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EPIDEMIOLOGY & RISK FACTORS

Family History for Cardio-Metabolic Diseases: A Predictor of Major Adverse Cardiovascular Events in Men With Erectile Dysfunction



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ABSTRACT

Background: Family history (FH) of cardiovascular (CV) disease is a known CV risk factor. However, it is rarely considered for CV risk stratification. Furthermore, FH for metabolic diseases is generally overlooked.

Aim: To evaluate, in a population of men with erectile dysfunction (ED), whether FH for cardio-metabolic diseases could provide insights into metabolic and sexual features and predict the occurrence of forthcoming major adverse CV events (MACE).

Methods: A consecutive series of 4,693 individuals (aged 51.3 ± 13.3 years) attending an Andrology outpatient clinic for ED was studied. A subset of these ($n = 1,595$) was evaluated retrospectively for MACE occurrence.

Outcomes: Several metabolic and sexual function-related parameters were studied. For the retrospective study, information on an incident MACE was collected over a mean follow-up of 4.2 ± 2.5 years.

Results: A greater number of cardio-metabolic FH factors were associated with a worse metabolic profile, including higher waist circumference, triglycerides, glucose, glycosylated hemoglobin, and diastolic blood pressure, as well as lower high-density lipoprotein cholesterol. An increased number of FH factors were associated with worse erectile function (odds ratio = $1.14[1.07;1.23]$, $P < .0001$), impaired penile dynamic peak systolic velocity, and lower testosterone levels. In the retrospective study, a positive cardiometabolic FH was associated with a significantly higher incidence of MACEs, even after adjusting for age and comorbidities (hazard ratio = $1.51[1.06-2.16]$, $P = .023$). Interestingly, when dividing the sample into high- and low-risk categories according to several CV risk factors (age, previous MACEs, high-density lipoprotein cholesterol, and comorbidities), FH was confirmed as a predictor of incident MACE only among the low-risk individuals.

Clinical Implications: Investigating FH for cardio-metabolic diseases is a quick and easy task that could help clinicians in identifying, among individuals with ED, those who deserve careful evaluation of CV and metabolic risk factors. Moreover, considering FH for CV risk stratification could predict MACEs in individuals who, according to conventional CV risk factors, would be erroneously considered at low risk.

Strengths & Limitations: The large sample size and the systematic collection of MACEs through an administrative database, with no risk of loss at follow-up, represent strengths. The use of administrative database for MACE collection may lead to some misclassifications. The specific population of the study limits the generalizability of the results.

Conclusion: FH is simple and inexpensive information that should be part of the CV risk assessment in all men with ED because it helps in the identification of those who need lifestyle and risk factor modifications and whose risk would otherwise be overlooked. **Rastrelli G, Yannas D, Mucci B, et al. Family History for Cardio-Metabolic Diseases: A Predictor of Major Adverse Cardiovascular Events in Men With Erectile Dysfunction. J Sex Med 2020;17:2370–2381.**

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Key Words: Medical History Taking; Cardiovascular Risk Stratification; Metabolic Impairment; Risk Factors; Sexual Dysfunction

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INTRODUCTION

There is an established and complex relationship between erectile dysfunction (ED) and cardiovascular disease (CVD).¹ It is well-known that ED represents a marker of subclinical CVD and an early and independent predictor for major adverse CV events (MACEs).^{2,3} Compared with traditional CV risk factors, such as dyslipidemia or smoking, ED seems to have a similar, or even greater, predictive value for incident CV events.^{4,5} Interestingly, the predictive role of ED appears particularly relevant among subjects conventionally deemed as at low CV risk, such as younger ones. Indeed, the Olmsted County study has shown that, in a population of more than 1,400 community-dwelling men aged 40 to 79 years, the difference in the incidence of coronary artery disease (CAD) between men with and without ED was dramatically high in younger men (almost 50-fold higher in men aged 40–49 years) and progressively decreased in older age classes.⁵ Not surprisingly, individuals with ED are a population with a high prevalence of metabolic and CV risk factors and a man with ED should be considered at increased CV risk, independently of his age, until recommended checks show otherwise.⁶ Thus, men seeking medical care for ED represent an unmissable opportunity for CV risk assessment.

In routine clinical practice, the risk for the occurrence of CV events is generally estimated using specific algorithms based on multiple variables that weight differently on risk determination. Each model has its features and sets of variables; however, age, gender, total and high-density lipoprotein (HDL) cholesterol, systolic blood pressure (BP), diabetes mellitus (DM), and current smoking are the most frequently used determinants throughout the estimation tools. Despite being simple and useful for clinical practice, these tools present also some limitations. Among these, it should be mentioned that they are fully reliable only when applied to populations similar to the original validation cohort. In addition, most CV risk algorithms are established to assess the risk over a relatively short-term period (eg, 10 years in the Framingham or SCORE risk score) without considering the lifetime risk, which might be substantially higher and particularly relevant in younger patients. Finally, risk calculators stratify patients according to a limited set of strong risk factors; however, overlooking multiple secondary or unconventional—albeit well accepted—CV risk markers. This may lead to misclassifications of individuals, whose CV risk may be underestimated, a problem that takes on great proportions in men with ED who represent a high-risk population independently of traditional risk factors. The concept of “residual risk” deals with this issue and describes the gap between estimated and observed CV events explainable by factors other than those considered in the standard risk algorithms. Identifying other markers that can limit the residual risk in relatively healthy and younger individuals is pivotal to perform the best policy of primary and secondary CV prevention. Ideally, a useful marker should be effective in CV risk prediction, reliable, easy and quick to obtain, widespread available, and as lower cost as possible. Investigating the family history (FH) with easy and quick

questions may meet these requisites. FH for CVD predisposes to early metabolic derangements in offspring, as recently shown in a population of 364 university students from Ghana where parental history for CVD was associated with a 25% increased risk for having metabolic syndrome (MetS) already at 99999 the age of 20–30 years.⁷ Not only FH for CVD provides adverse fingerprints in the offspring but also metabolic disorders are predicting factors, as observed in the Atherosclerosis Risk in Communities Study where the prevalence of MetS in offspring progressively increased with the number of metabolic derangements reported in parents.⁸ Furthermore, a positive FH for CVD or CV death in a first-degree relative (parents or siblings) is a well-accepted independent risk factor for early and lifetime CV events,^{9–11} particularly among younger individuals with an FH of premature disease.^{12–14} According to a meta-analysis—scrutinizing available studies evaluating the association between maternal or paternal history of CVD and the incidence of MACEs—individuals with a positive FH have an increased risk for MACEs that is 54–116% higher in comparison with offspring of non-CVD parents and even greater for FH of early CVDs.¹⁵

Although several studies have demonstrated that FH of CVD is an independent risk factor for future CV events, only few risk calculators, such as QRISK2¹⁶ and Reynolds Risk Score,¹⁷ include FH among their variables and none consider FH for metabolic diseases. In fact, limited data exist regarding the ability of FH to improve the prediction of CVD when added to an established risk score,¹⁸ and some studies showed a modest improvement in the reclassification of individuals into a more accurate risk category.¹² However, FH could be particularly useful in stratifying individuals whose risk factors may not be included in current risk calculators, such as men with ED.¹⁹ Hence, defining the role of a positive FH for single CV risk factors in the occurrence of MetS components or in an incident MACE in the offspring could help in understanding which men may need more attention in the evaluation of the cardiometabolic risk factor status.

The aim of the present study is to evaluate, in a population of men seeking medical care for ED, whether a positive FH for cardio-metabolic diseases, including hypertension, DM and CVD, can identify men with a worse CV and metabolic risk profile.

In addition, the value of FH for hypertension, DM, and CVDs in predicting forthcoming MACEs will be analyzed in a subset of the same population for which information on the occurrence of MACEs was retrospectively retrieved.

MATERIAL AND METHODS

Cross-Sectional Study

A consecutive series of 4,693 men attending an outpatient clinic for ED for the first time between 2002 and 2015 was studied with a retrospective collection of data.

The sociodemographic and clinical characteristics of the sample are summarized in Table 1.

Table 1. Characteristics of the cross-sectional and longitudinal samples

Characteristics	Cross-sectional sample n = 4,693	Longitudinal sample n = 1,595
Age (years)	51.3 ± 13.3	52.9 ± 12.6
Education (%)		
None/primary	12.7	17.0
Lower secondary	32.0	29.8
Upper secondary	35.5	33.3
Higher	19.8	19.9
Current smoking (%)	30.5	33.1
Alcohol intake > 4 drinks daily (%)	3.5	3.8
Family history of cardio-metabolic diseases (%)		
Diabetes mellitus	28.7	21.4
Hypertension	27.7	21.4
Coronary artery disease	26.9	24.2
Stroke/transient ischemic attack	9.7	10.1
Peripheral artery disease	2.1	2.3
Waist circumference (cm)	97.7 ± 10.8	97.4 ± 10.0
Glycemia(g/L)	1.1 ± 0.4	1.1 ± 0.4
HbA1c (%)	6.8 ± 1.6	7.2 ± 1.7
Total cholesterol (mg/dL)	201.5 ± 40.5	206.6 ± 43.1
HDL cholesterol (mg/dL)	48.3 ± 12.3	49.6 ± 12.1
Triglycerides (mg/dL)	115.0 [83.0-164.0]	120.0 [84.0-175.0]
Systolic blood pressure (mm Hg)	130.0 [120.0-140.0]	140.0 [130.0-150.0]
Diastolic blood pressure (mm Hg)	80.0 [80.0-90.0]	85.0 [80.0-90.0]
Metabolic syndrome (%)	39.5	39.8
Hypertension (%)	77.7	85.9
Diabetes mellitus (%)	21.4	20.8
Previous cardiovascular event (%)	11.9	11.4
Chronic Disease Score	0.0 [0.0-4.0]	0.0 [0.0-3.0]
Moderate-severe ED (%)	67.7	65.6
Total testosterone (nmol/L)	15.7 ± 6.4	15.8 ± 6.2
Total testosterone < 10.4 nmol/L (%)	19.9	14.0
Penile color Doppler ultrasound parameters		
Flaccid peak systolic velocity (cm/s)	17.1 ± 6.1	15.8 ± 5.6
Flaccid acceleration (m/s ²)	2.9 ± 1.4	2.8 ± 1.3
Dynamic end-diastolic velocity (cm/s)	4.0 [0.0-7.5]	3.0 [-0.5-7.0]
Dynamic peak systolic velocity (cm/s)	51.5 ± 19.7	53.0 ± 20.4
Dynamic peak systolic velocity <30 cm/s (%)	12.4	10.6

HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; ED = erectile dysfunction.

All participants underwent the usual diagnostic protocol applied at the Andrology Outpatient Clinic at the University Hospital (Careggi Hospital, University of Florence) to newly referred men. All data were collected as part of a routine clinical procedure. Informed consent for the study was obtained from all participants.

Information on the FH was obtained with these questions: “Have your parents or siblings ever been diagnosed as diabetic or have they ever been treated with antidiabetic drugs?” or “Have your parents or siblings ever been diagnosed as having hypertension or have they ever been treated with antihypertensive drugs?” or “Have your parents or siblings ever been diagnosed as having any of the following CVDs, including CAD, stroke/transient ischemic attack (TIA), or peripheral arterial disease (PAD), or have they ever been treated for this disease?” Answers were categorized

as “yes” or “no.” Men replying “not to be sure” or who did not know were excluded from the analyses.

Men were interviewed before the beginning of any treatment and before any specific diagnostic procedures using the Structured Interview on Erectile Dysfunction,²⁰ a 13-item structured interview made up of 3 scales, which identify and quantify components concurring with ED. The severity of ED was assessed using question 1A of Structured Interview on Erectile Dysfunction appendix A (presence of a full erection sufficient for penetration in >50%, absent or mild ED; ≤ 50% moderate-severe ED).

Men were asked to report any kind of drugs used. The Chronic Disease Score (CDS), an index of concomitant morbidities, was calculated as previously described.²¹ This is an aggregate

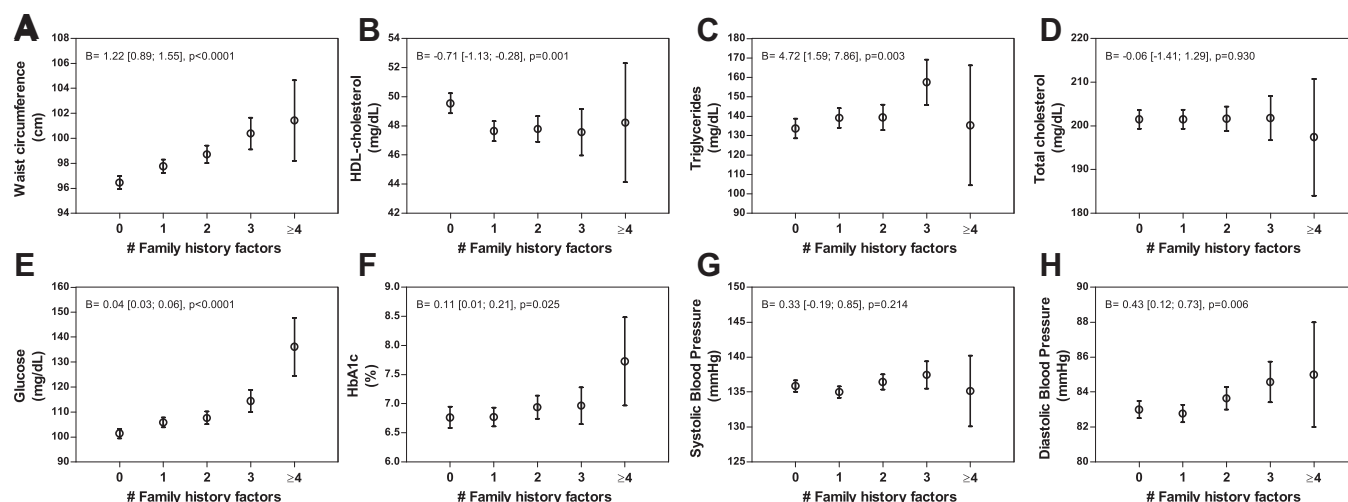


Figure 1. Relationship between family history (FH) factors for cardio-metabolic diseases and different metabolic parameters: Panel A: waist circumference; Panel B: HDL-cholesterol; Panel C: triglycerides; Panel D: total cholesterol; Panel E: glucose; Panel F: HbA1c; Panel G: systolic blood pressure; and Panel H: diastolic blood pressure. Data derive from linear regressions adjusted for age. Figures report estimated means and 95% confidence intervals. HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein.

comorbidity measure based on current medications and originally validated for use as a predictor of physician-rated disease status, self-rated health status, hospitalization, and mortality.²¹

Main Outcome Measures

All individuals underwent a complete physical examination, with measurement of the BP (the mean of 3 measurements 5 minutes apart, in the sitting position, with a standard sphygmomanometer), height, weight, and waist circumference along with testicular (Prader orchidometer) and prostate volume (digital rectal examination).

Blood samples were drawn in the morning, after an overnight fast, for determination of blood glucose (by glucose oxidase method; Aeroseal Abbott, Rome, Italy), total cholesterol, HDL cholesterol, triglycerides (TG) (by automated enzymatic colorimetric method; Aeroseal Abbott), glycated hemoglobin (HbA1c, with high-pressure liquid chromatography method; Menarini Diagnostics, Florence, Italy), total testosterone (TT), and luteinizing hormone (LH) (by electrochemiluminescent method; Modular Roche, Milan, Italy).

All men underwent penile color Doppler ultrasound (PCDU) examination with measurements performed once in the flaccid state and once 20 minutes after an alprostadil (10 µg) intracavernous injection (dynamic evaluation) as previously described.²² The measurement was carried out by 2 andrologists widely experienced in penile ultrasound. The following parameters were measured and collected: flaccid and dynamic peak systolic velocity (PSV), flaccid acceleration, and end-diastolic velocity. The PCDU procedure was performed as recommended in “Standard Operating Procedures for Duplex

Ultrasound”.²³ In particular, according to these, pathological dynamic PSV threshold <30 cm/s was considered.²³ No adverse effects were reported, including priapism or prolonged erections.

MetS and its single factors were defined according to the American Heart Association/National Heart, Lung, and Blood Institute criteria.²⁴

Study on Major Adverse Cardiovascular Events

For 1,595 individuals of the 4,693 cross-sectional cohorts, data concerning CV events as well as mortality and causes of death were retrieved retrospectively.

The characteristics of this subset are reported in Table 1.

Main Outcome Measures

CV events were identified through the regional hospital discharge system and the City of Florence Registry Office. Information on mortality up to December 31, 2007, including causes of death, was obtained from the City of Florence Registry Office, which contains complete and updated records of all persons living within city boundaries. For those who had moved away, queries were sent to the Registry Office of the new city of residence. Nonfatal cases of MACEs requiring hospitalization were identified through the regional hospital discharge system. Following the International Classification of Diseases, fatal and nonfatal MACEs were coded as 410–414 (ischemic heart disease), 420–429 (other heart diseases), or 798–799 (sudden death) for cardiac diseases, as 430–434 or 436–438 for cerebrovascular disease, and 440 for PAD. The data set of the regional hospital discharge system, which is used for

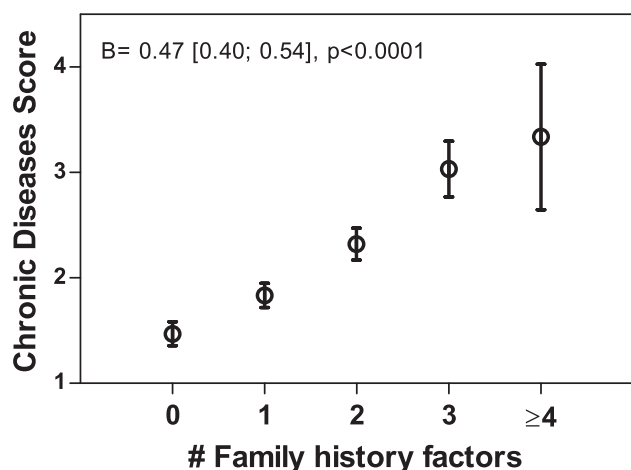


Figure 2. Relationship between the Chronic Disease Score and family history factors for cardio-metabolic disease. Data derive from linear regressions adjusted for age. Figures report the estimated means and 95% confidence intervals.

administrative (reimbursement) purposes, contains complete data on all hospital admissions of individuals residing within the borders of the local health district. Compilation in the register of causes of death is completed for any deceased individual. Therefore, these sources of data allow a complete retrieval of information on all participants, with no loss at follow-up.

Statistical Analysis

Data were expressed as the mean $\pm$ SD when normally distributed, and as the median and interquartile range for parameters with non-normal distribution, unless otherwise specified.

Multiple ordinal, linear, or binary logistic regressions were applied for multivariate analysis, whenever appropriate, with the estimation of B coefficients or odds ratio and 95% confidence intervals.

Survival analyses for MACEs were performed using Kaplan-Meier curves, with log-rank tests for between-group comparisons, with the estimation of hazard ratio and 95% confidence interval, and a stepwise Cox regression was carried out for multivariate analysis, adjusting all data for age and CDS and according to the presence or absence of CV risk factors.

All the analyses were carried out by using SPSS, version 25, statistical package (IBM Corp, Armonk, NY), and a $P < .05$ was considered statistically significant.

RESULTS

Cross-Sectional Study

Of 4,890 men in our casuistry, 197 (4.0%) were not able to provide information on their FH, leaving 4,693 individuals in

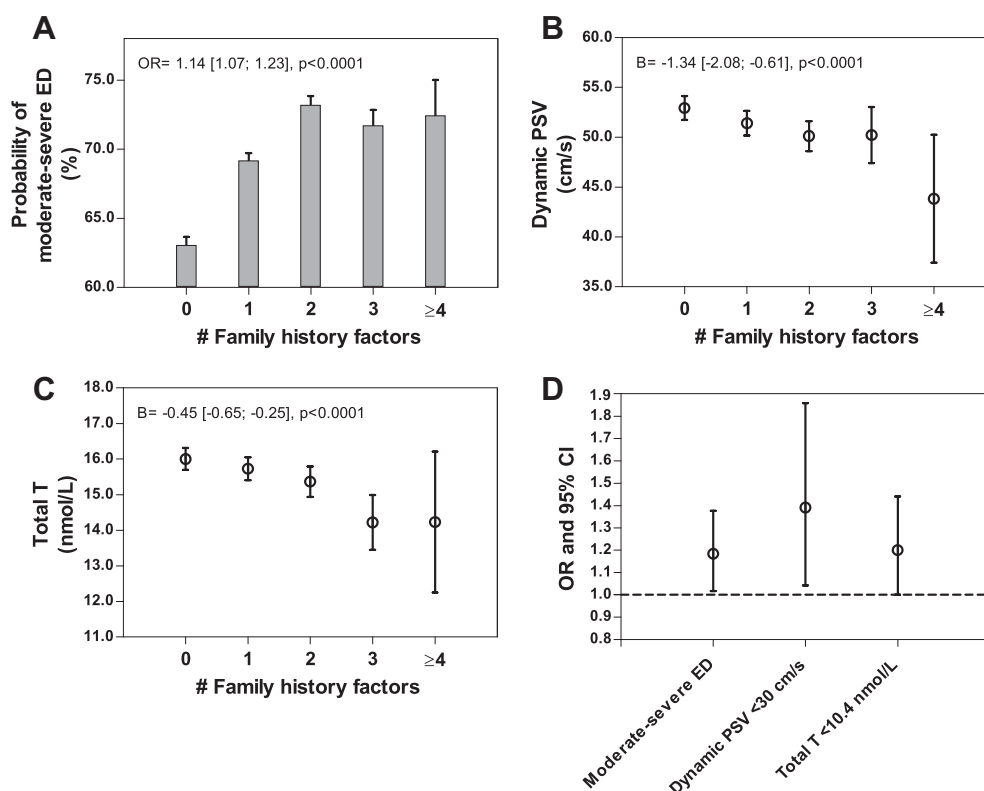


Figure 3. Probability of having a moderate-severe ED, hypogonadism, or impaired penile vascular flows as a function of family history factors for cardio-metabolic diseases. Data derive from age-adjusted ordinal regression (panel A) or linear regressions (panels B and C). Panel D reports data derived from binary logistic regressions adjusted for age and the Chronic Disease Score. Panel A reports estimated prevalence and the upper limit of the 95% confidence interval (CI), panels B and C report the estimated means and 95% CI, whereas panel D reports odds ratio (OR) and 95 CI. ED = erectile dysfunction; T = testosterone; PSV = peak systolic velocity.

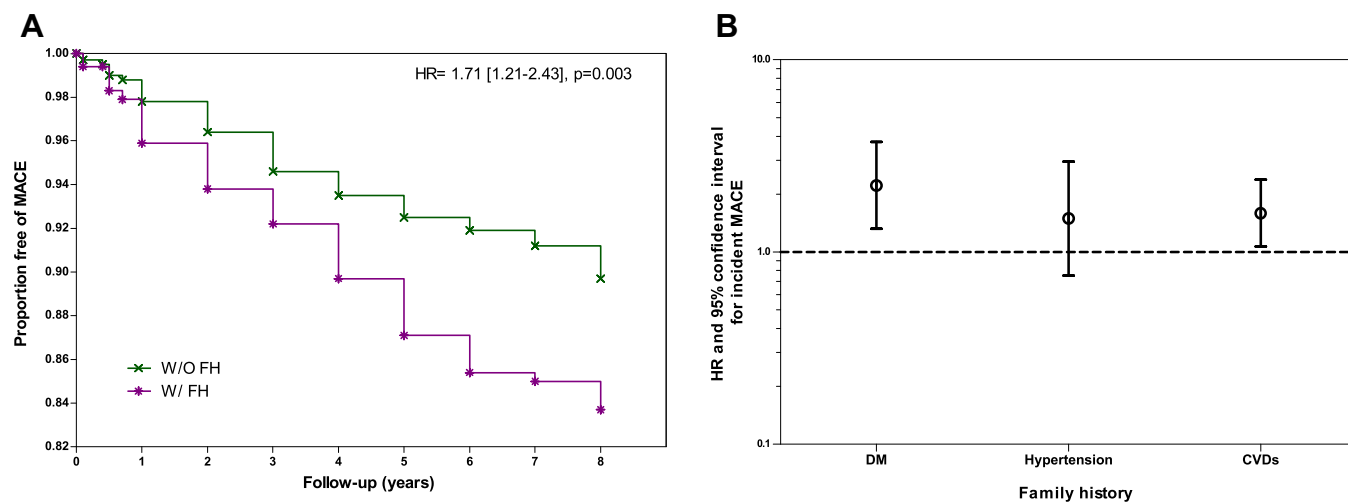


Figure 4. Risk of incident major adverse cardiovascular events as a function of family history for cardio-metabolic diseases. Panel A: Kaplan-Meier curve for the risk of incident MACE in subjects having or not FH for cardio-metabolic diseases. The green line represents a negative FH (factors = 0), and the purple line represents a positive FH (factors > 0). Panel B: Cox regression for the risk of an incident MACE in subjects having or not FH of DM, CVDs (CAD, stroke/TIA or PAD) or hypertension. MACE = major adverse cardiovascular events; FH = family history; W = with; W/O = without; DM = diabetes mellitus; CVDs = cardiovascular diseases; CAD = coronary artery disease; TIA = transient ischemic attack; PAD = peripheral artery disease. Figure 4 is available in color online at www.jsm.jsexmed.org.

the analytical sample. Among the 4,693 individuals studied, 1,348 (28.7%) had FH for DM, 1,299 (27.7%) for hypertension, 1,264 (26.9%) for CAD, 457 (9.7%) for stroke/TIA, and 99 (2.1%) for PAD.

Participants were categorized based on the number of family factors as mentioned previously. Of them, 1824 (38.9%) had negative FH for cardio-metabolic factors, 1,630 (34.7%) had one family factor, and 922 (19.6%), 276 (5.9%), and 41 (0.9%) had 2, 3, or ≥ 4 family factors, respectively.

When considering separately the MetS determinants and other biochemical parameters (Figure 1), after adjusting for age, a higher number of FH factors were associated with greater waist circumference (panel A), lower HDL cholesterol (panel B), higher TG (panel C), higher blood glucose (panel E), and higher HbA1c (panel F) levels. A higher number of FH factors were also associated with increased diastolic, but not systolic, BP (Figure 1, panels H and G, respectively). No association with total cholesterol levels was observed (Figure 1, panel D). Concerning chronic illnesses, a significant positive association was found between the number of FH factors and CDS (Figure 2). In an age-adjusted model, a direct relationship between the number of FH factors and the number of MetS components was found ($B = 0.18$ [0.13; 0.231]; $P < .0001$) and confirmed even after introducing the CDS in the model, as a further covariate ($B = 0.06$ [0.02; 0.11]; $P < .0001$).

When considering sexual function, after adjusting for age, a greater number of FH factors were associated with a higher probability of moderate-severe ED (Figure 3 panel A), lower dynamic PSV and TT levels (Figure 3 panels B and C) without any significant relationship with LH ($B = -0.11 \pm 0.09$, $P = .208$). Accordingly, panel D in Figure 3 shows the increased

probability of ED, impaired PCDU parameters (defined as dynamic PSV < 30 cm/s), and hypogonadism (defined as TT < 10.4 nmol/L) associated with cardio-metabolic FH, evaluated as dummy variables, in a model adjusted for age and the CDS. No other PCDU parameter (ie, flaccid PSV or acceleration and end-diastolic velocity) was significantly associated with FH factors (data not shown).

Study on Major Adverse Cardiovascular Events

Among the 1,595 individuals retrospectively evaluated, 341 (21.4%) had FH for DM, 341 (21.4%) for hypertension, 386 (24.2%) for CAD, 161 (10.1%) for stroke/TIA, and 37 (2.3%) for PAD. Overall, 739 (46.3%) men did not report any positive FH factor, whereas 856 (53.7%) had at least one of these. Of the entire population, 80 were free of previous MACEs and 59 reported previous CV events at baseline. During a mean follow-up of 4.2 ± 2.5 years, 136 MACEs were observed of which 87 (64.0%) were ischemic heart diseases, 36 (26.5%) were cerebral (stroke or TIA), and 13 (9.6%) were PAD. The median time to MACEs was 4.0 [2.0–7.0] years. Of the observed MACEs, 87 (64.0%) occurred in men with at least one positive FH factor.

The survival analysis showed a higher risk of MACEs in individuals with at least one positive FH factor than those without (Figure 4 panel A). This result was confirmed in a Cox regression model, after adjusting for age and the CDS (hazard ratio = 1.51 [1.06–2.16], $P = .023$). When considering separately FH for DM, hypertension, or CVDs (CAD, stroke/TIA, or PAD), FH for DM and MACE proved to be predictors, whereas hypertension did not reach the statistical significance for the association with forthcoming MACEs in the offspring (Figure 4 panel B). When categorizing the population according to the presence

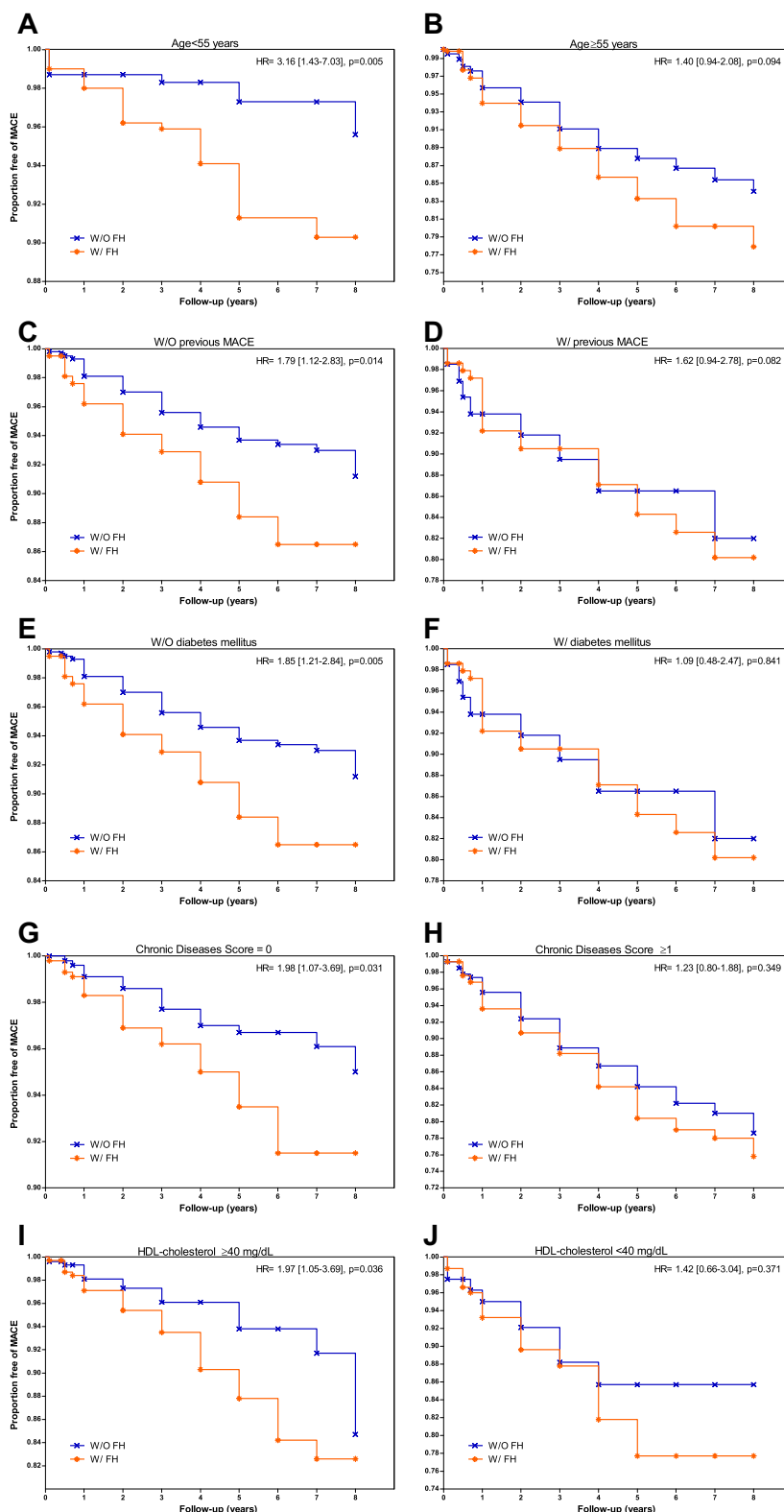


Figure 5. Risk of incident major adverse cardiovascular events as derived from Kaplan-Meier curves as a function of family history for cardio-metabolic diseases according to the presence or absence of different conventional risk factors: Panel A: younger subjects; Panel B: older subjects; Panel C: subjects W/O previous MACE; Panel D: subjects W/ previous MACE; Panel E: subjects W/O diabetes mellitus; Panel F: subjects W/ diabetes mellitus; Panel G: subjects W/O comorbidities; Panel H: subjects W/ at least one comorbidity; Panel I: subjects with normal HDL-cholesterol; and Panel J: subjects with low HDL-cholesterol. The blue line represents a negative FH (factors = 0), and the orange line represents a positive FH (factors > 0). HDL = high-density lipoprotein; MACE = major adverse cardiovascular events; FH = family history; W/ = with; W/O = without. Figure 5 is available in color online at www.jsm.jsexmed.org.

Table 2. Adjusted hazard ratio and 95% confidence interval for incident MACEs according to the presence or absence of different conventional risk factors

Risk factor	HR and 95% confidence intervals	
	Absence of risk factor	Presence of risk factor
Age (≥ 55 years)	2.28 [1.00-5.22], $P = .050$	1.24 [0.83-1.85], $P = .290$
Diabetes mellitus	1.66 [1.08-2.56], $P = .021$	1.05 [0.45-2.44], $P = .911$
HDL cholesterol (< 40 mg/dL)	1.95 [1.03-3.70], $P = .039$	1.34 [0.62-2.89], $P = .461$
Chronic Disease Score (≥ 1)	2.04 [1.10-3.80], $P = .025$	1.34 [0.87-2.07], $P = .183$
Previous cardiovascular events	1.63 [1.02-2.61], $P = .042$	1.54 [0.89-2.66], $P = .126$

Data are derived from Cox regression models adjusted for age and the Chronic Disease Score, except for the analysis according to age that was adjusted only for the Chronic Disease Score and the analysis according to the Chronic Disease Score that was adjusted only for age.

HR = hazard ratio; HDL = high-density lipoprotein; MACEs = major adverse cardiovascular events.

of several conventional risk factors considered as dummy variables, such as age (stratified according to the median age: < 55 or ≥ 55 years), DM (yes or no), HDL cholesterol (< 40 or ≥ 40 mg/dL), and the CDS ($= 0$ or ≥ 1), the association between cardio-metabolic FH and incident MACE was confirmed only in the low-risk groups (Figure 5). The predictive value of cardio-metabolic FH toward the incident MACE was confirmed even when only men free from previous CV events were considered, whereas a nonsignificant trend was observed for men with a previous personal history of CVD (Figure 5). All the aforementioned results were confirmed even after adjusting for confounding factors (Table 2).

DISCUSSION

In the present study, we demonstrated that, in a high CV risk population such as individuals with ED, a positive FH for cardio-metabolic factors (hypertension, DM, CVDs) in first-degree relatives is associated with a worse metabolic and CV risk profile and acts as a predictor for the incidence of forthcoming MACEs. Although investigating FH as a dichotomous variable does not consider important aspects, such as disease severity or the number of affected relatives, it is convenient for the clinical setting, providing useful information on several cardiometabolic conditions in men with ED. A higher number of family factors were clearly dose-dependently associated with most of the clinical features defining MetS, including a greater waist circumference, lower HDL cholesterol, higher TG, higher blood glucose, and HbA1c; when considering BP values, an association was found with a higher diastolic BP. Even when considering the corresponding pathological conditions, such as obesity, DM, hypertension, and dyslipidemia, a greater FH burden was associated with a higher number of MetS features. Other studies have shown an association between a parental history of single MetS components and the development of MetS in the offspring.^{8,25} In a recent study conducted in Ghana, including young adults aged 20-30 years, an association between a parental history of CVDs and MetS was found. In addition, abdominal obesity was associated with parental CVDs, DM, and hypertension.⁷ Consistently with these results, our findings suggest the

importance of a correct evaluation of MetS abnormalities in individuals with a positive FH for cardiometabolic diseases, namely in a high-risk population, such as men with ED. The discovery of multiple features of MetS may justify more aggressive interventions of primary prevention to reduce lifetime CV risk, especially in younger men, because of their long-life expectancy. In fact, although it is still controversial whether the CV risk associated with MetS is equal or greater than the risk associated with its single components,²⁶ MetS is a proven risk factor for CVD. Accordingly, we previously demonstrated that, among individuals with ED, those with MetS are characterized by the worst erectile function, essentially because of impairment in the penile blood flow,²⁷ thus highlighting the adverse effect of MetS on arterial health. Moreover, diagnosing MetS in patients with low-to-moderate CV risk is still important because MetS includes also risk factors, such as visceral obesity, which are not taken into consideration by most CV risk calculators.

Cardio-metabolic FH was associated with a greater probability of having a moderate-severe form of ED, defined as the absence of full erection sufficient for penetration in more than 50% of attempts. Besides the self-reported severity of ED, FH was also associated with a greater probability of having an abnormal PSV at dynamic PCDU, suggestive for impairment in the penile arterial circulation. We previously demonstrated the role of impaired PCDU parameters in identifying an adverse CV profile and in predicting silent CAD and MACE in men with ED.^{3,28,29} We also demonstrated that this association is particularly relevant in lower risk individuals.²⁹ Hence, an impairment in penile arterial circulation detected at PCDU not only enables to identify an arteriogenic component of ED but also provides a general overview of systemic arterial health status. To our knowledge, this is the first study to describe an association between a positive FH for cardio-metabolic factors and impairment in arterial penile circulation. However, other studies explored the role of a positive FH for CVD as a marker of arterial disorders. An FH of premature CAD has been associated, in young adults, to early changes in arterial structure and endothelial function, such as greater intima-media thickness of the common carotid artery³⁰ and reduced flow-mediated brachial-artery reactivity.^{30,31} Furthermore, these vascular abnormalities occurred

independently of several traditional CV risk factors, such as the lipid profile,³² and they were more evident in individuals free of conventional risk factors and in those whose CAD-affected first-degree relatives were free of risk factors themselves, thus suggesting a genetic influence on early arterial pathophysiology.³¹ These findings are consistent with our results that show a role for FH in predicting forthcoming CV events only in otherwise low-risk men, suggesting that FH has an impact that goes beyond the traditional atherogenic risk factors.

FH for cardio-metabolic diseases was associated with an increased risk of hypogonadism without significant changes in LH, suggesting a biochemical state of hypogonadotropic hypogonadism. These findings confirm the role of FH as a marker of an altered metabolic and hormonal status. Metabolic conditions, including obesity, DM, dyslipidemia, and MetS, are associated with a decline in TT levels, which are not accompanied by a compensatory increase in LH, thus configuring a hypothalamic-pituitary failure, rather than primary testicular damage.^{33,34} Interestingly, in our study, the association between FH and hypogonadism is independent of age and comorbidities, which are both linked with a decrease in TT levels.^{33,35}

A positive cardio-metabolic FH was associated with an increased incidence of forthcoming MACEs, independent of age and comorbidities. When evaluating the predicting role of FH in low- and high-risk groups, a positive FH showed a predicting value for forthcoming MACEs only in low-risk groups, such as younger and nondiabetic individuals without chronic conditions, and with normal HDL cholesterol levels. Similarly, FH demonstrated a predictive role even in men with ED and without previous history of MACEs. According to these findings, FH may represent a valuable tool for identifying, among ED men, those who, despite a low CV risk profile, require more efforts on lifestyle intervention. Although present algorithms for CV risk stratification include the most important and well-known risk factors whose prediction captures most of the MACEs actually observed,¹⁹ in specific subsets of patients, the presence of one or more additional risk factors, such as FH, may considerably alter the risk estimation.¹⁹ Different professional societies considered the evaluation of additional risk factors alongside traditional ones. The recent American Professional Society guidelines on cholesterol management state that considering additional risk factors, such as FH, can help in deciding whether to start or intensify statin therapy in patients aged between 40 and 75 years, without DM and at intermediate risk, as calculated by current risk calculators.³⁶ In a 2016 study that compared the effect of several negative risk markers on the risk of future CVD, a negative FH was, among the clinical features, the strongest modifier and had the greatest impact in downgrading the risk classification.³⁷

The role of a positive FH as a CV risk factor seems to be particularly important in younger and lower risk individuals.^{13,14} Data from the Offspring Framingham Study have shown that a parental history of CVD increases the risk of CV events in

middle-aged adults (30–59 years old) but not in older individuals (>60 years).⁹ Moreover, in the same study, parental history of CVD increased CV risk only in nondiabetic individuals and its effect is greater in patients with borderline levels of cholesterol and BP and among patients classified as low-intermediate risk by traditional risk factors.⁹ Accordingly, our results suggest the importance of a positive FH as a CV risk factor in men with ED, namely in those considered at lower risk by using traditional CV risk factors such as age and DM.

Multiple explanations could underlie the relationship between a positive cardio-metabolic FH and the adverse CV profile in the offspring. The impact of FH on CV risk reflects both the genetic trait and the environment shared among the family members. A familial component for several major risk factors, including hypertension³⁸ and diabetes,³⁹ has been largely studied and is well established. However, the recurrence within a family of conventional risk factors only partly explains the phenomenon. A possible explanation relies on a familial predisposition to a proinflammatory status, which is a well-known pathogenic step in plaque formation and destabilization. In a longitudinal study involving the offspring of patients with a history of CAD, it has been shown that affected patients and their offspring share a genetic signature with a greater prevalence of adverse genotypes for vascular endothelial growth factor, interleukin-10, and interferon- γ . In addition, the offspring, as compared with matched controls, has a 3-to-8 fold increased incidence of MACE.⁴⁰ Besides genetic fingerprints, behavioral risk factors may play a role. In fact, several lines of evidence show that unhealthy diet, physical inactivity, and maladaptive coping strategies to stress found in adulthood have roots in the family environment during childhood and adolescence.⁴¹

The vast majority of CV risk models consider age as a fundamental variable, and this usually leads to classifying young individuals as at low risk. As a result, young adults are generally not evaluated thoroughly regarding the CV risk. Data from the Pathobiological Determinants of Atherosclerosis in Youth Study showed that traditional risk factors for CAD are associated with a high probability of having advanced atherosclerotic lesions in the coronary arteries and the abdominal aorta in individuals aged between 15 and 34 years.⁴² These findings show that the same risk factors, which predict MACEs in older individuals, can be an indicator of preclinical atherosclerotic lesions even in younger subjects. In sexual medicine, the identification of additional risk factors for a correct risk assessment is particularly relevant, considering the role of ED as an independent risk factor for CVDs. ED is a sign of atherosclerotic disease in other vascular districts; in fact, it commonly occurs in subjects with silent CAD.^{43,44} Furthermore, ED is considered a harbinger of forthcoming CV events, preceding CVDs by 2–5 years.^{45,46} Several pathophysiologic mechanisms can explain the association between ED and CVD and their temporal relationship, such as endothelial dysfunction and the difference in the blood vessel diameter between penile and other vascular districts.⁵

The association between ED and CVD is particularly important in younger men and those without comorbidities.^{5,47} Both organic and psychological factors can contribute to ED. Younger men are often classified as affected by psychogenic ED, without carrying out a thorough assessment first, underestimating the possibility of organic pathogenesis. However, it is worth noticing that organic factors, either alone or associated with psychological aspects, might play a significant role in the pathogenesis of ED in young adults⁴⁸ and vascular factors may account for a considerable part of them.⁴⁹ Hence, young men with a known CV risk marker, such as ED, are the ideal candidates for an additional CV risk factor screening. FH can be a risk modifier in men with ED, particularly in those whose global risk may be underestimated by current risk calculators (eg, younger men, nondiabetic, with normal lipid profile, and free from previous CV events). In these men, the use of FH and other nonconventional CV factors may be helpful in guiding treatment decisions. Conversely, in individuals whose estimated risk is already high for the presence of major CV risk factors (eg, older men, diabetic, dyslipidemic, and with history of previous CV events), an additional assessment may not be as much helpful in adding insights to the global risk estimation.

The principal limitation of this study is that FH of DM, hypertension, and CVDs was obtained through participants' report and was not formally adjudicated. These data may be affected by recall bias, which may lead to misclassification of some study participants. However, the great sample size is likely to dilute possible mistakes. An additional limitation depends on the specific setting of recruitment. In fact, the results are derived from men consulting an Italian University Andrology Clinic for ED, which could have different characteristics from those consulting general practitioners or not seeking medical care. Finally, although the use of an administrative database for capturing MACEs minimizes the risk of loss at follow-up, it should be recognized that it may be a source of bias for the risk of misclassification.

CONCLUSIONS

In men with ED, FH for hypertension, DM, and CVDs is associated with an adverse cardio-metabolic profile, and it is a predictor for the incidence of new MACEs, in particular, in low-risk individuals.

FH is a simple and inexpensive information that should be always part of the CV risk assessment. Positive FH for cardio-metabolic diseases can help in the identification of men who need to undergo lifestyle and risk factor modifications and whose risk would otherwise be overlooked.

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STATEMENT OF AUTHORSHIP

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