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RESIDENTIAL PROXIMITY TO ENVIRONMENTAL SOURCES OF PERSISTENT ORGANIC POLLUTANTS AND FIRST-TIME HOSPITALIZATIONS FOR MYOCARDIAL INFARCTION WITH COMORBID DIABETES MELLITUS: A 12-YEAR POPULATION-BASED STUDY

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Abstract
Objectives: Environmental exposure to persistent organic pollutants (POPs) has been associated with an increased risk of both acute myocardial infarction (AMI) and diabetes mellitus (DM). A study of first-time hospitalizations for AMI with DM as a comorbidity in populations presumed to be exposed or not exposed on the basis of residence near POPs sites was conducted to investigate whether exposure to POPs increases the environmental burden of disease. **Materials and Methods:** We examined the association between residential proximity to environmental sources of POPs and hospitalization rates for first-time AMI with comorbid DM in 31 428 patients aged 25–74 years, using the New York Statewide Planning and Research Cooperative System data for a 12-year period (1993–2004). Environmental exposure status was assessed based on the zip code of residence. Adjusted relative risks (RR) of AMI hospitalization were estimated by multivariate Poisson regression. **Results:** Hospitalization rates for first-time AMI with comorbid DM were significantly greater in populations living near POPs sites (adjusted RR = 1.169, 95% CI: 1.014–1.347, $p < 0.05$). These rates were also significantly higher in African Americans than in Caucasians (adjusted RR = 1.902, 95% CI: 1.659–2.180, $p < 0.001$), in males (adjusted RR = 1.767, 95% CI: 1.695–1.843, $p < 0.001$), and for older ages (p for trend < 0.001). These findings, consistent with established non-modifiable risk factors, support the plausibility of our model. **Conclusions:** Residential proximity to environmental sources of POPs is associated with a significant increase in hospitalization rates for first-time AMI with comorbid DM, compared to respective rates in populations not exposed to POPs.

Key words:
Persistent organic pollutants, Cardiovascular disease, Myocardial infarction, Diabetes Mellitus

INTRODUCTION

The incidence and prevalence of cardiovascular disease (CVD) has reached alarming levels. CVD is the leading cause of death in the US and worldwide [1,2]; it also represents the highest economic impact with more than $475 billion costs in 2009 [2]. The CVD problem is made particularly worse with diabetes mellitus (DM), which is not only a major risk factor for CVD, but also a serious comorbidity that aggravates the burden of CVD by having unfavorable impact on the severity of the condition and prognosis in hospitalized AMI patients [3].

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Conventional risk factors (diabetes, hypertension, smoking, and dyslipidemia) have failed to explain 100% of atherosclerosis-related heart disease: coronary heart disease (CHD) and its most severe form — acute myocardial infarction (AMI) [4,5]. There is increasing evidence that exposure to other environmental contaminants, in addition to tobacco smoke, is a significant risk factor for CHD and AMI; 16% of CVD in North America is attributed to environmental exposure [6]. Of particular concern are persistent organic pollutants (POPs), the environmental exposure to which is associated with the development of atherosclerosis both in humans and animals. POPs are semi-volatile lipophilic organic compounds, including polychlorinated biphenyls (PCBs), dioxins, furans, and chlorinated pesticides that are resistant to chemical, biological, and photolytic degradation. These compounds are persistent both in the environment and human body. Exposure to POPs is associated with an increased risk of atherosclerosis and its clinical manifestations (CHD, AMI, and cerebrovascular disease) in humans [7–9] and animals [10,11]. We have previously reported that environmental exposure to POPs, assessed by the residence near a POPs waste site, is associated with increased CHD and AMI hospitalization rates [12]. Shcherbatykh et al. observed an increase in stroke hospitalization rates based on a similar exposure assessment [13].

Recent evidence also suggests that exposure to POPs is associated with an elevated risk of developing diabetes mellitus (DM) [14–19].

While several of the above-cited studies have investigated association between exposure to POPs and either CHD or DM, regardless of the presence or absence of the other disease, the problem of exposure to POPs and the risk of AMI aggravated by DM has not been addressed yet. This prompted us to investigate hospitalization rates for first-time AMI with DM as a comorbidity in POPs-exposed and unexposed populations.

MATERIALS AND METHODS

Study Population

Data on AMI hospitalizations for a 12-year period (1993–2004) were obtained from the New York State (NYS) Statewide Planning and Research Cooperative System (SPARCS) which is maintained by the NYS Department of Health. This database contains information on the principal diagnosis, up to 14 other diagnoses and up to 15 procedures coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and includes demographic information (such as age, gender, and race/ethnicity) and patient's residential zip code for every patient upon discharge from a state-regulated hospital. As the New York City maintains its own hospitalization data and its population structure is different from that of the rest of the state, we excluded the New York City from the analysis.

To assess environmental residential exposure, we classified the patients' zip codes of residence as "POPs" or "non-POPs" zip codes depending on whether they contain or abut hazardous waste sites with these pollutants, as described elsewhere [20]. A total of 196 zip codes were classified as POPs zip codes based on the information on 818 waste sites identified by the New York State Department of Environmental Conservation as "State Superfund" sites, the zip codes directly abutting POPs-contaminated portion of the Hudson River, and the six "Areas of Concern" identified by the US-Canadian International Joint Commission (Buffalo River, Niagara River, the Rochester Embayment and Genesee River, Eighteen Mile Creek, the St. Lawrence River, and Oswego River) [21]. The total number of non-POPs zip codes was 1207, of which 215 contained or abutted hazardous waste sites with contaminants other than POPs ("other" zip codes), and 992 zip codes were classified as "clean" (containing no known hazardous waste sites).

The demographic data (age, gender, race, and income) were obtained from Claritas, Inc. We analyzed data from only two racial groups — African Americans and Caucasians — because they comprised more than 97% of the residential population of New York State except for New York City. Income, a well-established and valid measure of the socioeconomic status [22,23], was controlled for by restriction. We included only residents of households in the two upper quartiles of the medium-household income distribution, because lower income can prevent patients from seeking medical care, especially in the cases with moderate and/or atypical clinical manifestations of AMI (no severe chest pain or other

prominent symptoms). After the above exclusions, there were a total of 31 428 first-time AMI hospitalizations (the principal diagnosis ICD-9-CM codes 410.xx and the absence of old myocardial infraction ICD-9-CM codes 412.x in the hospital record) in patients 25–74 years of age with either type 1 or type 2 DM (other diagnoses ICD-9-CM codes 250.xx) during the 12-year period of 1993–2004 out of a total of 53 260 344 person-years (Table 1). We restricted the upper age limit to 74 years inclusive, because in older age groups, the effect of age as an atherosclerosis risk factor becomes so prominent that it obscures the other risk factors.

Statistical Methods

The primary outcome variable was the hospitalization rate for first-time AMI (no history of previous AMI) with DM as a comorbidity among New York State's population. Relative risks (RR) of hospitalization for first-time AMI with comorbid DM were calculated as the hospitalization rate ratios. RR, with 95% confidence intervals (CI), were estimated by Poisson regression, adjusting for potential confounders including age, gender, and race. Conventional alpha-level (type I error) of 0.05 was used for testing statistical significance ($p < 0.05$). In unadjusted preliminary analysis, Bonferroni correction was used when multiple comparisons were performed. In adjusted analysis, multivariate Poisson regression was used to control for confounders. Overdispersion in the Poisson regression was adjusted for by using a scaling factor; the scaled Pearson chi-square equaled 1. To adjust for exposure measured at the zip code level, the generalized estimating equations (GEE) method was used. Significance for trend was assessed with the Wald statistics. Statistical analyses were conducted with SAS software, version 9.1 (SAS Institute, Inc.).

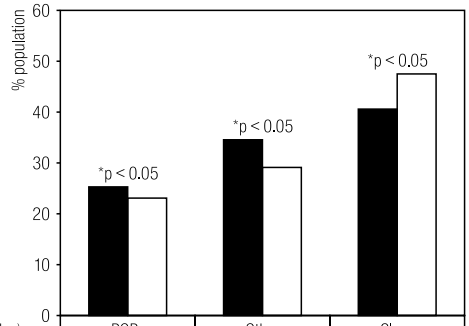
RESULTS

Almost one fourth of the study population (23.4%) was living in proximity to environmental sources of POPs (Table 1).

Table 1. Exposure status and demographic characteristics of the study population

Characteristics	Person-years studied (1993–2004) N (%)	First-time AMI hospitalizations with DM as a secondary diagnosis N (%)
Total	53 260 344 (100.0)	31 428 (100.0)
Exposure		
"POPs"	12 440 154 (23.4)	7 941 (25.3)
"clean"	25 144 332 (47.2)	13 869 (44.1)
"other"	15 675 858 (29.4)	9 618 (30.6)
Sex		
males	25 296 466 (47.5)	19 168 (61.0)
females	27 463 878 (52.5)	12 260 (39.0)
Age (years)		
25–34	12 484 038 (23.4)	140 (0.4)
35–44	14 010 060 (26.3)	1 269 (4.0)
45–54	11 614 524 (21.8)	4 935 (15.7)
55–64	8 436 606 (15.8)	9 804 (31.2)
65–74	6 715 116 (12.7)	15 280 (48.7)
Race		
Caucasian	49 940 352 (93.8)	29 071 (92.5)
African American	3 319 992 (6.2)	2 357 (7.5)

AMI — acute myocardial infarction; DM — diabetes mellitus; POPs — persistent organic pollutants.



Exposure (zip codes)	POPs	Other	Clean
■ African Americans (total 100.0%)	24.94%	34.49%	40.57%
□ Caucasians (total 100.0%)	23.25%	29.10%	47.65%

*African Americans compared to Caucasians, with Bonferroni correction.

Fig. 1. Distribution of exposure status by race.

African Americans were more likely to reside near environmental sources of POPs and other environmental pollutants, as compared to Caucasians, who were more likely to reside in "clean" zip code areas (Figure 1).

There were 31 428 first-time AMI hospitalizations with comorbid DM, which constituted 26.5% of all first-time AMI hospitalizations (118 637 cases with and without DM as a secondary diagnosis).

Unadjusted analysis, conducted prior to multivariate regression modeling, indicated that the crude rates of first-time AMI hospitalization with DM as a comorbidity were higher in POPs-exposed populations compared to residents of "clean" and "other" zip codes. Hospitalization rates (per 100 000 person-years) were 63.83 (95% CI: 62.43–65.24) for "POPs" zip codes, 61.36 (95% CI: 60.13–62.58) for "other" zip codes, and 55.16 (95% CI: 54.24–56.08) for the "clean" zip codes ($p < 0.05$ for "POPs–clean", "POPs–other", and "other–clean" pairwise comparisons, with Bonferroni correction).

The results of the adjusted analysis are presented in Table 2. A statistically significant 16.9% increase in hospitalization rates for first-time AMI with comorbid DM was observed among POPs-exposed populations as compared to unexposed populations ("clean" zip code residents): RR = 1.169 (95% CI: 1.014–1.347, p = 0.03). The increase in hospitalization rates among residents of "other" zip codes compared to "clean" zip codes was just at a borderline significance level (p = 0.08): RR = 1.133 (95% CI: 0.984–1.306).

Table 2. Adjusted RRs of hospitalization for first-time AMI with comorbid DM (1993–2004), GEE model results

Parameter	Beta Coefficient	SE	RR (95% CI)	*p*-value
"POPs" exposure (compared to "clean")[a]	0.1561	0.0725	1.169 (1.014–1.347)	0.03
"Other" exposure (compared to "clean")[a]	0.1253	0.0724	1.133 (0.984–1.306)	0.08
Males (compared to females)[b]	0.5695	0.0213	1.767 (1.695–1.843)	< 0.001
African Americans (compared to Caucasians)[c]	0.6428	0.0696	1.902 (1.659–2. 180)	< 0.001
Age (years)				
(compared to 25–34 years of age)[d]				< 0.001*
35–44	0.8887	0.1816	2.432 (1.704–3.472)	
45–54	2.3182	0.1960	10.157 (6.917–14.915)	
55–64	3.3276	0.1984	27.871 (18.893–41.116)	
65–74	4.0303	0.1987	56.278 (38.126–83.080)	

AMI — acute myocardial infarction; DM — diabetes mellitus; GEE model — generalized estimating equations model; RR(s) — relative risk(s); CI — confidence interval; POPs — persistent organic pollutants; SE — standard error of the beta coefficient.

[a] Adjusted for gender, race, and age.

[b] Adjusted for exposure status, race, and age.

[c] Adjusted for exposure status, gender, and age.

[d] Adjusted for exposure status, gender, and race.

* *p*-value for trend, Wald statistic.

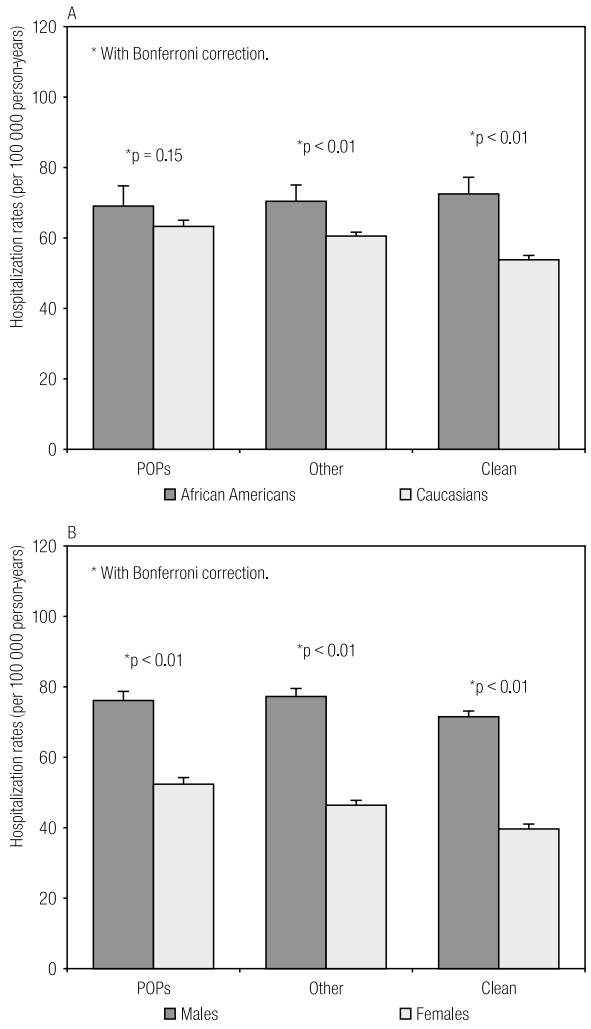
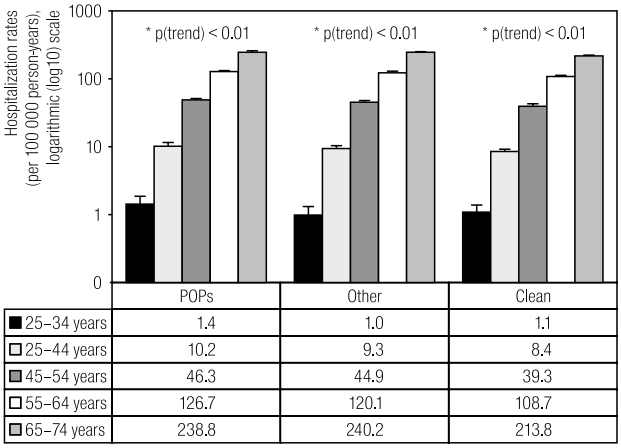


Fig. 2. (A) Crude (unadjusted) hospitalization rates (per 100 000 person-years) for first-time AMI with comorbid DM, by race. (B) Crude (unadjusted) hospitalization rates (per 100 000 person-years) for first-time AMI with comorbid DM, by gender.

Adjusted analysis demonstrated a significantly higher RR of hospitalization for first-time AMI with comorbid DM in males than in females (adjusted RR = 1.767, 95% CI: 1.695–1.843, $p < 0.001$) and in African Americans than in Caucasians (adjusted RR = 1.902, 95% CI: 1.659–2.180, $p < 0.001$). An increase in age was associated with a significant increase in RR of hospitalization as well (Table 2). These findings are consistent with the well-established risk factors for AMI — male gender, African American race, and older age — and thus can serve as indirect quality control indicators for the plausibility of our model.



	POPs	Other	Clean
25–34 years	1.4	1.0	1.1
25–44 years	10.2	9.3	8.4
45–54 years	46.3	44.9	39.3
55–64 years	126.7	120.1	108.7
65–74 years	238.8	240.2	213.8

* With Bonferroni correction.

Fig. 3. Crude (unadjusted) hospitalization rates (per 100 000 person-years) for first-time AMI with comorbid DM, by age (logarithmic scale log10).

While it was not a primary goal of our study, we also conducted exposure-stratified unadjusted analysis of hospitalization rates by race, gender, and age. In each of the three exposure status groups ("clean", "POPs", and "other"), the crude (unadjusted) RR of AMI hospitalization with DM as a comorbidity was higher in African Americans than in Caucasians: 1.342 (95% CI: 1.255–1.430, $p < 0.01$) in "clean" zip codes, 1.088 (95% CI: 0.996–1.182, $p = 0.15$) in "POPs" zip codes, and 1.161 (95% CI: 1.078–1.245, $p < 0.01$) in "other" zip codes (Figure 2A). The hospitalization rates for first-time AMI with comorbid DM were significantly higher in males than in females, both in POPs-exposed and unexposed groups: the crude (unadjusted) RR were 1.462 (95% CI: 1.399–1.529, $p < 0.01$) in "POPs" zip codes, 1.667 (95% CI: 1.601–1.737, $p < 0.01$) in "other" zip codes, and 1.795 (95% CI: 1.734–1.858, $p < 0.01$) in "clean" zip codes (Figure 2B).

Age was positively associated with an increase in hospitalization rates for first-time AMI with DM in each of the three groups (Figure 3).

DISCUSSION

In this study, we demonstrated that residential proximity to environmental sources of POPs is associated with a statistically significant ($p < 0.05$) 16.9% increase in hospitalization

rates for first-time AMI aggravated by comorbid DM. Although this finding does not establish a causal relationship between POPs and AMI, it is consistent with a growing body of evidence linking environmental exposure to POPs with AMI and other atherosclerosis-related diseases. This body of evidence contributed to the development of the emerging concepts of "environmental cardiovascular disease" [24] and "environmental burden of disease" [25]. In previous studies, increased mortality was observed among workers occupationally exposed to POPs (dioxins and furans) [26,27]. Vietnam veterans who sprayed or handled Agent Orange, a herbicide containing dioxin, were found to have an increase in CHD morbidity [8,9]. In our previous studies, we observed a significant increase in the rates of hospitalization for atherosclerosis-related diseases (CHD, AMI, and stroke) in populations living in proximity to environmental sources of POPs [12,13].

In this study, we investigated the association between POPs and hospitalization rates for first-time AMI aggravated by comorbid DM for a reason. As the patients with these conditions have a substantially worse prognosis than the hospitalized AMI patients without DM [3], a higher risk of hospitalization for AMI with DM as a secondary diagnosis in POP-exposed, compared to unexposed, populations is indicative of a substantial environmental burden of disease due to a significant increase in the use of healthcare services and a higher risk of lethal outcome.

Animal studies of atherosclerosis indicate that the major mechanism responsible for the atherogenic effect of POPs is the ability of these lipophilic compounds to alter lipid metabolism in the liver, causing atherogenic dyslipidemias [11,28,29]. This mechanism is also supported by the results of population-based studies [30–32]. POPs also contribute to other known mechanisms of the development of atherosclerosis; they induce an inflammatory process [33], cause dysfunction of the vascular endothelium [34,35], and stimulate the differentiation of macrophages into foam cells [36].

The major potential confounders of concern in this epidemiological study are race, age, gender, and socio-economic status (SES). We controlled for these factors by applying adjustment in multivariate analysis (age, race, gender) and restriction (SES approximated by income). Thus, the results of our study are unlikely to be attributed to confounding by these variables. We did not attempt to adjust for atherogenic dyslipidemias, because they are suggested to be a major mechanism linking POPs and AMI and thus are in a causal pathway between exposure and outcome.

Cardiovascular disease mortality is higher in African Americans than in Caucasians [2,37]. Also, AMI hospitalization rates can be affected by racial disparities in utilization of CHD treatment [38]. By including race as a predictor of hospitalization rate in our model, we obtained the results adjusted for racial differences. Thus, an increase in AMI hospitalization rates observed in relation to residential proximity to environmental sources of POPs cannot be attributed to the effect of race.

SES is another potential confounder in our study. Firstly, people of lower SES may be less likely to become hospitalized patients when they become ill, owing to the lack of health insurance coverage [39,40]. Secondly, people of lower SES may be at a higher risk of residential exposure to environmental pollutants because they are more likely to obtain residence in places near landfills and other waste sites, and new landfills are more likely to be placed in proximity to lower SES communities rather than higher SES communities [41,42]. We controlled for SES by using median household income and restricting our analysis to the two upper quartiles of household income. We applied restriction to control for SES (excluding two lower quartiles) because health care access disparities in the U.S. prevent many people of lower SES from being hospitalized due to the lack of health insurance coverage. To prevent distortion in the calculation of hospitalization rates, the same restriction was applied both to the numerator and the denominator of the hospitalization rate. Restriction is used widely as an effective method of control for confounding in large population-based studies [43,44]. Therefore, the results of our study cannot be attributed to confounding by SES.

As expected, our findings demonstrated that older age, male gender and African American race/ethnicity are associated with a significantly higher risk of AMI with DM hospitalization. These findings are consistent with well-established knowledge of the role of non-modifiable

cardiovascular risk factors, and provide additional evidence that our model is reasonable from the viewpoint of biological plausibility.

The observed borderline-significant ($p = 0.08$) increase in AMI with DM hospitalization rates among populations living near waste sites containing pollutants other than POPs (residents of "other" zip codes) may possibly be attributed to exposure to other chemicals, including metals such as mercury [45], which are known to be associated with cardiovascular disease.

There are some limitations to our study. The zip code of residence is a crude measure of exposure, but this sort of problem is usual for ecologic studies [46]. The SPARCS database does not contain data on discharges from federally-regulated hospitals, such as Veterans Affairs Department hospitals. First-time AMI hospitalization rate is a crude approximation of the AMI morbidity rate. Information on the smoking status and some other risk factors and potential confounders, such as modifiable behavioral factors, diet, and physical exercise, would be helpful, but are not available in this dataset. It should be noted, however, that these limitations are likely to cause bias towards the null, due to non-differential misclassification [43]. Such bias may have resulted in an underestimation of RR of AMI hospitalization in our study, compared to higher RR that would have been observed in an ideal study. In other words, bias towards the null cannot cause the positive association between POPs and AMI hospitalization rates to appear in populations where such an association does not truly exist. It should also be noted that these factors are associated with lower SES, and we controlled for SES in our study, although on a population, not an individual, level.

The causal pathways from POPs exposure to both AMI and DM are not known with certainty. In spite of a number of reports documenting an association between POPs exposure and DM [7,14,17,18], there is little information on specific causal pathways, apart from the fact that POP exposures result in up and down regulation of many different genes [47]. Further research, such as a study of AMI in a DM-only population, with individually measured POPs exposure levels, could clarify some of these questions.

In conclusion, the results of our population-based study demonstrate that residential proximity to environmental sources of POPs increases the healthcare burden. Our findings also suggest that exposure to POPs is associated with a higher risk of AMI. Further studies on the mechanisms responsible for this association and on the possible interactions between POPs and conventional risk factors are necessary at the individual level in order to further understand the atherogenic effect of POPs.

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