Ethnic Differences in Ambient Air Pollution and Risk of Acute Ischemic Stroke

Jeffrey J. Wing, PhD[a,d], **Sara D. Adar, ScD**[a], **Brisa N. Sánchez, PhD**[b], **Lewis B. Morgenstern, MD**[a,c], **Melinda A. Smith, DrPH**[c], and **Lynda D. Lisabeth, PhD**[a,c]

[a]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, United States

[b]Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, United States

[c]Department of Neurology, Stroke Program, University of Michigan, Ann Arbor, United States

Abstract

Objectives—To investigate the association between short-term changes in ambient pollution (particulate matter < 2.5μm in aerodynamic diameter ($PM_{2.5}$) and ozone (O_3)) and the risk of ischemic stroke among individuals living in a bi-ethnic community and whether this association is modified by ethnicity.

Methods—We identified incident ischemic stroke cases from the population-based Brain Attack Surveillance in Corpus Christi (BASIC) project between 2000 and 2012. Associations between $PM_{2.5}$ (mean 24-hour) and O_3 (maximal 8-hour) levels, measured on the same-day and lags of 1-3 days, and odds of ischemic stroke were assessed using a time-stratified case-crossover design and modeled using conditional logistic regression. We explored race/ethnicity (Mexican American versus non-Hispanic white) as a modifier by including interaction terms in the models.

Results—There were 2,948 ischemic strokes with median age 71 years (IQR: 59-80). We observed no overall associations between the air pollutants and odds of ischemic stroke at any lag. When stratified by ethnicity, higher O_3 was consistently associated with greater odds of ischemic stroke for non-Hispanic whites, but not for Mexican Americans. Higher $PM_{2.5}$ was generally associated with lower odds of ischemic stroke for non-Hispanic whites but modestly greater odds for Mexican Americans.

Corresponding Author Information: Jeffrey J. Wing, PhD, Department of Public Health, 307 Michigan Heath Hill, 545 Michigan St. NE, Suite 300, Grand Rapids, MI 49503, Tel. 616-331-5537, Fax. 616-331-5550, wingjeff@umich.edu.
[d]Present address: Department of Public Health, College of Health Professions, Grand Valley State University, Grand Rapids, Michigan, United States

Conclusion—Ethnic differences in the associations between ischemic stroke and short-term exposures to O_3 and $PM_{2.5}$ were suggested indicating that further study in diverse populations may be warranted.

Keywords

1. INTRODUCTION

Acute changes in air pollution have been linked to increased risk of cardiovascular events (Brook et al., 2010; Pope and Dockery, 2006; Simkhovich et al., 2008), but less is known in terms of the association with stroke specifically. Published studies of stroke have examined relationships with particulate matter less than 2.5μm in aerodynamic diameter ($PM_{2.5}$) and ozone (O_3), but inconsistent evidence exists regarding the associations between acute exposures to these pollutants and stroke incidence (Henrotin et al., 2007, 2010; Maheswaran et al., 2012; O'Donnell et al., 2011). One possible explanation for variation in associations across studies could be differing susceptibilities of the populations studied. For example, previous research in cardiovascular disease has suggested there may be differential associations by race/ethnicity, with Hispanics reported to be more susceptible to PM-induced health effects (Allen et al., 2009; Ostro et al., 2008; Sacks et al., 2011). Existing stroke research, however, has been conducted in predominantly non-Hispanic white populations and thus questions remain regarding enhanced susceptibility by race/ethnicity for this endpoint.

Our objective was to investigate associations between daily changes in ambient $PM_{2.5}$ and O_3 levels and the risk of ischemic stroke and to explore effect modification of these associations by ethnicity. Using data from individuals living in the bi-ethnic community of Nueces County, Texas between 2000 and 2012 and a time-stratified case-crossover design, this analysis builds upon past research in this community that documented borderline significant associations between $PM_{2.5}$ and O_3 and stroke (Lisabeth et al., 2008). By more than doubling the follow-up period, we improve our power to detect associations and are able to focus on a more specific endpoint of ischemic stroke using validated data that is not available in many studies. We furthermore add a new hypothesis that associations will be modified by ethnicity. Specifically, we hypothesized that higher levels of $PM_{2.5}$ and O_3 are associated with increased risk of incident ischemic stroke and that ethnicity modifies the associations between $PM_{2.5}$ and O_3 and incident ischemic stroke, such that the associations are greater in Mexican Americans compared with non-Hispanic whites.

2. MATERIAL AND METHODS

2.1 Study Population

Data are from the Brain Attack Surveillance in Corpus Christi (BASIC) project (Morgenstern et al., 2013; Smith et al., 2004). BASIC is an ongoing population-based stroke surveillance study in Nueces County, Texas. Nueces County is located on the Gulf Coast, geographically isolated from the larger cities in southeast Texas, being over 150 miles from

Houston and San Antonio making complete case capture for stroke possible. Approximately, 340,000 people live in Nueces County with the majority of the population (95%) residing in the urban city of Corpus Christi. Based on the 2010 Census, 61% of the population is Mexican American and 33% is non-Hispanic white (US Census Bureau, 2012). There were 2,948 ischemic strokes included in the current analysis after 268 strokes were excluded due to missing exposure data.

2.2 Study Design

We used a time-stratified case-crossover study design to assess the associations between ambient air pollution ($PM_{2.5}$ and O_3) and odds of incident ischemic stroke and evaluate whether ethnicity modifies these associations. This study design allowed for the comparison of each subject's exposure to air pollution prior to an acute stroke event with his or her own exposure during referent control periods where he/she did not have a stroke (Lumley and Levy, 2000). Control periods were selected on the same day of the week, falling in the same calendar month as the stroke event. Such that if an individual had a stroke on July 1st, the control dates would all be post-stroke dates of July 8th, 15th, 22nd, and 29th. Similarly, if an individual had a stroke on July 15th, the control dates would be the two pre-stroke dates (July 1st and 8th) and the two post-stroke dates (July 22nd and 29th). This selection approach avoids overlap bias and bias in time trends while controlling for seasonality and all time-invariant individual level characteristics (Janes et al., 2005).

2.3 Stroke Ascertainment

Methods for case identification in BASIC included active and passive surveillance techniques as has been previously described (Morgenstern et al., 2013; Smith et al., 2004). Briefly, between January 1, 2000 and June 30, 2012, trained abstractors screened ischemic stroke cases from seven hospitals in the county. Out of hospital surveillance was also conducted using other sources at various times in the study as previously described (Morgenstern et al., 2013). Admission and emergency department logs were screened daily for validated cerebrovascular diagnostic terms. Monthly admissions from the hospitals were also checked for cerebrovascular ICD-9 discharge codes for stroke. Study neurologists blinded to age and ethnicity validated strokes according to published international clinical criteria (Asplund et al., 1988) that require a focal neurologic deficit of acute onset specifically attributable to cerebrovascular distribution lasting longer than 24 hours. For the purposes of this study, we focused on first-ever completed ischemic strokes defined as no documented medical history of stroke/transient ischemic attack (TIA) in the medical record. Per the BASIC protocol, patients were excluded if they were younger than 45 years of age, lived outside of Nueces County, or if their strokes were traumatic. The BASIC project was approved by the University of Michigan Institutional Review Board and each of the Nueces County hospital systems.

2.4 Other Covariates Collected (Race/Ethnicity Ascertainment)

We ascertained race/ethnicity from medical records, which have been demonstrated to have a 97% agreement with self-reported race/ethnicity in this study community (kappa=0.94) (Smith et al., 2004). Additional information collected from medical records included date of first presentation for stroke, demographics, traditional stroke risk factors, including diabetes,

hypertension, atrial fibrillation, high cholesterol, heart disease, and smoking status. Home addresses were recorded from the medical record and sent to an external company for geocoding (Mapping Analytics, Rochester, New York). Approximately 97% of addresses were able to be geocoded, with 94% at the block-face-level.

2.5 Air Pollutant and Meteorology Data

We obtained ambient air pollutant concentration ($PM_{2.5}$ and O_3) and meteorological data for 2000 to 2012 from the Texas Commission on Environmental Quality's (TCEQ) Texas Air Monitoring Information System (TAMIS) (TCEQ (Texas Commission on Environmental Quality), 2012). Data for the air pollutants and wind direction were collected from one monitor centrally located within the urban population, Corpus Christi West C4 (483550025). $PM_{2.5}$ was measured using a tapered element oscillating microbalance (TEOM) and O_3 was measured using an ultraviolet absorption analyzer. Relative humidity was calculated using dew point temperature from the National Oceanic and Atmospheric Administration (NOAA) (NOAA (National Oceanographic and Atmospheric Administration), 2013) from the Corpus Christi International airport 6.5 km away from the pollutant monitor. $PM_{2.5}$, ambient temperature, and relative humidity were averaged daily (midnight to midnight) and the daily maximal 8-hour average was calculated for O_3. Of the 4,565 days in the study period, there were 329 days with insufficient data to calculate the mean 24-hour $PM_{2.5}$, one day with an unusually high average and peak $PM_{2.5}$ (greater than nine-times median level), and 106 days of missing O_3 data resulting in a total of 382 days excluded due to missingness of either air pollutant (8.4%).

2.6 Statistical Methods

We calculated descriptive statistics for the overall study population and by ethnicity. Chi-squared tests were used for categorical variables and Wilcoxon Rank Sum tests for continuous variables. We examined both air pollution and meteorological data with descriptive statistics as well as time-series plots. We used conditional logistic regression, stratifying on each stroke event, to calculate the odds ratios (ORs) and corresponding 95% confidence intervals associated with the air pollutant exposures. We assessed the functional forms of air pollutant and meteorological variables using penalized polynomial splines but found linear functional forms to be appropriate. Our primary analyses utilized single pollutant models with adjustment for ambient temperature and relative humidity at the same lag as the pollutant. We calculated ORs for a 10 μg/m^3 or 10 ppb change in $PM_{2.5}$ and O_3, respectively. Associations were examined separately for concentrations measured the same-day (lag 0), 1-day prior (lag 1), 2-days prior (lag 2), and 3-days prior (lag 3) to presentation for stroke. These lags were selected based on associations found in other studies, as well as the belief that this range includes the appropriate pathophysiologic window for triggering a stroke event (Henrotin et al., 2007, 2010; Lisabeth et al., 2008; Wellenius et al., 2012). Day of the week and month were inherently adjusted for by the study design (Lumley and Levy, 2000). We added interaction terms to the models to test effect modification by ethnicity (on the multiplicative scale) and reported ethnic-specific associations and considered p-values < 0.10 to provide evidence of effect modification. We also tested for additive interactions between ethnicity and the pollutants using methods described by Hosmer and Lemeshow (1992).

In secondary analyses, we explored the potential confounding effect of each pollutant with the other by running multi-pollutant models with both pollutants included. We conducted sensitivity analyses on the subset of cases with geocoded address within five kilometers of the ambient monitor to test the robustness of the results to potential exposure measurement error. We similarly examined effect modification of the air pollution-stroke association by season (summer vs. non-summer) as well as a binary indicator for residing downwind of a pollution point source using daily prevailing wind direction. We conducted all analyses using SAS version 9.3 (SAS Institute Inc, Cary, NC) and the R statistical package, version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. RESULTS

Median age of the stroke cases was 71 years (interquartile range (IQR): 59-80) with 56% (n=1,652) among Mexican Americans (Table 1). Mexican Americans were more likely than non-Hispanic whites to have their strokes at younger ages, have a history of diabetes, and have a history of hypertension, but less likely to be former smokers and have a history of atrial fibrillation. Most stroke cases (85%) resided within 20 km of the ambient monitoring site with a median distance of 6.9 km (IQR: 3.6-13.3). Median temperature for the study period was 23.3°C (IQR, 18.4-27.5) and median relative humidity was 78.3% (IQR: 70.2-84.0).

3.1 $PM_{2.5}$

The median pollutant level of $PM_{2.5}$ for the study period was 7.7 μg/m^3 (IQR: 5.7-10.6). Across all individuals, we found no associations between the odds of incident ischemic stroke and $PM_{2.5}$ concentrations (Figure 1). Effect modification of the $PM_{2.5}$ association by ethnicity was, however, borderline significant for same-day $PM_{2.5}$ levels (p-interaction=0.07). At this exposure time, a 4.9 μg/m^3 (IQR) higher same-day $PM_{2.5}$ was associated with a 6% higher odds of ischemic stroke in Mexican Americans (95% CI: 0.99-1.12), but a 3% lower odds of ischemic stroke in non-Hispanic whites (95% CI: 0.90-1.04). Effect modification $PM_{2.5}$ by ethnicity was not present for other lag days. Tests for additive interaction were non-significant for all lags (all p-interaction > 0.29).

3.2 O_3

The median pollutant level of O_3 for the study period was 35.7 ppb (IQR: 25.5-46.3). Across all individuals, higher O_3 levels corresponded with higher odds of incident ischemic stroke with the strongest associations for lags 1 and 2, but not significantly (Figure 2). In models with interaction terms by ethnicity, non-Hispanic whites were consistently found to have stronger associations between O_3 concentrations and incident ischemic stroke with strongest differences at the longer lag periods. This modification by ethnicity was strongest at lag 2 (p-interaction=0.06), where a 20.8 ppb (IQR) higher O_3 level was associated with a 12% higher odds of ischemic stroke (95% CI: 1.01-1.25) among non-Hispanic whites while Mexican Americans experienced no difference in odds (OR: 0.99, 95% CI: 0.90-1.09). Tests for additive interaction were non-significant for all lags (all p-interaction > 0.29).

3.3 Sensitivity Analysis

Multi-pollutant models yielded similar results as reported for single pollutant models (Supplementary Table 1). Results were similarly robust across season and presence of upwind pollution sources. Restriction to the 1,121 ischemic strokes residing within five km of the air pollution monitor were also consistent with our main results, with slightly stronger associations for $PM_{2.5}$ and slightly attenuated associations for O_3 (Supplementary Table 2).

4. DISCUSSION

In this population-based stroke study that included 13 years of validated ischemic strokes, we documented suggestive associations between higher short-term O_3 exposures and higher odds of incident ischemic stroke among non-Hispanic whites but not Mexican Americans. No consistent associations were found for $PM_{2.5}$. Although we did not find strong associations between incident ischemic stroke and short-term changes in air pollution, the suggestion of ethnic differences indicates that more research in diverse populations may be warranted.

These findings are in line with suggestive associations previously observed in this population over a 5-year follow-up period for O_3 and stroke, but not $PM_{2.5}$ (Lisabeth et al., 2008). In that study, borderline associations were found between risk of ischemic stroke/TIA and same-day and lag 1 $PM_{2.5}$ concentrations (RR: 1.03, 95% CI: 0.99-1.07 and RR: 1.03, 95% CI: 1.00-1.07 per 5.1 $\mu g/m^3$) and lag 1 O_3 concentrations (RR: 1.04, 95% CI: 0.99-1.09 per 15.7 ppb). This analysis added an additional 7 years of follow-up, restricted to validated incident ischemic stroke, and newly explored effect modification of associations between air pollution and stroke by ethnicity. Although we hypothesized that associations would be stronger when restricted to incident ischemic stroke, it is possible that we did not observe associations in the same area over a longer time period because we excluded recurrent events and TIAs, which could have stronger associations with air pollutants than ischemic stroke (Bedada et al., 2012; Henrotin et al., 2007). Power may also have been an issue even over the longer follow-up period given that the observed levels of ambient air pollution in Nueces County were quite low with relatively little variability.

We hypothesized that both $PM_{2.5}$ and O_3 would be associated with incident stroke risk, however the lack of overall associations found in our study is consistent with some previous studies. Studies from Canada with similar pollution levels also reported no association between ischemic stroke risk and $PM_{2.5}$ in a case-crossover design (O'Donnell et al., 2011; Villeneuve et al., 2012). Case-crossover studies in Massachusetts (Wellenius et al., 2012), Pennsylvania (Xu et al., 2013), and France (Henrotin et al., 2010) reported no associations between same day or previous day O_3 with risk of ischemic stroke; these studies also reported lower average daily concentrations of O_3 than we observed. Additionally, recent reviews and meta-analyses have suggested null to small associations between O_3 and ischemic stroke, with slightly stronger effects in case-crossover studies (Ljungman and Mittleman, 2014; Shah et al., 2015). Conversely to our results, some studies have found an association between $PM_{2.5}$ and incident stroke. A study in Boston, Massachusetts found that an IQR increase in $PM_{2.5}$ (6.4 $\mu g/m^3$) in the 24 hours preceding stroke was associated with an OR of 1.11 (95% CI: 1.03-1.20) for ischemic stroke (Wellenius et al., 2012). This could

be due in part to different chemical components of $PM_{2.5}$ across these areas (Bell et al., 2009, 2007). Further research is needed to examine the effects of PM species in the context of their association with ischemic stroke.

A unique contribution of our investigation of air pollution and stroke was the consideration of differences by ethnicity. Mexican Americans have an increased stroke risk compared to non-Hispanic whites (Morgenstern et al., 2013), but the modification of relationships between stroke and air pollution have not been investigated. A priori, we hypothesized a stronger association with $PM_{2.5}$ in Mexican Americans based on previous research that has demonstrated that Hispanics are more susceptible to PM-induced cardiovascular health effects (Sacks et al., 2011). Possible explanations for these differences may be that Mexican Americans have a higher prevalence of living in disadvantaged areas with different housing characteristics (Dvonch et al., 2009; Lisabeth et al., 2007) and hold more blue-collar occupations where they may have increased exposure to outdoor air pollution (Cattan, 1993). Another possibility is that biological impacts of air pollution on stroke risk vary by ethnicity, in part due to increased prevalence of diabetes in Mexican Americans (Lisabeth et al., 2006; Moon et al., 2012), as stronger associations have been found between $PM_{2.5}$ and ischemic stroke among diabetics as compared to nondiabetics (O'Donnell et al., 2011). A recent meta-analysis of air pollution and stroke data has also suggested that low income, a marker of disadvantaged areas, may modify the association between air pollution and stroke (Shah et al., 2015), which could also partly explain our observed ethnic differences.

Although associations with $PM_{2.5}$ were not strong in this study, the magnitude of the association we observed between $PM_{2.5}$ and stroke in Mexican Americans was larger than for non-Hispanic whites for the same-day lag as has been previously reported (Lisabeth et al., 2008; Wellenius et al., 2012). Greater short-term $PM_{2.5}$ exposure was associated with an increased risk of cardiovascular mortality among Hispanics as compared to non-Hispanic whites in a study of six California counties (Ostro et al., 2008); specifically, Hispanics had a 2.5-6% excess risk of mortality due to $PM_{2.5}$ compared a 0-2% excess risk of mortality for non-Hispanic whites. Similarly, the Multi-Ethnic Study of Atherosclerosis, with estimated $PM_{2.5}$ concentrations ranging from 10.6 to 24.7 μg/m^3, reported 10 μg/m^3 increases in $PM_{2.5}$ among Hispanics were associated with a 22% elevated risk of coronary calcification (Allen et al., 2009), while no increased risk was found in non-Hispanic whites.

In contrast, among non-Hispanic whites, increases in lag 2 O_3 were associated with higher odds of ischemic stroke, but not in Mexican Americans. The 6% higher odds of ischemic stroke that we found for lag 2 exposure in non-Hispanic whites was comparable to the results of Henrotin et al., who reported an OR of 1.04 for lag 2 O_3 exposure in a non-Hispanic white European population (Henrotin et al., 2010). The reasons for our contrasting findings for $PM_{2.5}$ and O_3 by ethnicity are not clear though it may represent a complex interplay of biologic susceptibility, infiltration of homes, or activity patterns. Chance is also a possible explanation. Our focus was on the existence of an ethnic disparity and as a result, additional research is needed in diverse populations to investigate ethnic-specific effects and their causes.

Our results have implications in terms of public health. The magnitude of the observed associations between O_3 concentrations and incident ischemic stroke may be modest, but the number of strokes that are attributable to O_3 may be high given that air pollution exposure affects almost everyone. Assuming that the association between O_3 and incident ischemic stroke is causal and a linear function, a 20% reduction in the mean O_3 levels (7.4 ppb) during the study period may have averted approximately 6,007 of the 387,000 stroke hospitalizations in the South region of US in 2010 alone (National Center for Health Statistics, 2010).

There are some limitations of this work that warrant discussion. The classification of the exposure for individuals was limited by the fact that we only had one monitor in the study community. The measurements from the single fixed monitor may introduce measurement error into our analysis if the daily fluctuations were not homogeneous across the county. However, another monitor in the county measuring 24-hour $PM_{2.5}$ every three to six days using the Federal Reference Method showed large correlations (ρ 80%) with the single monitor used in our study. This is consistent with the topography of Nueces County (flat, with elevation varying from sea level to a maximum elevation of 180 feet (TNRIS (Texas Natural Resources Information System), 2013)) which suggests that air pollution exposures are likely to be highly correlated across space. It is possible, however, that our observed ethnic differences may, in part, be due to differential measurement error if the communities resided in distinct neighborhoods in Nueces County although we did find similar associations when restricted to those that resided within a 5km buffer of the air pollution monitor. We are also assuming that ambient pollutant concentrations are surrogates for personal pollutant exposures, which may be the case for $PM_{2.5}$ but not O_3 (Sarnat et al., 2001). Another issue is that we do not have the exact time of stroke onset, but rather the day of hospital presentation. Although consistent with much of the existing literature on air pollution and stroke, this may have resulted in an underestimation of the strength of the association between air pollution and ischemic stroke (Lokken et al., 2009). Another possibility is that air pollution exposures could have triggered death such that competing risks would reduce the observed association between air pollution and incident stroke. Also, the ethnic distribution and air pollution exposures of Corpus Christi are unique, and therefore generalizability may be limited.

In summary, we observed suggestive associations between higher $PM_{2.5}$ and O_3 levels and incident ischemic stroke, with associations observed only among Mexican Americans for $PM_{2.5}$ and only among non-Hispanic whites for O_3. This study contributes to the literature by being the first study to our knowledge to address a possible ethnic difference in the influence of air pollution on stroke risk, and suggests that further study in diverse populations is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREIVIATIONS

$PM_{2.5}$ particulate matter less than 2.5μm in aerodynamic diameter

O_3 Ozone

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HIGHLIGHTS

First study to examine possible ethnic differences in air pollution on stroke risk.

Case-crossover design to assess associations between $PM_{2.5}$/O_3 and stroke incidence.

Suggestive association between $PM_{2.5}$ and ischemic stroke among Mexican Americans.

Suggestive association between O_3 and ischemic stroke among non-Hispanic whites.

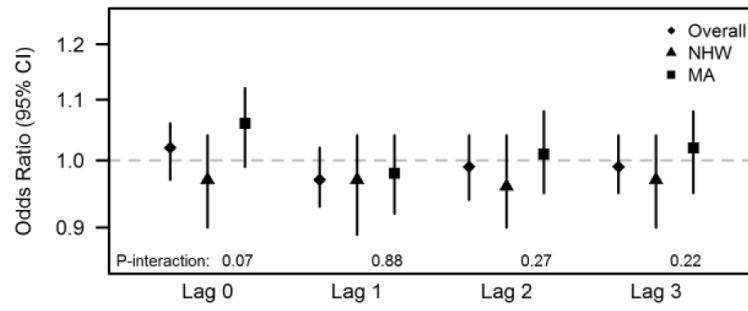Further study in diverse populations is warranted.

Figure 1.
Odds ratios associated with a 10 μg/m^3 increase in 24-hour PM$_{2.5}$ overall and stratified by ethnicity for 2000-2012 incident ischemic stroke cases in Nueces County, Texas. NHW corresponds to non-Hispanic White ethnicity and MA corresponds to Mexican American ethnicity.

Figure 2.
Odds ratios associated with a 10 ppb increase in maximal 8-hour O_3 overall and stratified by ethnicity for 2000-2012 incident ischemic stroke cases in Nueces County, Texas. NHW corresponds to non-Hispanic White ethnicity and MA corresponds to Mexican American ethnicity.
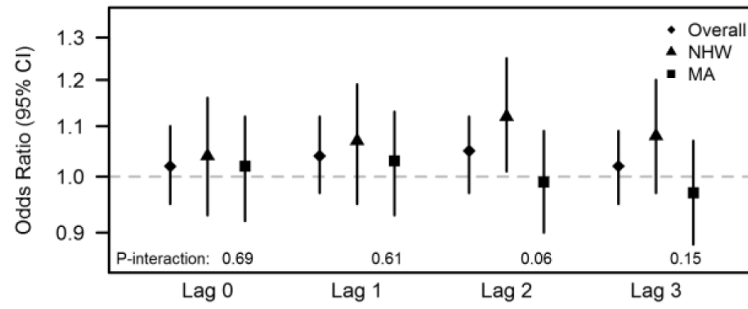
Table 1

Characteristics of 2948 Incident Ischemic Strokes in Nueces County, Texas, 2000-2012

Characteristic	Overall (N=2948)	Mexican American (N=1652)	Non-Hispanic White (N=1296)	P
Age, median (Q1, Q3), y	71 (59, 80)	67 (57, 78)	75 (63, 83)	<0.001
Female	1511 (51.3)	835 (50.5)	676 (52.2)	0.384
MA	1652 (56.0)	-	-	
Medical History				
Atrial fibrillation	390 (13.2)	152 (9.2)	238 (18.4)	<0.001
Coronary artery disease	895 (30.4)	499 (30.2)	396 (30.6)	0.846
Diabetes mellitus	1204 (40.8)	882 (53.4)	322 (24.9)	<0.001
High cholesterol	956 (32.4)	551 (33.4)	405 (31.3)	0.226
Hypertension	2204 (74.8)	1275 (77.2)	929 (71.7)	<0.001
Smoking History				
Current	610 (20.7)	340 (20.6)	270 (20.8)	0.867
Former	366 (12.4)	158 (9.6)	208 (16.1)	<0.001
Distance to monitor, median (Q1, Q3), km	6.9 (3.6, 13.3)	2.7 (1.4, 6.3)	5.9 (3.7, 10.8)	<0.001

Q = quartile.