Sex-Specific Trends in Midlife Coronary Heart Disease Risk and Prevalence

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Background: While recent data indicate that stroke prevalence in women at midlife is double that of similarly aged men in the United States, little is known about current sex-specific trends in symptomatic cardiovascular disease. This study aimed to determine sex-specific midlife prevalence of myocardial infarction (MI) and risk of future coronary heart disease.

Methods: We assessed the sex-specific MI prevalence and the Framingham coronary risk score (FCRS) among US adults aged 35 to 54 years who participated in the National Health and Nutrition Examination Surveys (NHANES), cross-sectional, nationally representative surveys, during 1988 to 1994 and 1999 to 2004.

Results: In both epochs, men aged 35 to 54 years had a higher prevalence of MI than similarly aged women, but the gap narrowed in recent years as MI prevalence decreased among men and increased among women (2.5% vs 0.7% in NHANES 1988-1994 [$P<.01$] and 2.2% vs 1.0% in NHANES 1999-2004 [$P<.01$]). Among men, the mean FCRS showed an improving trend (8.6% in NHANES 1988-1994 vs 8.1% in NHANES 1999-2004 [$P=.07$]), while among women, the mean FCRS worsened (3.0% in NHANES 1988-1994 vs 3.3% in NHANES 1999-2004 [$P=.02$]). Temporal trends in FCRS components revealed that men had more improvements in vascular risk factors than women, but diabetes mellitus prevalence increased in both sexes.

Conclusions: Over the past 2 decades, MI prevalence has increased among midlife women, while declining among similarly aged men. Also, although the risk of future hard cardiovascular events remains higher in midlife men compared with midlife women, the gap has narrowed in recent years. Greater emphasis on vascular risk factor control in midlife women might help mitigate this worrisome trend.

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WOMEN IN THEIR midlife years have historically been at a lower risk for overall vascular events than similarly aged men. We recently reported, however, that in a nationally representative sample of the US population that participated in the National Health and Nutrition Examination Surveys (NHANES), self-reported stroke prevalence among women aged 45 to 54 years was double that of similarly aged men.[1] This sex disparity in stroke prevalence appears to be a new phenomenon that is evolving as a result of increasing stroke prevalence among women.[2] Whether similar sex disparities are present or have recently developed in myocardial infarction (MI) prevalence or in the risk of future hard coronary heart disease (myocardial infarction or coronary death) remains unknown. We hypothesized that given the similar pathophysiologic underpinnings of most strokes and ischemic cardiovascular events, coronary heart disease has likely increased in parallel with strokes among midlife women. The aims of this study were 2-fold: (1) to assess temporal trends in sex disparities in MI prevalence among individuals at midlife, and (2) to assess temporal trends in sex disparities in the risk of future hard cardiovascular events among midlife individuals without a history of MI.

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METHODS

POPULATION FOR STUDY

The NHANES are composed of cross-sectional samples of the US noninstitutionalized civilian population conducted by the National Center for Health Statistics (NCHS), a branch of the Centers for Disease Control and Prevention.[3] The NHANES were conducted from 1988 to 1994 in 2 phases (1988-1991 and 1991-1994) and from 1999 to 2004 in 3 phases (1999-2000, 2001-2002, and 2003-2004), and the data from the 2 phases and the 3 phases, respectively, were combined herein following NCHS recommendations.[4,5] The protocols for conduct of the NHANES were approved by the

NCHS institutional review board, and informed consent was obtained from all participants.[6,7] The sampling plan followed a complex, stratified, multistage, probability cluster design, with oversampling of non-Hispanic blacks, Mexican Americans, and the elderly, to enhance the precision of prevalence estimates in those groups.

Interviews were conducted in sampled households, and all individuals were invited to participate in medical examinations that were conducted at nearby mobile examination centers. The interviews collected demographic, socioeconomic, dietary, and health-related information. Mobile examinations consisted of medical and dental examinations, physiologic measurements, and laboratory tests. Detailed descriptions of the plan and operation of each survey have been published.[6,8]

The total sample examined in NHANES 1988-1994 included 30 818 persons, while the total sample examined in NHANES 1999-2004 included 29 402 persons. The NHANES 1988-1994 included 5112 individuals aged 35 to 54 years; the NHANES 1999-2004 included 4594 individuals aged 35 to 54 years . Of those who participated, 4793 individuals in NHANES 1988-1994 and 4592 individuals in NHANES 1999-2004 answered the question regarding a history of a physician diagnosis of heart attack. For the Framingham coronary risk score (FCRS) analysis, 4326 individuals in NHANES 1988-1994 and 4075 individuals in NHANES 1999-2004 had complete data for the components of FCRS.

STUDY VARIABLES

A history of MI was determined by self-reported physician diagnosis of heart attack. To calculate FCRS, individuals with a self-reported history of a physician diagnosis of heart attack were excluded, and the following components were used: age, sex, total cholesterol level, high-density lipoprotein cholesterol level, systolic blood pressure measurement, the presence or absence of diabetes mellitus, and history of smoking.[9] Smoking was defined by a self-reported history of smoking more than 100 cigarettes. Diabetes mellitus was defined by a self-reported physician diagnosis, self-reported current medical therapy (insulin or oral agents), or a glycosylated hemoglobin concentration greater than 7%. Body mass index, calculated as weight in kilograms divided by height in meters squared, was measured using standardized examination protocols. Obesity was defined as a body mass index greater than or equal to 30.

STATISTICAL ANALYSIS

The distributions of each variable of interest were evaluated for normality. The normality of data was determined by the shape of histogram and the values of skewness and kurtosis (–1.0 to 1.0). Transformations (square root transformation of FCRS) were performed when the distributions were skewed. PROC SURVEYMEANS, PROC SURVEYREG, and PROC SURVEYFREQ were used for the comparisons between the 2 NHANES waves. According to the NHANES Analytic and Reporting Guidelines, sample weights and the stratification and clustering of the design were incorporated into our analyses to get proper estimates and standard errors of estimates.[4] All data analyses were conducted using SAS (version 9.1; SAS Institute Inc, Cary, North Carolina). Statistical hypotheses were tested using $P < .05$ as the level of statistical significance.

RESULTS

Table 1 shows the demographic characteristics of individuals aged 35 to 54 years who participated in NHANES 1988-1994 and 1999-2004. Among individuals aged 35 to 54 years, men were more likely than women to report a history of MI (2.5% vs 0.7% in NHANES 1988-1994 [$P < .01$] and 2.2% vs 1.0% in NHANES 1999-2004 [$P < .01$]). A comparison of history of MI between the 2 NHANES waves revealed that women's MI prevalence had increased (0.7% vs 1.0% [$P = .38$]) , while men's MI prevalence had declined (2.5% vs. 2.2% [$P = .65$]); however, the differences were not significant.

Table 1. Demographic Characteristics of Individuals Aged 35 to 54 Years Who Participated in NHANES 1988-1994 and NHANES 1999-2004

Characteristic	NHANES 1988-1994 (n=4326)	NHANES 1999-2004 (n=4075)	*P* Value
Age range, y			<.01
35-44	2692	2160	
45-54	1634	1915	
Sex, % female	52.1	50.3	.10
Race/ethnicity women, %			.31
Non-Hispanic white	75.7	72.0	
Non-Hispanic black	10.6	10.9	
Hispanic	9.8	12.4	
Other	3.9	4.7	
Race/ethnicity men, %			.09
Non-Hispanic white	78.0	73.6	
Non-Hispanic black	9.4	9.5	
Hispanic	9.3	12.6	
Other	3.3	4.3	

Abbreviation: NHANES, National Health and Nutrition Examination Survey.

In individuals without a history of MI, the mean FCRS was higher in men than in women (**Table 2** and **Table 3**). The mean FCRS increased with age in both men and women, as expected (Table 2). Analysis of temporal trends in sex-specific mean FCRS revealed that in both age groups, the men's mean FCRS declined ($P < .01$) from NHANES 1988-1994 to NHANES 1999-2004, while the women's mean FCRS remained stable (Table 2). Also, assessment of individuals with an FCRS of 20% or higher revealed that among men aged 35 to 44 years the prevalence of an FCRS of 20% or higher remained stable in both periods, while no women aged 35 to 44 years had an FCRS of 20% or higher. Among individuals aged 45 to 54 years, however, the prevalence of an FCRS of 20% or higher declined in men from 16% in NHANES 1988-1994 to 10.6% in NHANES 1999-2004 ($P = .01$) (Table 2). The prevalence of an FCRS of 20% or higher among women aged 45 to 54 years remained stable (0.5% in NHANES 1988-1994 vs 0.6% in NHANES 1999-2004 [$P = .78$]) (Table 2). As a result, the ratio of men to women with an FCRS of 20% or higher decreased from 32 in NHANES 1988-1994 to 18 in NHANES 1999-2004. When the age groups were collapsed, the men's mean FCRS showed an improving trend (8.6% in NHANES 1988-1994 vs 8.1% in NHANES 1999-2004 [$P = .07$]), but the women's mean FCRS worsened (3.0% in NHANES 1988-1994 vs 3.3% in NHANES 1999-2004 [$P = .02$]) (Table 3).

With regard to sex-specific temporal trends in the components of FCRS, all except 1 component remained stable or improved among men. Specifically, the total choles-

Table 2. Comparison Between Age- and Sex-Stratified Framingham Coronary Risk Scores (FRCS) in NHANES 1988-1994 vs NHANES 1999-2004

Age Range, y	NHANES 1988-1994 No.	NHANES 1988-1994 FCRS, Mean (SE), %	NHANES 1999-2004 No.	NHANES 1999-2004 FCRS, Mean (SE), %	*P* Value
Men					
35-44	1214	6.5 (0.2)	1059	5.9 (0.1)	<.01
45-54	768	11.9 (0.3)	953	10.6 (0.3)	<.01
Women					
35-44	1478	1.6 (0.04)	1101	1.6 (0.05)	.92
45-54	866	5.2 (0.1)	962	5.1 (0.1)	.43
		Transformed FCRS,[a] Mean (SE)		**Transformed FCRS,[a] Mean (SE)**	
Men					
35-44	1214	2.5 (0.03)	1059	2.3 (0.02)	<.01
45-54	768	3.3 (0.04)	953	3.2 (0.04)	<.01
Women					
35-44	1478	1.2 (0.01)	1101	1.2 (0.01)	.99
45-54	866	2.2 (0.03)	962	2.1 (0.03)	.48
		FCRS ≥ 20%, Mean (SE), %		**FCRS ≥ 20%, Mean (SE), %**	
Men					
35-44	25	1.0 (0.3)	12	1.0 (0.4)	.94
45-54	106	16.0 (1.7)	98	10.6 (1.4)	.01
Women					
35-44	0	0	0	0	NA
45-54	6	0.5 (0.3)	9	0.6 (0.3)	.78

Abbreviations: FCRS, Framingham coronary risk score; NA, not applicable; NHANES, National Health and Nutrition Examination Survey.
[a]The FRCS was transformed using square root transformation.

terol levels remained stable, the high-density lipoprotein levels improved slightly, the systolic blood pressure levels improved, and smoking prevalence declined (Table 3). Diabetes mellitus prevalence, however, increased among men. Women, on the other hand, saw fewer improvements; the mean high-density lipoprotein-cholesterol level was the only component of the FCRS to improve (Table 3). Total cholesterol levels, systolic blood pressure levels, and smoking prevalence remained stable, while diabetes mellitus prevalence increased (Table 3). Assessment of temporal trends in obesity prevalence revealed that the prevalence of obesity increased in both men and women from NHANES 1988-1994 to NHANES 1999-2004 (Table 3).

In NHANES 1999-2004, the mean (SE) FCRS was 3.0% (0.1%) among nondiabetic women and 8.6% (0.4%) among diabetic women, suggesting that the increase in FCRS in NHANES 1999-2004 compared with the previous decade was primarily attributable to the increase in the prevalence of diabetes mellitus.

COMMENT

This is the first study that we are aware of that has assessed recent temporal trends in sex-specific MI prevalence and risk of future hard cardiovascular events among midlife individuals. Data from this nationally representative study comparing the prevalence of MI across the 2 most recent decades showed a trend toward a decline in MI prevalence among men aged 35 to 54 years and an increase in MI prevalence among similarly aged women; however, these results did not reach statistical significance. These results are in accord with recent data among middle-aged individuals in the United States indicating that there is a rising stroke prevalence among women compared with men.[1]

In support of what seems to be an ominous trend in cardiovascular health among midlife women, evaluation of FCRS, a reliable indicator of future risk of coronary heart disease, revealed that although FCRS remains higher in men than in women, the difference has narrowed. While men's cardiovascular risk improved in recent years, women's risk worsened. Temporal trends in the components of the FCRS revealed that men's smoking rates declined and blood pressure improved in recent years, whereas similar improvements were lacking in women. Diabetes mellitus prevalence was the only component of the FCRS to worsen in both men and women, which might be indicative of rising insulin resistance in the context of the growing obesity epidemic. Because diabetes mellitus was defined by self-reported physician diagnosis, self-reported current medical therapy (insulin or oral agents), or a glycosylated hemoglobin concentration greater than 7%, an increase in the use of oral hypoglycemics or insulin or changes in screening for diabetes mellitus could also play a role in the higher prevalence observed in NHANES 1999-2004.

The lower rates of smoking, improved blood pressure levels, and improved high-density lipoprotein cholesterol levels among men suggest that educational campaigns and drug interventions likely have had a positive impact on cardiovascular risk factor control. These findings are in line with multiple other studies that have shown an overall improvement in hypertension, dyslipidemia, and smoking rates in the United States in recent years.[10-12]

Although men in their midlife years continue to have a higher prevalence of MI and a higher 10-year risk of hard coronary heart disease than women of similar age,

our study suggests that the risk is increasing in women, while decreasing in men. Therefore, intensification of efforts at screening for and treating vascular risk factors in women in their midlife years may be warranted. In the past, perhaps as a result of previous data on cardiovascular risk, women with cardiovascular risk factors were not identified and treated.[13-17] For example, previous studies of high-risk individuals have shown that men have cholesterol levels measured more often and treated more aggressively and have lower low-density lipoprotein levels than women[14,18-20] and that women are less likely than men to have their hypertension controlled.[13] Potential reasons for these sex disparities may include patient, clinician, and health system factors. Patient factors include poorer access to care among women, competing health concerns (eg, women think they are at a higher risk for cancer than for cardiovascular disease),[21,22] and higher number of comorbidities.[23] Clinician factors include underestimation of women's cardiovascular risks[24] and benefits of treatment, confidence in the ability to manage cardiovascular disorders, prioritization of other preventive services over cardiovascular risk factor management, and communication and decision-making styles.[23] Finally, health system factors such as disease management programs might play a role.

The patient, physician, and health system factors that affect sex disparities in cardiovascular disease are heavily influenced by the perception of relative risk. Because premenopausal women were historically thought to have a lower risk of cardiovascular disease than similarly aged men, cardiovascular disease prevention efforts have focused on men. Our recent findings of an increase in midlife women's stroke prevalence (resulting in twice as many women reporting having had a stroke than men) and the current findings of a trend toward worsening MI prevalence rates and hard coronary heart disease risk among women suggest that women are not absolutely protected. While the rate of coronary heart disease remains lower in women than in men, more attention should be paid to overall vascular risk factor prevention in women in their midlife years. In particular, efforts to reduce the rising trends in obesity and diabetes mellitus in women will likely be beneficial.

This study has some limitations. First, it relies on self-report of physician diagnosis of MI. While self-reported history of MI has not been evaluated in NHANES, other studies show a sensitivity of 80% to 82%[25,26] and a specificity of 99.4%.[25] Second, it is cross-sectional; therefore, caution should be exercised in making causal inferences. This cross-sectional design, however, is ideally suited for assessing sex-specific trends in cardiovascular disease prevalence and risk in a broad, nationally representative study. Third, sex differences in FCRS in individuals younger than 45 years must be interpreted with caution, as the score assumes that male sex confers a higher risk of coronary heart disease in individuals younger than 45 years. For example, with all other risk factors being equal, a man younger than 45 years will receive a higher FCRS than a woman of the same age. Finally, the lack of significance in the temporal trends in MI prevalence is likely attributable to the small sample size. Nevertheless, this trend is consistent with similar trends in both stroke and FCRS, suggesting that it is real. Further investigation will be required to determine if this trend has continued in more recent years.

Table 3. Trends in Framingham Coronary Risk Score, Components of Framingham Coronary Risk Score, and Obesity Prevalence Among Men and Women Aged 35 to 54 Years in the United States[a]

Variable	NHANES 1988-1994	NHANES 1999-2004	*P* Value
No. of men aged 35-54 y	1982	2012	
FCRS, %	8.6 (0.2)	8.1 (0.2)	.07
Transformed FCRS[b]	2.8 (0.03)	2.7 (0.03)	.09
FCRS ≥ 20%, % (SE)	6.8 (0.6)	5.5 (0.7)	.19
Total cholesterol, mg/dL	210.2 (1.3)	210.9 (1.4)	.72
HDL cholesterol, mg/dL	45.4 (0.5)	46.5 (0.4)	.08
SBP, mm Hg	124.2 (0.5)	121.9 (0.5)	<.01
History of smoking, % (SE)	68.5 (1.8)	56.8 (1.7)	<.01
History of diabetes mellitus, % (SE)	0	5.7 (0.5)	NA
BMI ≥ 30, % (SE)	20.9 (1.1)	30.4 (1.2)	<.01
No. of women aged 35-54 y	2344	2063	
FCRS, %	3 (0.1)	3.3 (0.1)	.02
Transformed FCRS[b]	1.6 (0.01)	1.7 (0.02)	.006
FCRS ≥ 20%, % (SE)	0.2 (0.1)	0.3 (0.1)	.52
Total cholesterol, mg/dL	201.7 (1.3)	204.0 (1.1)	.20
HDL cholesterol, mg/dL	55.3 (0.5)	57.2 (0.6)	.01
SBP, mm Hg	118.6 (0.4)	118.2 (0.4)	.47
History of smoking, % (SE)	46.9 (1.5)	45.2 (1.4)	.46
History of diabetes mellitus, % (SE)	0	4.7 (0.5)	NA
BMI ≥ 30, % (SE)	27.0 (1.5)	34.1 (1.4)	<.01

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FCRS, Framingham coronary risk score; HDL, high-density lipoprotein; NA, not applicable; NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure.

SI conversion factor: To convert cholesterol values to millimoles per liter, multiply by 0.0259.

[a] Values are expressed as mean (SE) unless indicated otherwise.

[b] The FRCS was transformed using square root transformation.

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Author Contributions: Dr Towfighi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Towfighi. *Acquisition of data:* Zheng. *Analysis and interpretation of data:* Towfighi, Zheng, and Ovbiagele. *Drafting of the manuscript:* Towfighi. *Critical revision of the manuscript for important intellectual content:* Towfighi, Zheng, and Ovbiagele. *Statistical analysis:* Zheng. *Obtained funding:* Towfighi. *Administrative, technical, and material support:* Towfighi. *Study supervision:* Ovbiagele.

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EDITORIAL

Women's Cardiovascular Health

Prevention Is Key

CARDIOVASCULAR ILLNESSES HAVE BEEN long neglected in their role as the primary cause of mortality in women, both by patients and physicians. More easily identifiable female illnesses, such as breast, uterine, and ovarian cancer, have been regarded as the primary concern for women's health.[1] Men are still believed to be at greater risk for myocardial infarction and stroke and are thus more aggressively informed, counseled, and treated for these diseases. The results from a survey sponsored by the American Heart Association and KOS Pharmaceuticals showed low levels of physicians' awareness of cardiovascular risk in women and undertreatment of risk factors.[2] In fact, most of the health and mortality disparities we see today are due to a combination of several factors.

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The need to specifically tailor medical therapy by sex and with attention to drug dosage adjustment or drug compound selection is gaining more and more acceptance.[3,4] The inclusion of female patients in clinical trials is improving, allowing for more information that can be transformed into sex-specific guidelines.[5] Sex-specific recommendations in guidelines are much needed and could considerably improve women's cardiovascular care. However, more and better sex-specific data are needed to inform coverage decisions.[6]

Nonetheless, the concept of cardiovascular risk identified after the original Framingham Heart Study[7] underlines what appears most important of all: the need for more aggressive prevention. In this issue of the *Archives*, Towfighi and colleagues[8] have addressed the impact of this concept by analyzing myocardial infarction prevalence and associated risk factors in women and men at midlife. Comparing 2 National Health and Nutrition Examination Survey cohorts (1988-1994 and 1999-2004), they detected not only a reduction in myocardial infarction prevalence in men and an increase in women, but, more importantly, similar trends in risk factor assessment. Men appeared to have progressively reduced their cardiovascular risk through effective prevention measures, while the risk in women has progressively increased. The only factor that did not differ between the populations was the increased incidence of diabetes (likely related to increasing obesity in men and women). This study demonstrates the continued opportunities for improvement in cardiovascular risk factors.

Towfighi and colleagues[8] concentrated on the younger female population. Women younger than 60 years experience a still unexplained increased mortality compared with men, as demonstrated by Vaccarino et al[9] more than 10 years ago. In this issue, Vaccarino and colleagues[10] have analyzed more recent data to identify potential improvements in the trend. In fact, overall female mortality has decreased, including the population younger than 55 years, despite lower rates of invasive procedures in women than in men. These results are encouraging. The most striking factor in this improvement, however, is changes in comorbidity and clinical severity on presentation. More awareness on the physicians' side has to be taken into account for part of this improvement. However, the major factor is likely the adequate pre-event risk management as the essential modulator of women's cardiovascular health and disease prevention.

These novel data, confirmed by our own experience, highlight for us the importance of risk management. In light of these results, inadequate control of risk factors, such as hypertension and diabetes, in women compared with men,[11,12] as well as reduced counseling and risk management programs, is not acceptable. The improvements described by the Towfighi et al[8] and Vaccarino et al[10] are encouraging and indicate that we are on the right track. However, much needs to be done, especially in consideration of the increase in prevalence of risk factors as obesity and type II diabetes mellitus in the general population. As these studies show, increased and continuous vigorous attention to the prevention of cardiovascular risk factors—by healthy diet, regular physical activity, and avoidance of smoke and smoking—is necessary for both men and women.

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