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Higher burden of cardiometabolic and socioeconomic risk factors in women with type 2 diabetes: an analysis of the Glycemic Reduction Approaches in Diabetes (GRADE) baseline cohort

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ABSTRACT

Introduction Type 2 diabetes mellitus (T2DM) is a powerful risk factor for cardiovascular disease (CVD), conferring a greater relative risk in women than men. We sought to examine sex differences in cardiometabolic risk factors and management in the contemporary cohort represented by the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE).

Research design and methods GRADE enrolled 5047 participants (1837 women, 3210 men) with T2DM on metformin monotherapy at baseline. The current report is a cross-sectional analysis of baseline data collected July 2013 to August 2017.

Results Compared with men, women had a higher mean body mass index (BMI), greater prevalence of severe obesity (BMI≥40 kg/m^2), higher mean LDL cholesterol, greater prevalence of low HDL cholesterol, and were less likely to receive statin treatment and achieve target LDL, with a generally greater prevalence of these risk factors in younger women. Women with hypertension were equally likely to achieve blood pressure targets as men; however, women were less likely to receive ACE inhibitors or angiotensin receptor blockers. Women were more likely to be divorced, separated or widowed, and had fewer years of education and lower incomes.

Conclusions This contemporary cohort demonstrates that women with T2DM continue to have a greater burden of cardiometabolic and socioeconomic risk factors than men, particularly younger women. Attention to these persisting disparities is needed to reduce the burden of CVD in women.

Trial registration number ClinicalTrials.gov (NCT01794143)

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Decades of research have shown that women with type 2 diabetes mellitus (T2DM) are less likely to receive evidence-based care for cardiometabolic risk factor management

WHAT THIS STUDY ADDS

⇒ In this contemporary cohort, disparities persist in the evidence-based management of traditional cardiovascular risk factor of dyslipidemia, and substantial differences in non-traditional adverse socioeconomic factors are evident, which may be more relevant for addressing cardiac risk in this population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ There is a need to optimize care strategies to reduce the heightened risk factor burden and treatment gaps for women with T2DM.

INTRODUCTION

Cardiovascular disease (CVD) is the primary cause of mortality among women, and women with type 2 diabetes mellitus (T2DM) have a threefold higher relative risk for cardiovascular (CV) death than women without diabetes, even after controlling for traditional cardiac risk factors including blood pressure (BP), cholesterol, body mass index (BMI) and smoking.[1–3] In comparison, diabetes doubles the CV mortality risk among men.[1]

The higher relative risk of CVD for women with diabetes has been attributed to multiple factors, including a higher baseline burden of traditional cardiometabolic risk factors (eg, hypertension, obesity, diabetes), novel risk factors (eg, inflammation, prothrombotic phenotype), non-traditional risk factors (eg, depression, lower socioeconomic status (SES)),[4–10] and less aggressive management of traditional cardiac risk factors for primary prevention.[11–14] Factors that contribute to worse outcomes compared with men include sex differences in cardiac symptom

presentation,[15 16] lower use of cardiac procedures and evidence-based treatment for secondary prevention,[17–22] and more postprocedural complications.[23–25]

The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) is a prospective, randomized controlled trial comparing four glucose-lowering medications on metabolic and patient-centered outcomes in adults with T2DM.[26] Unlike earlier studies which examined diabetes as a simple binary variable (yes/no) without accounting for duration of disease, degree of glycemic control, or specific glucose-lowering treatment, GRADE offers a unique opportunity to examine sex differences in a large contemporary group of individuals with an early clinical stage of T2DM who have undergone detailed clinical and metabolic phenotyping at baseline.

Our aim was to examine sex differences in baseline traditional and socioeconomic risk factors within this cohort, and to determine whether there were sex differences in the provision of evidence-based treatment for prevention of CV complications. Identified differences in this representative population may provide meaningful insight on current gaps that contribute to persistent disparities in CVD burden for women with T2DM.

RESEARCH DESIGN AND METHODS

Study design, setting, and participants

The design of the GRADE Study has been previously described (GRADE protocol).[26] In brief, GRADE is a parallel-group, randomized clinical trial that compares the effectiveness of four major classes of glucose-lowering medications in individuals with T2DM treated with metformin on glycemic, metabolic, and patient-centered outcomes. Participants provided written informed consent.

Recruitment occurred between 2013 and 2017 and follow-up continued through spring 2021. The present analysis is restricted to data collected during the screening/baseline period of the GRADE Study. The study was conducted at 36 funded clinical centers, including nine additional subsites, across the USA. Sites included academic hospitals, integrated health systems, and Veterans Affairs (VA) medical centers.

Eligibility criteria included individuals with a history of T2DM for <10 years in duration and ≥30 years of age at diagnosis (≥20 years of age at diagnosis for Native Americans) who were treated with metformin, but no other glucose-lowering medications, and who had a glycated hemoglobin (HbA1c) level of 6.8%–8.5% (51–69 mmol/mol) at randomization, measured at a central laboratory, after metformin therapy was maximized to a dose of at least 1000 mg daily and up to 2000 mg daily, as tolerated, during the run-in period. Exclusion criteria included individuals with type 1 diabetes mellitus, chronic kidney disease with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, congestive heart failure (NY State Heart Association Functional Classification≥III), history of a major CV event (myocardial infarction (MI), stroke, or vascular procedure such as coronary artery or peripheral bypass grafting, stent placements (peripheral or coronary) or angioplasty) within the preceding year, new diagnosis or treatment for cancer within the prior 5 years, planned pregnancy in women of childbearing potential, planned major surgery, and history of pancreatitis.

Demographic and clinical variables were collected by self-report including age, race, ethnicity, sex, diabetes duration (years), smoking history, marital status, years of education, employment, and income. Physical measurements including height (m), weight (kg), waist circumference (cm), hip circumference (cm), and BP (mm Hg) were obtained by trained clinical research staff; per protocol, each physical measurement was taken in duplicate and averaged. BMI (kg/m^2) and waist-to-hip ratio were calculated based on these physical measurements. Concomitant medications known to affect glycemia or CV risk were collected by self-report for all participants with the exception of querying for the use of medications for depression and anxiety; this question was added after study initiation and collected at baseline for 2494 participants only.

Hypertension was considered present if it was reported by the participant, the participant reported taking an antihypertensive medication, measured systolic BP was ≥130 mm Hg, or measured diastolic BP was ≥80 mm Hg. Hyperlipidemia was present if it was reported by the participant, the participant reported taking a lipid-lowering medication, or measured low-density lipoprotein cholesterol (LDL-C) was ≥100 mg/dL. Sex-specific thresholds were used to define increased waist circumference, ≥88 cm for women and ≥102 cm for men (for Asian Americans, ≥80 cm for women and ≥90 cm for men). Sex-specific thresholds were also used to define abnormal high-density lipoprotein cholesterol (HDL-C) levels, specifically HDL-C<50 mg/dL for women and <40 mg/dL for men. Metabolic syndrome was defined by the presence of at least three of the following criteria: abdominal obesity, high triglycerides (≥150 mg/dL, or lipid-lowering medication), low HDL-C; <50 mg/dL for women, <40 mg/dL for men, or lipid-lowering medication), hypertension (systolic BP ≥130 mm Hg, diastolic BP ≥80 mm Hg, or antihypertensive medication), or high fasting glucose (≥100 mg/dL, or glycemia-lowering medication);[27] since metformin was a criterion for enrolment in GRADE, all participants met at least 1 of the metabolic syndrome criteria (ie, using glycemia-lowering medication).

Laboratory data were analyzed at the Advanced Research and Diagnostic Laboratory at the University of Minnesota, using standardized laboratory procedures, including HbA1c (standardized per National Glycohemoglobin Standardization Program protocol). LDL-C was calculated using the Friedewald equation if the triglyceride concentration was <400 mg/dL (LDL-C=TC [total cholesterol]– HDL-C – triglyceride/5.0).[28] HDL-C was measured using the Roche HDL-Cholesterol direct method (Roche Diagnostics, Indianapolis, Indiana, USA). Triglycerides were measured using Triglyceride GB (glycerol-blanked) reagent (Roche Diagnostics, Indianapolis, Indiana, USA).

Statistical analyses

Analyses were presented by sex (female/male). Descriptive statistics included means±SD and nominal *t* tests to explore differences between men and women for all continuous variables, and proportions and nominal Pearson's χ^2 tests to explore differences between men and women for all categorical variables.

The proportion of participants receiving clinically indicated treatment for hypertension (ie, BP medications among those with hypertension), hyperlipidemia (ie, statin treatment among those with hyperlipidemia) and those achieving target levels of LDL-C<100 mg/dL (<2.59 mmol/L) and BP <140/90 mm Hg and <130/80 mm Hg were presented by sex. Differences between men and women for each of these variables were tested using Pearson's χ^2 tests, and a Holm adjustment was applied to the p values from these tests to control the type I error rate in this set of analyses.

Exploratory analyses were conducted to assess whether sex differences in cardiometabolic risk factors differed by sociodemographic factors, such as age (<45 years, 45–54 years, 55–64 years, 65+years), income (<US$10 000, US$10 000 to <US$50 000, US$50 000 to <US$75 000, ≥US$75 000), education (<high school, high school graduate/GED, some college, college graduate or more), race (white, black or African-American, other or more than one race), and ethnicity (Hispanic, non-Hispanic). Means or proportions for each cardiometabolic risk factor were calculated for men and women within each category of the sociodemographic factor. Exploratory analyses to assess sex differences in the cardiometabolic factor as a function of the sociodemographic factor and the interaction with sex were conducted using the following described procedures. Linear (for continuous risk factors) or logistic (for binary risk factors) regression models were fit for each risk factor with covariates for sex, the sociodemographic factor, and the interaction term. A nominal joint Wald test of the interaction term was then conducted to explore whether sex differences in that risk factor varied by that sociodemographic factor (ie, to test for homogeneity of sex differences in the cardiometabolic risk factor across the sociodemographic factor).

Medical centers affiliated with VA accounted for 10 of the 45 total sites across the 36 funded clinical centers in GRADE. Since the patient population within VA Medical Centers was expected to differ from a more general patient population,[29] a sensitivity analysis was conducted that repeated the previous analyses stratified by whether participants were enrolled at a VA study site, allowing for comparison of sex differences in sociodemographic factors and cardiometabolic risk factors between VA study sites and non-VA study sites.

RESULTS

A total of 5047 individuals with T2DM participated in the GRADE Study, including 1837 women and 3210 men, ranging in age from 22 years to 85 years. The average ages for women and men were 55.4 years and 58.2 years, respectively. The percentage of participants age 65 years or older was almost twice as high in men as in women (men 28.8% vs women 15.6%). Compared with men, women in this cohort were more likely to self-report as black, Native American, or Hispanic. The average duration of diabetes was approximately 4 years for both sexes (table 1).

Sex differences in cardiometabolic risk factors

At baseline, the average HbA1c for both women and men was 7.5% (58.3 mmol/mol). Compared with men, women had higher BMI across all demographic and socioeconomic groups (table 1; online supplemental table 1), and more women met criteria for class III obesity (BMI≥40 kg/m^2, women 23.6% vs men 14.5%). Women were more likely to meet sex-specific criteria for increased waist circumference than men (women 92.9% vs men 79%; table 1). Overall, women had lower systolic BP and diastolic BP, but the absolute differences were small (table 1). The overwhelming majority of all study participants (>90%) met criteria for metabolic syndrome.

Lipid levels varied by sex and race. Women had higher mean LDL-C levels than men (table 1). The sex differences in LDL-C levels were greater for white participants (white men 75.6 mg/dL (1.96 mmol/L) vs white women 84.5 mg/dL (2.19 mmol/L)); however, black participants had higher LDL-C levels overall (black men 91.3 mg/dL (2.36 mmol/L) vs black women 94.9 mg/dL (2.46 mmol/L)) (online supplemental table 2). Women consistently had a greater prevalence of low HDL-C than men across all demographic and socioeconomic groups, based on sex-specific criteria. Sex differences in low HDL-C levels varied across racial groups; black participants had a lower prevalence of low HDL-C (men 32.8% vs women 50.8%) than white participants (men 51.4% vs women 69%) (online supplemental tables 3 and 4). Men, on the other hand, had consistently higher triglyceride levels than women.

Sex differences in evidence-based therapies and treatment targets

Women with dyslipidemia were less likely to receive statin treatment than men overall (table 2). Stratified analyses showed that women treated with a statin had higher LDL-C levels and were less likely to achieve target LDL-C<100 mg/dL (<2.59 mmol/L) than men across demographic and socioeconomic groups (figure 1; online supplemental tables 2 and 5). Overall, younger women, black and Hispanic women, and women with lower education and income had higher LDL-C levels and lower prevalence of LDL-C<100 mg/dL (<2.59 mmol/L) while being treated with statin therapy (online supplemental table 2).

In contrast, there were no sex differences in the percentage of individuals with hypertension receiving BP-lowering medications and achieving BP targets; however, women with hypertension were less likely to receive angiotensin converting enzyme inhibitors (ACE

Table 1 Baseline characteristics by sex

	Overall (n=5047)	Men (n=3210)	Women (n=1837)	P value
Age at baseline visit (years)	57.2±10.0	58.2±10.1	55.4±9.6	<0.001
Categorized age				<0.001
Age <45 years	623 (12.3%)	346 (10.8%)	277 (15.1%)	
Age 45–54 years	1436 (28.5%)	856 (26.7%)	580 (31.6%)	
Age 55–64 years	1778 (35.2%)	1085 (33.8%)	693 (37.7%)	
Age ≥65 years	1210 (24.0%)	923 (28.8%)	287 (15.6%)	
Diabetes duration (years), mean	4.0±2.8	4.1±2.8	4.0±2.8	0.258
Demographics				
Race				<0.001
American Indian/Alaska Native	137 (2.7%)	56 (1.7%)	81 (4.4%)	
Asian	182 (3.6%)	140 (4.4%)	42 (2.3%)	
Hawaiian/Pacific Islander	28 (0.6%)	20 (0.6%)	8 (0.4%)	
Black or African-American	1000 (19.8%)	491 (15.3%)	509 (27.7%)	
White	3314 (65.7%)	2288 (71.3%)	1026 (55.9%)	
Other/multiple	319 (6.3%)	175 (5.5%)	144 (7.8%)	
Unknown/not reported	67 (1.3%)	40 (1.2%)	27 (1.5%)	
Ethnicity				<0.001
Hispanic/Latino	929 (18.4%)	502 (15.6%)	427 (23.2%)	
Not Hispanic/Latino	4077 (80.8%)	2685 (83.6%)	1392 (75.8%)	
Unknown	41 (0.8%)	23 (0.7%)	18 (1.0%)	
Marital status				<0.001
Married	2918 (57.8%)	2061 (64.2%)	857 (46.7%)	
Living with partner	288 (5.7%)	179 (5.6%)	109 (5.9%)	
Divorced/separated/widowed	1233 (24.4%)	631 (19.7%)	602 (32.8%)	
Single	606 (12.0%)	339 (10.6%)	267 (14.6%)	
Years of education				<0.001
Some high school	364 (7.2%)	174 (5.4%)	190 (10.3%)	
High school graduate/GED	1039 (20.6%)	632 (19.7%)	407 (22.2%)	
Some college	1463 (29.0%)	951 (29.6%)	512 (27.9%)	
College graduate or more	2180 (43.2%)	1453 (45.3%)	727 (39.6%)	
Employment				<0.001
Employed full-time or part-time, or seasonally	3004 (59.6%)	1875 (58.4%)	1129 (61.5%)	
Retired	1203 (23.9%)	902 (28.1%)	301 (16.4%)	
Full-time homemaker	152 (3.0%)	7 (0.2%)	145 (7.9%)	
Not employed	380 (7.5%)	229 (7.1%)	151 (8.2%)	
Never worked or disabled	145 (2.9%)	97 (3.0%)	48 (2.6%)	
Student or other	160 (3.2%)	98 (3.1%)	62 (3.4%)	
Income				<0.001
<US$10 000	296 (5.9%)	146 (4.5%)	150 (8.2%)	
US$10 000 to <US$50 000	1942 (38.5%)	1162 (36.2%)	780 (42.5%)	
US$50 000 to <US$75 000	788 (15.6%)	529 (16.5%)	259 (14.1%)	
US$75 000+	1401 (27.8%)	1009 (31.4%)	392 (21.3%)	
Refused	620 (12.3%)	364 (11.3%)	256 (13.9%)	
Current smoking	695 (13.8%)	514 (16.0%)	181 (9.9%)	<0.001
Medications				
Depression/anxiety medications	472* (18.9%)	283 (17.1%)	189 (22.5%)	0.001

Continued

Table 1 Continued

	Overall (n=5047)	Men (n=3210)	Women (n=1837)	P value
Exogenous estrogen and/or progesterone	156 (8.5%)	0	156 (8.5%)	n/a
Exogenous androgens	84 (2.6%)	84 (2.6%)	0	n/a
Anthropometrics				
Weight (kg)	100.0±22.3	104.0±21.7	92.9±21.6	<0.001
BMI (kg/m^2)	34.3±6.8	33.7±6.3	35.4±7.5	<0.001
BMI categories				<0.001
Underweight/normal weight (<25 kg/m^2)	233 (4.6%)	148 (4.6%)	85 (4.6%)	
Overweight (25 to <30 kg/m^2)	1213 (24.1%)	837 (26.1%)	376 (20.5%)	
Class I obesity (30 kg/m^2 to <35 kg/m^2)	1603 (31.8%)	1086 (33.9%)	517 (28.2%)	
Class II obesity (35 kg/m^2 to <40 kg/m^2)	1093 (21.7%)	668 (20.9%)	425 (23.1%)	
Class III obesity (≥40 kg/m^2)	896 (17.8%)	463 (14.5%)	433 (23.6%)	
Waist circumference (cm)	112.3±15.8	114.1±15.6	109.3±15.6	<0.001
Waist circumference >sex and race-specific threshold†	4244 (84%)	2538 (79%)	1706 (92.9%)	<0.001
Systolic BP (mm Hg)	128.3±14.7	129.0±14.6	127.3±14.9	<0.001
Diastolic BP (mm Hg)	77.3±9.9	77.8±9.8	76.5±9.9	<0.001
Laboratory tests				
HbA1c (%) (mmol/mol)	7.5±0.5 58.3 (5.3)	7.5±0.5 58.4 (5.2)	7.5±0.5 58.3 (5.3)	0.678
HbA1c ≤7% (≤53 mmol/mol)	1101 (21.8%)	696 (21.7%)	405 (22.0%)	0.790
Total cholesterol (mg/dL) (mmol/L)	163.8±37.8 4.24±0.98	158.7±37.2 4.10±0.96	172.7±37.1 4.47±0.96	<0.001
Triglycerides (mg/dL) (mmol/L)	154.0±121.6 1.74±1.37	160.9±134.1 1.82±1.51	142.0±94.7 1.60±1.07	<0.001
HDL-cholesterol (mg/dL) (mmol/L)	43.4±10.6 1.12±0.27	41.0±9.3 1.06±0.24	47.7±11.3 1.23±0.29	<0.001
HDL-cholesterol ≤sex-specific threshold‡	2686 (53%)	1510 (47%)	1175 (64%)	<0.001
LDL-cholesterol (mg/dL) (mmol/L)	90.5±31.7 2.34±0.82	86.8±30.9 2.25±0.80	96.9±32.1 2.51±0.83	<0.001
LDL-cholesterol<100 mg/dL (<2.59 mmol/L)	3152 (65.0%)	2118 (69.2%)	1034 (57.7%)	<0.001
Fasting glucose (mg/dL) (mmol/L)	151.5±30.9 8.42±1.72	153.3±30.8 8.52±1.71	148.3±30.9 8.24±1.72	<0.001

All variables presented as means (SD) except as noted otherwise. Nominal p values are presented from exploratory comparisons of sex differences, and so should not be interpreted as testing hypotheses.
*This question was added after study start and was answered by 2494 participants at baseline.
†Waist circumference <88 cm for women, <102 cm for men (for Asian Americans, <80 cm for women, <90 cm for men).
‡HDL ≥50 mg/dL for women, ≥40 mg/dL for men.
BMI, body mass index; BP, blood pressure; GED, Graduate Equivalency Degree; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

inhibitors) or angiotensin receptor blockers (ARBs) (women 57.4% vs men 62.7%, p=0.003; table 2).

Age analysis of cardiometabolic risk factors and evidence-based treatment

Younger women had higher mean BMI (figure 2) and there was a trend for greater sex differences in mean BMI in the younger age group. Likewise, younger women had the highest prevalence of low HDL-C levels and the sex difference in low HDL-C was most evident in the younger population (figure 2; online supplemental table 3).

Younger women treated with statins had modestly higher LDL-C levels and lower levels of achieving LDL-C<100 mg/dL (figure 1).

Socioeconomic factors

Compared with men, women in this cohort were more likely to be divorced, separated or widowed. Overall, women had fewer years of formal education and had lower incomes; the majority of women reported incomes below the median for the US population at that time (table 1). Women were more likely to take antidepressant and anxiolytic medications than men (table 1).

Sensitivity analysis by VA site

Sensitivity analyses did not indicate that the observed sex differences were due to differences in the cohort enrolled at VA study sites compared with non-VA study sites.

Table 2 Sex differences in treatment targets and evidence-based therapies at baseline

	Overall (n=5047)	Men (n=3210)	Women (n=1837)	P value
Lipid management				
Statin treatment (%) among those with elevated blood lipids	3210 (66.4%)	2181 (70.7%)	1029 (58.8%)	<0.001
LDL<100 mg/dL (%) in entire cohort	3152 (65%)	2118 (69.2%)	1034 (57.7%)	<0.001
Hypertension management				
BP medications (%) among those with hypertension	3495 (72.4%)	2263 (73.1%)	1232 (71.2%)	0.454
BP<140/90 (%)	3800 (75.3%)	2401 (74.8%)	1399 (76.2%)	0.58
BP<130/80 (%)	2170 (43%)	1347 (42%)	823 (44.8%)	0.211
ACE inhibitor or ARB for those with hypertension (%)	2933 (60.8%)	1939 (62.7%)	994 (57.4%)	0.003

A Holm adjustment was applied to all p values presented in this table to control the type I error rate in this set of analyses.
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure.

DISCUSSION

Compared with men with similar glycemic control and duration of diabetes, women with T2DM in the GRADE study were younger, and yet had a greater burden of traditional cardiometabolic risk factors (greater prevalence and severity of obesity, higher LDL-C and lower HDL-C), were less likely to receive evidenced-based treatment for dyslipidemia, and had a higher prevalence of adverse socioeconomic factors, all of which may ultimately contribute to greater burden of CV disease in women. Overall, the magnitude and severity of these risk factors appears to be more pronounced among younger women with T2DM. Unlike prior studies, women and men were equally likely to achieve target BP goals, although women with hypertension in the GRADE cohort were less likely to receive ACE inhibitors or ARB medications.

GRADE enrolled individuals under protocol-specified conditions of glycemic control, diabetes duration, and metformin monotherapy. Consequently, this cohort allows for a detailed assessment of sex differences in cardiometabolic risk factors across a wide age range without the confounding factors of variable levels of glycemic control and diabetes duration, and the metabolic impact of different pharmacologic agents, as seen in earlier studies. The sex-stratified and age-stratified data highlight the disproportionate cardiometabolic risk factor burden among women with T2DM, especially younger women. Despite a decade or more difference in age, younger women, compared with older women and men, had a higher BMI, higher prevalence of increased waist circumference and low HDL-C, and were less likely to achieve target LDL-C levels despite statin treatment. Although CVD is generally thought to be a disease of older individuals, the disproportionate cardiometabolic burden among younger women with T2DM may contribute to a higher relative risk for premature macrovascular disease. This was demonstrated in a recent analysis of the Women's Health Study which showed that diabetes is a powerful predictor of premature coronary heart disease (CHD) in women younger than 55 years

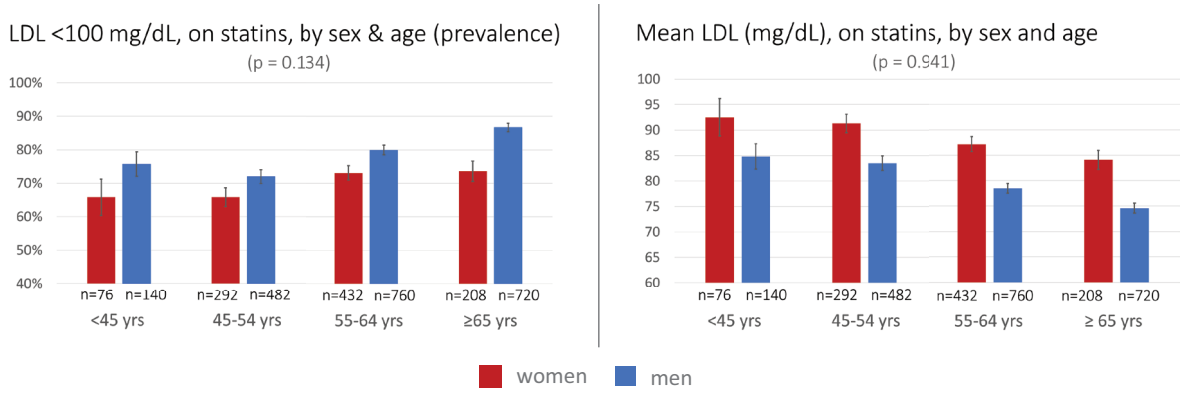

Figure 1 LDL-C<100 mg/dL and mean LDL-C among statin users by sex and age at baseline in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) cohort. Red bars=women; blue bars=men. Error bars reflect the SE of means and proportions. The nominal p value for the interaction term between sex and age is provided to explore whether sex differences vary by age group, and so should not be interpreted as testing a hypothesis.

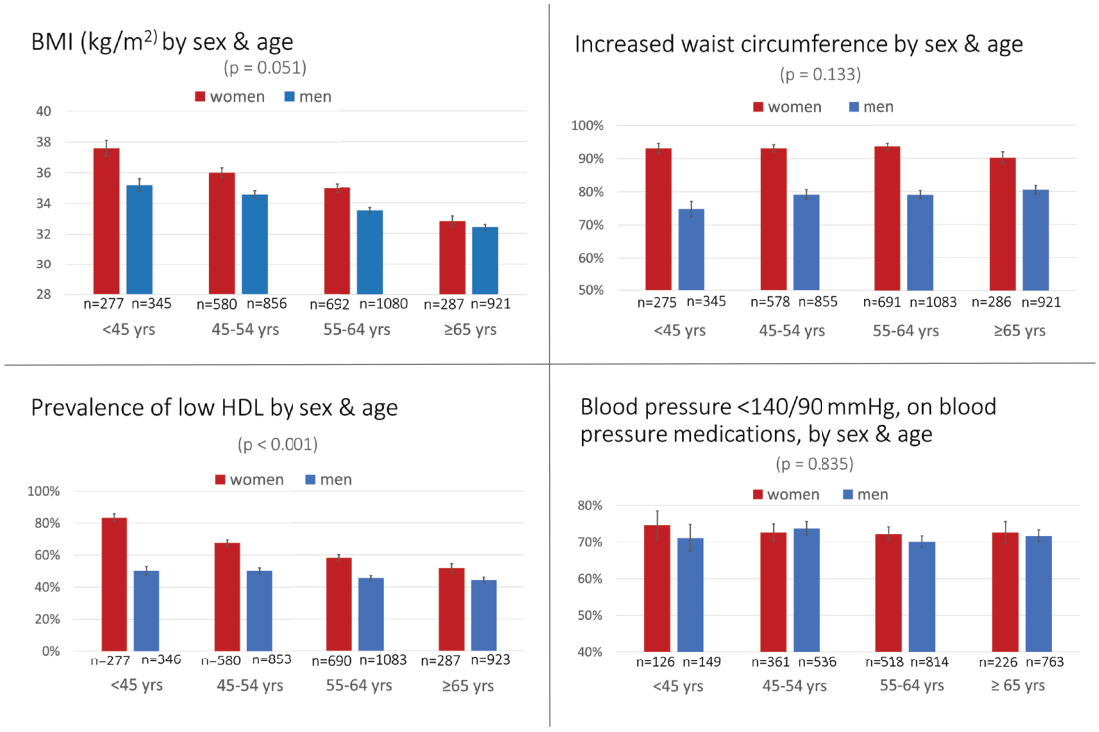

Figure 2 Baseline cardiometabolic risk factors by sex and age in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) cohort. Red bars=women; blue bars=men. Error bars reflect the SE of means and proportions. The nominal p value for the interaction term between sex and age is provided to explore whether sex differences vary by age group, and so should not be interpreted as testing hypotheses. BMI, body mass index.

(>10-fold higher adjusted relative risk),[30] and postacute MI studies that have shown higher mortality rates among younger women <50 years relative to men of comparable age.[31 32] A worldwide meta-analysis demonstrated that the relative risk for CV mortality is highest among younger women with diabetes after adjustment for traditional cardiometabolic risk factors.[1]

These results also demonstrate contemporary persistence of earlier reports of a high burden of cardiometabolic risk factors among women with T2DM and a lower likelihood of receiving evidence-based treatment for dyslipidemia.[11 13 33] Even among women in GRADE treated with statins, LDL-C levels remained higher than men of comparable age. Younger women, black and Hispanic women, and women from lower SES groups (lower income and lower education) had higher LDL-C levels while on statin therapy. The reasons women are less likely to achieve target lipid control are complex and multifactorial, including being less likely than men to be offered statins by healthcare providers and less likely to believe that statins are safe and effective.[13] Preferences for pharmacologic treatment and adherence to interventions differ by sex.[34] Women are more likely to decline statin treatment, be treated with less potent statins, have non-adherence due to cost, and to report discontinuing their statin because of a side effect.[13] Although the US Food and Drug Administration (FDA) recently recommended removal of labeling of statins as contraindicated in pregnancy, they still recommend against taking statins during pregnancy and breast feeding which impacts prescribing for women of childbearing potential.[35]

Our data expand on findings from earlier studies of sex differences in cardiometabolic risk factors in several areas. Prior studies have shown that women with T2DM were less likely to receive evidence-based hypertension treatment compared with men.[12 36] In contrast, women with hypertension in GRADE were as likely as men to receive antihypertensive medications and to achieve target BP goals. However, women with hypertension were less likely to receive ACE inhibitor or ARBs. While the reason for this finding in GRADE is unknown, earlier studies reported that women are more likely to experience side effects such as cough with ACE inhibitors and more likely to discontinue treatment.[37] The lower use of ACE inhibitors or ARBs in women has also been attributed to teratogenic risks of these agents in women of reproductive age.

In addition to traditional cardiometabolic risk factors, we identified sex differences in several adverse socioeconomic factors in GRADE. Women in GRADE were younger, had lower household income, lower levels of education, and were more likely to be single or divorced, separated or widowed than men. Several SES measures have been shown to have a strong inverse relationship with CHD including income, level of education, employment, and neighborhood socioeconomic factors,[38 39] and women are disproportionately represented among those living in poverty. In a recent study examining the

relationship of low SES and premature CHD, individuals aged 35–64 years with lower SES experienced double the incidence of MI and CHD-related deaths compared with individuals of higher SES, with less than half of the excess events attributable to traditional risk factors (eg, cigarette smoking, hypertension, dyslipidemia, high BMI).[40] Based on computer simulation, 60% of the excess risk for premature MI and CHD mortality was tied to SES, and women comprised the majority of individuals in the low SES cohort.

Depression is another non-traditional risk factor associated with an increased risk for CHD and stroke.[41–44] Women in GRADE were more likely to take antidepressants and anxiolytics than men across demographic and SES groups. A recent pooled analysis of prospective cohort studies showed that even mild depression (below the threshold for diagnosis of clinical depression) is associated with an increased incidence of CHD and stroke.[45]

Studies that examined both traditional and non-traditional risk factors in populations with CHD found similar sex differences in the pattern of cardiometabolic and psychosocial risk factors. In the Variation in Recovery: Role of Gender on Outcomes of Young AMI (acute myocardial infarction) Patients Study, women younger than 55 years had significantly higher rates of cardiometabolic risk factors including diabetes (women 38.8% vs men 26.7%) and obesity (women 51% vs men 44.5%) than men. These younger women also had higher rates of depression and stress, poorer physical and mental health status, lower income, higher unemployment, and a lower quality of life. The authors concluded that young women with acute MI have a unique risk profile compared with men of comparable age, and that cardiometabolic factors and SES factors play a prominent role.[6 46] Taken together, these data suggest that women with T2DM, especially younger women, have a unique pattern of cardiometabolic and socioeconomic risk that may worsen lifetime CVD outcomes, and that adjustment for traditional cardiometabolic risk factors does not fully account for their higher risk.

The strengths of our study include detailed cardiometabolic data on a large sample size of individuals across a wide age range at a comparable early stage of diabetes duration, glycemic control, and glucose-lowering therapy. We accounted for sex-specific criteria for increased waist circumference and low HDL-C, which revealed relevant sex differences in these CV risk factors, unlike earlier studies which reported population means without adjustment. Limitations include the lack of data on the reproductive status of GRADE participants and reproductive risk factors for CVD including polycystic ovary syndrome or gestational diabetes. In addition, individuals who choose to volunteer in clinical trials may not be fully representative of the general population of those with T2DM, including the distribution and clinical characteristics of participants based on sex.

A large proportion of the GRADE cohort (n=1216, 24.1%) was enrolled at VA Medical Centers. Since the patient population at VA-affiliated study sites was more likely to be male and older age, sensitivity analyses were conducted stratifying results by whether participants were enrolled in a VA study site or not and by age. Sensitivity analyses, along with age stratification, showed that results were similar among those enrolled at VA study sites compared with those at non-VA study sites.

There are different approaches for the statistical analysis of descriptive data. The statistical approach used in this descriptive analysis included the Holm procedure to control the type I error rate for hypothesis testing of the main analyses (sex differences in BP and lipid management) and nominal p values for the exploratory analyses. For outcome-based analyses, measures of discriminatory accuracy (such as multilevel analysis of individual heterogeneity and discriminatory accuracy)[47 48] might be appropriate; however, there were no outcomes in this analysis, being descriptive and cross-sectional in nature.

CONCLUSIONS

In conclusion, despite decades of research documenting that women with T2DM were less likely to receive evidence-based care for cardiometabolic risk factor management than men, data from the contemporary GRADE cohort demonstrates that women, particularly younger women, with T2DM continue to have a greater burden of adverse cardiometabolic and socioeconomic risk factors than men. Disparities persist in the evidence-based management of traditional cardiac risk factor of dyslipidemia, and substantial differences in non-traditional adverse socioeconomic factors remain evident, which may be more relevant for addressing cardiac risk in this population. Collectively, these data indicate the need to optimize care strategies to reduce the heightened risk factor burden and treatment gaps for women with T2DM.

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Ethics approval This study involves human participants. GRADE is a multicenter RCT, approved by over 30 institutional review boards (institutional review board approval was obtained at each participating institution). We have indicated the primary review board submission information from the most recent annual renewal below: The George Washington University Office of Human Research - Institutional Review Board (IRB Number: 071245; Last Approved: 8/15/2022; Expires: 8/23/2023.) Participants gave informed consent to participate in the study before taking part.

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