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ORIGINAL RESEARCH

Sex Differences in Outcomes of Young Adults Hospitalized With First Myocardial Infarction From 2011 to 2022

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BACKGROUND: Acute myocardial infarction (AMI) hospitalizations are increasing in young adults, but outcomes stratified by sex and AMI subtype are not well understood.

METHODS: First AMI hospitalizations among young adults 18 to 54 years old were analyzed from 2011 to 2022 in the United States from the National Inpatient Sample and stratified by subtype (ST-segment–elevation myocardial infarction [STEMI] and non–ST-segment–elevation myocardial infarction) and sex. In-hospital mortality by first AMI-subtype was the primary outcome, including in-hospital mortality trends using orthogonal polynomial contrasts; in-hospital complications were secondary outcomes. Patient characteristics included traditional and nontraditional risk factors. All analyses were performed sex-stratified with adjustment using a sequential additive multivariable logistic regression model.

RESULTS: Among 945 977 weighted first AMI hospitalizations in young adults, 356 115 (37.6%) were STEMI and 589 862 (62.4%) were non–ST-segment–elevation myocardial infarction. Overall, adjusted in-hospital mortality increased significantly for first STEMI (1.2% absolute increase, P_{trend}<0.001) and was unchanged for first non–ST-segment–elevation myocardial infarction (0.2% absolute decrease, P_{trend}=0.70) across the study period. Compared with young men, young women had higher in-hospital mortality compared with young men (STEMI: 3.1% versus 2.6%, P<0.001; non–ST-segment–elevation myocardial infarction: 1.0% versus 0.8%, P=0.03) and experienced similar in-hospital complications with lower receipt of cardiovascular procedures. Irrespective of sex, more nontraditional than traditional risk factors were independently associated with higher odds of in-hospital mortality.

CONCLUSIONS: There was a rise in first STEMI in-hospital mortality among young adults from 2011 to 2022. Mortality for both AMI subtypes was higher in young women and was associated with more nontraditional compared with traditional risk factors.

Key Words: first myocardial infarction ■ mortality ■ young adults

Mortality from acute myocardial infarction (AMI) has reportedly plateaued or decreased in young adults in observational studies extending into the 2010s in the United States.[1–4] However, although there has been an overall decline in AMI hospitalizations in the United States, the decline appears to be driven largely by older adults and men.[1–3] In parallel, the prevalence of modifiable traditional risk factors (eg, tobacco smoking) is increasing among young adults hospitalized with AMI, with notable sex differences in traditional risk profiles.[5–7] Collectively, these trends have called for a closer examination of sex differences

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CLINICAL PERSPECTIVE

What Is New?

- Among nearly 1 million first acute myocardial infarction hospitalizations in young adults (18–54 years old) from 2011 to 2022, in-hospital mortality for first ST-segment–elevation myocardial infarction increased significantly and remained unchanged for first non–ST-segment–elevation myocardial infarction after adjustment for both traditional and nontraditional risk.
- In-hospital mortality for both acute myocardial infarction subtypes was higher in young women compared with young men and was associated with more nontraditional than traditional risk factors.

What Are the Clinical Implications?

- Improved acute myocardial infarction risk assessments that include nontraditional risk factors could help reduce in-hospital acute myocardial infarction mortality, particularly among young women.

Nonstandard Abbreviations and Acronyms

NIS	National Inpatient Sample

in AMI outcomes among young adults, considering both nontraditional risk factors (eg, psychosocial risk) and differences by AMI subtype.[4,6–8]

However, there are 3 key knowledge gaps that remain in the evaluation of sex differences in AMI outcomes among young adults. First, prior studies documenting stable or declining AMI mortality in young adults have not extended into the most recent decade, warranting a contemporary reassessment in light of rising traditional risk factor prevalence and persistent sex-based disparities.[1–4,7,8] Second, prior analyses often included young adults with a prior myocardial infarction (MI) or revascularization (percutaneous coronary intervention or coronary artery bypass grafting), and did not consistently stratify by AMI subtype (ST-segment–elevation MI [STEMI] versus non–ST-segment–elevation MI [NSTEMI]).[1–4,9,10] As a result, there is a poor understanding of sex differences in outcomes following the first AMI among young adults without known cardiovascular disease, and whether there are differences by AMI subtype.[1–4,9,10] Finally, the influence of nontraditional risk factors (eg, inflammatory rheumatic diseases) on AMI outcomes remains poorly characterized, despite increasing recognition of their importance and a higher prevalence of these risk factors in young adults as compared with older adults.[7,11] Nontraditional risk factors, including those beyond atherosclerotic cardiovascular disease risk enhancers, may further modify outcomes, highlighting the importance of examining sex differences in AMI outcomes accounting for both traditional and nontraditional risk factors.[7]

To address these gaps, we evaluated sex differences in in-hospital outcomes among young adults (18–54 years old) hospitalized from 2011 to 2022 with first AMI in the United States, stratified by AMI subtype, and accounting for both traditional and nontraditional risk factors. We used data from the National Inpatient Sample (NIS) because it is a nationally representative all-payer inpatient health care database that includes young adults and enables evaluation of both AMI trends and outcomes in AMI enablers.[12]

METHODS

Data Availability Statement

The NIS Data Use Agreement precludes data sharing from this study, but all data are publicly available: https://hcup-us.ahrq.gov/tech_assist/centdist.jsp. Additionally, since all data in the NIS are de-identified, informed consent was not required.

Data Source

Hospitalization data were abstracted from the NIS, which is a part of the Healthcare Cost and Utilization Project family of databases sponsored by the Agency for Healthcare Research and Quality.[12] The NIS is a deidentified all-payer inpatient health care database in the United States and accounts for approximately a 20% stratified sample of all discharges in the United States. Therefore, when weighted, the calculation of national estimates is based on >35 million hospitalizations annually.

Study Population

We queried the NIS database from 2011 to 2022 to identify hospitalizations for first AMI, defined as those with a primary discharge diagnosis code of AMI (STEMI or NSTEMI), using the *International Classification of Diseases, Ninth Revision, Clinical Modification* and *Tenth Revision, Clinical Modification* (*ICD-9-CM* and *ICD-10-CM*) codes, and ascertained through the exclusion of *ICD-9-CM* and *ICD-10-CM* codes for either a prior MI, history of prior percutaneous coronary intervention or coronary artery bypass grafting, history of heart transplant, history of coronary artery disease in bypass graft or transplanted heart, chronic ischemic heart disease, a subsequent episode of AMI care, or unspecified acute or subacute MI, including unstable angina or post-MI syndrome. A complete list of all variables and corresponding *ICD-9* and *ICD-10* codes are provided in Table S1. We included

first AMI hospitalizations among those 18 to 54 years old, herein defined as young adult first AMI hospitalizations, and therefore excluded hospitalizations among those ≥55 years old to maintain consistency with prior definitions of young adults.[1,2,4,5,8] We excluded all hospitalizations with missing data (which accounted for 7% of the eligible sample). In accordance with prior NIS studies, we also excluded hospitalizations with 0-day length of stay from the primary analysis given possible ambiguity of whether these were true AMI hospitalizations.[1,5,13]

Clinical Characteristics

For each hospitalization, we extracted patient demographic characteristics including age, biological sex, race and ethnicity, and quartile of median household income. The lowest household income quartile was considered as a nontraditional risk factor. Further identification of both traditional and nontraditional risk factors of interest to describe hospitalization characteristics used relevant Elixhauser comorbidity data, or validated *ICD-9-CM* and *ICD-10-CM* codes from prior studies that are independent of medication prescription ascertainment (Table S1).[1,4,5,14–16] Traditional risk factors included hypertension, dyslipidemia, diabetes, tobacco use, and obesity. Nontraditional risk factors included metabolic syndrome, chronic kidney disease, inflammatory rheumatic disease (composite of rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, psoriatic arthropathies/psoriasis, ankylosing spondylitis, enteropathic arthropathies, systemic necrotizing vasculitides, dermatomyositis and polymyositis, Sjogren's syndrome, mixed connective tissue disease, and polymyalgia rheumatica), HIV or AIDS, hypercoagulable states, psychiatric disorders (composite of major depression or anxiety disorder), nontobacco drug use (a composite of cocaine/stimulant, cannabis, or opioid use), family history of ischemic heart disease, obstructive sleep apnea, hypothyroidism, and female-specific factors (a composite of preeclampsia/eclampsia, premature/early menopause, gestational diabetes, history of preterm delivery, history of pregnancy-related complications, or polycystic ovarian syndrome). We also extracted hospital characteristics including location/teaching status (rural, urban nonteaching, and urban teaching), and hospital bed size (small, medium, and large).[17,18]

Study Outcomes

The primary outcome of interest was all-cause in-hospital mortality. We also assessed annual in-hospital mortality trends. In addition, we evaluated the incidence of in-hospital complications: cardiogenic shock, cardiac tamponade, acute stroke (including hemorrhagic stroke), cardiac arrest or ventricular fibrillation, acute renal failure, and major bleed (a composite of intracranial, gastrointestinal, respiratory, or procedural sources of hemorrhage; excludes hemorrhagic stroke). In parallel, we also identified the receipt of coronary angiography or coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), and the receipt of mechanical circulatory support during the index first AMI hospitalization in young adults.

Statistical Analysis

All analyses (baseline clinical characteristics, outcome, and trend analyses) were stratified by first AMI subtype (STEMI or NSTEMI) and compared within subtype between biological sex. Continuous variables are presented as median and interquartile ranges, whereas categorical variables are presented as percentages. Age was analyzed both as a continuous and categorical variable. All baseline demographic and clinical characteristics were compared using standardized mean differences. Linear trends in in-hospital mortality were examined using orthogonal polynomial contrasts to allow differential weighting of year-specific mortality estimates and ensure appropriate degrees of freedom. In-hospital mortality and in-hospital complication outcomes were evaluated using 4 exploratory sequentially additive multivariable logistic regression models: Model 1, a conditional model for adjustment of linear year-over-year differences in the primary outcome of in-hospital mortality (and accounts for the impact of the COVID-19 pandemic years); Model 2, adjustment for Model 1 characteristics (applicable for in-hospital mortality) and patient age, patient demographics, hospital characteristics; Model 3, adjustment for Model 2 characteristics and traditional risk factors; and Model 4, adjustment for Model 3 characteristics and nontraditional risk factors. Models were compared with the preceding model using the likelihood ratio test and Akaike information criterion. After full sequential adjustment (Models 1–4), a 2-way interaction analysis between biological sex and all variables included in Models 1 to 4 was performed. All analyses accounted for NIS sampling design using updated hospital trend weights and were weighted to provide national-level estimates. SAS version 9.4 was used for all statistical analysis, with a 2-tailed $P<0.05$ to indicate statistical significance. No results were presented at any time when the unweighted number of hospitalizations was ≤10 as per the NIS Data Use Agreement. This study was considered exempt research by the Weill Cornell Medicine Institutional Review Board.

RESULTS

From 2011 through 2022, an estimated 945 977 hospitalizations in the United States had a principal discharge diagnosis of first AMI among young adults, of which an estimated 356 115 hospitalizations were STEMI (37.6%) and an estimated 589 862 were NSTEMI (62.4%).

Overall Cohort Characteristics

Baseline clinical characteristics of the total sample are presented in Table 1.

ST-Segment–Elevation MI

A higher proportion of first STEMI hospitalizations among young adults were men (77.2%) compared with women. Overall median age was similar between men and women for first STEMI. Irrespective of sex, a higher proportion of first STEMI hospitalizations were White people compared with non-White (defined as race or ethnicity that is either Black, Hispanic, Asian or Pacific Islander, Native American, or "Other race") people. Among traditional risk factors, tobacco use was the most prevalent in first STEMI hospitalizations irrespective of sex but was more prevalent in women compared with men (64.3% versus 61.0%; P<0.001). Among nontraditional risk factors, lowest income quartile was the most prevalent in first STEMI, irrespective of sex, and with a significantly higher prevalence in women compared with men (34.9% versus 28.7%; P<0.001).

Non–ST-Segment–Elevation MI

Among young adults, first NSTEMI hospitalizations were higher in men (66.2%) compared with women. Irrespective of sex, a higher proportion of both first NSTEMI hospitalizations were White people compared with non-White people. Hypertension was the most prevalent traditional risk factor in first NSTEMI hospitalizations irrespective of sex (69.9% in men versus 68.6% in women; P<0.001). Among nontraditional risk factors, the lowest income quartile was the most prevalent in first NSTEMI hospitalizations, irrespective of sex, and with a significantly higher prevalence in women compared with men (38.1% versus 32.3%; P<0.001).

In-Hospital Mortality

Overall, in-hospital mortality from 2011 to 2022 was higher in first STEMI hospitalizations as compared with first NSTEMI hospitalizations in young adults (2.6% versus 0.9%; Figure 1). Unadjusted trends in in-hospital mortality and sequentially adjusted odds for in-hospital mortality among cohort characteristics are shown in Figures 2 and 3 (STEMI and NSTEMI, respectively) and Tables 2 and 3 (STEMI and NSTEMI), respectively.

ST-Segment–Elevation MI

Unadjusted in-hospital mortality was significantly higher with first STEMI in women as compared with men (3.1% versus 2.5%; P<0.001; Figure 1). From 2011 to 2022, there was a significant increase in unadjusted in-hospital mortality for first STEMI (2.1% to 3.3%, 1.2% absolute increase; P_{trend}<0.001; Figure 2). When stratified according to sex, there was a significant increase in unadjusted in-hospital mortality for first STEMI in men (2.0% to 3.1%, 1.1% absolute increase; P_{trend}<0.001) but not in women (2.5% to 3.9%, 1.4% absolute increase; P_{trend}=0.081; Figure 2). The trend for the increase in in-hospital mortality with first STEMI remained significant throughout sequential adjustment (adjusted odds ratio [aOR], 1.04 [95% CI, 1.02–1.05]; Table 2). Young women had significantly higher adjusted odds of in-hospital mortality with first STEMI as compared with young men after full sequential adjustment (aOR, 1.24 [95% CI, 1.11–1.39]; Table 2). Other characteristics associated with higher odds of mortality with first STEMI after full sequential adjustment included Native American race (aOR, 1.83 [95% CI, 1.14–2.94]), 1 traditional risk factor: diabetes (aOR, 1.61 [95% CI, 1.44–1.80]), and 3 nontraditional risk factors: lowest income quartile (aOR, 1.24 [95% CI, 1.12–1.39]), chronic kidney disease (aOR, 3.19 [95% CI, 2.70–3.76]), and nontobacco drug use (aOR, 1.63 [95% CI, 1.37–1.93]; Table 2). There was no significant interaction of any characteristic with sex and a higher odds of in-hospital mortality (Model 4; Table 2).

Non–ST-Segment–Elevation MI

Unadjusted in-hospital mortality was higher with first NSTEMI in women as compared with men (1.0% versus 0.8%; P=0.03; Figure 1), but was not significant after adjustment for patient demographics and hospital characteristics (Model 2; Table 3). From 2011 to 2022, there was a significant decrease in unadjusted in-hospital mortality for first NSTEMI (1.0% to 0.8%, 0.2% absolute decrease; P_{trend}=0.021; Figure 3). When stratified according to sex, there was no significant decrease in unadjusted in-hospital mortality for first NSTEMI in both men (0.9% to 0.7%, 0.2% absolute decrease; P_{trend}=0.085) and women (1.2% to 1.0%, 0.2% absolute decrease; P_{trend}=0.077; Figure 3). Overall decreasing trends in in-hospital mortality with first NSTEMI were no longer significant after additive adjustment of traditional risk factors (aOR, 0.98 [95% CI, 0.96–1.01], Model 3; Table 3). Characteristics associated with higher odds of mortality with first NSTEMI after full sequential adjustment included 1 traditional risk factor: diabetes (aOR, 1.36 [95% CI, 1.17–1.57]) and 1 nontraditional risk factor: chronic kidney disease (aOR, 3.39 [95% CI, 2.89–3.98]; Table 3). There was no significant interaction of any characteristic with sex and a higher odds of in-hospital mortality (Model 4; Table 3).

In-Hospital Complications

The overall incidence of in-hospital complications from 2011 to 2022 was not significantly different in women compared with men in first STEMI (19.1% versus 18.6%; P=0.079; Figure 4), whereas men had a

Table 1. Overall Baseline Cohort Characteristics at Time of First Acute Myocardial Infarction

	NSTEMI				STEMI			
	Overall	Men	Women	SMD	Overall	Men	Women	SMD
Hospitalization count								
Unweighted	118 659	78 578	28 113	—	71 730	55 349	16 373	—
Weighted	589 862	390 567	139 767	—	356 115	274 789	81 286	—
Age, y [IQR]	48 [43–51]	48 [43–51]	48 [43–51]	0.02	48 [43–51]	48 [43–51]	48 [43–51]	0.01
18–34	5.2	5.3	5.1	0.01	4.6	4.6	4.6	0.00
35–44	24.0	23.6	24.7	−0.03	24.2	24.1	24.6	−0.01
45–54	70.8	71.1	70.2	0.02	71.2	71.2	70.8	0.01
Biological sex								
Men	66.2	—	—	—	77.2	—	—	—
Women	33.8	—	—	—	22.8	—	—	—
Race and ethnicity								
White	61.7	62.7	59.7	0.06	69.6	69.4	70.6	−0.03
Black	18.9	16.6	23.4	−0.17	11.5	10.1	16.0	−0.18
Hispanic	12.0	12.3	11.2	0.04	10.3	11.0	8.1	0.10
Asian or Pacific Islander	3.1	3.6	2.1	0.09	3.3	3.8	1.7	0.14
Native American	0.7	0.7	0.7	0.00	0.6	0.6	0.6	0.00
Other race (includes multiracial)	3.6	4.0	2.9	0.06	4.6	5.0	3.1	0.10
Hospital location, teaching status								
Rural	6.9	6.5	7.7	−0.05	6.3	6.0	7.1	−0.05
Urban nonteaching	26.7	26.9	26.3	0.01	27.2	27.4	26.3	0.03
Urban teaching	66.4	66.6	66.0	0.01	66.6	66.6	66.6	0.00
Hospital bed size								
Small	16.4	16.2	16.8	−0.02	13.5	13.5	13.3	0.01
Medium	29.0	29.0	29.0	0.00	28.3	28.5	27.8	0.02
Large	54.7	54.9	54.3	0.01	58.2	58.0	58.9	−0.02
Traditional								
Hypertension	69.4	69.9	68.6	0.03	59.2	58.5	61.6	−0.06
Dyslipidemia	59.0	62.1	53.0	0.18	58.7	59.9	54.6	0.11
Diabetes	32.6	30.7	36.5	−0.12	26.1	23.9	33.3	−0.21
Tobacco	56.5	57.8	54.0	0.06	61.8	61.0	64.3	0.07
Obesity	30.4	28.0	35.0	−0.15	22.5	20.4	29.8	−0.22
Nontraditional								
Lowest income quartile	34.2	32.3	38.1	−0.12	30.1	28.7	34.9	−0.14
Metabolic syndrome	0.8	0.8	0.7	0.01	0.6	0.6	0.7	−0.01
Chronic kidney disease	11.0	10.9	11.1	−0.01	4.2	4.0	4.6	−0.03
Inflammatory rheumatic disease	2.5	1.5	4.6	−0.18	1.8	1.2	4.0	−0.18
HIV/AIDS	0.9	1.0	0.7	0.03	0.8	0.8	0.6	0.02
Hypercoagulable state	0.7	0.5	1.0	−0.06	0.7	0.6	1.2	−0.07
Psychiatric disorders	17.7	12.6	27.7	−0.38	12.0	9.1	21.6	−0.35
Nontobacco drug use	8.8	9.5	7.5	0.07	7.2	7.4	6.5	0.03
Family history of ischemic heart disease	21.4	21.9	20.4	0.04	19.8	19.8	19.8	0.00
Obstructive sleep apnea	8.2	9.3	6.0	0.13	5.1	5.5	3.7	0.08
Hypothyroidism	6.6	3.6	12.4	−0.33	4.2	2.6	9.6	−0.30
Female-specific risk factors	0.8	—	0.8	—	0.8	—	0.8	—

IQR indicates interquartile range; NSTEMI indicates non–ST-segment–elevation myocardial infarction; SMD, standardized mean difference; and STEMI, ST-segment–elevation myocardial infarction.

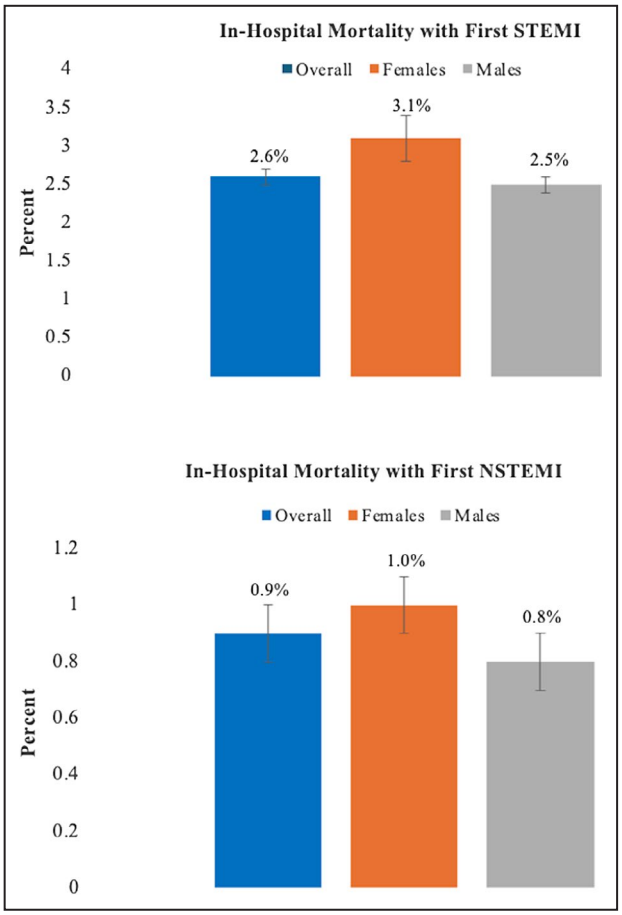

Figure 1. Unadjusted in-hospital mortality rates with first MI between sexes by MI subtype (STEMI and NSTEMI).
P<0.001 and *P*=0.03 for differences in unadjusted incidence rates between men and women in STEMI and NSTEMI, respectively. MI indicates myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

significantly higher rate of overall in-hospital complications with first NSTEMI (13.6% versus 11.6%; *P*<0.001; Figure 5). Receipt of either coronary angiography or

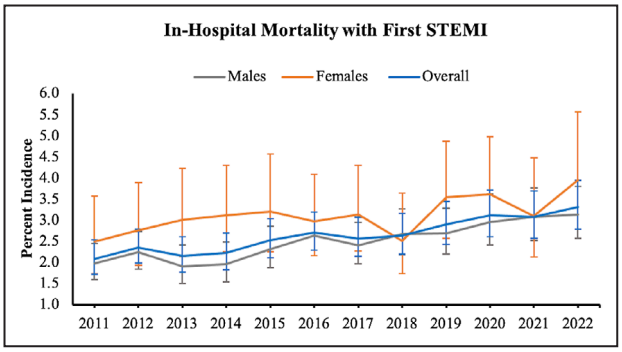

Figure 2. Overall and sex-specific unadjusted trends in in-hospital mortality with first STEMI.
P_{trend}<0.001 for all unadjusted trends except in women (P_{trend}=0.081). STEMI indicates ST-segment–elevation myocardial infarction.

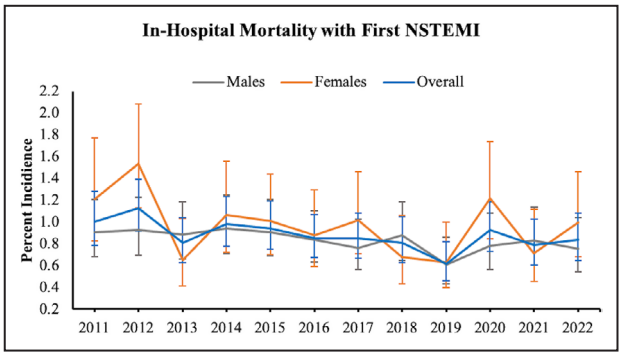

Figure 3. Overall and sex-specific unadjusted trends in in-hospital mortality with first NSTEMI.
P_{trend}=0.021 for overall unadjusted trend but was not significant in unadjusted trends in women (P_{trend}=0.077) or men (P_{trend}=0.085). NSTEMI indicates non–ST-segment–elevation myocardial infarction.

revascularization (both coronary artery bypass grafting and percutaneous coronary intervention) was significantly higher in men than women, with both first STEMI and NSTEMI, in addition to a significantly higher receipt of mechanical circulatory support for men in first NSTEMI as well (Table S2). Sequentially adjusted odds for each in-hospital complication are shown in Tables S3 (STEMI) and S4 (NSTEMI) between sexes.

ST-Segment–Elevation MI

Cardiac arrest or ventricular fibrillation had the highest incidence among all in-hospital complications with first STEMI and was similar in incidence between sexes (9.5% in women versus 9.2% in men; *P*=0.346; Figure 4), and in adjusted odds by sex (aOR, 1.04 [95% CI, 0.98–1.12]; Table S3). Compared with men, women had a significantly higher incidence of cardiogenic shock (8.1% versus 6.8%; *P*<0.001; Figure 4) with no significant difference in receipt of mechanical circulatory support (Table S2) and major bleed (1.5% versus 1.2%; *P*<0.001; Figure 4) with first STEMI, including higher adjusted odds of both in women (cardiogenic shock aOR, 1.20 [95% CI, 1.11–1.29], and major bleed aOR, 1.24 [95% CI, 1.05–1.45]; Table S3).

Non–ST-Segment–Elevation MI

In comparison, acute renal failure had the highest incidence among all in-hospital complications with first NSTEMI and was significantly higher in men compared with women (10.4% versus 8.2%; *P*<0.001; Figure 5), including higher adjusted odds in men (aOR, 0.66 [95% CI, 0.63–0.69]; referent group: men; Table S4). Additionally, incidence in cardiogenic shock was similar between sexes with first NSTEMI (1.8% versus 1.8%, *P*=0.324; Figure 5) and with no significant difference in odds after adjustment for nontraditional risk factors (aOR, 0.91 [95% CI, 0.83–1.01]; Model 4; Table S4). In parallel, receipt of mechanical circulatory support was

Table 2. Sequential Additive Multivariable Adjusted Odds Ratios for In-Hospital Mortality With First STEMI

	Odds for in-hospital mortality with first STEMI				
	Adjusted odds ratio (95% CI)				
	Model 1	Model 2	Model 3	Model 4	Interaction by sex *P* value
Trend (linear)	1.04 (1.02–1.05)	1.03 (1.02–1.05)	1.04 (1.02–1.05)	1.04 (1.02–1.05)	0.119
Demographics					
Age	—	1.02 (1.01–1.03)	1.03 (1.02–1.04)	1.03 (1.02–1.04)	0.510
Biological sex					
Women	—	1.30 (1.17–1.45)	1.20 (1.07–1.34)	1.24 (1.11–1.39)	—
Men	—	Reference	Reference	Reference	—
Race and ethnicity					
Black	—	1.38 (1.20–1.59)	1.26 (1.09–1.45)	0.97 (0.83–1.13)	0.779
Hispanic	—	1.15 (0.97–1.35)	0.95 (0.81–1.12)	0.85 (0.72–1.01)	0.285
Asian or Pacific Islander	—	1.13 (0.86–1.48)	1.01 (0.76–1.33)	1.01 (0.77–1.34)	*
Native American	—	2.30 (1.46–3.60)	2.07 (1.30–3.28)	1.83 (1.14–2.94)	*
White	—	Reference	Reference	Reference	Reference
Traditional risk factors					
Hypertension	—	—	0.76 (0.68–0.84)	0.69 (0.62–0.77)	0.445
Dyslipidemia	—	—	0.23 (0.20–0.26)	0.25 (0.22–0.28)	0.300
Diabetes	—	—	1.81 (1.62–2.02)	1.61 (1.44–1.80)	0.974
Tobacco	—	—	0.52 (0.47–0.57)	0.53 (0.48–0.59)	0.552
Obesity	—	—	0.87 (0.76–0.99)	0.90 (0.78–1.02)	0.031
Nontraditional risk factors					
Lowest income quartile	—	—	—	1.24 (1.12–1.39)	0.811
Metabolic syndrome	—	—	—	*	*
Chronic kidney disease	—	—	—	3.19 (2.70–3.76)	0.428
Inflammatory rheumatic disease	—	—	—	0.67 (0.44–1.02)	0.649
HIV/AIDS	—	—	—	0.75 (0.42–1.34)	*
Hypercoagulable state	—	—	—	1.18 (0.74–1.87)	*
Psychiatric disorders	—	—	—	0.81 (0.69–0.97)	0.390
Nontobacco drug use	—	—	—	1.63 (1.37–1.93)	0.813
Family history of ischemic heart disease	—	—	—	0.40 (0.33–0.48)	0.135
Obstructive sleep apnea	—	—	—	0.98 (0.76–1.27)	0.234
Hypothyroidism	—	—	—	0.98 (0.76–1.26)	0.880

Exploratory sequential additive multivariable adjustment model: Model 1, a conditional model for linear trend adjustment. Model 2, adjustment for Model 1 characteristics in addition to patient age, patient demographics, and hospital characteristics. Model 3, adjustment for Model 2 characteristics in addition to traditional risk factors (as delineated in Methods). Model 4, adjustment for Model 3 characteristics in addition to nontraditional risk factors (as delineated in Methods). After full sequential adjustment (Models 1–4), a 2-way interaction between biological sex and variables included in the preceding models is shown with their corresponding *P* values. Adjusted odds ratios are presented with 95% CIs. STEMI indicates ST-segment–elevation myocardial infarction.

*In accordance with the National Inpatient Sample Data Use Agreement, where no results are presented any time the unweighted number of hospitalizations is ≤10, and therefore also denote when statistical comparisons are invalid.

significantly higher in men as compared with women with first NSTEMI (aOR, 0.74 [95% CI, 0.67–0.82]; referent group: men; Table S4).

DISCUSSION

To our knowledge, this study is the largest nationally representative study to evaluate clinical outcomes in first AMI among young US adults, accounting for nearly 1 million weighted first AMI hospitalizations between 356 115 first STEMI and 589 862 first NSTEMI cases. There are 3 significant findings. First, after adjustment for traditional and nontraditional risk factors, in-hospital mortality for first STEMI is increasing in young adults, particularly in young men, and is unchanged with first NSTEMI. Second, irrespective of AMI subtype, young women have higher in-hospital mortality and receive fewer cardiovascular

Table 3. Sequential Additive Multivariable Adjusted Odds Ratios for In-Hospital Mortality With First NSTEMI

	Odds for in-hospital mortality with first NSTEMI				
	Adjusted odds ratio (95% CI)				
	Model 1	Model 2	Model 3	Model 4	Interaction by sex *P* value
Trend (linear)	0.97 (0.56–0.99)	0.97 (0.95–0.99)	0.98 (0.96–1.01)	0.99 (0.97–1.01)	0.975
Demographics					
Age	—	1.04 (1.02–1.05)	1.04 (1.03–1.06)	1.04 (1.03–1.05)	0.460
Biological sex					
Women	—	1.14 (0.99–1.30)	0.97 (0.85–1.11)	1.06 (0.92–1.22)	—
Men	—	Reference	Reference	Reference	—
Race and ethnicity					
Black	—	1.47 (1.26–1.73)	1.27 (1.08–1.49)	0.96 (0.80–1.14)	0.748
Hispanic	—	1.43 (1.19–1.73)	1.15 (0.95–1.40)	1.02 (0.83–1.23)	0.187
Asian or Pacific Islander	—	1.00 (0.67–1.49)	0.88 (0.58–1.32)	0.79 (0.52–1.18)	*
Native American	—	2.33 (1.34–4.05)	2.06 (1.18–3.60)	1.74 (1.00–3.03)	*
White	—	Reference	Reference	Reference	Reference
Traditional risk factors					
Hypertension	—	—	0.77 (0.67–0.89)	0.62 (0.54–0.72)	0.125
Dyslipidemia	—	—	0.31 (0.27–0.35)	0.35 (0.31–0.41)	0.354
Diabetes	—	—	1.81 (1.58–2.07)	1.36 (1.17–1.57)	0.102
Tobacco	—	—	0.49 (0.43–0.56)	0.56 (0.49–0.64)	0.642
Obesity	—	—	0.91 (0.79–1.06)	0.97 (0.84–1.13)	0.644
Nontraditional risk factors					
Lowest income quartile	—	—	—	1.06 (0.92–1.22)	0.832
Metabolic syndrome	—	—	—	1.01 (0.45–2.30)	*
Chronic kidney disease	—	—	—	3.39 (2.89–3.98)	0.116
Inflammatory rheumatic disease	—	—	—	1.00 (0.68–1.47)	*
HIV/AIDS	—	—	—	1.16 (0.66–2.05)	*
Hypercoagulable state	—	—	—	*	*
Psychiatric disorders	—	—	—	0.76 (0.63–0.93)	0.001
Nontobacco drug use	—	—	—	1.18 (0.95–1.48)	0.915
Family history of ischemic heart disease	—	—	—	0.31 (0.23–0.40)	0.099
Obstructive sleep apnea	—	—	—	1.03 (0.81–1.31)	0.029
Hypothyroidism	—	—	—	0.86 (0.66–1.12)	0.965

Exploratory sequential additive multivariable adjustment model: Model 1, a conditional model for linear trend adjustment. Model 2, adjustment for Model 1 characteristics in addition to patient age, patient demographics, and hospital characteristics. Model 3, adjustment for Model 2 characteristics in addition to traditional risk factors (as delineated in Methods). Model 4, adjustment for Model 3 characteristics in addition to nontraditional risk factors (as delineated in Methods). After full sequential adjustment (Models 1–4), a 2-way interaction between biological sex and variables included in the preceding models is shown with their corresponding *P* values. Adjusted odds ratios are presented with 95% CIs. NSTEMI indicates non–ST-segment–elevation myocardial infarction.

*In accordance with the National Inpatient Sample Data Use Agreement, where no results are presented any time the unweighted number of hospitalizations is ≤10, and therefore also denote when statistical comparisons are invalid.

procedures. Third, more nontraditional risk factors as compared with traditional risk factors were independently associated with higher in-hospital mortality for young men and women, particularly in first STEMI.

Trends in In-Hospital Mortality With First AMI

From 2011 to 2022, the significant increase in overall in-hospital mortality with first STEMI was driven largely by increases in young men. A prior study found that in-hospital mortality with AMI declined in young women and remained stable in young men (30–54 years old) from 2001 to 2010 in the United States.[1] Subsequent STEMI analyses in the United States extending to 2019 among adults 18 to 55 years old found no significant difference in adjusted in-hospital mortality compared with earlier years.[4,9] In contrast, our study shows that the odds of in-hospital mortality increased from 2011 to 2022 in young adults (18–54 years old) even after

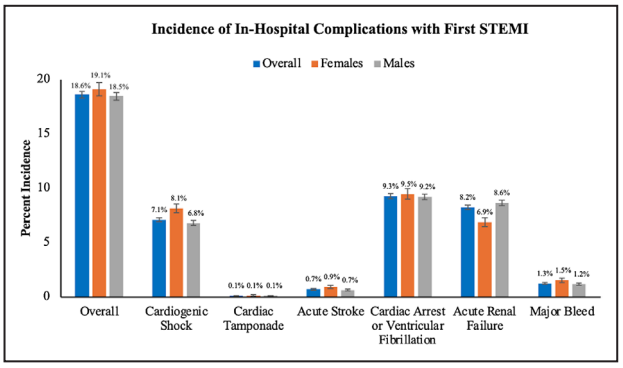

Figure 4. Overall and sex-specific rates of in-hospital complications with first STEMI.
P<0.001 for between-sex differences in individual in-hospital complications except overall complications (*P*=0.079), cardiac tamponade (*P*=0.467), and cardiac arrest or ventricular fibrillation (*P*=0.346). STEMI indicates ST-segment–elevation myocardial infarction.

adjustment of traditional and nontraditional risk factors, and with no interaction by sex. Additionally, we found that previously described declines in in-hospital mortality for first NSTEMI are no longer significant after adjustment of traditional and nontraditional risk factors, and with no interaction by sex. Likely explanations for the differences in our findings compared with prior studies are (1) use of a more contemporary data set, (2) adjustment for a larger number of nontraditional risk factors, and (3) inclusion of only patients with first AMI. Of note, the COVID-19 pandemic did occur during our study period but with continued increase or unchanged in-hospital mortality with first STEMI and first NSTEMI, respectively, despite adjustment for year-over-year differences. Therefore, our findings raise further concern of possible delays in both atherosclerotic cardiovascular disease risk recognition and treatment in young adults.

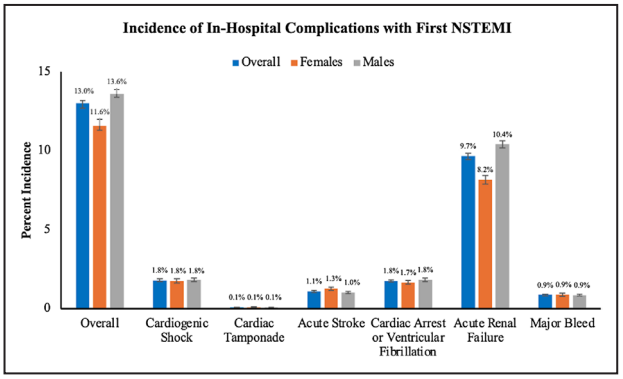

Figure 5. Overall and sex-specific rates of in-hospital complications with first NSTEMI.
P<0.001 for between-sex differences in individual in-hospital complications except cardiogenic shock (*P*=0.324), cardiac tamponade (*P*=0.789), and major bleed (*P*=0.763). NSTEMI indicates non–ST-segment–elevation myocardial infarction.

Sex Differences in Outcomes With First AMI Mortality

Although first STEMI mortality is increasing irrespective of sex, the significant increase observed in young men may be due to a disproportionate rise in contributory risk factors, and warrants further investigation given that no sex-based interaction in trends existed after adjustment of traditional and nontraditional risk in our study. However, compared with young men, young women had significantly higher overall rates of in-hospital mortality with first STEMI and first NSTEMI, in addition to higher odds of in-hospital mortality with first STEMI even after adjustment for traditional and nontraditional risk. Our findings demonstrate the persistence of higher AMI mortality in young women.[1,4,19] Furthermore, we observed distinct sex differences in traditional risk factor profile irrespective of AMI subtype that are in line with prior evidence, with young women having a higher prevalence of individual traditional risk factors.[8,20,21] Additionally, we also found that young women also have a higher prevalence of individual nontraditional risk factors as compared with young men, also irrespective of AMI subtype. However, we found that the association of traditional and nontraditional risk factors with in-hospital mortality did not differ between sexes. Sex-based disparities may therefore arise from deviations from guideline-directed therapies and delays in treatment initiation in young women, including the lower receipt of cardiovascular procedures our study and others have observed in young women.[1,4,8,20,21] Alternatively, as previously shown, delays in disease presentations in young women itself may also explain higher in-hospital mortality despite a lower receipt of cardiovascular procedures, but this could not be ascertained within the NIS.[22]

Additionally, we observed higher in-hospital mortality in young women in our study despite overall complication rates being similar in first STEMI and lower in first NSTEMI hospitalizations as compared with young men. However, young women had higher rates and adjusted odds of cardiogenic shock and major bleed in first STEMI, and acute stroke (irrespective of AMI subtype), in comparison with young men, who had higher rates and adjusted odds of acute renal failure (irrespective of AMI subtype). Further study is needed to understand causes for these differences.

Irrespective of sex, although traditional risk factors were overall more prevalent than nontraditional risk factors in young adults, more nontraditional risk factors (lowest income quartile, chronic kidney disease, and nontobacco drug use) were independently associated with higher in-hospital mortality in first AMI, particularly in STEMI. Interestingly, with the exception of diabetes and obesity, after the adjustment of both traditional and nontraditional risk, all traditional risk factors were

independently associated with lower in-hospital mortality in first AMI, irrespective of sex and AMI subtype. These findings do not suggest protective effects of traditional risk factors, but instead may either be the result of inequities in access to care, where those with documented risk factors have may have made increased health care interactions, or unrecognized intrinsic aspects of nontraditional risk factors that warrant further investigation.[23,24]

STUDY LIMITATIONS

This study has limitations. First, there is a possibility of misclassification due to miscoding or coding variability within the NIS. We used published crosswalks for *ICD-9* to *ICD-10* transitions for codes and validated definitions used to maintain consistency and comparability with prior published studies.[1,4,5,14–16] However, potential underreporting or misclassification of risk factors is possible with *ICD* code-based ascertainment, and with the absence of prehospital care data in the NIS, could lead to inaccurate or underestimated risk factor estimates (particularly among those with early death [eg, associated cardiac arrest]). Second, we lacked clinical data such as biomarkers, complete cardiac catheterization data (to differentiate between obstructive and nonobstructive MI), or in-hospital clinical care metrics (eg, door-to-balloon time) within the NIS, which would have all enabled better risk adjustment than administrative claims data alone. Third, although small, hospitalizations with missing data (7% of eligible sample) were excluded and could have introduced unmeasured bias in estimates reported. Finally, because data from prehospital care to further adjudicate first MI cases are not available within the NIS, misclassification of recurrent events as first MI events is possible. However, we did account for the omission of hospitalizations with a transferred-in status by performing a sensitivity analysis and did not identify a difference in outcomes or receipt of cardiovascular treatment as compared with the overall pooled cohort (Table S5).

CONCLUSIONS

In this large contemporary analysis of nearly 1 million AMI hospitalizations in young adults, we found that in-hospital mortality with first STEMI is rising and is unchanged with first NSTEMI. Young women had higher in-hospital mortality with first AMI and received fewer cardiovascular procedures as compared with young men. Although traditional risk factors were common, more nontraditional risk factors were independently associated with higher in-hospital mortality with first AMI irrespective of sex. Our findings suggest a need for further investigation into increasing first STEMI mortality in young adults, focusing on examining prevalent sex-based disparities and the impact of nontraditional risk factors.

ARTICLE INFORMATION

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None.

Supplemental Material

Tables S1–S5

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