University of Nevada, Reno

Air Pollution, Aging, and Cognitive Impairment

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by

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Abstract

Age-related cognitive impairment (CI) is a common health condition that affects millions of people worldwide. With population aging on the rise, CI will affect millions more. CI and dementia causality is multifactorial. Known causal factors include genetics, age, and sex. Recently, toxicological and epidemiological studies have implicated air pollution in the causation of these conditions. Air pollution is a well-known environmental hazard with millions of people exposed to high concentrations of air pollutants every day. Exposure to air pollutants such as volatile organic compounds (VOC), fine particles ($PM_{2.5}$), and ozone (O_3) can lead to chronic oxidative stress (OS), which is involved in the pathogenesis of CI and dementia. We reviewed the existing literature regarding the association among air pollutants, OS, and CI. Then, we implemented two epidemiological studies—using data from the National Health and Nutrition Examination Survey (NHANES) III and the Behavioral Risk Factor Surveillance System Survey (BRFSS) 2011—to explore the association between exposure to VOC, $PM_{2.5}$, and O_3; and, CI. After adjusting for demographic and health characteristics, results showed an inverse association between serum VOC and neurobehavioral functioning ($p < 0.05$). Similarly, we found a significant association between exposure to $PM_{2.5}$, and O_3, and self-reported CI ($p < 0.05$). These results indicated that air pollution combined with population aging could act synergistically on increasing the burden CI and dementia at the population level. Further research with larger sample size, longitudinal design, and objective exposure and outcome assessments is needed to identify modifiable risk factors for dementia and orient public health efforts.

Key words: Air Pollution, Cognitive Impairment, Aging, Oxidative Stress

Dedication

To Eliana and Juan, my grandparents…You will always live in my heart.

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A todos y cada uno de ustedes, ¡muchas gracias!

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CHAPTER I ROUTE MAP TO THIS DISSERTATION

1.1. Dissertation Outline

Chapter II presents an overall introduction to this research. Chapter III describes the methods and procedures used to gather and analyze the data for each study and thus is divided in three sections: (1) Study 1: Air Pollution, Oxidative Stress, and Alzheimer's Disease; Study 2: Serum Concentration of Volatile Organic Compounds, Oxidative Stress, and Neurobehavioral Functioning; and, Study 3: Exposure to Fine Particles and Ozone, and the Risk of Cognitive Impairment: A Population-Based Study in Eleven U.S. States. The results from study 1 (i.e. literature review) are presented in Chapter IV.

The results from study 2 and 3 are described in Chapter V and Chapter VI, respectively. Chapter VII consists of a summary of the overall findings. Conclusions drawn from the studies' findings and recommendations for future research are provided in this last chapter as well.

CHAPTER II INTRODUCTION

2.1. Background

The world's population is aging. Today's longer life expectancy, low birth rates, and the elevated birth rates of many countries after World War II—the Baby Boom of 1946 to 1964 [1,2]—are resulting in a growing number of older adults (i.e. individuals age 65 or older). Recent estimates indicate that 8% of the world's population (500 million people) are older adults [3]. The U.S. Census Bureau reported that in 2010, 13% Americans (40.3 million) were older adults [4]. It is projected that by 2030 the proportion of older adults will increase up to 13% (one billion people) worldwide and 19% (72.1 million people) in the U.S. [3,5].

The increasing number of older adults is shifting the global age distribution towards older age. The shift in age distribution will result in an increased frequency of age-related diseases such as dementia. Dementia is an age-related condition characterized by progressive decline in memory and other cognitive functions that leads to loss of independent functioning and disability [6]. The first sign of age-related cognitive impairment is forgetfulness. Over time, forgetfulness evolves into mild cognitive impairment (MCI); and in some cases, MCI progresses to dementia [7]. Dementia decreases individuals' cognitive functioning and can have broader impacts on individuals, families, and the healthcare system. Thus, the aging world population represents an important public health problem [6].

2.2. Air Pollution and Age-Related Cognitive Impairment

Dementia represent a major social, economic, and medical problem [8]. Despite the tremendous public health importance of cognitive impairment and dementia in older age, few modifiable risk factors have been identified. Evidence indicates age-related cognitive

impairment is at least partially mediated by oxidative stress [9–13]. Oxidative stress is the state of redox imbalance that results from a production of reactive oxygen species (ROS) that exceeds the capacity of antioxidant defense mechanisms [14]. Environmental exposures such as air pollution can increase an organism's generation of ROS and thus represent a potential risk factor for age-related cognitive impairment.

In the U.S., National Ambient Air Quality Standards (NAAQS) have been established for six criteria air pollutants proved to represent a threat for human health. These pollutants include: (1) ozone (O_3), (2) particulate matter (PM), (3) carbon monoxide (CO), (4) nitrogen oxides (NOx), (5) sulfur dioxide (SO_2), and (6) lead [15]. Notwithstanding standards that are currently in place, it is estimated that over one hundred million people in the U.S. live in areas that exceed the recommended NAAQS [16]. Primary and Secondary NAAQS for these six criteria air pollutants are summarized in Table 2.1.

Air pollution is a well-known environmental hazard and its association with respiratory and cardiovascular pathology has been consistently confirmed by several epidemiological studies [17–22]. The idea that air pollution might be associated with cognitive functioning has recently been the focus of many toxicological studies, but the epidemiological evidence is limited. While it has been established that cognitive impairment and dementia are well correlated with population aging, exposure to air pollution concentrations above the NAAQS could act synergistically with population aging to increase the prevalence of these conditions. The widespread occurrence of air pollution makes ascertaining its association with cognitive impairment a public health priority. Thus more epidemiological studies looking at this association are needed.

2.3. Purpose of the Study

Most studies investigating the association between air pollution and decline in cognitive functioning have focused on two criteria pollutants: PM and O_3. The effects of other air pollutants on cognitive functioning—such as volatile organic compounds (VOC)—have yet to be fully understood. Currently, there is a scarcity of data addressing VOC exposure in the general population and its effects on cognitive functioning. As air pollution consists of a mixture of different air pollutants (i.e. particles, liquid droplets, and gases), further investigation on the potential additive and/or synergistic effects between these pollutants is also needed.

Thus, the purpose of this epidemiological study was to explore the possible existence of associations between exposure to air pollutants such as PM, O_3, and VOC and age-related cognitive impairment. In the hypothesized causal model, these air pollutants were the exposures of interest affecting cognitive functioning. The performance on the Neurobehavioral Examination System 2 (NES2) tests as assessed in the National Health and Nutrition Examination Survey (NHANES) III; and, self-reported cognitive impairment as evaluated in the Behavioral Risk Factor Surveillance System (BRFSS) 2011, acted as proxies of age-related cognitive impairment (outcome).

In addition, oxidative stress was explored as the physiological mechanism explaining the potential association between air pollution and cognitive decline. The reasons for this are threefold: (1) aging is described as the result of the accumulation of ROS-induced damage to macromolecules by free radicals [23,24]; (2) oxidative stress have been implicated on the etiology and pathogenesis of dementia and cognitive

impairment [25–31]; and, (3) air pollutants can act as pro-oxidant or free radical generators and promote oxidative stress in the brain [32–34].

Any new knowledge gained from the determining potential modifiable predictors of cognitive impairment and dementia later in life will prove to be useful for guiding future public health policies and interventions. Evidence-based initiatives oriented toward decreasing the burden of dementia on individuals and society as a whole may be valuable for protecting population's health.

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Table 2.1. National Ambient Air Quility Standards (NAAQS) for Criteria Air Pollutants [15]

Criteria Air Pollutant	Primary Standard		Secondary Standard	
	Level	Averaging Time	Level	Averaging Time
1. Ozone	0.075 ppm (2008 std)	8-Hour	Same as Primary	
	0.08 ppm (1997 std)	8-Hour	Same as Primary	
2. Particulate Matter				
$PM_{2.5}$	15.0 μg/m^3	Annual	Same as Primary	
	35 μg/m3	24-Hour		
PM_{10}	150 μg/m^3	24-Hour	Same as Primary	
3. Carbon Monoxide	9 ppm (10 mg/m^3)	8-hour	None	
	35 ppm (40 mg/m^3)	1-hour		
4. Nitrogen Dioxide*	53 ppb	Annual	Same as Primary	
	100 ppb	1-hour	None	
5. Sulfur Dioxide	0.03 ppm (1971 std)	Annual	0.5 ppm	3-hour
	0.14 ppm (1971 std)	24-hour		
	75 ppb	1-hour	None	
6. Lead	0.15 μg/m^3	Rolling 3-Month Average	Same as Primary	

* Although NAAQS cover the entire group of NO_X, NO_2 is use as indicator for this group.

CHAPTER III METHOD

3.1. Study 1: Air Pollution, Oxidative Stress, and Alzheimer's Disease

A systematic literature review was conducted of studies examining the relationship between air pollution, oxidative stress, and Alzheimer's disease listed in the Medline-PubMed databases from 1956 to 2011. Search terms included combinations and variations of the following terms: aging, dementia, Alzheimer's disease, oxidative stress, air pollution, particulate matter, and ozone. The databases' search was complemented by reviewing the reference sections of all identified articles and extracting the references considered to be relevant to this topic.

Studies that examined the relationship between/among oxidative stress, aging, dementia, and/or air pollutants were included in this review. Unpublished studies, thesis, dissertations, and non-English publications were excluded from this review. The literature search and review of the references lists produced over 150 articles. After the selection criteria were applied, 78 articles remained in this study.

There was great heterogeneity across the 78 articles selected. Because the idea that air pollution might be associated with Alzheimer's disease is relatively new, the epidemiological evidence supporting this association is limited. However, several toxicological studies have shown an association between exposure to air pollution, oxidative stress, and cognitive impairment. As we were concerned that the vast evidence from toxicological studies may possibly be overlooked, both, toxicological and epidemiological studies that explored this association were included. Furthermore, both original research and review articles were included in this review.

3.2. Study 2: Serum Concentration of Volatile Organic Compounds, Oxidative Stress, and Neurobehavioral Functioning

3.2.1. Population and Sample. Participants were selected from the respondents to the NHANES III, which was conducted between October 1988 and October 1994 [1,2]. A total of 39,695 persons were selected to participate in NHANES III over the six years period [1,2]. Of these individuals, 11, 306 people were 20 to 59 years old [3]. About half of the participants 20-59 years old were randomly selected to complete a CNS function evaluation (i.e. NES2); and, 1,338 of them, voluntarily participated in a toxicological assessment (Priority Toxicant Reference Range Study [PTRRS]).

For this study, we used the following inclusion criteria: age ≥ 30 years, to have completed NES2; and, to have volunteered for the PTRRS. Among the NHANES III participants, a total of 15, 042 people, 30 years and older, were evaluated for eligibility. After applying these inclusion criteria and eliminating subjects with missing data, the final sample size was 341(Figure 3.1).

3.2.2. Data Source. Data for this study was retrieved from the NHANES III public release data files available at http://www.cdc.gov/nchs/nhanes/nh3data.htm. Specifically, the data files utilized in this study were the following: Household Adult file (adult), Household Adult Update file (adultx), Examination file (exam), Laboratory file (lab), Second Laboratory file (lab2), Prescription Medication file (prupremed), Drug Information (rxq_drug), Vitamin and Mineral file (puvitmin), Supplement Concentration file (suplconc), Supplement Product Information file (supliden), and Volatile Toxicant (voc).

3.2.3. Measures.

3.2.3.1. Volatile organic compounds. In NHANES III exposure to VOC was assessed from the cross-sectional blood concentrations of VOC collected in the PTRRS. The blood concentration of thirty VOC were measured, these included: 1,1,1-Trichloroethane, 1,1,2,2-Tetrachloroethane, 1,1,2-Trichloroethane, 1,1-Dichloroethane, 1,1-Dichloroethene, 1,2-Dichlorobenzene, 1,2-Dichloroethane, 1,2-Dichloropropane, 1,3-Dichlorobenzene, 1,4-Dichlorobenzene, 2-Butanone, Acetone, Benzene, Bromodichloromethane, Bromoform, Carbon tetrachloride, Chlorobenzene, Chloroform, cis-1,2-dichloroethene, Dibromochloromethane, Dibromomethane, Ethylbenzene, m-/p-Xylene, Methylene chloride, o-Xylene, Styrene, Tetrachloroethene, Toluene, trans-1,2-Dichloroethene, and Trichloroethene. If the blood concentration of VOC was below the lower detection limit, the values were replaced with a value equal to the detection limit divided by the square root of two.

3.2.3.2. Cotinine, serum C-reactive protein, and gamma glutamyl transferase. NHANES III's laboratory data included the values obtained from the blood specimens collected from participants aged one year and older. General biochemistry tests included the cross-sectional blood concentrations of serum cotinine (COP, mg/dL), C-reactive protein (CRP, mg/dL), and gamma glutamyl transferase (GGT, SI U/L). These biomarkers were utilized in this study as an indicator of participants' exposure to tobacco smoke and oxidative stress.

3.2.3.3. Neurobehavioral evaluation system 2. The NES2 is a set of computerized self-administered neurobehavioral tests used to evaluate psychomotor speed and control, perpetual speed, learning, memory, vocabulary ability, attention, and affect [4–6]. NES2 is widely used to relate neurobehavioral variables to neurotoxicant exposure in occupational and non-occupational settings [4,5]. The NES2 is a tool that has demonstrated to be a feasible, efficient, acceptable, and sensitive approach to evaluating the central nervous system functioning in populations exposed to neurotoxicants such as air pollutants [6].

As part of the NHANES III's CNS function evaluation, three computerized neurobehavioral tests were administered to the selected participants: (1) Simple Reaction Time Test (SRTT); (2) Symbol Digit Substitution Test (SDST); and, (2) Serial Digit Learning Test (SDLT). The scores (i.e. summary measures) obtained in SRTT, SDLT, and SDST tests were used as indicators of cognitive functioning. These tests are briefly described below.

The SRTT evaluated visuomotor speed (i.e. how quickly an individual responds to a given stimulus) in milliseconds [4,5,7] . Each participant completed fifty trials, and on each trial a 4x4 centimeters square was displayed on a computer screen. Participants were asked to press a blue button using the index finger of his/her preferred hand when the square appeared [4,5]. The latency (in milliseconds), between the appearance of the square on the computer's screen and the participant

pressing the button was measured and recorded [4,8]. The SRTT score was calculated as the average reaction time of trials eleven to fifty.

The SDST measured coding speed (i.e. visual motor speed, learning, and memory) in seconds [4,5,7]. The participant was presented with two grids: (1) a grid that paired one of nine different symbols with one of the digits from 1 to 9; and (2) a grid that displayed the same symbols in a scrambled order and the spaces for the corresponding digits left blank [4,5,7] . Each trial presented a different pairing of digits and symbols. The participant was asked to enter, as quickly as possible, the matching digit for each symbol [4,7,8]. The amount of time (in seconds) required to enter each digit and the number of errors on each trial were recorded [4]. The SDST score was the mean of the error corrected latencies (in second/correct digit) on the two best (lowest latency) trials [8].

The SDLT test measured learning, concentration, and memory [4,5,7]. Participants were asked to learn a series of digits which were presented slowly, one at a time, on the computer screen [4,5]. After all the digits were displayed, the respondent was asked to enter as many digits as he/she could remember in the order that they were shown [7]. The test continued until the participant responded correctly to two consecutive trials or until the subject attempted a maximum of eight trials [4]. The sequence of digits entered by the subject was recorded for each trial. Participants received a score of zero if all eight digits were entered correctly; one, if six or seven digits were entered correctly; and two, if fewer than six digits were

entered correctly [8] . The total SDLT score was calculated from the sum of the error scores for each trial [4,7,8].

3.2.3.4. Covariates. Of the demographic variables collected by NHANES III, age, sex, race/ethnicity, educational level, and poverty income ratio were utilized in this study. Health-related questions on health status (i.e. Is health in general excellent, very good, good, fair, poor?), history of cardiovascular disease (i.e. Doctor ever told you had…congestive health failure, stroke, hypertension/high blood pressure, cholesterol level high, heart attack), history of diabetes (i.e. Doctor ever told you had diabetes), history of chronic obstructive pulmonary disease (i.e. Doctor ever told you had…chronic bronchitis, emphysema); and, history of cancer (i.e. Doctor ever told you had…skin cancer, other cancer) were also used.

In addition, participants' information on medication use was retrieved. Specifically, we assessed the use of prescription drugs commonly prescribed for dementia and/or depression. Questions about behaviors such as physical activity status (i.e. In the past month, did you…jog/run, ride bicycle/exercise bicycle, swim, do aerobics/aerobic dancing/other dancing, do calisthenics/exercises, do garden/yard work; lift weights; do any other exercise/sport); tobacco use (i.e. Have you smoked 100+ cigarettes in life; Do you smoke cigarettes now?); and, alcohol consumption (i.e. How often did you have…beer and lite beer; wine; and hard liquor—times/month) were also included.

Finally, other variables of interest were the language (English or Spanish) used in the NES2, amount of sleep the subject had the night before the test, energy level at the test, computer and familiarity, and the effort made to perform the test. Indicator variables were created for all predictors with more than two categories.

3.2.4. Statistical Analysis. Descriptive statistical analysis was conducted using SAS 9.3 © statistical software, with the goal of describing NHANES III participants, who provided the blood samples for the PTRRS and completed the neurobehavioral tests. Proportions, mean, standard deviation were used to describe the participants' characteristics. In addition, the geometric mean (with its corresponding standard error, and lower and upper 95% confidence limits) and the 50^{th}, 75^{th}, and 95^{th} percentiles concentration values were used to describe the blood concentrations of VOC (ug/L) and other biomarkers in blood.

Inferential analysis was used to determine the predictors of cognitive decline as measured by NES2. Following Wu et al. methodology [3], VOC blood concentrations were divided into two groups using the 95^{th} percentiles as the cutoff value. Then, Student's t-test at 5% level of significance was used to compare the NES2 summary scores between the two groups for all VOC that had at least ten participants with blood concentrations higher than the 95^{th}. Finally, for all VOC for which the Student's t-test was significant ($p < 0.05$) multiple linear regression modeling was used to compare the mean difference in the NES2 summary scores.

The first step in the multiple linear regression analysis was to select the independent variables to be included in the final linear predictor. In order to do this, a

collinearity analysis was conducted to check if there were any independent variables with high collinearity. If there was a correlation greater or equal than |0.75| between predictor variables, all but one variable was removed from the analysis. Then, multiple linear regression analysis, with forward, backward, and stepwise selection was used to determine a preliminary linear predictor. Changes in the variables selected among the different selection methods were observed. Those variables that were by more than one selection method (i.e. forward, backward and stepwise) were kept in the model. Next, Square Residuals (R^2) was used to evaluate the predictive power of the preliminary linear predictor and the influence of each independent variable on the proportion of total variation explained by the model. R^2 obtained from the preliminary model and from the models obtained by eliminating one independent variable at a time were compared. Variables with small predictive power (i.e. variables which removal from the model did not significantly change the proportion of total variation explained by the preliminary model) were removed from the model.

Regression diagnostics such as Studentized residuals, leverage, Cook's distance (D), Dffits, and Dfbeta were used to detect unusual and influential observations. Data points that were identified as influential by most of these diagnostics methods were removed from the data. Then, to evaluate whether the data meet the assumptions of linear regression modeling (i.e. linearity, normality, homogeneity [heteroscedasticity], independence, errors in variables, and model specification) graphical methods and numeric tests were used. Shapiro-Wilk and the White tests at 5% level of significance were used for to check for normality and heteroscedasticity, respectively. If Shapiro-Wilk test for normality and the White test for heteroscedasticity were accepted ($p > 0.05$), the

data was considered to meet the assumptions for linear regression. Once the final linear predictor was obtained, multiple linear regression modeling was used to estimate the regression coefficients and examine if any of the VOC blood concentrations had a linear relationship with the NES2 scores. Because PTRRS was a convenience sample (i.e. volunteers), NHANES III sample weights were not considered in the inferential analysis.

3.3. Study 3: Exposure to Fine Particles and Ozone, and the Risk of Cognitive Impairment: A Population-Based Study in Eleven U.S. States

3.3.1. Population and Sample. Participants were selected from the respondents to the BRFSS in 2011. The BRFSS is a state-based telephone survey (i.e. cell phone and landline telephones) that includes information on health outcomes, risk behaviors, and chronic conditions for persons residing in the US states and territories [9]. All 50 states and the District of Columbia conducted the BRFSS by landline and cellular telephones in 2011. The median BRFSS response rate in 2011 was 49.7% [10].

BRFSS questionnaires include core questions—included in all telephone surveys—and several optional modules that vary by state. To assess and monitor self-reported cognitive decline and its associated burden in the US population, the Healthy Aging Program of the Center for Disease Control and Prevention developed a 10-question Cognitive Impairment Module (CIM) for its use in the BRFSS. In 2011, 21 states (i.e. Arkansas, California, Florida, Hawaii, Illinois, Iowa, Louisiana, Maryland, Michigan, Nebraska, New Hampshire, New York, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Utah, Washington, West Virginia, and Wisconsin) collected data using the CIM as an optional module in their state BRFSS.

For our study, inclusion criteria were applied at the individual and county levels. At the individual level we included respondents to the BRFSS 2011, who were 50 years of age and older, and, who had answered the CIM. At the county level, we included counties located in the continental US, that had at least fifty BRFSS respondents 50 years of age and older, and that had complete air pollution data from 2009 to 2011 (i.e. 3-year average of $PM_{2.5}$ 98th percentile, 3-year average of $PM_{2.5}$ annual mean, and 3-year average of O_3 annual 4th highest daily maximum 8-hour concentration).

Among the BRFSS 2011 respondents, who completed the CIM, 95,057 people were 50 years of age and older. After applying the inclusion criteria and eliminating subjects with missing data, the final sample size was 17, 461 individuals (Figure 3.2). Participants represented 73 counties and 11 U.S. states. The number of participants per county ranged from 50 (0.3%) to 838 people (4.8%).

3.3.2. Data Source. Data for this study was retrieved from the BRFSS 2011 data files available at http://www.cdc.gov/brfss/annual_data/annual_2011.htm. Specifically, five 2011 BRFSS datasets were used: (1) 2011 BRFSS Data (LLCP2011); (2) 2011 BRFSS Landline Questionnaire Data (LAND2011); (3) 2011 BRFSS Landline Multiple Version Questionnaire Version 1 Data (LAND11V1); (4) 2011 BRFSS Landline Multiple Version Questionnaire Version 2 Data (LAND11V2); and, (5) 2011 BRFSS Landline Multiple Version Questionnaire Version 3 Data (LAND11V3).

The LLCP2011 data file contained 506,467observations, from landline and cell phone combined data. The states included in this data set that collected CIM data via landline and cell phone surveys were Hawaii, Illinois, New Hampshire, South Carolina, Tennessee, West Virginia, and Wisconsin. The LAND2011 data file contained 435,208

observations, from landline survey data only. The states in this data set that used the CIM only on their landline survey were Arkansas, Florida, Iowa, Louisiana, and North Carolina. The LAND11V1, LAND11V2, and LAND11V3 contained the data from the states that in BRFSS 2011 conducted more than one version of their questionnaire and used optional modules. These data sets contained 83,548; 83,799; and, 36,270 observations, respectively. The states in these data sets that use the CIM were California, Maryland, Michigan, Nebraska, New York, Oklahoma, Texas, Utah, and Washington. From each data set, we extracted the states that implemented the CIM in BRFSS 2011. Then, the data were combined into one data set containing all states that collected CIM in BRFSS 2011.

3.3.3. Measures.

3.3.3.1. Fine particles. Individuals' exposure to fine particles ($PM_{2.5}$) was assessed at the county level. Fine particles concentration data was retrieved from the Air Quality Statistics Report, which is available at http://www.epa.gov/airdata/ad_rep _con.html. The Air Quality Statistics Report displays air pollution values of the six criteria air pollutants (i.e. carbon monoxide, lead, nitrogen dioxide, ozone, particle pollution, and sulfur dioxide) related to national standards for air quality. Summary statistics for the years 2009, 2010, and 2011 were used to calculate $PM_{2.5}$ concentrations of each county. Following the US Environmental Protection Agency primary and secondary National Air Quality Standards (NAAQS), $PM_{2.5}$ 98^{th} percentile, averaged over 3 years; was calculated and used as an estimate of an individual's exposure to ambient fine

particles[11]. For the inferential analysis, we grouped the counties' $PM_{2.5}$ concentrations in deciles.

3.3.3.2. Ozone. Individuals' exposure to O_3 was assessed at the county level. Ozone concentration data was retrieved from the Air Quality Statistics Report, which is available at http://www.epa.gov/airdata/ad_rep_con.html. Summary statistics for the years 2009, 2010, and 2011 were used to calculate O_3 concentrations of each county. Following the US Environmental Protection Agency primary and secondary NAAQS, the annual 4th-highest daily maximum 8-hour concentration, averaged over three years, was calculated and used as an estimate of an individual's exposure to ambient O_3 [12]. For the inferential analysis we grouped the counties' O_3 concentrations in deciles.

3.3.3.3. Cognitive impairment. The BRFSS 2011's CIM consisted of 10 questions, which were developed by the BRFSS, under the guidance of a national panel of experts, and then cognitively tested to determine the best approach for assessing cognitive impairment (Box 3.1). The CIM questions evaluated the severity and frequency of respondents' self-reported confusion or memory loss, in the past 12 months. Thus, CIM's questions captured the progression of cognitive decline over time. If respondents indicated they have experienced confusion or memory loss, questions about whether cognitive decline affects functioning or causes burden were asked next.

Because the outcome of interest in this study was self-reported cognitive impairment, this study was limited to the first question of the CIM (i.e. "During the past 12 months, have you experienced confusion or memory loss that is happening more often or is getting worse?"). Thus, the outcome variable was a dichotomous measure, assessed at the individual level (level-1). Cognitive impairment was considered occurring if the if participants answered "Yes" to this question.

3.3.3.4. Covariates. Of the demographic variables collected by the BRFSS 2011, age, sex, race/ethnicity, educational level, and income were utilized in this study. Health-related questions about health status (i.e. Would you say that in general your health is…excellent, very good, good, fair, poor?), history of cardiovascular disease (i.e. Doctor ever told you had…congestive health failure, stroke, hypertension/high blood pressure, cholesterol level high, heart attack?), history of diabetes (i.e. Doctor ever told you had diabetes?), and health-related quality of life (i.e. Now thinking about your mental health, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good?) were also used.

The question about health-related quality of life was used in this study as a measure of frequent mental distress (FMD). A person who reported 14 days or more of poor mental health in the past 30 days was identified as having FMD. In this study, FMD was the participant-level predictor of interest.

3.3.4. Statistical Analysis. Statistical analysis was conducted using SAS© statistical software. Descriptive analysis was used to describe the characteristics of BRFSS 2011 participants, 50 years and older, included in this study. Valid percentages, mean, and standard deviation (SD) were used to describe the participants' characteristics.

Inferential analysis was used to determine whether or not exposure to ambient $PM_{2.5}$ and O_3 was associated with self-reported cognitive impairment. Specifically, we assessed between and within county variations in participants self-reported cognitive impairment. In this hierarchical model, level-1 was the participant's level and level-2 was the county's level. Within each level-2 unit (i.e. county [c]) there are n_c participants in the c^{th} county. As we wanted to determine the differences between the counties, adjusting for other effects in the model such as participants' health status, county intercepts were treated as random variables. The multilevel modeling was performed in three steps, for $PM_{2.5}$ and O_3: (1) empty model, (2) random intercept model with fixed level-1 predictors; and, (3) hierarchical model with level-1 and level-2 predictors. Thus, the BRFSS 2011 and environmental data were used for three applications: (1) to fit a random intercept model without explanatory variables where β_0 is the average intercept, identical for the counties; (2) to fit the random intercept model with the participant-level fixed predictor (i.e. FMD) to identify county outliers; and, (3) to estimate a hierarchical model with participant-level and county-level to evaluate the effect of air pollution concentrations on self-reported cognitive impairment. Odds ratios (i.e. crude [OR] and adjusted [AOR]) and its corresponding p-values (p) are reported.

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Figure 3.1. Study 2: Serum Concentration of Volatile Organic Compounds, Oxidative Stress, and Neurobehavioral Functioning Population

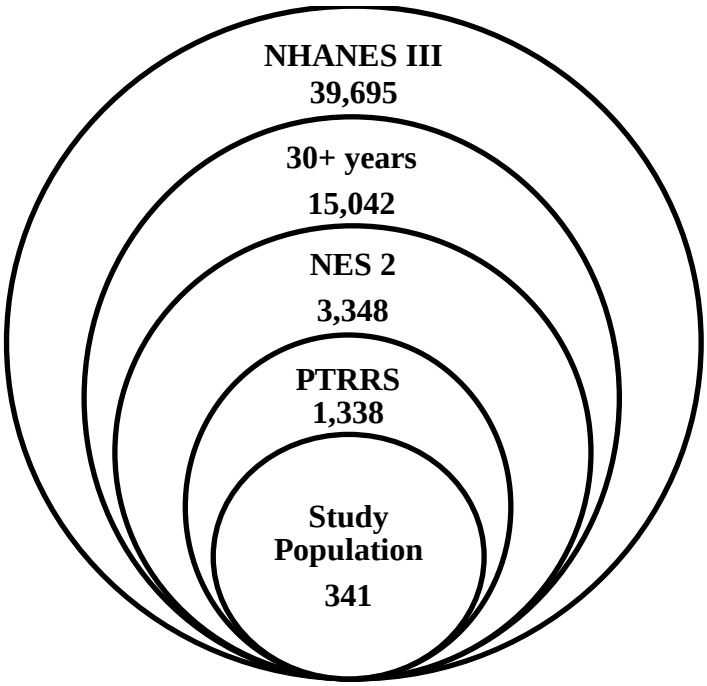
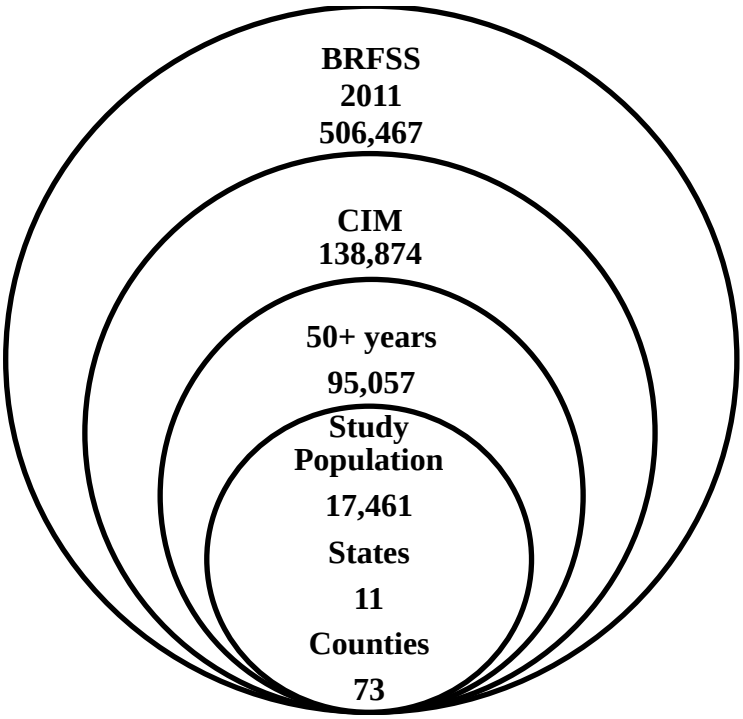


Figure 3.2. Study 3: Exposure to Fine Particles and Ozone, and the Risk of Cognitive Impairment: A Population-Based Study in Eleven U.S. States Population



Box 3.1. Behavioral Risk Factor Surveillance System Optional Impact of Cognitive Impairment Module

1. During the past 12 months, have you experienced confusion or memory loss that is happening more often or is getting worse?
   (1) Yes (2) No

2. How many adults 18 years or older in your household experienced confusion or memory loss that is happening more often or is getting worse during the past 12 months?

3. Of these people, please select the person who had the most recent birthday. How old is this person?

4. During the past 12 months, how often have you/ has this person given up household activities or chores you/ they used to do, because of confusion or memory loss that is happening more often or is getting worse?
   (1) Always (2) Usually (3) Sometimes (4) Rarely (5) Never

5. As a result of your/ this person's confusion or memory loss, in which of the following four areas do you/ does this person need the most assistance?
   (1) Safety
   (2) Transportation
   (3) Household activities
   (4) Personal care
   (5) Needs assistance, but not in those areas
   (6) Doesn't need assistance in any area

6. During the past 12 months, how often has confusion or memory loss interfered with your/this person's ability to work, volunteer, or engage in social activities?
   (1) Always (2) Usually (3) Sometimes (4) Rarely (5) Never

7. During the past 30 days, how often has a family member or friend provided any care or assistance for you/this person because of confusion or memory loss?
   (1) Always (2) Usually (3) Sometimes (4) Rarely (5) Never

8. Has anyone discussed with a health care professional, increases in your/this person's confusion or memory loss?
   (1) Yes (2) No [End of module]

9. Have you/ Has this person received treatment such as therapy or medications for confusion or memory loss?
   (1) Yes (2) No

10. Has a health care professional ever said that you have/ this person has Alzheimer's disease or some other form of dementia?
    (1) Yes, Alzheimer's Disease
    (2) Yes, other form of dementia but not Alzheimer's disease
    (3) No diagnosis has been given

CHAPTER IV STUDY 1: AIR POLLUTION, OXIDATIVE STRESS, AND ALZHEIMER'S DISEASE

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4.1. Abstract

Alzheimer's disease (AD) is the most common form of dementia affecting millions of people worldwide, and will continue to affect millions more with population aging on the rise. AD causality is multifactorial. Known causal factors include genetic predisposition, age, and sex. Environmental toxins such as air pollution (AP) have also been implicated in AD causation. Exposure to AP can lead to chronic oxidative stress (OS), which is involved in the pathogenesis of AD. Whereas AP plays a role in AD pathology, the epidemiological evidence for this association is limited. Given the significant prevalence of AP exposure combined with increased population aging, epidemiological evidence for this link is important to consider. In this review, we examine the existing evidence supporting the relationship between AP, OS, and AD and provide recommendations for future research on the population level, which will provide evidence in support of public health interventions.

Key Words: Air pollution, Oxidative Stress, Alzheimer's Disease, Particulate Matter, Ozone, Aging

4.2. Introduction

Air pollution is a well-known environmental hazard and its association with respiratory and cardiovascular pathology has been consistently confirmed by several epidemiological studies. In recent years, the idea that air pollution might be also associated with Alzheimer's disease (AD) and other neurodegenerative disorders has been the focus of many toxicological studies. However, the epidemiological evidence supporting this association is limited.

Alzheimer's disease—a progressive and irreversible neurodegenerative disorder—is the most common form of dementia among older adults affecting more than 4 million people in the U.S. and almost 30 million worldwide [1–3]. The most proven risk factor for AD is advanced age. Other common risk factors include a positive family history of AD [1], the presence of APOE-4 alleles [4,5], being a member of the female sex [6], cardiovascular disease [7], head injury [8], Down syndrome [1,9], and low educational level [10]. As people continue to live longer, it is likely the number of Alzheimer's cases will increase. By 2050, it is projected that approximately 13 million people in the U.S. and 100 million people worldwide will be affected by this disease [2,11]

Increasing evidence indicates AD and other neurodegenerative disorders are at least partially mediated by oxidative stress. Oxidative stress is the state of redox imbalance that results from a production of reactive oxygen species (ROS) that exceeds the capacity of antioxidant defense mechanisms [12]. Environmental exposures such as air pollution can enhance an organism's generation of ROS; thus, air pollution exposure could very well represent a risk factor for AD by enhancing oxidative stress processes capable of inducing physiological alterations of the central nervous system.

Air pollution is a prevalent environmental hazard. In the U.S., National Ambient Air Quality Standards (NAAQS) have been established for six principal air pollutants – criteria air pollutants—proved to represent a threat for human health. These pollutants include: (1) ozone (O_3), (2) particulate matter (PM), (3) carbon monoxide (CO), (4) nitrogen oxides (NOx), (5) sulfur dioxide (SO_2), and (6) lead. In spite of the current standards, it is estimated that in the U.S. over one hundred million people live in areas that exceed the recommended air quality levels [13].

The large number of individuals exposed to air pollution levels above the recommended standards and population aging are two factors that could act synergistically to increase the prevalence of AD. Even after accounting for the predicted increase in Alzheimer's frequency due to population aging, the significant prevalence of air pollution could very well exacerbate the impact of this disease on public health. Granting that air pollution could be one of the factors involved in AD causality, its widespread occurrence makes ascertaining its association with AD a public health priority. The association between air pollution—specifically PM and O_3—and AD via oxidative stress is the focus of this review.

4.3. Aging, Oxidative Stress, and Alzheimer's Disease

4.3.1. Oxidative Stress. Reactive oxygen species (ROS) is a term used to collec tively refer to "reactive" molecules containing oxygen, which include free radicals and derivates, and are capable of leading to oxidative changes within cells [14–16]. A wide variety of ROS are produced in healthy tissues in the course of normal metabolism at different cellular sites. However, the main source of ROS is the mitochondrial electron transport chain, specifically complex I (NADH dehydrogenase) and III (ubiquinone–

cytochrome *c* reductase) of the chain [16–21]. Other important generators of ROS in vivo include peroxisomal fatty acids metabolism, cytochrome P-450 reactions, phagocytic cells (respiratory burst), and numerous enzymes [19,22]. ROS are important for maintaining oxygen homeostasis in tissues and destructing microbial invaders [15]. However, they can also cause oxidative changes within the cell [16] and modify proteins, lipids, and nucleic acids to develop or enhance age-related manifestations [12,21,23].

Several antioxidant systems—enzymes, vitamins, and metabolites—protect the cell against ROS-mediated oxidative damage by three key mechanisms: (1) scavenging ROS and their precursors, (2) binding catalytic metals ions used for ROS formation, and (3) generating and up-regulating endogenous defense mechanisms [12,23–27]. The balance between ROS production and antioxidant defense system determines the degree of oxidative stress [17]. When ROS formation exceeds the capacity of the antioxidant defense systems oxidative stress occurs, which results in oxidative damage to macromolecules—lipids, proteins, and nucleic acids—mitochondria, and other cells compartments [12,16,19,22,24,25,27,28]. Box 4.1 lists some examples of ROS, ROS sources, and antioxidant defense mechanisms [17–19,22,26].

4.3.2. Oxidative Stress and Aging. From a biological perspective, aging is defined as the accumulation of changes over time responsible for the chronological alterations that occur with age and result in an increased risk of disease and death with advanced age [28,29]. No theory has been widely accepted to explain the aging process [28]. However, the oxidative stress hypothesis proposed by Denham Harman in 1956—the Free Radical Theory of Aging—offers the best mechanistic explanation of aging and age-related diseases [28,29]. Harman's theory posits a single common process modified by

genetic and environmental factors that is responsible for aging and subsequent death. Harman argues aging is primarily the result cumulative damage on macromolecules resulting from free radical attacks—oxidative stress [28,30,31]. This theory was later expanded to propose mitochondria as the main source of free radical production [28,31]. Consequently, aging can now be described as the result of the accumulation of ROS-induced damage to macromolecules by free radicals mainly of mitochondrial origin [19,28].

In addition to being a main source, mitochondria are also a major target of ROS. Mitochondrial DNA is especially vulnerable to oxidative damage because of its proximity to the site of mitochondrial ROS production (mitochondria), little protection of its structure (no full histone coat), and limited repair mechanisms [17,19–21,29,32]. During normal aging, free radical damage to mitochondria and ROS production increase; and, antioxidant mechanisms become progressively impaired [28,33]. Consequently, vulnerability to oxidative stress and accumulation of oxidatively damaged macromolecules increases with age and may contribute to aging and age-related degeneration [20,28].

Although fast-replicating cells with low levels of oxygen consumption do not suffer free radical damage, mitochondria of highly differentiated cells with high levels of oxygen utilization are highly vulnerable to oxidative stress [29]. Consequently, neurons are especially vulnerable to mitochondrial damage by free radicals [29,34]. Thus, the detrimental effects of the aging process are best observed in the brain, where irreversibly damaged cells cannot be replaced [21].

4.3.3. Oxidative Stress and Alzheimer's Disease. The brain—an organ rich in fatty acids, consumer of high levels of energy and physiological oxygen, and poor in antioxidant defense mechanisms—is particularly vulnerable to oxidative stress [16,23,27,34–

[38]. Depending on the macromolecule targeted by ROS, oxidative stress will manifest as lipid peroxidation, protein oxidation, or DNA oxidation. Accumulation of oxidation of lipids, proteins, and DNA by free radicals are responsible for the functional decline in aged brains, which manifests as a deterioration in cognitive function and motor skills [12,19].

Alzheimer's disease is a progressive and irreversible neurodegenerative disease manifested as a slowly progressive dementia, which begins with subtle memory loss and progresses to severe decline in cognitive function and disability [1,39,40]. The neuropathological hallmarks of AD are senile plaques and neurofibrillary tangles [41]. Evidence of an increased oxidation of macromolecules—lipids, carbohydrates, proteins, and DNA—and oxidative stress products has been found in senile plaques and neurofibrillary tangles [25]. Biomarkers of these forms of oxidation have been observed not only in AD brains, but also in peripheral tissues (e.g. blood cells), and biological fluids (e.g. urine) of individuals affected by AD [16,23,37,38,42–44].

The principal component of senile plaques found in Alzheimer's brains is amyloid-beta (Aβ) peptide [45,46], which plays an important role in the etiology and progression of this disease [45]. However, it is unclear whether Aβ peptide deposition is the cause or the result of the oxidative stress observed in Alzheimer's brains [27,46]. In the initial phase of the development the disease, Aβ peptide deposition and the formation of neurofibrillary tangles are consequences of oxidative stress and may serve as shields to protect neurons against oxidative damage. However, as the disease progresses, these evolve into pro-oxidants driving a self-sustained "auto-destructive" process and the progression of the disease [16,47].

Amyloid-beta peptide-related oxidative stress provides a theoretical framework that unites these two components in the pathogenesis of AD [46] and suggests two possible scenarios: first, neuronal degeneration could be the result of an oxidative stress response to senile plaques and neurofibrillary tangles rather than to these lesions as such [47]. Second, oxidative stress could be one of the earliest detectable events in the pathogenesis of AD—preceding the extracellular deposition of Aβ peptide and the formation of senile plaques and neurofibrillary tangles [16,47].

In addition to senile plaques and neurofibrillary tangles, olfactory dysfunction is a common feature of AD affecting approximately 90% of AD cases [48]. Evidence of lipid peroxidation has been found in the nuclear and cell membrane of AD's olfactory neurons and epithelial cells but not in age-matched normal neuroepithelial cells [49,50]. In addition, evidence from human models indicate that Aβ peptide deposition and paired helical filaments of tau protein (precursors of neurofibrillary tangles) are substantially more frequent and more abundant in the olfactory epithelium of AD cases than in controls [48,51].

Olfactory dysfunction in AD is related to the considerable cell loss and neurofibrillary tangles formation that precedes Aβ peptide deposition and occur in the olfactory bulb and olfactory centers (i.e. anterior olfactory nucleolus, periamygdaloid cortex, and anterior amygdala) in the early stages of AD [52,53]. Furthermore, epidemiological studies indicate that olfactory dysfunction predicts an increased risk of cognitive decline with advanced age and takes place before the clinical manifestations of AD [51,53,54]. The occurrence of olfactory pathology in the early stages of AD and the identification of the nose as the portal of entry of airborne xenobiotics into the brain suggest that AD pathology

could be mediated by environmental agents such as air pollutants that could reach the brain through the olfactory epithelium [53,55,56].

4.4. The Role of Air Pollution in Alzheimer's Disease

4.1.1. Air Pollution. Atmospheric air pollution can be defined as the introduce tion of any chemical, physical, or biological pollutant—in the indoor or outdoor air—that modifies the natural characteristics of the atmosphere and harms human health and welfare [57]. Air pollutants can be released into the atmosphere from both natural (e.g. windblown dust, volcanoes, and wildfires), and anthropogenic sources (e.g. power plants, industries, and transportation). However, man-made sources are identified as the major contributor to indoors and outdoors air pollution [58].

In the U.S., NAAQS for six principal air pollutants (i.e. O_3, PM, CO, NOx, SO_2, and lead) have been established to protect vulnerable populations (children, older adults, and individuals living with chronic diseases) against air pollutants toxicity. Primary and Secondary NAAQS for these six criteria air pollutants are summarized in Table 4.1 [59].

4.1.1.1. Routes of Exposure. Despite the improvements made in ambient air quality, air pollution continues to be a prevalent environmental hazard in urban and rural areas. It is estimated that in the U.S. 146 million people live in areas that exceed the recommended air quality standards for at least one criteria air pollutant—in most cases, O_3, PM, or both [13]. Human activities affect the timing, location, and degree of personal exposure to pollutants [60]. Adults, who generally spend most of their time inside (e.g. at home, workplace, and/or automobile), are more likely to be exposed to in-

door air pollution while children, who spend more time than adults outside, are more likely to encounter outdoor air pollution [61].

Exposure to air pollution can occur through multiple routes. The release of pollutants into the atmosphere exposes humans to hazardous substances primarily by direct inhalation. Transport and deposition of air pollutants into water and soil also exposes humans to air pollutants through the ingestion of contaminated water and food [62]. Although representing a minor route of exposure, dermal contact with contaminated soil, dust, or water; can also contribute to an individual's air pollutant intake [58,62].

4.1.1.2. Air pollution and Human Health. Short- and long-term exposure to air pollution has consistently been linked to adverse health outcomes. Exposure to PM and O_3 is associated with an increased cardiovascular and respiratory morbidity, mortality, and disability risk (54-59). Recent estimates indicated that globally about 3% of adult cardiopulmonary disease mortality, 5% of cancers of the respiratory system mortality, and about 1% acute respiratory infection mortality in children in urban areas are attributable to PM, which represents about one million premature deaths and 6.4 million years of life lost [64].

Epidemiologic studies have shown a positive association between cardiovascular hospitalizations and ambient NO_2, CO, and PM els [63,65,67,68]. Exposure to air pollution has also been associated with reduced lung capacity in healthy individuals and increased risk of exacerba-

tions, hospitalizations, and mortality in subjects with respiratory chronic diseases such as asthma and chronic obstructive pulmonary disease [66].

4.1.1.3. Air pollution and Oxidative Stress. Oxidative stress occurs when the production of ROS exceeds the natural antioxidant systems. This imbalance can result from exposure to pro-oxidant substances—ROS—present as air pollutants in the atmosphere [26,57,69]. The oxidative potential of air pollution relies on particle composition and size distribution, and on the presence of transition metals and semi-volatile and volatile organic chemicals [69]. Air pollutants can act directly as pro-oxidant of lipids and proteins or as free radical generators by promoting oxidative stress and inducing inflammatory responses after a threshold—a level at which natural antioxidant mechanisms are overwhelmed—is reached [58,69,70]. Once natural defense mechanism are overwhelmed pro-inflammatory effects follow via the activation of redox-sensitive transcription factors such as NFκB—nuclear factor kappa-light chain-enhancer of activated B cells [69]. Thus, given the large number of people exposed to air pollution, air pollutants could very well represent a prevalent source of environmentally-induced ROS production [71] and thus a risk factor for AD—a neurodegenerative disorder mediated by oxidative stress.

4.1.1.4. Air Pollution and Alzheimer's Disease. Evidence from toxicological studies using animal and cellular models indicate that individuals exposed to high levels of air pollution show damage in the olfactory mucosa, olfactory bulb, and frontal cortex region tissues—all similar to that

observed in the AD brains [53,71]. In addition, human studies have shown that exposure to air pollution impairs cognitive function [72]; and induces neuroinflammation, cerebrovascular damage, and neurodegenerative pathology [71,73,74]. Air pollution can also accelerate amyloid-beta-42 (Aβ-42) accumulation, which is a known cause of the neuronal dysfunction that precedes the formation of Aβ peptide plaques and neurofibrillary tangles [55,73,75].

Together, these findings support a plausible association between air pollution and AD. Also, they allow us to identify the human nose as the portal of entry of air pollutants into the brain [55,56]. Although AD causality is multifactorial and thus the result of the interaction of several factors rather than of a single identifiable cause, there is enough evidence to identify air pollution as an important contributing factor to the development and expression of the disease. The interaction between aging, genetic predisposition, and air pollution in the causation of AD is depicted in Figure 4.1 [1,4–11,17,19,28,35,71,73].

4.1.2. Oxidative Mechanisms of Particulate-Induced Alzheimer's Disease

Pathology. Atmospheric particulate matter is a complex mixture of solid particles and liquid droplets commonly found in urban air, and it has shown to be associated with a variety of adverse health outcomes [58,65,76,77]. The potential for PM to reach the central nervous system is directly associated to the particles' size. Fine particles with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$) and ultrafine particles of less than 0.1 μm of aerodynamic diameter (UFPM) are the most significant for the pathogenesis of diseases

of the central nervous system [71]. Ultrafine particles can reach the brain by trans-synaptic transport after inhalation through the olfactory epithelium and uptake through the blood-brain barrier [16,71,75]. Deleterious effects of PM on the brain also vary depending of the number of particles, their chemical composition and physical characteristics, the amount of surface components that are translocate from the lung to other organs, and the velocity at which these particles and components are cleared from the system [71,75].

The effects of PM on the brain are believed to be the result of two mechanisms. First, its ability to induce chronic respiratory and systemic inflammation by producing pro-inflammatory cytokines, which affect the blood-brain barrier, triggers neural-immune interactions, and lead to chronic oxidative stress [16,56,72]. Second, its ability to directly produce ROS can damage the blood-brain barrier and increases the production of Aβ peptides [72]. Together these mechanisms are responsible for causing brain inflammation and accelerating the accumulation of Aβ peptide, both of which are associated with the neuronal dysfunction that precede the appearance of senile plaques and formation of neurofibrillary tangles [55,75], which are the hallmarks of AD.

4.1.3. Oxidative Mechanisms of Ozone-Induced Alzheimer's Disease Pathology

Pathology. Ozone is a gaseous air pollutant originated from photochemical reactions between NO_X and VOC in the troposphere. Ozone is the main component of smog and represents an important problem in urban areas, especially during the summer when sunlight is abundant. Emissions from industrial facilities, motor vehicle exhaust, and gasoline vapors, are examples of important sources of NO_X and VOC—the precursors of O_3.

Ozone is a ROS and powerful oxidizing agent [71,78] capable of inducing oxidative stress state. Animal studies have indicated that the oxidative effects of O_3 on the brain vary with the duration of the exposure [78] and show a dose-response relationship [36,78]. This variation indicates that even though short O_3 exposure induces ROS production, this occurs at a level that can still be compensated by antioxidant defense mechanisms. However, as the duration of the exposure increases, the production of ROS rises, and finally reaches a threshold dose at what antioxidant defense mechanisms capacity is exceed causing brain dysfunction [36]. This brain dysfunction is manifested as short and long-term memory loss and motor deficiency in rats, all alterations that are positively related to the duration of O_3 exposure [36,78].

Besides causing motor deficiency and memory loss, O_3 can also cause neuroinflammation, neuronal damage, and alterations of the cerebral vasculature [36,71]. Moreover, O_3-induced oxidative stress can cause dysregulation of inflammatory processes, progressive neurodegeneration, chronic loss to brain repair in the hippocampus, and brain plasticity changes in rats, which are comparable to those observed in AD disease patients [78]. Although there is evidence showing the oxidative changes caused by O_3 on the brain, the mechanisms through which this gas reaches and affects the brain are yet to be understood [36,71] and should consequently motivate future research efforts.

4.5. Future Directions

In this review we discussed the current evidence describing an association between exposure to air pollution and AD. Although evidence from toxicological studies using animal and cellular models is abundant, epidemiological evidence is limited. Thus, the potential link between air pollution and AD at the population level remains unclear.

More research is needed to characterize the association between exposure to air pollution and AD and its implications for public health.

At the individual level, efforts should be oriented toward determining the routes through which each air pollutant reaches the brain, as well as the biological mechanisms through which they contribute to the development and clinical manifestation of AD. Specifically, the effects of PM and O_3 on the brain have been the focus of many studies; however, exposure to VOC is yet to be described. Also, and because air pollution consists of a mixture of different air pollutants (i.e. particles, liquid droplets, and gases), further investigation on the potential additive or synergistic effects between these pollutants is imperative.

The identification of air pollution as a factor in the pathogenesis and etiology of AD on the population level could provide a strong basis for implementing novel public health initiatives that could prevent AD for reaching epidemic proportions. By controlling the environmental factors that contribute to the pathogenesis of AD, public health professionals could also effectively minimize the burden AD is projected to place on worldwide healthcare systems in the decades to come.

4.6. Conclusion

Air pollution has consistently been identified as a significant environmental hazard and its association with cardiovascular and respiratory disease is well established. Recent reports from toxicological studies indicate the existence of an association between air pollution and central nervous system disease. Depending on their characteristics air toxicants can reach the brain through several pathways. The effects of air pollution on the brain then manifest as neuroinflammation, oxidative stress, and neurodegeneration.

Although AD causality is multifactorial, air pollution could increase an individual's risk of developing AD by accelerating age-related oxidative changes observed in the brain and hence represent a significant public health hazard. Therefore, the control of environmental factors such as air pollution could be a key factor in limiting the predicted increase in AD cases, as well as the burden it is expected to have on healthcare systems, worldwide.

Despite the many studies investigating the association between air pollution and AD, the role of air pollution in the causation and pathogenesis of this neurodegenerative disorder is not fully understood. Individual factors that could mediate the association between air pollution and AD such as age, nostril size, daily activities, and concomitant health conditions need further investigation. In addition, epidemiological studies looking at the association between air pollution and AD are few. Therefore, the implications of the association between air pollution and AD at a population level remain unclear. The predicted burden of AD on public health and the health care system should further motivate future research oriented toward providing evidence to obtain a better understanding of this association and guide preventive efforts.

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4.8. References

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Box 4.1. Reactive Oxygen Species (ROS), Sources, and Defense Mechanisms [17–19,22,26]

ROS

Superoxide (O_2•-)
Hydrogen peroxide (H_2O_2)
Hydroxyl radical (•OH)
Peroxyl radicals (ROO•)
Alkoxyl radicals (RO•)
Organic hydroperoxides (ROOR')
Hypochlorous acid (HOCl)
Peroxynitrite (ONOO–)
Singlet oxygen ($^1O_2$)

ROS Sources

Endogenous
Mitochondria (By-products of electron transport)
Oxidases (Oxidase-catalyzed reactions)
Inflammation (neutrophils, macrophages)
Cytochrome P450 reactions
Arginine metabolism
Peroxisomal fatty acid metabolism (Peroxisomes, Lipoxygenases)

Exogenous
Ionizing radiation (X-, γ-, UV)
Chemotherapeutics
Inflammatory cytokines (macrophages, neutrophils)
Environmental toxins

Antioxidant Defense Mechanisms

Enzymatic systems
Catalase (CAT)
Superoxide dismutase (SOD)
Glutathione peroxidase (GPx)

Non-enzymatic systems
DNA repair mechanisms
Glutathione
Vitamins (A,C, and E)
Carotenes

Table 4.1. National Ambient Air Quility Standards (NAAQS) for Criteria Air Pollutants [59]

Criteria Air Pollutant	Primary Standard		Secondary Standard	
	Level	Averaging Time	Level	Averaging Time
1. Ozone	0.075 ppm (2008 std)	8-Hour	Same as Primary	
	0.08 ppm (1997 std)	8-Hour	Same as Primary	
	0.12 ppm	1-Hour	Same as Primary	
2. Particulate Matter				
$PM_{2.5}$	15.0 µg/m^3	Annual	Same as Primary	
	35 µg/m3	24-Hour		
PM_{10}	150 µg/m^3	24-Hour	Same as Primary	
3. Carbon Monoxide	9 ppm (10 mg/m^3)	8-hour	None	
	35 ppm (40 mg/m^3)	1-hour		
4. Nitrogen Dioxide*	53 ppb	Annual	Same as Primary	
	100 ppb	1-hour	None	
5. Sulfur Dioxide	0.03 ppm (1971 std)	Annual	0.5 ppm	3-hour
	0.14 ppm (1971 std)	24-hour		
	75 ppb	1-hour	None	
6. Lead	0.15 µg/m^3	Rolling 3-Month Average	Same as Primary	

* Although NAAQS cover the entire group of NO_X, NO_2 is use as indicator for this group.

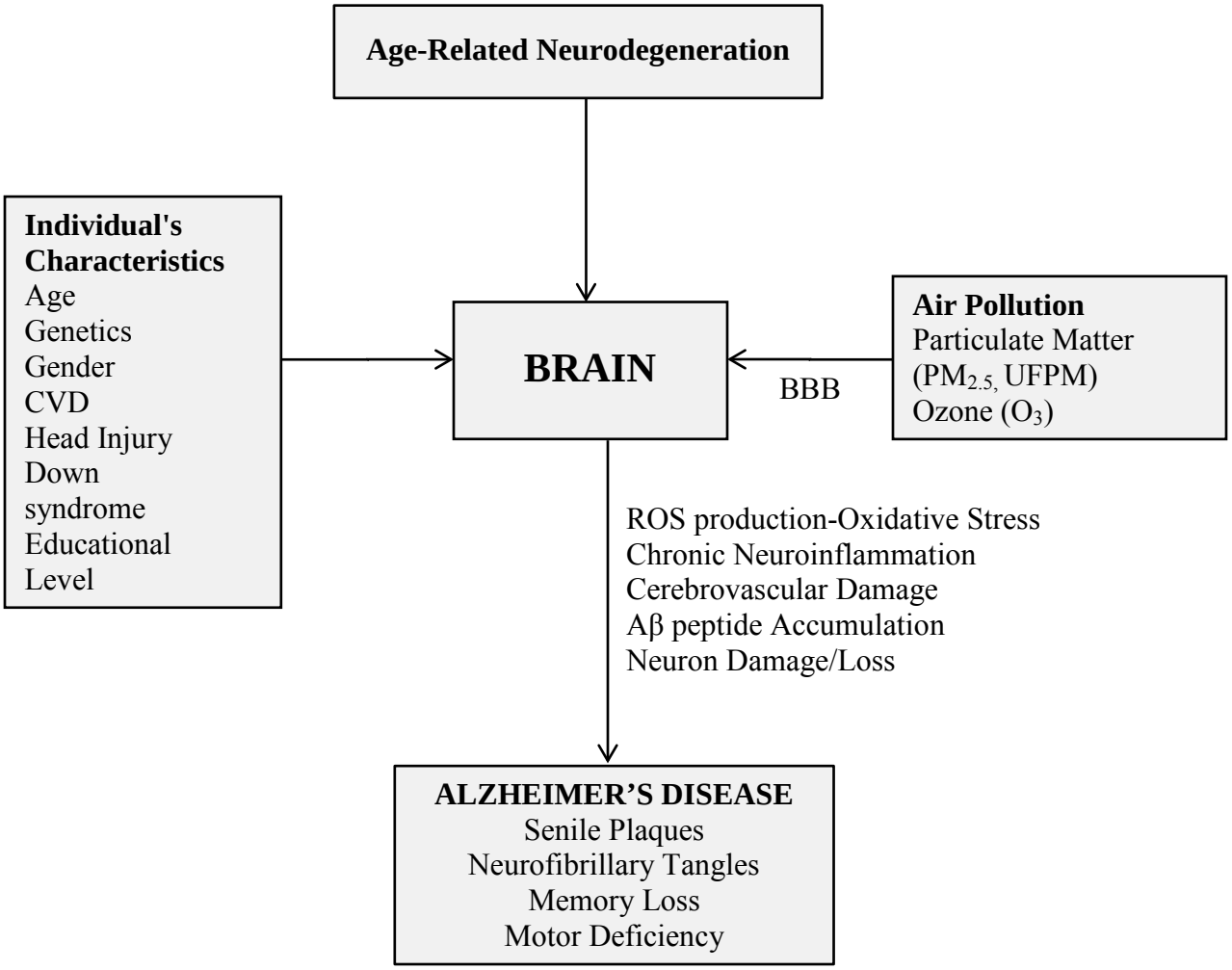

Figure 4.1. Interacting Factors in the Causality of Alzheimer's Disease [1,4–11,17,19,28,35,71,73]. Alzheimer's is the result of the interaction of aging, genetic predisposition, and environmental exposures such as air pollution in the etiology and pathogenesis of the disease. Air pollution is a prevalent environmental source of ROS that impacts the brain through the multiple pathways accelerating the development and clinical manifestation Alzheimer's disease. Abbreviations: BBB, Blood-Brain-Barrier; ROS, Reactive oxygen species; CVD, Cardiovascular Disease.

CHAPTER V STUDY 2: SERUM CONCENTRATION OF VOLATILE ORGANIC COMPOUNDS, OXIDATIVE STRESS, AND NEUROBEHAVIORAL FUNCTIONING

5.1. Abstract

Introduction: Oxidative stress (OS) has been used to explain the association between air pollution and cognitive impairment. Toxicological studies have demonstrated that exposure to air pollutants could act synergistically with age and increase the risk of age-related cognitive impairment. However, epidemiological studies exploring the association between cognitive functioning and common air pollutants (e.g. volatile organic compounds [VOC]) are scarce. **Method**: Participants included respondents to the National Health and Nutrition Examination Survey (NHANES) III; aged 30 to 59 years; who completed the Neurobehavioral Examination System 2 (NES 2) tests; and, voluntarily participated in the Priority Toxicant Reference Range Study. Cognitive functioning was estimated using the participants' summary scores in the NES 2 and exposure to VOC from the blood concentrations of VOC collected in the PTRRS. Blood concentration of biomarkers of OS, were also studied. **Results**: Linear regression analyses indicated an inverse association between blood concentrations of dibromochloromethane ($p < 0.05$), benzene ($p < 0.05$), and chloroform ($p < 0.01$); and, cognitive functioning. After adjusting for demographics and health characteristics, only dibromochloromethane was significantly associated with cognitive functioning ($p < 0.05$). Also, there was a positive association between benzene and biomarkers of OS (C-reactive protein, $p < 0.05$; gamma glutamyl transferase, $p < 0.01$). These associations were not significant in the adjusted model. **Discussion**: Exposure to VOC could negatively affect cognitive functioning via oxidative stress. Large longitudinal studies are needed to determine causality and guide public health initiatives.

Key words: Volatile Organic Compounds, Cognitive Impairment, Oxidative Stress

5.2. Results

5.2.1. Demographic Characteristics of Study Participants

Among the NHANES III participants who completed the NES2 and participated in the PTRRS (*N* = 341), the mean age of was 42.1 years (*SD* = 8.2). More than half of them (58.4%, *n* = 199) were men and 41.6% (*n* = 142) were women. Whites accounted for 32.0% (*n* = 109) of the study population; among them, 4.6% were Hispanic (*n* = 5) and 95.4% (*n* = 104) were non-Hispanic. Among all other races combined (68.0%, *n* = 232), including Black, Mexican-American, and other; 34.1 % (*n* = 79) were Hispanic.

5.2.2. Self-Reported Health

Almost 40.0% (*n* = 134) of the respondents reported their health status as "good", 40.5% (*n* = 138) as poor to fair, and 20.2% (*n* = 69) as very good to excellent. Also, 37.2% (*n* = 127) reported having at least one cardiovascular disease (i.e. congestive health failure, stroke, hypertension, cholesterol level high, and/or heart attack), 6.74% (*n* = 23) reported suffering from chronic obstructive pulmonary disease (i.e. emphysema and/or chronic bronchitis), and 4.7% (*n* = 16) reported a positive history of cancer (i.e. skin cancer and/or other cancer). Among those who provided information about their medications (*N* = 128), 8.6% (*n* = 11) indicated using at least one prescription drug indicated for the treatment of depression in adults.

Approximately a third of the participants (33.7%, *n* = 115) were current smokers, 22.0% (*n* = 74) were former smokers, and 44.6% (*n* = 152) had never smoked. In addition, 53.7% (*n* = 183) and 70.09 % (*n* = 239) reported consuming alcohol and engaging in physical activity regularly, respectively. Tables 5.1 and 5.2 summarize participants' demographic and health characteristics.

5.2.3. Volatile Organic Compounds

In almost half of the VOC measured as part of the PTRRS (i.e. 1,1,2,2-Tetrachloroethane, 1,1,2-Trichloroethane, 1,1-Dichloroethane, 1,1-Dichloroethene, 1,2-Dichlorobenzene, 1,2-Dichloroethane, 1,2-Dichloropropane, 1,3-Dichlorobenzene, Carbon tetrachloride, cis-1,2-Dichloroethene, Dibromomethane, Methylene chloride, and trans-1,2-Dichloroethene), less than 5% of participants had blood concentrations above the detection limit. The VOC's geometric means range from 2,197.2 ug/L (acetone, 95% Confidence Limit [CI]: 1,996.0 ug/L, 2,418.6 ug/L) and 0.15 ug/L (1,1,1-Trichloroethane, 95% CI: 0.1 ug/L, 0.2 ug/L). Summary statistics of VOCs are listed in Table 5.3.

5.2.4. Cotinine, Serum C-Reactive Protein, and Gamma Glutamyl Transferase

Only a third of participants had CRP blood concentrations above the detection limit (29.9%, $n = 102$). However, most participants had COP and GGT blood concentrations above the detection limits (91.2%, $n = 111$ and 83.9%, $n = 286$, respectively). Summary statistics of COP, CRP, and GGT are listed in Table 5.3.

5.2.5. Neurobehavioral Evaluation System 2 Scores. The mean reaction time in the SSRT was 239 milliseconds ($SD = 53.2$). The mean of the two lowest error-corrected latencies in the SDST was 3.1 seconds/correct digit ($SD = 1.1$). Finally, the summary total score in the SDLT, calculated from the sum of error scores for each trial, was 6.3 ($SD = 5.2$). NES 2 scores and test-related factors are summarized in Table 5.4.

5.2.6. Association between Neurobehavioral Evaluation System 2 Scores and Blood Concentrations of Volatile Organic Compounds

5.2.6.1. Student's t-test. Student's t-test revealed a significant difference in the NES2 means between participants with blood concentrations of VOC at or below 95th percentile and those whose VOC concentration was above 95th percentile a the 5% level of significance. Specifically, there was a significant difference in the SRTT mean between participants whose 1,2-dichloropropane blood concentration was at or below 95th percentile and those whose blood concentration was above 95th percentile ($p < 0.05$).

The general rule is to accept smaller significance level as evidence against the null hypothesis in large samples and to accept larger significance level as evidence against the null hypothesis in small samples[1]. Thus, there was also a significant difference in the SRTT mean between participants whose dibromochloromethane blood concentration was at or below 95th percentile and those whose blood concentration was above 95th percentile ($p < 0.1$), at 10% significance level. Similarly, Student's t-test revealed a significant difference in the SDST mean between participants whose chloroform, o-Xylene, and trichloroethene blood concentrations were at or below 95th percentile and those whose blood concentration were above 95th percentile ($p < 0.05$). In addition, we found significant difference in the SDLT mean between participants whose benzene blood concentration was at or below 95th percentile and those whose blood concentration was above 95th percentile ($p < 0.05$). Finally, there was also a significant difference in

the SDLT mean reaction time between participants whose chloroform blood concentration was at or below 95th percentile and those whose blood concentration was above 95th percentile ($p < 0.1$), at the10% significance level. Participants' NES2 scores grouped by 95th percentile of VOC blood concentration are summarized in Table 5.5.

5.2.6.2. Linear Regression.

5.2.6.2.1.Volatile organic compounds. The results from the crude linear regression analysis indicated a significant positive association between blood concentrations of dibromochloromethane ($p < 0.05$) and SRTT mean reaction time. Also, there was a positive association between the blood concentration of benzene ($p < 0.05$) and the SDLT score; and, between the blood concentration of chloroform ($p < 0.05$) and the SDLT score. After adjusting for demographic and health covariates, only the association between dibromochloromethane and SRTT mean reaction time continued to be significant ($p < 0.05$). No other VOC had a significant linear association with any of the NES2 summary scores (Table 5.6).

5.2.6.2.2.Cotinine, serum C-reactive protein, and gamma glutamyl transferase. The results from the crude linear regression analysis indicated a significant positive association between serum CRP and SDST ($p < 0.05$); and also between serum CRP and the SDLT ($p < 0.05$). However, after adjusting for demographic and health covariates, none of these associations continued to be statistically

significant. Neither cotinine nor GGT had a significant linear association with any of the NES2 summary scores (Table 5.6).

Additionally, linear regression analysis indicated a significant positive association between serum concentrations of benzene and CRP ($p < 0.05$); and, between serum concentration of benzene and GGT ($p < 0.05$). However, none of these associations continued to be significant in the adjusted model.

5.3. Discussion

This exploratory study provided a description of the serum concentrations of thirty VOC, among individuals 30 years and older, who participated in the NHANES III. Also, it explored the association between individuals' blood concentrations of VOC and their neurobehavioral functioning as measured by the NES2. Consistent with previous research [2], results revealed a significant difference in neurobehavioral functioning between participants whose blood VOC concentration (e.g. 1,2-dichloropropane) was at or below 95th percentile and those whose blood concentration was above 95th percentile ($p < 0.05$). Specifically, a blood VOC concentration above the 95th percentile was associated with poorer neurobehavioral functioning than a blood VOC concentration at or below the 95th percentile.

Multiple linear regression analyses indicated the existence of a significant positive association between blood concentrations of dibromochloromethane and SRTT mean reaction time ($p < 0.05$); between benzene and the SDLT score ($p < 0.05$); and, between chloroform and the SDLT score ($p < 0.05$). However, after adjusting for demographic and

health characteristics, only the association between dibromochloromethane and SRTT mean reaction time continued to be significant ($p < 0.05$).

Dibromochloromethane is formed when raw water is treated through chlorination for human consumption and, as a result, it is present in chlorinated water supplied to homes, work, and public places [3,4]. The most common routes of exposure to dibromochloromethane are ingestion (from drinking tap water), inhalation (from volatized compounds), and dermal routes (from showering and bathing) [4]. Although the long-term effects of exposure to dibromochloromethane in humans are still unclear, occupational epidemiologic studies have suggested an inverse association between serum concentration of dibromochloromethane and performance in neurobehavioral tests [4,5]. Although this was an exploratory, cross-sectional study; its findings warrant further investigation as they suggest that VOC may have adverse neurobehavioral effects in the general population as well. Specifically, findings suggest that exposure to dibromochloromethane at non-occupational settings (e.g. from contaminated tap water) could have a negative effect on neurobehavioral functioning in community-dwelling individuals.

The existence of a significant positive association between serum biomarkers of oxidative stress (i.e. CRP, $p < 0.05$; GGT, $p < 0.01$) and benzene support our hypothesis of oxidative stress as the physiological mechanism underlying the association between exposure to air pollutants—such as VOC—and cognitive impairment. However, CRP and GGT are not exclusive biomarkers of oxidative stress occurring in the central nervous system. Thus, their increased serological concentrations could be the result of oxidative processes occurring outside the brain and unrelated to cognitive impairment.

Epidemiological studies have identified cardiovascular diseases as precursor of age-related cognitive impairment [6–9]. Similarly, research has linked air pollution to cardiovascular pathology, and proposed oxidative stress as the physiological mechanism mediating this association [10–12]. In this study, almost 40% of participants (37.2%, *n* = 127) reported at least one cardiovascular disease. Thus, it is possible that the observed positive linear association between serum CRP and benzene concentrations; and, between serum GGT and benzene concentrations could be confounded by oxidative stress due to cardiovascular pathology.

Antioxidant compounds found in food and dietary supplements have been proposed to have a protective effect against cognitive impairment [13,14]. Thus, as air pollution can result in increased oxidative stress in the brain, dietary supplementation of antioxidants could modulate the oxidative effects of air pollutants on brain [15]. In this study we did not control for dietary factors that could fight oxidative stress. Consequently, future longitudinal and experimental research efforts are necessary to elucidate the effects of dietary antioxidants on cognitive functioning and to explore new opportunities for the prevention and management of cognitive impairment.

VOC are commonly found in indoor air in concentrations up to ten times higher than outdoor air [16–18]. Cigarette smoking constitutes an important source of VOC and can have a substantial effect on VOC blood concentrations [19]. In this study, a large proportion of participants had a positive history of smoking (55.4%, *n* = 189). Although we accounted for participants' smoking status and used cotinine as an indicator of exposure to tobacco smoke, we were unable to isolate the source of VOC exposure. Thus, it is possible that the observed blood concentration of VOC could be confounded by cigarette

smoking. Also, VOC have a very short half-life in the body [2]. Blood concentrations of VOC change rapidly upon exposure and after cessation of exposure, with most VOC having a half-life of just a few hours [20]. Thus, cross-sectional blood concentrations of VOC are only an indicator of recent VOC exposures. As a result, the findings from this study only provide information about the effect of short-term VOC exposures on neurobehavioral functioning and do not allow making conclusions about the effects of long-term and/or cumulative exposure to VOC.

Although VOC are commonly found indoors, no standards have been set for VOC in nonindustrial settings. Due to the existence of a potential causal relationship between VOC and cognitive impairment, assessing the neurobehavioral effects of VOC could have important implications on reducing the burden of neurobehavioral disorders, such as dementia, on the health care system. Moreover, if one considers the potential synergism between VOC and population aging in the causation cognitive impairment.

Dementia represent a major social, economic, and medical problem [21]. Despite the tremendous public health importance of cognitive impairment and dementia in older age, few modifiable risk factors have been identified. Environmental exposures such as air pollution can increase an organism's generation of ROS and thus represent a potential risk factor for age-related cognitive impairment. Thus, VOC found to have a significant association with participants' performance in the NES2 (i.e. dibromochloromethane, benzene, and chloroform), should merit particular attention.

Although participants in the NHANES III are a good representation of the general U.S. population, this may not be true for the participants in the NHANES III's PTRRS as they were not randomly selected. Consequently, the findings from this study may not be

generalizable to the general U.S. population and might be susceptible to bias from nonprobability sampling. In addition, the cross-sectional design of this study does not allow to establish a causal (i.e. temporal) association between exposure to VOC and a decline in neurobehavioral functioning. Nevertheless, they do highlight the need of large longitudinal studies to assess the potential causal association between serum VOC concentrations and neurobehavioral performance as a proxy of cognitive function.

5.4. Conclusion

This exploratory study provides some insight about the association between exposure to VOC, oxidative stress, and neurobehavioral functioning. Further research with larger sample size and longitudinal design is needed to determine causality and provide the basis for implementing public health initiatives oriented toward the prevention and management of dementia.

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Table 5.1. Participants' Characteristics (Numeric Variables)

Characteristic	*N*	Mean	SD	Minimum	Maximum
Age at interview (years)	341	42.1	8.2	30	59
Highest grade or year of school completed	339	11.7	3.5	0	17
Poverty Income Ratio*	322	2.7	1.9	0.1	9.7

*Poverty income ratio: 0.000-0.999 (Below poverty); 1.000 and above (At or above poverty)

Table 5.2. Participants' Characteristics (Categorical Variables)

Characteristic		*n*	Valid Percent
Gender			
	Male	199	58.4
	Female	142	41.6
Race			
	White	109	32.0
	Other	232	68.0
Ethnicity			
	Hispanic	84	24.6
	Non-Hispanic	257	75.4
Self-Reported Health Status			
	Poor	59	17.3
	Fair	79	23.2
	Good	134	39.3
	Very Good	59	17.3
	Excellent	10	3.0
History of Cardiovascular Disease			
	Yes	127	37.2
	No	214	62.8
Chronic Obstructive Pulmonary Disease			
	Yes	23	6.7
	No	318	93.3
Cancer			
	Yes	16	4.7
	No	325	95.3
Smoking			
	Current Smoker	115	33.7
	Former Smoker	74	21.7
	Never Smoke	152	44.6
Regular Alcohol Consumption			
	Yes	183	53.7
	No	158	46.3
Regular Physical Activity			
	Yes	239	70.1
	no	102	29.9
Prescription for Depression			
	Yes	11	8.6
	No	117	91.4

Table 5.3. Descriptive Statistics of Biomarkers

Biomarkers	*N*	DL	GMean	Percentiles			Min.	Max.
				50th	75th	95th		
1,1,1-Trichloroethane (ug/L)	177	0.086	0.149	0.125	0.218	0.8	0.061	5.377
1,1,2,2-Tetrachloroethane (ug/L)	325	0.008	0.006	0.006	0.006	0.006	0.006	0.013
1,1-Dichloroethane (ug/L)	314	0.009	0.006	0.006	0.006	0.006	0.006	0.034
1,1-Dichloroethene (ug/L)	313	0.018	0.013	0.013	0.013	0.013	0.013	0.058
1,2-Dichloroethane (ug/L)	322	0.012	0.008	0.008	0.008	0.008	0.008	0.017
1,2-Dichloropropane (ug/L)	290	0.008	0.006	0.006	0.006	0.006	0.006	0.026
1,3-Dichlorobenzene (ug/L)	307	0.019	0.013	0.013	0.013	0.013	0.013	0.040
1,4-Dichlorobenzene (ug/L)	301	0.073	0.486	0.357	0.882	8.796	0.052	51.889
2-Butanone (ug/L)	320	0.500	5.522	5.3205	9.002	16.467	0.956	50.477
Acetone (ug/L)	304	200.000	2197.156	1908	4201	9540	368.000	31184.000
Benzene (ug/L)	263	0.030	0.081	0.061	0.17	0.569	0.021	1.348
Bromodichloromethane (ug/L)	312	0.009	0.007	0.006	0.006	0.021	0.006	0.130
Bromoform (ug/L)	192	0.027	0.020	0.019	0.019	0.039	0.019	0.090
Carbon tetrachloride (ug/L)	312	0.019	0.013	0.013	0.013	0.013	0.013	0.056
Chlorobenzene (ug/L)	298	0.007	0.006	0.005	0.005	0.014	0.005	0.092
Chloroform (ug/L)	286	0.021	0.026	0.015	0.037	0.104	0.015	0.584
cis-1,2-Dichloroethene (ug/L)	309	0.013	0.009	0.009	0.009	0.009	0.009	0.014
Dibromochloromethane (ug/L)	307	0.013	0.010	0.009	0.009	0.022	0.009	0.059
Ethylbenzene (ug/L)	198	0.020	0.072	0.0675	0.125	0.272	0.014	3.731
m-/p-Xylene (ug/L)	341	0.033	0.088	0.112	0.237	0.622	0.023	7.461
Methylene chloride (ug/L)	194	0.089	0.067	0.063	0.063	0.063	0.063	1.248
o-Xylene (ug/L)	207	0.040	0.110	0.109	0.153	0.259	0.028	2.174

Table 5.3. Descriptive Statistics of Biomarkers (Continued)

Biomarkers	*N*	DL	GMean	Percentiles			Min.	Max.
				50th	75th	95th		
Styrene (ug/L)	206	0.019	0.047	0.0415	0.081	0.222	0.013	4.006
Tetrachloroethene (ug/L)	185	0.030	0.079	0.065	0.164	0.696	0.021	12.225
Toluene (ug/L)	182	0.092	0.364	0.2935	0.683	1.52	0.065	5.724
trans-1,2-Dichloroethene (ug/L)	317	0.014	0.010	0.010	0.01	0.01	0.010	0.022
Trichloroethene (ug/L)	212	0.010	0.008	0.007	0.007	0.022	0.007	2.678
Serum cotinine (ng/mL)	336	0.050	2.823	0.783	201.000	432.000	0.035	832.000
Serum C-reactive protein (mg/dL)	337	0.300	0.312	0.210	0.400	1.320	0.210	4.700
Gamma glutamyl transferase: SI(U/L)	286	5.000	27.328	26.000	37.000	99.000	6.000	1329.000

Note: *n*, number of participants with measured biomarker; DL, detection limit; Gmean, geometric mean; Min., minimum concentration; Max., maximum concentration.

Table 5.4. Summary Measures of the Neurobehavioral Evaluation System 2 Scores and Testing-Related Factors

NES2 Tests	*n*	Mean	SD	Min.	Max.
SRTT summary: Mean reaction time (msec)	341	238.9	53.2	158.5	615.0
SDST: Mean, 2 lowest corrected latencies	340	3.1	1.1	1.7	9.4
SDLT summary: Total score	341	6.3	5.2	0	16

Test-Related Factors	*n*	Valid Percent
How much sleep did you get last night		
About usual amount	225	66.0
Less than usual	93	27.3
More than usual	23	6.7
Now feeling energetic, ... exhausted		
Energetic	18	5.3
Fresh	40	11.7
Average	199	58.4
Tired	70	20.5
Exhausted	14	4.1
Familiarity w/ computers: none, some, a lot		
None	137	40.2
Some	163	47.8
A lot	41	12.0
How hard tried to perform computer test		
None/not at all	6	1.8
Some	62	18.2
A lot	85	24.9
As hard as I could	188	55.1

Note: *n*, number of participants; SD, standard deviation; Min., minimum score; Max., maximum score.

Table 5.5. Neurobehavioral Evaluation System 2 scores by Volatile Organic Compounds Blood Concentration

VOC	SRTT summary: Mean reaction time (msec)				
	n	Mean	SD	Min	Max
1,1-Dichloroethane (ug/L)					
> 95th percentile	15	234.8	24.2	197.7	280.7
≤ 95th percentile	299	238.7	55.0	163.4	615.0
1,3-Dichlorobenzene (ug/L)					
> 95th percentile	13	220.2	29.8	158.5	286.6
≤ 95th percentile	294	239.1	54.8	163.4	615.0
1,4-Dichlorobenzene (ug/L)					
> 95th percentile	15	252.1	36.7	204.9	346.1
≤ 95th percentile	286	238.3	55.6	163.4	615.0
Acetone (ug/L)					
> 95th percentile	15	250.1	71.8	200.8	495.6
≤ 95th percentile	289	239.2	53.9	158.5	615.0
Benzene (ug/L)					
> 95th percentile	13	278.9	110.3	193.3	607.9
≤ 95th percentile	250	236.1	46.6	163.4	502.0
Bromodichloromethane (ug/L)					
> 95th percentile	15	237.5	29.7	197.6	305.0
≤ 95th percentile	297	240.2	55.7	158.5	615.0
Chlorobenzene (ug/L)					
> 95th percentile	12	227.7	37.0	158.5	294.0
≤ 95th percentile	286	235.9	50.3	163.4	615.0
Chloroform (ug/L)					
> 95th percentile	13	255.2	55.8	186.3	385.3
≤ 95th percentile	273	239.1	56.5	158.5	615.0
Dibromochloromethane (ug/L)					
> 95th percentile	15	287.6	109.4	197.9	607.9
≤ 95th percentile	292	236.6	48.9	158.5	615.0
m-/p-Xylene (ug/L)					
> 95th percentile	17	223.3	42.9	181.6	349.8
≤ 95th percentile	324	239.7	53.6	158.5	615.0
o-Xylene (ug/L)					
> 95th percentile	10	223.1	43.2	181.6	299.9
≤ 95th percentile	197	240.5	54.7	163.4	615.0
Styrene (ug/L)					
> 95th percentile	10	233.8	55.1	181.6	367.0
≤ 95th percentile	196	240.0	54.6	163.4	615.0
Trichloroethene (ug/L)					
> 95th percentile	10	249.4	58.3	198.8	397.6
≤ 95th percentile	202	239.5	53.8	163.4	615.0

Table 5.5. Neurobehavioral Evaluation System 2 scores by Volatile Organic Compounds Blood Concentration (Continued)

VOC	CNPCBEST (SDST: Mean, 2 lowest corrected latencies)				
	n	Mean	SD	Min	Max
1,1-Dichloroethane (ug/L)					
> 95th percentile	15	3.0	1.1	2.0	5.9
≤ 95th percentile	298	3.1	1.1	1.7	9.4
1,3-Dichlorobenzene (ug/L)					
> 95th percentile	13	3.0	1.0	2.1	5.9
≤ 95th percentile	293	3.0	1.1	1.8	9.4
1,4-Dichlorobenzene (ug/L)					
> 95th percentile	15	3.1	0.7	1.8	5.0
≤ 95th percentile	285	3.1	1.1	1.7	9.4
Acetone (ug/L)					
> 95th percentile	15	3.2	0.9	2.1	5.3
≤ 95th percentile	289	3.1	1.1	1.7	9.4
Benzene (ug/L)					
> 95th percentile	13	3.4	0.9	2.6	5.3
≤ 95th percentile	249	3.1	1.1	1.7	9.4
Bromodichloromethane (ug/L)					
> 95th percentile	15	3.0	0.9	2.1	5.9
≤ 95th percentile	296	3.0	1.1	1.7	9.4
Chlorobenzene (ug/L)					
> 95th percentile	12	3.1	1.0	2.1	5.9
≤ 95th percentile	285	3.0	1.1	1.7	9.4
Chloroform (ug/L)					
> 95th percentile	13	3.6	1.0	2.4	5.9
≤ 95th percentile	272	3.0	1.1	1.8	9.4
Dibromochloromethane (ug/L)					
> 95th percentile	15	3.4	1.3	2.1	6.7
≤ 95th percentile	291	3.0	1.0	1.8	9.4
m-/p-Xylene (ug/L)					
> 95th percentile	17	2.8	0.8	2.0	5.3
≤ 95th percentile	323	3.1	1.1	1.7	9.4
o-Xylene (ug/L)					
> 95th percentile	10	2.6	0.4	2.0	3.4
≤ 95th percentile	196	3.0	1.1	1.7	8.6
Styrene (ug/L)					
> 95th percentile	10	3.4	1.1	2.0	5.3
≤ 95th percentile	196	3.0	1.1	1.7	8.6
Trichloroethene (ug/L)					
> 95th percentile	9	2.6	0.5	2.0	3.4
≤ 95th percentile	202	3.0	1.1	1.7	8.6

Table 5.5. Neurobehavioral Evaluation System 2 scores by Volatile Organic Compounds Blood Concentration (Continued)

VOC	CNPCBEST (SDST: Mean, 2 lowest corrected latencies)				
	n	Mean	SD	Min	Max
1,1-Dichloroethane (ug/L)					
> 95th percentile	15	4.4	4.1	0	14
≤ 95th percentile	299	6.6	5.3	0	16
1,3-Dichlorobenzene (ug/L)					
> 95th percentile	13	5.5	5.0	0	15
≤ 95th percentile	294	6.3	5.2	0	16
1,4-Dichlorobenzene (ug/L)					
> 95th percentile	15	8.3	5.2	0	16
≤ 95th percentile	286	6.3	5.2	0	16
Acetone (ug/L)					
> 95th percentile	15	8.1	5.3	2	16
≤ 95th percentile	289	6.5	5.2	0	16
Benzene (ug/L)					
> 95th percentile	13	10.1	4.7	3	16
≤ 95th percentile	250	6.4	5.3	0	16
Bromodichloromethane (ug/L)					
> 95th percentile	15	4.9	4.9	0	13
≤ 95th percentile	297	6.4	5.2	0	16
Chlorobenzene (ug/L)					
> 95th percentile	12	6.5	5.6	0	15
≤ 95th percentile	286	6.4	5.3	0	16
Chloroform (ug/L)					
> 95th percentile	13	8.9	6.1	1	16
≤ 95th percentile	273	6.4	5.3	0	16
Dibromochloromethane (ug/L)					
> 95th percentile	15	7.8	6.0	0	16
≤ 95th percentile	292	6.2	5.1	0	16
m-/p-Xylene (ug/L)					
> 95th percentile	17	5.5	5.7	0	15
≤ 95th percentile	324	6.4	5.2	0	16
o-Xylene (ug/L)					
> 95th percentile	10	4.2	4.9	0	15
≤ 95th percentile	197	6.6	5.4	0	16
Styrene (ug/L)					
> 95th percentile	10	9.1	6.4	0	16
≤ 95th percentile	196	6.4	5.3	0	16
Trichloroethene (ug/L)					
> 95th percentile	10	4.5	4.7	1	15
≤ 95th percentile	202	6.6	5.4	0	16

Table 5.6. Regression Coefficients for Neurobehavioral Evaluation System 2 Scores by Volatile Organic Compounds Blood Concentration

Biomarker	Crude estimate	*p*-value	Adjusted estimate	*p*-value
SRTT summary: Mean reaction time (msec)				
1,3-Dichlorobenzene (ug/L)	-975.923	0.318		
Dibromochloromethane (ug/L)	1157.916	0.01**	845.150	0.01**
Serum C-reactive protein (mg/dL)	5.842	0.29		
Gamma glutamyl transferase: SI(U/L)	0.015	0.68		
Serum cotinine (ng/mL)	0.025	0.15		
SDST: Mean, 2 lowest corrected latencies				
Chloroform (ug/L)	1.661	0.19		
o-Xylene (ug/L)	-0.274	0.53		
Trichloroethene (ug/L)	-0.034	0.93		
Serum C-reactive protein (mg/dL)	0.222	0.04*		
Gamma glutamyl transferase: SI(U/L)	0.001	0.31		
Serum cotinine (ng/mL)	0.000	0.16		
SDLT summary: Total score				
Benzene (ug/L)	4.236	0.01**		
Chloroform (ug/L)	15.750	0.01**		
Serum C-reactive protein (mg/dL)	1.066	0.05*		
Gamma glutamyl transferase: SI(U/L)	0.004	0.24		
Serum cotinine (ng/mL)	0.002	0.34		

*p-value ≤ 0.05

**p-value ≤ 0.01

CHAPTER VI STUDY 3: EXPOSURE TO FINE PARTICLES AND OZONE, AND THE RISK OF COGNITIVE IMPAIRMENT: A POPULATION-BASED STUDY IN ELEVEN U.S. STATES

6.1. Abstract

Introduction: Toxicological studies have identified fine particles and ozone as environmental factors that could act synergistically with age and increase the risk of cognitive impairment in older adults. However, epidemiological studies exploring these associations are limited. **Method**: Participants included respondents to the 2011 Behavioral Risk Factor Surveillance System (BRFSS), 50 years and older, who completed a self-assessment for cognitive impairment. Multilevel logistic regression models were implemented to identify risk factors for cognitive impairment at the individual and county levels. Individuals' data was retrieved from BRFSS 2011 databases and counties' air quality data was retrieved from the U.S. Environmental Protection Agency air quality statistics reports, from 2009 to 2011. **Results**: After adjusting from demographic and health characteristics, we found a statistical significant association between exposure to high ambient concentrations of fine particles and ozone, and self-reported cognitive impairment ($p < 0.05$). **Discussion**: Findings suggest that exposure to high concentrations of fine particles and ozone could increase an individual's risk of cognitive impairment and dementia with age. Air pollutants combined with an individual's characteristics could act together increasing the frequency of this disease at the population level as well. Further research with objective exposure and outcome assessments and longitudinal design is needed to determine dementia's causality and provide the basis evidence-based public health initiatives.

Key words: $PM_{2.5}$, Ozone, Cognitive Impairment, Aging

6.2. Results

6.2.1. Demographic Characteristics of Study Participants

The mean age of participants was 66.1 years (*SD* = 10.4 years). Most participants were between 50 to 64 years old (49.2 %, *n* = 8, 582), female (*n* = 63.7 %, 11,116), White Non-Hispanic (81.3%, *n* = 14,040), and were living with their spouse (60.0%, *n* = 8,878). More than a third of participants (36.3 %, *n* = 6,333) completed four or more years of college education and reported an annual household income of more than $50, 000 per year (39.9 %, *n* = 5,880). Participants' demographics characteristics are summarized in Table 6.1.

Most participants resided in the northeast and southeast of the U.S. Overall, they represented 11 continental states and 73 counties. Participants' geographic distribution is summarized in Table 6.2.

6.2.2. Self-Reported Health

The majority of participants reported their health status as being from good to excellent (77.2%, *n* = 13,422). However, a large proportion of participants (74.7%, *n* = 12,629), indicated having at least one cardiovascular disease (i.e. high blood pressure, high blood cholesterol, heart attack, coronary heart disease, and/or stroke). A smaller proportion of participants reported they have been told by a health professional they had diabetes (17.8%, *n* = 3,111).

In regards to mental health, more than a third of participants (35.9%, *n* = 1,658), reported experiencing FMD. In addition, approximately 10% (9.7%, *n* = 1,689) of participants reported that during the past 12 months, they have experienced confusion or memory loss that is happening more often or getting worse over time. The proportion of

participants reporting cognitive impairment per county, ranged from 3.8% (n = 5) to 25.5% (n = 13). Table 6.3 summarizes participants' self-reported health conditions and health-related behaviors.

6.2.3. Fine Particles

The 3-year average 98th percentile concentration of $PM_{2.5}$ ranged from14μg/m^3 to 41μg/m^3. Most counties (99.6%, n = 17,388) met the 24-hour NAAQS for $PM_{2.5}$ (i.e. a 3-year average 98th percentile concentration of 35μg/m^3).

6.2.4. Ozone

The 3-year average 4th highest daily maximum 8-hour concentration of O_3, ranged from 0.057 ppm to 0.083 ppm. The majority of the counties (81.1%, n = 14,168) met the primary and secondary NAAQS for O_3 (i.e. an annual 4th highest daily maximum 8-hour concentration of 0.075 ppm).

6.2.5. Association between Fine Particles, Ozone, and Self-Reported Cognitive Impairment

6.2.5.1. Empty Model. The estimated between-group variance different than zero ($\sigma_{uo}^2 = 0.08$) and the test of covariance parameters was significant ($X^2 = 40.31,\ p < 0.0001$) which indicates that there is a significant between-group variation among counties. In other words, there is a county effect on self-reported cognitive impairment. Similarly, the ICC—which represents the proportion of group-level variance in the total variance—indicated that 2.5% of the total variance was attributable to the county-level variance (ICC = 0.025). Since the estimated between-group variance was

statistically significant and the ICC was different than zero, the multilevel logistic modeling approach should be applied to this data.

The estimates for the fixed effects indicated that the overall mean of log-odds ($\hat{\gamma}_{00}$) of cognitive impairment was -2.25 ($p < 0.0001$). The corresponding probability ($\hat{p}$) of self-reported cognitive impairment on average in the population was approximately 0.1.

6.2.5.2. Random Intercept Model with Fixed Level-1 Predictor. Results indicated that an individual's FMD had a significant effect on self-reported cognitive impairment ($p < 0.0001$). The odds of an individual reporting FMD of reporting cognitive impairment were more than twice as high as the odds of those individuals who did not reported FMD (Table 6.4). The effect of FMD on cognitive impairment continued to be statistically significant in the adjusted model as described below.

6.2.5.3. Hierarchical Model with Level-1 and Level-2 Predictors.

6.2.5.3.1. Fine particles. The level-1 explanatory variables FMD, gender, education, annual household income, health status, history of cardiovascular disease, and history of diabetes had a statistically significant effect on self-reported cognitive impairment ($p < 0.05$). In this model, FMD, being male, having some education after high school but less than college, having an annual household income of less than $25,000, and having a positive history of cardiovascular disease and/or diabetes, significantly increased the odds of reporting cognitive impairment (Table 6.5). On the other hand,

rating health status from good to excellent significantly lowered the odds of reporting cognitive impairment when compared to those who rated their health from fair to poor (Table 6.5).

Also, we found a significant effect of $PM_{2.5}$ concentration on self-reported cognitive impairment ($p < 0.05$), where individuals in the lower $PM_{2.5}$ concentration counties having lower odds of reporting cognitive impairment. Specifically, the odds of individuals in the $PM_{2.5}$ sixth decile of reporting cognitive impairment were 40% lower than the odds of those in the highest $PM_{2.5}$ decile (AOR = 0.6, $p < 0.05$). Similarly, although marginally statistically significant, the odds of individuals in the $PM_{2.5}$ third decile of reporting cognitive impairment were 40% lower than the odds of those in the highest $PM_{2.5}$ decile (AOR = 0.6, $p = 0.05$). Results from this analysis are summarized in Table 6.5.

6.2.5.3.2. Ozone. Similar to the findings in the $PM_{2.5}$ model, in the O_3 model the level-1 explanatory variables FMD, gender, education, annual household income, health status, history of cardiovascular disease, and history of diabetes had a statistically significant effect on self-reported cognitive impairment ($p < 0.05$). In this model, FMD, being male, having some education after high school but less than college, having an annual household income of less than $25,000, and having a positive history of cardiovascular disease and/or diabetes, increased the odds of reporting cognitive

impairment. On the other hand, rating health status from good to excellent lowered the odds of reporting cognitive impairment when compared to those who rated their health from fair to poor.

Also, we found a significant effect of O_3 concentration on self-reported cognitive impairment, with individuals in counties with lower O_3 having lower odds of reporting cognitive impairment. Specifically, the odds of individuals in the O_3 third decile of reporting cognitive impairment were 30% lower than the odds of those in the highest O_3 decile (AOR = 0.7, $p < 0.05$). Strangely, and on the contrary to what we predicted, we found that the odds of individuals in the eight and ninth O_3 decile of reporting cognitive impairment were higher than the odds of individuals in the high O_3 concentration (10^{th} decile). Results from this analysis are summarized in Table 6.6.

6.3. DISCUSSION

This exploratory study provided an estimate of the prevalence of cognitive impairment and FMD, in the U.S., among individuals 50 years and older, who participated in the BRFSS 2011. Also, it explored the association between FMD and self-reported cognitive impairment; and, between ambient $PM_{2.5}$ and O_3 concentrations, and self-reported cognitive impairment as well. In this population, FMD—14 days or more of poor mental health in the past 30 days[1,2]—was reported by more than a third of participants (35.9%, n = 1,658). In addition, more than half of participants (53.0%, n = 473) responding to both mental health questions reported having experienced cognitive

impairment and FMD. This finding adds to the statistically significant association found between self-reported cognitive impairment and FMD in the multilevel logistic regression analysis. In addition, this result is consistent with previous longitudinal research showing a significant association between psychological stress and dementia [3].

The manifestations of age-related cognitive impairment vary among individuals and can include changes in attention, memory, learning, executive function, and language [4,5]. These symptoms eventually lead to functional difficulties and severely impact an individual's quality of life. As a result, dementia represents a major social, economic, and medical problem [6]. Thus, the identification of risk factors for cognitive impairment can aid in reducing its impact on public health and society as a whole. In studies of predictors of age-related cognitive impairment, associations with demographic characteristics such as education and income have been found [7,8]. In this study, having less than a college education and a household annual income of less than $25,000, were significantly associated with self-reported cognitive impairment, even after controlling for other related factors such as age ($p < 0.005$). This finding is consistent with the BRFSS 2011 national estimates of cognitive impairment which also showed a higher prevalence of cognitive impairment among less educated individuals [9].

As it is the case for cognitive impairment, self-reported health status has also shown to be associated with income and other social factors, with access to health care as one potential intervening mechanism [10,11]. In this study, self-reported good or better health was a protective factor against cognitive impairment, after controlling for health and demographic characteristics ($p < 0.0001$). It is possible that those who already feel in good to excellent health may make the extra effort to maintain and/or enhance their

cognitive health, or perhaps, good mental health create the context for feeling in good or excellent overall health [12].

In the multilevel logistic regression analyses—$PM_{2.5}$ and O_3 models—the odds of participants who reported suffering from at least one cardiovascular disease of also reporting cognitive impairment were higher than the odds of individuals without such history (AOR = 1.5, $p < 0.001$). In addition, those with other chronic health conditions such as diabetes had higher odds of reporting progressive cognitive impairment as well (AOR = 1.2, $p < 0.005$). These findings suggest that cardiovascular pathology could be the underlying factor responsible for the self-reported cognitive impairment. In addition, these results are consistent with previous epidemiological research identifying CVD and diabetes as risk factors for cognitive impairment [13,14].

The raw numbers for the other variables are similarly interesting. In the U.S., a large proportion of individuals live in areas where the concentrations of ambient air pollutants, such as $PM_{2.5}$ and O_3, are above the recommended NAAQS [15]. Several epidemiological studies have found an association between high concentrations of these air pollutants and negative health outcomes [16–21]. Just focusing on the respondents who reported cognitive impairment (N = 1,689), we found a substantial proportion of them were living in the counties in the highest decile of $PM_{2.5}$ and O_3 concentrations, 15.3% (n = 259) and 18.6% (n = 314), respectively. We hypothesized exposure to higher concentrations to $PM_{2.5}$ and O_3 to be a predictor of cognitive impairment. However, for $O_3$the data did not completely support this assumption, as those living in areas with lower O_3 concentrations (8^{th} and 9^{th} deciles) appeared to have higher odds of reporting cognitive impairment than those in the 10^{th} decile.

Other factors such as age group, marital status, and race/ethnicity were important to examine in the model as potential confounders but did not significantly contribute to the risk of self-reported cognitive impairment. Although $PM_{2.5}$ and O_3 seemed to be associated with self-reported cognitive impairment, no specific dose-response relationship was found in the adjusted model.

The results of this study are not free of limitations. The cross-sectional design of this study does not allow us to establish a temporal association between exposure to fine particles and ozone and outcome cognitive impairment. Thus, it is not possible to determine whether there is a causal association between exposure to these air pollutants and self-reported cognitive impairment. This study also analyzed a self-reported outcome measure of cognitive impairment, which is vulnerable to recall and interviewer bias. Also, only counties with 50 or more respondents and with complete air pollution data were included in the study, so selection bias could have affected the results as well. In addition, individuals' exposure to air pollutants was assessed at the county level. Thus, the actual level of exposure at the individual level might be different because of factors such as the mobility of the population from one county to another, the length of residency in a specific county, and/or exposure to air pollutants indoors (e.g. at home and workplace).

Exploratory studies such as this, offer an opportunity for public health professionals to identify potential modifiable risk factors for cognitive impairment by studying risk factors for cognitive impairment from a comprehensive approach, including the assessment of individual and environmental characteristics. Primary preventive actions at the individual and environmental levels could reduce the risk of cognitive

impairment with age. Individuals residing in more polluted areas could relocate to a less polluted area and take preventive actions at the individual level as well (e.g. regular physical activity, use of antioxidants supplements). These behaviors could reduce their risk of experiencing progressive cognitive impairment with age and support healthy aging.

In contrast with other epidemiological studies looking at the association between exposure to air pollutants and cognitive impairment, this study included a large sample of community-dwelling older adults, from across the U.S. In this study, besides environmental factors, FMD also emerged as a factor that diminishes cognition because the odds of individuals suffering from FMD of reporting cognitive impairment were higher than the odds of those who did not suffer from FMD. These findings suggest that studies in maintaining mental health are a vital part of promoting healthy aging and quality of life. They also warrant the need for public health research and interventions related to prevent and reduce the burden of cognitive impairment and dementia.

When identifying populations that may have a higher risk of cognitive impairment, the analysis revealed that males and individuals experiencing FMD had higher odds of reporting cognitive impairment. Social inequality such as income and education gaps create additional barriers to optimizing preventive interventions and could make more difficult for these individuals to take action and follow public health recommendations. In the present study, income could be a marker for diminished resources for taking action. Moreover, education may affect health communication and health literacy. Also the fact that males had higher odds of reporting cognitive decline could be evidence of occupational exposures that need to be addressed as well.

6.4. CONCLUSION

The prevention of multifactorial pathologies such as cognitive impairment implies addressing both individual and environmental risk factors. When people may be able to address individual risk factors, public health professionals and policy makers should take actions to control environmental risk factors and create the conditions in which individuals can be healthy. The results reported in this study encourage environmental public health interventions as individuals' cognitive health could benefit from living and working in healthier and less polluted environments.

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Table 6.1. Participants' Demographic Characteristics

Characteristic	*n*	Valid Percent
Age		
50-64 years	8,582	49.2
65-74 years	4,892	28.0
75 and older	3,987	22.8
Gender		
Male	6,345	36.3
Female	11,116	63.7
Race/Ethnicity		
Hispanic	405	2.3
Other/Multiethnic	425	2.5
Black, Non-Hispanic	2,409	13.9
White, Non-Hispanic	14,040	81.3
Marital Status		
Married/Partnered	8,878	51.0
Divorced/Widowed/	7,237	41.6
Never married	1,299	7.5
Education		
Less than HS	1,595	9.2
High School/GED	5,072	29.1
Some Post-High School Education	4,429	25.4
Complete College Education or More	6,333	36.3
Annual Household Income		
Less than $15,000	1,755	11.9
$15,000 – 24,999	2,907	19.7
$25,000 – 34,999	1,927	13.1
$35,000 – 49,999	2,282	15.5
$50,000 or More	5,880	39.9

Table 6.2. Participants Geographic Distribution

State	County		Participants	
	n	Valid Percent	*n*	Valid Percent
Arkansas	3	4.1	623	3.6
Florida	16	21.9	2,436	14.0
Illinois	6	8.2	1,643	9.4
Iowa	3	4.1	1,075	6.2
Louisiana	7	9.6	1,869	10.7
New Hampshire	6	8.2	2,736	15.7
North Carolina	12	16.4	2,371	13.6
South Carolina	4	5.5	1,600	9.2
Tennessee	6	8.2	1,414	8.1
West Virginia	6	8.2	909	5.2
Wisconsin	4	5.5	785	4.5

Table 6.3. Participants' Self-Reported Health

Characteristic		*n*	Valid Percent
Cardiovascular Disease			
	Yes	12,629	74.7
	No	4,276	25.3
Diabetes			
	Yes	3,111	17.8
	No	14,323	82.2
Frequent Mental Distress			
	Yes	1,658	35.9
	No	2,957	64.1
Self-Reported Cognitive Impairment			
	Yes	1,689	9. 7
	No	15,772	90.3
Self-Reported Health Status			
	Good or Better Health	13,422	77.2
	Fair or Poor Health	3,975	22.9

Table 6.4. Random Intercept Model with Fixed Level-1 Predictor—FMD

Effect	Estimate	*SE*	DF	*p-value*
Intercept	-1.82	0.06	72	<0.0001
FMD	0.90	0.08	72	<0.0001*

**p-value* < 0.001

Table 6.5. Hierarchical Model with Level-1 and Level-2 Predictors Estimates—$PM_{2.5}$

Variables	Estimate	*SE*	*DF*	*p-value*	AOR
$PM_{2.5}$ Deciles					
1^{st}	-0.94	0.23	63	0.68	0.9
2^{nd}	-0.07	0.24	63	0.76	0.9
3^{rd}	-0.47	0.24	63	0.05*	0.6
4^{th}	-0.34	0.21	63	0.11	0.7
5^{th}	-0.13	0.24	63	0.60	0.9
6^{th}	-0.52	0.25	63	0.04*	0.6
7^{th}	0.15	0.34	63	0.65	1.2
8^{th}	-0.24	0.26	63	0.37	0.8
9^{th}	-0.06	0.23	63	0.80	0.9
10^{th}	0				1.0
FMD					
14 days and more	0.62	0.09	72	<0.0001**	1.9
Less than 14 days	0				1.0
Age					
50-64 years	0.11	0.13	141	0.41	1.1
65-74 years	0.13	0.15	141	0.35	1.1
75 and older	0				1.0
Gender					
Male	0.21	0.09	72	0.03*	1.2
Female	0				1.0
Race/Ethnicity					
Hispanic	-0.31	0.26	140	0.24	0.7
Other/Multiethnic	-0.06	0.24	140	0.79	0.9
Black, Non-Hispanic	-0.08	0.12	140	0.55	0.9
White, Non-Hispanic	0				1.0
Marital Status					
Married/Partnered	0.33	0.18	137	0.07	1.4
Divorced/Widowed	0.33	0.17	137	0.05*	1.4
Never married	0				1.0
Education					
Less than HS	0.07	0.16	208	0.69	1.1
High School/GED	0.07	0.13	208	0.59	1.1
Some Post-High School Education	0.27	0.12	208	0.03*	1.3
Complete College Education or More	0				1.0

Table 6.5. Hierarchical Model with Level-1 and Level-2 Predictors Estimates—$PM_{2.5}$ (Continued)

Variables	Estimate	*SE*	*DF*	*p-value*	AOR
Annual Household Income					
Less than $15,000	0.67	0.16	279	<0.0001**	1.9
$15,000 - 24,999	0.33	0.14	279	0.02*	1.4
$25,000 - 34,999	0.27	0.16	279	0.10	1.3
$35,000 - 49,999	0.40	0.15	279	0.01*	1.5
$50,000 or More	0				1.0
Health Status					
Good or Better Health	-0.68	0.10	70	<0.0001**	0.5
Fair or Poor Health	0				1.0
History of CVD					
Yes	0.44	0.13	70	0.001**	1.5
No	0				1.0
History of Diabetes					
Yes	0.22	0.10	71	0.04*	1.2
No	0				1.0

**p-value* ≤ 0.05
***p-value* ≤ 0.001

Table 6.6. Hierarchical Model with Level-1 and Level-2 Predictors Estimates—O_3					
Variables	Estimate	*SE*	*DF*	*p-value*	AOR
O_3 Deciles					
1st	0.01	0.22	63	1.00	1.0
2nd	-0.10	0.19	63	0.72	0.9
3rd	-0.40	0.19	63	0.05*	0.7
4th	-0.20	0.30	63	0.57	0.8
5th	0.03	0.22	63	0.90	1.0
6th	-0.19	0.2	63	0.40	0.8
7th	0.05	0.21	63	0.81	1.1
8th	0.44	0.21	63	0.04*	1.5
9th	0.41	0.23	63	0.08	1.5
10th	0				1.0
FMD					
14 days and more	0.62	0.09	72	<0.0001**	1.9
Less than 14 days	0				1.0
Age					
50-64 years	0.12	0.13	141	0.36	1.1
65-74 years	0.16	0.14	141	0.28	1.2
75 and older	0				1.0
Gender					
Male	0.20	0.09	72	0.04*	1.2
Female	0				1.0
Race/Ethnicity					
Hispanic	-0.28	0.26	140	0.28	0.8
Other/Multiethnic	-0.08	0.24	140	0.75	0.9
Black, Non-Hispanic	-0.07	0.13	140	0.58	0.9
White, Non-Hispanic	0				1.0
Marital Status					
Married/Partnered	0.33	0.16	137	0.06	1.4
Divorced/Widowed	0.34	0.12	137	0.05*	1.4
Never married	0				1.0
Education					
Less than HS	0.09	0.16	208	0.59	1.1
High School/GED	0.07	0.12	208	0.56	1.1
Some Post-High School Education	0.27	0.12	208	0.03*	1.3
Complete College Education or More	0				1.0

Table 6.6. Hierarchical Model with Level-1 and Level-2 Predictors Estimates—O_3 (Continued)

Variables	Estimate	*SE*	*DF*	*p-value*	AOR
Annual Household Income					
Less than $15,000	0.68	0.16	279	<0.0001**	2.0
$15,000 - 24,999	0.34	0.15	279	0.02*	1.4
$25,000 - 34,999	0.27	0.16	279	0.09	1.3
$35,000 - 49,999	0.40	0.15	279	0.01*	1.5
$50,000 or More	0				1.0
Health Status					
Good or Better Health	-0.68	0.10	70	<0.0001**	0.5
Fair or Poor Health	0				1.0
History of CVD					
Yes	0.43	0.13	70	0.001**	1.5
No	0				1.0
History of Diabetes					
Yes	0.23	0.10	71	0.03*	1.2
No	0				1.0

*$p\text{-value} \leq 0.05$
**$p\text{-value} \leq 0.001$

Chapter VII Summary

7.1. Conclusion

Reports from toxicological studies have indicated the existence of an association between air pollution and impairment of cognitive function. The effects of air pollution on the brain include neuroinflammation, oxidative stress, and neurodegeneration; and can manifest as cognitive impairment later in life. Although the causality of cognitive impairment is multifactorial, air pollution could increase an individual's risk by accelerating age-related oxidative processes in the brain and hence represent a significant risk factor for cognitive impairment. Thus, the control of environmental factors such as air pollution could be crucial in limiting the predicted increase of the frequency of dementia due to population aging.

To our knowledge, this study constitutes one of the few epidemiological studies looking at the association between exposure to air pollution and cognitive impairment. Also, it is one of the first studies examining VOC exposure and its association with cognitive functioning in humans. An additional contribution of this study was the use of two national samples to determine the extent of air pollution exposure and its effects on age-related cognitive impairment at the population level. Findings indicated the existence of a statistically significant association between exposure to air pollutants such as VOC, $PM_{2.5}$, and O_3 and cognitive impairment. The results also indicated that exposure to VOC could negatively affect cognition via oxidative stress. However, due to the cross-sectional nature of the data and because CRP and GGT are not exclusive biomarkers of OS in the brain, these findings need to be carefully interpreted and require further review. In addition, O_3 data did not completely support an association between exposure to ambient pollutants and cognitive impairment, and it requires further investigation.

Individual factors such as age, gender, education, socioeconomic status, and concomitant health conditions were identified as individual characteristics that could mediate the association between these ambient air pollutants and cognitive impairment. Thus, effective prevention of cognitive impairment and dementia would require addressing both, individual and environmental characteristics, associated with cognitive impairment. When people may be able to address individual risk factors, public health professionals and policy makers should take actions to control environmental risk factors and create the conditions in which individuals can be healthy. The results from the presented studies must encourage environmental public health interventions as individuals' cognitive health could benefit from living and working in less polluted environments, which could provide the conditions for healthy aging.

7.2. Recommendations

This research provided an opportunity to explore modifiable risk factors for cognitive impairment by reviewing the current literature and using two national samples, to assess the association between exposure to air pollutants—such as VOC, $PM_{2.5}$, and O_3—and cognitive impairment. Although the results from these studies provided some insight in regards to the effects of ambient air pollutants on cognitive functioning, they warrant further investigation. Studies with a larger sample size, random selection of participants, longitudinal design, and objective exposure and outcome assessment are needed to elucidate the questions originated from these exploratory studies.

To our knowledge, this study represented one of the first epidemiological studies examining the association between VOC and cognitive functioning in humans. An

additional contribution of this study was to estimate the extent of exposure to ambient air pollutants and its effects on cognitive impairment at the population level, in the U.S.

Currently, there are not regulatory standards for VOC. The identification of VOC as potential risk factors for neurobehavioral functioning impairment highlight the need of developing and implementing policies oriented toward regulating the concentration of these pollutants in the indoor air. Similarly, when identifying vulnerable groups, the higher odds of males of reporting cognitive impairment compared to women could be evidence of occupational exposures that could be mediating the observed association between exposure to ambient air pollutants and cognitive impairment, which also merits further investigation. Therefore, further research should be oriented toward determining the causality of age-related cognitive impairment and provide the basis for implementing public health initiatives oriented toward the prevention and management of cognitive impairment and dementia.