# Pollution and Heart Failure

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# Disclosures

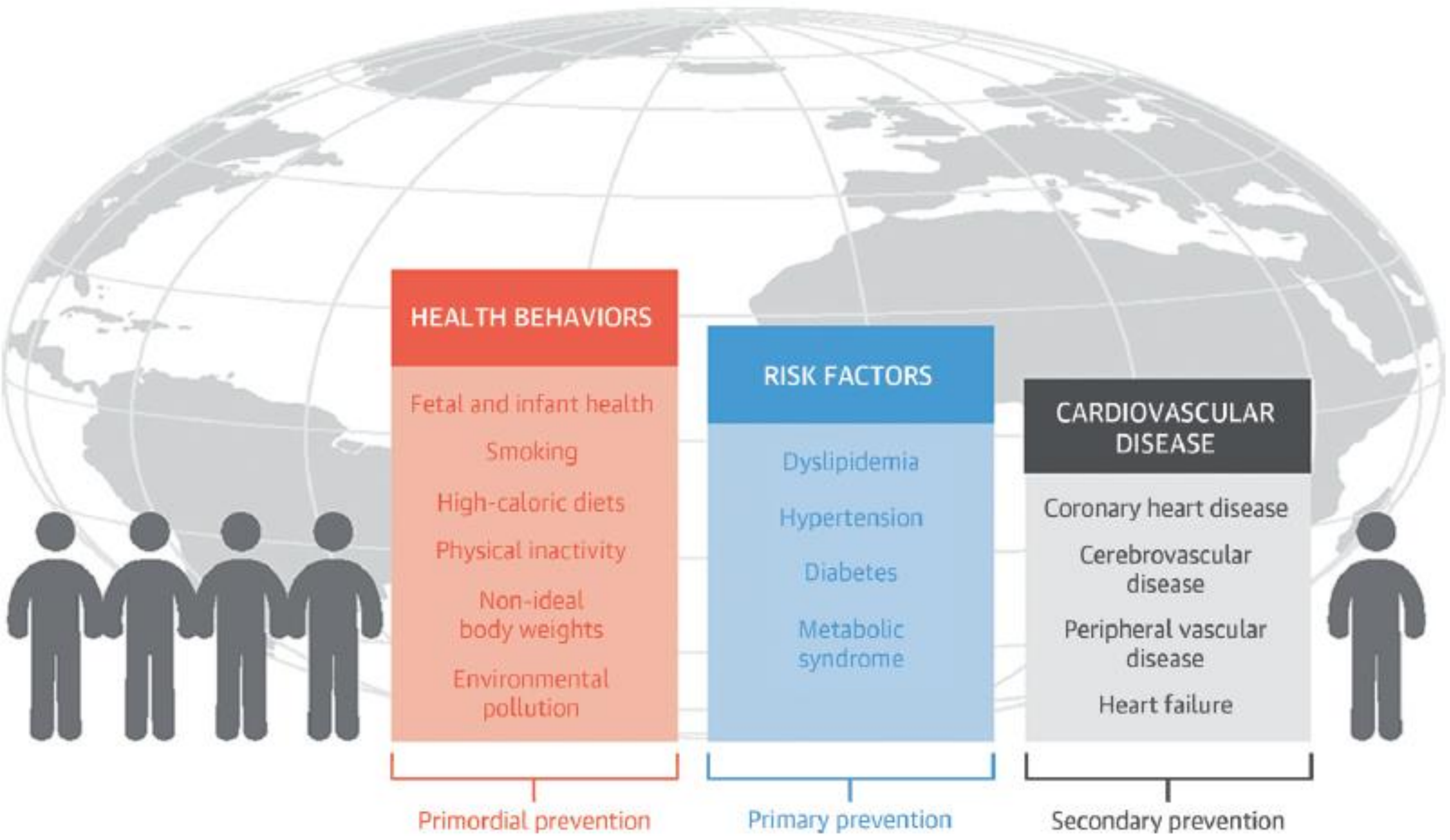
**Dr. Deepak L. Bhatt** discloses the following relationships - Advisory Board: Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex, Medscape Cardiology, MyoKardia, PhaseBio, PLx Pharma, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, MyoKardia, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, Takeda.

**This presentation may include off-label and investigational uses of drugs and devices.**

# Learning Objectives

- This talk will address
  - How poor air quality may worsen heart failure
  - Strategies to avoid negative impacts of pollution in everyday life
  - Ways in which COVID-19 may impact heart failure patients

# Primordial, Primary, Secondary Prevention




Vaduganathan M, Venkataramini AS, Bhatt DL. *JACC.* 2015.

*JACC* STATE-OF-THE-ART REVIEW

# Cardiopulmonary Impact of Particulate Air Pollution in High-Risk Populations

## *JACC* State-of-the-Art Review

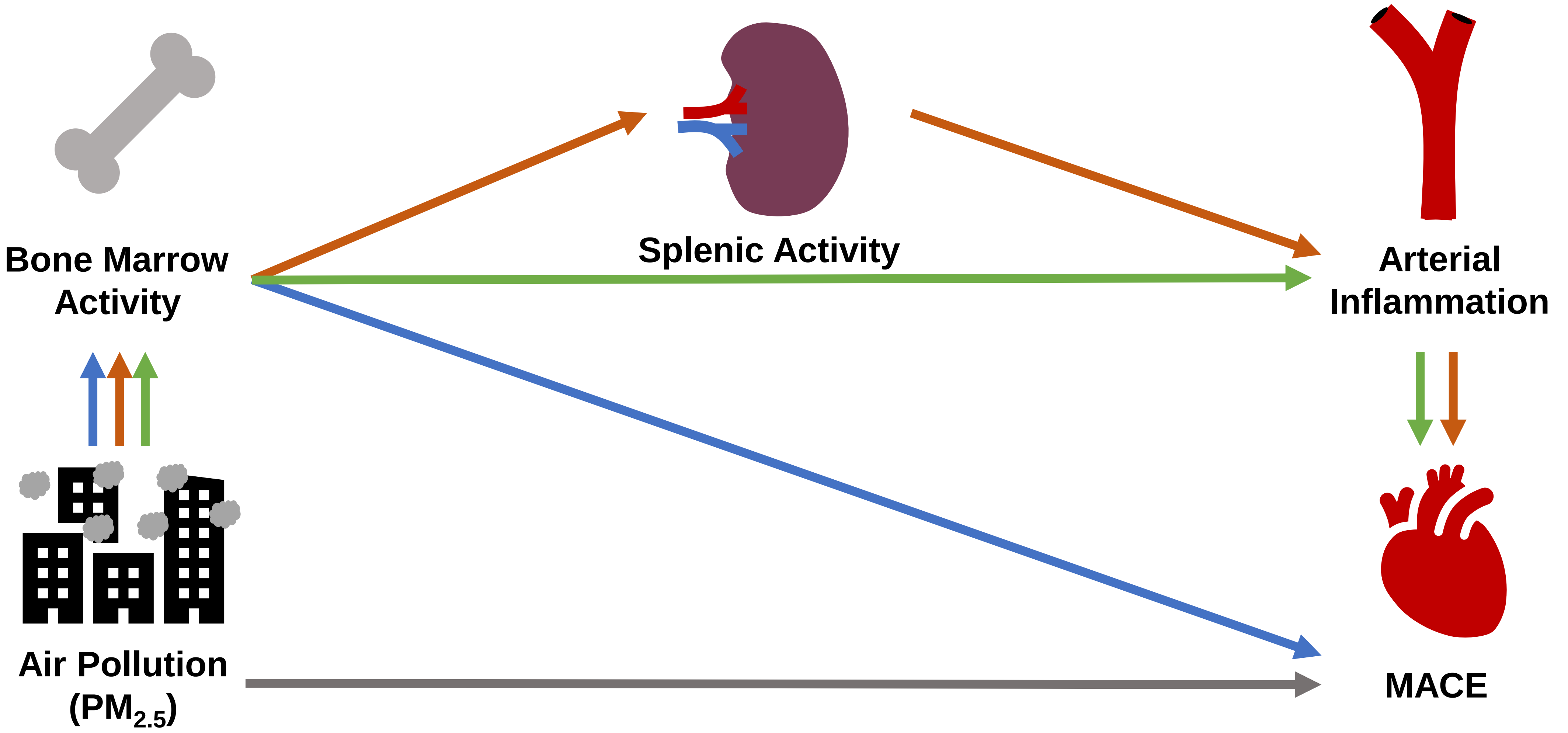
Jonathan D. Newman, MD, MPH,[a] Deepak L. Bhatt, MD, MPH,[b] Sanjay Rajagopalan, MD,[c] John R. Balmes, MD,[d] Michael Brauer, ScD,[e] Patrick N. Breysse, PhD,[f] Alison G.M. Brown, PhD, MS,[g] Mercedes R. Carnethon, PhD,[h] Wayne E. Cascio, MD,[i] Gwen W. Collman, PhD,[j] Lawrence J. Fine, MD, DrPH,[k] Nadia N. Hansel, MD, MPH,[l] Adrian Hernandez, MD, MHS,[m] Judith S. Hochman, MD, MA,[n] Michael Jerrett, PhD,[o] Bonnie R. Joubert, PhD,[p] Joel D. Kaufman, MD, MPH,[q] Ali O. Malik, MD, MSc,[r] George A. Mensah, MD,[s] David E. Newby, MD,[t] Jennifer L. Peel, PhD, MPH,[u] Jeffrey Siegel, PhD,[v] David Siscovick, MD, MPH,[w] Betsy L. Thompson, MD, MSPH, DrPH,[x] Junfeng Zhang, PhD,[y] Robert D. Brook, MD[z]

# Background

- Listed by the most recent Global Burden of Disease Study as the 4th leading risk factor for global mortality, air pollution results in an estimated mortality of 9 million people annually worldwide
- >50% of deaths due to air pollution are from cardiovascular causes
- Early data on use of air cleaners and facemasks support potential benefit on cardiovascular risk factors, but randomized clinical trials of $PM_{2.5}$ intervention are necessary
- Air pollution is also associated with COVID-19 mortality; HF patients are particularly at risk for developing and suffering serious complications from this infection

Rajagopalan S, et al. *Circulation*. 2020;142:00–00; Newman JD, et al. *JACC*. 2020;76(24):2878-94; Rajagopalan et al. *Eur J Heart*. 2021;00:1-3.

# Hypothesized Pathways Linking $PM_{2.5}$ Exposure and MACE




Abohashem S, et al. *Eur J Heart*. 2021;42(7):761-772.

# Biological Pathways Linking Air Pollution with CVD

**Cardiovascular disease progression** → **Cardiovascular events**

**Traditional risk factors**
- Vasoconstriction and elevated systemic and pulmonary BP
- Insulin resistance and hypoglycemia
- Dyslipidemia and HDL dysfunction

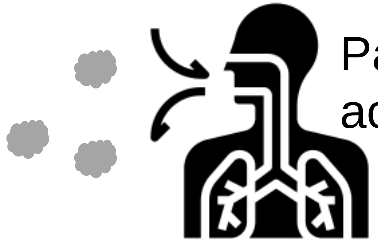
**Other risk factors**
- Activation of HPA axis
- Endothelial dysfunction and smooth muscle proliferation

**Development of subclinical CVD**
- Myocardial remodeling and fibrosis
- Progression of coronary and carotid atherosclerosis
- Systemic and pulmonary hypertension

Oxidative stress and inflammation
Pollutants enter systemic circulation
Neural reflex arcs and autonomic imbalance

**Mechanisms of acute CVD**
- Pulmonary and systemic vasoconstriction
- Impaired coronary vasodilation
- Endothelial dysfunction
- Platelet activation and thrombotic pathways
- Decreased fibrinolysis
- Increased myocardial oxygen demand
- Increased sympathetic tone
- Increased HR and decreased HR variability

Chronic exposure



Pathway activation

Acute exposure

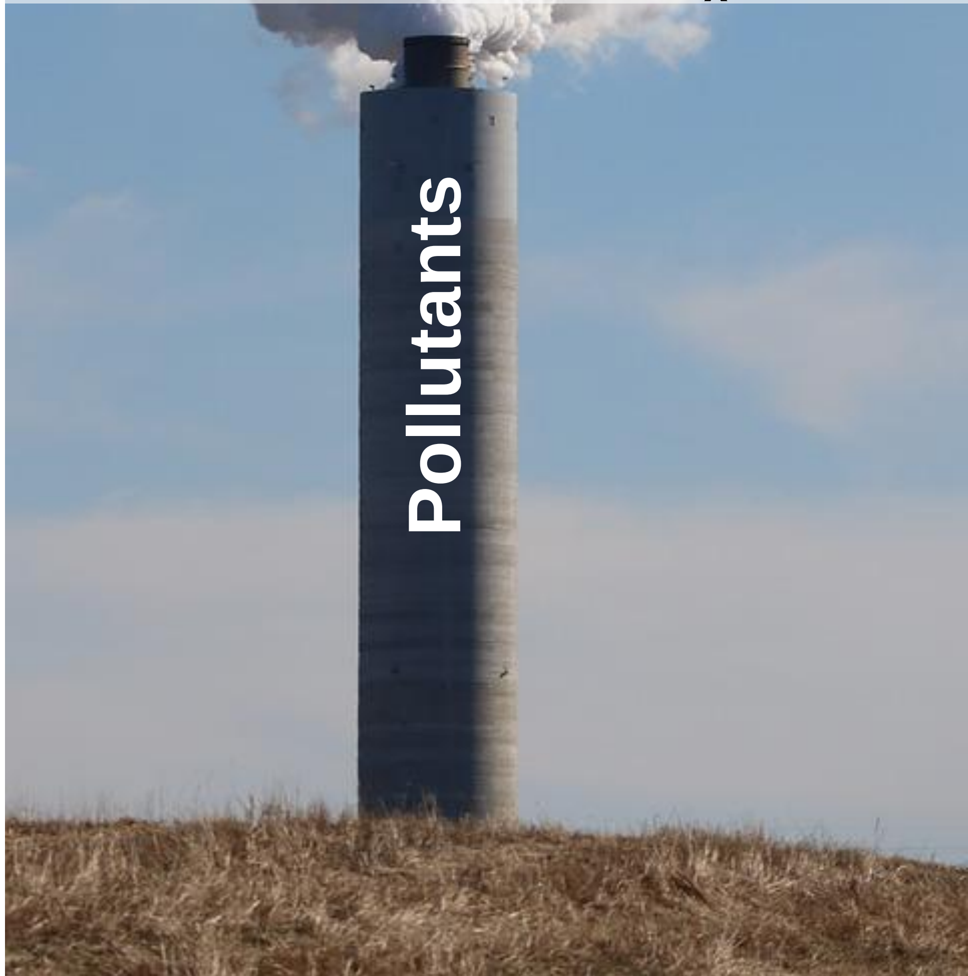
Brauer et al. *JACC*. 2021;In Press.

HPA = hypothalamic–pituitary–adrenal

# Air Pollution and HF

- Wang et. al explored the relationship between long-term exposure to various air pollutants (right) as well as impact of genetic susceptibility
- 432,530 participants free of HF, atrial fibrillation, or coronary heart disease from the UK Biobank Study were enrolled and followed for a median 10.1 years
- 4201 were documented with incident HF, and analysis showed the following:
  - Long-term joint exposure to various air pollutants is associated with an elevated risk of incident HF in an additive manner
  - The association between air pollution score and HF risk was strengthened by genetic susceptibility to HF

- **Particulate matter (PM) with diameters ≤2.5μm**
- **PM with diameters ≤10μm**
- **PM with diameters 2.5-10μm**
- **Nitrogen Dioxide ($NO_2$)**
- **Nitrogen Oxides ($No_x$)**




Wang M, et al. *Eur J Heart*. 2021;ehaa1031.

# Scoring

## Air Pollution Score

- The concentration of 5 pollutants was weighted by the multivariable-adjusted risk estimates in the analysis
- Participants were divided into 5 groups corresponding to the quintiles of air pollution score

**Air pollution score[1] =**

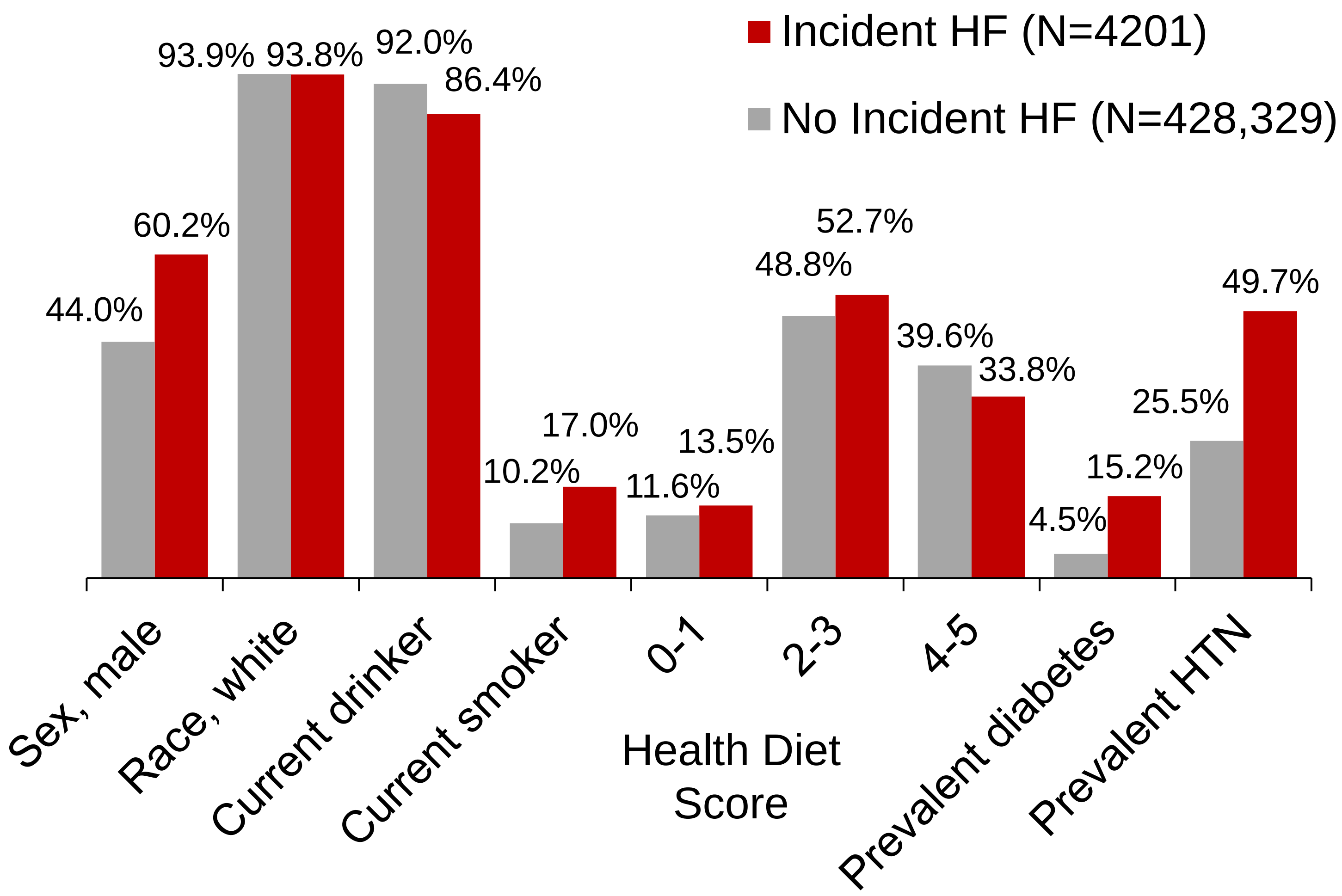
$(\beta[PM_{2.5}] \times PM_{2.5} + \beta[PM_{10}] \times PM_{10} + \beta[PM_{2.5\text{-}10}] \times PM_{2.5\text{-}10} + \beta[NO_2] \times NO_2 + \beta[NO_x] \times NO_x) \times$ (5/sum of the b coefficients)

## Genetic Risk Score (GRS)

- GRS for HF was calculated using 12 single-nucleotide polymorphisms based on a genome-wide association study[2]
- Participants were classified into 3 risk groups
  - Low (tertile 1)
  - Intermediate (tertile 2)
  - High (tertile 3)

1. Wang M, et al. *Eur J Heart*. 2021;ehaa1031. 2. Shah S, et al. *Nat Commun*. 2020;11:163.

# Baseline Characteristics of Participants in the UK Biobank Study

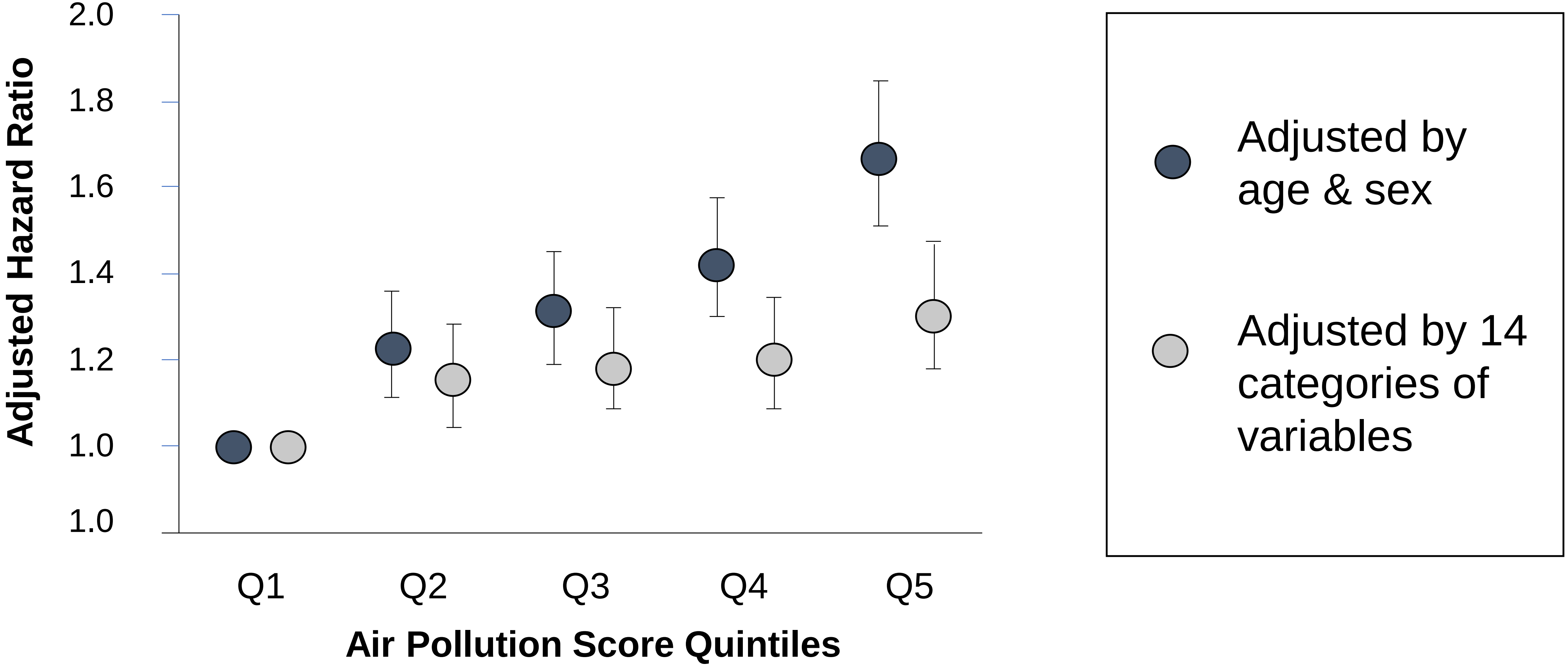



| Characteristic | HF | No HF |
|---|---|---|
| Age, years | 61.6 | 56.2 |
| BMI, kg/m$^2$ | 29.5 | 27.3 |
| TDI | -0.8 | -1.4 |
| MET, min/week | 2478.9 | 2666.8 |
| BP, mmHg | | |
| Systolic | 145.6 | 137.7 |
| Diastolic | 83.7 | 82.4 |
| Pollution, µg/m$^3$ | | |
| $PM_{2.5}$ | 10.2 | 10.0 |
| $PM_{10}$ | 19.4 | 19.3 |
| $PM_{2.5-10}$ | 6.5 | 6.4 |
| $NO_2$ | 30.0 | 29.3 |
| $NO_x$ | 46.1 | 43.9 |

TDI = Townsend Deprivation Index; BP = Blood Pressure

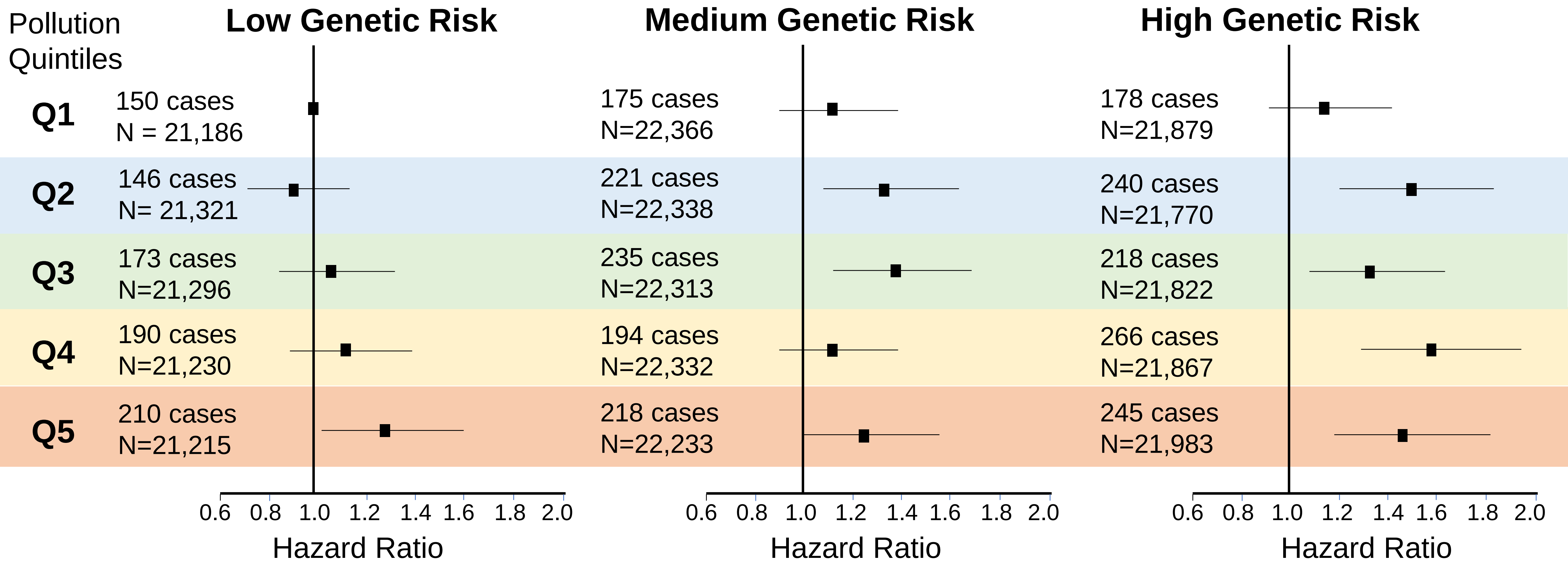
Wang M, et al. *Eur J Heart*. 2021;ehaa1031.

# Air Pollution Score Associated with Increased Risk of Incident HF, Strengthened by Genetic Susceptibility




Wang M, et al. *Eur J Heart*. 2021;ehaa1031.

# Joint Association of Air Pollution Score, HF GRS, and Risk of Incident HF




46% greater risk of HF in participants with high GRS and air pollution score

Wang M, et al. *European Heart Journal* (2021) 00, 1-10.

# Adjusted HR (95% CI) for Air Pollution Concentrations with the Risk of Incident HF

## Air Pollution Concentration (Quintiles)

| | $PM_{2.5}$ | $PM_{10}$ | $PM_{2.5-10}$ | $NO_2$ | $NO_X$ |
|---|---|---|---|---|---|
| Q1 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Q2 | 1.00 (0.90-1.11) | 1.17 (1.06-1.30) | 1.03 (0.93-1.13) | 1.11 (1.00-1.23) | 1.09 (0.98-1.21) |
| Q3 | 1.05 (0.94-1.16) | 1.24 (1.12-1.37) | 1.07 (0.97-1.18) | 1.18 (1.06-1.30) | 1.20 (1.08-1.33) |
| Q4 | 1.16 (1.05-1.29) | 1.16 (1.04-1.29) | 1.04 (0.94-1.15) | 1.23 (1.10-1.37) | 1.11 (1.00-1.24) |
| Q5 | 1.14 (1.02-1.27) | 1.31 (1.15-1.48) | 1.02 (0.93-1.13) | 1.24 (1.09-1.42) | 1.29 (1.16-1.45) |

## HR (95% CI) for a 10 μg/m³ increase and *P* for Trend

| $PM_{2.5}$ | $PM_{10}$ | $PM_{2.5-10}$ | $NO_2$ | $NO_X$ |
|---|---|---|---|---|
| 1.85 (1.34-2.55) | 1.61 (1.30-2.00) | 1.13 (0.80-1.59) | 1.10 (1.04-1.15) | 1.04 (1.02-1.06) |
| *P*<0.001 | *P*<0.001 | *P*=0.48 | *P*<0.001 | *P*<0.001 |

Wang M, et al. *Eur J Heart*. 2021;ehaa1031.

# Adjusted Hazard Ratios (95% CI) for Air Pollution Score and HF GRS with Risk of Incident HF

## Air Pollution Score

| | Cases (total N=86,506) | Adjusted for Age and Sex | Adjusted for 14 Variables |
|---|---|---|---|
| Q1 | 677 | 1.00 | 1.00 |
| Q2 | 819 | 1.23 (1.11-1.36) | 1.16 (1.05-1.28) |
| Q3 | 850 | 1.32 (1.19-1.46) | 1.19 (1.08-1.32) |
| Q4 | 890 | 1.43 (1.30-1.58) | 1.21 (1.09-1.35) |
| Q5 | 965 | 1.67 (1.51-1.84) | 1.31 (1.17-1.48) |
| | | *P*<0.001 | *P*<0.001 |

↑ 67% higher risk of incident HF in age- and sex-adjusted model in highest quintile vs lowest

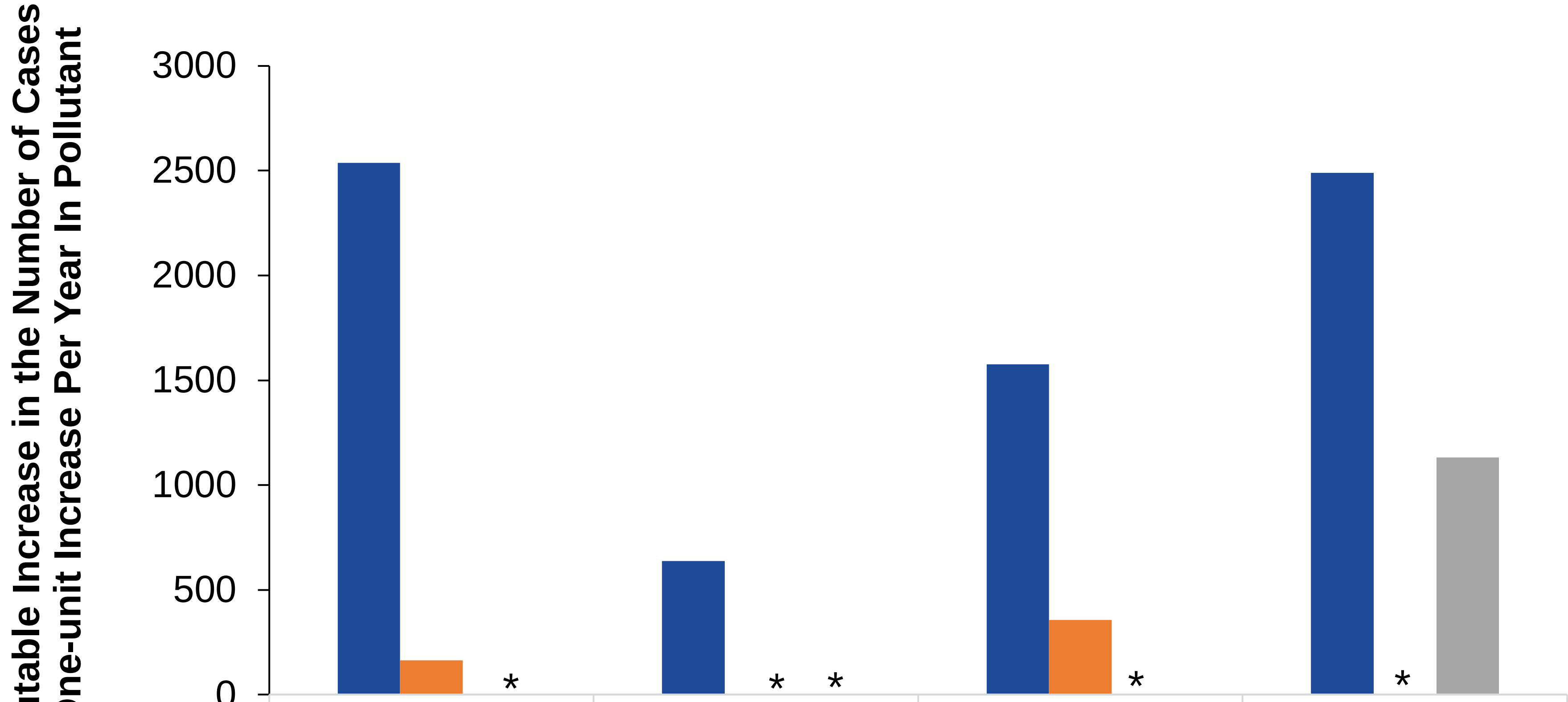
## HF Genetic Risk

| | Cases/N | Adjusted for Age and Sex | Adjusted for 14 Variables |
|---|---|---|---|
| Low | 869/ 106,248 | 1.00 | 1.00 |
| Medium | 1043/ 111,582 | 1.15 (1.05-1.26) | 1.15 (1.05-1.25) |
| High | 1147/ 109,321 | 1.31 (1.20-1.43) | 1.39 (1.19-1.42) |
| Continuous Variable | | 2.73 (2.05-3.62) | 2.65 (1.99-3.53) |
| | | *P*<0.001 | *P*<0.001 |

↑ 173% higher risk of incident HF associated with HF GRS in models adjusted for sex, age, assessment center, genotyping batch, and 1$^{st}$ 10 genetic principal components

Wang M, et al. *Eur J Heart*. 2021;ehaa1031.

# Long-Term Associations: Air Pollution and Hospital Admissions Among Medicare Participants




| | Ischemic stroke | Myocardial infarction | Atrial fibrillation | Pneumonia |
|---|---|---|---|---|
| PM2.5 | 2536 | 637 | 1575 | 2489 |
| NO2 | 163 | N/A | 357 | N/A |
| O3 | N/A | N/A | N/A | 1131 |

The study associated…

- $PM_{2.5}$ increases with hospitalizations across all studied outcomes
- $NO_2$ increases with stroke and AF
- And $O_3$ increases with pneumonia

*Negative values on probability scale are not logical. As such, attributable number of cases were not calculated

Yazdi MD, et al. *Circulation*. 2021 Feb 22. doi: 10.1161/CIRCULATIONAHA.120.050252. Online ahead of print.

# Long-Term Associations: Air Pollution and Hospital Admissions Among Medicare Participants (cont)

- On an additive scale, air pollution risks human health, especially among the **very old patients**
- The **largest increase** in the risk of admissions per unit change in exposure **occurs at lower concentrations of air pollutants**
- At these lower concentrations, increases in **any** of the studied air pollutants **increased the probability of hospitalization** with larger effect estimates than the primary results

**>50%** of the U.S. population is exposed to such levels

Yazdi MD, et al. *Circulation*. 2021 Feb 22. doi: 10.1161/CIRCULATIONAHA.120.050252. Online ahead of print.

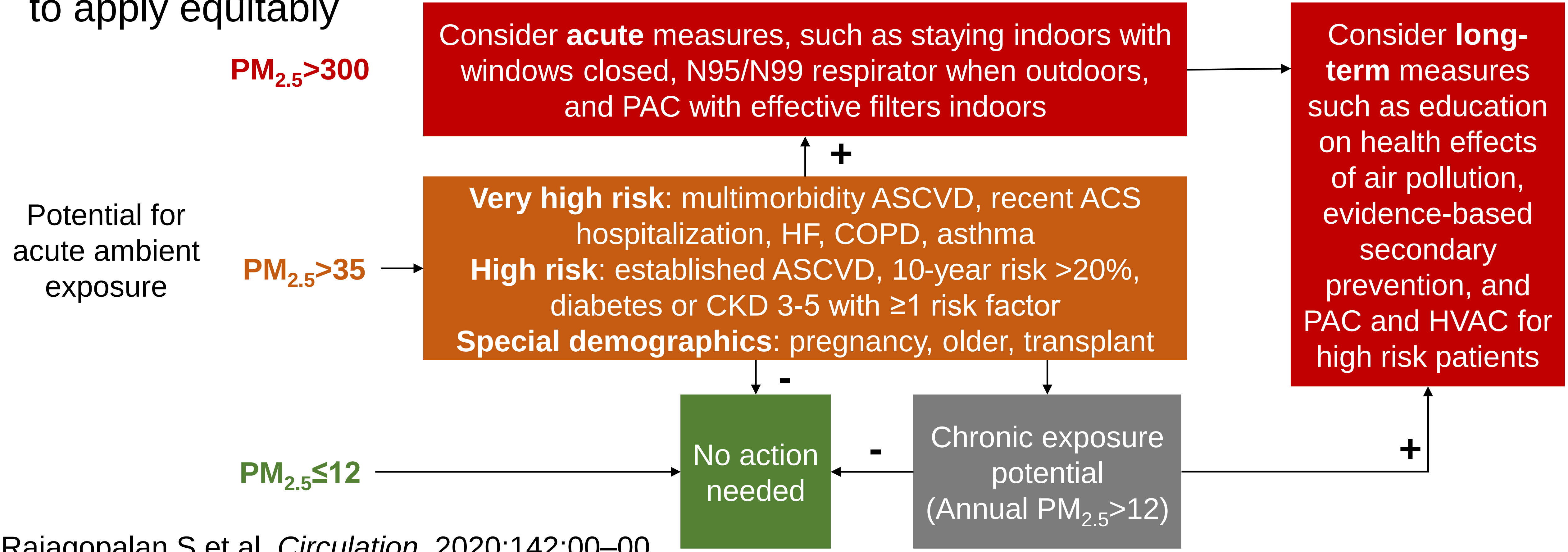
Circulation
Volume 142, Issue 23, 8 December 2020; Pages e411-e431
https://doi.org/10.1161/CIR.0000000000000931

# Personal-Level Protective Actions Against Particulate Matter Air Pollution Exposure: A Scientific Statement From the American Heart Association

**Sanjay Rajagopalan, MD, Chair, Michael Brauer, ScD, Aruni Bhatnagar, MD, Deepak L. Bhatt, MD, MPH, Jeffrey R. Brook, PhD, Wei Huang, ScD, Thomas Münzel, MD, PhD, David Newby, MD, PhD, Jeffrey Siegel, PhD, Robert D. Brook, MD, Vice Chair, and On behalf of the American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; and Stroke Council**

# Strategies to Avoid Negative Impacts of Pollution

For optimal impact the approach should be practical, safe, and low cost or no cost; to a degree congruent with the risk of the patient and level of exposure; and feasible to apply equitably

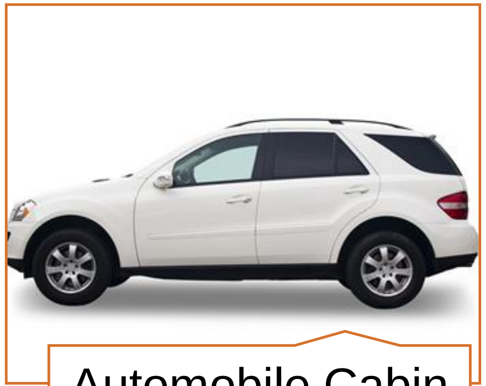



Rajagopalan S et al. *Circulation*. 2020;142:00–00.

# Personal Exposure Mitigation and Behavioral Tactics

HVAC filters

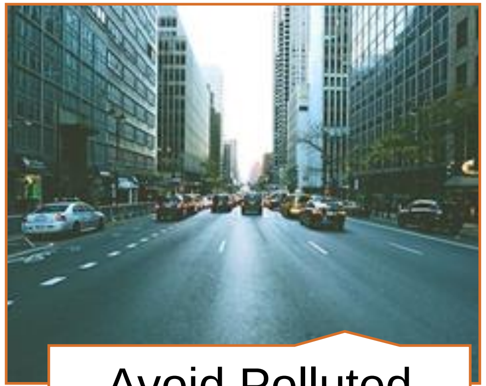
N95 Respirator



Automobile Cabin Filter

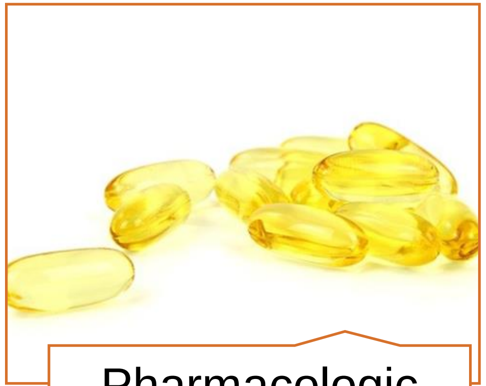
Portable Air Cleaner

Staying Indoors



Avoid Polluted Areas

Exercise

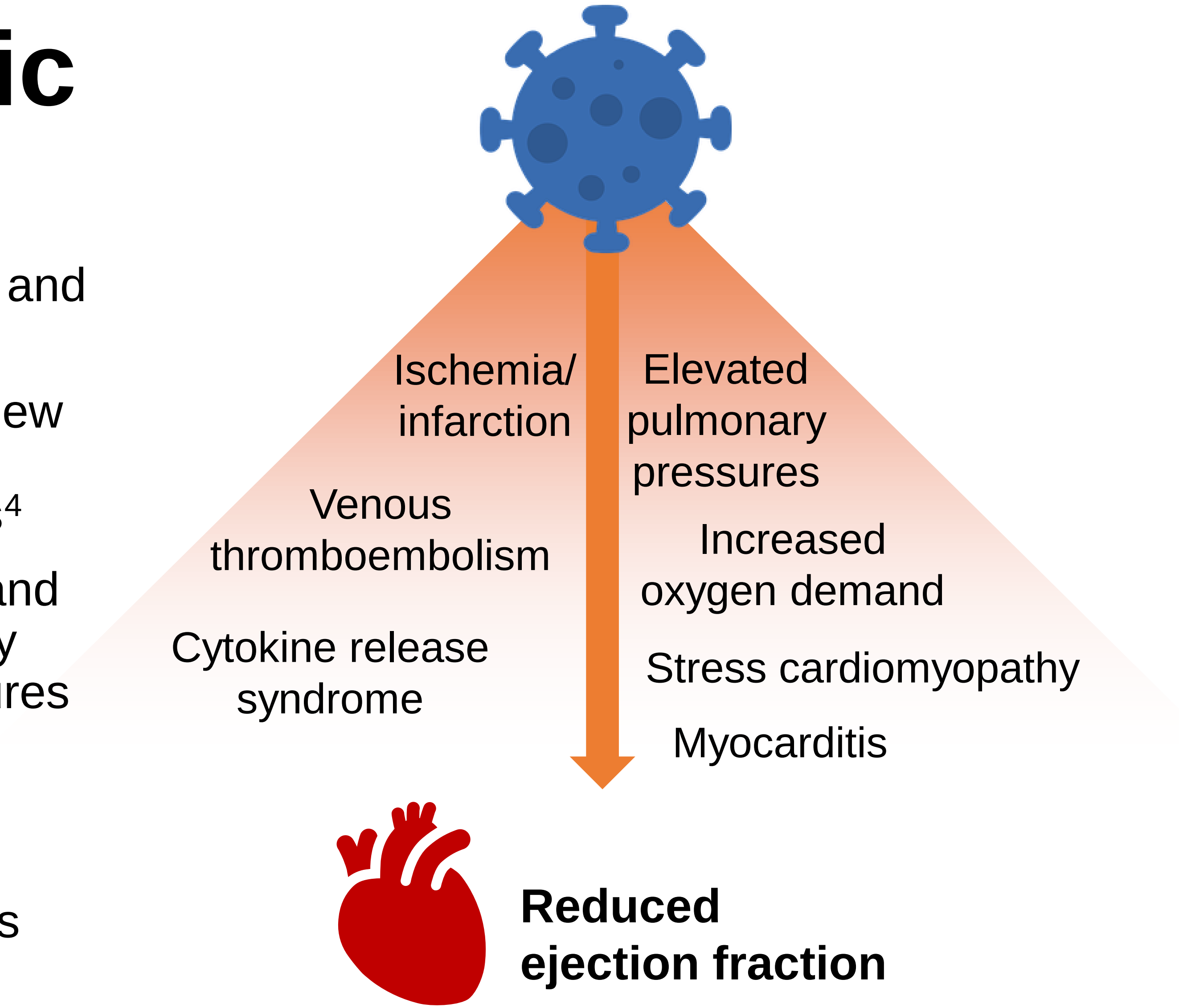


Pharmacologic Agents?

Rajagopalan S et al. *Circulation*. 2020;142:00–00.

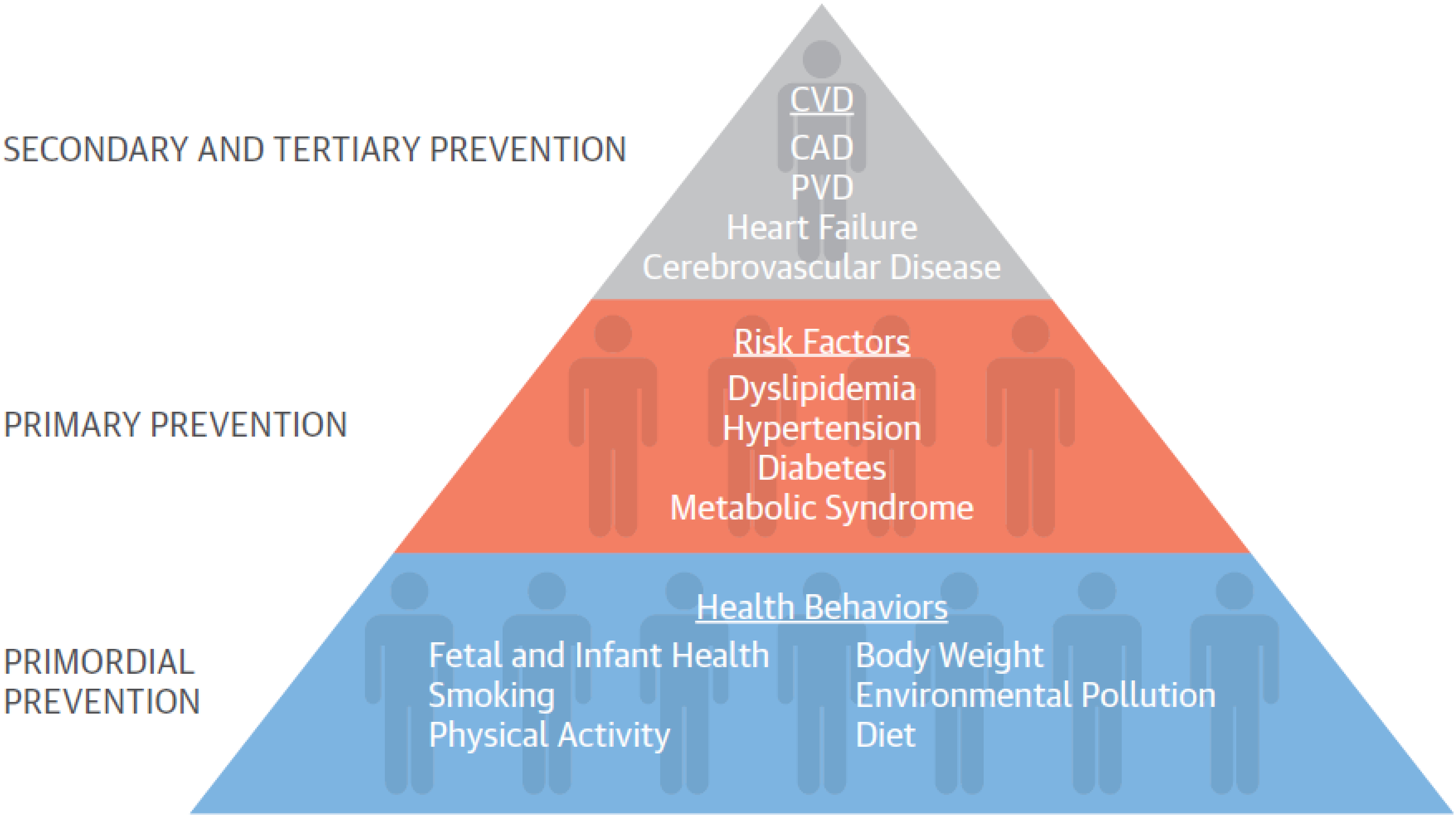
# In the Context of the COVID-19 Pandemic

- Several studies have reported significant associations between COVID-19 mortality and air pollution[1-3]
- The pandemic has affected patients with new or existing HF, potentially complicating presentation, management, and prognosis[4]
- Patients with HF are at risk of COVID-19 and serious associated complications, and they should strictly adhere to preventive measures as well as following personal exposure mitigation tactics for air pollution
- It is crucial to rule out COVID-19 in hospitalized patients with HF, as symptoms overlap




1. Liang D, et al. *Innovation (NY)*. 2020;1(3):100047. 2. Wu X, et al. *Sci Adv*. 2020;6(45):eabd4049.3. 3. Fattorini D, Regoli F. *Environ Pollut*. 2020;264:114732. 4. DeFilippis EM, et al. *JACC Heart Fail*. 2020 Aug; 8(8): 681–691. 5. Zhang Y, et al. *Eur J Heart Fail*. 2020;22(6):941-956.

# Pyramid of Risk




Hong KN, Fuster V, Rosenson RS, Rosendorff C, Bhatt DL. *JACC* 2017;70:2171-2185.

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## *Thank You!*


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