Long-term Association of Depression Symptoms and Antidepressant Medication Use With Incident Cardiovascular Events in the Look AHEAD (Action for Health in Diabetes) Clinical Trial of Weight Loss in Type 2 Diabetes

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OBJECTIVE

To examine whether depression symptoms or antidepressant medication (ADM) use predicts the probability of cardiovascular events in overweight/obese individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Preplanned analyses of depression and incident cardiovascular disease (CVD) were performed in the Look AHEAD (Action for Health in Diabetes) weight loss trial after a median follow-up of 9.6 years. Depression symptoms, assessed with the Beck Depression Inventory (BDI), were analyzed both as a continuous and dichotomized variable (BDI score <10 or ≥10). ADM use was coded from participants' prescription medications. Four composite CVD outcomes were defined in the study protocol. Sex-stratified Cox proportional hazards models were adjusted for a range of baseline covariates.

RESULTS

Depression symptoms were only significantly associated with a composite secondary outcome comprising CVD death, nonfatal myocardial infarction, nonfatal stroke, hospitalized angina, congestive heart failure, peripheral vascular disease, coronary artery bypass graft, and carotid endarterectomy. Significant sex interactions were observed for BDI score and BDI score ≥10. BDI score was significantly associated with higher probability of this composite outcome in men but was not associated with the outcome in women. BDI score ≥10 was positively associated with this composite outcome in men but was negatively associated in women. Exploratory analysis identified a significant BDI ≥10 × ADM use interaction for this composite outcome that differed in men versus women. Men with both BDI score ≥10 and ADM use compared with those with neither had 60% higher probability of the outcome, whereas women with both compared with those with neither had 50% lower probability.

CONCLUSIONS

Sex differences in the association of depression symptoms and ADM use with incident CVD warrant further investigation.

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Substantial evidence indicates that depression is an independent predictor of cardiovascular disease (CVD) morbidity and mortality in both noncardiac and cardiac populations (1–3). Depression has been estimated to confer a relative risk between 1.5 and 2.5 for cardiac morbidity and mortality in patients with existing coronary artery disease (CAD) and a relative risk of 1.5–2.0 for CAD onset in noncardiac populations (2). Diabetes, which affected 30.2 million people ≥18 years of age, or 12.2% of the U.S. adult population, in 2015 (4) not only is a major risk factor for CVD (5) but also doubles the odds of depression (6). The estimated prevalence of comorbid depression in persons with diabetes is 20% in community samples and 32% in clinical samples (6), and there is evidence suggesting that diabetes and depression may have synergistic effects on some CVD outcomes (3).

The effect of antidepressant medication (ADM) use on CVD risk has not been clearly established and may vary depending on the type of ADM used. Cardiotoxic side effects have been reported for tricyclic antidepressants (TCAs) (7,8). Newer medications such as selective serotonin reuptake inhibitors (SSRIs) have anticoagulation properties and may improve cardiovascular (CV) morbidity and mortality in patients with established CAD (2,7,8). This potential benefit, however, has not been observed in all studies (9), and, among postmenopausal women free of CAD at baseline, SSRI use was associated with increased risk of hemorrhagic and fatal stroke (10).

The Look AHEAD (Action for Health in Diabetes) trial was a multicenter randomized controlled trial in overweight/obese adults with type 2 diabetes, 45–76 years of age, that was designed to compare the efficacy of an intensive lifestyle intervention to promote 5–10% weight loss through reduced caloric intake and increased physical activity with a diabetes support and education control group for preventing incident CVD morbidity and mortality (11,12). Depression symptoms and ADM use were assessed at multiple time points during the trial, and two articles have been published examining the association of depression symptoms and ADM use with CV risk factors both at study entry (13) and over the subsequent 4 years (14). These articles provided evidence that depression

symptoms and ADM use were independently and positively associated both cross-sectionally and prospectively with a range of CV risk factors in this large cohort of individuals with type 2 diabetes. The purpose of the present article is to report the results of a preplanned analysis to determine whether depression symptom scores treated as either a continuous measure or dichotomous measure indicating the presence or absence of mild or greater depression or ADM use predict the probability of CVD events over a median of 9.6 years of follow-up.

RESEARCH DESIGN AND METHODS

Study Design
Details of the design and methods of this multicenter randomized controlled clinical trial have been described elsewhere (15). As previously reported (12), the trial was stopped early (median duration of follow-up 9.6 years) based on a futility analysis that found no significant difference between treatment arms on the primary CVD outcome. The Look AHEAD trial is now continuing as a prospective observational cohort study.

Participants
Participants in the Look AHEAD trial (N = 5,145) were recruited from 16 clinical centers in the U.S. (11). Eligibility requirements included the following: age 45–76 years; self-reported type 2 diabetes verified by tested glucose levels, use of glucose-lowering medication, or physician's report; BMI ≥25 kg/m^2 (≥27 kg/m^2 if taking insulin); glycosylated hemoglobin (HbA$_{1c}$) ≤11% (97 mmol/mol); systolic blood pressure (SBP) <160 mmHg; diastolic blood pressure (DBP) <100 mmHg; triglycerides (TGs) <600 mg/dL; the ability to complete a valid maximal exercise test, suggesting it was safe to exercise; and an established relationship with a primary provider. Individuals with a current diagnosis of bipolar disorder or psychosis or who had been hospitalized for depression in the past 6 months were excluded.

The study was approved by the Institutional Review Board at each center, and all participants provided informed consent prior to study participation.

Depression Indicators
Depression symptoms were assessed at baseline, annually in years 1–4, and again

at year 8, using the Beck Depression Inventory-1A (BDI-1A), a self-report symptom scale with well-documented psychometric properties (i.e., validity, reliability, and sensitivity to change) across a broad spectrum of clinical and nonclinical populations (16,17). The BDI-1A assesses 21 symptoms, scored 0–3 in order of increasing symptom severity, generating a total scale score ranging from 0 to 63. The presence of elevated depression symptoms, indicating likely mild or greater depression, was defined by a BDI-1A score ≥10. The BDI-1A may also be scored using two subscales by separating the 14 items that assess primarily cognitive and affective components of depression (e.g., guilt and negative mood) from the 7 items that evaluate predominantly somatic components (e.g., sleep and appetite).

Participants brought all prescription medications to their annual clinic assessment visits and these medications (but not the dosages) were recorded by study staff. ADMs were identified using the U.S. Food and Drug Administration classification system. Distinct types of ADM were also identified in the following five categories: serotonin-norepinephrine-dopamine reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor, SSRI, serotonin modulator, and TCA.

Outcome Measures
The four composite CVD outcomes (one primary and three secondary) specified in the Look AHEAD protocol were examined. The primary CVD outcome was the first occurrence of a composite of death from CV causes, nonfatal myocardial infarction (MI), nonfatal stroke, and angina requiring hospitalization. There were three secondary CVD outcomes. Secondary outcome 1 differed from the primary outcome in that it excluded hospitalized angina. Secondary outcome 2 differed from the primary outcome in that it included any death rather than CVD death only. Secondary outcome 3 expanded the scope of secondary outcome 2 to include two additional CV conditions (i.e., congestive heart failure [CHF] and peripheral vascular disease) and two CV procedures (i.e., coronary artery bypass graft [CABG] and carotid endarterectomy). CV events were classified by an Events Adjudication Committee, blinded to treatment arm, that reviewed all pertinent

medical records and death certificates to confirm CVD events.

Statistical Analyses

Analyses included all randomized participants (N = 5,145) and were performed using SAS version 9.3 (SAS Institute, Cary, NC). All data were censored at 14 September 2012, the date that the intervention was stopped by the National Institutes of Health (NIH) on recommendation of the Data and Safety Monitoring Board. Median follow-up at that time was 9.6 years. Because patterns in the data suggested that there may be sex differences in the association of depression indicators with CVD outcomes, the preplanned analyses were performed in sex-specific strata. Sex differences in relevant baseline characteristics were examined using χ^2 tests for categorical variables and t tests for continuous variables. The association of depression indicators with CVD outcomes was examined using three sequential Cox proportional hazard models. Model 1 included clinic as a stratification variable and intervention assignment as a covariate. Model 2 added baseline age, race/ethnicity, history of CVD, BMI, and waist circumference (WC). Model 3 added additional baseline CV risk factors (i.e., HbA_{1c}, insulin use, SBP, DBP, antihypertensive medication use, LDL cholesterol, HDL cholesterol, total cholesterol, TG, lipid-lowering medication use, ankle-brachial index outside the normal range (<0.9, >1.3) except in secondary outcome 3, smoking, estimated maximal equivalents of task (METs) achieved on stress test, and hormone replacement therapy for women only. Time to event was defined as the time from randomization to first occurrence of the outcome of interest. An individual's contribution to the number of person-years of exposure was censored at first occurrence of an outcome event, loss to follow-up, or the closing date of 14 September 2012. Tests of the proportional hazard assumptions were performed and met the criteria. Hazard ratios (HRs) and 95% CIs for each depression indicator and CVD outcome were calculated using PROC PHREG. For these preplanned analyses, Bonferroni correction was used to adjust for multiple comparisons within sex groups and for sex × depression indicator interaction effects; thus, a two-sided P value of <0.004 (0.05 ÷ 12) was

considered to indicate statistical significance. Separate forest plots were constructed for each depression indicator to display the fully adjusted sex-specific results and the sex × depression interaction effect for each CVD outcome. Depression indicators were analyzed both as baseline predictors of incident CVD events and as time-varying covariates. Because results obtained using the two approaches were very similar, only the results using baseline values of the depression indicators are presented here.

RESULTS

Table 1 shows baseline characteristics of the sample by sex. There was no difference in the distribution of men and women in the study arms. The mean age of women, however, was 2 years less than that of men, and there were significant sex differences in the distribution of race/ethnicity, prior CVD, BMI, and WC. Among women, there was a greater proportion of race/ethnic minorities and higher mean BMI compared with men, while prior CVD was almost 2.5 times higher in men than that in women, and mean WC was higher in men as well. Men and women did not differ significantly on the proportion using insulin, HbA_{1c} level, or mean SBP. Men had a higher mean level of maximal METs achieved; however, sex differences in all remaining covariates were suggestive of a higher level of CVD risk among men. On the other hand, women had values on the three depression indicators suggestive of a worse depression profile. Mean BDI and subscale scores were higher, prevalence of BDI score ≥10 was 1.5 times higher, and ADM use was 1.6 times higher in women compared with men.

The total number of events included in the composite CVD outcomes and the frequency of component events are shown in Supplementary Table 1. Some participants experienced multiple events during the same admission; all are included in Supplementary Table 1, but only one contributed to the composite outcome (see footnote in Supplementary Table 1). Supplementary Tables 2–4 provide results for the sequential models stepping in covariates. Among women, none of the depression indicators were significantly associated with CVD outcomes, even in model 1. Among men,

BDI score in model 1 was significantly associated with all CVD outcomes except secondary outcome 1. After model 2 covariate adjustments, BDI score remained significantly associated with secondary outcomes 2 and 3, but not with the primary outcome. After model 3 covariate adjustment, BDI score continued to be significantly associated with secondary outcome 3, but the association with secondary outcome 2 became nonsignificant when either lipids/lipid-lowering medication or maximal METs achieved were added to model 2. The results of multivariable models adjusted for all baseline covariates and including a sex × depression interaction term are shown in Figs. 1–3. The only CVD outcome significantly associated with any depression indicator was secondary outcome 3, which included events (CHF, peripheral vascular disease, CABG, carotid endarterectomy) not in other CVD outcomes.

For BDI score (Fig. 1), there was a statistically significant sex × BDI interaction effect (P = 0.0015). BDI score was not significantly associated with secondary outcome 3 in women but was significantly associated with increased likelihood of this outcome in men. Each 1-point increment in baseline BDI score was associated with a 3% greater likelihood of the outcome occurring (HR 1.03; 95% CI 1.01–1.04). Analyses examining the association of the separate BDI cognitive-affective and somatic subscales with the composite CVD outcomes showed a similar pattern of sex differences as that observed with the full BDI scale (data not shown).

For a BDI score ≥10 (Fig. 2), there was also a statistically significant BDI score ≥10 × sex interaction effect for secondary outcome 3 (P = 0.0009), with the direction of the association opposite in the two sex groups. Men had a 26% greater likelihood of the outcome occurring (HR 1.26; 95% CI 1.01–1.57), whereas women had a 22% lower likelihood of the outcome occurring (HR 0.78; 95% CI 0.62–0.98). However, neither of these associations was statistically significant after Bonferroni correction.

For ADM use (Fig. 3), there was some suggestion of a sex difference in its association with secondary outcome 3. ADM use was associated with a 25% lower likelihood of the outcome in women (HR 0.75; 95% CI 0.59–0.96),

Table 1—Baseline characteristics of sample by sex

Variable	Men	Women	P value
Treatment assignment, N (%)			0.8197
DSE	1,038 (49.9)	1,537 (50.2)	
Lifestyle intervention	1,044 (50.1)	1,526 (49.8)	
Age (years)	59.93 (0.15)	57.91 (0.12)	<0.0001
Race/ethnicity, N (%)			<0.0001
African American/Black (not Hispanic)	189 (9.08)	615 (20.1)	
American Indian/Native American/Alaskan Native	55 (2.64)	203 (6.63)	
Asian/Pacific Islander	16 (0.77)	34 (1.11)	
White	1,584 (76.1)	1,668 (54.5)	
Hispanic	197 (9.46)	483 (15.8)	
Other/mixed	41 (1.97)	59 (1.93)	
Prior CVD, N (%)	439 (21.1)	275 (8.98)	<0.0001
BMI (kg/m^2)	35.18 (0.12)	36.46 (0.11)	<0.0001
WC (cm)	118.5 (0.29)	110.8 (0.24)	<0.0001
Insulin use, N (%)	389 (18.7)	5 90 (19.3)	0.6040
HbA$_{1c}$ (% [mmol/mol])	7.26 [56] (0.03)	7.29 [56] (0.02)	0.4383
Antihypertensive use, N (%)	1,588 (76.3)	2,253 (73.6)	0.0292
SBP (mmHg)	128.5 (0.36)	129.0 (0.32)	0.2573
DBP (mmHg)	73.21 (0.20)	68.05 (0.17)	<0.0001
Lipid-lowering medication use, N (%)	1,238 (59.5)	1,384 (45.2)	<0.0001
LDL (mg/dL)	107.0 (0.68)	115.9 (0.60)	<0.0001
HDL (mg/dL)	38.04 (0.20)	47.20 (0.22)	<0.0001
Total cholesterol (mg/dL)	182.1 (0.80)	197.1 (0.69)	<0.0001
TGs (mg/dL)	191.5 (2.75)	175.0 (2.00)	<0.0001
ABI outside normal range (<0.9 or >1.3), N (%)	391 (18.8)	272 (8.88)	<0.0001
Smoking, N (%)			<0.0001
Never	782 (37.7)	1,795 (58.7)	
Former	1,198 (57.7)	1,132 (37.0)	
Current	95 (4.58)	132 (4.32)	
Maximal METs achieved	7.95 (0.05)	6.67 (0.03)	<0.0001
HRT use, N (%)	NA	501 (16.4)	<0.0001
BDI	4.87 (0.10)	6.21 (0.09)	<0.0001
Cognitive-affective subscale	1.98 (2.79	2.53 (3.08)	<0.0001
Somatic subscale	2.89 (2.37)	3.67 (2.74)	<0.0001
BDI ≥10, N (%)	283 (13.6)	649 (21.3)	<0.0001
ADM use, N (%)	253 (12.6)	595 (20.1)	<0.0001
Type of ADM used, N (%)			0.4214
SSRI	149 (55.6)	378 (57.8)	
TCA	52 (19.4)	124 (19.0)	
SNDRI	34 (12.7)	57 (8.7)	
SNRI	17 (6.3)	49 (7.5)	
SerMod	16 (6.0)	46 (7.0)	

Data are mean (SE) unless otherwise indicated. ABI, ankle-brachial index; DSE, diabetes support and education; HRT, hormone replacement therapy; NA, not applicable; SerMod, serotonin modulator; SNDRI, serotonin-norepinephrine-dopamine reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor. Among AMD users, 1.34% of men and 4.07% of women were taking two types of ADM; 0.44% of men and 0.49% of women were taking three types of ADM.

but was not associated with the outcome in men (HR 1.07; 95% CI 0.85–1.36). Neither the association in women, however, nor the ADM use × sex interaction was statistically significant after Bonferroni correction.

Two exploratory analyses were performed to gain further insights into the results of these preplanned analyses: 1) an analysis to examine whether there was a BDI ≥10 × ADM use interaction in men and women for secondary outcome 3, and 2) whether specific component events were driving the finding that depression indicators were associated only with composite secondary outcome 3. Bonferroni correction was not applied for these exploratory analyses.

For the first analysis, the following four indicator variables were created: BDI <10 + no ADM use, BDI <10 + ADM use, BDI ≥10 + no ADM use, and BDI ≥10 + ADM use. BDI <10 + no ADM use was used as the reference category. In women, BDI ≥10 + ADM use was significantly associated with a 50% decreased likelihood of secondary outcome 3 occurring (HR 0.50; 95% CI 0.32–0.78; P = 0.0020), whereas in men it was significantly associated with a 60% increased likelihood of this outcome occurring (HR 1.60; 95% CI 1.12–2.28;
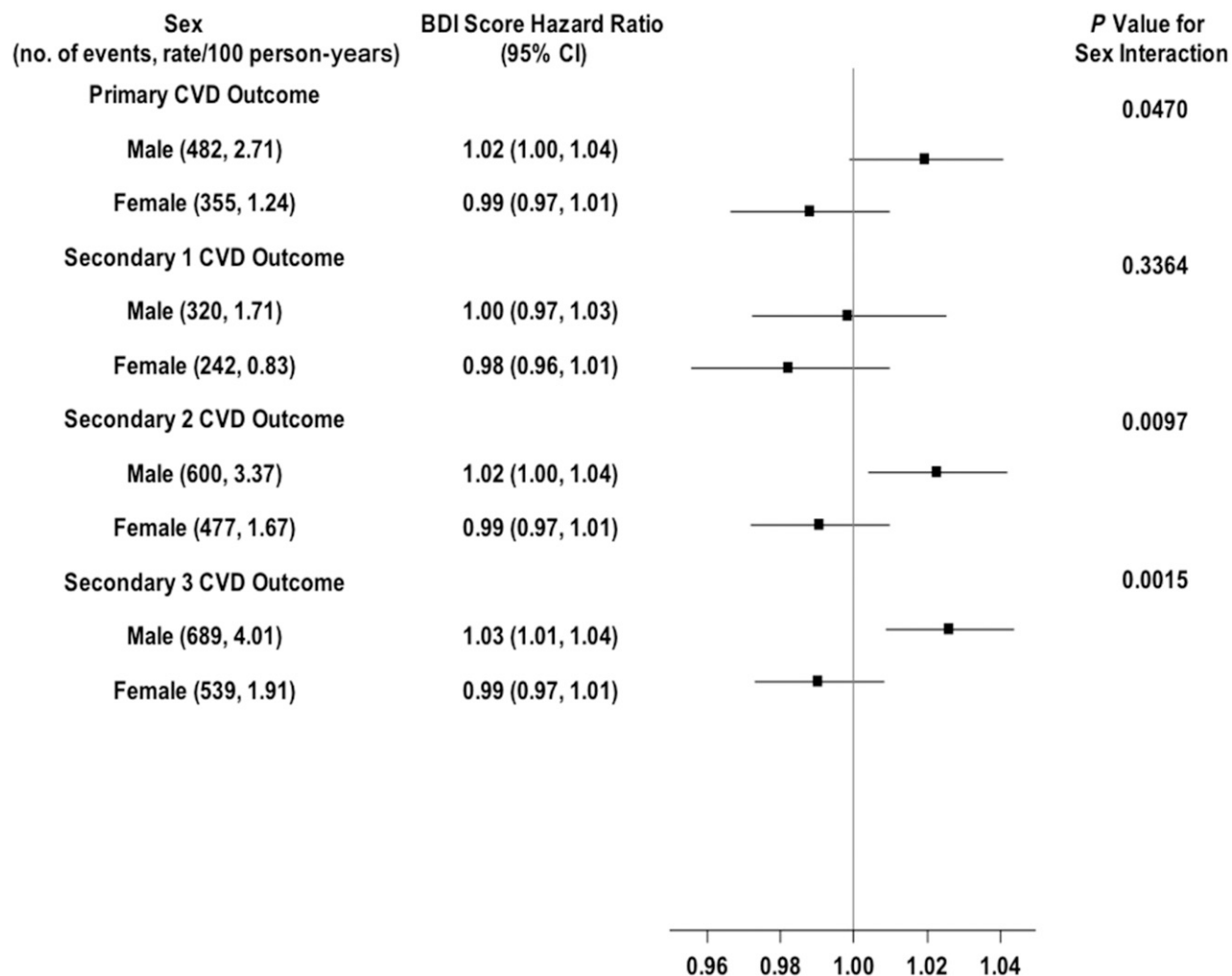
Figure 1—Shown are the number of CVD events and the rate per 100 person-years, the HRs (95% CIs) for a 1-point increment in BDI continuous score for the primary and secondary CVD outcomes in men and women, and the *P* value for the sex × BDI score interaction effect. The solid vertical line indicates an HR of 1.00 (i.e., no effect).

P = 0.0099). The BDI score ≥10 × ADM use interaction effect was statistically significant in men (*P* = 0.04) and trended toward significance in women (*P* = 0.07).

For the second exploratory analysis, there was a sufficient number of events for any death, nonfatal MI, hospitalized angina, CABG, and CHF (Supplementary Table 1) to examine associations with the depression indicators separately in men and women. In men, BDI score was associated with increased likelihood of hospitalized angina (HR 1.03; 95% CI 1.00–1.06; *P* = 0.0483), BDI ≥10 was associated with none of these events, and ADM use was significantly associated with decreased likelihood of nonfatal MI (HR 0.47; 95% CI 0.27–0.82; *P* = 0.0077). In women, BDI score and BDI score ≥10

were associated with none of these events, whereas ADM use was significantly associated with decreased likelihood of both hospitalized angina (HR 0.52; 95% CI 0.32–0.86; *P* = 0.0114) and CABG (HR 0.60; 95% CI 0.39–0.93; *P* = 0.0211).

CONCLUSIONS

In the current study, we performed sex-stratified analyses of the association of three depression indicators with incident CVD outcomes because patterns in the data suggested that this association might differ between men and women. The results of multivariable analyses, adjusting for trial design and a wide range of baseline covariates, identified significant sex differences in the association of depression indicators with secondary outcome 3, which was the only

CVD outcome significantly associated with any depression indicator. Depression symptoms treated as a continuous BDI score were significantly associated with higher probability of secondary outcome 3 in men but were not associated with this outcome in women. A similar pattern of sex differences was observed in separate analyses with the BDI subscales. The sex × BDI score interaction effect was statistically significant, supporting the conclusion that depression symptoms were differentially associated with this outcome in men compared with women. A statistically significant sex interaction effect with elevated depression symptoms (BDI score ≥10) was also observed for secondary outcome 3 (i.e., the direction of the association was opposite for men and women), with BDI score ≥10 associated with increased
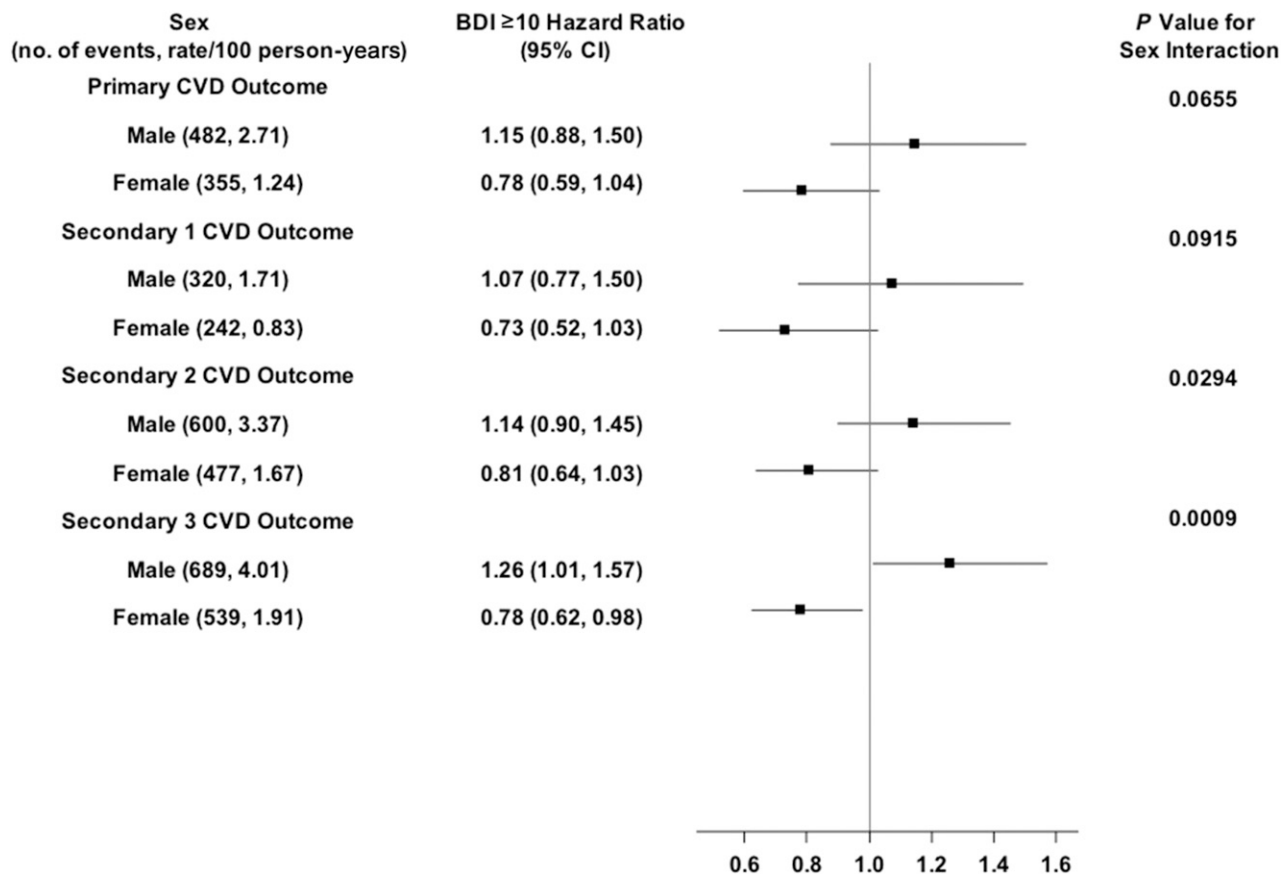
Figure 2—Shown are the number of CVD events and the rate per 100 person-years, the HRs (95% CIs) for BDI ≥10 for the primary and secondary CVD outcomes in men and women, and the P value for the sex × BDI ≥10 interaction effect. The solid vertical line indicates an HR of 1.00 (i.e., no effect).
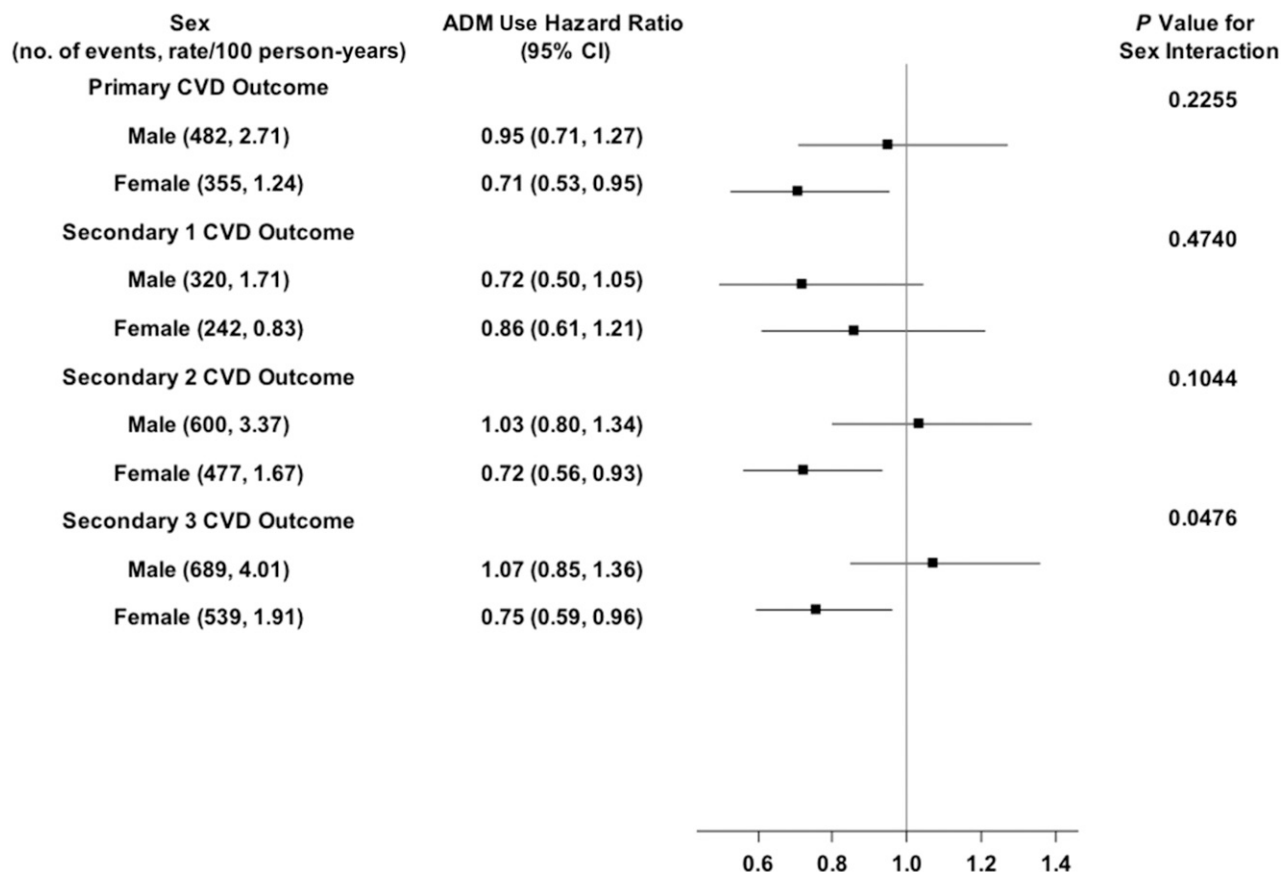
likelihood of the outcome in men and decreased likelihood in women. The ADM use × sex interaction effect was not statistically significant; however, exploratory analyses identified a significant BDI ≥10 × ADM use interaction that differed in the two sex groups. Men with both BDI score ≥10 and ADM use compared with those with neither had a 60% higher probability of this outcome (P = 0.0099), whereas women with both compared with those with neither had 50% lower probability (P = 0.0020). The BDI score ≥10 × ADM use interaction effect was statistically significant in men and trended toward significance in women.

The finding of no significant association between BDI score and CVD composite outcomes in women was unexpected as some evidence suggests that women with diabetes who are depressed have more rapid development of CVD compared with those who are not depressed (18). It should be noted, however, that previous population-based, prospective studies examining sex

differences in the depression-CVD association have yielded mixed results. Some studies found increased risk of incident CVD outcomes in women but not men (19–22), some found increased risk in men but not women (23), and others found increased risk in both men and women (1,24). These mixed results may be due, at least in part, to variations in design characteristics across studies, including the baseline age of the population, instrument to assess depression, CV/mortality end points, length of follow-up, and covariates included in multivariable analyses. Although they provide inconsistent evidence about whether men or women are at greater risk of CVD outcomes, these studies as well as our own suggest a need for a more careful and systematic investigation of sex differences in the association of depression with CVD and the mechanisms that account for observed differences. It has been noted (25) that the vast majority of mechanistic studies examining the link between depression and CVD have not reported sex-specific results.

Given the earlier Look AHEAD trial publication that reported higher 4-year incidence of CVD risk factors among participants using ADM (14), we hypothesized that both men and women who were ADM users would have a higher probability of incident CVD outcomes compared with those who were non-users. Thus, the lack of significant associations between ADM use and any of the CVD composite outcomes in either men or women in the preplanned analyses was unexpected, as was the finding in exploratory analyses of a significant BDI ≥10 × ADM use interaction effect for secondary outcome 3. Several studies in the psychiatry and psychopharmacology literature, however, have reported sex differences in antidepressant response to different types of ADM. For example, a randomized treatment trial comparing a TCA to an SSRI ADM found that men compared with women were more likely to show a favorable response to the TCA, while women were more likely than men to show a favorable response to the SSRI. Among

Sex (no. of events, rate/100 person-years)	ADM Use Hazard Ratio (95% CI)		P Value for Sex Interaction
Primary CVD Outcome			0.2255
Male (482, 2.71)	0.95 (0.71, 1.27)		
Female (355, 1.24)	0.71 (0.53, 0.95)		
Secondary 1 CVD Outcome			0.4740
Male (320, 1.71)	0.72 (0.50, 1.05)		
Female (242, 0.83)	0.86 (0.61, 1.21)		
Secondary 2 CVD Outcome			0.1044
Male (600, 3.37)	1.03 (0.80, 1.34)		
Female (477, 1.67)	0.72 (0.56, 0.93)		
Secondary 3 CVD Outcome			0.0476
Male (689, 4.01)	1.07 (0.85, 1.36)		
Female (539, 1.91)	0.75 (0.59, 0.96)		

Figure 3—Shown are the number of CVD events and the rate per 100 person-years, the HRs (95% CIs) for ADM use (ADM) for the primary and secondary CVD outcomes in men and women, and the P value for the sex × ADM use interaction effect. The solid vertical line indicates an HR of 1.00 (i.e., no effect).

postmenopausal women, however, there was no difference in response to these two types of ADM, leading investigators to hypothesize that female sex hormones may enhance response to SSRIs and inhibit response to TCAs. In this regard, it should be noted that 82.1% of women in the Look AHEAD trial were postmenopausal at baseline. Another study using data from 15 placebo-controlled trials found that the magnitude of women's antidepressant response with SSRIs was twice as high as that in men and posited that the higher concentration of adipose tissue in women may allow for greater accumulation and slower release of SSRIs, which are lipophilic in nature (26). That study, as well as a large treatment trial of SSRIs in which women demonstrated a 33% greater likelihood of depression remission versus men, also posited sex-specific biological differences in the serotonergic system as a plausible mechanism for observed sex differences (27). A comprehensive discussion of mechanisms underlying sex differences in antidepressant response to different types of ADM is provided by Yonkers and Brawman-Mintzer (28).

In addition to their antidepressant effects, both TCAs and SSRIs have effects that may directly impact cardiac risk. TCAs may increase cardiac risk by altering heart rate and rhythm; SSRIs may lower cardiac risk by decreasing platelet aggregation (2,7,29). ADMs may therefore affect CVD outcomes not only via their impact on depression but also on physiological/biological factors that alter cardiac risk. There was no statistically significant difference between sex groups in the type of ADM used, and over half of men and women (55.6% and 57.8%, respectively) who took ADMs were taking SSRIs. Women's greater antidepressant response to SSRIs compared with that of men may partially explain why women with a BDI score ≥10 and using ADM had a substantially lower probability of secondary outcome 3 relative to those with neither condition. The reason why men with a BDI score ≥10

and ADM use compared with those with neither had a 60% higher probability of secondary outcome 3 is less clear. Although men may have a smaller antidepressant response to SSRIs compared with women, there is no evidence to suggest that SSRIs adversely affect depression or cardiac risk in men. A possible explanation may be derived from an American Psychological Association report (30) indicating that men are less likely than women to seek help for all mental health problems and are particularly resistant to seeking help for depression and experience greater discomfort than women with emotional expression. Consistent with national trends (25), the proportion of ADM users in our study was 70% higher in women than in men, and women were more likely to use ADMs at lower levels of depression symptoms. Thus, men may not only have waited until they experienced higher levels of depression symptoms before seeking treatment, but once they began using ADMs were less

adherent and less likely to engage in concomitant cognitive behavioral therapy, resulting in a higher probability of adverse cardiac events.

Given its frequency and specificity to secondary outcome 3, it seems likely that CABG was a major component accounting for the fact that significant main effects were found only for this composite outcome. Exploratory component analyses also called attention to potential differences in the relationship of depression symptoms and ADM use to different types of CVD events and to potential sex differences in these relationships. The observed negative association of ADM use with nonfatal MI in men when the overall association with composite secondary outcome 3 was positive is consistent with the known concern that use of composite outcomes may sometimes mask relationships with individual component events when these differ from that observed for the composite outcome as a whole (31,32).

This study has several limitations. Although analyses were preplanned and based on data collected in a randomized controlled trial, the present analyses comprise an observational study controlling for treatment arms. More severe levels of depression symptoms were not represented in the sample; however, a dose-response relationship between depression and CVD across the full range of depression symptom scores has been found in other studies (33). ADMs are prescribed for indications other than depression (e.g., smoking cessation, social anxiety disorder, peripheral neuropathy), but we did not confirm that all participants taking ADMs were doing so because of depression. In addition, we did not obtain information about the dosage or duration of ADM treatment or about concomitant treatments such as cognitive behavioral therapy. Important areas for future investigation thus include sex differences in ADM prescribing, reaching therapeutic dose, treatment adherence in ADM use, and the use of concomitant treatments for depression also shown to be effective. We examined the moderating effect of sex on the association of depression indicators with CVD outcomes, but we did not explore the data further to identify other potential moderators or perform mediation analyses to identify potential intervening variables that might explain the moderating effects of sex on the association between depression indicators and CVD outcomes (34). Although we discuss factors that may mediate the observed sex × depression interaction effect, we did not have the necessary data to perform a formal mediation analysis. Last, these results may not apply to persons without diabetes or to people with diabetes who would not volunteer for a clinical trial or meet the strict eligibility criteria for this clinical trial. Notably, eligibility included passing a maximal exercise tolerance test (which suggests participants would have lower risk of CVD) and not having severe depression.

The study also has important strengths. It was conducted in a large, multiethnic cohort of individuals with type 2 diabetes and, to our knowledge, is the first study to examine sex differences in the association of depression with CVD in a cohort comprised exclusively of individuals with type 2 diabetes. The cohort had substantial numbers of both men and women with high rates of retention and no differential dropout, and sex × depression interaction effects were formally tested in the analyses. P values were corrected for multiple comparisons with the exception of the two exploratory analyses. CV events were classified by an Events Adjudication Committee, blinded to treatment arm, that reviewed all pertinent medical records and death certificates to confirm CVD events. Participants brought all prescription medications to the annual study visit, and ADM use and type were coded using a standardized classification system. The study examined not only depression symptoms but also ADM use as predictors of CVD outcomes. The latter is particularly important as data from the National Health and Nutrition Examination Surveys, 2011–2014, found that 12.7% of Americans ≥12 years old take ADM; among persons 40–59 years old, 11.6% of men and 21.2% of women take ADM; and among persons ≥60 years old, 12.6% of men and 24.4% of women take ADM (35).

Prevalence of depression is about twice as high in women as in men (24,36), and substantial evidence indicates that women differ from men in multiple aspects of CAD, including age of onset, presenting symptoms, traditional and psychosocial risk factors, and outcomes following MI and CABG (36,37). This is one of the few studies, however, that has examined sex differences in the association of depression symptoms and ADM use with CVD. The results provide evidence that, among individuals with type 2 diabetes, there are differences between men and women in the effects of both depression symptoms and ADM use on the probability of incident CVD events. Careful consideration should be given to the implications of these findings for the design of future studies and the management of depression and ADM use in the presence of type 2 diabetes.

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