

Roadway Proximity and Risk of Sudden Cardiac Death in Women

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Abstract

Background—Sudden cardiac death (SCD) is a major source of mortality and is the first manifestation of heart disease for the majority of cases. Thus, there is a definite need to identify risk factors for SCD that can be modified on the population level. Exposure to traffic, measured by residential roadway proximity, has been shown to be associated with an increased risk of cardiovascular disease. Our objective was to determine if roadway proximity was associated with an increased risk of SCD and to compare to the risk of other coronary heart disease (CHD) outcomes.

Methods and Results—A total of 523 cases of SCD were identified over 26 years of follow-up among 107,130 members of the prospective Nurses' Health Study. We calculated residential distance to roadways at all residential addresses from 1986-2012. In age- and race-adjusted models, women living within 50 meters of a major roadway had an elevated risk of SCD (HR=1.56; 95% CI: 1.18-2.05). The association was attenuated but still statistically significant after controlling for potential confounders and mediators (HR=1.38; 95% CI: 1.04-1.82). The equivalent adjusted HRs for nonfatal myocardial infarction and fatal CHD were 1.08 (95% CI: 0.96-1.23) and 1.24 (95% CI: 1.03-1.50), respectively.

Conclusions—Among this sample of middle-aged and older women, roadway proximity was associated with an elevated and statistically significant risks of SCD and fatal CHD, even after controlling for other cardiovascular risk factors.

Key words: traffic exposure, air pollution, death, sudden cardiac, death, sudden, coronary heart disease risk

Sudden cardiac death (SCD) accounts for approximately 180,000-400,000 deaths in the United States each year.¹ SCD is responsible for over half of cardiovascular deaths, 15-20% of total deaths each year, and is the first manifestation of heart disease for a large proportion of victims,² especially among women.³ Therefore, there is a need to identify risk factors that can be modified on a population level to broadly impact SCD risk.

Long-term exposures associated with traffic, such as air pollution and noise, have been associated with increased mortality from coronary heart disease (CHD),⁴⁻⁷ and associations with fatal CHD have typically been stronger than for non-fatal events.^{8,9} Acute exposure to air pollution and/or traffic has also been associated with ventricular arrhythmias in patients with ICDs,¹⁰ and with elevations in the risk of out-of-hospital cardiac arrest in most, but not all, studies.¹¹⁻¹⁹ Therefore, long-term exposure to traffic may be associated with SCD, both through the development of underlying atherosclerosis and by influencing myocardial vulnerability to lethal ventricular arrhythmias.²⁰

Previous studies, including our own, have observed modest elevations in incident CHD (combined nonfatal and fatal) among individuals who live closer to major roadways;²¹⁻²⁴ but the impact of this exposure on SCD risk is unknown. Our current objective was to determine if exposure to traffic, measured by roadway proximity, leads to an increased risk of SCD in women, in whom CHD has been demonstrated to underlie a lower percentage of SCDs than in men.^{25,26} We also sought to compare risk estimates for SCD to those for nonfatal and fatal CHD outcomes in this cohort.

Methods

Study Population

The Nurses' Health Study (NHS) is a prospective cohort study that began in 1976 with 121,701

married female registered nurses, 30 to 55 years old, who each completed a mailed questionnaire and provided implied informed consent. At the study inception the nurses resided in eleven states (CA, CT, FL, MA, MD, MI, NJ, NY, OH, PA, TX), however, due to residential mobility, there is now at least one cohort member in all fifty states. Follow-up questionnaires, with response rates above 90%, are mailed every two years to update information on risk factors and the occurrence of major illnesses. These also provide updated information on residential address. Women were included in the current study if they were still responding to questionnaires and had at least one home address 1986-2012 geocoded to the street segment level (so that roadway proximity could be calculated). Women were excluded if they had cancer (other than non-melanoma skin cancer), CVD, or had died prior to baseline. The study protocol was approved by the Institutional Review Board of Brigham and Women's Hospital.

Outcome Assessment

On all questionnaires, we inquire about the occurrence of physician-diagnosed CHD events, and deaths are identified by reports from next-of-kin, postal authorities, or by searching the National Death Index (NDI). Details on the method of classifying SCD in this cohort have been published previously.³ Briefly, SCDs were confirmed by physician review of medical records and next-of-kin reports regarding the circumstances surrounding the death if not adequately documented in the medical record. Cardiac deaths were considered sudden if the death or cardiac arrest occurred within 1 hour of the onset of symptoms. To increase specificity for arrhythmic death, we also required there be no evidence of circulatory collapse or a neurologic event prior to the disappearance of the pulse.²⁷ Unwitnessed deaths or deaths that occurred during sleep where the participant was documented to be symptom free within the preceding 24 hours were considered probable SCDs if an autopsy or circumstances suggested that the death could have been

arrhythmic.²⁸

Cases of definite fatal CHD (ICD-8 and ICD-9 codes 410-412, ICD-10 codes I21-I22) were confirmed by hospital records or autopsy, or if CHD was listed as the underlying and most plausible cause of death on the death certificate and there was prior evidence of CHD. Probable fatal CHD events include deaths where medical records surrounding the death were not available, but CHD was the underlying cause on the death certificate, NDI search, or a family member provided supporting information. Given the relatively low prevalence of CHD in female sudden cardiac death and arrest victims,^{25, 26, 29, 30} SCD cases not fulfilling the above definition and/or where another primary underlying cause of death was identified by history or autopsy were not included as fatal CHD events.

Non-fatal MI was classified as definite if the criteria of the World Health Organization were met, specifically, symptoms and either electrocardiograph-detected changes or elevated cardiac-enzyme concentrations. Cases of nonfatal MIs were designated as probable if an interview or letter confirming hospitalization was obtained and medical records were unavailable.

Roadway Proximity

We calculated roadway proximity at each mailing address from 1986 forward as a proxy for traffic exposure. Distance (in meters) was determined using Geographical Information System (GIS) software (ArcGIS 10.2, ESRI, Redlands, CA). ESRI StreetMap Pro 2007 road segments were selected to include the three largest US Census Feature Class Codes: A1 (primary roads, typically interstate highways, with limited access, division between the opposing directions of traffic, and defined exits), A2 (primary major, non-interstate highways and major roads without access restrictions), or A3 (smaller, secondary roads, usually with more than two lanes). Based

on the distributions in the cohort, and on exposure studies showing exponential decays in exposures with decreasing roadway proximity,³¹ we created distance categories of 0-49m, 50-199m, 200-499m and 500+m. In sensitivity analyses, we also examined continuous measures, and other cutpoints to determine the robustness of results to our *a priori* choices.

Potential Confounders

Information on potential confounders is available every two years (four years for diet) from the follow-up questionnaires and can be used to assign updated covariate values. We included a number of risk factors for SCD and/or CHD as possible confounders: age (in months), race (white, black, other or multiple races), calendar year, physical activity (hours/week), body mass index (kg/m²), alcohol consumption (grams/day), menopausal status (premenopausal, postmenopausal, and unknown/dubious) and hormone use (never, current, former), and family history of MI (none, < or ≥ age 60), and incidence of diabetes or cancer. We used lifetime smoking history to calculate pack-years and to determine smoking status (current/former/never). Diet was assessed by calculating a score based on the 2010 Alternate Healthy Eating Index (AHEI).³² This score includes eight components: higher intakes of vegetables, fruit, nuts, soy and cereal fiber, moderate alcohol consumption, high ratios of chicken plus fish to red meat and polyunsaturated to saturated fat, low intake of trans fat, and multivitamin use of ≥5 years. We also adjusted for aspirin, vitamin E and multivitamin use. Information on secondhand smoke exposure (during childhood, at home, and at work) was collected on the 1982 questionnaire. To control for regional differences in traffic and disease risk, we controlled for Census region (Northeast, Midwest, West, and South). To control for area-level socioeconomic status (SES) we included Census tract level median income and house value. In sensitivity analyses, we additionally adjusted for incident comorbidities that may be mediators of the association between

traffic exposure and SCD (high blood pressure, hypercholesterolemia, stroke, or CHD) or CHD (high blood pressure, hypercholesterolemia, or stroke).

Statistical Methods

Separate analyses were performed for each outcome. Person-months of follow-up time were calculated from June 1986 until the end of available follow-up (December 2012 for SCD, May 2010 for nonfatal MI and fatal CHD), death, or loss to follow-up. We did not censor person-time at the incidence of nonfatal MI for the fatal outcomes. Time-varying Cox proportional hazards models were used to assess the relationship of each outcome with roadway proximity. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each category of roadway proximity compared to the furthest category (500+m). We examined the linearity of the continuous associations 0-499m (compared to 500m+) using cubic splines.³³ The dataset was converted to an Anderson-Gill data structure with a record for each 2-year time period, including person-time, the exposure during that time period, whether the person was censored during the interval, and covariate information. All models were based on a biennial time scale and were stratified by age in months and time period. The proportional hazard assumption was verified for all analyses by including interaction terms for age and time period and performing a likelihood ratio test comparing models with and without the interaction terms. The percent of the roadway proximity-outcome association explained by the potential mediators was calculated as $[(HR_{\text{multivariable model}} - HR_{\text{multivariable and mediator model}})/(HR_{\text{multivariable model}} - 1)] \times 100\%$.³⁴ In sensitivity analyses, we considered models restricted to definite cases of each outcome to determine the impact of stricter case definitions on our conclusions. To examine possible effect modification by race (white vs. other) and smoking status (never vs. ever and current vs. former/never), we calculated stratum-specific effect estimates and examined the statistical significance of effect

modification using likelihood ratio tests. Using publically available software,³⁵ we also estimated the population attributable risk (PAR) associated with living closer than 500m from A1-A3 roadways. An alpha level of 0.05 was used to determine statistical significance.

Results

Characteristics of the study sample (N=107,130) over the full period of follow-up are presented in **Table 1** for the whole cohort and by roadway proximity category. The women were 64.3 years old on average, with an average BMI of 26.3, were mostly white (94%), postmenopausal (86%), never (44%) or former (42%) smokers, and most (58%) exercised less than 2 hours per week. Overall, there was little difference in these characteristics across the different categories of roadway proximity, with the exception of region; women in the Northeast tended to live closer to roadways than women in other regions.

Roadway proximity and SCD

During the 26 years of follow-up, a total of 523 cases (328 definite, 195 probable) of SCD were observed. The associations of roadway proximity with SCD are presented in **Table 2**. In basic models adjusted for age, race, and calendar time, women living within 50 meters of a roadway had a higher risk of SCD (HR= 1.56; 95% CI: 1.18-2.05) compared to women living further away (500+m). The dose-response relationship between roadway proximity and SCD risk was linear as determined by cubic splines, and each 100 m closer to roadways was associated with a 8% increased risk for SCD (95% CI: 3-14%). In multivariable models controlling for potential confounders, hazard ratios were attenuated but remained statistically significant in both the categorical (HR= 1.40; 95% CI, 1.06-1.85 for <50 versus 500m) and continuous (HR= 1.06; 95% CI, 1.01-1.12 per 100m) analyses. Additional adjustment for incident comorbidities, including

incident CHD, potentially on the causal pathway had little effect on the HRs (4.3% mediation). In sensitivity analyses excluding probable SCDs or non-whites, the magnitude of the associations were similar (multivariable HR; 95% CI = 1.33; 0.94-1.89 and 1.32; 0.99-1.76 for <50 versus 500m, respectively). These associations also did not significantly differ by region of residence, race or smoking status; however the HR associated with living <50m versus 500m from a roadway was higher among ever smokers (HR= 1.56; 95%CI: 1.08-2.23) as compared to nonsmokers (1.22; 95%CI: 0.80-1.97) (**Supplemental Table 1**).

Roadway proximity and nonfatal MI and fatal CHD

During 24 years of follow-up, 2,731 cases (1,813 definite, 918 probable) of nonfatal MI and 1,159 cases (794 definite, 365 probable) of fatal CHD were identified. The associations with roadway proximity and each outcome are shown in **Table 3**. In multivariable models, the risk of fatal CHD (HR=1.24; 95%CI: 1.03-1.49) was statistically significantly higher among women living within 50m of an A1-A3 road as compared to women living 500m or further away and the HR for each additional 100m closer in proximity was 1.04 (95%CI: 1.00-1.07). This association was slightly attenuated when fatal CHD events also considered SCDs (n=152) were excluded from the endpoint (multivariable HR=1.21; 95%CI: 0.99-1.48 for <50 versus 500 meters; and multivariable HR=1.03; 95%CI: 0.99-1.07 per 100m). Risks of nonfatal MI were more modest in magnitude and were not statistically significant in multivariable models. Similar to our results for SCD, results for fatal CHD and nonfatal MI were essentially unchanged when additionally adjusted for incidence of other comorbidities which might be in the causal pathway (0.1% and 0.2% mediation for nonfatal MI and fatal CHD, respectively), when other categorical cutpoints were considered, and in models excluding probable events or non-whites (data not shown). There was also no evidence of effect modification by race or region of residence (data not

shown) or smoking status (**Supplemental Table 2**).

Population Attributable Risks (PAR)

Over the course of the study, 75% percent of the total person-years observed were spent at residences within 499m of an A1-A3 roadway. The multivariable adjusted HRs for the categorical variable (0-49m, 50-199m, 200-499m versus 500m+) translate into PARs of 17.9% (95%CI: 0.1 – 34.7%), 11.6% (95%CI: -1.1 – 23.9%), and 6.8% (95%CI: -1.4 – 14.9%) for SCD, fatal CHD, and non-fatal MI respectively in this sample of women.

Discussion

Among this sample of middle-aged, older women, roadway proximity was associated with an elevation in the risk of SCD. Even after adjustment for potential confounders and mediators, women who lived within 50m of a major roadway had a 38% higher hazard (95% CI 1.04-1.82) of experiencing SCD as compared to women living 500m or further away. The association was linear, and each 100 meters closer to a major roadway was associated with a 6% elevation in the hazard ratio (95% CI: 1-11%). Proximity to a major roadway was also statistically significantly associated with fatal CHD, but to a lesser magnitude. These results suggest that traffic exposure, as measured by roadway proximity, may increase the risk of death from CHD, and may increase propensity toward fatal ventricular arrhythmias. If the observed relationships are causal, these results suggest that roadway exposures may underlie 17.9, 11.6, and 6.8% of SCDs, fatal CHDs, and nonfatal MIs in this population. For the endpoint of SCD, these PARs are comparable to or greater than the contributions made by smoking, diet, and obesity in this population.³⁶

To the best of our knowledge, this is the first study to examine the impact of residential roadway proximity on the risk of SCD. However, a few case-crossover studies have examined

the impact of short-term traffic-related air pollution exposures (most often fine particulate matter (PM_{2.5}), carbon monoxide, or oxides of nitrogen), and risk of out-of-hospital cardiac arrests. As summarized in a recent review,³⁷ the majority have utilized administrative databases to identify cases, and local air pollution monitoring networks to assign pollution measures for a variety of pollutants on the day of the event and a varying number of previous days. In studies based in Rome, Italy,¹³ Melbourne, Australia,¹¹ Helsinki, Finland,¹⁶ Stockholm, Sweden,³⁸ and Indianapolis, Indiana,¹⁵ New York City, New York,¹⁷ and Houston, Texas¹² from the United States, elevated risks were observed with increased levels of PM or other pollutants on the day of or up to 3 preceding days prior to cardiac arrest. However, in studies from Washington State, United States^{14, 18} and Copenhagen, Denmark,¹⁹ consistent associations were not found between levels of PM measured in the days prior to out-of-hospital cardiac arrest as compared to control days from the same month. Although it is not possible to directly compare these studies to ours, the preponderance of evidence suggests that short-term exposures to traffic related pollutants are associated with acute increases in risk of out-of-hospital cardiac arrests.

Regarding mechanisms underlying these associations, there is a growing body of literature supporting an association between short-term (hourly, daily) exposures to air pollution, especially those from traffic sources, and ventricular arrhythmias.¹⁰ The majority of these studies have been conducted in selected high risk populations of patients with implanted cardiac defibrillators, where the events can be identified with fine temporal resolution. In the first such study, based in the Boston, Massachusetts area, recent exposures to NO₂ were associated with an increased risk of arrhythmias, and multiple events were additionally associated with a number of other traffic related exposures.³⁹ A second study in the same geographic area observed a positive linear association between PM_{2.5} and the risk of arrhythmias.⁴⁰ Similar findings with different

measures of air pollution have been observed in studies from St. Louis, Missouri, and from Gothenburg, Germany and Stockholm, Sweden, but not in studies of patients in Vancouver, Canada and Atlanta, Georgia.¹⁰ As fatal ventricular arrhythmias underlie a large proportion of SCD, and thus, contribute to fatal CHD deaths as well, these data provide a potential biological mechanism underlying at least part of our observed association between traffic-related exposures and SCD and fatal CHD.

Our data suggest that there may also be a more general association between roadway proximity and fatal CHD events that may not be entirely explained by effects on SCD. Acute exposure to traffic has been associated with transiently increased risks of nonfatal MI,⁴¹ and long term exposure to traffic or roadways has been associated with higher risks of fatal and nonfatal CHD events.²¹⁻²³ In Atherosclerosis Risk in Communities (ARIC) study, living within 300m of a major road was associated with a 12% increased risk of CHD in a population of ~13,000 middle-aged men and women, with stronger risks for those living near roads with higher traffic density.²¹ In a case-control study in Massachusetts, each interquartile-range increase in traffic density was associated with a 4% (95% CI: 2-7%) increased risk of acute MI.²³ Our previous analyses in the NHS found that women living at residences consistently close to traffic over follow-up were at a higher risk for incident total CHD (HR=1.11; 95% CI: 1.01-1.21) than women who live consistently at addresses further away.²² Although these studies did not specifically compare associations for fatal and nonfatal events, other studies from Stockholm and Rome examining long-term exposures to traffic related air pollution have demonstrated stronger associations with fatal MI endpoints and out of hospital deaths as compared to nonfatal events,^{42,}⁴³ consistent with our results.

It is important to note that although there was minimal overlap between SCD and fatal

CHD events, some degree of undetected overlap between SCD and fatal CHD events undoubtedly exists and is unavoidable in this epidemiologic study. In prior studies,^{25, 26, 29} CHD is detected at autopsy or upon extensive clinical evaluation in slightly less than half of women who suffer a sudden cardiac arrest/death.^{25, 26, 29, 30} In our study, only 30% of SCDs were found to have evidence for CHD prior to or at the time of death, and thus, it is probable that undetected CHD underlies a proportion of the remaining SCDs. Therefore, despite controlling for known CHD in our models, residual confounding by undetected CHD could account for part of the association with SCD. Conversely, the strict, but standard,²⁸ definition of SCD employed in our study relies on the patient having been observed within the 24 hours prior to death, and it is probable that some of the fatal CHD events which occurred suddenly may not have been characterized as SCD, either because the deaths were unwitnessed for greater than 24 hours or details regarding the circumstances of the death were not available. Therefore, undetected SCDs may underlie some of the residual association between roadway proximity and fatal CHD.

There are a number of potential biological mechanisms associated with residential proximity to roadways that could predispose patients both to SCD and to fatal CHD apart from acute triggering of ventricular arrhythmias.⁴⁴ The primary comorbidities we examined as mediators (high cholesterol and high blood pressure) had little effect on our observed associations, as determined by the percent mediation, suggesting that the effects of roadway proximity on SCD and fatal CHD may be working through other mechanisms. Traffic related air pollution has also been associated with elevations in systemic inflammation, oxidative stress, heart failure, and alterations in autonomic function and heart rate variability.⁴⁴ Residential proximity to major roadways has been directly associated with higher left ventricular mass index⁴⁵ and severity of atherosclerosis as measured by coronary calcification.⁴⁶ Additionally,

traffic noise has also been linked to a number of these underlying mechanisms, including heart rate, cardiac output, and oxidative stress, suggesting that traffic exposures may act on cardiovascular disease through a number of underlying biologic mechanisms.⁴⁷

This study has several limitations. Our measure of exposure, roadway proximity, is a poor proxy for true traffic exposures, such as noise or pollution levels, and it does not provide us with information on temporal changes in exposures that may be associated with triggering of events. These limitations are expected to lead to nondifferential misclassifications of exposure, which would bias our results toward the null. It does have the advantage, however, of allowing us to assess the combined impact of all aspects of near-roadway exposure simultaneously.

Additionally, only 15% of the person time in the cohort was spent at addresses within 50m of an A1-A3 roadway, limiting our ability to detect statistically significant effects at the highest exposure levels. Our assumption of similar exposures from all roadways within a given roadway classification is another limitation of our study, as time-varying information on traffic volume during our follow-up period is not widely available for the entire contiguous US for the study period. We also lack information on the temporal and seasonal trends in traffic. This inability to differentiate roads and time periods with higher exposure levels likely leads to nondifferential exposure errors, which would lessen our ability to detect statistically significant effects.

Similarly, we do not have information on the amount of time each participant spends at her home, or characteristics of each home, such as age, ventilation rate, soundproofing, and orientation relative to prevailing winds and/or to the roadways. All of these factors would also lead to exposure misclassification and likely partially explain our wide confidence intervals.

As with any observational study, exposures and/or comorbidities may be incompletely or imperfectly measured resulting in residual confounding or inability to adequately detect effect

mediation by comorbidities. However, validation studies have suggested that the nurses accurately report many of the CHD risk factors and comorbidities risk factors examined in this study.⁴⁸ We also do not have information on medication use just prior to the death (such as QT prolonging agents), which may mediate our observed associations with SCD. Lastly, although women in this cohort live in all portions of the contiguous US and we did not observe evidence for effect modification by race, the latter analyses were limited by small numbers of non-white participants. The participants are also mostly middle-aged to elderly and of middle- to upper-class socioeconomic status. Therefore, it is possible that the results in this population are not generalizable to other races or populations with differing levels of susceptibility to the effects of roadway proximity or differing patterns of exposure.

This large prospective study also has major strengths. We had information on residential address and roadway proximity available over a 26 year period, allowing us to look at the long-term effects of roadway proximity on the risk of SCD over a long time scale, as opposed to the daily or weekly exposures commonly examined. Additionally, the large number of well validated cases of SCD, nonfatal MI, and fatal CHD allowed us to look at relatively fine scale changes in exposure with tight control for a number of time-varying risk factors. This wealth of outcome data also provided us with an opportunity to compare the impacts of traffic exposure for a number of outcomes. Finally, the availability of a host of time-varying information on other potential risk factors for our outcomes allowed us to examine the impacts of roadway proximity independent of diet, personal characteristics, socioeconomic status, and other comorbidities.

In conclusion, living near a major roadway was associated with a significant increase in SCD risk in this sample of US middle-aged women. Although the risk elevations are modest, given the ubiquitous nature of the exposure, the population attributable risk is significant and

comparable to that observed for other major SCD risk factors.³⁶ In the US, the EPA estimated that 35 million people lived within 300m of a major road in 2009,⁴⁹ and a growing number of individuals live in close proximity to major roads worldwide. Therefore, exposures related to traffic, such as air pollution and noise, are widely prevalent and potentially modifiable population level risk factors for SCD. Since the majority of SCDs occur in individuals considered to be at low risk within the general population, modification of population level exposures that elevate SCD risk represent an important component of a comprehensive strategy to reduce the burden of SCD in the population.

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Table 1. Selected characteristics of 107,130 Nurses' Health Study participants during the full period of follow-up (1986-2012) for the full analytic cohort and by residential proximity to A1-A3 roads.

Characteristics (Mean (SD) or %)	All	Residential Proximity to Nearest A1-A3 Road (m)			
		0-49	50-199	200-499	500+
Age (years)	64.3 (10.0)	64.8 (10.1)	64.3 (10.0)	64.1 (10.0)	64.1 (10.0)
Body Mass Index (kg/m ²)	26.3 (5.3)	26.5 (5.3)	26.3 (5.3)	26.2 (5.2)	26.3 (5.2)
Alternative Healthy Eating Index	49.6 (11.0)	49.3 (10.9)	49.5 (10.9)	49.6 (11.0)	49.8 (11.0)
Census tract median income (\$1,000)	65.4 (25.1)	64.1 (26.4)	64.8 (25.6)	65.9 (24.7)	66.1 (24.1)
Census tract median home value (\$10,000)	17.7 (13.1)	17.9 (14.5)	18.3 (14.0)	17.8 (12.8)	16.9 (11.3)
Race					
White	94	93	93	93	95
Black	2	2	2	2	1
Other/Multiple Races	5	5	5	5	4
Smoking Status					
Never	44	44	43	43	45
Former	42	41	42	42	42
Current	11	11	11	11	10
Secondhand Smoke During Childhood					
None	26	25	26	25	26
From Mother	4	4	4	4	4
From Father	35	35	34	34	35
From Both Parents	15	15	15	15	16
Missing	21	21	21	21	20
Home Secondhand Smoke					
None	34	33	33	34	35
Occasional	19	19	19	19	19
Regular	17	18	18	18	16
Missing	30	30	30	30	29
Occupational Secondhand Smoke					
None	15	15	15	16	16
Occasional	30	29	30	31	31
Regular	23	24	23	22	22
Missing/Not working	32	32	32	31	31
Menopause Status					
Premenopausal	9	9	9	9	9
Postmenopausal	86	86	86	86	86

Dubious	4	4	4	4	4
Postmenopausal Hormone Use					
Never	22	24	23	22	21
Former	28	27	27	28	31
Current	25	23	24	25	26
N/A or Missing	25	26	26	25	23
Aspirin Use (times/week)					
<1	57	56	55	56	59
1-6	18	17	18	18	17
7+	10	10	10	10	10
Parental History of Myocardial Infarction					
None	74	74	74	74	74
Before age 60	12	12	12	12	12
After age 60	15	14	15	15	14
Alcohol Consumption (g/day)					
0	37	38	37	36	37
0.1-4.9	27	26	27	27	27
5.0-14.9	17	16	17	17	17
15.0+	10	9	10	10	10
Physical Activity (hrs/week)					
0	22	23	22	22	20
0.1-1.9	36	35	36	36	36
2-3.9	17	16	17	17	18
4+	20	19	19	20	21
Other Diagnoses During Follow-Up					
Diabetes	8	9	9	8	8
High cholesterol	51	50	50	50	52
High blood pressure	44	45	45	44	44
Stroke	2	2	2	2	2
Coronary Heart Disease	6	7	6	6	6
Region of Residence					
Northeast	50	59	54	47	44
Midwest	18	16	15	18	21
West	14	12	17	16	12
South	18	13	14	19	23

Values are mean (SD) or percentages and besides age, are standardized to the age distribution of the study population. NOTE: Participants may be in multiple exposure categories during the study follow-up

Table 2. Hazard ratios (HRs) and 95 % confidence intervals (95% CI) for the association of risk of sudden cardiac death 1986-2012 with residential proximity to A1-A3 roads among Nurses' Health Study participants (N=107,130).

Distance (m)	Cases	Person-Years	Basic [*]	Multivariable [†]	Multivariable [‡]
0-49	103	354,901	1.56 (1.18-2.05)	1.40 (1.06-1.85)	1.38 (1.04-1.82)
50-199	150	661,072	1.27 (0.98-1.63)	1.19 (0.92-1.53)	1.17 (0.91-1.51)
200-499	169	770,257	1.26 (0.98-1.61)	1.20 (0.94-1.54)	1.20 (0.93-1.53)
500+	101	594,129	reference	reference	reference
Linear (per 100m closer) [§]	523	2,380,358	1.08 (1.03-1.14)	1.06 (1.01-1.12)	1.06 (1.01-1.11)

^{*} Models adjusted for age, race, and calendar time

[†] Models additionally adjusted for smoking status, secondhand smoke exposure during childhood, at home, and at work, BMI, menopausal status and postmenopausal hormone use, the Alternative Healthy Eating Index, alcohol consumption, physical activity, family history of MI, aspirin, multivitamin, and vitamin E use, region of residence, and Census tract median home value and median income, and incidence of diabetes or cancer

[‡] Models additionally adjusted for comorbidities -- incidence of high cholesterol, high blood pressure, stroke, or coronary heart disease

[§] Linear models for distances 0-499m, compared to addresses 500+m away

Note: N, person-years, and number of cases apply for all models

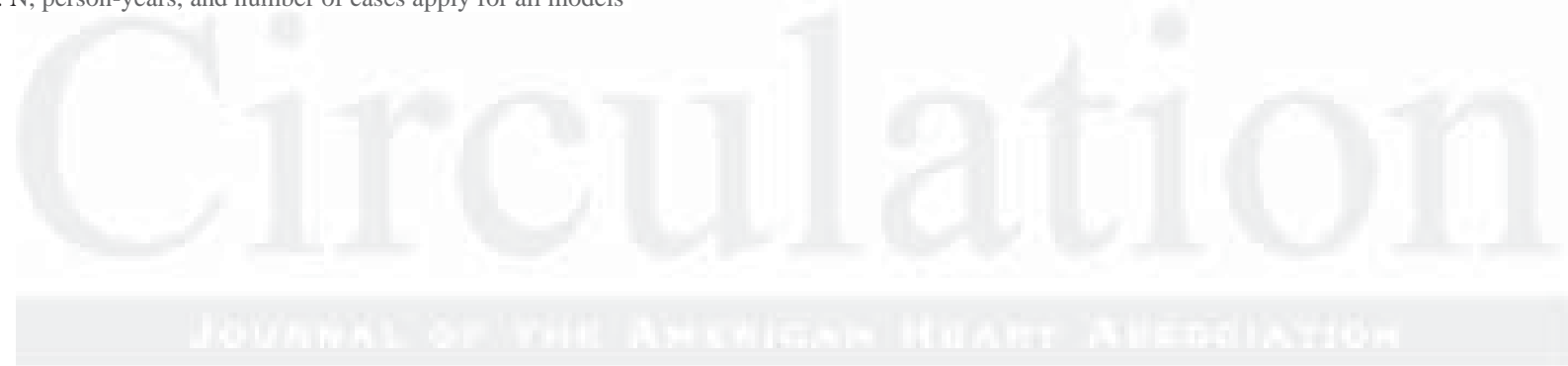


Table 3. Hazard ratios (HRs) and 95 % confidence intervals (95% CI) for associations of the risk of nonfatal myocardial infarction (MI) and fatal coronary heart disease (CHD) 1986-2010 with residential proximity to A1-A3 roads among Nurses' Health Study participants (N=107,130).

Outcome	Distance (m)	Cases	Person-Years	Basic [*]	Multivariable [†]	Multivariable [‡]
Nonfatal MI	0-49	445	326,705	1.14 (1.00-1.29)	1.08 (0.96-1.23)	1.08 (0.96-1.23)
	50-199	819	611,508	1.13 (1.02-1.26)	1.09 (0.98-1.22)	1.09 (0.98-1.21)
	200-499	861	711,732	1.05 (0.95-1.17)	1.03 (0.92-1.14)	1.03 (0.92-1.14)
	500+	606	541,065	reference	reference	reference
	Linear (per 100m) [§]	2,731	2,191,010	1.03 (1.01-1.05)	1.02 (1.00-1.04)	1.02 (1.00-1.04)
Fatal CHD	0-49	228	331,321	1.41 (1.17-1.70)	1.24 (1.03-1.49)	1.24 (1.03-1.50)
	50-199	341	619,706	1.18 (1.00-1.40)	1.07 (0.90-1.27)	1.07 (0.90-1.27)
	200-499	362	720,015	1.12 (0.95-1.33)	1.06 (0.90-1.25)	1.07 (0.90-1.26)
	500+	228	547,634	reference	reference	reference
	Linear (per 100m) [§]	1,159	2,218,407	1.07 (1.03-1.10)	1.04 (1.00-1.07)	1.04 (1.00-1.07)

^{*} Models adjusted for age, race, and calendar time

[†] Models additionally adjusted for smoking status, secondhand smoke exposure during childhood, at home, and at work, BMI, menopausal status and postmenopausal hormone use, the Alternative Healthy Eating Index, alcohol consumption, physical activity, family history of MI, aspirin, multivitamin, and vitamin E use, region of residence, and Census tract median home value and median income, and incidence of diabetes or cancer

[‡] Models additionally adjusted for comorbidities -- incidence of high cholesterol, high blood pressure, or stroke

[§] Linear models for distances 0-499m, compared to addresses 500+m away

Note: Ns, person-years, and number of cases apply for all models

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SUPPLEMENTAL MATERIAL

Supplemental Table 1: Hazard ratios (HRs) and 95 % confidence intervals (95% CI) for the multivariable and mediator adjusted association of risk of sudden cardiac death 1986-2012 with residential proximity to A1-A3 roads among Nurses' Health Study participants by active smoking status

Distance (m)	Never Smokers			Ever Smokers		
	Cases	Person-Years	HR (95%CI) [*]	Cases	Person-Years	HR (95%CI) [*]
0-49	33	153,559	1.22 (0.80-1.97)	67	186,407	1.56 (1.08-2.23)
50-199	57	282,979	1.22 (0.80-1.87)	89	352,552	1.17 (0.84-1.65)
200-499	60	329,767	1.25 (0.82-1.89)	105	412,495	1.23 (0.89-1.70)
500+	39	265,689	reference	58	310,025	reference
Linear (per 100m closer) [§]	189	1,031,994	1.06 (0.97-1.15)	319	1,261,479	1.07 (1.00-1.14)
p-for-interaction				0.88		

Models adjusted for age, race, and calendar time, secondhand smoke exposure during childhood, at home, and at work, BMI, menopausal status and postmenopausal hormone use, the Alternative Healthy Eating Index, alcohol consumption, physical activity, family history of MI, aspirin, multivitamin, and vitamin E use, region of residence, and Census tract median home value and median income, incidence of diabetes or cancer, high cholesterol, high blood pressure, stroke, or coronary heart disease

[§] Linear models for distances 0-499m, compared to addresses 500+m away

Supplemental Table 2: Hazard ratios (HRs) and 95 % confidence intervals (95% CI) for the multivariable and mediator adjusted associations of the risk of nonfatal myocardial infarction (MI) and fatal coronary heart disease (CHD) 1986-2010 with residential proximity to A1-A3 roads among Nurses' Health Study participants by active smoking status

Outcome	Distance (m)	Cases	Never Smokers		Ever Smokers		
			Person-Years	HR (95%CI)*	Cases	Person-Years	HR (95%CI)*
Nonfatal MI	0-49	108	141,168	1.06 (0.84-1.20)	162	171,856	1.10 (0.94-1.28)
	50-199	102	261,862	1.00 (0.84-1.20)	166	326,017	1.13 (0.99-1.29)
	200-499	89	304,673	0.94 (0.78-1.12)	150	381,281	1.08 (0.95-1.23)
	500+	92	241,918	reference	131	282,346	reference
	Linear (per 100m) §	911	949,621	1.01 (0.98-1.05)	1,762	1,161,499	1.02 (0.99-1.05)
	p-for-interaction					0.89	
Fatal CHD	0-49	47	244,065	1.21 (0.85-1.72)	145	174,848	1.37 (0.87-1.35)
	50-199	43	307,267	1.21 (0.89-1.65)	201	331,579	1.09 (0.87-1.36)
	200-499	42	264,344	1.37 (1.01-1.85)	200	386,787	0.96 (0.77-1.21)
	500+	28	142,672	reference	132	286,390	reference
	Linear (per 100m) §	379	958,349	1.03 (0.97-1.09)	678	1,179,603	1.07 (1.02-1.11)
	p-for-interaction					0.52	

* Models adjusted for age, race, calendar time, secondhand smoke exposure during childhood, at home, and at work, BMI, menopausal status and postmenopausal hormone use, the Alternative Healthy Eating Index, alcohol consumption, physical activity, family history of MI, aspirin, multivitamin, and vitamin E use, region of residence, and Census tract median home value and median income, and incidence of diabetes, cancer, high cholesterol, high blood pressure, or stroke

§ Linear models for distances 0-499m, compared to addresses 500+m away