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Adolescence Risk Factors Are Predictive of Coronary Artery Calcification at Middle Age

The Cardiovascular Risk in Young Finns Study

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Objectives The purpose of this study was to examine the roles of adolescence risk factors in predicting coronary artery calcium (CAC).

Background Elevated coronary heart disease risk factor levels in adolescence may predict subsequent CAC independently of change in risk factor levels from adolescence to adulthood.

Methods CAC was assessed in 589 subjects 40 to 46 years of age from the Cardiovascular Risk in Young Finns Study. Risk factor levels were measured in 1980 (12 to 18 years) and in 2007.

Results The prevalence of any CAC was 19.2% (27.9% in men and 12.2% in women). Age, levels of systolic blood pressure (BP), total cholesterol, and low-density lipoprotein cholesterol (LDL-C) in adolescence, as well as systolic BP, total cholesterol, diastolic BP, and pack-years of smoking in adulthood were higher among subjects with CAC than those without CAC. Adolescence LDL-C and systolic BP levels predicted CAC in adulthood independently of 27-year changes in these risk factors. The multivariable odds ratios were 1.34 (95% confidence interval: 1.05 to 1.70; $p = 0.02$) and 1.38 (95% confidence interval: 1.08 to 1.77; $p = 0.01$), for 1-SD increase in adolescence LDL-C and systolic BP, respectively. Exposure to both of these risk factors in adolescence (defined as values at or above the age- and sex-specific 75th percentile) substantially increased the risk of CAC (multivariable odds ratio: 3.5 [95% confidence interval: 1.7 to 7.2; $p = 0.007$]) between groups with no versus both risk factors.

Conclusions Elevated adolescence LDL-C and systolic BP levels are independent predictors of adulthood CAC, indicating that adolescence risk factor levels play an important role in the pathogenesis of coronary heart disease. (J Am Coll Cardiol 2012;60:1364–70) © 2012 by the American College of Cardiology Foundation

The development of coronary heart disease (CHD) starts in childhood decades before clinical symptoms. The presence of preclinical atherosclerotic lesions in adolescents and young adults and their associations with CHD risk factors have been shown in autopsy studies (1).

Coronary artery calcium (CAC) is a sign of coronary atherosclerosis (2) most frequently present in advanced lesions and older individuals (3). The amount of calcified

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plaque correlates with the total amount of atherosclerotic plaque (4), and there is a direct association between CAC and CHD events (5–7). The presence of atherosclerotic plaque is confirmed by a positive scan finding, whereas the absence of detectable CAC on computed tomography (CT) among asymptomatic subjects implies that the presence of atherosclerotic plaque is substantially less likely (3,4,8).

The CARDIA (Coronary Artery Risk Development in Young Adults) study has demonstrated that early adulthood risk factors, including dyslipidemia, high blood pressure (BP), cigarette smoking, and elevated plasma glucose, are associated with increased coronary calcification 2 decades later in middle age independently of contemporary risk factors (9,10). In the Muscatine study, elevated body mass index (BMI) in childhood was associated with adult CAC (11). However, it is unclear whether exposure to other risk factors in adolescence is predictive of increased CAC in adulthood and whether adolescence risk exposure has an independent effect after taking into account a change in risk factors. The residual effect of adolescence CHD risk factor exposures on CAC risk would have implications for primary prevention programs (12). Childhood risk factors, such as dyslipidemia and elevated BP, have been associated with increased preclinical carotid atherosclerosis in adulthood (13–15), but no direct evidence exists linking adolescence lipid and BP levels to coronary atherosclerosis in adulthood. In the present study, we aimed to examine the roles of adolescence risk factors in predicting CAC 3 decades later in adulthood. To distinguish the effects of adolescence risk factor exposure from that of adult exposure, we estimated the residual effect due to adolescence risk exposure by taking into account the change in CHD risk factors from adolescence to adulthood (16). The study subjects were 589 participants in the prospective Cardiovascular Risk in Young Finns Study.

Methods

For detailed methods, please see the Online Appendix.

Participants. The Cardiovascular Risk in Young Finns Study is an ongoing follow-up study of atherosclerosis risk factors of Finnish children and young adults. The first cross-sectional survey was conducted in 1980 on 3,596 participants 3 to 18 years of age. The latest adult follow-up survey was conducted in 2007, in which 2,204 individuals participated (17). In 2008, a cardiac CT study to measure CAC was conducted for 589 individuals, then 40 to 46 years of age. This was a convenience sample; the 3 oldest cohorts from 3 centers with a possibility to perform CAC imaging were invited (N = 711), and the attendance rate was 80%. Risk factor levels among those who participated and those who did not are shown in Online Table 1. Sixty-two participants were taking antihypertensive medication, 19 were taking lipid-lowering medication, 4 used injected insulin, and 2 were taking oral medication for diabetes. No significant difference in results was observed after these participants were excluded from the analyses. Participants gave written informed consent, and the study was approved by local ethics committees.

Clinical characteristics. BMI was calculated as: BMI = weight in kilograms/height in meters squared (kg/m^2). BP was measured using a standard mercury sphygmomanometer in 1980 and a random zero sphygmomanometer in 2007. Smoking was defined as daily smoking in adolescence and/or in adulthood. Pack-years of smoking were calculated as the number of cigarette packs smoked daily multiplied by the duration of daily smoking in years.

Abbreviations and Acronyms

BMI = body mass index
BP = blood pressure
CAC = coronary artery calcium
CHD = coronary heart disease
CI = confidence interval
CRP = C-reactive protein
CT = computed tomography
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
OR = odds ratio

Biochemical analyses. Venous blood samples were taken after an overnight fast. Standard methods were used to determine total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride concentrations. Low-density lipoprotein cholesterol (LDL-C) was calculated indirectly using the Friedewald formula. In 1980, serum insulin was measured using a modification of the immunoassay method. In 2007, serum insulin concentrations were measured by a microparticle enzyme immunoassay kit. Serum high-sensitivity C-reactive protein (CRP) was analyzed with a turbidimetric immunoassay kit.

CAC scoring. CT scans were performed at 3 study locations: Turku, Tampere, and Kuopio, Finland. The scans were performed with a GE Discovery VCT 64-slice CT/positron emission tomography device (GE Healthcare, Milwaukee, Wisconsin) (Turku), a Philips Brilliance 64-slice CT device (Philips Medical Systems, Best, the Netherlands) (Tampere), and a Siemens Somatom Sensation 16-slice CT device (Siemens Healthcare, Erlangen, Germany) (Kuopio). CAC scores were calculated using the Agatston method for each coronary artery (18). The coefficient of variation for intraobserver measurements was 4%. Absence of CAC was defined as an Agatston score of 0 and presence of CAC as an Agatston score of 1 or greater (9). A phantom with deposits of known calcium concentration was also scanned twice using 3 projections at all of the study centers, and the calcium scores from these scans were compared. The coefficient of variation between all of the phantom scans was 3.9%.

Statistical methods. Logistic regression analysis adjusted for sex and age was used to test how risk factors predict the presence or absence of CAC. A series of multivariable logistic regression models were fitted, positing the dichotomous CAC variable (0 = absence of CAC, 1 = presence of CAC) as the outcome. First, a stepwise multivariable model adjusting for age, sex, and all continuous adolescence risk factors was fitted. Second, a multivariable model in-