemed to be protective factors against risky behaviour clustering. The accumulation of risk behaviours was also associated with an atherogenic lipid and blood pressure profile. Thus, the concept of clustering is a complex phenomenon, where socioeconomic, demographic, dietary and behavioural factors determine the occurrence of risky behaviour clustering, which contribute to the development of an adverse metabolic risk profile.

Physical activity has been an intensive research topic in the Young Finns Study. For example, tracking of physical activity has been analysed on several occasions. A significant tracking was observed in physical activity from adolescence to early adulthood. These observations were confirmed in the 21-year follow-up study, when we could demonstrate that high level of physical activity at ages 9–18 years, especially when continuously, significantly predicted a high level of adult physical activity. Health effects of physical activity have also been examined. A cross-sectional analysis in 9–24-year-old subjects in 1986 (n = 2358) found that a high level of physical activity was associated with high-serum HDL-cholesterol, especially HDL-2 cholesterol concentrations, and low levels of serum triglycerides, apolipoprotein B and insulin in males. Recent analysis suggests that changes in physical activity patterns during the lifetime may contribute to the development of obesity, especially in women.

Psychological, behavioural and socioeconomic risk factors inside the families were highly accumulated comprising generally favourable and unfavourable developmental environments. Familial factors in subjects’ early childhood, such as parental job stress, Type A behaviour, life satisfaction and child rearing practices significantly predict adulthood risk factors like hostility and depression; and moderate other risk factors, such as early smoking and physical inactivity. In addition, a correlation between psychological and somatic risk factors of CHD is evident since childhood.

The 21-year follow-up study

At present, there are no prospective long-term data available that could be used to test the hypothesis that exposure to risk factors in childhood influence cardiovascular morbidity or mortality. Therefore, the main objective for the 21-year follow-up study in 2001 was to gather indirect evidence for this idea by examining how exposure to risk factors early in life influences the markers of sub-clinical atherosclerosis in young adulthood. The findings have been supportive of this hypothesis. We have observed that exposure to cardiovascular risk factors in early in life may induce changes in arteries that contribute to the development of structural and functional vascular changes related to atherosclerosis. For example, we have shown that exposure to high LDL cholesterol, elevated blood pressure, obesity and cigarette smoking in adolescence predict increased carotid IMT and decreased elasticity in young adulthood. In addition, the data suggest that elevated blood pressure during adolescence...
influences brachial FMD responses later on in adulthood.\textsuperscript{39} Most importantly, the effect of childhood risk factors on later sub-clinical atherosclerosis was independent of contemporaneous risk factors. Thus, these findings suggest that exposure to risk factors in childhood may increase the vulnerability of vascular wall to atherosclerosis.

Cross-sectional findings in 2001 regarding the inter-relations of vascular markers and biochemical risk have also provided interesting insights into the pathophysiology of atherosclerosis. Loss of normal endothelial function is hypothesized to be a fundamental step in the atherosclerotic disease process. The response-to-injury model of atherosclerosis\textsuperscript{40} predicts that arterial endothelial damage or activation is required before risk factors can induce atherosclerotic changes in the arterial wall. We have addressed this concept at the population level in the Young Finns Study. We demonstrated that the number of risk factors was associated with increased carotid IMT only among subjects with impaired FMD but not among those with enhanced FMD.\textsuperscript{41} The data thus support the concept that systemic endothelial function reflects the propensity of arteries to develop atherosclerosis in response to exposure to cardiovascular risk factors. Of the potential biochemical markers of endothelial function, we found that the levels of asymmetric dimethylarginine were, independently of conventional risk factors, associated with decreased brachial FMD response.\textsuperscript{41}

The analyses from the 21-year follow-up have also shown that socioeconomic, behavioural and psychological factors, e.g. depression and job strain are associated with cardiovascular risk factors and measures of sub-clinical atherosclerosis.\textsuperscript{42,43} For example, an association between job stress and carotid IMT was moderated by genetic dispositions, i.e. this association was related to certain genetic polymorphisms that sensitize the carriers to the stress.\textsuperscript{44} Childhood temperament, hyperactivity,\textsuperscript{45} and childhood eagerness-energy (a temperament-related sub-component of Type A behaviour)\textsuperscript{46} predict adult IMT over a follow-up periods of 21- and 15-years, respectively.

In addition to environmental factors, several genetic polymorphisms have been linked with cardiovascular risk factors, as well as with alterations in carotid and brachial artery structure or function in the Young Finns Study. We have utilized the candidate gene approach to explore potentially interesting relations between several known single nucleotide polymorphisms and clinical traits. Recently, genetic analyses have been an active part of the study. For example, by using the Mendelian randomization technique, we found no evidence of a causal association between CRP and carotid IMT.\textsuperscript{47} However, CRP genetics may influence arterial elasticity.\textsuperscript{38} In diabetes research, we found that variation of the transcription factor 7-like two gene predicted impaired fasting glucose in young adults.\textsuperscript{49} In addition, the role of apolipoprotein E polymorphism influencing serum lipid changes from childhood to adulthood was recently confirmed in the study.\textsuperscript{50}

Regarding risk factor trends over time, we observed a rapid decrease in total cholesterol levels between 1980 and 1986 and a modest decrease between 1986 and 2001.\textsuperscript{21} At the same time, a clear increase in BMI and triglycerides levels and a decrease in HDL-cholesterol and blood pressure levels was observed. In line with these findings, in 24-year-old subjects, the prevalence of the metabolic syndrome increased significantly from 1.0 to 7.5% in 15 years.\textsuperscript{51} Our reports have also shown that lifestyle adopted in childhood is clearly predictive of diet and physical activity in adulthood.\textsuperscript{31,52} Dietary patterns are established already in childhood, persist into adulthood and are significantly associated with CHD risk factors.\textsuperscript{53,54}

What are the main strengths and weaknesses?

The main strengths of the Young Finns Study include its longitudinal study design with regular follow-ups and collection of a diverse set of carefully measured phenotypes, lifestyle measures and socioeconomic background information. With the vascular measurements the study has the potential to provide important insights regarding the mechanisms of atherosclerosis, as it will be possible to test and integrate at the population level concepts that have emerged from experimental studies. The cohort provides a unique opportunity to study the development of lifestyle and risk factors from childhood to adulthood. The study makes it possible to relate the lifetime burden of risk factors on vascular ageing in these subjects. By linking morbidity and mortality statistics on the existing longitudinal database of this cohort, it will be possible to study the childhood determinants of adult health in a way that has not been previously possible. The cumulative data allow testing the hypothesis that common diseases and disorders have their origin in early life.

At this time, the main weakness of the study is that so far it is not possible to study the associations between childhood risk factors with disease end points. In addition, the generalizability of the findings is limited to white European subjects. Lost to follow-up is an inevitable problem in all long-term studies. Finally, original enrolment of the subjects occurred over a wide age range 3–18 years, therefore in a large proportion of subjects early childhood data are not available.

Can I get hold of the data?

Where can I find out more?

The Young Finns Study offers a unique opportunity to link detailed, longitudinal measures of conventional and novel cardiovascular risk factors, lifestyle, genetic
and psychological factors beginning from childhood with a range of outcomes in adulthood. Proposals for collaboration are welcome, and enquiries or requests for further information should be made to Olli Raitakari. Further information about the study, contact information and a bibliography are available on the website www.utu.fi/med/cardio/youngfinnssstudy

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