Prevalence and Clinical Determinants of Mitral, Tricuspid, and Aortic Regurgitation (The Framingham Heart Study)

Jagmeet P. Singh, MD, DPhil, Jane C. Evans, MPH, Daniel Levy, MD, Martin G. Larson, ScD, Lisa A. Freed, MD, Deborah L. Fuller, RDCS, Birgitta Lehman, RDCS, and Emelia J. Benjamin, MD, ScM

Little information is available on the prevalence and determinants of valvular regurgitation in the general population. This study sought to assess the prevalence and clinical determinants of mitral (MR), tricuspid (TR), and aortic (AR) regurgitation in a population-based cohort. Color Doppler echocardiography was performed in 1,696 men and 1,893 women (aged 54 ± 10 years) attending a routine examination at the Framingham Study. After excluding technically poor echocardiograms, MR, TR, and AR were qualitatively graded from trace to severe. Multiple logistic regression analysis was used to examine the association of clinical variables with MR and TR (more than or equal to mild severity) and AR (more than or equal to trace severity). MR and TR of more than or equal to mild severity was seen in 19.0% and 14.8% of men and 19.1% and 18.4% of women, respectively, and AR of more than or equal to trace severity in 13.0% of men and 8.5% of women. The clinical determinants of MR were age (odds ratio [OR] 1.3/9.9 years, 95% confidence interval [CI] 1.2 to 1.5), hypertension (OR 1.6; 95% CI 1.2 to 2.0), and body mass index (OR 0.8/4.3 kg/m^2; 95% CI 0.7 to 0.9). The determinants of TR were age (OR 1.5/9.9 years; 95% CI 1.3 to 1.7), body mass index (OR 0.7/4.3 kg/m^2; 95% CI 0.6 to 0.8), and female gender (OR 1.2; 95% CI 1.0 to 1.6). The determinants of AR were age (OR 2.3/9.9 years; 95% CI 2.0 to 2.7) and male gender (OR 1.6; 95% CI 1.2 to 2.1). A substantial proportion of healthy men and women had detectable valvular regurgitation by color Doppler echocardiography. These data provide population-based estimates for comparison with patients taking anorectic drugs. ©1999 by Excerpta Medica, Inc.

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In the wake of controversy surrounding anorectic drugs and valvular regurgitation[1,2] there has been a sudden surge of interest in the prevalence and predictors of valvular regurgitation. Little information, however, is available on the prevalence and determinants of regurgitant valvular lesions in the general population. Color Doppler echocardiography, a sensitive technique for detecting valvular regurgitation, provides a semiquantitative method for estimating the severity of regurgitation.[3] Previous color Doppler echocardiographic studies reporting prevalence of valvular regurgitation have been limited to small subsets of patients,[4–6] athletes,[7] children,[8] and to subjects with structurally normal hearts.[4,6,9] There are no published reports of the prevalence rates of mitral, tricuspid, or aortic regurgitation in a large unselected sample of middle-aged men and women. The purpose of this study was twofold: (1) to use color Doppler echocardiography to establish the prevalence and distribution of mitral (MR), tricuspid (TR), and aortic regurgitation (AR) in a population-based cohort; and (2) to study the clinical determinants of these regurgitant valvular lesions.

From the National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham; Massachusetts; National Heart, Lung and Blood Institute, Bethesda, Maryland; Divisions of Cardiology and Preventive Medicine, Boston University School of Medicine, Boston, Massachusetts; Divisions of Cardiology and Clinical Epidemiology, Beth Israel Hospital, and Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. This work was supported in part by NIH/NHLBI contract NO1-HC-38038 and NINDS Grant 2-RO1-NS-17950-11, Bethesda, Maryland. Manuscript received July 15, 1998; revised manuscript received and accepted November 18, 1998.

Address for reprints: Emelia J. Benjamin, MD, ScM, Framingham Heart Study, Boston University School of Medicine, 5 Thurber Street, Framingham, Massachusetts 01702. E-mail: emelia@fram.nhlbi.nih.gov.

METHODS

Study sample: The Framingham Heart Study is a prospective epidemiologic study established in 1948 to evaluate potential risk factors for coronary heart disease. The original study cohort included 5,209 men and women, aged 28 to 62 years. In 1971, 5,124 additional subjects were entered into the Framingham Offspring Study. Study design and selection criteria have been published.[10–12]

Subjects for the present investigation were Framingham Offspring Study subjects who had color Doppler echocardiographic examinations performed between 1991 and 1995 during their routine fifth examination cycle at the Framingham Heart Study clinic. Subjects were excluded if they met any of the following criteria: (1) technically poor echocardiogram (i.e., color Doppler of insufficient quality to assess accurately the severity of regurgitation); (2) mitral stenosis; (3) more than mild aortic stenosis, or (4) prosthetic or bioprosthetic heart valve.

The clinical variables included in this investigation were age, sex, hypertension, body mass index, smok-

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TABLE I Definitions of Grades of Regurgitation

Grades	MR	TR	AR
Absent	—	—	—
Trace	w/in 1 cm of valve	w/in 1 cm of valve	JH/LVOH < 10%
Mild	RJA/LAA<19%	RJA/RAA<19%	10%–24%
Moderate	20%–40%	20%–40%	25%–49%
Severe	>41%	>41%	>50%

Valvular regurgitation was assessed qualitatively using these semiquantitative categories as guidelines. JH = jet height; LAA = left atrial area; LVOH = left ventricular outflow height; RAA = right atrial area; RJA = regurgitant jet area; w/in = within.

TABLE IIa Prevalence of Valvular Regurgitation Stratified by Age and Severity in Men

	Age (yr)				
	26–39	40–49	50–59	60–69	70–83
Mitral regurgitation	(n = 91)	(n = 351)	(n = 432)	(n = 372)	(n = 90)
None (%)	14.4	13.3	11.3	12.7	9.0
Trace (%)	76.7	72.9	74.6	60.3	51.7
Mild (%)	8.9	13.5	12.5	24.6	28.1
≥Moderate (%)	0.0	0.3	1.6	2.4	11.2
Tricuspid regurgitation	(n = 77)	(n = 289)	(n = 320)	(n = 260)	(n = 66)
None (%)	14.3	17.8	19.0	18.3	16.7
Trace (%)	72.7	72.5	71.5	59.8	47.0
Mild (%)	13.0	9.4	9.2	21.9	25.8
≥Moderate (%)	0.0	0.3	0.3	0.0	1.5
Aortic regurgitation	(n = 91)	(n = 352)	(n = 433)	(n = 359)	(n = 91)
None (%)	96.7	95.4	91.1	74.3	75.6
Trace (%)	3.3	2.9	4.7	13.0	10.0
Mild (%)	0.0	1.4	3.7	12.1	12.2
≥Moderate (%)	0.0	0.3	0.5	0.6	2.2

TABLE IIb Prevalence of Valvular Regurgitation Stratified by Age and Severity in Women

	Age (yr)				
	26–39	40–49	50–59	60–69	70–83
Mitral regurgitation	(n = 93)	(n = 452)	(n = 515)	(n = 395)	(n = 90)
None (%)	14.0	8.6	9.0	7.2	5.6
Trace (%)	76.3	75.0	74.0	66.5	70.8
Mild (%)	9.7	15.5	16.0	24.0	23.6
≥Moderate (%)	0.0	0.9	1.0	2.3	0.0
Tricuspid regurgitation	(n = 84)	(n = 371)	(n = 414)	(n = 300)	(n = 71)
None (%)	20.5	16.0	14.5	10.4	14.1
Trace (%)	65.1	70.0	70.7	62.2	56.4
Mild (%)	13.2	13.5	14.1	25.7	23.9
≥Moderate (%)	1.2	0.5	0.7	1.7	5.6
Aortic regurgitation	(n = 93)	(n = 451)	(n = 515)	(n = 390)	(n = 90)
None (%)	98.9	96.6	92.4	86.9	73.0
Trace (%)	1.1	2.7	5.5	6.3	10.1
Mild (%)	0.0	0.7	1.9	6.0	14.6
≥Moderate (%)	0.0	0.0	0.2	0.8	2.3

Data are presented as percentage of subjects.

ing, total cholesterol level, diabetes mellitus, and history of myocardial infarction or congestive heart failure. The association between TR and percent predicted forced expiratory volume in 1 second was also examined. The diagnoses of myocardial infarction and congestive heart failure were confirmed by a committee of 3 physicians who evaluated records from the Framingham Heart Study clinic examinations, interim hospitalizations, and visits to personal physicians in accordance with published criteria.[13] Diabetes was defined as a fasting blood glucose level ≥140 mg/dl (>7.7 mmol/L) or the use of insulin or an oral hypoglycemic agent. Body height and weight measurements, medical history, physical examination, blood pressure measurements, and pulmonary function tests were performed routinely at the same examination.

Color Doppler echocardiography: Color Doppler examinations were performed with a commercially available system (Hewlett- Packard, Sonos 1000, Andover, Massachusetts) using a 2.5-MHz transducer. All images were recorded on videotape using a Panasonic VCR system (AG 7350, Matsushite Electrical Industrial Limited, Osaka, Japan). Conventional pulsed Doppler echocardiography was performed routinely in apical 4- and 5-chamber views by selective placement of the sample volume on the color Doppler echocardiographic regurgitation signals when present.

Color Doppler variations were represented by different groups of brightness and color intensity. Flow directed toward the transducer was conventionally coded in red and flow away from the transducer in blue. Valvular regurgitation was diagnosed using color-coded Doppler imaging proximal to the valve plane during its closure and extended into the chamber proximal to the valve. For color Doppler studies, gain settings were adjusted to eliminate background speckling and to maximize the extent of intracavitary velocity coding. MR was sought from the parasternal long-axis, apical 4- and 2-chamber, apical long-axis, and subcostal views. TR was sought from the parasternal right ventricular inflow, parasternal short-axis, apical 4-chamber, and subcostal views. AR was sought using the parasternal long-axis, parasternal short-axis, apical 5-chamber, and apical long-axis views.

MR was considered to be present if blue, green, or mosaic signals were seen originating from the mitral valve and spreading into the left atrium during systole. TR was considered to be present if blue, green, or mosaic signals were seen originating from the tricuspid valve and spreading into the right atrium during systole. AR was considered to be present if red, yellow, or mosaic signals (blue in the parasternal long

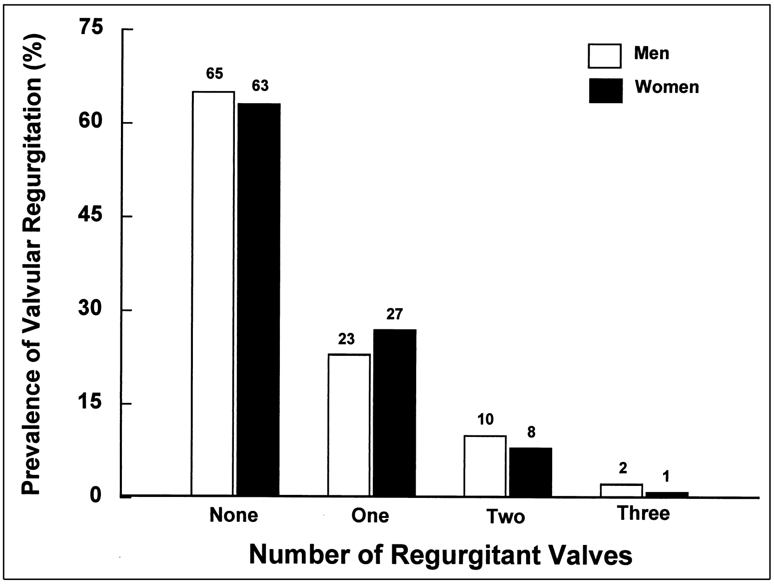

FIGURE 1. Histogram showing prevalence of valvular regurgitation by number of regurgitant valves. One indicates any single regurgitant valve; Two, any 2 regurgitant valves; Three, combined aortic, mitral, and tricuspid regurgitation. Regurgitation was defined as ≥mild severity for mitral and tricuspid regurgitation and ≥trace severity for aortic regurgitation.

axis) were seen originating from the aortic valve and spreading into the left ventricle during diastole. Valvular regurgitation was assessed qualitatively using semiquantitative guidelines and graded none, trace, mild, moderate, or severe (Table I).

Statistical analysis: All statistical analyses were valve specific. Prevalence rates of MR, TR, and AR were examined by grade of regurgitation in different age groups. Age- and sex-adjusted Spearman rank correlations were used to examine associations between clinical variables and each regurgitant lesion. The clinical variables included body mass index, hypertension, cholesterol, diabetes, smoking, history of myocardial infarction, or congestive heart failure.

Multivariable regression analyses[14] were performed to assess the strength and independence of the clinical variables with MR and TR (≥mild severity) and AR (≥trace severity). This analysis was performed after excluding subjects with a history of myocardial infarction or congestive heart failure, because these disease states are known to be associated with valve regurgitation. Results are expressed as odds ratios (OR) and 95% confidence intervals (CI). ORs are expressed for 1 SD of the continuous variables. Statistically significant values were defined as a 2-tailed $p < 0.05$. All analyses were done on a Sparcstation 2 (SUN Microsystems, Palo Alto, California) using the Statistical Analysis System (SAS, Cary, North Carolina).[15]

RESULTS

Subjects: Of 3,589 subjects (1,696 men and 1,893 women) who attended the baseline examination and underwent color Doppler echocardiographic examination, 21 were excluded for mitral stenosis or more than mild aortic stenosis and 9 for prosthetic heart valves. Subjects with technically poor color Doppler echocardiograms were also excluded (344 men and 334 women for MR, 354 men and 340 women for AR, and 668 men and 639 women for TR). A total of 2,881 subjects (1,336 men and 1,545 women) were eligible for assessing MR, 2,252 (1,012 men and 1,240 women) were eligible for assessing TR, and 2,865 (1,326 men and 1,539 women) were eligible for assessing AR. Subjects selected for analyses (age [mean ± SD], 54 ± 10 years) had a lower body mass index (mean ± SD: men, 27.6 ± 3.6 kg/m^2; women, 26.0 ± 4.7 kg/m^2) compared with subjects excluded from analysis for technically poor echocardiograms (men, 30.1 ± 4.7 kg/m^2; women, 29.8 ± 6.9 kg/m^2, $p < 0.0001$).

Prevalence of valvular regurgitation: MR was detectable in 87.7% of men and 91.5% of women, whereas TR was detectable in 82.0% of men and 85.7% of women. AR was less prevalent and was observed in 13.0% of men and 8.5% of women (Table II). The prevalence of MR of more than or equal to mild severity was 19.0% in men and 19.1% in women and of TR, 14.8% in men and 18.4% in women. The prevalence of regurgitation of more than or equal to mild severity was much lower for all 3 valves in both sexes (range 0.4% to 2.0%). When examined across different age groups, the prevalence of MR and TR of more than or equal to mild severity, and AR of more than or equal to trace severity, increased with advancing age in both sexes (Tables IIa and IIb).

A total of 944 men and 1,225 women had color Doppler echocardiograms technically adequate for all 3 valves. Regurgitation (MR or TR of more than or equal to mild severity or AR more than or equal to trace severity) involving a single valve was more common than regurgitation of ≥2 valves (Figure 1).

Determinants of valvular regurgitation: Age was related positively to the severity of MR, TR, and AR ($p < 0.0001$) (Table III). The prevalence of AR was greater in men, whereas tricuspid regurgitation was more common in women. In models that adjusted for age and sex, the severity of MR and TR correlated with lower body mass index and history of congestive heart failure and myocardial infarction (Tables IIIa and IIIb). Mitral regurgitation was also related to presence of systemic hypertension. Figure 2 shows the predicted prevalence of MR, TR, and AR in the population in relation to body mass index.

Multiple logistic regression analyses were performed after excluding subjects with a history of myocardial infarction or congestive heart failure (Table IV). The clinical determinants of MR (more than or equal to mild severity) were age, lower body mass

TABLE IIIa Clinical Characteristics and Severity of Mitral Regurgitation

Clinical Characteristics	Degree of Regurgitation: None	Trace	Mild	≥Moderate	r	p Value
Men/women (%)	55/45	45/55	45/55	60/40	0.03	0.09
Age (yrs)	54 ± 10	54 ± 10	57 ± 10	62 ± 9	0.13	0.0001
BMI (kg/m^2)	26.9 ± 0.2	26.8 ± 0.1	26.1 ± 0.2	26.3 ± 0.6	−0.06	0.0006
Systemic HTN (%)	29	30	35	43	0.05	0.004
Total Chol (mg/dl)	210 ± 2	204 ± 1	204 ± 2	200 ± 5	−0.04	0.052
Diabetes mellitus (%)	6	5	7	4	0.02	0.30
Smoking (pack-years)	17	16	15	22	−0.02	0.23
CHF or MI (%)	2	3	5	10	0.09	0.0001

BMI = body mass index; CHF = congestive heart failure; Chol = cholesterol; HTN = hypertension; MI = myocardial infarction.

TABLE IIIb Clinical Characteristics and Severity of Tricuspid Regurgitation

Clinical Characteristics	Degree of Regurgitation: None	Trace	Mild	≥Moderate	r	p Value
Men/women (%)	50/50	45/55	39/61	38/62	0.06	0.003
Age (yrs)	53.0 ± 9.9	53.1 ± 9.7	57.0 ± 10.5	62.2 ± 12.8	0.12	0.0001
BMI (kg/m^2)	27.2 ± 0.2	26.2 ± 0.1	25.3 ± 0.2	23.9 ± 0.8	−0.15	0.0001
Systemic HTN (%)	33	28	28	13	−0.03	0.11
Diabetes mellitus (%)	6	5	3	2	−0.03	0.20
Smoking (pack-years)	15 ± 1	16 ± 1	14 ± 1	19 ± 4	−0.01	0.60
CHF or MI (%)	2	3	4	4	0.04	0.04
Airflow obstruction (%)	12	9	10	9	−0.14	0.50

Abbreviations as in Table IIIa.

index, and systemic hypertension; the determinants of TR (more than or equal to mild severity) were age, lower body mass index, and female sex; and the determinants of AR (more than or equal to trace severity) were age and male sex.

DISCUSSION

The results of our study show that valvular regurgitation detectable by color Doppler echocardiography was highly prevalent in the general population. MR and TR were most common, followed by AR. Obesity was associated with a lower prevalence of TR and MR. These data provide population-based estimates for comparison with patients taking anorectic drugs.

Prevalence of valvular regurgitation: Previous studies using conventional pulsed Doppler methodology have varied widely in their estimates of the prevalence of valvular regurgitation. In normal subjects, prevalence rates of TR have been 24% to 96%, MR 10% to 80%, and AR 0% to 33%.[16–20] Color Doppler flow imaging, which superimposes color-coded flow patterns on the real-time 2-dimensional image, is a more comprehensive and sensitive, yet less tedious, method than conventional pulsed-wave Doppler echocardiography.[4,21] Consequently, color Doppler echocardiography has become the procedure of choice to detect and measure valvular regurgitation. The reported prevalence has varied widely, from 15% to 100% for TR, 38% to 58% for MR, and 0% to 18% for AR.[4–6,9] The discrepancies in prevalence rates can be explained by the fact that the earlier studies have been limited to small numbers of subjects[4–6] and have varied in their definitions of regurgitation.[4–6,9] Also, in contrast to previous reports, our study is not limited by selection bias (by virtue of echocardiography laboratory referral patterns)[4–6,9] or by interpretation of echocardiograms unblinded to the clinical status of patients.[4–9]

Prevalence rates in the Framingham Heart Study sample differed markedly according to threshold definitions (i.e., trace vs mild severity). The high prevalence of trace regurgitation suggests that this may be an artifact of valve closure[17] or may be a feature related to closure of anatomically normal valves.[16]

Clinical determinants: Age was observed to exert a profound influence on the prevalence of valve regurgitation in the population. Our findings that the prevalence of MR, TR, and AR increased with age are consistent with earlier Doppler studies.[6,9,16] Long-standing mechanical stress may play a role in the wear and tear of the valve, resulting in valvular regurgitation.[22] Although left-sided valves (aortic and mitral) are exposed to high pressures and are likely to undergo degenerative changes earlier than right-sided valves, the prevalence rates of MR and TR were comparable at all ages.

Systemic hypertension was associated with MR but not with AR. Increased afterload may play an important role in the genesis of minor degrees of MR. Earlier reports have suggested that hypertension predisposes to aortic root enlargement and, consequently, to AR.[23] Our observation of a lack of association between hypertension and AR is supported by a recent study demonstrating the lack of an association between blood pressure and dilation of the aortic root at the site of commissural attachment and AR.[24] The present investigation and previous studies[24,25] have

TABLE IIIc Clinical Characteristics and Severity of Aortic Regurgitation						
	Degree of Regurgitation					
Clinical Characteristics	None	Trace	Mild	≥Moderate	r	p Value
Men/women (%)	45/55	54/46	60/40	54/46	−0.07	0.0001
Age (yrs) (mean ± SD)	53 ± 10	60 ± 10	63 ± 8	63 ± 10	0.24	0.0001
BMI (kg/m²)	26.7 ± 0.8	26.5 ± 0.3	26.5 ± 0.4	25.6 ± 1.2	−0.009	0.62
Systemic HTN (%)	30	34	32	12	0.029	0.12
Total cholesterol (mg/dl)	205 ± 1	201 ± 3	207 ± 3	195 ± 10	−0.01	0.54
Diabetes mellitus (%)	5	6	10	0	0.03	0.18
Smoking (pack-years)	16 ± 1	15 ± 2	16 ± 2	11 ± 6	−0.24	0.19
CHF or MI (%)	3	4	6	0	0.006	0.76

Data expressed as mean ± SEM.
r = Spearman rank correlations.
Abbreviations as in Table IIIa.

TABLE IV Results of Multivariable Regression Analyses				
Clinical Determinants		MR	TR	AR
	Unit	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age (yr)	9.9	1.3 (1.2, 1.5)	1.5 (1.3, 1.7)	2.3 (2.0, 2.7)
Sex	M/F	1.1 (0.9, 1.3)	1.2 (1.0, 1.6)	0.6 (0.5, 0.8)
BMI (kg/m²)	4.3	0.8 (0.7, 0.9)	0.7 (0.6, 0.8)	1.0 (0.8, 1.1)
HTN	Y/N	1.6 (1.2, 2.0)	1.1 (0.8, 1.4)	1.2 (0.9, 1.5)

Data expressed as odds ratio (95% confidence intervals). Odds ratios for continuous variables expressed for 1 SD of age and BMI.
Abbreviations as in Table IIIa.

shown a strong association between AR and age, which in turn may explain the lack of association between hypertension and AR after adjusting for age in the multivariable model.

Obesity and regurgitation: The severity and prevalence of MR and TR decreased as a function of increasing body mass index. This may be because ultrasonic penetration becomes poorer in obese persons, and ultrasound may be too attenuated to permit adequate detection of Doppler signals from distally located areas. To minimize this bias, we purposefully excluded subjects with technically poor Doppler echocardiograms. The inverse relation between body mass index and MR and TR persisted despite exclusion of technically limited studies. Because obesity is associated with changes in cardiac structure, hemodynamics, and altered ventricular inflow patterns,[26,27] it may be speculated that mechanisms other than technical factors are involved in the inverse association between body mass index and valvular regurgitation. Further studies are needed to examine this association.

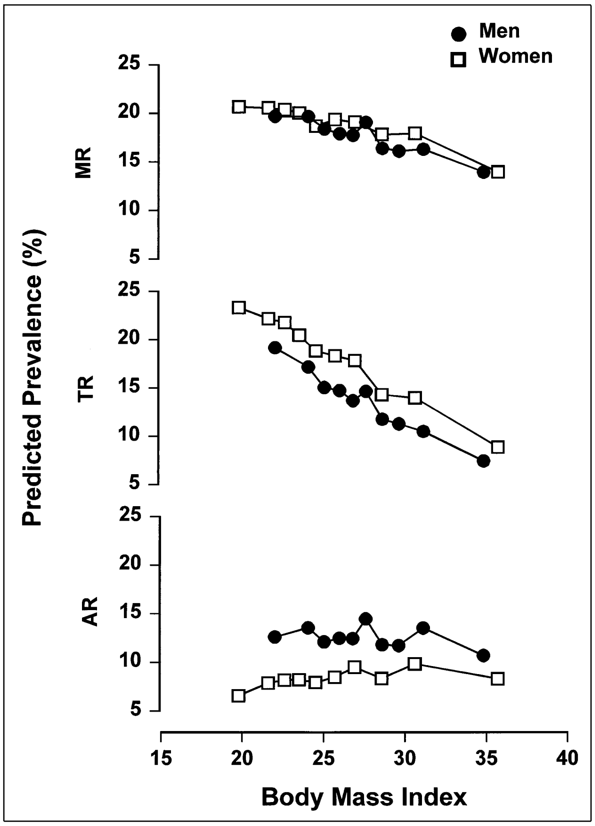

FIGURE 2. Graphic representation of the mean predicted prevalence of mitral, tricuspid, and aortic regurgitation for the population subdivided into deciles, on the basis of their body mass index (kg/m²).

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