Journal of the American Heart Association

ORIGINAL RESEARCH

Temporal Changes in Pollen Concentration Predict Short-Term Clinical Outcomes in Acute Coronary Syndromes

Omar Al-Mukhtar, MBChB; Sara Vogrin, MBBS, MBiostat; Edwin R. Lampugnani, PhD; Samer Noaman, MBChB; Diem T. Dinh, BSc, PhD; Angela L. Brennan, RN, BSC; Christopher Reid, BA, MSc, PhD; Jeffrey Lefkovits, MBBS; Nicholas Cox, MBBS; Dion Stub, MBBS, PhD; William Chan, MBBS, PhD

BACKGROUND: Atmospheric changes in pollen concentration may affect human health by triggering various allergic processes. We sought to assess if changes in pollen concentrations were associated with different acute coronary syndrome (ACS) subtype presentations and short-term clinical outcomes.

METHODS AND RESULTS: We analyzed data in consecutive patients presenting with ACS (unstable angina, non–ST-segment–elevation myocardial infarction, and ST-segment–elevation myocardial infarction) treated with percutaneous coronary intervention between January 2014 and December 2017 and enrolled in the VCOR (Victorian Cardiac Outcomes Registry). Baseline characteristics were compared among patients exposed to different grass and total pollen concentrations. The primary outcome was occurrence of ACS subtypes and 30-day major adverse cardiac and cerebrovascular events (composite of mortality, myocardial infarction, stent thrombosis, target vessel revascularization, or stroke). Of 15 379 patients, 7122 (46.3%) presented with ST-segment–elevation myocardial infarction, 6781 (44.1%) with non–ST-segment–elevation myocardial infarction, and 1476 (9.6%) with unstable angina. The mean age was 62.5 years, with men comprising 76% of patients. No association was observed between daily or seasonal grass and total pollen concentrations with the frequency of ACS subtype presentation. However, grass and total pollen concentrations in the preceding days (2-day average for grass pollen and 7-day average for total pollen) correlated with in-hospital mortality (odds ratio [OR], 2.17 [95% CI, 1.12–4.21]; P=0.021 and OR, 2.78 [95% CI, 1.00–7.74]; P=0.05), respectively, with a trend of 2-day grass pollen for 30-day major adverse cardiac and cerebrovascular events (OR, 1.50 [95% CI, 0.97–2.32]; P=0.066).

CONCLUSIONS: Increased pollen concentrations were not associated with differential ACS subtype presentation but were significantly related to in-hospital mortality following percutaneous coronary intervention, underscoring a potential biologic link between pollen exposure and clinical outcomes.

Key Words: acute coronary syndrome ■ environment ■ pollen count

Several observational studies have linked the development of specific disease states with changes in environmental factors, for example exacerbation of asthma.[1,2] The variability and quality of inhaled air is one such environmental factor. Changes to the constituents of inhaled air can occur naturally because of changes in airborne pollen levels[3] or as a result of human activities resulting in pollutants and airborne particulate matter.[4] It was recently suggested that environmental factors, such as pollen concentration, air pollutants, and temperature, can exert a synergistic effect in susceptible individuals leading to poor

Correspondence to: William Chan, MBBS, PhD, FRACP, Department of Cardiology, Western Health, St. Albans, VIC 3021, Australia. E-mail: william.chan@unimelb.edu.au

The abstract of this research was presented at the Annual Meeting of the Cardiac Society of Australia and New Zealand in August 2021, Adelaide, Australia.

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.023036

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Temporal changes in daily or seasonal pollen concentration were not associated with the frequency of acute coronary syndrome admission needing treatment with percutaneous coronary intervention.
- Grass and total pollen concentrations in the preceding days of acute coronary syndrome admission were predictive of in-hospital mortality, with a trend for 30-day major adverse cardiac and cerebrovascular events (grass pollen only).

What Are the Clinical Implications?

- Climatic perturbations resulting in changes in pollen concentration could potentially be linked to adverse short-term clinical outcomes following acute coronary syndrome.
- The pathophysiology behind this association might be because of the heightened inflammatory response following pollen exposure, but it requires further research.

Nonstandard Abbreviations and Acronyms

MACCE	major adverse cardiac and cerebrovascular events
VCOR	Victorian Cardiac Outcomes Registry

health outcomes, such as exacerbation of respiratory conditions, increased hospital admissions, and overall mortality.[5]

Pollen grains from different plant species contain allergens,[6] with evidence supporting increased frequency of respiratory allergic reactions associated with increased pollen levels in the air.[7] In Melbourne, Australia, high levels of grass pollen grains have been reported to be strongly correlated with development of allergic rhinitis symptoms.[8] Furthermore, Erbas et al observed that the grass pollen level was a strong nonlinear predictor for asthma hospital admissions.[9] Allergic reactions occur through the interaction of allergens carried by pollen grains stimulating the immune system and the resulting inflammatory responses adversely affecting various biological processes and organ function.[10] Although exposure to pollen grain allergens is predominantly limited to the upper respiratory tract, the inflammatory response and subsequent biological effects could impact organ systems remote from the site of exposure, such as the cardiovascular system.[11] Inflammation is known to play a key role in both acute and chronic coronary syndromes.[12,13] The extent of inflammation in patients with acute coronary syndrome (ACS), as reflected by higher inflammatory markers such as C-reactive protein, is well-described and predicts worse cardiovascular outcomes.[14]

The link between exposure to environmental pollutants, such as particulate matter and poor cardiovascular outcomes, is well documented.[15,16] Extreme temperature changes have also been implicated in the observed seasonality in cardiovascular disease peaks and associated outcomes.[17] However, there is a paucity of data linking pollen grain exposure and cardiovascular outcomes. We therefore aimed to evaluate the relationship between exposure to pollen grains and the frequency of different ACS subtype presentations and short-term clinical outcomes. Identification of such a relationship would have important public health implications pertaining to public health policies and defining susceptible populations during vulnerable climatic periods.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The study was approved by Western Health's Ethics Committee (LNR/18/WH/100 LREP). Written consent was waived because only nonidentifiable data were used.

Study Design

We analyzed data from the VCOR (Victorian Cardiac Outcomes Registry), a statewide sponsored clinical governance registry of all patients undergoing percutaneous coronary intervention (PCI) in 30 participating public and private hospitals across the state of Victoria, Australia. Monash University coordinates VCOR in conjunction with the Victorian Cardiac Clinical Network and Department of Health and Human Services. The ethics committee approved the VCOR registry operation at each participating hospital. The registry records PCI-related demographic, clinical, and procedural data, including complications and outcomes with a 30-day follow-up period. All patients undergoing PCI at each hospital are included unless they opt out.[18]

Pollen data from 2014 to 2017 were obtained from the Melbourne Pollen registry (http://www.MelbournePollen.com.au/) operated by the University of Melbourne that records daily grass and total pollen concentrations during the peak grass pollen season between October 1 to December 31 of each year in Melbourne, Victoria, Australia. Additional details of the study sites and methodologies used to record pollen concentrations are described by Silver et al.[8] Grass pollen concentrations are not recorded from the January 1 to September 30 of each year, because this period typically has negligible grass pollen levels, as reported previously.[19]

Daily grass and total pollen concentrations are categorized according to previously published levels in studies by Ong et al[20] and Weichenthal et al.[21] High grass pollen days are defined as days with an average concentration of 50 or more grass pollen grains per cubic meter of air, whereas average concentrations below 50 are defined as non–high grass pollen days. Total pollen concentrations are categorized as high total pollen days when the recorded concentration was in the highest tertile of recorded values (>111 grains/m^3) and low total pollen days when the concentration was in the lowest tertile of recorded values (<34 grains/m^3). Between 2014 and 2016, air samples were collected at 4:00 PM, with the measured pollen concentrations representing the 24-hour average concentration before the collection time. Because this period covered 67% of the day the samples were obtained, the measured concentration was taken as the grass and total pollen concentration on the collection day. In 2017 the sample collection period changed to 9:00 AM. Because the sample period represented 63% of the previous day, grass and total pollen measurements were defined as grass and total pollen concentration of the previous day.

Data for daily mean temperature, humidity, and particulate matter (PM2.5) as an air pollution index were obtained from the Australian Bureau of Meteorology (www.bom.gov.au).

Study Population and End Points

This study included consecutive patients enrolled in the VCOR who underwent PCI between January 2014 and December 2017, where the initial presentation was 1 of 3 ACS subtypes. ST-segment–elevation myocardial infarction was defined as an elevation in cardiac biomarker levels coupled with ECG changes of either new ST-segment elevation, new left bundle branch block, or new pathological Q waves. Non–ST-segment–elevation myocardial infarction was defined as elevated cardiac biomarkers with either ECG changes of ST-segment depression/T-wave changes or history of ischemic symptoms. Unstable angina was defined as new onset of severe angina, prolonged angina at rest, or worsening anginal symptoms. Patients who had missing data (demographic, procedural, or clinical outcomes) or received PCI for non-ACS indications were excluded.

The study's primary objective was to determine if there was an association between the frequency of different ACS subtype presentations and 30-day clinical outcomes with changes in daily and seasonal grass and total pollen concentrations. The primary outcome was occurrence of ACS subtypes and 30-day major adverse cardiac and cerebrovascular events (MACCE), defined as a composite of all-cause mortality, new or recurrent myocardial infarction, stent thrombosis, target vessel revascularization, and stroke.

Statistical Analysis

Data for continuous variables were expressed as means and standard deviations or medians and interquartile ranges. Categorical variables were expressed as numbers and percentages. Between-group differences were evaluated by χ^2 test for categorical variables and independent samples *t* test or rank sum test for continuous variables.

The effect of daily grass and total pollen concentration on frequency of ACS presentations, in-hospital mortality, and 30-day MACCE was evaluated using time series regression. Long-term pattern in the outcome was modeled using a time-stratified model,[22] where monthly baseline outcome risk was predicted and included in subsequent generalized linear models. Poisson distribution was used to examine pollen concentration with ACS subtype frequency. Because of overdispersion, standard errors were scaled using Pearson χ^2 statistic. Binary distribution with logit link was used to evaluate pollen association with in-hospital mortality and 30-day MACCE. All models were adjusted for average temperature, humidity, and PM2.5 count. Models for in-hospital mortality and 30-day MACCE were also adjusted for the clinical predictors listed in Table S1.

Because the relationship between the timing of pollen exposure with potential clinical outcomes remains debatable,[23] we analyzed different time intervals of pollen exposure (day 0, 1-, 2-, 3-day average and 7-day average) preceding the occurrence of ACS and clinical outcomes. This is in accord with the methodology used in previous studies that evaluated the association of exposure to environmental triggers, including air pollutants and subsequent health outcomes.[24–27] Grass pollen count was grouped into high (≥50 grains/m^3) and low count (<50 grains/m^3),[20] whereas total pollen count was grouped into tertiles.[21]

A 2-sided *P* value of <0.05 was considered statistically significant. All analyses were performed using Stata 16 (StataCorp, College Station, TX).

RESULTS

A total of 15 379 patients with ACS underwent PCI over the 4-year study period, with ACS subtype being ST-segment–elevation myocardial infarction in 7122 patients, non–ST-segment–elevation myocardial infarction in 6781 patients, and unstable angina in 1476 patients. Baseline clinical characteristics of the study population during peak and nonpeak grass pollen seasons, high and nonhigh grass pollen days, and high total pollen days and low total pollen days are presented

in Table 1. The mean age of patients was 62 years, and men comprised over three-quarters of patients. About one-fifth of patients had diabetes. The majority (78%) of patients had no previously known coronary artery disease. Only 17% had received previous PCI, and <5% had a history of previous coronary artery bypass graft surgery. Other baseline demographic characteristics were similar between the groups of nonpeak grass pollen season versus peak grass pollen season, non–high grass pollen days versus high grass pollen days, and high total pollen days versus low total pollen days. Specifically, no significant differences in presentation with out-of-hospital cardiac arrest or cardiogenic shock were observed. More patients were noted to have severe left ventricular systolic dysfunction during high total pollen days compared with low total pollen days (6.8% versus 5.7%, *P*=0.05).

Concentrations of grass and total pollen grains varied throughout the study period and are displayed in Table 2. Grass pollen accounted for between 14% and 23% of the total seasonal measured pollen grains, whereas other pollen grains constituted between 77% and 86%. The seasonal mean daily grass and total pollen count varied between 11.1 grains/m^3 and 28.9 grains/m^3 and 68.2 grains/m^3 and 130.2 grains/m^3, respectively.

The mean number of daily and monthly presentations of different ACS subtypes during the peak grass pollen season and nonpeak grass pollen season are shown in Table 3 and the Figure. No differences were observed in the mean daily or monthly presentations during peak grass pollen season and nonpeak grass pollen season (10.5±3.7 versus 10.5±3.4, *P*=0.8 and 281.9±119.2 versus 317.6±36.4, *P*=0.11, respectively). Similarly, the daily and monthly frequency of ACS subtypes were comparable between peak grass pollen season and nonpeak grass pollen season. Prevalence of in-hospital mortality and 30-day MACCE were similar during peak grass pollen season and nonpeak grass pollen season (3.5% versus 3.6%, *P*=0.75 and 6.5% versus 7.3%, *P*=0.11, respectively).

During the peak grass pollen season, no association was found between ACS presentation frequency and different timeframes of exposure to grass and total pollen concentrations. The incidence rate ratio for different grass and total pollen exposure periods preceding ACS presentation is shown in Table 4. Multivariable analysis of clinical predictors for in-hospital mortality and 30-day MACCE are shown in Table S1. Specifically, out-of-hospital cardiac arrest, severe left ventricular systolic dysfunction, and stage IV chronic kidney disease carried the highest risk for in-hospital mortality (odds ratio [OR], 11.92 [95% CI, 9.00–15.8] and OR, 7.11 [95% CI, 5.23–9.67] and OR, 6.06 [95% CI, 4.09–8.98]) and 30-day MACCE (OR, 4.31 [95% CI, 3.44–5.39] and OR, 4.25 [95% CI, 3.39–5.33] and OR, 2.65 [95% CI, 1.94–3.60]), respectively (all *P*<0.001). However, neither overall peak grass pollen season nor high total pollen days during the peak grass pollen season were associated with in-hospital mortality (OR, 1.11 [95% CI, 0.86–1.44]; *P*=0.414 and OR, 0.99 [95% CI, 0.55–1.79]; *P*=0.96), respectively, or 30-day MACCE (OR, 0.93 [95% CI, 0.79–1.10]; *P*=0.407 and OR, 0.89 [95% CI, 0.61–1.31]; *P*=0.56), respectively.

We explored the effect of pollen exposure in the days preceding in-hospital mortality and 30-day MACCE. A multivariable regression analysis for different timeframes of exposure to pollen grains and clinical outcomes is shown in Table 5. Exposure to high grass pollen concentration 2 days before presentation with ACS carried a significant risk of in-hospital mortality (OR, 2.17 [95% CI, 1.12–4.21]; *P*=0.021) and trend to increased risk of 30-day MACCE (OR, 1.50 [95% CI, 0.97–2.32]; *P*=0.066). A high preceding 7-day average total pollen concentration was associated with increased risk of in-hospital mortality (OR, 2.78 [95% CI, 1.00–7.74], *P*=0.050) but not 30-day MACCE (OR, 1.40 [95% CI, 0.81–2.41]; *P*=0.230).

DISCUSSION

In this multicenter, observational study of a large Australian population of patients with ACS undergoing PCI, we sought to examine the association of exposure to different grass and total pollen concentrations with the frequency of ACS subtype presentation and also subsequent short-term clinical outcomes. Although we did not observe any relationship between the frequency of ACS presentation with the variability in pollen concentration, whether during peak grass pollen season compared with nonpeak grass pollen season or on days of high versus low pollen concentration during the peak grass pollen season, there was an association between the concentration of grass and total pollen in the preceding days with the occurrence of in-hospital mortality. This observed effect was independent of the variability in metrological factors of mean temperature, humidity, and PM2.5 level. Because we do not have any information on the allergy status of the cohort on which our analysis was based, we must currently assume that the effect of grass and total pollen is relevant for the entire population. Nevertheless, these data raise the possibility of a biological link between allergen exposure with adverse clinical outcomes following the development of acute cardiovascular illness, as suggested by other studies.[28,29] To our knowledge, this is the first Australian study and one of only a few published studies[30,31] to assess the association of exposure to pollen grains and subsequent adverse cardiovascular outcomes.

Environmental factors could trigger ACS and other cardiovascular events through various mechanisms,

Table 1. Baseline Clinical Characteristics

Characteristic	Nonpeak vs peak grass pollen seasons		Low vs high total pollen days during peak grass pollen season		Nonhigh vs high grass pollen days during peak grass pollen season	
	Nonpeak grass pollen season, January–September	Peak grass pollen season, October–December	Low total pollen count days, lowest tertile	High total pollen count days, highest tertile	Non–high grass pollen count days	High grass pollen count days
No. of patients	11 433	3946	1260	1334	3450	490
Age, y, mean±SD	62.9±12.5	62.5±12.1	62.1±12.4	62.9±12.1	62.4±12.2	63.1±12.0
Male sex, n (%)	8741 (76.5%)	3057 (77.5%)	989 (78.5%)	1038 (77.8%)	2675 (77.5%)	378 (77.1%)
Body mass index	28.8±5.7	28.7±5.5	28.4±5.5*	28.9±5.6*	28.6±5.6	29±5.5
eGFR, median (IQR)	91.5 (67–118)	92.5 (68–118)	93.1 (68–119)	91.5 (67–120)	92.9 (68.5–118)	91.1 (68–119)
Diabetes, n (%)	2300 (20.1%)	809 (20.5%)	265 (21.0%)	263 (19.7%)	712 (20.7%)	94 (19.2%)
Cerebrovascular disease, n (%)	437 (3.8%)	144 (3.7%)	48 (3.8%)	48 (3.6%)	125 (3.6%)	19 (3.9%)
Chronic oral anticoagulant therapy, n (%)	436 (3.8%)	142 (3.6%)	50 (4.0%)	45 (3.4%)	122 (3.5%)	19 (3.9%)
Previous CABG, n (%)	564 (4.9%)	181 (4.6%)	54 (4.3%)	68 (5.1%)	165 (4.8%)	16 (3.3%)
Previous PCI, n (%)	1972 (17.2%)	669 (17%)	214 (17.0%)	234 (17.6%)	577 (16.7%)	91 (18.6%)
Dialysis, n (%)	168 (1.5%)	45 (1.1%)	14 (1.1%)	16 (1.2%)	39 (1.1%)	6 (1.2%)
Cardiogenic shock, n (%)	604 (5.3%)	194 (4.9%)	66 (5.2%)	60 (4.5%)	173 (5.0%)	20 (4.1%)
Out-of-hospital cardiac arrest, n (%)	549 (4.8%)	180 (4.6%)	64 (5.1%)	55 (4.1%)	162 (4.7%)	18 (3.7%)
ACS-STEMI, n (%)	5318 (46.5%)	1804 (45.7%)	591 (46.9%)	615 (46.1%)	1590 (46.1%)	212 (43.3%)
ACS-NSTEMI, n (%)	5015 (43.9%)	1766 (44.8%)	557 (44.2%)	607 (45.5%)	1529 (44.3%)	233 (47.6%)
ACS-UA, n (%)	1100 (9.6%)	376 (9.5%)	112 (8.9%)	112 (8.4%)	331 (9.6%)	45 (9.2%)
Severe left ventricular systolic dysfunction, n (%)	677 (5.9%)*	242 (6.1%)*	72 (5.7%)*	91 (6.8%)*	204 (5.9%)	37 (7.6%)
Moderate left ventricular systolic dysfunction, n (%)	1470 (12.9%)*	548 (13.9%)*	189 (15.0%)*	174 (13.0%)*	480 (13.9%)	67 (13.7%)
Mild left ventricular systolic dysfunction, n (%)	2596 (22.7%)*	909 (23.0%)*	306 (24.3%)*	303 (22.7%)*	800 (23.2%)	108 (22.0%)
Normal left ventricular systolic function, n (%)	5406 (47.3%)*	1874 (47.5%)*	590 (46.8%)*	618 (46.3%)*	1646 (47.7%)	225 (45.9%)

ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and UA, unstable angina.

*Significant *P*-value ≤0.05.

Table 2. Recorded Pollen Concentrations and Basic Seasonal Characteristics

Pollen count	2014	2015	2016	2017
Total grass pollen recorded in grains/m^3	1198 (14.1%)	1021 (16.3%)	2659 (22.1%)	2487 (23.1%)
No. of high grass pollen days	2	3	20	18
Minimum daily grass pollen recorded in grains/m^3	0	0	0	0
Maximum daily grass pollen recorded in grains/m^3	54	58	154	172
Mean daily grass pollen recorded in grains/m^3	13.0	11.1	28.9	27.1
Total pollen recorded in grains/m^3	8469	6274	11 984	10 766
Minimum daily total pollen recorded in grains/m^3	5	0	9	3
Maximum daily total pollen recorded in grains/m^3	392	425	843	709
Mean daily total pollen recorded in grains/m^3	92.1	68.2	130.26	117.0

including plaque rupture, acute thrombosis,[32] and altered autonomic control.[33] Despite an abundance of data linking exposure to air pollutants and the onset of cardiovascular events,[24,25,32] only a few published studies have assessed if a similar association with exposure to pollen grains exists. Interestingly, this relationship was examined within the general population, and no details were provided about the history of preexisting allergic diseases or the use of antiallergy medications. One such study is a study from the United States by Low et al involving 16 900 patients, where there was an observed weak association of higher grass pollen exposure and the risk of ischemic stroke (correlation coefficient *r*, 0.011; *P*=0.034).[34] In a population-based study by Weichenthal et al in the province of Ontario, Canada, the risk of presentation with myocardial infarction was reported to be higher on days of highest tertile of total pollen concentration (>95 grains/m^3) compared with days with the lowest tertile of total pollen concentration (<20 grains/m^3) (OR, 1.055 [95% CI, 1.034–1.076]; *P*<0.001).[21] Our study findings are different from the Weichenthal et al results. Although the 2 studies used registry data,[35] significant differences between the 2 studies exist. First, the mean daily total pollen count during peak grass pollen season was as high as 122 grains/m^3 in the Weichenthal et al study compared with 101.7 grains/m^3 in our study. This difference could be attributed to the different geographic locations of the 2 study populations. Second, the total pollen count cutoff for comparing the highest and lowest tertiles differed between the 2 studies. In contrast to our study, where pollen count >111 grains/m^3 was considered as high exposure, Weichenthal et al used a cutoff of >95 grains/m^3 to indicate high exposure and a much lower cutoff of <20 grains/m^3 to indicate low exposure. Third, our study's inclusion criteria required a diagnosis of ACS as

Table 3. Frequency of ACS Subtypes, In-Hospital Mortality, and 30-Day MACCE During Peak and Nonpeak Grass Pollen Seasons

ACS subtypes and clinical outcomes	Peak grass pollen season, October, November, December	Nonpeak grass pollen season, January to September	*P* value
Daily frequency, no. of patients/d			
Overall ACS, mean (SD)	10.5 (3.7)	10.5 (3.4)	0.8
NSTEMI, mean (SD)	4.77 (2.28)	4.67 (2.25)	0.4
STEMI, mean (SD)	4.90 (2.22)	4.94 (2.21)	0.8
Unstable angina, mean (SD)	1.66 (0.97)	1.67 (0.88)	0.9
Monthly frequency, no. of patients/mo			
Overall ACS, mean (SD)	281.9 (119.2)	317.6 (36.4)	0.1
STEMI, mean (SD)	138.8 (54.8)	147.7 (21.4)	0.3
NSTEMI, mean (SD)	126.1 (53.5)	139.3 (19.9)	0.2
Unstable angina, mean (SD)	28.9 (9.95)	30.6 (6.08)	0.5
In-hospital mortality, no. of patients during the study period (%)	139 (3.5%)	415 (3.6%)	0.8
30-d MACCE, no. of patients during the study period (%)	258 (6.5%)	834 (7.3%)	0.1
30-d rehospitalization, no. of patients during the study period (%)	445 (11.3%)	1450 (12.7%)	0.05

ACS indicates acute coronary syndrome; MACCE, major adverse cardiac and cerebrovascular events; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

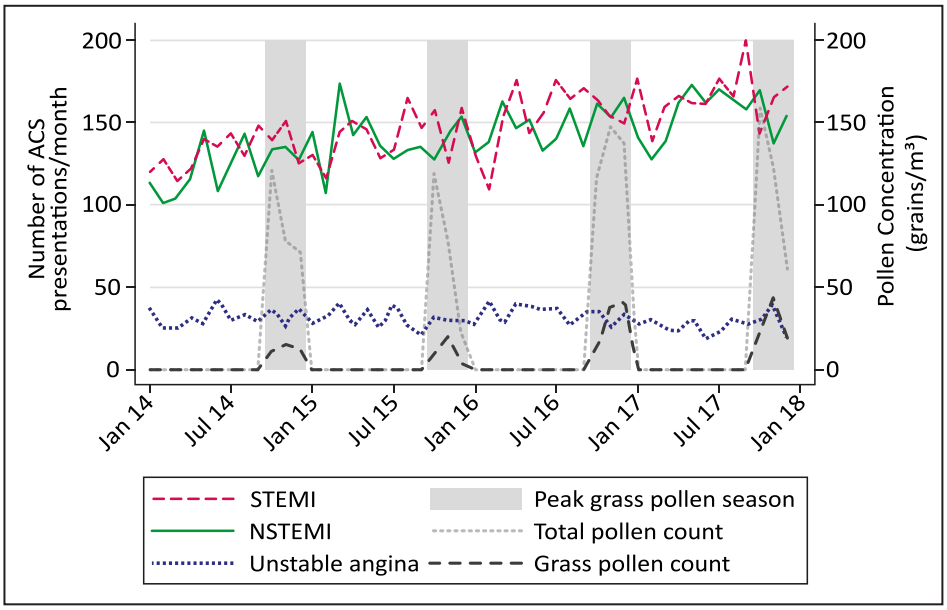

Figure 1. Relationship of acute coronary syndrome subtypes and pollen concentrations. ACS indicates acute coronary syndrome; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

per VCOR definition, where patients underwent diagnostic angiography with identification of culprit lesion(s) treated with PCI. On the other hand, the Weichenthal et al study included patients who had an ACS diagnosis based on clinical and biochemical assessment in the emergency department. This approach could have overestimated the ACS frequency, given that myocardial injury might have arisen from non-ACS causes.[36] Our study findings are more in accord with the study results by Carracedo-Martinez et al. in Spain,[26] where elevated pollen concentrations were not associated with increased emergency services use attributed to cardiovascular causes. Taken together, the association between changes in temporal pollen concentration and the occurrence of ACS remains contentious and not well defined. This could be explained by the complex interaction between geographical and patient-related factors that lead to different sensitization and symptom development thresholds after exposure to pollen.[37]

Few published studies have described a relationship between a history of allergic reactions and cardiovascular outcomes. In the study by Brunetti et al, patients presenting with unstable angina treated with PCI[28] with a history of allergy had increased occurrence of major adverse cardiac events in the 6-month follow-up period (hazard ratio, 7.17% [95% CI, 1.71–29.98]; $P<0.01$). In another study from Hospers et al[29] after 30 years of follow-up, patients with increased blood eosinophil counts were at higher risk of all cardiovascular and ischemic heart disease mortality (risk ratio [RR], 1.7 [95% CI, 1.4–2.2]; $P=0.05$) and (RR, 1.6 [95% CI, 1.2–2.2]; $P=0.05$), respectively. Eosinophils are thought to actively participate in the inflammatory process associated with myocardial infarction along with their traditional role in allergic reactions.[38] In the study by Niccoli et al, eosinophil degranulation, as a marker of allergic inflammation, appeared to be a predictor of MACCE in patients with ST-segment–elevation myocardial

Table 4. Association Between Different Timeframes of Pollen Grains Exposure and Frequency of Acute Coronary Syndrome Presentation

	Grass pollen concentration		Total pollen concentration	
Timeframes of pollen grains exposure	IRR (95% CI)	*P* value	IRR (95% CI)	*P* value
On day of admission, d 0	1.01 (0.90–1.12)	0.9	1.03 (0.94–1.12)	0.5
1 day before admission, d –1	1.07 (0.96–1.19)	0.2	1.03 (0.94–1.12)	0.6
2 days before admission, d –2	0.98 (0.88–1.10)	0.8	0.98 (0.90–1.07)	0.7
3 days before admission average, d 0, d –1, d –2	1.02 (0.91–1.14)	0.7	0.99 (0.90–1.09)	0.9
7 days before admission average, d 0, d –1, d –2, d –3, d –4, d –5, d –6	1.04 (0.91–1.20)	0.6	1.01 (0.90–1.13)	0.9

IRR indicates incidence rate ratio.

Table 5. Cumulative Pollen Exposure as Predictor of In-Hospital Mortality and 30-Day MACCE

Timeframes of pollen grains exposure	30-d MACCE		In-hospital mortality	
Grass pollen concentration, grains/m^3	OR (95% CI)	*P* value	OR (95% CI)	*P* value
On day of admission	1.24 (0.62–2.50)	0.544	1.06 (0.67–1.67)	0.817
1 day before admission, d –1	1.44 (0.73–2.85)	0.292	1.21 (0.78–1.87)	0.404
2 days before admission, d –2	2.17 (1.12–4.21)†	0.021†	1.50 (0.97–2.32)	0.066
3 days before admission average, d 0, d –1, d –2	1.70 (0.87–3.31)	0.119	1.46 (0.94–2.26)	0.093
7 days before admission average, d 0, d –1, d –2, d –3, d –4, d –5, d –6	1.20 (0.50–2.87)	0.688	0.97 (0.55–1.74)	0.932
Total pollen concentration, grains/m^3				
On day of admission	0.99 (0.55–1.79)	0.965	0.89 (0.61–1.31)	0.565
1 days before admission, d –1	1.08 (0.58–2.00)	0.805	0.91 (0.62–1.35)	0.643
2 days before admission, d –2	1.27 (0.69–2.34)	0.446	1.27 (0.86–1.88)	0.233
3 days before admission average, d 0, d –1, d –2	1.32 (0.65–2.67)	0.440	1.08 (0.70–1.67)	0.725
7 days before admission average, d 0, d –1, d –2, d –3, d –4, d –5, d –6	2.78 (1.00–7.74)†	0.050†	1.40 (0.81–2.41)	0.230

MACCE indicates major adverse cardiac and cerebrovascular events; and OR, odds ratio.

Variables in the model include age, stage III chronic kidney disease, stage IV chronic kidney disease, out-of-hospital cardiac arrest, in-hospital periprocedural cardiac arrest, procedural intubation, mechanical ventricular support, percutaneous coronary intervention for moderate and severely complex lesions, percutaneous coronary intervention with 1 stent only, multivessel coronary disease, moderate left ventricular dysfunction, severe left ventricular dysfunction, mean daily temperature, humidity, and particulate matter PM2.5 level.

†*P*-values with statistical significance.

infarction after 24 months of follow-up (OR, 1.041 [95% CI, 1.012–1.071]; *P*=0.005).[39] A few studies have also examined the relationship between exposure to environmental factors such as air pollutants and subsequent cardiovascular outcomes. One example is the Australian study of Barnet et al,[40] where exposure to pollutants from common emission sources increased the risk of hospital cardiovascular admissions in elderly patients. Other studies reported a similar significant association between exposure to pollutants with short-term[41] and long-term[42] cardiovascular mortality.

There is, however, a lack of data evaluating the association of exposure to pollen grains and subsequent cardiovascular outcomes. One study that mirrored the findings from our study is that of Brunekreef et al[30] in the Netherlands, where daily cardiovascular deaths were found to be associated with high compared with low average weekly grass pollen concentration (RR, 1.06 [95% CI, 1.03–1.08]) during their high pollen season. This effect was independent of other seasonal and environmental factors such as influenza infections, ambient temperature, and air pollution. Another study that parallels our findings is from Jaakkola et al,[31] which involved 153 378 patients and was conducted in Helsinki, Finland. Exposure to high concentrations of Mugwort pollen grains (>30 grains/m^3) in the preceding 10 days was associated with increased risk of cardiovascular mortality (adjusted mortality rate ratio, 1.414 [95% CI, 1.024–1.953]) after adjusting for exposure to mean daily temperature and particulate matter PM2.5. Both of the 2 aforementioned studies also did not record a history of allergic disorders or use of allergy medications, such as antihistamines or steroids, presumably because these variables were not available. It is also noteworthy that the pollen grains examined varied across the studies being Poaceae grass in the Netherlands, mugwort plants in Finland, and perennial ryegrass in our study. The degree of sensitization and severity of subsequent allergic reactions is known to be different between countries and populations even after exposure to the same plant pollen grains.[43] These data would suggest that exposure to grass pollen grains (irrespective of species) are associated with adverse cardiovascular outcomes, although the magnitude might differ depending on the degree of individual susceptibility and sensitization, and ultimately the phenotypic expression of cardiovascular disease.

A possible explanation of pre-ACS exposure to pollen grains and subsequent in-hospital mortality is the development of heightened inflammatory response adversely impacting different organ function, thereby leading to a clinical adverse event.[44,45] Increased inflammation is a hallmark of ACS,[46,47] and raised inflammatory markers in patients with ACS treated with PCI[48] were associated with increased risk of poor cardiovascular outcomes. The precise mechanisms underpinning inflammation to adverse cardiovascular outcomes remains to be elucidated.[14,49] Potentiation of myocardial damage and pathologic remodeling because of inflammatory processes, with subsequent development of severe left ventricular dysfunction,[50] heart failure, and malignant arrhythmias,[51] have been suggested

to be a potential link to increased risk of adverse cardiovascular outcomes.[52] Interest in identifying and refining biochemical markers of inflammation[53] and anti-inflammatory therapies, such as colchicine, for patients presenting with ACS have led to multiple randomized controlled trials,[54,55] with conflicting results.

Our study findings need to be considered in the context of several limitations. First, given the retrospective nature, there are likely to be confounders that could not be adjusted for that might have influenced the study findings. Second, relevant clinical variables, such as the proportion of patients with a preexisting allergy or asthma diagnosis, were not available because VCOR did not capture them. Notably, it is also unclear what proportion of patients were on preexisting steroids or antihistamine medications. Third, it is challenging to quantify geographic exposure to pollen grains in any individual. Exposure to pollen was assessed based on the average pollen count measured by fixed stations often separated by large distances. Finally, we did not have data on patients' socioeconomic background, which could impact their general cardiovascular health and the clinical outcomes after ACS.

In conclusion, in this multicenter observational study, seasonal and daily variations in levels of grass and total pollen concentrations did not correlate with the frequency of different subtypes of ACS presentation. However, in-hospital mortality after presentation with ACS was related to preceding grass and total pollen concentrations, underscoring a potential biologic link between grass and total pollen exposure and clinical outcomes requiring validation in future studies. Future prospective studies with linkage of individual patient data to pollen data within predefined geographic locations may help better define the relationship between pollen exposure and incident cardiac events and outcomes.

ARTICLE INFORMATION

Received June 26, 2021; accepted December 21, 2021.

Affiliations

Department of Cardiology, Western Health (O.A., S.N., N.C., D.S., W.C.) and Department of Medicine, Western Health, Melbourne Medical School, University of Melbourne (S.V., N.C., W.C.), Melbourne, Victoria, Australia; Department of Cardiology, Alfred Health, Melbourne, Victoria, Australia (S.N., D.S., W.C.); School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia (D.T.D., A.L.B., C.R., J.L.); School of Biosciences, The University of Melbourne, Melbourne, Victoria, Australia (E.R.L.); NHMRC Centre of Research Excellence in Cardiovascular Outcomes Improvement, Curtin University, Perth, Western Australia, Australia (C.R.); Department of Cardiology, Royal Melbourne Hospital, Melbourne, Victoria, Australia (J.L.); and Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia (D.S., W.C.).

Acknowledgments

The authors acknowledge the support from the Department of Cardiology, Western Health, Victoria, Australia. We thank E. Newbigin, U. Nattala, and Dr Silver for supporting Melbourne Pollen Count activities.

Sources of Funding

This research was investigator-initiated, and no funding was required for any part of the conduct of the research. E.R.L. acknowledges funding support for the Melbourne Pollen monitoring program from the University of Melbourne and the National Health and Medical Research Council AusPollen Partnership (grant number GNT1116107), as well as additional support from the University of Melbourne William Stone Trust and the Botany Foundation.

Disclosures

None.

Supplemental Material

Table S1

REFERENCES

1. Leaf A. Potential health effects of global climatic and environmental changes. *N Engl J Med*. 1989;321:1577–1583. doi: 10.1056/NEJM198912073212305
2. Liang F, Liu F, Huang K, Yang X, Li J, Xiao Q, Chen J, Liu X, Cao J, Shen C. Long-term exposure to fine particulate matter and cardiovascular disease in china. *J Am Coll Cardiol*. 2020;75:707–717. doi: 10.1016/j.jacc.2019.12.031
3. Ziello C, Sparks TH, Estrella N, Belmonte J, Bergmann KC, Bucher E, Brighetti MA, Damialis A, Detandt M, Galán C, et al. Changes to airborne pollen counts across Europe. *PLoS One*. 2012;7:e34076. doi: 10.1371/journal.pone.0034076
4. Nel A. Air pollution-related illness: effects of particles. *Science*. 2005;308:804–806. doi: 10.1126/science.1108752
5. Anenberg SC, Haines S, Wang E, Nassikas N, Kinney PL. Synergistic health effects of air pollution, temperature, and pollen exposure: a systematic review of epidemiological evidence. *Environ Health*. 2020;19:1–19. doi: 10.1186/s12940-020-00681-z
6. Levetin E, Buck P. Hay fever plants in Oklahoma. *Ann Allergy*. 1980;45:26–32.
7. D'amato G, Spieksma FTM, Liccardi G, Jäger S, Russo M, Kontou-Fili K, Nikkels H, Wüthrich B, Bonini S. Pollen-related allergy in Europe. *Allergy*. 1998;53:567–578. doi: 10.1111/j.1398-9995.1998.tb03932.x
8. Silver JD, Spriggs K, Haberle S, Katelaris CH, Newbigin EJ, Lampugnani ER. Crowd-sourced allergic rhinitis symptom data: the influence of environmental and demographic factors. *Sci Total Environ*. 2020;705:135147. doi: 10.1016/j.scitotenv.2019.135147
9. Erbas B, Chang JH, Dharmage S, Ong E, Hyndman R, Newbigin E, Abramson M. Do levels of airborne grass pollen influence asthma hospital admissions? *Clin Exp Allergy*. 2007;37:1641–1647. doi: 10.1111/j.1365-2222.2007.02818.x
10. Taylor PE, Flagan RC, Valenta R, Glovsky MM. Release of allergens as respirable aerosols: a link between grass pollen and asthma. *J Allergy Clin Immunol*. 2002;109:51–56. doi: 10.1067/mai.2002.120759
11. Traidl-Hoffmann C, Kasche A, Menzel A, Jakob T, Thiel M, Ring J, Behrendt H. Impact of pollen on human health: more than allergen carriers? *Int Arch Allergy Immunol*. 2003;131:1–13. doi: 10.1159/000070428
12. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999;340:115–126. doi: 10.1056/NEJM199901143400207
13. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131. doi: 10.1056/NEJMoa1707914
14. Barron HV, Cannon CP, Murphy SA, Braunwald E, Gibson CM. Association between white blood cell count, epicardial blood flow, myocardial perfusion, and clinical outcomes in the setting of acute myocardial infarction: a thrombolysis in myocardial infarction 10 substudy. *Circulation*. 2000;102:2329–2334. doi: 10.1161/01.CIR.102.19.2329
15. De Marco A, Amoatey P, Khaniabadi YO, Sicard P, Hopke PK. Mortality and morbidity for cardiopulmonary diseases attributed to PM2. 5 exposure in the metropolis of Rome, Italy. *Eur J Intern Med*. 2018;57:49–57. doi: 10.1016/j.ejim.2018.07.027
16. Liu Y, Pan J, Fan C, Xu R, Wang Y, Xu C, Xie S, Zhang H, Cui X, Peng Z. Short-term exposure to ambient air pollution and mortality

from myocardial infarction. *J Am Coll Cardiol*. 2021;77:271–281. doi: 10.1016/j.jacc.2020.11.033
17. Stewart S, Keates AK, Redfern A, McMurray JJ. Seasonal variations in cardiovascular disease. *Nat Rev Cardiol*. 2017;14:654. doi: 10.1038/nrcardio.2017.76
18. Stub D, Lefkovits J, Brennan AL, Dinh D, Brien R, Duffy SJ, Cox N, Nadurata V, Clark DJ, Andrianopoulos N, et al. The establishment of the victorian cardiac outcomes registry (VCOR): monitoring and optimising outcomes for cardiac patients in victoria. *Heart Lung Circ*. 2018;27:451–463. doi: 10.1016/j.hlc.2017.07.013
19. Ong EK, Singh MB, Knox RB. Seasonal distribution of pollen in the atmosphere of Melbourne: an airborne pollen calendar. *Aerobiologia*. 1995;11:51–55. doi: 10.1007/BF02136145
20. Ong EK, Singh MB, Knox RB. Grass pollen in the atmosphere of Melbourne: seasonal distribution over nine years. *Grana*. 1995;34:58–63. doi: 10.1080/00173139509429034
21. Weichenthal S, Lavigne E, Villeneuve PJ, Reeves F. Airborne pollen concentrations and emergency room visits for myocardial infarction: a multicity case-crossover study in Ontario, Canada. *Am J Epidemiol*. 2016;183:613–621. doi: 10.1093/aje/kwv252
22. Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B. Time series regression studies in environmental epidemiology. *Int J Epidemiol*. 2013;42:1187–1195. doi: 10.1093/ije/dyt092
23. Pfaar O, Bastl K, Berger U, Buters J, Calderon MA, Clot B, Darsow U, Demoly P, Durham SR, Galán C, et al. Defining pollen exposure times for clinical trials of allergen immunotherapy for pollen-induced rhinoconjunctivitis–an EAACI position paper. *Allergy*. 2017;72:713–722. doi: 10.1111/all.13092
24. Kwon OK, Kim S-H, Kang S-H, Cho Y, Oh I-Y, Yoon C-H, Kim S-Y, Kim O-J, Choi E-K, Youn T-J, et al. Association of short-and long-term exposure to air pollution with atrial fibrillation. *Eur J Prev Cardiol*. 2019;26:1208–1216. doi: 10.1177/2047487319835984
25. Ishii M, Seki T, Kaikita K, Sakamoto K, Nakai M, Sumita Y, Nishimura K, Miyamoto Y, Noguchi T, Yasuda S, et al. Association of short-term exposure to air pollution with myocardial infarction with and without obstructive coronary artery disease. *Eur J Prevent Cardiol*. 2020;2047487320904641. doi: 10.1177/2047487320904641
26. Carracedo-Martinez E, Sanchez C, Taracido M, Saez M, Jato V, Figueiras A. Effect of short-term exposure to air pollution and pollen on medical emergency calls: a case-crossover study in Spain. *Allergy*. 2008;63:347–353. doi: 10.1111/j.1398-9995.2007.01574.x
27. Andrew E, Nehme Z, Bernard S, Abramson MJ, Newbigin E, Piper B, Dunlop J, Holman P, Smith K. Stormy weather: a retrospective analysis of demand for emergency medical services during epidemic thunderstorm asthma. *BMJ*. 2017;359. doi: 10.1136/bmj.j5636
28. Brunetti ND, De Gennaro L, Cuculo A, Gaglione A, Di Biase M. History of allergy is a predictor of adverse events in unstable angina treated with coronary angioplasty. *Allergol Immunopathol*. 2013;41:25–29. doi: 10.1016/j.aller.2011.12.009
29. Hospers JJ, Rijcken B, Schouten JP, Postma DS, Weiss ST. Eosinophilia and positive skin tests predict cardiovascular mortality in a general population sample followed for 30 years. *Am J Epidemiol*. 1999;150:482–491. doi: 10.1093/oxfordjournals.aje.a010037
30. Brunekreef B, Hoek G, Fischer P, Spieksma FTM. Relation between airborne pollen concentrations and daily cardiovascular and respiratory-disease mortality. *Lancet*. 2000;355:1517–1518. doi: 10.1016/S0140-6736(00)02168-1
31. Jaakkola JJ, Kiihamäki S-P, Näyhä S, Ryti NR, Hugg TT, Jaakkola MS. Airborne pollen concentrations and daily mortality from respiratory and cardiovascular causes. *Eur J Pub Health*. 2021. doi: 10.1093/eurpub/ckab034
32. Servoss SJ, Januzzi JL, Muller JE. Triggers of acute coronary syndromes. *Prog Cardiovasc Dis*. 2002;44:369–380. doi: 10.1053/pcad.2002.123470
33. Gold DR, Litonjua A, Schwartz J, Lovett E, Larson A, Nearing B, Allen G, Verrier M, Cherry R, Verrier R. Ambient pollution and heart rate variability. *Circulation*. 2000;101:1267–1273. doi: 10.1161/01.CIR.101.11.1267
34. Low RB, Bielory L, Qureshi AI, Dunn V, Stuhlmiller DF, Dickey DA. The relation of stroke admissions to recent weather, airborne allergens, air pollution, seasons, upper respiratory infections, and asthma incidence, september 11, 2001, and day of the week. *Stroke*. 2006;37:951–957. doi: 10.1161/01.STR.0000214681.94680.66
35. Janes H, Sheppard L, Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. *Epidemiology*. 2005:717–726. doi: 10.1097/01.ede.0000181315.18836.9d
36. Park KC, Gaze DC, Collinson PO, Marber MS. Cardiac troponins: from myocardial infarction to chronic disease. *Cardiovasc Res*. 2017;113:1708–1718. doi: 10.1093/cvr/cvx183
37. De Weger LA, Bergmann KC, Rantio-Lehtimäki A, Dahl Å, Buters J, Déchamp C, Belmonte J, Thibaudon M, Cecchi L, Besancenot J-P. Impact of pollen. In: *Allergenic Pollen*. Springer. 2013;161–215.
38. Hällgren R, Venge P, Cullhed I, Olsson I. Blood eosinophils and eosinophil cationic protein after acute myocardial infarction or corticosteroid administration. *Br J Haematol*. 1979;42:147–154. doi: 10.1111/j.1365-2141.1979.tb03707.x
39. Niccoli G, Calvieri C, Flego D, Scalone G, Imaeva A, Sabato V, Schiavino D, Liuzzo G, Crea F. Allergic inflammation is associated with coronary instability and a worse clinical outcome after acute myocardial infarction. *Circ Cardiovasc Interv*. 2015;8:e002554. doi: 10.1161/CIRCINTERVENTIONS.115.002554
40. Barnett AG, Williams GM, Schwartz J, Best TL, Neller AH, Petroeschevsky AL, Simpson RW. The effects of air pollution on hospitalizations for cardiovascular disease in elderly people in Australian and New Zealand cities. *Environ Health Perspect*. 2006;114:1018–1023. doi: 10.1289/ehp.8674
41. Zhang C, Ding R, Xiao C, Xu Y, Cheng H, Zhu F, Lei R, Di D, Zhao Q, Cao J. Association between air pollution and cardiovascular mortality in Hefei, China: a time-series analysis. *Environ Pollut*. 2017;229:790–797. doi: 10.1016/j.envpol.2017.06.022
42. Dehbi H-M, Blangiardo M, Gulliver J, Fecht D, de Hoogh K, Al-Kanaani Z, Tillin T, Hardy R, Chaturvedi N, Hansell AL. Air pollution and cardiovascular mortality with over 25 years follow-up: a combined analysis of two British cohorts. *Environ Int*. 2017;99:275–281. doi: 10.1016/j.envint.2016.12.004
43. Heinzerling L, Burbach G, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S, Bousquet J, Bousquet-Rouanet L, Bousquet P, Bresciani M. GA²LEN skin test study I: GA²LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. *Allergy*. 2009;64:1498–1506. doi: 10.1111/j.1398-9995.2009.02093.x
44. Dahl Å. Pollen lipids can play a role in allergic airway inflammation. *Front Immunol*. 2018;9:2816. doi: 10.3389/fimmu.2018.02816
45. Floris I, Chenuet P, Togbe D, Volteau C, Lejeune B. Potential role of the micro-immunotherapy medicine 2LALERG in the treatment of pollen-induced allergic inflammation. *Dose-Response*. 2020;18:1559325820914092. doi: 10.1177/1559325820914092
46. Nanchen D, Klingenberg R, Gencer B, Räber L, Carballo D, von Eckardstein A, Windecker S, Rodondi N, Lüscher TF, Mach F, et al. Inflammation during acute coronary syndromes—risk of cardiovascular events and bleeding. *Int J Cardiol*. 2019;287:13–18. doi: 10.1016/j.ijcard.2019.03.049
47. Fiechter M, Ghadri JR, Jaguszewski M, Siddique A, Vogt S, Haller RB, Halioua R, Handzic A, Kaufmann PA, Corti R, et al. Impact of inflammation on adverse cardiovascular events in patients with acute coronary syndromes. *J Cardiovasc Med*. 2013;14:807–814. doi: 10.2459/JCM.0b013e3283609350
48. Corrada E, Cappelleri A, Belli G, Genovese S, Barbaro C, Gasparini G, Pagnotta P, Rossi M, Zavalloni D, Presbitero P. Admission glycemia and markers of inflammation are independent outcome predictors in primary PCI in non-diabetic patients. *Minerva Cardioangiol*. 2008;56:445–452.
49. Retterstol L, Eikvar L, Bohn M, Bakken A, Erikssen J, Berg K. C-reactive protein predicts death in patients with previous premature myocardial infarction—a 10 year follow-up study. *Atherosclerosis*. 2002;160:433–440. doi: 10.1016/S0021-9150(01)00595-0
50. Mouton AJ, Rivera OJ, Lindsey ML. Myocardial infarction remodeling that progresses to heart failure: a signaling misunderstanding. *Am J Physiol-Heart Circ Physiol*. 2018;315:H71–H79. doi: 10.1152/ajpheart.00131.2018
51. St John Sutton M, Lee D, Rouleau JL, Goldman S, Plappert T, Braunwald E, Pfeffer MA. Left ventricular remodeling and ventricular arrhythmias after myocardial infarction. *Circulation*. 2003;107:2577–2582. doi: 10.1161/01.CIR.0000070420.51787.A8
52. Westman PC, Lipinski MJ, Luger D, Waksman R, Bonow RO, Wu E, Epstein SE. Inflammation as a driver of adverse left ventricular remodeling after acute myocardial infarction. *J Am Coll Cardiol*. 2016;67:2050–2060. doi: 10.1016/j.jacc.2016.01.073
53. Mani P, Puri R, Schwartz GG, Nissen SE, Shao M, Kastelein JJ, Menon V, Lincoff AM, Nicholls SJ. Association of initial and serial

C-reactive protein levels with adverse cardiovascular events and death after acute coronary syndrome: a secondary analysis of the vista-16 trial. *JAMA Cardiol*. 2019;4:314–320. doi: 10.1001/jamacardio.2019.0179

54. Vaidya K, Arnott C, Martínez GJ, Ng B, McCormack S, Sullivan DR, Celermajer DS, Patel S. Colchicine therapy and plaque stabilization in patients with acute coronary syndrome: a CT coronary angiography study. *JACC Cardiovasc Imaging*. 2018;11:305–316. doi: 10.1016/j.jcmg.2017.08.013
55. Tong DC, Quinn S, Nasis A, Hiew C, Roberts-Thomson P, Adams H, Sriamareswaran R, Htun NM, Wilson W, Stub D, et al. Colchicine in patients with acute coronary syndrome: the Australian cops randomized clinical trial. *Circulation*. 2020;142:1890–1900. doi: 10.1161/CIRCULATIONAHA.120.050771

SUPPLEMENTAL MATERIAL

Table S1. Clinical Multivariate Predictors of in-hospital mortality and 30-day MACCE

Clinical Multivariate Predictors	In-hospital Mortality		30-day MACCE	
	OR (95% CI)	*P-Value*	*OR (95% CI)*	*P-Value*
Age	1.04 (1.03-1.06)	< 0.001	1.02 (1.02-1.03)	< 0.001
Body Mass Index	1.02 (1.00-1.04)	0.04	1.01 (1.00- 1.03)	0.07
Stage III Chronic Kidney Disease	2.41 (1.81-3.21)	<0.001	1.48 (1.21-1.81)	<0.001
Stage IV Chronic Kidney Disease	6.06 (4.09- 8.98)	<0.001	2.65 (1.94- 3.60)	<0.001
Out of hospital cardiac arrest	11.92 (9.00-15.8)	<0.001	4.31 (3.44-5.39)	<0.001
In hospital periprocedural cardiac arrest	2.86 (2.05-3.98)	<0.001	2.37 (1.80 – 3.10)	<0.001
Procedural Intubation	5.73 (3.97-8.28)	<0.001	4.33 (3.12- 6.00)	<0.001
Mechanical Ventricular Support	4.12 (2.75-6.15)	<0.001	4.26 (3.02- 6.02)	<0.001
PCI for Moderate and severely complex lesions	1.31 (1.02-1.68)	0.03	1.23 (1.05- 1.43)	<0.01
PCI with 1 stent only	0.79 (0.61-1.02)	0.06	0.74 (0.63-0.88)	0.001
Multivessel coronary disease	2.49 (1.77-3.48)	<0.001	1.46 (1.13- 1.89)	0.004
Moderate left ventricular dysfunction	2.75 (2.02-3.75)	<0.001	2.01 (1.63- 2.48)	<0.001
Severe left ventricular dysfunction	7.11 (5.23-9.67)	<0.001	4.25 (3.39-5.33)	<0.001

*Abbreviations: PCI= Percutaneous Coronary Intervention.

†Variables included in the model include age, stage III Chronic Kidney Disease, Stage IV Chronic Kidney Disease, Out of hospital cardiac arrest, In hospital periprocedural cardiac arrest, Procedural Intubation, Mechanical Ventricular Support, PCI for Moderate and severely complex lesions, PCI with 1 stent only, Multivessel coronary disease, Moderate left ventricular

dysfunction, Severe left ventricular dysfunction, mean daily temperature, humidity and particulate matter PM 2.5 level.