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Living Near Major Traffic Roads and Risk of Deep Vein Thrombosis

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Abstract

Background—Particulate air pollution has been consistently linked to increased risk of arterial cardiovascular disease. Few data on air pollution exposure and risk of venous thrombosis are available. We investigated whether living near major traffic roads increases the risk of deep vein thrombosis (DVT), using distance from roads as a proxy for traffic exposure.

Methods and Results—Between 1995-2005, we examined 663 patients with DVT of the lower limbs and 859 age-matched controls from cities with population>15,000 inhabitants in Lombardia Region, Italy. We assessed distance from residential addresses to the nearest major traffic road using geographic information system methodology. The risk of DVT was estimated from logistic regression models adjusting for multiple clinical and environmental covariates.

The risk of DVT was increased (Odds Ratio [OR]=1.33; 95% CI 1.03-1.71; p=0.03 in age-adjusted models; OR=1.47; 95%CI 1.10-1.96; p=0.008 in models adjusted for multiple covariates) for subjects living near a major traffic road (3 meters, 10th centile of the distance distribution) compared to those living farther away (reference distance of 245 meters, 90th centile). The increase in DVT risk was approximately linear over the observed distance range (from 718 to 0 meters), and was not modified after adjusting for background levels of particulate matter (OR=1.47; 95%CI 1.11-1.96; p=0.008 for 10th vs. 90th distance centile in models adjusting for area levels of particulate matter <10 μm in aerodynamic diameter [PM_{10}] in the year before diagnosis).

Conclusions—Living near major traffic roads is associated with increased risk of DVT.

Keywords

Deep vein thrombosis; air pollution; risk factors; coagulation

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CONFLICT OF INTEREST DISCLOSURES
The Authors do not have any potential conflicts of interest relevant to the subject of this manuscript.

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Exposure to particulate air pollution has been consistently associated with increased morbidity and death from heart disease and stroke.[1-4] Among the mechanistic pathway that mediates such effects,[4, 5] elevated plasma levels of coagulation proteins such as factor VIII, von Willebrand factor, and fibrinogen, as well as shortened prothrombin time, have been associated with the exposure.[5-8] Recently, an association between particulate air pollution and an increased risk of deep vein thrombosis (DVT) was reported by some of us.[9] Determinants of arterial and venous thrombosis are in part different, as hypercoagulability due to a series of heritable or acquired risk factors, including the gain-of-function mutations in coagulation factor V (factor V Leiden) and prothrombin (prothrombin G20210A), deficiencies of the natural anticoagulant proteins antithrombin, protein C and protein S, and use of oral contraceptive or hormone replacement therapy,[10-12] is much more associated with venous than arterial thrombosis. Venous thromboembolism is the third most common cardiovascular disease behind acute coronary syndromes and stroke.[13] In our previous study on DVT conducted in Lombardia Region, Italy, the average background ambient concentrations of PM_{10} (ambient particulate matter <10 μm in aerodynamic diameter) measured in the year before diagnosis in the areas of residence of the study subjects were positively associated with DVT risk, and air pollution related risks were found to be stronger in men than in women, particularly those using oral contraceptives or hormone replacement therapy.[9] After this initial report, additional evidence is needed to confirm the link between air pollution and DVT and identify the responsible sources of exposure.[14, 15]

Road traffic is a major determinant of exposure to particulate pollution in urban environments,[16, 17] and residential proximity to major traffic roads has been used in several studies to demonstrate the effects of traffic-related air pollution on cardiovascular and respiratory disease.[16-24] In the present study, we investigated whether individuals living near major traffic roads have a higher risk of DVT than those living farther away, and tested whether such risk is independent from background average exposure to particulate matter, as well as from clinical risk factors for DVT.

METHODS

Study population

The study included 663 patients (314 men, 349 women), who were Lombardia Region, Northern Italy residents and had been referred from January 1995 through September 2005 to the Thrombosis Center, University of Milan and IRCCS Maggiore Hospital, Milan, Italy, for a thrombophilia screening after an episode of lower-limb DVT with or without symptomatic pulmonary embolism. Patients were asked to bring to the Center all available clinical documentation. Diagnosis of DVT was accepted on the evidence from objective methods such as compression ultrasonography or venography, and, in case of concurrent pulmonary embolism, substantiated by perfusion/ventilation scan, computed tomography or pulmonary angiography. Patients were asked about the presence of transient DVT risk factors in the month preceding the event, including surgery, trauma, immobilization (>=10 days), oral contraceptives or hormone replacement therapy, pregnancy/puerperium (6 week period after delivery). DVT was complicated by symptomatic pulmonary embolism in 122 patients (18.4%) Five hundred and eighty patients (87.5%) had had a first DVT, whereas 83 (12.5%) had recurrent DVT in the study period.

Controls were 859 healthy individuals residents in Lombardia Region (320 men, 539 women), who volunteered to be investigated at the Thrombosis Center in the same study period as the patients. Controls for the present study were randomly selected among a larger population of controls recruited by asking each of the patients referred to the Thrombosis Center to be accompanied by a friend or nonblood relative. Selection of controls was made using an

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algorithm that balanced their age distribution to that of the patients. To increase power to evaluate a potential effect modification by oral contraceptives and hormone replacement therapy, female controls were recruited in excess of female patients. Thrombosis was excluded in controls with a structured questionnaire validated for the retrospective diagnosis of venous thromboembolism.[25] All patients and controls lived in cities with population>15,000 inhabitants. Information on clinical, lifestyle, and reproductive factors was collected from all participants during an in-person interview. Participants's written informed consent and local Institutional Review Board approvals were obtained before the study.

Distance from Major Roads and Background Exposure to Particulate Matter

All residential addresses of the study subjects were geocoded using TeleAtlas Multinet (Ver 2006.10; Tele Atlas Italia srl, Milan, Italy). We used ArcGIS software (version 9; ESRI, Redlands, WA) to calculate the distance of the geocoded address of each study subject from the nearest major traffic road (limited-entrance highways, other multilane highways, primary urban roads) based on electronic maps provided by the Territory Information System of the Lombardia Region (CT10 Version 1.0, map scale 1:10,000; released on December 15th 2000).

Methods for PM exposure assignment were previously described in detail.[9, 26] Briefly, average mean concentrations of PM_{10} were computed using data from monitors located at 53 different sites throughout the Region. All participants were assigned to one of five geographic areas (Milan urban area; Milan suburban area; Bergamo/Brescia; Po River Valley; Varese/Como/Lecco), based on their residence at the index date, and average levels of PM_{10} were computed for each area. Index dates were the date of diagnosis of DVT for patients and the date of the examination for controls. PM_{10} level was evaluated in our statistical analyses using ambient PM_{10} concentrations averaged over the 365 days preceding the index date, taking also into account changes of residence during the same time-window. Because PM_{10} represented the average background PM_{10} of each of the five geographic areas, distance from major traffic roads and PM_{10} levels were only weakly, non significantly correlated in our data (r=0.05, p=0.07).

Statistical Analysis

To test for the association between proximity to major roads and risk of DVT, we first assigned the study participants to categories of distance from major roads based on the quartiles of controls. We computed Odds Ratios (ORs) and 95% confidence intervals (CIs) using conditional logistic regression models that included as independent variables either age only (matching variable); or age, sex, age, body mass index, area of residence, education (elementary/middle school, high school, college), factor V Leiden or G20210A prothrombin mutation (yes/no), and current oral contraceptive use or hormone replacement therapy (yes/no). In addition, we fit additional models that also included the mean PM_{10} area level as independent variable to assess whether the association between DVT and proximity to major roads was modified after adjustment for background levels of particulate matter. Using statistical models that fit a penalized spline[27] for distance to major road, we determined that the association between the risk of DVT and proximity to major traffic roads was linear. This approach uses piecewise polynomials with up to 10 degrees of freedom to model the risk response, and chooses the optimal curve based on a goodness of fit criterion. Therefore, we also used linear models to estimate DVT risk, which we report using ORs computed for a decrease equal to the difference between the 90th and the 10th percentile of the distance to major roadways. These ORs from linear models express the risk for individuals living on a hypothetical line set at the 10th percentile of distance from the nearest major traffic road (3 meters), compared with individuals living on a reference line located at the 90th percentile (245 meters). In other words, the ORs express the risk associated with living 242 meters closer to major traffic roads. T-tests and ANOVA were used to test for the association of proximity to

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major roads with subjects' characteristics separately for patients and controls. All analyses were performed in Stata/SE, version 10.0 (Stata Corp., College Station, TX), except for models fitting penalized splines, which were run in R, version 2.2.0 (R Project for Statistical Computing, Vienna, Austria). All statistical tests are two sided.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Characteristics of the study population

Table 1 shows the main characteristics of patients and controls, as well as the mean distance from major traffic roads, according to demographic and clinical variables. Distance from major traffic roads of patients and controls was not significantly associated with sex, age, body mass index, education, use of oral contraceptives or hormone replacement therapy, and factor V Leiden or G20210A prothrombin mutation. Distance from major traffic road tended to be lower for subjects from the Varese/Como/Lecco area, particularly in DVT patients.

Proximity to Major Traffic Roads and Relative Risk of Deep Vein Thrombosis

The risk of DVT increased in association with proximity to major traffic roads (Table 2). When we assigned the study participants to categories of distance from major traffic roads based on the quartiles of the control groups, we found that the risk of DVT was lowest in the subjects who lived farther away (between 162.1 and 718.0 meters, taken as the reference category) and increased progressively with proximity to major roads. Individuals who lived closest to major traffic roads (between 0 and 20.5 meters) had an age-adjusted OR of 1.43 (95% 1.06-1.91; p=0.01 for trend across distance categories). The ORs for DVT did not differ after adjustment for age, sex, body mass index, education, current use of oral contraceptives, Leiden V or prothrombin mutations, and area of residence (OR=1.50; 95% 1.08-2.09 for the category closest to major traffic roads; p-trend=0.01), as well as after additional adjustment for the average background levels of particulate matter in each of the geographical areas of residence (OR=1.50; 95% 1.08-2.09; p-trend=0.01, adjusted for area average level of background PM_{10} in the year before diagnosis, in addition to the other covariates) [Table 1].

The increase in risk of DVT was nearly linear over the entire range of distances (from 718 to 0 meters) observed in this population [Figure 1]. In linear models (Table 3), we estimated an age-adjusted OR for DVT of 1.33 (95% CI 1.03-1.71; p=0.03) for individuals living in proximity of a major traffic road (3 meters, 10th centile of the distance distribution) compared to those living farther away (reference distance of 245 meters, 90th centile). This OR was equal to 1.47 (95% CI 1.10-1.96; p=0.008) in a model adjusted for multiple covariates. Again, the risk estimate for DVT associated with proximity to major traffic road did not change after adjustment for background levels of particulate matter (OR=1.47; 95% CI 1.11-1.96; p=0.008 for 10th vs. 90th centile of distance in a model adjusting for area average level of background PM_{10} in the year before diagnosis, in addition to the other covariates).

The association between proximity to major traffic roads and DVT was weaker in women (OR=1.30, 95% CI 0.86-1.94; p=0.21) than in men (OR=1.67, 95% CI 1.11-2.51; p=0.014), and absent in women using oral contraceptives or hormone replacement therapy (OR=0.72; 95% CI=0.32-1.61; p=0.42). The results on the association between proximity to major traffic roads and DVT appeared to be driven by the associations found among individuals who lived in the Milan urban and suburban areas, which included the majority of the study subjects. The other characteristics evaluated, such as age, body mass index, education, study period, and factor V Leiden or G20210A prothrombin mutations, did not modify the association between

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proximity to major traffic roads and DVT (Table 3). For all the variables considered, none of the p-values for the interaction between proximity to major traffic roads and subjects' characteristics reached statistical significance.

As a sensitivity analysis, we evaluated the effect of adding current smoking (yes/no) to the statistical models. In the model fully adjusted for all covariates used above, PM_{10} levels, and current smoking, the OR for individuals living in proximity of a major traffic road (10th centile) compared to those living farther away (90th centile) was equal to 1.47 (95% CI 1.10-1.97; p=0.008); the smoking-adjusted ORs by subjects' characteristics did not show relevant departures from those reported in Table 3. Similarly, adding a categorical variable for the study period (1995-1997, 1998-2000, or 2001-2005) in the models did not modify the results (OR=1.49, 95% CI 1.1-2.0, p=0.007 for 10th vs. 90th centile in the fully adjusted model).

We also repeated all the analyses after excluding patients with a recurrent (non-first) episode of DVT (n=83). Risk estimates were very similar to those obtained on the entire study population. The OR for DVT was 1.42 (95% CI 1.06-1.91; p=0.02) for individuals living in proximity of a major traffic road (10th centile) compared to those living farther away (90th centile). In the subsample of 580 patients with a single episode of DVT, the variations in the association between proximity to major traffic roads and DVT by demographic characteristics, presence of thrombophilia or use of hormone therapies were similar to those observed in the entire study population.

DISCUSSION

In this study of patients with DVT and healthy controls, residential proximity to major traffic roads was associated with an increased risk of DVT after controlling for individual characteristics and clinical covariates. The increased risk of DVT associated with proximity to major traffic roads was smaller in women than in men and limited to those who were not using oral contraceptives or hormone replacement therapy at the time of diagnosis.

Residential distance from major traffic roads is considered to reflect exposure to traffic emissions,[16, 17, 24] as concentrations of particulate matter and other exhaust pollutants have been reported to be higher nearby major roads and then decline exponentially within 500 meters.[28, 29] Several previous investigations have shown an association between proximity to major roads and arterial cardiovascular diseases.[16-18, 24, 30] In a case-control study in Massachusetts, Tonne and collaborators[18] found that living near a major roadway was associated with a 5% increase per kilometer in the risk of acute myocardial infarction. A cohort-study in the Netherlands showed a 1.95-fold increase in cardiopulmonary mortality for subjects living within 100 meters of a freeway or within 50 meters of a major urban road,[16] and, more recently, mortality of patients with heart failure has been shown to be 30% greater among subjects from Worcester, Massachusetts living within 100 meters of a major traffic road.[17] In an investigation in England and Wales, mortality from stroke was 7% higher in men living within 200 meters of a main road compared to those living =>1000 meters away.[30] In our study, the estimates for the increase in DVT risk associated with road proximity were similar in models with or without background PM_{10} levels as an independent variable, which we estimated using PM_{10} measurements from ambient monitoring stations that were averaged over broad areas of Lombardia region.[9] Background PM_{10} and road distance were only weakly correlated in our data. This suggests that distance from major traffic roads provided additional information on local spatial variations of air pollution in our study.

A systemic increase in thrombotic tendency, secondary to the induction of inflammatory mediators produced in the lungs and released in the circulation, or to the translocation of particles of smaller diameter from the lungs into the circulation, has been frequently proposed

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to account for the cardiac and cerebrovascular effects of particulate air pollution[6] and may also operate to increase the risk of DVT. The pattern of DVT-road proximity association was remarkably consistent with the results on DVT risks we recently described for background PM_{10} exposure,[9] particularly as both environmental risk factors showed weaker effects in women and no effect in those women who were taking oral contraceptives or hormone replacement therapy.

This study has the advantage of being based on a large number of patients with DVT and controls recruited using a standardized protocol. Patients had objective diagnoses of DVT, and both patients and controls were carefully characterized for inherited and acquired risk factors for DVT. Healthy controls, also due to their selection among non-blood relatives and friends of DVT patients, tended to be distributed in the five study areas with proportions that were very similar to those of the patients. This might have generated overmatching in our study, i.e., distance to major roads of controls might have been more similar to that of patients than they actually are in the population at risk. Therefore, it is possible that the risk of DVT was underestimated in our study. Although the multivariate analysis was adjusted for the major risk factors for DVT, we cannot exclude that other unmeasured confounders might have influenced our results. Living near major traffic roads might have been associated with factors other than exposure to high traffic pollution. Residential location may reflect differences in socioeconomic status. However, no association was found between distance from major road and educational level, a major determinant of socioeconomic status, which was also included in our multivariable models. In addition, one might hypothesize that distance from major traffic roads may be differentially associated with patterns of physical activity. Although we did not have information on physical activity in this study, major differences in physical activity would have likely been reflected in differences in body mass index, which is a strong risk factor for DVT.[31] On the contrary, body mass index did not vary in relation to distance from major traffic roads. Also, estimates of DVT risk were adjusted for BMI in multivariable models. Other factors which have been proposed as potential confounders of the association between living near to major traffic roads and arterial cardiovascular disease, such as traffic noise and tobacco smoking, were less of a concern in our analysis, as neither of them is an established risk factor for DVT.[31] A recent meta-analysis indicated that diabetic patients might have a moderately increased risk of DVT.[32] As diabetes was not known as a risk factor for DVT at the time the present study was initiated, we did not collect information on diabetes that could have been used in our multivariate analyses. Another limitation of the present study is that no information was collected about the floor on which the study subjects lived. Therefore, we were unable to take into account vertical elevation from street level in our analyses.

In our study, the increase in DVT risk associated with proximity to major traffic roads was approximately linear across the range of distances we observed. In previous work, we showed that DVT risk also increased linearly in relation with increasing PM_{10} concentrations. As particle concentrations have been shown to decrease exponentially with distance from major roads,[28, 29] one might have expected a non-linear relationship between DVT risk and distance from major traffic roads. However, some of the previous studies that have associated proximity to major traffic roads to arterial cardiovascular outcomes have also shown no departures from a linear increase in risk,[23, 33] or modeled distance from major roads using a linear function.[17, 18] The lack of an exponential increase in DVT risk with proximity to major traffic roads may be accounted for by limitations inherent to the use of this surrogate measure as a proxy for traffic exposure. For example, distance of the subjects' residence from major traffic roads does not take into account individual differences in the time spent at home and in other environments, such as workplaces or in traffic while commuting.[22] In our study, we did not have information on low physical activity, a risk factor for DVT that might be associated with distance from major traffic roads and modify the shape of the DVT-traffic road relationship.

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In conclusion, our study indicates that subjects living near major traffic roads are at increased risk of DVT. Our findings, particularly if confirmed in future investigations, would demonstrate a common and easy to identify risk factor for DVT, and give further support to the measures aimed at reducing traffic emissions that have been adopted or considered in major metropolitan cities.

CLINICAL SUMMARY

Venous thromboembolism is the third most common cardiovascular disease behind acute coronary syndromes and stroke. Exposure to particulate air pollution has been associated with increased risk of arterial cardiovascular disease, but only a few data are available on venous thrombosis. Because road traffic is a major source of exposure to particulate pollution, individuals living closer to major traffic roads might be at higher risk for air pollution effects. In a study of 663 patients with Deep Vein Thrombosis (DVT) of the lower limbs and 859 age-matched controls from Lombardy, Italy, we found that individuals living near major traffic roads had a higher risk of DVT than those living farther away. Using multivariable modeling adjusting for multiple clinical and environmental covariates, we estimated that an individual living AT (within?) 3 meters of distance from a major traffic road had a 47% increase in DVT risk compared to an individual living at a reference distance of 245 meters. The increase in DVT risk was approximately linear over the observed distance range (from 718 to 0 meters), and was not modified after adjusting for background levels of particulate matter measured in the areas of residence of the study participants.

These findings provide novel evidence that living near major traffic roads is associated with increased risk of DVT.

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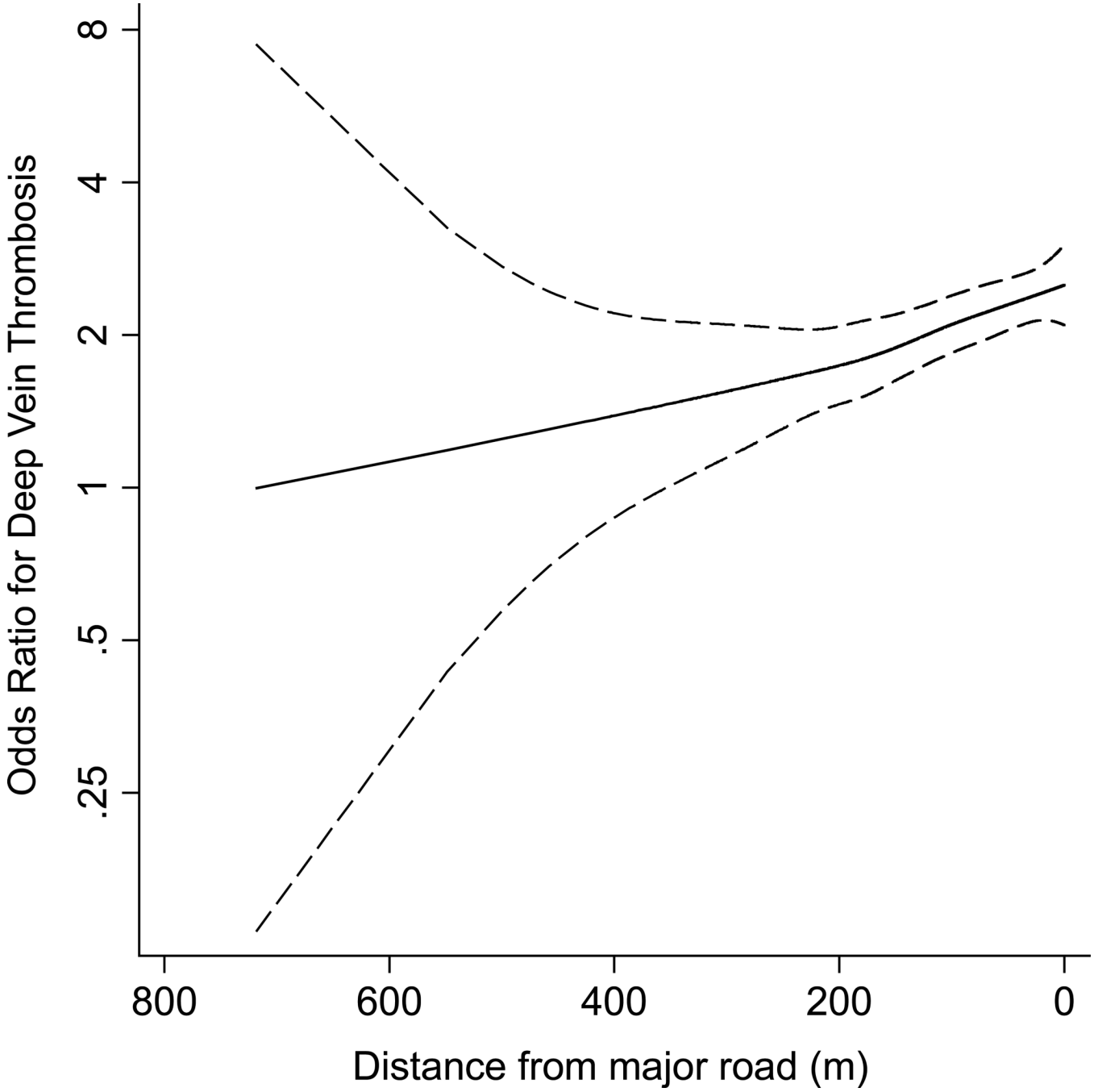

Figure 1.

Proximity to Major Roads and Risk of Deep Vein Thrombosis.

The graph demonstrates the observed relationship between proximity to the nearest major road and risk of deep vein thrombosis. These results suggest a linear relationship between exposure and risk, though the 95% confidence intervals (dashed lines) are wide at the farther extreme of road distance. Risk is depicted in comparison with a reference value of 718 meters (maximum observed distance). Risk estimates, obtained using penalized splines with four degrees of freedom, are adjusted for age, sex, body mass index, education, current use of oral contraceptives or hormone replacement therapy, factor V Leiden and prothrombin G20210A mutation in logistic regression analysis.

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Table 1

Characteristics and distance from major traffic roads of patients with deep vein thrombosis and healthy controls

	Patients (n=663)					Controls (n=859)				
	n	(%)	Distance from major roads			n	(%)	Distance from major roads		
			Mean	(SD)	p-value*			Mean	(SD)	p-value*
Sex										
Male	314	(47.4%)	99.9	(97.0)		320	(37.2%)	117.8	(111.8)	
Female	349	(52.6%)	97.9	(97.4)	0.79	539	(62.8%)	104.6	(95.5)	0.27
Age										
18-35 years	208	(31.4%)	101.1	(97.3)		270	(31.4%)	107.8	(95.3)	
35-50 years	209	(31.5%)	93.4	(94.6)		274	(31.9%)	106.2	(110.2)	
50-84 years	246	(37.1%)	101.6	(99.4)	0.62	315	(36.7%)	113.9	(100.4)	0.63
Body Mass Index										
13.3-22.0 kg/m^2	151	(24.4%)	93.3	(100.8)		305	(35.7%)	107.2	(101.4)	
22.0-24.9 kg/m^2	154	(24.8%)	98.2	(92.4)		290	(33.9%)	107.8	(96.6)	
24.9-53.3 kg/m^2	315	(50.8%)	100.4	(98.2)	0.77	260	(30.4%)	114.4	(109.1)	0.66
Education										
Elementary/Middle School	204	(32.3%)	96.3	(100.1)		198	(23.3%)	107.8	(95.2)	
High School	283	(44.9%)	100.3	(100.4)		425	(50.0%)	112.4	(107.2)	
College	144	(22.8%)	101.0	(87.9)	0.87	227	(26.7%)	106.5	(99.0)	0.75
Area of residence										
Milan, Urban Area	381	(57.5%)	98.5	(91.4)		505	(58.8%)	106.4	(96.9)	
Milan, Suburban Area	201	(30.3%)	103.0	(104.8)		249	(29.0%)	121.4	(117.7)	
Bergamo/Brescia	8	(1.2%)	145.8	(173.4)		18	(2.1%)	104.9	(103.3)	
Po River Valley	47	(7.1%)	105.0	(104.9)		67	(7.8%)	97.0	(78.3)	
Varese, Como, Lecco	26	(3.9%)	47.6	(55.9)	0.05	20	(2.3%)	87.9	(81.0)	0.21
Current use of oral contraceptives or hormone replacement therapy†										
No	181	(51.9%)	93.0	(91.4)		388	(75.2%)	106.7	(97.3)	
Yes	168	(48.1%)	106.1	(106.6)	0.22	128	(24.8%)	94.6	(88.6)	0.29
Factor V Leiden or G20210A prothrombin mutation										

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	Patients (n=663)					Controls (n=859)				
	n	(%)	Distance from major roads			n	(%)	Distance from major roads		
			Mean	(SD)	p-value*			Mean	(SD)	p-value*
No mutation	480	(72.4%)	96.9	(94.6)		807	93.9%)	108.9	(101.7)	
Any mutation	183	(27.6%)	104.2	(103.8)	0.39	52	(6.1%)	120.0	(107.8)	0.44

*Test for difference of average distance from major traffic roads across subjects' characteristics categories.

†Only female subjects are shown

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Table 2

Relative risk of deep vein thrombosis by quartile-based categories of proximity to major traffic roads

Distance from major roads*	Patients		Controls		Adjusted for age†			Adjusted for multiple covariates‡			Adjusted for multiple covariates & PM_{10} level§		
	n	%	n	%	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p
718.0-162.1 m	138	(20.8%)	214	(24.9%)	1.00	-		1.00	-		1.00	-	
162.0-92.1 m	160	(24.1%)	217	(25.3%)	1.14	(0.84-1.53)	0.40	1.16	(0.83-1.63)	0.39	1.16	(0.82-1.62)	0.40
92.0-20.6 m	174	(26.2%)	214	(24.9%)	1.30	(0.96-1.74)	0.09	1.39	(0.99-1.95)	0.05	1.39	(0.99-1.95)	0.05
20.5-0 m	191	(28.8%)	214	(24.9%)	1.43	(1.06-1.91)	0.02	1.50	(1.08-2.09)	0.01	1.50	(1.08-2.09)	0.01
					p for trend=0.01			*p for trend=0.01*			*p for trend=0.01*		

*Subjects were assigned to distance categories based on quartiles of the control group

†Controls were matched by age to the cases. Odds Ratios (ORs), 95% Confidence Intervals (95% CIs) and p-values were adjusted for age to account for the age-matching

‡Risk estimates adjusted for age, sex, area of residence, body mass index, education, current use of oral contraceptives, and Leiden V or prothrombin mutations.

§Risk estimates adjusted for age, sex, area of residence, body mass index, education, current use of oral contraceptives, Leiden V or prothrombin mutations, and average PM_{10} levels in the year before diagnosis (patients) or examination (controls)

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Table 3

Relative risk of deep vein thrombosis associated with proximity to major traffic roads by subjects' characteristics, adjusted for multiple risk factors.

	OR*	(95% CI)	p-value	p -interaction
All subjects, age-adjusted	1.33	(1.03-1.71)	0.03	NA
All subjects, adjusted for multiple covariates†	1.47	(1.10-1.96)	0.008	NA
All subjects, adjusted for background PM_{10} exposure‡	1.47	(1.11-1.96)	0.008	NA
Sex‡				
Male	1.67	(1.11-2.51)	0.014	
Female	1.30	(0.86-1.94)	0.21	0.39
Age‡				
18-35 years	1.30	(0.76-2.13)	0.36	
35-50 years	1.33	(0.82-2.15)	0.24	
50-84 years	1.71	(1.06-2.74)	0.03	0.65
Body Mass Index‡				
13.3-22.0 kg/m^2	1.61	(0.92-2.80)	0.09	
22.0-24.9 kg/m^2	1.41	(0.80-2.47)	0.23	
24.9-53.3 kg/m^2	1.41	(0.93-2.15)	0.11	0.92
Education‡				
Elementary/Middle School	1.58	(0.91-2.77)	0.11	
High School	1.40	(0.94-2.07)	0.09	
College	1.53	(0.82-2.84)	0.18	0.93
Area of residence‡				
Milan, Urban Area	1.50	(1.01-2.21)	0.04	
Milan, Suburban Area	1.58	(0.98-2.53)	0.06	
Bergamo/Brescia	0.32	(0.05-1.82)	0.20	
Po River Valley	0.93	(0.28-3.09)	0.91	
Varese, Como, Lecco	9.51	(0.80-113.6)	0.07	0.21
Study period				
1995-1997	1.71	(1.05-2.79)	0.03	
1998-2000	1.34	(0.78-2.29)	0.29	
2001-2005	1.36	(0.83-2.23)	0.22	0.79
Current use of oral contraceptives or hormone replacement therapy‡*				
No	1.67	(1.01-2.78)	0.047	
Yes	0.72	(0.32-1.61)	0.42	0.08
Factor V Leiden or G20210A prothrombin mutation‡				
No mutation	1.52	(1.11-2.08)	0.008	
Any mutation	1.21	(0.58 -2.54)	0.61	0.58

*Odds Ratio (OR) and 95% Confidence Interval (CI) estimating the risk of DVT associated with living in the proximity of a major road (3 meters, 10th centile of the distance distribution) compared to living farther away (reference distance of 245 meters, 90th centile of the distance distribution)

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[†]Risk estimates adjusted for age, sex, area of residence, body mass index, education, current use of oral contraceptives and Leiden V or prothrombin mutations in logistic regression analysis

[‡]Risk estimates adjusted for age, sex, area of residence, body mass index, education, current use of oral contraceptives and Leiden V or prothrombin mutations, and average PM_{10} levels in the year before diagnosis (patients) or examination (controls) in logistic regression analysis.