

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Prevalence of Angina in Women Versus Men. A Systematic Review and Meta-Analysis of International Variations Across 31 Countries

Harry Hemingway, Claudia Langenberg, Jacqueline Damant, Chris Frost, Kalevi Pyörälä and Elizabeth Barrett-Connor

Circulation published online Mar 17, 2008;

DOI: 10.1161/CIRCULATIONAHA.107.720953

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2008 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org>

Subscriptions: Information about subscribing to *Circulation* is online at
<http://circ.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Prevalence of Angina in Women Versus Men A Systematic Review and Meta-Analysis of International Variations Across 31 Countries

Harry Hemingway, FRCP; Claudia Langenberg, MD; Jacqueline Damant, MPhil; Chris Frost, PhD;
Kalevi Pyörälä, MD; Elizabeth Barrett-Connor, MD

Background—In the absence of previous international comparisons, we sought to systematically evaluate, across time and participant age, the sex ratio in angina prevalence in countries that differ widely in the rate of mortality due to myocardial infarction.

Methods and Results—We searched MEDLINE and EMBASE until February 2006 for healthy population studies published in any language that reported the prevalence of angina (Rose questionnaire) in women and men. We obtained myocardial infarction mortality rates from the World Health Organization. A total of 74 reports of 13 331 angina cases in women and 11 511 cases in men from 31 countries were included. Angina prevalence varied widely across populations, from 0.73% to 14.4% (population weighted mean 6.7%) in women and from 0.76% to 15.1% (population weighted mean 5.7%) in men, and was strongly correlated within populations between the sexes ($r=0.80$, $P<0.0001$). Angina prevalence showed a small female excess with a pooled random-effects sex ratio of 1.20 (95% CI 1.14 to 1.28, $P<0.0001$). This female excess was found across countries with widely differing myocardial infarction mortality rates in women (interquartile range 12.7 to 126.5 per 100 000), was particularly high in the American studies (1.40, 95% CI 1.28 to 1.52), and was higher among nonwhite ethnic groups than among whites. This sex ratio did not differ significantly by participant's age, the year the survey began, or the sex ratio for mortality due to myocardial infarction.

Conclusions—Over time and at different ages, independent of diagnostic and treatment practices, women have a similar or slightly higher prevalence of angina than men across countries with widely differing myocardial infarction mortality rates. (*Circulation*. 2008;117:1526-1536.)

Key Words: angina ■ meta-analysis ■ population ■ women

The causes of angina pectoris are poorly understood. Despite stable angina being a common initial presentation of coronary disease¹ and exerting a major impact on quality of life,² ability to work, and costs to society,³ there have been few large-scale epidemiological investigations and no meta-analyses of risk factors for angina. The pathological hallmarks of myocardial infarction (MI)—plaque rupture and thrombosis—are not shared with angina,⁴⁻⁷ which suggests that the population causes might differ. The incidence of acute MI shows a universal excess among males across countries with widely differing absolute rates of MI mortality,^{8,9} and this has been taken as evidence of an inherent biological cause. By contrast, male sex was not associated with physician-defined angina occurrence in either a small (146 cases in women) healthy population study (Framingham)¹⁰ or a large (67 832 cases in women) study of primary

care patients.¹¹ Although these physician-defined angina cases were related to subsequent MI mortality in women, the lack of male excess could be biased if women with atypical symptoms were included,^{12,13} if women sought healthcare more often than men,¹² or if physicians selected nitrates as a diagnostic test more often for women than for men.

Editorial p 1505 Clinical Perspective p 1536

Thus, it is not known whether male sex is a risk factor for angina in unselected populations, independent of diagnostic and treatment practices.¹⁴ Addressing this question is fundamental both to etiological understanding of the complex phenotypes aggregated in the term "coronary heart disease" and to the development of appropriate clinical services, which have been beset by inequitable underuse of investigation and

Continuing medical education (CME) credit is available for this article. Go to <http://cme.ahajournals.org> to take the quiz.

Received June 18, 2007; accepted December 31, 2007.

From the Department of Epidemiology and Public Health (H.H., J.D.), University College London Medical School, London, United Kingdom; Medical Research Council Epidemiology Unit (C.L.), Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK; Medical Statistics Unit (C.F.), London School of Hygiene and Tropical Medicine, London, United Kingdom; Department of Medicine (K.P.), University of Kuopio, Kuopio, Finland; and Department of Family and Preventive Medicine (E.B.-C.), School of Medicine, University of California, San Diego.

Reprint requests to Harry Hemingway, FRCP, Professor of Clinical Epidemiology, Department of Epidemiology and Public Health, University College London Medical School, 1-19 Torrington Place, London WC1E 6BT, United Kingdom. E-mail h.hemingway@ucl.ac.uk

© 2008 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.107.720953

treatment among women.¹⁵ The 7-item Rose angina questionnaire¹⁶ is largely free of biases due to the diagnostic practices of physicians and is the only standardized instrument for assessing typical angina that has been used in different countries. In women, Rose-determined angina is associated with coronary risk factors,¹⁷ resting ECG abnormalities,¹⁷ carotid intima-media thickness,¹⁸ and coronary artery calcification.¹⁹ Women with angina ascertained by use of the Rose questionnaire have greater cardiovascular²⁰ and coronary^{21–24} mortality than women without angina, with relative risks similar to those of men.^{20–24} Clinical studies suggest that angina in women is more commonly microvascular in origin than is the case in men,²⁵ and in the general population, microvascular disease is associated with increased risk of MI and coronary death in women but not men.²⁶

We hypothesized that if male sex is a cause of angina, this would be reflected in its population prevalence across countries that differ widely in MI mortality rates, risk factors, cultural factors, and healthcare systems, and it would be robust across both participant age and study year. In the absence of any previous studies on this hypothesis, we performed a meta-analysis according to the standards proposed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Investigators.²⁷

Methods

Study Eligibility

The review included reports of angina prevalence that used the Rose angina questionnaire in population-based surveys of women and men. We included cross-sectional and prospective cohort study designs and articles in any language; there were no exclusion criteria.

Search of Data Sources

We searched MEDLINE and EMBASE for articles published up to February 27, 2006, using a search strategy developed with an experienced librarian. The strategy used search terms (including MeSH [Medical Subject Headings]) most sensitive for identifying epidemiological studies of prevalence: “angina pectoris/epidemiology [MAJR:NoExp] OR angina [tw] AND prevalence [tw].” We individually searched on each of the 70 unique countries included in previous international comparisons of MI in women and men.^{8,28,29} We hand-searched the bibliography of each eligible study. We obtained unpublished tabular data for countries with particularly high (Russia, Poland, and Czech Republic) or particularly low (Japan) MI mortality rates and obtained data from India and Sri Lanka from investigators when their surveys had measured but not yet reported angina prevalence.

Selecting Studies and Data Abstraction

A total of 2068 titles, and abstracts if available, and 136 full-text papers (25 of which were written in languages other than English) were reviewed against the eligibility criteria, and 53 unique articles were included. We excluded 83 full-text papers because they did not report angina prevalence (n=26 papers), did not use the Rose questionnaire (n=26), did not report separate estimates for women and men (n=15), and other reasons. From each article, we abstracted the following information: definition of angina (classified as “definite” if cases met all 7 Rose criteria³⁰ [Table 1] or “other” if fewer than 7 items were used to define a case, or if it was not stated explicitly), prevalence of angina in women and men, language of administration (English versus non-English), survey response rate, country, year the study began, and age range. Where mean age was not stated, the population weighted mean or midpoint of the range was derived (in the 14 studies for which both were available, the

Table 1. Angina Questionnaire Items*

1. Have you ever had any pain or discomfort in your chest? (yes)
2. Do you get it when you walk uphill or hurry?
3. Do you get it when you walk at an ordinary pace on the level?
If the answer to question 2 or question 3 is “yes,” then proceed to question 4:
4. What do you do if you get it while walking? (stop or slow down)
5. If you stand still what happens? (relieved)
6. How soon? (10 minutes or less)
7. Location? (central chest or left arm)

Responses required to define a case.
Taken from Rose et al.³⁰

mean difference was 1.9 years). The mean age of women and men was similar in all studies, differing by a mean of 0.11 years. With the exception of the British-Norwegian Migrant Study,²⁰ all articles reported estimates within 1 country. Of the 52 articles investigating a single country, 10 gave more than 1 report according to ethnicity or geographic region. Because of this and the use of unpublished data, there were a total of 74 populations (separate reports) from 53 unique articles that contributed data for 31 countries for the present analyses. Interreader correlation for angina prevalence was high (reliability coefficient of 0.973 for women and 0.978 for men).

Country-Level Mortality Data

We obtained country- and sex-specific mortality rates for acute MI from the World Health Organization (WHO) mortality database (http://www3.who.int/whosis/mort/table1.cfm?path=whosis,mort,mort_table1&language=english). Acute MI was defined by the International Classification of Diseases (ICD), 9th revision (ICD-9; code 410) or, when available, the 10th revision (ICD-10; codes I21 and I22). For the Russian Federation and Switzerland, only the aggregated term “ischemic heart diseases” (ICD-10 I20 to I25) was available. Masked to angina prevalence, 2 reviewers independently selected MI mortality rates that were closest in time to the start year of each survey and that corresponded to the mean age of survey participants. The interreader agreement between 2 independent reviewers for acute MI mortality was high, with a reliability coefficient of 0.978 for women and 0.976 for men. To assess whether the level of economic development influenced the sex ratio in angina, we classified each country according to the 6 WHO geographic regions and according to 5 mortality strata based on mortality in children younger than 5 years and in males between the ages of 15 and 59 years³¹: A, very low child and adult mortality; B, low child and adult mortality; C, low child and high adult mortality; D, high child and adult mortality; and E, very high child and adult mortality.

Statistical Analyses

Prevalence ratios comparing women with men were calculated and logarithmically transformed for each study. As is standard practice for ratios, all analyses were performed on these logarithmically transformed values, with back-transformation for reported results. Standard errors for each (log) prevalence ratio were calculated. Pooled (log) prevalence ratios with 95% CIs were calculated with the STATA (version 9.2) meta-analysis program (Stata Corp, College Station, Tex; <http://www.stata.com>), and a forest plot was obtained. Heterogeneity of effects across studies was assessed by the Cochran Q statistic. Because this was significant, and to allow for clustering of data from the same country, a random-effects model was used. Stratified meta-regression analyses were performed according to participants' mean age, start year of the survey, absolute levels of MI mortality in women (categorized by quartiles), the sex ratio in MI mortality (quartiles), birth cohorts, WHO region and subregion, angina definition, language, and response rate of the study. The statistical significance of differences between estimates in these

Table 2. Angina Prevalence Studies Included in the Meta-Analysis (74 Reports, 31 Countries)

WHO Region	Country/Study Author	Year of Study	Mean Age, y	Women			Men		
				Angina, No. of Cases/Total No. Surveyed	Prevalence*	AMI Mortality (WHO)†	Angina, No. of Cases/Total No. Surveyed	Prevalence*	AMI Mortality (WHO)‡
Subregion AFRO, mortality stratum D									
	Ghana/Watkins ³³	1981	50	44/442	9.9	NA	11/366	3.0	NA
Subregion AFRO, mortality stratum E									
	South-Africa/Rossouw ³⁴	1979	40.6	182/3831	4.8	NA	113/3357	3.4	NA
Subregion AMRO, mortality stratum A									
	Canada/Reeder ³⁵	1990	39.9	45/1093	4.1	2.3	33/1074	3.1	15.7
	USA/Ford (white) ³⁶	1971	57.0	98/2141	4.6	126.5	87/1929	4.5	409.2
	USA/Ford (black) ³⁶	1971	57.0	18/328	5.5	126.5	6/292	1.9	409.2
	USA/Wilcosky ³⁷	1972	54.5	95/2191	4.3	36.1	78/2431	3.2	157.3
	USA/Ford (white) ³⁶	1976	57.0	272/3357	8.1	126.5	187/3010	6.2	409.2
	USA/Ford (black) ³⁶	1976	57.0	35/428	8.1	126.5	22/346	6.5	409.2
	USA/LaCroix (white) ³⁸	1976	52.0	289/4345	6.7	36.1	190/3978	4.8	157.3
	USA/LaCroix (black) ³⁸	1976	50.3	45/619	7.3	36.1	31/516	6.0	157.3
	USA/LaCroix (Hispanic) ³⁸	1976	44.2	83/1533	5.4	7.5	33/1242	2.7	35.4
	USA/LaCroix ²²	1981	73.8	272/5292	5.2	346.6	115/3067	3.8	799.0
	USA/Langford (white) ³⁹	1981	49.5	102/1180	8.6	36.1	97/1896	5.1	157.3
	USA/Langford (black) ³⁹	1981	49.5	133/1344	9.9	36.1	82/1065	7.7	157.3
	USA/Sorlie (white) ¹⁸	1987	54.5	422/6041	7.3	24.7	275/5418	5.0	90.3
	USA/Sorlie (black) ¹⁸	1987	54.5	169/2625	6.4	24.7	67/1623	4.1	90.3
	USA/Ford (white) ⁴⁰	1988	57.0	159/2695	5.9	87.4	156/2889	5.4	231.2
	USA/Ford (black) ⁴⁰	1988	57.0	112/1273	8.8	87.4	48/1297	3.7	231.2
	USA/Ford (Hispanic) ⁴⁰	1988	57.0	74/1057	7.0	87.4	52/1156	4.5	231.2
	USA/Mittelmark ⁴¹	1989	72.3	37/2946	1.3	242.4	17/2250	0.8	497.1
	USA/Smith (white) ⁴²	1990	59.1	22/460	4.8	79.9	18/316	5.7	216.4
	USA/Smith (black) ⁴²	1990	56.0	51/7372	7.0	79.9	21/416	5.0	216.4
Subregion AMRO, mortality stratum B									
	Jamaica/Miall ⁴³	1962	49.5	51/541	9.4	NA	40/526	7.6	NA
Subregion EMRO, mortality stratum B									
	Iran/Sarraf-Zadegan ⁴⁴	1996	50.6	145/3362	4.3	NA	82/2411	3.4	NA
Subregion EURO, mortality stratum A									
	Belgium/DeBacquer ⁴⁵	1978	46.1	758/12 637	6.0	20.8	1737/34 731	5.0	111.7
	Czech Republic/Bobak§	2002	57.9	346/4649	7.4	52.1	283/4068	7.0	196.8
	Denmark/Hagerup ⁴⁶	1964	50	8/366	2.2	9.0	19/436	4.3	47.8
	Denmark/Hagerup ⁴⁶	1976	40	4/548	0.7	1.9	7/5049	1.4	10.6
	Denmark/Jensen ⁴⁷	1976	52.3	464/7699	6.0	9.0	404/6491	6.2	47.8
	Denmark/Agner ⁴⁸	1967	70	11/210	5.0	222.7	23/230	10.0	522.1
	Finland/Reunanen ⁴⁹	1966	44.1	281/5224	5.4	3.1	239/5738	4.2	26.3

(Continued)

Table 2. Continued

WHO Region	Country/Study Author	Year of Study	Mean Age, y	Women			Men		
				Angina, No. of Cases/Total No. Surveyed	Prevalence*	AMI Mortality (WHO)†	Angina, No. of Cases/Total No. Surveyed	Prevalence*	AMI Mortality (WHO)‡
	Finland/Ahto ⁵⁰	1990	76	35/708	4.9	1564.4	44/488	9.0	2479.5
	Finland/Lahelma ⁵¹	2000	50	299/4991	6.0	10.3	50/1252	4.0	64.6
	Germany/Todzy ⁵²	1975	41.1	116/1207	9.6	21.6	62/898	6.9	131.9
	Germany/Helmert ⁵³	1984	53.4	907/12 125	7.5	16.5	867/12 093	7.2	100.9
	Ireland/Shelley ⁵⁴	1985	47.8	19/396	5.1	36.9	8/415	1.9	167.9
	Israel/Librach ⁵⁵	1967	80.7	9/116	7.8	1429.6	1/44	2.3	1872.6
	Italy/Krogh ⁵⁶	1978	41.6	134/3433	3.9	3.8	71/3140	2.3	26.4
	Italy/Cacciatore ⁵⁷	1991	74.2	103/772	13.4	116.6	54/567	9.6	337.8
	Netherlands/Grobbee ⁵⁸	1990	70.6	337/4878	6.9	239.8	211/3105	6.8	642.9
	Norway/Feinleib ²⁰	1962	52.1	1322/14 066	9.4	19.4	1040/12 089	8.6	123.3
	Spain/Masia ⁵⁹	1995	50.3	35/909	3.9	7.1	25/839	3.0	49.0
	Spain/Cosin ⁶⁰	1995	61.5	382/4961	7.7	26.9	386/5287	7.3	130.8
	Sweden/Lernfelt ⁶¹	1971	70	52/524	10	306.8	58/499	13.0	910.1
	Sweden/Cederholm ⁶²	1981	50.5	17/443	3.9	12.7	21/376	5.7	77.9
	Sweden/Glader ⁶³	1986	49.8	36/610	5.9	12.7	22/627	3.4	77.9
	Sweden/Glader ⁶³	1994	49.5	17/607	2.8	10.4	18/580	3.1	49.4
	Switzerland/Gutzwiller ⁶⁴	1977	40.9	137/4148	3.3	1.7	83/3607	2.3	14.8
	UK/Feinleib ²⁰	1962	52.1	1028/9607	10.7	42.1	946/8089	11.7	221.8
	England/Nicholson ¹⁷	1985	45	134/3350	4.0	27.2	164/6830	2.4	151.5
	England/Dewhurst ⁶⁵	1988	73.9	13/116	11.2	410.4	15/143	10.5	918.5
	England/Harland (Chinese) ⁶⁶	1991	44.5	8/197	4.1	16.9	6/183	3.2	93.0
	England/Harland (Europid) ⁶⁶	1993	44.5	21/315	6.7	14.1	26/310	3.2	75.3
	England/Patel ⁶⁷	1994	47.0	8/184	4.3	12.7	6/192	3.1	65.6
	England/Fischbacher (South-Asian) ⁶⁸	1995	50.1	14/359	3.9	13.1	13/325	4.0	63.1
	Scotland/Kitchin ⁶⁹	1970	76	32/272	11.6	1764.4	22/215	10.3	2965.0
	Scotland/Hart ²⁴	1972	54.4	799/8350	9.6	72.4	671/7057	9.5	300.8
	Scotland/Smith ²³	1984	49.5	445/5236	8.5	55.6	323/5123	6.3	224.0
	Scotland/Smith ⁷⁰	1988	64.5	89/796	11.2	670.7	118/796	14.8	1344.5
Subregion EURO, mortality stratum B									
	Georgia/Balabadze ⁷¹	1985	44.5	154/1636	9.4	15.6	111/1371	8.1	96.3
	Poland/Bobak§	2002	52.3	728/5427	13.4	52.3	497/5140	9.7	223.8
	Turkey/Onat ⁷²	1990	40.7	41/1822	2.3	NA	49/1867	2.6	NA
Subregion EURO, mortality stratum C									
	Lithuania/Bluzhas ⁷³	1983	49.5	90/2801	3.2	7.0	62/2694	2.3	49.5
	Russian Federation/Bobak§	2002	57.1	359/4735	7.6	361.8	231/3551	6.5	1236.9
Subregion SEARO, mortality stratum B									
	Sri Lanka/Mohideen§	2003	47.5	188/3792	4.95	NA	137/3044	4.5	NA

(Continued)

Table 2. Continued

WHO Region	Country/Study Author	Year of Study	Mean Age, y	Women			Men		
				Angina, No. of Cases/Total No. Surveyed	Prevalence*	AMI Mortality (WHO)†	Angina, No. of Cases/Total No. Surveyed	Prevalence*	AMI Mortality (WHO)‡
Subregion SEARO, mortality stratum D									
	India/Gopinath ¹⁰²	1985	40.1	137/7325	1.9	60.5¶	156/6235	2.5	62.5¶
	India/Singh (urban) ⁷⁴	1994	39.9	10/902	1.1	60.5¶	33/904	3.7	62.5¶
	India/Singh (rural) ⁷⁴	1994	39.9	10/875	1.1	28.0#	12/894	1.3	31.0#
	India/Nazareth ⁷⁵	2003	52.2	27/930	2.9	60.5¶	6/626	1.0	62.5¶
Subregion WPRO, mortality stratum A									
	Japan/Sekine§	2005	41.9	13/8284	4.6	1.1	30/598	5.0	6.1
Subregion WPRO-Mortality Stratum B									
	Hong Kong/Woo ^{76‡}	1990	79.4	9/101	8.9	484.8	7/96	7.3	628.6
	Hong Kong/Lam ^{77‡}	1995	45.5	44/1385	3.2	3.4	33/1348	2.5	17.1
	Taiwan/Chen ^{78‡}	1992	76.0	45/2094	2.2	NA	14/1732	0.8	NA
	Taiwan/Lin ^{79‡}	2001	79.0	79/547	14.4	NA	229/1513	15.1	NA

AMI indicates acute MI; AFRO, African region; AMRO, Americas region; EMRO, Eastern Mediterranean region; EURO, European region; UK, United Kingdom; SEARO, Southeast Asian region; and WPRO, Western Pacific region.

*Per 100 in population.

†Per 100 000 in population.

‡Hong Kong and Taiwan are not WHO member states; therefore, geographic region and mortality stratum are based on classification for China.

§Personal communication: 5 reports from 3 investigators.

¶Mortality rate for ICD-10 codes I20–I25.

¶Represents midpoint of coronary heart disease mortality range for urban areas.⁸⁰

#Represents midpoint of coronary heart disease mortality range for rural areas.⁸⁰

subgroup analyses was assessed with random-effects meta-regression models. Global tests of heterogeneity were used to investigate differences when the source of variability under investigation was unordered, and trend tests were used for ordered sources. We calculated τ -squared, a moment-based estimate of the residual between-studies variance, as part of the random-effects meta-regression analysis.³²

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Individual Study Estimates

We included a total of 74 population samples of 13 331 angina cases in 199 494 women and 11 511 cases in 201 821 men from 31 countries, 5 countries being English speaking (Table 2) (I. Nazareth, G. D'Costa, G. Levy, D. Naik, R. Vaidya, M. King, unpublished data, 2007).^{17,18,20,22,23,24,33–74,76–80} Mortality estimates for acute MI were available for 66 of the 74 studies. Angina prevalence varied widely, from 0.73% to 14.4% (population weighted mean 6.7%) in women and from 0.76% to 15.1% (population weighted mean 5.7%) in men. There was a strong and significant correlation between female and male angina prevalence across studies (correlation coefficient 0.80, 95% CI 0.70 to 0.87, $P<0.0001$; Figure 1). Figure 1 illustrates that most studies lie above the line of equality between the sexes, which denotes a female excess. There were significant ecological correlations between study-level angina prevalence and country-level MI mortality rates in

women ($r=0.27$, 95% CI 0.03 to 0.48, $P=0.03$) and men ($r=0.42$, 95% CI 0.20 to 0.60, $P=0.0005$).

Pooled Results From Meta-Analysis

The pooled sex ratio of angina prevalence from the random-effects model was 1.20 (95% CI 1.14 to 1.28, $P<0.0001$), with significant heterogeneity between studies ($P<0.0001$; Figure 2); the between-studies variance of the log (prevalence ratio) was 0.0347, which corresponds to a geometric SD of 1.20 [$1.20=\exp(\text{square root of } 0.0347)$] acting in a multiplicative fashion. In other words, the average weighted prevalence ratio was 1.20, with a geometric SD of 1.21 (exponentiated value of the SD of the log-transformed values). The British sample in the Norwegian Migrant Study, performed in 1962, was the largest study that differed from the pooled estimate; 2 of the 3 estimates from India showed a male excess. The sex ratio in angina was similar in the subset of studies with complete information on MI mortality rates ($n=66$, sex ratio 1.20, 95% CI 1.12 to 1.27).

Meta-Regression of Influence of Country, Study, and Participant Characteristics on the Sex Ratio of Angina

Stratified analyses showed that the angina sex ratio did not differ significantly according to participant's age ($P=0.12$), start year of the survey ($P=0.89$), the sex ratio in MI ($P=0.09$), or birth cohort ($P=0.15$; Table 3). A female excess was found across countries with MI mortality rates in women

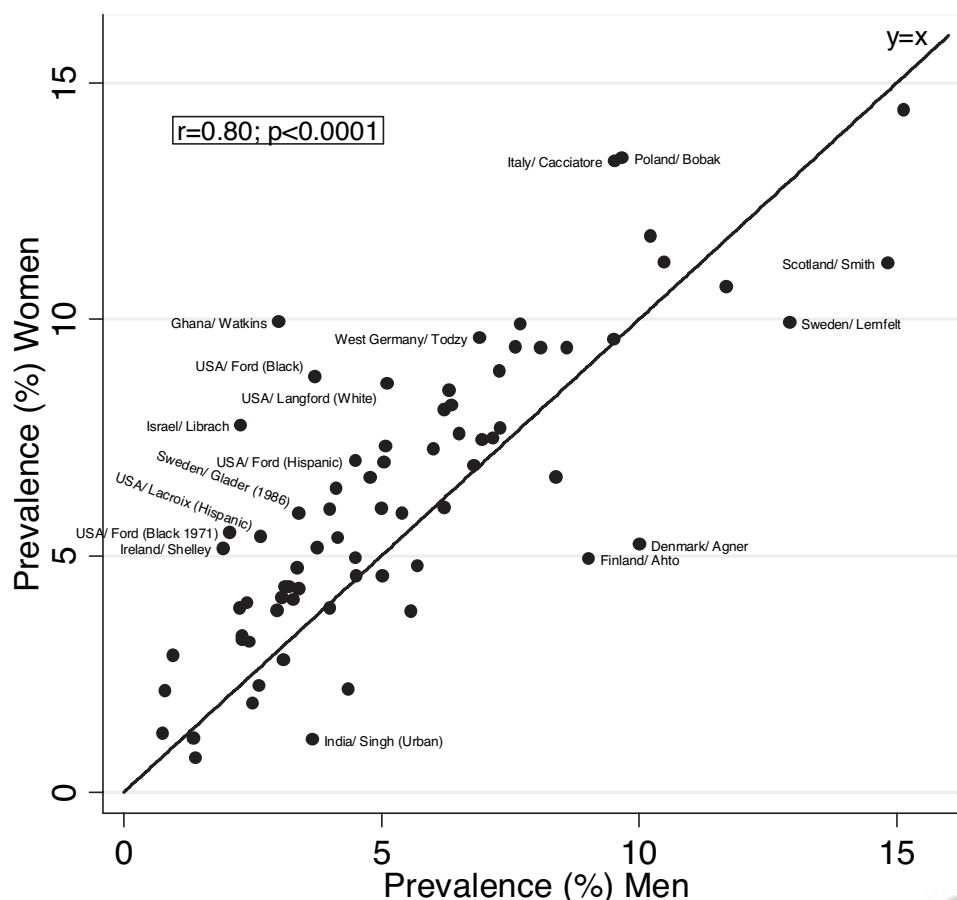


Figure 1. Angina prevalence in women vs men. Labels are given for populations in which the prevalence differs by at least 2.5% between women and men.

that ranged from 1 to 1764.4 per 100 000, with some evidence that the excess declined as MI mortality increased. This female excess was particularly high among American studies (1.40, 95% CI 1.28 to 1.52) and was higher among nonwhite ethnic groups than among whites. Estimates differed according to WHO region ($P=0.0004$), with Southeast Asia (4 studies from India, 1 from Sri Lanka) being the only region that did not show an overall female excess (sex ratio 0.88, 95% CI 0.56 to 1.38). The female excess effect did not differ according to definition of angina ($P=0.83$), questionnaire language ($P=0.10$), administration method ($P=0.43$), or response rate to survey ($P=0.09$). In meta-regression analyses of the subset of studies with complete information on all covariates ($n=66$), adjustment for all factors mentioned above reduced the residual variance between studies by 8%, which indicates that these factors explained only a small proportion of the heterogeneity between studies.

Discussion

Objective Addressed

In the present meta-analysis, which was based on almost 25 000 angina cases in women and men from 31 countries, we found that women had a slightly higher prevalence of stable angina pectoris than men, with a pooled sex ratio of 1.20. The present study adds to current understanding by demonstrating for the first time that the female excess is

remarkably consistent across countries with widely differing MI mortality rates, spanning 4 decades of study period and 4 decades of participant age. Such generalizability suggests an inherent biological basis rather than artifactual explanations. The sex ratio of angina contrasts with the male excess of MI, is unexplained, and warrants further study. There have been no previous international comparisons focusing on angina in women and men, and as far as we are aware, this is the first systematic review of any etiological risk factor for stable angina, as distinct from aggregate end points of nonfatal MI and coronary death. The male focus of randomized trials and clinical guidelines in angina is at odds with the global public health burden and should be addressed.

Lack of Male Excess

Clinicians have been faced with a paradox, with the male preponderance of patients who reach coronary angiography contrasting with individually small reports from epidemiological studies that suggest that male sex may not be a risk factor for angina in the general population. The contribution of the present meta-analysis is to provide large-scale evidence that this lack of male excess in angina prevalence is highly robust across countries that differ markedly in rates of MI mortality (interquartile range 12.7 to 126.5 per 100 000 in women) and in angina prevalence. This contrasts with the

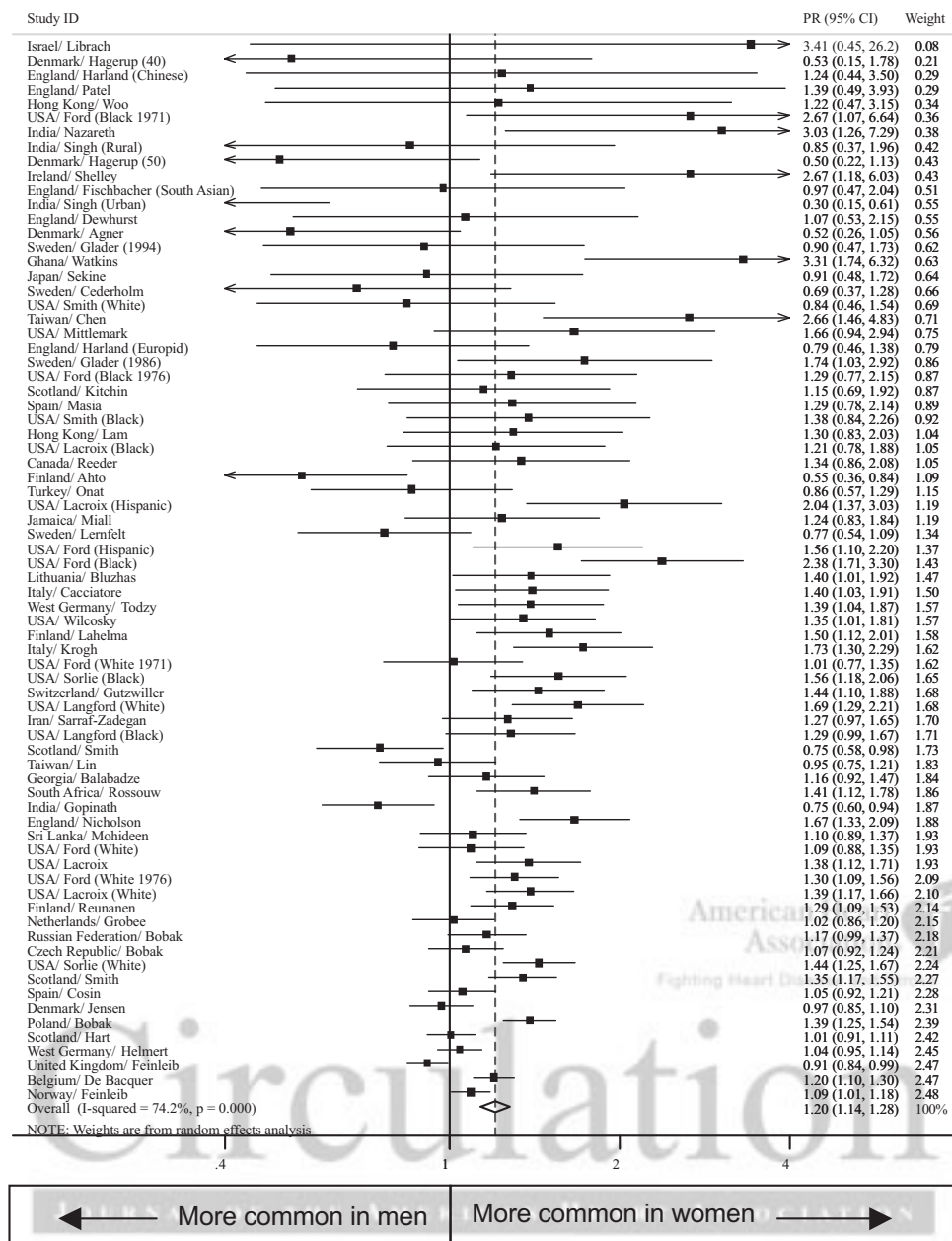


Figure 2. Sex ratios in Rose angina prevalence ([PR] 95% CIs) ordered by study weight and pooled estimate from a random-effects model. Numbers in parentheses denote patients' ages or year of study.

male excess in MI that is present and of similar magnitude among countries with low, medium, and high rates of coronary death. The countries included in the present review span widely differing social conditions and smoking, diet, physical activity, and other health-related behaviors that influence MI mortality.⁸¹ Furthermore, we found a lack of male excess in angina at all ages, including women before and after menopause. This suggests that the changes in hormone, lipid, hemostatic, hemodynamic, and inflammatory factors⁹ at the time of the menopause are not important modifiers of the angina sex ratio. So why, then, do women have lower rates of MI than men but not of angina? Neither the observational studies on women's reproductive history nor the trials of exogenous estrogens⁸² have addressed the development of stable angina, with all such studies focusing

on MI. Further research is required to establish whether risk factors that are unique to women (eg, cyclic hormones with menses, pregnancy-associated remodeling of the coronary arteries, pregnancy-induced hypertension, and gestational diabetes), that are more common in women (eg, clustering of risk factors, lower levels of physical exercise, and higher mean heart rates), or that have stronger effects in women (eg, diabetes mellitus^{11,83}), as well as their underlying genetic basis,⁸⁴ differentially predict angina compared with MI.

Vasculopathy in Women With Angina

Angina in women is associated with myocardial ischemia through mechanisms that both overlap with and differ from those in men.²⁵ The prevalence of atherosclerosis in the large epicardial coronary arteries in unbiased samples of women has

Table 3. Sex Ratio in Angina Prevalence in Specified Subgroups (Random Effects Models)

Subgroup	No. of Populations	Crude Prevalence Women/Men	Pooled Sex Ratio (95% CI)
Mean age of participants, y			
<45	15	3.8/3.2	1.11 (0.92–1.34)
45–54	33	7.1/5.9	1.27 (1.17–1.38)
55–64	13	8.2/6.7	1.26 (1.12–1.41)
65–74	9	6.2/6.9	1.02 (0.85–1.23)
≥75	4	7.1/8.8	0.95 (0.53–1.71)
P_{trend}			0.12
Start year of study			
Before 1970	7	9.0/8.5	1.04 (0.88–1.22)
1970–1979	17	6.3/5.2	1.25 (1.12–1.38)
1980–1989	21	6.0/4.8	1.34 (1.18–1.52)
1990–1999	20	5.2/4.8	1.06 (0.92–1.23)
2000 or later	8	8.0/7.4	1.19 (1.04–1.37)
P_{trend}			0.89
MI mortality rate*			
Q1 (1.1–12.7/100 000)	17	4.7/3.8	1.27 (1.09–1.47)
Q2 (13.1–36.1/100 000)	18	7.3/5.7	1.25 (1.16–1.36)
Q3 (36.9–116.6/100 000)	15	8.2/7.4	1.19 (1.02–1.38)
Q4 (126.5–1764.4/100 000)	16	6.2/5.8	1.05 (0.91–1.22)
P_{trend}			0.03
Sex ratio MI*			
Q1 (0.11–0.18)	17	6.5/5.4	1.28 (1.16–1.42)
Q2 (0.19–0.23)	17	7.1/5.9	1.19 (1.06–1.34)
Q3 (0.23–0.37)	16	8.4/7.1	1.20 (1.09–1.33)
Q4 (0.38–0.97)	16	4.1/3.9	1.06 (0.83–1.36)
P_{trend}			0.09
Birth cohort			
Before 1920	20	8.2/8.1	1.07 (0.97–1.18)
1920–1929	8	6.4/6.0	1.13 (0.97–1.33)
1930–1939	24	6.3/5.0	1.41 (1.28–1.56)
1940–1949	15	6.0/4.8	1.14 (1.00–1.30)
1950 or later	7	4.6/3.6	1.08 (0.76–1.54)
P_{trend}			0.004
WHO region			
1–Africa	2	5.3/3.3	2.05 (0.89–4.70)
2–Americas	21	6.2/4.5	1.40 (1.28–1.52)
3–Southeast Asia	5	2.7/2.9	0.88 (0.56–1.38)
4–Europe	40	7.5/6.3	1.13 (1.05–1.21)
5–Eastern Mediterranean	1	4.3/3.4	1.27 (0.97–1.65)
6–Western Pacific	5	4.3/5.9	1.26 (0.87–1.83)
$P_{\text{interaction}}$			0.0004
Ethnicity			
White	8	6.8/5.3	1.26 (1.10–1.44)
Nonwhite	10	7.2/4.5	1.58 (1.35–1.86)
$P_{\text{interaction}}$			0.03

Q1 through Q4 indicate quartiles 1 through 4.

*N=66 reports.

been difficult to study. In a large primary care study (7906 coronary deaths), women with angina were at markedly increased risk of subsequent coronary mortality, even among women not known to have abnormal angiography findings.¹¹

Intracoronary ultrasound studies of young heart transplant recipients shows a similar prevalence (52%) of intimal thickening in women and men.⁸⁵ Studies in heart transplant⁸⁶ and transsexual⁸⁷ patients show that large arteries are inherently smaller in women, independent of body size, and such smaller coronary arteries may be associated with ischemia at a lower plaque burden.⁸⁸ Many women with unobstructed coronary arteries have magnetic resonance spectroscopy changes consistent with ischemia,⁸⁹ and these are associated with an increased risk of subsequent coronary events.⁹⁰ Microvascular disease of the coronary arteries is more common in women than men and is associated with anginal symptoms and ischemia.⁹¹ Although some studies have suggested that retinal markers of microvascular disease might be stronger predictors of coronary events in women than men,^{26,92,93} this has not been found in other studies.^{94,95} Moreover, in the Multi-Ethnic Study of Atherosclerosis (MESA), retinal microvascular abnormalities showed similar associations in women and men in concentric left ventricular remodeling,⁹⁶ aortic distensibility,⁹⁷ and coronary artery calcification.⁹⁸

Study Strengths and Limitations

A key strength of the present study is the use of a standard questionnaire to detect typical symptoms of angina pectoris, which is largely free of the potential underrecognition and selection biases that might affect angina diagnosed by physicians.^{11,12} However, several limitations require consideration. The first limitation is reporting bias. Importantly, the sex ratio we observed (1.2, small female excess) is identical to that observed when angina is defined clinically by the initiation of antianginal therapy in an entire country (Finland; sex ratio 1.2).¹¹ This strongly suggests that the sex ratio is not an artifact of reporting on the Rose questionnaire. Second, the Rose angina questionnaire was originally developed and validated in men⁹⁹ in western Europe and the United States; however, we found that angina prevalence in women was associated with country-level MI mortality rate, consistent with the impact of angina on mortality in individual women in cohort studies.^{20–24} Misdiagnosis of MI in women might explain why these associations were stronger in men. The lack of male excess in angina was found in each of the 31 countries studied, with their attending differences in public and professional awareness of heart disease in women and healthcare provision. Such a stable finding supports an inherent, valid underlying association. Third, the only available data for meta-analysis concerned prevalent rather than incident (new) cases. Although women with incident angina might have a better survival than men, the small size of this difference cannot account for the lack of male excess in angina occurrence. Furthermore, the present results are in accordance with studies of new cases of angina without a previous history of MI.^{10,11} Lastly, although we may have missed data sets, we estimate that 35 larger studies (with the 75th centile in study weight) each reporting the most extreme observed male excess (sex ratio 0.30) would be required to change the pooled estimate to 0.77 (the least extreme male excess in MI mortality). It is unlikely that such a volume of such extreme data would not have been reported or would have been reported but not found.

Clinical Implications

The present finding of the global phenomenon of a female excess in angina, independent of diagnostic and treatment practices, has clinical implications for understanding quality of care in women. First, inequities in management of women may be underestimated, because studies begin with populations that are selected by clinical contact rather than because of the presence of typical anginal symptoms in the general population. With each step in the presentation, investigation, and referral cascade, the ratio of women to men declines. Second, clinical guidelines should consider the population perspective. Recent guidelines specific to women recommend investigation among those with typical symptoms,¹⁰⁰ but these and other guidelines are silent on the issue of whether women with typical symptoms present to a physician and, if so, whether their physician will label their symptoms as typical. Women with typical symptoms on Rose questionnaire who are not diagnosed with angina by a doctor have an increased mortality compared with women with no symptoms.^{12,101}

Conclusions

Women have a similar or slightly higher prevalence of angina across countries that differ widely in MI mortality. Understanding the dichotomy of why men, who have a universal excess of fatal MI, do not have an excess of angina presents an important challenge for further research.

Acknowledgments

We would like to thank Dr M. Bobak, Professor R. Mohideen, and Professor M. Sekine for kindly permitting us to use angina estimates from their unpublished data.

Sources of Funding

Dr Hemingway is supported by a public health career scientist award from the Department of Health. Dr Langenberg is supported by a Health of the Public PhD Fellowship from the Medical Research Council.

Disclosures

None.

References

1. Sekhri N, Feder GS, Junghans C, Hemingway H, Timmis AD. How effective are rapid access chest pain clinics? Prognosis of incident angina and non-cardiac chest pain in 8762 consecutive patients. *Heart*. 2007;93:458–463.
2. Spertus JA, Jones P, McDonnell M, Fan V, Fihn SD. Health status predicts long-term outcome in outpatients with coronary disease. *Circulation*. 2002;106:43–9.
3. Javitz HS, Ward MM, Watson JB, Jaana M. Cost of illness of chronic angina. *Am J Manag Care*. 2004;10(suppl):S358–S369.
4. Ahmed WH, Bittl JA, Braunwald E. Relation between clinical presentation and angiographic findings in unstable angina pectoris, and comparison with that in stable angina. *Am J Cardiol*. 1993;72:544–550.
5. Bogaty P, Brecker SJ, White SE, Stevenson RN, el Tamimi H, Balcon R, Maseri A. Comparison of coronary angiographic findings in acute and chronic first presentation of ischemic heart disease. *Circulation*. 1993;87:1938–1946.
6. Hong MK, Mintz GS, Lee CW, Kim YH, Lee SW, Song JM, Han KH, Kang DH, Song JK, Kim JJ, Park SW, Park SJ. Comparison of coronary plaque rupture between stable angina and acute myocardial infarction: a three-vessel intravascular ultrasound study in 235 patients. *Circulation*. 2004;110:928–933.
7. Tunstall-Pedoe H. Angina pectoris: epidemiology and risk factors. *Eur Heart J*. 1985;6(F):1–5.

8. Kalin MF, Zumoff B. Sex hormones and coronary disease: a review of the clinical studies. *Steroids*. 1990;55:330–352.
9. Barrett-Connor E. Sex differences in coronary heart disease: why are women so superior? The 1995 Ancel Keys Lecture. *Circulation*. 1997;95:252–264.
10. Murabito JM, Evans JC, Larson MG, Levy D. Prognosis after the onset of coronary heart disease: an investigation of differences in outcome between the sexes according to initial coronary disease presentation. *Circulation*. 1993;88:2548–2555.
11. Hemingway H, McCallum A, Shipley M, Manderbacka K, Martikainen P, Keskimäki I. Incidence and prognostic implications of stable angina pectoris among women and men. *JAMA*. 2006;295:1404–1411.
12. Hemingway H, Shipley M, Britton A, Page M, MacFarlane P, Marmot M. Prognosis of angina with and without a diagnosis: 11 year follow up in the Whitehall II prospective cohort study. *BMJ*. 2003;327:895.
13. Philpott S, Boynton PM, Feder G, Hemingway H. Gender differences in descriptions of angina symptoms and health problems immediately prior to angiography: the ACRE study: Appropriateness of Coronary Revascularisation study. *Soc Sci Med*. 2001;52:1565–1575.
14. Rose G, Ahmetelli M, Checacci L. Ischaemic heart disease in middle-aged men: prevalence comparisons in Europe. *Bull WHO*. 1968;38:885–895.
15. Pinn VW. Sex and gender factors in medical studies: implications for health and clinical practice. *JAMA*. 2003;289:397–400.
16. Rose G. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull WHO*. 1962;27:645–658.
17. Nicholson A, White IR, MacFarlane P, Brunner E, Marmot M. Rose questionnaire angina in younger men and women: gender differences in the relationship to cardiovascular risk factors and other reported symptoms. *J Clin Epidemiol*. 1999;52:337–346.
18. Sorlie PD, Cooper L, Schreiner PJ, Rosamond W, Szklo M. Repeatability and validity of the Rose questionnaire for angina pectoris in the Atherosclerosis Risk in Communities Study. *J Clin Epidemiol*. 1996;49:719–725.
19. Oei HH, Vliegenthart R, Deckers JW, Hofman A, Oudkerk M, Witteman JC. The association of Rose questionnaire angina pectoris and coronary calcification in a general population: the Rotterdam Coronary Calcification Study. *Ann Epidemiol*. 2004;14:431–436.
20. Feinleib M, Lambert PM, Zeiner-Henriksen T, Rogot E, Hunt BM, Ingster-Moore L. The British-Norwegian Migrant Study: analysis of parameters of mortality differentials associated with angina. *Biometrics*. 1982;38(suppl):55–74.
21. Lapidus L, Bengtsson C, Lindquist O, Sigurdsson JA, Rafnsson V. Prognosis for women with different symptoms and signs suggesting ischaemic heart disease: a 12-year follow-up: the population study of women in Gothenburg, Sweden. *J Chronic Dis*. 1985;38:741–748.
22. LaCroix AZ, Guralnik JM, Curb JD, Wallace RB, Ostfeld AM, Hennekens CH. Chest pain and coronary heart disease mortality among older men and women in three communities. *Circulation*. 1990;81:437–446.
23. Smith WC, Kenicer MB, Tunstall-Pedoe H, Clark EC, Crombie IK. Prevalence of coronary heart disease in Scotland: Scottish Heart Health Study. *Br Heart J*. 1990;64:295–298.
24. Hart CL, Watt GC, Davey SG, Gillis CR, Hawthorne VM. Pre-existing ischaemic heart disease and ischaemic heart disease mortality in women compared with men. *Int J Epidemiol*. 1997;26:508–515.
25. Pepine CJ, Kerensky RA, Lambert CR, Smith KM, von Mering GO, Sopko G, Bairey Merz CN. Some thoughts on the vasculopathy of women with ischemic heart disease. *J Am Coll Cardiol*. 2006;47(suppl):S30–S35.
26. Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, Tielsch JM, Klein BE, Hubbard LD. Retinal arteriolar narrowing and risk of coronary heart disease in men and women: the Atherosclerosis Risk in Communities Study. *JAMA*. 2002;287:1153–1159.
27. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting: Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008–2012.
28. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations: Monitoring Trends and Determinants in Cardiovascular Disease. *Lancet*. 1999;353:1547–1557.
29. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries

- (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952.
30. Rose GA, Blackburn H, Gillum RF, Prineas RJ, eds. *Cardiovascular Survey Methods*. 2nd ed. Geneva, Switzerland: World Health Organization; 1982.
 31. World Health Organisation. WHO mortality database. 2006. Geneva, Switzerland. Available at: <http://www.who.int/whosis/mort/en/>.
 32. Thompson GS, Pyke SDM, Hardy RJ. The design and analysis of paired cluster randomized trials: an application of meta-analysis techniques. *Stat Med*. 1997;16:2063–2079.
 33. Wakins LO. Coronary heart disease and coronary disease risk factors in black populations in underdeveloped countries: the case for primordial prevention. *Am Heart J*. 1984;108:850–862.
 34. Rossouw JE, Weich HF, Steyn K, Kotze JP, Kotze TJ. The prevalence of ischaemic heart disease in three rural South African communities. *J Chronic Dis*. 1984;37:97–106.
 35. Reeder BA, Liu L, Horlick L. Sociodemographic variation in the prevalence of cardiovascular disease. *Can J Cardiol*. 1996;12:271–277.
 36. Ford ES, Giles WH. Changes in prevalence of nonfatal coronary heart disease in the United States from 1971–1994. *Ethn Dis*. 2003;13:85–93.
 37. Wilcosky T, Harris R, Weissfeld L. The prevalence and correlates of Rose Questionnaire angina among women and men in the Lipid Research Clinics Program Prevalence Study population. *Am J Epidemiol*. 1987;125:400–409.
 38. LaCroix AZ, Haynes SG, Savage DD, Havlik RJ. Rose Questionnaire angina among United States black, white, and Mexican-American women and men: prevalence and correlates from the Second National and Hispanic Health and Nutrition Examination Surveys. *Am J Epidemiol*. 1989;129:669–686.
 39. Langford HG, Oberman A, Borhani NO, Entwisle G, Tung B. Black-white comparison of indices of coronary heart disease and myocardial infarction in the stepped-care cohort of the Hypertension Detection and Follow-Up Program. *Am Heart J*. 1984;108(pt 2):797–801.
 40. Ford ES, Giles WH, Croft JB. Prevalence of nonfatal coronary heart disease among American adults. *Am Heart J*. 2000;139:371–377.
 41. Mittelmark MB, Psaty BM, Rautaharju PM, Fried LP, Borhani NO, Tracy RP, Gardin JM, O’Leary DH. Prevalence of cardiovascular diseases among older adults: the Cardiovascular Health Study. *Am J Epidemiol*. 1993;137:311–317.
 42. Smith KW, McGraw SA, Crawford SL, McKinlay JB. Do blacks and whites differ in reporting Rose Questionnaire angina? Results of the Boston Health Care Project. *Ethn Dis*. 1993;3:278–289.
 43. Miall WE, Del Campo E, Fodor J, Nava R Jr, Ruiz L, Standard KL, Swan AV. Longitudinal study of heart disease in a Jamaican rural population, I: prevalence, with special reference to ECG findings. *Bull World Health Organ*. 1972;46:429–441.
 44. Sarraf-Zadegan N, Sayed-Tabatabaei FA, Bashardoost N, Maleki A, Totonchi M, Habibi HR, Sotodehmaran E, Tafazoli F, Karimi A. The prevalence of coronary artery disease in an urban population in Isfahan, Iran. *Acta Cardiol*. 1999;54:257–263.
 45. De Bacquer D, De Backer G, Kornitzer M. Prevalences of ECG findings in large population based samples of men and women. *Heart*. 2000;84:625–633.
 46. Hagerup L, Eriksen M, Schroll M, Hollnagel H, Agner E, Larsen S. The Glostrup population studies: collection of epidemiologic tables: reference values for use in cardiovascular population studies. *Scand J Soc Med Suppl*. 1981;20:1–112.
 47. Epidemiology of chest pain and angina pectoris, with special reference to treatment needs. *Acta Med Scand Suppl*. 1984;682:1–120.
 48. Agner E. Natural history of angina pectoris, possible previous myocardial infarction and intermittent claudication during the eighth decade: a longitudinal epidemiologic study. *Acta Med Scand*. 1981;210:271–276.
 49. Reunanen A, Aromaa A, Pyorala K, Punsar S, Maatela J, Knekt P. The Social Insurance Institution’s coronary heart disease study: baseline data and 5-year mortality experience. *Acta Med Scand Suppl*. 1983;673:1–120.
 50. Ahto M, Isoaho R, Puolijoki H, Laippala P, Romo M, Kivela SL. Prevalence of coronary heart disease, associated manifestations and electrocardiographic findings in elderly Finns. *Age Ageing*. 1998;27:729–737.
 51. Lahelma E, Martikainen P, Rahkonen O, Roos E, Saastamoinen P. Occupational class inequalities across key domains of health: results from the Helsinki Health Study. *Eur J Public Health*. 2005;15:504–510.
 52. Todzy I, Tannenberg B. Results of a questionnaire study on coronary disease and its relation to electrocardiographic changes and respiratory symptoms in a North German population [in German]. *Soz Präventivmed*. 1981;26:237–247.
 53. Helmert U, Shea S, Bammann K. The impact of occupation on self-reported cardiovascular morbidity in western Germany: gender differences. *Rev Environ Health*. 1997;12:25–42.
 54. Shelley E, Daly L, Kilcoyne D, Graham I, Mulcahy R. Risk factors for coronary heart disease: a population survey in County Kilkenny, Ireland, in 1985. *Ir J Med Sci*. 1991;160(suppl 9):22–28.
 55. Librach G. Prevalence of ischemic heart disease among elderly Yemenites and Europeans, residents of homes for the aged in Israel. *J Am Geriatr Soc*. 1967;15:1125–1136.
 56. Krogh V, Trevisan M, Panico S, Farinoro E, Mancini M, Menotti A, Ricci G. Prevalence and correlates of angina pectoris in the Italian nine communities study: Research Group ATS-RF2 of the Italian National Research Council. *Epidemiology*. 1991;2:26–32.
 57. Cacciatore F, Gallo C, Ferrara N, Abete P, Paolisso G, Canonico S, Signoriello G, Terracciano C, Napoli C, Varricchio M, Rengo F. Morbidity patterns in aged population in southern Italy: a survey sampling. *Arch Gerontol Geriatr*. 1998;26:201–213.
 58. Grobbee DE, van der Bom JG, Bots ML, de Bruijne MC, Mosterd A, Hoes AW. Coronary heart disease in the elderly: the ERGO study (Erasmus Rotterdam Health and the Elderly) [in Dutch]. *Ned Tijdschr Geneesk*. 1995;139:1978–1982.
 59. Masia R, Pena A, Marrugat J, Sala J, Vila J, Pavesi M, Covas M, Aubo C, Elosua R; REGICOR Investigators. High prevalence of cardiovascular risk factors in Gerona, Spain, a province with low myocardial infarction incidence. *J Epidemiol Commun Health*. 1998;52:707–715.
 60. Cosin J, Asin E, Marrugat J, Elosua R, Aros F, de los Reyes M, Castro-Beiras A, Cabades A, Diago JL, Lopez-Bescos L, Vila J; PANES Study Group. Prevalence of angina pectoris in Spain. *Eur J Epidemiol*. 1999;15:323–330.
 61. Lernfelt B, Landahl S, Svanborg A. Coronary heart disease at 70, 75 and 79 years of age: a longitudinal study with special reference to sex differences and mortality. *Age Ageing*. 1990;19:297–303.
 62. Cederholm J. Findings in a health survey of middle-aged subjects in Uppsala 1981–82: risk factors for diabetes mellitus and cardiovascular disease. *Ups J Med Sci*. 1985;90:201–227.
 63. Glader EL, Stegmayr B. Declining prevalence of angina pectoris in middle-aged men and women: a population-based study within the Northern Sweden MONICA Project: Multinational Monitoring of Trends and Cardiovascular Disease. *J Intern Med*. 1999;246:285–291.
 64. National Research Program 1A: incidence and nature of thoracic pain in 4 Swiss towns [in German]. *Soz Präventivmed*. 1980;25:275–279.
 65. Dewhurst G, Wood DA, Walker F, Lampe FC, Jeffreys M, Cooper M, Williams JD. A population survey of cardiovascular disease in elderly people: design, methods and prevalence results. *Age Ageing*. 1991;20:353–360.
 66. Harland JO, Unwin N, Bhopal RS, White M, Watson B, Laker M, Alberti KG. Low levels of cardiovascular risk factors and coronary heart disease in a UK Chinese population. *J Epidemiol Community Health*. 1997;51:636–642.
 67. Patel DJ, Winterbotham M, Sutherland SE, Britt RG, Keil JE, Sutton GC. Comparison of methods to assess coronary heart disease prevalence in South Asians. *Nat Med J India*. 1997;10:210–213.
 68. Fischbacher CM, Bhopal R, Unwin N, White M, Alberti KG. The performance of the Rose angina questionnaire in South Asian and European origin populations: a comparative study in Newcastle, UK. *Int J Epidemiol*. 2001;30:1009–1016.
 69. Kitchin AH, Lowther CP, Milne JS. Prevalence of clinical and electrocardiographic evidence of ischaemic heart disease in the older population. *Br Heart J*. 1973;35:946–953.
 70. Smith FB, Fowkes FG, Rumley A, Lee AJ, Lowe GD, Hau CM. Tissue plasminogen activator and leucocyte elastase as predictors of cardiovascular events in subjects with angina pectoris: Edinburgh Artery Study. *Eur Heart J*. 2000;21:1607–1613.
 71. Balabadze MB, Chumburidze IT, Bakradze ND, Tataradze RA. Possibility of using WHO questionnaires, distributed by mail, for detecting stenocardia during mass screening [in Russian]. *Kardiologiya*. 1989;29:42–44.
 72. Onat A, Senocak MS, Surdum-Avci G, Ornek E. Prevalence of coronary heart disease in Turkish adults. *Int J Cardiol*. 1993;39:23–31.
 73. Bluzhas I, Reklaitene R, Tamoshiunas A, Domarkene S, Shidlauskene D. Prevalence of ischemic heart disease and mortality among Kaunas

- population aged 35–64 years in the prospective study [in Russian]. *Kardiologiia*. 2002;42:72–75.
74. Singh RB, Sharma JP, Rastogi V, Raghuvanshi RS, Moshiri M, Verma SP, Janus ED. Prevalence of coronary artery disease and coronary risk factors in rural and urban populations of north India. *Eur Heart J*. 1997;18:1728–1735.
 75. Deleted in proof.
 76. Woo J, Ho SC, Lau J, Yuen YK, Chan SG, Masarei J. Cardiovascular symptoms, electrocardiographic abnormalities, and associated risk factors in an elderly Chinese population. *Int J Cardiol*. 1993;42:249–255.
 77. Lam TH, Liu LJ, Janus ED, Lau CP, Hedley AJ. Fibrinogen, angina and coronary heart disease in a Chinese population. *Atherosclerosis*. 2000;149:443–449.
 78. Chen CH, Chuang JH, Kuo HS, Chang MS, Wang SP, Chou P. Prevalence of coronary heart disease in Kin-Chen, Kinmen. *Int J Cardiol*. 1996;55:87–95.
 79. Lin YC, Chu FY, Fu CC, Chen JD. Prevalence and risk factors for angina in elderly Taiwanese. *J Gerontol A Biol Sci Med Sci*. 2004;59:161–165.
 80. Ahmad N, Bhopal R. Is coronary heart disease rising in India? A systematic review based on ECG defined coronary heart disease. *Heart*. 2005;91:719–725.
 81. World Health Organisation. *World Health Report 2003: Shaping the Future*. Geneva, Switzerland: World Health Organisation; 2003.
 82. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321–333.
 83. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischaemic heart disease in women than in men? *JAMA*. 1991;265:627–631.
 84. Weiss LA, Pan L, Abney M, Ober C. The sex-specific genetic architecture of quantitative traits in humans. *Nat Genet*. 2006;38:218–222.
 85. Tuzcu EM, Kapadia SR, Tutar E, Ziada KM, Hobbs RE, McCarthy PM, Young JB, Nissen SE. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound. *Circulation*. 2001;103:2705–2710.
 86. Herity NA, Lo S, Lee DP, Ward MR, Filardo SD, Yock PG, Fitzgerald PJ, Hunt SA, Yeung AC. Effect of a change in gender on coronary arterial size: a longitudinal intravascular ultrasound study in transplanted hearts. *J Am Coll Cardiol*. 2003;41:1539–1546.
 87. New G, Timmins KL, Duffy SJ, Tran BT, O'Brien RC, Harper RW, Meredith IT. Long-term estrogen therapy improves vascular function in male to female transsexuals. *J Am Coll Cardiol*. 1997;29:1437–1444.
 88. Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. *Radiology*. 2003;228:826–833.
 89. Buchthal SD, den Hollander JA, Merz CNB, Rogers WJ, Pepine CJ, Reichel N, Sharaf BL, Reis S, Kelsey SF, Pohost GM. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. *N Engl J Med*. 2000;342:829–835.
 90. Johnson BD, Shaw LJ, Buchthal SD, Bairey Merz CN, Kim HW, Scott KN, Doyle M, Olson MB, Pepine CJ, den Hollander J, Sharaf B, Rogers WJ, Mankad S, Forder JR, Kelsey SF, Pohost GM. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health–National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation*. 2004;109:2993–2999.
 91. Kaski JC. Cardiac syndrome X. In: Wenger NK, Collins P, eds. *Women and Heart Disease*. 2nd ed. London, United Kingdom: Taylor & Francis; 2005:205–216.
 92. Wang JJ, Liew G, Wong TY, Smith W, Klein R, Leeder SR, Mitchell P. Retinal vascular calibre and the risk of coronary heart disease-related death. *Heart*. 2006;92:1583–1587.
 93. Juutilainen A, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Retinopathy predicts cardiovascular mortality in type 2 diabetic men and women. *Diabetes Care*. 2007;30:292–299.
 94. Wang JJ, Liew G, Klein R, Rochtchina E, Knudtson MD, Klein BE, Wong TY, Burlutsky G, Mitchell P. Retinal vessel diameter and cardiovascular mortality: pooled data analysis from two older populations. *Eur Heart J*. 2007;28:1984–1992.
 95. Targher G, Bertolini L, Zoppini G, Lippi G, Zenari L. Retinopathy predicts cardiovascular mortality in type 2 diabetic men and women: response to Juutilainen et al. *Diabetes Care*. 2007;30:e51.
 96. Cheung N, Bluemke DA, Klein R, Sharrett AR, Islam FM, Cotch MF, Klein BE, Criqui MH, Wong TY. Retinal arteriolar narrowing and left ventricular remodeling: the Multi-Ethnic Study of Atherosclerosis. *J Am Coll Cardiol*. 2007;50:48–55.
 97. Cheung N, Sharrett AR, Klein R, Criqui MH, Islam FM, Macura KJ, Cotch MF, Klein BE, Wong TY. Aortic distensibility and retinal arteriolar narrowing: the Multi-Ethnic Study of Atherosclerosis. *Hypertension*. 2007;50:617–622.
 98. Wong TY, Cheung N, Islam FM, Klein R, Criqui MH, Cotch MF, Carr JJ, Klein BE, Sharrett AR. Relation of retinopathy to coronary artery calcification: the Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol*. 2008;167:51–58.
 99. Rose G. Chest pain questionnaire. *Milbank Mem Fund Q*. 1965;43:32–39.
 100. Mieres JH, Shaw LJ, Arai A, Budoff MJ, Flamm SD, Hundley WG, Marwick TH, Mosca L, Patel AR, Quinones MA, Redberg RF, Taubert KA, Taylor AJ, Thomas GS, Wenger NK. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. *Circulation*. 2005;111:682–696.
 101. Owen-Smith V, Hannaford PC, Elliott AM. Increased mortality among women with Rose angina who have not presented with ischaemic heart disease. *Br J Gen Pract*. 2003;53:784–789.
 102. Gopinath N, Chadha SL, Jain P, Shekhawat S, Tandon R. An epidemiological study of coronary heart disease in different ethnic groups in Delhi urban population. *J Assoc Physicians India*. 1995;43:30–33.

CLINICAL PERSPECTIVE

Is male sex a risk factor for stable angina pectoris in the same way that it is for acute coronary syndromes? In this meta-analysis based on almost 25 000 angina cases in women and men from 31 countries, we found that women had a slightly higher prevalence of stable angina pectoris than men. This study adds to current understanding by demonstrating for the first time that the female excess of angina is remarkably consistent across countries with widely differing myocardial infarction mortality rates, spanning 4 decades of study period and 4 decades of participant age. Such generalizability may suggest an inherent biological basis rather than artifactual explanations. The sex ratio of angina contrasts with the ubiquitous male excess of myocardial infarction, is unexplained, and warrants further study. The observation of a female excess of angina, independent of diagnostic and treatment practices, has clinical implications for understanding the quality of care in women.

Go to <http://cme.ahajournals.org> to take the CME quiz for this article.