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Adult dyslipidemia prediction is improved by repeated measurements in childhood and young adulthood. The Cardiovascular Risk in Young Finns Study

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ABSTRACT

Background: Prediction of adult dyslipidemia has been suggested to improve with multiple measurements in childhood or young adulthood, but there is paucity of specific data from longitudinal studies.
Methods and results: The sample comprised 1912 subjects (54% women) from the Cardiovascular Risk in Young Finns Study who had fasting lipid and lipoprotein measurements collected at three time-points in childhood/young adulthood and had at least one follow-up in later adulthood. Childhood/young adult dyslipidemia was defined as total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C) or triglycerides (TG) in the highest quintile, or high-density lipoprotein cholesterol (HDL-C) in the lowest quintile. Adult dyslipidemia was defined according to European cut-points (TC > 5.0 mmol/L, LDL-C >3 mmol/L, Non-HDL-C >3.8 mmol/L, HDL-C <1.0 mmol/L (in men)/<1.2 mmol/L (in women) and TG > 1.7 mmol/L). With the exception of triglycerides, Pearson correlation coefficients for predicting adult levels significantly improved when two lipid or lipoprotein measurements in childhood/young adulthood were compared with one measurement (all $P < 0.01$). For triglycerides, there was significant improvement only when three measurements were considered ($P = 0.004$). Two measurements significantly improved prediction of dyslipidemia levels in adulthood for non-HDL-C, LDL-C, HDL-C and TG compared with one measurement ($P < 0.05$ for improved area-under the receiver-operating characteristic curve). Risk of dyslipidemia in adulthood grew according to the number of times a person had been at risk in childhood.
Conclusions: Based on these results, it seems that compared to a single measurement two lipid measures in childhood/early adulthood significantly improve prediction of adult dyslipidemia. A lack of dyslipidemia in childhood does not strongly exclude later development of dyslipidemia. Multiple measurements increase the prediction accuracy, but the incremental prognostic/diagnostic accuracy of especially third measurement is modest.

1. Introduction

Atherosclerotic cardiovascular disease (CVD) is the leading cause of death and disability in the world [1,2]. Atherosclerosis

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begins in childhood with its progression related to the presence and intensity of known CVD risk factors such as an atherogenic diet, high blood pressure and dyslipidemia [3,4]. Risk factor levels in childhood have a tendency to track [5–8], resulting in a sustained increase to the risk of experiencing a cardiovascular event later in life [9].

Dyslipidemia, a recognized risk factor for atherosclerotic cardiovascular disease [10–12], is defined as an abnormal lipid profile: elevated triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (Non-HDL-C) or total cholesterol (TC), or low high-density lipoprotein cholesterol (HDL-C). Childhood dyslipidemias have been associated with adult dyslipidemias [13] and surrogate markers of atherosclerosis such as carotid intima-media thickness [14,15], which has been shown to predict future cardiovascular events [16].

Current pediatric guidelines [17] for primary prevention of CVD recommend both a selective and a universal approach for screening of lipid and lipoprotein levels. The selective approach suggests that a fasting lipid profile should be obtained from children who have either a positive family history for CVD, dyslipidemia in either parent, or any other risk factors present (e.g. hypertension, obesity and diabetes), from the age of 2 years onward. The universal, population-wide, approach recommends screening of non-fasting lipid profile among all children aged 9–11 years and repeated among young adults aged 17–21 years – with the decision for a fasting lipid profile assigned by non-HDL-C levels above or equal to 3.75 mmol/l (145 mg/dl). However, there is paucity of specific evidence from longitudinal studies demonstrating whether obtaining multiple measurements in childhood and young adulthood improves prediction of adult dyslipidemias. Therefore, our aim was to examine whether prediction of abnormal lipid levels in adulthood becomes more accurate with repeated measurements in childhood or young adulthood compared with a measurement obtained at a single time-point.

2. Materials and methods

2.1. Population

Participants were drawn from the Cardiovascular Risk in Young Finns Study (YFS), which is a population-based follow-up study in Finland [18]. The study began in 1980 when 3596 children and adolescents aged 3–18 years were examined. Since then, follow-ups have been performed in 1983, 1986, 2001, 2007 and 2011. The present study is based on 1912 participants (53.9% women, mean age 12.4 years in 1983), who were aged 6–21 years in 1983, had participated in baseline examination in 1980 and child follow-up in 1986, and who had at least one adulthood measurement in either 2001, 2007 or 2011. Lipid measurements in adulthood were from the 2011 follow-up (75% of the adulthood measurements), except in case of missing data from 2011, measurements from 2007 (15%) or 2001 (10%) were used. Data on childhood smoking status from participants aged 12–18 years at baseline, and physical activity from participants aged 3–18 years at baseline were acquired with questionnaires.

The study was performed according to the Declaration of Helsinki and approved by local ethics committees. Written informed consent was given by participants or parents.

2.2. Measurement of serum lipids in childhood and adulthood

In childhood, venous blood samples were drawn after a 12-h fast. Serum samples were stored at −20 °C until thawed for the first time for the analyses. In 1980, 1983 and 1986, TC concentrations were measured using a fully enzymatic CHOD-PAP method (Boehringer Mannheim, Mannheim, Germany) with OLLI 3000 and Kone CD analyzers (Kone Co., Espoo, Finland). In 1980, serum HDL cholesterol concentrations were measured from the supernatant after precipitation of very low density lipoprotein cholesterol and LDL-C with dextran sulphate 500,000 (Pharmacia, Uppsala, Sweden) [19]. During 1980–1986, serum TG were determined by using a fully enzymatic method (Boehringer Mannheim). The concentration of LDL-C was calculated by using the Friedewald formula [20].

In adulthood, venous blood samples were drawn after an overnight fast and serum was separated, aliquoted and stored at −70 °C until analysis. TG concentration was determined using the enzymatic glycerol kinase–glycerol phosphate oxidase method (Triglyceride reagent, Beckman Coulter Biomedical, Ireland). TC levels were measured by the enzymatic cholesterol esterase–cholesterol oxidase method (Cholesterol reagent, Beckman Coulter Biomedical). The same reagent was used for estimating HDL-C levels after precipitation of LDL-C with dextran sulfate- Mg^{2+} [19]. All the above assays were performed on an AU400 instrument (Olympus, Japan) and the same methods were used both in 2007 and 2011. Due to changes in reagents or methods in 2001–2007, TG values were corrected by using correction factor equations [21]. LDL-C was calculated by the Friedewald formula in participants with TG levels <4.0 mmol/L [20]. Non-HDL-C was calculated as TC − HDL-C. The analysis methods for TC and TG have been accredited by the Finnish Accreditation Service according to standard ISO/IEC17025. Use of lipid-lowering medication in adulthood was examined by self-administrated questionnaires.

2.3. Definition of dyslipidemia risk in childhood and of adult dyslipidemia

We defined dyslipidemia in childhood based on either TC, LDL-C, non-HDL-C or TG being in the uppermost quintile of the age- and sex-specific distribution, or HDL-C in the lowest quintile. European cut-points were used in adulthood to denote abnormal serum lipid values: TC > 5.0 mmol/L (~190 mg/dL), LDL-C >3.0 mmol/L (~115 mg/dL), HDL-C in men <1.0 mmol/L (~40 mg/dL) and in women <1.2 mmol/L (~45 mg/dL), Non-HDL-C >3.8 mmol/L (~145 mg/dL), TG > 1.7 mmol/L (~150 mg/dL) [9].

2.4. Statistical methods

Attrition analyses were performed to examine differences in risk factor variables in 1983 by participant status at follow-up (non-participants vs. participants) to determine if loss to follow-up was differential. Descriptive values for childhood and adulthood variables were expressed as mean ± SD. Childhood and young adulthood lipid measurements were performed in 1980, 1983 and 1986. All values were transformed into age-, sex- and year-specific Z-scores. Year 1983 was used to represent the single measurement, the mean of 1980 and 1986 was used to represent two measurements, and the mean of 1980, 1983 and 1986 was used to represent three measurements. We took this approach to assign the single and combined measurements to negate any confounding introduced as a result of different length of follow-ups between the child/young adult measures and those collected in later adulthood. In adulthood, analyses of absolute values were performed using measurements from year 2011, except in cases of missing data when values from 2007 or 2001 were used. The mean of all adulthood measurements from 2001, 2007 or 2011 (between 1 and 3 measurements) transformed into age-, sex, and year-specific Z-scores was used to represent the adulthood lipid level in calculation of quintiles and in correlation analyses.