Published in final edited form as:
Prev Med. 2013 November ; 57(5): 525–532. doi:10.1016/j.ypmed.2013.07.006.

Weight and metabolic effects of dietary weight loss and exercise interventions in postmenopausal antidepressant medication users and non-users: a randomized controlled trial

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Abstract

Objective—Antidepressants may attenuate the effects of diet and exercise programs. We compared adherence and changes in body measures and biomarkers of glucose metabolism and inflammation between antidepressant users and non-users in a 12-month randomized controlled trial.

Methods—Overweight or obese, postmenopausal women were assigned to: diet (10% weight loss goal, N=118); moderate-to-vigorous aerobic exercise (225 minutes/week, N=117); diet +exercise (N=117); and control (N=87) in Seattle, WA 2005–2009. Women using antidepressants at baseline were classified as users (N=109). ANCOVA and generalized estimating equation approaches, respectively, were used to compare adherence (exercise amount, diet session attendance, and changes in percent calorie intake from fat, cardiopulmonary fitness, and pedometer steps) and changes in body measures (weight, waist and percent body fat) and serum

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Conflict of interest
Dr. McTiernan has received compensation as a consultant for Metagenics and holds stock in Merck.

biomarkers (glucose, insulin, homeostasis assessment-insulin resistance, and high-sensitivity C-reactive protein) between users and non-users. An interaction term (intervention × antidepressant use) tested effect modification.

Results—There were no differences in adherence except diet session attendance was lower among users in the diet+exercise group ($P<0.05$ vs. non-users). Changes in body measures and serum biomarkers did not differ by antidepressant use ($P_{interaction}>0.05$).

Conclusion—Dietary weight loss and exercise improved body measures and biomarkers of glucose metabolism and inflammation independent of antidepressant use.

Keywords

Obesity; weight loss intervention; antidepressants; diet; exercise

Introduction

Antidepressant medications are frequently prescribed in the United States; prevalence of use in adults has increased more than threefold (Paulose-Ram et al., 2007). Several studies show that individuals taking antidepressants have increased risk for obesity or weight gain (Kivimaki et al., 2010; Patten et al., 2011; Rubin et al., 2010a; Serretti and Mandelli, 2010), diabetes (Kivimaki et al., 2010; Pan et al., 2012; Rubin et al., 2008; Rubin et al., 2010b), and cardiovascular disease (Cohen et al., 2000; Hamer et al., 2011b; Smoller et al., 2009).

It is not clear if antidepressant use has a physiological effect on weight loss efficacy and risk factors associated with chronic disease, or if the impact of antidepressants is tied to behavioral factors. *In vitro* studies show that fluoxetine (Garcia-Colunga et al., 1997), paroxetine (Fryer and Lukas, 1999), nefazodone (Fryer and Lukas, 1999), and venlafaxine (Fryer and Lukas, 1999), commonly prescribed antidepressants, non-competitively inhibit muscle nicotinic acetylcholine receptors, which may reduce energy expenditure. Paroxetine and sertraline inhibit insulin signaling in rat hepatoma cells (Levkovitz et al., 2007), suggesting potential direct effects of antidepressants on energy balance and insulin resistance. Among adults with type 2 diabetes, antidepressant users were more likely to have clinical and behavioral cardiovascular disease risk factors including high blood pressure or antihypertensive use, high cholesterol or lipid lowering drug use, high triglyceride or lipid lowering drug use, current smoking, and BMI ≥30kg/m^2 (Rubin et al., 2010a).

Dietary weight loss and exercise interventions can reduce weight in patients with depression (Ludman et al., 2010; Pagoto et al., 2007; Richardson et al., 2005). Whether antidepressant use modifies intervention effects on weight is not well established, however. In a 24-month exercise and dietary weight loss intervention in 1632 overweight adult women, antidepressant users lost less weight vs. non-users (Linde et al., 2004). In 131 obese adults, participants with major depressive disorder lost less weight compared to those without the disorder (Pagoto et al., 2007), using the Diabetes Prevention Program (DPP) (Knowler et al., 2002). In 190 obese women with or without major depressive disorder attending a 12-month group-based caloric reduction and exercise weight loss intervention, there were no significant differences in weight loss between the two groups; those who attended ≥12 sessions reduced weight independent of depression status (Ludman et al., 2010).

Several dietary weight loss and exercise intervention studies have shown that individuals with depression have low adherence (Flegal et al., 2007; Somerset et al., 2011) and high dropout rates (Pagoto et al., 2007). Lower intervention adherence among antidepressant users may account for differences in weight loss between antidepressant users and non-users.

The primary aim of this analysis was to compare the effects of 12-month dietary weight loss and/or exercise interventions on body composition (weight, waist circumference, and percent body fat); and biomarkers of glucose metabolism (fasting glucose, insulin, and homeostasis assessment-insulin resistance [HOMA-IR]) and inflammation (high-sensitivity c-reactive protein [hs-CRP]) between overweight or obese postmenopausal women taking or not taking antidepressants. To our knowledge, no studies have tested whether antidepressant use modifies changes in biomarkers of glucose metabolism and hs-CRP, an inflammatory biomarker used to assess risk of coronary heart disease (Buckley et al., 2009). The secondary aim of this analysis was to compare adherence to the diet and exercise programs between those using and not using antidepressants.

Methods and Subjects

Study design and participants

The Nutrition and Exercise for Women (NEW) study was a 12-month, randomized controlled trial conducted from 2005–2009 at the Fred Hutchinson Cancer Research Center (FHCRC), Seattle, WA. The study examined the individual and combined effects of 12-months of reduced calorie diet and/or exercise interventions on breast cancer biomarkers. The primary outcome was serum estrone (Campbell et al., 2012). Secondary outcomes were additional sex hormones (Campbell et al., 2012), glucose metabolism (Mason et al., 2011), body composition (Foster-Schubert et al., 2011), quality of life (Imayama et al., 2011), and complete blood count (Imayama et al., 2012). In an ancillary study we assessed the interventions' effects on inflammatory biomarkers (Imayama et al., 2012). The trial was designed to have at least 80% power for a 0.05/3 level test to detect a difference of 10% in 12-month estrone changes for 3 primary comparisons. Because of funding limitation and expected adherence and retention after half of the women completed the trial, power calculations were repeated and the recruitment goal was changed from 503 to 439. The study procedures were reviewed and approved by the FHCRC Institutional Review Board. All participants provided signed Informed Consent.

The study design, recruitment, and intervention methods have been reported elsewhere (Foster-Schubert et al., 2011). Participants were recruited from the greater Seattle area (Figure 1). Eligibility criteria included: 50–75 years of age; BMI ≥25.0 kg/m^2 (if Asian-American ≥23.0 kg/m^2); <100 minutes/week of moderate activity; postmenopausal; not taking postmenopausal hormone therapy for the past 3 months; no history of breast cancer, heart disease, diabetes mellitus, or other serious medical conditions; fasting glucose <126 mg/dL; non-smoking; ≤2 alcohol drinks/day; able to attend diet/exercise sessions at the intervention site; and a normal exercise tolerance test.

Randomization and interventions

A total of 439 women were randomized to dietary weight loss with a goal of 10% weight reduction (N=118); moderate-to-vigorous intensity aerobic exercise for 45 minutes/day, 5 days/week (N=117); combined exercise and diet (N=117); or control (N=87). Computerized randomization was stratified by BMI (<30.0, ≥30.0 kg/m^2) and race/ethnicity (non-Hispanic white, black, other). Permuted blocks allocated a smaller number of women to the control group. The sequence was concealed until the allocation was determined. Study staff enrolled and informed participants of group assignment. Other than statisticians, all study staff involved in assessments and investigators were blinded to randomization.

The dietary weight loss intervention was based on the DPP (Knowler et al., 2002) and the Action for Health in Diabetes trial lifestyle interventions (Ryan et al., 2003) with the following goals: caloric intake of 1200–2000 kcal/day based on weight, ≤30% calories from fat, and 10% weight loss by week 24, with weight maintenance thereafter. Dietitians with

training in behavior modification conducted the diet intervention. Participants had 2–4 individual sessions with a study dietitian, attended weekly group sessions (5–10 women) until week 24, and completed daily food logs for at least 6 months or until they reached their weight loss goal. Afterwards they attended monthly group sessions and had e-mail/phone contact. The diet+exercise group attended separate diet sessions from the diet-only group.

The exercise goal was 45 minutes/day, 5 days/week of moderate-to-vigorous intensity exercise for 12 months. Participants attended 3 supervised sessions/week at the facility and exercised 2 days/week at home. They gradually increased exercise training to 70–85% of maximal heart rate (based on baseline VO_2max treadmill test) for 45 minutes/session by week 7 and maintained thereafter. At each session participants wore Polar heart rate monitors (Polar Electro, New Hyde Park, NY, USA) and recorded exercise mode, duration, peak heart rate, and perceived exertion in facility and home activity logs. Activities with ≥4 METs were counted toward the prescribed exercise target (Ainsworth et al., 2000).

Exercise-only and diet-only participants were asked not to change their respective diet and exercise habits. Controls were asked not to change their diet or exercise habits. At the end of 12 months, controls were offered 4 group diet sessions and 8 weeks of supervised exercise sessions.

Measurements

Demographics, medication use, depressive symptoms, exercise and diet behaviors, cardiopulmonary fitness, pedometer counts, weight, waist circumference, and percent body fat were assessed at baseline and at 12 months. We used standardized questionnaires to collect demographic information. Participants brought current prescription and over-the-counter medication bottles to clinic visits. Participants regularly taking prescription antidepressant medications (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclics, and atypical antidepressants) at baseline were classified as antidepressant users. Because of concerns about a subgroup analysis using post-randomization factors, we defined user status according to baseline data (Yusuf et al., 1991).

Depression was measured using the validated Brief Symptom Inventory-18 (Derogatis, 2001; Derogatis and Melisaratos, 1983). Type, intensity and duration of exercise over the previous 3 months were assessed (Taylor et al., 1978). We used the 120-item food frequency questionnaire (FFQ) to assess usual dietary intake, and calculated percent of caloric intake from fat (Patterson et al., 1999). Cardiopulmonary fitness was assessed using a modified branching treadmill protocol (Foster-Schubert et al., 2011; Pate et al., 1991; Schauer and Hanson, 1987). Participants wore pedometers (Accusplit, Silicon Valley, CA, USA) for 7 consecutive days from which the mean steps/day was determined. Height, weight and waist circumference were measured and BMI was calculated as kg/m^2 (Foster-Schubert et al., 2011). Body fat was measured by a dual-energy x-ray absorptiometry whole-body scanner (GE Lunar, Madison, WI, USA).

Twelve-hour fasting blood samples were collected at baseline and 12 months, with no exercise for 24 hours. The intra- and inter-assay coefficients of variations (CVs) for glucose were 1.1% and 3.5%, respectively. The intra-assay CV was 4.5% for insulin. We calculated HOMA-IR=fasting insulin(mU/L)×fasting glucose(mmol/L)/22.5 (Matthews et al., 1985). The lower detection limit was 0.2 mg/L for hs-CRP. Intra- and inter-batch CVs were 4.1% and 4.7%, respectively, for hs-CRP.

Change in percent of calorie intake from fat (FFQ) and diet session attendance were used as indicators of diet intervention adherence. Total minutes of moderate-to-vigorous exercise/week were calculated from the facility and home exercise logs. We used minutes/week of

moderate-to-vigorous exercise, and 12-month changes in cardiopulmonary fitness and pedometer steps as indicators of exercise adherence.

Statistical analysis

Baseline characteristics between antidepressant users and non-users within each study group were compared using a *t*-test or χ^2 test as appropriate. Numbers of participants who started using antidepressants (non-user at baseline and user at 12 months) and stopped using antidepressants (user at baseline and non-user at 12 months) among the study groups were compared using a Fisher's exact test. The association between antidepressant use and depression score (tertiles) at baseline was examined by χ^2 test. Based on intention-to-treat principle, we analyzed the data using last observation carried forward (LOCF) for missing data at 12 months. We also repeated the analysis using available data (Supplementary Table 1–3). There were no substantial differences in the findings; thus, we report the result of LOCF analysis. Rates of dropouts and adherence to the diet and exercise sessions between antidepressant users and non-users within each intervention arm and across tertiles of baseline depression score in non-users were compared using a logistic regression model and analysis of covariance (ANCOVA), respectively. We used generalized estimating equations to compare changes from baseline to 12 months. An interaction term of intervention × antidepressant user status was included in the model to test effect modification by antidepressant use. As several interaction terms showed marginal statistical significance ($p<0.20$), and a previous report suggested possible modifying effects of antidepressant use on weight loss (Linde et al., 2004), we performed further analyses to investigate the effect size and statistical significance in each intervention arm vs. control within each antidepressant user status. Additionally, we compared 12-month weight loss between antidepressant users and non-users within each study arm using ANCOVA. Outcomes were also compared between users and non-users in all participants, intervention arms and control using ANCOVA adjusted for group assignment. To account for differences in intervention adherence, models were adjusted for intervention adherence variables that were significantly different between antidepressant users and non-users (i.e., diet session attendance). Models were further adjusted for depression symptoms to test for confounding effects. All analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Briefly, the diet, diet+exercise, and exercise groups decreased weight from baseline by 8.5% ($p<0.01$), 10.8% ($p<0.01$), and 2.4% ($p=0.03$) respectively (vs. controls, Foster-Schubert et al., 2011). All intervention groups decreased percent body fat (Δdiet=−4.2%; Δdiet +exercise=−5.9%; Δexercise=−1.6%; all $p<0.01$ vs. controls) (Foster-Schubert et al., 2011). Compared to controls (+1.1 cm), waist circumference decreased in diet (−4.4 cm, $p<0.01$), diet+exercise (−7.0 cm, $p<0.01$), and exercise (−2.0 cm, $p=0.02$) groups (Foster-Schubert et al., 2011).

Among the diet and diet+exercise groups, 41.5% (N=49) and 59.5% (N=69), respectively, achieved the 10% weight loss goal at 12 months. The exercise and diet+exercise groups completed respective means of 80.2% and 84.7% of the exercise goal (225 minutes/week). The exercise and diet+exercise groups increased pedometer counts by an average of 2415 and 3468 steps/day, respectively (both $p<0.01$ vs. controls). Aerobic fitness increased by 0.17 L/min in the exercise and 0.12 L/min in the diet+exercise groups (both $p<0.01$ vs. control). The diet and diet+exercise groups significantly reduced fasting glucose (Δdiet= −2.4%, Δdiet+exercise=−2.8%); insulin (Δdiet=−22.3%, Δdiet+exercise=−24.0%); HOMA-IR (Δdiet=−24.3%, Δdiet+exercise=−26.4%); and hs-CRP (Δdiet=−36.1%, Δdiet+exercise= −41.7%) compared to controls ($p\leq0.002$). In the exercise group, there were no significant changes in these biomarkers (Imayama et al., 2012; Mason et al., 2011).

Baseline characteristics of participants

At baseline and 12-months, 109 (24.8%) and 85 (21.3%) women, respectively, were taking antidepressants (Supplementary Table 4). Of the 400 women who completed both baseline and 12-month assessments, 76 reported using antidepressants at both time-points, with 21 stopping them and 9 starting their use. There were no differences in the numbers of participants who started and stopped antidepressants during the study between the groups ($p>0.05$).

There were no significant baseline differences in demographics, anthropometrics, biomarkers of glucose metabolism and inflammation, and exercise and diet behaviors between antidepressant users and non-users within each study arm except for higher percent body fat among antidepressant users in the diet+exercise group (vs. non-users, $p=0.04$, Table 1). Antidepressant users had more depressive symptoms compared to non-users in both the diet-only and exercise-only groups ($p<0.01$). Prevalence of antidepressant use increased with increasing tertile of baseline depression score ($p=0.006$, Supplementary table 8).

Adherence to intervention between antidepressant users and non-users

The number of dropouts between antidepressant users and non-users did not differ in any intervention groups ($p>0.05$, Table 2). We observed no differences in 12-month change in cardiopulmonary fitness and weekly minutes of moderate-to-vigorous exercise between antidepressant users and non-users ($p>0.05$).

Diet session attendance was higher among antidepressant non-users in the diet+exercise group (vs. users, $p=0.03$),which attenuated after adjusting for depressive symptoms at baseline and 12 months (vs. users, $p>0.05$, results not shown).

Among non-users there were no differences in adherence by tertile of baseline depression symptom except for a smaller reduction in %calorie intake from fat in the highest tertile in the diet+exercise group (vs. lowest or middle tertile, Supplementary table 9).

Changes in body composition between antidepressant users and non-users

The intervention effects on weight, waist circumference, and percent body fat were not modified by antidepressant user status in any intervention arm ($P_{interaction}>0.05$, Table 3). Percent body fat and waist circumference were reduced regardless of antidepressant use in all intervention groups ($p<0.05$ vs. control). Weight was significantly reduced in both antidepressant users and non-users in all intervention groups (vs. controls, $p<0.01$), with the exception of non-users randomized to exercise alone ($p=0.09$). Adjusting for depressive symptoms at baseline and 12 months had negligible effects on the changes in body composition among both antidepressant users and non-users (results not shown).

Changes in biomarkers of glucose metabolism and inflammation

The diet and diet+exercise groups significantly reduced fasting glucose in antidepressant non-users (vs. controls, $p<0.05$), but not in users (Table 4). The diet and diet+exercise groups reduced insulin in both antidepressant users and non-users ($p<0.01$ vs. control). The exercise group reduced insulin among users only ($p=0.03$, vs. control). The diet and diet +exercise groups reduced HOMA-IR and hs-CRP in both antidepressant users and non-users ($p<0.05$, vs. control). All tests for interaction between anti-depressant use and intervention effects were nonsignificant, however.

To assess the effect of continuous antidepressant use, all analyses were repeated by comparing continuous antidepressant users (i.e., antidepressant use at both baseline and 12 months [N=76] versus non-users at both time points [N=294]). Except for a significant

interaction in changes in fasting glucose between women who were continuous users and non-users in the diet group ($P_{interaction}$=0.05, Supplementary Table 5–7), there were no substantial differences in the results.

Direct comparisons between antidepressant users and non-users

We also contrasted 12-month weight loss between antidepressant users and non-users within each study arm. We found a smaller weight loss among antidepressant users in the exercise (p=0.002, vs. non-users) and control groups (p=0.0008, vs. non-users), while there were no differences in the diet (p=0.20, vs. non-users) and the diet+exercise groups (p=0.35, vs. non-users; results not shown).

When all participants were combined, with adjustment for group assignment and diet session attendance, users had significantly lower decreases in weight, percent body fat and waist circumference (Supplementary table 10).

Discussion

In this study, we found no differences in most adherence variables and 12-month changes in body composition, biomarkers of glucose metabolism, and hs-CRP between antidepressant users and non-users during a 12-month diet and/or exercise intervention. Our findings suggest that when adherence is similar between antidepressant users and non-users, the dietary weight loss and exercise programs improve body composition, glucose metabolism, and inflammation independent of antidepressant use.

To our knowledge, only one previous intervention study compared the differences in weight loss between antidepressant users and non-users (Linde et al., 2004). A 24-month randomized trial of 1632 overweight adults that compared low-cost telephone-based, mail-based, and usual care interventions for weight loss, reported a smaller weight loss among female antidepressant users (mean weight loss 0.91 kg) compared to non-users (mean weigh loss 2.68 kg) at 12 months (Linde et al., 2004). We did not observe significant differences in weight loss between antidepressant users and non-users; however, a closer observation of the 12-month changes in weight showed 1.4–2.6 kg differences in absolute weight changes between antidepressant users and non-users (1.4 kg in diet, 2.6 kg in exercise, 1.9 kg in diet +exercise and 4.0 kg in controls). Differences in our statistical approaches to compare the differences between antidepressant users and non-users may have partially contributed to conflicting findings with the prior study.

When we contrasted 12-month weight loss between antidepressant users and non-users within each study arm, we found a smaller degree of weight loss among antidepressant users in the exercise and control but not in the diet groups. Our statistical approach examined the intervention effects relative to controls. However, among controls, antidepressant users showed greater weight gain compared to non-users. Several studies have similarly shown that antidepressants users are more likely to gain weight compared to non-users (Kivimaki et al., 2010; Patten et al., 2011). Thus, the differences in natural body weight trajectory between antidepressant users and non-users may need to be considered when evaluating the effects of weight loss programs.

The diet and diet+exercise groups significantly reduced insulin, fasting glucose, HOMA-IR, and hs-CRP independent of antidepressant use. Observational studies have shown that antidepressant use is associated with higher CRP (Hamer et al., 2011a) and increased risk for diabetes (Ma et al., 2011; Pan et al., 2012; Rubin et al., 2008; Rubin et al., 2010b) and cardiovascular disease (Cohen et al., 2000; Hamer et al., 2011b; Smoller et al., 2009). An analysis of a cohort study of 4584 adults showed that antidepressant use at baseline (1997–

1999) and follow-up (2003–2004) was associated with higher CRP compared to non-users at both time points (Hamer et al., 2011a). The biological mechanisms of how antidepressants increase the risk of diabetes and cardiovascular disease are not established. Our findings suggest that dietary weight loss and exercise interventions reduce weight and improve biomarkers of glucose metabolism and inflammation independently of antidepressant use given similar adherence to interventions.

Since antidepressant users may have reduced adherence, this underscores the need for more intensive strategies to increase adherence in behavioral intervention studies. Several studies (Flegal et al., 2007; Somerset et al., 2011), but not all (Ludman et al., 2010), have shown that depression is associated with low adherence to diet and/or exercise programs. Our antidepressant users had a mean depression score similar to the norm of non-depressed women (Derogatis, 2001), which may account for our observed, non-significant differences in most adherence variables between antidepressant users and non-users.

Although most adherence differences did not reach statistical significance, we observed a consistent tendency of smaller increases in pedometer counts and reductions in percent calorie intake from fat among antidepressant users compared with non-users in all intervention arms.

Our antidepressant users in the diet and diet+exercise groups reduced weight by 7.6% and 9.2% and hs-CRP by 42.6% and 33.2%, respectively. A review concluded that 5% weight loss has beneficial effects on health outcomes, including lipid profile and blood pressure control (Blackburn, 1995). Another review estimated that individuals with CRP>3.0mg/L have an estimated relative risk of 1.58 (95%CI=1.37–1.83) for coronary heart disease compared to those with CRP<1.0 mg/L (Buckley et al., 2009). The observed reduction of hs-CRP in the diet and diet+exercise programs could have a significant health benefits among antidepressant users and nonusers alike.

Strengths of this study includes a large sample size, study design allowing direct comparisons of three intervention arms, low dropout rate (9%), and valid measures to assess outcomes. There are several limitations. Our participants, even those taking antidepressants, had only mild or no symptoms of depression. The findings therefore cannot be generalized to patients with moderate or severe depression. The study was not large enough to differentiate types of antidepressant medications which may have different effects on weight change and other outcomes (Serretti and Mandelli, 2010). We did not take into account the length of antidepressant use. This was a secondary analysis of the trial; thus, we had limited power to detect differences in intervention effects between antidepressant users and non-users.

Conclusion

In this study, we found that antidepressant use does not interfere with the effects of dietary weight loss and exercise on body composition and biomarkers of glucose metabolism and inflammation. Because antidepressant use is associated with increased risk of obesity and obesity-related comorbidities, practitioners are encouraged to promote dietary weight loss and exercise programs to reduce risks of obesity, diabetes, and cardiovascular disease especially among individuals who are prescribed antidepressant medications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The NEW trial was supported by R01 CA105204-01A1 and U54-CA116847 from National Cancer Institute (NCI). Part of this study was conducted at the University of Washington, Clinical Nutrition Research Unit supported by National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) 61–7015. While working on the trial, CMA was employed at the Ohio State University, and located to NCI following completion of her effort on the NEW trial. CM is and KC was supported by a fellowship from the Canadian Institutes of Health Research. AK was supported by NCI R25CA094880 at the time of this study and is currently supported by NCI 2R25CA057699. KEF is supported by 5KL2RR025015-03 from National Center for Research Resources, a component of the National Institute of Health (NIH) and NIH Roadmap for Medical Research. These funding agencies had no role in study design, data collection, data analysis and interpretation of the results, writing of the article and decision to submit it for publication.

Trial registration:

Clinicaltrials.gov NCT00470119

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Highlights

- We compared intervention adherence and effects by antidepressant use.
- There were no differences in most adherence variables between users and non-users.
- Intervention effects on body measures did not differ by antidepressant use.
- Intervention effects on serum biomarkers did not differ by antidepressant use.

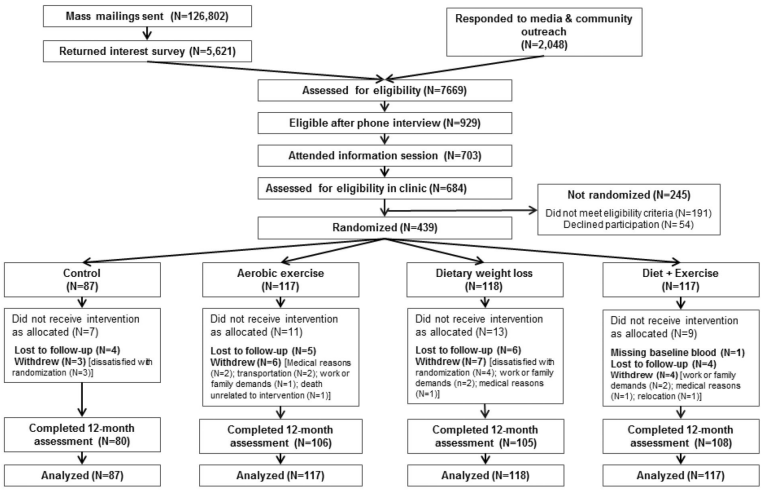

Figure 1.
CONSORT diagram of the Nutrition and Exercise for Women (NEW) trial, Seattle WA 2005–2009

Table 1

Baseline characteristics of study participants stratified by baseline antidepressant use in Seattle, WA 2005–2009

	Control		Diet		Exercise		Diet + Exercise	
	Users (N=19)	**Non-users (N=68)**	**Users (N=26)**	**Non-users (N=92)**	**Users (N=29)**	**Non-users (N=88)**	**Users (N=35)**	**Non-users (N=82)**
Age, mean (SD)	56.8 (4.4)	57.6 (4.4)	58.4 (6.1)	58.0 (5.9)	57.5 (5.5)	58.3 (4.8)	57.3 (3.4)	58.4 (4.9)
Ethnicity, n (%)								
Non-Hispanic white	17 (89.5)	57 (83.8)	21 (80.8)	80 (87.0)	27 (93.1)	71 (80.7)	30 (85.7)	70 (85.4)
Education, n (%)								
College degree	13 (68.4)	46 (67.6)	16 (61.5)	60 (65.2)	12 (41.4)	58 (65.9)	26 (74.3)	56 (68.3)
Marital status, n (%)								
Married/living with a partner	12 (63.2)	47 (69.1)	15 (57.7)	64 (69.6)	15 (57.7)	51 (58.0)	21 (60.0)	49 (60.5)
Anthropometrics, mean (SD)								
Body mass index, kg/m^2	30.8 (3.9)	30.7 (3.9)	31.4 (3.4)	30.9 (4.1)	31.3 (4.4)	30.5 (3.5)	31.4 (4.0)	30.8 (4.4)
Waist circumference, cm	93.7 (9.7)	95.2 (10.4)	97.9 (10.3)	93.7 (10.0)	94.5 (10.4)	95.2 (10.1)	95.5 (10.3)	92.9 (9.7)
Percent body fat, %	48.0 (5.0)	47.8 (4.4)	47.5 (3.5)	47.6 (4.6)	47.9 (4.1)	47.9 (4.2)	49.3 (4.9)*	47.4 (4.3)
Cardiopulmonary fitness, mL/kg/min	23.0 (3.5)	23.1 (4.3)	22.8 (2.9)	22.6 (4.0)	22.5 (3.1)	22.4 (4.4)	22.5 (5.0)	24.0 (3.7)
Biomarkers, mean (SD)								
Fasting glucose, mg/dL	96.4 (6.0)	97.2 (8.9)	96.9 (8.9)	96.8 (8.6)	95.4 (10.5)	96.0 (7.2)	95.2 (7.7)	96.4 (7.8)
Insulin, mU/L	12.7 (4.6)	13.6 (6.9)	14.3 (8.3)	12.8 (8.9)	13.9 (13.2)	12.1 (5.4)	11.7 (5.7)	12.9 (9.6)
HOMA-IR	3.0 (1.2)	3.3 (1.8)	3.4 (2.1)	3.1 (2.3)	3.4 (3.7)	2.9 (1.3)	2.7 (1.4)	3.1 (2.5)
C-reactive protein, mg/L	2.61 (2.30)	3.40 (3.80)	5.15 (6.00)	3.69 (3.28)	4.29 (5.22)	3.69 (3.39)	3.05 (2.58)	3.12 (2.70)
Exercise & Diet habits, mean (SD)								
Physical activity, min/week	14.6 (14.7)	26.4 (45.7)	25.9 (35.1)	35.8 (48.0)	49.1 (47.3)	34.0 (42.1)	23.3 (49.0)	38.0 (42.2)
Physical activity, min/week, median (25^{th} – 75^{th} percentile)	13.8 (0.0 – 23.0)	1.4 (0.0 – 36.7)	14.5 (0.0 – 55.1)	13.8 (0.0 – 66.6)	41.3 (9.2 – 76.9)	25.2 (0.0 – 54.0)	0.0 (0.0 – 23.0)	23.0 (0.0 – 67.3)
Pedometer counts, steps/day	5035 (2029)	5765 (2403)	5146 (2086)	5652 (2302)	5424 (2190)	5886 (2111)	6171 (2516)	5903 (2354)
Daily calorie intake, kcal	2158 (602)	1945 (682)	2084 (676)	1831 (651)	2022 (581)	1974 (595)	2027 (708)	1830 (599)
% calorie intake from fat, %	36.1 (5.8)	35.4 (7.2)	31.6 (5.6)	33.5 (6.4)	33.9 (6.7)	33.5 (7.0)	33.8 (5.7)	36.0 (7.9)
Depression, mean (SD)								
Depression symptoms	50.6 (8.6)	47.3 (9.0)	53.6 (9.0)†	48.2 (9.7)	52.3 (10.2)†	47.0 (8.7)	49.5 (9.3)	47.7 (8.4)

	Control		Diet		Exercise		Diet + Exercise	
	Users (N=19)	Non-users (N=68)	Users (N=26)	Non-users (N=92)	Users (N=29)	Non-users (N=88)	Users (N=35)	Non-users (N=82)
Antidepressants use, n (%)								
SSRI	14 (73.7)	---	13 (50.0)	---	17 (58.6)	---	21 (60.0)	---
SNRI	1 (5.3)	---	3 (11.5)	---	5 (17.2)	---	6 (17.1)	---
Atypical antidepressant	7 (36.8)	---	12 (46.2)	---	7 (24.1)	---	7 (20.0)	---
Tricyclic antidepressant	0 (0.0)	---	4 (3.8)	---	4 (13.8)	---	5 (14.3)	---

SSRI: Selective serotonin reuptake inhibitor SNRI: Serotonin–norepinephrine reuptake inhibitor

*p<0.05 for the differences between antidepressants users and non-users within each intervention group

†p<0.01 for the differences between antidepressants users and non-users within each intervention group

Table 2

Adherence to a 12-month lifestyle intervention among antidepressant users and non-users in Seattle, WA 2005–2009

	Diet			Exercise			Diet + Exercise		
	Users	**Non-users**		**Users**	**Non-users**		**Users**	**Non-users**	
	(N=26)	**(N=92)**		**(N=29)**	**(N=88)**		**(N=35)**	**(N=82)**	
	Odds ratio (95% CI)		**p-value**	**Odds ratio (95% CI)**		**p-value**	**Odds ratio (95% CI)**		**p-value**
Drop outs	1.07 (0.21 to 4.21)	ref	0.92	1.15 (0.29 to 4.67)	ref	0.84	4.39 (0.99 to 19.6)	ref	0.052
	Mean (SD)	Mean (SD)	p-value	Mean (SD)	Mean (SD)	p-value	Mean (SD)	Mean (SD)	p-value
Exercise Adherence									
ΔCardiopulmonary fitness, L/min*	---	---	---	0.18 (0.17)	0.16 (0.40)	0.77	0.14 (0.34)	0.12 (0.35)	0.92
Exercise adherence, min/week	---	---	---	160.2 (65.1)	164.3 (72.7)	0.78	157.4 (79.2)	177.9 (53.6)	0.13
ΔPedometer counts, steps/day*	---	---	---	1646 (2709)	2636 (2750)	0.10	2573 (2885)	3796 (2996)	0.06
Diet Adherence									
ΔCalorie intake from fat, %*	−3.1 (6.1)	−6.5 (7.2)	0.08	---	---	---	−5.7 (6.3)	−7.7 (7.8)	0.48
Diet session attendance, percent of sessions attended	91.2 (29.0)	89.5 (29.0)	0.77	---	---	---	84.3 (25.1)	95.6 (21.0)	**0.03**

P values compared drop out and exercise and dietary adherence between antidepressant users and non-users.

ANCOVA models for changes in cardiopulmonary fitness, pedometer counts, percent calorie intake from fat were adjusted for baseline values.

Table 3

12-month changes in anthropometric outcomes among antidepressant users and non-users in Seattle, WA 2005–2009

	Antidepressant users					Non-users					
		baseline	12 months	Change	P value		baseline	12 months	Change	P value	Pinteraction
	N	Geo Means (95% CI)	Geo Means (95% CI)	Absolute (%)		N	Geo Means (95% CI)	Geo Means (95% CI)	Absolute (%)		
Weight, kg											
Control	19	83.2 (77.5–89.3)	85.6 (80.0–91.7)	2.5 (3.0)	Ref	68	83.3 (80.5–86.3)	81.8 (79.0–84.7)	−1.5 (−1.8)	Ref	
Diet	26	84.9 (80.8–89.1)	78.4 (74.0–83.2)	−6.4 (−7.6)	**<0.0001**	92	82.8 (80.4–85.2)	75.0 (72.3–77.8)	−7.8 (−9.4)	**<0.0001**	0.18
Exercise	29	82.9 (78.5–87.6)	82.8 (78.4–87.5)	−0.1 (−0.1)	**0.0006**	88	82.7 (80.3–85.3)	80.1 (77.6–82.7)	−2.7 (−3.2)	0.09	0.19
Diet + Exercise	35	83.0 (79.5–86.8)	75.4 (71.4–79.5)	−7.7 (−9.2)	**<0.0001**	82	81.3 (79.1–83.6)	71.7 (69.4–74.0)	−9.6 (−11.9)	**<0.0001**	0.38
Percent body fat, %											
Control	19	47.1 (44.9–49.5)	48.1 (46.0–50.3)	0.9 (2.0)	Ref	68	47.0 (46.0–48.1)	46.5 (45.2–47.8)	−0.5 (−1.2)	Ref	
Diet	26	46.8 (45.5–48.2)	43.5 (41.6–45.4)	−3.4 (−7.2)	**<0.0001**	92	46.8 (45.8–47.7)	41.9 (40.5–43.5)	−4.8 (−10.3)	**<0.0001**	0.92
Exercise	29	47.1 (45.7–48.6)	46.4 (44.9–47.9)	−0.8 (−1.6)	**0.002**	88	47.1 (46.2–48.0)	45.2 (44.0–46.3)	−1.9 (−4.1)	**0.005**	0.71
Diet + Exercise	35	48.4 (46.8–50.0)	43.8 (41.4–46.2)	−4.6 (−9.5)	**<0.0001**	82	46.7 (45.8–47.6)	39.8 (38.3–41.3)	−7.0 (−14.9)	**<0.0001**	0.16
Waist circumference, cm											
Control	19	93.2 (89.0–97.6)	96.9 (93.0–101.0)	3.7 (3.9)	Ref	68	94.6 (92.2–97.1)	94.8 (92.5–97.2)	0.2 (0.2)	Ref	
Diet	26	97.4 (93.6–101.0)	92.8 (88.8–97.0)	−4.6 (−4.7)	**<0.0001**	92	93.2 (91.1–95.2)	88.5 (86.2–90.9)	−4.7 (−5.0)	**<0.0001**	0.33
Exercise	29	94.0 (90.4–97.7)	93.3 (90.2–96.6)	−0.6 (−0.7)	**0.005**	88	94.7 (92.7–96.8)	92.3 (90.2–94.5)	−2.4 (−2.6)	**0.01**	0.37
Diet + Exercise	35	95.0 (91.7–98.4)	89.1 (85.2–93.2)	−5.9 (−6.2)	**<0.0001**	82	92.5 (90.5–94.5)	84.6 (82.4–86.9)	−7.9 (−8.5)	**<0.0001**	0.90

P values compared changes from baseline to 12 months in intervention group vs. controls within strata defined by antidepressant use.

P interaction compared differences in 12-month changes in intervention group vs. controls between antidepressant users and non-users.

All models were adjusted for diet session attendance.

Table 4

12-month changes in serum biomarkers among antidepressant users and non-users in Seattle, WA 2005–2009

	Antidepressant users					Non-users					
		baseline	12 months	Change	P value		baseline	12 months	Change	P value	Pinteraction
	N	Geo Means (95% CI)	Geo Means (95% CI)	Absolute (%)		N	Geo Means (95% CI)	Geo Means (95% CI)	Absolute (%)		
Fasting glucose, mg/dL											
Control	19	96.2 (93.5–99.1)	96.1 (93.2–99.0)	−0.2 (−0.2)	Ref	68	96.8 (94.8–98.9)	96.7 (94.9–98.6)	−0.1 (−0.1)	Ref	
Diet	26	96.5 (93.2–99.9)	95.9 (92.2–99.6)	−0.6 (−0.7)	0.81	92	96.4 (94.6–98.2)	93.5 (91.9−95.0)	−3.0 (−3.1)	**0.004**	0.19
Exercise	29	94.9 (91.3–98.7)	94.7 (91.3–98.2)	−0.2 (−0.2)	0.99	88	95.7 (94.3–97.2)	94.4 (93.0–95.9)	−1.3 (−1.3)	0.23	0.55
Diet + Exercise	35	94.9 (92.4–97.5)	92.8 (90.1–95.6)	−2.1 (−2.2)	0.30	81	96.1 (94.4–97.8)	92.7 (91.1–94.3)	−3.3 (−3.5)	**0.002**	0.56
Insulin, µU/mL											
Control	19	11.8 (9.9–14.1)	13.6 (11.2–16.6)	1.8 (15.3)	Ref	68	12.0 (10.7–13.6)	11.3 (10.0–12.7)	−0.8 (−6.3)	Ref	
Diet	26	12.5 (10.3–15.3)	9.6 (7.7–12.1)	−2.9 (−23.1)	**<0.0001**	92	10.6 (9.4–12.0)	8.3 (7.4–9.3)	−2.3 (−22.0)	**0.004**	0.14
Exercise	29	11.2 (9.1–13.9)	10.6 (8.8–12.7)	−0.6 (−5.7)	**0.03**	88	10.8 (9.8–12.0)	9.9 (9.0–11.0)	−0.9 (−8.5)	0.68	0.11
Diet + Exercise	35	10.4 (8.8–12.3)	8.7 (7.4–10.2)	−1.7 (−16.2)	**0.0009**	81	10.8 (9.5–12.3)	7.9 (6.9–8.9)	−2.9 (−27.2)	**0.0002**	0.51
HOMA-IR (Homeostasis assessment - insulin resistance)											
Control	19	2.8 (2.3–3.4)	3.2 (2.6–4.0)	0.4 (15.1)	Ref	68	2.8 (2.5–3.2)	2.7 (2.4–3.0)	−0.2 (−6.4)	Ref	
Diet	26	3.0 (2.4–3.6)	2.3 (1.8–2.9)	−0.7 (−23.6)	**0.0002**	92	2.5 (2.2–2.9)	1.9 (1.7–2.1)	−0.6 (−24.4)	**0.002**	0.25
Exercise	29	2.6 (2.0–3.3)	2.5 (2.0–3.0)	−0.2 (−5.9)	0.054	88	2.5 (2.3–2.8)	2.3 (2.1–2.6)	−0.2 (−9.7)	0.56	0.17
Diet + Exercise	35	2.4 (2.0–2.9)	2.0 (1.7–2.4)	−0.4 (−18.0)	**0.002**	81	2.5 (2.2–2.9)	1.8 (1.6–2.0)	−0.8 (−29.7)	**<0.0001**	0.62
High-sensitivity C-reactive protein, mg/L											
Control	19	1.7 (1.0–2.7)	1.7 (1.1–2.6)	0.0 (0.9)	Ref	68	2.0 (1.5–2.6)	2.0 (1.5–2.6)	0.0 (0.8)	Ref	
Diet	26	2.9 (1.9–4.4)	1.7 (1.1–2.6)	−1.2 (−42.6)	**0.0002**	92	2.5 (2.1–3.1)	1.6 (1.3–1.9)	−0.9 (−36.4)	**<0.0001**	0.82
Exercise	29	2.7 (1.9–3.9)	2.8 (2.0–4.1)	0.1 (3.4)	0.90	88	2.4 (2.0–3.0)	2.2 (1.7–2.8)	−0.8 (−8.7)	0.30	0.35
Diet + Exercise	35	2.2 (1.6–2.9)	1.5 (1.0–2.1)	−0.7 (−33.2)	**0.02**	81	2.1 (1.7–2.6)	1.1 (0.9–1.4)	−1.0 (−46.4)	**<0.0001**	0.16

P values compared changes from baseline to 12 months in intervention group vs. controls within strata defined by antidepressant use.

P interaction compared differences in 12-month changes in intervention group vs. controls between antidepressant users and non-users.

All models were adjusted for diet session attendance.