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Association between Oxidative Stress and Depressive Symptom Score in Elderly Population :A Repeated Panel Study

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Abstract

Association between Oxidative Stress and Depressive Symptom Score in Elderly Population : A Repeated Panel Study

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Objectives

Previous epidemiological studies about oxidative stress and depression are limited by hospital-based case-control design, single time measurement of oxidative stress biomarkers, and small number of study participants. Therefore in this study, we analyzed the association between biomarker of oxidative stress and scores of depressive symptom using repeatedly measured panel data from community dwelling elderly population.

Methods

From 2008 to 2010, a total of 478 elderly subjects residing in Seoul, Korea, were evaluated 3 times. Subjects underwent the Korean Version of the Short Form Generic Depression Scale test (SGDS-K) for screening depression and

urinary malondialdehyde (MDA) level was measured as oxidative stress biomarker. We used generalized estimating equation with compound symmetry covariance structure to estimate effects of oxidative stress on depressive symptom scores.

Results

A two fold increase in urinary MDA concentration were significantly associated with 33.08% (95% confidence interval (CI): 21.59%, 47.42%) increase of total SGDS-K score. In subgroup analyses by sex, a two fold increase in urinary MDA concentration were significantly associated with increased SGDS-K score in both men and women. (Men: 30.88%, 95%CI: 10.24%, 55.37%; Women: 34.77%, 95%CI: 20.09%, 51.25%) In bivariate analysis after the SGDS-K score ≥ 8 was defined as depression, the third and the fourth urinary MDA quartile showed significantly increased odds ratio of depression compared to the lowest urinary MDA quartile. (Third quartile, OR: 6.51, 95%CI: 1.77-24.00; Fourth quartile, OR: 7.11, 95%CI: 1.99-25.42)

Conclusion

In conclusion, our study suggests significant association between oxidative stress and depressive symptoms in elderly population.

Keywords: Oxidative stress, Depressive Disorder, Aged, Malondialdehyde, Depression, Epidemiologic Study

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Introduction

Depression is a disease of serious global public health burden. The World Health Organization is speculating more than 350 million people suffers from depression worldwide and nearly 1 million people dies with depression-related suicide annually. [1] Enormous and increasing disease burden emphasizes the needs to understand etiologies and underlying pathogenic mechanisms of depression.

Social, psychological, and biological risk factors of depression are believed to develop complex interactions in depression pathogenesis. [2, 3] Interestingly, some of the risk factors of depression increases oxidative stress in human tissues, [4, 5] suggesting a common pathway between oxidative stress and depression.

Oxidative stress refers imbalanced state between free radical generation and antioxidant potential. [6] Oxidative phosphorylation from mitochondria produces not only ATP but also byproducts such as reactive oxygen species (ROS) and reactive nitrogen species. When generation of free radicals exceeds the antioxidant capacity of the body, oxidative stress occurs and induces damage to all major groups of cellular macromolecules. [7]

The association between oxidative stress and depression has been reported in various epidemiological, brain imaging and molecular studies. [4, 8-11] Recently published meta-analysis also showed significant association between

oxidative stress and depression. [8] In another systematic review, depression was significantly associated with increased oxidative stress marker 8-hydroxydeoyguanosine and F2-isoprostanes. [9] Because oxidative stress is a major contributor of neuronal degeneration in the brain region, it is biologically plausible to explain the causal relationship between oxidative stress and depression. [4]

However, many of the previous epidemiological studies between oxidative stress and depression has several limitations. First, most of the studies were performed without repeated measurement of oxidative stress biomarkers. Regarding changeable nature of one's oxidative stress and depressive symptoms, single measurement may limit the reliability of previous findings. Second, most of the previous studies are hospital-based case-control studies comparing oxidative stress markers of depression patient and healthy controls. Therefore, dose-response relationship between oxidative stress and severity of depressive symptom in population without clinically diagnosed depression could not be assessed. [8] Third, although imbalance between oxygen radical generation and antioxidant potential increases with age, most of the studies are conducted in young adult population with small number of study participants. [12]

Therefore in this study, we analyzed the association between oxidative stress biomarker and depressive symptom scores from the panel data of community dwelling elderly participants. Due to changeable nature of oxidative stress and

depressive symptom, repeatedly measured data may reasonably capture the possible association. In addition, we evaluated the association in population without clinically diagnosed depression. Lastly, we focused on elderly population which has reduced capacity to respond against external stress and increased imbalance between radical generation and antioxidant potential compared to younger population. [12, 13] In other words, we analyzed vulnerable population against oxidative stress, making it more likely to observe the association between oxidative stress and depressive symptoms.

Material and Methods

Study population and data collection

This study evaluated 560 participants who regularly visited a community welfare center located in Seoungbuk-Gu, Seoul, Korea, as part of the Korean Elderly Environmental Panel (KEEP) study. The KEEP study was launched in March 2008 to explore relationship between environmental exposure and health outcomes in the elderly. The study participants visited the community welfare center for medical examination and filled out a structured questionnaire up to 5 times. Among their visits, urinary measurement of oxidative stress marker and depressive symptom test were conducted 3 times. The first examination of oxidative stress marker and depressive symptom were conducted from September to December 2008. The second and third examination were

conducted from April to October 2009 and from March to August 2010, respectively. We obtained detailed information of the participants using a structured questionnaire, including demographics, lifestyle habits, and medical history. The study protocol was approved by the institutional review board at Seoul National University Hospital, Seoul, Republic of Korea (IRB no. H-0804–045–241).

Among the panel, we excluded participants with missing urine samples and depression screening test (n=42). Because depression screening was assessed by self-reporting questionnaire, we excluded participants with low Mini Mental Status Examination (MMSE) score because of concerns regarding reliability of the depression screening tests (n=13). In addition, to focus on participants without clinically diagnosed depression, we also excluded participant who are taking depression medication (n=4). After further eliminating participants with missing covariates, a total of 917 observations from 478 participants were included in our analyses. (Figure 1) Excluded participants were tend to have history of hypertension more frequently and consume less alcohol. However, there was no statistically significant difference from the included study subjects in other general characteristics. (Supplementary Table S1) Among our final study population, 127 participated in urine MDA measurement and depressive symptom test 3 times, 185 participated 2 times, and 166 participated just 1 time.

Urinary malondialdehyde (MDA) measurement

We used urinary MDA as an oxidative stress biomarker. Urinary MDA levels were determined by measuring thiobarbituric acid reactive substances. 50μL of urine was mixed with 300μL of 0.5M phosphoric acid solution and 150μL of 12mM TBA solution (Sigma-Aldrich T-5500, Steinheim, Germany) and heated at 95℃ for 1 hour. After cooling on ice, the mixture was vortexed with 500μL of methanol and centrifuged at 5000 x g. Absorbance of the supernatant was measured at 532nm using HPLC-UV. The mobile phase was potassium phosphate (0.05mol/L; pH 6.8) and methanol (58:42, v/v).

Measurement of depressive symptoms

To evaluate the depressive symptoms during the previous week, we used Korean version of the Geriatric Depression Scale-Short Form (SGDS-K) questionnaire. [14] The Geriatric Depression Scale (GDS)-Short Form [15] is a 15-item short version of the 30-item Geriatric Depression Scale. [16] Each 15 items of SGDS-K is answered “yes” or “no,” and higher scores indicate more severe depressive symptom. The SGDS-K is composed of 3 different components asking about personal emotional, somatic, and affective symptoms. [Emotional symptoms (Satisfied with life, In good spirits, Fear bad things, Happy most of time, Often feel helpless, and Wonderful to live), Somatic symptoms (Prefer to stay home, Problems with memory, and Full of energy),

Affective symptoms (Dropped activities/interests, Life is empty, Often get bored, Feel pretty worthless, Situation is hopeless, and Others are better off)] Therefore after conducting analysis with total score, subgroup analyses for each component of SGDS-K were also conducted. In addition, a prior validation study found that a cut-off score of 8 or more achieved 85% sensitivity and 70% specificity for major depression. [14] Therefore, a participant who scored 8 or more on the SGDS-K was defined as a depression case in bivariate analyses between urinary MDA quartile and risk of depression.

Other Variables

Information on age, sex, smoking status, alcohol consumption, education level, and history of hypertension and diabetes mellitus was collected by the structured questionnaire. Alcohol intake was considered as “yes” for participants who had consumed alcohol at least once a month for 10 years or longer, and smoking status was classified into never, former, and current smokers. Although primary and secondhand smoking is major causes of oxidative stress, we had a limited number of smokers in the final study population. Therefore we included creatinine-adjusted urinary cotinine levels in our analyses to adjust for primary and secondhand smoke exposure of each participants. Urinary cotinine levels were analyzed by an enzyme-linked immunosorbent assay method. [17] Education level was classified into below

elementary school graduate (< elementary school), over elementary school graduate to below high school graduate (elementary school < ≤ high school), and over high school graduate (high school ≤). Height and weight were measured at each time of visits and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squares. Blood pressure was measured 2 times with automatic sphygmomanometer (HEM-780, Omron, Kyoto, Japan) after 10 minutes of rest, with at least 10 minutes of interval. We used mean of both systolic blood pressure measurement in our analysis as covariates.

Statistical analysis

Urinary MDA concentration was adjusted by urinary creatinine (μg/g creatinine) and natural log transformed to approximate normal distribution. Due to panel design of KEEP study, the number of study visits varied among the participants. If number of study visits are not random, it may leads to selection bias. [18] Therefore we gave weight to subsequent visits of each participants using inverse probability of attaining follow up visits. [19] We used chi square test to compare the general characteristic between final study population and excluded study participants. By using initial visit data of final study participants, we calculated arithmetic means of urinary MDA and their statistical values for each demographic characteristics using ANOVA.

Covariates which may confound the relationship between oxidative stress and depressive symptom scores are selected *a priori* and adjusted in the analyses. In model 1, participants' age, sex, history of diabetes mellitus, and education levels were adjusted. In model 2, we adjusted for model 1 variables plus history of hypertension, alcohol consumption, BMI, fasting glucose, urinary cotinine, and systolic blood pressure. The initial covariates were selected based on earlier literature review. [20-22] After applying bivariate analysis, only significant covariate ($p < 0.25$) which predicted depressive symptoms in the first visit were selected for model 1. (Supplementary Table S2) In model 2, we adjusted for all the initial covariates selected for the analysis.

Association between urinary MDA and depressive symptom scores were assessed by following steps. First, to confirm linear association between depressive symptom score and urinary MDA concentration, nonparametric analysis using generalized additive mixed models were used. After assuming linear association, generalized estimating equation was used to estimate effects of oxidative stress on depressive symptom score. To account for correlation within subject in repeated data analysis, we assumed *compound symmetry* structure to give same covariance regardless of the length of the time interval between the measurements. We expressed estimate effects of 2 fold increase in urinary MDA levels as the percent change in depressive symptom score using following equation.

$\ln SGDS1 = \beta(\ln MDA)$ 2 fold increase in urinary MDA levels causes

$\ln SGDS2 = \beta(\ln(MDA * 2))$ $(2^{\beta}-1)$*100% changes in SGDS score

$\ln SGDS2/SGDS1 = \beta(\ln 2)$

$\frac{SGDS2}{SGDS1} = 2^{\beta}$

We also calculated odds ratios (ORs) for risk of depression by urinary MDA quartiles. Cut point for quartile was 0.20, 0.30, and 0.42μg/g creatinine for men and 0.25, 0.35, and 0.48μg/g creatinine for women, respectively.

Several sensitivity analysis were conducted to secure the robustness of our study findings. First, additional analysis after including participants with low MMSE score and previous history of depression was conducted. Second, because urinary MDA is susceptible to confounders such as dietary antioxidants, additional analyses after further adjusting dietary Vitamin E intake in model 1 and 2 was conducted. Last, we applied different cutoff point for SGDS-K scores in bivariate analysis to differentiate sensitivity and specificity for depicting major depression [cutoff point 6 (sensitivity: 90%, specificity: 52%), cutoff point 10 (sensitivity: 74%, specificity: 85%)]. [14]

All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC) and R version 3.2.2 (The Comprehensive R Archive Network: http://cran.r-project.org). The statistical testing was conducted with the conventional two-tailed alpha level of 0.05.

Results

Study participants' characteristics at the first visit and mean MDA levels are presented in Table 1. The mean age of 478 study participants were 70.7 years and BMI was 24.7kg/m^2. 74% of participants were women and 87% of the participants were non-smokers. Women, Non-alcohol drinker, and thinner participants showed increased urinary MDA levels in the first visit. In addition, level of urinary MDA concentration was different according to the educational level.

Table 2 show**s** average of SGDS-K scores and the subgroup scores for each components of SGDS-K. The average SGDS-K score was 3.66 at the first examination period, 2.33 at the second and 1.17 at the third examination periods. Similar patterns were observed in each components of SGDS-K.

Figure 2 shows the nonparametric associations between urinary MDA concentration and SGDS-K score. SGDS-K score increased with increasing concentration of urinary MDA concentration and it showed almost linear association. Therefore after assuming linearity, we used generalized estimating equation model in our analysis.

Figure 3 displays the estimated percent changes in SGDS-K score per two fold increase in urinary MDA concentration. Two fold increase in urinary MDA concentration were significantly associated with 33.88% [95% confidence interval (CI): 21.59%, 47.42%] increase of total SGDS-K score.

(Supplementary Table S3) In subgroup analyses, two fold increase in urinary MDA concentration were significantly associated with increased SGDS-K score in both men and women. (Men: 30.88%, 95%CI: 10.24%, 55.37%; Women: 34.77%, 95%CI: 20.09%, 51.25%) In analysis by each component of SGDS-K score, we found significant association between urinary MDA concentration with emotional and affective symptom scores, but not with somatic symptom score. Two fold increase in urinary MDA concentration were associated with 37.96% (95%CI: 23.34%, 54.30%), 13.89% (95%CI: -1.31%, 31.42%), and 39.76% (95%CI: 25.85%, 55.22%) increase in emotional, somatic, and affective symptom score respectively. Similar patterns were observed in subgroup analyses by sex. In men, two fold increase in urinary MDA concentration were associated with 29.59% (95%CI: 8.74%, 54.43%), 8.69% (95%CI: -21.53%, 50.55%), and 39.81% (95%CI: 16.48%, 67.82%) increase in emotional, somatic, and affective symptom score respectively. In women, two fold increase in urinary MDA concentration were associated with 39.73% (95%CI: 21.91%, 60.15%), 14.15% (95%CI: -2.76%, 34.00%), and 40.88% (95%CI: 23.96%, 60.12%) increase in emotional, somatic, and affective symptom score respectively.

Table 3 shows odds ratios (OR) and 95%CI for depression according to quartile of the urinary MDA levels. Compared to the lowest urinary MDA quartile, we found statistically significant increase of depression risk in the third and the fourth quartile. (Third quartile, OR: 6.51, 95%CI: 1.77-24.00; Fourth quartile,

OR: 7.11, 95%CI: 1.99-25.42) It also showed a significant OR when we restricted the analyses to women. Although we could not find significant association in analysis with men, the associations were still positive and increased with dose dependent fashion.

In the sensitivity analysis after including participants with low MMSE score and previous history of depression, two fold increase in urinary MDA concentration were significantly associated with 31.95% [95% confidence interval (CI): 19.98%, 45.12%] increase of total SGDS-K score, showing similar results as Figure 3. (Supplementary Table S4) In analysis with additional adjustment for dietary Vitamin E intake, two fold increase in urinary MDA concentration were significantly associated with 36.60% [95% confidence interval (CI): 22.54%, 52.29%] increase of total SGDS-K score. (Supplementary Table S5) We also found similar results in bivariate analysis after applying different cutoff points for depicting major depression. (Supplementary Table S6, S7)

Discussion

We observed a significant association between oxidative stress marker and depressive symptom scores in our analysis with the elderly panel. A two fold increase in urinary MDA concentration was associated with about 30 percent increase in depressive symptom scores and similar findings were noted in

several subgroup analyses. In bivariate analysis after the SGDS-K score ≥ 8 was defined as depression, we found statistically significant increase of depression risk in the third and the fourth MDA quartiles compared to the lowest MDA quartile.

Epidemiological, brain imaging, postmortem, and molecular study suggests possible association between oxidative stress and depression. Most of the case-control studies found increased oxidative stress markers in depression patients compared to healthy controls. [23-35] In recent meta-analysis and systematic review of previous studies, significant association between oxidative stress and depression was suggested. [8, 9] By meta-analyzing 23 studies with 4980 participants, there was 0.55 of 1 standard deviation increase of oxidative stress markers in individual with depression compared with those without depression. [8] In another meta- analysis by specific individual oxidative stress markers, depression patients showed increased level of 8-OHdG and F2-isoprostanes with pooled effect size of 0.31 (10 studies, 1308 subjects) and 0.48 (8 studies, 2471 subjects), respectively. [9] Brain imaging studies and postmortem studies showed reduced volume of prefrontal cortex, hippocampus, and reduced number of glial cells in depression patients which supports the notion that oxidative stress-related apoptosis is involved in depression pathogenesis. [4] By comparing ROS detoxification enzyme levels in recurrent depression patients and healthy controls, increased superoxide dismutase was noticed in depression patient's frontal brain tissue. [10] Reduced gene

expression of metallothionein 1M protein which regulates oxidative stress are also noticed in prefrontal cortex of major depression patients. [11]

However, only few studies evaluated oxidative stress and severity of depressive symptom in participants without clinically diagnosed depression. By analyzing 3,867 participants from 2005-2006 National Health and Nutrition Examination Survey data, researchers found significant association between depressive symptom scores and oxidative stress marker serum gamma-glutamyltransferase (GGT) and antioxidant marker serum Vitamin C. [36] GGT showed upward dose response relationship between depressive symptom and highest quartile of Vitamin C showed lower risk of depression. In studies of acute leukemia and colorectal carcinoma patients, researchers found higher levels of MDA and nitric oxide levels and lower antioxidant capacity in high depression questionnaire score group compared to low depression questionnaire score group. [37, 38] In our study, we found significant association between oxidative stress and depressive symptom scores among elderly individuals without clinically diagnosed depression. Moreover, degree of depressive symptom score was linearly associated with MDA levels, thus showing dose-response relationship.

Although many studies and our study results indicate the intimate association between oxidative stress and depression, the direction of the association is still unclear. In other words, oxidative stress may work as key pathogenic mediator of depression, but increased oxidative stress could also be an outcome of

depression. For example, major depression is characterized by elevation of immune activation which leads to excessive production of ROS. [39, 40] Increased catecholamine metabolism in depression patients also induces lipid peroxidation and ROS production. [41, 42] Decreased oxidative stress parameter after depression medication could be another reason for regarding oxidative stress as outcome of depression. [23, 27, 29, 33]

However, oxidative stress is receiving attention as a possible pathogenic mediator for developing various diseases. [43] In the same fashion, many researchers are suggesting oxidative stress as one of possible pathogenic mediators for depression pathogenesis based on following biological reasons. First, many of the risk factors in depression have been shown to cause changes in oxidative stress markers. For example, psychosocial stress, substance abuse, aging and environmental factors such as air pollution and various chemicals which are found to be associated with depression may induce oxidative stress in various human tissues. [5, 44-46] Second, brain is regarded as one of the most vulnerable tissue against oxidative stress. Due to the high oxygen state and modest antioxidant defense mechanism, oxidative stress could be intensified in the brain lesion. [5] In addition, there are abundant lipid substrates such as polyunsaturated fatty acid (PUFA) for oxidation and various ions chemicals of the brain may work as catalase for free radical reaction. [47] Therefore oxidative stress may easily impact neuronal cell functions of the brain.

Third, increased oxidative stress could show several characteristic features which underlies the pathogenesis of clinical depression. ROS induces oxidation of PUFA and reduced PUFA level is believed to contribute depression pathophysiology. [48] After exposed to ROS, protein undergoes deterioration which may leads to changes in tertiary structure or enzymatic activity. [49] For instance, number of glycoprotein Neural Cell Adhesion Molecule (NCAM) decreases at surface of neuronal and glial cell after oxidative stress exposure. [50] In line with this study, NCAM knockout mice shows decreased hippocampal neurogenesis and depression like symptoms. [51]

Therefore, association between oxidative stress and depression seems to be apparent despite the undetermined exact causal direction. Oxidative stress and depression may be forming complex vicious circle which reinforces each other. Thus by avoiding imbalance between free radical generation and antioxidant potential, we may reduce the occurrence or exacerbation of depression.

In case of the elderly, the effect of oxidative stress on depression could be intensified due to physiological changes of aging. Regarding reduced antioxidant potential and poor prognosis of elderly depression compared with depression in younger age, [12, 52] elderly people should receive exceptional care against oxidative stress to prevent or manage depression. As far as we know, only one study evaluated the association between oxidative stress and depression among elderly population aged over 60. [28] Compared to 33 healthy controls, 36 subjects with psychiatrist diagnosed depression showed

increased level of F2-isoprostane, which is the quantitative marker of lipid peroxidation. In addition, levels of F2-isoprostane were positively correlated with severity of depression among depression patients. In our study, we noticed linear positive association between oxidative stress marker and depressive symptom score among elderly population without diagnosis of clinical depression. Even with the participant with SGDS-K score below 8, we found linear positive association suggesting close association between oxidative stress and depressive symptom.

To our knowledge, this is the first panel study to report an association between oxidative stress levels and depressive symptoms in the elderly population. By analyzing repeatedly measured data from elderly population without clinical depression, our results may support the findings from previous studies. Regarding constantly changing properties of oxidative stress and depressive symptom, panel data analysis may provide higher level of evidences in the association between oxidative stress and depression. Furthermore, self-reported depression questionnaire asked depressive symptom of past 1 week. Because MDA is short-term marker of oxidative stress, we may reasonably speculate association between short term oxidative stress exposure and depressive symptom.

However, there are several limitations that need to be noticed in this study. First, using of MDA as an only oxidative stress biomarker may limit our findings. MDA is short-term oxidative stress marker which is susceptible to confounders

such as dietary antioxidants. However, because central nervous system is composed with neurons and high lipid tissues, MDA, the byproduct of polyunsaturated fatty acid peroxidation may reasonably represent oxidative stress of the brain. Second, although various time dependent and independent factors were adjusted in analytical models, other potential confounders may have been overlooked. Third, because our study participants were elderly people residing in Seoul, Korea, our finding may not be generalizable to elderly population in other cities or countries. Fourth, although we found significant association between oxidative stress levels and depressive symptoms with panel data, exact causal direction is still unclear due to cross-sectional nature of this study.

In conclusion, our study suggests the positive association between oxidative stress and depressive symptoms in elderly population without clinically diagnosed depression.

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Table 1. Demographic properties of the study population from the first visit of participants (n= 478)

		Numbers (N)	Percentage (%)	MDA levels median, range (μg/g creatinine)	p value
Sex	Men	124	25.94	0.34, 0.03-1.92	<0.01
	Women	354	74.06	0.39, 0.10-2.00	
Age group	60 to 69	220	46.03	0.37, 0.04-1.66	0.58
	70 to 79	237	49.58	0.38, 0.05-2.00	
	80≤	21	4.39	0.43, 0.08-1.41	
History of hypertension	No	225	47.07	0.39, 0.08-2.00	0.19
	Yes	253	52.93	0.37, 0.03-1.92	
History of diabetes mellitus	No	397	83.05	0.38, 0.03-1.92	0.35
	Yes	81	16.95	0.38, 0.05-2.00	
Alcohol consumption	No	364	76.15	0.39, 0.04-2.00	<0.01
	Yes	114	23.85	0.36, 0.03-1.16	
Smoking status	Smoker	28	5.86	0.35, 0.10-0.75	0.27
	Ex-smoker	33	6.90	0.36, 0.04-0.80	
	Non smoker	417	87.24	0.38, 0.03-2.00	
Education level	< Elementary school	138	28.87	0.42, 0.08-1.65	<0.01
	Elementary school < ≤ High school	213	44.56	0.39, 0.04-2.00	
	High school ≤	127	26.57	0.33, 0.03-1.66	
Body Mass Index	<25.0	271	56.69	0.38, 0.04-1.92	<0.01
	25.0-29.9	188	39.33	0.39, 0.06-2.00	
	>30	19	3.97	0.32, 0.03-0.69	

Table 2. SGDS-K (Depressive symptom) scores (Mean±S.D)

	Total score	Emotional symptoms	Somatic symptoms	Affective symptoms
1st follow up				
Total (n=277)	3.66±3.33	1.35±1.67	0.69±0.80	1.61±1.66
Men (n=60)	3.33±3.15	1.25±1.54	0.53±0.77	1.55±1.61
Women (n=217)	3.75±3.38	1.38±1.71	0.73±0.81	1.63±1.67
2nd follow up				
Total (n=330)	2.33±3.19	0.80±1.43	0.37±0.64	1.16±1.61
Men (n=80)	1.86±2.80	0.64±1.21	0.26±0.55	0.96±1.37
Women (n=250)	2.48±3.30	0.86±1.49	0.41±0.67	1.22±1.67
3rd follow up				
Total (n=310)	1.17±2.40	0.40±0.92	0.38±0.87	0.39±0.91
Men (n=84)	0.57±1.40	0.18±0.42	0.18±0.62	0.21±0.60
Women (n=226)	1.39±2.64	0.48±1.04	0.46±0.93	0.46±0.99

Table 3. Odds ratio for depression according to urinary MDA levels

	No. of events	1Q OR (95%CI)	2Q OR (95%CI)	3Q OR (95%CI)	4Q OR (95%CI)
Total					
No. of observation	917	229	245	221	222
Depression (+)/(-)	81/836	ref	3.78 (1.01-14.03)	6.51 (1.77-24.00)	7.11 (1.99-25.42)
Men					
No. of observation	224	54	56	58	56
Depression (+)/(-)	14/210	ref	2.76 (0.33-23.41)	2.87 (0.34-24.54)	3.06 (0.51-18.42)
Women					
No. of observation	693	177	164	180	172
Depression (+)/(-)	67/626	ref	5.26 (1.23-22.42)	7.49 (1.70-33.11)	8.36 (1.916-36.63)

Adjusted for age, sex, history of hypertension and diabetes mellitus, alcohol consumption, educational level, body mass index, urinary cotinine, fasting glucose level, and systolic blood pressure.

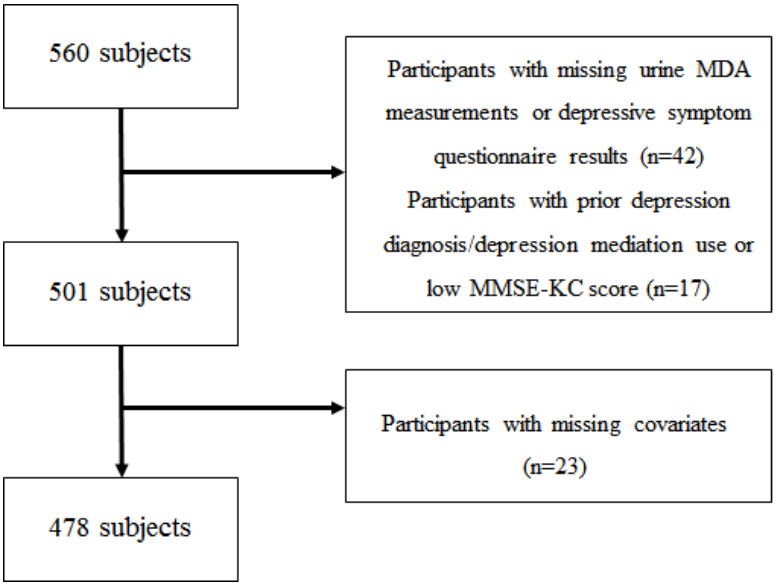

Figure 1. Flow diagram of study population

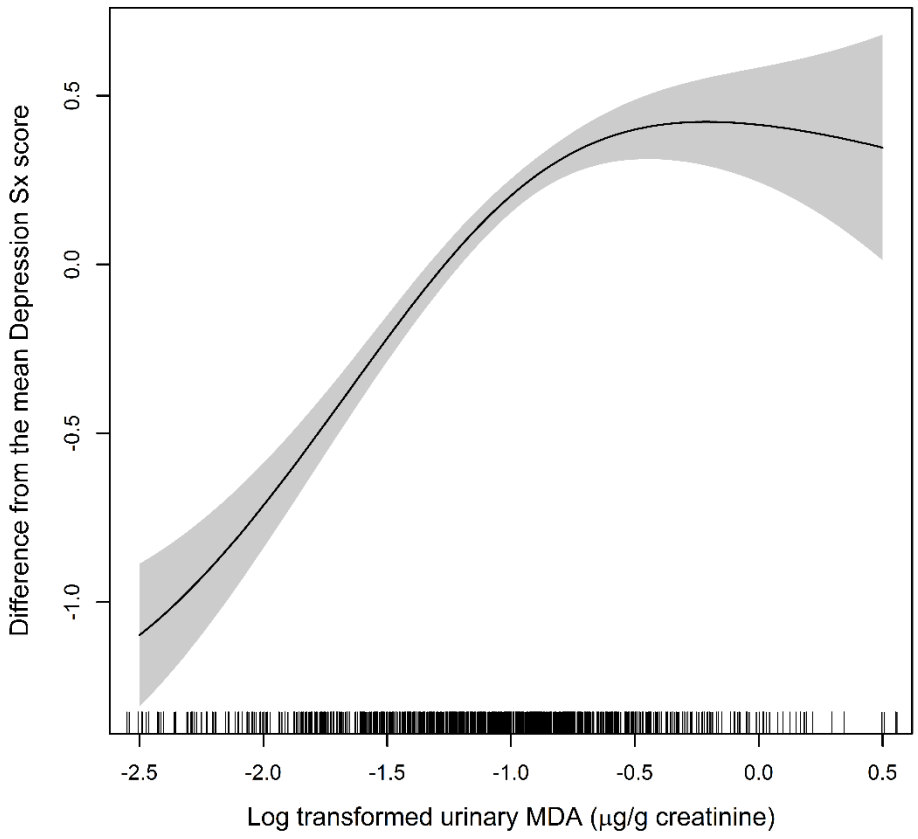

Figure 2. Non parametric association between urinary MDA concentration with depression symptom score. Data was adjusted for age, sex, history of hypertension and diabetes mellitus, alcohol consumption, educational level, body mass index, urinary cotinine, fasting glucose level, and systolic blood pressure.

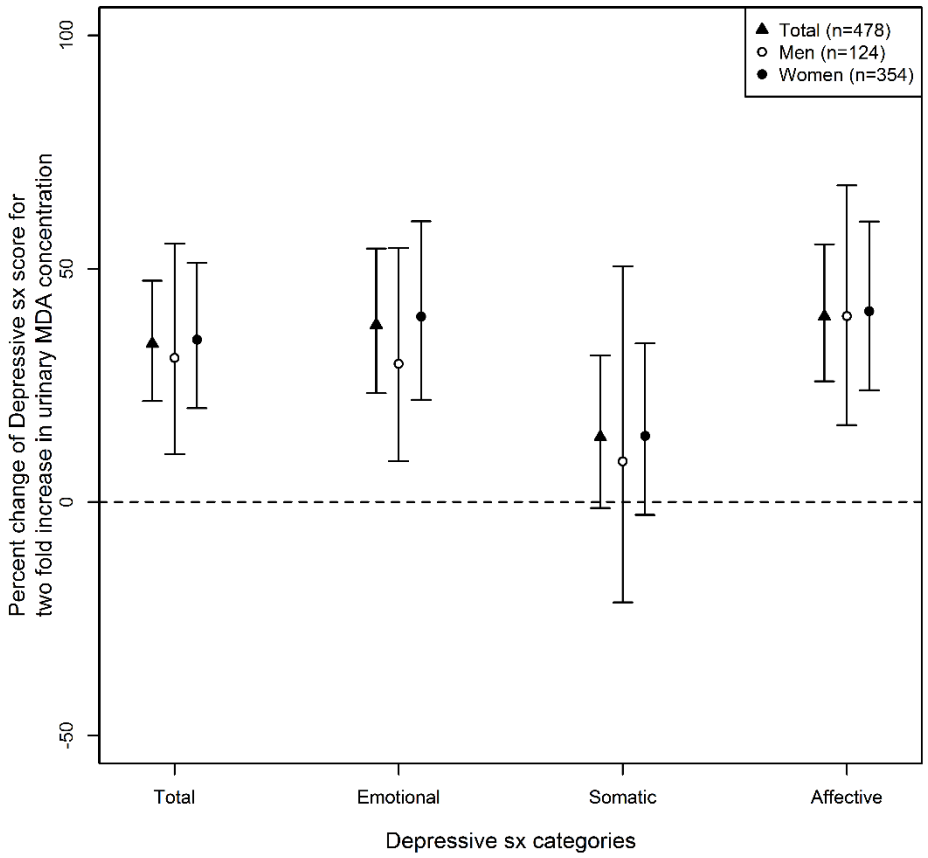

Figure 3. Percent change in SGDS-K scores per 2 fold increase in urinary MDA concentration. Data was adjusted for age, sex, history of hypertension and diabetes mellitus, alcohol consumption, educational level, body mass index, urinary cotinine, fasting glucose level, and systolic blood pressure.

Table S1. General characteristics of study subjects across final study population and excluded participants N(%)

		Final study population (n=478)	Excluded study participants (n=82)	p-value
Sex	Men	124(25.94)	22(26.83)	0.87
	Women	354(74.06)	60(73.17)	
Age group	60 to 69	220(46.03)	27(36.59)	0.15
	70 to 79	237(49.58)	44(60.98)	
	80≤	21(4.39)	2(2.44)	
History of hypertension	No	225(47.07)	52(63.41)	<0.01
	Yes	253(52.93)	30(36.59)	
History of diabetes mellitus	No	397(83.05)	72(87.80)	0.28
	Yes	81(16.95)	10(12.20)	
Alcohol consumption	No	364(76.15)	58(89.23)	0.02
	Yes	114(23.85)	7(10.77)	
	Did not answer		n=17	
Smoking status	Smoker	28(5.86)	3(4.41)	0.79
	Ex-smoker	33(6.90)	3(4.41)	
	Non smoker	417(87.24)	62(91.18)	
	Did not answer		n=14	
Education level	< Elementary school	138(28.87)	17(25.76)	0.78

	Elementary school < ≤ High school	213(44.56)	29(43.94)	
	High school ≤	127(26.57)	20(30.30)	
	Did not answer		n=16	
Body Mass Index	<25.0	271(56.69)	45(54.88)	0.19
	25.0-29.9	188(39.33)	30(36.59)	
	>30	19(3.97)	7(8.54)	

Tables S2. Demographic properties of the study population from the first visit of participants (n=478) N(%)

		Depression (-) (n=421)	Depression (+) (n=57)	p-value
Sex	Men	113(26.84)	11(19.30)	0.22
	Women	308(73.16)	46(80.70)	
Age group	60 to 69	199(47.27)	21(36.84)	0.03
	70 to 79	207(49.17)	30(52.63)	
	80≤	15(3.56)	6(10.53)	
History of hypertension	No	198(47.03)	27(47.37)	0.96
	Yes	223(52.97)	30(52.63)	
History of diabetes	No	353(83.85)	44(77.19)	0.21
	Yes	68(16.15)	13(22.81)	
Alcohol consumption	No	318(75.53)	46(80.70)	0.39
	Yes	103(24.47)	11(19.30)	
Smoking status	Smoker	24(5.70)	4(7.02)	0.86
	Ex-smoker	30(7.13)	3(5.26)	
	Non smoker	367(87.17)	50(87.72)	
Education level	Below elementary school	114(27.08)	24(42.11)	0.02
	Middle school graduation	188(44.66)	25(43.86)	
	High school graduation	119(28.27)	8(14.04)	

Body Mass Index	<25.0	235(55.82)	36(63.16)	0.42
	25.0-29.9	170(40.38)	18(31.85)	
	>30	16(3.80)	3(5.26)	

Table S3. Associations of log transformed urinary concentration of MDA with depressive symptom score

	Crude			Model 1			Model 2		
	Beta	S.E.	p value	Beta	S.E.	p value	Beta	S.E.	p value
Total (n=478)									
Depressive Sx score									
Total	0.49	0.08	<.0001	0.42	0.07	<.0001	0.42	0.07	<.0001
Emotion	0.52	0.08	<.0001	0.45	0.08	<.0001	0.46	0.08	<.0001
Somatic	0.29	0.11	0.009	0.20	0.11	0.057	0.19	0.11	0.075
Affective	0.56	0.08	<.0001	0.47	0.07	<.0001	0.48	0.08	<.0001
Men (n=124)									
Depressive Sx score									
Total	0.40	0.13	0.003	0.37	0.13	0.004	0.39	0.13	0.002
Emotion	0.39	0.13	0.002	0.37	0.13	0.003	0.37	0.13	0.004
Somatic	0.19	0.25	0.439	0.15	0.22	0.491	0.12	0.24	0.616
Affective	0.48	0.14	0.001	0.45	0.14	0.001	0.48	0.13	<0.001
Women (n=354)									
Depressive Sx score									
Total	0.49	0.09	<.0001	0.42	0.08	<.0001	0.43	0.08	<.0001
Emotion	0.52	0.10	<.0001	0.46	0.09	<.0001	0.48	0.10	<.0001
Somatic	0.29	0.12	0.020	0.21	0.12	0.072	0.19	0.12	0.106
Affective	0.56	0.10	<.0001	0.48	0.09	<.0001	0.49	0.09	<.0001

Model 1: Adjusted for age, sex, history of diabetes mellitus, and educational level

Model 2: Model 1+ history of hypertension, alcohol consumption, body mass index, fasting glucose, urinary cotinine, and systolic blood pressure

Table S4. Associations of log transformed urinary concentration of MDA with depressive symptom score (Sensitivity analysis including participants with low MMSE-KC score and depression history)

	Crude			Model 1			Model 2		
	Beta	S.E.	p value	Beta	S.E.	p value	Beta	S.E.	p value
Total (n=495)									
Depressive Sx score									
Total	0.47	0.08	<.0001	0.39	0.07	<.0001	0.40	0.07	<.0001
Emotion	0.48	0.09	<.0001	0.41	0.08	<.0001	0.42	0.09	<.0001
Somatic	0.28	0.11	0.009	0.19	0.10	0.064	0.18	0.10	0.075
Affective	0.54	0.08	<.0001	0.46	0.08	<.0001	0.47	0.08	<.0001
Men (n=124)									
Depressive Sx score									
Total	0.42	0.13	0.001	0.39	0.13	0.002	0.41	0.13	0.001
Emotion	0.42	0.13	0.001	0.41	0.13	0.002	0.41	0.13	0.002
Somatic	0.22	0.24	0.366	0.16	0.21	0.440	0.15	0.23	0.525
Affective	0.50	0.14	0.000	0.46	0.14	0.001	0.49	0.13	<0.001
Women (n=371)									
Depressive Sx score									
Total	0.46	0.09	<.0001	0.39	0.08	<.0001	0.40	0.09	<.0001
Emotion	0.47	0.11	<.0001	0.40	0.10	<.0001	0.42	0.11	<.0001
Somatic	0.27	0.12	0.023	0.19	0.11	0.091	0.17	0.11	0.125
Affective	0.54	0.10	<.0001	0.46	0.09	<.0001	0.48	0.10	<.0001

Model 1: Adjusted for age, sex, history of diabetes mellitus, and educational level

Model 2: Model 1+ history of hypertension, alcohol consumption, body mass index, fasting glucose, urinary cotinine, and systolic blood pressure

Table S5. Associations of log transformed urinary concentration of MDA with depressive symptom score (Sensitivity analysis including dietary intake of Vitamin E in Model 1 and Model 2)

	Crude			Model 1			Model 2		
	Beta	S.E.	p value	Beta	S.E.	p value	Beta	S.E.	p value
Total (n=392)									
Depressive Sx score									
Total	0.49	0.08	<.0001	0.45	0.08	<.0001	0.45	0.08	<.0001
Emotion	0.52	0.08	<.0001	0.47	0.09	<.0001	0.48	0.09	<.0001
Somatic	0.29	0.11	0.009	0.22	0.11	0.059	0.19	0.11	0.091
Affective	0.56	0.08	<.0001	0.53	0.08	<.0001	0.54	0.08	<.0001
Men (n=97)									
Depressive Sx score									
Total	0.40	0.13	0.003	0.35	0.13	0.008	0.33	0.12	0.005
Emotion	0.39	0.13	0.002	0.36	0.13	0.006	0.34	0.12	0.005
Somatic	0.19	0.25	0.439	0.15	0.21	0.479	0.07	0.23	0.774
Affective	0.48	0.14	0.001	0.43	0.14	0.003	0.44	0.12	<0.001
Women (n=295)									
Depressive Sx score									
Total	0.49	0.09	<.0001	0.46	0.09	<.0001	0.46	0.10	<.0001
Emotion	0.52	0.10	<.0001	0.48	0.11	<.0001	0.50	0.12	<.0001
Somatic	0.29	0.12	0.020	0.22	0.13	0.090	0.19	0.13	0.143
Affective	0.56	0.10	<.0001	0.57	0.10	<.0001	0.57	0.11	<.0001

Model 1: Adjusted for age, sex, history of diabetes mellitus, and educational level

Model 2: Model 1+ history of hypertension, alcohol consumption, body mass index, fasting glucose, urinary cotinine, and systolic blood pressure

Table S6. Odds ratio for depression according to urinary MDA levels (applying SGDS-K cutoff value 6)

	No. of events	1Q OR (95%CI)	2Q OR (95%CI)	3Q OR (95%CI)	4Q OR (95%CI)
Total					
No. of observation	917	229	245	221	222
Depression (+)/(-)	81/836	ref	1.84 (0.87-3.92)	4.23 (2.09-8.57)	3.32 (1.62-6.78)
Men					
No. of observation	224	54	56	58	56
Depression (+)/(-)	14/210	ref	1.97 (0.30-12.88)	2.66 (0.47-15.18)	2.60 (0.51-13.15)
Women					
No. of observation	693	177	164	180	172
Depression (+)/(-)	67/626	ref	2.35 (1.03-5.41)	4.30 (1.99-9.28)	3.81 (1.71-8.48)

Adjusted for age, sex, history of hypertension and diabetes mellitus, alcohol consumption, educational level, body mass index, urinary cotinine, fasting glucose level, and systolic blood pressure.

Table S7. Odds ratio for depression according to urinary MDA levels (applying SGDS-K cutoff value 10)

	No. of events	1Q OR (95%CI)	2Q OR (95%CI)	3Q OR (95%CI)	4Q OR (95%CI)
Total					
No. of observation	917	229	245	221	222
Depression (+)/(-)	41/876	ref	6.69 (1.29-34.67)	8.23 (1.49-45.57)	10.23 (1.87-56.09)
Men					
No. of observation	224	54	56	58	56
Depression (+)/(-)	6/218	ref	1.94 (0.18-21.00)	1.73 (0.14-20.55)	4.31 (0.64-28.96)
Women					
No. of observation	693	177	164	180	172
Depression (+)/(-)	35/658	ref	8.81 (1.28-60.58)	11.57 (1.64-81.52)	9.05 (1.32-61.99)

Adjusted for age, sex, history of hypertension and diabetes mellitus, alcohol consumption, educational level, body mass index, urinary cotinine, fasting glucose level, and systolic blood pressure.

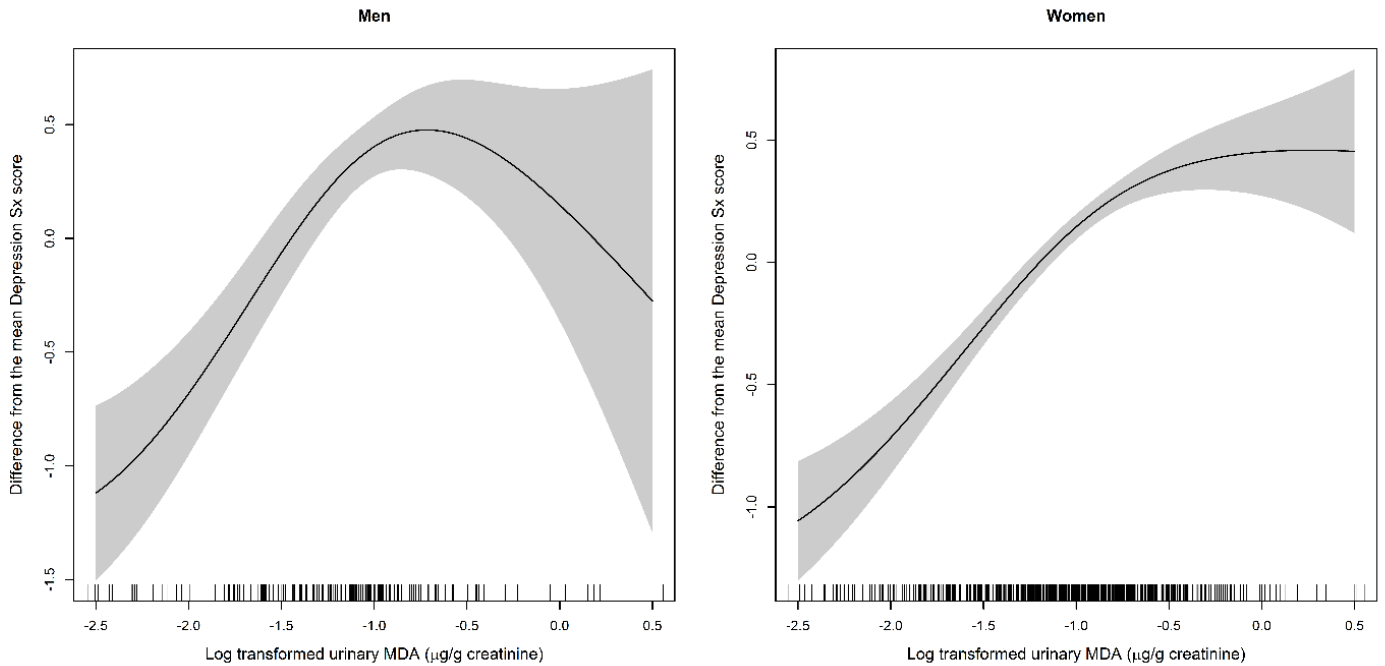

Figure S1. Non parametric association between urinary MDA concentration with depression symptom score. Data was adjusted for age, sex, history of hypertension and diabetes mellitus, alcohol consumption, educational level, body mass index, urinary cotinine, fasting glucose level, and systolic blood pressure.

초록

노인인구의 산화손상 지표와 우울증상과의 관계

한창우

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배경

과거 산화손상과 우울증간의 역학연구는 병원기반 환자-대조군 연구, 산화손상 지표의 단발성 측정, 소수의 연구 대상자에서 수행된 연구라는 한계점을 가지고 있었다. 이에 본 연구에서는 산화손상 지표와 우울증 사이의 관계를 지역사회 거주 노인인구를 대상으로 수행된 반복조사 자료를 통해 분석하였다.

방법

2008년에서 2010년에 걸쳐, 서울 성북구 지역에 거주하는 478명의 60세 이상 노인인구에 대한 평가가 3회 이루어 졌다. 대상자들은 한국형 노인우울척도 단축형 검사를 통해 우울증을, 소변 말론디알데히드 검사를 통해 산화손상의 정도를 평가 받았다. 일반화 선형 방정식을 사용하여 산화손상의 지표가 우울증상의 정도에 미치는 영향을 평가하였다.

결과

소변 말론디알데히드 농도가 2배 증가한 경우 노인우울척도의

점수가 33.88% 유의하게 증가하는 것으로 나타났다. (95%신뢰구간: 21.59-47.42%) 성별에 따른 분석에서도 소변 말론디알데히드 농도의 2배 증가할 경우 노인우울척도 점수가 유의하게 증가하는 것으로 나타났다. (남성: 30.88%, 95%신뢰구간: 10.24-55.37%; 여성: 34.77%, 95%신뢰구간: 20.09-51.25%) 8점 이상의 노인우울척도점수를 기록한 대상자를 우울증 환자로 정의하고 수행한 이변량 분석에서는, 제1사분위 소변 말론디알데히드 그룹과 비교하여 제3사분위, 제4사분위 소변 말론디알데히드 그룹에서 우울증의 오즈비가 유의하게 증가하는 것으로 나타났다. (제 3사분위그룹: 오즈비, 6.51, 95%신뢰구간: 1.77-24.00; 제 4사분위그룹: 오즈비, 7.11, 95%신뢰구간: 1.99-25.42)

결론

본 연구를 통해 노인인구에서 산화손상과 우울증상과의 유의한 관련성을 확인할 수 있었다.

주요어: 산화손상, 우울증, 노인, 말론디알데히드, 우울증, 역학연구

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