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Improving long-term prediction of first cardiovascular event: The contribution of family history of coronary heart disease and social status

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ABSTRACT

Objective. The aim of this study is to assess whether family history of coronary heart disease (CHD) and education as proxy of social status improve long-term cardiovascular disease risk prediction in a low-incidence European population.

Methods. The 20-year risk of first coronary or ischemic stroke events was estimated using sex-specific Cox models in 3956 participants of three population-based surveys in northern Italy, aged 35–69 years and free of cardiovascular disease at enrollment. The additional contribution of education and positive family history of CHD was defined as change in discrimination and Net Reclassification Improvement (NRI) over the model including 7 traditional risk factors.

Results. Kaplan–Meier 20-year risk was 16.8% in men (254 events) and 6.4% in women (102 events). Low education (hazard ratio = 1.35, 95%CI 0.98–1.85) and family history of CHD (1.55; 1.19–2.03) were associated with the endpoint in men, but not in women. In men, the addition of education and family history significantly improved discrimination by 1%; NRI was 6% (95%CI: 0.2%–15.2%), raising to 20% (0.5%–44%) in those at intermediate risk. NRI in women at intermediate risk was 7%.

Conclusion. In low-incidence populations, family history of CHD and education, easily assessed in clinical practice, should be included in long-term cardiovascular disease risk scores, at least in men.

Introduction

Primary prevention of cardiovascular disease in clinical practice is based on subject's absolute risk of event within a certain time period, according to a set of established risk factors (Grover and Lowensteyn, 2011). Many efforts are nowadays dedicated to the contribution of novel markers to improve subjects' stratification beyond traditional risk factors (Hlatky et al., 2009). At this stage, promising biomarkers are recommended for secondary screening of subjects at intermediate risk, due also to the costs of assessment (The emerging risk factors collaboration, 2012; Wierzbicki, 2012), while non-laboratory risk factors assessed in clinical practice at lower costs may be especially beneficial at a population level. Family history of coronary heart disease (CHD) and low socio-economic status are well-established independent risk factors with the same level of evidence as high-sensitivity CRP or fibrinogen (Greenland et al., 2010; Perk et al., 2012). Family history remains to date the most accessible way of measuring disease heritability, and it reflects both the genetic trait and the environment shared among household members (Banerjee, 2012). Level of education is a frequently adopted proxy of social status, because it is easily measured, it remains stable over time, and it reflects both intellectual and material resources, as well as early lifetime conditions (Galobardes et al., 2006; Vescio et al., 2001). Despite the strong evidence coming from association studies, their contribution to short-term risk prediction beyond traditional risk factors has been examined to a lesser degree and with controversial findings (Fiscella et al., 2009; Franks et al., 2010; Ramsay et al., 2011; Sivapalaratnam et al., 2010; Woodward et al., 2007; Yeboah et al., 2012). Primary prevention of atherosclerotic cardiovascular disease is shifting towards the concept of long-term risk (International Atherosclerosis Society) for early identification and treatment of subjects at low short-term but at elevated lifetime risk of event. To this extent, the addition of a measure of disease inheritance and education, two time-invariant conditions in middle-aged adults, might improve long-term risk prediction beyond traditional risk factors.

In this paper, we aim to evaluate the contribution of family history and educational level as an indicator of social status to long-term risk prediction in a southern European population considered at low incidence of major cardiovascular events.

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Methods

Study population

We used data from three independent population-based surveys carried out between 1986 and 1990 as part of either the WHO-MONICA Project (2 surveys; Ferrario et al., 2001) or the PAMELA study (Cesana et al., 1991) in Brianza, an area located in northern Italy between Milan and the Swiss border. The underlying population is characterized by high levels of industrialization and urbanization, with one of the highest average incomes in Italy. Participation rates were 70.1% and 67.2% for the MONICA surveys, respectively, and 64% for the PAMELA Study. Detailed information on the study population by cohort is reported as supplementary material. Both the baseline screening and the follow-up for all the surveys were approved by the ethical committee of the Monza Hospital.

Baseline assessment of risk factors

Cardiovascular risk factors were collected at baseline according to the standardized procedures and quality standards of the WHO-MONICA Project (WHO). Serum total cholesterol, HDL-cholesterol and blood glucose were determined using the enzymatic method on a fasting blood sample. Systolic blood pressure was assessed twice, at 5 min apart, using a standard mercury sphygmomanometer; the study variable for systolic blood pressure is the average of the two measurements. A standardized interview was administered to participants by trained interviewers. Information on the use of anti-hypertensive treatment in the previous two weeks was dichotomized as yes/no; similarly, cigarette smoking habit was dichotomized as current versus past/never smokers. Diabetes mellitus was defined using self-reported diagnoses, information on insulin and oral hypoglycemic treatments and fasting blood glucose exceeding 126 mg/dl. The presence at baseline of a previous history of MI, unstable angina pectoris, cardiac revascularization or stroke was defined based on self-reported information.

Definition of family history of CHD and socio-economic position

First-degree family history of coronary heart disease ("Has one or more of your first degree relatives suffered from coronary heart disease?", with possible answers: yes/no) was ascertained at baseline as part of the interview, with no reference to age limit. The number of years of schooling ("How many years have you spent at school or in full time study?") was also investigated. As year of schooling is subject to modifications across different birth cohorts, we derived a three-class study variable (high, intermediate and low education) by comparing the years of schooling of any given subject with the distribution within his gender-specific birth cohort. Sample tertiles were used as cut-points. More details on this method have been previously published (Karvanen et al., 2007).

Study endpoint and follow-up procedures

The study endpoint is the occurrence of first major coronary event (myocardial infarction, acute coronary syndrome and coronary revascularization) or first ischemic stroke or carotid endarterectomy, fatal and non-fatal. Vital status and death certificates were available for 99% of the subjects. Suspected out-of-hospital deaths were investigated through interview of relatives. Suspected hospitalized coronary (discharge code ICD-IX 410 or 411 and ICD-IX CM 36.0–9 for coronary revascularization) and stroke events (ICD-IX 430–432, 434, 436; ICD-IX CM 38.01–39.22 or 39.50–39.52 with at least one 430–438 as discharge code, for carotid endarterectomy) were identified through deterministic and probabilistic record linkages with regional hospital discharge databases, obtaining a satisfactory performance in case finding, as reported (Ferrario et al., 2001, 2005; Fornari et al., 2008). All acute events were investigated and validated according to the MONICA diagnostic criteria (WHO); the ischemic subtype for stroke was attributed after review of the available clinical information.

Statistical analysis

To estimate the 20-year absolute risk of first major atherosclerotic event for the study subjects, we considered gender-specific Cox regression models on pooled data, as there was no evidence of any cohort effect in men (2 df chi-square test p-value: 0.35) nor in women (p-value: 0.24). Following a consolidated standard for the Italian population (Ferrario et al., 2005; Veronesi et al., 2013), the reference model included age, total cholesterol, HDL-cholesterol, systolic blood pressure, anti-hypertensive treatment, cigarette smoking and diabetes. Model calibration was assessed through the Grønnesby–Bogan goodness-of-fit test (May and Hosmer, 1998). The additional contribution of education and family history of CHD to long-term risk prediction was measured in terms of association, change in discrimination and reclassification improvement over the reference model (Hlatky et al., 2009). The reference category for education was "high education"; we report the overall 2 df Wald chi-square test p-value for significance. We also formally tested the interaction between education and family history. Change in discrimination was assessed as difference in the Area under the ROC-Curve (Δ-AUC) as well as Integrated Discrimination Improvement (IDI). The improvement in risk stratification was measured by a three-category Net Reclassification Improvement (NRI), with threshold values to define the categories (men: 10% and 20%; women: 2% to 10%) chosen based on previous assessment of clinical utility (Veronesi et al., 2013). In a sensitivity analysis we considered different thresholds as NRI is sensible to the choice of the cut-off values (Cook, 2012), but the findings did not change substantially from those presented here. We also present the reclassification plot for the full model with education and family history of CHD versus the reference one. We estimated Δ-AUC, IDI and NRI taking censorship into account (Chambless et al., 2011), and providing bootstrapped confidence intervals as well. Finally we replicated the analysis on 35–50 year old subjects, as in this age group genetics play a major role as cardiovascular event determinant (Kathiresan et al., 2009). All the analyses were conducted using the SAS software, release 9.2.

Results

4099 subjects were enrolled in the age range 35–69 years. 130 subjects with a positive history of CVD at baseline were excluded, as well as subjects with missing data on covariates of interest ($n = 11$). The available sample size for the analysis was 1941 men and 2015 women. Baseline characteristics of the study population, by gender, are shown in Table 1. The prevalence of family history of CHD at baseline was 27% in men and 34% in women; 42% of men and 37% of women were in the low education group. During a median follow-up time of 18 years (interquartile range: 12–20), we observed 254 first CVD events in men (188 coronary events) and 102 in women (68 coronary events). The Kaplan–Meier estimate for 20-year risk was 16.7% and 6.4% in men and women, respectively.

Association

In men, education was associated with incidence of cardiovascular events (2 df chi-square p-value 0.049) when controlling for age; in particular, men in the low education class had a significant 40% risk excess when compared to men in the high education group (95% confidence interval: 1.01, 1.88; Table 2). After the adjustment for traditional risk factors and family history of CHD, the association remained statistically

Table 1
Baseline characteristics (mean (SD) or %) of the study population and number of incident events, by gender. Men and women, 35–69 years old, CVD-free at baseline.

	Men ($n = 1941$)	Women ($n = 2015$)
Age (years)	50.7 (9.2)	50.5 (9.1)
Education (%)		
High education	30.0	32.1
Intermediate education	27.9	31.2
Low education	42.1	36.7
Family history of CHD (%)	27.2	34.3
Total cholesterol (mg/dl)	220.6 (42.2)	220.7 (44.1)
HDL-cholesterol (mg/dl)	50.2 (13.2)	61.3 (14.6)
Body mass index (kg/m^2)	26.1 (3.5)	25.5 (4.7)
Systolic blood pressure (mm Hg)	135.4 (19.1)	132.6 (20.4)
Anti-hypertensive treatment (%)	11.3	17.2
Diabetes (%)	7.1	4.4
Current smoker (%)	38.8	19.2
Incident coronary event (n)	188	68
Incident ischemic strokes (n)	81	37
Incident CVD event (n)	254	102