
The 7th annual BREATHE Workshop
Environmental Aerosols and Health Effects
MAY 24, 2024
UCR
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BREATHE CENTER

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Welcome to the 7th BREATHE Workshop!!

I am David Lo, Director of the BREATHE Center at UCR. We were founded as part of a faculty cluster recruitment nearly ten years ago, building on a strong collaborative network across campus, focusing on Bridging Regional Ecology, Aerosolized Toxins, and Health Effects. That is, we study air quality and health effects. Over the past several years, we have hosted workshops and "data dump" sessions on a broad range of topics, from wildfire smoke, air quality monitoring, humanities perspectives, and we have certainly not exhausted the possible topics for discussion. This year, our main focus is Environmental Aerosols and Health Impacts, and we have a great group of talks and exciting keynote speakers.

The BREATHE Center has been maturing in its active research programs, some of which will be presented today, and we hope that our continued discussions and collaborations will begin to develop into some novel research grant proposals. But meanwhile, please enjoy the presentations and conversations!!

Main partners in this work include faculty from:

UC Riverside, Biomedical Sciences, School of Medicine (SOM)

College of Engineering Center for Environmental Engineering and Technology (CE-CERT)

Center for Conservation and Biology (CCB)

Environmental Dynamics and GeoEcology (EDGE)

BREATHE Affiliates:

Bourns College of Engineering (BCOE)

The College of Natural and Agricultural Sciences (CNAS)

The College of Humanities, Arts, and Social Sciences (CHASS)

The School of Public Policy (SPP)

The School of Medicine (SOM)

The Science and Technology Studies group in the UCR Center for Ideas and Society

Health Assessment and Research for Communities (HARC)

7th Annual Breathe Workshop Agenda

- MAY 24TH, 2024 | 11:00AM - 5:00 PM -

UC Riverside, School of Medicine Education II Building, Room 106

11:00 am	**Registration**
11:30-12:00pm	**Workshop Lunch**
12:00-12:10pm	**Welcome and Introduction** ***David Lo, MD., PhD.*** *| University of California, Riverside*

AFTERNOON MODERATOR I, EMMA ARONSON, PHD.

	Keynote Speaker
12:15-1:15pm	**You can't manage what you can't measure: our current knowledge, challenges, and future directions for evaluating dust emissions from the dry lakebed of Great Salt Lake"** ***Molly Ann Blakowski,*** *Graduate Student | University of Utah*
1:15-1:35pm	**"Source-Specific Acute Cardio-Respiratory Effects of Ambient Dust Exposure in California's Salton Sea Region"** ***Will Porter, PhD.,*** *Assistant Professor, Department of Environmental Sciences, University of California, Riverside*
1:35-1:45pm	**"Physical and Chemical Characterization of Salton Sea Playa Dust"** ***Alexander MacDonald,*** *Postdoctoral Scholar, Roya Bahreini lab University of California, Riverside*
1:45-1:55pm	**"A Likely Suspect: LPS from the Salton Sea Drives Neutrophilic Pulmonary Inflammation"** ***Keziyah Yisrael,*** *Graduate student, David Lo lab University of California, Riverside*
1:55-2:35pm	**Afternoon Break and Poster Session**

AFTERNOON MODERATOR II, WILLIAM PORTER, PHD.

2:35-2:45pm

"The Core Dust Microbiome and its Pathogenic Potential"

Linton Freund, *Graduate Student, Emma Aronson lab*
University of California, Riverside

2:45-3:05pm

"Microbial-Mediated Pyrogenic Organic Matter and Nitrogen Cycling genes increase over time after a Chaparral wildfire"

Fabiola Pulido, *Post-doctoral Fellow, Sydney Glassman lab*
University of California, Irvine

3:05-3:15pm

"Inflammation and respiratory control: mechanisms and clinical consequences"

Veronica Penuelas, *Graduate student, Erica Heinrich lab*
University of California, Riverside

3:15-3:30pm

"Dynamic chemistry and toxicity of secondhand e-cigarette aerosols"

Ying-Hsuan Lin, PhD., *Associate Professor*
University of California, Riverside

3:30-3:40pm

"Lung-Brain Interactions: Sex-dependent Responses to allergic inflammation"

Monica Carson, *Professor | University of California, Riverside*

3:40-4:00pm

Afternoon Break II and Poster session

4:00-5:00pm

Keynote Speaker

"Unraveling the Ocean's Influence on Air Quality and Human Health in a Changing Climate"

Kimberly Prather, *Distinguished Professor | University of California, San Diego*

5:00pm

Closing remarks and expression of gratitude

David Lo, MD., PhD. *| University of California, Riverside*

UC RIVERSIDE BREATHE

Talk Abstracts

1.“You can't manage what you can't measure: our current knowledge, challenges, and future directions for evaluating dust emissions from the dry lakebed of Great Salt Lake”

BLAKOWSKI, MOLLY A.

Utah State University

Dust from desiccating saline lakes can have significant impacts on the environment, air quality, human health, and the economy. Yet, there's no one-size-fits all approach to monitoring, measuring, or mitigating dust emissions from dry lakebeds, and each has its own challenges to consider. In this presentation, I will discuss the state of the science on Great Salt Lake dust and its many potential impacts on human and ecosystem health. I will summarize key findings from different research efforts and share new results from my dissertation research, including the first multi-year record of wind erosion on the dry lakebed of Farmington Bay and evidence that metals can be transferred from Great Salt Lake dust to food crops. I will relate the current knowns and unknowns of Great Salt Lake dust to recently funded proposals, priorities discussed during last week’s Great Salt Lake Dust Forum, and the many research and management opportunities that lie ahead.

2. "Source-Specific Acute Cardio-Respiratory Effects of Ambient Dust Exposure in California's Salton Sea Region"

PORTER C., WILLIAM; Miao, Yaning; Benmarhnia, Tarik; Lyons, Timothy; Hung, Caroline; Diamond, Charlie

California Air Resources Board
University of California, San Diego
University of California Riverside

Windblown dust is an ongoing air quality and public health concern among residents living around California's Salton Sea, a region characterized by serious socioeconomic and health outcome disparities. Dropping water levels and unique biogeochemistry at the Salton Sea have raised concerns regarding the human health impacts of drying sediments exposed on shrinking shorelines, as well as potential lake spray emissions from the water surface itself. As particles emitted from different surface types can differ greatly in terms of composition, size distribution, and other properties, variability in the resulting health impacts of windblown dust reaching communities in the region may likewise be source dependent but remain understudied. Here we use observed coarse particulate matter (PM2.5-10) concentrations and then modeled back trajectories as well as land surface data to estimate individual source region types for particulates observed at long distance monitoring sites in the Salton Sea region. We then apply this data product to an analysis of source-specific acute cardio-respiratory impacts using a time-stratified case crossover design with conditional logistic regression based on 171,465 hospitalizations cases recorded from 2008 to 2019. We quantify and compare the acute health effects of dust arriving from different directions and estimated likely source surfaces on respiratory and cardiovascular hospitalizations. Using a remote sensing chlorophyll-a data product, we further investigate the possible influence of periodic bloom events – a result of ongoing nutrient loading – on surrounding hospitalizations.

3."Physical and Chemical Characterization of Salton Sea Playa Particles"

MACDONALD, ALEXANDER B.[1]; Bond[2] , Robin; Botthoff[2] , Jon; Humphreys[3], Jennifer; Brounce[3], Maryjo; Aronson[2,4], Emma; Lo[5,6,7], David D.; Bahreini[1] , Roya

[1] Department of Environmental Sciences
[2] Center for Conservation Biology
[3] Department of Earth and Planetary Sciences
[4] Department of Microbiology and Plant Pathology
[5] Division of Biomedical Sciences, School of Medicine
[6] BREATHE Center
[7] Center for Health Disparities Research
University of California, Riverside, Riverside, CA, USA

The Salton Sea is a terminal saline lake in California that is shrinking due to natural and anthropological causes. The exposed dry lakebed soil (playa) can experience frequent dissolution and reprecipitation of salt minerals, thus creating a crust made of loose aggregates which emits copious amounts of dust into the air. These dust emissions are linked to a high prevalence of asthma among residents of the Salton Sea. This study examines the physical and chemical characteristics of playa particles to better understand how these particles are entrained (i.e., become airborne). Particle/soil samples were collected in November 2023 at a site on the Salton Sea shore (Red Hill Bay, RHB), a site near the shore and heavily influenced by the Salton Sea dust emissions (Dos Palmas, DP), and at a control site north of the Salton Sea (Boyd Deep Canyon, BDC). Samples were collected at three depths (0–5 mm, 6–10 mm, and 60–70 mm) to study the effect of surface processes. The dried and sieved samples were analyzed with a laser diffraction particle sizer to determine particle size distribution, and by scanning electron microscopy-energy dispersive x-ray spectrometry (SEM-EDS) to determine particle morphology and elemental composition. For the three sites, the volume size distribution is the same at the two top depths (0–5 mm and 6–10 mm) and different at the bottom depth (60–70 mm), suggesting that the playa/soil is homogenous in the top 10 mm. This was qualitatively corroborated with the SEM-EDS images. Number size distribution at the top 10 mm between all three sites showed that number concentration peaks at ~1.0 µm for the control site (BDC) and at ~0.5 µm for the two sites on or near the Salton Sea shore (RHB and DP), thus showing that the playa/soil particles collected closer to the Salton Sea are finer than those collected farther away. SEM-EDS elemental maps show particles from RHB and DP to be covered in smaller halide particles (NaCl), whereas this was not clearly observed in the BDC sample. The abundant concentration of small halide particles in the samples from RHB and DP together with the smaller size distribution are consistent with the hypothesis that salt mineral dissolution and reprecipitation contributes to the formation of a loose playa crust made of fine particles that are easily entrained.

4. "A Likely Suspect: LPS from the Salton Sea Drives Neutrophilic Pulmonary Inflammation"

YISRAEL KEZIYAH; Castillo, Diana del; Shapiro Malia; Alaama, Troy; Gonzalez, Daniel; Dingilian, Hovaness; Topacio, Talyssa; Freund, Linton; Aronson, Emma; Lo, David; Cocker, David; Morin, Chris; LeComte-Hinley, Jenna

Health Assessment and Research for Communities
University of California, Riverside

California's largest lake, the Salton Sea, situated at the Riverside-Imperial County border, is linked to rising asthma cases in nearby communities. In environmental chamber exposure studies, we found that mice exposed to material collected from across the region showed responses characteristic of innate immunity rather than allergic immunity, with a pattern suggesting LPS as the likely toxin. To confirm the toxin identity, wildtype (WT) C57BL/6J mice, Toll-like receptor 4 (TLR4) -/- mice, Toll-like receptor 2 (TLR2) -/- mice, and MYD88 -/- mice were exposed to Salton Sea dust for 48 hours. WT and TLR2 -/- mice exhibited similar inflammatory cell cellular recruitment, but TLR4 -/- and MYD88 -/- mice were unresponsive to the dust, suggesting that LPS is indeed the aerosol toxin. Quantification of LPS concentrations in dust samples gathered from across the region revealed surprisingly high concentrations of LPS, with a distinct gradient from the Northern to Southern end of the lake. To determine whether this was relevant to the incidence of clinical disease, we conducted an epidemiological study on immune-related symptoms and diagnoses. Strikingly, we found that asthma incidence followed a North to South gradient very similar to the LPS dust concentration gradient, peaking at upwards of 30+% in Imperial County. These results strongly implicate aerosolized LPS, likely entrained from the Salton Sea water microbiome into playa dust, as a key driver of the region's pulmonary health issues.

5. "The Core Dust Microbiome and its Pathogenic Potential"

FREUND, LINTON; Topacio, Talyssa; Miao, Yaning; Porter, William; Aronson, Emma

University of California, Riverside

The Salton Sea is a hypersaline lake in Southern California that is rapidly shrinking due to water diversion and ecological negligence. As the lake recedes, its playa becomes exposed and made airborne, increasing local dust emissions. Dust proliferation continues to threaten the health of nearby communities, many of whom lack access to health care and are disproportionately burdened by respiratory illnesses. While it is understood that high particulate matter load in the atmosphere is detrimental to human health, the effects of environmental dust microorganisms on respiratory health are under studied. Here we aim to establish a connection between the aeolian (i.e., windblown) dust microbiome, ecological stability, and public health. Dust samples were collected from four sites around the Salton Sea in the Summer and Fall of 2020 and 2021. Several bacterial genera dominated the aeolian microbiomes across locations and collection periods, most notably Massilia species, which were found at relative abundances of greater than 25% in multiple samples. While a set of core microbial taxa were identified across our study sites, environmental drivers of microbial composition were significantly different in each location. Furthermore, shotgun metagenomes isolated from our samples revealed that aeolian dust microorganisms contain a variety of lipopolysaccharide (LPS) biosynthesis genes (i.e., LpxL, kdta) as well as endospore-formation genes (i.e., spoIVCA). These traits not only support the survival and transport of dust microorganisms but are also commonly found in pathogens. Our results demonstrate the potential of airborne dust microorganisms to adapt to their harsh environment and disperse across broad distances, thus posing a growing health risk to exposed communities.

6. “Microbial-Mediated Pyrogenic Organic Matter and Nitrogen Cycling genes increase over time after a Chaparral wildfire”

PULIDO-CHAVEZ, FABIOLA, M.; Nelson, Amelia R.; Wilkins Michael J.; Glassman, Sydney I.

Wildfires alter soil chemistry and microbial communities, creating niche space for pyrophilous, “fire-loving”, microbes to initiate secondary succession. Wildfires also increase soil nitrogen (N) and transform woody vegetation into difficult-to-decompose pyrogenic organic matter (PyOM), a potential carbon source for pyrophilous microbes. The degradation of post-fire resources by pyrophilous microbes impacts global carbon and N cycling, including carbon sequestration and greenhouse gas emissions. We previously found that microbial richness decreased, and microbial communities changed substantially and experienced rapid post-fire secondary succession. Here, we used shotgun metagenomics on 30 burned and unburned samples collected across 5 timepoints to determine if changes in microbial community composition led to functional changes in carbon and N cycling. Specifically, soils were collected at 17, 25, 34, 131, and 376 days after a southern California wildfire in a fire-adapted chaparral shrubland. Not only did overall profiles of carbon and N cycling genes differ between burned and unburned plots, but burned plots showed dramatic increases in genes responsible for degrading PyOM (167%) and cycling N (117%). This is in stark contrast to unburned plots, where gene abundances for PyOM degradation and N cycling remained stable over time. Moreover, genes encoding degradation of two PyOM intermediates, catechol and protocatechuate, revealed that the easier-to-degrade ortho-cleavage pathways dominated across time in burned plots, as did genes encoding N retention. Finally, the dominant pyrophilous bacteria Massilia and Noviherbaspirillium encoded different PyOM and N processing pathways, suggesting that niche complementarity or trade-offs in traits enable the adaptation to post-fire resource acquisition.

7. “Inflammation and respiratory control: mechanisms and clinical consequences”

PENUELAS, VERONICA; Pham, Kathy; Frost, Shyleen; Vargas, Abel; Harahap-Carrillo; Indira Kaul, Marcus; Nair, Meera; Heinrich, Erica

University of California, Riverside

Breathing is controlled by an intricate interplay between a central pattern generator, multiple reflexes, and several inputs to the respiratory center of the brainstem. Recent evidence suggests that some of these ventilatory reflexes may be modified by inflammatory signals in the periphery. Specifically, the sensitivity of the ventilatory response to hypoxia seems to be impacted by systemic inflammation. Such a relationship is significant because modifications of the hypoxic ventilatory response can cause sleep disordered breathing and can impact outcomes in critical lung injury. Thus, to gain a better understanding of how inflammation may be associated with ventilatory reflexes, we examined the relationship between systemic inflammatory marker expression and ventilatory reflexes to oxygen and carbon dioxide in a cohort recovered from COVID-19 (known to induce an acute cytokine storm and vascular damage), as well as a matched control group. We identified long-term impacts of COVID-19 on ventilatory control, as well as significant correlations between the sensitivity of the hypoxic ventilatory response and levels of systemic inflammation. These results highlight the potential contribution of inflammatory signaling in the neural control of breathing.

8. "Dynamic chemistry and toxicity of secondhand e-cigarette aerosols"

LIN, YING-HSUAN; Woo, Wonsik; Tian, Linhui; Lum, Michael; Canchola, Alexa; Chen, Kunpeng

Department of Environmental Sciences
Environmental Toxicology Graduate Program, University of California, Riverside

E-cigarette aerosols represent a complex mixture of gases and suspended particles or droplets that can linger in the air. The emitted e-cigarette aerosols can undergo chemical transformation in the surrounding environment, known as the aging process. This process leads to significant alterations in the chemical composition and toxicity of the aged e-cigarette aerosols, in contrast to the aerosols that are freshly emitted. Terpenes are common flavor additives used in e-liquids. When terpenes are released into the indoor environment, they can quickly react with ambient atmospheric oxidants like ozone to generate highly oxygenated and condensable species, including reactive oxygen species (ROS). While vaping emissions may become a significant source of secondary indoor air pollutants, the exposure to these aged (i.e., transformed) vaping emission products have not been well characterized. In this study, we simulated the indoor aging of terpene-flavored e-cigarette emissions in a 2 m3 FEP film chamber with 100 ppb of O3. ROS production was determined in both freshly emitted and aged e-cigarette aerosols using complementary analytical approaches, including electron paramagnetic resonance (EPR) spin-trapping, the DCFH2 assay, iodometry, and high-resolution mass spectrometry. Human bronchial epithelial lung cells (BEAS-2B) were exposed to both freshly emitted and aged e-cigarette aerosols to assess oxidative stress-related gene expression. Our findings indicate that the formation of organic hydroperoxides via ozonolysis of terpene flavor additives in aged e-cigarette aerosols is key to elevated aerosol-phase ROS production. Furthermore, exposure to aged e-cigarette aerosols resulted in significant upregulation of the oxidative stress-related genes (HMOX-1 and GSTP1) in BEAS-2B cells. These differential results between fresh vaping emissions and aged e-cigarette aerosols highlight the dynamic changes in chemical composition and inhalation toxicity of e-cigarette aerosols in the indoor environment, while the surrounding environment plays an important role in modulating the production of ROS and the consequent health effects.

9. “Lung-Brain Interactions: Sex-dependent Responses to allergic inflammation”

CARSON, MONICA

University of California, Riverside

While the brain is often viewed as being isolated and protected from systemic insults by the blood-brain-barrier (BBB), systemic inflammation can trigger neuroinflammatory responses within the brain. Here, we examined the consequences of allergic lung inflammation triggered by one-week airborne exposure to non-infectious Alternaria alternata fungal particulates on gliosis and neuronal synapses in adult mice. We found that airborne exposures sufficient to cause allergic lung inflammation was sufficient to cause a reduction in synaptic molecules in the brainstem region regulating respiration but only in exposed female mice and not male mice. Furthermore, this reduction was dependent on the vagal nerve connecting the lung to the brainstem. These data suggest that lung inflammation may alter neuronal regulation of breathing in a sex-dependent mechanism.

10. “Unraveling the Ocean's Influence on Air Quality and Human Health in a Changing Climate”

PRATHER, KIMBERLY

University of California, San Diego

As our climate undergoes rapid change, understanding the intricate interplay between the ocean and atmosphere is crucial. Human-induced pollution exacerbates environmental challenges, yet current models do not begin to account for the massive impact of human pollution on the ocean and atmosphere. Particularly understudied are the impacts of waterborne microbes and pollution on coastal air quality and human health.

This presentation will discuss insights gleaned from innovative laboratory experiments conducted at the NSF Center for Aerosol Impacts on Chemistry of the Environment (CAICE). Emphasizing coastal environments, scientists are exploring the composition, cloud-forming abilities, and ice nucleation properties of marine aerosols.

Using the Scripps Ocean-Atmosphere Research Simulator (SOARS), we are investigating ocean-atmosphere exchange dynamics under varying conditions with control of winds, waves, microbiology, and temperature. Additionally, we are performing studies to better understand the transfer mechanisms involved aerosolization of bacteria, viruses, and gases from the ocean to the atmosphere.

This presentation will discuss the implications of human-induced environmental changes on human health, ecosystems, and climate. As we confront unprecedented warming, this presentation underscores the urgency of comprehensively understanding coastal water pollution impacts on air quality and human health in the southern San Diego region.

Poster Abstracts

1. "Risks and Outcomes Associated with Chronic Particulate Matter Exposure in Non-smoker Obese Adults; a Retrospective Clinical Investigation"

SEYLANI, ALLEN; Haile, Yohannes; Lowe, Catherine; Golestany, Batis; Tinh, Elise; Yosief, Pheben

University of California, Riverside - School of Medicine

The World Bank estimated air pollution health damages amount to $8.1 trillion globally, corresponding to 6.1% of the global GDP, with low- and middle-income countries bearing significant consequences. In the U.S. asthma alone imposes an annual cost of 50 billion dollars. Meanwhile, according to the CDC, obesity costs the U.S healthcare system more than 260 billion dollars annually. The relationship between obesity and particulate matter exposure is a circular one which ends in widespread multiorgan oxidative stress. The increased risk of adverse health outcomes has been associated with higher serum levels of inflammatory markers, including CRP, IL-6, as well as other proinflammatory biomarkers. While prior studies have examined the impact of PM on health outcomes and vice versa, our retrospective study seeks to elucidate the effects of chronic exposure to particulate matter among obese and non-obese individuals. Therefore, we hope to elucidate how these factors interact, exacerbate health risks, and propose targeted health and policy interventions.

2. “Measuring and Mitigating Indoor Air Quality Threats Around the Salton Sea”

TRINIDAD, ASHLEY; Porter, William; Cheney, Ann

Department of Environmental Science, University of California, Riverside
School of Medicine, University of California, Riverside

Ambient atmospheric particulate matter (PM) shows source-specific seasonal patterns and variability due to seasonal changes in emissions and transport. Indoor air quality can likewise show strong seasonal cycles due not only to changes in indoor emissions such as cooking and cleaning, but also to variability in ventilation, heating, and cooling practices. In areas strongly impacted by ambient air pollution, indoor/outdoor air quality coupling can be an important source of prolonged air pollution exposure, as well as an additional source of exposure disparities related to differences in building insulation and filtration. In this study, we analyze seasonality impacts on ambient and indoor air quality around environmental justice communities in the Coachella Valley, a region strongly influenced by windblown dust storms worsened by the shrinking Salton Sea, using air quality monitors deployed within participant homes. To quantify the amount of exchange with outdoor air we examine daily temperature correlations between indoor and outdoor systems, using the strength of this correlation to help explain observed indoor air quality patterns. We also share preliminary results showing the impact of low-cost DIY indoor air filtration on indoor air quality and the coupled indoor/outdoor air quality relationship. Indoor air filtration is a cost-effective intervention capable of reducing direct impacts from particulates as well as airborne disease transmission. Using novel measurements collected by deployed monitors along with existing outdoor station measurements, we explore connections between the indoor and outdoor regimes, evaluate the reduction of PM after DIY air filtration deployment, and quantify observed variability and similarities between participant homes.

3.“Beyond Breath; The Gut-Lung Axis in COPD Exacerbations and Particulate Matter Exposure”

SADIGHIAN, ASSAL; Sadighian, Sadaf; Seylani, Allen; Haile, Yohannes; Shahin, Hania; Lowe, Catherine; Tinh, Elise; Yosief, Pheben

Introduction

Chronic obstructive pulmonary disease (COPD) impacts approximately 300 million individuals globally, ranking as the third leading cause of mortality, claiming the lives of 3.23 million people in 2019. While the prevalence of COPD in the general population stands at around 1% across all age groups, it escalates to over 10% among individuals aged 40 and above, with even higher rates observed with advancing age. Although the prevalence of COPD remained relatively stable from 2011 to 2021, it exhibited a decline among adults aged 18–44, while showing an increase among those aged 75 and older. In 2022, approximately 11.7 million individuals, comprising 4.6% of the U.S adults were diagnosed with COPD. Women exhibit a 37% higher likelihood of COPD diagnosis compared to men, with over half of those diagnosed being women. COPD ranks as the sixth leading cause of death in the United States, with 85% of COPD-related deaths occurring among individuals aged 65 years or older. According to the American Lung Association, the annual medical cost of Chronic Obstructive Pulmonary Disease (COPD) among adults aged 45 and older in the United States amounts to $24 billion, averaging $4,322 per patient. Mannino et al. projected that national medical costs associated with COPD are anticipated to rise to $60.5 billion by 2029. While smoking constitutes the primary cause of COPD, it's noteworthy that only one in five smokers will develop significant COPD. Moreover, COPD can manifest in individuals who have experienced prolonged exposure to hazardous pollutants in their workplace, including certain chemicals, dust, or fumes. Exposure to particulate matter (PM) has been linked to increased inflammation in lung tissue, exacerbation of COPD symptoms, and decreased lung function. Additionally, PM exposure can elevate the frequency of COPD exacerbations, which are correlated with heightened rates of hospitalization, heart failure and mortality. The lung microbiome in individuals with chronic obstructive pulmonary disease (COPD) exhibits distinct differences from that of the upper airway in terms of bacterial composition. Specifically, the bronchial microbiome of COPD patients often demonstrates an elevated abundance of Proteobacteria, including the genus Haemophilus, along with a reduced abundance of Bacteroidetes and Firmicutes. In advanced stages of the disease, the microbial flora tends to shift towards a predominance of the Pseudomonas genus. The gut-lung axis (GLA) is a concept proposing that alterations in the gut's microbiota can impact lung health and disease. This axis is closely linked with chronic obstructive pulmonary disease (COPD) and plays a pivotal role in lung immunity and overall health. The gut microbiota has the potential to influence lung health outcomes across a spectrum of diseases, including asthma, cystic fibrosis, and COPD. For instance, microbial presence may trigger recognition by host immune cells, leading to systemic cytokine release. Additionally, in certain scenarios, microbes secrete bioactive compounds that are absorbed into circulation and directly modulate lung function.

The gut microbiome exerts a crucial influence on inflammation and immune responses within the lungs, thereby contributing to the mitigation of lung inflammation. Microbial populations from the gut microbiota can translocate across the intestinal mucosa and be engulfed by antigen-presenting cells (APCs). Subsequently, these APCs migrate to the lungs, where they stimulate T cells, eliciting an immune response. Additionally, metabolites produced by the gut microbiota, such as short-

chain fatty acids (SCFAs), have the capacity to facilitate the differentiation of T cells in the lung and inducing pro and anti-inflammatory based on the type of SCFA. Butyrate demonstrates anti-inflammatory properties by down regulating TNF-α, IL-1β, IL-6, MMP9, and MMP12, in models of COPD. Furthermore, butyrate can down-regulate the expression of GATA3 in type-2 innate lymphoid cells (ILC2), thereby inhibiting the activity of ILC2 cells within the lungs. This modulation of ILC2 cells contributes to a reduction in pulmonary airway hyperresponsiveness. Additionally, certain strains of Lactobacillus have been shown to mitigate respiratory hyperresponsiveness induced by chronic PM2.5 inhalation. Furthermore, in murine models of lung cancer, daily oral administration of Lactobacillus Acidophilus was associated with reduced tumor size via reduced VEGFa and Ras oncogenes expression which led to an increased overall survival rate.

Hypothesis

We propose that regular consumption of beneficial probiotics, particularly Lactobacillus Acidophilus strains, among COPD patients exposed to chronic PM, could potentially mitigate the risk of acute COPD exacerbations. By leveraging the anti-inflammatory properties of probiotics and their ability to modulate GLA communication, especially in the context of PM-induced inflammation, we anticipate a reduction in COPD exacerbations and risk of neoplasm formation. This approach holds promise for improving the management and outcomes of COPD in individuals facing environmental challenges such as PM exposure.

Methods

We conducted a retrospective cohort study utilizing de-identified patient data from the TriNetX platform, a comprehensive electronic health records (EHR) system. Cohorts included nonsmokers without chronic exposure to PM who reported taking daily L. Acidophilus (Cohort A) and nonsmokers exposed to PM with no history of L. Acidophilus (Cohort B). Propensity score matching was utilized to balance baseline characteristics between the cohorts, including age, sex, ethnicity, and comorbidities.

Results

Risk of acute COPD exacerbation in patients with chronic exposure to PM who did not report consuming daily Lactobacillus Acidophilus was 9.439% (N=5,318,255, Total Number of Patients with the Outcome= 502,007) while the risk of acute exacerbation in patients with chronic exposure to PM who reported intake of Lactobacillus Acidophilus was 9.053% (N=5,318,255, Total Number of Patients with the Outcome= 481,456), (P< 0.0001, 95% CI (1.039,1.047), Risk Ratio 1.043).

Risk of malignant neoplasm of bronchus and lung in patients with chronic exposure to PM who did not report consuming daily Lactobacillus Acidophilus was 1.808% (N=5,198,054, Total Number of Patients with the Outcome= 93,977) while the risk of acute malignancy in patients with chronic exposure to PM who reported intake of Lactobacillus Acidophilus was 1.746% (N=5,203,436, Total Number of Patients with the Outcome= 90,859) (P< 0.0001, 95% CI (1.026,1.045), Risk Ratio 1.035).

Discussion

Given the culmination of daily exposure to particulate matter and other environmental influences that induce epigenetic changes, it is of vital importance to explore how the gut, lung and microbiome and the GLA may influence pulmonary disease. The decreased risk of COPD exacerbation among patients who reported daily intake of Lactobacillus Acidophilus with chronic

exposure to PM support previous findings suggesting that Lactobacillus Acidophilus may mitigate inflammatory cell infiltration, enhancing the GLA communication thus, protecting against excess proinflammatory cytokines leading to airway hyperresponsiveness, the hallmark of COPD exacerbation. In addition to this, previous work has shown that Western diets are associated with increased risk of COPD, giving credence to the notion that dietary changes, in addition to smoking, may be integral in the development and severity of the disease.

Previous mouse models have supported the delicate interplay between the lung and gut as it relates to COPD exacerbation. Specific intestinal organisms have been shown to enhance Interleukin-22 (IL-22) levels, a cytokine which has been shown to protect against non-typeable Haemophilus influenzae infection, one of the most common causes of COPD exacerbation.

Further work supports that alveolar macrophages in mice with depleted gut microbiota have a blunted immune response against Streptococcus pneumoniae, another common culprit of COPD exacerbation. The gold standard for COPD exacerbation management remains bronchodilators with possible steroids and/or antibiotics depending on symptoms. A well-known side effect of antibiotics is gut microbiome depletion, which may contribute to increased bacterial load in the lung and blood as well as decreased intestinal cytokine expression. This begs the question of whether the standard of care for hospitalized patients with COPD exacerbation should include adequate gut microbiome repletion with probiotic intake during and after antibiotic administration.

The observed decrease in lung cancer risk among COPD patients taking Lactobacillus acidophilus could be attributed to its impact on gene expression. Studies have suggested this probiotic increases the expression of tumor suppressor genes such as Cdkn1b and Bax while decreases expression of genes related to progression of dysplasia and even metastasis. The efficacy of daily oral probiotic supplements remains a subject of controversy and incomplete understanding. Recent studies propose that the significant benefits of probiotic supplementation may not stem directly from bacteria retention but rather from the influence exerted by transient probiotics on the native gut microbiome. This influence may involve epigenetic modifications and the uptake of bacterial genomic material by the gut microbiome. In acute exacerbations of COPD, the predominant bacterial phylum is Proteobacteria (30.29%), followed by Firmicutes (29.85%) and Bacteroidetes (14.02%). Conversely, in stable COPD conditions, Firmicutes (31.63%) emerges as the major phylum, trailed by Bacteroidetes (28.94%) and Proteobacteria (19.68%). A clinical trial showcased a notable alteration in the composition of the lung microbiome following oral probiotic intake, leading to substantial enhancements in lung function. In a study by Wenger et al., individuals with asthma who underwent four weeks of oral probiotic supplementation exhibited a significant shift in their gut microbiome composition. Additionally, the study reported marked improvements in respiratory function and alleviation of asthma symptoms. While the Gut-Lung Axis (GLA) continues to emerge as a focal point in medical research, further investigation, and a more meticulous exploration of the GLA axis and its impact on conditions like COPD, asthma, and other inflammatory respiratory diseases are warranted. Such endeavors are essential for gaining a deeper understanding of this intriguing connection.

4.“The Hidden Connection; Psoriasis, Particulate Matter Exposure, and Cardiovascular Disease Risk”

VO, CAROLYNNE; Seylani, Allen; Haile, Yohannes; Shahin, Hania; Lowe, Catherine; Yosief, Pheben; Tinh, Elise

University of California, Riverside

Psoriasis, impacting approximately 2–3% of the global population and about 2% of the United States population, poses a considerable healthcare burden. While classically viewed as a dermatological condition, emerging research has unveiled the cardiovascular implications of psoriasis. Several cytokines and immune cells have been implicated in the pathogenesis of psoriasis and its cardiovascular-related ramifications. These include CD4 T cells, Th1 and Th17 cells, as well as cytokines such as IL-17, IL-22, and IL-21. Exposure to particulate matter (PM) has been linked to the development of a systemic proinflammatory environment in the body. Purpose: To investigate the association between chronic particulate matter exposure and psoriasis with the risk of developing CAD, acute MI, peripheral arterial disease, and dementia using the TrinetX database. Methods: Analysis included de-identified patient data from the TriNetX platform, a comprehensive electronic health records (EHR) system. Cohorts included patients with a diagnosis of psoriasis and chronic exposure to particulate matter (Cohort A) and psoriatic patients without exposure to PM (Cohort B). Propensity score matching was utilized to balance baseline characteristics between the cohorts, including age, sex, ethnicity, and comorbidities. The two cohorts were compared for the risk of developing CAD, acute MI, peripheral arterial disease, and dementia. Results: Risk of developing CAD in Cohort A was 7.483% while the risk for Cohort B was 6.685% (P< 0.0001, 95% CI (0.882,0.905). Risk of developing acute MI among Cohort A was 3.062% while the risk for Cohort B was 2.478% (P< 0.0001, 95% CI (0.842,0.87). Risk of developing PAD in Cohort A was 3.164% while the risk for Cohort B was 2.684% (P< 0.0001, 95% CI (0.831,0.865). Risk of developing dementia among Cohort A was 0.89% while the risk for Cohort B was 0.566% (P< 0.0001, 95%CI (0.61,0.662). Conclusion: Our findings support the association between psoriasis and CAD and PAD, secondary to PM exposure as systemic inflammation from psoriasis. Our results indicate that PM exposure is associated with the advent of myocardial infarction among patients with psoriasis. Increased risk of dementia was also observed among patients with PM exposure in our cohort with psoriasis.

5."Investigating the Invisible Threat- The Link Between Particulate Matter Exposure and Non-Alcoholic Fatty Liver Diseases"

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Fine particulate matter, defined as 2.5 micrometers and smaller (PM2.5), is an inhaled air pollutant that can deposit deep into the lung, where it can promote acute and chronic tissue injury through neutrophil-induced airway inflammation and lung scarring, respectively. PM2.5 exposure is associated with the largest proportion of adverse health effects related to air pollution. Although the most established adverse health implications associated with PM2.5 involve respiratory and cardiovascular disease, the association between PM2.5 and liver disease has also been examined in light of the significant prevalence and global health impact of liver disease, particularly nonalcoholic fatty liver disease (NAFLD). PM exposure has been linked to elevated liver enzymes, oxidative stress on the liver, and cell-signaling dysregulation, all of which promote fatty deposition in the liver and progressive hepatic damage. NAFLD is the leading cause of liver disease worldwide and is associated with type 2 diabetes, hypertension, obesity, and smoking. Using the TrinetX clinical database consisting of de-identified patient data, we found that documented PM exposure was associated with a higher risk of developing elevated liver enzymes and a variety of liver diseases. We also found an increased mortality risk in those with documented NAFLD and exposure to PM. These findings contribute to the mounting evidence that PM2.5 exposure may pose significant unintended health consequences and warrants further investigation with regard to its potential to contribute to significant disease burden.

6.“Beneath the Haze; Uncovering the Cardiovascular Ramifications of Particulate Matter Exposure”

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Introduction:

According to the World Health Organization (WHO), air pollution contributes to approximately 8 million premature deaths globally each year. In 2023, the United States emitted approximately 1.7 million metric tons of particulate matter (PM2.5), marking a reduction of 35% compared to levels recorded in 2000. Notably, numerous counties in the United States, particularly those situated within California, exhibit heightened pollution levels. In recent years, air pollution has emerged as an independent risk factor for cardiovascular diseases (CVD). According to statistics provided by the California Department of Public Health, between 2015 and 2019, 5.9% of Californian adults, totaling 1.7 million individuals, received diagnoses of various CVDs, including angina, stroke, heart attack, or coronary heart disease (CHD). This study delves into the outcomes and association between PM exposure and CVD, along with angioplasty and post-cardiac infarction comorbidities such as pulmonary edema, as well as clinically pertinent biomarkers across diverse cohorts.

Methods:

We conducted a retrospective cohort study utilizing de-identified patient data from the TriNetX platform, a comprehensive electronic health records (EHR) system. Cohorts included healthy non-smoker patients who were exposed to PM, smokers exposed to PM, non-smokers with diabetes, hypertension exposed to PM, and smokers with diabetes. Propensity score matching was utilized to balance baseline characteristics between the cohorts, including age, sex, ethnicity, and comorbidities.

Results:

Exposure to PM among non-smoker patients with D2T and HTN was associated with 1.5 years earlier onset of ischemic cardiomyopathy (ISC) with the exposed group experienced a 19% increase in serum Troponin, 11% increase in BNP, 5 % increase in incidence of pulmonary edema, 5% increase in coronary artery angioplasty. The rate of arrival for ISC among non-smokers with D2T and HTN who are exposed to PM was 1,737 new cases per month per year which translates to 20,844 new cases per year in the U.S. Incidence proportion of ISC among non-smokers with D2T, HTN and exposure to PM for Females 27/1,000,000 and for Males 5/100,000. Overall, there is a 2 fold increased risk of pulmonary edema development among non-smokers diagnosed with D2T and HTN who were exposed to PM for more than five years of their lives when compared to non-smokers diagnosed with D2T, HTN but without exposure to PM. The exposed group witnessed a total 4.4% increased risk of developing ISC. The worst outcome was seen among smokers with diagnosis of D2T, HTN and exposure to PM in comparison to their unexposed counterparts. A 29%, 16%, 9% and 11% increase in Troponin, BNP, pulmonary edema coronary artery angioplasty respectively were seen among smokers diagnosed with D2T and HTN who were exposed to PM.

Conclusion:

This study found that PM exposure among nonsmoker diabetic individuals with hypertension resulted in earlier onset of myocardial infarction (MI), possibly mediated by increased cellular oxidative stress leading to hypoxia and mitochondrial damage. Consistent with previous studies, this research noted a higher prevalence of ischemic MI among males but revealed a novel finding of a disproportionate incidence of pulmonary edema among females exposed to PM. These findings highlight the need for tailored post-MI care for females and increased preventive efforts to reduce MI incidence, particularly among males.

7. “Particulate Matter Exposure in Obese Adults Is Associated with Higher Major Depressive Disorder Risk”

SADIGHIAN, SADAF; Sadighian, Assal; Haile, Yohannes; Lowe, Catherine; Yosief, Pheben; Shahin, Hania; Seylani, Allen

Depression triggers changes in the brain's structure, function, and molecular composition, particularly in the prefrontal and limbic areas, notably the hippocampus. These alterations extend to activity patterns within neuroanatomical structures. The earliest hypothesis of depression, the monoamine deficiency hypothesis, emphasizes the role of chemical imbalances, particularly serotonin, dopamine, and norepinephrine. However, recent studies have uncovered additional molecules linked to neuron growth, synaptic maintenance, and reduction of oxidative stress, expanding our understanding of depression's molecular mechanisms.

The PKA/CREB/BDNF signaling pathway plays a crucial role in promoting neuronal survival, regulating synaptic morphology and enhancing synaptic transmission efficiency. However, the health effects of particulate matter (PM) are not fully understood due to its rapid redistribution and high point-source production. Several studies have suggested that exposure to PM can induce neurodegenerative-like pathology in both humans and animals. These effects include neurotoxicity, neuroinflammation, oxidative stress, and damage to the blood-brain barrier and neurovascular units. Interleukin-6 (IL-6) is a cytokine associated with depression and stress reactions, especially in individuals with metabolic syndrome and obesity, factors that are known to increase risk of depression. Both clinical and animal studies have demonstrated that elevated levels of IL-6 in the periphery or brain are correlated with depression and can influence a variety of depressive symptoms. Indeed, depressed patients tend to exhibit higher levels of IL-6 in their serum, and there exists a direct correlation between IL-6 levels and depression ratings. Exposure to particulate matter (PM) has been linked to a range of adverse neurological effects, including neuroinflammation, neurotoxicity, and disruption of the blood-brain barrier and neurovascular units. These outcomes potentially heighten the risk of neurodegenerative conditions.
Oxidative stress plays a crucial role in the initiation and progression of depression, stemming from an imbalance of reactive oxygen species (ROS) and inadequate antioxidant defenses. ROS can inflict harm on essential cellular components such as DNA, proteins, and fatty acids, culminating in inflammatory responses, neurodegeneration, and ultimately neuronal demise. Given the brain's elevated metabolic activity, it is particularly susceptible to oxidative damage, underscoring the significance of oxidative stress in depression pathology.

Hypothesis

We propose that PM, particularly fine particulate matter (PM2.5), can penetrate the blood-brain barrier and accumulate in brain regions implicated in mood regulation. In obese individuals who are already predisposed to chronic low-grade inflammation and oxidative stress due to adipose tissue dysfunction, PM exposure may further exacerbate these processes. This heightened inflammatory response, coupled with increased oxidative stress, can lead to dysregulation of neurotransmitter systems involved in mood regulation, such as serotonin and dopamine. Additionally, PM-induced disruption of neuroendocrine pathways, including the hypothalamic-pituitary-adrenal (HPA) axis, may contribute to depressive symptoms in obese adults. Overall, we

hypothesize that the combined effects of PM exposure and obesity create a synergistic environment that increases the risk of depression through neuroinflammation, oxidative stress, and neuroendocrine dysregulation.

Method

We conducted a retrospective cohort study utilizing de-identified patient data from the TriNetX platform, a comprehensive electronic health records (EHR) system. The risk of developing MDD in association with chronic PM exposure in nonsmoker obese adults was assessed. Cohorts included nonsmoker obese adults with no history of MDD or chronic exposure to PM (Cohort A) and nonsmoker obese adults with no history of MDD, but with chronic exposure to PM. Propensity score matching was utilized to balance baseline characteristics between the cohorts, including age, sex, ethnicity, and comorbidities.

Results

Risk of developing MDD for nonsmoker obese adults with five years of exposure to PM was 13.856%, (N=258,581, Patients with the outcome= 35,828) while the risk was 9.409% for nonsmoker obese adults with no history of chronic exposure to PM (N=252,706, Patients with the outcome= 23,777) (P< 0.0001, 95% CI (0.669,0.69)).

Discussion

Our results support our hypothesis that obese, nonsmoking adults with documented exposure to PM have increased rates of MDD when compared to those without documented PM exposure, suggesting PM may act as an independent risk factor implicated in mood dysregulation. This result brings to attention the significance of air pollution and its potential for adverse health effects, particularly in the psychiatric realm. Our work supports previous findings that PM2.5 acts as an independent risk factor for major depressive episodes. Air pollution, in addition to other environmental factors such as housing, location of housing, and chronic stress may play a multifactorial role that may induce epigenetic changes associated with depression. These social determinants of health in conjunction with the health implications of obesity, including chronic low-grade inflammation, may be implicated in the development of depression.

Potential biological mechanisms from human and animal studies indicate that PM exposure induces oxidative and nitrosative stress including systemic and neuroinflammation while being directly neurotoxic and associated with structural brain changes. The neuroinflammatory processes that are implicated in PM exposure are linked to circulating cytokines produced in systemic inflammation, such as TNF alpha and IL-1B, which are well known to cause cerebral vascular damage and direct neurotoxicity. Other hypotheses illustrate the premise that PM may stimulate the innate immunity of the brain through pattern recognition receptors on the brain's immune cells, microglia. Additionally, ultrafine particulate matter has also been implicated in the production of pro-inflammatory cytokines in olfactory bulb cells within animal models. This finding demonstrates that PM exhibits a pro-inflammatory stimulus through surface molecule complexes CD36, α6β1 integrin, and CD47. In addition to neuron damage, it has also been proposed that systemic inflammation caused by PM can contribute to deterioration within the blood-brain barrier, as evidenced by dysregulated levels of GFAP expression on astroglia to alter the integrity of the BBB and accelerate neuropathology. As a result, PM has the potential to foster both neuroinflammation and neuropathology, leading to the accumulation of adverse effects. These mechanisms underlie the

association between PM exposure and inflammation-associated major depressive disorders. A number of hypotheses have been postulated with the most common pathway for this pathophysiology being demonstrated through the kynurenine pathway. Through exposure to cytokines IFN-γ and TNF-α, indoleamine 2,3 dioxygenase (IDO) and tryptophan 2,3 dioxygenase (TDO) are activated and metabolize tryptophan. This metabolism has important neuropsychiatric implications which influence serotonergic transmission as tryptophan is the precursor to serotonin and its bioavailability determines the synthesis of serotonin. Additionally, as IDO is present within several immune brain cells, including macrophages and dendritic cells, the net result may illustrate an altered chemical environment that triggers the necessary conditions for the development of depression.

8.“Novel Genetic Mutations in Non-Smoker Pancreatic Cancer Patients with Chronic Particulate Matter Exposure”

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Particulate matter (PM) is a complex mixture of solids and aerosols of varying sizes and compositions including PM10 and PM2.5. Global estimates show that PM is a major contributor to various morbidities and even mortality risk in both developed and developing countries. In the US, analysis of PM levels was highest at rural communities, reaching nearly ~66 µm, about seven times higher than the standard regulation by the environmental protection agency [1]. Throughout the US, wintertime concentrations of PM were highest in the Midwest and California. The deleterious effects of PM exposure are directly imposed and compounded upon cigarette smokers through the additional exposure of carcinogens leading to cancer. While lung cancer is the most implicated organ system affected by inhalation of tobacco and PM, other organ systems are also involved. While the risk of pancreatic cancer (PC) from tobacco smoke has been well established, the risk of PC also increases by 1% per 10µg/m3 inhaled PM [2]. One study revealed that with each additional 10 micrograms per cubic meter (µg/m3) of exposure to PM2.5, the risk of mortality from any cancer increases by 22 percent. Specifically, the mortality risk for cancers affecting accessory digestive organs, such as the pancreas, liver, bile ducts, and gallbladder, rises by 35 percent [3]. There currently is no effective screening tool or treatment for PC and the mortality rate closely parallels incidence. The low survivability among patients with PC is most likely due to the late stage patients with 5-year survival of 12% and overall mortality rate of 89% based on the age-adjusted incidence and incidence-based mortality rates. Inherited germline mutations implicated in PC include CDKN2A, TP53, MLH1, BRCA2, ATM, BRCA. However, notable genetic mutations from tobacco use include KRAS, TP53, SMAD4, and CDKN2A [4].

Several studies reported a positive association between PM exposure and PC, however to the best of our knowledge, no study has been conducted to examine genetic mutations in PC associated with PM exposure in nonsmokers. This study investigates the associated mutations garnered from PM exposure.

Methods

We conducted a retrospective cohort study utilizing de-identified patient data from the TriNetX platform, a comprehensive electronic health records (EHR) system. Cohorts included smokers without chronic exposure to PM (Cohort A) to nonsmokers exposed to PM (Cohort B). Propensity score matching was utilized to balance baseline characteristics between the cohorts, including age, sex, ethnicity, and comorbidities. We utilized the genomic database within TriNetX to procure abnormal genetic anomalies among both cohorts.

Result

Cohort A (N=1,394,779) consisted of smokers without chronic exposure to PM with a median age of 54.8 years, 50.9% male, 43.6% female, 17.1% black, 2.0% Asian, and 60.7% white. In this cohort, 0.009% (N=130) developed mutations within Erythroblastic Oncogene B (ERBB2), 0.005% (N=73) within protein tyrosine phosphatase non-receptor type 11 (PTPN11), and 0.001% (N=12) within ETS Translocation Variant 6 (ETV6). Cohort B (N=2,510,482) consisted of non-smokers with chronic exposure to PM with a median age of 47.1 years, 49.3% male, 46.2% female, 15.5% black, 2.3% Asian, and 61.4% white. In this cohort, 0.015% (N=374) developed ERBB2 mutations, 0.011% (N=265) developed PTPN11 mutations, 0.005% (N=134) developed ETV6 genetic mutations. PM exposure among nonsmokers was associated with 0.015% risk of developing PC while smoking alone among patients not exposed to PM was associated with 0.026% risk of PC development ($P<0.0001$, 95% CI (1.509,2.018)). Cohort B (nonsmoker with chronic PM exposure) and Cohort A (smoker without PM exposure) had average Partial Activated Time (PT) of 14.1 seconds and 12.8 seconds, respectively, while both cohorts had an average aPPT of 32 seconds. Risk of acute pancreatitis was 0.956% in cohort A and 0.576% in cohort B ($P < 0.0001$, 95% CI (1.622,1.699)). Risk of DIC was 0.141% in nonsmokers with chronic exposure to PM and 0.106% among smokers without exposure to PM ($P<0.0001$, 95% CI (0.708,0.799).

Discussion

This study uncovered three distinct genetic mutations seen more frequently among non-smokers with chronic exposure to PM. ERBB2 mutation is often seen in breast cancer cells, which leads to increased Matrix Metalloproteinase-9 expression. Increased expression and activity of MMPs is linked to invasiveness and metastasis. Additionally, ERBB2 promotes angiogenesis by increasing VEGF expression, which together with MMP-9 leads to higher metastatic potential. PTPN11 is required for RAS/ERK pathway activation and provides adaptive resistance to therapeutic intervention from MEK inhibitors (MEKi). PTPN11 inhibition downregulates KRAS mutants with GTPase activity, allowing targeted impediment of ERK1/2-dependent reactivation in response to MEKi. Therefore, PTPN11/MEKi combinations can prevent adaptive resistance specifically among PC patients expressing KRAS, which is highly active among this patient population. Primarily recognized for its fusion partners in hematological malignancies, the ETV6 gene has also been implicated in solid tumors. Of particular significance in pancreatic carcinoma is the ETV6-NTRK3 fusion gene, given that the NTRK3 gene encodes a membrane-bound receptor capable of phosphorylating itself and members of the MAPK pathway. This fusion facilitates the dimerization of ETV6 with NTRK3, thereby activating tyrosine kinase and promoting cell cycle progression. As a result, the ETV6-NTRK3 gene is considered as a pathogenic germline variant that is associated with early-onset PC whose genetic stability may be negatively affected by PM exposure and the subsequent cellular oxidative stress.

Tissue factor (TF) functions as a transmembrane receptor pivotal in activating factor VII (FVII). Normally concealed on intact blood vessel surfaces, TF is released upon vascular lumen damage. TF then binds to circulating factors FVII and VIIa, promoting the conversion of factor VII to its activated form, factor VIIa (FVIIa). TF expression is notably upregulated in exocrine pancreatic cells upon malignancy, suggesting its potential significance in cancer-related thrombosis and accelerated metastatic dissemination. TF levels demonstrate a strong correlation with the

procoagulant activity exhibited in patients diagnosed with PC, particularly those who develop cancer-associated thromboembolism. Thrombus associated with PC can also cause pulmonary embolism leading to right heart failure. Pancreatic cancer cells can also activate platelets and produce procoagulant factors such as thrombin and tissue factor. This activity may result in the formation of arterial thromboembolisms. Additionally, these hematologic abnormalities may trigger disseminated intravascular coagulopathy (DIC). The increased risk of DIC among non-smokers with chronic exposure to PM may be explained by the chronic inflammation and cellular assaults on pancreatic cells mediated by PM and heavy metals and the subsequent accumulation of additional mutations and upregulation of TF on the surface of the affected cells. Research indicates that heavy metals, including cadmium, arsenic, and nickel, bound to the surface of PM2.5, may act as carcinogenic factors in pancreatic cancer development. Furthermore, PM exposure has been associated with the promotion of cancer metastasis. PM has been shown to elevate the expression of heparin-binding EGF-like growth factor (HBEGF) in macrophages, leading to the induction of epithelial-to-mesenchymal transition (EMT) in cancer cells, consequently enhancing metastatic potential.

Altogether, our data suggests an increased risk of PC and DIC due to chronic PM exposure among non-smokers. More research is needed to fully elucidate the role of PM, novel genetic mutations, and risk of metastasis in pancreatic cancer patients with chronic exposure to PM.