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Associations between short-term exposure to $PM_{2.5}$ and cardiomyocyte injury in myocardial infarction survivors in North Carolina

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ABSTRACT

Objective Short-term ambient fine particulate matter ($PM_{2.5}$) is associated with adverse cardiovascular events including myocardial infarction (MI). However, few studies have examined associations between $PM_{2.5}$ and subclinical cardiomyocyte damage outside of overt cardiovascular events. Here we evaluate the impact of daily $PM_{2.5}$ on cardiac troponin I, a cardiomyocyte specific biomarker of cellular damage.

Methods We conducted a retrospective cohort study of 2924 patients identified using electronic health records from the University of North Carolina Healthcare System who had a recorded MI between 2004 and 2016. Troponin I measurements were available from 2014 to 2016, and were required to be at least 1 week away from a clinically diagnosed MI. Daily ambient $PM_{2.5}$ concentrations were estimated at 1 km resolution and assigned to patient residence. Associations between log-transformed troponin I and daily $PM_{2.5}$ were evaluated using distributed lag linear mixed effects models adjusted for patient demographics, socioeconomic status and meteorology.

Results A 10 µg/m^3 elevation in $PM_{2.5}$ 3 days before troponin I measurement was associated with 0.06 ng/mL higher troponin I (95% CI=0.004 to 0.12). In stratified models, this association was strongest in patients that were men, white and living in less urban areas. Similar associations were observed when using 2-day rolling averages and were consistently strongest when using the average exposure over the 5 days prior to troponin I measurement.

Conclusions Daily elevations in $PM_{2.5}$ were associated with damage to cardiomyocytes, outside of the occurrence of an MI. Poor air quality may cause persistent damage to the cardiovascular system leading to increased risk of cardiovascular disease and adverse cardiovascular events.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Exposure to particulate matter ($PM_{2.5}$) is associated with cardiovascular-related mortality and increased risk of myocardial infarction (MI).
⇒ Limited evidence for elevations of cardiac-specific troponins (a highly sensitive indicator of cardiac tissue damage) in relation to short-term air pollution exposure.
⇒ Few studies have used cardiac specific troponins to assess air pollution associated impacts, particularly outside of a triggered MI.

WHAT THIS STUDY ADDS

⇒ Evaluation of the association between $PM_{2.5}$ exposure and cardiac-specific troponins in a large cohort study.
⇒ Understanding of age, race and sex-specific associations which have yet to be evaluated.
⇒ Validation that associations between $PM_{2.5}$ and cardiac-specific troponins are not solely driven by the occurrence of a clinically diagnosed MI.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Our findings indicate that poor air quality may cause continual damage to the cardiovascular system leading to accelerated cardiovascular disease and increase risk of future adverse events.
⇒ Clinicians should consider communicating environmental health risks to patients who might be particularly sensitive to poor air quality, including those with a history of MI.

INTRODUCTION

Air pollution, particularly elevated concentrations of particulate matter <2.5 µm in diameter ($PM_{2.5}$), is responsible for nearly 4 million deaths annually, of which over 2 million are cardiovascular related.[1] $PM_{2.5}$ has been repeatedly associated with cardiovascular events and mortality and is proposed to have a causal effect on the development of cardiovascular disease.[2–4] Observations from animal and controlled human exposure studies have explored mechanisms through which short-term $PM_{2.5}$ exposures prompt both acute cardiovascular events and disease progression by examining subclinical biochemical and physiological changes in response to PM exposure.[5] Understanding factors that

influence disease progression is important and one-way to assess progression is to use a proxy measure of cardiovascular damage outside of acute events, troponin.

Cardiac-specific troponins (troponin I and troponin T) are regulatory proteins that are released when damage to cardiac muscle cells occur. In normal conditions they occur in very small concentrations in the blood; however, insults that damage cardiomyocytes can rapidly increase the concentration of troponins in the blood.[6 7] Elevation of troponin T can also be associated with damage to other tissues such as renal tissue. However, troponin I is only found in cardiomyocytes and is considered to be a highly specific biomarker for cardiac tissue damage.[8 9] Elevated levels of these proteins can be used to detect the occurrence of a myocardial infarction (MI)[10] and may also detect damage to the myocardium without meeting the clinical criteria of an MI.[11] Despite the evidence that air pollution may cause continual damage to cardiac tissue, only a few studies have used cardiac specific troponins to investigate the damage that air pollution may cause outside of an MI. In a study of patients who underwent a cardiac catheterisation, short-term $PM_{2.5}$ exposure was associated with significant increases in troponin T. Similar results for cardiac troponin I have been observed in both an observational study of healthy, young adults[12] as well as a controlled exposure study of diesel exhaust particulates.[13]

Here we examine the association between short-term exposure to $PM_{2.5}$ and the cardiac-specific troponin, troponin I, in a large cohort of MI survivors. We use a repeated measures analysis to estimate the immediate and delayed association between $PM_{2.5}$ and troponin I. A novel aspect of this study is that it uses electronic health records to exclude time periods before and after the occurrence of an MI, in order to specifically examine effects outside of the occurrence of an MI, which will provide evidence on cardiac tissue damage from $PM_{2.5}$ distinct from its known association with acute MI. Observations from this study should provide additional information on cardiovascular risks associated with short-term air pollution exposure.

METHODS

Cohort and health outcome description

The participants in this study came from the Environmental Protection Agency Clinical and Archived records Research for Environmental Studies (EPA CARES) resource which has been previously described.[14 15] EPA CARES is a collection of electronic health records from the University of North Carolina Healthcare System (UNCHCS), collected via a series of queries to extract patient data sets based on specific characteristics. These electronic health records are then cleaned and merged with environmental data to power a variety of environmental health studies using the detailed clinical phenotyping and longitudinal follow-up from electronic health records. Previous analyses of EPA CARES focused on patients with heart failure; however, this analysis examined a patient cohort of individuals with a prior MI. Patients were selected randomly from all patients who had a recorded MI in UNCHCS from 1 July 2004 until 31 December 2016, and then further restricted to those with troponin data available. As troponin data only became available in 2014 this restricted our patient cohort to individuals observed between 2014 and 2016. Figure 1 gives a flowchart of the cohort selection.

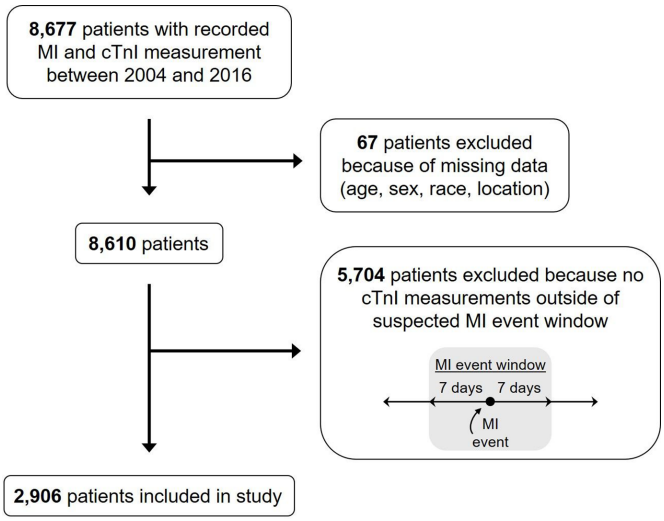

Figure 1 Inclusion and exclusion criteria used to select study population. cTnI, cardiac troponin I; MI, myocardial infarction.

Daily $PM_{2.5}$ exposure was assessed using an ensemble model that included aerosol optical depth measurements from satellite monitoring, land use regression and ground based $PM_{2.5}$ monitors. $PM_{2.5}$ was estimated at 1 km×1 km resolution for the entire continental USA. This model had high agreement with ground-based monitoring with an R^2 of 0.89 for the Mid-Atlantic region where this study takes place.[16] We linked individuals with a prior MI to $PM_{2.5}$ exposure based on their residential address at the time of troponin I measurement. Residential address was determined according to hospital records which were updated during patient interactions (eg, hospital visits).

The troponin I measurements used in this analysis came from the patient's electronic health records. Troponin I data were only available from 2014 to 2016 were used, which is after the introduction of high sensitivity troponin measurements into hospital systems. However, since the exact method of measurement was not attached to patient records some measurements may have been taken under older troponin assays, though we expect this to be minimal. Though troponin T and troponin I are both used for diagnoses of MI and may be used as indicators of cardiomyocyte damage, troponin I was chosen as the primary endpoint over other forms since only troponin I is inherently specific for cardiac tissue, with high specificity for myocardial injury.[17 18] Additionally, the use of a single biomarker simplified the data harmonisation and helped to prevent potential cross-assay biases.

This analysis focused on troponin measurements taken outside the period immediately before or after a clinically diagnosed acute MI. The primary exclusion period was defined by excluding troponin I measurements that occurred 7 days before or after a clinically diagnosed MI event, which was determined using International Classification os Disease, tenth revision (ICD-10) codes (I21.*, I22.*). MI events including MI or ischaemic damage cause large increases in troponin I concentrations that can remain elevated for days. The half life of troponin I is approximately 2 hours[19] and blood concentrations typically return to baseline after 4–10 days.[20] Assay specific information such as the manufacturer, assay kit and associated limit of detection for troponin I measurements was not recorded in the electronic health records. The minimum non-zero value observed within our data set was 0.01 ng/mL which is at or below most reference ranges for high sensitivity troponin I assays.[21] Typical concentrations of troponin I are often and the limit of detection can serve as a cut-off for acute MI.[21] For this analysis we retained all troponin values so as to not bias analyses by excluding healthy individuals with undetectable troponin I.

Statistical analysis

The association between daily $PM_{2.5}$ and troponin I was examined using immediate (lag 0) and delayed (lags 1–4) $PM_{2.5}$ effects assessed via unconstrained distributed lag models with a linear lag-response. As the troponin I distribution was skewed values were log-transformed prior to analyses. As undetectable troponin was reported as a value of 0 we added 0.001 (1/10 of the minimum observed value) to all values to avoid losing healthy individuals and biasing towards a less healthy population. Distributed lags for $PM_{2.5}$ as well as time-varying meteorological variables allowed us to evaluate immediate (same day) and delayed effects. We also examined the 5-day average (average $PM_{2.5}$ on lags 0–4) to determine if average air quality over the preceding days is associated with troponin I. Models were adjusted for sex, race, age at troponin I measurement, temperature, relative humidity and census block group-level socioeconomic (SES) variables and included a random intercept for patient to account for repeated measurements. SES variables were based on the 2010 census and included median income, median house value, percentage of individuals on public assistance, urbanicity and percentage of households below the federal poverty line. Temperature and relative humidity were included as natural splines with 3 df.

In secondary analyses, we stratified models to assess potential effect modification by sex, race, age at first incidence of MI and urbanicity as all of these might be expected to modify the relationship between air quality and health outcomes. Greater associations have been observed in older and more rural patients in similar cohorts in this study region. Age at first incidence of MI was assessed for two age groups, <65 years and ≥65 years. Urbanicity was evaluated for patients residing in fully urban (100% urban) and less than fully urban (<100% urban) areas.

Sensitivity analyses were performed to assess the robustness of $PM_{2.5}$ estimates with respect to the time window around MI events excluded from analyses, lag consideration, dose-response relationship, adjustment for a time trend and troponin I values above and below the median patient troponin I level. Models using rolling averages in 2-day intervals, and the average of the 5-day period before troponin I measurement were used to evaluate cumulative effects. Sensitivity to non-linear associations with $PM_{2.5}$ were also examined by substituting the linear term for $PM_{2.5}$ in the main model with a natural cubic spline for $PM_{2.5}$.

All analyses were performed using R (V.4.0.4).[22] Results are presented as the per cent increase in troponin I per 1 $\mu g/m^3$ increase in $PM_{2.5}$ and the associated 95% CI.

RESULTS

Characterisation of clinical cohort, clinical events and daily ambient $PM_{2.5}$

As described in the Methods the study cohort was comprised of individuals who had a prior MI. There were 8677 individuals with a prior MI who had at least one recorded troponin I measurement. Mean troponin I across all measurements was 7.41 ng/mL. As this study was specifically interested in $PM_{2.5}$ associations occurring outside of an MI, to construct the study cohort we excluded troponin I measurements in the week prior to and after a clinically diagnosed MI, leaving 2906 patients with 20 709 troponin I measurements (on average 7.1 measurements per patient). Mean troponin I in the final study cohort was 1.94 ng/mL for all measurements, reflecting the exclusion of elevated troponin I occurring during a clinically diagnosed acute MI. The average age was 69.4 years, 55.9% were men, 67.5% were white and 46.0% resided in a fully urban area (table 1). The average daily $PM_{2.5}$ was 9.15 $\mu g/m^3$ (table 2).

Associations between $PM_{2.5}$ and troponin I

We observed evidence of an association between prior ambient $PM_{2.5}$ and elevated troponin I. In distributed lag models with a linear lag-response, a 1 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with an increase in troponin I at lag 3 (0.61%; 95% CI=0.05% to 1.19%). The associations with 1 was similar in magnitude but to lag 3, and no evidence of association was observed for the other lags. Associations with the 5-day average were stronger than associations with individual lags (figure 2, online supplemental table S2).

The association between troponin I and $PM_{2.5}$ at lag 3 was particularly elevated among men (0.90% increase; 95% CI=0.04% to 1.77%) and patients who resided in less than fully urban areas (0.90% increase; 95% CI=0.03% to 1.78%). However, these differences were not seen across all lags. (figure 3, online supplemental table S1). For the 5-day average $PM_{2.5}$ associations were strongest

Table 1 Descriptive statistics of the study cohort

	Patients with troponin I within criteria
Total study participants	2906
Age (years), mean (SD)	69.4 (14.3)
Troponin I (ng/mL)	1.95 (12.19)
Troponin measurements (#)	20709
Race	
White	1961 (67.5)
Black	799 (27.5)
Other	146 (5.0)
Sex	
Male	1282 (44.1)
Female	1624 (55.9)
Urbanicity	
Urban	1337 (46.0)
Rural	1569 (54.0)
Comorbidities	
Type 2 diabetes	1432 (49.3)
Ischaemic heart disease	2045 (70.4)
Chronic obstructive pulmonary disease	894 (30.8)
Chronic kidney disease	1246 (42.9)
Emphysema	301 (10.4)
Hypertension	2425 (83.4)
Hyperlipedaemia	2210 (76.0)
Peripheral artery disease	751 (25.8)

among men, white study participants, those with an age a first MI <65 years, and those whose average troponin I measurements were above the median for the study cohort (figure 3, online supplemental table S2). Individuals with underlying cardiovascular often have increased sensitivity to air pollution exposure. We examined this by stratifying based on an individual's average troponin measurement being above versus below the median of the population. As compared with individuals with below median troponin I blood concentrations, those with above median concentrations had substantially elevated associations in both the distributed lag models as well as

Table 2 Summary statistics (minimum [Min], 25th percentile, mean, standard deviation [SD], median, 75th percentile, maximum [Max]) of $PM_{2.5}$ and meteorological variables

Characteristic	Mean (SD)	Min, 25%, median, 75%, max
$PM_{2.5}$ (μg/m^3)	9.15 (4.9)	0.00, 6.17, 8.38, 11.2, 93.4
Temperature (C)	16.1 (8.6)	−11.4, 9.00, 17.2, 23.6, 32.3
Relative humidity (%)	61.4 (26.3)	0.00, 53.8, 68.6, 78.8, 100

$PM_{2.5}$, particulate matter .

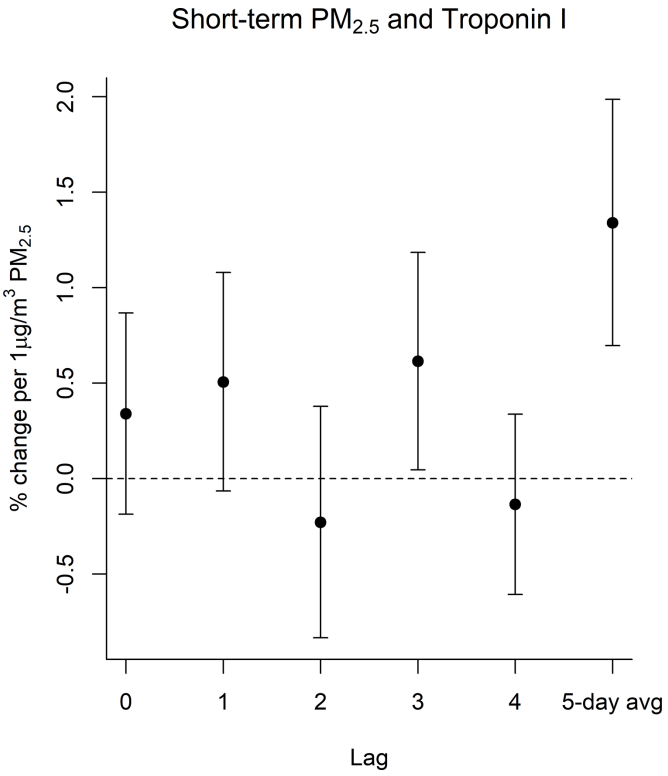

Figure 2 Associations between $PM_{2.5}$ and troponin I. Associations for lags 0–4 were estimated using distributed lag models with a linear lag-response. Associations for the 5-day average $PM_{2.5}$ (5-day average) were estimated using a linear mixed effects model which was outside the distributed lag framework as there was only one 'lag' for that model. All models included a random intercept for individual and confounder adjustment as described in the Methods. $PM_{2.5}$, particulate matter.

the 5-day average exposures (online supplemental table S1 and S2).

Sensitivity analyses were conducted to assess the strength of the observed associations under a variety of modelling scenarios. In addition to considering $PM_{2.5}$ effect as linear we also examined non-linear relationships using splines with different df. Models with non-linear considerations did not provide model improvement and had similar results (online supplemental figure S1). Additional lags improved model fit as interpreted by Akaike information criterion (AIC) and Bayesian information criterion (BIC) and supported the main observation of a delayed impact of $PM_{2.5}$ on troponin I concentrations (online supplemental table S3 and figure S2), and inclusion of a time trend did not meaningfully modify associations (online supplemental table S4). Associations also remained stable when increasing the window around a diagnosed MI from 7 to 14 and finally 30 days, and strengthened for some of the earlier lags (online supplemental table S5). When adjusting the distributed lag models for comorbidities we did not observe any change in the associations (online supplemental figure S3). When examining the association using 2-day rolling average $PM_{2.5}$, we observed associations at lag 0–1 (1.15% increase; 95% CI=0.2% to

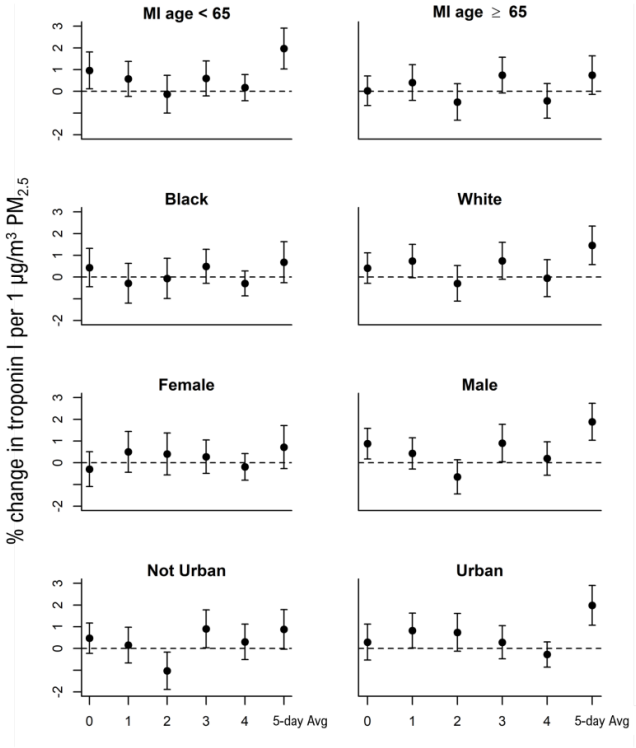

Figure 3 Associations between $PM_{2.5}$ and troponin I stratified by demographics. Associations maintained the same confounder adjustment as described in the Methods except removing the stratifying variable from each of the stratified associations. Associations for lags 0–4 were estimated using distributed lag models with a linear lag-response. Associations for the 5-day average $PM_{2.5}$ (5-day average) were estimated using a linear mixed effects model which was outside the distributed lag framework as there was only on 'lag' for that model. All models included a random intercept for individual and confounder adjustment as described in the Methods. $PM_{2.5}$, particulate matter.

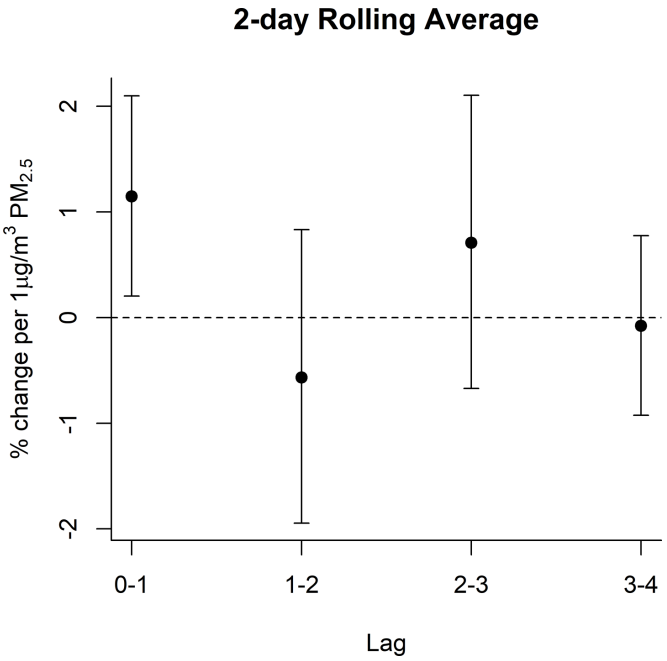

Figure 4 A 2-day rolling average associations between $PM_{2.5}$ and troponin I. A 2-day rolling average models used the same adjustment approach as the primary distributed lag models including a linear lag-response, random intercept for individual and identical confounder adjustment as described in the Methods. $PM_{2.5}$, particulate matter.

2.1%) (figure 4, online supplemental table S6). Two-day rolling average associations were strongest among men, individuals with a younger (<65 years) age a first MI, and those not residing in fully urban areas (online supplemental table S6). In models that measured the association on individual lag days, unadjusted for autocorrelation between days, associations mirrored what was observed in the distributed lag models with an even stronger association. Associations were seen for lags 1–4 with the strongest association (by magnitude) on lag 3—though only marginally so with substantially overlapping CIs for lags 1, 2 and 4 (online supplemental figure S4 and table S7).

DISCUSSION

Our analyses demonstrate that short-term exposure to air pollution is associated with increases in troponin I in MI survivors. This association was most evident among men, white participants and those who were <65 years old when they had their first recorded MI. These results were robust to specification of the exposure period, individual lags versus rolling averages and are in line with previous studies as well as the wider body of scientific knowledge linking particulate air pollution and cardiovascular health. Troponin I is highly sensitive indicators of cardiac tissue damage. While there has been substantial effort placed on quantifying the cardiovascular risks faced by exposure to elevated air pollution, we still understand little about potential associations between poor air quality and continual damage to cardiomyoctyes outside of the immediate acute MI time period.

There have been a few previous studies of cardiac troponins and air pollution. In a study of 2732 participants, all of whom had a prior cardiac catheterisation, researchers observed that an IQR increase (7.6 µg/m^3) in $PM_{2.5}$ was associated with a 7.7% increase in circulating concentrations of cardiac troponin T on the day prior to measurement. This was similar to the associations observed on lag 3 in distributed lag non-linear models in our study (figure 2, online supplemental table S1) when scaled to the same $PM_{2.5}$ exposure increment. For the model without distributed lags (online supplemental table S7 and figure S4), which closely matched their model, associations were even more similar for the day prior exposure. This indicates high congruence across these studies and also highlights that delayed effects of $PM_{2.5}$ on troponin may become most apparent in models that account for multiple lagged effects like distributed lag models. The Zhang, *et al* study also observed that associations were slightly stronger among men and that

associations were substantially stronger among less urban participants.[23]

In a smaller study of 73 non-smoking, younger (mean age 23.0) healthy adults, average $PM_{2.5}$ over lag days 0–4 was associated with elevated troponin I.[24] These associations between troponin I and $PM_{2.5}$ closely match our own despite the cohort being significantly younger and having a lower mean troponin I measurement (1.0 ng/mL vs 1.9 ng/mL) likely due to our cohort being composed survivors of MI. Overall, these previous studies are consistent with our own observations that daily variation in $PM_{2.5}$ is associated with increased circulating cardiac troponins indicating cardiac muscle tissue damage. Our study focused on cardiac troponin I as it is only released from cardiac tissue. Cardiac troponin T is found in non-cardiac muscle, though is still highly indicative of cardiac tissue damage. While the literature suggests that both cardiac troponins are elevated post-$PM_{2.5}$ exposure, a systematic assessment of these troponins to compare associations and better elucidate potential mechanisms would enhance our understanding of the association between $PM_{2.5}$ exposure and troponin release.

Air quality associations with troponin that exclude periods where elevated troponins may be driven by a clinically diagnosed MI are of particular interest because these associations would indicate continued damage to cardiac tissue mediated in part by poor air quality. In the study of patients who underwent a cardiac catheterisation, measurements that occurred up to 2 weeks following an MI were excluded.[23] In the study of healthy Chinese adults, the young age and close monitoring make the occurrence of an unobserved MI unlikely.[24] In the current study, we used electronic health records to specifically exclude measurements that occurred 1 week before or 1 week after the occurrence of an MI. While the use of ICD-10 codes to diagnose an MI is not perfect, it is a widely accepted standard and it is unlikely that an MI occurring during a period of troponin measurements would not be noted in the medical record. MI events not captured by ICD-10 codes would mostly likely also not be accompanied by troponin measurements and therefore still not present in our study. Thus, our study provides the latest, strongest evidence that the cardiovascular risks from short-term elevations in air pollution extend beyond the triggering event causing an MI and also includes continued cardiac tissue damage which may weaken the myocardium increasing risks of future cardiovascular events, such as heart failure and arrhythmia and potentially increasing sensitivity to future cardiovascular ischaemic events. Previous studies were not able to examine associations stratified by levels of circulating troponins. Individuals with elevated circulating troponins may have more underlying cardiac tissue damage and thus be more sensitive to the environment. We observed this in our study, adding to the literature suggesting that cardiovascular damage (or disease) is a sensitivity factor for $PM_{2.5}$-related health effects.

There are multiple mechanisms that may account for the observed associations. As mentioned earlier, air pollution induced dysregulation of the autonomic nervous system may be a mechanism underlying the observed associations. Imbalances within the autonomic nervous system, particularly increased sympathetic activity, can cause myocardial tissue damage.[25–27] In a controlled exposure study of healthy volunteers, authors observed that short-term exposure to diesel exhaust directly increased the activity of the sympathetic nervous system.[13] Another mechanism may be increased oxidative stress and inflammation which has been proposed as one of the central hallmarks of exposure to environmental pollutants.[28] Oxidative stress and inflammation are known consequences of $PM_{2.5}$ exposure.[29] Additionally, both of these outcomes are linked with myocardium damage[30] and troponin release.[26 31 32] In our associations we did not observe evidence of an immediate (lag 0 or lag 1) association between $PM_{2.5}$ and cardiac troponins. Thus, potential mechanisms linking $PM_{2.5}$ and troponin release should be able to account for delayed effects. Inflammation and oxidative stress can rise and remain elevated after $PM_{2.5}$ exposure and thus may account for delayed effects of $PM_{2.5}$ on troponin release. However, this should not be taken to exclude other mechanisms, even though with typically more immediate action such as autonomic nervous system modulation. In vivo mechanistic studies may be required to fully elucidate mechanisms and their relative contribution to these observed associations.

There are several strengths and limitations of this study. One of the primary strengths is the sample size. The current study eclipses the samples size of previous studies of troponin and air pollution both in terms of participants as well as number of observations. Additionally, this study focuses on individuals who survived an MI, a highly relevant patient population as individuals with previous cardiovascular events or underlying cardiovascular disease may be at increased risk for cardiovascular damage and have heightened environmental sensitivities. While the use of electronic health records allowed for extensive capture of disease diagnoses and hospital administered troponin measurements, the fact that we used only a single hospital system may limit generalisability. This is a limitation faced by all the current studies on troponin and air pollution, however studies in both USA and China-based populations have yielded highly concurrent results. Still, there is a clear need for geographically diverse studies on this topic. Medications usage has been reported to modify responses to air pollution. We did not examine medication usage in this study, but did adjust for comorbidities which would correspond with use of medications, for example, use of diabetic medications among those diagnosed with diabetes. There was not alteration in the associations observed (online supplemental figure S3), however future studies should more deeply explore the role of medications. The use of electronic health records also limited the demographic information available, such as information on income. However, we still applied a robust confounder adjustment and the study design, with a random intercept

for each individual, is robust to time-invariant confounders. We did not extend this study to examine multipollutant exposures or other joint effects like temperature. However, these effects should certainly be examined in future studies with the geographical diversity to have populations exposed to multiple sources of air pollution. We used air pollution exposure models with high correlation with ground-based monitoring and high spatiotemporal resolution.[16] These models have been used in previous studies[14 15 33] including ones of troponin[23] and allowed for uniform, daily capture of exposures for the entire study period which would not have been possible with monitor or other sensor data. However, these models do not fully capture personal exposures, only ambient exposure at the residence. Ambient exposures do still have high relevance given the amount of time spent at or near the primary residence, as well as the fact that public policy and federal regulations are often based on ambient pollutant concentrations and not personal exposures or inhaled doses.

CONCLUSION

In conclusion, this study adds substantially to a growing body of literature indicating that daily variations in ambient $PM_{2.5}$ can mediate damage to cardiomyocytes potentially accelerating cardiovascular disease and increasing risks of adverse cardiovascular events. This study helps to resolve the relevant time periods of exposure as well as potential subpopulations that might have increased health risks. Future work should aid in establishing the biological mechanisms linking air pollution and myocardial tissue damage as well as establish the impact of exposure mixtures on biomarkers of tissue damage.

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Contributors LW and CW-C conceived and designed the study. WC provided subject matter expertise input into the interpretation of evidence. QD, JDS and CW-C provided access to the data for the study; AMW, CW-C and JM cleaned, annotated and structured the data; LW, GK and JM managed the analytical data. LW and GK analysed the data and LW guided the analysis. LW, GK and CW-C wrote the first draft of the manuscript. LW, GK, JM, JDS, QD, DD-S, WC and CW-C critically contributed to the manuscript and approved the final draft. LW and CW-C are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests CW-C is a paid advisor for the Clock Foundation. The Clock Foundation had no involvement in any aspect of this work. The remaining authors have nothing to disclose.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the institutional review board at the University of North Carolina at Chapel Hill (IRB# 17-0150).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data access to electronic health records from the University of North Carolina Healthcare System is through an internal data use agreement. PM2.5 data was obtained through collaboration with Drs Joel Schwartz (Harvard TH Chan School of Public Health) and Qian Di (Tsinghua University). For general data sharing inquiries, contact ward-caviness.cavin@epa.gov.

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REFERENCES

1 Cohen AJ, Brauer M, Burnett R, *et al*. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the global burden of diseases study 2015. *Lancet* 2017;389:1907–18.
2 Brook RD. Cardiovascular effects of air pollution. *Clin Sci* 2008;115:175–87.
3 Shrey K, Suchit A, Deepika D, *et al*. Air pollutants: the key stages in the pathway towards the development of cardiovascular disorders. *Environ Toxicol Pharmacol* 2011;31:1–9.
4 US EPA. *Integrated science assessment for particulate matter*. EPA/600/R-19/188. Washington, DC: U.S. Environmental Protection Agency, 2019. https://www.epa.gov/isa/integrated-science-assessment-isa-particulate-matter
5 Patel V, Kantipudi N, Jones G, *et al*. Air pollution and cardiovascular disease: a review. *Crit Rev Biomed Eng* 2016;44:327–46.
6 Newby LK, Jesse RL, Babb JD, *et al*. ACCF 2012 expert consensus document on practical clinical considerations in the interpretation of troponin elevations: a report of the American College of cardiology Foundation Task force on clinical expert consensus documents. *J Am Coll Cardiol* 2012;60:2427–63.
7 Thygesen K, Alpert JS, Jaffe AS, *et al*. Fourth universal definition of myocardial infarction (2018). *Circulation* 2018;138:e618–51.
8 Lindner G, Pfortmueller CA, Braun CT, *et al*. Non-Acute myocardial infarction-related causes of elevated high-sensitive troponin T in the emergency room: a cross-sectional analysis. *Intern Emerg Med* 2014;9:335–9.
9 Rubini Gimenez M, Twerenbold R, Reichlin T, *et al*. Direct comparison of high-sensitivity-cardiac troponin I vs. T for the

early diagnosis of acute myocardial infarction. *Eur Heart J* 2014;35:2303–11.
10 Larue C, Calzolari C, Bertinchant JP, *et al*. Cardiac-Specific immunoenzymometric assay of troponin I in the early phase of acute myocardial infarction. *Clin Chem* 1993;39:972–9.
11 Higgins JP, Higgins JA. Elevation of cardiac troponin I indicates more than myocardial ischemia. *Clin Invest Med* 2003;26:133–47.
12 Xu H, Brook RD, Wang T, *et al*. Short-Term effects of ambient air pollution and outdoor temperature on biomarkers of myocardial damage, inflammation and oxidative stress in healthy adults. *Environ Epidemiol* 2019;3:e078–e78.
13 Rankin GD, Kabéle M, Brown R, *et al*. Acute exposure to diesel exhaust increases muscle sympathetic nerve activity in humans. *J Am Heart Assoc* 2021;10:e018448.
14 Ward-Caviness CK, Danesh Yazdi M, Moyer J, *et al*. Long-Term exposure to particulate air pollution is associated with 30-day readmissions and hospital visits among patients with heart failure. *J Am Heart Assoc* 2021;10:e019430.
15 Ward-Caviness CK, Weaver AM, Buranosky M, *et al*. Associations between long-term fine particulate matter exposure and mortality in heart failure patients. *J Am Heart Assoc* 2020;9:e012517.
16 Di Q, Amini H, Shi L, *et al*. An ensemble-based model of $PM_{2.5}$ concentration across the contiguous United States with high spatiotemporal resolution. *Environ Int* 2019;130:104909.
17 Apple FS. Tissue specificity of cardiac troponin I, cardiac troponin T and creatine kinase-MB. *Clin Chim Acta* 1999;284:151–9.
18 Adams JE, Bodor GS, Dávila-Román VG, *et al*. Cardiac troponin I. A marker with high specificity for cardiac injury. *Circulation* 1993;88:101–6.
19 Coudrey L. The troponins. *Arch Intern Med* 1998;158:1173–80.
20 Stark M, Kerndt CC, Sharma S. *Troponin*. Treasure Island (FL): StatPearls Publishing LLC, 2021.
21 Body R, Morris N, Collinson P. Single test rule-out of acute myocardial infarction using the limit of detection of a new high-sensitivity troponin I assay. *Clin Biochem* 2020;78:4–9.
22 A language and environment for statistical computing. R Foundation for Statistical Computing [program] Vienna, Austria 2019.
23 Zhang S, Breitner S, Cascio WE, *et al*. Association between short-term exposure to ambient fine particulate matter and myocardial injury in the CATHGEN cohort. *Environ Pollut* 2021;275:116663.
24 Xu H, Brook RD, Wang T, *et al*. Short-Term effects of ambient air pollution and outdoor temperature on biomarkers of myocardial damage, inflammation and oxidative stress in healthy adults. *Environ Epidemiol* 2019;3:e078.
25 Barber M, Morton JJ, Macfarlane PW, *et al*. Elevated troponin levels are associated with sympathoadrenal activation in acute ischaemic stroke. *Cerebrovasc Dis* 2007;23:260–6.
26 Patil H, Vaidya O, Bogart D. A review of causes and systemic approach to cardiac troponin elevation. *Clin Cardiol* 2011;34:723–8.
27 Tung P, Kopelnik A, Banki N, *et al*. Predictors of neurocardiogenic injury after subarachnoid hemorrhage. *Stroke* 2004;35:548–51.
28 Peters A, Nawrot TS, Baccarelli AA. Hallmarks of environmental insults. *Cell* 2021;184:1455–68.
29 Feng S, Gao D, Liao F, *et al*. The health effects of ambient PM2.5 and potential mechanisms. *Ecotoxicol Environ Saf* 2016;128:67–74.
30 Marchant DJ, Boyd JH, Lin DC, *et al*. Inflammation in myocardial diseases. *Circ Res* 2012;110:126–44.
31 Nie J, Close G, George KP, *et al*. Temporal association of elevations in serum cardiac troponin T and myocardial oxidative stress after prolonged exercise in rats. *Eur J Appl Physiol* 2010;110:1299–303.
32 Ostermann M, Ayis S, Tuddenham E, *et al*. Cardiac troponin release is associated with biomarkers of inflammation and ventricular dilatation during critical illness. *Shock* 2017;47:702–8.
33 Alexeeff SE, Deosaransingh K, Liao NS. Particulate matter and cardiovascular risk in adults with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*;204.