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Anti-Depression Medication Taking and Risk of Metabolic Syndrome among US Ctizens Aged 60+ Years: an Across-Sectional Analysis of the NHANES 2007-2008

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Abstract:

OBJECTIVE: To examine whether having metabolic syndrome (MS) among seniors is associated with using anti-depression medication.

METHODS: A total of 1366 (617 men and 749 women) individuals aged 60+ years from the NHANES 2007/08 survey who had no reported heart disease and/or cancers but had information on prescribed medications in previous month were included in this analysis. All subjects were categorized into three prescribed drug use status, ie, none (group 1); no anti-depressants (group 2); and with anti-depressants (group 3). MS was defined with the criteria of the ATP III.

RESULTS: Over 80% of individuals reported taking prescribed medications with 6% of men and 16% of women respectively having used anti-depressants. About 36% of men and 40% of women respectively were considered to have MS. Results from multiple logistic regression analyses indicated that in comparing to group 1, the odds ratios (95% CI) of MS was 2.73 (1.96, 3.82) for group2 and 2.25 (1.07, 4.69) for group 3, respectively. Both group 2 and 3 had a similar metabolic risk profile, in comparing to group 1, they had higher odds of having diabetes and high level of blood pressures.

CONCLUSION: Seniors with medications are more likely to be with MS, diabetes, and high level blood pressures. However, the observed the cardio-metabolic risk association seems similar between seniors using anti -depressant drugs and using other prescribed medications.

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Introduction:

Available epidemiological evidence suggests that depression among the elderly is a significant public health problem both for its effect on quality of life and for its impact on expected lifespan[1, 2]. With an estimated prevalence of 4% among the US household population aged 60+, approximately 2.5 million in this age group suffer from depression based on 2010 – 2014 American Community Survey estimated figures [3]. Moreover, depression in seniors is considered as one of the most common conditions associated with suicide. Although people aged 60+ comprise only 19.5 percent of US population in 2014, they accounted 25.5 percent of total suicide deaths [4]. In that year, 18.6 of every 100,000 people aged 60 and older died by suicide; it is significantly higher than the rate of 13.4 per 100,000 in the general population.

There is no doubt that medication treatment for seniors with serious depression is important and necessary. However, seniors are often with large degree of medical co-morbidity, especially vascular diseases, or with much unfavorable profile of inflammatory and metabolic dysregulations, which may contribute to the development of depression in late life [5-10]; while antidepressants use are often associated with weight gain and metabolic abnormalities [11-13]. As drug therapy is often selected as a primary mode of management in depression and the antidepressants now rank as the most frequently dispensed prescription medication in the US [14], the risk for metabolic syndrome (MS) among seniors is particularly a concern. MS is a clustering of risk factors known to promote or increase the risk of cardiovascular disease including impaired glucose metabolism, hypertension, dyslipidemia and abdominal obesity [15-17]. Thus, it is necessary to be caution in regarding using antidepressants among the elderly to minimize cardiovascular risk. However, it seems no study only focus on seniors to examine how MS and its risk profile are affected by taking antidepressant drugs and whether using anti-depressant drugs is the only explanation for the observed cardio-metabolic risk association with using anti-depressant drugs. In this study, using the National Health and Nutrition Examination Survey (NHANES) 2008 dataset, we explored whether such an association can be identified.

Methods

Study Population:

Our study was based on public domain data abstracted from the 2007-2008 National Health and Nutritional Examination Survey (NHANES). A detailed description of the database may be found online (http://wwwn.cdc.gov/nchs/nhanes/search hanes07_08.aspx). The original NHANES database included self-reports on 2145 persons aged 60 and older. Within this age bracket we excluded from analysis those who provided incomplete information on prescription drug use in the preceding month and those who reported a history of either CVD (i.e., yes with either coronary heart disease, congestive heart failure, heart attack, stroke, or angina) or cancer (i.e., any type cancer or malignancy), leaving a sample size of 1366 subjects (617 men and 749 women).

Prescription 'Drug Use' Variable:

When survey participants responded 'yes' to the question on prescription medication use during the past month, further information would be gathered regarding each generic drug name and its duration of use. In 86% of cases a check of medication containers made verification of details possible. In this study, we defined three drug use categories: (1) no prescription drug use, (2) no anti-depressants among prescription drugs, and

(3) anti-depressants among prescription drugs. We have further categorized two subgroups from Group 3 according to relative duration of drug exposure: (3a), duration of taking non-antidepressant drugs is longer than that of taking anti-depressant drugs, and (3b), duration of taking anti-depressant drugs alone or is longer than that of taking non-antidepressant drugs.

Depression Status:

The 2007-2008 NHANES questionnaire included a depression screening tool, the Patient Health Questionnaire (PHQ-9) used to assess mood over the previous two weeks. The PHQ-9 has been extensively validated with performance characteristics reported in peer-reviewed publications[18]. In this paper we reported only the background rate of mild to severe depression (PHQ-9 score ≥ 5) among those who did not take anti-depressant prescription drugs.

Classification criteria for metabolic syndrome (MS) and diabetes: Survey respondents were identified as having MS based on criteria adopted by theThird Adult Treatment Panel Report of the National Cholesterol Education Program (ATP III) [19]. Component parameters of MS are shown in Table 2 with a diagnosis of MS established when 3 or more parameters reached threshold. Cases were classified as 'diabetic' conditional upon either a self-report of the disease, use of diabetic medications, HbA1c>6.5% or fasting glucose≥125 mg/dL.

Covariates:

Covariates included in the analysis were age (years), sex (male vs. female), highest education (< high school: yes vs. no), marital status (married or living with a partner: yes vs. no), home income (<$25k: yes vs. no), cigarette smoking (never, ex-smoker, current smoker), alcohol consumption (drinks/day), and physical activity (10+ min vigorous recreation activity/day: yes vs. no).

Statistical Analysis:

All analyses were conducted using survey procedures in SAS 9.2 (SAS Institute Inc., Cary, NC, USA), taking into account the weighted and clustered sampling design of NHANES. Logistic regression models were used to estimate odds ratios for the association between anti-depressant drug use and the corresponding risk of MS. Our analysis was built around two primary regression constructs each modeled three ways by adjusting for different sets of covariates. In the first construct, we used those who reported having taken no prescribed medications during the past month as the reference group and created two indicators, one for those without antidepressants in their prescribed medications, and another for those with antidepressants in their prescribed medications. In the second construct we included for analysis only those who reported prescription drug use. Those without antidepressants in their prescribed drugs were the referent group. We then specified two indicator variables from among those on anti-depressants, i.e., one for the duration of taking non-anti-depressant medications is longer than that of taking anti-depressant medications for those in group 3a, and one for the duration of taking antidepressants alone or is longer than that of taking non-anti-depressant medications for those in group 3b. Duration of taking anti-depressant and non-anti-depressant drugs respectively was calculated as the longest period of use, in years, reported for any of the drugs in each category. To examine whether depression as detected by the PHQ-9 screening tool may be associated with a risk of MS, we specified a binary indicator to classify summary scores as either screen-positive for mild to severe depression (PHQ-9≥5) or screen-negative (PHQ-9 <5). Analysis was conducted only among persons in group 1

and group 2. The level for statistical significance was set up as a 2-tailed type I error of 0.05.

Result:

Overall, approximately 80% of males and 86% of females reported taking prescribed medications during the prior month, with 6% of males

Table 2. Variables related to metabolic syndrome by sex and prescribed drug status, NHANES 2007-2008

	None	Without antidepressants in prescribed drugs	With antidepressants in prescribed drugs
Men			
n (unweighted)	140	439	38
Demographic Characteristics			
Age (yrs, mean [SE])	66.2 [0.7]	68.6 [0.5]	70.5 [0.7][a]
Less than high school (%)	19.7	26.3	25.6
Non-Hispanic White (%)	69	78.9	81.1
Married or live with a partner (%)	62.4	78.9	75.5
Home income <$25K (%)	30.3	25.1	30.4
Cigarette smoking (%)			
None	68.3	64.7	67.1
Ex-smoker	13.8	16.8	13.5
Current smoker	17.9	18.5	19.5
10+ min vigorous re-creativities (%)	29.2	25.3	27.8
Metabolic syndrome components (%)			
Fasting glucose ≥ 100 mg/dL	74.5	77.6	67.2
HDL cholesterol <40 mg/dL	16.8	29	17.5
SBP≥130 or DBP ≥85 mmHg or taking medicine	52.8	78.9[a]	71.7[a]
Triglyceride >150 mg/dL	18.2	41.9[a]	52.7[a]
Waist circumference≥102 cm	41.2	61.4	44.3
Metabolic syndrome (%)#	10.8	43.0[a]	35.2[a]
Diabetes (%)	7.1	28.3[a]	26.6[a]
Years of taking mediations (yrs, mean [SE])	n/a	8.2 [0.5]	10.5 [1.9]
Women			
n (unweighted)	134	526	89
Demographic Characteristics			
Age (yrs, mean [SE])	67.8 [0.8]	70.8 [0.4]a	67.6 [0.7]
Less than high school (%)	22.1	28	24.6
Non-Hispanic White (%)	68.4	76.8	90.3[a,b]
Married or live with a partner (%)	51.1	49.3	61.6
Home income <$25K (%)	26.3	36.6	31.2
Cigarette smoking (%)			
None	65.4	60.2	64.6
Ex-smoker	18.7	23.7	15
Current smoker	15.9	16.1	20.4
10+ min vigorous re-creativities (%)	27.2	25.3	27.9

Metabolic syndrome components (%)			
Fasting glucose ≥ 100 mg/dL	58.7	59.4	67.9
HDL cholesterol <50 mg/dL	34.9	27.6	27.7
SBP≥130 or DBP ≥85 mmHg or taking medicine	66.8	81.7[a]	76.9
Triglyceride >150 mg/dL	35.7	30.6	35.9
Waist circumference≥88 cm	67.8	72.3	78.3
Metabolic syndrome (%)#	33.8	41.7	40.7
Diabetes (%)	6.3	19.4[a]	12.4
Years of taking mediations (yrs, mean [SE])	n/a	12.0 [0.6]	12.2 [1.6]

three or more metabolic syndrome components

[a] p <0.05 compared to non-drug users; [b] p <0.05 compared to without anti-depressants in prescription.

females respectively having used anti-depressants. Among those who reported taking anti-depressant drugs, approximately 82% of them were on selective serotonin reuptake inhibitors (SSRIs). Characteristics of the sample selected for analysis are shown in Table 1. Gender differences were few in statistically significance. Females were slightly older (69.9 years vs. 68.2 years), had a lower proportion of persons married or living with a partner (51.2 % vs. 75.4%), and higher proportion of taking antidepressants (16.2 % vs. 5.7%).

Table 2 provides a breakdown of subjects by gender, prescription medication use and prevalence of variables associated with MS. Anti-depressant drug users were marginally younger in females compared with non-drug and other drug users, while marginally older among males. The other selected characteristics were similar

Table 1. Basic characteristics of the NHANES participants aged 60+ by sex, NHANES 2007-2008.

	Men	Women
	n=617	n=749
Age (yrs, mean [SE]	68.2 [0.4]	69.9 [0.3] ^
Less than high school (%)	24.9	26.7
Non-Hispanic White (%)	77	77.9
Married or live with a partner (%)	75.4	51.2^
Home income <$25K (%)	26.5	34.4
Cigarette smoking (%)		
None	65.6	61.6
Ex-smoker	16	21.6
Current smoker	18.4	16.8
10+ min vigorous re-creativities (%)	26.2	26
Medications use (%)		
None	20.4	13.5
Group1	73.8	70.3
Group2	5.7	16.2^
Metabolic syndrome (%)	36	40.5

Group1 –without antidepressants in the prescribed drugs
Group2 – with antidepressants in the prescribed drugs
^ p < 0.05 between genders

between groups by gender except that the proportion of non-Hispanic white in female anti-depressant drug users were much higher than other groups. Prevalence rates of MS were quite similar between the two drug use subgroups in females (41.7% for other drug users vs. 40.7% for anti-depressant drug users), but slightly lower in males with using anti-depressant drug (43.0% vs. 35.2%). Not surprisingly, those not taking any form of prescription medication were less likely to have MS, in particular among men (10.8% for males and 33.8% for females). Duration of drug exposure was positively related to anti-depressant use in males. When on antidepressants, the average duration of use was 10.5 years compared with 8.2 years for those solely on other drugs. No such difference appeared for females (12.0 years vs. 12.2 years).

Table 3 presents the results of logistic and 16% of regression analyses designed to measure adverse metabolic affects which may be associated with anti-depressant use. The results from model 1 indicated that after adjusting for age, sex and ethnicity, prescription drug use was associated with an increased odds for MS whether on anti-depressants (odds ratio [OR, 95% CI]:2.25 [1.07, 4.69]) or off (2.73 [1.96, 3.82]). When further adjusting for other covariates (model 2 and 3) the results were similar. Those who took anti-depressants were from two subgroups, i.e., a) the duration of taking non-anti-depressant medications is longer than that of taking anti-depressant medications, and b) taking antidepressants alone or its duration is longer than that of taking non-anti-depressant medications. However, when further dividing those who took anti-depressants into two subgroups in the models, the results were similar to Table 3 except none of them reached statistical significance (data not shown). The risk associations between prescribed drugs and each component of MS were also examined. The same covariates as in the previous model 3 were included in the logistic regression analyses. Compared to those non-drug users, prescription drug use, with or without anti-depressants, was associated with a statistically significant rise in the odds for diabetes (5.29 [2.81, 9.90] for those without anti-depressant drugs and 3.73 [1.12, 12.50] for those with anti-depressant drugs) and elevated blood pressure (8.40 [4.93, 14.30] for those without anti-depressant drugs and 5.30 [2.80, 9.70] for those with anti-depressant drugs). The ORs of having high waist circumference were similar for both drug users (OR = 1.90), but only non-antidepressant reached statistical significance. The OR estimates for the remaining variables (TG, HDL) were increased by drug use relative to the non-user reference group; however, neither reached statistical significance. No excess risk on any of the variables was found for anti-depressant drug users relative to non-antidepressant drug users, i.e., Group 3 versus Group 2.

Table 3. Odds ratio of metabolic syndrome for different prescribed drug status, NHANES 2007-2008

None			Without antidepressant in prescribed drugs		With antidepressants in prescribed drugs	
			OR	95% CI	OR	95% CI
Model 1	n=1366	1	2.73	1.96 -3.82	2.25	1.07 - 4.69
Model 2	n=1365	1	2.65	1.88 -3.74	2.16	1.07 - 4.37
Model 3	n=1237	1	2.89	1.80 - 4.63	2.65	1.18 - 5.95

Model 1 adjusting for age, gender and ethnicity
Model 2 further adjusting for family income, education, and marriage status
Model 3 further adjusting for smoking and physical activity

To generate the results in Table 4, we used a surrogate measure of drug exposure as described in the Methods section above. No increased odds of MS was evident as a result of relatively prolonged exposure to anti-depressants where non-antidepressant drug users became the referent.

The prevalence of depression detected by the PHQ-9 screening tool (PHQ-9≥5) was 8.6% for males and 11.4% for females among group 1 (non- users) and 14.1% for males 16.7% for females among group 2 (non-anti-depressant drugs in the prescribed

medications). Compared to a group who screened negative for depression (PHQ-9<5), the OR (95%CI) of MS was 1.16 (0.90, 1.49) for PHQ-9 ≥5 (mild or more severe depression) and 1.06 (0.44, 2.56) for PHQ-9≥10 (moderate or more severe depression).

to be explained well as the result of taking antidepressants because in comparing to those who were not on any prescribed drugs, the seniors with antidepressants had a similar level of odds of MS as those with non-antidepressant drugs. In addition, the cardio-metabolic risk

Table 4. Odds ratio of metabolic syndrome for different prescribed drug users, NHANES 2007-2008

		Drug user[a]	Drug user[b]		Drug user[c]	
			OR	95% CI	OR	95% CI
Model 1	n=1020	1	0.79	0.39 -1.61	1.05	0.40 -2.72
Model 2	n=1020	1	0.78	0.40 - 1.54	1.05	.041 -2.70
Model 3	n=934	1	0.84	0.46 -1.55	1.36	0.47 -3.91

a. without antidepressants in prescribed drugs

b. duration of taking non-antidepressant drugs is longer than that of taking antidepressants

c. duration of taking antidepressants alone or is longer than that of taking non-antidepressant drugs.

Model 1 adjusting for age, gender, ethnicity and yrs of taking medications

Model 2 further adjusting for family income, education, and marriage status

Discussion:

Using the NHANES 2007-08 data we examined the cardio-metabolic risk association with anti-depressants drug use among US seniors and found that in comparing to no drug users, seniors with prescribed anti-depressants were in more than two times higher odds of having MS. The high odds of MS association with using anti-depressant drugs have been observed by several different studies [12, 13, 20]. For instance, results from the PPP-Botnia Study conducted among Finns aged 18-75 years indicated that users of anti-depressant drugs had more than 50% higher odds of MS in comparing to non-users [12], and the cohort study conducted in Italy showed that in the general population without treated cardiovascular risk, pharmacologic treatment for depression was associated with about two-fold higher risk in all-cause mortality and major cardiovascular outcomes[20]. However, the observed cardio-metabolic risk association in our study seems not profiles were very similar between these two groups; in general, both of them had much higher odds of diabetes and hypertension in comparing to non-drug users.

Although results from some other studies suggested that the increased cardio-metabolic risk may be associated with the severity of mental health status [13, 21], our results from those who were not on antidepressants, however, failed to support the association. It seems the odds of having MS for those with depression measured by PHQ-9 score equal or higher than five was similar to those with a score less than five. The different results could be due to the differences between our study and others on age of the study subjects (ours were aged 60+ vs. others were with much wide age ranges) and the evaluation methods (we examined the MS risk association with depression only among those who did not take anti-depressants, while other studies did not exclude them).

However, results from some studies indicate an

alternative direction that depression, in particular seniors' depression, may be contributed by their cardio-metabolic abnormality. The term "vascular depression" has been proposed to describe a subset of depressive disorders that occurs in old age as a consequence of cerebrovascular disease[5, 22]. It has been estimated that approximately 3.4% or 2.64 million American adults 50-years and older might be considered having vascular depression[23] and treating late-life depression could improve cognitive function[24]. The change of white matter lesion volume is considered to have a causal association with vascular depression[25], but it seems more research is needed to explore the bi-directional relationship between depression and vascular disease [26].

Several limitations should be aware when interpreting the results from this study. First, like any cross-sectional study, the observed relationship cannot be explained as a causal relationship. Second, the depression measured with PHQ-9 screening tool score among those without taking anti-depressant drugs may not be so sensitive. However, the questionnaire has been validated and applied in many larger population studies; using it as a screening tool to identify the possible depression cases is still useful. Third, the prescribed medications and their duration were self-reported. Although the majority of these medications were verified with the medication containers it might still have some misclassification. The durations particularly for those seniors who took multiple medications might be less accurate. Furthermore, it was difficulty to examine the truly impact of antidepressants on MS due to the small size in that group, which was mixed with people who took the medications for depression at the first place and people who took it after other health problems. Nevertheless, the strengths of the study include the exclusion of those with serious disease history, such as CVD and cancer, the standardized measurements of MS components, detail information on demographic and potential confounding variables, and the data quality since it was from a well-organized and national representative survey.

In conclusion, seniors with prescribed medications, regardless whether taking anti-depressants or not, are more likely to have MS, diabetes, and high level blood pressure. However, the observed the cardio-metabolic risk association seems similar between seniors taking prescribed medications either with or without antidepressants. Thus, more research may be needed to explore the relationship between depression and cardio-metabolic risk among the elderly.

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