A Neurobiological Link between Transportation Noise Exposure and Metabolic Disease in Humans

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Abstract

Background: Chronic transportation noise exposure associates with cardiovascular events through a link involving heightened stress-associated neurobiological activity (as amygdalar metabolic activity, AmygA) on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT). Increased AmygA also associates with greater visceral adipose tissue (VAT) and type 2 diabetes mellitus (DM). While relationships between noise exposure and VAT and DM have been reported, the underlying mechanisms remain incompletely understood. We tested whether: 1) transportation noise exposure associates with greater a) baseline and gains in VAT and b) DM risk, and 2) heightened AmygA partially mediates the link between noise exposure and these metabolic diseases.

Methods: VAT was measured in a retrospective cohort (N=403) who underwent clinical ^{18}F-FDG-PET/CT. AmygA was measured in those with brain imaging (N=238). Follow-up VAT was remeasured on available imaging (N=67). Among individuals (N=224) without baseline DM, incident DM was adjudicated over two years from clinical records. Noise (24-hour average) was modeled at each individual's home address. Linear regression, survival, and mediation analyses were employed.

Results: Higher noise exposure (upper tertile vs. others) associated with greater: baseline VAT (standardized β [95% confidence interval (CI)]=0.230 [0.021, 0.438], p=0.031), gains in VAT (0.686 [0.185, 1.187], p=0.008 adjusted for baseline VAT), and DM (hazard ratio [95% CI]=2.429 [1.031, 5.719], p=0.042). The paths of: ↑noise exposure→↑AmygA→↑baseline VAT and ↑noise exposure→↑AmygA→↑subsequent DM were significant (p<0.05).

Conclusions: Increased transportation noise exposure associates with greater VAT and DM. This relationship is partially mediated by stress-associated neurobiological activity. These findings suggest altered neurobiology contributes to noise exposure's link to metabolic diseases.

Graphical abstract
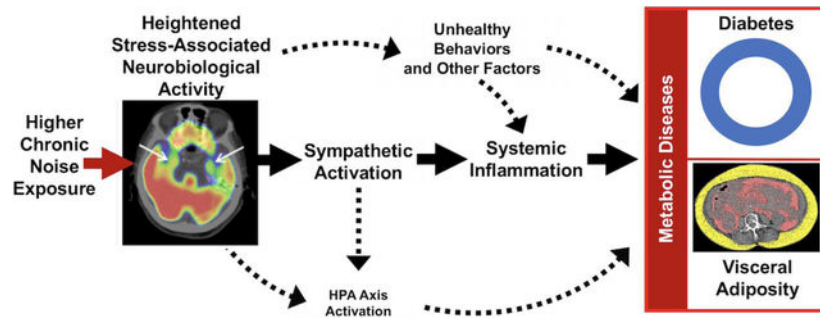
Keywords

amygdalar activity; diabetes mellitus; noise exposure; positron emission tomography; visceral adiposity

1. Introduction

Chronic noise exposure is an important contributor to human diseases, including metabolic diseases (i.e., obesity and diabetes mellitus (DM)) and cardiovascular disease (CVD). (Christensen et al., 2015; Christensen et al., 2016; Clark et al., 2017; Eze et al., 2017; Fritschi et al., 2011; Munzel et al., 2018; Osborne et al., 2020; Pyko et al., 2015; Pyko et al., 2017; Shin et al., 2020; Sorensen et al., 2013) The relationships between noise and anthropometric measures of adiposity as well as DM are known to be independent of key confounders in several populations (e.g., air pollution, socioeconomic factors, medical comorbidities, diseases, smoking, malignancy); however, no study has comprehensively evaluated these endpoints using objective imaging-based measurements.(Christensen et al., 2015; Christensen et al., 2016; Clark et al., 2017; Eze et al., 2017; Pyko et al., 2015; Pyko et al., 2017; Shin et al., 2020; Sorensen et al., 2013) Furthermore, the mechanisms linking noise exposure to these metabolic diseases remain incompletely understood.

Chronic noise exposure generates a stress response that activates the sympathetic nervous system (SNS) leading to increased downstream inflammation and oxidative stress.(Munzel et al., 2018; Osborne et al., 2020; Schmidt et al., 2013) Noise exposure also stimulates the hypothalamic-pituitary-adrenal (HPA) axis and leads to impaired glucose metabolism and increased adiposity.(Munzel et al., 2018) These changes culminate in metabolic and cardiovascular diseases.(Munzel et al., 2017; Munzel et al., 2018; Osborne et al., 2020; Recio et al., 2016; Schmidt et al., 2013) High transportation noise exposure triggers increased stress-associated neural activity of the amygdala, a limbic brain center that participates in the response to psychosocial and environmental stressors.(Osborne et al., 2020; Tawakol et al., 2019; Zald and Pardo, 2002) ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) imaging provides a unique opportunity to detail neurobiological mechanisms by simultaneously evaluating regional brain activity (e.g., amygdalar metabolic activity, or AmygA) and the structures of extra-neural tissues (e.g., visceral adipose tissue, or VAT).(Ishai et al., 2019; Osborne et al., 2020; Tawakol et al., 2017) ^{18}F-FDG-PET/CT imaging has previously been implemented to show that heightened stress-associated neurobiological activity (AmygA) associates with

greater: VAT, type 2 DM, atherosclerotic inflammation, and CVD events.(Ishai et al., 2019; Osborne et al., 2018; Tawakol et al., 2017) Because higher transportation noise exposure associates with increased AmygA,(Osborne et al., 2020) we hypothesized that AmygA has an important role in linking noise exposure to metabolic diseases (e.g., increased VAT and DM).

Accordingly, we sought to investigate the independence of the associations between transportation noise exposure and: a) baseline and change in VAT and b) type 2 DM risk from key confounding factors. Further, we tested whether the relationship between higher noise exposure and these metabolic diseases is mediated by AmygA.

2. Methods

2.1 Study Samples

The study samples were derived from a retrospective cohort of 1,777 individuals without known CVD or active malignancy who underwent clinically indicated ^{18}F-FDG-PET/CT imaging at Massachusetts General Hospital (Boston, MA) from 2005 to 2008 (largely for malignancy screening or surveillance). None received chemotherapies within one year before imaging or during follow-up, and none developed cancer during follow-up. Four hundred ninety-eight (498) individuals met additional inclusion criteria: 1) age >30 years, 2) no clinically diagnosed inflammatory disease, 3) 3 clinical notes to establish baseline health, 4) >1 follow-up note, 5) available ^{18}F-FDG-PET/CT imaging, and 6) home address data to derive 24-hour average transportation noise levels. Of this group, 403 provided abdominal imaging data for the measurement of VAT and comprised the VAT sample. A subset of 238 individuals provided imaging data that allowed assessment of AmygA, and 67 individuals provided clinically indicated ^{18}F-FDG-PET/CT imaging data approximately one year after baseline imaging that allowed measurement of follow-up VAT. Of the 498 total subjects, a separate group of 224 without baseline DM provided up to two years of follow-up data for the determination of incident type 2 DM. Complete details are provided in Figure 1. This retrospective study was approved by the Partners Institutional Review Board and was completed in compliance with the Declaration of Helsinki. Informed consent was not required for this retrospective study.

2.2 ^{18}F-FDG-PET/CT Imaging Acquisition

^{18}F-FDG-PET/CT imaging was performed with a hybrid scanner (e.g., Biograph 64 Siemens Healthcare, Erlangen, Germany, or similar). Each individual was injected with intravenous ^{18}F-FDG after an overnight fast. After an interval of 60 minutes in a quiet waiting area, resting state PET imaging was performed according to standard clinical protocol without programmed stimulation. A low-dose, non-contrast CT was performed for attenuation correction prior to PET imaging.

2.3 ^{18}F-FDG-PET/CT Imaging Analysis

Imaging measurements were performed by trained and experienced investigators blinded to noise and clinical data. On baseline attenuation correction CT images, VAT was measured as the volume of adipose tissue with Hounsfield units from −195 to −45 using the abdominal,

intercostal, and paraspinal musculature as boundaries on one 3 mm slice at the level of the umbilicus.(Ishai et al., 2019; Maurovich-Horvat et al., 2007) Subcutaneous adipose tissue (SAT) was measured as tissue of the same radiographic density within the subcutaneous space. VAT:SAT ratio, a known correlate of metabolic disease, was quantified.(Kaess et al., 2012)

Among the 238 individuals with brain imaging data, baseline AmygA was measured by a single reader. Using CT images and circular regions of interest with radii of approximately 15 mm, the mean bilateral amygdalar ^{18}F-FDG uptake was measured as a standardized uptake value (SUV) and then averaged. This mean value was corrected for mean temporal lobe activity to obtain a ratio of amygdalar to regulatory brain tissue activity (AmygA).(Ishai et al., 2019; Osborne et al., 2018; Osborne et al., 2020; Tawakol et al., 2017) Among randomly selected subjects from the parent cohort from which the current study samples were derived, the inter- and intra-reader variability of the AmygA measurement were a mean (standard deviation) of 0.06 (0.16) or 5.77% (16.13%) among a sample of 265 individuals and 0.01 (0.13) or 1.16% (12.52%) among a sample of 50 subjects, respectively.(Tawakol et al., 2017)

2.4 Adjudication of Noise Exposure, DM Events, and Covariables

Clinical status was evaluated by a separate team of blinded and trained investigators. Average transportation noise exposure over a 24-hour period was evaluated in 5 A-weight decibel (dBA) increments from <35 dBA to 65–70 dBA at the street-facing façade of each individual's home address using the United States Department of Transportation's Road and Aviation Noise Map from 2014.(United States Department of Transportation, 2014) The model approximated average traffic and aircraft noise over 24-hours in dBA to adjust instrument-measured sound to reflect the human ear's perception of relative loudness. Aircraft noise was quantified with the Aviation Environmental Design Tool version 2b service pack 2 and data on aircraft flight operation. Traffic noise was evaluated using roadway average annual traffic distributions, the Newly built National Transportation Noise Modeling Tool, and the Federal Highway Administration Traffic Noise Model version 2.5. For the DM sample, baseline type 2 DM was based on a clinical diagnosis, active medication, and existing laboratory values (i.e., two fasting blood glucose values >126 mg/dl or glycohemoglobin values >6.5%) applied to the American Diabetes Association (ADA) criteria.(American Diabetes Association, 2016) Individuals without baseline DM were evaluated over two years for the adjudication of incident type 2 DM using available notes and clinically acquired laboratory values and any of the same ADA criteria that were used to establishing a baseline diagnosis. For the DM sample, we additionally evaluated for the presence baseline of pre-DM (defined as a single fasting blood glucose ranging from 100–125 mg/dL or glycohemoglobin of 5.7–6.4%) with ADA criteria.(American Diabetes Association, 2016) For multivariable adjustment, clinically relevant covariables (e.g., age, sex, race, current smoking, hypertension, hyperlipidemia, malignancy and malignancy treatment history) were derived from the medical record. To assess and control for confounders that may be present in noisier neighborhoods, median neighborhood income was evaluated using the United States Census Bureau's 2015 American Community Survey's 5-Year Estimates.(United States Censusl Bureau, 2015) Crime rates were evaluated

using the United States Federal Bureau of Investigation's Massachusetts Offenses Known to Law Enforcement from 2015 for Massachusetts residents,(United States Federal Bureau of Investigation, 2015) and air pollution was assessed as the mean annual concentration of particulate matter with diameter <2.5 μm using 2017 United States Environmental Protection Agency data.(United States Environmental Protection Agency, 2017; McGuinn et al., 2017)

2.5   Statistical Analysis

For the primary prespecified analysis, noise exposure was divided into tertiles, after which those exposed to higher levels of noise (upper tertile, >45 dBA) were compared to those with lower exposure. Chi-square tests and t-tests (or Mann-Whitney U tests when skewed) were performed to assess for group differences between baseline categorical and continuous variables, respectively. Continuous variables were standardized for analyses. Linear regression was used to evaluate univariable and multivariable relationships with measures of adiposity and AmygA as standardized β and 95% confidence intervals (CIs). Cox proportional hazard ratios (HRs) were implemented to assess the relationship between noise exposure and subsequent type 2 DM. Kaplan-Meier curves were used to estimate DM-free survival. Individuals were censored at the date of DM diagnosis or last follow-up. Sensitivity analyses were performed to assess for the relationships between noise exposure in 5 dBA increments and >55 dBA (threshold established as unhealthy by the World Health Organization) with measures of visceral adiposity and incident type 2 DM.(Munzel et al., 2018) For multivariable analyses, covariables were selected a priori as those factors that were deemed to be potentially clinically relevant, including demographics (e.g., age, sex, race), markers of metabolic impairment (e.g., body mass index (BMI), adipose tissue measures, baseline DM, hypertension (HTN), hyperlipidemia, baseline pre-DM, and glucose measures), current smoking, prior malignancy and malignancy treatment, socioeconomic factors (e.g., neighborhood income and crime), air pollution exposure, and amygdalar activity. Combined models were implemented to assess the impact of higher transportation noise exposure on baseline VAT, change in VAT, and DM in models adjusted for combined demographic and clinical factors and combined socioeconomic and environmental factors. Backwards selection was employed in these combined models. Unadjusted mediation analysis was used to evaluate the prespecified single mediator paths:

1.   ↑noise exposure →↑AmygA→↑baseline VAT and

2.   ↑noise exposure →↑AmygA→↑DM risk.

The analyses estimate direct and indirect effects and CIs based upon 5,000 bias-corrected bootstrap samples by implementing an ordinary least squares or logistic regression framework.(Hayes, 2013) Given the use of bootstrapping, exact p-values for mediation analyses are not available; however, indirect pathways with CIs that do not cross zero are significant with p<0.05. Individuals with missing data were excluded from analysis. All analyses were performed using SPSS version 24 and the SPSS PROCESS macro version 3.4 Models 4 and 6 (IBM Corporation, Armonk, NY). A two-sided p-value <0.05 was determined to be significant for all analyses.

3. Results

3.1 Baseline Characteristics

The study cohorts were selected from an overall sample of 498 eligible individuals with a median age of 55 (interquartile range (IQR) 45–66) years, which was 42.0% male; 84.3% had prior malignancy. The VAT cohort of 403 eligible individuals (i.e., those in the overall sample with abdominal imaging to allow VAT measurement) had a median age of 55 (IQR 44–65) years and was 42.4% male; 86.4% had prior malignancy. Individuals with VAT > sample median (N=202) were older, had a higher BMI and glucose at the time of imaging, and were more likely to be male and have baseline HTN, hyperlipidemia, and DM. The DM cohort (i.e., those in the overall population without baseline type 2 DM and up to two years of clinical follow-up, N=224) had a median age of 54.5 (IQR 44–63) years and was 42.9% male; 89.3% had prior malignancy. Glucose at the time of imaging, maximum glucose within two years of imaging, pre-DM, amygdalar activity, and transportation noise exposure differed significantly between those who did and did not develop subsequent type 2 DM. Complete details are shown (Tables 1A & 1B). The distribution of transportation noise exposure in each of the three study samples is shown (Supplemental Tables 1A, 1B, and 1C).

3.2 Association between Noise Exposure and VAT

There were no significant relationships between higher transportation noise exposure and baseline: BMI, SAT, or VAT:SAT ratio (Table 2A). However, higher noise exposure associated with greater baseline VAT (standardized β [95% CI]: 0.230 [0.021, 0.438], unadjusted p=0.031). Furthermore, among the 67 individuals with follow-up VAT measured a median 358 (IQR 286–374) days after index scanning, noise exposure associated with greater gains in VAT (0.686 [0.185, 1.187], p=0.008) in a model adjusted for baseline VAT. Models for baseline VAT remained significant after adjustment for many covariables; however, the relationship was attenuated by adjustment for age, other baseline metabolic diseases (i.e., DM, HTN, and hyperlipidemia), and amygdalar activity. Further, the relationship remained in a model combining socioeconomic and environmental factors but was attenuated in a model combining demographic and clinical factors. Models for change in VAT remained robust to the addition of all covariables to baseline VAT in multivariable models and in both combined models (Table 2B). In sensitivity analyses, the relationship between noise exposure in 5 dBA increments and baseline (p=0.052) and change in VAT (p=0.066 when adjusted for baseline VAT) trended towards significance. The relationships with baseline and change in VAT were not significant when a threshold of >55 dBA was used (p=0.10 and p=0.53, respectively).

3.3 Association between Noise Exposure and DM Risk

During two years of follow-up, twenty-one individuals developed incident type 2 DM with confirmation by available laboratory values for all cases. Higher noise exposure predicted subsequent DM (HR [95% CI]: 2.429 [1.031, 5.719], p=0.042), and this remained significant after adjustment for age and sex (2.393 [1.015, 5.368], p=0.046) as well as additional adjustment for baseline adiposity measures, baseline HTN, baseline hyperlipidemia, glucose >100 mg/dL within two years before imaging, pre-DM, prior malignancy and malignancy treatment, or air pollution. The results were attenuated by addition of maximum glucose

value within two years before imaging, glucose at the time of imaging, neighborhood crime rate, or amygdalar activity. The relationship remained significant in models adjusted for combined demographic and clinical factors and combined socioeconomic and environmental factors (Table 3). Furthermore, those with noise exposure >45 dBA had decreased DM-free survival (log-rank p=0.036, Figure 2). In sensitivity analyses, the relationship between transportation noise exposure in 5 dBA increments and incident type 2 DM remained significant (1.272 [1.031, 1.568], p=0.025), but the relationship was not significant when a threshold of >55 dBA was used (p=0.19).

3.4 The Link between Noise Exposure to Visceral Adiposity and Incident Diabetes Involves Increased Amygdalar Activity

Consistent with prior observations, heightened transportation noise exposure associated with higher AmygA (standardized β [95% CI]: 0.572 [0.325, 0.820], p<0.001, Table 2A). (Osborne et al., 2020) Moreover, in unadjusted path analysis, the indirect path of noise >45 dBA→↑AmygA→↑baseline VAT was significant (standardized β [95% CI]: 0.108 [0.005, 0.225], p<0.05, Figure 3A). Similarly, the indirect path of noise exposure >45 dBA→↑AmygA→↑incident DM was significant in an unadjusted model (standardized log odds ratio [95% CI]: 0.229 [0.036, 0.647], p<0.05, Figure 3B).

4. Discussion

This study leveraged multi-system imaging to show that increased chronic transportation noise exposure associates with increased baseline VAT and gains in VAT as well as type 2 DM risk independently of many important covariables. Additionally, heightened amygdalar metabolic activity on ^{18}F-FDG-PET/CT imaging mediated the relationship between noise exposure and baseline VAT as well as incident type 2 DM. Although these pathways do not account for all the factors (e.g., health behaviors) that link noise exposure to metabolic diseases, the findings implicate stress-associated neural centers in participating in the initiation of this pathologic mechanism.

4.1 Relationship between Noise Exposure and Obesity and DM

Our results corroborate the known associations between noise exposure and obesity and DM.(Christensen et al., 2015; Christensen et al., 2016; Clark et al., 2017; Eze et al., 2017; Fritschi et al., 2011; Munzel et al., 2018; Pyko et al., 2015; Pyko et al., 2017; Shin et al., 2020; Sorensen et al., 2013) Notably, herein we extend prior findings by adjusting for a number of potential confounders in the same population, including radiographic adiposity measures and baseline blood glucose assessments, to show that there is a predominantly independent relationship between noise exposure and new onset type 2 DM within two years that persists even after accounting for baseline measures of metabolic impairment (e.g., pre-DM and baseline VAT). By using imaging to objectively quantify adipose tissue, we also build upon prior work by showing that individuals with higher noise exposure also have greater baseline VAT as well as gains in VAT over approximately one year. These results identify higher noise exposure as a largely independent and under-recognized risk factor for metabolic disease.

4.2 Mechanistic Insights

The amygdala is a limbic brain center that has a prominent role in responding to noise stress. (Osborne et al., 2020; Spreng, 2000; Zald and Pardo, 2002) When activated, amygdalar blood flow and metabolism increase, and its efferent neurons activate the SNS, leading to increased leukopoiesis, systemic inflammation, endothelial dysfunction, and oxidative stress.(Munzel et al., 2018; Osborne et al., 2020; Schmidt et al., 2015) Concurrently, HPA axis activity is increased, leading to increased cortisol with associated dysregulation of glucose metabolism and increased adiposity.(Munzel et al., 2018) Importantly, endothelial dysfunction, a known cardiovascular consequence of noise exposure, also predicts future prediabetes and DM and may directly contribute to the link between noise and metabolic disease.(Hahad et al., 2019; Munzel et al., 2017; Munzel et al., 2018) In addition, increased bone marrow activity, a marker of leukopoietic activity, is a known mediator of the relationship between increased AmygA and greater VAT as well as heightened atherosclerotic inflammation.(Ishai et al., 2019; Tawakol et al., 2017) Collectively, these changes ultimately lead to downstream cardiovascular and metabolic diseases, such as VAT, DM, and inflammatory atherosclerosis.(Heidt et al., 2014; Ishai et al., 2019; Munzel et al., 2017; Munzel et al., 2018; Osborne et al., 2018; Osborne et al., 2020; Spreng, 2000; Zald and Pardo, 2002) The current study expands upon the link from AmygA to VAT and type 2 DM to show that increased transportation noise exposure drives the front end of this pathway to incite these metabolic diseases, suggesting that the amygdala serves as an important conduit by which noise stress enters the body and triggers subsequent pathology.

Furthermore, these findings may provide further clarification of the complex interplay between noise exposure, AmygA, VAT, atherosclerotic inflammation, and CVD events. (Figueroa et al., 2016; Ishai et al., 2019; Osborne et al., 2020; Tawakol et al., 2017) Heightened AmygA leads to greater visceral adiposity. VAT itself has high levels of local inflammation that potentiate its own expansion and increase systemic inflammation. (Despres, 2012; Lau et al., 2005) Mechanistically, greater VAT volume further perpetuates the inflammatory milieu by augmenting monocytosis and priming local monocytes to produce cytokines, resulting in further peripheral monocyte migration and the development of inflammatory pathologies, including atherosclerosis.(Lau et al., 2005; Lumeng et al., 2007; Nagareddy et al., 2014) The current study suggests that noise-induced metabolic diseases likely participate in the multi-organ neuroinflammatory mechanism linking increased noise exposure to downstream CVD events.

Noise's deleterious impact on sleep may play an important role in these findings. While nocturnal transportation noise could not be directly measured in this study that implemented mean 24-hour noise measurements, poor sleep has been linked to increased perceived stress, neurohormonal changes, and heightened inflammation and oxidative stress.(Killgore, 2013; Munzel et al., 2017; Schmidt et al., 2013) These sleep-induced changes culminate in metabolic and cardiovascular diseases.(Cappuccio et al., 2010; Schmidt et al., 2015) Furthermore, impaired sleep increases amygdalar activity and reactivity and negatively modifies its connectivity with the inhibitory prefrontal cortex and other regulatory regions. (Killgore, 2013; Motomura et al., 2014) The impact of nocturnal noise on sleep, stress-

associated neural activity, and metabolic health should be simultaneously evaluated in subsequent research.

4.3   Clinical Implications

This study not only supports efforts to limit noise exposure in our communities but also identifies biological targets for possible therapeutic interventions in situations where noise mitigation alone is inadequate. The impact of behavioral therapies on the brain's stress response and downstream systemic inflammation as well as the impact of anti-inflammatory therapies could be evaluated in studies of individuals with high noise exposure and increased metabolic risk.(Creswell et al., 2012; Holzel et al., 2010; Taren et al., 2015; Tawakol et al., 2013)

4.4   Limitations

This study has notable limitations that relate to the retrospective study design. The sample was largely derived from patients with prior or suspected malignancy and may only represent a portion of the broad population at risk for health complications from noise exposure. In addition, there were relatively few individuals (approximately 10–15%) in the study populations with noise exposure greater than the World Health Organization threshold (>55 dBA), limiting the statistical power to detect significant differences at this threshold. Clinical follow-up occurred in a non-uniform fashion at the discretion of individual physicians, which may have influenced the results. Transportation noise exposure was estimated as a 24-hour average at each individual's home address; thus, nocturnal exposure and exposure at other locations (e.g., work) could not be assessed. In addition, measures of SNS and HPA axis activity (including cortisol) as well as those of systemic inflammation and oxidative stress, perceived stress, and health behaviors (e.g., sleep, diet, physical activity) were not available. The duration of time each individual lived at their home address prior to imaging was not known. Individual level socioeconomic factors were unavailable; thus, they were evaluated at the zip code or town level, a proxy which has been validated in prior studies.(Diez Roux, 2001) Future prospective studies that account for these limitations are warranted to further clarify the relationship between noise exposure and metabolic disease.

5.   Conclusions

Increased transportation noise exposure associates with greater VAT and type 2 DM risk. Amygdalar metabolic activity mediates the relationships between higher noise exposure and VAT as well as DM. These findings suggest that altered stress-associated neurobiological activity partially mediates the relationship between noise exposure and metabolic diseases in humans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

Data Availability

The data for this study can be made available upon reasonable request.

Abbreviations

AmygA	amygdalar metabolic activity
BMI	body mass index
CI	confidence interval
CVD	cardiovascular disease
DM	diabetes mellitus
^{18}F-FDG-PET/CT	^{18}F-fluorodeoxyglucose positron emission tomography/ computed tomography
HPA	hypothalamic-pituitary-adrenal
HR	hazard ratio
HTN	hypertension
IQR	interquartile range
SAT	subcutaneous adipose tissue
SNS	sympathetic nervous system
SUV	standardized uptake value
VAT	visceral adipose tissue

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Highlights

- Noise exposure associates with greater baseline and gains in visceral adiposity.

- Noise exposure also associates with greater diabetes risk over two years.

- Noise exposure's link to these diseases involves altered neurobiological activity.

- These findings suggest novel therapies for metabolic disease due to noise exposure.
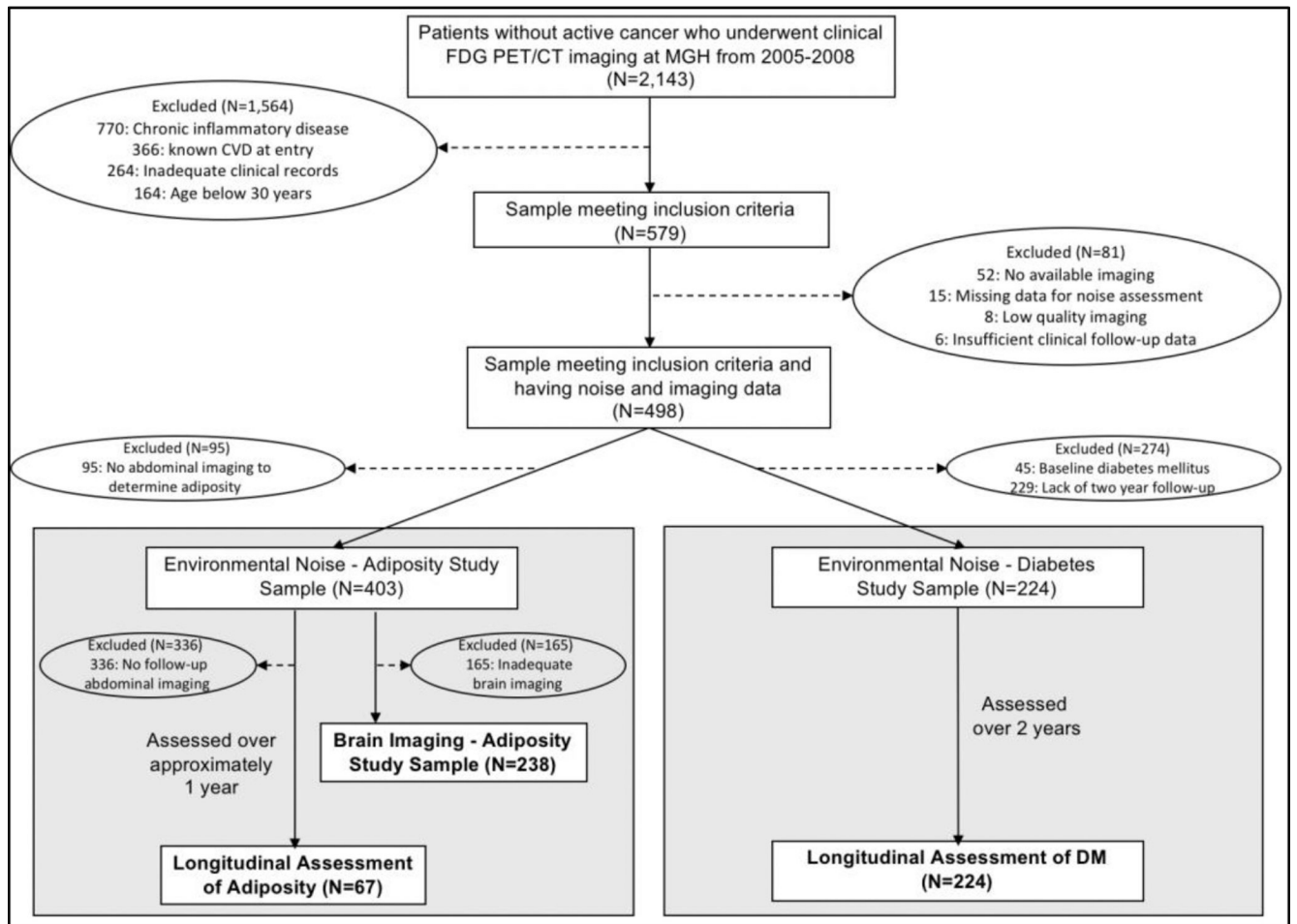
Figure 1:
Patient selection for the adiposity and DM samples. Abbreviations: CVD-cardiovascular disease, DM-diabetes mellitus, FDG PET/CT-fluorodeoxyglucose positron emission tomography/computed tomography, HTN-hypertension, VAT-visceral adipose tissue.
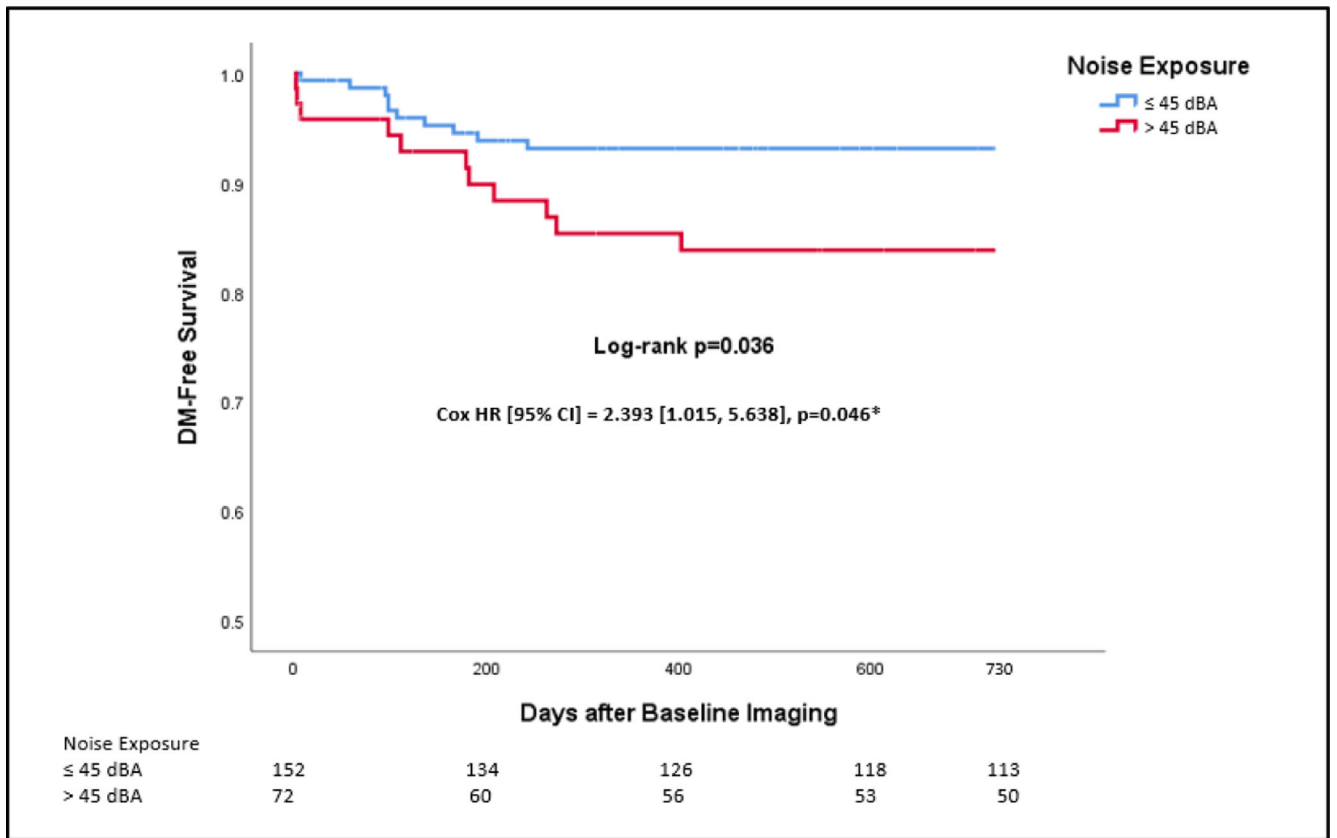
Figure 2:
Kaplan-Meier plot of type 2 DM-free survival by transportation noise exposure (upper tertile or >45 dBA vs. others). Log-rank p-value and a multivariable Cox model adjusted for age and sex are shown. Abbreviations: CI-confidence interval, DM-diabetes mellitus, HR-hazard ratio.

A)
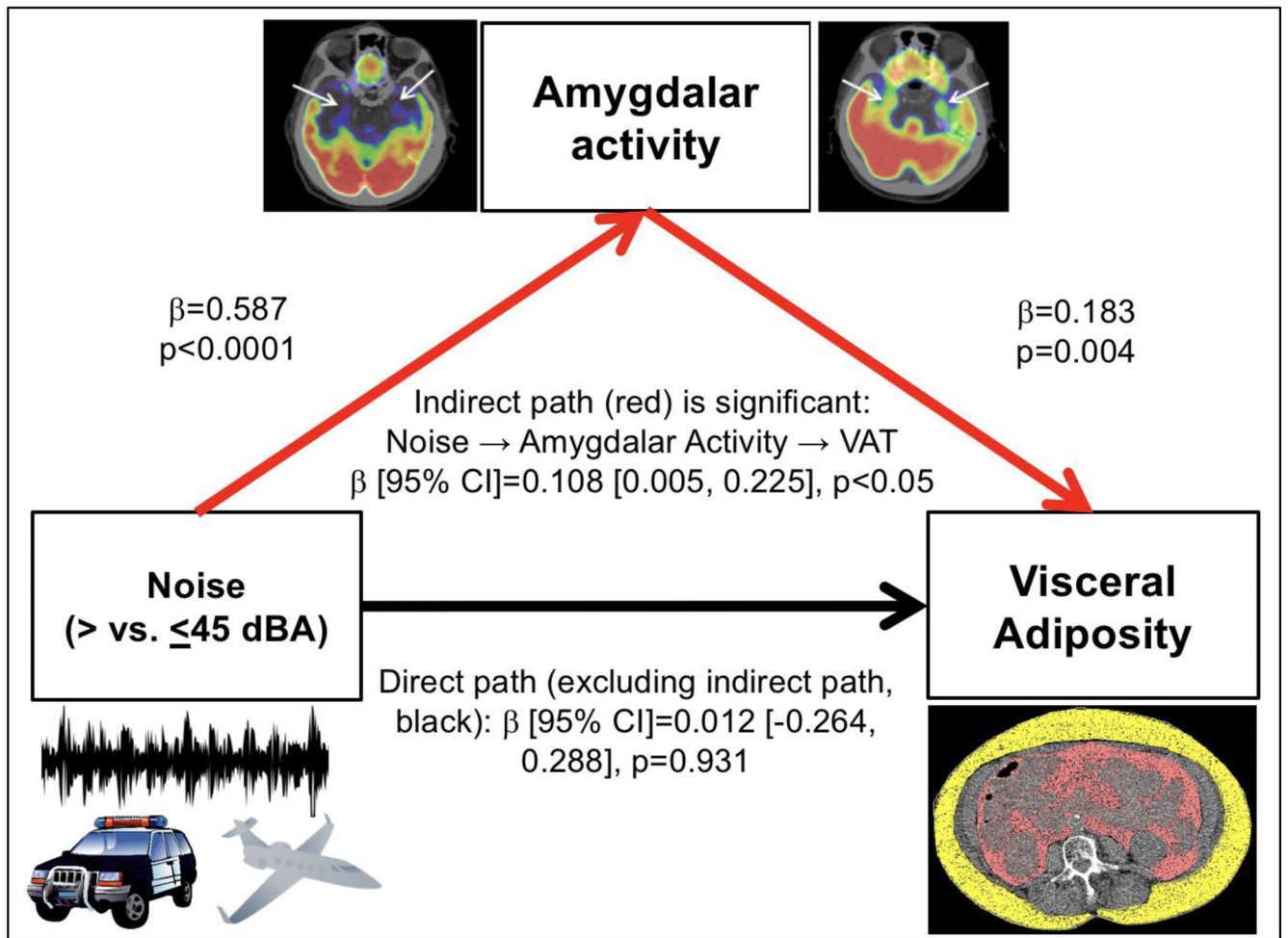
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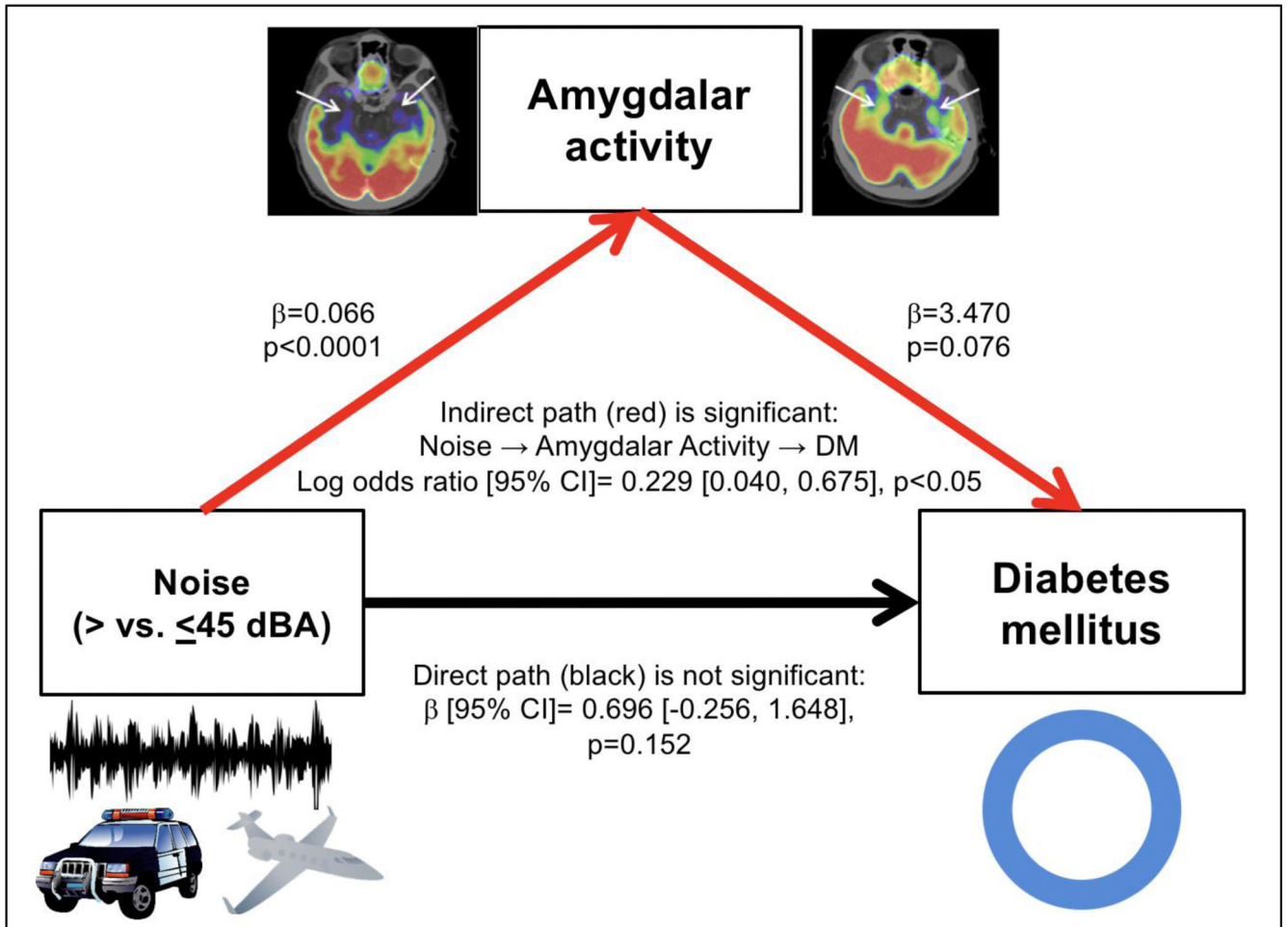
Figure 3:
Mediation models evaluating the pathways linking increased transportation noise exposure (>45 dBA) to: A) increased VAT through increased amygdalar metabolic activity and B) increased type 2 DM risk through increased amygdalar metabolic activity. Models are unadjusted. Indirect pathways are shown in red and direct pathways are shown in black. Abbreviations: AmygA-amygdalar metabolic activity, CI-confidence interval, VAT-visceral adipose tissue.

Table 1A:

Visceral adiposity sample baseline characteristics.

	Overall Sample (N=403)	Baseline VAT Volume ≥ median (N=202)	Baseline VAT Volume < median (N=201)	p-value
Median age, years (IQR)	55.00 (44.00–65.00)	60.00 (51.00–68.00)	49.00 (39.00–60.00)	**<0.001**
Male, N (%)	171 (42.4%)	117 (57.9%)	54 (26.9%)	**<0.001**
Caucasian, N (%)	367 (91.1%)	186 (92.1%)	181 (90.0%)	0.48
Median baseline BMI, kg/m² (IQR)	26.31 (23.41–30.89)	29.82 (26.63–32.72)	23.75 (21.61–26.05)	**<0.001**
Baseline DM, N (%)	33 (8.2%)	26 (12.9%)	7 (3.5%)	**0.001**
Baseline HTN, N (%)	136 (33.7%)	99 (49.0%)	37 (18.5%)	**<0.001**
Baseline hyperlipidemia, N (%)	110 (27.3%)	65 (32.2%)	35 (17.4%)	**<0.001**
Median glucose at time of imaging, mg/dL (IQR)	99.00 (90.00–108.00)	96.00 (87.00–103.00)	102.00 (94.00–114.25)	**<0.001**
Current smoking, N (%)	41 (10.2%)	26 (12.9%)	15 (7.5%)	0.067
History of cancer, N (%)	348 (86.4%)	171 (84.7%)	177 (88.1%)	0.32
History of chemotherapy or radiation, N (%)	317 (78.7%)	155 (76.7%)	162 (80.6%)	0.34
Median air pollution, particulate matter 2.5 μm, μg/m³ (IQR)	5.23 (4.83–6.00)	5.20 (4.83–6.00)	5.61 (4.83–6.00)	0.18
Median neighborhood income, $ (IQR)	79540 (61618–100286)	77425.5 (61148.5–100286)	80266 (63353.5–100604.5)	0.28
Median local crime rate (IQR)	21.69 (13.98–36.96)	22.46 (13.83–36.96)	20.53 (13.98–34.22)	0.74
Median average transportation noise exposure, dBA (IQR)	35–40 (<35–50)	35–40 (<35–50)	35–40 (<35–55)	0.12
Median amygdalar activity (IQR)	0.80 (0.73–0.85)	0.80 (0.72–0.84)	0.79 (0.74–0.86)	0.73

Median baseline VAT for population=48.38 cm³

Air pollution available in 384 subjects, crime in 304 subjects, and amygdalar activity in 238 subjects.

Bold type indicates p<0.05.

Abbreviations: BMI-body mass index, DM-diabetes mellitus, HTN-hypertension, IQR-interquartile range, VAT-visceral adipose tissue

Table 1B:

Diabetes sample baseline characteristics.

	Overall Sample (N=224)	DM Event (N=21)	No DM Event (N=203)	p-value
Median age, years (IQR)	54.50 (44.00–63.00)	56.00 (46.00–67.50)	54.00 (43.00–63.00)	0.32
Male, N (%)	96 (42.9%)	13 (61.9%)	83 (40.9%)	0.064
Caucasian, N (%)	210 (89.3%)	19 (90.5%)	181 (89.2%)	0.85
Median baseline BMI, kg/m^2 (IQR)	26.26 (23.02–30.84)	28.45 (23.15–32.04)	26.10 (23.01–30.68)	0.21
Median baseline VAT volume, cm^3 (IQR)	47.09 (26.00–72.51)	66.34 (23.32–102.94)	46.88 (26.27–71.25)	0.23
Baseline HTN, N (%)	69 (30.8%)	6 (28.6%)	63 (31.0%)	0.82
Baseline hyperlipidemia, N (%)	58 (25.9%)	7 (33.3%)	51 (25.1%)	0.41
Fasting glucose > 100 mg/dL within 2 years prior to imaging, N (%)	109 (48.7%)	8 (61.9%)	96 (47.3%)	0.20
Median maximum fasting glucose < 2 years before imaging, mg/dL (IQR)	102.00 (90.00–112.00)	116.00 (98.00–128.00)	101.00 (89.25–109.75)	**0.003**
Median fasting glucose at time of imaging, mg/dL (IQR)	98.00 (90.00–107.00)	104.50 (97.50–131.00)	97.00 (90.00–106.00)	**0.006**
Pre-DM, N (%)	113 (50.4%)	15 (71.4%)	6 (28.6%)	**0.043**
Current smoking, N (%)	17 (7.6%)	2 (9.5%)	15 (7.4%)	0.73
History of cancer, N (%)	200 (89.3%)	20 (95.2%)	180 (88.7%)	0.35
History of chemotherapy or radiation, N (%)	186 (83.0%)	20 (95.2%)	166 (81.8%)	0.12
Median air pollution, particulate matter 2.5 μm, μg/m^3 (IQR)	5.61 (4.83–6.13)	5.76 (4.83–6.06)	5.61 (4.83–6.13)	0.95
Median neighborhood income, $ (IQR)	80399 (61919–101597.75)	92300 (71467.50–111612)	79540 (61619–100286)	0.084
Median local crime rate (IQR)	21.69 (14.16–34.22)	16.50 (10.76–35.93)	22.46 (14.50–34.22)	0.51
Median average transportation noise exposure, dBA (IQR)	35–40 (<35–50)	45–50 (35–55)	35–40 (<35–50)	**0.019**
Median amygdalar activity (IQR)	0.79 (0.73–0.85)	0.84 (0.80–0.91)	0.78 (0.72–0.84)	**0.005**

Air pollution available in 384 subjects, crime in 304 subjects, and amygdalar activity in 238 subjects.

Abbreviations: BMI-body mass index, DM-diabetes mellitus, HTN-hypertension, IQR- interquartile range, VAT-visceral adipose tissue

Table 2A:

Associations between higher transportation noise exposure (>45 dBA or upper tertile vs. others) and tissue measurements.

Tissue Measurement	Standardized p (95% CI)	p-value
Baseline VAT volume (cm^3)	0.230 [0.021, 0.438]	**0.031**
Baseline BMI (kg/m^2)	0.156 [−0.044, 0.356]	0.13
Baseline SAT volume (cm^3)	0.034 [−0.175, 0.243]	0.75
Baseline VAT:SAT ratio	0.184 [−0.024, 0.392]	0.082
Subsequent change in VAT volume (cm^3)[a]	0.686 [0.185, 1.187]	**0.008**
Amygdalar activity	0.572 [0.325, 0.820]	**<0.001**

[a]Adjusted for baseline VAT volume (follow-up data available in 67 subjects). The remaining models are unadjusted.

Bold type indicates p<0.05.

Abbreviations: BMI-body mass index, SAT-subcutaneous adipose tissue, VAT-visceral adipose tissue

Table 2B:

Associations between higher transportation noise exposure (>45 dBA or upper tertile vs. others) and VAT volumes adjusted for covariables.

Covariable	Baseline VAT (cm³)		Change in VAT (cm³)[a]	
	Standardized β [95% CI]	p-value	Standardized β [95% CI]	p-value
Age	0.149 [−0.051, 0.349]	0.14	0.693 [0.188, 1.198]	**0.008**
Sex	0.222 [0.025, 0.420]	**0.027**	0.655 [0.153, 1.157]	**0.011**
Caucasian race	0.239 [0.030, 0.448]	**0.025**	0.684 [0.184, 1.185]	**0.008**
Baseline DM	0.179 [−0.025, 0.382]	0.086	0.673 [0.167, 1.178]	**0.010**
Baseline HTN	0.129 [−0.071, 0.330]	0.21	0.669 [0.161, 1.176]	**0.011**
Baseline hyperlipidemia	0.170 [−0.035, 0.374]	0.10	0.657 [0.152, 1.162]	**0.012**
Fasting glucose at time of imaging	0.043 [−0.179, 0.265]	0.71	0.790 [0.186, 1.394]	**0.011**
Current smoking	0.212 [0.002, 0.423]	**0.048**	0.706 [0.204, 1.207]	**0.007**
History of cancer	0.230 [0.021, 0.440]	**0.031**	0.686 [0.185, 1.187]	**0.008**
History of cancer treatment	0.228 [0.019, 0.437]	**0.033**	0.708 [0.201, 1.214]	**0.007**
Combined demographic and clinical factors	−0.061 [−0.261, 0.140]	0.55	0.745 [0.189, 1.300]	**0.010**
Median neighborhood income	0.216 [0.007, 0.426]	**0.043**	0.684 [0.179, 1.190]	**0.009**
Neighborhood total crime rate[b]	0.289 [0.053, 0.525]	**0.017**	0.622 [0.078, 1.166]	**0.026**
Air pollution[c]	0.302 [0.082, 0.522]	**0.007**	0.552 [0.070, 1.033]	**0.025**
Combined socioeconomic and environmental factors[c]	0.282 [0.068, 0.496]	**0.010**	0.741 [0.222, 1.261]	**0.006**
Amygdalar activity[d]	0.012 [−0.264, 0.288]	0.93	0.591 [0.090, 1.093]	**0.022**

Each row represents a separate model aside from the combined models: Combined demographic and clinical factors (age, sex, Caucasian race, baseline DM, baseline HTN, baseline hyperlipidemia, fasting glucose at time of imaging, current smoking, history of cancer, and history of cancer treatment) and combined socioeconomic and environmental factors (median neighborhood income and air pollution). Backwards selection was implemented for combined models.

[a]Also adjusted for baseline VAT.

[b]Crime data available in 304 subjects with baseline VAT and 50 patients with follow-up VAT.

[c]Air pollution data available in 384 subjects with baseline VAT and 63 patients with follow-up VAT.

[d]Amygdalar activity available in 238 patients with baseline VAT and all patients with follow-up VAT.

Bold type indicates p<0.05.

Abbreviations: CI-confidence interval, DM-diabetes mellitus, VAT-visceral adipose tissue

Table 3:

Cox models assessing the unadjusted and adjusted relationships between higher transportation noise exposure (>45 dBA or upper tertile vs. others) and subsequent type 2 DM.

Covariable	HR [95% CI]	p-value
None (univariable)	2.429 [1.031, 5.719]	**0.042**
Age and sex	2.393 [1.015, 5.638]	**0.046**
Caucasian race	2.431 [1.022, 5.785]	**0.045**
Baseline BMI	2.434 [1.033, 5.739]	**0.042**
Baseline VAT volume	2.619 [1.032, 6.643]	**0.043**
Baseline VAT/SAT ratio	2.666 [1.049, 6.774]	**0.039**
Baseline HTN	2.438 [1.033, 5.755]	**0.042**
Baseline hyperlipidemia	2.369 [1.003, 5.595]	**0.049**
Current smoking	2.385 [1.011, 5.626]	**0.047**
Fasting glucose > 100 mg/dL within 2 years prior to imaging	2.484 [1.050, 5.878]	**0.038**
Maximum fasting glucose < 2 years before imaging	1.723 [0.680, 4.368]	0.25
Fasting glucose at time of imaging	2.416 [0.989, 5.901]	0.053
Pre-DM	2.472 [1.044, 5.849]	**0.040**
History of cancer	2.424 [1.027, 5.721]	**0.043**
History of cancer treatment	2.397 [1.016, 5.655]	**0.046**
Combined demographic and clinical factors	2.658 [1.091, 6.475]	**0.036**
Median neighborhood income	2.668 [1.112, 6.398]	**0.028**
Neighborhood total crime rate[a]	2.258 [0.851, 5.993]	0.10
Air pollution[b]	2.601 [1.068, 6.334]	**0.035**
Combined Socioeconomic and environmental factors	2.613 [1.102, 6.194]	**0.029**
Amygdalar activity	1.968 [0.795, 4.873]	0.14

Each row represents a separate model (all multivariable models additionally adjusted for age and sex) aside from combined models: Combined demographic and clinical factors (age, sex, Caucasian race, baseline BMI, baseline HTN, baseline hyperlipidemia, pre-DM, current smoking, history of cancer, and history of cancer treatment) and combined socioeconomic and environmental factors (median neighborhood income and air pollution). Backwards selection was implemented for combined models.

[a]Crime data available in 171 subjects.

[b]Air pollution data available in 212 subjects.

Bold type indicates p<0.05.

Abbreviations: BMI-body mass index, CI-confidence interval, HTN-hypertension, SAT-subcutaneous adipose tissue, VAT-visceral adipose tissue.