Associations Between Residential Proximity to Traffic and Vascular Disease in a Cardiac Catheterization Cohort

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Objective—Exposure to mobile source emissions is nearly ubiquitous in developed nations and is associated with multiple adverse health outcomes. There is an ongoing need to understand the specificity of traffic exposure associations with vascular outcomes, particularly in individuals with cardiovascular disease.

Approach and Results—We performed a cross-sectional study using 2124 individuals residing in North Carolina, United States, who received a cardiac catheterization at the Duke University Medical Center. Traffic-related exposure was assessed via 2 metrics: (1) the distance between the primary residence and the nearest major roadway; and (2) location of the primary residence in regions defined based on local traffic patterns. We examined 4 cardiovascular disease outcomes: hypertension, peripheral arterial disease, the number of diseased coronary vessels, and recent myocardial infarction. Statistical models were adjusted for race, sex, smoking, type 2 diabetes mellitus, body mass index, hyperlipidemia, and home value. Results are expressed in terms of the odds ratio (OR). A 23% decrease in residential distance to major roadways was associated with higher prevalence of peripheral arterial disease (OR=1.29; 95% confidence interval, 1.08–1.55) and hypertension (OR=1.15; 95% confidence interval, 1.01–1.31). Associations with peripheral arterial disease were strongest in men (OR=1.42; 95% confidence interval, 1.17–1.74) while associations with hypertension were strongest in women (OR=1.21; 95% confidence interval, 0.99–1.49). Neither myocardial infarction nor the number of diseased coronary vessels were associated with traffic exposure.

Conclusions—Traffic-related exposure is associated with peripheral arterial disease and hypertension while no associations are observed for 2 coronary-specific vascular outcomes.

Visual Overview—An online visual overview is available for this article. **(*Arterioscler Thromb Vasc Biol*. 2018;38:275-282. DOI: 10.1161/ATVBAHA.117.310003.)**

Key Words: air pollution ■ hypertension ■ myocardial infarction ■ peripheral arterial disease ■ vascular diseases

Worldwide in 2010, ischemic heart disease and stroke combined to cause ≈1 in 4 deaths,[1–3] and ambient air pollution accounted for ≈3.4 million of the 52.8 million deaths (6.4%).[1] Traffic is a major source of air pollution exposure, and exposure to traffic-related air pollution, such as nitrogen oxides, has been associated with coronary atherosclerosis,[4,5] carotid artery calcification,[6,7] deep vein thrombosis,[8] hypertension in women,[9–11] peripheral arterial disease (PAD),[5,6] and myocardial infarction (MI).[12] In addition to these epidemiological studies, recent publications have highlighted molecular factors that may underlie the associations between traffic exposure and cardiovascular outcomes.[13–15] Despite this wealth of evidence, there are still conflicting signals on the association between traffic exposure and vascular outcomes; some epidemiological studies have failed to show associations between exposure to traffic and vascular outcomes, such as abdominal and aortic calcification,[6,16] coronary atherosclerosis progression,[17] and cardiac function.[18] In addition, observations from a mixed sex European cohort yielded little evidence of an association between nitrogen oxides and incident hypertension.[19] Possible reasons for this effect heterogeneity include sex differences, geographic region differences, association differences between disease occurring in coronary versus peripheral vascular beds, and potentially stronger associations in populations with underlying disease.

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Nonstandard Abbreviations and Acronyms	
DV	number of diseased coronary vessels
MI	myocardial infarction
OR	odds ratio
PAD	peripheral arterial disease
TEZ	traffic exposure zone

To better resolve the association between traffic exposure and vascular disease, we used the CATHGEN cohort (CATHeterization GENetics) to examine the relationship between multiple measures of traffic exposure and vascular outcomes. CATHGEN comprises individuals who received a cardiac catheterization at Duke University Hospital in Durham, NC.[20] Because of a higher prevalence of cardiovascular disease, individuals in CATHGEN may exhibit stronger associations with air pollution than the general population.[21]

Materials and Methods

Materials and Methods are available in the online-only Data Supplement. Briefly, we used a cohort composed of cardiac catheterization patients to examine associations between residential exposure to traffic and 4 cardiovascular outcomes: MI, the number of diseased coronary vessels at catheterization (DV), hypertension, and PAD. Residential exposure to traffic was assessed via 2 methods: the perpendicular distance the nearest roadway and traffic exposure zones (TEZ) which classified regions of the study area according to traffic type. We examined race- and sex-stratified models and compared observed associations to those seen using published, categorical models of residential exposure to traffic.

Results

Of the 2124 CATHGEN participants in the final study cohort (Figure 1), 60% (1274) were men and 71% (1499) were white. The average age was 61 years, and 45% (947) were current smokers or recently quit smoking. The interquartile range for distance to the nearest roadway was 990 m. The interquartile range for the negative logarithm transform was 1.46; this translated to a 23% decrease in residential distance to a major roadway for every 1-unit increase in the interquartile range (Table 1). Results were similar for both the basic and full model (Tables I and II in the online-only Data Supplement); therefore, we present results for the full model throughout the text. The decision to remove rural CATHGEN participants (those residing >2 miles from a roadway; n=130) did not alter or bias the observed associations (Table IB in the online-only Data Supplement).

Hypertension

Hypertension was significantly associated with proximity to major roadways (odds ratio [OR]=1.15; 95% confidence interval, 1.01–1.31; Figure 2; Table IA in the online-only Data Supplement). This association was stronger in blacks (OR=1.42; 95% confidence interval, 1.05–1.93) than in whites (OR=1.10; 95% confidence interval, 0.96–1.26); however, the confidence intervals overlapped, and the interaction by race was not significant (Table II in the online-only Data Supplement). We observed an association between residence in TEZ 5+ and hypertension (OR=2.97); however, this association had a wide 95% confidence interval (1.20–7.37) likely because of the small sample size in TEZ 5+. No other association with the TEZs was observed, indicating that any increased risk might be exclusive to high traffic volume roadways (Figure 3; Table III in the online-only Data Supplement).

Peripheral Arterial Disease

PAD was significantly associated with proximity to major roadways in the full model (OR=1.29; 95% confidence interval, 1.08–1.55). Unlike hypertension, this association was stronger in whites (OR=1.41; 95% confidence interval, 1.14–1.74) than blacks (OR=1.10; 95% confidence interval, 0.79–1.53). The PAD association was also stronger in men

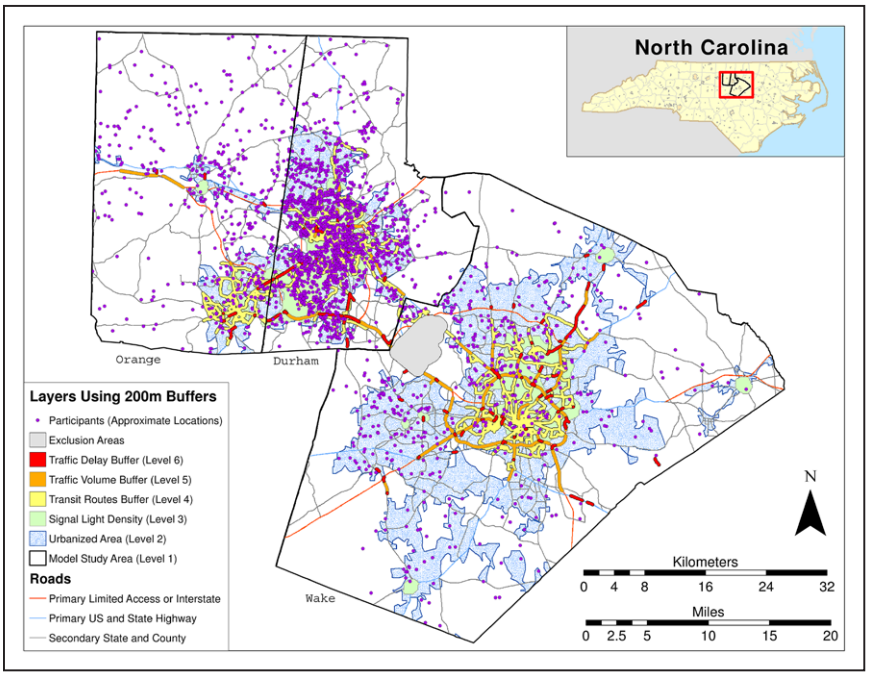

Figure 1. CATHGEN (CATHeterization GENetics) participants in study area. The distribution of CATHGEN participants within the study area of Durham, Wake, and Orange counties, NC, is given in the figure below. The participant locations are overlaid on a map of the primary and secondary roadway networks, as well as the traffic exposure zones. Reproduced from Environmental Health Perspectives, http://dx.doi.org/10.1289/ehp.1306980.[38]

Table 1. Demographic and Clinical Variables

Continuous clinical variable	Mean	SD	n missing (%)
Age, y	61.3	12.2	0 (0)
BMI, kg/m^2	30.3	7.36	12 (0.6)
Median home value ($1000s)	179	93.8	24 (1.1)
Binary clinical variable	**n**	**%**	**n missing (%)**
Sex (male)	1274	60.0	0 (0)
Smokers (yes)	947	44.6	0 (0)
Race (white)	1499	70.6	0 (0)
Type 2 diabetes mellitus (cases)	606	28.5	0 (0)
PAD (cases)	144	6.78	0 (0)
Hypertension (cases)	1472	69.3	0 (0)
MI (cases)	174	8.19	0 (0)
DV (0)	853	44.2	192 (9.0)
DV (1)	410	21.2	…
DV (2)	294	15.2	…
DV (3+)	375	19.4	…
Distance measure	**Mean**	**SD (IQR)**	**n missing (%)**
Proximity to major roadways, m	898	747 (990)	0 (0)
−log(Proximity to major roadways; log[m])	−6.29	1.28 (1.46)	0 (0)
Traffic exposure zone	**n**	**%**	**n missing (%)**
1 (Baseline)	407	19.2	0 (0)
2 (Urban areas)	765	36.0	…
3 (High signal light density)	318	15.0	…
4 (Transit routes)	581	27.4	…
5+ (High volume roadways)	53	2.50	…

Continuous variables are given as the mean and SD with the interquartile range also given for the distance measures. Binary and categorical variables are given as the number in the given level of that variable along with the percentage (%) of the cohort represented by that variable level, with levels of the variable in parentheses next to the binary/categorical variable name. The final column (missing) gives the percentage of missing values for each variable. For DV and the traffic exposure zones, the percentage missing for all values are listed alongside the baseline category. BMI indicates body mass index; DV, number of diseased coronary vessels; IQR, interquartile range; MI, myocardial infarction; N missing, number of missing observations; and PAD, peripheral arterial disease.

than women though the race- and sex-stratified confidence intervals overlapped (Figure 2; Table II in the online-only Data Supplement). We did not observe any associations among PAD and the TEZs (Figure 3; Table III in the online-only Data Supplement).

MI and DV

CATHGEN participants residing in urbanized areas (TEZ 2) had an increased prevalence of MI relative to those in TEZ 1 (OR=1.71; 95% confidence interval, 1.04–2.79). No significant associations with MI were observed with the other TEZs or residential proximity to roadways. We also observed no association between DV and any of the traffic exposure metrics.

Comparison of Roadway Metrics

We compared the observed associations with those observed when using traffic exposure metrics defined by classifying individuals into categorical bins based on their residential proximity to major roadways. To allow for direct comparison with previous publications,[4,5,10] comparisons were made for the most extreme exposure bins, that is, 0 to 100 m compared with 1000+ m from a major roadway for categorical 1000 and 0 to 50 m compared with 200+ m for categorical 200. Both metrics produced similar ORs, and we again observed associations with hypertension and PAD (Table IV in the online-only Data Supplement; Figure I in the online-only Data Supplement).

To compare models with the Akaike Information Criterion, we estimated associations using a binomial distribution that has a defined likelihood. The estimates from the binomial model were nearly identical to those seen using a quasibinomial model (Figure II in the online-only Data Supplement). The negative logarithm transform provided a better fit (smaller Akaike Information Criterion) to the data than the untransformed distance to roadways for all outcomes. The negative logarithm transform also yielded a smaller Akaike Information Criterion than the categorical 1000 m and categorical 200 m for all outcomes except DV (Table 2). The Akaike Information Criterion weight ratio indicates that for hypertension and PAD, the 2 outcomes with significant associations for all exposure metrics, the negative logarithm transform was between 2.32 and 8.99 times as likely to provide the best fit to the data as the other exposure metrics assessed (Table 2).

Discussion

Although the association of ambient air pollution with cardiovascular disease mortality is well documented,[22,23] there is still much to learn about the specificity of association among traffic exposure and various cardiovascular outcomes. Recent studies have suggested that traffic exposure may be less associated with coronary artery disease phenotypes than with atherosclerosis in other vascular beds.[6,18] Using the CATHGEN cohort, we observed that exposure to traffic is strongly associated with hypertension and PAD, outcomes indicative of systemic cardiovascular disease. Little to no association with traffic exposure was observed for the coronary-specific outcomes MI and DV.

Of the 4 outcomes assessed, PAD was the most significantly associated with residential proximity to major roadways. In a European cohort study of urban air pollution, residence within 50 m of a major roadway was associated with a 77% increase in the risk of PAD when compared with residence >200 m from a roadway.[5] In a study of blacks from Jackson, MS, participants living <150 m from a major roadway had a 17% higher prevalence of PAD than those living ≥300 m from a major roadway,[6] lower than estimates of risk observed in the European cohort. We expanded on these previous studies by examining individuals of both European and African ancestry

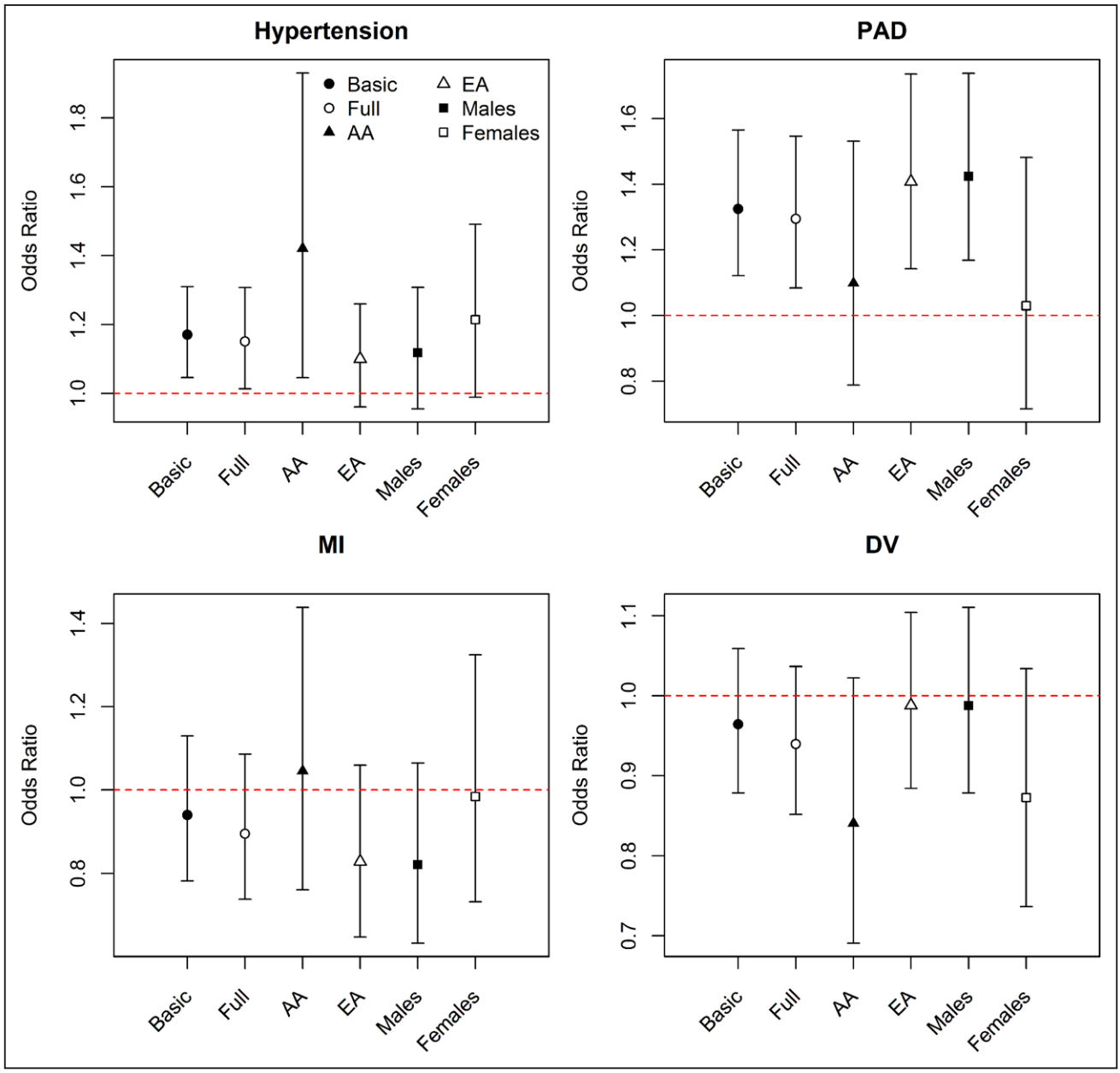

Figure 2. Association between clinical outcomes and residential proximity to roadways. The *x* axis represents each of the models considered, and the *y* axis is the odds ratio and associated 95% confidence interval for each model for the outcome given in the plot title. AA and EA indicate the race-stratified models while males and females indicate the sex-stratified models. All stratified models were run using the full model that adjusted for race, sex, body mass index, smoking, hyperlipidemia, type II diabetes mellitus, and median home value at the census tract level. The basic model adjusted for race and sex. AA indicates African Americans (blacks); DV, number of diseased coronary vessels; EA, European-Americans (whites); MI, myocardial infarction; and PAD, peripheral arterial disease

residing in the same geographic area. Using categorical 200 m, the identical exposure used for the European cohort[5] and similar to that used for the black cohort,[6] we observed associations with PAD stronger than those seen in these previous studies (OR=2.16; 95% confidence interval, 1.14–4.11). This association was elevated for individuals of European ancestry compared with those with African ancestry (Table IV in the online-only Data Supplement); this is consistent with previous studies,[5,6] but to our knowledge had never been directly examined. There are several factors that may underlie this potential ethnicity difference, including ethnicity-specific genetic variation, diet, or differences in the types of traffic to which they are exposed. Also, although we adjusted for socioeconomic status, we cannot discount the persistence of unmeasured confounding. However, given the width of the overlapping confidence intervals, we also cannot discount that the underlying association is approximately equivalent in both ethnicities, and further studies with larger ethnicity-specific sample sizes are needed to more fully resolve this observation.

Hypertension was also associated with proximity to major roadways. Most previous studies showing a positive association between hypertension and traffic focused on populations composed mainly or entirely of women.[9–11] In our analysis, hypertension was associated with traffic exposure in the

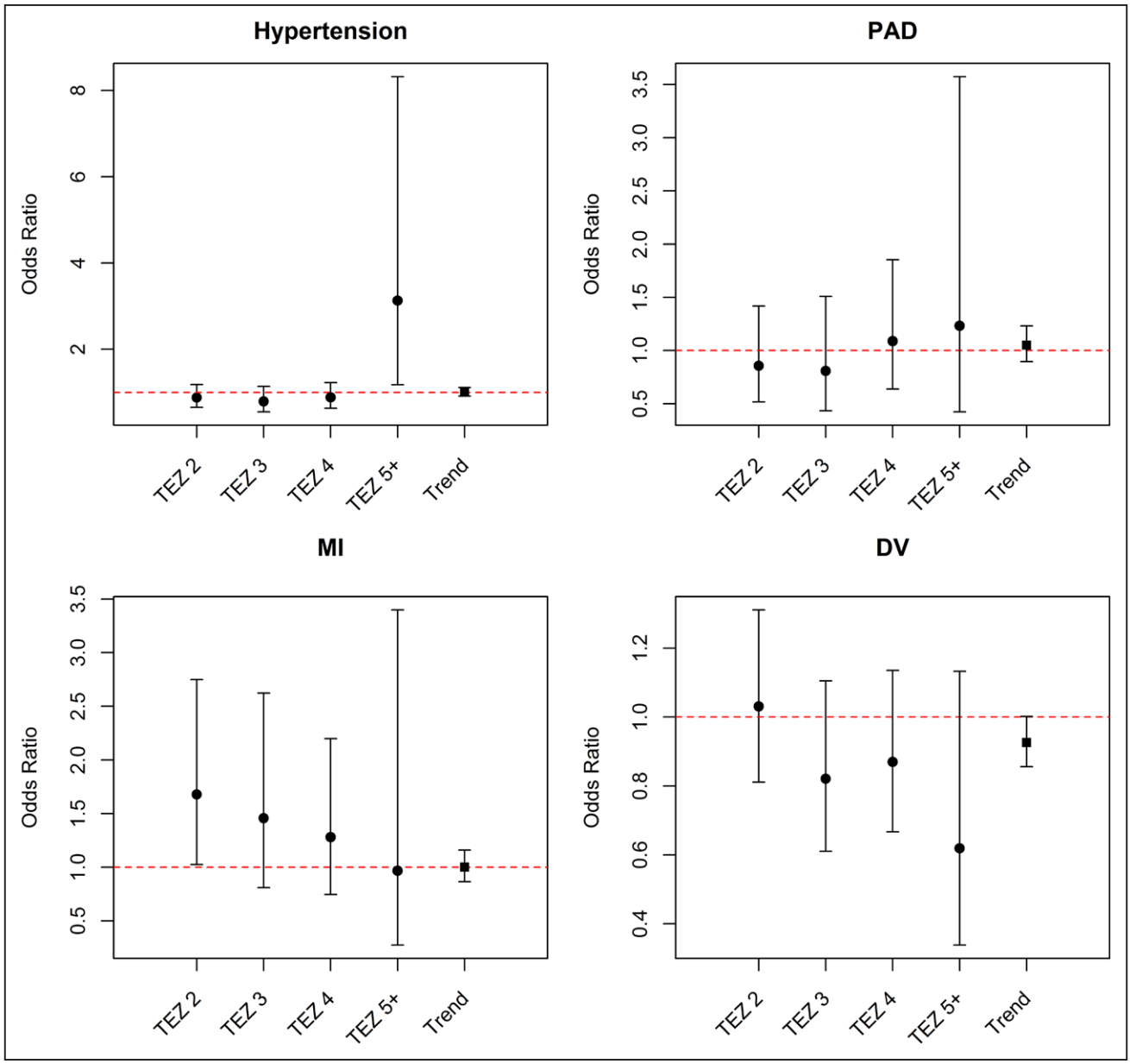

Figure 3. Association between clinical outcomes and traffic exposure zones. The *x* axis represents each of the models considered, and the *y* axis is the odds ratio and associated 95% confidence interval for each model for the outcome given in the plot title. Models were adjusted for race, sex, body mass index, hyperlipidemia, smoking, type II diabetes mellitus, and median home value at the census tract level. Traffic exposure zone (TEZ) 2 represents urban areas, TEZ 3 areas with high signal light density, TEZ 4 represents a 200-m buffer around transit routes, and TEZ 5+ represents a 200-m buffer around high volume roadways. Trend represents a linear association treating the TEZs as a linear variable. DV indicates number of diseased coronary vessels; MI, myocardial infarction; and PAD, peripheral arterial disease.

combined sex population; however, this association was strongest in women (Table II in the online-only Data Supplement). Our categorical 1000 m model matches the exposure used by Kirwa et al[10] in a general population study that also associated traffic exposure with prevalent hypertension in women. The estimated OR for hypertension in CATHGEN (1.73; 95% confidence interval, 0.93–3.23) is substantially higher than that observed previously (1.22; 95% confidence interval, 1.07–1.39).[10] Although the wide confidence interval from CATHGEN overlaps the estimate observed from a general population cohort, the difference in the odds ratios is suggestive of our underlying hypothesis that as a high-risk coronary disease cohort CATHGEN is enriched for individuals with increased sensitivity to traffic-related air pollution.

We did not observe associations between MI or DV and traffic exposure. MI was only associated with residence in urban areas in our analyses. Although short-term exposure to traffic is associated with MI,[12] a review of 26 articles on the associations between MI and exposure to air pollution yielded mixed results. Seven of the 26 studies examined long-term exposures, with 5 examining nitrogen dioxide, a gaseous pollutant primarily derived from traffic sources, or residential proximity to traffic. Among these 5 long-term traffic exposure studies, 2 showed no association and 3 showed an increased

Table 2. Comparison of Exposure Metrics

Outcome	Exposure	OR*	LCI	UCI	*P* Value	AIC	AICw	AICw Ratio
Hypertension	–log (distance)	1.15	1.02	1.30	0.02	2275.3	0.49	…
Hypertension	Distance	1.10	0.96	1.26	0.15	2278.7	0.09	5.34
Hypertension	Categorical 1000 m	1.58	1.06	2.36	0.02	2277.0	0.21	2.32
Hypertension	Categorical 200 m	1.66	1.00	2.75	0.048	2277.1	0.20	2.44
PAD	–log (distance)	1.31	1.10	1.57	0.003	953.4	0.63	…
PAD	Distance	1.37	1.06	1.77	0.02	955.5	0.22	2.86
PAD	Categorical 1000 m	2.26	1.28	3.99	0.005	957.5	0.08	7.81
PAD	Categorical 200 m	2.16	1.14	4.11	0.02	957.8	0.07	8.99
MI	–log (distance)	0.90	0.74	1.09	0.27	1175.3	0.51	…
MI	Distance	0.94	0.76	1.15	0.53	1176.2	0.33	1.56
MI	Categorical 1000 m	0.90	0.50	1.63	0.72	1179.4	0.07	7.65
MI	Categorical 200 m	0.73	0.33	1.61	0.44	1178.7	0.10	5.24
DV	–log (distance)	0.95	0.86	1.05	0.30	4689.8	0.23	…
DV	Distance	1.00	0.89	1.12	0.96	4690.9	0.13	1.70
DV	Categorical 1000 m	0.97	0.71	1.33	0.86	4689.4	0.28	0.81
DV	Categorical 200 m	0.85	0.58	1.25	0.42	4688.9	0.36	0.63

For each outcome, 4 exposure metrics were compared. The negative logarithm transform of distance to nearest roadway (–log [distance]), untransformed distance to the nearest roadway (distance), and 2 categorical exposure metrics. Categorical 1000 m gives the estimates based on comparison of residence 0 to 100 m and 1000+ m from a roadway. Categorical 200 m gives the estimates based on comparison of residence 0 to 50 m and 200+ m from a roadway. Both categorical 1000 m and categorical 200 m were chosen to allow for direct comparisons with previous studies of proximity to roadways and vascular outcomes.[4,5,10] AIC indicates Akaike Information Criterion; AICw, Akaike Information Criterion weight; DV, number of diseased coronary vessels; LCI, 95% lower confidence interval; MI, myocardial infarction; OR, odds ratio; PAD, peripheral arterial disease; and UCI, 95% upper confidence interval.

*A binomial distribution was used for these models so that a likelihood could be obtained. The binomial and quasibinomial models are highly correlated (Figure II in the online-only Data Supplement).

risk of MI with traffic-related air pollution exposure.[24] A previous study of associations between residential proximity to roadways and various vascular phenotypes noted no association with coronary artery calcification but a significant association with carotid intima–media thickness.[6] Although this study focused on subclinical phenotypes, our study examined hard cardiovascular disease outcomes. These 2 studies together suggest that associations with traffic exposure may be stronger for peripheral or systemic vascular phenotypes than with coronary-specific phenotypes.

An increasing volume of molecular epidemiology literature supports associations between exposure to traffic-related air pollution and health outcomes. Exposure to traffic-related air pollution is associated with markers of oxidative stress and inflammation.[25–27] Recently, traffic air pollution exposure has been linked with cellular markers of vascular injury and repair.[15] Even short-term exposure to nitric oxides may alter metabolic homeostasis.[28] Interaction studies have shown that genetic variants related to inflammatory pathways may modify associations between cardiovascular outcomes and traffic exposure.[13,14,29] Short-term exposure to nitrogen dioxide is associated with altered concentrations of metabolites, particularly long-chain fatty acids.[28] With respect to long-term exposure, traffic-derived pollutants are associated with accelerated epigenetic aging[30,31] and high-density lipoprotein cholesterol.[32] The majority of these studies involve either small sample sizes or observational associations; therefore, further research is needed to establish causal links between traffic exposure, molecular phenotypes, and clinical outcomes.

Strengths and Limitations

One of our primary limitations is that indirect measures of traffic-related air pollution cannot disentangle the various air pollution components that contribute to observed health effects, including traffic noise. Traffic noise is associated with health outcomes[33,34] and thus it must be considered a potential confounder of near roadway exposures. However, traffic noise and air pollution may independently contribute to vascular phenotypes,[35] and estimates suggest that the confounding of traffic noise on air pollution is <10%.[36] All geocoding procedures carry some degree of imprecision. This can lead to mismeasurement of the distance to a primary roadway, as well as misclassification for those residents who reside alongside the boundary of a TEZ or categorical exposure classification. Also, the roadway network used may not perfectly capture roadway networks over the entire time course of exposure. Given the near permanent nature of major roadways and rarity of modifications that would cause new roadways to seem, errors in the roadway network are expected to be minor. Both errors with respect to geocoding and the roadway network would not be expected to differ with respect to our outcome and thus should not increase the number of false positives but might attenuate the observed effect size.

The use of CATHGEN as a study cohort—a patient population enriched for those with known and unobserved cardiovascular disease—is both a strength and a limitation. Individuals with underlying cardiovascular disease have shown increased sensitivity to air pollution exposures,[6,37] an observation possibly responsible for the higher ORs observed in this study as compared with previous studies. However, it can be difficult to generalize these observations to the effects that might be observed in the general population. That said, it is important to study cohorts enriched for disease because those with underlying vascular diseases may disproportionately contribute to the health risks associated with air pollution exposure.

Another strength of CATHGEN is the large sample size and deep clinical phenotyping. The sample size allowed us to examine race- and sex-specific effects and validate in a single cohort racial and sex differences in associations that were previously observed across multiple publications. In addition, the phenotyping depth of CATHGEN allowed us to examine multiple vascular disease outcomes and to observe the specificity of traffic exposure associations for noncoronary vascular disease that was previously noted for subclinical phenotypes.[6]

Conclusion

Residential proximity to roadways is associated with PAD and hypertension in a cardiac catheterization cohort. The observed associations were stronger than those from general population-based studies but followed similar patterns of associations with respect to sex and race. Further studies are needed to fully understand the specificity and causality of these associations.

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References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2095–2128. doi: 10.1016/S0140-6736(12)61728-0.
2. Murray CJ, Lopez AD. *Global Burden of Disease*. Boston, MA: Harvard University Press; 1996.
3. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet*. 1997;349:1269–1276. doi: 10.1016/S0140-6736(96)07493-4.
4. Hoffmann B, Moebus S, Möhlenkamp S, Stang A, Lehmann N, Dragano N, Schmermund A, Memmesheimer M, Mann K, Erbel R, Jöckel KH; Heinz Nixdorf Recall Study Investigative Group. Residential exposure to traffic is associated with coronary atherosclerosis. *Circulation*. 2007;116:489–496. doi: 10.1161/CIRCULATIONAHA.107.693622.
5. Hoffmann B, Moebus S, Dragano N, Möhlenkamp S, Memmesheimer M, Erbel R, Jöckel KH; Heinz Nixdorf Recall Investigative Group. Residential traffic exposure and coronary heart disease: results from the Heinz Nixdorf Recall Study. *Biomarkers*. 2009;14(suppl 1):74–78. doi: 10.1080/13547500902965096.
6. Wang Y, Wellenius GA, Hickson DA, Gjelsvik A, Eaton CB, Wyatt SB. Residential proximity to traffic-related pollution and atherosclerosis in 4 vascular beds among African-American adults: results from the Jackson Heart Study. *Am. J. Epidemiol*. 2016;184:732–743.
7. Bauer M, Moebus S, Möhlenkamp S, Dragano N, Nonnemacher M, Fuchsluger M, Kessler C, Jakobs H, Memmesheimer M, Erbel R, Jöckel KH, Hoffmann B; HNR Study Investigative Group. Urban particulate matter air pollution is associated with subclinical atherosclerosis: results from the HNR (Heinz Nixdorf Recall) study. *J Am Coll Cardiol*. 2010;56:1803–1808. doi: 10.1016/j.jacc.2010.04.065.
8. Baccarelli A, Martinelli I, Pegoraro V, Melly S, Grillo P, Zanobetti A, Hou L, Bertazzi PA, Mannucci PM, Schwartz J. Living near major traffic roads and risk of deep vein thrombosis. *Circulation*. 2009;119:3118–3124. doi: 10.1161/CIRCULATIONAHA.108.836163.
9. Coogan PF, White LF, Jerrett M, Brook RD, Su JG, Seto E, Burnett R, Palmer JR, Rosenberg L. Air pollution and incidence of hypertension and diabetes mellitus in black women living in Los Angeles. *Circulation*. 2012;125:767–772. doi: 10.1161/CIRCULATIONAHA.111.052753.
10. Kirwa K, Eliot MN, Wang Y, Adams MA, Morgan CG, Kerr J, Norman GJ, Eaton CB, Allison MA, Wellenius GA. Residential proximity to major roadways and prevalent hypertension among postmenopausal women: results from the Women's Health Initiative San Diego Cohort. *J Am Heart Assoc*. 2014;3:e000727. doi: 10.1161/JAHA.113.000727.
11. Kingsley SL, Eliot MN, Whitsel EA, Wang Y, Coull BA, Hou L, Margolis HG, Margolis KL, Mu L, Wu WC, Johnson KC, Allison MA, Manson JE, Eaton CB, Wellenius GA. Residential proximity to major roadways and incident hypertension in post-menopausal women. *Environ Res*. 2015;142:522–528. doi: 10.1016/j.envres.2015.08.002.
12. Peters A, von Klot S, Heier M, Trentinaglia I, Hörmann A, Wichmann HE, Löwel H; Cooperative Health Research in the Region of Augsburg Study Group. Exposure to traffic and the onset of myocardial infarction. *N Engl J Med*. 2004;351:1721–1730. doi: 10.1056/NEJMoa040203.
13. Ward-Caviness CK, Neas LM, Blach C, Haynes CS, LaRocque-Abramson K, Grass E, Dowdy E, Devlin RB, Diaz-Sanchez D, Cascio WE, Lynn Miranda M, Gregory SG, Shah SH, Kraus WE, Hauser ER. Genetic variants in the bone morphogenic protein gene family modify the association between residential exposure to traffic and peripheral arterial disease. *PLoS One*. 2016;11:e0152670. doi: 10.1371/journal.pone.0152670.
14. Van Hee VC, Adar SD, Szpiro AA, Barr RG, Diez Roux A, Bluemke DA, Sheppard L, Gill EA, Bahrami H, Wassel C, Sale MM, Siscovick DS, Rotter JI, Rich SS, Kaufman JD. Common genetic variation, residential proximity to traffic exposure, and left ventricular mass: the Multi-Ethnic Study of Atherosclerosis. *Environ Health Perspect*. 2010;118:962–969. doi: 10.1289/ehp.0901535.
15. DeJarnett N, Yeager R, Conklin DJ, Lee J, O'Toole TE, McCracken J, Abplanalp W, Srivastava S, Riggs DW, Hamzeh I. Residential proximity to major roadways is associated with increased levels of ac133+ circulating angiogenic cells. *Arterioscler Thromb Vasc Biol*. 2015;35:2468–2477. doi: 10.1161/ATVBAHA.115.305724.
16. Allen RW, Davies H, Cohen MA, Mallach G, Kaufman JD, Adar SD. The spatial relationship between traffic-generated air pollution and noise in 2 US cities. *Environ Res*. 2009;109:334–342. doi: 10.1016/j.envres.2008.12.006.
17. Gan WQ, Allen RW, Brauer M, Davies HW, Mancini GB, Lear SA. Long-term exposure to traffic-related air pollution and progression of carotid artery atherosclerosis: a prospective cohort study. *BMJ Open*. 2014;4:e004743. doi: 10.1136/bmjopen-2013-004743.
18. Weaver A, Wellenius G, Wu W-C, Hickson D, Kamalesh M, Wang Y. Residential proximity to major roadways is not associated with cardiac

function in African Americans: results from the Jackson Heart Study. *Int J Environ Res Publ Health*. 2016;13:581–592.
19. Sørensen M, Hoffmann B, Hvidberg M, Ketzel M, Jensen SS, Andersen ZJ, Tjønneland A, Overvad K, Raaschou-Nielsen O. Long-term exposure to traffic-related air pollution associated with blood pressure and self-reported hypertension in a Danish cohort. *Environ Health Perspect*. 2012;120:418–424. doi: 10.1289/ehp.1103631.
20. Kraus WE, Granger CB, Sketch MH Jr, Donahue MP, Ginsburg GS, Hauser ER, Haynes C, Newby LK, Hurdle M, Dowdy ZE, Shah SH. A guide for a cardiovascular genomics biorepository: the CATHGEN experience. *J Cardiovasc Transl Res*. 2015;8:449–457. doi: 10.1007/s12265-015-9648-y.
21. McGuinn LA, Ward-Caviness CK, Neas LM, Schneider A, Diaz-Sanchez D, Cascio WE, Kraus WE, Hauser E, Dowdy E, Haynes C, Chudnovsky A, Koutrakis P, Devlin RB. Association between satellite-based estimates of long-term PM2.5 exposure and coronary artery disease. *Environ Res*. 2016;145:9–17. doi: 10.1016/j.envres.2015.10.026.
22. Brook RD, Urch B, Dvonch T, et al. Insights into the mechanisms and mediators of the effects of air pollution exposure on blood pressure and vascular function in healthy humans. *Hypertension*. 2009;54:18.
23. Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC Jr, Whitsel L, Kaufman JD; American Heart Association Council on Epidemiology and Prevention; Council on the Kidney in Cardiovascular Disease; and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*. 2010;121:2331–2378. doi: 10.1161/CIR.0b013e3181dbece1.
24. Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L. Effects of air pollution on the incidence of myocardial infarction. *Heart*. 2009;95:1746–1759. doi: 10.1136/hrt.2009.175018.
25. Chuang KJ, Chan CC, Su TC, Lee CT, Tang CS. The effect of urban air pollution on inflammation, oxidative stress, coagulation, and autonomic dysfunction in young adults. *Am J Respir Crit Care Med*. 2007;176:370–376. doi: 10.1164/rccm.200611-1627OC.
26. Li N, Sioutas C, Cho A, Schmitz D, Misra C, Sempf J, Wang M, Oberley T, Froines J, Nel A. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. *Environ Health Perspect*. 2003;111:455–460.
27. Lane KJ, Levy JI, Scammell MK, Peters JL, Patton AP, Reisner E, Lowe L, Zamore W, Durant JL, Brugge D. Association of modeled long-term personal exposure to ultrafine particles with inflammatory and coagulation biomarkers. *Environ Int*. 2016;92–93:173–182. doi: 10.1016/j.envint.2016.03.013.
28. Ward-Caviness CK, Breitner S, Wolf K, Cyrys J, Kastenmüller G, Wang-Sattler R, Schneider A, Peters A. Short-term NO2 exposure is associated with long-chain fatty acids in prospective cohorts from Augsburg, Germany: results from an analysis of 138 metabolites and three exposures. *Int J Epidemiol*. 2016;45:1528–1538. doi: 10.1093/ije/dyw247.
29. Ward-Caviness CK, Neas LM, Blach C, Haynes CS, LaRocque-Abramson K, Grass E, Dowdy ZE, Devlin RB, Diaz-Sanchez D, Cascio WE, Miranda ML, Gregory SG, Shah SH, Kraus WE, Hauser ER. A genome-wide trans-ethnic interaction study links the PIGR-FCAMR locus to coronary atherosclerosis via interactions between genetic variants and residential exposure to traffic. *PLoS One*. 2017;12:e0173880. doi: 10.1371/journal.pone.0173880.
30. Ward-Caviness CK, Nwanaji-Enwerem JC, Wolf K, Wahl S, Colicino E, Trevisi L, Kloog I, Just AC, Vokonas P, Cyrys J, Gieger C, Schwartz J, Baccarelli AA, Schneider A, Peters A. Long-term exposure to air pollution is associated with biological aging. *Oncotarget*. 2016;7:74510–74525. doi: 10.18632/oncotarget.12903.
31. Nwanaji-Enwerem JC, Colicino E, Trevisi L, Kloog I, Just AC, Shen J, Brennan K, Dereix A, Hou L, Vokonas P. Long-term ambient particle exposures and blood DNA methylation age: findings from the VA normative aging study. *Environ Epigenet*. 2016;2:1–10.
32. Bell G, Mora S, Greenland P, Tsai M, Gill E, Kaufman JD. Association of air pollution exposures with high-density lipoprotein cholesterol and particle number: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2017;37:976–982. doi: 10.1161/ATVBAHA.116.308193.
33. Sørensen M, Andersen ZJ, Nordsborg RB, Becker T, Tjønneland A, Overvad K, Raaschou-Nielsen O. Long-term exposure to road traffic noise and incident diabetes: a cohort study. *Environ Health Perspect*. 2013;121:217–222. doi: 10.1289/ehp.1205503.
34. Leon Bluhm G, Berglind N, Nordling E, Rosenlund M. Road traffic noise and hypertension. *Occup Environ Med*. 2007;64:122–126. doi: 10.1136/oem.2005.025866.
35. Kälsch H, Hennig F, Moebus S, Möhlenkamp S, Dragano N, Jakobs H, Memmesheimer M, Erbel R, Jöckel KH, Hoffmann B; Heinz Nixdorf Recall Study Investigative Group. Are air pollution and traffic noise independently associated with atherosclerosis: the Heinz Nixdorf Recall Study. *Eur Heart J*. 2014;35:853–860. doi: 10.1093/eurheartj/eht426.
36. Tétreault LF, Perron S, Smargiassi A. Cardiovascular health, traffic-related air pollution and noise: are associations mutually confounded? A systematic review. *Int J Public Health*. 2013;58:649–666. doi: 10.1007/s00038-013-0489-7.
37. Pope CA 3rd. Epidemiology of fine particulate air pollution and human health: biologic mechanisms and who's at risk? *Environ Health Perspect*. 2000;108(suppl 4):713–723.
38. Ward-Caviness CK, Kraus WE, Blach C, et al. Association of roadway proximity with fasting plasma glucose and metabolic risk factors for cardiovascular disease in a cross-sectional study of cardiac catheterization patients. *Environ Health Perspect*. 2015;123:1007–1014.

Highlights

- Exposure to traffic is associated with peripheral arterial disease and hypertension in individuals at high risk of cardiovascular disease.
- Associations between traffic and vascular outcomes are stronger in individuals at greater risk of cardiovascular disease than the general population but follow similar sex and race effects.
- No association is observed between residential exposure to traffic and coronary-specific outcomes (recent myocardial infarction and coronary vessel disease).