

# Relations of Depressive Symptoms and Antidepressant Use to Body Mass Index and Selected Biomarkers for Diabetes and Cardiovascular Disease

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Postmenopausal women have been identified as being at elevated risk for both depression and diabetes.<sup>1</sup> Depression has been well documented to be associated with increased risk of diabetes.<sup>2–9</sup> Using data on postmenopausal women from the Women's Health Initiative (WHI), we previously observed that depressive symptoms and antidepressant use were independently associated with diabetes risk and cardiovascular disease.<sup>10,11</sup> Recent studies<sup>12–15</sup> have suggested that this relationship may be prospective and independent of traditional risk factors for type 2 diabetes such as family history of diabetes, body weight, diet, physical activity, and smoking, although 1 study found no association between depressive symptoms and unrecognized diabetes.<sup>16</sup>

Few studies have examined the association of body mass index (BMI; defined as weight in kilograms divided by height in meters squared), waist circumference, and biomarkers of glucose dysregulation and inflammation with depression, antidepressant medication use, or both. However, identifying these markers is important for diabetes prevention because they can be monitored for possible action before progression to full-blown diabetes. We therefore investigated the associations of elevated depressive symptoms and antidepressant use with body habitus, glucose dysregulation, and inflammatory biomarkers using longitudinal data from the WHI. In particular, we examined these hypotheses: (1) elevated depressive symptoms and antidepressant use are independently associated with increased BMI and waist circumference; (2) elevated depressive symptoms and antidepressant use are independently associated with increased levels of fasting glucose and insulin, insulin resistance, blood pressure, and triglycerides and reduced high-density lipoprotein (HDL) cholesterol; and

**Objectives.** We investigated whether depressive symptoms and antidepressant use are associated with biomarkers for glucose dysregulation and inflammation, body mass index (BMI), and waist circumference.

**Methods.** Postmenopausal women were recruited into the Women's Health Initiative from 1993 to 1998, and data were collected at regular intervals through 2005. We used multiple linear regression models to examine whether depressive symptoms and antidepressant use are associated with BMI, waist circumference, and biomarkers.

**Results.** Analysis of data from 71 809 women who completed all relevant baseline and year 3 assessments showed that both elevated depressive symptoms and antidepressant use were significantly associated with higher BMI and waist circumference. Among 1950 women, elevated depressive symptoms were significantly associated with increased insulin levels and measures of insulin resistance. Analyses of baseline data from 2242 women showed that both elevated depressive symptoms and antidepressant use were associated with higher C-reactive protein levels.

**Conclusions.** Monitoring body habitus and other biomarkers among women with elevated depression symptoms or taking antidepressant medication may be prudent to prevent diabetes and cardiovascular disease. (*Am J Public Health.* 2013;103:e34–e43. doi:10.2105/AJPH.2013.301394)

(3) elevated depressive symptoms and antidepressant use are independently associated with increased levels of high-sensitivity C-reactive protein (CRP), tumor-necrosis factor- $\alpha$  receptor 2 (TNF- $\alpha$  R2), and interleukin-6 (IL-6) as markers of systemic inflammation.

## METHODS

The design of WHI and participants' characteristics have been described in detail elsewhere.<sup>17–20</sup> Briefly, the WHI enrolled postmenopausal women aged 50 to 79 years who were able to provide written informed consent and had an expected survival and local residency of 3 or more years. Exclusion criteria included current alcoholism, drug dependency, dementia, or other conditions that would limit full participation in the study. A total of

161 808 women were enrolled—68 132 participants into clinical trials (WHI-CT) and 93 676 participants into an observational study (WHI-OS) between 1993 and 1998, with an average of 7.6 years of follow-up by the end of intervention on March 31, 2005.<sup>17</sup> Medication use, depressive symptoms, and diabetes and cardiovascular disease risk factors were collected repeatedly during follow-up. Participant retention and data collection completion rates were greater than 95%.<sup>21</sup>

## Measures

**Body weight, height, and waist circumference.** Height was measured with a stadiometer and weight with a balance-beam scale. We defined waist circumference as the smallest circumference between the lower rib and the iliac crest. For the WHI-OS participants, body

weight, height, and waist circumference were measured at baseline and at the year 3 clinic visits. For all WHI-CT participants, weight and height were measured at baseline and at each annual clinic visit; waist circumference was measured at baseline and year 1 for all WHI-CT participants and for 6% of WHI-CT participants at years 3, 6, and 9.

**Fasting blood measures.** We collected blood samples at baseline and at the year 3 clinic visits for WHI-OS participants and at baseline; at the year 1 clinic visits for WHI-CT participants; and for a random sample of 6% of WHI-CT participants at the year 3, 6, and 9 clinical visits. We stratified random sampling by age, clinical site, hysterectomy status, and race/ethnicity to correct for potential oversampling of minority populations. Blood samples were obtained in the fasting state ( $\geq 12$  hours) in the morning. Blood was analyzed for 20 assays including glucose, insulin, HDL cholesterol, and triglycerides for the WHI-CT participants. A random 1% of WHI-OS participants had the same core analyses. Plasma glucose was analyzed by using the hexokinase method (Hitachi 747; Boehringer Mannheim Diagnostics, Indianapolis, IN), with interassay coefficients of variation less than 2%.<sup>22</sup> Insulin was measured by enzyme-linked immunosorbent assay. Triglycerides were measured enzymatically, and HDL cholesterol was measured by manganese sulfate precipitation. We calculated insulin resistance from fasting glucose and insulin according to the homeostasis model assessment of insulin resistance (HOMA-IR) model:  $\text{insulin}/\{22.5 \exp[-\ln(\text{glucose}/18)]\}$ , where the unit for insulin was microunits per milliliter and the unit for glucose was millimoles per liter.<sup>23</sup>

We measured CRP, IL-6, and TNF- $\alpha$  R2 among approximately 4000 women in the WHI-OS cohort at baseline as part of an ancillary study.<sup>24</sup> CRP was assayed by high-sensitivity latex-enhanced immunonephelometry (interassay correlation of variation [CV] = 4%; Behring Diagnostics, San Jose, CA), IL-6 was assayed by an ultra-sensitive solid-phase enzyme-linked immunosorbent assay (interassay CV = 9%; R&D Systems, Minneapolis, MN), and TNF- $\alpha$  R2 was assayed by a multiplex assay (interassay CV of 18%; Milliplex Human Adipokine Panel B, Millipore, Billerica, MA).

**Depression symptom assessment and score.** We measured depression symptoms using the

Center for Epidemiological Studies Depression Scale 6-item short form.<sup>25</sup> The short form scores are highly correlated with the full 20-item scale ( $r = .88$ ),<sup>11</sup> which has been shown to be highly correlated with clinical diagnoses of depression.<sup>26,27</sup> Consistent with previous studies, we used a cut point of 5 or more to categorize participants as having elevated depressive symptoms.<sup>10,11</sup> We assessed depressive symptoms in all women at baseline, at year 3 in WHI-OS participants, at years 1 and 9 in WHI-CT participants, and at years 3 and 6 in a random 6% subsample of WHI-CT participants.

**Measurement and classification of antidepressant medication.** WHI-CT participants were instructed to bring all current prescription and nonprescription medications in original containers to clinic visits at baseline and years 1, 3, 6, and 9. We collected WHI-OS medication data at baseline and year 3. The Master Drug Database (Medi-Span, Indianapolis, IN) was used to categorize the medications. On the basis of the Master Drug Database classification, we created a binary indicator for antidepressant medication use. Antidepressants were classified into 6 major groups:

1. selective serotonin reuptake inhibitors (SSRIs),
2. monoamine oxidase inhibitors,
3. tricyclic antidepressants (TCAs),
4.  $\alpha$ -2 receptor antagonists (tetracyclics),
5. modified cyclics (triazolopyridines), and
6. other miscellaneous medications classified as antidepressants, which would include serotonin-norepinephrine reuptake inhibitors and aminoketones (norepinephrine-dopamine reuptake inhibitors).

We created a variable for type of antidepressant use with the following categories:

1. none,
2. only TCAs,
3. only SSRIs,
4. TCAs and SSRIs in combinations, and
5. others.

### Statistical Analyses

On the basis of availability of data in the WHI, we tested the hypotheses using different subsets of women. Women with self-reported

diabetes or use of diabetes drugs at baseline were excluded from all analyses.

**Association of elevated depressive symptoms and antidepressant use with body mass index and waist circumference.** Analysis was based on 71 809 women in the WHI-OS who completed all relevant baseline and year 3 assessments. We used linear mixed models<sup>28</sup> to examine the relationship between elevated depressive symptoms or antidepressant medication use and BMI. In these models, we treated BMI as the dependent variable and depression status and antidepressant use as independent categorical variables. We considered depression status a binary variable (with elevated depression score or not) at each available time point. Antidepressant use was also considered a binary variable (medication user or nonuser) at each available time point. Unadjusted models included depression status or antidepressant use separately as primary variables of interest. Multivariate models adjusted for depression status and antidepressant use simultaneously, while accounting for various characteristics at baseline—age, race/ethnicity, education, smoking status, alcohol intake, menopausal hormone therapy, reported physical activity, and reported caloric intake. Mixed-effects models assumed a compound symmetry covariance structure, and we based statistical significance on 2-sided likelihood ratio tests. We assessed evidence of multiplicative interaction between antidepressant use and elevated depressive symptoms on the basis of likelihood ratio tests comparing nested multivariate models with and without the multiplicative interaction term. We conducted similar analyses for waist circumference as an outcome variable.

**Association of elevated depressive symptoms and antidepressant use with metabolic measures.** Evaluation was based on 1950 women in the WHI-CT who had measures of fasting glucose, blood pressure, and HDL cholesterol and triglycerides at baseline and years 1, 3, and 6 and measures of insulin and HOMA-IR at baseline and years 1 and 3. We fit linear mixed models to examine the associations. Because the distributions of the outcome variables (i.e., inflammatory markers, insulin) were skewed, all outcomes were transformed to the natural logarithm scale. Multivariate models adjusted for depressive symptoms and antidepressant use simultaneously, while accounting for

various characteristics at baseline—namely, age, race/ethnicity, BMI, education, smoking status, alcohol intake, hormone therapy, physical activity, reported sleep patterns, and assignment to different WHI–CT arms. We assessed evidence of multiplicative interaction between elevated depressive symptoms and antidepressant use on the basis of likelihood ratio tests comparing nested multivariate models.

*Association of elevated depressive symptoms and antidepressant use with systemic inflammation markers.* Analyses were based on 2242 women in the WHI–OS who had complete data at baseline. We conducted a cross-sectional analysis and used linear regression models to examine the association of elevated depressive symptoms and antidepressant use with levels of CRP, IL-6, and TNF- $\alpha$  R2. Each inflammation marker was natural logarithm transformed and considered individually as the outcome in multiple linear regression models. Multivariate models adjusted for depression status and antidepressant use simultaneously, while accounting for characteristics at baseline—namely, age, race/ethnicity, BMI, statin use, education, sleep duration, saturated fat intake, physical activity, and family history of cardiovascular disease.

*Association of persistent depression, use of antidepressants, and outcomes with longitudinal measurements.* The goal of these analyses was to evaluate whether prolonged depression or antidepressant use resulted in stronger associations with each diabetes and cardiovascular disease risk factor. We assessed the effect of persistent depression with respect to each outcome (BMI, waist circumference, insulin, fasting glucose, HOMA-IR, blood pressure, HDL cholesterol, and triglycerides) at every visit after baseline in linear mixed-effects models including time-varying depression status and an additional time-varying binary (0–1) covariate to capture the effect of persistent elevated depressive symptoms. This additional covariate was coded as 1 at each follow-up visit beyond baseline only for those participants who were depressed at both the previous and the current visits. We used a 2-sided likelihood ratio test of this new covariate to assess the effect of persisting depressive symptoms. The effect of persistent antidepressant use was assessed similarly.

## RESULTS

Sample size differed according to the 3 major analyses. The largest sample consisted of 71 809 women, who had a mean age of 63.5 years (SD = 7.3 years). Approximately 14% of the women were from racial/ethnic minority groups, and the largest representation of minorities were Black (6.5%) and Hispanic (3.0%). Approximately 15% of women had baseline depressive symptoms above the cut-off point of 5 on the short-form Center for Epidemiological Studies Depression Scale. In all, 7.0% women reported using antidepressant medications. Participants' characteristics for the other 2 analysis cohorts are included in Table 1 and were similar except for a much higher representation of racial/ethnic minorities.

### Associations With Body Mass Index and Waist Circumference

At all time points, women with elevated depressive symptoms had higher average BMI and waist circumference than did women without elevated depressive symptoms (Table 2). Similarly, at all time points, women using antidepressants had higher average BMI and waist circumference than women not using antidepressants. Evaluation of mean BMI by class of antidepressant use showed that women taking combinations of SSRI and TCA medications had significantly elevated BMI compared with women taking SSRI or TCA medications alone. At baseline, the mean BMIs among women taking combination SSRI and TCA ( $n = 136$ ), SSRI alone ( $n = 2248$ ), and TCA alone ( $n = 1910$ ) were 29.20 kilograms per meter squared (SD = 1.2), 27.60 kilograms per meter squared (SD = 1.2), and 27.03 kilograms per meter squared (SD = 1.2), respectively (data not tabulated). We also observed similar results for waist circumference. At baseline, the mean waist circumferences among women taking combination SSRI and TCA, SSRI alone, and TCA alone were 89.57 centimeters (SD = 1.2), 85.73 centimeters (SD = 1.2), and 85.52 centimeters (SD = 1.2), respectively (data not tabulated).

After adjustment for potential confounders, both elevated depressive symptoms and antidepressant use were significantly associated with higher BMI and waist circumference

(Table 3). However, the associations were stronger for waist circumference (i.e., a difference of 2.0 in relation to an SD of 1.2 for waist circumference and a difference of 0.9 in relation to an SD of 1.2 for BMI). The multiplicative interaction term between elevated depressive symptoms and antidepressant use was not significant ( $P = .33$ ), indicating that elevated depressive symptoms and antidepressant use were independently associated with BMI and waist circumference.

In linear mixed-effects models, persistent antidepressant use at baseline and at the year 3 visit was associated with significantly increased BMI when compared with antidepressant use at the year 3 visit alone ( $P \leq .001$ ). The mean BMI among those using antidepressants only at year 3 was 27.32 kilograms per meter squared (SD = 1.2), whereas the mean among those using antidepressants at both baseline and year 3 was 27.91 kilograms per meter squared (SD = 1.2).

### Associations With Metabolic Measures

Analysis of 1950 women in the WHI–CT with metabolic measures at baseline and at years 1 and 3 indicated that elevated depressive symptoms were significantly associated with increased serum insulin ( $P = .01$ ) and insulin resistance ( $P = .01$ ) after adjustment for potential confounders (Table 3). We found no evidence of an increased effect of persistent elevated depressive symptoms with respect to HOMA-IR and serum insulin. In multivariate models adjusting for confounders, antidepressant use was not associated with levels of insulin ( $P = .55$ ) or insulin resistance ( $P = .67$ ).

In multivariate models adjusting for confounders, neither elevated depressive symptoms nor antidepressant use were significantly associated with blood pressure ( $P > .3$ ), HDL cholesterol ( $P > .6$ ), or triglycerides ( $P > .5$ ). We found no evidence of a multiplicative interaction between depression status and antidepressant use with respect to levels of insulin, fasting glucose, HOMA-IR, blood pressure, HDL cholesterol, and triglycerides (all  $P > .05$ ).

### Associations With Systemic Inflammation Markers

Cross-sectional analyses of 2242 women in the WHI–OS with complete data at baseline

**TABLE 1—Baseline Characteristics of Participants: Women’s Health Initiative (WHI), United States, 1993–2005**

Variable	Weight Analyses (n = 71 809), No. (%) or Mean ±SD	Metabolic Measure Analyses (n = 2242), No. (%) or Mean ±SD	Inflammatory Marker Analyses (n = 1950), No. (%) or Mean ±SD
Age at screening, y	63.5 ±7.28	62.3 ±6.93	62.0 ±6.84
Race/ethnicity			
American Indian or Alaskan Native	242 (0.3)	0 (0)	39 (2.0)
Asian or Pacific Islander	2112 (3.0)	173 (7.7)	174 (8.9)
Black	4624 (6.5)	663 (29.6)	430 (22.1)
Hispanic or Latino	2172 (3.0)	260 (11.6)	220 (11.3)
White	61 725 (86.2)	1145 (51.1)	1042 (53.4)
Other	755 (1.0)	1 (<0.1)	45 (2.3)
Education			
< high school	2802 (3.9)	196 (8.8)	131 (6.7)
High school or GED	11 102 (15.6)	355 (16.0)	381 (19.6)
> high school, < 4 y college	25 657 (36.0)	845 (38.1)	729 (37.5)
≥ 4 y college	31 705 (44.5)	821 (37.0)	705 (36.2)
Smoking status			
Never	36 611 (51.6)	1196 (54.1)	1040 (54.1)
Former	30 433 (42.9)	878 (39.7)	739 (38.4)
Current	3950 (5.6)	137 (6.2)	144 (7.5)
Hormone therapy use			
Never used hormones	20 275 (28.8)	779 (35.5)	831 (44.0)
Past hormone user	14 511 (20.6)	459 (20.9)	554 (29.4)
Current hormone user	35 721 (50.7)	957 (43.6)	502 (26.6)
Family history of diabetes			
Yes	21 520 (31.4)	942 (44.9)	711 (38.7)
No	47 068 (68.6)	1155 (55.1)	1128 (61.3)
Elevated depressive symptoms at baseline			
Yes	10 474 (14.6)	357 (15.9)	263 (13.5)
No	61 335 (85.4)	1885 (84.1)	1687 (86.5)
Taking antidepressant medication at baseline			
Yes	5061 (7.0)	144 (6.42)	67 (3.4)
No	66 748 (93.0)	2098 (93.6)	1883 (96.6)
Taking antidepressant medication and having elevated depressive symptoms at baseline			
Not depressed, not taking antidepressant medication	57 713 (80.4)	1790 (79.8)	1642 (84.2)
Not depressed, taking antidepressant medication	3622 (5.0)	95 (4.2)	45 (2.3)
Depressed, not taking antidepressant medication	9035 (12.6)	308 (13.7)	241 (12.4)
Depressed, taking antidepressant medication	1439 (2.0)	49 (2.2)	22 (1.1)
WHI participation condition			
Observation study	71 809 (100.0)	2242 (100.0)	1950 (100)
Estrogen-alone trial only			284 (14.6)
Estrogen plus progestin trial only			453 (23.2)
Dietary modification trial only			797 (40.9)
HRT and dietary trials			416 (21.3)

Note. GED = general equivalency diploma; HRT = hormone replacement therapy.

**TABLE 2—Geometric Means and Standard Deviations by Elevated Depressive Symptoms Status and Antidepressant Use at Each Time Point: Women's Health Initiative (WHI), United States, 1993–2005**

Variable	Baseline		Year 1 <sup>a</sup>		Year 3		Year 6	
	Yes	No	Yes	No	Yes	No	Yes	No
BMI <sup>c</sup> (kg/m <sup>2</sup> )	27.1 (1.22)	26.2 (1.21)	≤.001	<b>Elevated depressive symptoms? (Yes/No)</b>		27.4 (1.23)	26.5 (1.21)	≤.001
Weight <sup>c</sup> (kg)	70.5 (1.23)	68.6 (1.22)	≤.001	27.4 (1.23)	26.5 (1.21)	26.5 (1.21)	26.5 (1.21)	≤.001
Waist circumference <sup>c</sup> (cm)	84.5 (1.17)	82.5 (1.16)	≤.001	70.9 (1.24)	68.9 (1.22)	68.9 (1.22)	68.9 (1.22)	≤.001
Insulin <sup>d</sup> (μU/mL)	10.4 (1.70)	10.1 (1.60)	.34	85.7 (1.17)	83.3 (1.16)	83.3 (1.16)	83.3 (1.16)	≤.001
HOMA-IR <sup>d</sup>	2.5 (1.81)	2.4 (1.73)	.45	10.3 (1.67)	9.8 (1.65)	10.9 (1.62)	10.9 (1.62)	.006
Fasting glucose <sup>d</sup> (mg/dL)	95.7 (1.13)	96.2 (1.16)	.51	2.4 (1.82)	2.3 (1.79)	2.6 (1.77)	2.6 (1.77)	.05
Systolic blood pressure <sup>d</sup> (mm Hg)	126.0 (1.14)	127.4 (1.14)	.21	96.0 (1.17)	95.4 (1.17)	94.6 (1.15)	96.0 (1.21)	.12
Diastolic blood pressure <sup>d</sup> (mm Hg)	75.4 (1.13)	75.9 (1.13)	.45	124.5 (1.13)	125.3 (1.14)	126.2 (1.13)	125.9 (1.14)	.79
HDL <sup>d</sup> (mg/dL)	55.0 (1.29)	56.5 (1.29)	.1	74.4 (1.13)	74.1 (1.13)	74.1 (1.14)	73.6 (1.14)	.45
Triglycerides <sup>d</sup> (mg/dL)	140.9 (1.67)	133.6 (1.60)	.11	56.6 (1.29)	57.7 (1.29)	56.7 (1.30)	56.4 (1.29)	.73
CRP <sup>d</sup> (mg/L)	2.1 (3.00)	2.0 (2.85)	.28	138.5 (1.62)	138.8 (1.59)	142.8 (1.56)	138.7 (1.56)	.38
IL-6 <sup>d</sup> (pg/mL)	2.1 (2.23)	1.9 (2.25)	.05	2.1 (3.00)	2.0 (2.85)	2.0 (2.85)	2.0 (2.85)	.28
TNF-α R2 <sup>d</sup> (pg/mL)	2547.1 (1.36)	2414.6 (1.36)	.003	1.9 (2.25)	1.9 (2.25)	1.9 (2.25)	1.9 (2.25)	.05
				2547.1 (1.36)	2414.6 (1.36)	2414.6 (1.36)	2414.6 (1.36)	.003
				<b>On antidepressants? (Yes/No)</b>		27.6 (1.22)	26.5 (1.21)	≤.001
BMI <sup>c</sup> (kg/m <sup>2</sup> )	27.4 (1.22)	26.3 (1.21)	≤.001	27.6 (1.22)	26.5 (1.21)	26.5 (1.21)	26.5 (1.21)	≤.001
Weight <sup>c</sup> (kg)	72.1 (1.23)	68.6 (1.22)	≤.001	72.2 (1.24)	69.0 (1.22)	69.0 (1.22)	69.0 (1.22)	≤.001
Waist circumference <sup>c</sup> (cm)	85.7 (1.17)	82.5 (1.16)	≤.001	86.7 (1.17)	83.3 (1.16)	83.3 (1.16)	83.3 (1.16)	≤.001
Insulin <sup>d</sup> (μU/mL)	9.9 (1.62)	10.1 (1.62)	.72	11.6 (1.54)	11.0 (1.63)	11.0 (1.63)	11.0 (1.63)	.32
HOMA-IR <sup>d</sup>	2.3 (1.74)	2.4 (1.74)	.56	2.7 (1.72)	2.6 (1.78)	2.6 (1.78)	2.6 (1.78)	.4
Fasting glucose <sup>d</sup> (mg/dL)	94.4 (1.12)	96.2 (1.16)	.19	95.8 (1.21)	95.8 (1.20)	95.8 (1.20)	95.8 (1.20)	.98
Systolic blood pressure <sup>d</sup> (mm Hg)	125.3 (1.15)	127.3 (1.14)	.36	125.6 (1.16)	126.0 (1.14)	126.0 (1.14)	126.0 (1.14)	.84
Diastolic blood pressure <sup>d</sup> (mm Hg)	74.1 (1.14)	75.9 (1.13)	.12	72.9 (1.14)	73.8 (1.14)	73.8 (1.14)	73.8 (1.14)	.35
HDL <sup>d</sup> (mg/dL)	54.9 (1.33)	56.3 (1.29)	.42	55.7 (1.32)	56.5 (1.29)	56.5 (1.29)	56.4 (1.28)	.61
Triglycerides <sup>d</sup> (mg/dL)	158.7 (1.63)	133.7 (1.61)	.004	149.2 (1.64)	139.1 (1.58)	139.1 (1.58)	133.1 (1.56)	.12
CRP <sup>d</sup> (mg/L)	2.9 (2.62)	2.0 (2.88)	≤.001	149.2 (1.64)	139.1 (1.58)	139.1 (1.58)	133.1 (1.56)	.12
IL-6 <sup>d</sup> (pg/mL)	2.2 (2.17)	1.9 (2.25)	.04	150.4 (1.57)	150.4 (1.57)	150.4 (1.57)	150.4 (1.57)	.001
TNF-α R2 <sup>d</sup> (pg/mL)	2621.8 (1.35)	2422.9 (1.36)	.003	150.4 (1.57)	150.4 (1.57)	150.4 (1.57)	150.4 (1.57)	.001

Note. BMI = body mass index; CRP = C-reactive protein; CT = clinical trials; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment of insulin resistance; IL-6 = interleukin-6; OS = observational study; TNF-α R2 = tumor necrosis factor-α receptor 2.

<sup>a</sup>Empty cells indicate that data were not collected in these time points.

<sup>b</sup>P value from 2 simple means *t*-test.

<sup>c</sup>Means based on 71 809 women in the WHI-OS who completed all relevant at baseline and year-3 assessments.

<sup>d</sup>Means based on 1950 women in the WHI-CT who had longitudinal measures of fasting glucose, blood pressure, HDL cholesterol, triglycerides and insulin.

<sup>e</sup>Means based on 2242 women in the WHI-OS with who had complete data at baseline.

**TABLE 3—Association of Natural Log of BMI, Waist Circumference, Metabolic Measures, and Inflammatory Markers with Elevated Depressive Symptoms and Antidepressant Use: Women’s Health Initiative (WHI), United States, 1993–2005**

Variable	Unadjusted Model		Multivariate Adjusted Model <sup>a</sup>		Multivariate Adjusted Model <sup>b</sup>	
	b (95% CI)	P <sup>c</sup>	b (95% CI)	P <sup>c</sup>	b (95% CI)	P <sup>c</sup>
<b>WHI-OS data from baseline and year 3 (n = 71 809)</b>						
Elevated depressive symptoms: BMI		≤ .001		≤ .001		≤ .001
Not at all (Ref)	1.00		1.00		1.00	
Yes at baseline, no at year 3	0.03 (0.02, 0.03)		0.01 (0.003, 0.01)		0.01 (0.003, 0.01)	
No at baseline, yes at year 3	0.03 (0.03, 0.04)		0.01 (0.01, 0.02)		0.01 (0.01, 0.02)	
Yes at baseline, yes at year 3	0.05 (0.04, 0.06)		0.01 (0.01, 0.02)		0.01 (0.01, 0.02)	
Antidepressant use: BMI		≤ .001		≤ .001		≤ .001
Not at all (Ref)	1.00		1.00		1.00	
Yes at baseline, no at year 3	0.04 (0.03, 0.05)		0.03 (0.02, 0.04)		0.03 (0.02, 0.04)	
No at baseline, yes at year 3	0.03 (0.02, 0.03)		0.02 (0.01, 0.02)		0.02 (0.01, 0.02)	
Yes at baseline, yes at year 3	0.04 (0.04, 0.05)		0.03 (0.02, 0.04)		0.03(0.03, 0.04)	
Elevated depressive symptoms: waist circumference		≤ .001		≤ .001		≤ .001
Not at all (Ref)	1.00		1.00		1.00	
Yes at baseline, no at year 3	0.02 (0.02, 0.02)		0.01 (0.001, 0.01)		0.01 (0.003, 0.01)	
No at baseline, yes at year 3	0.02 (0.02, 0.03)		0.01 (0.01, 0.02)		0.01 (0.01, 0.02)	
Yes at baseline, yes at year 3	0.04 (0.03, 0.04)		0.01 (0.01, 0.02)		0.02 (0.01, 0.02)	
Antidepressant use: waist circumference		≤ .001		≤ .001		≤ .001
Not at all (Ref)						
Yes at baseline, no at year 3	0.03 (0.02, 0.04)		0.02 (0.01, 0.03)		0.02 (0.02, 0.03)	
No at baseline, yes at year 3	0.02 (0.02, 0.03)		0.01 (0.01, 0.02)		0.02 (0.01, 0.02)	
Yes at baseline, yes at year 3	0.04 (0.04, 0.05)		0.03 (0.03, 0.04)		0.03 (0.03, 0.04)	
<b>WHI-CT data from baseline, year 1, and year 3 (n = 1950)</b>						
Elevated depressive symptoms: Insulin		.03		.01		.01
Yes	-0.04 (-0.08, -0.001)		-0.05 (-0.09, -0.01)		-0.05 (-0.10, -0.01)	
No (Ref)	1.00		1.00		1.00	
Antidepressant use: Insulin		.18		.55		.55
Yes	-0.03 (-0.10, 0.05)		-0.01 (-0.08, 0.07)		-0.01(-0.09, 0.07)	
No (Ref)	1.00		1.00		1.00	
Elevated depressive symptoms: HOMA-IR		.03		.01		.01
Yes	-0.05 (-0.09, -0.01)		-0.06 (-0.10, -0.01)		-0.06 (-0.10, -0.01)	
No (Ref)	1.00		1.00		1.00	
Antidepressant use: HOMA-IR		.25		.67		.67
Yes	-0.04 (-0.12, 0.05)		-0.01 (-0.10, 0.08)		-0.01 (-0.11, 0.07)	
No (Ref)	1.00		1.00		1.00	
<b>WHI-OS data from baseline (n = 2242)<sup>d</sup></b>						
Elevated depressive symptoms: CRP		.27		.02		
Yes	0.07 (-0.05, 0.18)		-0.13 (-0.25, -0.02)			
No (Ref)	1.00					
Antidepressant use: CRP		≤ .001		.004		
Yes	0.38 (0.20, 0.56)		0.23 (0.07, 0.40)			
No (Ref)	1.00					

Continued

TABLE 3—Continued

Elevated depressive symptoms: TNF- $\alpha$ R2		.003		.07
Yes	0.05 (0.02, 0.09)		0.03 (-0.002, 0.07)	
No (Ref)	1.00		1.00	
Antidepressant use: TNF- $\alpha$ R2		.003		.13
Yes	0.08 (0.03, 0.13)		0.04 (-0.01, 0.09)	
No (Ref)	1.00		1.00	

Note. BMI = body mass index; CI = confidence interval; CRP = C-reactive protein; CT = clinical trials; CVD = cardiovascular disease; HOMA-IR = homeostasis model assessment of insulin resistance; HRT = hormone replacement therapy; OS = observational study; TNF- $\alpha$  R2 = tumor-necrosis factor- $\alpha$  receptor 2.

<sup>a</sup>Multivariate models included elevated depressive symptoms status, antidepressant use, age, race/ethnicity, education, smoking status, alcohol intake, family history of diabetes, HRT use, total physical activity and total caloric intake as independent variables.

<sup>b</sup>Multivariate models included elevated depressive symptoms status, antidepressant use, age, race/ethnicity, education, smoking status, alcohol intake, HRT use, total physical activity, and total caloric intake as independent variables, and excluded family history of diabetes.

<sup>c</sup>P values from linear mixed models included association of elevated depressive symptoms and antidepressant use with BMI, insulin, HOMA-IR, high-sensitivity CRP and TNF- $\alpha$  R2, respectively.

<sup>d</sup>Multivariate models included elevated depressive symptoms status, antidepressant use, age, race/ethnicity, BMI, statin use, education, sleep duration, saturated fat intake and physical activity, and family history of CVD as independent variables.

showed that elevated depressive symptoms were significant in their association with serum levels of CRP after adjustment for potential confounders ( $P=.02$ )—the mean levels of serum CRP among those with and without depressive symptoms were 2.1 milligrams per liter ( $SD=3.0$ ) and 2.0 milligrams per liter ( $SD=2.8$ ), respectively. Antidepressant use was significantly associated with serum level of CRP after adjustment for potential confounders ( $P=.04$ ). Women taking antidepressants had an average CRP of 2.9 milligrams per liter ( $SD=2.6$ ), whereas women not taking antidepressants had an average CRP of 2.0 milligrams per liter ( $SD=2.9$ ).

In the bivariate analyses, both IL-6 and TNF- $\alpha$  R2 were significantly associated with depression status and antidepressant use. However, after adjustment for potential confounders, both IL-6 and TNF- $\alpha$  R2 were not significantly associated with depression status. We found no consistent evidence of a multiplicative interaction of elevated depressive symptoms and antidepressant use with the systemic inflammation markers. In addition, we evaluated the association between CRP and antidepressant use in 3 subgroups, defined as BMI less than 25 kilograms per meter squared ( $n=676$ ), BMI between 25 and 30 kilograms per meter squared ( $n=759$ ), and BMI greater than 30 kilograms per meter squared ( $n=807$ ). Although CRP levels increased steadily with increasing BMI, within all 3 subgroups CRP levels were significantly elevated among women taking antidepressants.

## DISCUSSION

This investigation resulted in 3 main findings. First, both elevated depressive symptoms and antidepressant use are each significantly associated with higher BMI and waist circumference. Second, elevated depressive symptoms are associated with increased levels of insulin and insulin resistance. Third, both elevated depressive symptoms and antidepressant use are associated with increased CRP levels. We found no multiplicative effect of elevated depressive symptoms and antidepressant use, indicating that elevated depressive symptoms and antidepressant use are independently associated with BMI, waist circumference, and CRP.

Our results are consistent with those of several previous studies that found that both elevated depressive symptoms and antidepressant use were associated with increased body weight and waist circumference. Elevated depressive symptoms can influence anthropometric measurements such as weight and waist circumference. Elevated depressive symptoms often lead to weight gain,<sup>29</sup> particularly in the abdominal region,<sup>30</sup> which is associated with type 2 diabetes. Weight gain can result from elevated depressive symptoms as a result of increased sedentary behavior,<sup>29,31</sup> increased appetite, or sleep dysregulation, which are 3 main symptoms of depression. Many antidepressant medications have also been associated with weight gain, with possible etiologies involving variable and complex interactions with neurotransmitter pathways.<sup>32,33</sup> Our finding

that BMI and waist circumference are increased with the combination of TCA plus any SSRI validates the findings of Brown et al.<sup>13</sup>

In a cross-sectional study of 1732 participants aged between 26 and 36 years, Pearson et al.<sup>34</sup> found a positive association between depressive disorders and insulin resistance. Our prospective study extends those findings by showing that elevated depressive symptoms are significantly associated with the development of increased serum levels of insulin and insulin resistance in postmenopausal women.

Elevated depressive symptoms are linked to inflammation, which increases the risk of type 2 diabetes and cardiovascular disease.<sup>10,11,24</sup> Consistent with our findings, several studies have found that elevated depressive symptoms are associated with elevated CRP and proinflammatory cytokines.<sup>35-39</sup> Previous work has shown that proinflammatory cytokines, including IL-6 and CRP, tend to decrease over the course of antidepressant treatment.<sup>40-48</sup> Whether the changes are attributable to depression treatment response, to antidepressant action effects, or to an unrelated effect is unclear. In some studies, the degree of improvement in depression was associated with a decrease in inflammatory markers,<sup>48,49</sup> whereas others have not found this relationship.<sup>50</sup>

We found that CRP, but not IL-6 or TNF- $\alpha$  R2, was increased with antidepressant use. Although some studies have suggested that antidepressant use may promote proinflammatory cytokine production,<sup>46</sup> others have produced conflicting results, indicating no

change in inflammatory biomarkers over the course of antidepressant treatment.<sup>51–53</sup> Evidence has shown that an increase in inflammatory markers varies according to certain antidepressants.<sup>54–58</sup> Weight gain may influence these results,<sup>55,56</sup> and different classes or specific antidepressants and doses may differentially affect inflammatory biomarkers,<sup>46,59</sup> as well as the risk or presence of immune dysfunction, infection, injury, and other disease states.

We did not find the expected associations of elevated depressive symptoms and antidepressant use with HDL cholesterol and triglycerides, contradicting previous studies that linked depressive symptoms to low HDL cholesterol levels<sup>60,61</sup> and high triglyceride levels.<sup>5</sup> Other studies found links between lipid changes and antidepressant medication use. Using cross-sectional data from the Hordaland Health Study, Raeder et al.<sup>62</sup> found an association between use of SSRIs (n = 461) with high total cholesterol, low HDL, hypertriglyceridemia, and diabetes (odds ratio = 1.36, 95% confidence interval = 1.07, 1.73). People may take antidepressants for reasons other than depression, which may have influenced our results.<sup>63</sup> Limited information about antidepressant type and dose, concurrent medications, and comorbidities may have had an impact on our ability to find an association.

Our study included a large, racially and ethnically diverse sample of postmenopausal women who were well characterized by a comprehensive range of covariates for the analyses. However, the WHI did not adjudicate depression diagnosis. Instead, we used the cutoff score of 5 or more on the Center for Epidemiological Studies Depression Scale short form to represent those with elevated depressive symptoms. Although this particular score has not been psychometrically validated using clinically diagnosed depression as a gold standard, the elevated depressive symptoms cutoff used in the WHI has been shown to be highly correlated with diagnosed depression.<sup>26,27</sup> We note that antidepressants are often prescribed for anxiety disorders and for other conditions, and may not be indicative of specific treatment of depression. Antidepressant medication prescribing practices for depression are usually long term,<sup>64</sup> but specific antidepressants, doses, and concurrent medications may change over

time. We did not have measures of medication dose, duration, or compliance to confirm specific associations with biomarkers for CVD and diabetes such as insulin and CRP. Additionally, we could not track changes in CRP after baseline. Because our analysis was epidemiological, we could not determine a causal relationship. Further study is needed to confirm these relationships through clinical trials. Finally, the WHI is not a representative national sample, and we only included subsets of women with follow-up data for longitudinal analyses; therefore, we cannot generalize results to a larger population without making additional inferential assumptions.

In conclusion, in this large population-based study of older women, we found a strong relation between elevated depressive symptoms and antidepressant use and increased BMI, waist circumference, and CRP. The results of these analyses indicate the prudence of monitoring BMI, waist circumference, and other risk factors including serum glucose, insulin resistance, and CRP among women with elevated depression symptoms or who are taking antidepressant medication to prevent diabetes and CVD. Further study is needed to identify the specific patterns of change associated with diabetic and cardiovascular disease risk markers and individual antidepressants and depression. ■

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### Contributors

Y. Ma researched the data and wrote the article. R. Balasubramanian and M. Zorn performed the data analyses and reviewed and edited the article. S. L. Pagoto, K. L. Schneider, J. R. Hébert, L. S. Phillips, J. S. Goveas, A. L. Culver, B. C. Olenzki, J. Beck, J. W. Smoller, D. M. Sepavich, J. K. Ockene, L. Uebelacker, and S. Liu contributed to discussion and reviewed and edited the article.

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### Human Participant Protection

All protocol and consent forms were approved by institutional review boards of participating institutions of the WHI, and an institutional review board exemption was obtained at the University of Massachusetts Medical School for the use of deidentified data for the current analysis.

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