Cardiovascular risk factors and global risk of fatal cardiovascular disease are positively correlated between partners of 802 married couples from different European countries

Report from the *IMMIDIET* project

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Summary

Shared environmental factors may confer to spouses a similar risk for cardiovascular disease. We aimed at investigating in pairs the concordance in risk factors for cardiovascular disease and in global risk of cardiovascular events. In the framework of the *IMMIDIET* Project, married couples, recruited randomly from general practice, were studied. One thousand six hundred and four apparently healthy subjects aged 25–74 years from three different European populations were enrolled. Individual cardiovascular risks were estimated using *SCORE* risk equations. Age was strongly correlated within couples (r=0.86, P<0.0001). In multivariate model, within-pair correlation was high for social status (r=0·49; percentage of explained variation=24%) and percent of calories from lipids (r=0.34; 12%). Concerning conventional metabolic risk factors, percentage of explained variation varied from 0.5% (triglycerides) to 11% (glucose). Among new risk factors, activated factor VII showed the strongest correlation (r=0.28) and C-reactive protein the lowest (r=0.13). Either total, coronary or non-coronary risk estimates at 10 years were strongly correlated within pairs: the risk of a member explained about two thirds of the cardiovascular risk of the partner. Spouse pairs share common lifestyle habits, common and new metabolic risk factors and the predicted global risk of cardiovascular events. If the individual risk of a person is influenced by the risk of his/her partner, decreasing the risk in a member of the pair should also decrease the risk in the partner. These concepts may have important public health consequences in targeting screening or disease prevention measures towards partners of people with cardiovascular risk.

Keywords

Epidemiology, prevention, risk factors, cardiovascular disease

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Introduction

Married couples allow the assessment of determinants of diseases related to environmental or behavioural characteristics, since they share the same life-style and socio-economic environment but are genetically unrelated.

Previous studies showed a spousal aggregation of risk factors for cardiovascular disease (CVD) (1–19) and several other conditions such as asthma, depression, peptic ulcer or cancer (20–23). Similarity in blood pressure or history of hypertension was observed in the majority of the previous studies (2, 4–15), while it was slight or absent in a few of them (3, 16). Lipid pro-

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file concordance was found in some studies (3, 5, 7, 11, 12, 14) but was negligible (1, 10, 13, 17) or absent (16, 17) in others. Hippisley-Cox et al. (20) showed that subjects from the general population were significantly more likely to have hypertension and hyperlipidemia, but not ischemic heart disease or stroke, if their marital partner had the same disease. Lately, Qureshi et al. (18) found that smoking women whose spouses also smoked had a higher risk of stroke than those married to non-smokers.

Likewise, an intervention program for coronary artery disease (CAD) targeted to reduce smoking, blood pressure and cholesterol in men, produced beneficial effects also in their wives (19).

Until now, studies regarding spousal concordance concerned individual risk factors and mainly included life-style habits or common metabolic risk factors. At present, however, the prevention of cardiovascular disease is based on the assessment of the absolute global individual risk, rather than on single risk factors. Scoring systems for evaluation of global cardiovascular risk based on European populations, such as that developed by the investigators of the *SCORE* project (24), are now available. Moreover, a number of new risk factors linked to inflammation, coagulation system and homocysteine have been identified.

The aim of the present study was to investigate the degree of concordance of both common and new risk factors for cardiovascular disease with global risk of fatal cardiovascular events as provided by the SCORE equations in European spouse pairs, recruited in the framework of the *IMMIDIET* study: Dietary Habit Profile in European Communities with Different Risk of Myocardial Infarction: the Impact of Migration as a Model of Gene-Environment Interaction, http://www.moli-sani.org/progetti/immidiet_site/welcome.html) (25).

Methods

Subjects

The *IMMIDIET* project and the selection of subjects have been described in detail (25, 26). Briefly, the *IMMIDIET* project is a population-based cross-sectional study aimed at comparing healthy couples from regions of Italy, Belgium and England in order to evaluate the risk components in the three communities at different risk of myocardial infarction. Apparently healthy pairs were male-female spouses living together and were recruited through general practices (GP). To protect against selection bias, the selection of potential pairs was randomized in each country, where three local GP networks were established to recruit approximately 270 pairs each. The required number of pairs was recruited from the Abruzzo region in Italy (n=270), the Flemish territory of Limburg in Belgium (n=268) and South-East England (n=263), A computerized list of all potential pairs in each practice was preliminarily generated and an invitation was made by letter and/or by phone call.

Abruzzo, Limburg and South-East England (London) were chosen as areas at lower, medium and higher CAD risk, according to MONICA data (27). Between October 2001 and October 2003, 1,604 subjects (802 pairs), aged 25–74 years were enrolled in the study. The participation rate ranged between 70–90% in the different centres. Exclusion criteria for all groups were: history of CVD, type 2 diabetes mellitus, familial hypercholesterolemia, malignancies, chronic diseases like heart, liver or renal failure, hypo/hyperthyroidism and epilepsy.

The principal aim of the *IMMIDIET* project was to investigate how dietary habits interact with the genetic background of populations in determining changes in risk factors for CAD. For this reason, "emerging" risk factors for CVD as coagulation factor (F) VII, homocysteine metabolism, C-reactive protein (CRP) and a number of metabolic factors associated with the so-called "metabolic syndrome" were measured; these factors most likely are under the combined influence of dietary components and genetic polymorphisms.

Interviews were taken using a well-standardised questionnaire previously adopted in the *Olivetti Prospective Heart Study* (28). To evaluate dietary factors we used the *EPIC* semi-quantitative food frequency questionnaires (29).

The study was approved by the ethics committees of all the participating institutions. All study participants agreed by written informed consent.

Blood pressure and anthropometric measurements

Trained research personnel in the different centres of recruitment carried out blood pressure and anthropometric measurements using methods that had been standardised beforehand during a preliminary meeting in which all *IMMIDIET* consortium partners participated. Blood pressure (BP) was measured with an automatic device (OMRON-HEM-705CP) (30). Blood pressure values were recorded three times on the non-dominant arm, and the last two values were taken as the BP. Measurements were performed in a quiet room with comfortable temperature with the participants resting in seated position for at least 5 min. Body weight and height were measured on a standard beam balance scale with an attached ruler, in subjects wearing no shoes and only light indoor clothing. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). Waist circumferences were measured according to the National Institutes of Health, National Heart, Lung, and Blood Institute guidelines (31).

Biochemical measurements

Blood samples were obtained between 7.00 and 9.00 a.m. from participants who had been fasting overnight and had refrained from smoking for at least six hours. Blood samples were centrifuged within three hours for 15 minutes (min) at 3,000 rpm. Biochemical analyses were performed in centralised laboratories after shipping of aliquots in dry ice.

The measurements of serum lipids and blood glucose were performed by an automated analyser (Cobas-Mira-Plus, Roche, Milan, Italy). LDL-cholesterol was calculated according to Friedewald (32).

High-sensitivity (hs) CRP was measured in frozen plasma samples with a hs-CRP assay (IL Coagulation Systems on ACL9000, IL, Milan, Italy), a latex particle enhanced immunoturbidimetric assay, including a double quality control at 2.59 mg/l and 6.19 mg/l, respectively.

Coagulation factor VII (FVII) activity levels were determined with a clotting based assay (Stagoclot® VIIa-rTF, Diagnostica Stago, Asnières-sur-Seine, France). Activated FVII levels were determined by a one-stage clotting assay using FVII im-

muno-depleted plasma (FVII deficient plasma Hemoliance, Instrumentation Laboratory, Lexington, MA, USA) as substrate and a recombinant tissue factor based thromboplastin (Innovin®, DadeBehring, Marburg, Germany). FVII antigen levels were determined by a manual ELISA (Affinity Biologicals Inc., Ontario, Canada). Homocysteine levels were determined by a semi-automated Fluorescence Polarisation Immunoassay on an Imx analyzer (ABBOTT Diagnostic division, Abbott Park, IL, USA).

The insertion/deletion polymorphism in the coagulation FVII gene was measured as described (33).

Definition of risk factors

Subjects were classified as non-smokers (if they had never smoked cigarettes), ex-smokers (if they had smoked cigarettes in the past), and current smokers (if they were currently smoking on a regular daily basis one or more cigarettes per day). Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, or being on pharmacological treatment for hypertension. Hypercholesterolemia was considered as cholesterol levels ≥240 mg/dl or being on pharmacological treatment for hypercholesterolemia. Physical activity was assessed by a standardised questionnaire (25). Subjects were grouped in three categories of physical activity ("low", "middle" or "high"). Socio-economic status was defined as a score based on three variables: education, job and housing; the highest the score, the highest the level of socio-economic status.

Statistical analysis

Univariate within-pair correlations were calculated using Pearson's correlation coefficient. Multivariate within-pair correlations were obtained by analysing dyadic data in the context of the Actor-Partner Interdependence Model (APIM) (34). APIM was developed as a framework for analyzing dyadic data, primarily by stressing the importance of considering the interdependence that exists between dyad members. The model can test for multivariate within-dyad correlation. To estimate the APIM model we used multilevel modelling (procedure PROC-MIXED within SAS software) (35). Within-pair correlations for a metabolic factor may differ according to within-pair concordance in environmental factors; to explore such differences of effects we conducted APIM analysis stratified for indicators of within-pair concordance in the environmental factor. Concordance for a categorical variable was defined when both the members of the couple belonged to the same category of the variable; non-concordance was defined when the members of the pair belonged to extremely distant categories of the variable. Stratification according to the concordance in BMI was obtained dividing the pairs in thirds of the inter-spouse absolute difference in BMI.

Fatal cardiovascular global risk for each *IMMIDIET* subject was calculated applying the risk equations of the *SCORE* project (24). Due to the known difference in vascular risk between men and women, analysis of the within-pair correlation of global risk was carried out using ranks (deciles) of the global risk, calculated separately in men and women. Data for triglycerides and glucose were natural-logarithmic transformed to reduce positive skewness.

All computations were carried out using the SAS statistical package (Version 8.2 for Windows. SAS Institute Inc., Cary, NC, USA: SAS Institute Inc., 1989).

Results

The main characteristics of men and women in 802 couples are shown in Table 1. Social status and physical activity were similar in men and women; however, men were older, smoked more and

Table 1: General characteristics of the population studied.

	Women (n=802)	Men (n=802)	P*
Age (years)	45 (8)	47 (8)	<0·0001
Environmental factors			
Smoking habits (frequency and percentage)			
– Never	636 (79·3)	569 (71·0)	0·0022
– Current	158 (19·7)	218 (27·2)	
– Former	8 (1·0)	15 (1·9)	
Social status (frequency and percentage)			
– Low	120 (15·0)	98 (12·2)	0·12
– Middle	454 (56·6)	448 (55·9)	
– High	228 (28·4)	256 (31·9)	
Physical activity (frequency and percentage)			
– Low	254 (31·7)	288 (36·0)	0·53
– Middle	300 (37.4)	226 (28·3)	
– High	248 (30.9)	286 (35·7)	
Alcohol consumption (g/day)	9 (13)	27 (29)	<0·0001
Percent of calories from lipids (%)	36 (5)	35 (6)	0.62
Metabolic factors (mean and SD)			
Systolic blood pressure (mmHg)	117 (17)	129 (16)	<0·0001
Diastolic blood pressure (mmHg)	75 (10)	82 (10)	<0·0001
Body mass index (kg/m^2)	25·9 (4·9)	27·3 (3·7)	<0·0001
Waist circumference (cm)	85 (11)	96 (10)	<0·0001
Waist/hip ratio (pure number)	0·82 (0·06)	0·93 (0·06)	<0·0001
Cholesterol (mM)	5.5 (1.0)	5.8 (1.0)	0·022
Triglycerides (mM)	1.1 (0.6)	1.6 (1.0)	<0·0001
HDL-cholesterol (mM)	1.50 (0.36)	1.24 (0.31)	<0·0001
LDL-cholesterol (mM)	3.5 (1.0)	3.8 (1.0)	<0·0001
Glucose (mM)	4.38 (0.83)	4.66 (0.94)	<0·0001
FVII activity (%)	110 (24)	105 (20)	<0·0001
FVII activated (mU/ml)	94 (47)	93 (41)	0.13
FVII antigen (%)	90 (27)	83 (28)	<0·0001
Homocysteine (uM)#	9.6 (8.1–11.2)	11.9(10.1–14.1)	<0·0001
C-reactive protein (mg/l)#	1.5 (0.7–3.1)	1.2 (0.6–2.5)	0.0010

*Adjusted for population and age. SD = standard deviation. # Median and range; Q1-Q3 = 25%-75% inter quartile range.

consumed more alcohol than women. Anthropometric and metabolic factors were all higher in men than in women, with the exception of HDL, CRP, FVII activity and FVII antigen that were higher in women and of activated FVII that did not show any sex-related difference.

Within-pair correlation in risk factors

Age was strongly correlated between pairs (r=0.86, P<0.0001). Spousal correlations for lifestyle are listed in Table 2. The correlation for different environmental factors ranged between 0.57 and 0.22. The multivariate r values provide an estimate of the degree of non-independence within a pair after controlling for covariates measured for both members. All the correlations remained significant after adjustment for age and population and further adjustment for other confounders; the strongest was found for social status (r=0.49, P<0.0001, percentage of explained variation ($100xr^2$)=24.0%) while the lowest for physical activity (r=0.18, P<0.0001, percentage of explained variation=3.2%) (Table 2).

Spousal correlations for anthropometric, conventional and new metabolic risk factors are shown in Table 2. All factors were correlated within pairs in univariate analysis. The correlations ranged between 0.44 and 0.12. Fasting glucose levels showed the strongest spousal concordance. All correlations remained significant after adjustment for age of the spouses and population and further adjustment for other confounders, although a reduction in the strength of the correlation was generally observed. Concerning conventional metabolic factors, the percentage of explained variation varied from 0.5% (triglycerides) to 11% (glucose). Among the new risk factors, activated FVII showed the strongest within-pair correlation (r=0.28) while CRP the lowest (r=0.13).

Within-pair correlation in total cardiovascular risk

Estimations of 10-year risk (%) of fatal cardiovascular disease calculated using the *SCORE* equations are shown in Table 3. The median predicted value for total cardiovascular risk in men was 1.09% and indicates that – on average – half of the men participating to the *IMMIDIET* study had a chance greater than 1.09% to be confronted with a fatal cardiovascular event within the following 10 years.

Total, coronary and non-coronary risk estimates at 10 years were strongly correlated within pairs. Being a pair explained about two thirds of the cardiovascular risk. Figure 1 depicts the univariate within-pair correlations in total cardiovascular risk. The degree of correlation was not changed by adjustment for

Table 2: Univariate and multivariate within-pair correlation of common risk factors for cardiovascular disease and dietary components in the whole *IMMIDIET* population (n=802 pairs).

	Univariate		Adjusted for age and population		Fully adjusted*	
	r	P	r	P	r	P
Environmental factors						
Smoking habits	0·30	<0·0001	0·28	<0·0001	0·26	<0·0001
Social status	0·57	<0·0001	0·51	<0·0001	0·49	<0·0001
Physical activity	0·22	<0·0001	0·18	<0·0001	0·18	<0·0001
Alcohol consumption	0·23	<0·0001	0·19	<0·0001	0·20	<0·0001
Percent of calories from lipids	0·37	<0·0001	0·34	<0·0001	0·34	<0·0001
Metabolic factors						
Systolic blood pressure	0·21	<0·0001	0·14	<0·0001	0·11	0·0015
Diastolic blood pressure	0·16	<0·0001	0·11	0·0026	0·09	0·012
Body Mass Index	0·25	<0·0001	0·23	<0·0001	0·21	<0·0001
Waist circumference	0·27	<0·0001	0·25	<0·0001	0·23°	<0·0001
Waist/hip ratio	0·16	<0·0001	0·11	0·0017	0·10°	0.0037
Cholesterol	0·16	<0·0001	0·11	0·0025	0·11	0·0023
Triglycerides	0·12	0.0005	0·08	0·019	0·07	0·042
HDL-cholesterol	0·16	<0·0001	0·13	0.0002	0·11	0.0021
LDL-cholesterol	0·17	<0·0001	0·13	0.0003	0·14	0·0002
Glucose	0·44	<0·0001	0·33	<0·0001	0·33	<0·0001
FVII activity	0·19	<0·0001	0·17	<0·0001	0·16	<0·0001
FVII activated	0·30	<0·0001	0·29	<0·0001	0·28	<0·0001
FVII antigen	0·26	<0·0001	0·16	<0·0001	0·15	<0·0001
Homocysteine	0·19	<0·0001	0·18	<0·0001	0·17	<0·0001
C-reactive protein	0·17	<0·0001	0·16	<0·0001	0·13	0.0006

Analysis for smoking was based on a comparison of current or former versus never. *Adjusted for age, population, BMI, social status, physical activity, smoking habit and percent of calories from lipids. °Adjusted for age, population, social status, physical activity, smoking habit and percent of calories from lipids.

	Estimated risk		Within-pairs correlations			
	Women	Men	Univariate		Multivariate*	
	(n=802)	(n=802)	r	P	r	P
Total cardiovascular risk (%)			0·81	<0·0001	0·79	<0·0001
Mean (SD)	0·34 (0·51)	1·89 (2·29)				
Median	0·12	1·09				
Quartiles Q1-Q3	(0·04–0·45)	(0·42–2·44)				
Coronary risk (%)			0·80	<0·0001	0·78	<0·0001
Mean (SD)	0·20 (0·30)	1·43 (1·73)				
Median	0·07	0·84				
Quartiles Q1-Q3	(0·02–0·25)	(0·34–1·78)				
Non-coronary risk (%)			0·83	<0·0001	0·82	<0·0001
Mean (SD)	0·14 (0·22)	0·46 (0·60)				
Median	0·05	0·25				
Quartiles Q1-Q3	(0·02–0·18)	(0·09–0·60)				

Population means, standard deviation, median value and 25%-75% inter quartile range (quartiles Q1-Q3) are provided in the left part of the table. R and *P* values for the within pairs correlation in estimated risks are provided in the right part of the table. *Adjusted for population, BMI, social status, physical activity, percent of calories from lipids and alcohol consumption.

Table 3: Estimation of 10-year global risk of fatal cardiovascular disease from the *SCORE* equations, in men and women.

population, social status, physical activity, BMI, total lipid intake and alcohol consumption (Table 3). *SCORE* equations are based on age, sex, systolic blood pressure, total cholesterol and smoking. Age was the major determinant of the high within-pair correlation of the *SCORE* function. In fact, the within-pair correlation of the *SCORE* function (total cardiovascular risk) decreased to 0.18 (P<0.0001) when age was included in the multivariate analysis, and to 0.11 (P=0.0018) when systolic blood pressure, total cholesterol and smoking were further added (similar results were found for coronary and non coronary *SCORE*).

The influence of centre-related variables on the within pair correlation was studied by country stratification. The adjusted within pair correlations were homogeneous among the three countries for the majority of risk factors, except for smoking habits, HDL-cholesterol and CRP. The within-pair correlation in smoking habits decreased from England to Belgium and Italy (test for difference, P=0.0030). The within pair correlation in HDL-cholesterol or CRP was low in England but high in Belgium and Italy (test for difference, P=0.0077 and P=0.020 for HDL and CRP, respectively).

In addition, we calculated the within pair correlation for each specific risk factor after stratification of the pairs according to below or above the median value calculated in men. We failed to observe differences for the majority of risk factors, except BMI, waist circumference, glucose and activated FVII levels. In particular, the within pair correlation in BMI, waist circumference and activated FVII was higher when the male partner exceeded the median value. On the contrary, when the glucose level of the male partner was below the median, the within pair correlation disappeared.

Furthermore, between person variability in the risk factors did not affect the within pair correlation (data not shown).

Finally, we tested the intra-pairs correlation of a genetic polymorphism (the deca-nucleotide polymorphism of the coagulation FVII gene). As one would have expected from genetically unrelated subjects, no correlation was found (r=-0.014, P=0.67). In addition, we performed a series of "spouse-swapping" exercises in which men and women were randomly linked and analysis of within-pair correlations were performed after each random pairing; both univariate and multivariate correlations for all variables disappeared.

Discussion

Engagement of people in spouse relationships influences each other's cognitions, emotions and behaviour (36); however, it might also impact the risk of disease of the other pair member (18, 20). Cohabitant pairs share a similar environment but have a different genetic background; therefore, they might help in understanding the role of environmental factors in determining the risk of multifactorial diseases. We investigated the degree of concordance of traditional and new risk factors with global individual risk for cardiovascular disease in European couples.

Within-pair correlation in risk factors

All major risk factors were correlated between the spouses, even after adjusting for age. In particular *environmental* and *dietary* factors, for which genetic components can reasonably be excluded, were well correlated within pairs, confirming that pair members really shared a similar environment. *Common metabolic* risk factors, such as blood pressure, glucose or lipid components, likely to be influenced by both genetic and environmental factors, were also positively correlated within pairs, although to a lower extent. A major determinant of within-pair correlations of such risk factors was the partners' age, since they all decreased after age adjustment. However age, as well as other shared measurable risk factors, cannot fully explain such correlations, being the strength of the correlations only reduced but still statistically significant after multivariate analysis.

Positive spousal correlations of common cardiovascular risk factors have been reported previously (1–19). Our data show for the first time that there is a strong within-pairs concordance also for emerging factors, reportedly associated with cardiovascular risk, such as CRP, homocysteine and especially FVII levels. Al-

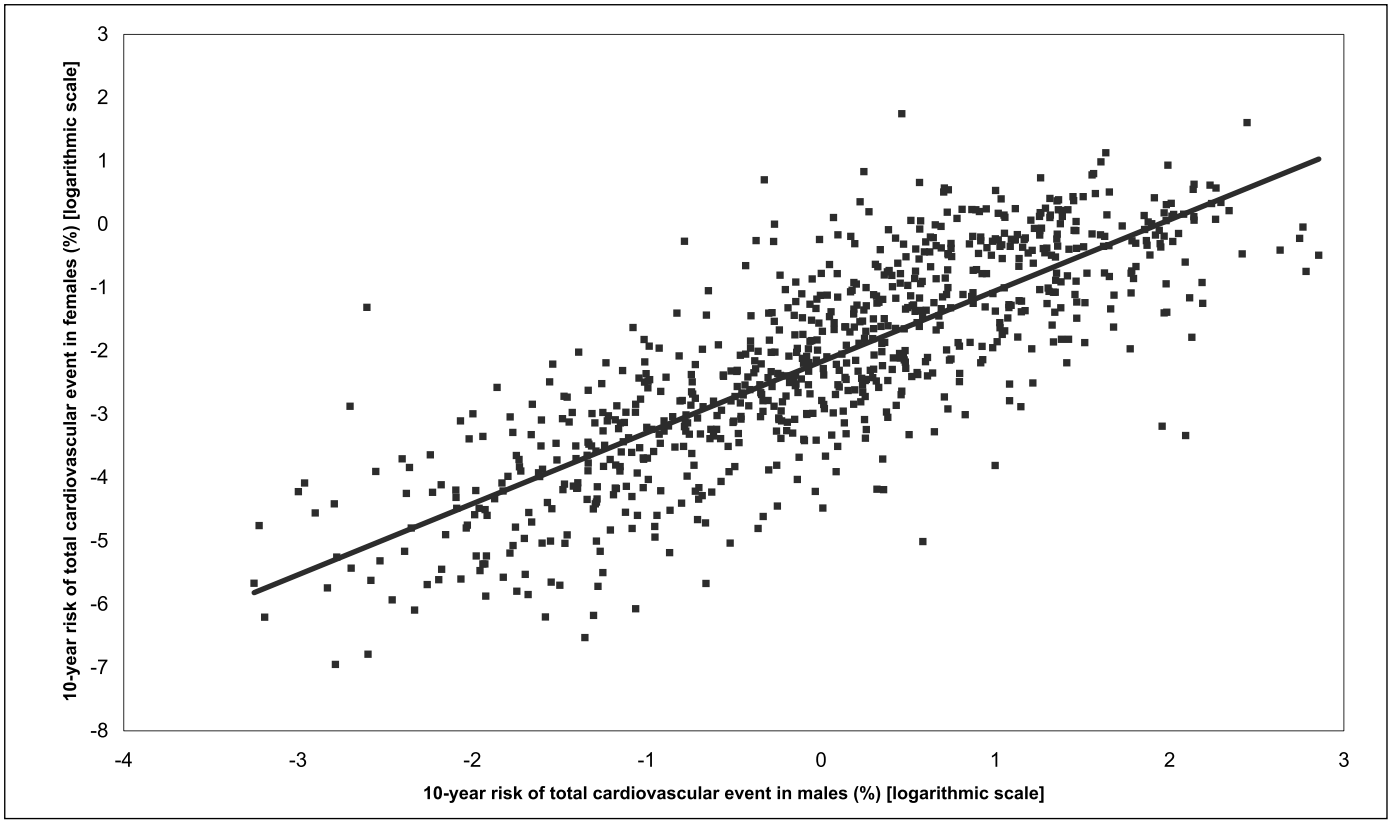

Figure 1: Within-pairs (n=802 pairs) univariate correlations in the 10-year risk of total fatal cardiovascular disease estimated from the *SCORE* equation.

though all these factors have a relevant genetic component (25, 37–40), the strong correlations observed here within pairs underline the relevance of life-style factors also as their determinants. As expected, a common genetic polymorphism in FVII gene did not show any within-pair correlation.

As FVII levels correlate with lipids, (33) the within pair correlation of FVII levels would be marginally explained by the within pair correlation in lipids. However, the within-pair correlation of FVII levels remained virtually unchanged when lipids were further introduced in the multivariate model of Table 2 (data not shown). Our data confirm that FVII levels are higher in females. We previously observed that hormones or other gender-specific factors could be important in the genetic regulation of FVII levels, by interacting with regulatory elements of the FVII gene (33). In fact, the factor VII promoter contains hormone-responsive elements that can up-regulate the synthesis of FVII levels in females. Despite these differences in the regulation and distribution of FVII levels in males and females, FVII levels were clearly correlated within our couples (composed by a male and a female). Thus, sharing environment (dietary habits in particular) is a strong enough determinant to produce within pairs a significant correlation of an emerging risk factor such as FVII levels. The close dependence of factor VII activity levels on fat intake and their role as a marker of CAD risk both in men and in women has been recently reviewed (41).

The major proportion of FVII circulates in plasma in the zymogene form. However, low but significant levels of activated FVII are also present and appear to serve as a primer for triggering the clotting cascade (42). FVII activation is also dependent on both environmental and genetic factors, although the effect of the environment seems to be prevalent. Indeed, the strongest determinants of FVII activation are lipid levels and dietary lipemia (43, 44). These can justify our finding of a stronger within-pairs correlation of activated FVII as compared to activity or antigen FVII levels.

The within-pair correlation of environmental or metabolic risk factors could be partially influenced by centre-related attributes or by risk factors average level. We tested these hypotheses by stratifying our population by centre and by average level of risk factors. The within-pair correlations were homogeneous among the three countries for the majority of risk factors, except for smoking habit, HDL-cholesterol and CRP. While the difference in smoking habits correlation could be explained by cultural disparities among countries, those in HDL or CRP correlation may be due to difference in unobserved variables, such as dietary or genetic factors.

The average level of risk factors did not influence the majority of risk factors, except BMI, waist circumference, glucose and activated FVII levels. Moreover, between-person variability in the risk factors did not affect the within-pair correlation.

Spousal concordance of each risk factor can be mediated by both "cohabitation effect" and "assortative mating". Previous studies suggested that concordance for metabolic conditions is mainly due to positive "assortative mating" (9), i.e. the tendency

to marry a person with similar constitution and behaviours. Nevertheless, Hippisley-Cox et al. (20) excluded the importance of a strong "assortative mating" on the association between exposure to a marital partner with a disease and the risk of that disease. We are not able to clearly discriminate the effects of sharing the same environment and those of "assortative mating" in determining the observed spousal concordance. However, the high spousal concordance of dietary intake such as total fat intake could suggest that non-genetic life-style factors at least partially explain the spousal concordance of several conventional and new metabolic risk factors. Moreover, adjustment for BMI of both partners, used as a surrogate of "assortative mating" for body weight, did not modify the strength of the association.

Within-pair correlation in total cardiovascular risk

Prevention of cardiovascular disease is based on the assessment of the absolute global individual risk rather than on the effect of any particular risk factor (45). We used the risk equations provided by the *SCORE* Project (24). Whilst *SCORE* only allows to predict fatal events, it uses country-specific data, thus overcoming the problem of applicability of risk equations to diverse populations. Our results show that members of a cohabitant pair were significantly more likely to have a higher risk of fatal cardiovascular events if their marital partner belonged to a high risk category and *vice versa*. The correlation in global cardiovascular risk was not modified by stratification for either single environmental factors or BMI, suggesting that members of a pair tend to share the majority of risk factors, even if not all at a strong level, rather than strongly sharing a single factor.

If the absolute individual risk of a person is substantially influenced by the risk of his/her partner, we should expect that decreasing or increasing the risk in a member of the pair should also decrease or increase the risk in the partner. Both concepts can have important public health consequences in targeting screening and addressing prevention campaigns or counselling for cardiovascular disease.

Limitations of the study

As our study includes couples from three European countries at different cardiovascular risk, our findings do not appear to be restricted to a given population. However, it has a cross-sectional design; thus, we do not know how long the pairs had lived together. This might be an important piece of information as, when the pattern of spouse resemblance in blood pressure was studied as a function of marriage duration, a decreasing trend in the magnitude of the correlations was observed (5, 11–13). Moreover, happiness or distress of living together may also affect cardiovascular risk of the dyad members (46). Further studies are necessary to establish the role of such factors.

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References

1. Barrett-Connor E, Suarez L, Criqui MH. Spouse concordance for plasma cholesterol and triglyceride. J Chronic Dis 1982; 35: 333–340.
2. Suarez L, Criqui MH, Barrett-Connor E. Spouse concordance for systolic and diastolic blood pressure. Am J Epidemiol 1983; 118: 345–351.
3. Brenn T. Adult family members and their resemblance of coronary heart disease risk factors: the cardiovascular disease study in Finnmark. Eur J Epidemiol 1997; 13: 623–630.
4. Speers MA, Kasl SV, Freeman DH, Ostfeld AM. Blood pressure concordance between spouses. Am J Epidemiol 1986; 123: 818–829.
5. Sackett DL, Anderson GD, Milner R, et al. Concordance for coronary risk factors among spouses. Circulation 1975; 52: 589–595.
6. Perusse L, Leblanc C, Tremblay A, et al. Familial aggregation in physical fitness, coronary heart disease risk factors, and pulmonary function measurements. Prev Med 1987; 16: 607–615.
7. Pyke SD, Wood DA, Kinmonth AL, et al. Change in coronary risk and coronary risk factor levels in couples following lifestyle intervention. The British Family Heart Study. Arch Fam Med 1997; 6: 354–360.
8. Bloch KV, Klein CH, de Souza e Silva NA, et al. Socioeconomic aspects of spousal concordance for hypertension, obesity, and smoking in a community of Rio de Janeiro, Brazil. Arq Bras Cardiol 2003; 80: 179–186.

9. Jurj AL, Wen W, Li HL, et al. Spousal correlations for lifestyle factors and selected diseases in Chinese couples. Ann Epidemiol 2006; 16: 285–291.
10. Hunt SC, Hasstedt SJ, Kuida H, et al. Genetic heritability and common environmental components of resting and stressed blood pressures, lipids, and body mass index in Utah pedigrees and twins. Am J Epidemiol 1989; 129: 625–638.
11. Knuiman MW, Divitini ML, Welborn TA, et al. Familial correlations, cohabitation effects, and heritability for cardiovascular risk factors. Ann Epidemiol 1996; 6: 188–194.
12. Knuiman MW, Divitini ML, Bartholomew HC, et al. Spouse correlations in cardiovascular risk factors and the effect of marriage duration. Am J Epidemiol 1996; 143: 48–53.
13. Inoue K, Sawada T, Suge H, et al. Spouse concordance of obesity, blood pressures and serum risk factors for atherosclerosis. J Hum Hypertens 1996; 10: 455–459.
14. Jee SH, Suh I, Won SY, et al. Familial correlation and heritability for cardiovascular risk factors. Yonsei Med J 2002; 43: 160–164.
15. Stimpson JP, Peek MK. Concordance of chronic conditions in older Mexican American couples. Prev Chronic Dis 2005; 2: A07.
16. Macken LC, Yates B, Blancher S. Concordance of risk factors in female spouses of male patients with coronary heart disease. J Cardiopulm Rehabil 2000; 20: 361–368.
17. Garrison RJ, Castelli WP, Feinleib M, et al. The association of total cholesterol, triglycerides and plasma lipoprotein cholesterol levels in first degree relatives and spouse pairs. Am J Epidemiol 1979; 110: 313–321.
18. Qureshi AI, Suri MF, Kirmani JF, et al. Cigarette smoking among spouses: another risk factor for stroke in women. Stroke 2005; 36: e74–76.
19. Sexton M, Bross D, Hebel JR, et al. Risk-factor changes in wives with husbands at high risk of coronary heart disease (CHD): the spin-off effect. J Behav Med 1987; 10: 251–261.
20. Hippisley-Cox J, Coupland C, Pringle M, et al. Married couples' risk of same disease: cross sectional study. Br Med J 2002; 325: 636.
21. Dufouil C, Alperovitch A. Couple similarities for cognitive functions and psychological health. J Clin Epidemiol 2000; 53: 589–593.
22. Kato I, Tominaga S, Suzuki T. Correspondence in cancer history between husbands and wives. Jpn J Cancer Res 1990; 81: 584–589.
23. Walach N, Novikov I, Milievskaya I, et al. Cancer among spouses: review of 195 couples. Cancer 1998; 82: 180–185.
24. Conroy RM, Pyorala K, Fitzgerald AP, et al.; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003; 24: 987–1003.
25. Iacoviello L, Arnout J, Buntinx F, et al., on behalf of the European Collaborative Group of the IIMIDIET Project. Dietary habit profile in European Communities with different risk of myocardial infarction: the impact of migration as a model of gene-environment interaction-the IMMIDIET study. Nutr Metab Cardiovasc Dis (Suppl) 2001; 11: 122–126.
26. Dean SC, Harper CE, Cappuccio FP, et al., on behalf of the European Collaborative Group of the IMMIDIET Project. The challenges of cross-national research in primary health care across Europe. Fam Pract 2005; 22: 1–6.
27. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, et al. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. Lancet 1999; 353: 1547–1557.
28. Cappuccio FP, Strazzullo P, Farinaro E, et al. Uric acid metabolism and tubular sodium handling: Results from a population-based study. J Am Med Assoc 1993; 270: 354–359.
29. Slimani N, Kaaks R, Ferrari P, et al. European Prospective Investigation into Cancer and Nutrition (EPIC) calibration study: rationale, design and population characteristics. Public Health Nutr 2002; 5: 1125–1145.
30. O'Brien E, Waeber B, Parati G, et al. Blood pressure measuring devices: recommendations of the European Society of Hypertension. Br Med J 2001; 322: 531–536.
31. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults- The Evidence Report. National Institutes of Health. Obes Res 1998; 6 (Suppl 2): 51S-209S.
32. 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.
33. Di Castelnuovo A, D'Orazio A, Amore C, et al. Genetic modulation of coagulation factor VII plasma levels: contribution of different polymorphisms and gender-related effects. Thromb Haemost 1998; 80: 542–545.
34. Kashy DA, Kenny DA. The analysis of data from dyads and groups. In: Handbook of research methods in social psychology. New York: Cambridge University Press, 2000: 451–477.
35. Campbell LJ, Kashy DA. Estimating actor, partner, and interaction effects for dyadic data using PROC MIXED and HLM5: A brief guided tour. Personal Relationships 2002; 9: 327–342.
36. Gallo LC, Troxel WM, Kuller LH, et al. Marital status, marital quality, and atherosclerotic burden in postmenopausal women. Psychosom Med 2003; 65: 952– 962.
37. Brattstrom L, Wilcken DE, Ohrvik J, et al. Common methylenetetrahydrofolate reductase gene mutation leads hyperhomocysteinemia but not to vascular disease: the result of a meta-analysis. Circulation 1998; 98: 2520–2526.
38. Carlson CS, Aldred SF, Lee PK, et al. Polymorphisms within the C-reactive protein (CRP) promoter region are associated with plasma CRP levels. Am J Hum Genet 2005; 77: 64–77.
39. Bennermo M, Held C, Ericsson CG, et al. Genotype-specific increase in plasma concentrations of activated coagulation factor VII in response to experimental inflammation. A link between infection and acute myocardial infarction? Thromb Haemost 2005; 94: 427–431.
40. Gueant-Rodriguez RM, Juilliere Y, Candito M, et al. Association of MTRRA66G polymorphism (but not of MTHFR C677T and A1298C, MTRA2756G, TCN C776G) with homocysteine and coronary artery disease in the French population. Thromb Haemost 2005; 94: 510–515.
41. Donati MB, Iacoviello L. Fibrinogen and factor VIIc levels:independent risk factors or markers of coronary disease risk. J Thromb Haemost 2007; 5: 458–460.
42. Morrissey JH, Macik BG, Neuenschwander PF, et al. Quantitation of activated factor VII levels in plasma using a tissue factor mutant selectively deficient in promoting factor VII activation. Blood 1993; 81: 734–744.
43. Miller GJ, Cooke CJ, Nanjee MN, et al. Factor VII activation, apolipoprotein A-I and reverse cholesterol transport: possible relevance for postprandial lipaemia. Thromb Haemost 2002; 87: 477–482.
44. Mariani G, Bernardi F, Bertina R, et al. Serum phospholipids are the main environmental determinants of activated factor VII in the most common FVII genotype. European Union Concerted Action "Clotart". Haematologica 1999; 84: 620–626.
45. Robson J, Feder G. Predicting and reducing cardiovascular risk. Heart 2001; 85: 487–488.
46. Rosengren A, Hawken S, Ounpuu S, et al. INTERHEART investigators. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364: 953–962.