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ORIGINAL RESEARCH

Exposure to Persistent Organic Pollutants Increases Hospitalization Rates for Myocardial Infarction with Comorbid Hypertension

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Abstract: Studies suggest that environmental exposure to persistent organic pollutants (POPs) may be an emerging risk factor for ischemic heart disease, including acute myocardial infarction (AMI). However, some studies indicate that exposure to POPs may also be a risk factor for hypertension, a well-established risk factor for AMI. To investigate effect of POPs on the environmental burden of cardiovascular disease, a study of AMI with comorbid hypertension in populations environmentally exposed to persistent organic pollutants, based on the zip code of residence, was conducted. Data on hospital discharges for AMI with comorbid hypertension were obtained from the New York Statewide Planning and Research Cooperative System for 1993–2004. Patients residing in zip codes containing or abutting POPs contaminated sites were considered environmentally exposed. Relative risks (RR) — with corresponding 95% confidence intervals (95% CI) — of hospitalization for AMI with comorbid hypertension were estimated by Poisson regression, adjusting for known confounders. Adjusted hospitalization rates for AMI with comorbid hypertension were 12.4% higher in populations residing in proximity to a POPs site (adjusted RR = 1.124, 95% CI 1.025–1.233, $p < 0.05$), compared to not in proximity to a POPs site. Also, hospitalization rates for AMI with comorbid hypertension were higher in males than in females (adjusted RR = 2.157, 95% CI 2.100–2.215, $p < 0.05$), in African Americans than in Caucasians (adjusted RR = 1.631, 95% CI 1.483–1.794, $p < 0.05$), and in older age groups (p for trend <0.05). These findings are consistent with the established effects of non-modifiable risk factors and serve as indirect quality indicators for our model. In conclusion, our results support the hypothesis that environmental exposure to POPs increases the burden of cardiovascular disease in exposed populations.

Keywords: myocardial infarction, hypertension, hazardous waste, persistent organic pollutants

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Introduction

Ischemic heart disease (IHD) is the leading cause of death in developed countries, and it is followed by cerebrovascular disease.[1–3] Hypertension (HTN) is known to be a major risk factor for IHD; both systolic HTN and diastolic HTN increase risk of IHD.[4–7] Other well-documented risk factors include hypercholesterolemia, obesity, diabetes, cigarette smoking, and sedentary life style.[4–6,8–11]

These conventional risk factors, however, do not explain 100% of IHD. Khot et al. analyzed results of 14 international randomized clinical trials with a total of 122,458 enrolled patients and found that of the four conventional risk factors for IHD — hypertension, smoking, diabetes, and hyperlipidemia — at least one is present in 84.6% of females and 80.6% of males.[12] Other researchers have emphasized that as many as 50% of IHD patients do not have any of the "traditional" risk factors.[13]

Recent evidence indicates that exposure to persistent organic pollutants (POPs) is a significant risk factor for atherosclerosis and atherosclerosis-related diseases, such as IHD. POPs are a group of semi-volatile lipophilic toxic compounds, including polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins and dibenzofurans, chlorinated and brominated aromatic compounds, persistent pesticides, such as dichlorodiphenyltrichloroethane (DDT), and polybrominated diphenyl ethers. POPs are persistent in the environment and bioaccumulate in the adipose tissue of human body. They alter normal functioning of endocrine, immune, and nervous systems.[14,15]

Exposure to POPs has been found to stimulate development of atherosclerosis in laboratory animals.[16,17] Epidemiological studies have demonstrated that occupational and environmental exposure to POPs increases risk of development of IHD.[18–20] Exposure to PCBs also increases risk of development of hypertension,[21,22] as do some non-POP environmental pollutants, such as lead[23] and arsenic.[24,25] This prompted us to conduct a study of hospitalization rates for AMI (the severest form of IHD) with HTN as a comorbidity in populations environmentally exposed to POPs.

Methods

A cross-sectional, ecological study of hospitalization rates for AMI with comorbid HTN in relation to presumed environmental exposure to POPs, based on whether or not the patient resided near to a hazardous waste site containing POPs, was conducted. Data on hospital discharges were obtained from the New York State Statewide Planning and Research Cooperative System (SPARCS), which is maintained by the New York State Department of Health. This administrative database, like other administrative databases, contains formalized data derived from clinical datasets such as hospital charts. Upon discharge from New York State hospitals (all except federal hospitals such as those run by the Veterans Administration), the hospital must report the principal diagnosis and up to 14 other diagnoses, coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM),[26] for each patient to the New York State Department of Health. The data includes patient age, sex, race, and zip code of residence. This study was approved by the Institutional Review Boards of Ohio University and the University at Albany. SPARCS data for a 12-year period (1993–2004) were used. Because New York City maintains its own hospitalization data and its population structure is different from that of the rest of the state, New York City was excluded from the study.

The primary outcome variable was the hospitalization rate for AMI with comorbid HTN. Hospitalization rate (per 100,000 person-years, over a 12-year period) was calculated as a number of hospitalizations divided by the total population living in a given zip code multiplied by 100,000. Information on patient age, gender, and race was used to adjust for potential confounding. Since racial groups other than Caucasians and African-Americans (Native Americans, Asians, and Pacific Islanders) all-together comprised less than 1% of the total number of hospitalizations for AMI with comorbid HTN, they were not included in the study to prevent extra variability and compromised parsimony of the model. Income data (median household income on the zip code level) used as a proxy measure of socio-economic status (SES) were obtained from Claritas, Inc. (San Diego, CA). To control for confounding effect of income, residents of the lowest quartile of the medium-household income distribution were excluded. This approach was applied to minimize confounding effect of lower SES level that can prevent cardiovascular patients from seeking health care, especially in situations with

AMI not being accompanied by severe chest pain (asymptomatic AMI).

Because effect of age as a risk factor for atherosclerosis becomes very prominent in older age groups and obscures effect of other risk factors, the upper age limit was limited to 74 years (inclusive).

After the above restrictions were applied, there were a total of 65.5 million person-years for the 12-year period of 1993–2004, during which there were 79,262 discharges of patients between the ages of 25 to 74 years with AMI as a principal diagnosis (ICD-9-CM codes category: 410) and essential HTN as a non-principal, secondary, diagnosis (ICD-9-CM codes categories: 401–404). Secondary HTN (ICD-9-CM codes category: 405) was not included, because it is a symptom of some diseases of certain organs and systems participating in blood pressure regulation, not a disease per se.

Environmental residential exposure status was classified by patients' zip codes of residence as "POPs", "other" (pollutants other than POPs) or "clean" (areas with no known sources of environmental pollution) depending on whether they contain or abut hazardous waste sites containing these pollutants. Overall, 196 zip codes were classified as "POPs", 215 — as "other", and 992 — as "clean" zip codes in New York State, exclusive of New York City. Hazardous waste sites were identified by the U.S. Environmental Protection Agency (EPA) (National Priority List sites), the New York State Department of Environmental Conservation (NYSDEC) (State Superfund sites), and the International Joint Commission (polluted portions of the Great Lakes and St. Lawrence River known as Areas of Concern). The POPs group of pollutants included PCBs, dioxins/furans, and/or persistent chlorinated pesticides. The "other" category was a zip code which contained or abutted a waste site, but not one for which the U.S. EPA or NYDEC have identified POPs as a major component. Details of these classifications have been previously described.[21]

Relative risks (RR) of hospitalization for AMI with comorbid HTN and their 95% confidence intervals (95% CI) were calculated as hospitalization rate ratios, using Poisson regression. Overdispersion was adjusted for by using a scaling factor; the scaled Pearson chi-square was equal 1. To adjust for clustering of observations within zip codes, generalized estimating equations (GEE) method was used. Adjustment for potential confounders, such as age, gender, and race, was accomplished by including the respective variables in the model. Another potential confounder — income — was controlled for by restriction: the lowest household income quartile was excluded. All data analyses were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC). The PROC GENMOD procedure was used for Poisson regression analysis. Conventional level of type I error (alpha-level) of 0.05, i.e. $p < 0.05$, was used for statistical significance testing. For multiple comparisons, Bonferroni correction was used.

Results

Demographic characteristics of the population residing in "clean", "POPs" and "other" areas are shown in Table 1. Nearly a quarter of the study population (24.2%) was residing in the "POPs" areas, 45.1% — in "clean" areas, and 30.7% — in "other" areas.

While Caucasians were more likely to live in areas without identified waste sites, African-Americans were more likely to live in proximity to POPs and other waste sites (Fig. 1). These observations indicate race as an important confounder to be considered in this investigation.

Prior to multivariate Poisson regression modeling, an unadjusted (not controlled for confounders) pairwise comparison of hospitalization rates for AMI with comorbid HTN across populations residing in "POPs", "other", and "clean" areas was conducted, with Bonferroni correction for multiple pairwise comparisons. Hospitalization rates (per 100,000 person-years) were 125.09 (95% CI 123.35–126.83) for "POPs" zip codes, 127.52 (95% CI 125.96–129.08) for "other" zip codes, and 114.31 (95% 113.09–115.53) for "clean" zip codes ($p < 0.05$ for "POPs-clean" and "other-clean" pairwise comparisons, non-significant $p > 0.05$ for "POPs-other", with Bonferroni correction).

Table 2 presents RR (with corresponding 95% CI) of hospitalization for AMI with comorbid HTN in relation to residence in "clean", "POPs" and "other" zip codes, adjusted for race, gender, and age. These 95% CI reflect traditionally used significance level of $\alpha = 0.05$ ($p < 0.05$ for RR with 95% CI that do not include 1.000). The study findings indicate that residence near to either POPs or other waste sites, which we hypothesize results in environmental exposure to pollutants, is associated with higher

Table 1. Demographic characteristics of the study population by residential exposure status (1993–2004), person-years (%).

Study population groups	"Clean"	"POPs"	"Other"
Total 65,519,028 p-yrs (100%)	29,528,568 (45.1)	15,899,448 (24.2)	20,091,012 (30.7)
Race			
Caucasians	28,083,654 (42.9)	14,831,886 (22.6)	18,465,624 (28.2)
African Americans	1,444,914 (2.2)	1,067,562 (1.6)	1,625,388 (2.5)
Gender			
Females	15,168,474 (23.2)	8,201,682 (12.5)	10,353,468 (15.8)
Males	14,360,094 (21.9)	7,697,766 (11.7)	9,737,544 (14.9)
Age, years			
25–34	6,801,606 (10.4)	3,911,562 (6.0)	4,852,836 (7.4)
35–44	7,796,688 (11.9)	4,185,696 (6.4)	5,253,462 (8.0)
45–54	6,580,230 (10.0)	3,236,862 (4.9)	4,288,044 (6.6)
55–64	4,661,940 (7.1)	2,430,336 (3.7)	3,156,318 (4.8)
65–74	3,688,104 (5.6)	2,134,992 (3.3)	2,540,352 (3.9)

hospitalization rates for populations residing in the contaminated areas, compared to non-contaminated areas.

Residence in a "POPs" zip code was associated with a 12.4% increase in RR of hospitalization for AMI with comorbid HTN, which was statistically significant ($p = 0.013$). There was also a significant increase in hospitalization rates for AMI with comorbid HTN in the population exposed to other pollutants (17.5% increase, $p = 0.002$).

Regarding gender differences, males were more than two times as likely to be hospitalized with AMI and HTN than females (RR = 2.157, $p < 0.001$), regardless of residency in clean or polluted areas.

As expected, risk of being hospitalized for AMI with comorbid HTN increased significantly with age.

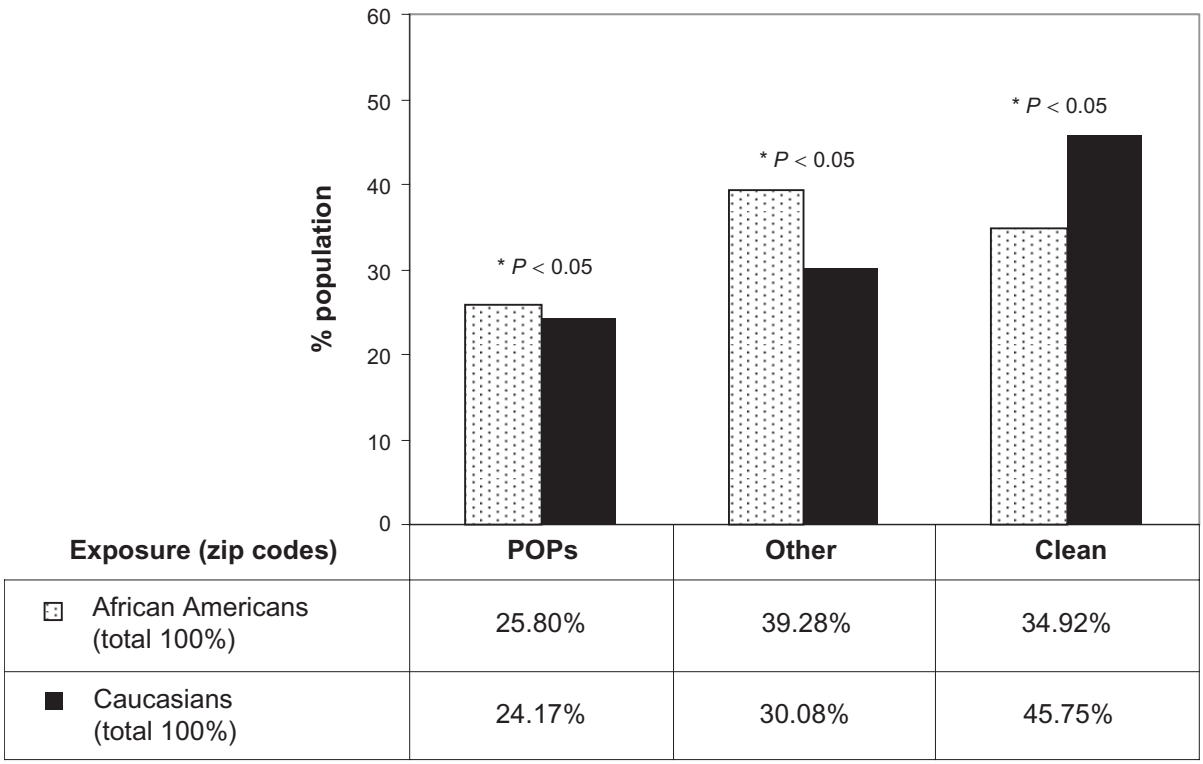

Figure 1. Distribution of residential environmental exposure status by race.

Table 2. Adjusted RR of hospitalization for AMI with comorbid HTN (1993–2004) in relation to residence in "clean", "POPs" or "other" zip codes, gender, age and race.

Parameter	RR (95% CI)	*p*-value
"POPs" exposure (compared to "clean")[a]	1.124 (1.025–1.233)	0.013
"Other" exposure (compared to "clean")[a]	1.175 (1.059–1.303)	0.002
Males (compared to females)[b]	2.157 (2.100–2.215)	<0.001
African Americans (compared to Caucasians)[c]	1.631 (1.483–1.794)	<0.001
Age, yrs (compared to 25–34 years old)[d]		<0.001*
35–44	5.198 (4.208–6.421)	
45–54	22.956 (18.214–28.933)	
55–64	52.873 (41.963–66.613)	
65–74	96.149 (76.272–121.219)	

[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.
Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HTN, hypertension; POPs, persistent organic pollutants; RR, relative risk.

Results of the study also indicate that African Americans were at 63.1% higher risk of hospitalization compared to Caucasians ($p < 0.001$).

Findings from separate analyses of the effects of age, gender, and race on RR of hospitalization for AMI with comorbid HTN in populations residing in "POPs" and "other" zip codes are presented in Tables 3 and 4 respectively. These findings indicate that in each of the two groups male gender, African American race and older age are associated with higher hospitalization risk.

Discussion

Results of this study support the hypothesis that residential exposure to hazardous waste sites is associated with an elevated risk of AMI with comorbid HTN. Residence near to a waste site that did not contain POPs ("other" zip codes) was also associated with an elevated risk in hospitalization.

HTN is a well-documented risk factor for IHD including its severest form — AMI.[4–7] Middle age females tend to have lower mean systolic (6 to 7 mm Hg lower) and diastolic (3 to 5 mm Hg lower) blood pressure than males; after 59 years of age, a raise in systolic blood pressure is observed in females.[27]

Since conventional risk factors (HTN, obesity, hypercholesterolemia, diabetes, smoking) do not explain 100% of IHD,[12,13] it is imperative to investigate the role of other potential risk factors, such as exposure to POPs and other environmental pollutants.

Table 3. Adjusted RR of hospitalization for AMI with comorbid HTN (1993–2004) in populations residing in proximity to environmental sources of "POPs".

Parameter	RR (95% CI)	*p*-value
Gender (males compared to females)[a]	2.028 (1.938–2.121)	<0.001
Race (African Americans compared to Caucasians)[b]	1.591 (1.352–1.872)	<0.001
Age, yrs (compared to 25–34 years old)[c]		<0.001*
35–44	4.475 (3.462–5.785)	
45–54	20.340 (15.442–26.792)	
55–64	44.719 (34.312–58.282)	
65–74	79.091 (60.190–103.928)	

[a]Adjusted for race and age.
[b]Adjusted for gender and age.
[c]Adjusted for gender and race.
*_p_-value for trend, Wald statistic.
Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HTN, hypertension; POPs, persistent organic pollutants; RR, relative risk.

Table 4. Adjusted RR of hospitalization for AMI with comorbid HTN (1993–2004) in populations residing in proximity to environmental sources of "other" pollutants.

Parameter	RR (95% CI)	*p*-value
Gender (males compared to females)[a]	2.144 (2.034–2.261)	<0.001
Race (African Americans compared to Caucasians)[b]	1.410 (1.246–1.595)	<0.001
Age, yrs (compared to 25–34 years old)[c]		<0.001*
35–44	6.268 (3.974–9.887)	
45–54	29.752 (18.307–48.347)	
55–64	68.559 (42.738–109.980)	
65–74	125.939 (78.539–201.926)	

[a]Adjusted for race and age.
[b]Adjusted for gender and age.
[c]Adjusted for gender and race.
**p*-value for trend, Wald statistic.
Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HTN, hypertension; RR, relative risk.

There is increasing evidence that environmental exposure to POPs is a previously under-appreciated risk factor both for IHD[18–20,28] and hypertension.[21,22] Because environmental exposure to POPs and other pollutants is an involuntary risk factor, it is important to investigate whether it is associated with higher burden of cardiovascular disease in order to provide health policy makers with evidence that justifies reduction and elimination of environmental exposure as a primary prevention measure.

Findings from our study are consistent with results obtained in other population-based studies indicating that environmental exposure to PCBs, dioxins/furans, and other POPs can increase risk of IHD. Collins et al. found that exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is associated with IHD mortality.[29] Various adverse health effects, including an increase in IHD mortality, were reported in a population exposed to TCDD after the industrial accident that occurred in Seveso, Italy in July 1976.[30,31]

If the hypothesis that environmental exposure to POPs increases risk of AMI on a population level is correct, then association between blood levels of POPs and risk of AMI should exist on an individual level to satisfy a reasonable assumption of biological plausibility and causation. Indeed, results of other studies have demonstrated a direct relationship between serum levels of POPs and atherosclerosis-associated diseases. Morgan et al. reported positive association between serum levels of organochlorine pesticides and development of atherosclerotic cardiovascular disease in workers occupationally exposed to the pesticides.[32] Using NHANES data, Ha et al. found that background exposure to dioxin-like PCBs, non-dioxin-like PCBs, and organochlorine pesticides is associated with a higher prevalence of self-reported cardiovascular disease in general population.[19] Our findings are consistent with these reports.

Because atherosclerosis is the primary morphological basis for AMI and other forms of IHD, if this hypothesis is true there should be evidence that POPs increase the risk of development of atherosclerosis. Experimental studies have demonstrated that exposure to POPs results in development of atherosclerosis in laboratory animals. Jokien et al. reported development of degenerative cardiovascular lesions in rats exposed to dioxin and a dioxin-like compound (PCB126).[33] Exposure to dioxins caused earlier and more prominent development of atherosclerosis in mice.[16] Thus our findings are consistent with results of experimental animal studies.

The mechanism whereby POPs promote development of atherosclerosis and its clinical manifestations, such as AMI, is likely through alterations in lipid metabolism. Human studies have demonstrated that exposure to PCBs and other POPs increase total serum lipids. Pelclova et al. reported that occupational exposure to TCDD was associated with elevation in serum levels of triglycerides and cholesterol as well as increased intima-media thickness and atherosclerotic plaques in carotid arteries.[34] A statistically significant association between increased serum levels of PCBs, dichloro-diphenyl-dichloro-ethylene and hexachlorobenzene and elevation of serum lipids in humans has been demonstrated recently.[35] Experimental studies

indicate that PCBs interfere with lipid metabolism in rat liver.[36] Exposure to dioxins and dioxin-like PCBs increase serum levels of triglycerides and cholesterol in animals.[16,37]

These results from both human and animal studies indicate a biologically plausible mechanism for a causal pathway explaining effect of environmental exposure to POPs on significant increase in AMI hospitalization rates: POPs → lipid metabolism alteration in liver → elevated serum lipids → atherosclerosis → IHD. The specific chemicals responsible for this finding have not been identified, but may include volatile organics. It has been previously hypothesized that inhalation is the major route of exposure to the semi-volatile POPs,[20] and inhalation would be even more likely for more volatile compounds, many of which are also chlorinated. While exposure assessment in our present study is limited in that only zip code of residence is available, our recent demonstration of a direct relation between levels of PCBs and some pesticides with total serum lipids and with self-reported heart disease and hypertension[35] adds support for the hypothesis that simple residence near to one of these waste sites poses a risk of exposure and of disease.

With regard to the effects of gender as a cardiovascular disease risk factor, gender differences in hospitalization rates for AMI with comorbid HTN, as demonstrated in our study, are consistent with knowledge of male gender being a risk factor for cardiovascular diseases.[4]

The major confounders of concern to this study are race, SES, and age. There are known differences in rates of IHD and its risk factors (including HTN) in African Americans and Caucasians, and IHD mortality in African Americans is higher than in any other racial group in the United States.[38] Also, hospitalization rates can be affected by racial disparities in utilization of IHD treatment.[39] By including race as a hospitalization rates predictor in our model, obtained results were adjusted for racial differences. Thus, an increase in hospitalization rates for AMI with comorbid HTN in patients residentially exposed to POPs and other environmental pollutants cannot be attributed to effect of race.

SES is another potential confounder in our study. People of lower SES have limited access to health care and may be less likely to become hospitalized patients when they become ill due to lack of health insurance coverage.[40–42] Although this issue may be more important for chronic diseases rather than for acute conditions (such as AMI) accompanied by very prominent clinical manifestations like sudden and severe chest pain, it must still be considered. People of lower SES may be at higher risk of residential exposure to environmental pollutants because they are more likely to reside 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.[43,44]

To adjust for potential confounding effect of SES, income, which a well-established and widely-used proxy measure of SES, was used in our study.[45,46] SES was controlled for by using median household income and applying restriction, which is an effective method of confounding control in population-based studies.[47–49] So, results of our study cannot be attributed to confounding by SES.

Results of our study, as expected, demonstrated that older age is associated with significantly higher risk of cardiovascular disease hospitalization. These findings are consistent with well-established role of age as a non-modifiable cardiovascular risk factor.[4] Inclusion of age into model allowed us to prevent confounding by age and to be assured that the study results cannot be attributed to effect of age. Because of their consistency with the well-established role of age as a risk factor for AMI and other atherosclerosis-associated diseases, these findings indicate that our model has a good quality from viewpoint of biological plausibility.

From policy makers' perspective, separate analyses of hospitalization rates in populations residing in "POPs" and "other" zip codes may be of interest. Study results suggest that effects of demographic characteristics remain statistically significant in presence of environmental pollutants which indicates that while elimination of environmental pollutants is warranted, demographic characteristics should also be considered in health policy decision making.

While other than POPs pollutants were not of primary interest in our study, it is worth mentioning that residence in "other" zip codes was also associated with an increased risk of hospitalization for AMI with comorbid HTN. This observation may possibly be attributed to effect of some other chemicals — such as mercury,[50] lead,[23] and arsenic[24,25] — shown to be associated with cardiovascular disease.

There are some limitations to our study. Zip code of residence is a very crude measure of exposure, but this sort of problem is usual for ecologic studies.[51] The ecological (group-level) approach to estimating exposure status is an acknowledged method that is used, along with the individual-level approach, in the area of environmental epidemiology.[52] The SPARCS database does not contain data on discharges from federally-regulated hospitals, such as Veterans Affairs Department hospitals. Repeated hospitalization of one individual from hospitalizations of different individuals cannot be distinguished in this study. However, multiple repeated hospitalizations is not a typical characteristic of AMI.

Conclusion

Results of this study support the hypothesis that environmental exposure to environmental contaminants by place of residence is associated with a statistically significant increase in hospitalization rates for AMI with comorbid HTN. More research is needed to elucidate the role of POPs and other environmental pollutants in development of atherosclerosis and cardiovascular diseases specifically including IHD and HTN, and to obtain further information on the mechanisms behind the causal pathways and susceptibility to POPs. Both observational epidemiological studies in human populations, such as prospective cohort studies in residential and occupational settings, and experimental studies on laboratory animals are warranted in order to further understanding of biological processes behind atherogenic effect of POPs.

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Abbreviations

AMI, acute myocardial infarction; CI, confidence interval; HTN, hypertension; IHD, ischemic heart disease; PCBs, polychlorinated biphenyls; POPs, persistent organic pollutants; RR, relative risk; SES, socioeconomic status; TCDD, tetrachlorodibenzo-p-dioxin.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

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