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ORIGINAL RESEARCH ARTICLE

Joint Exposure to Ozone and Temperature and Acute Myocardial Infarction Among Adults Aged 18 to 64 Years in the United States

Lingzhi Chu, PhD*; Rong Wang, PhD*; Cary P. Gross, MD; Jing Wei, PhD; Yuan Lu, ScD; Harlan M. Krumholz, MD; Xiaomei Ma, PhD†; Kai Chen, PhD†

BACKGROUND: Previous research suggests that exposures to air pollution and nonoptimal temperatures are associated with a higher risk of acute myocardial infarction (AMI), but few studies examined the exposures jointly. Furthermore, moderate exposures were often overlooked. We evaluated short-term exposure to ambient ozone pollution and ambient temperature jointly and over the entire range of exposures, with the occurrence of AMI among adults aged 18 to 64 years (an understudied population) in the contiguous United States.

METHODS: We identified eligible individuals with incident AMI insured by a nationwide private insurance company from 2016 to 2020. We designed a time-stratified case-crossover study in which each patient's ambient exposure to ozone and temperature on the day of their AMI was compared with their exposures on a nearby day. We used a 2-stage model to investigate the associations with joint exposures: (1) fitting climate- and region-specific models with statistical interaction terms between ozone and temperature, and (2) using a multivariate random-effects meta-analysis to pool the region-specific estimates.

RESULTS: We included 270 123 adults with incident AMI and observed a significant association between joint ozone-temperature exposures and increased AMI. Compared with the reference of ozone at 35 ppb and temperature at the first percentile, joint exposure to ozone at 60 ppb and temperature at the 95th percentile at lag 0 day was associated with a 33% (95% CI, 16%–51%) increase in incident AMI, and joint exposure to ozone at 50 ppb and temperature at the median was associated with a 15% (95% CI, 4%–28%) increase. There was heterogeneity by sex, with women showing increased odds when both ozone and temperature were high and men showing increased odds when either ozone or temperature was high.

CONCLUSIONS: Joint exposure to ozone pollution and high temperature increased the probability of AMI among younger adults, even when 1 of the exposures was moderate. This study highlights the importance of addressing exposures to ozone and nonoptimal temperature simultaneously in AMI prevention strategies.

Key Words: acute myocardial infarction ■ ambient temperature ■ ground-level ozone

Globally, acute myocardial infarction (AMI) is among the leading causes of human death, and ~3 million people experience AMI occurrences annually.[1] In the United States, there were >800 000 new or recurrent AMI events in 2020.[2] Despite a trend of declining AMI incidence and mortality in the United States in recent years,[3] a higher proportion of AMI now occurs in younger adults. Among AMI hospitalizations in the United States from 1995 to 2014 among adults aged 35 to 74 years, ~30% occurred in younger patients

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Clinical Perspective

What Is New?

- Joint exposure to ozone and higher ambient temperature is associated with an increased probability of incident acute myocardial infarction among younger adults aged 18 to 64 years in the contiguous United States.
- Joint exposure to ozone at 60 ppb and temperature at the 95th percentile at lag 0 day increased probability of acute myocardial infarction by 33% (95% CI, 16%–51%) compared with the reference exposure to ozone at 35 ppb and temperature at the first percentile.
- Even when 1 of the exposures (ie, ozone or temperature) is moderate, there is increased occurrence of acute myocardial infarction, especially among men.

What Are the Clinical Implications?

- It is essential to consider both ambient ozone pollution and temperatures when designing health strategies to reduce acute myocardial infarction morbidity and mortality among younger adults.
- Our findings underline the necessity of health strategies and actions against not only extreme exposures but also moderate levels of exposure to ozone and temperature.

Nonstandard Abbreviations and Acronyms

AMI	acute myocardial infarction
ICD-10	*International Classification of Diseases, Tenth Revision*
NSTEMI	non–ST-segment–elevation myocardial infarction
OR	odds ratio
$PM_{2.5}$	fine particulate matter
STEMI	ST-segment–elevation myocardial infarction

aged 35 to 54 years, and this proportion increased by 5% between the periods 1995 to 1999 and 2010 to 2014.[4] For women, the proportion increased an even larger percentage, from 21% to 31%.[4] In addition, the pathogenesis of AMI may vary by age, so previous research findings primarily based on an older patient population may not be generalizable to the younger population.[3] Thus, it is critical to identify modifiable risk factors for younger adults to reduce the rising AMI burden in this age group, including environmental risk factors, like air pollution and nonoptimal temperatures (ie, temperatures lower or higher than the temperature with minimum morbidity risk, which is usually cause-, location-, and population-specific[5,6]).

Whether at home, at work, or at play, humans are exposed to joint exposures, which means being simultaneously exposed to >1 exposure, and the evaluation of joint exposure may reveal more accurate and comprehensive health implications beyond the evaluation of independent exposures. However, few studies have examined the influence of joint exposure to environmental factors, an evaluation of particular significance when such exposures can interact chemically in the atmosphere or biologically in the human body. For example, the ground-level ozone becomes more reactive at high atmospheric temperatures, and high temperatures catalyze the chemical reactions of nitrogen oxides and volatile organic compounds to form ozone. Moreover, the joint exposure to ground-level ozone and nonoptimal temperature triggered similar physiological pathways in an animal study.[7] Therefore, we hypothesized that there may be associations with joint exposures to ambient ozone and temperature regarding risk of AMI. It should be noted that this study focused on ground-level ozone, which may have adverse human health impacts and is different from stratospheric ozone (which protects humans against ultraviolet radiation).[8]

Moreover, previous studies on joint exposures have typically used categorical or linear variables for at least 1 exposure, leading to knowledge gaps about moderate exposures and complex real-world interactions. Specifically, categorical variables focusing on the extreme events overlook the health impacts of moderate exposures, and linear variables are unable to distinguish the potentially differential associations with extreme versus moderate exposures. Considering that moderate exposures may be more frequent compared with extreme exposures, moderate exposures could attribute to larger health burdens. It is thus crucial to conduct a comprehensive evaluation of joint exposures over the entire ranges of exposures (as opposed to only at the extreme ends) and to explore potential nonlinearity beyond linear relationships between joint exposures and health outcomes.

To address important knowledge gaps and inform future interventions to reduce the burden of AMI among younger adults aged 18 to 64 years, we designed a large, nationwide study to evaluate the relation of short-term joint exposure to ozone and ambient temperature to incident AMI, incorporating a recently established method for interaction analysis.[9] Given that the prevalence and pathophysiology of AMI risk factors vary by demographic characteristics and AMI subtypes, we also conducted stratified analyses by sex (women, men), age (18–54 years, 55–64 years), and AMI subtypes (ST-segment–elevation MI [STEMI], non–ST-segment–elevation MI [NSTEMI]).

METHODS

The Institutional Review Board of Yale University approved this study with determination that investigators are not engaged in research involving human subjects (ID: 2000037456).

Data Availability Statement

Health data are available upon request from a third party. Because of the sensitive nature of the health data, we are not allowed to disseminate the data or to publish the identity of the third party per the data use agreement. Ozone data are available upon request from the author (Dr. Jing Wei, weijing@umd.edu). Temperature data are publicly available at https://daymet.ornl.gov/. The analytic codes are available from the authors upon request.

Study Design

To investigate possible associations between short-term joint exposure to ozone and ambient temperature and the occurrence of AMI, we designed a time-stratified case-crossover study.[10] In case-crossover studies, a participant's exposure on the day when an outcome of interest occurred (ie, a case day) is compared to the exposures on selected "control" days. Control days are assumed to share characteristics with case days, except for the level of exposure, outcome of interest, and dates. In other words, participants on control days serve as their own controls for case days. Such a design enables automatic control of time-invariant confounders (eg, age, sex, personal behavior).

In this time-stratified case-crossover study, we selected days on the same day of the week within the same month in the same calendar year as control days, which in addition controlled for the potential influences of the day of the week (eg, Monday versus Friday), seasonality (eg, summer versus winter), and long-term trends (eg, 2009 versus 2019). That is, for a patient who experienced an AMI, we compared the local ozone concentration and temperature on the day of their AMI occurrence (eg, 40 ppb and 18 °C on the second Tuesday in October 2018) to the ozone concentration and temperature in their area on nearby days (ie, on other Tuesdays in October 2018).

Study Population

We obtained health claims data for individuals who were insured by a nationwide private health insurance company and experienced AMI during the period 2016 to 2020. This insurance company is a large provider of commercial insurance in the United States, covering every zip code in the United States. Claims in this insurance database came from a vast majority of hospitals in the United States and provide individual-level information on residential zip code, hospital visit date, causes of disease coded in the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes, age, and sex. Age and sex were ascertained at the insurance enrollment.

In this study, we restricted the study population to younger individuals who (1), had claims for incident AMI (*ICD-10*: I21 according to the World Health Organization definition) from an inpatient or outpatient visit during the period 2016 to 2020[11,12]; (2), were aged 18 to 64 years on the day of AMI occurrence; (3), were continuously insured by the company providing the data during the month of AMI and the preceding month; and (4), had no history of AMI in the insurance database during the period 2016 to 2020.

Exposure Assessment

We obtained daily 1-km level maximum 8-hour ozone concentration and mean fine particulate matter ($PM_{2.5}$) concentration from the high-resolution and high-quality USHighAirPollutants dataset.[13] Ozone and $PM_{2.5}$ were estimated by deep learning models described in detail in a previous work.[14] The daily estimates of ground-level ozone are highly accurate with a coefficient of determination (R^2) of 0.88 in a 10-fold cross-validation during the period 2016 to 2020 (Figure S1). The daily $PM_{2.5}$ estimate also has excellent performance with an R^2 of 0.82 in a 10-fold cross-validation.[14]

We also extracted daily minimum and maximum air temperatures and vapor pressure at a 1-km resolution from the Daymet Version 4 dataset, which has a very small bias and is widely used for heat exposure assessment.[15,16] We then calculated daily mean temperature as the mean of daily minimum and maximum temperatures and dew point temperature from daily mean temperature and vapor pressure.

In addition, we obtained annual population data at a 1-km resolution from LandScan Global,[17] resampled the population data to the grids same as the exposure data, and then calculated grid-based average exposure levels weighted by population for each zip code. We linked environmental exposures to each participant using their residential zip code and case/control dates.

Statistical Analysis

Considering the spatially differential temperature distributions and potential adaptation (either physiological or behavioral) to local climate, the temperature associations on the absolute scale (ie, degrees Celsius) may have spatial heterogeneity. For example, a hot day of 35 °C may be common in hot areas, and because of adaptation, individuals in these areas may be less vulnerable to such hot days than individuals in cooler areas, where days of 35 °C could be extreme and rare. To address such potential spatial heterogeneity, we used 2-stage models to assess possible associations between ozone, ambient temperature, and incident AMI.

In the first stage, we conducted separate models for each of the 9 climate regions in the contiguous United States according to definitions by the National Center for Environmental Information (Figure 1).[18] For each region, we fitted a conditional logistic model regressing the case status of outcome (case=1, control=0) on the moving averages of daily maximum 8-hour ozone concentration and of daily mean temperature over a lagged period of up to 3 days (ie, separate models for lag 0 day, lag 0–1 days [cumulative association with exposure over the 2-day period: the case/control day and 1 preceding day], lag 0–2 days, and lag 0–3 days). Considering potential nonlinearity, we specified the ozone term as a natural cubic spline with knots at the 25th, 50th, and 75th percentiles of pollution distribution in the contiguous United States and the temperature term as a natural cubic spline with knots at the climate- and region-specific 25th, 50th, and 75th percentiles given potential adaptation to local temperatures. To assess the influence of joint exposures to ozone and temperature, we included an interaction term between the ozone natural cubic spline and the temperature natural cubic spline.[9] In addition, we adjusted for the moving averages of $PM_{2.5}$ and dew point temperature over the same lagged period in the model, which were also specified as natural cubic splines (knots for $PM_{2.5}$ were placed at the 25th, 50th, and 75th percentiles of pollution distribution in the contiguous United States, and knots for dew point temperature were equally placed for each climate region), to

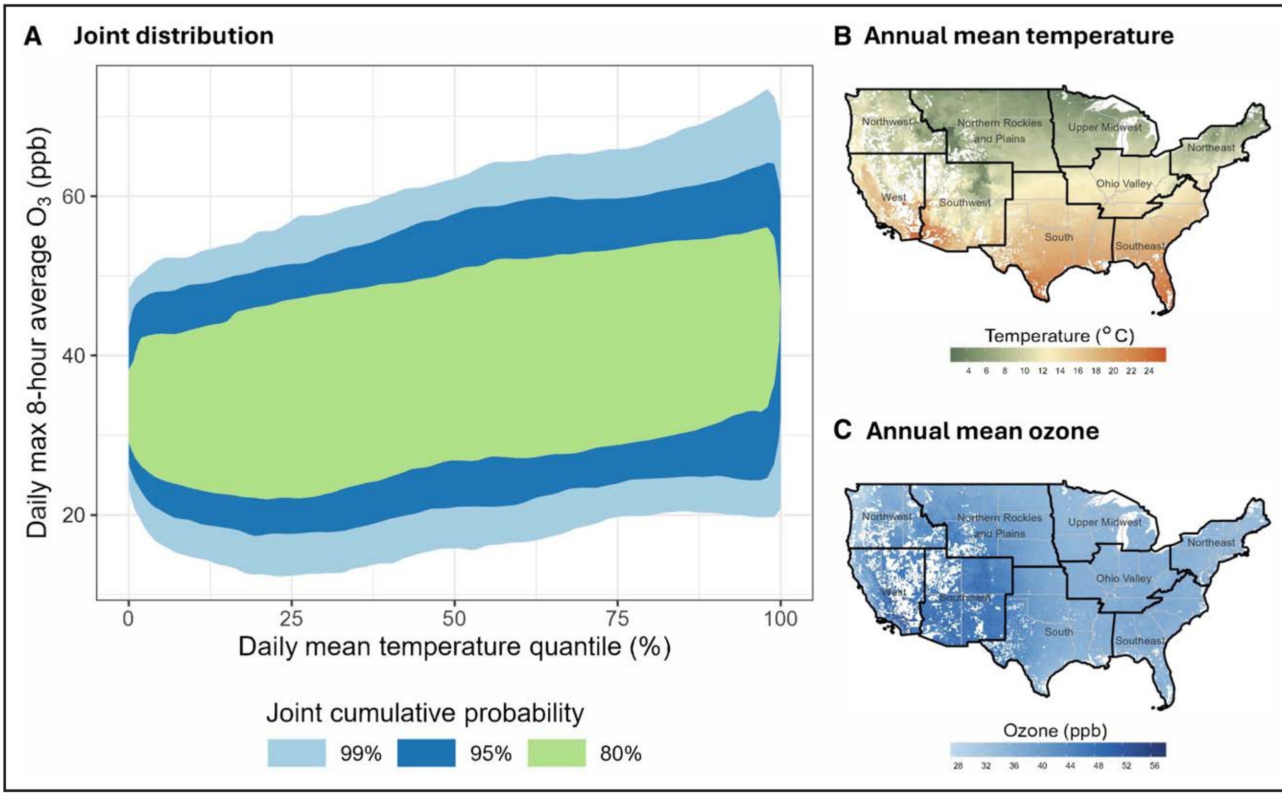

Figure 1. Joint distribution of zip code–level daily ozone and temperature and maps of annual mean temperature and of annual mean value of daily maximum 8-hour ozone concentrations in the contiguous United States (2016–2020).
Areas without zip codes appear in white in the maps of exposures (**B** and **C**).

control potential confounding because they are risk factors for AMI and potentially correlated with exposures of interest (ie, ground-level ozone and temperature).[19,20]

In the second stage, we used multivariate random-effects meta-analysis to pool the climate-and region-specific coefficients obtained in the first stage. Based on the pooled coefficients, we could calculate the association estimates (along with their variances) at any combination of ozone and temperature levels, which were then plotted as points determining the exposure-response surface for the joint exposure to ozone and temperature.[9] We assessed heterogeneity across climate regions by Q statistics and *P* values thereof based on the coefficients of the natural cubic splines.

Based on our comparison of models using different lagged periods (ie, 0, 1, 2, or 3 days), the association between joint exposure to ozone and temperature and AMI reached the largest magnitude at lag 0 day (Figure S2). Therefore, we used lag 0 day as the primary time window in subsequent analyses. With no significant heterogeneity across regions (Table S1), we reported pooled odds ratio (OR) estimates across climate regions. We reported for a total of 9 combinations of ozone and temperate levels (ie, ozone concentration at 35 ppb, 50 ppb, and 60 ppb, and temperature at the 50th, 80th, and 95th percentiles), with the combined exposure to ozone at 35 ppb and temperature at the 1st percentile as the reference. The 3 ozone concentrations reported in this study (ie, 35 ppb, 50 ppb, and 60 ppb) are selected to showcase the association estimates at the ozone levels below the World Health Organization guideline (100 μg/m^3, which is ~51 ppb), approximately at the World Health Organization guideline, and between the World Health Organization and the US Environmental Protection Agency National Ambient Air Quality Standards for ozone (70 ppb). On interpretation and discussion, we considered the ozone level of 60 ppb and the temperature level of the 95th percentile as extreme exposures and the other 2 levels for respective exposures as moderate.

To evaluate potential effect modification, we conducted stratified analyses by sex (women, men), AMI subtype (STEMI [*ICD-10*: I21.0–I21.3], NSTEMI [*ICD-10*: I21.4]), and age (18–54 years, 55–64 years). For all stratified analyses, we evaluated heterogeneity across subpopulations by Q statistics and *P* values, similar to what we did to evaluate interregion heterogeneity.

To investigate the robustness of our estimates, we performed sensitivity analyses by (1) varying the knots of ozone at the 10th, 50th, and 90th percentiles; and (2) varying the knots of temperature at the 10th, 75th, and 90th percentiles in the natural cubic splines. We conducted all statistical analyses in R (version 4.2.2) and interpreted $P<0.05$ as statistically significant. All tests are 2-sided.

RESULTS

Characteristics of the Study Population

A total of 270 123 participants with incident AMI during the period 2016 to 2020 were included in this study (Table). Most of our AMI occurrence samples came from the Southeast (23.3%), Northeast (19.9%), Ohio Valley

Table. Characteristics of the Study Population

	No. (%)
Total	270 123
Climate region	
Northeast	53 650 (19.9)
Northern Rockies and Plains	6545 (2.4)
Northwest	10 663 (3.9)
Ohio Valley	45 801 (17.0)
South	44 144 (16.3)
Southeast	62 886 (23.3)
Southwest	7372 (2.7)
Upper Midwest	23 827 (8.8)
West	15 235 (5.6)
Sex	
Women	81 940 (30.3)
Men	188 183 (69.7)
Subtype	
STEMI	93 401 (34.6)
NSTEMI	150 662 (55.8)
Others	26 060 (9.6)
Age (y)	
18–54	119 150 (44.1)
55–64	150 973 (55.9)

NSTEMI indicates non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

(17.0%), and South (16.3%) regions. It should be noted that these proportions reflect the sample composition rather than the actual incidence distribution of AMI, which is influenced by the underlying distribution of policyholders across regions in our dataset. More than two-thirds (69.7%) of AMI events were observed in men. Approximately 56% were NSTEMI, and about one-third were STEMI. The younger group aged 18 to 54 years accounted for 44.1% and individuals aged 55 to 64 years accounted for 55.9% of all AMIs.

In general, the ozone concentration tended to be higher when the temperature was higher, and most of the daily maximum 8-hour ozone concentration levels ranged from 20 ppb to 60 ppb in the contiguous United States (2016–2020) (Figure 1). Annual mean ozone concentrations were higher in the western part of the contiguous United States compared with the eastern part.

Associations Between Joint Exposure to Ozone and Temperature and AMI

In the pooled exposure-response surface for the entire population, with the reference of joint exposure to ozone at 35 ppb and temperature at the 1st percentile, we observed a significantly increased odds of AMI at most combinations of ozone concentrations and ambient temperatures at lag 0 day, especially when temperature was above the median (Figure 2).

We observed an OR of 1.14 (95% CI, 1.03–1.27) at the ozone level of 35 ppb and the 50th percentile of temperature (Table S2). Keeping the ozone level at 35 ppb, when the temperature increased to the 80th or the 95th percentiles, the OR increased to 1.28 (95% CI, 1.15–1.44) and 1.30 (95% CI, 1.13–1.50), respectively. Keeping the temperature at the 50th percentile, when the ozone level increased to 50 or 60 ppb, the OR was 1.15 (95% CI, 1.04–1.28) and 1.15 (95% CI, 1.02–1.30), respectively. The joint exposure to ozone of 60 ppb and temperature at the 95th percentile resulted in an OR of 1.33 (95% CI, 1.16–1.51).

The associations between joint exposure to ozone and ambient temperature and the occurrence of AMI generally diminished to the null after 1 or 2 days, mainly depending on the temperature (Figure 3; Figure S2). When temperature was above the median (generally regardless of the ozone level), we still observed significantly increased AMI odds at lag 0–1 days, although the magnitude of the associations was weaker than those at lag 0 day.

Effect Modification by Sex, AMI Subtype, and Age

Both women and men had an increased odds of AMI occurrence when ozone concentration and temperature were high at lag 0 day (Figure 4). Compared with the joint exposure of ozone at 35 ppb and temperature at the 1st percentile, exposure to ozone at 60 ppb and temperature at the 95th percentile had an OR of 1.29 (95% CI, 1.03–1.61) among women and 1.35 (95% CI, 1.16–1.57) among men (Table S3). However, only men had significantly increased odds when either temperature or ozone was relatively lower: (1) when temperature was mild (between the 25th and 50th percentiles) and ozone was relatively high (above ~40 ppb) or (2) when temperature was relatively high (above the median) and ozone was low (below ~30 ppb). Men had an OR of 1.17 (95% CI, 1.03–1.34; women: 1.13 [95% CI, 0.95–1.34]) with temperature at the 50th percentile and ozone at 50 ppb, and an OR of 1.34 (95% CI, 1.17–1.53; women: 1.23 [95% CI, 0.99–1.53]) with temperature at the 80th percentile and ozone at 30 ppb.

In the stratified analysis by AMI subtype, the pattern of associations with NSTEMI was similar to that from the analysis of AMI overall. We found increased odds associated with mild to moderate heat only for NSTEMI, but observed increased odds for both STEMI and NSTEMI when temperature was higher (approximately >75th percentile) (Figure 5; Figure S3). As for the stratified analysis by age, individuals in both age groups experienced an increased odds of AMI when temperature was above

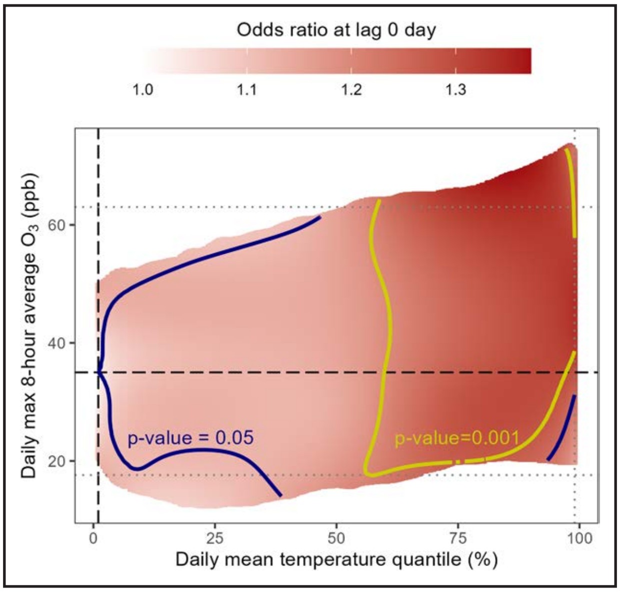

Figure 2. The exposure-response surface regarding joint exposure to ozone and ambient temperature and incident acute myocardial infarction at lag 0 day, with joint exposure to ozone at 35 ppb and temperature at the 1st percentile as the reference.

The blue solid contour indicates P=0.05. Yellow solid contour indicates P=0.001 (which was not interpreted as a statistical significance threshold) to help identify the area where P<0.05.

~60th percentile, regardless of the ozone concentrations. However, when the temperature was lower than the median, the younger group tended to have increased odds when the ozone concentration was high, whereas the older group had significantly increased AMI odds when ozone was approximately <40 ppb.

We observed statistically significant heterogeneity in the pattern of the associations in the stratified analysis by sex (P value=0.016; Table S4) but not in the stratified analysis by AMI subtype or age.

Sensitivity Analyses

The exposure-response surface patterns and magnitudes in the sensitivity analyses were consistent with those observed in the primary analyses (Figure S4).

DISCUSSION

In this large, nationwide study, we observed significant associations between joint exposure to ozone and higher ambient temperature and AMI incidence among adults aged 18 to 64 years, even when there was moderate ozone pollution or moderate heat. The exposure-response patterns differed between women and men, with the latter being vulnerable when exposure to either ozone or heat is relatively mild. There were also indications of vulnerability for NSTEMI and among individuals aged 55 to 64 years.

This study advanced the understanding of AMI risk associated with joint exposures to temperature and ozone beyond the previous studies on respective independent associations. On the independent role of temperature, 2 meta-analysis studies and a review found increased AMI or acute coronary syndrome risk associated with low temperature, high temperature, or both.[21–23] However, it should be noted that considerable heterogeneity existed across the original studies in both meta-analyses, and there was no in-depth evaluation of the potential effect modification by demographic characteristics or AMI subtypes. In recent years, more original epidemiologic studies have been conducted on temperature-AMI association, but the findings are inconclusive: cold-only associations,[24,25] heat-only associations,[26] or both.[12,27] In general, the heat association appears to be immediate, whereas the time window for cold exposures may range from hours to weeks. Furthermore, most studies supported vulnerability among the older population,[24] whereas some found no heterogeneity[28,29] or heat associations only in the younger group.[12] Evidence related to the vulnerability by sex and AMI subtype is still insufficient and inconsistent, and existing research has primarily focused on the older population, which underscores the novelty of our study but makes it challenging to interpret our findings in the context of the current literature.

As for the potential role of ozone exposure, a meta-analysis in 2012 based on 19 original studies found no association between ozone and AMI risk, with notable heterogeneity across studies.[30] Recent original research still reported heterogeneous associations with increased ozone concentrations, showing null,[31,32] protective,[25] harmful,[33] or "U-shaped" associations,[34] with many studies simply assuming a linear relationship between ozone exposure and AMI risk and not evaluating potential nonlinearity. The only consistent finding is that the time window for ozone is generally short, often within days. Subgroup analyses by demographic characteristics and AMI subtypes remain insufficient for a reliable comparison.

Existing epidemiologic evidence is scarce on the joint exposure to ozone and ambient temperature regarding AMI. We identified 3 relevant studies. A study based in a Chinese city found no statistically significant interaction between apparent temperature and ozone but did not report the association magnitudes with joint exposure.[35] A Singaporean study clustered days based on environmental parameters and found that days with high temperature and high pollution levels had higher AMI incidence, whereas a composite pollution index combining multiple pollutants (ie, particulate matter [PM_{10}], $PM_{2.5}$, sulfur dioxide, nitrogen dioxide, ozone, and carbon monoxide) was used instead of ozone concentration alone.[36] In a German study, researchers evaluated the myocardial infarction–ozone relationship conditional on the weather types combining multiple meteorological factors instead

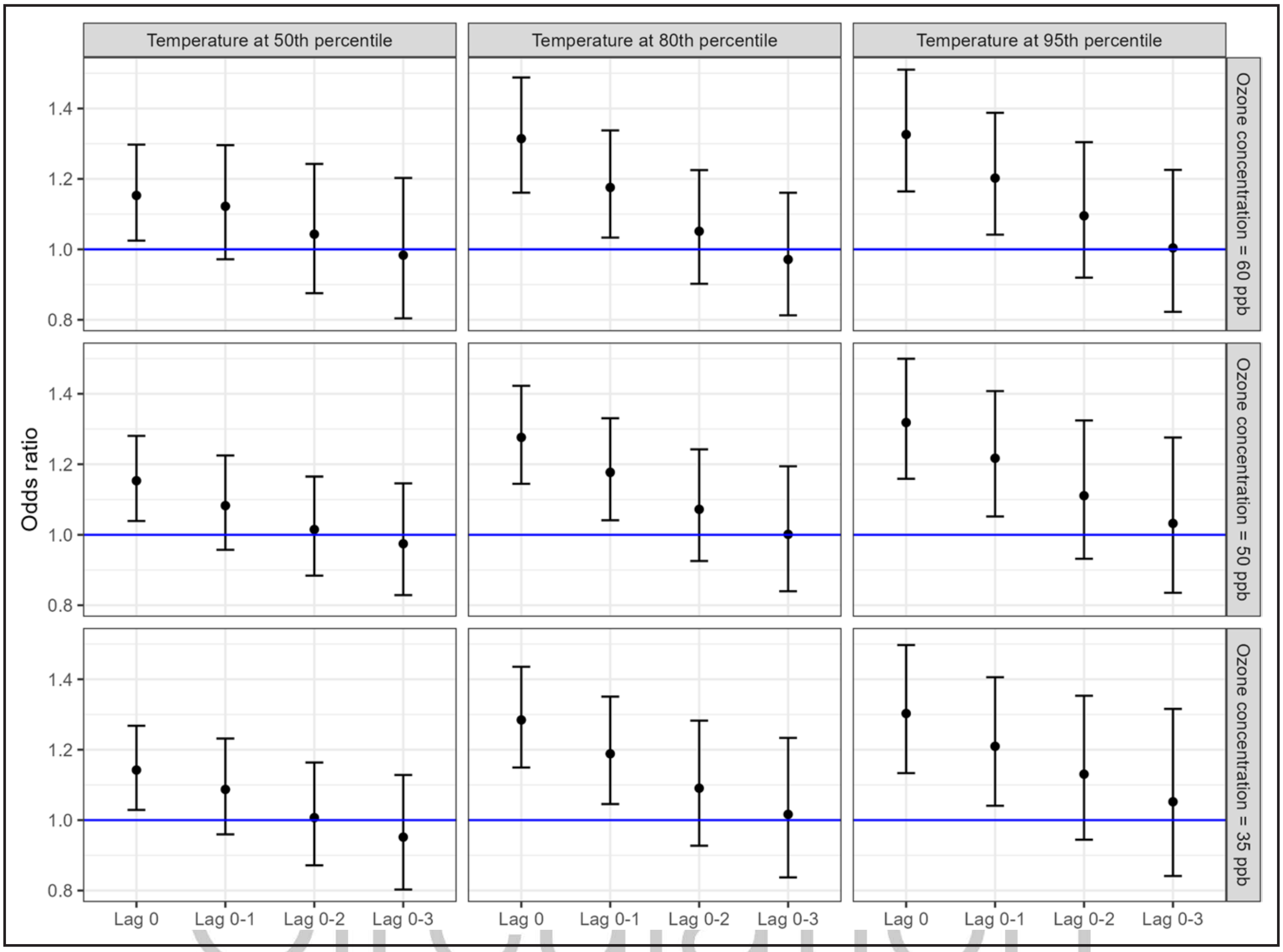

Figure 3. The exposure-response association estimates (with 95% CI) from lag 0 to lag 0–3 days regarding joint exposure to ozone and ambient temperature and risk of incident acute myocardial infarction, with joint exposure to ozone at 35 ppb and temperature at the 1st percentile as the reference.

of ambient temperature alone.[37] It should be noted that the latter 2 studies did not specifically investigate joint ozone-temperature exposure in relation to AMI risk. Existing evidence remains insufficient for meaningful comparison, and further studies across regions with different weather and air pollution conditions are warranted, given the complex atmospheric chemistry of ozone under diverse environmental conditions.

Biologically, heat exposure could increase the cardiac burden, heart rate disturbances, platelet activation, and endothelial injury.[23,38,39] As for ozone exposure, the related myocardial damage may be mediated by autonomic modulation, oxidative stress, inflammation, endothelial cell function, and metabolic homeostasis.[40–42] On the other hand, several underlying mechanisms have been proposed for the potential interaction between ozone and heat exposure, including pathways through inflammation, hypertension, increased blood lipid, and formation of microthrombus.[7] Furthermore, low levels of ozone exposure could induce subclinical adverse effects that may be only detectable with joint exposure to another stressor.[40]

Strengths and Implications

This study leveraged comprehensive and contemporary data from a large nationwide provider of commercial insurance in the United States, encompassing a broad range of geographic areas. The unique resources enabled us to evaluate a large number of younger adults, who are underrepresented and understudied in existing environmental epidemiologic research on AMI. Furthermore, among younger individuals, the prevalence of traditional cardiovascular risk factors like hypertension, diabetes, and obesity is increasing,[43,44] alongside emerging nontraditional risk factors such as HIV, recreational substance uses, and chronic lead toxicity.[45–47] These will induce a foreseeable increasing burden of AMI among younger adults. This study facilitates health policies and strategies to reduce the morbidity and mortality burden of AMI among younger adults. We also encourage future research on other cardiovascular outcomes, including out-of-hospital cardiac arrest, sudden cardiac death, and stroke, for which joint environmental exposures may hold equal relevance. Moreover, the large sample size

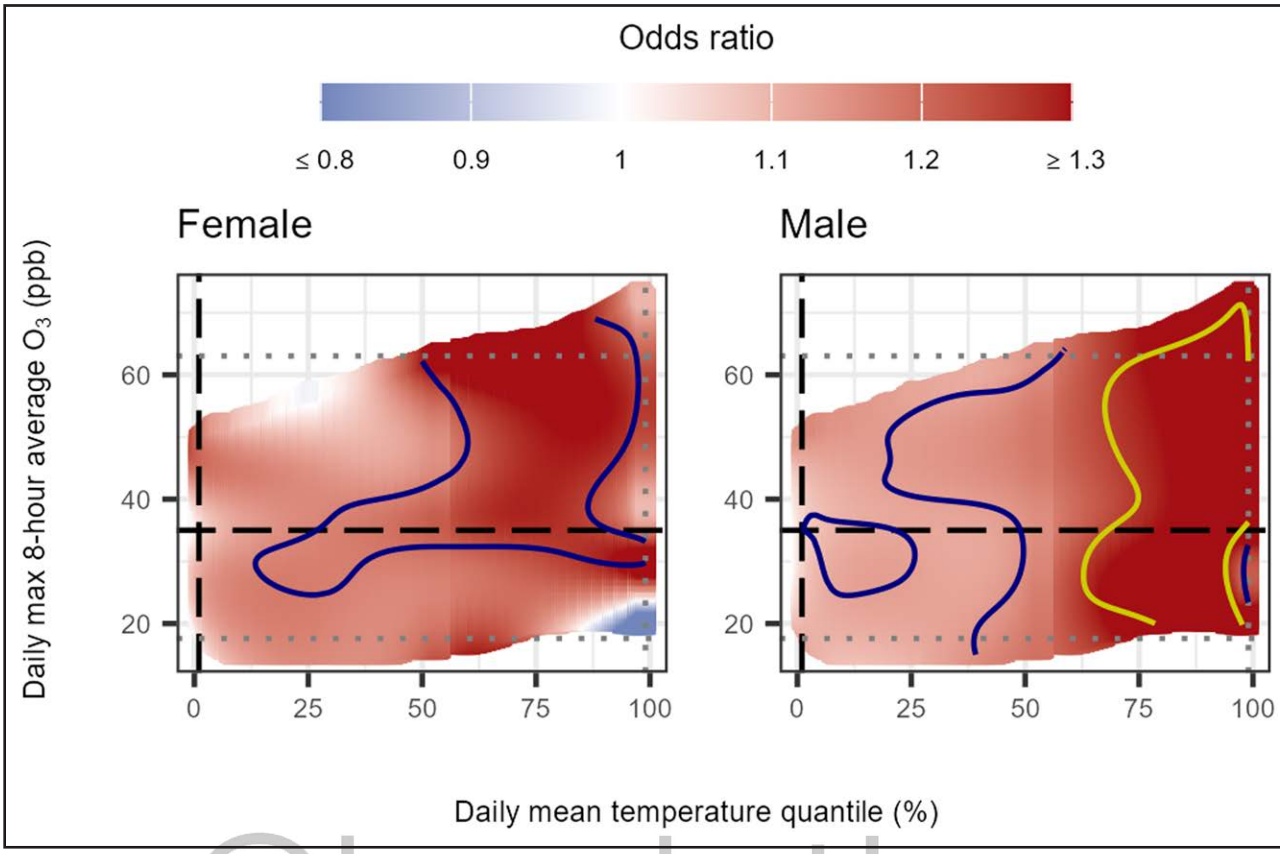

Figure 4. The exposure-response surface by sex (women and men) regarding joint exposure to ozone and ambient temperature and risk of incident acute myocardial infarction at lag 0 day, with joint exposure to ozone at 35 ppb and temperature at the 1st percentile as the reference.
The blue solid contour indicates P=0.05. Yellow solid contour indicates P=0.001 (which was not interpreted as a statistical significance threshold) to help identify the area where P<0.05.

also allowed us to conduct stratified analyses by sex, AMI subtype, and age, which has the potential to contribute to the body of evidence in support of environmental health policies and regulations at the federal, state, and tribal levels to generally protect human health from ozone, especially those individuals most at risk. The current data provide insight into specific risks incurred by joint exposures to increasing temperatures and ozone concentration even when the ozone concentrations are below the current ozone National Ambient Air Quality Standards. Such knowledge when developed into guidance for public health practitioners and clinicians could motivate behavior to reduce exposure and risk among the most at risk.

Furthermore, compared with existing studies on independent associations with ambient ozone or temperature, this study tried to avoid neglecting or oversimplifying the interactive relationships between ozone and temperature. When evaluating independent associations with ozone in previous work, temperature is usually considered as a confounder and adjusted in models, which, however, took no consideration of joint impacts and may end up in coarse or even distorted estimation of the health impacts of ozone.

In addition, previous studies on joint exposure also had the problem of simplification of exposures as categorical or linear variables, which overlooked the complexity of response surfaces of joint exposures. In contrast, we modeled both exposures as continuous, nonlinear forms to ensure the flexibility of analysis, which could better reflect the complex associations in the real world. Moreover, by using this novel approach, we were able to show the exposure-response relationship throughout the entire range of both exposures, instead of focusing only on the extreme levels. Although extreme levels of pollution and temperature could exert higher risk for health outcomes, they may induce a smaller health burden at the population level because they are less frequent, compared with exposures to moderate pollutions and moderate temperatures. Our findings further underlined the necessity of health strategies and actions against moderately nonoptimal exposures, in addition to extreme exposures.

Study Limitations

All participants in this study were insured by a private insurance company, so our findings may not be

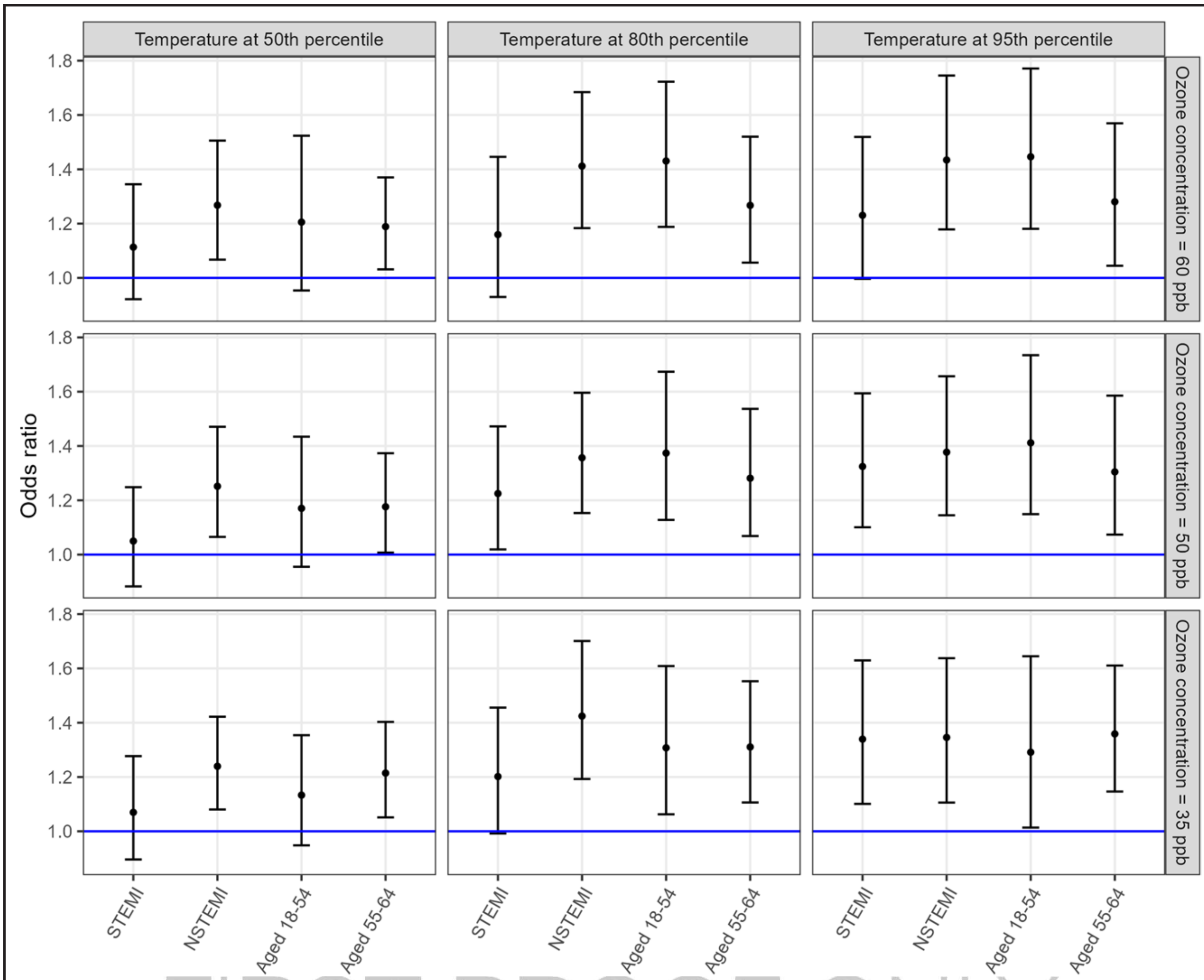

Figure 5. The exposure-response association estimates (with 95% CI) by acute myocardial infarction type (ST-segment–elevation myocardial infarction [STEMI] and non–ST-segment–elevation myocardial infarction [NSTEMI]) and age (18–54 years and 55–64 years) regarding joint exposure to ozone and ambient temperature and risk of incident acute myocardial infarction at lag 0 day, with joint exposure to ozone at 35 ppb and temperature at the 1st percentile as the reference.

generalizable to individuals using public insurance (eg, Medicaid population who may have higher health risks) or those without any insurance (who may have higher risks possibly because of education attainment, employment, citizenship status, etc.). These populations underrepresented in this study are worth further evaluation. Moreover, although AMI can develop and progress within hours, we only know the date and do not have access to the exact time of day when AMI occurred. In addition, because this study was based on claims, we do not have information on other factors that may be related to AMI risk, such as diet, physical activity, and alcohol intake. Furthermore, with two-thirds of the study population lacking race/ethnicity data, we did not conduct stratified analyses by race/ethnicity. Last, we used zip code–level exposure assessment, which may not represent personal exposures, and we did not evaluate other criteria pollutants (eg, nitrogen oxides), which may play important roles in real-world joint exposures and AMI risk.

CONCLUSIONS

This study investigated the association between short-term joint exposure to ozone and ambient temperature and the occurrence of AMI among younger adults aged 18 to 64 years in the contiguous United States during the period 2016 to 2020. Joint exposure to ozone and higher temperature was associated with an increased risk of AMI, even when 1 of the exposures was moderate. These findings underscore the health impact of joint exposure to ozone and ambient temperature among a previously understudied population (ie, younger adults) regarding AMI, and call for health policies and strategies to reduce joint exposure to ozone and heat, not only extreme exposures, but also exposures at the moderate levels.

ARTICLE INFORMATION

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Supplemental Material

Figures S1–S4
Tables S1–S4

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