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Exposure to Air Pollution and Noise, Metabolic Dysfunction and Late-life Cognitive Impairment - A Cohort Study in Elderly Mexican-Americans in Sacramento Area

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Exposure to Air Pollution and Noise, Metabolic Dysfunction and Late-life Cognitive Impairment

- A Cohort Study in Elderly Mexican-Americans in Sacramento Area

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by

Yu Yu

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ABSTRACT OF THE DISSERTATION

Exposure to Air Pollution and Noise, Metabolic Dysfunction and Late-life Cognitive Impairment

- A Cohort Study in Elderly Mexican-Americans in Sacramento Area

by

Yu Yu

University of California, Los Angeles, 2020

Professor Beate Ritz, Chair

Cognitive impairment is a major concern for older adults especially in societies with increasing life expectancy and aging populations, since it reduces health related quality of life and increases caregiver burden. Possible and established factors for cognitive impairment not only include age, genetics, race/ethnicity, life style factors, but also metabolic syndrome, and evidence is accumulating that links environmental risk factors to cognitive impairment such as air pollution and noise exposure. As one of the risk factors of cognitive impairment, metabolic syndrome (MetS) refers to a collection of reversible pathophysiologic conditions including insulin resistance, obesity, dyslipidemia and hypertension. It is highly prevalent in the Hispanic population especially among those aged 60 years or older. In this dissertation, our aim was to investigate the influence of exposures to traffic-related air pollution and noise on incident metabolic syndrome and cognitive impairment, and whether the presence of metabolic syndrome

would modify the association between air pollution or noise exposure and cognitive decline in elderly Mexican-Americans.

The following studies used data from the Sacramento Area Latino Study on Aging (SALSA), a prospective cohort study of 1789 Mexican-Americans aged 60-101, who were living in the Sacramento Area of California between 1998 and 2007. Based on participants' residential addresses at baseline, we estimated local traffic-related nitrogen oxides (NOx) exposure using the California Line Source Dispersion Model version 4 (CALINE4), and traffic noise employing the SoundPLAN software package.

For 1,554 SALSA participants who were free of all five components of MetS at baseline according to the recommendations of the Third Adult Treatment Panel of the National Cholesterol Education Program (NCEP ATP III), we investigated associations between modeled traffic-related NOx or noise pollution and incident metabolic syndrome or its components using Cox regression models with calendar time as the underlying time scale. We found that per unit increase in traffic-related NOx (2.29 parts per billion (ppb)) the hazard ratio (HR) for having low level of high-density lipoprotein cholesterol (HDL-cholesterol) increased by 15% (HR=1.15, 95% CI: 1.04–1.28), and for each 11.6 decibels (dB) increase in noise the risk of developing metabolic syndrome increased by 17% (HR=1.17, 95% CI: 1.01–1.35).

Some epidemiological studies started to focus on associations between air pollution and cognitive function recently, while the role of traffic noise in relation to cognitive impairment is under-studied. Here, we examined association between traffic-related noise pollution and

dementia/ cognitive impairment without dementia (CIND) that developed newly over a 10-year follow-up period among 1,612 participants who were free of dementia/CIND at enrollment. Using Cox proportional hazard models, we observed that per 11.6dB (interquartile range, IQR) increase in 24-hour noise, the hazard of developing dementia/CIND increased (HR = 1.24, 95% CI: 1.00, 1.53) during follow-up; estimates were slightly lower (HR = 1.19, 95% CI: 0.95, 1.49) when adjusting for modeled local air pollution exposure from traffic sources. Overall, the risk of dementia/CIND was elevated when 24-hour and nighttime noise were higher than 75dB and 65dB, respectively.

In the third study, we investigated whether the presence of metabolic dysfunction (obesity, hyperglycemia and low HDL-cholesterol) modifies associations between air pollution or noise exposures and incident dementia or CIND. Among the 1,612 participants from SALSA study who were cognitively normal at the baseline, we used Cox proportional hazard models with calendar time as the underlying time scale to estimate the joint effects of air pollution and noise exposures and several metabolic dysfunctions, specially obesity, hyperglycemia, or low HDL-cholesterol. We found that the risk of developing dementia/CIND increased most (more than 2-fold) among SALSA participants who were exposed to high levels of traffic-related NOx ($\geq$ 3.44 ppb [75th percentile]) (HR = 2.36, 95% CI = 1.41, 3.97) or 24-hour noise ($\geq$ 65 dB) (HR = 2.21, 95% CI = 1.26, 3.89), respectively, and had hyperglycemia. The estimated hazard ratios for dementia/CIND were similarly increased with traffic related air pollution or noise exposures among participants with low HDL-cholesterol but no difference were seen for obesity.

Employing data from one of the large population-based studies of Mexican-Americans, in which repeated anthropometric measurements and sampling of biomarkers as well as repeated cognitive function testing, we added for the linkage between traffic-related air pollution and noise exposures with metabolic syndrome and cognitive impairment. We additionally improve the understanding for the role that metabolic dysfunctions play in the association between traffic-related exposures and cognitive decline. Early identification and treatment of people with metabolic dysfunction as well as prevention approaches that restricting the traffic-related exposures in residential neighborhoods might provide an effective avenue to generate public health benefits in vulnerable populations of elderly.

The dissertation of Yu Yu is approved.

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2020

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ABBREVIATIONS AND ACRONYMS

AADT	Annual Average Daily Traffic
AD	Alzheimer's disease
AHA	American Heart Association
aMCI	Amnestic MCI
ANS	Autonomic Nervous System
apoB	Apolipoprotein B
APOE	Apolipoprotein E
AT II	Angiotensin II
BMI	Body Mass Index
CALINE4	California Line Source Dispersion Model version 4
CARB	California Air Resources Board
CETP	Cholesterol Ester Transport Protein
CIND	Cognitive Impairment without Dementia
CNS	Central Nervous System
CVD	Cardiovascular Disease
dB	Decibel
DOT	Department of Transportation
EGIR	European Group for the Study of Insulin Resistance
eNOS	Endothelial Nitric Oxide Synthase
ET-1	Endothelin-1
FFA	Free Fatty Acid
FHWA	Federal Highway Administration

GPS	Global Positioning System
HDL	High-Density Lipoprotein
HPA	Hypothalamic–Pituitary–Adrenal
IDF	International Diabetes Foundation
IL-6	Interleukin-6
IQR	Interquartile Range
IRS	Insulin Receptor Substrates
LDL	Low Density Lipoprotein
MAP	Mitogenactivated Protein
MCI	Mild Cognitive Impairment
MetS	Metabolic Syndrome
3MSE	Modified Mini-mental State Examination
mPFC	Medial Prefrontal Cortex
MPO	Metropolitan Planning Organizations
MRI	Magnetic Resonance Imaging
NCEP ATP III	National Cholesterol Education Program
NFTs	Neurofibrillary Tangles
NO_2	Nitrogen Dioxide
NOx	Nitrogen Oxides
NSES	Neighborhood Socioeconomic Status
O_3	Ozone
PDK1	3-Phosphoinositide-Dependent Protein Kinase 1
PI3K	Phosphoinositide 3-kinase

$PM_{2.5}$	Particulate Matter $\leq 2.5\mu$
RAS	Renin Angiotensin System
SALSA	Sacramento Area Latino Study on Aging
SEVLT	Spanish English Verbal Learning Test
TG	Triglyceride
TNF	Tumor Necrosis Factor
TNM	Traffic Noise Model
VLDL	Very Low Density Lipoprotein
WHO	World Health Organization

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Chapter 1. Introduction

1.1 Exposure to Air Pollution and Noise

Exposure to air pollution and noise are growing and common concerns due to global urbanization trends that increase exposures (Paul et al. 2019). There are multiple exposure pathways including inhalation, ingestion and dermal contact (Genc et al. 2012). Experimental, clinical and epidemiologic studies have provided evidence for links to various diseases including hypertension, diabetes, cardiovascular disease and neurodegenerative disorders (Kilian and Kitazawa 2018; Lim et al. 2012).

Possible mechanisms underlying the associations between exposure to air pollution and adverse health effects include excessive oxidative stress, generation of reactive oxygen species and elevated cytokine levels such as tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6), induction of the activity of cellular kinases and activation of signal transduction cascades leading to systemic inflammation (Clementi et al. 2019). Systemic inflammation can disrupt insulin signaling pathways leading to insulin resistance, result in hyper-activity of the autonomic nervous system, lipolysis imbalance or enzyme and endothelial dysfunction (Brook et al. 2004; Clementi et al. 2019; Sun et al. 2009; Weiss et al. 2013). Air pollutants may also affect the central nervous system either by direct transport of nanosized particles to the central nervous system (CNS) through nasal pathway, or by triggering the release of soluble inflammatory factors from primary entry organs or secondary deposition sites leading to neuro-inflammation and neurodegeneration (Cipriani et al. 2018; Genc et al. 2012).

Noise can be a source of stress resulting in adverse health effects, possibly explained by two inter-connected pathways ─ sleep disturbance and stress. Noise exposure causes sleep disturbances followed by activation of stress-responsive regulatory systems and behavioral disturbance (Passchier-Vermeer and Passchier 2000) and metabolic dysregulation (Cappuccio et al. 2010; Chaput et al. 2007; Van Cauter et al. 2008). Noise acting as a stressor may also induce activation of the ANS and the hypothalamic–pituitary–adrenal (HPA) axis, causing elevated cortisol levels during sleep (Griefahn and Robens 2010; Schmidt et al. 2013) followed by insulin resistance and metabolic alterations (Björntorp and Rosmond 2000; Cui et al. 2016). Additionally, noise may reduce brain volume in the medial prefrontal cortex (mPFC) area and cortical thickness in the hippocampus and amygdala areas ─ the essential components of the neural circuitry mediating stress responses (Czeh et al. 2007; Jafari et al. 2018). Noise stressors also cause the amygdala to activate stress pathways in the hypothalamus and brainstem, increase the release of noradrenaline and dopamine, and lead to dysregulation of the prefrontal cortex responsible for executive function (Arnsten 2009; Arnsten and Goldman-Rakic 1998; Jafari et al. 2019).

1.2 Metabolic Syndrome

The metabolic syndrome refers to a cluster of multiple adverse pathophysiologic conditions consisting of insulin resistance, visceral obesity, atherogenic dyslipidemia and hypertension (J Stein et al. 2008). Since the World Health Organization (WHO) developed its definition in 1998 (Alberti and Zimmet 1998), there are five most commonly used criteria for MetS, including the definitions from the European Group for the Study of Insulin Resistance (EGIR) (Balkau 1999),

the International Diabetes Foundation (IDF) (Zimmet et al. 2005) the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) and American Heart Association (AHA) (Scott M Grundy et al. 2005), all of them employed a constellation of interconnected physiological, biochemical and metabolic measurements for the MetS diagnosis.

According to the IDF estimation, approximately 25% of adults worldwide have metabolic syndrome (IDF, http://www.idf.org/metabolic-syndrome), but the prevalence varies from 10% to 80%, depending on the region, urbanization, age, gender and ethnicity composition of the population (Kaur 2014). Using 2003-2012 NHANES data, it indicated that overall prevalence of the metabolic syndrome increased from 32.9% in 2003-2004 to 34.7% in 2011-2012 in the United States (US), while the overall prevalence of the metabolic syndrome remained stable from 36.1% in 2007-2008 to 34.7% in 2011-2012 (Aguilar et al. 2015). Individuals in their 40's and 50's were more than three times as likely to have metabolic syndrome, compared with those in their 20's and 30's. Males aged 60 and over were more than four times as likely to have the syndrome than females in the same age group. When taking into account ethnicity, non-Hispanic black males were less likely to have MetS than non-Hispanic white males. However, non-Hispanic black and Mexican American females were more likely to meet the criteria than non-Hispanic white females. It has also been reported that overweight persons were about five to six times as likely to have MetS, and obese persons were more than 32 (males) and 17 (females) times more likely to meet MetS criteria compared with normal weight males and females respectively (Kaur 2014).

Pathophysiologically, MetS can be distilled into four interrelated central features: insulin resistance, visceral obesity, atherogenic dyslipidemia and endothelial dysfunction. Usually atherogenic dyslipidemia follows from insulin resistance and visceral obesity, and can be captured in the definition by including separate criteria for high serum triglyceride (TG) levels and low HDL levels. Endothelial dysfunction, which is captured by hypertension, also follows from insulin resistance and from adipokines and free fatty acids (FFAs) that are released from visceral adipose tissue (Eckel et al. 2005; Kaur 2014).

Insulin resistance

Insulin, which is produced by the pancreas and removes glucose from the circulation i.e. it is taken up by various tissues including skeletal muscle and liver, where it is also converted into its storage molecules, glycogen or fat (Kim et al. 2006). Insulin resistance means that there is a decrease in the responsiveness of peripheral tissues (skeletal muscle, fat and liver) to insulin. Generally, tyrosine phosphorylation of insulin receptor substrates (IRS) activates phosphoinositide 3-kinase (PI3K) — one of the most important regulatory proteins involving in different key functions of the cell such as growth and survival, aging, and malignant transformation (Krasilnikov 2000), followed by the activation of the 3-phosphoinositide-dependent protein kinase 1 (PDK1) kinase and Akt kinase. PDK1 is a protein kinase that can be activated by several growth factors and hormones including insulin signaling (Nicholson and Anderson 2002). Akt is a serine/threonine-specific protein kinase that plays a key role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription and cell migration (Fyffe and Falasca 2013). Akt kinase phosphorylates and activates endothelial nitric oxide synthase (eNOS) and stimulates translocation of the insulin-

responsive glucose transporter GLUT4 to the cell surface in skeletal muscle and adipose tissue. On the other hand, the mitogenactivated protein (MAP) kinase, a type of protein kinase which is involved in directing cellular responses to a diverse array of stimuli, such as mitogens, osmotic stress, heat shock and proinflammatory cytokines, regulates key cell functions including proliferation, gene expression, differentiation, mitosis, cell survival, and the apoptosis pathway (Morrison 2012) that mediates the production of endothelin-1 (ET-1) - a potent vasoconstrictor, leading to vasoconstriction, greater leukocyte-endothelial interactions and growth and mitogenesis of vascular smooth muscle cells. Thus, the inhibition of the PI3K-Akt pathway results in a reduction of nitrous oxide (NO) production, causing endothelial dysfunction, and a reduction in GLUT4 translocation, leading to decreased glucose uptake in skeletal muscle and fat. Since the MAP kinase pathway is unaffected, it continues to produce ET-1, expression of vascular cell adhesion molecules and mitogenic stimulus of vascular smooth muscle cells; consequently insulin resistance leads to vascular abnormalities that predispose to atherosclerosis (Huang 2009).

Visceral obesity

Adipose tissue is a heterogeneous mix of adipocytes, stromal preadipocytes, immune cells, and endothelium. It does not only store and mobilize lipids but also is involved in multiple physiologic processes including insulin sensitivity, oxidant stress, energy metabolism, blood coagulation, and inflammatory responses. Visceral obesity is associated with insulin resistance, leading to a decrease in insulin-mediated glucose uptake. Probable mechanisms include (1) disrupted adipocytokine (cell signaling proteins that are secreted by adipose tissue) levels leading to elevated levels of proinflammatory mediators including TNF-α and IL-6, (2)

activation of the renin angiotensin system in adipose tissue resulting in hypertension and insulin resistance, (3) decreasing levels of adiponectin ─ a protective adipocytokine that couples insulin sensitivity with energy metabolism, (4) release of FFAs from visceral fat, which will interact with other bioactive lipid intermediators to impair the PI3K-Akt pathway and increase oxidative stress. Thus, obesity is considered by some researchers to be fundamental to metabolic syndrome as it appears to precede the emergence of the other features (O'Neill and O'Driscoll 2015).

Dyslipidemia

Atherogenic dyslipidemia refers to a spectrum of qualitative lipid abnormalities consisting of high plasma TG levels, low HDL cholesterol levels and increased low-density lipoprotein (LDL) levels, which is related to insulin resistance and visceral obesity. In insulin resistance, impairments of the insulin signaling pathway increase lipolysis in adipose tissues, followed by elevated FFA levels and very low density lipoprotein (VLDL) production. Also in a state of insulin resistance, insulin cannot degrade apolipoprotein B (apoB) through PI3K-dependent pathways and regulate the activity of lipoprotein lipase which is the rate-limiting and primary mediator of VLDL clearance, thus increasing VLDL production. VLDL is metabolized to remnant lipoproteins and small dense LDL, both of which can promote atheroma formation. The TGs in VLDL are transferred to HDL by the cholesterol ester transport protein (CETP) in exchange for cholesteryl esters, leading to TG-enriched HDL and cholesteryl ester-enriched VLDL particles. The TG-enriched HDL is a better substrate for hepatic lipase, such that it is cleared rapidly from the circulation, leaving fewer HDL particles to participate in reverse cholesterol transport from the vasculature. Thus, dyslipidemia associated with insulin resistance is the result of both an increase in VLDL production and a decrease in VLDL clearance. These

anomalies are related to increased oxidative stress and endothelial dysfunction, reinforcing the proinflammatory nature of macrovascular atherosclerotic disease (Huang 2009; Kaur 2014).

Endothelial dysfunction

Endothelial dysfunction occurs when the endothelium fails to play its protective role in physiological mechanisms, including (1) responding to physiological and pathological stimuli, producing vasoactive substances such as NO, endothelin and prostacyclin; (2) interacting with circulating leukocytes, and platelets by expression of cell adhesion molecules, affecting inflammation and hemostasis and thrombosis respectively; (3) modulating the response of the vascular smooth muscle layer which is associated with the development of atherosclerotic plaques. Many factors can influence endothelial function including inflammatory cytokines, oxidative stress or hyperglycemia. Insulin resistance impairs the PI3K-Akt pathway, decreasing Akt kinase activity and diminishing eNOS phosphorylation and activity, which in turns reduce the bioavailability of NO in vasculature. Visceral adiposity also causes endothelial dysfunction through several pathways, including (1) inhibition of eNOS phosphorylation and activity through resistin, IL-6 and TNFα; (2) decrease in adiponectin levels (also resulting in a reduction of eNOS phosphorylation); (3) increased generation of reactive oxygen species due to leptin resistance in visceral fat, (4) increased production of FFAs and diminished PI3K-Akt signaling, again increasing reactive oxygen species levels and ET-1 production. Thus, endothelial dysfunction is the consequence of these metabolic abnormalities, leading to the development of hypertension. For example, hypertension may be caused by the expression of angiotensinogen, Angiotensin II (AT II), and the AT1 receptor and these have been shown to be elevated by hyperglycemia and hyperinsulinemia through the activation of the Renin angiotensin system (RAS). Also, insulin

resistance and hyperinsulinemia lead to sympathetic nervous system (SNS) activation and increased sodium reabsorption by the kidneys, subsequently increasing cardiac output by the heart, and vasoconstriction of arteries resulting in hypertension (Morse et al. 2005).

Metabolic syndrome has been considered to be related to multiple risk factors including age, genetics, ethnicity, diet, socioeconomic status and lifestyle factors (Aguilar et al. 2015; Grundy 2008; Rochlani et al. 2015). Recently, it has been linked to environmental risk factors including air pollution and noise exposures (Brook and Kousha 2015; Wallwork et al. 2017; Yu et al. 2019). Also, the concept of MetS has been used to identify a subgroup of people who are at higher risk of developing cardiovascular disease and Type II diabetes. Growing evidence also implicates MetS as a risk factor for chronic renal disease (Locatelli et al. 2006), sleep problems (Lam and Ip 2010), dementia and other neurodegenerative-diseases (Genc et al. 2012). Compared with those not affected by MetS, individuals with MetS are about 3 times more likely to develop a stroke; 4 times more likely to suffer from myocardial infarction; and twice as likely to die from a cardiovascular incident, even when controlling for cardiovascular disease history (Kaur 2014). Therefore, a diagnosis of MetS might motivate patients and doctors to undertake steps to reduce the risk for cardiovascular disease, endocrine or neurodegenerative-disease, including life-style improvement and appropriate pharmacological management (Huang 2009). Moreover, since the definition of the MetS incorporates five components which are known to be interrelated, it can serve as a shorthand to better understand the common underlying pathophysiological processes and the genetic basis and environmental risk factors for this syndrome, and to develop and test new treatment approaches.

1.3 Late-life Cognitive Impairment

Cognitive decline and dementia are gaining concern due to increasing life expectancy and a growing elderly population and the social and economic burden of these disorders for communities (Paul et al. 2019). It has been reported that ~5.7 million people are living with dementia in the US in 2018, and the prevalence of Alzheimer's disease (AD) will reach 13.9 million by 2060 (Matthews et al. 2019).

The deposition of tau and β-amyloid (Aβ) is considered the principle pathological mechanism underlying AD and cognition damage (Paul et al. 2019). Aβ aggregates and forms neuritic amyloid plaques - the primary pathological marker of AD. Aβ is produced throughout the body and plays physiological roles at low concentration. In AD, increased Aβ levels contribute to the formation of insoluble aggregates in the brain which are known as senile plaques, and damage nearby brain cells and - importantly- activate microglia. Neurofibrillary tangles (NFTs) are another pathological hallmark of AD and consist of a modified structural protein known as tau. Normally tau proteins play a role in stabilizing the structure of the neuron, while in AD they may aggregate inappropriately and lead to cellular dysfunction. It is still unclear what links NFTs and amyloid plaques, however, the dual proteinopathy is considered necessary for progression toward cognitive impairment (Elahi and Miller 2017; Jill Stein et al. 2008).

According to the Alzheimer's Association, possible or established risk factors for cognitive impairment include age, family history, apolipoprotein E (APOE) ε4, cardiovascular disease (CVD), diabetes, hypertension, and life style factors such as smoking and alcohol consumption (https://www.alzheimers.org.uk/sites/default/files/pdf/factsheet_risk_factors_for_dementia.pdf)

Evidence that links cognitive impairment to environmental risk factors especially air pollution and noise exposures is starting to accumulate (Oudin et al. 2016; Power et al. 2016; Tzivian et al. 2015; Tzivian et al. 2016; Weuve et al. 2012). Common mechanisms of how environmental risk factors may be affecting the brain include inflammation, oxidative stress and disruption of insulin signaling pathways and also may play critical roles not only in the development but also progression of the disease (Cipriani et al. 2018; Genc et al. 2012; Kilian and Kitazawa 2018). Moreover, insulin resistance, one of the key pathological features of metabolic dysfunction, is closely related to oxidative stress and inflammation (Clementi et al. 2019; Dik et al. 2007; Dubowsky et al. 2006; Razay et al. 2007; Stampfer 2006). Thus, given the associations among environmental exposures, cardiovascular risk factors and cognitive impairment and dementia risk, environmental exposures might damage brain health directly or indirectly through vascular neuropathology and the mechanisms listed above (Paul et al. 2019).

Chapter 2. Air Pollution, Noise Exposure, and Metabolic Syndrome – A Cohort Study in Elderly Mexican-Americans in Sacramento Area

2.1 Abstract

Introduction: Previous studies suggested that air pollutants may increase the incidence of metabolic syndrome, but the potential impact from traffic sources is not well-understood. This study aimed to investigate associations between traffic-related nitrogen oxides (NOx) or noise pollution and risk of incident metabolic syndrome and its components in an elderly Mexican-American population.

Methods: A total of 1,554 Mexican-American participants of the Sacramento Area Latino Study on Aging (SALSA) cohort were followed from 1998 to 2007. We used anthropometric measures and biomarkers to define metabolic syndrome according to the recommendations of the Third Adult Treatment Panel of the National Cholesterol Education Program (NCEP ATP III). Based on participants' residential addresses at baseline, estimates of local traffic-related NOx were generated using the California Line Source Dispersion Model version 4 (CALINE4), and of noise employing the SoundPLAN software package. We used Cox regression models with calendar time as the underlying time scale to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations of air pollution or noise with metabolic syndrome or its components.

Results: Each per unit increase of traffic-related NOx (2.29 parts per billion (ppb)) was associated with a 15% (HR = 1.15, 95% CI: 1.04, 1.28) lower level of high-density lipoprotein cholesterol (HDL-cholesterol), and each 11.6 decibels (dB) increase in noise increased the risk of developing metabolic syndrome by 17% (HR = 1.17, 95% CI: 1.01, 1.35).

Discussion: Policies aiming to reduce traffic-related air pollution and noise might mitigate the risk of metabolic syndrome and its components in vulnerable populations.

2.2 Introduction

Metabolic syndrome refers to a cluster of adverse pathophysiologic conditions including insulin resistance, visceral obesity, atherogenic dyslipidemia and hypertension (J Stein et al. 2008). The prevalence of metabolic syndrome has been increasing and in 2011–2012 in the United States (US) nearly 35% of all adults and 50% of those age 60 years or older were estimated to live with metabolic syndrome (Aguilar et al. 2015). Compared with those not affected by metabolic syndrome, individuals with metabolic syndrome are about two to four times more likely to suffer a cardiovascular related event (Kaur 2014). Growing evidence implicates metabolic syndrome as a risk factor for many chronic diseases including neurodegenerative-diseases (Genc et al. 2012; Lam and Ip 2010; Locatelli et al. 2006). It has been estimated that the average annual health care cost for people with metabolic syndrome is $5,732 compared with $3,581 for those without it (Boudreau et al. 2009). Thus, given 326 million adults in the US, a 35% prevalence of metabolic syndrome adds approximately 221.7 billion dollars in health care costs annually.

Risk factors for metabolic syndrome include age, genetics, race/ethnicity, life style factors such as physical activity, and socioeconomic status, and across the globe metabolic syndrome varies geographical along with these factors (Aguilar et al. 2015; Grundy 2008; Kaur 2014; Misra et al. 2010; Rochlani et al. 2015). Recently, it has been suggested that environmental risk factors, specifically air pollution, might play a role in metabolic syndrome occurrence possibly by affecting inflammatory pathways (Brook et al. 2008; Kramer et al. 2010; Rao et al. 2015). Yet, the role of exposures from different sources – traffic-related air pollutants or noise pollution – is unclear. Previous epidemiologic studies mostly explored the relationship between specific air

pollutants and one or two of the five components of metabolic syndrome (abdominal obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low HDL-cholesterol) (Brook and Kousha 2015; Christensen et al. 2016; Eze et al. 2014; Halonen et al. 2011; Valdes et al. 2014). Furthermore, no studies focused on Mexican-Americans, a fast-growing segment of the US population with an especially high occurrence of metabolic syndrome (Aguilar et al. 2015).

Here, we investigated the effects of local traffic-related air pollution and noise on the incidence of metabolic syndrome or its components in a cohort of elderly Mexican-Americans living in the Sacramento Area of California.

2.3 Methods

Research Ethics

All procedures described here were approved by the Institutional Review Boards of the University of California San Francisco, Los Angeles, and Davis and the University of Michigan.

Study population

The Sacramento Area Latino Study on Aging (SALSA) started as a prospective cohort study of 1789 Mexican-Americans aged 60-101 at baseline who were living in the Sacramento Area of California. The overall response rate was 85% and about 22% of total eligible residents were recruited in 1998 and 1999. The average annual attrition rate from mortality and loss to follow-up was 5%. A total of 462 deaths occurred during the study period.

Participants were eligible if they (i) were 60+ years of age, (ii) resided in the six-county area of the California Sacramento Valley (Sacramento, Yolo, Sutter, Solano, Yuba, and Placer counties); and (iii) self-identified as Latino. Participants were interviewed at their homes every 12–15 months for up to seven study visits, ending in December 2007. Between home visits, we updated contact information, health status and medication changes in a 10-minute phone interview every 6 months. The median length of follow-up was ~7.5 years with a maximum of 10 years (for more details see (Haan et al. 2003)). After excluding those who (1) did not participate in the baseline visit (n=3), (2) had no exposure estimates (living too far away from traffic sources (n=3)), (3) already exhibited all 5 components of metabolic syndrome (n=175) at baseline, and (4) lacked follow-up visits (n=54), the remaining 1,554 participants make up our baseline sample. For each specific outcome incidence analysis (metabolic syndrome or its components), we furthermore excluded participants who already met the criteria for the designated outcome at baseline (Figure S2-1).

Outcome measurements

At each follow-up visit, anthropometric measurements including waist circumference and blood pressure were collected. Waist circumference measurements (cm) were taken at the level of the umbilicus in mid-respiration while the participant was standing. After sitting for 10 minutes, systolic and diastolic blood pressure (mmHg) were measured twice within a 5-minute interval, and the two measurements were averaged (González et al. 2011; Odden et al. 2012). Fasting blood draws were performed at baseline and most follow-up visits to assess lipid, triglyceride, glucose and other biomarkers.

Each individual metabolic syndrome component was considered to be present according to the definition of NCEP ATP III (Scott M Grundy et al. 2005): (i) abdominal obesity: waist circumference of ≥ 40 inches in men; ≥ 35 inches in women); (ii) borderline elevation of blood glucose (fasting glucose ≥ 100 mg/dl, or use of glucose-lowering medications; (iii) elevated blood pressure (≥ 140/90 mmHg), or use of anti-hypertensive medication; (iv) elevated triglycerides (≥ 150 mg/dl), or use of statins; and (v) low HDL-cholesterol (men: < 40 mg/dl; women: < 50mg/dl), or use of statins. Metabolic syndrome was defined as the presence of three or more of these components.

Exposure measurements

Annual average traffic-related NOx exposure was estimated at baseline for each participant's geocoded residential address from the CALINE4 line dispersion model (Benson and Pinkerman 1989; Wu et al. 2009; Wu et al. 2016). This model captures the contributions from local traffic emissions within 1500 meters of the subject's baseline residence and the influence of meteorology (i.e. wind speed and direction, atmospheric stability, mixing height and ambient temperature). Roadway (freeways, highways, and major arterial roads) and 2002 traffic volume data were obtained from the California Department of Transportation. Emission factors were retrieved from the California Air Resources Board (CARB)'s EMFAC2011 model (California_EPA 2011). Meteorological data was obtained from the CARB Air Quality and Meteorological Information System (CARB 2015). We used the NOx estimates based on 2002 traffic data to generate our exposure estimate. However, traffic counts, meteorological and emission factors are highly correlated across the years of interest in the Sacramento area. Thus, the NOx estimates generated by CALINE4 are also highly correlated over all of these years.

Noise exposure levels for participants' baseline addresses were calculated using the SoundPLAN (Version 8.0, NAVCON, Fullerton, CA, USA) software package with the input of Annual Average Daily Traffic (AADT) data obtained from the local Metropolitan Planning Organizations (MPO). The Federal Highway Administration Traffic Noise Model (TNM) is one of the noise prediction models implemented in SoundPLAN. For each participant, A-weighted nighttime (22:00–07:00) and day-night average sound levels (Leq,n and Ldn, respectively) were estimated. SoundPLAN adds a constant penalty of 10dB for noise during the nighttime, to account for a higher impact of nighttime hour noise compared to daytime noise. The geocoded residential address of study subjects was used as the receiver point. At each receiver location, the TNM algorithm computed noise levels by incorporating vehicle speed, distance between receiver and roadway, ground classification (soft vs. hard ground) and counts of different types of vehicles. More information about TNM can be found elsewhere (US_DOT 1998, 2002). For the ambient noise predictions, we only considered roadway traffic as the source of noise in the study population. Hourly traffic counts collected from the State Department of Transportation (DOT) in 2002 were used to calculate an average diurnal pattern, and to adjust the MPO AADT values to hour-of-day specific traffic counts for each noise receptor location. Only light duty and heavy duty vehicles classified according to the Federal Highway Administration (FHWA) were counted and the average vehicle speed was assumed to be 55 miles per hour. Noise exposures were treated as continuous or categorical variables using cut-points according to the World Health Organization community noise guidelines (2009) and results from noise studies conducted in US and European countries (Lee et al. 2014; Seong et

al. 2011). Specifically, annual average 24-hour noise was categorized as < 65 dB and ≥ 65 dB and nighttime noise as < 55 dB and ≥ 55 dB.

All participants were recruited in 1998 and 1999 and 75% of participants reported to have resided at their baseline residence for more than five years; we did not have information on prior residences. Thus, our NOx estimates for the address at enrollment are all within a 2-year window. Since the average length of having lived at this residence was 22 years, 90% of participants remained in California throughout the study period, and the spatial pattern of traffic in the Sacramento area did not change much during the study period, our exposure measures might represent the overall long-term traffic patterns around each participants' residence well for periods long before and throughout follow-up.

Covariates

Demographic information including birthplace, years of education, and occupation during most of the lifetime were collected during enrollment. During each interview, participants were asked about lifestyle behaviors such as smoking, alcohol drinking, physical activity, medical diagnoses, and medication use. An urban/rural residential location indicator was created based on Census tract 2000 information (http://www.ers.usda.gov/data-products/rural-urbancommuting-area-codes.aspx). We also generated a neighborhood socioeconomic status (NSES) score ranging from 1 (low NSES) to 5 (high NSES) relying on six census (2000) estimates: percentage of (1) individuals who are 25 years or older without a high school diploma, (2) the population living below the poverty line, (3) individuals at ages 16+ years who at one time had been in the workforce but are unemployed, (4) households owning their home,

(5) vacant housing units; and (6) median number of rooms in a household (Yost et al. 2001). Physical activity level was based on the information that participants reported about time they had spent on 18 different activities common in older adults during a regular week (for details see (Shih et al. 2018)).

Statistical methods

Metabolic syndrome and its five components were investigated as separate outcomes. Cox proportional hazards regression models with calendar time as the underlying time scale were used to assess the impact of traffic-related NOx and noise exposures at baseline on the risk of developing metabolic syndrome or its components. Participants were censored at their last date of contact if they did not return for examinations or at their time of death before the end of 2007 whichever came first.

Exposures were treated as continuous variables normalized by their respective interquartile ranges (IQRs), and for noise exposures we also employed binary variables. We first adjusted for baseline age, gender and years of education, and then added the NSES indicator, occupation, smoking status, alcohol consumption, and physical activity level to the models. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Sensitivity analyses comprised of including both traffic-related NOx and noise exposures in the same model to address potential confounding by these co-exposures and investigating interactions between traffic-related NOx and noise exposures. We also further adjusted for birth country, residential location, and health status such as cardiovascular disease and stroke. Lastly,

we used different cut-off points (130/85 mmHg) to define hypertension for air pollution and noise models.

2.4 Results

At baseline, the average age of the participants in each sub-cohort was ~70 years, the average body mass index (BMI) 28 to 29 (except for the obesity sub-cohort). In each sub-cohort, ~60% reported having held a manual labor job during most of their life, 87% lived in an urban area and more than 70% in Sacramento County. One-third of the SALSA participants already suffered from CVD and ~8% reported a stroke at baseline. More than 20% were considered physically active according to our criteria, while only 12% were current smokers and 10% consumed alcohol daily (Table 2-1). Characteristics of subjects with prevalent metabolic syndrome or its components at baseline, who were excluded, are summarized in Table S2-1; they were less physically active and reported higher prevalence of cardiovascular disease and stroke.

CALINE4 estimated local traffic-generated NOx levels ranged from 0.01 to 14.5 ppb with an annual average concentration of 2.6 ppb across the cohort. The annual 24-hour-average and nighttime noise exposures were 68 dB and 60 dB respectively (Table2-1, Table S2-2), and these two noise measures were perfectly correlated (Pearson r = 1.00); however, our traffic-related NOx and noise measures were only moderately correlated (Pearson r = 0.41) (Table S2-3).

In single exposure models, the adjusted hazard ratio for incident low HDL-cholesterol level was 1.15 with each 2.29 ppb increase in traffic-related NOx (95% CI: 1.04, 1.28). Higher traffic-related NOx exposure was also positively associated with hypertension, hyperglycemia, hypertriglyceridemia and metabolic syndrome but not obesity, yet the 95% CIs of these estimates crossed the null (Table 2-2).

In single noise exposure models, elevated annual 24-hour noise levels were positively associated with the new occurrence of metabolic syndrome, hypertension, hyperglycemia, hypertriglyceridemia and low HDL-cholesterol during follow-up, but negatively with obesity. The hazard of developing metabolic syndrome was 1.17 (95% CI: 1.01, 1.35) per 11.6 dB 24-hour noise level increase. The incidence of hypertension, hyperglycemia, hypertriglyceridemia and low HDL-cholesterol increased by ~10% per 11.6 dB 24-hour noise level increase (Table 2-3). The effect of nighttime noise exposure on metabolic syndrome and its components was the same as for 24-hour noise exposure. When the 24-hour and nighttime noise levels were higher than 65 dB or 55 dB respectively, they were also positively associated with incident metabolic syndrome, hypertension, hyperglycemia, hypertriglyceridemia and low HDL-cholesterol (Table S2-4). When using a finer quartile-based scale, we found the risk of metabolic syndrome and its components to be especially elevated when annual average 24-hour and nighttime noise exposures were higher than 75 dB or 65 dB, respectively (Figure2-1).

In sensitivity analysis, additionally adjusting for birth country, residence area, and other health status indicators did not change the effect estimates for air pollution or noise exposures. When traffic-related NOx and noise exposures were both included in the same models, associations

between the exposures and metabolic syndrome or each component remained similar (Table S2-5), and no joint effect or interaction between traffic-related NOx and noise was found. When using a cut-off of 130/85 mmHg to define hypertension, associations between traffic-related NOx and metabolic syndrome and its components remained similar. For noise, the estimated effect on hypertension at this lower cut-off (per 11.6 dB 24-hour average noise level increase) was attenuated to the null (HR = 1.00, 95% CI: 0.85, 1.16), while the estimated noise effects on metabolic syndrome were retained (HR = 1.16, 95% CI: 1.00, 1.34).

2.5 Discussion

Air pollution and noise exposures from traffic sources are increasing with worldwide urbanization trends, and – with a growing elderly population – it is concerning that both exposures have recently been linked to metabolic disorders (Eze et al. 2014; Eze et al. 2017) that are prodromal to many chronic diseases of aging (Cui et al. 2012; Cui et al. 2015). In elderly Mexican-Americans, we found positive associations between traffic-related NOx air pollution exposures and low HDL-cholesterol. Noise exposure affected the incidence of metabolic syndrome during follow-up. Moreover, positive relationships between traffic-related NOx or noise exposures and other components of metabolic syndrome except for abdominal obesity were also suggested.

Associations between traffic-related NOx and metabolic syndrome or its components are supported by some but not all previous studies (Coogan et al. 2012; Fuks et al. 2017). Another study followed 1023 Mexican-American participants for 6 years and observed that higher nitrogen dioxide (NO_2) was positively related to lower HDL-cholesterol levels and a decreased

HDL-to-LDL cholesterol ratio (Chen et al. 2016). A Spanish cohort study – REGICOR (Registre Gironí del Cor , Girona Heart Registry), reported that each 5.32 ppb increase in NO_2 increased systolic blood pressure in non-medicated individuals by 1.34 mmHg (95% CI: 0.14, 2.55) (Foraster et al. 2014). Plausible mechanisms for air pollution effects on metabolic dysfunction are the induction of oxidative stress and systemic inflammation, followed by disruptions of the insulin signaling pathway and hyper-activation of the autonomic nervous system (ANS) leading to insulin resistance, endothelial dysfunction, alterations in lipolysis and enzyme function as documented previously (Brook et al. 2004; Farbstein and Levy 2012; Sun et al. 2009; Weiss et al. 2013).

The role of noise in generating adverse health effects has been gaining increasing credibility (de Souza et al. 2015; Mehrdad et al. 2011; Sorensen et al. 2012). Our results are corroborated by previous studies. A study in Sweden (n=667) reported a strong association between traffic-related noise and hypertension (Odds Ratio [OR] = 2.47, 95% CI: 1.38, 4.43) (Bluhm et al. 2007). A meta-analysis of 15 studies (444,460 adult participants and 17,430 diabetes cases) of noise exposure, mainly related to air and road traffic, estimated an increased risk of diabetes (Zare Sakhvidi et al. 2018). A cross-sectional study in Denmark (n=508) reported that noise levels increased levels of triglycerides, cholesterol–HDL ratio, while decreasing levels of HDL-cholesterol (Arlien-Søborg et al. 2016). Two proposed inter-connected pathways – sleep disturbance and stress – could explain the impact of noise on metabolic dysfunction. It is well-established that sleep disturbances caused by noise exposure may in turn result in behavioral (Passchier-Vermeer and Passchier 2000) and metabolic dysregulation (Cappuccio et al. 2010; Chaput et al. 2007; Van Cauter et al. 2008) through activation of stress-responsive regulatory

systems. Psychological stress induced by noise could activate the ANS and the hypothalamic–pituitary–adrenal (HPA) axis, causing increased cortisol levels during sleep (Griefahn and Robens 2010; Schmidt et al. 2013), and this may be followed by insulin resistance and consequently metabolic alterations (Björntorp and Rosmond 2000; Cui et al. 2016).

In our study, models that included both traffic-related NOx and noise exposures showed similar results as single exposure models, suggesting independent effects of these exposures on metabolic syndrome. This supports the notion that different traffic-generated environmental exposures – air pollution and noise – contribute to different pathophysiologic mechanisms (Fuks et al. 2017) but nevertheless converge to increase the occurrence of metabolic syndrome in elderly populations.

In the SALSA cohort, we did not find positive associations between traffic-related NOx or noise exposure and abdominal obesity. This might be explained by the fact that on average participants were 70 years old at enrollment and abdominal obesity was probably already established decades earlier (Table S2-1); thus, while these exposures may still contribute to the mechanisms that lead to metabolic syndrome or other components among the elderly, it is too late for abdominal obesity to be newly occurring. Additionally, these elderly participants might even have a decreasing waist circumference due to other chronic diseases.

Our study has several strengths. The SALSA study is a population-based longitudinal cohort study of elderly Mexican-Americans living in California. Repeated anthropometric measurements and sampling of biomarkers allowed us to study incident metabolic syndrome

and its components over a relatively long period. It is also one of the few studies in North America exploring the effect of noise on metabolic dysfunction. We generated traffic noise exposure metrics at the residential addresses and co-adjusted these measures for local traffic-generated air pollution. The geocoded-addresses used for exposure assessment, were based on Global Positioning System (GPS) readings available at the door step (readings were performed at home visits), thus geo-location quality is high. The traffic-related NOx exposure was generated using the CALINE4 dispersion model with the input of traffic density, emissions and meteorology, which employs a mixing zone concept to characterize pollutant dispersion along the roadway. Previously, studies (Franklin et al. 2012; Gauderman et al. 2005; Urman et al. 2014) reported moderate to strong correlations between traffic-related NOx estimates generated by CALINE4 model and monitored estimates, providing evidence that the Gaussian dispersion model it employs reflects local traffic exposures well. Additionally, we adjusted for various demographic and health-related covariates in our analyses.

There are also several limitations. The elderly participants in SALSA had a high prevalence of metabolic syndrome at baseline, shrinking our sample size and limiting the generalizability of our results to other age and ethnic groups. We lacked lifetime residential histories and information on potential use of sound-insulated windows, bedroom locations (facing the street) or the use of earplugs or other equipment (Fuks et al. 2017), which may have resulted in measurement error for both exposures. However, we expect that our participants' low mobility and the high percentage of retirees make it likely that they have been present in their homes during the day as well as nighttime which improves exposure assessment accuracy. In our study, NOx CALINE4 estimates solely represent the contribution from local traffic emissions,

without accounting for background pollution or contributions from traffic farther than 1500m away from the residence; thus, the estimated traffic-generated NOx concentrations are very low. Similarly, for noise, we only considered major roadway traffic as its source; i.e. the model does not include airport and railway noise or contributions from local small roadways. Thus noise levels overall are possibly underestimated. In addition, the noise model had to rely on limited traffic data specifically limited diurnal traffic flow pattern information such that we applied the same percentage of light and heavy duty vehicles to all roadways and hours of the day. This resulted – as expected – in high correlations between the two (daytime and nighttime) noise metrics. Selection bias due to loss of follow-up would be a concern if continued participation was dependent on exposure history and also differed between diseased and non-diseased. In our study, however, the percentage of subjects lost to follow-up was minimal (2.3% per year), and subjects were not asked to report environmental exposures or metabolic syndrome status. Thus, differential loss to follow-up due to awareness about exposures and disease status is unlikely. We additionally investigated the influences of NOx and noise exposure on mortality in prevalent cases at baseline and our results indicated that the influence of left truncation issue on results is minimal (Table S2-6 and S2-7). Additionally, if all of the noise effects on metabolic syndrome are assumed to be related to hearing but not vibrations, hearing loss may possibly contribute to differences between ambient and personal-level exposures. Thus, we repeated the analyses after either additionally adjusting for hearing loss status at baseline or after restricting to participants without hearing problems, this made no difference for our results (Table S2-8 and S2-9). We also repeated the analyses after additionally adjusting for baseline self-reported CVD/stroke or after deleting those with CVD/stroke at baseline and the results remained similar (Table S2-10 and S2-11), suggesting

that the estimated effects of exposure were not affected by baseline CVD/stroke status. Lastly, our study lacked information on diet and other unmeasured confounders. However, previous studies (Gilliland et al. 2003; Jerrett et al. 2014) found no or weak associations between caloric intake or carbohydrate consumption and noise or air pollution exposures making residual confounding due to these factors unlikely. Furthermore, the lack of an association between air pollution/noise exposure and obesity suggest that our results are not confounded by possible obesity-related lifestyle factors such as diet, because these would be expected to elevate the risk of obesity and we observed the opposite (Wallwork et al. 2017).

This study provides evidence that traffic-related NOx and noise elevate the risk of having lower HDL-cholesterol and metabolic syndrome in older Mexican-Americans. Prevention approaches therefore should not only target exhaust emissions but also traffic noise. Stricter emission controls and changes in land-use and transportation programs that encourage public transit, car-sharing, and active travel and generally reduce traffic may provide an effective avenue for reducing metabolic syndrome and generate large public health benefits.

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Co-authors contributions

Yu Yu conducted and interpreted the statistical analysis, and drafted the manuscript. Onyebuchi Arah, Elizabeth Rose Mayeda, Kimberly Paul and I-Fan Shih helped conduct and interpret statistical analyses. Eunice Lee, Michael Jerrett and Jason Su did the noise estimates and provided comments to the manuscript. Jun Wu contributed the traffic-related air pollution assessment and provided comments to manuscript. Mary Haan designed the study, and provided critical comments to manuscript. Beate Ritz obtained funding, interpreted statistical analysis, and helped writing of the manuscript.

2.6 Tables and Figures

Table 2-1. Characteristics of the participants used for incidence analyses at baseline, Sacramento Area Latino Study of Aging, 1998-2007.

	Total, No. (%)	Subpopulation used in metabolic syndrome and each individual symptom incidence analyses [a,b] , No. (%)[c]		
Baseline characteristics	(n=1554)	Metabolic syndrome (n=811)	Abdominal obesity (n=658)	Hypertension (n=636)
Baseline age, mean ± SD, years	70.7 ± 7.2	70.9 ± 7.6	70.9 ± 7.4	69.4 ± 6.7
Male	678 (43.6)	386 (47.6)	367 (55.8)	252 (39.6)
Years of education, mean ± SD, years	7.4 ± 5.3	7.4 ± 5.4	7.8 ± 5.4	7.4 ± 5.4
Sacramento County residence	1199 (77.2)	627 (77.3)	524 (79.6)	493 (77.5)
Urban Residence	1349 (86.8)	711 (87.7)	573 (87.1)	558 (87.7)
Birth country				
Mexico	699 (45.2)	386 (48.0)	299 (45.4)	299 (47.5)
United States	757 (48.9)	365 (45.3)	317 (48.2)	290 (46.0)
Others (i.e. Central or South America)	92 (5.9)	54 (6.7)	42 (6.4)	41 (6.5)
Occupation held during most of the lifetime				
Non-Manual	317 (20.8)	172 (21.7)	153 (23.7)	134 (21.6)
Manual	943 (61.7)	484 (61.2)	404 (62.4)	368 (59.3)
Other (Housewives and Unemployed)	268 (17.5)	135 (17.1)	90 (13.9)	119 (19.2)
Neighborhood socioeconomic status (NSES)				
Lowest NSES	526 (33.9)	264 (32.6)	220 (33.4)	206 (32.4)
Lower-Middle NSES	538 (34.6)	271 (33.5)	202 (30.7)	222 (34.9)
Middle NSES	340 (21.9)	193 (23.8)	172 (26.1)	148 (23.3)
Higher-Middle NSES	142 (9.1)	79 (9.8)	61 (9.3)	57 (9.0)
Highest NSES	8 (0.5)	3 (0.4)	3 (0.5)	3 (0.5)
Baseline smoking status				
Never/Non-Smoker	706 (45.7)	386 (48.1)	281 (42.8)	298 (47.4)
Former Smoker	655 (42.4)	315 (39.2)	272 (41.5)	247 (39.3)
Current Smoker	184 (11.9)	102 (12.7)	103 (15.7)	84 (13.4)
Baseline alcohol status				
Frequent (Daily) Drinker	147 (9.6)	93 (11.7)	81 (12.5)	53 (8.5)
Moderate (Weekly) Drinker	168 (11.0)	98 (12.3)	89 (13.7)	71 (11.3)
Occasional (Monthly) Drinker	147 (9.6)	81 (10.2)	64 (9.9)	59 (9.4)
Yearly/Rarely/Never Drinker	1071 (70.0)	525 (65.9)	415 (63.9)	443 (70.8)
Baseline high physical activity [d]	332 (21.4)	195 (24.0)	169 (25.7)	138 (21.7)
Baseline self-reported cardiovascular disease	540 (35.1)	241 (29.9)	203 (30.9)	185 (29.4)
Baseline self-reported stroke	135 (8.7)	59 (7.3)	51 (7.8)	38 (6.0)
Baseline BMI, mean ± SD	29.4 ± 5.8	27.8 ± 5.7	26.2 ± 4.1	28.9 ± 5.6

Traffic-related NOx, mean ± SD, ppb	2.6 ± 2.2	2.6 ± 2.2	2.6 ± 2.2	2.6 ± 2.1
24-hour noise, mean ± SD, dB	68.4 ± 8.7	68.5 ± 8.7	68.6 ± 8.9	68.2 ± 8.5
Nighttime (10PM - 7AM) noise, mean ± SD, dB	60.4 ± 8.7	60.4 ± 8.7	60.5 ± 8.9	60.1 ± 8.5

Note: HDL, high-density lipoprotein; SD, standard deviation; ppb, parts per billion; dB, decibels; BMI, body mass index; NOx, nitrogen oxides.

a. Definitions for metabolic syndrome and each individual symptom: (i) abdominal obesity: waist circumference of ≥ 40 inches in men; ≥ 35 inches in women); (ii) borderline elevation of blood glucose (fasting glucose ≥ 100 mg/dl, or use of glucose-lowering medications; (iii) elevated blood pressure (≥ 140/90 mmHg), or use of anti-hypertensive medication; (iv) elevated triglycerides (≥ 150 mg/dl), or use of statins; and (v) low high-density lipoprotein (HDL) cholesterol (men: < 40 mg/dl; women: < 50mg/dl), or use of statins. Metabolic syndrome was defined as the presence of three or more of these components.

b. In the main analyses, the participants with prevalent metabolic syndrome and individual components at baseline were excluded.

c. Percentages have been rounded and may not total 100.

d. Physical Activity measures were created by summing the MET-hour/week values over 8 activities that required a 3-fold or more increase over the metabolic rate required by quiet sitting (≥ 3 METs); specifically walking, dancing, hunting or camping or boating, swimming or engaging in workouts, golfing or other moderate exercise, gardening or yardwork, house repairs, and heavy housework. Then binary variables were generated by dichotomizing at 35 MET-hour/week as the cut-off. High physical activity was defined as MET scores ≥ 35 MET-hour/week.

Table 2-1 continued. Characteristics of the participants used for incidence analyses at baseline, Sacramento Area Latino Study of Aging, 1998-2007.

	Subpopulation used in metabolic syndrome and each individual symptom incidence analyses [a,b], No. (%)c		
Baseline characteristics	Hyperglycemia (n=892)	Hypertriglyceridemia (n=808)	Low HDL-cholesterol (n=1093)
Baseline age, mean ± SD, years	71.2 ± 7.3	71.4 ± 7.5	70.7 ± 7.3
Male	358 (40.1)	369 (45.7)	517 (47.3)
Years of education, mean ± SD, years	7.3 ± 5.3	6.9 ± 5.3	7.5 ± 5.3
Sacramento County residence	686 (76.9)	614 (76.0)	836 (76.5)
Urban Residence	777 (87.1)	705 (87.3)	955 (87.4)
Birth country			
Mexico	424 (47.9)	383 (47.8)	492 (45.3)
United States	398 (44.9)	370 (46.1)	535 (49.2)
Others (i.e. Central or South America)	64 (7.2)	49 (6.1)	60 (5.5)
Occupation held during most of the lifetime			
Non-Manual	185 (21.1)	158 (20.0)	229 (21.4)
Manual	539 (61.6)	486 (61.6)	671 (62.7)
Other (Housewives and Unemployed)	151 (17.3)	145 (18.4)	171 (16.0)
Neighborhood socioeconomic status (NSES)			
Lowest NSES	297 (33.3)	282 (34.9)	376 (34.4)
Lower-Middle NSES	319 (35.7)	273 (33.8)	361 (33.0)
Middle NSES	179 (20.1)	177 (21.9)	248 (22.7)
Higher-Middle NSES	93 (10.4)	73 (9.0)	102 (9.3)
Highest NSES	4 (0.5)	3 (0.4)	6 (0.6)
Baseline smoking status			
Never/Non-Smoker	430 (48.6)	381 (47.6)	499 (46.0)
Former Smoker	344 (38.9)	324 (40.5)	459 (42.3)
Current Smoker	110 (12.4)	95 (11.9)	127 (11.7)
Baseline alcohol status			
Frequent (Daily) Drinker	92 (10.5)	87 (11.0)	130 (12.1)
Moderate (Weekly) Drinker	109 (12.4)	82 (10.4)	132 (12.2)
Occasional (Monthly) Drinker	81 (9.2)	73 (9.2)	104 (9.6)
Yearly/Rarely/Never Drinker	595 (67.8)	550 (69.4)	713 (66.1)
Baseline high physical activity [d]	213 (23.9)	174 (21.5)	247 (22.6)
Baseline self-reported cardiovascular disease	288 (32.5)	279 (34.8)	356 (32.8)
Baseline self-reported stroke	65 (7.3)	68 (8.5)	88 (8.1)
Baseline BMI, mean ± SD	28.4 ± 5.5	29.0 ± 6.1	29.3 ± 6.0

Traffic-related NOx, mean ± SD, ppb	2.5 ± 2.1	2.6 ± 2.2	2.6 ± 2.2
24-hour noise, mean ± SD, dB	68.3 ± 8.7	68.5 ± 8.7	68.5 ± 8.8
Nighttime (10PM - 7AM) noise, mean ± SD, dB	60.2 ± 87	60.4 ± 8.7	60.4 ± 8.8

Note: HDL, high-density lipoprotein; SD, standard deviation; ppb, parts per billion; dB, decibels; BMI, body mass index; NOx, nitrogen oxides.

a. Definitions for metabolic syndrome and each individual symptom: (i) abdominal obesity: waist circumference of ≥ 40 inches in men; ≥ 35 inches in women); (ii) borderline elevation of blood glucose (fasting glucose ≥ 100 mg/dl, or use of glucose-lowering medications; (iii) elevated blood pressure (≥ 140/90 mmHg), or use of anti-hypertensive medication; (iv) elevated triglycerides (≥ 150 mg/dl), or use of statins; and (v) low high-density lipoprotein (HDL) cholesterol (men: < 40 mg/dl; women: < 50mg/dl), or use of statins. Metabolic syndrome was defined as the presence of three or more of these components.

b. In the main analyses, the participants with prevalent metabolic syndrome and individual components at baseline were excluded.

c. Percentages have been rounded and may not total 100.

d. Physical Activity measures were created by summing the MET-hour/week values over 8 activities that required a 3-fold or more increase over the metabolic rate required by quiet sitting (≥ 3 METs); specifically walking, dancing, hunting or camping or boating, swimming or engaging in workouts, golfing or other moderate exercise, gardening or yardwork, house repairs, and heavy housework. Then binary variables were generated by dichotomizing at 35 MET-hour/week as the cut-off. High physical activity was defined as MET scores ≥ 35 MET-hour/week.

Table 2-2. Effect estimates (and 95% CIs) from adjusted Cox models for traffic-related NOx exposure (per 2.29 ppb increase) and the risk of metabolic syndrome or each individual component.

Metabolic Syndrome OR Components [c]			***Crude Model*** [a]		***Adjusted Model*** [b]	
	Events	**Subjects**	**HR**	**95% CI**	**HR**	**95% CI**
Abdominal Obesity	200	658	0.86	(0.73, 1.02)	0.87	(0.74, 1.03)
Hypertension	433	636	1.02	(0.91, 1.14)	1.02	(0.91, 1.15)
Hyperglycemia	317	892	1.01	(0.89, 1.15)	1.01	(0.89, 1.15)
Hypertriglyceridemia	278	808	1.06	(0.93, 1.21)	1.03	(0.90, 1.18)
Low HDL-cholesterol	417	1093	1.16	(1.04, 1.28)	1.15	(1.04, 1.28)
Metabolic Syndrome	321	811	1.05	(0.93, 1.19)	1.04	(0.92, 1.17)

Note: HDL, high-density lipoprotein; ppb, parts per billion; 95% CI, 95% confidence interval; NOx, nitrogen oxides.

a. Adjusted for baseline age, gender, years of education.

b. Adjusted for baseline age, gender, years of education, neighborhood socioeconomic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status and physical activity level.

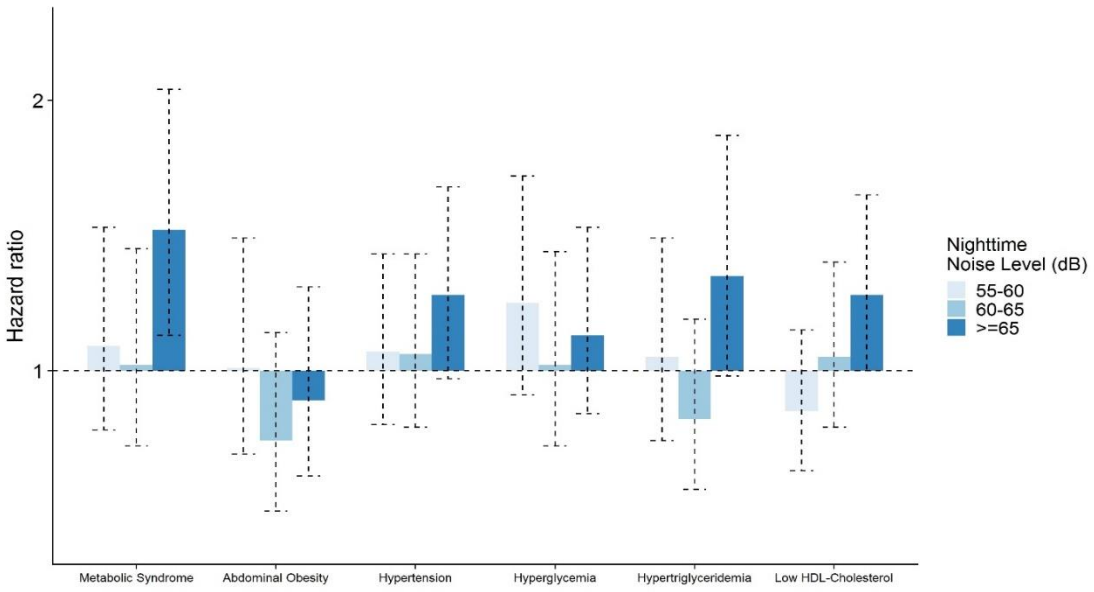
c. Definitions for metabolic syndrome and each individual symptom: (i) abdominal obesity: waist circumference of ≥ 40 inches in men; ≥ 35 inches in women); (ii) borderline elevation of blood glucose (fasting glucose ≥ 100 mg/dl, or use of glucose-lowering medications; (iii) elevated blood pressure (≥ 140/90 mmHg), or use of anti-hypertensive medication; (iv) elevated triglycerides (≥ 150 mg/dl), or use of statins; and (v) low high-density lipoprotein (HDL) cholesterol (men: < 40 mg/dl; women: < 50mg/dl), or use of statins. Metabolic syndrome was defined as the presence of three or more of these components.

Table 2-3. Effect estimates (and 95% CIs) from adjusted Cox models for 24-hour noise exposure (per 11.6 dB increase) and the risk of metabolic syndrome or each individual component.

Metabolic Syndrome OR Components [c]			***Crude Model*** [a]		***Adjusted Model*** [b]	
	Events	**Subjects**	**HR**	**95% CI**	**HR**	**95% CI**
Abdominal Obesity	200	658	0.90	(0.74, 1.09)	0.91	(0.75, 1.10)
Hypertension	433	636	1.10	(0.96, 1.25)	1.10	(0.96, 1.26)
Hyperglycemia	317	892	1.05	(0.90, 1.22)	1.06	(0.91, 1.23)
Hypertriglyceridemia	278	808	1.16	(0.99, 1.37)	1.14	(0.97, 1.34)
Low HDL-cholesterol	417	1093	1.11	(0.98, 1.27)	1.11	(0.98, 1.27)
Metabolic Syndrome	321	811	1.19	(1.03, 1.38)	1.17	(1.01, 1.35)

Note: HDL, high-density lipoprotein; dB, decibels; 95% CI, 95% confidence interval.
a. Adjusted for baseline age, gender, years of education.
b. Adjusted for baseline age, gender, years of education, neighborhood socioeconomic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status and physical activity level.
c. Definitions for metabolic syndrome and each individual symptom: (i) abdominal obesity: waist circumference of ≥ 40 inches in men; ≥ 35 inches in women); (ii) borderline elevation of blood glucose (fasting glucose ≥ 100 mg/dl, or use of glucose-lowering medications; (iii) elevated blood pressure (≥ 140/90 mmHg), or use of anti-hypertensive medication; (iv) elevated triglycerides (≥ 150 mg/dl), or use of statins; and (v) low high-density lipoprotein (HDL) cholesterol (men: < 40 mg/dl; women: < 50mg/dl), or use of statins. Metabolic syndrome was defined as the presence of three or more of these components.

(A)



(B)

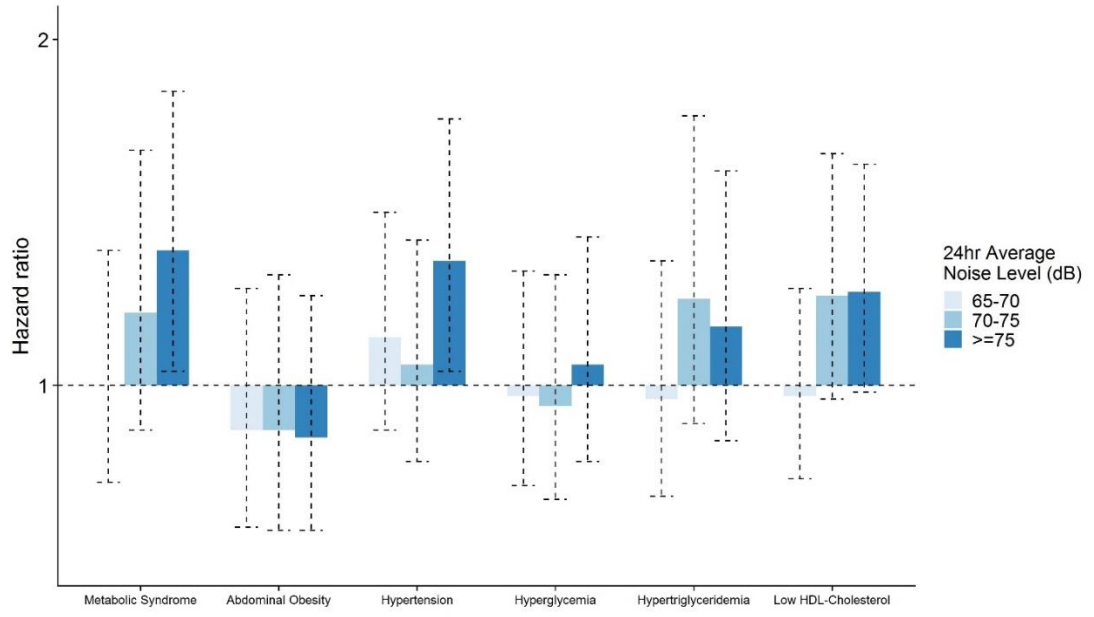


Figure 2-1. Effect estimates (and 95% confidence intervals) from adjusted Cox models for annual average of 24-hour (A) or nighttime noise (B) exposure at a quartile-based scale levels and the risk of metabolic syndrome or each individual component. (A) 24-hour noise level was divided into 4 categories (<65 dB, 65-70 dB, 70-75 dB, and ≥75 dB) according to (rounded) quartile values. The reference group included those with 24-hour average noise exposure <65 dB. P-value for trend are 0.02 for metabolic syndrome, 0.40 for abdominal obesity, 0.05 for hypertension, 0.81 for hyperglycemia, 0.21 for hypertriglyceridemia and 0.03 for low HDL-cholesterol. (B) Nighttime noise level was divided into 4 categories (<55 dB, 55-60 dB, 60-65 dB, and ≥ 65 dB). The reference group included those with nighttime noise exposure <55 dB. P-value for trend are 0.01 for metabolic syndrome, 0.34 for abdominal obesity, 0.09 for hypertension, 0.63 for hyperglycemia, 0.16 for hypertriglyceridemia and 0.03 for low HDL-cholesterol. Definitions for metabolic syndrome and each individual symptom: (i) abdominal obesity: waist circumference of ≥ 40 inches in men; ≥ 35 inches in women); (ii) borderline elevation of blood glucose (fasting glucose ≥ 100 mg/dl, or use of glucose-lowering medications; (iii) elevated blood pressure (≥

140/90 mmHg), or use of anti-hypertensive medication; (iv) elevated triglycerides (≥ 150 mg/dl), or use of statins; and (v) low high-density lipoprotein (HDL) cholesterol (men: < 40 mg/dl; women: < 50mg/dl), or use of statins. Metabolic syndrome was defined as the presence of three or more of these components. All models were adjusted for baseline age, gender, years of education, neighborhood socioeconomic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status and physical activity level. The dashed lines display the 95% confidence intervals.

2.7 Supplementary Tables and Figures

Table S2-1. Characteristics of the participants with prevalent metabolic syndrome or individual components at baseline, Sacramento Area Latino Study of Aging, 1998-2007.

	Subpopulation of metabolic syndrome and individual symptoms cases at baseline [a,b]					
	Metabolic syndrome (n=926)		Abdominal obesity (n=967)		Hypertension (n=1099)	
Baseline characteristics	N (%)	p-value [c]	N (%)	p-value [c]	N (%)	p-value [c]
Baseline age, mean ± SD, years	70.4 ± 6.7	0.20	70.3 ± 6.8	0.11	71.4 ± 7.3	0.01
Male	340 (36.7)	<0.01	303 (31.3)	<0.01	475 (43.1)	0.10
Years of education, mean ± SD, years	7.2 ± 5.3	0.71	7.1 ± 5.3	0.01	7.3 ± 5.3	0.90
Sacramento County residence	725 (78.3)	0.59	746 (77.2)	0.23	857 (78.0)	0.81
Urban residence	800 (86.4)	0.39	841 (87.0)	0.96	951 (86.5)	0.42
Birth country		<0.01		0.32		0.04
Mexico	398 (43.0)		429 (44.4)		482 (43.9)	
United States	487 (52.6)		491 (50.8)		562 (51.1)	
Others (i.e. Central or South America)	41 (4.4)		47 (4.9)		55 (5.0)	
Occupation held during most of the lifetime		0.53		<0.01		0.48
Non-Manual	193 (21.0)		195 (20.4)		230 (21.2)	
Manual	544 (59.2)		552 (57.6)		662 (60.9)	
Other (Housewives and Unemployed)	182 (19.8))		211 (22.0)		195 (17.9)	
Neighborhood socioeconomic status (NSES)		0.31		0.01		0.73
Lowest NSES	323 (34.9)		328 (33.9)		382 (34.8)	
Lower-Middle NSES	330 (35.6)		359 (37.1)		377 (34.3)	
Middle NSES	186 (20.1)		186 (19.2)		231 (21.0)	
Higher-Middle NSES	82 (8.9)		90 (9.3)		104 (9.5)	
Highest NSES	5 (0.5)		4 (0.4)		5 (0.5)	
Baseline smoking status		0.04		<0.01		0.07
Never/Non-Smoker	410 (44.3)		468 (48.5)		498 (45.4)	
Former Smoker	414 (44.8)		413 (42.8)		481 (43.9)	
Current Smoker	101 (10.9)		85 (8.8)		118 (10.8)	
Baseline alcohol status		<0.01		<0.01		0.70
Frequent (Daily) Drinker	59 (6.4)		59 (6.1)		100 (9.2)	
Moderate (Weekly) Drinker	82 (8.9)		87 (9.1)		108 (9.9)	
Occasional (Monthly) Drinker	80 (8.7)		91 (9.5)		102 (9.4)	
Yearly/Rarely/Never Drinker	698 (76.0)		724 (75.3)		778 (71.5)	
Baseline high physical activity [d]	162 (17.5)	<0.01	161 (16.7)	<0.01	220 (20.0)	0.55
Baseline self-reported cardiovascular disease	405 (43.7)	<0.01	391 (40.4)	<0.01	460 (41.9)	<0.01
Baseline self-reported stroke	104(11.2)	<0.01	95 (9.8)	0.14	125 (11.4)	<0.01
Baseline BMI, mean ± SD	31.3 ± 5.6	<0.01	32.1 ± 5.7	<0.01	30.2 ± 6.0	0.04

Traffic-related NOx, mean ± SD, ppb	2.6 ± 2.2	0.36	2.6 ± 2.1	0.58	2.6 ± 2.2	0.86
24-hour noise, mean ± SD, dB	68.6 ± 8.9	0.88	68.4 ± 8.9	0.72	68.7 ± 9.0	0.22
Nighttime (10PM - 7AM) noise, mean ± SD, dB	60.5 ± 8.9	0.88	60.4 ± 8.9	0.72	60.6 ± 9.0	0.22

Note: HDL, high-density lipoprotein; SD, standard deviation; ppb, parts per billion; dB, decibels; BMI, body mass index; NOx, nitrogen oxides.

a. Definitions for metabolic syndrome and each individual symptom: (i) abdominal obesity: waist circumference of ≥ 40 inches in men; ≥ 35 inches in women); (ii) borderline elevation of blood glucose (fasting glucose ≥ 100 mg/dl, or use of glucose-lowering medications; (iii) elevated blood pressure (≥ 140/90 mmHg), or use of anti-hypertensive medication; (iv) elevated triglycerides (≥ 150 mg/dl), or use of statins; and (v) low high-density lipoprotein (HDL) cholesterol (men: < 40 mg/dl; women: < 50mg/dl), or use of statins. Metabolic syndrome was defined as the presence of three or more of these components.

b. Theses subgroups were excluded from the main analyses.

c. P-value based on t-test or chi-square.

d. Physical Activity measures were created by summing the MET-hour/week values over 8 activities that required a 3-fold or more increase over the metabolic rate required by quiet sitting (≥ 3 METs); specifically walking, dancing, hunting or camping or boating, swimming or engaging in workouts, golfing or other moderate exercise, gardening or yardwork, house repairs, and heavy housework. Then binary variables were generated by dichotomizing at 35 MET-hour/week as the cut-off. High physical activity was defined as MET scores ≥ 35 MET-hour/week.

Table S2-1 continued. Characteristics of the participants with prevalent metabolic syndrome or individual components at baseline, Sacramento Area Latino Study of Aging, 1998-2007.

	Subpopulation of metabolic syndrome and individual symptoms cases at baseline [a,b]					
	Hyperglycemia (n=844)		Hypertriglyceridemia (n=928)		Low HDL cholesterol (n=642)	
Baseline characteristics	N (%)	p-value [c]	N (%)	p-value [c]	N (%)	p-value [c]
Baseline age, mean ± SD, years	70.1 ± 6.9	0.08	70.0 ± 6.6	<0.01	70.6 ± 6.8	0.04
Male	369 (43.8)	0.09	358 (38.6)	0.01	210 (32.7)	<0.01
Years of education, mean ± SD, years	7.3 ± 5.4	0.50	7.5 ± 5.4	0.48	6.9 ± 5.3	0.03
Sacramento County residence	667 (79.0)	0.22	738 (79.5)	0.07	514 (80.1)	0.08
Urban residence	734 (87.0)	0.93	806 (86.9)	0.80	554 (86.3)	0.48
Birth country		<0.01		0.03		0.95
Mexico	358 (42.4)		401 (43.2)		290 (45.1)	
United States	455 (53.9)		481 (51.8)		317 (49.5)	
Others (i.e. Central or South America)	31 (3.7)		46 (5.0)		35 (5.4)	
Occupation held during most of the lifetime		0.47		0.34		0.01
Non-Manual	180 (21.6)		207 (22.5)		136 (21.4)	
Manual	489 (58.6)		543 (59.0)		357 (56.0)	
Other (Housewives and Unemployed)	165 (19.8)		170 (18.5)		144 (22.6)	
Neighborhood socioeconomic status (NSES)		0.25		0.82		0.40
Lowest NSES	290 (34.3)		304 (32.8)		211 (32.9)	
Lower-Middle NSES	283 (33.5)		330 (35.6)		240 (37.4)	
Middle NSES	199 (23.6)		201 (21.7)		130 (20.3)	
Higher-Middle NSES	68 (8.1)		88 (9.5)		59 (9.2)	
Highest NSES	4 (0.5)		5 (0.5)		2 (0.3)	
Baseline smoking status		0.01		0.33		0.98
Never/Non-Smoker	365 (43.3)		414 (44.7)		296 (46.2)	
Former Smoker	385 (45.7)		404 (43.6)		268 (41.8)	
Current Smoker	93 (11.0)		109 (11.8)		77 (12.0)	
Baseline alcohol status		<0.01		0.07		<0.01
Frequent (Daily) Drinker	61 (7.3)		65 (7.0)		22 (3.5)	
Moderate (Weekly) Drinker	71 (8.5)		98 (10.6)		47 (7.4)	
Occasional (Monthly) Drinker	80 (9.5)		88 (9.5)		58 (9.1)	
Yearly/Rarely/Never Drinker	626 (74.7)		672 (72.8)		508 (80.0)	
Baseline high physical activity [d]	145 (17.2)	<0.01	183 (19.7)	0.41	110 (17.1)	0.01
Baseline self-reported cardiovascular disease	357 (42.3)	<0.01	366 (39.4)	0.03	288 (44.9)	<0.01
Baseline self-reported stroke	98 (11.6)	<0.01	95 (10.2)	0.21	75 (11.7)	0.01
Baseline BMI, mean ± SD	31.1 ± 6.0	0.01	30.3 ± 5.7	0.03	30.5 ± 5.7	0.12
Traffic-related NOx, mean ± SD, ppb	2.7 ± 2.2	0.59	2.6 ± 2.2	0.68	2.5 ± 2.2	0.49
24-hour noise, mean ± SD, dB	68.8 ± 8.9	0.64	68.6 ± 9.0	0.32	68.5 ± 8.9	0.88

Nighttime (10PM - 7AM) noise, mean ± SD, dB	60.7 ± 8.9	0.63	60.5 ± 9.0	0.32	60.5 ± 8.8	0.88

Note: HDL, high-density lipoprotein; SD, standard deviation; ppb, parts per billion; dB, decibels; BMI, body mass index; NOx, nitrogen oxides.

a. Definitions for metabolic syndrome and each individual symptom: (i) abdominal obesity: waist circumference of ≥ 40 inches in men; ≥ 35 inches in women); (ii) borderline elevation of blood glucose (fasting glucose ≥ 100 mg/dl, or use of glucose-lowering medications; (iii) elevated blood pressure (≥ 140/90 mmHg), or use of anti-hypertensive medication; (iv) elevated triglycerides (≥ 150 mg/dl), or use of statins; and (v) low high-density lipoprotein (HDL) cholesterol (men: < 40 mg/dl; women: < 50mg/dl), or use of statins. Metabolic syndrome was defined as the presence of three or more of these components.

b. Theses subgroups were excluded from the main analyses.

c. P-value based on t-test or chi-square.

d. Physical Activity measures were created by summing the MET-hour/week values over 8 activities that required a 3-fold or more increase over the metabolic rate required by quiet sitting (≥ 3 METs); specifically walking, dancing, hunting or camping or boating, swimming or engaging in workouts, golfing or other moderate exercise, gardening or yardwork, house repairs, and heavy housework. Then binary variables were generated by dichotomizing at 35 MET-hour/week as the cut-off. High physical activity was defined as MET scores ≥ 35 MET-hour/week.

Table S2-2. Distributions of traffic-related NOx and noise exposure.

Metabolic Syndrome OR Components [a]	Subject	Mean	Variance	Percentile								
				0	5	10	25	50	75	90	95	100
				Traffic-related NOx (ppb)								
Total	1554	2.60	4.70	0.01	0.42	0.67	1.15	1.90	3.44	5.30	6.93	13.20
Metabolic Syndrome	811	2.60	4.84	0.01	0.42	0.67	1.16	1.90	3.33	5.46	7.00	13.20
Abdominal Obesity	658	2.59	4.72	0.01	0.45	0.66	1.15	2.00	3.36	5.15	6.78	13.20
Hypertension	636	2.55	4.61	0.01	0.42	0.66	1.10	1.85	3.33	5.22	7.15	12.20
Hyperglycemia	892	2.50	4.60	0.01	0.37	0.65	1.09	1.81	3.12	5.25	6.80	13.20
Hypertriglyceridemia	808	2.57	4.60	0.01	0.37	0.67	1.17	1.86	3.29	5.31	6.75	13.20
Low HDL-cholesterol	1093	2.64	4.79	0.01	0.42	0.68	1.17	1.95	3.56	5.46	6.82	13.20
				24- hour Noise dB)								
Total	1554	68.43	76.14	39.40	55.20	57.60	62.50	67.65	74.10	80.80	84.20	100.00
Metabolic Syndrome	811	68.47	76.51	39.40	55.30	57.70	62.40	67.50	74.20	81.00	84.20	92.60
Abdominal Obesity	658	68.58	78.91	39.40	55.10	57.50	62.60	67.55	74.50	81.40	84.40	92.60
Hypertension	636	68.18	72.24	39.40	54.80	57.60	62.65	67.40	73.30	80.20	83.50	90.00
Hyperglycemia	892	68.26	75.53	39.40	55.20	57.70	62.10	67.30	74.20	80.60	83.80	92.60
Hypertriglyceridemia	808	68.43	73.73	39.40	55.90	58.10	62.60	67.40	73.70	80.90	84.40	100.00
Low HDL-cholesterol	1093	68.51	76.67	39.40	55.30	57.60	62.40	68.00	74.20	80.90	84.40	100.00
				Nighttime (10PM - 7AM) Noise (dB)								
Total	1554	60.35	76.17	31.40	47.20	49.50	54.40	59.55	66.00	72.80	76.10	91.90
Metabolic Syndrome	811	60.40	76.54	31.40	47.20	49.60	54.30	59.40	66.10	73.00	76.10	84.50
Abdominal Obesity	658	60.51	78.96	31.40	47.00	49.40	54.40	59.50	66.40	73.30	76.30	84.50
Hypertension	636	60.11	72.24	31.40	46.70	49.50	54.55	59.30	65.20	72.20	75.50	82.00
Hyperglycemia	892	60.18	75.53	31.40	47.10	49.60	54.10	59.20	66.10	72.50	75.70	84.50
Hypertriglyceridemia	808	60.35	73.77	31.40	47.80	50.10	54.50	59.30	65.60	72.80	76.30	91.90
Low HDL-cholesterol	1093	60.44	76.72	31.40	47.20	49.50	54.30	60.00	66.10	72.80	76.30	91.90

Note: HDL, high-density lipoprotein; ppb, parts per billion; dB, decibels; NOx, nitrogen oxides.

a. Definitions for metabolic syndrome and each individual symptom: (i) abdominal obesity: waist circumference of ≥ 40 inches in men; ≥ 35 inches in women); (ii) borderline elevation of blood glucose (fasting glucose ≥ 100 mg/dl, or use of glucose-lowering medications; (iii) elevated blood pressure (≥ 140/90 mmHg), or use of anti-hypertensive medication; (iv) elevated triglycerides (≥ 150 mg/dl), or use of statins; and (v) low high-density lipoprotein (HDL) cholesterol (men: < 40 mg/dl; women: < 50mg/dl), or use of statins. Metabolic syndrome was defined as the presence of three or more of these components.

Table S2-3. Pearson correlations between traffic-related NOx and noise exposures.

	Traffic-related NOx	24-hour noise
Traffic-related NOx	-	-
24-hour noise	0.41	-
Nighttime (10PM─7AM) noise	0.41	1.00

Note: NOx, nitrogen oxides.

Table S2-4. Effect estimates (and 95% CIs) from adjusted Cox models [a] for noise exposure (categorical variables) and metabolic syndrome or each individual component.

Metabolic Syndrome OR Components [b]			24-hour noise exposure ≥ 65 dB (Ref. group: 24hr Noise exposure < 65 dB)		Nighttime noise exposure ≥ 55 dB (Ref. group: Nighttime Noise exposure <55 dB)	
	Events	**Subjects**	**HR**	**95% CI**	**HR**	**95% CI**
Abdominal Obesity	200	658	0.87	(0.65, 1.16)	0.89	(0.65, 1.22)
Hypertension	433	636	1.19	(0.96, 1.47)	1.14	(0.91, 1.44)
Hyperglycemia	317	892	1.00	(0.79, 1.26)	1.14	(0.88, 1.46)
Hypertriglyceridemia	278	808	1.12	(0.86, 1.44)	1.08	(0.82, 1.42)
Low HDL-cholesterol	417	1093	1.16	(0.94, 1.43)	1.08	(0.87, 1.34)
Metabolic Syndrome	321	811	1.21	(0.95, 1.53)	1.23	(0.95, 1.60)

Note: HDL, high-density lipoprotein; dB, decibels; 95% CI, 95% confidence interval.

a. Adjusted for baseline age, gender, years of education, neighborhood socioeconomic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status and physical activity level.

b. Definitions for metabolic syndrome and each individual symptom: (i) abdominal obesity: waist circumference of ≥ 40 inches in men; ≥ 35 inches in women); (ii) borderline elevation of blood glucose (fasting glucose ≥ 100 mg/dl, or use of glucose-lowering medications; (iii) elevated blood pressure (≥ 140/90 mmHg), or use of anti-hypertensive medication; (iv) elevated triglycerides (≥ 150 mg/dl), or use of statins; and (v) low high-density lipoprotein (HDL) cholesterol (men: < 40 mg/dl; women: < 50mg/dl), or use of statins. Metabolic syndrome was defined as the presence of three or more of these components.

Table S2-5. Effect estimates (and 95% CIs) from adjusted Cox models [a] for traffic-related NOx and noise exposures and metabolic syndrome or each individual component.

	Metabolic Syndrome OR Components[b]					
Air Pollutants	Metabolic syndrome (n=811)	Abdominal obesity (n=658)	Hypertension (n=636)	Hypergly-cemia (n=892)	Hypertrigly-ceridemia (n=808)	Low HDL-cholesterol (n=1093)
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Traffic-related NOx exposure, per 2.29 ppb increase	0.98 (0.86, 1.13)	0.87 (0.73, 1.05)	0.99 (0.88, 1.12)	0.99 (0.86, 1.14)	0.98 (0.84, 1.13)	1.14 (1.01, 1.27)
24-hour noise exposure, per 11.6 dB increase	1.18 (1.00, 1.38)	0.97 (0.79, 1.20)	1.11 (0.96, 1.27)	1.06 (0.90, 1.25)	1.15 (0.96, 1.38)	1.05 (0.91, 1.21)
Traffic-related NOx exposure, per 2.29 ppb increase	0.98 (0.86, 1.12)	0.87 (0.73, 1.05)	0.99 (0.88, 1.12)	0.99 (0.86, 1.14)	0.98 (0.84, 1.13)	1.14 (1.01, 1.27)
Nighttime noise exposure, per 11.6 dB increase	1.18 (1.01, 1.38)	0.97 (0.79, 1.20)	1.11 (0.96, 1.27)	1.06 (0.90, 1.25)	1.15 (0.96, 1.38)	1.05 (0.91, 1.21)

Note: HDL, high-density lipoprotein; ppb, parts per billion; dB, decibels; 95% CI, 95% confidence interval; NOx, nitrogen oxides.
a. Adjusted for baseline age, gender, years of education, neighborhood socioeconomic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status and physical activity level.
b. Definitions for metabolic syndrome and each individual symptom: (i) abdominal obesity: waist circumference of ≥ 40 inches in men; ≥ 35 inches in women); (ii) borderline elevation of blood glucose (fasting glucose ≥ 100 mg/dl, or use of glucose-lowering medications; (iii) elevated blood pressure (≥ 140/90 mmHg), or use of anti-hypertensive medication; (iv) elevated triglycerides (≥ 150 mg/dl), or use of statins; and (v) low high-density lipoprotein (HDL) cholesterol (men: < 40 mg/dl; women: < 50mg/dl), or use of statins. Metabolic syndrome was defined as the presence of three or more of these components.

Table S2-6. Cross-sectional analyses [a] for traffic-related NOx and ambient noise exposures and metabolic syndrome or each individual component at baseline.

	Traffic-related NOx exposure, per 2.29 ppb increase	24-hour noise, per 11.6 dB increase
Metabolic Syndrome OR Components [b]	OR (95% CI)	OR (95% CI)
Metabolic Syndrome	0.98 (0.89, 1.08)	0.97 (0.85, 1.10)
Abdominal Obesity	0.99 (0.88, 1.10)	0.95 (0.83, 1.09)
Hypertension	1.05 (0.95, 1.16)	1.06 (0.93, 1.20)
Hyperglycemia	1.10 (0.99, 1.21)	1.06 (0.94, 1.21)
Hypertriglyceridemia	1.01 (0.91, 1.12)	1.00 (0.88, 1.14)
Low HDL-cholesterol	0.93 (0.84, 1.04)	0.95 (0.83, 1.09)

Note: HDL, high-density lipoprotein; ppb, parts per billion; dB, decibels; 95% CI, 95% confidence interval; NOx, nitrogen oxides.

a. Adjusted for baseline age, gender, years of education, neighborhood socioeconomic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status and physical activity level.

b. Definitions for metabolic syndrome and each individual symptom: (i) abdominal obesity: waist circumference of ≥ 40 inches in men; ≥ 35 inches in women); (ii) borderline elevation of blood glucose (fasting glucose ≥ 100 mg/dl, or use of glucose-lowering medications; (iii) elevated blood pressure (≥ 140/90 mmHg), or use of anti-hypertensive medication; (iv) elevated triglycerides (≥ 150 mg/dl), or use of statins; and (v) low high-density lipoprotein (HDL) cholesterol (men: < 40 mg/dl; women: < 50mg/dl), or use of statins. Metabolic syndrome was defined as the presence of three or more of these components.

Table S2-7. Effect estimates (and 95% CIs) from adjusted Cox models [a] for traffic-related NOx and ambient noise exposures and mortality.

Including prevalent cases at baseline						
Metabolic Syndrome OR Components [b]			Traffic-Related NOx exposure, per 2.29 ppb increase		24-hour noise, per 11.6 dB increase	
	Events	**Subjects**	**HR**	**95% CI**	**HR**	**95% CI**
Abdominal Obesity	335	967	1.05	(0.93, 1.19)	1.01	(0.87, 1.18)
Hypertension	459	1099	0.99	(0.89, 1.09)	1.06	(0.93, 1.21)
Hyperglycemia	358	844	1.08	(0.97, 1.20)	1.13	(0.97, 1.31)
Hypertriglyceridemia	312	928	1.00	(0.89, 1.12)	1.04	(0.89, 1.21)
Low HDL-cholesterol	253	642	1.01	(0.88, 1.16)	1.05	(0.88, 1.27)
Metabolic Syndrome	362	926	1.03	(0.92, 1.15)	1.05	(0.91, 1.23)
Excluding prevalent cases at baseline						
Metabolic Syndrome OR Components [b]			Traffic-Related NOx exposure, per 2.29 ppb increase		24-hour noise, per 11.6 dB increase	
	Events	**Subjects**	**HR**	**95% CI**	**HR**	**95% CI**
Abdominal Obesity	178	664	1.21	(0.95, 1.32)	1.22	(0.99, 1.49)
Hypertension	133	684	1.32	(1.07, 1.64)	1.02	(0.77, 1.35)
Hyperglycemia	211	939	1.03	(0.85, 1.25)	1.03	(0.84, 1.26)
Hypertriglyceridemia	246	855	1.11	(0.94, 1.31)	1.13	(0.93, 1.36)
Low HDL-cholesterol	281	1141	1.23	(1.07, 1.42)	1.14	(0.96, 1.36)
Metabolic Syndrome	206	857	1.19	(1.00, 1.42)	1.14	(0.92, 1.41)

Note: HDL, high-density lipoprotein; ppb, parts per billion; dB, decibels; 95% CI, 95% confidence interval; NOx, nitrogen oxides.

a. Adjusted for baseline age, gender, years of education, neighborhood socioeconomic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status and physical activity level.

b. Definitions for metabolic syndrome and each individual symptom: (i) abdominal obesity: waist circumference of ≥ 40 inches in men; ≥ 35 inches in women); (ii) borderline elevation of blood glucose (fasting glucose ≥ 100 mg/dl, or use of glucose-lowering medications; (iii) elevated blood pressure (≥ 140/90 mmHg), or use of anti-hypertensive medication; (iv) elevated triglycerides (≥ 150 mg/dl), or use of statins; and (v) low high-density lipoprotein (HDL) cholesterol (men: < 40 mg/dl; women: < 50mg/dl), or use of statins. Metabolic syndrome was defined as the presence of three or more of these components.

Table S2-8. Effect estimates (and 95% CIs) from adjusted Cox models of traffic-related NOx exposure (per 2.29 ppb increase) on the risk of Metabolic Syndrome and each individual component, after considering baseline hearing loss status.

Metabolic Syndrome OR Components [a]	***Adjusted Model 1*** [b]		***Adjusted Model 2*** [c]	
	HR	**95% CI**	**HR**	**95% CI**
Abdominal Obesity	0.87	(0.74, 1.03)	0.92	(0.76, 1.10)
Hypertension	1.03	(0.92, 1.16)	1.03	(0.94, 1.19)
Hyperglycemia	1.02	(0.90, 1.16)	1.10	(0.96, 1.27)
Hypertriglyceridemia	1.02	(0.89, 1.17)	1.06	(0.90, 1.24)
Low HDL-cholesterol	1.15	(1.03, 1.27)	1.17	(1.03, 1.33)
Metabolic Syndrome	1.03	(0.91, 1.16)	1.06	(0.92, 1.22)

Note: HDL, high-density lipoprotein; NOx, nitrogen oxides; 95% CI, 95% confidence interval.
a. Outcome definition: 1) abdominal obesity: waist circumference, men: >= 40 inches; women >= 35 inches); 2) hyperglycemia: borderline elevations of blood glucose (fasting glucose >= 100 mg/dl), or use of medication; 3) hypertension: elevated blood pressure (>= 140/90 mmHg), or use of medication; 4) hypertriglyceridemia: elevated triglycerides (>= 150 mg/dl), or use of medication; and 5) low HDL cholesterol: men: < 40 mg/dl; women: < 50mg/dl, or use of medication. A binary categorical variable for each metabolic syndrome component was created.
b. Adjusted for baseline age, gender, years of education, neighborhood social economic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status, physical activity level, and hearing loss status at baseline.
c. Adjusted for baseline age, gender, years of education, neighborhood social economic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status and physical activity level, restricting to those without hearing problems at baseline.

Table S2-9. Effect estimates (and 95% CIs) from adjusted Cox models of ambient noise exposure (per 11.6 dB increase) on the risk of Metabolic Syndrome and each individual component, after considering baseline hearing loss status.

Metabolic Syndrome OR Components [a]	***Adjusted Model 1*** [b]		***Adjusted Model 2*** [c]	
	HR	**95% CI**	**HR**	**95% CI**
Abdominal Obesity	0.91	(0.74, 1.10)	0.98	(0.80, 1.23)
Hypertension	1.10	(0.96, 1.27)	1.12	(0.97, 1.30)
Hyperglycemia	1.05	(0.91, 1.23)	1.10	(0.93, 1.30)
Hypertriglyceridemia	1.13	(0.95, 1.33)	1.19	(0.99, 1.43)
Low HDL-cholesterol	1.10	(0.96, 1.25)	1.10	(0.95, 1.27)
Metabolic Syndrome	1.15	(0.99, 1.33)	1.23	(1.05, 1.46)

Note: HDL, high-density lipoprotein; ppb, parts per billion; dB, decibels; 95% CI, 95% confidence interval.
a. Outcome definition: 1) abdominal obesity: waist circumference, men: >= 40 inches; women >= 35 inches); 2) hyperglycemia: borderline elevations of blood glucose (fasting glucose >= 100 mg/dl), or use of medication; 3) hypertension: elevated blood pressure (>= 140/90 mmHg), or use of medication; 4) hypertriglyceridemia: elevated triglycerides (>= 150 mg/dl), or use of medication; and 5) low HDL cholesterol: men: < 40 mg/dl; women: < 50mg/dl, or use of medication. A binary categorical variable for each metabolic syndrome component was created.
b. Adjusted for baseline age, gender, years of education, neighborhood social economic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status, physical activity level, and hearing loss status at baseline.
c. Adjusted for baseline age, gender, years of education, neighborhood social economic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status and physical activity level, restricting to those without hearing problems at baseline.

Table S2-10. Effect estimates (and 95% CIs) from adjusted Cox models of traffic-related NOx exposure (per 2.29 ppb increase) on the risk of Metabolic Syndrome and each individual component, after considering baseline self-reported CVD and stroke status.

Metabolic Syndrome OR Components [a]	***Adjusted Model 1*** [b]		***Adjusted Model 2*** [c]	
	HR	**95% CI**	**HR**	**95% CI**
Abdominal Obesity	0.87	(0.74, 1.02)	0.76	(0.61, 0.94)
Hypertension	1.03	(0.92, 1.16)	1.04	(0.91, 1.19)
Hyperglycemia	1.02	(0.90, 1.16)	1.00	(0.85, 1.16)
Hypertriglyceridemia	1.04	(0.91, 1.20)	1.05	(0.88, 1.26)
Low HDL-cholesterol	1.15	(1.04, 1.28)	1.15	(1.01, 1.31)
Metabolic Syndrome	1.04	(0.92, 1.17)	1.07	(0.93, 1.24)

Note: HDL, high-density lipoprotein; ppb, parts per billion; NOx, nitrogen oxides; 95% CI, 95% confidence interval; CVD, cardiovascular disease.

a. Outcome definition: 1) abdominal obesity: waist circumference, men: >= 40 inches; women >= 35 inches); 2) hyperglycemia: borderline elevations of blood glucose (fasting glucose >= 100 mg/dl), or use of medication; 3) hypertension: elevated blood pressure (>= 140/90 mmHg), or use of medication; 4) hypertriglyceridemia: elevated triglycerides (>= 150 mg/dl), or use of medication; and 5) low HDL cholesterol: men: < 40 mg/dl; women: < 50mg/dl, or use of medication. A binary categorical variable for each metabolic syndrome component was created.

b. Adjusted for baseline age, gender, years of education, neighborhood social economic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status, physical activity level additionally adjusted with baseline self-reported CVD and stroke status.

c. Adjusted for baseline age, gender, years of education, neighborhood social economic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status and physical activity level, restricting with those participants without self-reported CVD and stroke at baseline.

Table S2-11. Effect estimates (and 95% CIs) from adjusted Cox models of ambient noise exposure (per 11.6 dB increase) on the risk of Metabolic Syndrome and each individual component, after considering baseline self-reported CVD and stroke status.

Metabolic Syndrome OR Components [a]	***Adjusted Model 1*** [b]		***Adjusted Model 2*** [c]	
	HR	**95% CI**	**HR**	**95% CI**
Abdominal Obesity	0.91	(0.75, 1.10)	0.85	(0.67, 1.08)
Hypertension	1.09	(0.95, 1.25)	1.15	(0.98, 1.35)
Hyperglycemia	1.04	(0.89, 1.21)	1.05	(0.86, 1.27)
Hypertriglyceridemia	1.09	(0.93, 1.29)	1.15	(0.92, 1.45)
Low HDL-cholesterol	1.10	(0.97, 1.26)	1.07	(0.91, 1.25)
Metabolic Syndrome	1.13	(0.98, 1.31)	1.14	(0.95, 1.37)

Note: HDL, high-density lipoprotein; ppb, parts per billion; dB, decibels; 95% CI, 95% confidence interval; CVD, cardiovascular disease.

a. Outcome definition: 1) abdominal obesity: waist circumference, men: >= 40 inches; women >= 35 inches); 2) hyperglycemia: borderline elevations of blood glucose (fasting glucose >= 100 mg/dl), or use of medication; 3) hypertension: elevated blood pressure (>= 140/90 mmHg), or use of medication; 4) hypertriglyceridemia: elevated triglycerides (>= 150 mg/dl), or use of medication; and 5) low HDL cholesterol: men: < 40 mg/dl; women: < 50mg/dl, or use of medication. A binary categorical variable for each metabolic syndrome component was created.

b. Adjusted for baseline age, gender, years of education, neighborhood social economic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status, physical activity level additionally adjusted with baseline self-reported CVD and stroke status.

c. Adjusted for baseline age, gender, years of education, neighborhood social economic status indicator, occupation during most of life, baseline smoking status, baseline alcohol consumption status and physical activity level, restricting with those participants without self-reported CVD and stroke at baseline.

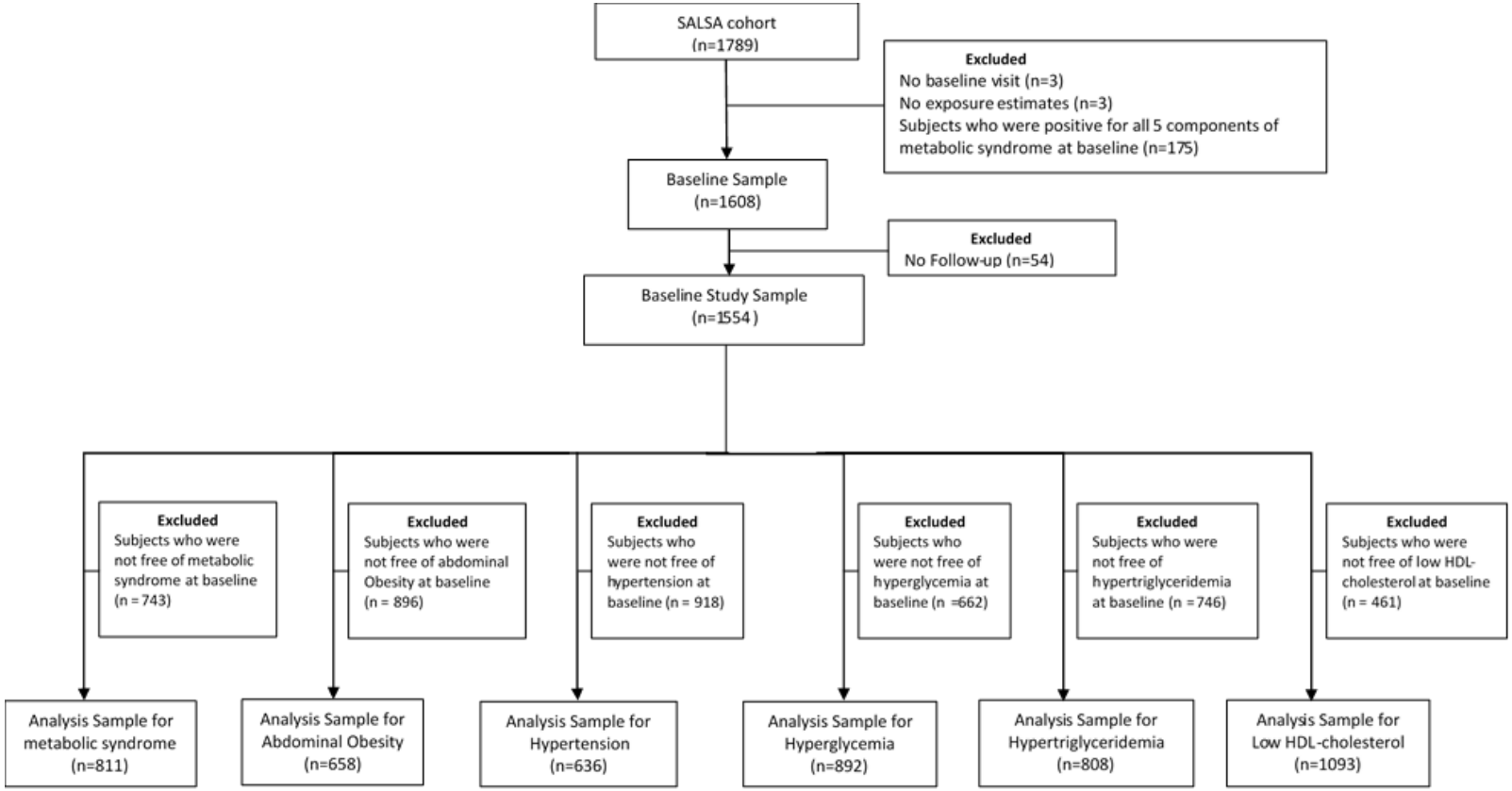


Figure S2-1. Flow chart of study participants, Sacramento Area Latino Study on Aging (SALSA), 1998 to 2007.

Chapter 3. Traffic-Related Noise Exposure on Late-life Dementia and Cognitive Impairment in Mexican-Americans

3.1 Abstract

Introduction: Recently, it has been suggested that environmental exposures from traffic sources including noise may play a role in cognitive impairment in the elderly. The objective of the study was to investigate the association between local traffic-related noise pollution and incident dementia, cognitive impairment without dementia (CIND) during a 10-year follow-up period.

Methods: 1,612 Mexican-American participants from the Sacramento Area Latino Study on Aging (SALSA) were followed every 12-15 months via home visits from 1998 to 2007. We used the SoundPLAN software package to estimate local noise originating from traffic with the input of Annual Average Daily Traffic (AADT) data from Metropolitan Planning Organizations (MPO) based on geocoded residential addresses at baseline (1998-99). We estimated the risks of incident dementia/CIND from 24-hour and nighttime noise exposure using Cox proportional hazard models.

Results: During the follow-up, 159 incident dementia/CIND cases were identified in total. Per 11.6dB (interquartile range, IQR) increase in 24-hour noise, the hazard of developing dementia/CIND increased (HR = 1.24, 95% CI =1.00, 1.53) during follow-up; estimates were slightly lower (HR = 1.19, 95% CI = 0.95, 1.49) when adjusting for modeled local air pollution exposure from traffic sources. Overall, the risk of dementia/CIND was elevated when 24-hour and nighttime noise were higher than 75 dB and 65 dB respectively.

Discussion: Traffic-related noise exposure increases risks of dementia/CIND in elderly Mexican-Americans. Programs to reduce traffic noise are needed to mitigate the development of cognitive impairment in vulnerable populations.

3.2 Introduction

Cognitive impairment is a major concern for older adults due to its relationship with morbidity and mortality. It also reduces health related quality of life and increases caregiver burden. In societies with increasing life expectancy and aging populations, preventing these outcomes becomes ever more urgent (Paul et al. 2019). According to the Alzheimer's Association in 2018, ~5.7 million people are living with dementia in the US, and by 2060 it projects that the prevalence of Alzheimer's disease (AD) will reach 13.9 million (Matthews et al. 2019). Possible or established risk factors for cognitive impairment include age, family history, apolipoprotein E (APOE) ε4, cardiovascular disease, diabetes, hypertension, and life style factors such as smoking and alcohol consumption (https://www.mayoclinic.org/diseases-conditions/dementia/symptoms-causes/syc-20352013).

Recently, studies have indicated that environmental exposures including air pollution from traffic sources are consistently associated not only with cardiovascular and respiratory diseases and all-cause mortality (Lim et al. 2012; Stieb et al. 2012), but also with cognitive impairment (Tzivian et al. 2015). Most epidemiological studies focused on investigating the association between air pollution and cognition function, however, the role of noise in relation to cognitive impairment is far less studied. Those studies that examined the influence of noise exposures mostly measured short-terms effects, or used cross-sectional or case-control study designs

(Tzivian et al. 2015). To our knowledge, to date there are three longitudinal studies in Switzerland (Brink 2011), France (Bocquier et al. 2014) and England (Carey et al. 2018) investigating traffic-related noise exposure but none of them has explored the influence of long-term noise exposure on the incidence of dementia/CIND in Mexican-Americans, a fast-growing and vulnerable segment of the US elderly population.

The objective of our study was to investigate whether residential-based traffic-related noise exposure at baseline increases the risk of dementia/CIND in older Mexican-Americans over 10 years of follow-up.

3.3 Methods

Research Ethics

All procedures described here were approved by the Institutional Review Boards of the University of California San Francisco, Los Angeles, and Davis, University of North Carolina, and the University of Michigan.

Study population

We relied on data from the Sacramento Area Latino Study on Aging (SALSA), a prospective cohort study of older Mexican-Americans which was originally designed to evaluate the effects of metabolic or cardiovascular risk factors for dementia and cognitive decline. Participants were eligible if (i) they were 60 years of age or older, (ii) resided in the six counties of the California Sacramento Valley (Sacramento, Yolo, Sutter, Solano, Yuba, and Placer counties), and (iii) self-identified as Mexican (78.4%), Latino (6%), Hispanic (10.8%), Anglo (1.6%),

Chicano (1.16%) or other (1.8%). Of those eligible and contacted, 83.5% agreed to be in the study. 1789 participants were recruited in 1998 to 1999 and interviewed at their homes; and they were re-contacted every 12–15 months for up to seven study visits, ending in December 2007. Between home visits, a 10-minute phone call was made every 6 months to update contact information, health status and change in medication information. The average annual attrition rate from mortality and loss to follow-up was 2.6% and 2.3% respectively. The average length of follow-up was 6.5 years and the maximum was 10 years (Haan et al. 2003). The written informed consent was provided by all the participants. Those who (1) did not participate in the interview at baseline (n=3), (2) lived too far away from traffic sources to generate noise measures (n=3), (3) already had CIND/dementia at baseline (n=114), (4) did not have a follow-up visit (n=57) were excluded, leaving 1,612 participants in total for this analysis (Figure3-1).

Outcome measurement

Two cognitive screening tests - the Modified Mini–Mental State Examination (3MSE) and a delayed word recall trial from the Spanish English Verbal Learning Test (SEVLT) – were administered to each patient at baseline and follow-up visits. A geriatrician referred the participants for a neuropsychological test battery and a standard neuropsychological examination (Informant Questionnaire on Cognitive Decline in the Elderly) if their scores (1) were below the 20th percentile at baseline on the 3MSE or SEVLT, or (2) had decreased ≥ 8 points on the 3MSE or ≥ 3 points on the SEVLT between baseline and follow-up. These cases were reviewed by a team of neurologists and neuropsychologist and given a diagnosis of ‘cognitively normal’, ‘cognitively impaired but not dementia (CIND)’ or ‘dementia’ according to standard diagnostic criteria. Those diagnosed with dementia and CIND were also referred for

a magnetic resonance imaging (MRI) examination (American Psychiatric Association 2000). Detailed procedures for dementia and CIND screening and classification are described elsewhere (Haan et al. 2003). Here, all-cause dementia and CIND were combined to capture both cognitive decline prior to dementia and dementia to improve our statistical power.

Noise Exposure measurement

The SoundPLAN (Version 8.0, NAVCON, Fullerton, CA, USA) software package was used to estimate the ambient noise exposure levels during the baseline year based on AADT data we received from the local MPO. The noise prediction model — Federal Highway Administration (FHWA) Traffic Noise Model (TNM) - was implemented in SoundPLAN. Each subject's geocoded residential address at baseline was used as the receiver point, and the TNM algorithm estimated the noise levels from the following input - speed of the vehicles, counts of different types of vehicles, ground classification (soft vs. hard ground), and distance from receptor points to the roadway (Seong et al. 2011). More information about the TNM has been detailed elsewhere (US_DOT 1998, 2002). Average diurnal traffic patterns were calculated using hourly traffic counts we obtained from the State Department of Transportation (DOT) in 2002, these were also used to adjust the MPO AADT values to generate hour-of-day specific traffic counts at each receptor point. A-weighted day-night average (Ldn) and nighttime (22:00–07:00, Leq,n) sound levels were estimated for each participant's residence. A constant penalty of 10dB for noise during the nighttime was added to allow for a potentially higher sensitivity to noise during nighttime hours, as has been done previously (Fecht et al. 2016).

Thus, only roadway traffic was considered a source of noise in our study. Also, we only counted the FHWA classified light and heavy-duty vehicles and assumed that the average vehicle speed was 55 miles per hour when we generated noise estimates. Noise exposure metrics were generated as 24-hour averages (A-weighted) and nighttime averages (22:00–07:00). Noise exposures estimates were treated as both continuous and categorical variables (24-hour average noise: < 65 dB, ≥ 65 dB; nighttime noise: <55 dB, ≥55 dB) following recommendations by the World Health Organization community noise guidelines (2009) comparable to noise studies conducted in the United States and European countries (Lee et al. 2014; Seong et al. 2011). Alternatively, a four-category scale according to (rounded) quartile values was also used to categorize both noise metrics.

Other covariates

Considering that the noise exposure we modeled originates from traffic only, we addressed potential confounding by co-exposure to traffic-related air pollution. Estimates for traffic-related nitrogen oxides (NOx) was generated based on participants' residential addresses at baseline using the California Line Source Dispersion Model version 4 (CALINE4)(Benson and Pinkerman 1989; Wu et al. 2009; Wu et al. 2016), with traffic volume data from California DOT in 2002 and meteorology data from the California Air Resources Board (CARB) Air Quality and Meteorological Information System (https://www.arb.ca.gov/aqmis2/metselect.php). Details have been described elsewhere (Yu et al. 2019).

Demographic information was collected during cohort recruitment such as birthplace (Mexico, United States, or other), years of education, and occupation held longest during the lifetime (non-manual labor, manual labor, or other). At each interview, participants also reported information regarding smoking, alcohol drinking, physical activity, medical diagnoses including cardiovascular diseases and stroke, as well as medication use. An indicator for urban or rural residential location was generated relying on Census tract 2000 information (http://www.ers.usda.gov/data-products/rural-urbancommuting-area-codes.aspx). Neighborhood socioeconomic status (NSES) is represented as a score ranging from 1 to 5 (low -high NSES) depending on six census (2000) estimates: percentage of (1) individuals aged 25+ years without a high school diploma, (2) individuals under the poverty limit, (3) individuals aged 16+ who had been in the workforce at one time but are unemployed, (4) households owning their home, (5) vacant housing units, and (6) median number of rooms in a household (Yost et al. 2001). Physical activity level was evaluated according to time spent performing 18 different activities that older adults commonly engage in during a regular week (Shih et al. 2018). To control for comorbidity at baseline, a modified Charlson index was created by assigning a point each for a history of certain medical diagnoses including myocardial infarction, congestive heart failure, stroke, liver disease, diabetes, renal disease, any malignancy, and leukemia or lymphoma; then, an index score was generated by summing across these items (Aiello et al. 2008).

Statistical methods

Cox proportional hazards regression models with calendar time as the underlying time scale were used to assess the impact of noise exposures on incident dementia/CIND. Participants

were censored at their last date of contact if they did not return for a follow-up examinations or at their time of death if they died before the end of 2007.

Ambient noise exposure was entered into Cox regression models as a continuous variable normalized by its IQR. We also repeated these models with dichotomized and a quartile-based scale for noise exposures, and stratified on a series of risk factors to further explore the association between noise exposure and dementia/CIND. We selected covariates for adjustment based on the prior literature mostly for air pollution but also noise exposures and cognition function (Tzivian et al. 2015). We also adjusted for NSES and residential county in the models, considering that our noise estimates are primarily varying spatially. When examining the impacts of noise exposures on dementia/CIND, we first adjusted for baseline age, gender and years of education, and then added NSES, occupation, smoking, alcohol consumption, physical activity level, and baseline Charlson index; as an additional step, we co-adjusted traffic-related NOx. We also investigated the association between noise and air pollution exposures and all-cause mortality as it is well-known that air pollution affects mortality (Appendix). Finally, we also used competing risk models considering death as a competing risk when estimating effects between noise and dementia/CIND (Fine and Gray 1999). SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for Cox regression analyses.

3.4 Results

The average age of SALSA participants at baseline was 70 years, 42% were men. Around 60% reported having held a manual labor job during most of their life, 87% lived in an urban area, and more than 70% in Sacramento County. At baseline, about one-third of the participants

already had received a diagnosis of cardiovascular disease or diabetes, two-thirds had hypertension and ~8% reported a stroke. Around 20% of these elderly participants were considered physically active, while about 12% and less than 10% were current smokers and daily alcohol drinkers respectively. Compared with those who did not develop dementia/CIND or died during active follow-up, participants who developed events were older and less educated, more often manual laborers, had experienced stroke or diabetes and had a higher Charlson score at baseline (Table3-1). Participants who were exposed to higher 24-hour (≥ 65 dB) or nighttime noise levels (≥ 55 dB) were more likely to live in the urban area and higher NSES areas (TableS3-1). The annual average 24-hour and nighttime noise exposure levels ranged from 39 – 100 dB and 31 – 92 dB, with the mean values 68.5 and 60.4 dB respectively; and these two noise measures were highly correlated (Pearson r = 0.999). The average NOx exposure level was 2.6 ppb, the correlation with noise exposures was 0.43 (TableS3-2).

A total of 159 incident dementia/CIND cases were identified from 1998 to 2007. For 24-hour noise exposure, the hazard ratio of developing dementia/CIND adjusting for personal characteristics and life-style factors was increased (per 11.6 dB increase, HR = 1.24, 95% CI =1.00, 1.53). The effect estimate was slightly attenuated (HR = 1.19, 95% CI = 0.95, 1.49) when we further adjusted for traffic-related air pollution. Further inclusion of baseline cognition function, primary language used did not change results (Table3-2). Relying on nighttime noise only generated the same results likely due to the perfect correlation between 24-hour and nighttime noise exposures. As defined by our cut-off, high 24-hour (≥ 65 dB) and nighttime (≥ 55 dB) noise exposures were also positively associated with incident dementia/CIND, but the 95% CIs were wider (TableS3-3). Overall, the risk of incident

dementia/CIND was elevated with increasing noise exposure (FigureS3-1), and the risk of dementia/CIND increased with each (rounded) noise quartiles and was highest when 24-hour and nighttime noise were higher than 75 dB or and 65 dB respectively (Figure3-2).

In the stratified analyses, higher 24-hour noise was consistently and positively associated with the occurrence of dementia/CIND in almost all categories (Table3-3). The effects of noise exposure on dementia/CIND were similar but slightly decreased with wider 95% CI in the competing risk model. When we also co-adjusted for traffic-related air pollution, the association between noise and dementia/CIND or mortality were slightly attenuated and the 95% CIs were a bit wider (TableS3-4).

3.5 Discussion

Worldwide, a growing population of elderly combined with strong urbanization trends fostering noise exposure from traffic sources raises concerns that noise may have adverse effects on chronic neurodegenerative-diseases (Cui et al. 2012; Cui et al. 2015; Eze et al. 2014; Eze et al. 2017). In this study of older Mexican-American residents living in the California Sacramento Valley, noise exposures were positively associated with incidence of dementia/CIND even after adjusting for a host of other risk factors including traffic-related air pollution.

Associations between noise exposure and cardio-metabolic diseases have been reported in previous epidemiologic studies (Arlien-Søborg et al. 2016; Cappuccio et al. 2010; de Souza et al. 2015), but investigations of noise effects on cognitive outcomes are still rare. A small cross-sectional study in Italy observed differences in logical reasoning (Raven's progressive matrices

1938 [Raven PM38]: t = 3.24, p = 0.002; arithmetic reasoning: t = 2.30, p = 0.024) between noise exposed traffic police officers (n=39) and noise unexposed office employees (n= 42) but not in their attention abilities, or state and trait anxiety (Chiovenda et al. 2007). A much larger cross-sectional study conducted within the Heinz Nixdorf Recall study in Germany consisting of 4,086 participants aged 50–80 years reported that for each 10 A-weighted decibel [dB(A)] increase in traffic noise modeled at the participants' residences, the risk of mild cognitive impairment (MCI) (Odds Ratio [OR] = 1.40, 95% CI = 1.03, 1.91), as well as amnestic MCI (aMCI) (OR = 1.53, 95% CI = 1.05, 2.24) increased (Tzivian et al. 2016). Most recently, a longitudinal cohort study in England of 130,978 adults aged 50-79 years observed a small positive association between incident dementia and traffic nighttime noise at the postcode level (HR = 1.02, 95% CI = 1.00, 1.05) per 2.68 dB increase in nighttime noise)(Carey et al. 2018). Other studies of noise did not find any associations (Bocquier et al. 2014; Brink 2011; Gomes et al. 1999; Hardoy et al. 2005), which might be explained by differences in study designs, methods of measuring noise exposure or sources of noise investigated (i.e. occupational-related noise), the time-frame for which noise was estimated (i.e. only nighttime), or how cognitive function was assessed (Tzivian et al. 2015).

Although the evidence from epidemiological studies is still inconsistent, animal studies have linked noise exposure to decreased cognitive performance. Experimental studies indicated that noise is acting as a stressor that can influence brain structures such as reducing the brain volume in the medial prefrontal cortex (mPFC) area and cortical thickness in the hippocampus and amygdala area, which are essential components of the neural circuitry mediating stress responses (Czeh et al. 2007; Jafari et al. 2018). Noise stressors could cause the amygdala to

activate stress pathways in the hypothalamus and brainstem, followed by elevated release of noradrenaline and dopamine, and consequently lead to dysregulation of the prefrontal cortex responsible for cognitive abilities such as executive function (Arnsten 2009; Arnsten and Goldman-Rakic 1998; Jafari et al. 2019). Furthermore, noise could affect insulin resistance and endothelial dysfunction via activation of the hypothalamic–pituitary–adrenal (HPA) axis (Björntorp and Rosmond 2000; Cui et al. 2016; Griefahn and Robens 2010; Schmidt et al. 2013) that influences corticosterone and adrenocorticotropic hormone secretion followed by metabolic dysregulation (Cappuccio et al. 2010; Chaput et al. 2007; Passchier-Vermeer and Passchier 2000; Van Cauter et al. 2008)and cognition damage. A recent animal study reportedfound increased catechol-O-methyltransferase (COMT) gene DNA methylation in the medulla oblongata after theof rats were exposed to environmental noise (70–75 dB) for three days during nighttime and in the inferior colliculus after long-term exposure (70–75 dB for 21 days during nighttime). COMT serves as a key enzyme for the inactivation of prefrontal dopamine and is closely related to stress response and cognition. This experiment suggests one possible pathway through which noise exposure may influence cognition function i.e. through by modulating stress-responses (Guo et al. 2017).

When we stratified for several risk factors, the risk of having dementia/CIND seemed higher among those who held non-manual jobs and those who lived in high NSES areas; however, individuals within the same occupation or NSES category might still differ according to personal (Yost et al. 2001) and lifestyle characteristics (TableS3-5 and TableS3-6). Moreover, stratification reduces the numbers of events and subjects considerably resulting in much wider confidence intervals such that it is hard to draw firm conclusions from these analyses.

The SALSA study is one of few studies focusing on brain health in older Mexican-Americans and other Hispanics (Haan et al. 2003), and also one of few studies in North America exploring the long-term effect of noise on cognitive impairment. We estimated noise exposure at baseline residential addresses geocoded employing Global Positioning System (GPS) readings at the door step during home visits (performed during home visits), which guarantees high geo-location quality. During follow-up visits, incident dementia/CIND was diagnosed after repeated cognitive function testing and further confirmed by imaging examination (MRI), i.e. we did not have to rely on self-reports or records, thus ensuring a high accuracy of the dementia/CIND diagnosis in SALSA.

There are nevertheless several limitations. First, we did not have lifetime history of residential addresses of the participants, as well as information regarding bedroom orientation, window insulation or habits of opening windows or using noise protective equipment such as earplugs (Fuks et al. 2017), all of which may have contributed to measurement error for noise exposures. However, participants had on average lived at their baseline residence for 22 years, and 90% remained in California during the whole study period with only 339 changing addresses between baseline and last follow-up visit. In our study, altogether 221 participants changed their addresses before the dementia/CIND events or last follow-up occurred, and among them only 96 moved out of the county. Excluding these participants did not change the results more than minimally (TableS3-7). Thus, the observed results suggest that the baseline address based noise measurements are appropriate surrogates for long-term exposure. Additionally, study participants were mostly retired and consequently are expected to be at home during the day.

Since our noise exposure was residential address-based, exposure misclassification should be expected to be smaller than in a working population. While the difference between ambient and personal-level exposure owing to individual behavior would be expected to cause exposure misclassification at the individual level, estimates of noise exposure at residences can be considered instrumental variables for personal exposures. That is, personal exposure is the common descendant of ambient exposure and individual behaviors, while individual behaviors are unlikely to influence ambient exposure (Weisskopf et al. 2015); therefore our results are less likely to be affected by confounding from personal behaviors. Additionally, we also have adjusted for personal demographic, lifestyle factors, health status, NSES and type of residential location related to personal health behaviors and brain health, but residual confounding can never be ruled out completely. Selection bias resulting from loss of follow-up was minimal in our study because the percentage of subjects lost to follow-up was 2.3% per year. Furthermore, environmental exposures and cognitive impairment status were not reported by the subjects themselves, making the differential loss-to-follow-up unlikely. Additionally, noise exposure is commonly considered to be highly related to traffic-related air pollution since they both originate from traffic and occur in time and space simultaneously, therefore, we also adjusted for air pollution. Although the 95% CI became wider with such adjustments, the associations between noise and dementia/CIND or mortality remained similar, indicating an independent effect of noise exposure on dementia/CIND (Carey et al. 2018). Our results for all-cause mortality and air pollution are consistent with what we would expected according to the literature, thus corroborating the validity of our exposure measures (TableS3-8). Lastly, we only took into account continuous roadway traffic as the source of residential noise exposures, we did not assess stop-and-go traffic, noise from the airport or railways, or occupational noise

exposure before retirement, which likely contributed to non-differential exposure misclassification. Also, our noise model applied the same percentages for vehicle types (light or heavy) for day and night time to all roadways since we did not have sufficient information to model diurnal fluctuations. Thus, our 24-hour and nighttime noise estimates are by design highly correlated. Future noise studies taking into account diurnal traffic changes, additional major sources of noise as well as details about occupational exposures are needed.

Our study indicates that noise exposure elevated the risk of cognitive impairment and mortality among older Mexican-Americans, adding evidence that noise affects brain health. Given increasing health burdens in an aging population, programs restricting traffic-related noise in residential neighborhoods might provide an effective avenue to avoid chronic brain damage in vulnerable populations of elderly.

3.6 Tables and Figures

Table3-1. Summary of characteristics of the participants used for incidence analyses at baseline, Sacramento Area Latino Study of Aging, 1998-2007.

	Total	***Dementia/CIND***	
	(n=1612)	Event (n=159)	Non-event (n=1453)
Characteristics, Mean ± SD / N (%)	N (%)	N (%)	N (%)
Baseline Age (Year, SD)	70.2 (±6.8)	75.3 (±7.8)	69.7 (±6.5)
Male	680 (42.2)	58 (36.5)	622 (42.8)
Years of Education (Year, SD)	7.4 (±5.3)	5.8 (±5.2)	7.6 (±5.3)
Sacramento County Residence	1255 (77.9)	118 (74.2)	1137 (78.3)
Urban Residence	1400 (86.9)	136 (85.5)	1264 (87.0)
Birth Country			
Mexico	721 (44.9)	76 (47.8)	645 (44.6)
United States	797 (49.6)	75 (47.2)	722 (49.9)
Others (i.e. Central or South America)	88 (5.5)	8 (5.0)	80 (5.5)
Occupation Held During Most of Lifetime			
Non-Manual	346 (21.8)	14 (9.0)	332 (23.2)
Manual	960 (60.5)	104 (66.7)	856 (59.8)
Other (Housewives and Unemployed)	282 (17.8)	38 (24.4)	244 (17.0)
Neighborhood Socio-Economic Status (NSES)			
Lowest (NSES = 1)	544 (33.8)	64 (40.3)	480 (33.0)
Lower-middle/middle (NSES = 2 or 3)	912 (56.6)	80 (50.3)	832 (57.3)
High-middle/high (NSES = 4 or 5)	156 (9.7)	15 (9.4)	141 (9.7)
Baseline Smoking Status			20
Never/Non-Smoker	735 (45.8)	75 (47.2)	660 (45.6)
Former Smoker	681 (42.4)	64 (40.3)	617 (42.7)
Current Smoker	189 (11.8)	20 (12.6)	169 (11.7)
Baseline Alcohol Status			
Frequent (Daily) Drinker	146 (9.1)	8 (5.0)	138 (9.6)
Moderate (Weekly) Drinker	172 (10.7)	11 (6.9)	161 (11.2)
Occasional (Monthly) Drinker	158 (9.9)	12 (7.6)	146 (10.1)
Yearly/Rarely/Never Drinker	1125 (70.3)	128 (80.5)	997 (69.1)
Baseline Physically Active	341 (21.2)	27 (17.0)	314 (21.6)
Baseline Self-reported Cardiovascular Disease	574 (35.7)	70 (44.0)	504 (34.8)
Baseline Self-reported Stroke	126 (7.9)	26 (16.4)	100 (6.9)
Baseline Hypertension	1093 (67.8)	115 (72.3)	978 (67.3)
Baseline Diabetes	513 (31.9)	71 (44.7)	442 (30.6)
Baseline Charlson Index (Mean, SD)	0.9 (± 1.2)	1.1 (±1.2)	0.9 (±1.2)
Baseline BMI (Mean, SD)	29.9 (±6.0)	29.1 (±5.2)	29.9 (±6.1)
Traffic-related NOx (ppb, Mean ± SD)	2.6 (±2.2)	2.7 (±2.3)	2.6 (±2.5)
24hr Average Noise (dB)	68.5 (±8.9)	69.5 (±8.9)	68.3 (±8.9)
Nighttime (10PM - 7AM) Noise (dB)	60.4 (±8.9)	61.5 (±8.9)	60.3 (±8.9)

Note: CIND, cognitive impairment without dementia; dB, decibels; BMI, body mass index.

Table 3-2. Effect estimates (and 95% CIs) from Cox models for 24-hour average noise exposure (per 11.6 dB increase) and the risk of dementia/CIND.

	Single Exposure model	**After additionally adjusted with traffic-related NOx**
	24hour noise, per 11.6 dB increase	24hour noise, per 11.6 dB increase
	HR (95% CI)	HR (95% CI)
Model 1[a]	1.20 (0.98, 1.48)	1.16 (0.93, 1.45)
Model 2[b]	1.21 (0.98, 1.49)	1.17 (0.94, 1.46)
Model 3[c]	1.23 (1.00, 1.51)	1.19 (0.95, 1.49)
Model 4[d]	1.24 (1.00, 1.53)	1.19 (0.95, 1.49)
Model 5[e]	1.28 (1.03, 1.58)	1.23 (0.98, 1.55)
Model 6[f]	1.27 (1.02, 1.57)	1.23 (0.97, 1.55)

Note: CIND, cognitive impairment without dementia; dB, decibels; HR, hazard ratio; 95% CI, 95% confidence interval. For the noise exposure, we used 11.6 dB increase as the unit to estimate effects.

a. Adjusted for baseline age, gender, years of education.

b. Adjusted for baseline age, gender, years of education, occupation.

c. Adjusted for baseline age, gender, years of education, occupation, smoking status, alcohol consumption status, physical activity level.

d. Adjusted for baseline age, gender, years of education, occupation during most of life, smoking status, alcohol consumption status, physical activity level, neighborhood socioeconomic status indicator, residential county.

e. Adjusted for baseline age, gender, years of education, occupation during most of life, smoking status, alcohol consumption status, physical activity level, neighborhood socioeconomic status indicator, residential county, baseline Charlson index.

f. Adjusted for baseline age, gender, years of education, occupation during most of life, smoking status, alcohol consumption status, physical activity level, neighborhood socioeconomic status indicator, residential county, baseline Charlson index, baseline cognition function and primary language.

Table 3-3. Effect estimates (and 95% CIs) from Cox models [a] for 24-hour average noise exposure (per 11.6 dB increase) and the risk of dementia/CIND, stratified by other major risk factors.

	N (Total=1612)	**Number of Cases** (Total = 159)	**HR (95% CI)**
Age			
60-80	1454	114	1.21 (0.95 -1.55)
>=80	143	44	1.36 (0.86 -2.14)
Gender			
Male	680	58	1.23 (0.87 -1.74)
Female	932	101	1.27 (0.97 -1.67)
Occupation held during most of life			
Non-Manual	346	14	1.57 (0.78 -3.14)
Manual	960	104	1.17 (0.91 -1.51)
Other (Housewives and Unemployed)	282	38	1.39 (0.87 -2.24)
Smoking Status			
Never	735	75	1.10 (0.79 -1.53)
Former	681	64	1.35 (0.98 -1.85)
Current	189	20	1.25 (0.69-2.26)
Neighborhood Socio-Economic Status (NSES)			
Lowest (NSES =1)	544	64	1.16 (0.83-1.64)
Lower-middle/middle (NSES =2 or 3)	912	80	1.15 (0.86 -1.55)
High-middle/high (NSES =4 or 5)	156	15	1.91 (0.89 -4.13)
Comorbidity			
No comorbidity (Charlson Index = 0)	819	56	1.31 (0.92 -1.86)
Comorbidity (Charlson Index > 0)	787	103	1.18 (0.90 -1.54)
County			
Sacramento	1255	118	1.26 (0.98 -1.61)
Non-Sacramento	357	41	1.06 (0.70 -1.60)
Living in Urban or Rural Area			
Urban	1400	136	1.24 (0.98 -1.56)
Rural	212	23	1.10 (0.63 -1.92)

Note: CIND, cognitive impairment without dementia; dB, decibels; HR, hazard ratio; 95% CI, 95% confidence interval. For the noise exposure, we used 11.6 dB increase as the unit to estimate effects.

a. Adjusted for baseline age, gender, years of education, neighborhood socioeconomic status indicator, occupation during most of life, residential county, smoking status, alcohol consumption status, physical activity level.

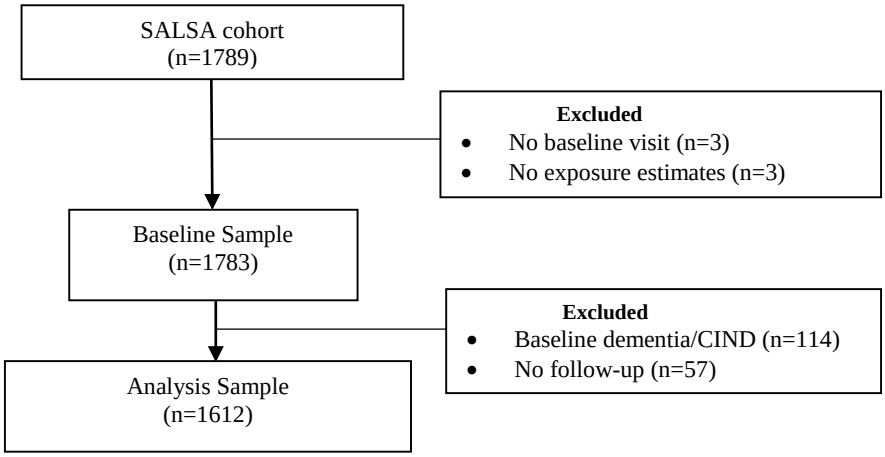


Figure 3-1. Flow chart of study population, Sacramento Area Latino Study on Aging (SALSA), 1998-2007. Abbreviations: CIND, cognitive impaired without dementia.

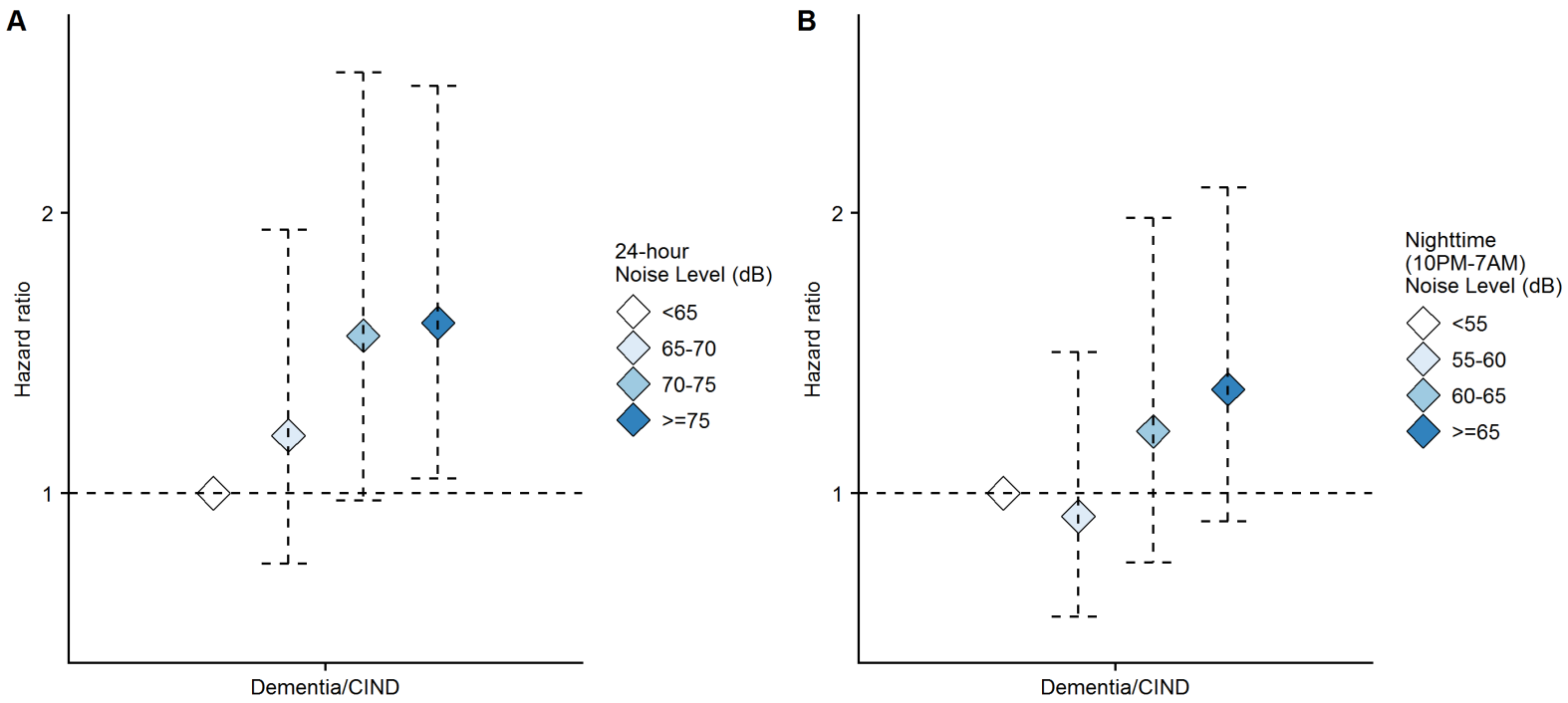


Figure 3-2. Effect estimates (and 95% confidence intervals) from adjusted Cox models for annual average of 24-hour (A) or nighttime noise (B) exposure at a quartile-based scale levels and the risk of dementia/CIND. A: 24-hour noise level was divided into 4 categories (<65 dB, 65-70 dB, 70-75 dB, and ⩾ 75 dB) according to (rounded) quartile values. The reference group included those with 24-hour average noise exposure <65 dB. B: Nighttime noise level was divided into 4 categories (<55 dB, 55-60 dB, 60-65 dB, and ⩾65 dB), according to (rounded) quartile values. The reference group included those with nighttime noise exposure <55 dB. Models were adjusted for baseline age, gender, years of education, neighborhood socioeconomic status indicator, occupation during most of life, residential county, smoking status, alcohol consumption status, and physical activity level. CIND, cognitive impairment without dementia; dB, decibels. The dashed lines display the 95% confidence intervals.

3.7 Supplemental Materials, Tables and Figures

Appendix for all-cause mortality analyses

Mortality data was collected through interviews with family members when we attempted to reach participants for annual follow-up visits or during interim 6-months phone calls, by reviewing online death notices, checking the Social Security Death Index, the National Death Index and California state vital statistics data. The mortality information used in this study was restricted to deaths (n=386) that occurred during active follow-up of the study population (1998–2007).

Cox proportional hazards regression models with calendar time as the underlying time scale were used to assess the impact of traffic-related air pollution and noise exposures on all-cause mortality. Participants were censored at their last date of contact if they did not return for a follow-up examinations or at their time of death if they died before the end of 2007. The analyses were same as the analyses for dementia/CIND. Both exposures were treated as continuous variables normalized by their respective interquartile ranges (IQRs), and for noise exposures we also employed binary variables and a quartile-based scale for noise exposures. stratified analyses on a series of risk factors were also employed to further explore the association between noise exposure and all-cause mortality.

TableS3-1. Characteristics of the participants used for incidence analyses at baseline, stratified by noise exposure.

	24-hour noise		*Nighttime noise*	
Characteristics, Mean ± SD / N (%)	<65 dB (n=598) N (%)	≥65 dB (n=1014) N (%)	<55 dB (n=453) N (%)	≥55 dB (n=1159) N (%)
Baseline Age (Year, SD)	70.3 (±6.8)	70.2 (±6.8)	70.2 (±6.9)	70.2 (±6.8)
Male	261 (43.7)	419 (41.3)	201 (44.4)	252 (55.6)
Years of Education (Year, SD)	7.5 (±5.3)	7.3 (±5.3)	7.4 (±5.3)	7.4 (±5.4)
Sacramento County Residence	443 (74.1)	812 (80.1)	343 (75.7)	912 (78.7)
Urban Residence	494 (82.6)	906 (89.4)	373 (82.3)	1027(88.6)
Birth Country				
Mexico	259 (43.5)	462 (45.7)	193 (42.8)	528 (45.7)
United States	299 (50.3)	498 (49.3)	232 (51.4)	565 (48.9)
Others (i.e. Central or South America)	37 (6.2)	51 (5.0)	26 (5.8)	62 (5.4)
Occupation held during most of the lifetime				
Non-Manual	131 (22.2)	215 (21.5)	99 (22.1)	247 (21.7)
Manual	360 (61.0)	600 (60.1)	281 (62.7)	679 (59.6)
Other (Housewives and Unemployed)	99 (16.8)	183 (18.3)	68 (15.2)	214 (18.8)
Neighborhood Socio-Economic Status (NSES)				
Lowest (NSES = 1)	211 (35.3)	333 (32.8)	172 (38.0)	372 (32.1)
Lower-middle/middle (NSES = 2 or 3)	320 (53.5)	592 (58.4)	226 (49.9)	686 (59.2)
High/high-middle (NSES = 4 or 5)	67 (11.2)	89 (8.8)	55 (12.1)	101 (8.7)
Baseline Smoking Status				
Never/Non-Smoker	289 (48.6)	446 (44.2)	220 (48.8)	515 (44.4)
Former Smoker	238 (40.0)	443 (43.9)	182 (40.4)	499 (43.2)
Current Smoker	68 (11.4)	121 (12.0)	49 (10.9)	140 (12.1)
Baseline Alcohol Status				
Frequent (Daily) Drinker	56 (9.4)	90 (8.9)	5 (10.0)	101 (8.8)
Moderate (Weekly) Drinker	58 (9.8)	114 (11.3)	47 (10.4)	125 (10.9)
Occasional (Monthly) Drinker	61 (10.3)	97 (9.6)	49 (10.9)	109 (9.5)
Yearly/Rarely/Never Drinker	419 (70.5)	706 (70.1)	309 (68.7)	816 (70.9)
Baseline Physically Active	447 (78.4)	760 (77.7)	341 (78.8)	866 (77.7)
Baseline Cardiovascular Disease	390 (34.5)	369 (36.5)	158 (35.0)	416 (36.0)
Baseline Stroke	50 (8.4)	76 (7.5)	39 (8.7)	87 (7.5)
Baseline Hypertension	404 (67.6)	689 (68.0)	309 (68.2)	784 (67.6)
Baseline Diabetes	175 (29.4)	338 (33.4)	137 (30.4)	376 (32.6)
Baseline Charlson Index (Mean, SD)	0.9 (±1.2)	0.9 (±1.2)	0.9 (±1.2)	0.9 (±1.2)
Baseline BMI (Mean, SD)	29.9(±5.5)	29.9(±6.3)	30.0(±5.0)	29.8(±6.3)
Traffic-related NOx (ppb, Mean, SD)	1.5 (±1.0)	3.3 (±2.4)	1.3 (±0.8)	3.1 (±2.3)
24hr Average Noise (dB, Mean, SD)	59.7(±4.2)	73.7(±6.5)	58.3(±4.0)	72.4(±6.9)
Nighttime (10PM - 7AM) Noise (dB, Mean, SD)	51.6(±4.2)	65.6(±6.5)	50.2(±4.0)	64.4(±6.9)

Note: CIND, cognitive impairment without dementia; dB, decibels; ppb, part per billion; BMI, body mass index.

TableS3-2. Distributions of 24-hour and nighttime noise and traffic-related NOx exposures.

				Percentile								
	Subject	**Mean**	**Variance**	**0**	**5**	**10**	**25**	**50**	**75**	**90**	**95**	**100**
24hr average noise (dB)	1612	68.5	78.8	39.4	55.1	57.5	62.4	67.6	74.2	81.3	84.4	100.0
Nighttime (10PM - 7AM) noise (dB)	1612	60.4	78.8	31.4	47.0	49.4	54.3	59.5	66.1	73.2	76.3	91.9
Traffic-related NOx (ppb)	1612	2.6	4.7	0.01	0.4	0.7	1.2	1.9	3.3	5.2	6.9	13.2

Note: dB, decibels; ppb, part per billion, NOx, nitrogen oxides.

Table S3-3. Effect estimates (and 95% CIs) from adjusted Cox models [a] for noise exposure (categorical variables) and the risk of dementia/CIND.

	24-hour Noise exposure ≥ 65 dB (Ref. group: 24-hour Noise exposure < 65 dB)		Nighttime Noise exposure ≥ 55 dB (Ref. group: Nighttime Noise exposure <55 dB)	
	HR	**95% CI**	**HR**	**95% CI**
Model 1[a]	1.36	(0.96, 1.93)	1.14	(0.79, 1.64)
Model 2[b]	1.36	(0.96, 1.93)	1.13	(0.79, 1.63)
Model 3[c]	1.41	(0.99, 2.01)	1.16	(0.80, 1.67)
Model 4[d]	1.46	(1.02, 2.08)	1.18	(0.82, 1.71)
Model 5[e]	1.45	(1.02, 2.07)	1.20	(0.83, 1.73)
Model 6[f]	1.42	(0.99, 2.03)	1.16	(0.80, 1.68)

Note: CIND, cognitive impairment without dementia; dB, decibels; HR, hazard ratio; 95% CI, 95% confidence interval.

a. Adjusted for baseline age, gender, years of education.

b. Adjusted for baseline age, gender, years of education, occupation.

c. Adjusted for baseline age, gender, years of education, occupation, smoking status, alcohol consumption status, physical activity level.

d. Adjusted for baseline age, gender, years of education, occupation during most of life, smoking status, alcohol consumption status, physical activity level, neighborhood socioeconomic status indicator, residential county.

e. Adjusted for baseline age, gender, years of education, occupation during most of life, smoking status, alcohol consumption status, physical activity level, neighborhood socioeconomic status indicator, residential county, baseline Charlson index.

f. Adjusted for baseline age, gender, years of education, occupation during most of life, smoking status, alcohol consumption status, physical activity level, neighborhood socioeconomic status indicator, residential county, baseline Charlson index, baseline cognition function and primary language.

Table S3-4. Effect estimates (and 95% CIs) from Competing risk models for 24-hour and nighttime noise exposure and the risk of dementia/CIND.

	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Exposure Parameter	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Continuous				
24hr average noise, per 11.6 dB	1.19 (0.96, 1.47)	1.22 (0.99, 1.50)	1.18 (0.95, 1.47)	1.20 (0.96, 1.49)
Nighttime noise, per 11.6 dB	1.19 (0.96, 1.46)	1.22 (0.99, 1.50)	1.18 (0.95, 1.47)	1.20 (0.96, 1.49)
Categorical				
24-hour noise exposure ≥ 65 dB (Ref group: <65 dB)	1.34 (0.94, 1.90)	1.44 (1.00, 2.06)	1.37 (0.93, 2.00)	1.36 (0.92, 2.00)
Nighttime noise exposure ≥ 55 dB (Ref group: <55 dB)	1.10 (0.76, 1.59)	1.15 (0.79, 1.67)	1.05 (0.70, 1.56)	1.06 (0.71, 1.58)

Note: CIND, cognitive impairment without dementia; dB, decibels; HR, hazard ratio; 95% CI, 95% confidence interval.
a. Adjusted for baseline age, gender, years of education.
b. Adjusted for baseline age, gender, years of education, occupation during most of life, smoking status, alcohol consumption status, physical activity level, neighborhood socioeconomic status indicator, residential county.
c. Adjusted for baseline age, gender, years of education, occupation during most of life, smoking status, alcohol consumption status, physical activity level, neighborhood socioeconomic status indicator, residential county, traffic-related NOx.
d. Adjusted for baseline age, gender, years of education, occupation during most of life, smoking status, alcohol consumption status, physical activity level, neighborhood socioeconomic status indicator, residential county, traffic-related NOx, baseline Charlson index.

TableS3-5. Characteristics of the participants used for incidence analyses at baseline, stratified by occupation.

	Occupation		
Characteristics, Mean ± SD / N (%)	Non-Manual (n=346) N (%)	Manual (n=960) N (%)	Others (n=282) N (%)
Baseline Age (Year, SD)	68.4 (±6.0)	70.8 (±6.8)	70.7 (±7.3)
Male	136 (39.3)	531 (55.3)	2 (0.7)
Years of Education (Year, SD)	12.7 (±4.5)	5.8 (±4.5)	5.9 (±4.4)
Sacramento County Residence	44 (12.7)	246 (25.6)	61 (21.6)
Urban Residence	328 (94.8)	805 (83.9)	245 (86.9)
Birth Country			
Mexico	61 (17.6)	511 (53.2)	145 (51.4)
United States	249 (72.0)	417 (43.4)	119 (42.2)
Others (i.e. Central or South America)	36 (10.4)	32 (3.3)	18 (6.4)
Neighborhood Socio-Economic Status (NSES)			
Lowest (NSES = 1)	96 (27.8)	348 (36.3)	93 (33.0)
Lower-middle/middle (NSES = 2 or 3)	184 (53.2)	544 (56.7)	169 (60.0)
Higher-middle/High (NSES = 4 or 5)	66 (19.1)	68 (7.1)	20 (7.1)
Baseline Smoking Status			
Never/Non-Smoker	171 (49.4)	377 (39.3)	178 (63.1)
Former Smoker	148 (42.8)	447 (46.6)	79 (28.0)
Current Smoker	27 (7.8)	136 (14.2)	25 (8.9)
Baseline Alcohol Status			
Frequent (Daily) Drinker	35 (10.1)	105 (11.0)	5 (1.8)
Moderate (Weekly) Drinker	50 (14.5)	114 (11.9)	7 (2.5)
Occasional (Monthly) Drinker	43 (12.4)	91 (9.5)	20 (7.1)
Yearly/Rarely/Never Drinker	218 (63.0)	647 (67.6)	249 (88.6)
Baseline Physically Active	2560 (77.8)	696 (75.4)	239 (86.3)
Baseline Cardiovascular Disease	120 (34.7)	336 (35.0)	116 (41.1)
Baseline Stroke	22 (6.4)	80 (8.3)	24 (8.5)
Baseline Hypertension	232 (67.1)	661 (68.9)	189 (67.0)
Baseline Diabetes	111 (32.1)	309 (32.2)	89 (31.6)
Baseline Charlson Index (Mean, SD)	0.9 (±1.2)	0.9 (±1.2)	0.9 (±1.2)
Baseline BMI (Mean, SD)	29.7 (±6.3)	29.7 (±5.5)	30.8 (±7.0)
Baseline Hearing loss	22 (6.4)	84 (8.9)	32 (11.5)
Traffic-related NOx (ppb, Mean, SD)	2.7 (±2.3)	2.5 (±2.1)	2.7 (±2.2)
24hr Average Noise (dB, Mean, SD)	68.6 (±8.9)	68.4 (±9.0)	68.6 (±8.5)
Nighttime (10PM - 7AM) Noise (dB, Mean, SD)	60.5 (±8.9)	60.3 (±9.0)	60.5 (±8.5)

Note: dB, decibels; ppb, part per billion; BMI, body mass index.

TableS3-6. Characteristics of the participants used for incidence analyses at baseline, stratified by neighborhood socio-economic status (NSES).

Characteristics, Mean ± SD / N (%)	**Neighborhood SES**		
	Lowest (n=544)	Lower-middle/middle (n=912)	High-middle/high (n=156)
Baseline Age (Year, SD)	70.4 (±7.0)	70.3 (±6.8)	69.3 (±5.9)
Male	245 (45.0)	365 (40.0)	70 (44.9)
Years of Education (Year, SD)	6.6 (±5.2)	7.3 (±5.2)	10.4 (±5.5)
Sacramento County Residence	498 (91.5)	623 (68.3)	134 (85.9)
Urban Residence	539 (99.1)	713 (78.2)	148 (94.9)
Birth Country			
Mexico	262 (48.3)	416 (45.9)	43 (27.6)
United States	254 (46.8)	445 (49.1)	98 (62.8)
Others (i.e. Central or South America)	27 (5.0)	46 (5.1)	15 (9.6)
Occupation held during most of the lifetime			
Non-Manual	96 (17.9)	184 (20.5)	66 (42.9)
Manual	348 (64.8)	544 (60.7)	68 (44.2)
Other (Housewives and Unemployed)	93 (17.3)	169 (18.8)	20 (13.0)
Baseline Smoking Status			
Never/Non-Smoker	240 (44.2)	418 (46.1)	77 (49.4)
Former Smoker	232 (42.7)	379 (41.8)	70 (44.9)
Current Smoker	71 (13.1)	109 (12.0)	9 (5.8)
Baseline Alcohol Status			
Frequent (Daily) Drinker	49 (9.1)	81 (8.9)	16 (10.3)
Moderate (Weekly) Drinker	50 (9.3)	102 (11.3)	20 (12.9)
Occasional (Monthly) Drinker	47 (8.7)	93 (10.3)	18 (11.6)
Yearly/Rarely/Never Drinker	394 (73.0)	630 (69.5)	101 (65.2)
Baseline Physically Active	114 (22.1)	187 (21.2)	40 (26.7)
Baseline Cardiovascular Disease	201 (37.0)	314 (34.6)	59 (37.8)
Baseline Stroke	37 (6.8)	75 (8.3)	14 (9.0)
Baseline Hypertension	379 (69.7)	603 (66.1)	111 (71.2)
Baseline Diabetes	183 (33.7)	290 (32.0)	40 (25.6)
Baseline Charlson Index (Mean, SD)	0.9 (±1.3)	0.9 (±1.1)	0.9 (±1.2)
Baseline BMI (Mean, SD)	30.3 (±6.6)	29.6 (±5.6)	29.7 (±5.6)
Traffic-related NOx (ppb, Mean, SD)	2.7 (±2.1)	2.5 (±2.0)	2.4 (±2.9)
24hr Average Noise (dB, Mean, SD)	68.5 (±8.7)	68.7 (±8.7)	66.9 (±10.5)
Nighttime (10PM - 7AM) Noise (dB, Mean, SD)	60.5 (±8.7)	60.6 (±8.7)	58.8 (±10.5)

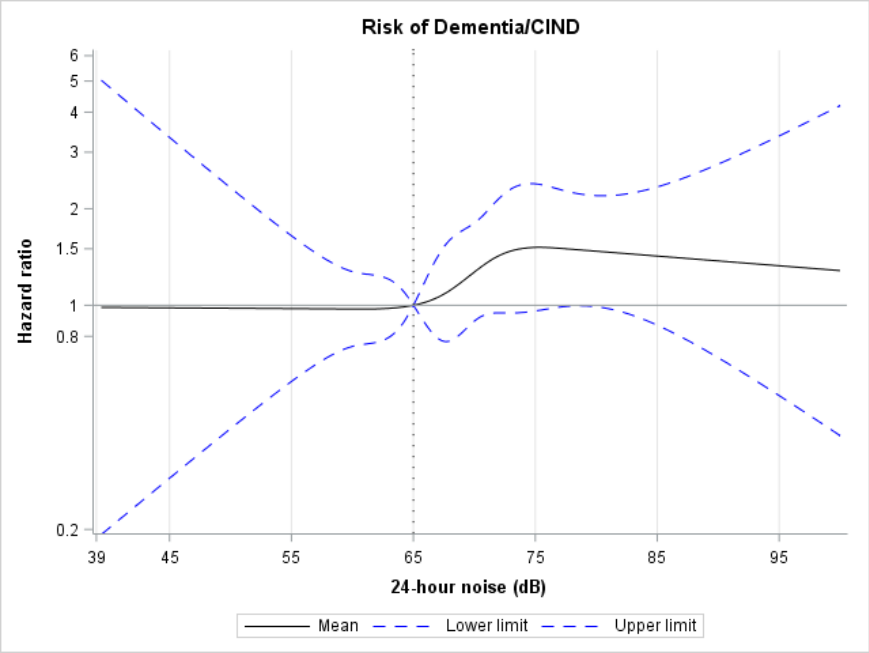
Note: dB, decibels; ppb, part per billion; BMI, body mass index.

TableS3-7. Effect estimates (and 95% CIs) from Cox models for 24-hour average noise exposure (per 11.6 dB increase) and the risk of dementia/CIND, after excluding those changed the addresses during the study period.

	After excluding all those changed address (case/subject = 138/1391)	After excluding those only moved to different county (case/subject = 148/1516)
	HR (95% CI)	HR (95% CI)
Model 1[a]	1.17 (0.93, 1.48)	1.20 (0.97, 1.49)
Model 2[b]	1.21 (0.96, 1.53)	1.24 (1.00, 1.54)
Model 3[c]	1.17 (0.91, 1.51)	1.20 (0.95, 1.51)
Model 4[d]	1.21 (0.94, 1.55)	1.24 (0.98, 1.56)

Note: CIND, cognitive impairment without dementia; dB, decibels; HR, hazard ratio; 95% CI, 95% confidence interval. For the noise exposure, we used 11.6 dB increase as the unit to estimate effects.
a. Adjusted for baseline age, gender, years of education.
b. Adjusted for baseline age, gender, years of education, occupation during most of life, smoking status, alcohol consumption status, physical activity level, neighborhood socioeconomic status indicator, residential county.
c. Adjusted for baseline age, gender, years of education, occupation during most of life, smoking status, alcohol consumption status, physical activity level, neighborhood socioeconomic status indicator, residential county, traffic-related NOx.
d. Adjusted for baseline age, gender, years of education, occupation during most of life, smoking status, alcohol consumption status, physical activity level, neighborhood socioeconomic status indicator, residential county, traffic-related NOx, baseline Charlson index.

(A)



(B)

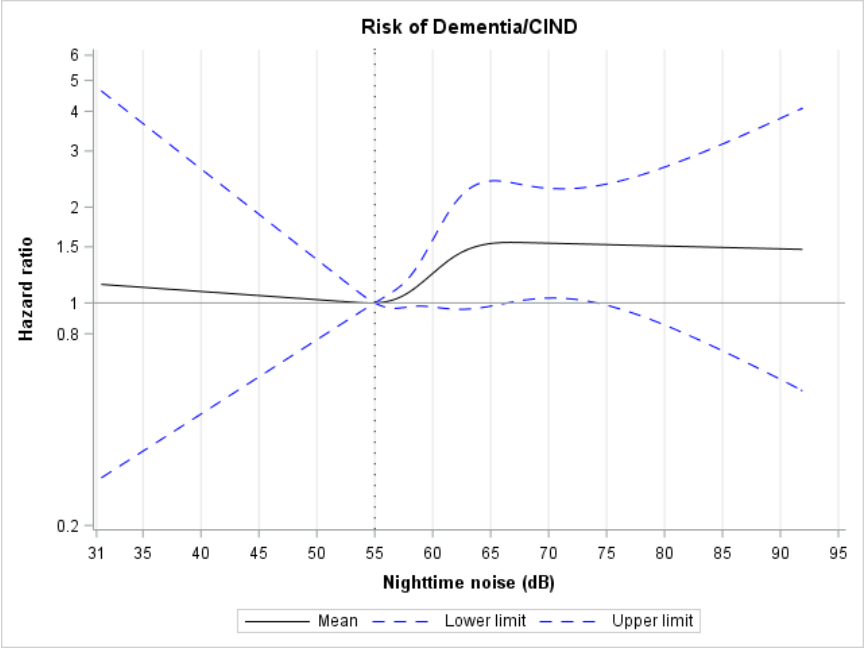


Figure3S-1. The estimated effects of 24-hour (A) and nighttime (B) noise exposure on incident dementia/CIND using restricted cubic spline function models. Models were adjusted for baseline age, gender, years of education, occupation during most of life, smoking status, alcohol consumption status, physical activity level, neighborhood socioeconomic status indicator, residential county, traffic-related NOx. CIND, cognitive impairment without dementia; dB, decibels.

Chapter 4. Metabolic Dysfunction Modifies the Influence of Traffic-Related Air Pollution and Noise Exposure on Late-life Dementia and Cognitive Impairment - A cohort study of elder Mexican-Americans

4.1 Abstract

Introduction: Cognitive impairment has been linked to traffic-related air pollution and noise exposure, as well as to metabolic syndrome or some of its individual components. Here we investigate whether the presence of metabolic dysfunction (obesity, hyperglycemia and low HDL-cholesterol) modifies associations between air pollution or noise exposures and incident dementia or cognitive impairment without dementia (CIND).

Methods: For 1,612 elderly Mexican-American participants of the Sacramento Area Latino Study on Aging (SALSA) followed for up to 10 years, we estimated local traffic-related exposures at residential addresses at enrolment relying on the California Line Source Dispersion Model version 4 (CALINE4) to model nitrogen oxides (NOx) and the SoundPLAN software package that implements the Federal Highway Administration Traffic Noise Model (TNM) to model 24-hour average noise exposures. We used Cox proportional hazard models with calendar time as the underlying time scale to estimate the joint effects of air pollution and noise exposures and metabolic dysfunction, specially obesity, hyperglycemia, or low HDL-cholesterol.

Results: The risk of developing dementia/CIND increased more than 2-fold among SALSA participants with hyperglycemia who also were exposed to high levels of traffic-related NOx (≥ 3.44 ppb [75th percentile]) (HR = 2.36, 95% CI = 1.41, 3.97) or 24-hour noise (≥ 65 dB) (HR = 2.21, 95% CI = 1.26, 3.89) respectively. For participants with low HDL-cholesterol or obesity

who were also exposed to high levels of NOx or noise, the estimated hazard ratios for dementia/CIND were similarly increased compared with those without metabolic dysfunction and low traffic air pollution or noise exposures.

Discussion: Exposure to traffic-related air pollution or noise most strongly increase the risk of dementia/CIND among older Mexican-Americans living in California who also exhibit metabolic dysfunction especially hyperglycemia and low HDL-cholesterol.

4.2 Introduction

Air pollution is a complex mixture of toxic compounds from different sources. Exposure to air pollution has been linked to endothelial dysfunction, microvasculature damage and atherosclerosis in both clinical and animal experiments (Kilian and Kitazawa 2018). There is growing epidemiologic evidence that both short and long-term exposures to ambient air pollutants, namely nitrogen dioxides (NO_2), Particular matter ($PM_{2.5}$), and Ozone (O_3) may increase the risk of neuro-degenerative disease including cognitive impairment (Carey et al. 2018; Oudin et al. 2016; J Stein et al. 2008; Tzivian et al. 2015; Weuve et al. 2012). Recently, noise exposure – also originating from traffic raised concerns due to associations observed with cardiovascular diseases (Hahad et al. 2019; Munzel et al. 2018) and cognitive impairment (Carey et al. 2018; Tzivian et al. 2015; Tzivian et al. 2016).

Metabolic syndrome, describes a cluster of reversible pathophysiologic conditions including insulin resistance, obesity, dyslipidemia and hypertension that are widely recognized in clinical practice and research for their potential to increase risk of chronic diseases including cardiovascular and neurodegenerative-diseases (Eckel et al. 2005; Kahn et al. 2005; Kaur

2014), and late-life cognitive impairment (Stampfer 2006). Considering the temporal issue correlated to associations between cognitive impairment and hypertension or hypertriglyceridemia reported by previous studies (Abell et al. 2018; Iadecola 2014; Kalmijn et al. 2000; Nagga et al. 2018), and the cohort characteristics, thus we only restricted metabolic dysfunctions to obesity, hyperglycemia and low HDL-cholesterol in this study.

Mexican-Americans, especially those aged 60 years or older, have a particularly high prevalence of obesity (Hales et al. 2017) and diabetes (Aguilar et al. 2015; Benjamin et al. 2018; Chukwueke and Cordero-MacIntyre 2010) and are also amongst the highly environmentally exposed populations in California, including traffic-related air pollution and noise (California_EPA 2018). Thus far, very few studies investigated the influence of noise exposures on cognition function, and to our knowledge no study has examined whether metabolic dysfunction contributes to the associations between noise exposure and cognition function; i.e. increases vulnerability to cognitive decline. The SALSA cohort offers the opportunity to examine this hypothesis in on a longitudinal cohort that enrolled and followed elderly Mexican-Americans.

4.3 Methods

Research Ethics

All procedures described here were approved by the Institutional Review Boards of University of California San Francisco, Los Angeles, and Davis, University of North Carolina, and University of Michigan.

Study design

We are using data from the Sacramento Area Latino Study on Aging (SALSA), a prospective population-based cohort study of older Mexican-Americans living in the Sacramento Area of California (1998–2007). A total of 1,789 participants were originally recruited. Participants were enrolled if they were 60 years or older, resided in the California Sacramento Valley and self-identified as Latino; they were followed with interviews and exams at their homes every 12–15 months for up to seven visits and every 6 months they were contacted in a 10-minute phone call to update contact information, health status and medication information between home visits. More information about the sampling process has been detailed elsewhere (Haan et al. 2003). In this study, those who (1) did not participate in the interview at baseline (n=3), (2) lived too far away from traffic sources to generate air pollution or noise measures (n=3), (3) already had dementia/CIND at baseline (n=114), (4) did not have any follow-up visit (n=57) were excluded, leaving 1,612 participants in total as our baseline sample. For analysis purposes, we further excluded those who at baseline did not have information on HDL levels, obesity or hyperglycemia (see Figure4-1).

Exposure assessment

All air pollution and noise exposure levels were estimated based on participants' geocoded residential addresses at baseline.

Estimation of traffic-related NOx Details about the generation of traffic-related NOx exposure measures for SALSA have been provided elsewhere (Yu et al. 2019). In brief, traffic-related NOx was estimated by the CALINE4, which captures local traffic emissions within 1500

meters of a participant's baseline address using traffic volume data in 2002 from the California Department of Transportation (DOT), while taking into account meteorological influences such as wind speed and direction, mixing height and temperature. The emission factors were obtained from the California Air Resources Board (CARB)'s EMFAC2011 model (California_EPA 2013). Meteorological data was obtained from the CARB Air Quality and Meteorological Information System (CARB 2015)

Estimation of traffic-related noise The creation of traffic-related noise exposure in SALSA has also been detailed elsewhere (Yu et al. 2019). Briefly, noise exposure was assessed using the SoundPLAN (Version 8.0, NAVCON, Fullerton, CA, USA) software package that implemented the Federal Highway Administration Traffic Noise Model (TNM) for noise prediction – based on input of Annual Average Daily Traffic (AADT) data from the local Metropolitan Planning Organizations (MPO). The TNM incorporates vehicle speed, distance between receiver (geocoded residential address of study subjects) and roadway, ground classification and counts of different types of vehicles. Continuous roadway traffic was considered the only source for our noise estimates. The 2002 State DOT hourly traffic counts were used to generate average diurnal patterns and to adjust the MPO AADT values to hour-of-day specific traffic counts for each noise receptor location.

Metabolic dysfunction

Three metabolic dysfunctions were defined according to the Third Adult Treatment Panel of the National Cholesterol Education Program (NCEP ATP III) (S. M. Grundy et al. 2005) as: (i) obesity: waist circumference of $\geq$ 40 inches in men, or $\geq$ 35 inches in women; (ii)

hyperglycemia: fasting glucose ≥ 100 mg/dl, or use of glucose-lowering medications; (iii) low HDL-cholesterol: HDL-cholesterol < 40 mg/dl in men, or < 50 mg/dl in women; or use of statins.

Dementia and CIND

The main outcome of interest is incident dementia/CIND. Cognition function was first evaluated with two cognitive screening tests (Modified Mini–Mental State Examination (3MSE) and Spanish English Verbal Learning Test (SEVLT)) administered to each participant at baseline and again during each follow-up visit. Participants were referred for a neuropsychological test battery and a standard neuropsychological examination (Informant Questionnaire on Cognitive Decline in the Elderly) by a geriatrician if their scores (1) on the 3MSE or SEVLT were below the 20th percentile at baseline, or (2) had decreased ≥ 8 points on 3MSE or ≥ 3 points on SEVLT from baseline. A team of neurologists and a neuropsychologist reviewed and classified them as cognitively normal, dementia or CIND according to standard diagnostic criteria. Those diagnosed with CIND or dementia were also referred for a magnetic resonance imaging (MRI) examination (details have been published elsewhere (Haan et al. 2003)). For the following analyses all-cause dementia and CIND were combined to improve statistical power and CIND captures the onset of cognitive decline prior to dementia.

Other covariates

Demographic information was collected during enrollment including birthplace, years of education, and occupation held longest during the lifetime. At each interview, participants were asked about lifestyle behaviors such as smoking, alcohol drinking, physical activity, medical

diagnoses, and medication use. We derived a neighborhood socioeconomic status (NSES) indicator calculated as a score ranging from 1 (low NSES) to 5 (high NSES) according to six census block (2000) measures including the percentages of individuals 25+ years old without a high school diploma, population living below the poverty line, individuals 16+ years old who at one time had been in the workforce but are unemployed, households with ownership of their home, vacant housing units, and the median number of rooms in a household (Yost et al. 2001). Physical activity level was evaluated according to spending time on 18 different activities in which older adults commonly engage in during a regular week (Shih et al. 2018).

Statistical analysis

We employed Cox proportional hazards regression models with calendar time as the underlying time scale and calculated hazard ratios (HRs) and 95% confidence intervals. Participants were censored at their last date of contact if they did not return for a follow-up examination or at their time of death if they died before the end of 2007.

For models with two-way interactions between each metabolic dysfunction (present vs absent) and environmental exposures, we dichotomized NOx exposure as low and high comparing the first three to the last (4th) quartile (< 3.44 ppb vs ≥ 3.44 ppb), and noise exposure based on the cut point (< 65 dB vs ≥ 65 dB) suggested in the World Health Organization community noise guidelines (2009) and in noise studies from US and European countries (Lee et al. 2014; Seong et al. 2011). We explored two-way interactions between NOx or noise exposure and obesity, hyperglycemia, and low HDL-cholesterol, respectively. Age, gender, education, occupation, household income level, smoking and alcohol status, physical activity and NSES and

residential location were entered into all models as covariates. We also calculated the relative excess risk due to interaction (RERI) to evaluate interactions on an additive scale (Li and Chambless 2007).

Additionally, we also redefined metabolic dysfunction in the following manner: for hyperglycemia and low HDL-cholesterol status, we generated four categories: (1) normal, (2) untreated, (3) treated and well-controlled, and (4) treated but not well-controlled. Traffic-related NOx and 24-hour noise exposures were entered into Cox regression models as continuous variables normalized by their interquartile ranges (IQRs), and hazard ratios were calculated for developing incident dementia/CIND per IQR increase in NOx or noise exposure for each categorized metabolic dysfunction.

In sensitivity analyses, we redefined metabolic dysfunction in an alternative manner ignoring medication information (Table S4-1), and repeated analyses using 75 dB as cut-off points to define high noise exposure, as well as using the highest tertile (< 2.68 ppb vs ≥ 2.68 ppb) for traffic-related NOx exposure.

Statistical analyses were performed using SAS 9.4 and an α-level of 0.05 was employed to assess formal statistical significance (two-tailed).

4.4 Results

Participants with prevalent obesity, hyperglycemia or low HDL-cholesterol at baseline were of similar average age but had less education, a lower household income and neighborhood socio-

economic status than those unaffected. There were more current-smokers and moderate/frequent alcohol drinkers among those without metabolic dysfunction. At baseline females had a higher prevalence of obesity, hyperglycemia and low HDL-cholesterol, while average exposure to traffic-NOx and noise were similar across all groups (Table 4-1). The distribution of air pollutants and noise are described in Tables S4-2, the traffic-related NOx and noise exposures were moderately correlated (Pearson r = 0.43).

Among 1,612 cognitively intact participants, 159 developed dementia/CIND during follow-up. As expected, having obesity, hyperglycemia or low HDL-cholesterol were positively associated with the risk of incident dementia/CIND, compared with those without metabolic dysfunction; (Table S4-3). When examining the joint effects for each environmental exposure and each metabolic dysfunction that affected CIND/dementia, we found that the risk estimates for developing dementia/CIND among participants exposed to high levels of traffic-related NOx (≥ 3.44 ppb) exposure and also classified as being obese, hyperglycemic or with low HDL-cholesterol were 1.73 (95% CI = 0.99, 3.03), 2.36 (95% CI = 1.41, 3.97) and 2.47 (95% CI = 1.43, 4.28) respectively, compared with those exposed to low level of traffic-related NOx and without the respective metabolic dysfunction. For highly 24-hour noise (≥ 65 dB) levels exposed and being hyperglycemic or having low HDL-cholesterol, the hazard ratios for developing incident dementia/CIND were 2.21 (95% CI = 1.26, 3.89) and 1.78 (95% CI = 1.04, 3.04) respectively (Table 4-2). However, only the interaction of low HDL-cholesterol and high traffic-related NOx was formally statistically significant and suggested superadditivity (RERI = 1.08, 95% CI = 0.03, 2.13). The joint effects for obesity, hyperglycemia or low HDL-cholesterol did not change when we used alternative cut-off thresholds for NOx and 24-hour

noise exposure (Table S4-4). Analyses based on alternative definitions for hyperglycemia and low HDL-cholesterol (Table S4-5 and S4-6) also did not make a difference for our effect estimates.

Finally, we estimated that participants treated with glucose-lowering medications who still had glucose levels ≥ 126 mg/dl were at highest risk (HR = 1.44, 95% CI = 1.04, 1.98) of developing dementia/CIND when exposed to traffic-related NOx, followed by those with treated and well-controlled glucose levels (< 126 mg/dl), those untreated with borderline glucose level (100mg/dl ≤ fasting glucose level < 126 mg/dl) or higher (≥ 126 mg/dl) and those with normal glucose level (Table 4-3). Also, the risk of developing incident dementia/CIND when exposed to traffic-related NOx exposure was higher among those having low HDL-cholesterol who were treated with medications (Table 4-4), however, no difference was found between those obese or not (obese group: HR = 1.13, 95% CI = 0.89, 1.45; not-obese group: HR = 1.11, 95% CI = 0.82, 1.51 per 2.29 ppb increase in traffic-related NOx exposure). When exposed to 24-hour noise, no difference for the risk of dementia/CIND was found across the different levels of hyperglycemia, low HDL-cholesterol or obesity respectively.

4.5 Discussion

We found that high exposure to traffic-related air pollution or noise in those with hyperglycemia, low HDL-cholesterol, and obesity exacerbates the risk of developing incident dementia/CIND among older Mexican-Americans. We further observed that those whose glucose level were not well-controlled when treated and similarly those who are obese or still

have low HDL-cholesterol when treated with statins were more likely to develop incident dementia/CIND when exposed to high traffic-related air pollution.

Air pollution, especially traffic-related air pollution, is a growing global problem along with other detrimental aspects of urbanization such as noise exposure and these exposures have been connected with various chronic health outcomes including adverse effects on cognition (Carey et al. 2018; Hong Chen et al. 2017; Jerrett et al. 2009; Jerrett et al. 2014; Jerrett et al. 2017; Jung et al. 2015). Both experimental and animal studies have shown that air pollutants provoke oxidative stress and systemic inflammatory responses, and can disrupt the blood-brain barrier, precipitate β-amyloid (Aβ) and activate microglia (Block et al. 2004; Calderón-Garcidueñas et al. 2008; Genc et al. 2012; Levesque et al. 2011). Traffic-related air pollution and noise exposures' possible roles in neuro-degenerative diseases has started to raise concerns (Paul et al. 2019). Possible mechanisms for noise include sleep disturbance and stress, which in turn lead to an activation of the autonomic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis i.e. stress-responsive regulatory systems including those involved in insulin resistance (Björntorp and Rosmond 2000; Cui et al. 2016; Griefahn and Robens 2010; Schmidt et al. 2013). Noise has also been shown to reduce brain volume in the medial prefrontal cortex area and cortical thickness in the hippocampus and amygdala in animal experiments (Czeh et al. 2007; Jafari et al. 2018), along with elevated level of noradrenaline and dopamine from the activation of stress pathways in the hypothalamus and brainstem, followed by prefrontal cortex dysregulation (Arnsten 2009; Arnsten and Goldman-Rakic 1998; Jafari et al. 2019). Epidemiological studies have also provided some limited evidence for a link between air pollution or noise exposure and cognitive impairment. A cohort study (Ontario Population

Health and Environment Cohort [ONPHEC]) in Canada used the health records of 20,666,639 subjects and found that per 1.2 ppb increase in NO2, dementia incidence increased by 10% (95% CI = 1.08, 1.12) (H. Chen et al. 2017). The longitudinal Betula study in Northern Sweden (1806 participants) reported a risk for incident dementia of 1.60 (95% CI = 1.02, 2.10) among those with highest traffic-related NOx exposure (> 26 ug/m3) compared to those with the lowest exposure (4.8 -9 ug/m3), and estimated a hazard ratio of 1.05 (95% CI = 0.98, 1.12) per 10ug/m^3 increase in NOx (Oudin et al. 2016). A longitudinal cohort study in England reported a 2% increase in risk of dementia per 2.68 dB increase in traffic-related nighttime noise exposure (Carey et al. 2018). A cross-sectional study in Germany of 4086 participants aged 50-80 years found that higher residential noise from traffic (per 10 dB(A) increase) was positively associated with mild cognitive impairment (MCI) ((Odds Ratio [OR] = 1.40, 95% CI = 1.03, 1.91) and amnestic MCI (OR = 1.53, 95% CI =1.05, 2.24) (Tzivian et al. 2016).

Metabolic dysfunctions including obesity, hyperglycemia and dyslipidemia have widely been considered to play a role in the development of dementia. Insulin resistance, one of the key pathological features of metabolic syndrome, is closely related to oxidative stress and inflammation and may induce alterations in β-amyloid deposition or clearance, a pathological mechanism considered important for AD related dementia and cognitive impairment (Paul et al. 2019; Yaffe et al. 2009). Evidence linking metabolic syndrome to decline in cognitive performance is growing and includes also structural changes such as volume loss in the hippocampus and frontal lobes, white matter alterations, as well as altered brain metabolism (Bokura et al. 2010; Yates et al. 2012). Our findings agree with previous studies that reported on metabolic syndrome and cognition. The longitudinal Aging Study Amsterdam (1183

participants aged 65 – 88 years) reported that hyperglycemia was most strongly associated with decline in cognition function (information processing speed: $\beta = -1.18$, $p<0.01$; immediate recall ($\beta = - 0.39$, $P = 0.02$) (Dik et al. 2007). The population-base PROOF study in France (n=895) observed a positive association between low HDL-cholesterol (HDL-cholesterol <1.03 mmol/L in men or <1.29 mmol/L in women) and poor executive function (OR = 2.60, 95% CI = 1.68, 4.02) (Rouch et al. 2014). In a sub-study of Longitudinal Older Veteran (LOVE) study in Taiwan with 276 men aged 75 years or older, central obesity was positively associated with cognitive decline (OR = 4.19, 95% CI =1.26, 13.91) (Liu et al. 2013).

We also investigated the roles of obesity, hyperglycemia and low HDL-cholesterol in more detail to account for treatment effects and found that the risk of developing incident dementia/CIND when exposed to traffic-related NOx exposure was higher among those treated but with glucose levels not well-controlled, those who were obese, or those having low HDL-cholesterol even with treatment of statins; however, we did not find such a risk pattern for 24-hour noise exposure, possible due to the different pathophysiologic mechanisms underlying air pollution (inflammation pathway) and noise exposure (stress pathway) (Fuks et al. 2017) or random variation and small sample size. Since our study is the first study to investigate the role that different metabolic dysfunctions play for noise exposure effects on cognitive impairment, further investigations are needed.

The SALSA study is a population-based longitudinal cohort study with over 10 years of follow-up and one of few studies focusing on brain health in older Mexican-Americans. To our knowledge, no study has thus far investigated the combined effect of high levels of traffic-

related air pollution and noise exposure and metabolic dysfunctions, and our study is one of few investigating the modification of effect measures by metabolic dysfunction on cognitive impairment, or to account for treatment effects. For air pollution and noise exposures, we derived the exposure estimates based on geocoded residential addresses using Global Positioning System (GPS) readings at the home visits with high geo-location quality. Additionally, we employed the CALINE4 dispersion model — a well-validated model — to characterize pollutant exposures from traffic sources in close proximity to homes. We used anthropometric, biochemical measurements and medication information to assess metabolic function and repeated cognitive function testing and imaging (MRI) to diagnose incident dementia/CIND, thus guaranteeing high accuracy for metabolic dysfunction and dementia/CIND diagnoses.

There are some limitations to be noted. First, SALSA study is a cohort of elder Mexican-Americans with average age of 70 years, restricting our analyses in terms of investigating the role of hypertension for cognition decline given the temporal relationship between hypertension and cognitive decline. Although hypertension's association with cognitive impairment are well established, the elevated blood pressure has to occur in midlife; while in late life reduced but not elevated blood pressure increases dementia risk (Abell et al. 2018; Iadecola 2014), likely reflective of a loss of the cerebral autoregulation to maintain adequate blood flow to the brain (Gottesman 2018). As for hypertriglyceridemia, temporal relationship was also reported by the longitudinal Honolulu-Asia Aging Study (Kalmijn et al. 2000) and the prospective Swedish BioFINDER Study (Nagga et al. 2018). Similar as previous studies, no associations between baseline hypertension (definition: blood pressure ≥ 130/85 mmHg, or use of anti-hypertensive

medication; HR = 0.88, 95% CI = 0.59, 1.32) or hypertriglyceridemia (definition: triglycerides ≥ 150 mg/dl, or use of statins; HR = 0.78, 95% CI = 0.56, 1.09) and incident dementia/CIND were observed in our study. Thus, since we lacked the participants' health status and medication information in early life, here we only restricted metabolic dysfunctions including obesity, hyperglycemia and low HDL-cholesterol. We were unable to have participants' historical exposures to air pollution and noise before enrollment in the study due to the lack of lifetime residential addresses and of adequate air monitoring or traffic density data prior to 1990. However, SALSA participants' low residential mobility – the average length of living at the baseline address was 22 years and more than 80% did not changing addresses during the study period – suggests that by using the baseline addresses we likely generated exposure measures that represent long-term spatially distinct exposures before and throughout the study period. Furthermore, we lack the information about use of protective measures including window insulation, bedroom orientation (facing to street or not) and use of ear plugs, which might contribute to exposure measurement error. As for NOx exposure, our CALINE4 dispersion model only captures local traffic emissions within 1500 m of the residence, without taking into account background air pollution and emissions farther away, thus while the estimated concentration is very low, they serve as a spatially dense proxy for local traffic pollution. Noise exposure estimates only considered major roadway traffic as a source, and did not include railway and airport noises or contributions from other sources such as construction sites, thus overall noise levels are possibly underestimated for some participants. The attrition rate in SALSA was 5%, and environmental exposures, metabolic syndrome and cognitive impairment status were not self-reported, making selection bias less likely. Lastly, residual confounding cannot be completely ruled out even though we have adjusted for a number of

important covariates that are related to both exposures and dementia incidence including demographic and life-style factors and NSES.

In conclusion, our study indicates that high levels of exposure to traffic-related air pollution or noise among those who are obese or suffer from hyperglycemia or low HDL-cholesterol may increase risk of cognitive impairment among older Mexican-Americans disproportionately. These findings provide evidence that metabolic dysfunction may not only act as a risk factors for cognitive decline, but also modify the negative impacts of environmental exposures. Early identification and treatment of people with metabolic dysfunction as well as prevention approaches that restricting the traffic-related exposures might mitigate the cognitive impairment in elders.

4.6 Tables and Figures

Table4-1. Characteristics of the study population at baseline by status of metabolic dysfunction [a], Sacramento Area Latino Study on Aging, 1998-2007.

	Total	***Obesity***		
Characteristics, Mean ± SD / N (%)	(n=1612) N (%)	NO (n=607) N (%)	YES (n=901) N (%)	p
Baseline Age (Year, SD)	70.2 (±6.8)	70.2 (±6.9)	70.0 (±6.6)	0.35
Male	680 (42.2)	340 (56.0)	287 (31.9)	<0.01
Education (Year, SD)	7.4 (±5.3)	8.0 (±5.4)	7.2 (±5.3)	0.01
Sacramento County Residence	1255 (77.9)	485 (79.9)	694 (77.0)	0.18
Urban Residence	1400 (86.9)	528 (87.0)	783 (86.9)	0.96
Neighborhood Socio-Economic Status (NSES, Mean, SD)	2.1 (1.0)	2.1 (1.0)	2.1 (1.0)	0.17
Birth Country				0.36
Mexico	721 (44.9)	269 (44.3)	399 (44.3)	
United States	797 (49.6)	299 (49.3)	459 (50.9)	
Others	88 (5.5)	39 (6.4)	43 (4.8)	
Occupation held during most of the lifetime				<0.01
Non-Manual	346 (21.8)	144 (24.1)	185 (20.7)	
Manual	960 (60.5)	374 (62.5)	519 (58.1)	
Other	282 (17.8)	80 (13.4)	189 (21.2)	
Household Income (US Dollar/Month)				0.01
Less than 1000	691 (43.7)	227 (37.9)	409 (46.1)	
1000 TO 1499	321 (20.3)	117 (19.5)	179 (20.2)	
1500 TO 1999	184 (11.6)	80 (13.4)	95 (10.7)	
2000 TO 2499	154 (9.7)	68 (11.4)	85 (9.6)	
2500 or more	233 (14.7)	107 (17.9)	119 (13.4)	
Baseline Smoking Status				<0.01
Never/Non-Smoker	735 (45.8)	256 (42.2)	435 (48.3)	
Former Smoker	681 (42.4)	254 (41.9)	389 (43.2)	
Current Smoker	189 (11.8)	96 (15.8)	77 (8.6)	
Baseline Alcohol Status				<0.01
Frequent Drinker	146 (9.1)	76 (12.6)	58 (6.5)	
Moderate Drinker	172 (10.7)	87 (14.4)	81 (9.0)	
Occasional Drinker	158 (9.9)	63 (10.4)	88 (9.8)	
Yearly/Rarely/Never Drinker	1125 (70.3)	378 (62.6)	672 (74.8)	
Baseline Physically Active	341 (21.2)	158 (26.0)	156 (17.3)	<0.01
Baseline CESD (Mean, SD)	0.9 (± 1.2)	8.9 (±9.9)	10.1 (±10.7)	0.03
Baseline BMI (Mean, SD)	29.9 (±6.0)	26.2 (±4.1)	32.3 (±5.8)	<0.01
24-hour Noise (dB)	68.5 (±8.9)	68.6 (±8.9)	68.4 (±8.9)	0.75
Traffic-related NOx (ppb)	2.6 (±2.2)	2.6 (±2.2)	2.6 (±2.1)	0.74

Note: CIND, cognitive impairment without dementia; HDL, high density lipoprotein; dB, decibels; ppb, part per billion; BMI, body mass index; CESD, the center for Epidemiological Studies-Depression; SD, standard deviation; NOx, nitrogen oxides.

a. Definitions for metabolic dysfunction: (i) obesity: waist circumference of ≥40 in. in men; ≥35 in. in women; (ii) borderline elevation of blood glucose (fasting glucose ≥100 mg/dl, or use of glucose-lowering medications; (iii) low high-density lipoprotein (HDL) cholesterol: men:<40 mg/dl; women:<50 mg/dl, or use of statins.

Table4-1continued. Characteristics of the study population at baseline by status of metabolic dysfunction a, Sacramento Area Latino Study on Aging, 1998-2007.

	Hyperglycemia			*Low HDL-Cholesterol*		
Characteristics, Mean ± SD / N (%)	NO (n=840) N (%)	YES (n=772) N (%)	p	NO (n=1026) N (%)	YES (n=586) N (%)	p
Baseline Age (Year, SD)	70.8 (±7.0)	69.7 (±6.5)	<0.01	70.3 (±7.0)	70.1 (±6.5)	0.67
Male	338 (40.2)	342 (44.3)	0.10	486 (47.4)	194 (33.1)	<0.01
Education (Year, SD)	7.3 (±5.3)	7.5 (±5.4)	0.51	7.6 (±5.3)	7.0 (±5.4)	0.04
Sacramento County Residence	644 (76.7)	611 (79.2)	0.23	787 (76.7)	468 (79.9)	0.14
Urban Residence	728 (86.7)	672 (87.1)	0.82	895 (87.2)	505 (86.2)	0.55
Neighborhood Socio-Economic Status (NSES, Mean, SD)	2.1 (1.0)	2.1 (1.0)	0.90	2.1 (1.0)	2.1 (1.0)	0.67
Birth Country			0.01			0.91
Mexico	400 (48.0)	321 (41.6)		462 (45.3)	259 (44.2)	
United States	375 (45.0)	422 (54.7)		502 (49.2)	295 (50.3)	
Others	59 (7.1)	29 (3.8)		56 (5.5)	32 (5.5)	
Occupation held during most of the lifetime			0.67			0.02
Non-Manual	177 (21.5)	169 (22.2)		216 (21.5)	130 (22.3)	
Manual	507 (61.5)	453 (59.4)		631 (62.7)	329 (56.5)	
Other	141 (17.1)	141 (18.5)		159 (15.8)	123 (21.1)	
Household Income (US Dollar/Month)			0.20			0.28
Less than 1000	355 (43.3)	336 (44.0)		432 (43.0)	259 (44.8)	
1000 TO 1499	177 (21.6)	144 (18.9)		198 (19.7)	123 (21.3)	
1500 TO 1999	101(12.3)	83(10.9)		125 (12.4)	59 (10.2)	
2000 TO 2499	81 (9.9)	73 (9.6)		92 (9.2)	62 (10.7)	
2500 or more	106 (12.9)	127 (16.6)		158 (15.7)	75 (13.0)	
Baseline Smoking Status			0.04			0.92
Never/Non-Smoker	401 (48.1)	334 (43.3)		470 (46.1)	265 (45.2)	
Former Smoker	328 (39.4)	353 (22.0)		431 (42.3)	250 (42.7)	
Current Smoker	104 (12.5)	85 (11.0)		118 (11.6)	71 (12.1)	
Baseline Alcohol Status			<0.01			<0.01
Frequent Drinker	90 (10.8)	56 (7.3)		124 (12.2)	22 (3.8)	
Moderate Drinker	106 (12.8)	66 (8.6)		130 (12.8)	42 (7.2)	
Occasional Drinker	78 (9.4)	80 (10.4)		102 (10.0)	56 (9.6)	
Yearly/Rarely/Never Drinker	557 (67.0)	568 (73.8)		663 (65.1)	462 (79.4)	
Baseline Physically Active	203 (24.2)	138 (17.9)	<0.01	240(23.4)	101(17.2)	<0.01
Baseline CESD (Mean, SD)	9.5(±10.3)	10.1(±10.5)	0.30	9.4(±10.1)	10.5(±10.9)	0.03
Baseline BMI (Mean, SD)	28.5 (±5.6)	31.2 (±6.1)	<0.01	29.4 (±6.1)	30.6 (±5.7)	<0.01
24-hour Noise (dB)	68.2 (±8.8)	68.7 (±9.0)	0.26	68.5 (±8.8)	68.4 (±9.0)	0.84
Traffic-related NOx (ppb)	2.5 (±2.1)	2.7 (±2.2)	0.12	2.6 (±2.2)	2.5 (±2.1)	0.33

Note: CIND, cognitive impairment without dementia; HDL, high density lipoprotein; dB, decibels; ppb, part per billion; BMI, body mass index; CESD, the center for Epidemiological Studies-Depression; SD, standard deviation; NOx, nitrogen oxides.

a. Definitions for metabolic dysfunction: (i) obesity: waist circumference of ≥40 in. in men; ≥35 in. in women; (ii) borderline elevation of blood glucose (fasting glucose ≥100 mg/dl, or use of glucose-lowering medications; (iii) low high-density lipoprotein (HDL) cholesterol: men:<40 mg/dl; women:<50 mg/dl, or use of statins.

Table4-2. Joint effects [a] between traffic-related air pollution or noise exposures and metabolic dysfunction on incident dementia/CIND.

	Traffic-related NOx					
	NOx <3.44 ppb			**NOx ≥ 3.44 ppb**		
Risk Factor	Case/Total	HR	95% CI	Case/Total	HR	95% CI
Obesity [b]						
No	38/463	1.00	-	13/144	1.31	(0.67, 2.58)
Yes	69/678	1.14	(0.72, 1.80)	25/223	1.73[c]	(0.99, 3.03)
Hyperglycemia [b]						
No	56/656	1.00	-	17/184	1.12	(0.57, 2.21)
Yes	59/562	1.47	(0.96, 2.26)	27/210	2.36[c]	(1.41, 3.97)
Low HDL-Cholesterol [b]						
No	72/759	1.00	-	22/267	1.02	(0.58, 1.81)
Yes	43/459	1.10	(0.71, 1.69)	22/127	2.47[c]	(1.43, 4.28)
	24-hour noise					
	24-hour noise < 65dB			**24-hour noise ≥ 65dB**		
Risk Factor	Case/Total	HR	95% CI	Case/Total	HR	95% CI
Obesity [b]						
No	16/226	1.00	-	35/381	1.45	(0.76, 2.78)
Yes	31/339	1.31	(0.67, 2.53)	63/562	1.65[c]	(0.89, 3.07)
Hyperglycemia [b]						
No	23/325	1.00	-	50/515	1.35	(0.75, 2.42)
Yes	27/273	1.67	(0.90, 3.10)	59/499	2.21[c]	(1.26, 3.89)
Low HDL-Cholesterol [b]						
No	30/379	1.00	-	64/647	1.40	(0.84, 2.33)
Yes	20/219	1.45	(0.79, 2.66)	45/367	1.78[c]	(1.04, 3.04)

Note: CIND, cognitive impairment without dementia; HDL, high density lipoprotein; NOx, nitrogen oxides; dB, decibels; ppb, part per billion; HR, hazard ratio; 95% CI, 95% confidence interval.

a. All the models were adjusted with baseline age, gender, education, occupation held during most of the life, neighborhood SES, smoking status, alcohol status, residential county, physical activity and household income, baseline cognition function.

b. Definitions for metabolic dysfunction: (i) obesity: waist circumference of ≥40 in. in men; ≥35 in. in women; (ii) borderline elevation of blood glucose (fasting glucose ≥100 mg/dl, or use of glucose-lowering medications; (iii) low high-density lipoprotein (HDL) cholesterol: men:<40 mg/dl; women:<50 mg/dl, or use of statins.

c. HR for interaction term (95% CI): NOx and obesity 1.16 (0.51, 2.67); NOx and hyperglycemia 1.43 (0.62, 3.31); NOx and low HDL-cholesterol 2.19 (1.00, 4.83); noise and obesity 0.87 (0.39, 1.93), noise and hyperglycemia 0.99 (0.46, 2.11), noise and low HDL-cholesterol 0.88 (0.42, 1.86).

Table 4-3. Effect estimates (and 95% CIs) from Cox models [a] for traffic-related NOx (per 2.29 ppb increase) and 24-hour average noise exposure (per 11.6 dB increase) and the risk of dementia/CIND, stratified by status of finer-scale of hyperglycemia status.

Hyperglycemia Status	Subjects	Dementia/CIND	Traffic-related NOx, per 2.29 ppb increase
			HR (95% CI)
Normal glucose level	840	73	1.00 (0.71, 1.40)
Untreated but hyperglycemia [b]	440	39	1.24 (0.88, 1.74)
Treated and well-controlled [c]	108	16	1.32 (0.70, 2.48)
Treated but not well-controlled [d]	220	31	1.44 (1.04, 1.98)

Note: CIND, cognitive impairment without dementia; NOx, nitrogen oxides; dB, decibels; ppb, part per billion; HR, hazard ratio; 95% CI, 95% confidence interval.

a. All the models were adjusted with baseline age, gender, education, occupation held during most of the life, neighborhood SES, smoking status, alcohol status, residential county, physical activity and household income, baseline cognition function.

b. Include the untreated participants whose glucose level either ≥ 126 mg/dl or 100mg/dl ≤ fasting glucose level < 126 mg/dl.

c. Include the treated participants whose glucose level either < 100 mg/dl or 100mg/dl ≤ fasting glucose level < 126 mg/dl.

d. Include the treated participants whose glucose level ≥ 126 mg/dl.

Table 4-4. Effect estimates (and 95% CIs) from Cox models [a] for traffic-related NOx (per 2.29 ppb increase) and 24-hour average noise exposure (per 11.6 dB increase) and the risk of dementia/CIND, stratified by status of finer-scale of HDL-cholesterol.

HDL-Cholesterol Status	Subjects	Dementia/CIND	Traffic-related NOx, per 2.29 ppb increase
			HR (95% CI)
Normal HDL-cholesterol level	1026	94	1.04 (0.80, 1.35)
Untreated but low HDL-cholesterol	453	52	1.12 (0.80, 1.55)
Treated low HDL-cholesterol [b]	132	13	1.67 (1.00, 2.77)

Note: CIND, cognitive impairment without dementia; HDL, high density lipoprotein; NOx, nitrogen oxides; dB, decibels; ppb, part per billion; HR, hazard ratio; 95% CI, 95% confidence interval.

a. All the models were adjusted with baseline age, gender, education, occupation held during most of the life, neighborhood SES, smoking status, alcohol status, residential county, physical activity and household income, baseline cognition function.

b. Include the treated participants whose HDL-cholesterol level either ≥ 40 mg/dl or < 40 mg/dl in men, either ≥ 50 mg/dl or < 50 mg/dl in women.

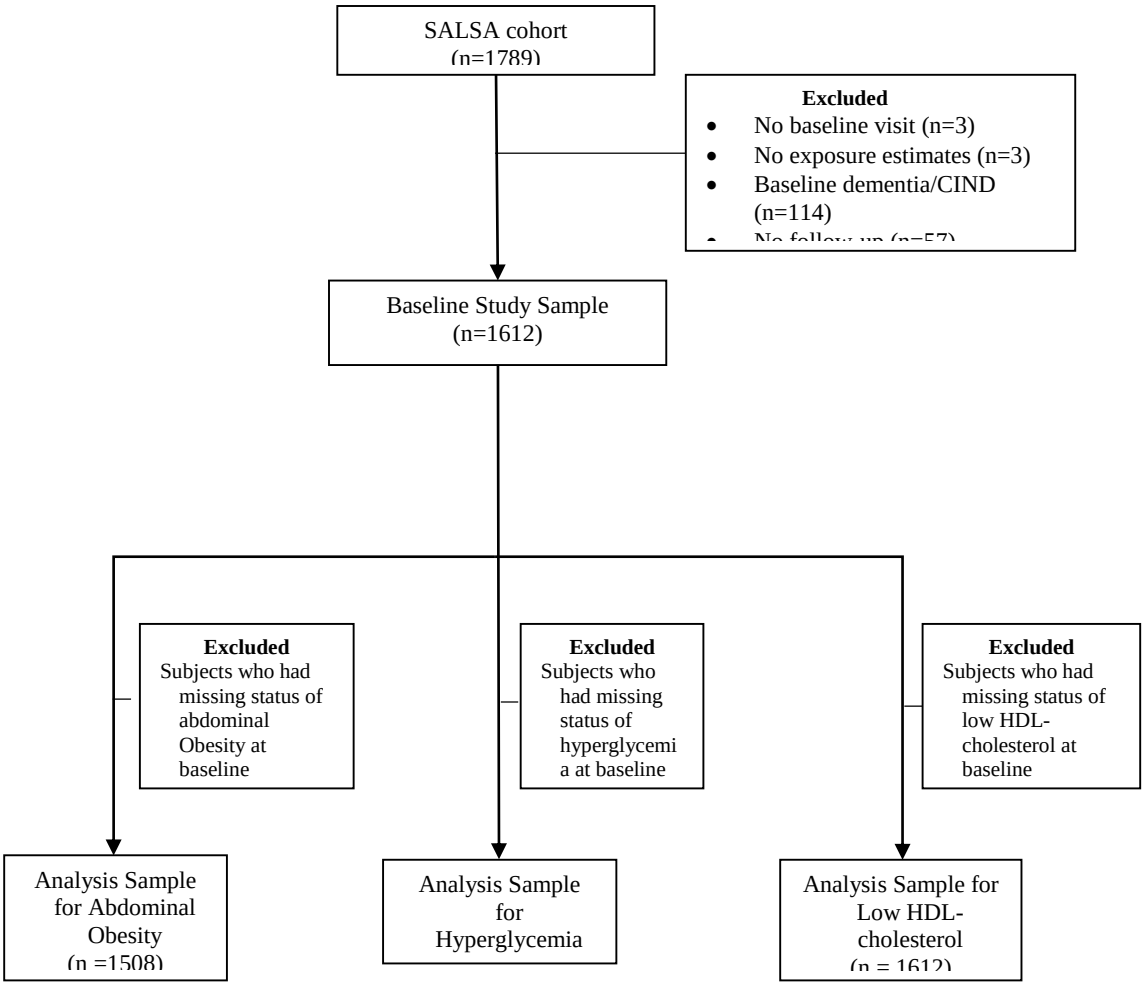


Figure 4-1. Flow chart of study population, Sacramento Area Latino Study on Aging (SALSA), 1998-2007. Abbreviations: CIND, cognitive impaired without dementia; HDL, high density lipoprotein.

4.7 Supplemental Tables and Figures

Table S4-1. Definition of metabolic syndrome according to the recommendations of the Third Adult Treatment Panel of the National Cholesterol Education Program (NCEP ATP III).

Metabolic Dysfunction	**NCEP ATP III Criteria**
Abdominal Obesity	Waist Circumference: ≥ 40 inches (Male), ≥ 35 inches (Female)
Hyperglycemia	Fasting glucose ≥ 100 mg/dl
Low HDL-cholesterol	HDL-Cholesterol:< 40 mg/dl (Male), < 50 mg/dl (Female)

Note: HDL, high density lipoprotein.

Table S4-2. Distributions of the air pollutions and noise exposure estimates.

Exposure	Subjects	Mean	Variance	Percentile								
				0	*5*	*10*	*25*	*50*	*75*	*90*	*95*	*100*
Traffic-related NOx (ppb)[a]	1612	2.59	4.69	0.01	0.43	0.67	1.15	1.90	3.34	5.22	6.93	13.20
24-hour noise (dB) [a]	1612	68.46	78.78	39.4	55.1	57.5	62.4	67.6	74.2	81.3	84.4	100.0

Note: NOx, nitrogen oxides; dB, decibels; ppb, part per billion.

a. The Pearson correlation among the air pollution and noise exposures estimates is 0.43.

TableS4-3. Effect estimates (and 95% CI) from adjusted Cox proportional hazards regression models [a] for traffic-related NOx and 24-hour noise exposures and five metabolic dysfunctions and the risk of dementia/CIND.

Parameter	Traffic-related NOx, per 2.29 ppb increase			24-hour noise exposure, per 11.6 dB increase		
	HR	95% CI		HR	95% CI	
Environmental exposure	1.18	0.99	1.42	1.23	1.00	1.53
Environmental exposure	1.19	0.99	1.44	1.20	0.96	1.48
Obesity [b]	1.13	0.78	1.64	1.13	0.78	1.64
Environmental exposure	1.18	0.98	1.42	1.23	1.00	1.52
Hyperglycemia [b]	1.46	1.04	2.05	1.47	1.05	2.06
Environmental exposure	1.19	0.99	1.43	1.24	1.00	1.53
Low HDL-Cholesterol [b]	1.29	0.91	1.82	1.28	0.91	1.81

Note: CIND, cognitive impairment without dementia; HDL, high density lipoprotein; dB, decibels; ppb, part per billion.

a. All the models were adjusted with baseline age, gender, education, occupation held during most of the life, neighborhood SES, smoking status, alcohol status, residential county, physical activity and household income, baseline cognition function.

b. Definitions for metabolic dysfunction: (i) obesity: waist circumference of ≥40 in. in men; ≥35 in. in women); (ii) hyperglycemia: fasting glucose ≥100 mg/dl, or use of glucose-lowering medications; (iii) elevated blood pressure (≥130/85 mmHg), or use of anti-hypertensive medication; (iv) elevated triglycerides (≥150 mg/dl), or use of statins; and (v) low high-density lipoprotein (HDL) cholesterol: men:<40 mg/dl; women:<50 mg/dl, or use of statins.

Table S4-4. Joint effects [a] between traffic-related NOx (<2.68 vs ≥ 2.68 ppb) or 24-hour noise exposure (<75 dB vs ≥ 75dB) and metabolic dysfunction on incident dementia/CIND.

	Traffic-related NOx					
	NOx <2.68 ppb			**NOx ≥ 2.68 ppb**		
Risk Factor	Case/Total	HR	95% CI	Case/Total	HR	95% CI
Obesity [b]						
No	33/400	1.00	-	18/207	1.25	(0.67, 2.32)
Yes	62/589	1.15	(0.70, 1.88)	32/312	1.59[c]	(0.92, 2.73)
Hyperglycemia [b]						
No	52/581	1.00	-	21/259	1.01	(0.55, 1.87)
Yes	51/481	1.41	(0.89, 2.23)	35/291	2.09[c]	(1.29, 3.40)
Low HDL-Cholesterol [b]						
No	62/671	1.00	-	32/355	1.29	(0.78, 2.11)
Yes	41/391	1.31	(0.83, 2.07)	24/195	1.85[c]	(1.08, 3.18)
	24-hour noise					
	24-hour noise < 75dB			**24-hour noise ≥ 75dB**		
Risk Factor	Case/Total	HR	95% CI	Case/Total	HR	95% CI
Obesity [b]						
No	40/466	1.00	-	11/141	1.07	(0.52, 2.18)
Yes	65/696	1.05	(0.67, 1.64)	29/205	1.79[c]	(1.05, 3.06)
Hyperglycemia [b]						
No	48/648	1.00	-	25/192	1.72	(0.95, 3.12)
Yes	66/594	1.79	(1.16, 2.76)	20/178	2.35[c]	(1.34, 4.13)
Low HDL-Cholesterol [b]						
No	64/788	1.00	-	30/238	1.79	(1.07, 3.00)
Yes	50/454	1.53	(0.99, 2.34)	15/132	1.76[c]	(0.96, 3.23)

Note: CIND, cognitive impairment without dementia; HDL, high density lipoprotein; NOx, nitrogen oxides; dB, decibels; ppb, part per billion; HR, hazard ratio; 95% CI, 95% confidence interval.

a. All the models were adjusted with baseline age, gender, education, occupation held during most of the life, neighborhood SES, smoking status, alcohol status, residential county, physical activity and household income, baseline cognition function.

b. Definitions for metabolic dysfunction: (i) abdominal obesity: waist circumference of ≥40 in. in men; ≥35 in. in women; (ii) borderline elevation of blood glucose (fasting glucose ≥100 mg/dl, or use of glucose-lowering medications; (iii) low high-density lipoprotein (HDL) cholesterol: men:<40 mg/dl; women:<50 mg/dl, or use of statins.

c. HR for interaction term (95% CI): NOx and obesity 1.11 (0.51, 2.38); NOx and hyperglycemia 1.47 (0.68, 3.18); NOx and low HDL-cholesterol 1.10 (0.53, 2.29); noise (<75 vs. ≥ 75dB) and obesity 1.60 (0.68, 3.79), noise (<75 vs. ≥ 75dB) and hyperglycemia 0.76 (0.35, 1.68), noise (<75 vs. ≥ 75dB) and low HDL-cholesterol 0.65 (0.29, 1.42).

Table S4-5. Effect estimates (and 95% CI) from adjusted Cox proportional hazards regression models [a] for traffic-related NOx and 24-hour noise exposures and metabolic dysfunctions defined without medication information and the risk of dementia/CIND.

Parameter	Traffic-related NOx, per 2.29 ppb increase			24-hour noise, per 11.6 dB increase		
	HR	95% CI		HR	95% CI	
Environmental exposure	1.19	0.99	1.44	1.20	0.96	1.48
Obesity [b]	1.13	0.78	1.64	1.13	0.78	1.64
Environmental exposure	1.19	0.98	1.43	1.21	0.97	1.50
Hyperglycemia [b]	1.56	1.10	2.20	1.57	1.11	2.22
Environmental exposure	1.20	0.99	1.44	1.20	0.96	1.49
Low HDL-cholesterol [b]	1.39	0.97	1.98	1.37	0.96	1.96

Note: CIND, cognitive impairment without dementia; HDL, high density lipoprotein; NOx, nitrogen oxides; dB, decibels; ppb, part per billion; HR, hazard ratio; 95% CI, 95% confidence interval.

a. All the models were adjusted with baseline age, gender, education, occupation held during most of the life, neighborhood SES, smoking status, alcohol status, residential county, physical activity and household income, baseline cognition function.

b. Definitions for metabolic dysfunction: (i) obesity: waist circumference of ≥40 in. in men; ≥35 in. in women; (ii) hyperglycemia: fasting glucose ≥100 mg/dl; (iii) low high-density lipoprotein (HDL) cholesterol: men:<40 mg/dl; women:<50 mg/dl.

Table S4-6. Joint effects [a] between traffic-related NOx or 24-hour noise exposure and metabolic dysfunction defined without medication information on incident dementia/CIND.

	Traffic-related NOx					
	NOx <3.44 ppb			**NOx ≥ 3.44 ppb**		
Risk Factor	Case/Total	HR	95% CI	Case/Total	HR	95% CI
Obesity [b]						
No	38/463	1.00	-	13/144	1.31	(0.67, 2.58)
Yes	69/678	1.14	(0.72, 1.80)	25/223	1.73[c]	(0.99, 3.03)
Hyperglycemia [b]						
No	51/614	1.00	-	12/168	1.07	(0.54, 2.09)
Yes	54/519	1.45	(0.95, 2.22)	27/200	2.42[c]	(1.44, 4.04)
Low HDL-Cholesterol [b]						
No	69/756	1.00	-	18/256	0.97	(0.55, 1.69)
Yes	37/379	1.13	(0.73, 1.77)	21/112	2.85[c]	(1.65, 4.91)
	24-hour noise					
	24hr noise < 65dB			**24hr noise ≥ 65dB**		
Risk Factor	Case/Total	HR	95% CI	Case/Total	HR	95% CI
Obesity [b]						
No	16/226	1.00	-	35/381	1.45	(0.76, 2.78)
Yes	31/339	1.31	(0.67, 2.53)	63/562	1.65[c]	(0.89, 3.07)
Hyperglycemia [b]						
No	19/303	1.00	-	44/479	1.29	(0.73, 2.29)
Yes	26/256	1.60	(0.87, 2.95)	55/463	2.21[c]	(1.27, 3.85)
Low HDL-Cholesterol [b]						
No	29/383	1.00	-	58/629	1.31	(0.80, 2.14)
Yes	17/178	1.48	(0.79, 2.75)	41/313	1.89[c]	(1.12, 3.20)

Note: CIND, cognitive impairment without dementia; HDL, high density lipoprotein; NOx, nitrogen oxides; dB, decibels; ppb, part per billion; HR, hazard ratio; 95% CI, 95% confidence interval.

a. All the models were adjusted with baseline age, gender, education, occupation held during most of the life, neighborhood SES, smoking status, alcohol status, residential county, physical activity and household income, baseline cognition function.

b. Definitions for metabolic dysfunction: (i) obesity: waist circumference of ≥40 in. in men; ≥35 in. in women; (ii) hyperglycemia: fasting glucose ≥100 mg/dl; (iii) low high-density lipoprotein (HDL) cholesterol: men:<40 mg/dl; women:<50 mg/dl.

c. HR for interaction term (95% CI): NOx and obesity 1.16 (0.51, 2.67); NOx and hyperglycemia 1.56 (0.67, 3.61); NOx and low HDL-cholesterol 2.60 (1.18, 5.74); noise and obesity 0.87 (0.39, 1.93), noise and hyperglycemia 1.07 (0.50, 2.29), noise and low HDL-cholesterol 0.98 (0.46, 2.09).

Chapter 5. Public Health Relevance and Expected Contributions

This dissertation assesses the contributions of traffic-related exposures specifically air pollution (NOx) and noise to the incidence of metabolic syndrome and dementia/cognitive impairment using a population-based cohort of older Mexican-Americans who participated in the SALSA cohort study. We found that exposure to traffic-related NOx or noise were associated with lower levels of high-density lipoprotein cholesterol and metabolic syndrome respectively. In addition, we found that traffic-related noise exposure increased the risk of developing dementia/CIND even after adjusting for local air pollution exposure from traffic sources. Finally, we found that the risk of developing dementia/CIND increased most (more than 2-fold) among participants who were exposed to high levels of traffic-related NOx or 24-hour noise, respectively, and exhibited the metabolic dysfunctions of hyperglycemia and low HDL-cholesterol.

Cognitive impairment and dementia are major concern due to their associations with mortality and morbidity, especially with increasing life expectancy and aging population, as well as the social and economic burden to the communities (Paul et al. 2019). Metabolic syndrome has been widely recognized in clinical practice and research for their potential to increase risk of chronic diseases including cardiovascular and neurodegenerative-diseases (Eckel et al. 2005; Kahn et al. 2005; Kaur 2014), and a particular high prevalence was see in the older Mexican-Americans (Aguilar et al. 2015), who are also amongst the highly environmentally exposed populations in California (California_EPA 2018). Thus, it is of public health relevance to study the associations between traffic-related exposure and metabolic dysfunction and cognitive

impairment using life-course approach if possible. Early identification and treatment of people with metabolic dysfunction as well as prevention approaches that restricting the traffic-related exposures might mitigate the cognitive impairment in elders.

Chapter 6. References

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