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Joint Effects of Air Pollution and Neighborhood Socioeconomic Status on Cognitive Decline - Mediation by Depression, High Cholesterol Levels, and High Blood Pressure

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2019

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Abstract

Joint Effects of Air Pollution and Neighborhood Socioeconomic Status on Cognitive Decline - Mediation by Depression, High Cholesterol Levels, and High Blood Pressure

By Yiyang Mei

Background: Air pollution and neighborhood socioeconomic status (N-SES) are associated with adverse cardiovascular health and neuropsychiatric functioning in older adults.

Objectives: This study examines the degree to which the joint effects of air pollution and N-SES on cognitive decline are mediated by high cholesterol levels, high blood pressure (HBP), and depression.

Methods: In the Emory Healthy Aging Study, 14,390 participants aged 50+ years from Metro Atlanta, GA, were assessed for subjective cognitive decline using the cognitive function instrument (CFI). Information on the prior diagnosis of high cholesterol, HBP, and depression was collected through the Health History Questionnaire. Participants' census tracts were matched to the 3-year average concentrations of 12 air pollutants and 16 N-SES characteristics. We used the unsupervised clustering algorithm Self-Organizing Maps (SOM) to create 6 exposure clusters based on the joint distribution of air pollution and N-SES in each census tract. Linear regression analysis was used to estimate the effects of the cluster indicator on CFI, adjusting for age, race/ethnicity, education, and neighborhood residential stability. The proportion of the association mediated by high cholesterol levels, HBP, and depression was calculated by comparing the total and direct effects.

Results: Depression mediated 19 - 87% of the association between SOM clusters and CFI. Participants living in the high N-SES and high air pollution cluster had CFI scores 0.05 (95% CI: 0.01, 0.09) points higher on average compared to those from the high N-SES and low air pollution cluster. After adjusting for depression, this association was attenuated (0.01 (95% CI: -0.04, 0.05)). HBP mediated up to 8% of the association between SOM clusters and CFI and high cholesterol up to 5%.

Conclusions: Air pollution and N-SES associated cognitive decline was partially mediated by depression. Only a small portion (<10%) of the association was mediated by HBP and high cholesterol.

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Table of Contents

Introduction

At present, aging is one of the most pressing public health issues. According to the World Health Organization, by 2030, 1 in 6 people in the world will be aged 60 years or over (Rudnicka et al., 2020). As people age, several diseases may occur at the same time. Age-related diseases accelerate the rate of neuronal dysfunction, neuronal loss, and cognitive decline, with many persons developing cognitive impairments severe enough to impair their everyday functional abilities (Murman, 2015).

Numerous studies have investigated the association between exposure to air pollution and accelerated cognitive decline across multiple stages of life (Clifford et al., 2016; Kilian & Kitazawa, 2018; Power et al., 2016). Two recent critical reviews examining the association between exposure to ambient air pollutants and acceleration of cognitive decline suggested that their relationship is likely to be causal (Delgado-Saborit et al., 2021; Weuve et al., 2021). This result is further supported by animal model studies suggesting that particulate matter (PM) adversely impacts neuroanatomical and neuropathological changes in the brain, leading to the development of Alzheimer's disease (AD)-like pathology via a multifactorial mechanism, including neurodegeneration, altered glial cell levels, amyloid processing, and immune response (Kilian & Kitazawa, 2018). However, the causal pathway through which air pollution leads to cognitive decline, and particularly the role of common comorbidities such as cardiovascular and neuropsychiatric diseases in this association, is not yet clearly understood.

Cardiovascular and neuropsychiatric comorbidities have been associated with air pollution and cognitive decline. A number of epidemiologic studies on air pollution and cardiovascular health have identified air pollution as a risk factor for cardiovascular morbidity

and mortality (Zong et al., 2022). Cardiovascular diseases and cognitive decline are also strongly associated with each other (C. Qiu & Fratiglioni, 2015).

Similarly, neuropsychiatric comorbidity such as depression is also associated with air pollution and cognitive decline (Altuğ et al., 2020). Previous studies have suggested that exposure to air pollution contributed to depression onset (Kioumourtzoglou et al., 2017; X. Qiu et al., 2022) as well as to the risk of acute hospital admissions for psychiatric disorders (X. Qiu et al., 2022). Furthermore, there is strong evidence that depression is associated with an increased risk of subsequent cognitive decline and dementia (Jorm, 2000; Perini et al., 2019).

Despite the clear association between air pollution and cardiovascular and neuropsychiatric comorbidities of cognitive decline, little is known about the potential mediating effects of these comorbidities on the association between air pollution and cognitive decline. Few studies have investigated the interrelationship between air pollution, depression, and cognitive decline. Among the limited number of papers that have done so, the analyses were done in the context of effect modification rather than mediation (Altuğ et al., 2020). So far, there are no studies investigating the mediation effects of depression on the association between outdoor air pollution and cognitive decline. Furthermore, only two studies have explored the mediation effects of cardiovascular disease on the association between outdoor air pollution and cognitive decline (Grande et al., 2020; Ilango et al., 2020). Both studies found that some of the association between air pollution and dementia was mediated through CVD, but estimated proportions mediated ranged from 9% (Ilango et al., 2020) to 50% (Grande et al., 2020), emphasizing the need for additional studies on this topic.

Another aspect concerning air pollution's effect on cognitive decline which is currently understudied is its joint effects with adverse neighborhood socioeconomic characteristics as a co-

exposure. Individuals living in disadvantaged neighborhoods are often exposed to a higher level of air pollution than individuals living in socioeconomically advantaged neighborhoods (Hajat et al., 2015). According to the theory of triple jeopardy, communities with low SES not only suffer from higher exposure to air pollutants and other environmental hazards but also have increased susceptibility to poor health because of psychosocial stressors (Ailshire & Clarke, 2015). These psychosocial stressors lower the brain's threshold for neurotoxicity, making those living in disadvantaged neighborhoods more vulnerable to the harmful effects of air pollution (Christensen et al., 2022; Li et al., 2022; McEwen & Tucker, 2011). For those living in high SES communities, however, the more advantageous SES can buffer the adverse effects of air pollution on cognitive decline, which can cause biased effect estimates when ignoring the interconnections between air pollution and neighborhood SES (N-SES) (Christensen et al., 2022; Li et al., 2022).

This study aims to investigate the degree by which the joint effects of air pollution and N-SES on cognitive decline are mediated by high cholesterol levels, high blood pressure, and depression using data from 14,390 older adults of the Emory Healthy Aging Study (EHAS) in Metro Atlanta, GA.

Methods

Study Population

Started in 2015, The Emory Healthy Aging Study (EHAS) is a large gerontology-based prospective study that focuses on the diseases of older adults. Anyone over the age of 18, living in the United States, and sufficiently fluent in English are encouraged to enroll. Individuals receiving health services at Emory Healthcare are the main focus of recruitment in the Metro-

Atlanta area as well as their spouses, family members, and associated non-relatives. The recruitment is also open to the public. In general, EHAS aims to advance the understanding of healthy aging and the pathogenesis of age-related illnesses in well-characterized, community-based prospective cohorts and to identify biomarkers for the earliest manifestations of Alzheimer's disease for the facilitation of preventative interventions (Goetz et al., 2019). EHAS participants that were included in this analysis were enrolled during the 2015-2020 period, were 50 years and older at baseline, and lived in the Metro Atlanta area. At enrollment, the participants were asked to complete a Health History Questionnaire which included demographic questions such as age, race and ethnicity, general and perceived health status, and memory decline. Prior to enrollment, all participants completed an online consent process. This study was approved by the Emory University Institutional Review Board.

Exposure Assessment

As described previously (Christensen et al., 2022), our exposure of interest was the joint exposure to air pollution and N-SES, which was estimated using Self-Organizing Maps (SOM), as described in the statistical analysis section.

The average ambient air pollution concentrations from 2008-2010 were derived from the Community Multiscale Air Quality (CMAQ) chemical transport model. We included 12 pollutants: Nitrogen Oxides (NO_x), Nitrogen Dioxide (NO_2), Nitrate (NO_3), Sulfur Dioxide (SO_2), Ozone (O_3), Carbon Monoxide (CO), Ammonium (NH_4), Sulfate (SO_4), Elemental Carbon (EC), Organic Carbon (OC), and Particulate Matter with a diameter 10 microns or less (PM_{10}) and 2.5 microns or less ($PM_{2.5}$) (Senthilkumar et al., 2019). Each participant was assigned CMAQ pollutant concentrations based on their census tract of residence by geospatially

matching the center of each CMAQ grid cell to its closest respective residential census tract. The residential census tract rather than the street addresses was used here because the SOM requires all inputs, i.e., air pollution and N-SES, to be at the same spatial resolution.

The N-SES data were obtained from the United States Census Bureau's American Community Survey for 2013-2018 for each Metro Atlanta census tract. The 5-year average estimate was calculated through the R package *tidycensus*. To be in line with the other N-SES characteristics, the variable representing the median home value was multiplied by -1. A total of 16 N-SES variables in the domains of income, racial composition, education, employment, occupation, and housing properties were selected to represent the mixture of exposure to N-SES (Messer et al., 2006). To control for the confounding effect of residential mobility, an indicator for residential stability representing the percentage of households that moved into their current residence before 2010 was also added to the analysis (Christensen et al., 2022).

Outcome Assessment

The Cognitive Function Instrument (CFI) was employed to measure subjective cognitive decline. The CFI was self-administered online. It consisted of 14 questions related to the participants' subjective cognitive concerns in daily life. Participants gave themselves scores based on their daily feelings. The total CFI score was calculated by scoring responses, with "yes" equals 1, "no" equals 0, and "maybe" equals 0.5. The higher the score, the more advanced they were for perceived memory and cognitive decline (Amariglio et al., 2015). A higher CFI score is predictive of cognitive decline for the elderly because subjective experience of cognitive decline often occurs at the late stage of the preclinical, cognitively unimpaired phase of the Alzheimer's disease continuum (Jack Jr. et al., 2018). Unlike other tests that assess cognitive impairment, the

CFI can be completed remotely. It does not require an in-person interview or physician review. In our regression analyses, the CFI score was log-transformed because the total score was right-skewed in this sample.

Assessment of Potential Confounders

Potential confounders under consideration included participants' individual age, race and ethnicity, education, and residential stability of the census tract. All information related to the confounders except residential stability was collected through an online Health History Questionnaire (HHQ), which is incorporated in a Qualtrics Survey (Qualtrics.com) and completed at baseline and annually thereafter (Goetz et al., 2019).

Race was divided into four categories: White, Black, and others. Ethnicity was classified as Hispanic yes or no. Education has 7 levels: less than high school, high school or General Education Development (GED), some college, associate degrees, bachelor's degrees, masters' degrees, and professional or doctorate degrees. Residential stability was measured through the percentage of residents living in the same household moving in before 2010. The median and interquartile range were calculated for continuous variables (age and residential stability). For categorical variables (education, race, and ethnicity), their percentages were calculated.

Assessment of Potential Mediators

Information on participants' cholesterol, blood pressure, and depression was collected through HHQ. Participants were asked whether they have ever been diagnosed by a doctor with high cholesterol levels, high blood pressure, or depression. All three variables were binary.

Statistical Analysis

As described previously (Christensen et al., 2022), we used the SOM algorithm (Pearce et al., 2014) to identify clusters of census tracts with similar air pollution and N-SES characteristics, which reflect the joint exposure of air pollution and N-SES. The number of clusters identified by the SOM algorithm was determined by identifying group structure using within-cluster sum of squares and between-cluster sum of square statistics, as well as visual inspection of cluster star plots. The method identifies clusters with exposure levels homogeneous within and heterogeneous between clusters. Then, census tract clusters were matched to EHAS participants using the census tract of the participants' addresses. The SOM exposure clusters were then used as categorical exposure variables in the subsequent regression analyses to estimate the joint effects of air pollution and N-SES. The reference cluster designates the metro Atlanta area with the highest N-SES and lowest air pollution concentrations.

Specifically, we estimated 1) the associations between SOM clusters and high cholesterol levels, high blood pressure, and depression (using logistic regression analysis); 2) the association between high cholesterol levels, high blood pressure, and depression and log-transformed CFI scores (lnCFI) (using linear regression models); and 3) the proportion of the association between SOM clusters and lnCFI mediated by high cholesterol levels , high blood pressure, and depression by comparing the total and direct effects from linear regression models (Robins & Greenland, 1992). The total effects were estimated using linear regression analysis for the association between SOM exposure clusters and lnCFI scores adjusting for individual age, race and ethnicity, education, and residential stability. The direct effects were derived by additionally adjusting these models for the potential mediators in individual linear regression models. The proportion mediated (PM) was calculated as (total effect – direct effect) / total effect.

Mediation analyses rely on three assumptions. The first assumption is that there was no confounding between exposure (SOM cluster) and mediator (high cholesterol level, high blood pressure, and depression). The second assumption is that there was no confounding relationship between mediators and outcome (cognitive decline). The third assumption is that there was no confounding between exposure (SOM cluster) and outcome (cognitive decline). Confounders were selected using directed acyclic graphs (DAGs) informed by the existing literature (Figure 5).

Results

Population Characteristics

The final study sample contained 14,390 individuals, 50 years and older, living in the Metro Atlanta areas. These participants had an average age of 61 years and were mostly white (80.3%). Participants of EHAS were highly educated – 74.3% of them had a bachelor's degree or higher. The median CFI score was 1.5 (IQR: 2.5) (Table 1).

Exposure Characteristics

Based on the air pollution and N-SES characteristics of the census tracts, the SOM identified 6 clusters (Figure 1A). Most participants lived in cluster 4 (n=5427; 37.71%) while relatively few lived in cluster 2 (n = 707, 4.91%) and 3 (n=521, 3.62%). In the map of Metro Atlanta (Figure 1B), census tracts were color-coded based on their SOM cluster assignment. Cluster 4, seen on the map in grey, primarily appears in the northern half of the Metro-Atlanta outside the City of Atlanta. Clusters 1, 2, and 3 appear primarily in the City of Atlanta around highways (black lines on the map). These three clusters have the highest proportions of rented

homes and percentage of dwellers not owning a car. Historically, because of Atlanta's segregation policies, the highest proportion of non-Hispanic Black participants reside within clusters 3 and 6, which are located in southern Atlanta. Cluster 2 has the highest percentage of Hispanic residents. Participants in all clusters had similar median ages, with the youngest residing in cluster 3 (median 57 years; IQR: 13.82) and the oldest in cluster 4 (median 62 years; IQR: 11.68). Cluster 4 was the most residentially stable compared to the other clusters with only 27.8% (IQR: 21.12) of residents moving in before 2010. Cluster 4 was used as the reference group for regression and mediation analyses because of its low concentration of air pollution and high N-SES.

Association between Exposure and Mediators

SOM cluster was associated with high cholesterol levels, particularly when comparing clusters 1 and 5 to the reference cluster 4. The odds of participants having high cholesterol levels were 0.86 (95% CI: 0.78, 0.94) times as likely among those living in cluster 1 compared to those in cluster 4. Participants assigned to cluster 4 had higher O_3 and PM_{10} exposure concentrations, lower exposure concentrations of the other air pollutants, and a similarly high N-SES as those in cluster 1. The odds of CHOL were 1.18 (95% CI: 1.06, 1.31) times higher among those living in cluster 5 compared to those living in cluster 4 (Figure 2A, Table S2A). Participants assigned to cluster 5 had similar air pollution concentrations as participants assigned to cluster 4 (reference category) but a lower N-SES.

We observed slightly stronger associations with narrower confidence intervals for associations with high blood pressure, with significant associations observed for the comparison of clusters 1, 2, 5, and 6 to the reference cluster 4. Similar to the associations with high

cholesterol, cluster 1 was protective of high blood pressure (OR: 0.89; 95% CI: 0.81, 0.98) and we observed higher odds for cluster 5 (OR: 1.11; 95% CI: 1.00, 1.24). In addition, we observed adverse effects for clusters 2 (OR: 1.22; 95% CI: 1.02, 1.45) and 6 (OR: 1.27; 95% CI: 1.11, 1.45), which are both characterized by high air pollution concentrations and low N-SES.

The association between SOM cluster and depression was not statistically significant, but we observed higher odds for clusters 2, 3, 5 and 6 in comparison to reference cluster 4 (Figure 2C, Table S2A).

Association between Mediator and Outcome

High cholesterol level, high blood pressure, and depression were associated with higher lnCFI scores (Figure 3). Participants with these health conditions had lnCFI scores 0.39 (95% CI: 0.36, 0.42; high cholesterol level), 0.12 (95% CI: 0.09, 0.15; high blood pressure), and 0.13 (95% CI: 0.10, 0.15; depression) points higher than those without these conditions (Table 2B).

Mediation by high cholesterol level, high blood pressure, and depression

The mediation analysis focused on the mediating effects of high cholesterol levels, high blood pressure, and depression on the association between SOM exposure clusters and lnCFI scores (Figure 4). The largest mediated proportion was found for depression with 19% (for cluster 3) to 87% (for cluster 1) of the association between SOM cluster and lnCFI being mediated by depression (Figure 4, table S1). For example, prior to adjusting for depression, on average, participants living in cluster 1 had CFI scores 0.05 (CI: 0.01, 0.09) (total effect) higher than those from cluster 4. After adjusting for depression, the association was attenuated (0.01; CI: -0.04, 0.05; direct effect).

The maximum proportion mediated by high cholesterol and high blood pressure for the association between SOM clusters and cognitive decline did not exceed 10%. Up to 8% of the association between SOM clusters and cognitive decline was mediated by high blood pressure (for cluster 3), with only 5% at maximum for high cholesterol levels (for cluster 6).

Discussion

In this study of 14,390 individuals 50 years and older from Metro Atlanta, we showed that 19 to 87% of the association between air pollution and N-SES on cognitive decline was mediated by depression, whereas only a small portion (<10%) was mediated by high blood pressure and high cholesterol levels. High blood pressure, high cholesterol levels, and depression were all associated with cognitive decline. We further identified a significant joint effect of air pollution and N-SES on high blood pressure and cholesterol. Associations with depression were weaker and not significant.

We observed adverse joint effects of exposure to air pollution and low N-SES on depression, but the associations were not statistically significant, potentially due to a lack of statistical power. While research on the joint effects of air pollution and N-SES on depression is scarce, the direction of association is in line with several studies that have reported an association between air pollution and increased odds of depression or the use of antidepressants (Ali & Khoja, 2019; Fan et al., 2020; Kioumourtzoglou et al., 2017; Lim et al., 2012; Vert et al., 2017) as well as between low N-SES and depression (Jakobsen et al., 2022; Mair et al., 2008; Richardson et al., 2015).

Depression was associated with cognitive decline in our study and the strongest predictor of subjective cognitive decline in comparison to other comorbidities (high blood pressure, high

cholesterol). This result is consistent with the existing literature. Substantial evidence has suggested that cognitive deficits could persist after remission of a major depressive episode (Formánek et al., 2020; Perini et al., 2019; Semkovska et al., 2019). In a review of biological mechanism discussing the putative mechanisms of cognitive decline in depression, Dobielska and colleagues explained that in two-thirds of the depressed patients and at least one-third of the remitted patients studied, reduced cognitive function occurred (Dobielska et al., 2022). The hypothesis is that inflammation processes drive a decrease in neuroplasticity and damage the brain structure, mainly the hippocampus. The atrophy of the hippocampus has proven to be a strong predictor of cognitive decline; therefore, the depression-associated inflammation process may contribute to cognitive decline. Of note, inflammation is also one of the biological pathways hypothesized to link air pollution exposure with cognitive decline (Dobielska et al., 2022).

In our study, depression mediated 19 to 87% of the association between SOM cluster and cognitive decline. So far, very few studies have investigated the interconnections between air pollution and N-SES, depression, and cognitive decline. One study investigated the role of cognitive impairment as a potential effect modifier of the association between air pollution and depression (Altuğ et al., 2020). Another study investigated the association between natural outdoor environments (parks, forests, and recreation areas) and cognitive functions, and used loneliness and mental health as potential mediators. However, they did not find indications for mediation by loneliness and mental health (Zijlema et al., 2017). Therefore, our findings contribute to the current literature by providing the first evidence of a mediating role of depression for the association between the joint exposure to air pollution and low N-SES and cognitive decline.

We found significant associations between SOM cluster and cardiovascular comorbidities, particularly with high blood pressure. This finding is consistent with the current literature, which shows a robust association between air pollution and high blood pressure (Giorgini et al., 2016) as well as some evidence of an association with high cholesterol levels (McGuinn et al., 2019). Low N-SES has also been consistently reported to be associated with higher blood pressure and cholesterol levels (Espírito Santo et al., 2019; Grotto et al., 2008; Jenkins & Ofstedal, 2014; Leng et al., 2015).

High blood pressure and high cholesterol were associated with cognitive decline, though the effect estimates were smaller than for depression. This result is consistent with a systematic review conducted in 2019 summarizing results from 50 studies (Forte et al., 2019). High blood pressure affects cerebral perfusion which can cause alterations in the physiological processes of cerebral blood flow regulation, making hypertensive patients more vulnerable to the development of cerebrovascular damage and vascular dementia (Jennings et al., 2005; Moretti et al., 2008). As for the association between high cholesterol levels and dementia, our findings contribute to the currently mixed results by adding to the pool of evidence that increased cholesterol level is a risk factor for dementia (Anstey et al., 2008; Peters et al., 2021).

High blood pressure and high cholesterol level mediated a small percentage of the association between SOM clusters and cognitive decline. This study is one of very few exploring cardiovascular comorbidities as potential mediators of the association between air pollution and cognitive decline. One study evaluated the role of CVD as a mediator of the association between indoor unclean fuel and adult cognitive function and indoor unclean fuel (Cong et al., 2021). They found that hypertension explained more than 50% of such a fuel-related decline in the verbal memory (Cong et al., 2021). So far, only two studies have investigated CVD as a potential

mediator of the association between outdoor air pollution and cognitive decline (Grande et al., 2020; Ilango et al., 2020). The proportions of the association mediated by CVD varied widely and ranged from 9% (Ilango et al., 2020) to 50% (Grande et al., 2020). In our study, up to 8% of the association between air pollution and N-SES on subjective cognitive decline was mediated by high blood pressure and high cholesterol levels, which is more in line with the estimates from Ilango et al. (2020). However, important differences between their and our study are that we looked at the joint effects of air pollution and N-SES, whereas they only focused on air pollution, and differences in the definition of CVD. Both previous studies focused on severe cardiovascular events (e.g., ischemic heart disease, heart failure, atrial fibrillation, and stroke) (Grande et al., 2020; Ilango et al., 2020), whereas we captured with high blood pressure and high cholesterol levels more common and less severe CVD, which are often well-controlled with medications. This difference in mediator assessment could explain the smaller proportions mediated observed for CVD in our study.

Strengths and Limitations

A strength of this study is its large sample size. EHAS collected information from a diverse city. The racial, ethnic, and socioeconomic landscape in Atlanta allowed for the definition of diverse profiles of the exposure mixture by SOM clustering algorithm. The second strength is the use of CFI to determine subjective cognitive decline. This measurement strengthens this analysis because subjective cognitive decline is one of the first signs of progression to dementia (Amariglio et al., 2015; Jessen et al., 2014)

There are several limitations in this study. The first is the cross-sectional nature of the study data with subjective cognitive decline over the last year (outcome) being assessed at the

same time as the mediators (ever diagnosed with high blood pressure, high cholesterol, or depression). However, while the mediator and outcome assessment were done on the same day, the doctor's diagnosis of comorbidities (high blood pressure, high cholesterol levels, and depression) must have occurred prior to their baseline visit to be reported, which limits the risk of reverse causality. The second limitation is the lack of representativeness for the information being collected. EHAS is not a population-based sample. The majority of the participants are white and live in areas with high N-SES, which is not representative of all residents in Atlanta. This could have limited the statistical power of our association analysis, particularly for the association between SOM clusters and depression. The grid size of the CMAQ chemical transport model is also a limitation. The 4 km resolution grids may not capture granule enough variation within air pollution levels in Atlanta. However, another study using 250m resolution did report similar harmful effects of air pollutants on cognitive decline (Li et al., 2022). The fourth limitation focuses on the self-reporting status of high cholesterol levels, high blood pressure, depression, and subjective cognitive decline. Participants were asked to report doctors' diagnoses. Recall bias may be present in data collection leading to misclassification of the mediator. There is also possible misclassification of the exposure based on participants moving prior to their enrollment in EHAS, although this is likely to be non-differential based on their CFI scores. The final limitation is that due to the categorical nature of the exposure, we cannot use widely used R packages to calculate mediation effects. Instead, we compared total and direct effects to calculate proportion mediated and could not provide confidence intervals for that proportion.

Conclusions

In our study of 14,390 participants from metro Atlanta, GA, depression explained most of the association between the joint effects of air pollution and N-SES on cognitive decline, whereas <10% of the association was mediated by high blood pressure and high cholesterol levels. Future studies are needed to replicate our findings and to investigate whether these results can help to understand the type of dementia that is most commonly caused by air pollution exposure (e.g., vascular dementia or Alzheimer's disease).

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Tables and Figures

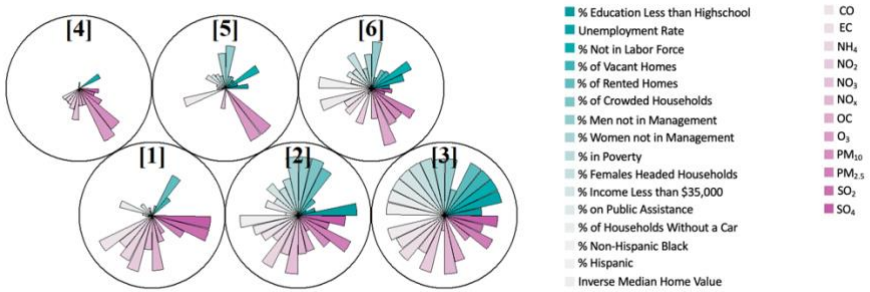
Table1. A. Emory Healthy Aging Study (EHAS) study population characteristics by Self-Organized Map (SOM) cluster. **B**. Air pollution measurements by SOM clusters. **C**. Neighborhood Socioeconomic Status (N-SES) indicators by SOM clusters. **D**. Mediators (cardiovascular and neuropsychiatric comorbidities).

		SOM Cluster*					
	Total	**1**	**2**	**3**	**4**	**5**	**6**
A. Study Population Characteristics							
N (%)	14390	3914(27.2)	707(4.9)	521(3.6)	5427(37.7)	2258(15.7)	1563(10.9)
Median CFI (IQR)	1.50 (2.50)	1.50 (2.50)	2.00 (2.50)	2.00 (3.00)	1.50 (2.50)	2.00 (2.50)	2.00 (2.50)
Median Age (IQR)	60.67 (12.81)	59.25 (14.67)	59.87 (13.11)	57.14 (13.82)	62.00 (11.68)	61.67 (11.07)	59.68 (12.76)
% Residents Moved in Before 2010 (IQR)	20.84 (18.94)	13.43 (12.21)	13.57 (13.02)	16.23 (14.26)	27.80 (21.12)	21.68 (15.86)	25.32 (19.70)
Race (%)							
White	11441 (80.3)	3436 (88.6)	540 (77.8)	196 (37.8)	4849 (90.2)	1850 (82.9)	570 (36.8)
Black	2034 (14.3)	237 (6.1)	97 (14.0)	296 (57.1)	235 (4.4)	259 (11.6)	910 (58.8)
Other	767 (5.4)	204 (5.3)	57 (8.2)	26 (5.0)	290 (5.4)	123 (5.5)	67 (4.3)
Hispanic (%)	547 (3.8)	160 (4.1)	32 (4.6)	20 (3.8)	196 (3.6)	90 (4.0)	49 (3.1)
Education (%)							
Less than High School	35 (0.2)	5 (0.1)	2 (0.3)	6 (1.2)	5 (0.1)	11 (0.5)	6 (0.4)
High School /GED	531 (3.7)	61 (1.6)	35 (5.0)	54 (10.4)	149 (2.7)	146 (6.5)	86 (5.5)
Some College, but no Degree	2133 (14.8)	355 (9.1)	128 (18.3)	109 (20.9)	704 (13.0)	516 (22.9)	321 (20.6)
Associates Degree	993 (6.9)	160 (4.1)	63 (9.0)	48 (9.2)	320 (5.9)	258 (11.4)	144 (9.2)
Bachelor's Degree	4872 (33.9)	1376 (35.2)	233 (33.2)	147 (28.2)	1968 (36.3)	658 (29.2)	490 (31.5)
Master's Degree	3837 (26.7)	1218 (31.2)	173 (24.7)	111 (21.3)	1510 (27.8)	443 (19.7)	382 (24.5)
Professional or Doctorate Degree	1963 (13.7)	730 (18.7)	67 (9.6)	46 (8.8)	769 (14.2)	222 (9.8)	129 (8.3)

B. Air Pollution Measurements – Median (IQR)							
CO (ppm)	0.62 (0.21)	0.67 (0.13)	0.69 (0.13)	0.65 (0.15)	0.54 (0.23)	0.40 (0.24)	0.56 (0.16)
EC ($\mu g/m^3$)	0.95 (0.33)	1.00 (0.26)	1.05 (0.25)	1.20 (0.45)	0.91 (0.22)	0.67 (0.38)	0.97 (0.29)
NH4($\mu g/m^3$)	1.04 (0.05)	1.05 (0.06)	1.08 (0.07)	1.04 (0.06)	1.04 (0.04)	1.02 (0.09)	1.02 (0.06)
NO_2 (ppb)	23.63 (5.56)	24.79 (2.58)	25.12 (3.09)	25.10 (6.30)	22.59 (5.73)	17.20 (9.36)	22.54 (3.62)
NO_3 (ppb)	0.62 (0.05)	0.61 (0.03)	0.64 (0.03)	0.62 (0.03)	0.63 (0.06)	0.62 (0.09)	0.61 (0.04)
NO_X (ppm)	0.04 (0.02)	0.05 (0.02)	0.05 (0.00)	0.05 (0.02)	0.04 (0.02)	0.03 (0.02)	0.04 (0.01)
OC($\mu g/m^3$)	2.84 (0.20)	2.84 (0.13)	2.92 (0.37)	2.92 (0.26)	2.82 (0.20)	2.82 (0.27)	3.00 (0.17)
O_3 (ppm)	0.04 (0.00)	0.04 (0.00)	0.04 (0.00)	0.04 (0.00)	0.04 (0.00)	0.04 (0.00)	0.04 (0.00)
PM_{10}($\mu g/m^3$)	20.96 (0.20)	20.86 (0.13)	20.95 (0.19)	20.97 (0.16)	20.98 (0.19)	21.08 (0.16)	21.01 (0.23)
$PM_{2.5}$($\mu g/m^3$)	12.56 (0.51)	12.52 (0.37)	12.83 (1.01)	12.85 (0.78)	12.52 (0.46)	12.54 (0.61)	12.85 (0.61)
SO_2 (ppb)	8.37 (2.52)	8.92 (1.99)	8.98 (2.7)	8.19 (2.8)	8.33 (2.27)	6.48 (3.11)	7.18 (1.42)
SO_4 (ppb)	2.95 (0.10)	2.97 (0.09)	3.01 (0.15)	2.95 (0.14)	2.95 (0.09)	2.87 (0.15)	2.89 (0.05)
C. N-SES Indicators – Median (IQR)							
% Education Less than High School	5.50 (7.56)	3.60 (4.85)	21.39 (14.05)	16.25 (7.02)	3.20 (3.43)	11.04 (6.44)	9.75 (5.62)
Unemployment Rate	6.38 (4.03)	5.40 (3.76)	7.79 (3.85)	16.08 (5.35)	5.34 (2.89)	7.51 (2.71)	12.37 (4.89)
% Not in Labor Force	24.47 (8.33)	21.45 (8.86)	19.41 (13.30)	32.62 (12.42)	24.17 (7.13)	25.48 (6.84)	28.55 (6.73)
% Homes Vacant	8.12 (6.98)	10.11 (7.78)	11.79 (4.68)	16.71 (8.35)	5.13 (4.11)	7.53 (4.87)	11.33 (5.03)
% Homes Rented	28.76 (32.13)	48.72 (18.90)	64.55 (16.33)	63.97 (13.72)	12.39 (13.22)	23.66 (15.23)	30.04 (15.66)
% Homes Crowded	0.98 (1.85)	1.00 (1.58)	5.58 (3.04)	2.99 (2.61)	0.23 (0.93)	1.65 (1.91)	1.63 (1.93)
Median Home Value ($ in thousands)	247833.33 (183216.67)	316.33 (133.18)	158.85 (79.72)	99.05 (45.26)	329.20 (170.87)	166.48 (43.35)	128.93 (42.00)
% Male not in Management	48.12 (31.89)	37.64 (13.17)	76.28 (9.99)	79.71 (17.94)	39.61 (17.91)	68.17 (10.51)	70.44 (9.72)

% Female not in Management	46.17 (21.75)	35.83 (14.19)	65.03 (16.01)	69.66 (13.38)	39.28 (13.53)	59.62 (8.84)	58.45 (11.48)
% In Poverty	5.68 (7.82)	5.68 (6.44)	17.90 (8.49)	29.30 (8.77)	3.23 (2.63)	8.40 (5.78)	12.02 (8.27)
% Female Headed Households	5.09 (5.81)	4.08 (3.92)	9.24 (3.66)	14.52 (5.12)	3.52 (2.67)	6.73 (3.69)	11.28 (4.52)
	21.03 (15.97)	24.79 (11.75)	39.33 (8.22)	54.24 (9.44)	12.69 (5.68)	23.80 (8.55)	31.09 (12.08)
		0.80 (0.96)	1.67 (1.49)	3.18 (2.49)	0.52 (0.71)	1.50 (1.32)	1.85 (1.72)
		1.48 (5.66)	22.27 (3.91)	30.12 (7.49)	8.37 (5.05)	11.10 (4.73)	16.17 (7.10)
		(13.58)	20.66 (18.52)	79.64 (26.51)	6.82 (9.06)	19.88 (18.32)	74.94 (30.69)
		1.13)	36.41 (22.72)	3.62 (4.46)	4.55 (3.30)	9.93 (9.80)	4.17 (3.88)
		)	307 (44.8)	252 (49.2)	2118 (39.8)	986 (44.9)	848 (55.4)
			339 (49.3)	216 (42.5)	2638 (49.9)	1177 (54.0)	715 (47.2)
			218 (36.9)	154 (34.4)	1366 (30.5)	659 (34.9)	367 (28.3)

A.



B.

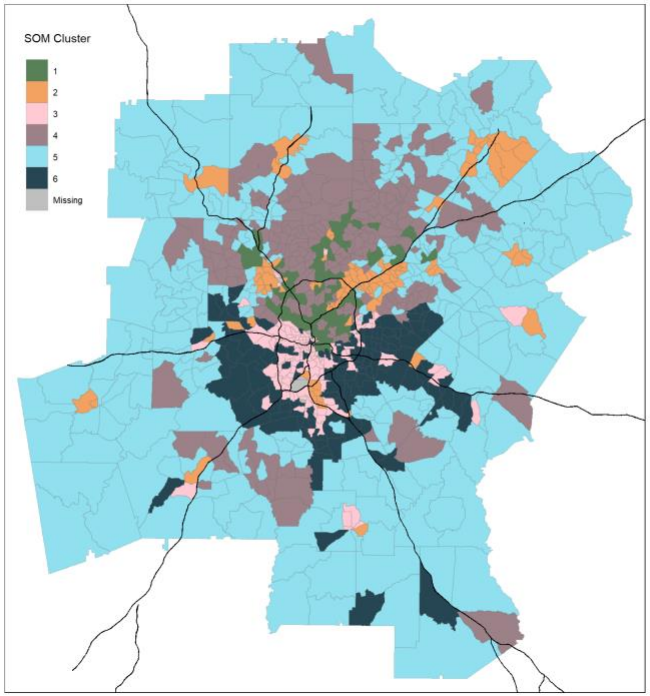


Figure1. Figure SOM. A. SOM cluster star plot, slices represent median values of a mixture component, each circle is a SOM cluster. Blue slices correspond with N-SES indicators, while pink slices correspond with air pollutants. **B.** Map of census tracts in Metro-Atlanta by cluster. Black lines represent major highways.

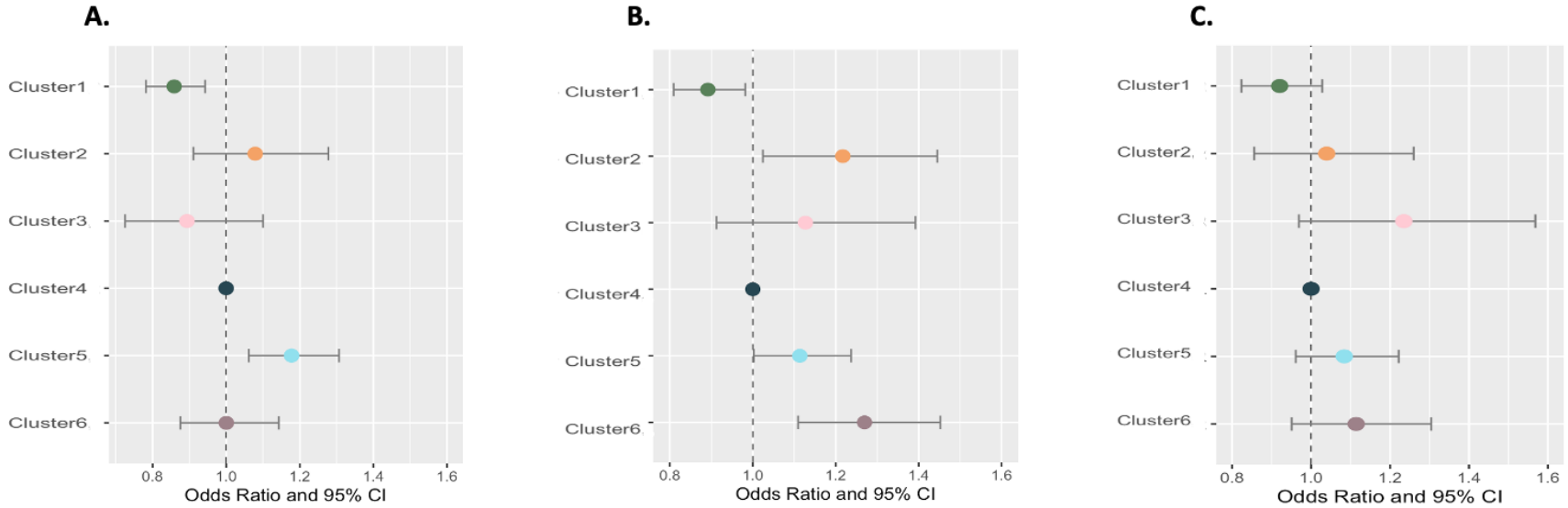


Figure 2. Association between SOM clusters (joint effects of air pollution and N-SES) and common cardiovascular and neuropsychiatric comorbidities. Association between the joint effects of air pollution and N-SES and **A.** high blood pressure, **B.** high cholesterol levels, and **C.** depression. Associations were adjusted for individual age, race/ethnicity, education, and neighborhood residential stability.

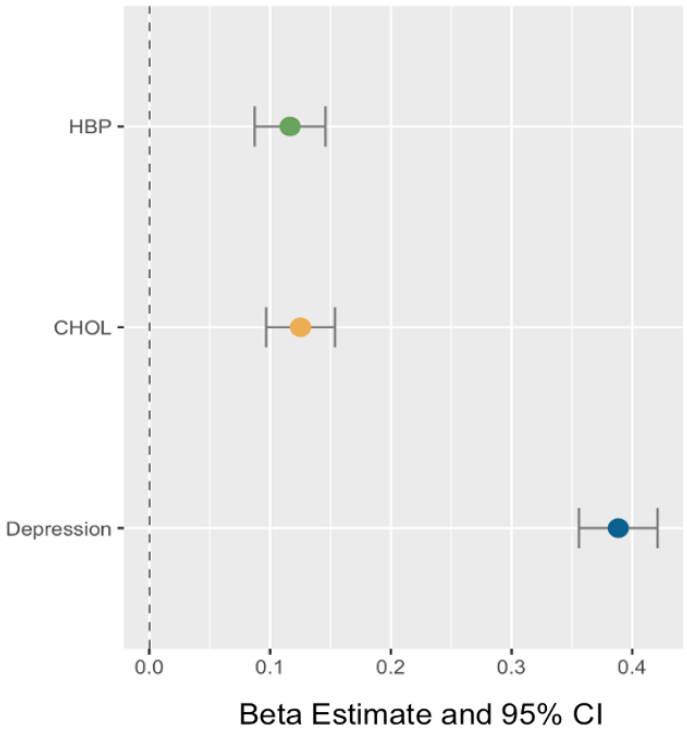


Figure 3. Association Between a prior diagnosis of common cardiovascular and neuropsychiatric comorbidities and cognitive functioning. Association between high blood pressure (HBP), high cholesterol level (CHOL), depression and cognitive decline. The association was adjusted for individual age, race/ethnicity, education, and neighborhood residential stability

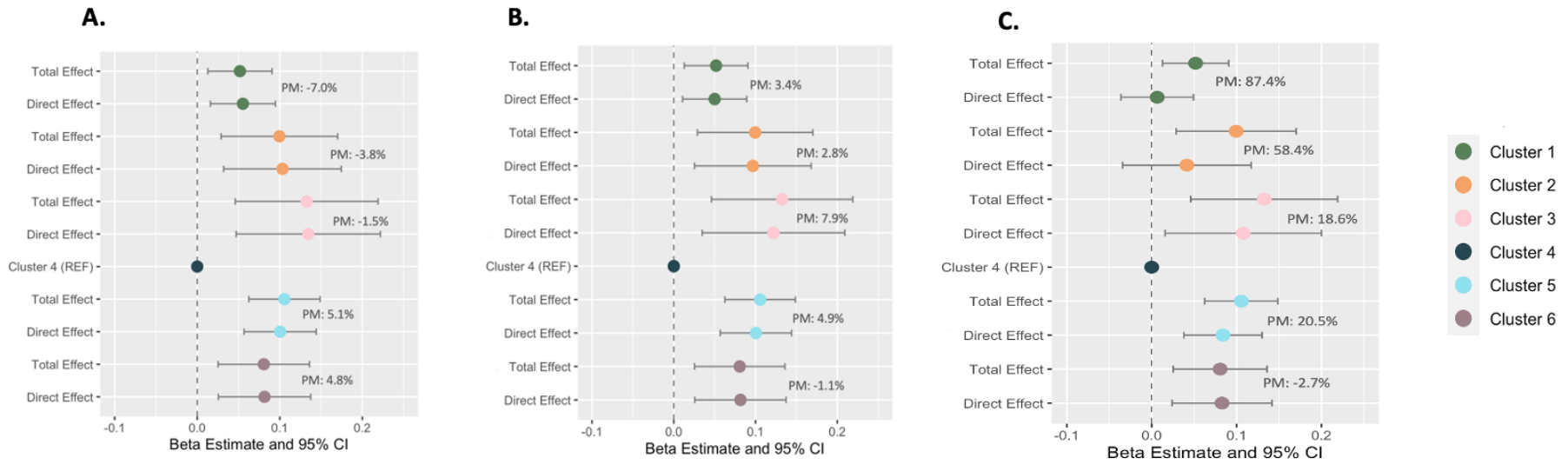


Figure 4. Mediation by common cardiovascular and neuropsychiatric comorbidities (A. Mediation by high cholesterol levels, B. Mediation by high blood pressure, C. Mediation by depression). Associations between SOM clusters (joint effects of air pollution and N-SES) and cognitive functioning before (total effects) and after adjusting for potential mediators (direct effects). Proportion mediated (PM) was calculated as (total effect – direct effect) / total effect. Associations were adjusted for individual age, race/ethnicity, education, and neighborhood residential stability.

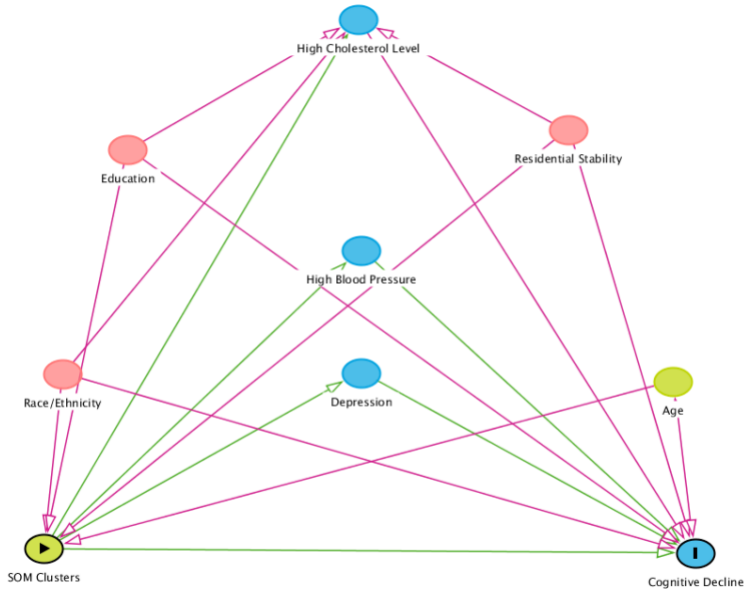


Figure 5. Directed acyclic graphs (DAG) for exposure-mediator-outcome associations. The graph represents the causal pathway relevant to our mediation analysis.

Supplements:

Table 1. Mediation. Mediation by common cardiovascular and neuropsychiatric comorbidities. Associations between SOM clusters (joint effects of air pollution and N-SES) and cognitive functioning before (total effects) and after adjusting for potential mediators (direct effects) using linear regression analysis. Proportion mediated (PM) was calculated as (total effect – direct effect) / total effect. Associations were adjusted for individual age, race/ethnicity, education, and neighborhood residential stability.

		Adjusted for depression		Adjusted for high blood pressure		Adjusted for high cholesterol level	
Clusters	**Total effect (95%-CI)**	**Direct effect (95%-CI)**	**Proportion mediated**	**Direct effect (95%-CI)**	**Proportion mediated**	**Direct effect (95%-CI)**	**Proportion mediated**
1	0.05 (0.01, 0.09)	0.01 (-0.04, 0.05)	0.87	0.05 (0.01, 0.09)	0.03	0.06 (0.02, 0.09)	-0.07
2	0.1 (0.03, 0.17)	0.04 (-0.03, 0.12)	0.58	0.1 (0.03, 0.17)	0.03	0.10 (0.03, 0.17)	-0.04
3	0.13 (0.05, 0.22)	0.11 (0.02, 0.20)	0.19	0.12 (0.03, 0.21)	0.08	0.13 (0.05, 0.22)	-0.02
4 (reference)	0 (n/a, n/a)	0 (n/a, n/a)	n/a	0 (n/a, n/a)	n/a	0 (n/a, n/a)	n/a
5	0.11(0.06, 0.15)	0.08 (0.04, 0.13)	0.21	0.1 (0.06, 0.14)	0.05	0.1 (0.06, 0.14)	0.05
6	0.08 (0.03, 0.14)	0.08 (0.02, 0.14)	-0.03	0.08 (0.03, 0.14)	-0.01	0.08 (0.02, 0.13)	0.05

Table 2. A. Association between SOM clusters (air pollution and N-SES) and cardiovascular and neuropsychiatric comorbidities (depression, high blood pressure, and high cholesterol levels). B. Association between cognitive decline and depression, high blood pressure, and high cholesterol levels.

A. Association between SOM clusters and depression, high blood pressure and high cholesterol			
	Depression	**High blood pressure**	**High cholesterol level**
Clusters	**OR (95%-CI)**	**OR (95%-CI)**	**OR (95%-CI)**
1	0.92 (0.82, 1.03)	0.89 (0.81, 0.98)	0.86 (0.78, 0.94)
2	1.04 (0.86, 1.26)	1.22 (1.02, 1.45)	1.08 (0.91, 1.28)
3	1.24 (0.97, 1.57)	1.13 (0.91, 1.39)	0.89 (0.73, 1.10)
4 (reference)	1 (n/a, n/a)	1 (n/a, n/a)	1 (n/a, n/a)
5	1.08 (0.96, 1.22)	1.11 (1.00, 1.24)	1.18 (1.06, 1.31)
6	1.11 (0.95, 1.30)	1.27 (1.11, 1.45)	1.00 (0.88, 1.14)
B. Association between depression, high blood pressure, high cholesterol level and CFI scores			
	Depression	**High blood pressure**	**High cholesterol level**
	Beta estimate (95%-CI)	**Beta estimate (95%-CI)**	**Beta estimate (95%-CI)**
CFI	0.13(0.10,0.15)	0.12(0.09,0.15)	0.39(0.36,0.42)