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Key Points:

- Short-term ozone exposure was associated with increased risk for acute myocardial infarction at lag 4–5 days in patients aged 18–55 years
- Association with ozone was more pronounced for non-ST-segment elevation myocardial infarction and type 2 myocardial infarction
- Non-Hispanic Black patients tended to be more vulnerable to the effect of ozone

Supporting Information:

Supporting Information may be found in the online version of this article.

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Short-Term Associations Between Ambient Ozone and Acute Myocardial Infarction Onset Among Younger Patients: Results From the VIRGO Study

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Abstract The association between ambient ozone (O_3) and acute myocardial infarction (AMI) onset is unclear, particularly for younger patients and AMI subtypes. This study examined the short-term association of O_3 with AMI onset in patients aged 18–55 years and explored differences by AMI subtypes and patient characteristics. We analyzed 2,322 AMI patients admitted to 103 US hospitals (2008–2012). Daily maximum 8-hr O_3 concentrations estimated using a spatiotemporal deep learning approach were assigned to participants' home addresses. We used a time-stratified case-crossover design with conditional logistic regression to assess the association between O_3 and AMI, adjusting for fine particulate matter, air temperature, and relative humidity. We conducted stratified analyses to examine associations for AMI subtypes and effect modification by sociodemographic status, lifestyle factors, and medical history. An interquartile range (16.6 ppb) increase in O_3 concentrations was associated with an increased AMI risk at lag 4 days (odds ratio [OR] = 1.21, 95% confidence interval [CI]: 1.08–1.34) and lag 5 days (OR = 1.11, 95% CI: 1.00–1.24). The association was more pronounced for non-ST-segment elevation AMI and type 2 AMI compared with ST-segment elevation AMI and type 1 AMI, respectively. Stronger O_3-AMI associations were observed in non-Hispanic Blacks than in non-Hispanic Whites. Our study provides evidence that short-term O_3 exposure is associated with increased AMI risk in younger patients, with varying associations across AMI subtypes. The effect modification by race/ethnicity highlights the need for population-specific intervention strategies.

Plain Language Summary Our study examined how ozone pollution may affect heart attacks in young adults. We analyzed data from 2,322 heart attack patients aged 18–55 years admitted to 103 US hospitals between 2008 and 2012. We found that higher ozone levels increased heart attack risk, particularly 4–5 days after exposure. This risk was higher for non-ST elevation and type 2 heart attacks, and was more pronounced in non-Hispanic Black patients. This research helps us better understand how air pollution affects hearts in young adults and could inform efforts to reduce air pollution and protect vulnerable populations.

1. Introduction

Ambient ozone (O_3) pollution has been identified as a modifiable risk factor for cardiovascular hospitalizations and mortality (Jiang et al., 2023; Murray et al., 2020). However, evidence on the association between O_3 and acute myocardial infarction (AMI) remains limited and inconsistent (Argacha et al., 2016; Jiang et al., 2023; Mustafic et al., 2012; Sahlén et al., 2019). In addition, a research gap exists in understanding the exposure-response relationship between O_3 and AMI onset among younger patients, who have often been underrepresented in previous studies despite their increasing proportion and different vulnerability to air pollution compared to older adults (Arora et al., 2019; Chen et al., 2022). This research gap is particularly of concern given the projected increase in O_3 levels due to climate change under a high greenhouse gas emission scenario (Gao et al., 2013).

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Different AMI subtypes may have varying susceptibilities to O_3 due to different pathophysiological mechanisms. Identifying the association of O_3 with each AMI subtype helps refine risk assessment and advance understanding of the pathways through which O_3 contributes to AMI onset. While numerous studies have reported short-term associations between air pollution exposure and ST-segment elevation AMI (STEMI), research on non-ST-segment elevation AMI (NSTEMI) has been scarce and inconclusive (Argacha et al., 2016; Gardner et al., 2014; Liu et al., 2018; Pope et al., 2015; Sahlén et al., 2019). To our knowledge, no previous studies have differentiated the association of O_3 with type 1 versus type 2 AMI, highlighting the need for further research to elucidate the specific impacts on these subtypes.

Marginalized subpopulations, including racial/ethnic minorities and people with lower socioeconomic status, have shown greater vulnerability to air pollution (Josey et al., 2023; Ma et al., 2023). However, few studies have specifically addressed disparities in the impact of O_3 on AMI onset. While previous studies have examined air pollution-related AMI by age and sex (Gardner et al., 2014; Liu et al., 2018; Ruidavets et al., 2005), effect modification by other individual characteristics, such as race, socioeconomic status, lifestyle factors, or comorbidities, remains largely unknown.

In this case-crossover study, we assessed the short-term association of ambient O_3 with the onset of overall AMI and its subtypes in a cohort of younger AMI patients in the US. We also explored how patient characteristics, including age, sex, race/ethnicity, socioeconomic status, lifestyle factors, and medical history, influenced this relationship.

2. Materials and Methods

2.1. Study Population

We analyzed data from the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study. This prospective cohort recruited 3,501 AMI patients aged 18–55 years from 103 geographically diverse hospitals across the US between August 2008 and January 2012 (Lichtman et al., 2010). Patients admitted for AMI were screened for eligibility based on the following AMI criteria: elevated cardiac biomarkers (with at least one value above the 99th percentile of the upper reference limit) within 24 hr of admission plus evidence of acute myocardial ischemia, including at least one of the following: symptoms of ischemia, electrocardiographic changes indicative of new ischemia (new ST-T changes, new or presumably new left bundle-branch block, or the development of pathological *Q* waves), or other evidence of myocardial necrosis (imaging or pathology). Patients were enrolled at a 2:1 ratio of women to men. All participants provided written informed consent in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and institutional review board regulations.

We obtained the date of AMI onset and clinical information for each participant from the medical record. Individual characteristics at baseline, including sociodemographic status, lifestyle factors, and medical history, were collected during the index hospitalization via in-person interviews by local site coordinators. Physical activity was categorized as (a) inactive: no participation or fewer than 10 min of moderate or vigorous physical activity per week, (b) insufficient: between 10 and 149 min per week of moderate physical activity or between 10 and 74 min per week of vigorous physical activity, and (c) active: 150 min or more of moderate physical activity or 75 min or more of vigorous physical activity per week. A body mass index (BMI) $\geq$ 30 kg/m^2 was used to define obesity. A history of cardiovascular disease (CVD) was defined as having any prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, angina, heart failure, stroke, transient ischemic attack, or peripheral artery disease. Depression was defined by self-reported lifetime history of depression or presence of depressive symptoms as assessed by the nine-item version of the Patient Health Questionnaire (PHQ-9). A PHQ-9 score $\geq$10 was used as the criterion for depressive disorder. All site coordinators received standardized training and underwent routine evaluation by the Yale Coordinating Center.

The investigated subtypes of AMI included STEMI compared with NSTEMI and type 1 AMI compared with type 2 AMI. STEMI or NSTEMI was classified based on the adjudicated ECG diagnosis. Type 1 or type 2 AMI was determined according to a taxonomy developed for the young patients in the VIRGO cohort (Spatz et al., 2015). Briefly, the VIRGO participants were grouped into the following classes based on disease mechanisms: class I, plaque-mediated culprit lesion; class IIa, obstructive coronary artery disease (CAD) with myocardial oxygen supply demand mismatch; class IIb, obstructive CAD without supply demand mismatch; class IIIa, non-obstructive CAD with supply demand mismatch; class IIIb, nonobstructive CAD without supply demand

mismatch; class IV, other defined mechanism (e.g., spontaneous coronary artery dissection and vasospasm); and class V, indeterminate. We defined type 1 AMI as class I, which was related to plaque rupture, ulceration, fissuring, erosion, or dissection with resulting thrombus. Type 2 AMI combined class IIa and class IIIa, involving an imbalance between myocardial oxygen supply and demand. We excluded classes IIb, IIIb, and V from the analysis since the mechanism of these AMI subtypes was not well-determined. Class IV was also excluded because of a small sample that included a range of other mechanisms.

Of the 3,501 VIRGO participants, we excluded 1,094 individuals without matched home address coordinates for exposure assignment and 57 patients with missing AMI onset dates. Furthermore, to ensure that the data collected at hospitalization more accurately reflected the conditions present at the onset of AMI, we excluded 28 patients with more than 28 days between AMI onset and hospitalization. We finally included 2,322 participants in the current study. The home addresses of these participants are shown in Figure S1 of Supporting Information S1. The dates of AMI onset of these participants were between September 2008 and June 2011, which was defined as the study period.

2.2. Exposure Data

Daily maximum 8-hr concentrations of surface O_3 and daily mean concentrations of fine particulate matter ($PM_{2.5}$) at a spatial resolution of 1 km across the conterminous US were obtained from the USHighAirPollutants (USHAP) database (Wei et al., 2022, 2023b). Air pollutant concentrations were estimated using a developed spatiotemporally deep learning approach that integrated big data from satellites, models, and surface observations, and accounted for spatial autocorrelation to improve the estimates. The daily air pollution estimates agree with ground measurements with an average ten-fold cross-validation coefficient of determination of 0.88 for O_3 and 0.82 for $PM_{2.5}$.

Daily mean air temperature and mean dew point temperature at a spatial resolution of approximately 4 km were collected from the PRISM Daily Spatial Climate Data set AN81d (Parameter-elevation Regression on Independent Slopes Model (PRISM) Climate Group, 2016) (Daly et al., 2008). We calculated the daily relative humidity using a version of the August-Roche-Magnus equation (Lawrence, 2005).

2.3. Statistical Analysis

We employed a time-stratified case-crossover study design. For each participant, we matched the day of AMI onset (case day) with days on the same day of the week within the same month and calendar year (control days). We then assigned air pollutant concentrations, temperature, and relative humidity in the grid with the centroid closest to the residential address on the case and control days and their preceding 1–6 days. By making within-participant comparisons of exposure profiles between the case and control days, we controlled for the potential confounding effects of time-invariant participant characteristics, long-term time trend, seasonality, and day of the week.

Two-pollutant conditional logistic regression models including O_3 and $PM_{2.5}$ of the same lag were used to estimate the short-term associations between air pollution and the risk for AMI onset at single-day lags of 0–6 days. The two-pollutant model allowed for disentangling the independent association with AMI for each pollutant. The air pollutants were examined as linear terms. We adjusted for daily mean air temperature and relative humidity, both included as a natural spline with three degrees of freedom. Effect estimates are presented as the odds ratios (ORs) with 95% confidence intervals (95% CIs) for an interquartile range (IQR) increase in daily maximum 8-hr concentration of O_3 as well as daily mean $PM_{2.5}$.

For the lag day(s) showing a statistically significant association with overall AMI, we performed separate analyses for STEMI versus NSTEMI and type 1 versus type 2 AMI to explore potential effect differences between AMI subtypes. Additionally, seasonal analyses were performed in the warmer months (April–September) and colder months (October–March) to examine potential seasonal patterns in the exposure-response relationship. The statistical significance of the difference in effect estimates between AMI subtypes and seasons was assessed by the two-sided Z-test (Altman & Bland, 2003).

We conducted stratified analyses to examine effect modification on the association between air pollution and AMI by individual characteristics, including age (≤45 years vs. >45 years), sex (males vs. females), race/ethnicity (non-Hispanic White vs. non-Hispanic Black), education level (less than high school or high school vs.

more than high school), obesity (no vs. yes), physical activity (inactive or insufficient vs. active), smoking in the past 30 days (no vs. yes), and history of cardiovascular disease (CVD; no vs. yes), diabetes (no vs. yes), and depression (no vs. yes). The statistical significance of the difference in effect estimates between subgroups was assessed by the two-sided Z-test (Altman & Bland, 2003). We reported the *p*-values of the Z-tests after Benjamini-Hochberg false discovery rate (FDR) correction for multiple testing (Benjamini & Hochberg, 1995).

In sensitivity analyses, we first examined the exposure-response function between O_3 and AMI onset by replacing the linear term of O_3 concentrations with a natural spline with three degrees of freedom in the two-pollutant model. Second, we restricted analyses to participants exposed to O_3 levels below the World Health Organization (WHO) air quality guidelines (100 μg/m^3 [51 ppb at 1,013 mbar and 298 K] for daily maximum 8-hr concentrations of O_3) on 0–6 days prior to AMI onset to examine the impact of low O_3 exposure. Third, we restricted the analyses to participants with AMI occurring within 1 day prior to hospitalization to reduce the influence of changes in time-varying factors.

The statistical analyses were performed with *R* software (version 4.3.2) using packages "survival" and "splines." All statistical tests were 2-sided with a 5% significance level.

3. Results

3.1. Description

Of the analyzed 2,322 patients, 1,154 (49.7%) were diagnosed with STEMI, 1,168 (50.3%) with NSTEMI, 1,869 (80.5%) with type 1 AMI, and 102 (4.4%) with type 2 AMI. The participants had a mean age of 47.1 years [standard deviation (SD) = 6.2 years] and 68.8% were female (Table 1). The majority were non-Hispanic White (70.4%), married or living with a partner as if married (56.2%), obese (52.1%), current smokers (57.4%), had education beyond high school (57.2%), had inactive or insufficient physical activity (62.9%), or had a history of depression (52.9%). Compared with the group with STEMI, the group with NSTEMI had a higher proportion of females and non-Hispanic Blacks, lower levels of physical activity, lower percentage of current smokers, a higher prevalence of CVD and depression, and a higher proportion of type 2 AMI.

The average daily maximum 8-hr O_3 and daily mean $PM_{2.5}$ concentrations during the study period were 37.6 ppb (SD = 11.9 ppb) and 9.8 μg/m^3 (SD = 5.0 μg/m^3), respectively (Table 2). Most participants' daily exposures to O_3 (85.7%) were below the recommended levels set by the WHO air quality guidelines (51 ppb). The air pollutants and meteorological factors were weakly correlated, except for a moderate positive correlation between O_3 and temperature (Pearson correlation coefficient $r = 0.47$, Table 2).

3.2. Short-Term Associations Between Air Pollution and Acute Myocardial Infarction

The daily maximum 8-hr O_3 concentration was positively associated with the risk for overall AMI (Table 3, Table S1 in Supporting Information S1). For an IQR (16.6 ppb) increment in O_3, the ORs for overall AMI were 1.21 (95% CI: 1.08–1.34) and 1.11 (95% CI: 1.00–1.24) at lag 4 and lag 5 days, respectively. The association at lag 4 days was stronger for NSTEMI (OR = 1.34, 95% CI: 1.15–1.56) than for STEMI (OR = 1.09, 95% CI: 0.93–1.27), with borderline significant difference in effect estimates (*p*-value = 0.05; Table 3). Moreover, O_3 was associated with an increased risk for type 1 AMI at lag 4 days (OR = 1.16, 95% CI: 1.03–1.31) and with type 2 AMI at lag 4 days (OR = 1.79, 95% CI: 1.04–3.07) and lag 5 days (OR = 1.70, 95% CI: 1.02–2.81). The between-group difference in effect estimates of type 1 versus type 2 AMI was non-significant (*p*-value = 0.13) at lag 4 days and borderline significant (*p*-value = 0.07) at lag 5 days. Additionally, the association between O_3 and AMI was more evident in the warmer months (OR = 1.27, 95% CI: 1.09–1.47) compared with the colder months (OR = 1.16, 95% CI: 0.96–1.41) at lag 4 days, but the difference was non-significant (*p*-value = 0.50). We found no statistically significant associations between O_3 and STEMI at any lag and no statistically significant positive associations between $PM_{2.5}$ and AMI (Table 3, Table S1 in Supporting Information S1).

3.3. Effect Modification by Individual Characteristics

The assessment of effect modification focused on the O_3 effect at lag 4–5 days based on the results of the main analysis. The association between O_3 and overall AMI was stronger in patients who were non-Hispanic Black

Table 1
Descriptive Statistics of Study Participants During the Study Period

Characteristic	Overall AMI[a] (n = 2,322)	STEMI[a] (n = 1,154)	NSTEMI[a] (n = 1,168)	p-value for difference[b]
Age (Years)	47.1 ± 6.2	46.9 ± 6.2	47.3 ± 6.1	0.06
Age >45 years (yes)	1,556 (67.0)	760 (65.9)	796 (68.2)	0.25
Sex (female)	1,598 (68.8)	740 (64.1)	858 (73.5)	<0.001
Race/ethnicity				<0.001
Hispanic	175 (7.5)	82 (7.1)	93 (8.0)	
Non-Hispanic White	1,633 (70.4)	870 (75.5)	763 (65.4)	
Non-Hispanic Black	401 (17.3)	154 (13.4)	247 (21.2)	
Others	110 (4.7)	46 (4.0)	64 (5.5)	
Marital status				0.54
Single	334 (14.5)	170 (14.9)	164 (14.1)	
Married/live as married	1,293 (56.2)	649 (56.8)	644 (55.5)	
Divorced/separated/widowed	675 (29.3)	323 (28.3)	352 (30.3)	
Education level				0.08
≤High school	985 (42.8)	480 (41.9)	505 (44.6)	
More than high school	1,318 (57.2)	665 (58.1)	653 (56.4)	
BMI (kg/m^2)	31.6 ± 7.8	31.3 ± 7.5	31.9 ± 8.1	0.12
Obesity (yes)	1,210 (52.1)	585 (50.7)	625 (53.5)	0.18
Physical activity				0.001
Inactive	782 (33.9)	350 (30.5)	432 (37.2)	
Insufficient	669 (29.0)	362 (31.6)	307 (26.5)	
Active	856 (37.1)	435 (37.9)	421 (36.3)	
Smoked in the past 30 days (yes)	1,332 (57.4)	733 (63.5)	599 (51.3)	<0.001
Prior CVD (yes)	826 (35.9)	351 (30.6)	475 (41.1)	<0.001
Diabetes (yes)	828 (35.7)	390 (33.8)	438 (37.5)	0.06
Depression (yes)	1,229 (52.9)	577 (50.0)	652 (55.8)	0.01
Type of AMI				<0.001
Type 1	1,869 (80.5)	1,013 (87.8)	856 (73.3)	
Type 2	102 (4.4)	15 (1.3)	87 (7.4)	

Note. Descriptive statistics are mean ± standard deviation (SD) for continuous variables and n (%) for categorical variables. AMI, acute myocardial infarction; BMI, body mass index; CVD, cardiovascular disease; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction. [a]Numbers in sub-groups may not sum to the total n due to missing values. AMI other than type 1 or type 2 was not included in this description. [b]Statistical difference in characteristics between patients with STEMI and NSTEMI was derived using Kruskal–Wallis rank sum tests for continuous variables and Fisher's exact tests for categorical variables.

compared to non-Hispanic White with a FDR-adjusted p-value of 0.06 (Figure 1, Table S2 in Supporting Information S1). No significant effect modification was found for the other characteristics examined.

3.4. Sensitivity Analyses

The sensitivity analyses focused on the O_3 effect at lag 4–5 days based on the results of the main analysis. The exposure-response relationship between O_3 concentration and overall AMI, STEMI, NSTEMI, type 1 AMI, or type 2 AMI did not deviate substantially from linearity (Figure 2). After excluding 425 participants with O_3 exposure levels above the WHO air quality guideline, the CIs of the effect estimates for O_3 widened due to the reduced sample size, and only the association with overall AMI remained significant (Table S3 in Supporting Information S1). Furthermore, these associations remained stable after excluding 344 participants who were hospitalized more than 1 day following AMI onset (Table S3 in Supporting Information S1).

Table 2
Distribution and Pearson Correlation Coefficients of Air Pollution and Meteorological Factors During the Study Period (September 2008 to June 2011)

Exposure	Mean	SD	Min	P25	Median	P75	Max	IQR	Correlation coefficient		
									O_3	$PM_{2.5}$	Temperature
Daily maximum 8-hr O_3 (ppb)	37.6	11.9	0.5	29.0	36.8	45.6	114.0	16.6	1		
Daily mean $PM_{2.5}$ ($\mu g/m^3$)	9.8	5.0	0.4	6.2	8.8	12.3	89.1	6.1	0.13	1	
Daily mean temperature (°C)	12.8	10.3	−27.2	5.7	14.1	21.0	35.4	15.3	0.47	0.07	1
Relative humidity (%)	67.9	15.2	9.2	57.9	68.7	78.3	100	20.4	−0.33	−0.03	−0.13

Note. IQR, interquartile range; Max, maximum; Min, minimum; O_3, ozone; P25, 25th percentile; P75, 75th percentile; $PM_{2.5}$, fine particulate matter; SD, standard deviation.

4. Discussion

In this large cohort of younger AMI patients with a higher proportion of females, short-term exposure to O_3 was significantly associated with an increased risk for AMI onset at lag 4 and 5 days, adjusted for concurrent $PM_{2.5}$ exposure. The association was more pronounced for NSTEMI and type 2 AMI compared with STEMI and type 1 AMI, respectively. Furthermore, non-Hispanic Black patients tended to be more vulnerable to the adverse effect of O_3. We found no evidence of adverse effects of $PM_{2.5}$ on AMI in this study population.

Although previous research mainly reported non-significant associations between O_3 and AMI morbidity (Chen et al., 2022; Mustafic et al., 2012; Qiu et al., 2020), our finding of the O_3-related increase in the AMI risk was consistent with studies from China, southwestern France, and Iran (Jiang et al., 2023; Mohammadian-Khoshnoud et al., 2023; Ruidavets et al., 2005; Tsai et al., 2012). The associations in these studies were mostly significant within 2 days after exposure, indicating a more acute effect compared to our results. This inconsistency may be due to our younger study population, who have shown more delayed responses to nitrogen dioxide and PM_{10} (although not O_3) compared to older individuals (Collart et al., 2017). Notably, our association remained at O_3 levels below the WHO 2021 guideline, suggesting the need for stricter air quality regulations below current limit values.

Our study contributes to the existing knowledge by differentiating between AMI subtypes. While previous research has linked air pollution to STEMI (Bañeras et al., 2018; Sahlén et al., 2019; Zhu et al., 2022), evidence for NSTEMI, particularly concerning O_3, remains inconclusive. For instance, large-scale studies in eastern Poland and China found associations of STEMI and NSTEMI with $PM_{2.5}$ but not with O_3 (Kuźma et al., 2024). In contrast, another multi-city study in China (Liu et al., 2018) and a case-crossover study in the US (Gardner et al., 2014) found $PM_{2.5}$-related increases in the risk for STEMI but not for NSTEMI. Moreover, Milojevic et al. (2014) did not observe significant air pollution associations with either STEMI or NSTEMI in England and Wales. Contrary to prior findings, our study demonstrated an association of O_3 with NSTEMI but not with STEMI. This discrepancy may be partly explained by patient characteristics. Specifically, patients with NSTEMI in the VIRGO cohort were more likely to be non-Hispanic Black, potentially increasing their vulnerability to O_3.

Table 3
Odds Ratios and 95% Confidence Intervals for Overall AMI, STEMI, NSTEMI, Type 1 AMI, and Type 2 AMI Associated With an Interquartile Range (16.6 ppb) Increase in Daily Maximum 8-hr Ozone Concentrations in Two-Pollutant Models at Lag 4 days and Lag 5 days

Outcome	Lag 4 days	Lag 5 days
Overall AMI	1.21 (1.08, 1.34)	1.11 (1.00, 1.24)
STEMI	1.09 (0.93, 1.27)	1.11 (0.95, 1.29)
NSTEMI	1.34 (1.15, 1.56)	1.12 (0.96, 1.30)
Type 1 AMI	1.16 (1.03, 1.31)	1.04 (0.93, 1.18)
Type 2 AMI	1.79 (1.04, 3.07)	1.70 (1.02, 2.81)

Note. AMI, acute myocardial infarction; IQR, interquartile range; NSTEMI, non-ST-elevation myocardial infarction; O_3, ozone; STEMI, ST-elevation myocardial infarction.

Our study is the first to discern the O_3-associated risk between type 1 and type 2 AMI, providing insights into the potential pathogenic pathways. Type 1 AMI is primarily caused by atherosclerotic plaque rupture and thrombosis. The association between O_3 and type 1 AMI supports the hypothesis that ozone-induced inflammation contributes to plaque instability and subsequent rupture (Bentzon et al., 2014; González-Guevara et al., 2014). Additionally, O_3 is associated with higher levels of coagulation and thrombosis factors, potentially exacerbating thrombosis following plaque rupture (Day et al., 2017). For type 2 AMI, which results from an imbalance between myocardial oxygen supply and demand, the association with O_3 implies several potential mechanisms. First, O_3 exposure may increase myocardial oxygen demand due to conditions such as elevated heart rate or blood pressure (Day et al., 2017; Devlin et al., 2012). Inflammation and broader effects of

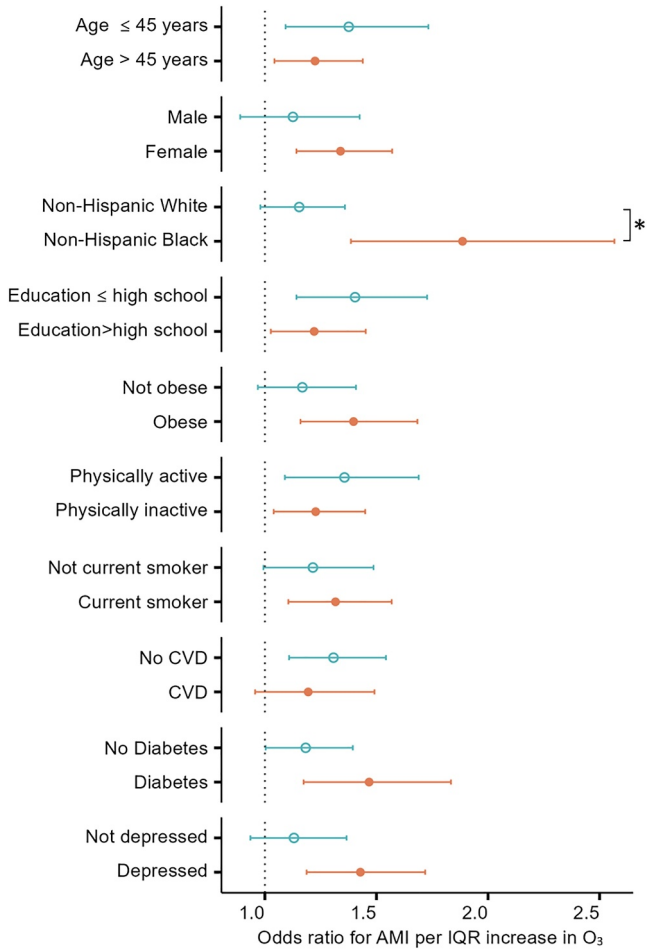

Figure 1. Odds ratios and 95% confidence intervals for overall acute myocardial infarction associated with an interquartile range (16.6 ppb) increase in daily maximum 8-hr ozone concentrations at lag 4–5 days in different subgroups. *FDR-adjusted *p*-value for between-group difference = 0.06. AMI, acute myocardial infarction; CVD, cardiovascular disease; FDR, false discovery rate; IQR, interquartile range.

increased sympathetic tone may also play a role. Second, O_3 may decrease oxygen supply via impaired pulmonary function (Rice et al., 2013). These findings advance our understanding of how O_3 exposure may trigger AMI through different mechanisms.

In contrast to prior research, our study found no significant association between $PM_{2.5}$ and AMI. This discrepancy may arise from age-related differences in susceptibility. Previous studies reporting $PM_{2.5}$-AMI associations typically included all age groups, with a substantial representation of people aged over 55 years, who have shown greater susceptibility to $PM_{2.5}$ than younger persons (Chen et al., 2022; Kuźma et al., 2024). Moreover, there is evidence suggesting an immediate effect of $PM_{2.5}$ exposure on AMI risk within hours after exposure. For instance, Chen et al. (2022) reported that the association between $PM_{2.5}$ and AMI onset was strongest in the concurrent hour of exposure and was attenuated thereafter. Due to the lack of hourly data on AMI onset time for a large number of VIRGO participants, we were unable to assess the effect of hourly air pollution. Therefore, our null findings for $PM_{2.5}$ should be interpreted in the context of our cohort consisting of younger adults, as well as the limitation of a daily exposure window.

Our effect modification analysis should be interpreted with caution due to the multiple comparisons performed. Nevertheless, our finding of a stronger association between O_3 exposure and AMI risk among non-Hispanic Blacks compared to non-Hispanic Whites is consistent with previous research showing greater vulnerability to $PM_{2.5}$ exposure in relation to mortality among Blacks (Di et al., 2017; Ma et al., 2023). The greater risk observed among Black Americans might be due to their socioeconomic disadvantage, limited access to health care, and higher prevalence of comorbidities, which may exacerbate the cardiovascular effects of air pollution (Williams & Mohammed, 2013). Our findings suggest that efforts to reduce air pollution, to address socioeconomic inequalities, and to improve access to health care are critical public health measures in communities with a high proportion of Black residents.

4.1. Strengths and Limitations

One major strength of our study is the focus on a young adult population with a high proportion of females, a population that has been underrepresented in previous studies. Our finding of a significant association of AMI with O_3 but not $PM_{2.5}$, which largely contradicts prior research, suggests potentially different responses to air pollution in this subpopulation versus subpopulations with older adults or a lower proportion of females. Second, by differentiating subtypes of AMI, our study elucidates the understudied associations of O_3 with NSTEMI, type 1 AMI, and type 2 AMI, and provides insights into the underlying biological mechanisms. Third, the use of model-estimated exposure data at high spatial resolutions improved the accuracy of exposure assessment compared to measured data from a limited number of monitoring sites. Moreover, the comprehensive collection of individual socioeconomic and medical history data in the VIRGO cohort allowed examination of effect modification by characteristics that have been rarely explored, suggesting valuable insights for the development of targeted prevention strategies to reduce the burden of CVD and address health inequalities.

This study also has limitations. First, the examination of seven lag days might lead to multiple testing issue. However, our finding of significant associations between O_3 and AMI on two consecutive lag days (lag 4 and 5 days) is biologically plausible and less likely to represent chance associations. Second, we did not examine the effects of hourly air pollution exposure due to unavailability of hourly exposure data and the precise AMI onset time. Hence, the potential for immediate effects of air pollution within hours of exposure cannot be excluded. Third, our findings are specific to our younger, mainly female study population and may not be generalizable to other populations, especially older adults. Finally, ambient air pollution concentrations at the participant's place of

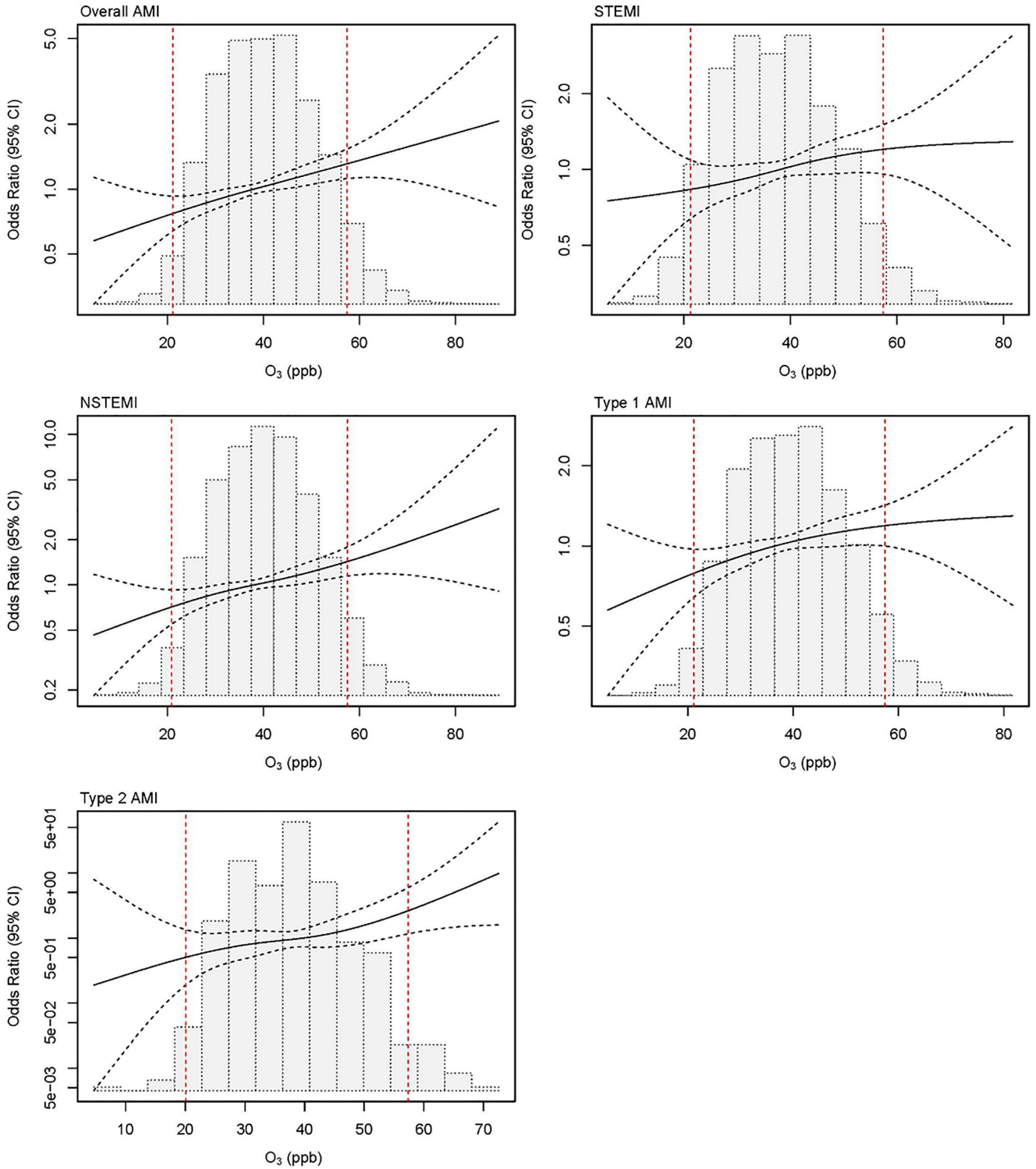

Figure 2. Exposure-response functions between daily maximum 8-hr ozone concentrations and overall AMI, STEMI, NSTEMI, type 1 AMI, and type 2 AMI at lag 4–5 days. Histograms show the distribution of ozone concentrations 4 days prior to the case and control days. Red dashed lines indicate the 5th and 95th percentiles of the ozone distribution. AMI, acute myocardial infarction; CI, confidence interval; NSTEMI, non-ST-elevation myocardial infarction; O_3, ozone; STEMI, ST-elevation myocardial infarction.

residence may not accurately reflect the actual exposure for some participants. Additionally, recall bias in the self-reported date of AMI onset may exist. These two factors could contribute to non-differential exposure misclassification, potentially biasing the results toward the null.

5. Conclusion

This case-crossover study of 2,322 younger AMI patients from 103 hospitals in the US provides evidence that short-term exposure to O_3 may increase the risk of AMI onset. Our findings contribute to the understanding of air pollution effects on subtypes of AMI and suggest a potentially vulnerable subpopulation of non-Hispanic Blacks, underscoring the necessity of targeted intervention strategies to reduce the burden of disease associated with air pollution.

Conflict of Interest

The authors declare no conflicts of interest relevant to this study.

Data Availability Statement

Daily air pollution data on $PM_{2.5}$ and O_3 for the US from 2008 to 2012 are available at Wei et al. (2023a). Meteorological data on daily mean air temperature and dew point temperature are available at PRISM Climate Group (PRISM Climate Group, 2014). Data were analyzed with *R* version 4.3.2 (R Core Team, 2023). The hospital admission data used in this study are not publicly available due to confidentiality of patient information.

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