Genetic variation in behavioral risk factors for atherosclerosis: twin-family study of smoking and cynical hostility

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Abstract. Genetic and environmental components of two behavioral risk factors for atherosclerosis, smoking and cynical hostility, were assessed in a twin-family population from Finland. Questionnaire assessment of smoking and MMPI Cook-Medley cynical hostility were obtained from twins aged 16 and their parents, with data on all four family members in 1,228 families. Decomposition of the phenotypic correlation between smoking and hostility, by bivariate twin analysis, found effects of idiosyncratic and common environments in both adolescent sisters and brothers, with additive genetic effects differing across gender. Twin-family analyses indicated a major role of common environmental factors shared by offspring for both variables, but little role for cultural transmission.

Etiological factors for atherosclerosis operate at many different levels such as genetic factors, cellular, organ-specific or societal. At the personal level, behavioral risk factors such as smoking and hostility have been associated with the risk for atherosclerosis and its clinical manifestations. Smokers are more prone to atherosclerosis than nonsmokers and also have an increased risk of CAD, but the mechanisms by which components of cigarette smoke increase the risk of atherosclerosis and CAD are not fully understood [1]. Risk of carotid atherosclerosis in monozygotic twins who smoke is greater than in their nonsmoking cotwins [2]. Data on families and twins show that various aspects of smoking behavior aggregate in families [3] and may have a genetic component.

Epidemiological studies during the last 20 years suggest that individual differences in personality characteristics reflecting various aspects of coronary-prone behavior are related to future risk of cardiovascular illness. This Type A coronary-prone behavior pattern (TABP) was defined by Rosenman and Friedman in 1974. However, subsequent studies support the hypothesis that the hostility/cynicism dimension is the major component of TABP. The Minnesota Multiphasic Personality Inventory (MMPI) Cook-Medley Hostility (Ho) scale is a useful questionnaire-based instrument to measure hostility/anger and shows a stronger effect in relation to coronary atherosclerosis assessed by arteriography than TABP categorization. These findings have been strengthened by results from several prospective studies (see the review by Dembroski and Williams [4]). Although not all prospective studies have found this association, these negative findings may be due to methodological limitations, such as the invalidity of hostility scores resulting from subject selection procedures and the instability of such scores in younger populations. The mechanisms which could explain the deleterious effect of hostility are not clear. It has been suggested that hostile persons respond to some events with more pronounced increases in blood pressure and neuroendocrine levels than do nonhostile persons. Repeated frequently, this phenomenon may have a role in the development and expression on cardiovascular disease. Stronger pathophysiological responses among hostile individuals than in less

hostile persons may arise in response to interpersonal challenge or conflict. When assessing various mechanisms for the association of hostility and coronary heart disease, behavioral aspects should be considered. Recently, it has been reported that hostility may contribute to health problems through its influence on other coronary risk factors [5,6].

Genetic determinants of hostility have been analyzed in several studies of twins, and most of them reported that individual differences in Cook-Medley Ho scores have a heritable component [7—9]. Different results may be due to small and selected samples of twins and also due to different measures of hostility. We assessed genetic and environmental components of smoking and cynical hostility in twin-families in Finland.

Materials and Methods

Twin pairs born between 1958 and 1986 have been identified from the Central Population Register of Finland [10]. For twins born in 1974 or after, the number of twins identified from the CPR is practically identical to the number of twins born annually according to birth statistics compiled by the Central Statistical Office of Finland. In February 1991, a health and lifestyle survey of 16-year-old twins was initiated after a pilot study had been carried out to test the questionnaire and mailing procedures. Questionnaires were mailed to twins born in 1975, 1976 and 1977 within 2 months of their 16th birthday. The data reported in these analyses is thus based on 3 years of responses. During this period, 1858 families of twins were contacted. In 1684 families at least one family member replied (91%), while the response rate among individuals was 85% for all boys and 91% for all girls. The parents were also asked to reply separately to a questionnaire on their own health and lifestyle; the response rates for mothers was 85% and 79% for fathers. Among the 1661 families with both twins and both parents alive and with a valid address, all family members replied in 1228 families (74%).

Twin zygosity was determined by the validated questionnaire method, which uses a set of decision rules supplemented by discriminant analysis, to classify the twin pairs as monozygotic (MZ), dizygotic (DZ) or undetermined zygosity [11]. Additional information on zygosity was derived from the family questionnaire filled out by the parents. Uncertainty about zygosity after these procedures remained for 3% of pairs, and these pairs were excluded from these analyses. Sample size in analyses varies, depending on which family members have been included and on the presence of missing data for the dependent variables.

Measures

Three questions were used to assess cigarette smoking status among the adolescents, while adult cigarette smoking was probed using six questions. Because the adolescents' smoking habits are still in their formative stages, the current analyses are based on a dichotomous trait for the presence or absence of some smoking exposure. We defined smokers as those adolescents who had smoked a total of more than 50 cigarettes, whether or not they currently smoked; 32% of sons and 29% of daughters were classified as smokers. For adults (mother and fathers), we applied a similar measure: smokers were defined as those who had smoked more than 100—200 cigarettes — nearly all had been or were regular, daily smokers as adults. Of fathers 71% fulfilled this criterion compared to 46% of mothers, which proportions reflect historical trends in smoking among men and women in Finland. Hostility was assessed using a 17-item cynical hostility subscale of the Cook-Medley Ho scale [9]. The mean score was 10.69 (SD 4.52) for fathers, 10.13 (4.48) for mothers, 11.65 (4.23) for sons and 11.51 (3.98) for daughters.

Statistical methods

To estimate genetic and environmental components of variance, a structural equations model [12] approach using the LISREL [13] program was used. The analysis of twin data alone permits the estimation of three parameters: an additive genetic (a) component, unique environmental (e) components and either effects due to dominance (d) or common (c) environmental components [12]. Familial similarity was estimated by computing polychoric correlations, while parameter estimation was done by using the weighted least squares approach.

A bivariate twin analysis was performed to examine whether the genetic and environmental effects on smoking are correlated with the genetic and environmental effects on hostility. The analysis explores to what extent the observed covariance between smoking and hostility can be accounted for by a correlation between additive genetic effects (r_a), a correlation between common environmental effects (r_c), and a correlation between the unique environmental effects on smoking and hostility (r_e) (p. 269 [12]). Models were fitted separately for male and female twins; opposite-sex twins were excluded from these analyses.

With the inclusion of parental data, other parameters can be estimated from twin-family data. We used a model of phenotypic assortment (p. 334 [12]) to estimate, in addition to a, c and e, the correlation between parental phenotypes (μ), cultural transmission (z), and the correlation (s) between additive genetic and shared environmental effects induced by parental transmission of both genetic and environmental factors to their offspring. The expected correlations under the full phenotypic assortment model are for MZ twins: a^2+c^2+2asc, for DZ twins: $\frac{1}{2}a^2[1 + (a + sc)^2\mu] + c^2 + 2asc$, for spouses ($\mu$), and finally, for mother–offspring and father–offspring: $[\frac{1}{2}a(a + sc) + cz](1 + \mu)$. Chi-square ($\chi^2$) goodness-of-fit statistics were used to assess how well each model fit the data [12].

Results and Discussion

Parent–offspring and spousal correlations for hostility and smoking ranged from 0.11 to 0.42 (Table 1), with the parent–offspring correlations lower than spousal or twin correlations (Table 2). The correlation in the offspring between hostility and smoking was 0.25 with no sex difference. The twin correlations for hostility showed a different pattern from the correlations for smoking in both girls and boys.

The bivariate twin analysis model fitted well in boys ($\chi^2 = 0.87$, df = 4, p = 0.93), yielding estimates that 49% of phenotypic variance in hostility was due to additive genetic effects, 5% to shared environmental effects, and 46% to unique environmental effects.

Table 1. Familial correlations [and standard errors] for hostility (above diagonal) and smoking (below diagonal). Numbers in curved parentheses indicate the number of parent–offspring and spouse pairs

Correlation	Father	Mother	Sons	Daughters
Father	—	0.28 [0.029] (1226)	0.11 [0.047] (1209)	0.12 [0.047] (1314)
Mother	0.42 [0.018] (1317)	—	0.17 [0.043] (1319)	0.16 [0.040] (1473)
Sons	0.22 [0.029] (1290)	0.10 [0.27] (1410)	—	—
Daughters	0.24 [0.28] (1391)	0.30 [0.026] (1537)	—	—

Table 2. Pairwise polychoric correlations (and standard errors) for hostility and smoking among 16-year-old twin pairs

Zygosity and sex	Hostility	Smoking	Pairs
Male MZ	0.54 (0.050)	0.93 (0.032)	176
Male DZ	0.27 (0.058)	0.84 (0.046)	224
Female MZ	0.51 (0.036)	0.93 (0.025)	281
Female DZ	0.40 (0.044)	0.78 (0.056)	225
Opposite-sex	0.26 (0.042)	0.46 (0.063)	513

Corresponding effects for smoking were 17% (additive genes), 75% (shared environment) and 8% (unique environment) respectively. There was no correlation between genetic effects, while the correlation between shared environmental effects was 1.0 (at boundary) and 0.25 for unique environmental effects. The corresponding bivariate twin analysis model for girls also fitted well (χ^2 = 2.29, df = 4, p = 0.68), yielding estimates that 25% of phenotypic variance in hostility was due to additive genetic effects, 26% to shared environmental effects, and 49% to unique environmental effects. Corresponding effects for smoking were 30% (additive genes), 63% (shared environment) and 7% (unique environment) respectively. The correlation between genetic effects was 0.37, between shared environmental effects 0.40, and 0.04 for unique environmental effects.

For each trait, the twin-family data were fitted to the full phenotypic assortment model. In none of the models was the cultural transmission parameter significantly different from zero, and reduced models with this parameter fixed at zero fitted the data well. A similar result was found in analyses of smoking initiation in Dutch twin-families [13]. Compared to the bivariate twin analysis, the family models yielded smaller estimates of additive genetic effects and higher estimates of common environment for hostility, while for smoking the two analyses yielded quite similar results. Spousal correlations were higher for smoking than for hostility. Our results confirm that individual differences in hostility have a heritable basis, while the genetic component in smoking initiation appears to be of lesser importance than common environmental effects shared by children in a family.

Acknowledgements

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