ELSEVIER

Atherosclerosis 179 (2005) 111–117

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

Correlation of parents' longevity with carotid intima–media thickness in patients attending a Lipid Clinic

Damiano Baldassarre[a,b,1], Mauro Amato[a,b], Fabrizio Veglia[b], Linda Pustina[a], Samuela Castelnuovo[a], Silvia Sanvito[a], Lorenzo Gerosa[a], Cesare R. Sirtori[a], Elena Tremoli[a,b,*]

[a] *Center E. Grossi Paoletti, Department of Pharmacological Sciences, University of Milan, Via Balzaretti 9, 20133 Milan, Italy*
[b] *Center Cardiologico "Monzino", IRCCS, Milan, Italy*

Received 28 October 2003; received in revised form 26 July 2004; accepted 31 August 2004
Available online 18 October 2004

Abstract

The relationship between carotid intima–media thickness (IMT) and the subject's parents' longevity has been investigated. The association between parents' age at death and IMT was estimated in 593 consecutive patients attending a Lipid Clinic by survival-analysis methods. Average maximum IMT (Avg-IMT), maximum IMT (Max-IMT), clinical and laboratory variables and parental age at death, were assessed. Kaplan–Meier analyses showed significant differences in survival curves, low IMTs being associated with long-lived parents ($p = 0.0003$ and 0.001 by log-rank test for fathers and mothers, respectively). A Cox proportional hazards regression model showed that higher carotid IMT values were associated with father's and mother's deaths at an early age, even after adjusting for conventional cardiovascular risk factors. These data were confirmed after the stratification of patients into younger (<65 y) and older (≥65 y) or into subjects with and without a family history of dyslipidemia or vascular diseases. In addition, by stratifying subjects into those with no, one or two long-lived parents, we observed a significant trend for the combination of father's and mother's longevity on their offspring's IMTs ($p < 0.01$ and 0.05 for Avg-IMT and Max-IMT, respectively). These data highlight a significant relationship between carotid artery IMT and a familial predisposition to be long-lived that is independent of the individual's vascular risk profile.

Keywords: Carotid arteries; Intima–media thickness; Atherosclerosis; Parental age; Longevity

1. Introduction

Subjects with a parental history of coronary heart disease (CHD) are at higher risk of developing atherosclerosis. A higher familial prevalence of established atherosclerosis risk factors (i.e. hypercholesterolemia, hypertension, diabetes, smoking habit and obesity) may partially explain the familial aggregation of CHD [1–4]. Since conventional risk factors do not fully justify the variability in CHD incidence [5–7], a number of authors have suggested that also other unknown determinants may be involved in the atherosclerotic process and probably also in the familial predisposition to this disease [1,2,8–13]. Intimal thickening of the coronary arteries in infancy, determined in autopsy studies, has been shown to be associated with the grandparents' history of coronary disease [14]. Angiographic [15–17] and ultrasonic [18–20] studies of atherosclerosis show that patients with a familial aggregation of CHD have more advanced atherosclerosis than appropriate controls. Although a family history of CHD has long been recognized as a major risk factor for atherosclerosis, the possible protective effect of genetic factors or specific family behaviours in a family with long-lived members has not been investigated before.

Longevity is the result of health-promoting behaviours plus genetic factors that promote disease resistance and

* Corresponding author. Present address: Department of Pharmacological Sciences, University of Milan, Via Balzaretti 9, 20133 Milan, Italy.
Tel.: +39 02 503 18318; fax: +39 02 503 18250.
E-mail addresses: damiano.baldassarre@unimi.it (D. Baldassarre), elena.tremoli@unimi.it (E. Tremoli).
[1] Tel.: +39 02 503 19907/19908; fax: +39 02 503 19900.

0021-9150/$ – see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2004.08.032

long-term survival. If environmental factors did not change from one generation to the next, parents' and children's longevity would be expected to be similar. Studies do, in fact, show similarities in the age of death in parents and offspring [21–23], while other studies confirm that parental survival is an independent predictor of offspring's longevity [24].

In this study, we have investigated whether familial predisposition to longevity is a determinant of intima–media thickness (IMT) in patients attending a Lipid Clinic, by assessing the relationship between their parents' longevity and the IMT of extracranial carotid arteries, a widely accepted non-invasive surrogate index of CHD [25].

2. Methods

2.1. Subjects

Five hundred and ninety-three consecutive patients (299 men and 294 women) attending the Ultrasound Laboratory of the E. Grossi Paoletti Centre (Niguarda Hospital, Milan, Italy) were analysed by carotid B-mode ultrasound imaging. The ultrasonic procedure is routinely performed in each patient attending for the first time at our Lipid Clinic.

Patients attend our Lipid Clinic either spontaneously or when referred by basic practitioners and as such they can have lipid or lipoprotein abnormalities (plasma LDL cholesterol >4.14 mmol/L; triglycerides >2.28 mmol/L, HDL-cholesterol ≤1.04 mmol/L), borderline hyperlipidemias (plasma LDL cholesterol 3.37–4.12 mmol/L, triglycerides 1.71–2.27 mmol/L) and even a normal lipoprotein pattern (plasma LDL cholesterol <3.34 mmol/L, triglycerides <1.70 mmol/L, HDL-cholesterol >1.04 mmol/L).

In the group studied, 480 patients (80.9%) were hyperlipidemic, 86 (14.5%) were borderline hyperlipidemic, and 27 (4.6%) had a normal lipoprotein pattern. Two hundred and fourteen patients (36.08%) were hypertensive (systolic or diastolic blood pressure ≥140 mmHg and ≥90 mmHg, respectively, or under treatment with hypotensive drugs). Thirteen patients (2.2%) were diabetic or were taking oral hypoglycemic drugs. Seventy-seven patients (13.0%) had a previous history of coronary heart disease (CHD), 29 (4.95%) of cerebrovascular disease (CVD) and 43 (7.3%) of peripheral arterial disease (PAD). The patients (46.7%) had a self-reported family history of CHD, 28.8% of CVD and 4.2% of PAD. About 56% of the patients reported a family history of hyperlipidemia, supported by medical records of at least one first-degree relative (siblings, parents, offspring).

More than 45.9% of the patients (272) were being treated with hypolipidemic drugs (statins, resins, probucol or fibrates), 20.1% with hypotensive drugs (beta-blockers, calcium antagonists, ACE inhibitors, sartans or diuretics), 15.3% with antiplatelet drugs, 2.2% with oral anticoagulants, 5.1% with hypoglycemic agents and 2.2% with uricosuric drugs or hormone replacement therapy. One hundred and twenty-four patients (20.9%) were current smokers, and 187 (31.5%) were previous smokers (at least 1 year after cessation of smoking).

Carotid IMT [26] was determined manually in real time [27]. Clinical and laboratory variables were also assessed. Oral informed consent was obtained from all the patients. The study was approved by the Institutional Review Board.

2.2. Lipids

Blood samples were collected from the antecubital vein after overnight fasting. Total and HDL cholesterol and triglyceride levels were determined in fresh serum by enzymatic methods [28,29]; HDL cholesterol levels were obtained by selective precipitation with dextran–$MgCl_2$ [30]. Serum LDL cholesterol levels were calculated by the Friedewald's formula [31].

2.3. Parental history of longevity

To define the parental history of longevity, subjects were asked by means of a standardized questionnaire whether their parents were still alive and how old they were. If a parent was deceased, the age and the reason of death were recorded. In the same questionnaire, first-degree family history of hyperlipidemia, hypertension, diabetes, obesity, CHD (fatal and nonfatal acute myocardial infarction, unstable angina, and coronary revascularization procedures), CVD (fatal and nonfatal stroke, transitory ischemic attack, and carotid surgery) or PAD (critical limb ischemia and revascularization procedures of the lower limbs) were also recorded. Apart from certification of family history of hyperlipidemias (required by Italian health system to allow patients to obtain lipid lowering drugs free of charge), no further medical records were obtained to validate the self-reported information.

For the deceased parents, fathers' and mothers' median ages of death were 69 and 73 years, respectively. Parents dead or still alive after these cut-offs were defined as "Long Lived" and those dead before, as "Short Lived". Parents still alive but younger than these cut-off ages (42 fathers and 113 mothers) were excluded from some analyses because of the impossibility to be correctly classified.

To investigate if a familial predisposition to be long lived inherited from both parents yields a more favourable IMT profile than having just one or no 'long-lived' parent, the association between carotid IMT and the number of long-lived parents was also investigated. The analysis was performed after data adjustment for relevant covariates (see Section 2.5). In these analyses, patients with parents younger than 40 years of age (alive or dead) and/or patients with fathers alive but younger than 69 years and/or mothers alive but younger than 73 years were considered as confounding because of the impossibility to be defined with sureness as long lived ($n = 95$) and as such, excluded.

2.4. Ultrasonography

Ultrasound scanning of the carotid arteries was performed by a single expert sonographer (DB) with a 8-MHz transducer

having axial and lateral resolutions of about 0.385 and 0.500 mm, respectively. The sonographer was blinded to the subject's characteristics. The near and far walls of the right and left common, internal and external carotid arteries (CCA, ICA and ECA) and bifurcations (BIF) in three different projections (anterior, lateral and posterior) were scanned using a standard protocol [32]. Eight segments of the right and left carotid arteries in each projection were examined, and the 48 IMT measurements were averaged to calculate the average maximum IMT (Avg-IMT) for each subject. Fewer than 1% of all IMT measurements were missed for anatomical reasons. The highest IMT value among the 48 segments was defined as the maximum IMT (Max-IMT).

2.5. Statistical analysis

As we were dealing with mortality data, with many censored times (still living parents), we used survival-analysis methods. Total mortality was used in place of putative cardiovascular mortality reported by the offspring, because although less specific, it is far more reliable in the absence of medical records.

Unadjusted survival curves for tertiles of patients' carotid IMTs were computed by the Kaplan–Meier method. Since the survival curves for patients in the lowest two tertiles overlapped, patients were divided into only two categories: those with 'high' (top tertile) or 'low' (lower two tertiles) carotid Max-IMTs.

Multivariable analysis, controlling for therapy (lipid lowering, antihypertensive and hypoglycemic) and conventional cardiovascular risk factors: age, gender, smoking habits, diabetes, total-cholesterol, HDL-cholesterol, triglycerides, blood glucose, systolic and diastolic blood pressure and family history of vascular diseases, of hyperlipidemia and of hypertension, was performed using Cox proportional hazards regression model. Furthermore, a Cox analysis stratified for age classes of 10-year spans was performed.

To assess the combined effect of father's and mother's longevity, patients were classified as having no, one or two long-lived parent(s). The independent contribution of fathers' and mothers' longevities was tested in a factorial model by covariance analysis after data adjustment for the same potential confounders mentioned above.

Results are reported as means ± S.D., if not otherwise stated. Logarithmic transformation was performed when the distribution of values was skewed, namely for lipoprotein (a) and triglycerides. For categorical variables, group differences were examined with the use of contingency tables and a χ^2 test of significance. Values of $p < 0.05$ were considered statistically significant.

3. Results

Patients' characteristics are shown in Table 1. The group was balanced by gender. Ages ranged from 14 to 79 years, mean ± S.D. 55 ± 11.6 years. About one-third of the patients were ex-smokers and one-fifth current smokers. As expected, most patients were dyslipidemic.

Table 1
Characteristics of patients ($n = 593$)

Age (years)	55 ± 11.6
Male (%)	50.4
BMI (kg/m^2)	23.9 ± 3.0
Never smokers (%)	47.6
Former smokers (%)	31.5
Current smokers (%)	20.9
Systolic BP (mmHg)	133 ± 16
Diastolic BP (mmHg)	82 ± 10
Total cholesterol (mmol/L)	6.99 ± 1.49
LDL-cholesterol (mmol/L)	4.86 ± 1.44
HDL-cholesterol (mmol/L)	1.33 ± 0.36
Triglycerides (mmol/L)	1.51 (1.37−9.9)
Lipoprotein(a) (mmol/L)	0.75 (0.04−4.82)
Blood glucose (mmol/L)	5.25 ± 0.84
Uric acid (mmol/L)	0.29 ± 0.09
Fathers' age (years)	67.4 ± 13.0
Mothers' age (years)	70.3 ± 13.4
Avg-IMT (mm)	0.76 ± 0.28
Max-IMT (mm)	1.59 ± 0.93

Data are expressed as means ± S.D., with the exception of gender and smoking habits shown as % and triglycerides and lipoprotein(a) as the median (range). BMI: body mass index. HDL-C and LDL-C, high- and low-density lipoprotein cholesterol, respectively. Avg-IMT and Max-IMT, average maximum IMT and maximum-IMT, respectively.

At the time of the study, 19.6% of the fathers and 43.2% of the mothers were still alive. The median age was 70 and 73 years for fathers and mothers, respectively. About 54.5% of the fathers and 51.7% of the mothers had lived longer than 69 and 73 years, respectively. Carotid IMT values were widely distributed from normal to overtly atherosclerotic, with an Avg-IMT ranging from 0.4 to 2.1 mm and Max-IMT ranging from 0.4 to 5.9 mm.

The association between parents' ages and IMT variables was first evaluated by Kaplan–Meier survival analysis (Fig. 1). By considering total mortality, a significant difference in survival curves of the parents of patients with high or low carotid Max-IMTs was observed ($p = 0.02$ and 0.006 by log-rank test for fathers and mothers, respectively), low IMTs being associated with long-lived parents. Similar results were observed if Avg-IMT was used instead of Max-IMT (data not shown).

A Cox proportional hazards regression model was used to calculate the adjusted hazard ratio (HR) for parent's death (Table 2). Both Avg-IMT and Max-IMT were explored as predictors. In the whole group of patients Avg-IMT (HR = 1.68, 95% CI 1.17, 2.42; $p = 0.005$) and Max-IMT (HR = 1.15, 95% CI 1.03, 1.29; $p = 0.013$) were significantly associated with earlier father's death after adjustment for covariates listed in the legend of the table. Similarly, Avg-IMT (HR = 1.53, 95% CI 1.03, 2.26 $p = 0.035$) and Max-IMT (HR = 1.17, 95% CI 1.04, 1.32 $p = 0.01$) were significantly associated with earlier mother's death.

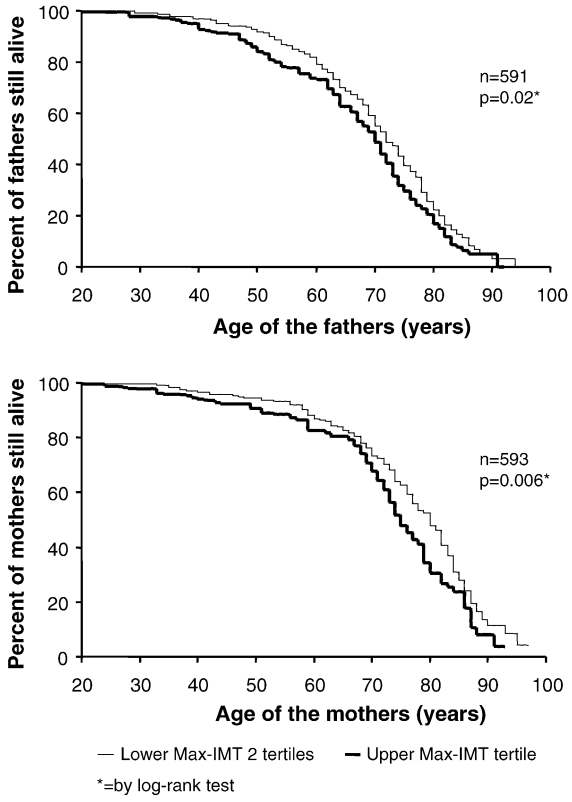

Fig. 1. Fathers' (top panel) and mothers' (bottom panel) survival-distribution curves estimated by Kaplan–Meier analysis of subjects having high (upper tertile: ▬) or low (lower two tertiles: —) age-adjusted carotid Max-IMTs.

Since a potential bias might arise from parents' differences in social, nutritional and medical status between old and young subjects (Cohort effect), the analyses were repeated after dividing the patient population into young (<65 years) and old (≥65 years) subjects. Even after this stratification, the differences in father's and mother's Kaplan–Meier survival curves associated with high or low Max-IMT were still significant in both groups (data not shown). The HRs obtained by applying the Cox model to the two groups are shown in Table 2. The differences in HRs between the two strata were tested by computing the interaction terms between IMT size and age group. In no case, was the interaction significant, either for Avg- or Max-IMT, which suggests that any Cohort effect is not strong. Lastly, when a stratified Cox analysis was performed, considering age classes in 10-year spans, the association between both Max-IMT and Avg-IMT with parent's longevity was still significant (data not shown). No gain in precision was obtained when total mortality was replaced with offspring reported putative cardiovascular mortality. In this analysis, indeed, after adjustment for the same covariates listed in Table 2, Avg-IMT (HR = 1.74, 95% CI 1.10, 2.73; $p = 0.017$) but not Max-IMT (HR = 1.12, 95% CI 0.97, 1.29; $p = 0.115$) were significantly associated with earlier father's death; and both Avg-IMT (HR = 1.46, 95% CI 0.91, 2.36 $p = 0.035$) and Max-IMT (HR = 1.18, 95% CI 1.03, 1.36 $p = 0.02$) were significantly associated with earlier mother's death.

Kaplan–Meier and Cox analyses were also repeated after dividing the patient population into those reporting a family history of vascular disease ($n = 373$) or not ($n = 220$). The differences in the parents' survival curves of patients with high or low Max-IMT were still present (data not shown); no significant interaction between IMT size and reported family history was observed. Significances were not modified even after dividing the patient population into those reporting a family history of hyperlipidemias ($n = 259$) or not ($n = 334$) (data not shown).

3.1. Combined effect of father's and mother's longevity on offspring's IMT

After stratification into patients having no ($n = 69$), one ($n = 212$) or two long-lived parents ($n = 217$), the three groups did not differ in terms of anamnestic clinical or biochemical variables, with the exception of the slightly higher age of patients with no long-lived parents (60.9 ± 8.1; 58.1 ± 8.6; 57.9 ± 7.7 y for "none", "only one" and "both parents" long lived, respectively; $p = 0.05$) and a marginally higher total cholesterol in those with both long-lived parents (6.78 ± 1.12;

Table 2
Associations between patients' IMTs and fathers' and mothers' survival evaluated by Cox's proportional hazards regression model in the whole group and after stratification into young (<65 y) and old (≥65 y) patients

	n	Avg-IMT		Max-IMT	
		Hazard ratio[a] (95% CI)	*p*	Hazard ratio[a] (95% CI)	*p*
Father's death					
Whole group	591	1.68 (1.17–2.42)	0.005	1.15 (1.03–1.29)	0.013
Young patients	460	1.50 (0.91–2.48)	0.114	1.06 (0.92–1.23)	0.427
Old patients	131	2.15 (1.14–4.05)	0.017	1.37 (1.10–1.69)	0.004
Mother's death					
Whole group	593	1.53 (1.03–2.26)	0.035	1.17 (1.04–1.32)	0.010
Young patients	462	1.27 (0.70–2.29)	0.436	1.08 (0.92–1.26)	0.360
Old patients	131	1.94 (1.01–3.73)	0.047	1.41 (1.12–1.77)	0.003

Analyses performed after data adjustment for: age, gender, smoking habits, diabetes, triglycerides, HDL-C, total cholesterol, blood glucose, systolic and diastolic blood pressure, therapy (lipid lowering, antihypertensive and hypoglycemic drugs) and family history of vascular diseases of hyperlipidemia and of hypertension.

[a] For 1 mm of IMT increase.

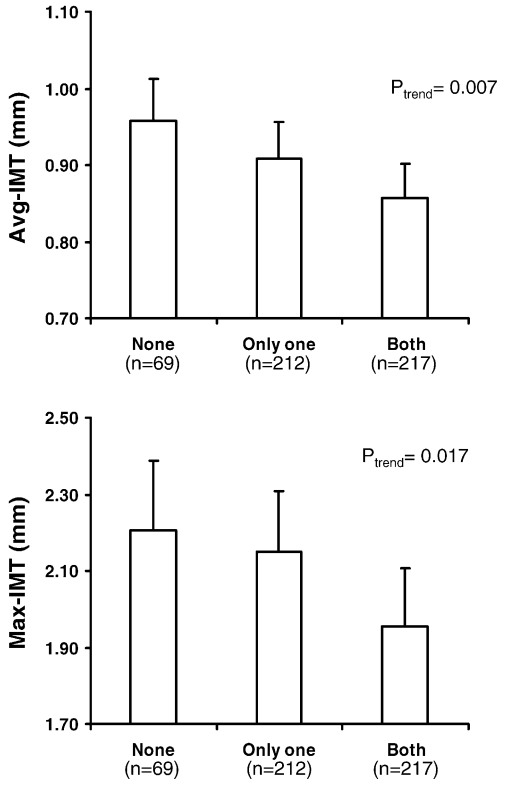

Fig. 2. Average (Avg-IMT, top panel) and maximal (Max-IMT, bottom panel) carotid IMT of patients stratified according to the number of their long-lived parents. Fathers and mothers were considered as long-lived when they lived at least 69 and 73 years, respectively. The significance of a trends was calculated after data adjustment for: age, gender, smoking habits, diabetes, triglycerides, HDL-C, total cholesterol, blood glucose, systolic and diastolic blood pressure, therapy (lipid lowering, antihypertensive and hypoglycemic drugs), and family history of vascular diseases, of hyperlipidemia and of hypertension. Results are expressed as means ± S.E.M.

6.67 ± 1.08; 7.09 ± 1.57 mmol/L for "none", "only one" and "both parents" long lived, respectively; $p = 0.002$). A significant trend for both Avg-IMT and Max-IMT was observed across the groups even after adjustment for relevant covariates (Fig. 2).

4. Discussion

This study, performed in a fairly large group of subjects attending a Lipid Clinic, suggests that parents' longevity is associated with lower IMT values of extracranial carotid arteries even when potentially confounding variables are taken into account. Thus, parents' longevity may affect IMT, independent of the individual vascular risk profile.

Inheritance of a predisposition to longevity from both parents results in the most favourable IMT profile. This protection against atherosclerosis is evident at the highest cholesterol levels of subjects with both long-lived parents, which suggests that heritable protective factors, not yet identified, influence the development of carotid atherosclerosis and act synergistically when inherited from both parents. Our data, based on an early surrogate index of atherosclerosis, agree with those reported by Rosengren et al., who showed [33] that the risk of fatal and non-fatal cardiovascular events decreases continuously with increasing parental age, this association being, like that observed in our study, independent of the major cardiovascular risk factors.

A number of epidemiological studies have shown an association between family history of cardiovascular diseases and the incidence of clinical events [2,10,34], but only a few have examined the role of a family history of cardiovascular events as a predictor of early carotid artery atherosclerosis. In the Cardiovascular Health Study (CHS), a positive association between family history of myocardial infarction and carotid IMT was found [18]. Similarly, Zureik et al. reported an association between parental history of premature death for CHD and the presence of carotid plaques [19]. In contrast, in a Finnish study [35], the severity of carotid atherosclerosis was not associated with a family history of ischemic heart disease. All these studies, however, have focused on the familial pattern of risk factors. This traditional approach, especially when performed in elderly populations, has been recently criticized [19] because of potential survival and self-selection biases. For instance, the survivors might present a low prevalence of carotid plaques merely because subjects with a positive family history of CHD may have died at an earlier age, thus not contributing to the statistical analysis. Our study, instead of evaluating the familial pattern of risk factors or the parents' history of premature death, has focused on parents' longevity and strongly suggests that a family history of long-living parents determines carotid IMT in a positive way.

It might be postulated that this relationship arises from a Cohort effect because mothers or fathers of young patients had lifestyles different from those of older ones (e.g. exposure to war or other). This hypothesis was ruled out by the same results being obtained after stratification of the patients into young and old or into 10-year-age classes.

The possibility that the effect observed in the whole group was attributable to a higher prevalence of subjects with a family history of vascular diseases in the subjects included in the highest IMT tertile group was also excluded.

All cause mortality rather than cardiovascular mortality was used in the present study because of the impossibility to obtain in each patient the medical records necessary to validate the putative cardiovascular mortality reported by offspring. Despite this, all the analyses were also repeated by using this information and the associations between parents' longevity and ultrasonic variables remained significant but did not improve. This lack of improvement suggests that the offspring reported parents' cardiovascular mortality is not sufficiently trustworthy to be used in this kind of analyses.

The study examined subjects with dyslipidemias in a large majority. This choice could have introduced a bias selection, which could render the reported conclusions not applicable to the general population. Familial hypercholesterolemia, indeed, is associated with premature cardiovascular disease [36,37] and decreased life expectancy [38–40].

Since many of the patients recruited in a Lipid Clinic may have familial hypercholesterolemia or familial combined hyperlipidemia, which means that also many of their parents may have suffered from dyslipidemia as well, the observed parents longevity protective effects might be "lipid-specific" and do not by definition, confer "general genetic protection" against atherosclerosis. This possibility, however, was ruled out by the same results being obtained also after stratification of the patients into those reporting a family history of hyperlipidemia or not.

To the best of our knowledge, this is the first study showing that longevity may be considered as a heritable protective factor for carotid atherosclerosis. Longevity is affected by a health-promoting environment interacting with genes coding for disease resistance and long survival [33]. If environmental factors remained unchanged from one generation to another, a similarity between parents and offspring with respect to longevity would be expected. Similarities in age at death in parents and offspring were already shown in the first part of the last century [21–23], and later studies confirmed that parental survival is an independent predictor of longevity [24,41]. The results reported here provide for the first time a potential explanation for this association by showing that independent of the presence of conventional vascular risk factors, individuals with long-lived fathers or mothers may inherit a familial resistance to atherosclerosis.Obviously, before parents' longevity can be effectively included as a protective factor in models for the prediction of atherosclerotic disease, further studies in larger and prospectively characterized groups of patients are needed to confirm the association between this parameter and (a) coronary atherosclerosis, (b) occurrence of cardiovascular events, and even (c) offspring's longevity. In addition, since the mechanism by which parental longevity and offspring's atherosclerosis are related is not known, and since it is not known to what extent genetic and/or environmental variables affect this relationship, appropriate studies need to be carried out in order to identify the factor(s) involved. If such factors could be identified, it would be possible by acting on it/them, to improve clinical results, till now obtained only by prevention and treatment of vascular risk factors.

Finally, if the protective nature of a long-lived family history is confirmed, the addition of this variable to algorithms for the cardiovascular global risk calculation [42–44] might improve their predictive power. Asymptomatic atherosclerotic patients who may need preventive treatment may thus be identified, as well as patients lucky enough to have had long-lived parents and low carotid IMTs, who may not need preventive drug treatment despite an unfavourable vascular risk profile.

References

[1] Colditz GA, Stampfer MJ, Willett WC, et al. A prospective study of parental history of myocardial infarction and coronary heart disease in women. Am J Epidemiol 1986;123:48–58.
[2] Myers HR, Kiely DK, Cupples A, Kannel WB. Parental history is an independent risk factor for coronary artery disease: the Framingham study. Am Heart J 1990;120:963–9.
[3] Burke GL, Savage PJ, Sprafka M, et al. Relation of risk factor levels in young adulthood to parental history of disease: the CARDIA study. Circulation 1991;84:1176–87.
[4] Rosseneu M, Fruchart JC, Bard JM, et al. Plasma apolipoprotein concentrations in young adults with a parental history of premature coronary heart disease and in control subjects: the EARS study. Circulation 1994;89:1967–73.
[5] Wilhelmsen L, Wedel H, Tibblin G. Multivariate analysis of risk factors for coronary heart disease. Circulation 1973;48(5):950–8.
[6] Goldbourt U, Medalie JH, Neufeld HN. Clinical myocardial infarction over a five-year period, III. A multivariate analysis of incidence, the Israel ischemic heart disease study. J Chronic Dis 1975;28(4):217–37.
[7] Gordon T, Castelli WB, Hjortoland ML, Kannell WB, Dawber TR. Predicting coronary heart disease in middle-aged and older persons: the Framingham study. JAMA 1977;238:497–9.
[8] Nora JJ, Lortscher HR, Spangler RD. Genetic–epidemiologic study of early-onset ischemic heart disease. Circulation 1980;61:503–8.
[9] Heller RF, Kelson MC. Family history in "low-risk" men with coronary heart disease in young adults. J Epidemiol Comm Health 1983;37:29–31.
[10] Shea S, Ottman R, Gabrieli C, Stein Z, Nichols A. Family history as an independent risk factor for coronary artery disease. J Am Coll Cardiol 1984;4:793–801.
[11] Barrett-Connor E, Khaw K. Family history of heart attack as an independent predictor of death due to cardiovascular disease. Circulation 1984;69:1065–9.
[12] Colditz GA, Rimm EB, Giovannucci E, et al. A prospective study of parental history of myocardial infarction and coronary heart disease in men. Am J Cardiol 1991;67:933–8.
[13] Friedlander Y, Siscovick DS, Weinmann S, et al. Family history as a risk factor for primary cardiac arrest. Circulation 1998;97:155–60.
[14] Kaprio J, Norio R, Pesonen E, Sarna S. Intimal thickening of the coronary arteries in infants in relation to family history of coronary artery disease. Circulation 1993;87:1960–8.
[15] Berg K. Genetics of coronary heart disease. In: Steinberg AG, Bearn AG, Motulsky A, editors. Progress in Medical Genetics, vol. 5. Philadelphia: Pa: WB Saunders; 1983. p. 35–89.
[16] Mukerji V, Holman AJ, Artis AK, Alpert MA, Hewett JE. Risk factors for coronary atherosclerosis in the elderly. Angiology 1989;40:88–93.
[17] Wang XL, Tam C, McCredie RM, Wilcken DEL. Determinants of severity of coronary artery disease in Australian men and women. Circulation 1994;89:1974–81.
[18] Kuller L, Borhanl N, Furberg C, et al. Prevalence of subclinical atherosclerosis and cardiovascular disease and association with risk factors in the cardiovascular health study. Am J Epidemiol 1994;139:1164–79.
[19] Zureik M, Touboul PJ, Bonithon-Kopp C, et al. Differential association of common carotid intima–media thickness and carotid atherosclerotic plaques with parental history of premature death from coronary heart disease: the EVA study. Arterioscler Thromb Vasc Biol 1999;19(2):366–71.
[20] Gaeta G, De Michele M, Cuomo S, et al. Arterial abnormalities in the offspring of patients with premature myocardial infarction. N Engl J Med 2000;343(12):840–6.
[21] Beeton M, Pearson K. Data for the problem of evolution in man II. A first study on the inheritance of longevity and the selective death rate in man. Proc R Soc Lond 1899;65:290–305.
[22] Beeton M, Pearson K. On the inheritance of the duration of life and on the intensity of natural selection in man. Biometrica 1901;1:50–891.

[23] Pearl R. Studies on human longevity, IV. The inheritance of longevity. Hum Biol 1931;3:245–69.
[24] Vandenbroucke JP, Matroos AW, van der Heide-Wessel C, van der Heide R. Parental survival, an independent predictor of longevity in middle-aged persons. Am J Epidemiol 1984;119:742–50.
[25] Barth JD. An update on carotid ultrasound measurement of intima–media thickness. Am J Cardiol 2002;89(4A):32B–8B.
[26] Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation 1986;74(6):1399–406.
[27] Baldassarre D, Amato M, Bondioli A, Sirtori CR, Tremoli E. Carotid artery intima–media thickness measured by ultrasonography in normal clinical practice correlates well with atherosclerosis risk factors. Stroke 2000;31(10):2426–30.
[28] Bucolo G, David H. Quantitative determination of serum triglycerides by the use of enzymes. Clin Chem 1973;19(5):476–82.
[29] Röschlau P, Bernt E, Gruber W. Enzymatische Bestimmung des Gesamt Cholesterins in serum. Z Klin Chem Klin Biochem 1974;12:403–7.
[30] Warnick GR, Benderson J, Albers JJ. Dextran sulfate precipitation procedure for quantitation of high-density lipoproteins. Clin Chem 1982;28:1379–88.
[31] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.
[32] Baldassarre D, Werba JP, Tremoli E, et al. Common carotid intima–media thickness measurement: a method to improve accuracy and precision. Stroke 1994;25(8):1588–92.
[33] Rosengren A, Thelle D, Wilhelmsen L. Parental age and coronary disease in the general male population. J Int Med 2002;251(3):258–67.
[34] Sesso HD, Lee IM, Gaziano JM, et al. Maternal and paternal history of myocardial infarction and risk of cardiovascular disease in men and women. Circulation 2001;104(4):393–8.
[35] Salonen JT, Seppänen, Rauramaa R, Salonen A. Risk factors for carotid atherosclerosis: the Kuopio ischaemic heart disease risk factor study. Ann Med 1989;21:227–9.
[36] Müller C. Angina pectoris in hereditary xanthomatosis. Arch Int Med 1939;64:675–700.
[37] Stone NJ, Levy RI, Fredrickson DS, Verter J. Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. Circulation 1974;49:476–88.
[38] Williams RR, Hasstedt SJ, Wilson DE, et al. Evidence that men with familial hypercholesterolemia can avoid early coronary death. JAMA 1986;255:219–24.
[39] Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. BMJ 1991;303:893–6.
[40] Sijbrands EJ, Westendorp RG, Paola Lombardi M, et al. Additional risk factors influence excess mortality in heterozygous familial hypercholesterolaemia. Atherosclerosis 2000;149:421–5.
[41] Abbott MH, Abbey H, Bolling DR, Murphy EA. The familial component in longevity: a study of offspring of nonagenarians, III. Intrafamilial studies. Am J Med Genet 1978;2(2):105–20.
[42] Anderson KM, Odell PM, Wilson PWF, Kannel WB. Cardiovascular disease risk profiles. Am Heart J 1990;121:293–8.
[43] Schulte H, Assmann G. CHD risk equations, obtained from the Framingham heart study, applied to the PROCAM study. Cardiovasc Risk Factors 1991;1:126–33.
[44] Thomsen TF, Davidsen M, Jorgensen HIT, Jensen G, Borch-Johnsen K. A new method for CHD prediction and prevention based on regional risk scores and randomized clinical trials: PRECARD and the Copenhagen Risk Score. J Cardiovasc Risk 2001;8(5):291–7.