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# Heart Disease Risk Factors Predict Erectile Dysfunction 25 Years Later

## The Rancho Bernardo Study

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<b>OBJECTIVES</b>	We examined whether common coronary heart disease (CHD) risk factors measured in mid-life predict erectile dysfunction (ED) 25 years later.
<b>BACKGROUND</b>	Retrospective and cross-sectional studies have suggested that ED is associated with classic CHD risk factors, but few prospective studies have studied these associations.
<b>METHODS</b>	In this prospective study of community-dwelling men age 30 to 69 years, seven classic CHD risk factors (age, smoking, hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, and obesity) were assessed from 1972 to 1974. In 1998, after an average follow-up of 25 years, surviving male participants were asked to complete the International Index of Erectile Function (IIEF-5), which allows stratification of ED into five groups.
<b>RESULTS</b>	Sixty-eight percent of the surviving men returned, and 60% completed the IIEF-5 questionnaire. Respondents had more favorable levels of all heart disease risk factors at baseline than non-respondents. At baseline, the average age of the 570 ED study participants was 46 years; at follow-up, their average age was 72 years. Mean age, body mass index, cholesterol, and triglycerides were each significantly associated with an increased risk of ED. Cigarette smoking was marginally more common in those with severe/complete ED, as compared with those without ED. Blood pressure and fasting blood glucose were not significantly associated with ED, likely due to selective mortality.
<b>CONCLUSIONS</b>	Improving CHD risk factors in mid-life may decrease the risk of ED as well as CHD. Erectile dysfunction should be included as an outcome in clinical trials of lipid-lowering agents and lifestyle modifications. (J Am Coll Cardiol 2004;43:1405-11) © 2004 by the American College of Cardiology Foundation

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According to the National Institutes of Health, erectile dysfunction (ED), the persistent inability to attain and maintain a penile erection adequate for satisfactory sexual performance, affects 30 million men in the U.S. alone (1). In recent years, the emphasis on the likely etiology of ED has shifted from psychogenic causes to those of vascular origin (2,3)—based largely on retrospective and cross-sectional studies of patients (4–7). These studies showed that ED is associated with many coronary heart disease (CHD) risk factors, including diabetes mellitus (4,6,7), hypertension (4,6,7), smoking (4,5,7), and abnormal lipids (5,6). It has been suggested that ED may be a clinical marker of coronary, peripheral, or cerebrovascular disease as well as hypertension and diabetes (8,9). Small studies have linked ED with angiographic evidence of coronary disease (10,11). One study of 132 men correlated angiographic results with ED symptoms and scores on the 5-item International Index of Erectile Function (IIEF-5); 58% reported experiencing ED before the diagnosis of CHD (11). To our knowledge,

no studies have reported the degree to which mid-life heart disease risk factors predict ED 25 years later.

We report here a prospective study of common CHD risk factors assessed in men age 30 to 69 years from 1972 to 1974 and ED by the IIEF-5, as reported by 60% of the surviving cohort in 1998.

### METHODS

Between 1972 and 1974, 82% of adult residents of Rancho Bernardo, California, a planned community of predominantly middle-class to upper middle-class Caucasian adults, participated in a survey of CHD risk factors. The baseline clinical evaluation included a brief medical and medication history and measurement of height, weight, blood pressure (BP), fasting plasma glucose (FPG), cholesterol, and triglyceride levels. High-density lipoprotein cholesterol was not measured. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in seated, rested subjects, using a standard protocol; height and weight were measured with subjects wearing light clothing and no shoes. Fasting plasma cholesterol and triglycerides were measured in a Centers for Disease Control-certified lipid research clinic laboratory, using an Auto Analyzer I (Technicon Instruments, Tarrytown, New York). Fasting plasma cholesterol was measured by a hexokinase method in a clinical laboratory. Body mass index (BMI) ( $\text{kg}/\text{m}^2$ ) was calculated as an estimate of obesity.

Baseline hypertension was defined as SBP  $\geq 140$  mm Hg,

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**Abbreviations and Acronyms**

BMI	=	body mass index
BP	=	blood pressure
CHD	=	coronary heart disease
CI	=	confidence interval
DBP	=	diastolic blood pressure
ED	=	erectile dysfunction
FPG	=	fasting plasma glucose
IIEF-5	=	5-item International Index of Erectile Function
MMAS	=	Massachusetts Male Aging Study
OR	=	odds ratio
SBP	=	systolic blood pressure

DBP  $\geq 90$  mm Hg, use of BP medications, or a history of high BP; diabetes mellitus as FPG  $\geq 7.0$  mmol/l (126 mg/dl), use of diabetes medications, or a personal history of diabetes; hypercholesterolemia as fasting total cholesterol  $\geq 5.2$  mmol/l (200 mg/dl), use of medication for cholesterol, or a history of high cholesterol; hypertriglyceridemia as a fasting triglyceride level  $\geq 2.6$  mmol/l (200 mg/dl); and obesity as BMI  $\geq 28$  kg/m<sup>2</sup>.

In 1998, all surviving non-institutionalized men were invited to complete a mailed questionnaire that included the short 5-item ED questionnaire (IIEF-5). Of 944 surviving members of the original cohort of 1,810 men age 30 to 69 years at baseline, 641 returned the survey (response rate 67.9%). Of these, 71 were excluded for incomplete responses to questions, leaving 570 men for this report. The main reason (74.1%) for non-response was death before the 1998 questionnaire (Fig. 1).

The IIEF is a widely accepted international standard for clinical trials involving sexual function, with four domains composing a multidimensional 15-item questionnaire

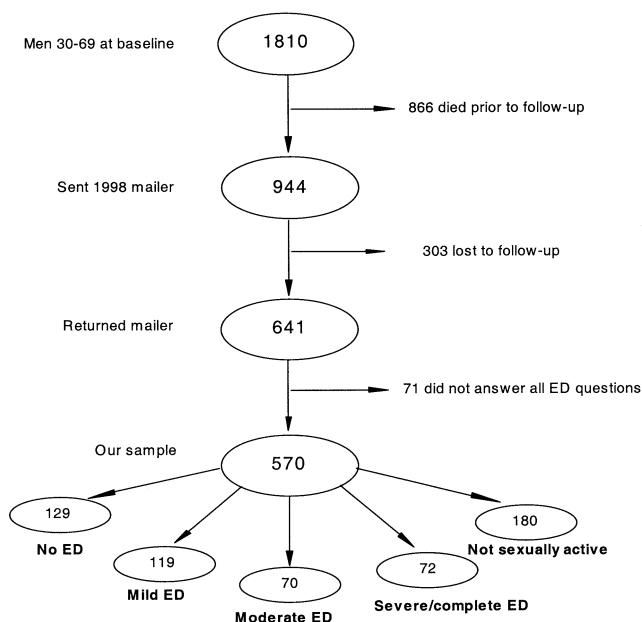


Figure 1. Flow chart of study participants. ED = erectile dysfunction.

(12,13). The IIEF-5 questionnaire is an abbreviated form of the IIEF, used to classify ED, with four items selected from the erectile domain portion of the IIEF and one addressing sexual satisfaction (14). The IIEF-5 has been validated (14,15) and correlated with patient reports of ED (15). The erectile function domain score is calculated as the sum of questions 1 through 4 for men with complete answers to the IIEF-5. The degree of ED is classified by the erectile function domain score as complete ( $\leq 4$ ), severe (5 to 10), moderate (11 to 14), mild (15 to 18), or none (19 to 20). The IIEF-5 protocol (Table 1) does not categorize men who fail to provide complete responses or report “no sexual activity” as a response to any of the questions on the IIEF-5 questionnaire.

Statistical analyses were performed using Statistical Analysis System software (SAS Institute, Cary, North Carolina). The internal consistency of the questionnaire construct was confirmed with a Cronbach’s alpha coefficient of 0.96 for all five questions and 0.95 for the four erectile function questions.

All baseline measures, except triglyceride levels, were sufficiently normally distributed so that transformation was unnecessary. For triglyceride levels, log-transformed values were used, with the values returned to original units for presentation. For continuous variables, the overall *F* statistic from general linear model procedures was used to determine whether the age-adjusted mean values differed significantly from each other across ED categories. Age-adjusted individual mean comparisons were assessed using analysis of covariance with linear contrasts across ED categories. Chi-square statistics were used to determine whether age-adjusted values for categorical variables differed significantly across ED categories. Age-adjusted proportions were computed by estimating probabilities for the ED groups at the overall average age by logistic regression. The end points of the 95% confidence intervals were computed based on methods described by Hosmer and Lemeshow (16).

Stepwise logistic regression was used to assess the relationship between age and the categorical risk factors (hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, ever smoker, and obesity) and ED until a final model was reached. Significance was  $p < 0.05$  for the odds ratio. Stepwise logistic regression was also used to estimate a cumulative logit model to predict the odds of being in a more severe ED category. Statistical significance was set at  $p < 0.05$  (two-sided).

**RESULTS**

Of 1,810 men age 30 to 69 years at the baseline visit between 1972 and 1974, 48% ( $n = 994$ ) had died by the time of the 1998 ED questionnaire. Figure 1 shows the 67.9% response rate among survivors, 570 of whom completed all of the IIEF-5 questions. Table 2 compares the baseline characteristics of the study sample included in this analysis with men not included due to death, lost to

**Table 1.** 5-Item International Index of Erectile Function (IIEF-5)\*

1. How do you rate your <i>confidence</i> that you can get and keep an erection?					
	Very low	Low	Moderate	High	Very high
	1	2	3	4	5
2. With sexual stimulation, <i>how often</i> have your erections been sufficient to allow for penetration (entering your partner)?					
I'm not at all sexually active.	Almost never/never	Rarely (much less than half the time)	Occasionally (about half the time)	Most of the time (much more than half the time)	Almost always/always
0	1	2	3	4	5
3. During sexual intercourse, <i>how often</i> were you able to maintain an erection after penetration?					
I'm not at all sexually active.	Almost never/never	Rarely (much less than half the time)	Occasionally (about half the time)	Most of the time (much more than half the time)	Almost always/always
0	1	2	3	4	5
4. During sexual intercourse, <i>how difficult</i> has it been to maintain your erections until completion of intercourse?					
I haven't tried to have sexual intercourse.	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
0	1	2	3	4	5
5. When you attempted sexual intercourse, <i>how often</i> was it satisfactory to you?					
I'm not at all sexually active.	Almost never/never	Rarely (much less than half the time)	Occasionally (about half the time)	Most of the time (much more than half the time)	Almost always/always
0	1	2	3	4	5

\*All questions preceded by "over the past six months." Reproduced by permission from Rosen et al. (14).

follow-up, or not answering all IIEF-5 questions. The mean ages for those deceased, lost to follow-up, and with incomplete questionnaires were  $61.8 \pm 7.4$  years,  $48.3 \pm 12.2$  years, and  $50.9 \pm 10.6$  years, respectively, compared with  $45.6 \pm 10.2$  years for respondents. At baseline, non-respondents to IIEF-5 were less likely to be married, less likely to have completed one year of college, and more likely to be past smokers ( $p < 0.05$ ). Levels of FPG, SBP, DBP, total cholesterol, and BMI were each significantly more favorable in the ED study sample ( $p < 0.05$ ).

At baseline, the mean ( $\pm$ SD) age of respondents was  $45.6 \pm 10.2$  years (range 30 to 69 years), with 63% being  $<50$  years of age. Age showed a strong linear correlation with

ED ( $p < 0.00001$ ), with increasing severity, as shown in Figure 2. Nearly all (99.1%) were married and living with their spouses. Medication use was uncommon, with only 4% reporting BP medication, 2% lipid-lowering medication, and  $<1\%$  diabetes medication. At baseline, 2.6% reported heart disease (40% in the sexually inactive group) and 2.1% a history of diabetes (42% in the sexually inactive group). The average ( $\pm$ SD) duration of follow-up was  $25.4 \pm 0.57$  years (range 24.3 to 26.9 years), and the average age at follow-up was  $71.5 \pm 10.3$  years (range 54.7 to 95.6 years).

Table 3 shows age-adjusted CHD risk factors by ED category or absent sexual activity. Age-adjusted, positive linear trends as ED severity progressed from no ED to

**Table 2.** Baseline Characteristics for Men in the Rancho Bernardo Study, 1972 to 1974

	Nonresponders* (n = 1,240)	Our Sample (n = 570)	p Value
Mean $\pm$ SD values			
Age (yrs)	$57.9 \pm 10.8$	$45.6 \pm 10.2$	$<0.0001$
Fasting plasma glucose (mmol/l)	$6.2 \pm 1.3$	$6.0 \pm 1.2$	0.0023
Total cholesterol (mmol/l)	$5.5 \pm 0.9$	$5.3 \pm 0.9$	0.0006
Systolic blood pressure (mm Hg)	$137.0 \pm 21.3$	$122.5 \pm 14.5$	$<0.0001$
Diastolic blood pressure (mm Hg)	$82.1 \pm 11.4$	$77.9 \pm 9.8$	$<0.0001$
Body mass index (kg/m <sup>2</sup> )	$26.0 \pm 3.1$	$25.7 \pm 2.7$	0.0489
Triglycerides (mmol/l)	1.3	1.3	0.3686
Percentages			
Married	97.5	99.1	0.0219
$\geq 1$ year of college	76.3	87.2	$<0.0001$
Current smoking	25.2	25.0	0.9268
Past smoking	49.1	42.3	0.0067

\*Deceased, lost to follow-up, or missing responses.

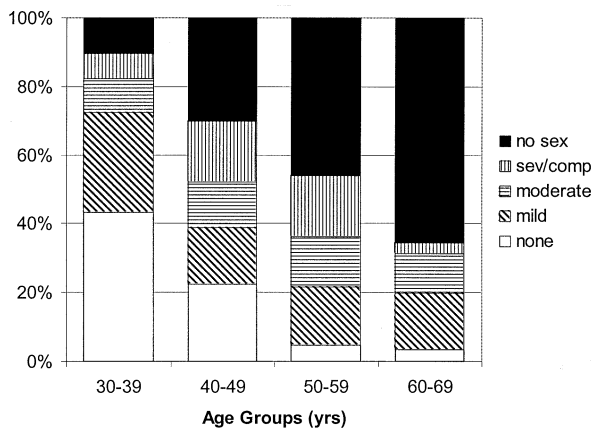


Figure 2. Erectile dysfunction by age.

severe/complete ED and no sexual activity were significant for triglycerides ( $p < 0.01$ ) and for BMI ( $p = 0.01$ ). In age-adjusted analyses, men without ED had lower cholesterol levels than men with moderate ED ( $p < 0.05$ ), and men with severe/complete ED or who were not sexually active had higher triglyceride levels than men without ED ( $p < 0.05$ ). Men with mild ED had lower triglyceride levels than sexually inactive men ( $p < 0.05$ ). Age-adjusted baseline BMI was also significantly lower in men without ED than in men with severe/complete ED or with sexually inactive men ( $p < 0.05$ ).

The overall prevalence of categorically defined CHD risk factors at baseline was 58% for hypercholesterolemia, 25% for current cigarette smoking, 25% for hypertension, 18% for being overweight, 15% for hypertriglyceridemia, and 12% for diabetes. Age-adjusted categorical CHD risk factors were assessed in bivariate and multivariate analyses. With marginal significance, men with hypercholesterolemia at baseline were more likely to have moderate ED than no ED at follow-up, and men with severe/complete ED were more likely to have been current smokers at baseline than those without ED.

Multivariate analyses for age and all categorical risk factors (diabetes, hypertension, hypercholesterolemia, hy-

pertriglyceridemia, obesity, and smoking) were performed to detect independent associations for any ED or for increasing severity of ED, after exclusion of the sexually inactive group. Other than age, the statistically significant associations were limited to hypercholesterolemia and obesity. The model for any ED shows significant independent predictors to be age (per year, odds ratio [OR] 1.09, 95% confidence interval [CI] 1.06 to 1.13;  $p < 0.0001$ ) and hypercholesterolemia (OR 1.93, 95% CI 1.21 to 3.06;  $p = 0.006$ ). When this model included men who were not sexually active in the ED group, obesity (OR 2.02, 95% CI 1.05 to 3.89;  $p = 0.035$ ) was also a significant independent predictor, in addition to age (per year, OR 1.12, 95% CI 1.09 to 1.16;  $p < 0.0001$ ) and hypercholesterolemia (OR 1.76, 95% CI 1.12 to 2.74;  $p = 0.014$ ). In a cumulative logit model, age (per year, OR 1.07, 95% CI 1.04 to 1.09;  $p < 0.0001$ ), presence of hypercholesterolemia (OR 1.54, 95% CI 1.05 to 2.26;  $p = 0.027$ ), and obesity (OR 1.93, 95% CI 1.18 to 3.17;  $p = 0.009$ ) were each independent significant predictors of a stepwise increase in severity of ED.

The results from a separate multivariate analysis limited to men who were  $< 50$  years of age at baseline were similar to the results from the entire cohort in terms of age (OR 1.07, 95% CI 1.02 to 1.12;  $p = 0.005$ ) and hypercholesterolemia (OR 1.88, 95% CI 1.15 to 3.08;  $p = 0.012$ ), each significant independent predictors of any ED.

Finally, to determine whether men with more than one risk factor would have an increased risk of ED, we examined the frequency of any ED by the number of risk factors. At baseline, 21% of men had no categorically defined risk factors, 33% had one, 26% had two, and 20% had three or more risk factors. In men who had only one risk factor, high cholesterol was the most common single factor (55.8%), followed by current smoking (16.5%), hypertension (11.2%), obesity (8%), diabetes (7.4%), and high triglycerides (1.1%). For men with two risk factors, the most common combinations were high cholesterol and current smoking (32%) and high cholesterol and hypertension (26%). For men with three risk factors, the most common combination was high cholesterol, current smoking, and

Table 3. Age-Adjusted Mean Heart Disease Risk Factors by Erectile Dysfunction Category for Men in the Rancho Bernardo Study, 1972 to 1974

	Category of Erectile Dysfunction					Test for Trend
	None (n = 129)	Mild (n = 119)	Moderate (n = 70)	Severe/Complete (n = 72)	Not Sexually Active (n = 180)	
Age (yrs)	38.1 ± 0.6	43.4 ± 0.9	46.7 ± 1.2	46.5 ± 1.0	51.5 ± 0.7	<0.00001
Fasting plasma glucose (mmol/l)	6.0 ± 0.1	6.0 ± 0.1	5.8 ± 0.1	5.8 ± 0.1	6.0 ± 0.1	NS
Total cholesterol (mmol/l)	5.2 ± 0.1	5.4 ± 0.1	5.5 ± 0.1*	5.3 ± 0.1	5.3 ± 0.1	NS
Triglycerides (mmol/l)	1.2	1.2	1.3	1.4*	1.4*†	<0.01
SBP (mm Hg)	123.3 ± 1.3	122.7 ± 1.3	123.0 ± 1.6	123.2 ± 1.6	121.2 ± 1.1	NS
DBP (mm Hg)	77.8 ± 0.9	78.1 ± 0.9	78.5 ± 1.2	78.8 ± 1.1	77.1 ± 0.8	NS
Pulse pressure (SBP - DBP)	45.5 ± 1.0	44.6 ± 1.0	44.5 ± 1.2	44.4 ± 1.2	44.1 ± 0.8	NS
Body mass index (kg/m <sup>2</sup> )	25.3 ± 0.3	25.5 ± 0.2	25.7 ± 0.3	26.1 ± 0.3*	26.0 ± 0.2*	<0.05

\* $p < 0.05$  compared with "None" group. † $p < 0.05$  compared with "Mild" group. Data are presented as the mean value ± SE. DBP and SBP = diastolic and systolic blood pressure, respectively; NS = not significant.

high triglycerides (16%); a similar proportion (15%) had high cholesterol, hypertension, and obesity. In an age-adjusted analysis with no risk factors set as the referent OR of 1, there was a linear trend toward increasing risk of any ED by number of risk factors; the ORs of ED were 1.50, 1.72, and 2.20 for men with one, two, or three or more risk factors, respectively.

## DISCUSSION

To our knowledge, this is the only long-term, population-based, prospective study of mid-life CHD risk factors and subsequent ED. In this cohort of community-dwelling men, common CHD risk factors (age, BMI, current smoking, high BP, and high cholesterol and triglyceride levels) 25 years earlier predicted an increased risk and severity of ED and/or sexual inactivity. The 25-year 68% response rate among survivors was less than the 77% response rate after nine years of follow-up in Massachusetts Male Aging Study (MMAS) (17), the only other published prospective study of multiple CHD risk factors and ED. The risk factor associations observed in the Rancho Bernardo cohort are likely to have been underestimated because the men who did not survive the 25 years to the ED questionnaire had significantly less favorable levels of all CHD risk factors at baseline.

**Age.** Age is the best-established risk factor for the development and severity of ED, as reported first by Kinsey et al. (18) in 1948, with 25% of 65-year-old men and up to 75% of men age  $\geq 80$  years reporting ED. Modern cross-sectional prevalence and incidence studies have shown similar age-related trends (4,6,7,9). We previously reported that the prevalence of ED in the Rancho Bernardo cohort increased from 16% in men  $< 50$  years of age to more than 71% in men age  $\geq 70$  years (19). Although ED was not queried at baseline, two-thirds of the men reported here were  $< 50$  years of age at baseline, when moderate or severe ED would be unusual. (Furthermore, analyses restricted to men age  $< 50$  years at baseline showed similar results.) Consistent with their relatively young age at baseline, only 2.6% reported heart disease and 2.1% reported a history of diabetes, 40% of whom were sexually inactive 25 years later.

**Weight.** Obesity was a strong predictor of ED, with the age-adjusted BMI significantly higher in men with later reported severe/complete ED or who were sexually inactive. On multivariate analysis, obesity remained a significant independent predictor of increasingly severe ED. Although obesity is associated with generally accepted ED risk factors, such as diabetes, hyperlipidemia, and hypertension, surprisingly few community-based studies have reported weight as an independent risk factor for ED (6,7). Although the original cross-sectional MMAS (4) did not show a significant association between BMI and ED, the nine-year follow-up study (17) reported that a BMI  $\geq 28$  kg/m<sup>2</sup> predicted incident ED (OR 1.96,  $p = 0.01$ ), similar to our results. In a separate prospective MMAS report, baseline

obesity defined as BMI  $\geq 30$  kg/m<sup>2</sup> was associated with a higher risk of ED, despite any subsequent weight loss. In MMAS, a sedentary lifestyle, not studied in the Rancho Bernardo cohort at baseline, also predicted a higher risk of ED (20). On average, men in MMAS were more overweight (BMI of 27.5 kg/m<sup>2</sup>) than the men at Rancho Bernardo (BMI of 25.7 kg/m<sup>2</sup>) (4).

**Lipids.** In the present study, high fasting plasma cholesterol and triglyceride levels were significant risk factors for more severe ED. On multivariate analysis, categorically defined hypercholesterolemia was a strong independent predictor of any ED and of a stepwise graded association for increasingly severe ED. Hypercholesterolemia was the most common risk factor in men with only a single risk factor (present in 55%) and was present in most men who had more than one risk factor—85% of men with two risk factors and 87% of men with three risk factors.

Cholesterol was also an ED risk factor in a 22-month follow-up study of 3,250 men age 25 to 83 years seen in preventive medicine clinics; in this study, each mmol/l increase in baseline total cholesterol was associated with 1.32 times the risk of ED (21). In contrast, in the MMAS prospective study, total cholesterol did not predict future ED, and triglycerides were not measured (17). The significant predictive role of hypercholesterolemia with ED at Rancho Bernardo may reflect the participants' younger age at baseline, longer duration of follow-up, or the nearly complete absence of lipid-lowering medication use at baseline from 1972 to 1974.

**Smoking.** Cross-sectional studies have reported that smoking is an independent risk factor for ED (4,22,23). For example, a study that excluded diabetic patients and controlled for age, trauma history, and hypertension found smoking to be independently associated with atherosclerosis in the internal pudendal artery ( $p < 0.05$ ); the relative risk for each 10 pack-years smoked was 1.31 (23). In a meta-analysis of 19 studies, Tengs and Osgood (24) reported that 40% of impotent men were current smokers, compared with 28% of men in the general population. In the Rancho Bernardo Study, with 25% of men being current smokers at baseline, current smoking at baseline was marginally more significant in men with severe/complete ED in an age-adjusted model, but was not an independent predictor of ED in the multivariate models. Nearly all surviving Rancho Bernardo men had quit smoking some time before the follow-up questionnaire. A prospective study of heavy smokers noted improvement in penile tumescence and rigidity within one month of smoking cessation (25). Thus, the minimal association of ED and smoking likely reflects the selective survival of men who had successfully discontinued their habit and lived to complete the follow-up questionnaire.

**Blood pressure.** Hypertension clinics report a high prevalence of ED (26,27). Men in the Treatment of Mild Hypertension Study with SBP  $\geq 140$  mm Hg were twice as likely as men with SBP  $< 140$  mm Hg to report erectile

problems (28). The prospective MMAS (17) reported a borderline significant ( $p = 0.06$ ) association of ED with hypertension, applying the same definition used in the present study. In the Rancho Bernardo cohort, neither categorical hypertension nor BP measurements significantly predicted moderate or severe ED 25 years later. Most men were classified as hypertensive based on elevated SBP and/or DBP. Only 30 men were classified as hypertensive based on history alone (i.e., without confirmatory BP levels), 21 of whom were taking BP medication. Thus, the majority of those classified as hypertensive had no history of hypertension. Either white-coat hypertension or misclassification, reflecting the very high BP levels used to diagnose hypertension in the 1970s, could have obscured a true association. The 3.7% of Rancho Bernardo men who reported taking BP medication at baseline is low compared with 19% of the prospective MMAS cohort (17), which may have changed the associations. Common antihypertensive medications are associated with ED (29), but aggressive antihypertensive therapy can aid in the recovery of erectile function in animal models (30).

**Diabetes.** Erectile dysfunction is said to follow within 10 years of the diagnosis of diabetes mellitus in at least 50% of men and may be the presenting manifestation of diabetes in 10% to 15% (31). Surprisingly, diabetes as a risk factor for ED has not been evaluated prospectively in a population, and the lag time between the onset of diabetes and the increased risk of ED is unknown. There is some evidence that ED commonly precedes the diagnosis of diabetes (32). Previous studies of the relationship between ED and diabetes or glycemia are retrospective or cross-sectional (4-7). In the MMAS cross-sectional study, men with a history of treated diabetes had at least a threefold risk of ED (4), but neither diabetes nor hyperglycemia was reported in the prospective study of cardiovascular risk factors (17).

Neither diabetes nor FPG was significantly associated with incident ED in the Rancho Bernardo Study, although 12% had diabetes, most defined by fasting hyperglycemia ( $\geq 126$  mg/dl [7.0 mmol/l]) at baseline. Only 12 men (2.1%) gave a history of diabetes in the period from 1972 to 1974, nine of whom did not have fasting hyperglycemia. When these baseline data were obtained (1972 to 1974), screening for diabetes was uncommon; known diabetes was more common (7%) in the 1987 to 1989 MMAS (4). Post-challenge glucose levels, which are more sensitive than fasting glucose for the diagnosis of diabetes in older adults (33), were not measured in Rancho Bernardo at baseline. Men with higher levels of FPG were less likely to survive the 25-year follow-up to the ED questionnaire. Also, within the 25-year follow-up period, other study participants probably developed diabetes. Thus, a combination of a low prevalence of known diabetes at baseline, misclassification, and survivor bias may explain the absence of the expected association between diabetes and ED. Alternatively, because glycemic control may be inversely associated with the level

of ED (34), careful management of diabetes in the educated Rancho Bernardo cohort could have reduced the risk of ED.

**Study limitations.** The Rancho Bernardo cohort is a homogeneous group of older, educated, middle-class to upper middle-class Caucasian men. Therefore, the associations or lack of associations reported here may not apply to other socioeconomic or ethnic groups. The prevalence of ED in Rancho Bernardo was similar to that reported in the other large Caucasian cohort (4). The 25-year follow-up is an advantage in assessing mid-life exposure to common CHD risk factors but allows unknown interval risk factor changes to obscure associations and does not consider new medications, psychological states, or comorbidities. Men in the ED cohort had significantly more favorable levels of all CHD risk factors measured than decedents, thus introducing a conservative bias and reducing the ORs toward the null. Survival bias does not negate the relevance of the results, because it is the survivors who live long enough to develop ED.

Although Rancho Bernardo medical and medication histories were self-reported, only 30 men were classified as hypertensive based on history without confirmatory BP levels, only eight men were classified as diabetic based on history without confirmatory plasma glucose levels, and only 14 men were classified as hypercholesterolemic without confirmatory plasma cholesterol levels. Furthermore, at baseline, only 6% of the entire cohort was being treated with medication for one of these risk factors.

Although the IIEF-5 is a convenient, validated screening tool to define ED in populations (14,15,35), all five questions must be answered for ED classification. According to protocol, men without recent sexual activity for any reason cannot be classified. In the Rancho Bernardo Study, sexually inactive men had CHD risk profiles and increased comorbidities similar to those of men with severe/complete ED. This suggests that severe ED will be underestimated by excluding sexually inactive men (31% of respondents in this study), in that ED may be a prominent reason for sexual inactivity.

**Conclusions.** The CHD risk factors measured in mid-life, including age, current cigarette smoking, obesity, hypercholesterolemia, and hypertriglyceridemia, were associated with incident ED 25 years later. This long interval allows time for modification of CHD risk factors, which could decrease the risk of ED as well as CHD. To test this hypothesis, ED should be included as an outcome in future CHD prevention trials.

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