HHS Public Access

Author manuscript

Environ Int. Author manuscript; available in PMC 2023 September 27.

Published in final edited form as:

Environ Int. 2023 August ; 178: 108086. doi:10.1016/j.envint.2023.108086.

Can traffic-related air pollution trigger myocardial infarction within a few hours of exposure? Identifying hourly hazard periods

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Abstract

Introduction: Traffic-related air pollution can trigger myocardial infarction (MI). However, the hourly hazard period of exposure to nitrogen dioxide (NO_2), a common traffic tracer, for incident MI has not been fully evaluated. Thus, the current hourly US national air quality standard (100 ppb) is based on limited hourly-level effect estimates, which may not adequately protect cardiovascular health.

Objectives: We characterized the hourly hazard period of NO_2 exposure for MI in New York state (NYS), USA, from 2000 to 2015.

Methods: For nine cities in NYS, we obtained data on MI hospitalizations from the NYS Department of Health Statewide Planning and Research Cooperative System and hourly NO_2

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Jenni A. Shearston: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing – original draft, Visualization. **Sebastian T. Rowland:** Methodology, Software, Writing – review & editing. **Tanya Butt:** Validation, Writing – review & editing. **Steven N. Chillrud:** Conceptualization, Writing – review & editing. **Joan A. Casey:** Conceptualization, Writing – review & editing. **Donald Edmondson:** Conceptualization, Writing – review & editing. **Markus Hilpert:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition. **Marianthi-Anna Kioumourtzoglou:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108086.

concentrations from the US Environmental Protection Agency's Air Quality System database. We used city-wide exposures and a case-crossover study design with distributed lag non-linear terms to assess the relationship between hourly NO_2 concentrations over 24 h and MI, adjusting for hourly temperature and relative humidity.

Results: The mean NO_2 concentration was 23.2 ppb (standard deviation: 12.6 ppb). In the six hours preceding MI, we found linearly increased risk with increasing NO_2 concentrations. At lag hour 0, a 10 ppb increase in NO_2 was associated with 0.2 % increased risk of MI (Rate Ratio [RR]: 1.002; 95 % Confidence Interval [CI]: 1.000, 1.004). We estimated a cumulative RR of 1.015 (95 % CI: 1.008, 1.021) for all 24 lag hours per 10 ppb increase in NO_2 Lag hours 2–3 had consistently elevated risk ratios in sensitivity analyses.

Conclusions: We found robust associations between hourly NO_2 exposure and MI risk at concentrations far lower than current hourly NO_2 national standards. Risk of MI was most elevated in the six hours after exposure, consistent with prior studies and experimental work evaluating physiologic responses after acute traffic exposure. Our findings suggest that current hourly standards may be insufficient to protect cardiovascular health.

Keywords

Traffic-related air pollution; Myocardial infarction; Air quality standards; Nitrogen dioxide; Distributed lag models; Case-crossover

1. Introduction

Coronary heart disease (CHD), which includes myocardial infarction (MI), is a leading cause of morbidity and mortality, resulting in an estimated 9.1 million deaths globally in 2019 (Roth et al., 2020). In the United States (US) alone, around 697,000 deaths from CHD —one in every five deaths—occurred in 2020 (Tsao et al., 2022; Centers for Disease Control and Prevention National Center for Health Statistics, 2022). Traffic is a major modifiable trigger of MI (Nawrot et al., 2011). In health studies of traffic-related air pollution (TRAP), ambient nitrogen dioxide (NO_2) is often used as a tracer for TRAP (Beckerman et al., 2008; Kendrick et al., 2015). Studies across the globe have found increased risk for MI after exposure to ambient NO_2, using different study populations and exposure periods (de Bont et al., 2022; Stieb et al., 2020; Wu et al., 2022). Research has suggested that increased risk begins shortly after exposure (Wu et al., 2022; Sahlén et al., 2019), but the hazard period—or time windows of elevated risk—of sub-daily NO_2 exposure and incident MI has not been fully evaluated.

Fully characterizing the hourly hazard period is particularly important for regulation. Hourly NO_2 is currently regulated by the US Environmental Protection Agency (EPA) at 100 ppb (United States Environmental Protection Agency, 2022), but because the hourly hazard period is insufficiently characterized, it is unclear if this standard is adequately protective of cardiovascular health. Studies reporting associations between various measures of traffic or TRAP (e.g., black carbon, NO_2) and MI have identified sub-daily hazard windows as soon as 0–18 h after exposure (Wu et al., 2022; Sahlén et al., 2019; Peters et al., 2004; Straney et al., 2014; Zhu et al., 2022; Bhaskaran et al., 2011; Chen et al., 2022). Although some studies

investigating sub-daily associations between NO_2 and cardiovascular outcomes have not reported significant findings (Straney et al., 2014; Peters et al., 2001; Rosenthal et al., 2013; Ensor et al., 2013; Evans et al., 2017; Li et al., 2019; Raza et al., 2014; Raza et al., 2019; Cheng et al., 2021), likely due to decreased power, a recent meta-analysis found increased risk of MI within 6 h of exposure to NO_2 (Wu et al., 2022). The hazard period, however, was not disaggregated into individual hours because studies reported varying exposure windows (Wu et al., 2022). Few studies have identified an hourly hazard period for NO_2, and those either took place in China (Zhu et al., 2022; Chen et al., 2022), where mean NO_2 levels and TRAP composition differ from the US, or used a moving 3-hour NO_2 average instead of hourly concentrations (Sahlén et al., 2019). Of note, these studies (Sahlén et al., 2019; Zhu et al., 2022; Chen et al., 2022) found health effects at mean hourly concentrations far lower than 100 ppb. Thus, it is critical to evaluate the hourly health effects of NO_2 exposure in a US context to best inform standards that maximally protect the US population.

Building upon this work, our objective was to characterize the hourly hazard period for MI after short-term NO_2 exposure, in the US state of New York (NYS). We used data from the NYS Department of Health Statewide Planning and Research Cooperative System (SPARCS) (New York State Department of Health, 2020), which contains hour of admission and covers ~98 % of all hospital admissions in the state. We hypothesized that increased NO_2 concentrations are associated with increased MI risk in the hours shortly after exposure, even at hourly NO_2 concentrations below 100 ppb.

2. Materials & methods

2.1 Study area

Hospital records from all nine NYS cities that hosted an NO_2 monitoring site during at least one year from 2000 to 2015 were included in the analysis. These cities were: Amherst, Buffalo, Cheektowaga, Corning, East Meadow, Hogansburg, Holtsville, New York City (NYC), and Rochester (Fig. 1). The nine cities are fairly representative of urban areas in New York and included the largest city in the state (NYC), three large central metro areas (Amherst, Buffalo, Rochester), two large fringe metros on Long Island (East Meadow and Holstville), and two micropolitan areas (Corning and Hogansburg). The cities are spread across the entire geographic area of New York state and make up 46 % of New York's population. Specific years of inclusion are shown in Table 1. Additionally, we conducted a secondary analysis for NYC alone, as its population and exposure profile are different than in other NYS cities. We also conducted a secondary analysis assessing effect modification by rush hour vs non-rush hour time periods. We focus on cities in this analysis (rather than, e.g., counties) to reduce exposure measurement error from reliance on central monitors which are usually located in urban centers.

2.2 Case ascertainment

The NYS SPARCS database (New York State Department of Health, 2020) was used to obtain MI hospitalizations for the study period. SPARCS is an administrative database established in 1979 that covers ~98 % of hospitalizations that occur in NYS, and includes hour of admission and patients' residential addresses. To identify cases, we used

International Classification of Disease, 9th Revision (*ICD*-9) diagnostic code 410.x for the years 2000–2014 and *ICD*-10 code I21 for 2015, in the first four diagnostic positions. These codes are valid and reliable measures of MI cases (Kiyota et al., 2004; McCormick et al., 2014). We estimated time of event by subtracting 3 h from the admission time of every case, based on a nationwide US study of median delay to admission for non ST-segment elevation MI (STEMI) (Ting et al., 2010). While it is likely that symptom severity (e.g., STEMI vs non-STEMI) influences time to admission (Ting et al., 2010; Ting et al., 2008), in a previous analysis of temperature and MI using a similar study design, we found no difference in effect estimates with variable delay times for STEMI vs non-STEMI MI (Rowland et al., 2020); thus we used a single delay time of 3 h. We included only adult cases, used both inpatient and outpatient admissions, and excluded newborn or trauma admissions. Fatal MIs were included in the dataset, as long as cases were admitted to the hospital prior to death (if death occurred prior to admission, the record was not included in SPARCS). Reinfarctions (events that occur within 28 days of a previous MI) and recurrent MIs (any MI occurring after 28 days of a patient's first MI) were included (Thygesen et al., 2018). However, readmissions for the same MI event were excluded by removing admissions that took place within two days of a previous admission. Approval to use human subjects data was obtained from the Columbia Univeristy Institutional Review Board (protocol # AAAR0877); informed consent was waived.

2.3 Hourly NO_2 exposure assessment

City-level hourly ambient NO_2 concentrations were obtained from the US EPA's Air Quality System (AQS) database (United States Environmental Protection Agency, 2020). Additional information about the monitoring sites, including EPA measurement scale, urban–rural county designation, and comments on the location, is included in Supplemental Table 1. We used information from all monitoring sites that were active during at least one year from 2000 to 2015 and hourly NO_2 concentrations as reported. If a city had more than one monitoring site, we aggregated hourly NO_2 concentrations to the city level by averaging concentrations from all monitors in the city.

Cases were assigned the hourly NO_2 concentrations of the city corresponding to their residential address ZIP code (SPARCS data at the ZIP code level were used to protect patient privacy). Hourly exposures were constructed for each unique city/date-hour combination for which at least one MI case was identified and corresponding control periods (Section 2.4) for a 24-hour period prior to the estimated time of event. We excluded city-months where more than 5 % of cases and controls were missing NO_2 observations (11.8 % of cases, Supplemental Figure 1).

2.4 Study design and statistical analyses

We employed a case-crossover study design—a form of case-control study—for our analyses (Maclure, 1991; Mittleman, 2005). This design is particularly useful for transient exposures that change rapidly (such as air pollution or temperature) because each case serves as its own control. Effectively, we compare a case's transient exposure to their exposure at a similar time when the outcome did not occur. For each case, we matched the city/date-hour when the MI occurred with comparable control city/date-hours. Control

hours were matched by city, year, month, and hour, and bi-directionally by day-of-week (Supplemental Figure 2) (Mittleman, 2005; Janes et al., 2005). This sampling scheme results in 3–4 control city/date-hours for every case and prevents confounding by both non-time varying or slowly varying factors, as well as long-term, seasonal, and diurnal trends. We additionally adjusted for hourly temperature and relative humidity from the National Aeronautics and Space Administration's (NASA) North American Land Data Assimilation System (NLDAS) in the health models, as these measures vary rapidly and are associated with MI (Rowland et al., 2020; Lee et al., 2010) and NO_2 (Jayamurugan et al., 2013).

We used conditional logistic regression to estimate the relationship between 24 h of NO_2 exposure and MI while accounting for the matching scheme. We weighted each case stratum by the number of MIs that occurred during that specific case city/date-hour. We coupled this with a Distributed Lag Non-linear Model (DLNM) (Gasparrini, 2011; Gasparrini et al., 2010) to account for temporal autocorrelation across hourly NO_2 concentrations. DLNMs allow for the independent estimation of the association at each lag (hour) by adjusting for all other lags. They additionally allow for the estimation of cumulative associations by summing the lag-specific contributions for specifiable ranges of lags (Gasparrini, 2011; Gasparrini et al., 2010). To capture potential non-linearities, we modeled the exposure- and lag-response relationships using natural splines with a range of plausible degrees of freedom (df): for the exposure–response constraint, we evaluated a linear relationship and a non-linear relationship modeled with a natural spline with 3–5 df, and for the lag-response constraint, a non-linear relationship modeled with a natural spline with 4–6 df. This range of df was selected based on existing literature (Rowland et al., 2020), biological plausibility, and to provide enough constraints in the model to effectively deal with collinearity and overly influential outliers. We selected the optimal df for both relationships using the Akaike Information Criterion (AIC) (Gasparrini, 2016). Hourly temperature and relative humidity were each also modeled as distributed lag non-linear terms, with a natural spline with 3 df set as the exposure–response relationship and a natural spline with 4 df set as the lag-response relationship (Rowland et al., 2020). The same model and constraints were used for the secondary analysis of NYC alone and for the rush hour effect modification analysis. Effect modification was assessed through stratification; rush hour time periods were defined as 6–10 AM and 4–8 PM on weekdays. All other weekday hours and all weekend hours were considered non-rush hour.

2.5 Sensitivity analyses

To evaluate the robustness of our results, we conducted several sensitivity analyses. All analyses used the the same model constraints as described above for the main model (unless otherwise specified). The sensitivity analyses are as follows: (1) We repeated the analysis using 48 lag hours of NO_2 rather than 24, in case 24 h of exposure were not sufficient to capture short-term risk. For this analysis, we used the same exposure–response constraint as the main model, but conducted an additional grid search to identify the optimal lag-response constraint. (2) To assess robustness to exposure measurement error from using city-wide NO_2 concentrations, we repeated the analysis restricting inclusion to only those ZIP codes surrounding monitoring sites. Specifically, five km circular buffers were drawn around each NO_2 monitor; ZIP-code centroids that fell within a single buffer were assigned

concentrations from that monitor. Centroids that overlapped multiple buffers were assigned the mean of the associated monitors. All cities were included in this analysis but ZIP codes outside of any buffer were excluded. (3) We restricted cases to those with *ICD*-9 code 410.x1 or ICD-10 code I21 in the first diagnostic position only to assess robustness to the case definition. (4) To assess the potential for confounding bias by relative humidity, we excluded the relative humidity distributed lag terms from the model. In other studies from our group using a similar design (e.g., (Rowland et al., 2020; Rowland et al., 2020)) relative humidity did not seem to induce confounding bias. However, as our exposure is different than in the previous analysis, we wanted to evaluate the role of relative humidity as a potential confounder of the association between NO_2 and MI. (5) We assessed potential confounding by non-traffic and total $PM_{2.5}$ in NYC using a subset of data for which hourly $PM_{2.5}$ concentrations were available. $PM_{2.5}$ data were obtained from the EPA's AQS database (United States Environmental Protection Agency, 2020). Hourly $PM_{2.5}$ data were only available for NYC for the years 2014–2015 and one other city; we chose to conduct the sensitivity analyses for NYC for the years 2014–2015 to facilitate comparison with our secondary NYC-only analysis. The sensitivity analysis involved completing three additional regressions: first, following the same parameters as the main model, second, additionally adjusting for hourly non-traffic $PM_{2.5}$ concentrations, and third, additionally adjusting for hourly total $PM_{2.5}$ concentrations. To obtain non-traffic $PM_{2.5}$, we first regressed NO_2 on $PM_{2.5}$, and then used the residuals to represent non-traffic $PM_{2.5}$. Both hourly total and non-traffic $PM_{2.5}$ concentrations were added to the model as a DLNM with a linear exposure–response relationship and a non-linear lag-response relationship (natural spline with 4 df). (6) To ensure the results were not being unduly influenced by cities with only one or two years of data, we excluded these cities (Cheektowaga, Corning, Rochester) from the main model. (7) Finally, to assess the potential for confounding bias by ozone, we additionally adjusted for hourly ozone concentrations in the NYC secondary analysis. Hourly ozone concentrations were obtained from the EPA AQS database (United States Environmental Protection Agency, 2020). We did not conduct the sensitivity analysis in the main model because hourly ozone concentrations were not available for all cities during the study period. Ozone was added to the model as a DLNM with a linear exposure–response relationship and a non-linear lag-response relationship (natural spline with 4 df).

All statistical analyses were completed in R, version 4.1.1 (R: A language and environment for statistical computing, 2021). The tidyverse package version 1.3.1 (Wickham et al., 2019) was used for data management, dlnm version 2.4.7 was used to construct the exposure crossbases, (Gasparrini, 2011) survival version 3.2.11 (Therneau, 2015; Therneau and Grambsch, 2000) was used to run the regression models, and ggplot2 version 3.3.5 (Wickham, 2016) was used for plotting all results. Identifying which ZIP code centroids fell with 5 km of an NO_2 monitoring site was done in QGIS, version 3.16 (Geographic Information System, 2021). All code is publicly available on GitHub at https://github.com/jenni-shearston/r_NO2-MI. Health data are publicly available upon request from SPARCS; NO_2 and meterological data are publicly available from respective organizations.

3. Results

3.1 Study population and NO_2 conditions

In the main analysis, a total of nine NYS cities, representing a population of more than 8.9 million people (~46 % of NYS population), were included (Table 1). Some cities only contributed one or two years of data, while others contributed the full 16 years. MI case counts for the months included for each city ranged from 51 in Corning (4 years of data) to 351,188 in NYC (16 years of data); 92 % of cases occurred in NYC. A total of 344,501 cases had complete data on exposure and covariates for all lags and were included in the main model (Supplemental Figure 1).

Over time, NO_2 concentrations decreased in most cities, with the exception of Cheektowaga, Corning, and Rochester (Supplemental Figure 3). Mean hourly NO_2 concentrations (Table 1) ranged from a low of 1.6 ppb (standard deviation [SD]: 2.0) in Corning to a high of 24.9 ppb (SD: 12.3) in NYC. The overall mean NO_2 concentration was 23.2 ppb (SD: 12.6) for case hours and 23.1 ppb (SD: 12.6) for control hours. Within-day NO_2 concentrations were bi-modally distributed with peaks from approximately 5–9 AM and at 9 PM (yellow peaks in Fig. 2); there was less variability in concentrations around noon (red area in Fig. 2). City-level mean temperatures ranged from 9.4 °C (SD: 11.7) to 12.3 °C (SD: 10.1), while relative humidity ranged from 75 % to 79 %. The NO_2 hourly standard, calculated as three-year averages of the 98th percentile of 1-hour daily maximum concentrations for each year, ranged from 43.80 to 62.11 ppb (Table 2).

3.2 Main analysis: Hourly city-level NO_2 and MI for nine NYS cities

For the main analysis, a linear exposure–response constraint for the relationship between NO_2 concentrations and MI and a non-linear lag-response constraint of 4 df yielded the optimal model fit, based on AIC. NO_2 concentrations in the 6 h before MI occurrence were positively and significantly associated with increased MI rates (Figs. 3 and 4). The highest rate ratio (RR) was found for lag hour 0, where a 10 ppb increase in NO_2 was associated with a 0.2 % increased risk of MI (RR = 1.002, 95 % Confidence Interval [CI]: 1.000, 1.004). We estimated a cumulative RR of 1.012 (95 % CI: 1.007, 1.017) for lags 0–6 (Fig. 5, y value at x =6). Additionally, we estimated a cumulative RR of 1.015 (95 % CI: 1.008, 1.021) for all 24 lags, per 10 ppb increase in NO_2 concentration (Fig. 5, y value at x = 23). Rate ratios for all 24 individual lags can be found in Supplemental Tables S2 and S3 for 10 ppb and 1 ppb increases in NO_2, respectively.

3.3 Secondary analysis: Hourly city-level NO_2 and MI for NYC alone and effect modification by rush hour

In NYC, NO_2 concentrations in the 7 h preceding the MI were associated with increased risk of MI. At lag hour 0, a 10 ppb increase in NO_2 was associated with a 0.2 % increase in MI (RR = 1.002, 95 % CI: 1.000, 1.004) (Supplemental Figure 4A). We estimated a cumulative RR of MI of 1.015 (95 % CI: 1.008, 1.021) per 10 ppb increase in NO_2 for all 24 lags (Supplemental Figure 4B).

In the secondary analysis assessing effect modification by rush hour time period, we did not observe evidence of effect modification. There was considerable overlap in the 95 % confidence intervals of the rush hour and non-rush hour strata (Fig. 6). For the rush hour strata, NO_2 concentrations in lags 0–5 were positively and significantly associated with increased MI rates, while for the non-rush hour strata, NO_2 concentrations at lags 3–7 were positively and significantly associated with increased risk of MI.

3.4 Sensitivity analyses

Sensitivity analyses generally replicated our main results, consistently finding an increased risk for MI of approximately 0.2–0.5 % in each of the first few hours after exposure to NO_2. There were some slight variations in the estimated hazard period: when removing relative humidity from the model, estimates were nearly identical to the main analysis (Supplemental Figure 5); when restricting to ZIP codes with centroids within 5 km of an NO_2 monitoring site, lags 0–3 had a stronger association with MI while lags 5–6 were not associated with increased risk (Supplemental Figure 6). When restricting cases to those with an MI code in the first position only, lags 0–4 had a slightly stronger association with MI (Supplemental Figure 7). When assessing 48 prior hours of exposure, lags 0–12 were positively associated with MI (Supplemental Figure 8). The sensitivity analyses adjusting for non-traffic and total $PM_{2.5}$ in the NYC 2014–2015 subset of data were also generally consistent with the full NYC sub-analysis (Supplemental Figures 9 and 10). The correlation between NO_2 and total $PM_{2.5}$ was 0.55, while the correlation between NO_2 and non-traffic $PM_{2.5}$ was 0.07. Confidence intervals were quite wide in these sub-analyses as the sample size was very small (n = 14,098 cases) relative to the full study. When removing Cheektowaga, Corning, and Rochester from the analysis, results were nearly identical to the main analysis (Supplemental Figure 11). When adjusting for ozone in the NYC secondary analysis, effect estimates were slightly attenuated and had larger confidence intervals but were generally very consistent (Supplemental Figure 12).

4. Discussion

In a population-wide study in NYS, we assessed the relationship between MI and an important tracer of TRAP, ambient NO_2, with the aim of identifying hourly hazard windows of exposure. In the first six hours before onset, we found increased risk for MI with increasing NO_2 concentrations, in a population exposed to a mean hourly NO_2 concentration of 23.2 ppb. We found null associations for lags 7 through 23. Our findings were consistent for lag hours 0 to 6 for all sensitivity analyses, including when assessing for outcome misclassification, exposure measurement error, analyzing up to 48 hourly lags, removing relative humidity as a confounder from the model, adjusting for total and non-traffic hourly $PM_{2.5}$, removing cities with only one or two years of data, and adjusting for hourly ozone. Results for NYC were consistent with those of NYS, and we did not find evidence of effect modification by rush hour time period.

Our study builds upon previous work identifying sub-daily hazard periods for NO_2 exposure and MI by characterizing the hourly hazard period in a US population with a mean NO_2 exposure concentration of 23.2 ppb. Our results are strikingly similar to a study conducted

in China by Chen et al. (2022) among 475,326 STEMI cases and 260,079 non-STEMI cases that assessed hourly hazard periods. While we found elevated risk of MI after exposure to NO_2 at individual lag hours 0 to 6 (ranging from 0.13 to 0.21 %), Chen et al. (2022) found that exposure to NO_2 in individual lag hours 0 to 21 increased risk of STEMI by approximately 0.1–0.25 %, and that exposure to NO_2 in individual lag hours 0 to 29 increased risk of non-STEMI by approximately 0.1–0.2 %, per 29.0 μg/m^3 (15.4 ppb at STP). Similar to our findings, increased risk was greatest at lag hour 0, decreasing thereafter. While Chen et al. (2022) identified a longer hazard period than we did, they also had a greater number of cases and larger statistical power. The mean NO_2 concentration for Chen et al. was 33.7 μg/m^3 (17.9 ppb at STP), lower than that reported in our study. Additionally, our cumulative risk ratio for lags 0–6 (1.012 [1.2 %] per 10 ppb [18.8 μg/m^3 at STP], 95 % CI: 1.007, 1.017) was very similar to that found in a *meta*-analysis by Wu et al. (2022) (2.07 % per 10 ppb, 05 % CI: 1.09 %, 3.06 %), and our 24-hour cumulative risk of 1.5 % per 10 ppb was very similar to that found by Chen et al. (2022) (1.22–1.24 % per 10 μg/m^3 [5.3 ppb at STP]).

Experimental work evaluating physiologic responses after acute exposure to TRAP suggests plausible mechanisms through which NO_2 and other traffic-related pollutants might trigger MI (Long & Carlsten, 2022). Changes in heart rate variability, (Han et al., 2021) fibrinolytic capacity, (Mills et al., 2007) and oxidative stress (Cosselman et al., 2020) after acute exposure to TRAP are a few such pathways. Notably, studies have shown that these pathways are altered even during exposure, with peak changes occurring a few hours after exposure. For example, Han et al. measured heart rate variability, blood pressure, and heart rate before, during, and after a 2-hour exposure to TRAP near a road during morning rush hour (Han et al., 2021). They found that heart rate variability parameters increased from baseline, peaking in the 0–3 h after exposure, while blood pressure increased during exposure but decreased in the hours after, and heart rate decreased throughout, with greatest decreases in the 0–2 h after exposure (Han et al., 2021). Mills et al. found that endothelial tissue plasminogen activator decreased by 35 % 6–8 h after exposure to diluted diesel exhaust, in a population of men with history of prior MI (Mills et al., 2007). In a study evaluating the acute impacts of TRAP on oxidative stress, Cosselman et al. found decreased antioxidant levels and increased antioxidant response leukocyte gene expression up to 24-hours post exposure to 2 h of diesel exhaust (Cosselman et al., 2020). Of note, IL-6, a pro-inflammatory marker, was more elevated at 5 h post-exposure than 24 h post-exposure (Cosselman et al., 2020). Overall, low-level systemic inflammation, impaired vasodilation, and changes in autonomic balance in the acute period after exposure to TRAP may combine to trigger MI.

Considering the likely causal relationship between TRAP/NO_2 exposure and MI (Stieb et al., 2020; Wu et al., 2022), consistent findings of previous studies (Chen et al., 2022; Stieb et al., 2020; Wu et al., 2022), experimental mechanistic evidence (Cosselman et al., 2020; Han et al., 2021; Long and Carlsten, 2022; Mills et al., 2007), and the work of ourselves and others describing hazard windows for the NO_2-MI relationship (Sahlén et al., 2019; Bhaskaran et al., 2011), there are important implications for air quality policy. Under the US Clean Air Act (CAA), NO_2 is regulated in two ways: with a 1-hour daily maximum averaged over 3 years, and as an annual mean (United States Environmental Protection Agency, 2022).

The 1-hour maximum standard is 100 ppb, while the annual mean is 53 ppb (United States Environmental Protection Agency, 2022). We report a significantly increased risk of MI of 0.2 % per 10 ppb increase in NO_2 for a single hour of exposure (lag 0), during a time period with an average hourly NO_2 concentration of 23 ppb and when the hourly standard was never exceeded. Additionally, we found a cumulative increased risk for the 24-hour period following exposure, indicating that the increased hourly risk is not due to short-term harvesting. Thus, we find health impacts at NO_2 concentrations substantially lower than the 100 ppb hourly standard and increases in risk of MI for every additional 10 ppb increase. Given ubiquitous exposure to TRAP and NO_2 in the United States, our findings could suggest that the current hourly standard should be lowered to adequately protect population health. We encourage the consideration of risk from ultra-short-term exposures to NO_2 on cardiovascular health in future reassessments of the maximum hourly standard.

Our work also has implications for health care practioners and people more at-risk of having an MI. For example, it may be reasonable to advise at-risk individuals to more closely monitor themselves for MI symptoms in the six hours following higher exposure to TRAP. Similarly, after high TRAP pollution episodes, health care practioners may expect to see an increased number of MI cases in the six hours following a high-pollution episode.

Throughout this analysis, we use NO_2 as a marker of TRAP. While we cannot separate the contributions of other emissions sources, traffic is the largest contributor to NO_2 emissions in NY state and city (34–44 %) (New York City Department of Health and Mental Hygiene, 2022; Office of the New York State Comptroller, 2020; United States Environmental Protection Agency, 2016). Unfortunately, there were not sufficient near-road NO_2 monitors in our study period to conduct a sensitivity analysis separating exposures from near-road vs. non-near-road monitors. Some studies, such as Poulsen et al in Denmark, have found associations between non-traffic NO_2 and MI, but not between traffic NO_2 and MI (Poulsen et al., 2023). Our results suggest that the mixture of air pollutants represented by NO_2 at central monitors in NY state, of which traffic contributes the largest fraction, is harmful to health.

Our analysis had several strengths and limitations. First, as our outcome data source—SPARCS—collects admission times, we were able to assess hourly hazard periods, an important contribution to the literature with critical policy relevance. Second, we used a case-crossover study design, which substantially reduces confounding bias by design. However, while we did adjust for temperature and relative humidity, there is still the possibility of confounding by other factors that vary on a similar time scale as NO_2 and are also MI predictors, such as noise (Heritier et al., 2019; Roswall et al., 2017). Third, we used city-averaged rather than neighborhood or individual-level exposure data for our main analysis, as we were limited by the distribution of NO_2 monitors. This could lead to exposure mismeasurement and/or limit generalizability. However, we conducted a sensitivity analysis restricting to ZIP codes with centroids within 5 km from a monitoring site to assess for exposure mismeasurement and found similar results. It is possible that city-wide NO_2 concentrations at central monitors are not generalizable to the full study population, but we do expect NO_2 concentrations to increase and decrease consistently across the hours of the day and following a similar pattern across a city, given the dominance of

traffic emissions. Because SPARCS is a population-wide administrative dataset, our results are likely generalizable not only to the cities included in the analysis, but to NYS more broadly, as we include cities representing 46 % of the state's population, with patients who reside in both urban and more rural counties. However, our findings are potentially less generalizable to the broad US population. Fourth, DLNMs can be sensitive to choice of knot placement. To address this, we used a grid search to choose optimal parameters and previous literature to identify parameters for temperature and relative humidity (Rowland et al., 2020). Fifth, we used ICD codes to identify MI cases. While these have been validated extensively (Kiyota et al., 2004; McCormick et al., 2014), there is still the possibility of outcome misclassification. Our sensitivity analysis assessing this showed both a slightly stronger association at earlier lags, and a slightly earlier association (only lags 0–4 were associated with increased risk). Any outcome misclassification, thus, biased our effect estimates towards the null. Finally, we assumed an average of 3 h delay between MI and hospitalization for all cases, regardless of severity of symptoms. We expect any random measurement error induced by using a single delay time will be non-differential to exposure. In a previous study of temperature and MI, we found no difference in effect estimates when using different delay times for STEMI vs non-STEMI MI (Rowland et al., 2020).

5. Conclusions

This study is one of the first to identify hourly hazard periods for NO_2 exposure and MI, finding increased risk of MI from NO_2 in the six hours prior to onset. We found robust associations between hourly NO_2 exposure and MI risk at levels far lower than the current hourly NO_2 national standards. Our findings suggest that current standards may be insufficient to protect population health and should be reconsidered to address the risk of ultra-short-term NO_2 exposure on cardiovascular health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to acknowledge Dr. Amelia K. Boehme for facilitating access to SPARCS data.

Funding

JAS was supported by grants from the National Institute of Environmental Health Sciences (NIEHS), grant # F31 ES033098 and grant # T32 ES007322. Funding was also provided by NIEHS grants # R01 ES030616 and # R21 ES030093. DE was supported by National Institutes of Health (NIH) grants # R01 HL128497 and # U24 AG052175.

Data availability

Code is available at https://github.com/jenni-shearston/r_NO2-MI. Health data are available upon request from SPARCS; NO_2 and meterological data are publicly available from respective organizations.

Abbreviations:

AIC	Akaike Information Criterion
CAA	Clean Air Act
CHD	Coronary Heart Disease
CI	confidence interval
df	degrees of freedom
EPA	Environmental Protection Agency
ICD	International Classification of Disease
MI	myocardial infarction
NASA	National Aeronautics and Space Administration
NYC	New York City
NYS	New York State
NLDAS	North American Land Data Assimilation System
NO_2	nitrogen dioxide
$PM_{2.5}$	particulate matter ≤ 2.5 μm
RR	rate ratio
SPARCS	Statewide Planning and Research Cooperative System
STEMI	ST-segment elevation MI
SD	standard deviation
TRAP	traffic-related air pollution
US	United States

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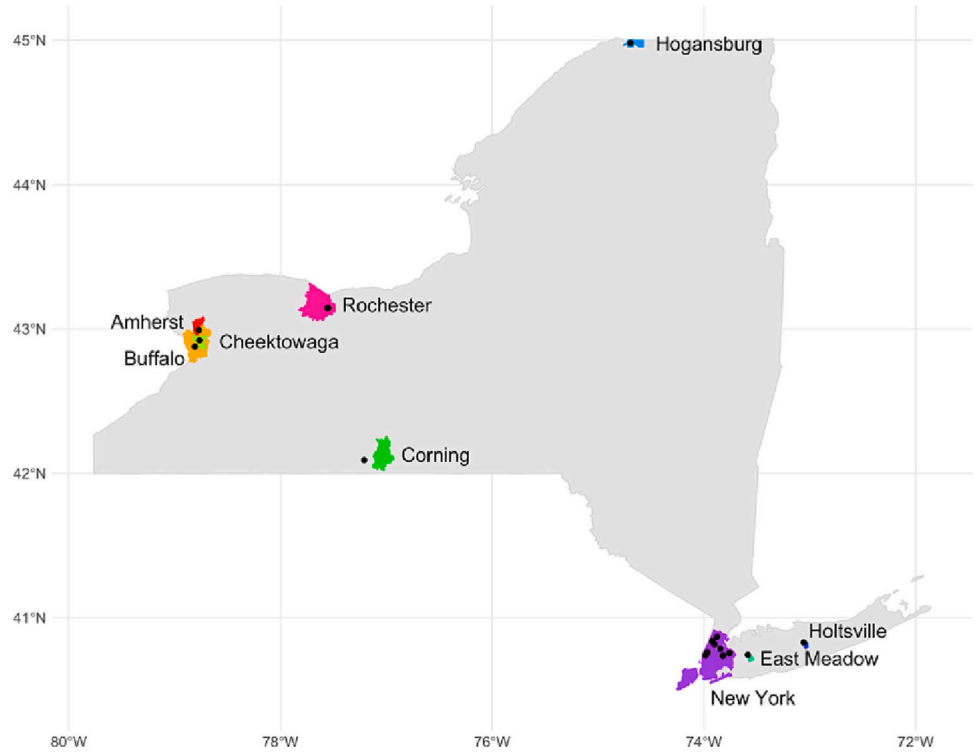

Fig. 1.

The nine New York cities included in the analysis. Colored polygons represent the area of each city, while black dots represent monitor locations.

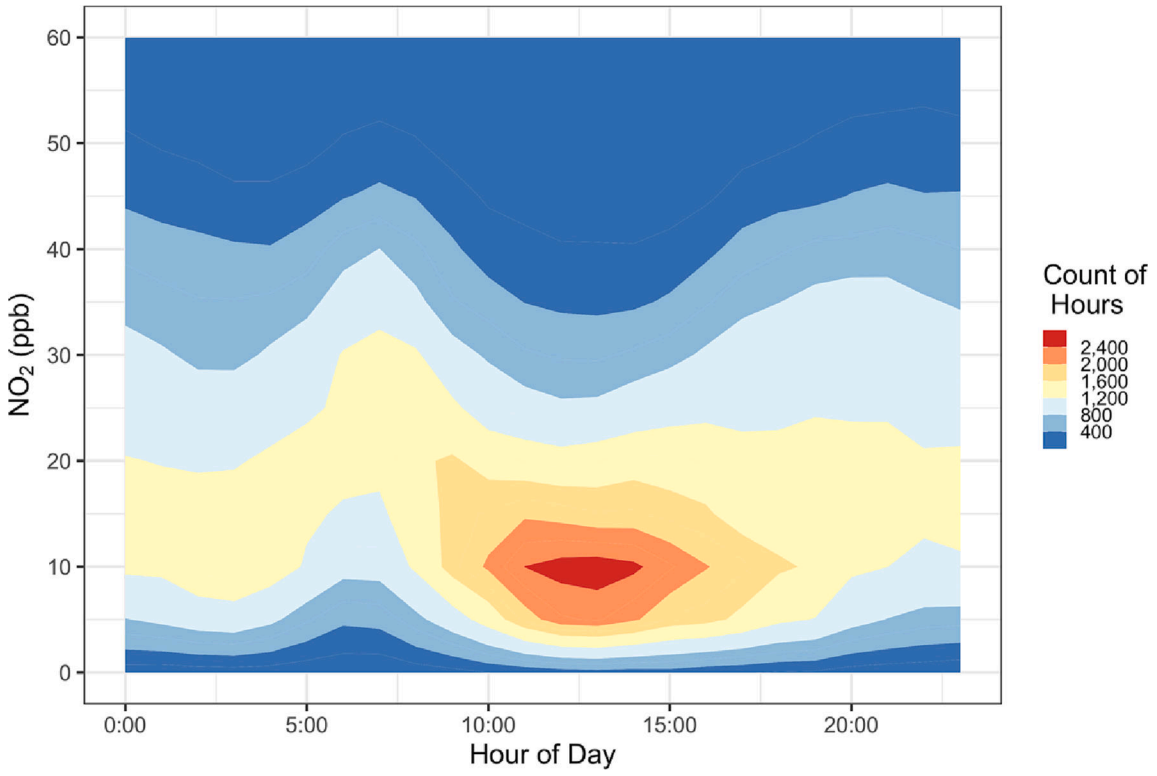

Fig. 2.

Filled contour plot showing within-day variability of hourly, city-level NO_2 concentrations over the entire study period, for all cities and years. Colors show the count of hours (observations) in the full study period with NO_2 at a given 5 ppb concentration interval and hour of day. For example, at 20:00 in the evening (x axis), the NO_2 concentration ranged from 17.5 to 22.4 ppb (y axis) for 1,200–1,600 (pale yellow color) hourly observations during the study period. Note: Observations over 60 ppb have been removed for visualization purposes.

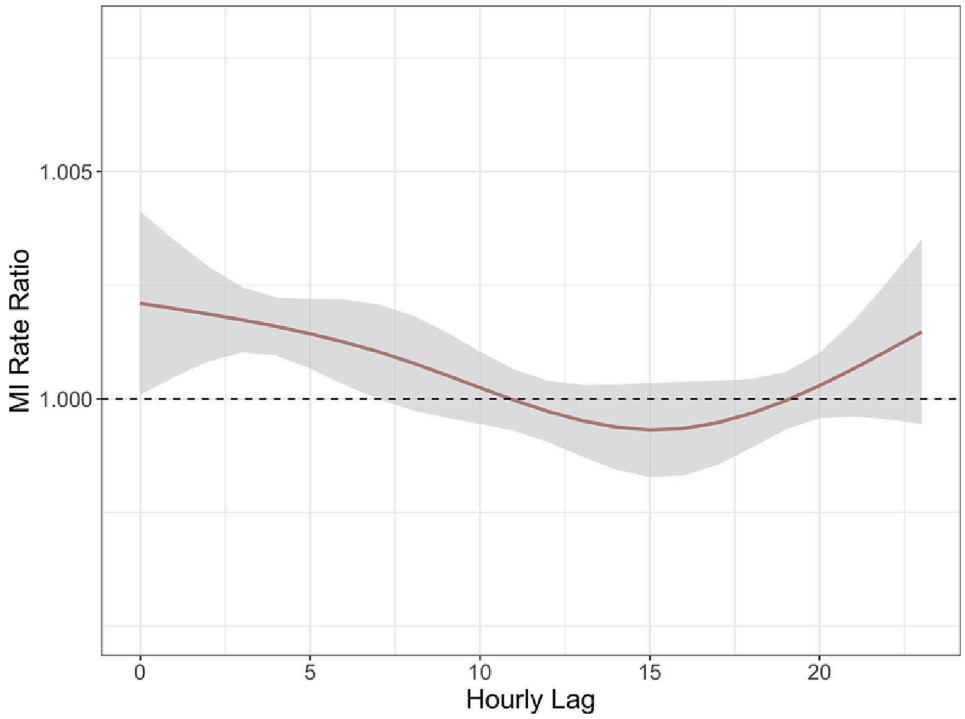

Fig. 3.

Exposure-response relationship for nitrogen dioxide (NO_2) and myocardial infarction (MI), across 24 hourly lags. Rate ratios correspond to a 10 ppb increase in hourly NO_2. Gray bands represent 95 % confidence intervals.

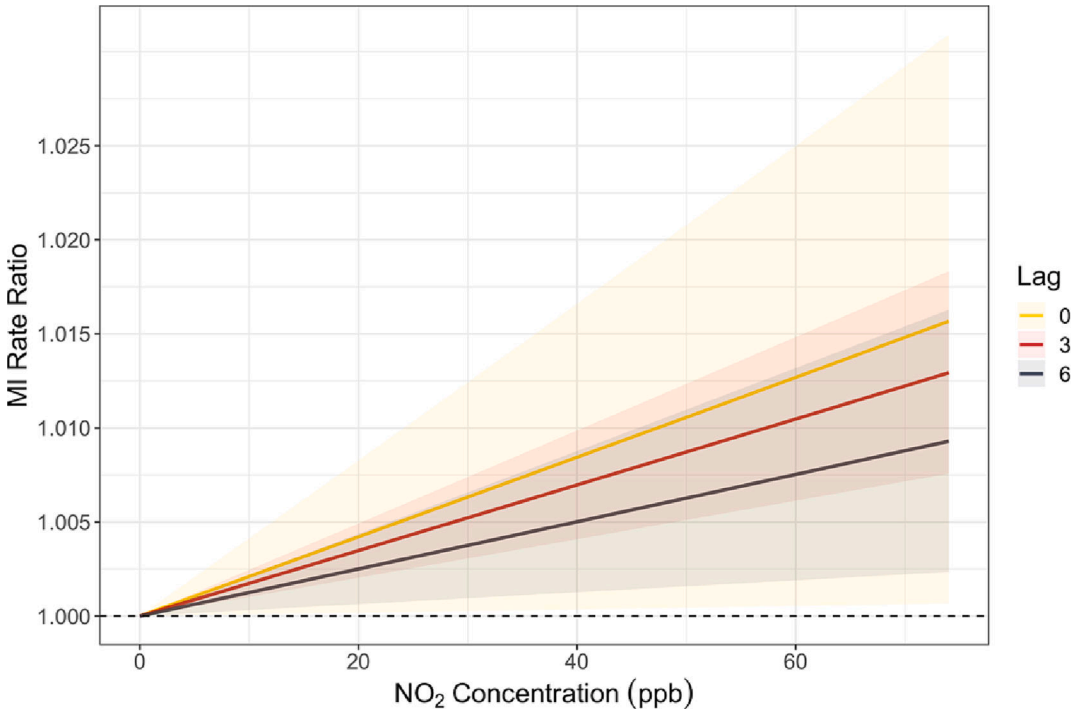

Fig. 4.

Exposure-response curve for nitrogen dioxide (NO_2) and myocardial infarction (MI) for selected lags (lag 0, lag 3, lag 6), for a 10 ppb increase in NO_2. Shaded bands represent 95 % confidence intervals.

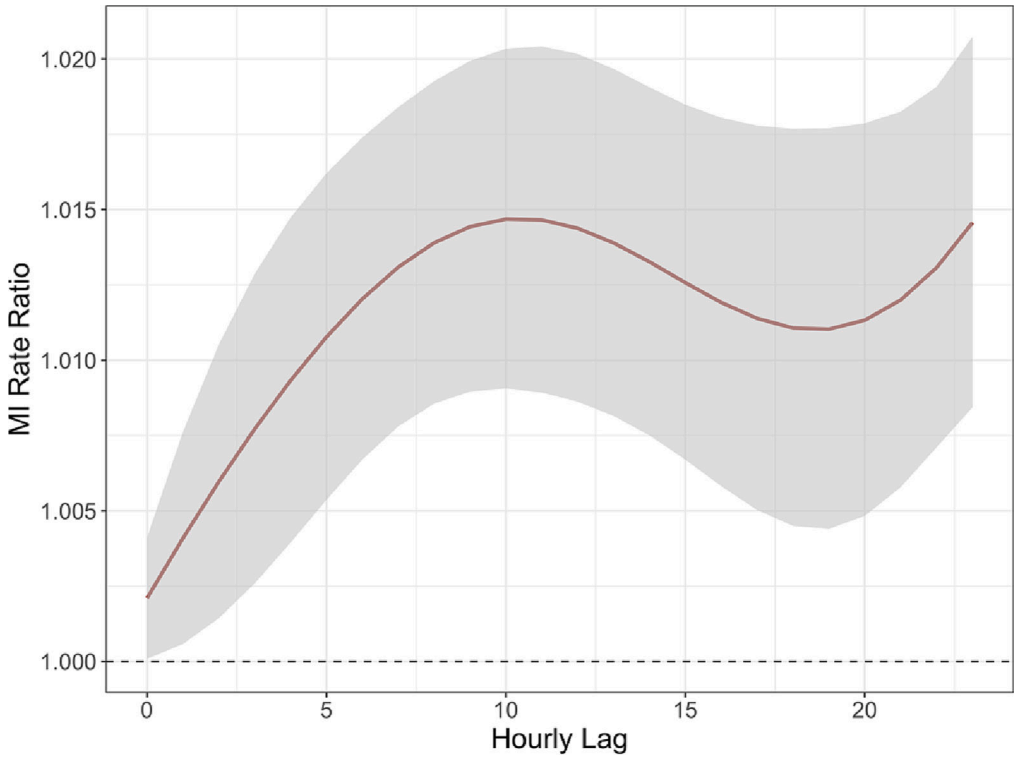

Fig. 5.

Cumulative exposure–response relationship for nitrogen dioxide (NO_2) and myocardial infarction (MI), across 24 hourly lags. Rate ratios correspond to a 10 ppb increase in NO_2. Gray bands represent 95 % confidence intervals.

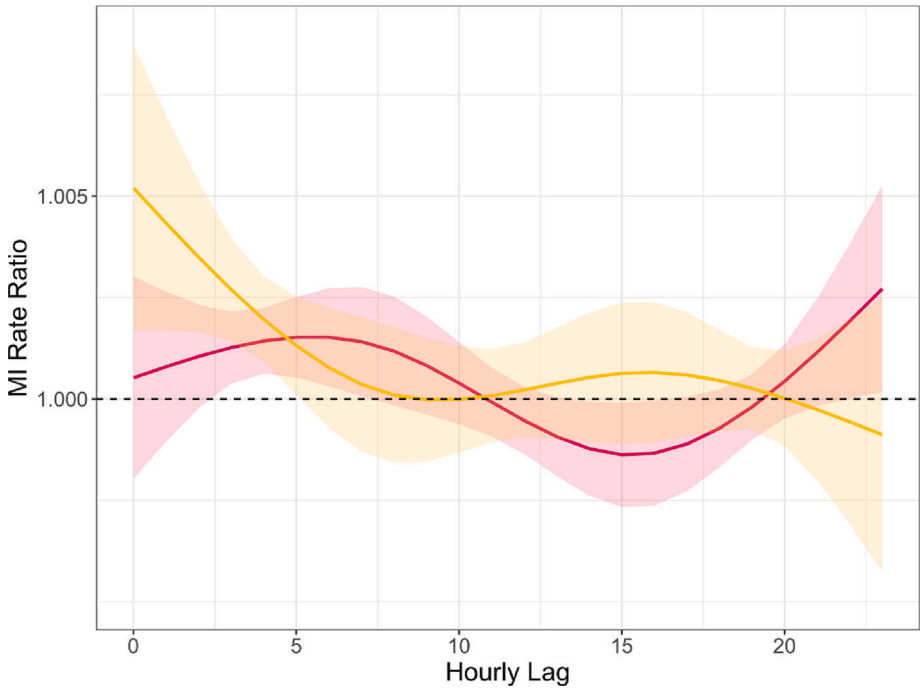

Fig. 6.

Secondary analysis assessing effect modification by rush hour: Exposure-response relationship for nitrogen dioxide (NO_2) and myocardial infarction (MI) across 24 hourly lags. Yellow color corresponds to cases that occurred during rush hour (6–10 AM and 4–8 PM on weekdays), while pink color corresponds to cases that did not occur during rush hour (all other hour/day-of-week combinations). Rate ratios correspond to 10 ppb increases in NO_2. Shaded bands represent 95 % confidence intervals.

Table 1

Descriptive statistics for New York State cities included in the analysis.

City	Years of inclusion	Population[a]	MI Case Count[b]	Mean (SD)[c]		
				NO_2 Concentration [ppb]	Temperature [°C]	Relative Humidity [%]
Amherst	2000–2012	122,366	5,238	11.1 (9.2)	9.7 (10.6)	78 (13)
Buffalo	2000–2015	261,310	19,390	16.4 (11.2)	9.7 (10.8)	78 (13)
Cheektowaga	2014–2015	88,226	466	11.2 (8.2)	10.3 (10.8)	76 (13)
Corning	2007–2008 2010–2011	11,183	51	1.6 (2.0)	9.6 (10.0)	77 (12)
East Meadow	2000–2010	38,132	1,094	19.9 (11.6)	11.4 (9.0)	77 (14)
Hogansburg	2009–2015	3,512	75	3.0 (3.7)	10.5 (11.5)	79 (12)
Holtsville	2000–2010	19,714	413	12.8 (9.5)	11.0 (8.6)	79 (13)
New York City	2000–2015	8,175,133	323,013	24.9 (12.3)	12.3 (10.1)	75 (17)
Rochester	2015	210,565	1,448	10.2 (6.8)	9.4 (11.7)	78 (12)
Total		**8,930,141**	**351,188**	**23.2 (12.6)**	**11.9 (10.3)**	**75 (16)**

[a] Data from 2010 US Census, all ages.

[b] Count of MI hospitalizations included in the main analysis after removing city-months where more than 5 % of hourly NO_2 concentrations were missing.

[c] Includes all case and control hours for lag 0.

Table 2

National Ambient Air Quality Standard for hourly NO_2 during the study period.

Averaging Years	98th Percentile of 1-hour Daily Maximum Concentrations, Averaged Over 3 Years (ppb)[a]
2000–2002	62.12
2001–2003	59.80
2002–2004	57.87
2003–2005	59.97
2004–2006	55.00
2005–2007	57.00
2006–2008	54.00
2007–2009	54.00
2008–2010	52.00
2009–2011	50.00
2010–2012	44.31
2011–2013	43.80
2012–2014	47.10
2013–2015	50.17

[a] Calculated from hourly city-level NO_2 averages using all monitors included in the analysis.