Universidade Estadual de Londrina

HENRIQUE OCHOA SCUSSIATTO

ASSOCIATION OF AIR POLLUTION WITH OLFACTORY IDENTIFICATION PERFORMANCE OF SÃO PAULO RESIDENTS: A CROSS SECTIONAL STUDY

LONDRINA
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Dissertation presented to the Postgraduate Program in Health Sciences at the Health Sciences Center of the State University of Londrina.
Mentor: Prof. Dr. Marco Aurélio Fornazieri

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SCUSSIATTO, HENRIQUE OCHOA. **Association of air pollution with olfactory identification performance of São Paulo residents: a cross sectional study.** Thesis (Doctor of Philosophy in Health Sciences) - Universidade Estadual de Londrina, 2024.

ABSTRACT

Objective: Exposure to particulate matter of 10 μm or less in diameter (PM_{10}) has been implicated in pulmonary and cardiovascular diseases. However, the effect of PM_{10} on olfaction has not been well established. We estimated individual acute and chronic PM_{10} exposure levels in a large Brazilian cohort and related them to the ability to identify odors.

Methods: Adults from São Paulo (n=1,358) were recruited from areas with different levels of air pollution. To verify individual exposure to air pollution, the averages of 30, 60, 90, 180 and 364 days of PM_{10} were interpolated to subjects' zip codes using the kriging method. Olfactory identification performance was tested using the University of Pennsylvania Smell Identification Test (UPSIT®). Multiple linear regressions were used to calculate the effect of air pollution on olfactory identification performance, controlling for demographic and other variables that affect the sense of smell.

Results: Acute exposures to PM_{10} were related to worse UPSIT® scores, including 30- (β = -0.94, 95% Confidence Interval [CI] -0.98, -0.89), 60- (β = -1.09, 95% CI = -1.13, -1.04) and 90-day intervals (β = -1.06, 95% CI -1.10, -1.02) (reference for β: 1 μm/m3 increase in PM_{10} exposure per point decrease in UPSIT® score). Chronic exposures were also associated with worse olfaction for both 180- (β = -1.06, 95% CI -1.10, -1.03) and 364-day (β = -0.87, 95% CI -0.90, -0.84) intervals. As in prior work, men, older, low-income, and low-schooling people demonstrated worse olfactory performance.

Conclusion: Acute and chronic exposure to PM_{10} is strongly associated with olfactory identification performance in Brazilian adults. Understanding the mechanisms which underlie these relationships could help to improve chemosensory function with a large public health impact.

Key words: Smell, smell disorders, olfactometry, air pollution, olfaction, PM_{10}.

SCUSSIATTO, HENRIQUE OCHOA. **Associação da poluição aérea com o desempenho de identificação olfatória de moradores de São Paulo: um estudo transversal.** Tese (Doutorado em Ciências da Saúde) - Universidade Estadual de Londrina, 2024.

RESUMO

Objetivo: A exposição a material particulado de 10 µm ou menos de diâmetro (MP_{10}) tem sido implicada em doenças pulmonares e cardiovasculares. No entanto, o efeito do MP_{10} no olfato não foi bem estabelecido. Estimamos os níveis individuais de exposição aguda e crônica ao MP_{10} em uma grande coorte brasileira e os relacionamos à capacidade de identificar odores.

Métodos: Adultos paulistas (n=1.358) foram recrutados em áreas com diferentes níveis de poluição atmosférica. Para verificar a exposição individual à poluição atmosférica, as médias de 30, 60, 90, 180 e 364 dias de MP_{10} foram interpoladas para os CEPs dos sujeitos por meio do método de krigagem. O desempenho da identificação olfativa foi testado usando o Teste de Identificação de Olfato da Universidade da Pensilvânia (UPSIT®). Regressões lineares múltiplas foram utilizadas para calcular o efeito da poluição do ar no desempenho da identificação olfativa, controlando variáveis demográficas e outras variáveis que afetam o sentido do olfato.

Resultados: As exposições agudas ao MP_{10} foram relacionadas a piores pontuações UPSIT®, incluindo 30- (β = -0,94, intervalo de confiança [IC] de 95% -0,98, -0,89), 60- (β = -1,09, IC 95% = - 1,13, -1,04) e intervalos de 90 dias (β = -1,06, IC 95% -1,10, -1,02) (referência para β: aumento de 1 µm/m3 na exposição a MP_{10} por ponto de diminuição na pontuação UPSIT®). Exposições crônicas também foram associadas a pior olfato nos intervalos de 180 dias (β = -1,06, IC 95% -1,10, -1,03) e 364 dias (β = -0,87, IC 95% -0,90, -0,84). Assim como em trabalhos anteriores, homens, idosos, pessoas de baixa renda e baixa escolaridade demonstraram pior desempenho olfativo.

Conclusão: A exposição aguda e crônica ao MP_{10} está fortemente associada ao desempenho de identificação olfativa em adultos brasileiros. Compreender os mecanismos subjacentes a estas relações poderia ajudar a melhorar a função quimiossensorial com um grande impacto na saúde pública.

Palavras-chave: Olfato, distúrbios do olfato, olfatometria, poluição do ar, olfato, MP_{10}.

FIGURES

TABLES

ABREVIATIONS AND ACRONYMS` LIST

CO – Carbon monoxide;
CO_2 – Carbon dioxide;
TSP – Total suspended particles;
$PM_{2,5}$ – Particulate matter of ≤ 2.5μm;
MP_{10} – Particulate matter of ≤ 10μm;
NO_2 – Nitrogen dioxide;
O_3 – Ozone;
SO_2 – Sulfur dioxide;
PPM – Particles per million;
GIS – Geographic Information System;
CETESB – Environmental company of the State of São Paulo;
CC – Correlation Coefficient;
CONAMA – National Board of the Environment;
OR – Odds-ratio.

SUMMARY

I. INTRODUCTION

Olfactory loss, or the reduction in the ability to smell, is significantly linked to a decrease in the quality of life, impacting not just simple pleasures like the taste and enjoyment of food and sexual behavior, but also crucial safety aspects such as recognizing the smell of smoke from fire or the presence of toxic substances. The olfactory epithelium, which is in direct contact with the environment, is particularly vulnerable to damage from various airborne substances, thereby making olfactory loss a considerable concern for public health (AUINGER et al., 2020; DENG et al., 2020; LIU et al., 2021; SCHÄFER; SCHRIEVER; CROY, 2021).

Exposure, whether temporary or continuous, to a myriad of airborne toxic agents such as metallic organic compounds and other chemical particles, is known to cause total or partial olfactory loss. This can range from transient to permanent impairment, significantly affecting individuals' quality of life (GUARNEROS et al., 2009; UPADHYAY; HOLBROOK, 2004a). Notably, air pollution has a substantial impact on the olfactory identification abilities of individuals living in large industrial and urban centers, exposed continuously to industrial emissions and road exhaust. Early population-scale studies indicate that exposure to pollutants like nitrogen dioxide and fine particulate matter of ≤ 2.5μm in diameter ($PM_{2.5}$) correlates with diminished olfactory capabilities, with the extent of impact varying based on the exposure duration and the age of the individual (ADAMS et al., 2016; AJMANI et al., 2016; CALDERÓN-GARCIDUEÑAS et al., 2010a; HUDSON et al., 2006) exposed to industrial and road exhaust based pollutants. This broad range of research underscores the importance of addressing air quality issues not only for environmental health but also for maintaining the vital sensory function of smell in populations worldwide.

I.1. JUSTIFICATION

Other previous studies have measured the influence of pollution on smell by comparing people in less polluted regions or cities with those living in more polluted ones; however, they did not quantify individual exposure to pollutants (CALDERÓN-GARCIDUEÑAS et al., 2010a; GUARNEROS et al., 2009; HUDSON et al., 2006; SOROKOWSKA et al., 2013; SOROKOWSKA; SOROKOWSKI; FRACKOWIAK, 2015). Other obstacles to better understanding of this topic include small samples (CALDERÓN-GARCIDUEÑAS et al., 2010a; GUARNEROS et al., 2009), failure to assess olfactory identification with validated tests (HUDSON et al., 2006), limited or unknown exposure windows (CALDERÓN-GARCIDUEÑAS et al., 2010a; GUARNEROS et al., 2009; SOROKOWSKA et al., 2013; SOROKOWSKA; SOROKOWSKI; FRACKOWIAK, 2015), or restricted age ranges (ADAMS et al., 2016; AJMANI et al., 2016; LUCCHINI et al., 2014). Besides that, to our knowledge, there are no studies analyzing the relationship between PM_{10} and olfactory identification in adults (nitrogen oxides and $PM_{2.5}$ have been previously studied) (ADAMS et al., 2016; AJMANI et al., 2016). Therefore, the aim of this study was to determine whether there is an association between the olfactory identification performance with acute and chronic exposures to particulate matter of 10 μm or less in diameter (PM_{10}) in adults living in São Paulo, Brazil.

Due to these gaps in the existing literature, this study aims to examine the possible association between olfactory identification performance and acute and chronic exposures to PM_{10} among adults residing in São Paulo, Brazil. By addressing these research gaps and focusing on PM_{10}, we seek to contribute valuable insights into the complex relationship between air pollution and olfactory function in the adult population of this urban environment. The specificity of our investigation not only broadens the scope of knowledge in this field, but also has potential implications for public health interventions and urban planning strategies aimed at mitigating the impact of air pollution on sensory perception in densely populated areas.

II. OBJETIVES

II.1. GENERAL

To examine the possible association between olfactory identification performance and acute and chronic exposures to PM_{10} among adults residing in São Paulo, Brazil.

II.2. ESPECIFIC

Verify the olfactory identification function of each individual by applying the University of Pennsylvania Smell Identification Test (UPSIT®);

Calculate the level of exposure to PM_{10} each individual is exposed to using an interpolation method;

Relate the final score of the UPSIT® questionnaire with the average (short and long term) exposure to PM_{10} using linear regressions.

III. LITERATURE REVIEW

Atmospheric pollution involves the degradation of indoor or outdoor air by chemical, physical, or biological elements altering the atmosphere's natural properties. Sources like domestic heating systems, vehicles, industrial complexes, and wildfires are prevalent sources of this pollution. Critical contaminants affecting public health include particulate matter, carbon monoxide, ozone, nitrogen dioxide, and sulfur dioxide. Both indoor and outdoor contaminants are significant causes of diseases affecting the respiratory system and other health conditions, leading to widespread illness and death (“WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide”, 2005).

World Health Organization indicate that virtually the entire world's population (99%) inhales air that surpasses the recommended WHO pollution thresholds, loaded with excessive pollutant concentrations. This is particularly severe in low- and middle-income nations, where exposure levels are most extreme. The condition of our air is intimately connected with global climate and ecological systems. Many factors contributing to air pollution, such as the burning of fossil fuels, are also significant sources of greenhouse gas emissions. Therefore, implementing policies aimed at reducing air contamination can serve a dual purpose. They not only reduce the health impacts associated with poor air quality but also contribute to both immediate and long-term efforts to mitigate climate change (XIAO et al., 2023). A summary of the main pollutants that affect human health is provided in Table 1.

Table 1. Main atmospheric pollutants, their sources, areas of systemic absorption by the respiratory system and effects on human health.

Pollutants	Sources	Respiratory system entry	Pathophysiology
TPS	Anthropogenic sources: street and road dust, agricultural and construction activities. Natural sources: sea salt, pollen, spores, fungi and volcanic ash.	Nose and Throat.	Decreases ciliary mucus and macrophage activity. It causes irritation in the respiratory tract. They can cause oxidative stress. Chronic exposure that produces bronchial remodeling and COPD. It has carcinogenic activity.
PM_{10}		Trachea, bronchi, bronchioles.	
$PM_{2,5}$	Burning of fossil fuels and biomass, thermoelectric plants.	Alveoli.	
$PM_{0,1}$		Alveoli.	
O_3	It is not emitted directly into the atmosphere. Its formation occurs through complex chemical reactions between volatile organic compounds (VOCs) and nitrogen oxides (NOx) in the presence of sunlight. Sunlight and temperature stimulate such reactions, so that on hot, sunny days, peaks in ozone concentration occur. Sources of VOC and NOx emissions are vehicles, chemical industries, laundries and activities that use solvents.	Trachea, bronchi, bronchioles, alveoli.	It is a photochemical oxidizing agent and very irritating. It causes inflammation of the respiratory tract mucosa. In high concentrations, it irritates the eyes, nasal and oropharyngeal mucous membranes. Causes coughing and chest discomfort. Exposure for several hours leads to damage to the epithelial tissue lining the airways. It causes greater sensitivity to inflammation and airway obstruction to stimuli such as cold and exercise.

NO_2	Anthropogenic sources: nitric and sulfuric acid and combustion engine industries (main source), burning of fuels at high temperatures, in thermal plants that use gas or incineration. Natural sources: electrical discharges in the atmosphere.	Trachea, bronchi, bronchioles, alveoli.	Irritating. It affects the mucosa of the eyes, nose, throat, and lower respiratory tract, increasing bronchial reactivity and susceptibility to infections and allergies. It is considered a good marker of vehicle pollution.
SO_2	Anthropogenic sources: petroleum refineries, diesel vehicles, furnaces, metallurgy, and papermaking. Natural sources: volcanic activity.	Upper airways, trachea, bronchi, bronchioles.	Affects the mucosa of the eyes, nose, throat, and respiratory tract. It causes coughing and increases bronchial reactivity, facilitating bronchoconstriction.
CO	Anthropogenic sources: forest fires, incomplete combustion of fossil fuels or other organic materials and road transport. The sector that most contributes to emissions of this pollutant are urban areas with intense traffic. Natural sources: volcanic eruptions and chlorophyll decomposition.	Alveoli.	Union with hemoglobin, interfering with oxygen transport. It causes headache, nausea, and dizziness. It has fetal teratogenic effects. It is associated with low-birth-weight newborns and fetal death.

TPS: Total particles in suspension; PM: Particulate matter; PM_{10}: Particulate matter of ≤ 10μm in diameter; $PM_{2,5}$: Particulate matter of ≤ 2.5μm in diameter; e $PM_{0,1}$: Particulate matter of ≤ 2.5μm in diameter. Adapted from Kunzli et al (KÜNZLI et al., 2000).

It is well understood that in large urban areas, air quality deteriorates due to the vast number of vehicles powered by diesel, ethanol, or gasoline. These vehicles emit pollutants such as carbon monoxide (CO), hydrocarbons, nitrogen oxides, and sulfur oxides or dioxide, significantly impacting the atmospheric conditions of densely populated regions. The congestion and density of these areas exacerbate the situation, leading to higher concentrations of these harmful substances and further degrading the air that residents breathe (BRAUER et al., 2003). A more detailed description of each pollutant is provided below.

III.1 PARTICULATE MATTER

The World Health Organization (WHO) has identified particulate matter (PM) air pollution as a significant contributor to premature deaths globally, ranking it as the 13th leading cause of death (ANDERSON; THUNDIYIL; STOLBACH, 2012). This statistic, while alarming, only scratches the surface of a more intricate and profound relationship between PM and human health. Composed of minute particles and droplets that include substances like acids, organic compounds, metals, and dust, PM's role in air pollution is highly scrutinized due to its strong connection with various diseases (ANDERSON; THUNDIYIL; STOLBACH, 2012).

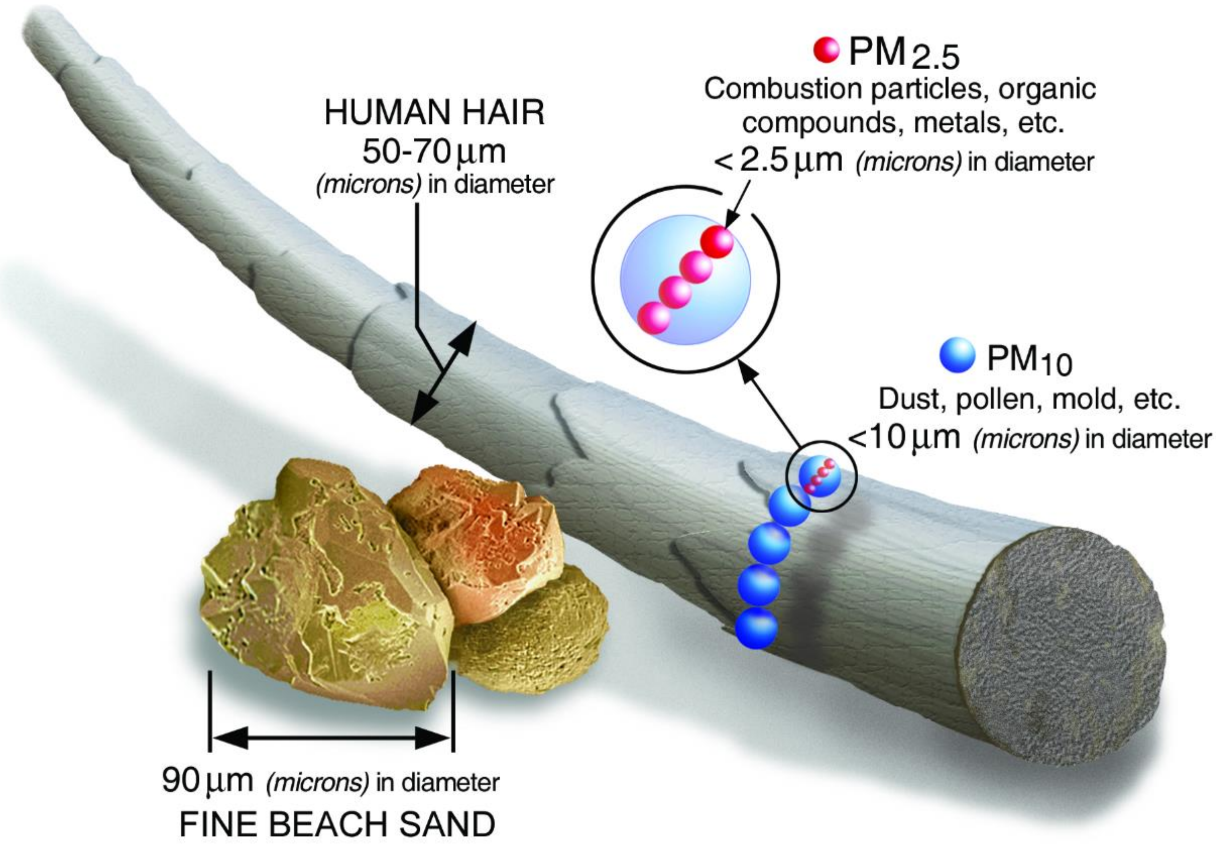

Figure 1. Particulate matter size. Source: https://www.epa.gov/pm-pollution/particulate-matter-pm-basics.

The impact of PM on human health is most notably seen in its contribution to heart and blood vessel diseases. It is believed to incite cardiovascular and cerebrovascular diseases through systemic inflammation, stimulation of coagulation processes, and potentially by directly entering the bloodstream (CHEN; NADZIEJKO, 2005; CHUANG et al., 2007; RIDKER et al., 2000; SUN et al., 2005; WENNBERG et al., 2012). The evidence connecting PM to cardiovascular health is particularly compelling; individuals exposed to PM over long durations exhibit a marked increase in cardiovascular incidents and related deaths (BROOK et al., 2010). Even short-term exposure can lead to a subtle but discernible rise in cardiovascular events following days when pollution levels are high (BROOK et al., 2010; DOCKERY et al., 1993; POPE et al., 2002, 2004).

While the evidence is less robust for PM's influence on cerebrovascular disease, similar biological processes indicate that it may have a consequential, albeit smaller, impact.

Respiratory health is also adversely affected by PM, with studies indicating that exposure leads to oxidative stress and inflammation in the lungs, resulting in structural and functional changes (DRISCOLL et al., 1990; NORDENHÄLL et al., 2001; QUAY et al., 1998; SILBAJORIS et al., 2011). This exposure escalates respiratory symptoms, medication usage, and emergency health care visits, and it also contributes to a decline in lung function and increased mortality rates (AVOL et al., 2001; GAUDERMAN et al., 2004; KARR et al., 2007; MCCONNELL et al., 1999; SLAUGHTER et al., 2003; WONG et al., 2008; ZEKA; ZANOBETTI; SCHWARTZ, 2005).

Research has consistently shown a dose-response relationship between PM exposure and adverse health effects, suggesting that reducing exposure to PM can decrease the prevalence of related diseases (MILLER et al., 2007; NAESS et al., 2007). Despite the need for further investigation into how different components and chemical makeups of PM affect various at-risk groups, the overarching conclusion is that PM exposure is tied to a significant uptick in morbidity and mortality (OMORI et al., 2003; SAMET et al., 2000).

Common sense measures, though backed by limited data, are widely recommended to mitigate PM exposure. These include using air conditioning and particulate filters indoors, reducing indoor combustion for heating and cooking, and avoiding smoking (“AirNow.gov”, [s.d.]; US EPA, 2014b). Particularly vulnerable groups, such as the elderly or those with asthma, are advised to limit outdoor activities during high traffic times or when air quality is poor. Implementing these simple modifications could offer substantial benefits, not only in managing short-term symptoms but also in reducing the long-term risk of cardiovascular and respiratory conditions (“AirNow.gov”, [s.d.]).

PM pollution is a major health hazard identified by the WHO, significantly contributing to premature deaths globally. These particles, which include acids, organic compounds, metals, and dust, are linked to a wide range of health problems, notably cardiovascular and respiratory diseases. Exposure to PM can cause systemic inflammation, stimulate coagulation processes, and enter the bloodstream, leading to increased incidents of heart attacks and strokes. It also exacerbates respiratory conditions by inducing oxidative stress and inflammation in the lungs, leading to more emergency healthcare visits and higher mortality rates.

III.2 OZONE (O_3)

In the process of conducting an exhaustive literature review and critical analysis, the US EPA assessed the impact of ozone on public health and documented its findings in the 2013 US EPA Integrated Science Assessment for Ozone (NUVOLONE; PETRI; VOLLER, 2018). This rigorous evaluation led to a revision of the national ambient air quality standard for 8-hour daily maximum ozone levels, which were reduced from 75 ppb to 70 ppb in 2015, as corroborated by recent reviews (KOMAN; MANCUSO, 2017; NUVOLONE; PETRI; VOLLER, 2018).

The US EPA`s revision was informed by evidence showing that ozone contributes to a range of adverse respiratory effects, from breathing difficulties and pain on taking deep breaths to inflammation of the airways. Such effects can intensify lung diseases including asthma, emphysema, chronic bronchitis, and COPD. The assessment also recognized that chronic exposure to ozone might play a role in the development of asthma and is likely to result in premature deaths, particularly from respiratory illnesses (NUVOLONE; PETRI; VOLLER, 2018).

The vulnerability of children to ozone is particularly concerning due to their still-developing lungs and higher dose of ozone per body mass compared to adults. The setting of the revised standard prompts a question regarding its implication on public health: does adherence to the standard eliminate the risk of the adverse effects mentioned? Although the standard may imply a level of safety, the actual safety threshold can appear arbitrary. For instance, the WHO recommends a stricter 8-hour daily max ozone guideline of around 50 ppb (100 µg/m^3), based on similar evidence to that of the US EPA but with additional observed effects such as coughing, throat irritation, and increased susceptibility to lung infections, and continuing damage to the lungs even after symptoms have ceased (DAI et al., 2018; NHUNG et al., 2018).

While the 2013 EPA assessment did not find the link between ozone and COPD to be particularly strong, other documented effects of ozone exposure include increased school absences, emergency room visits, and hospital admissions on days with high ozone levels (LIN et al., 2008; MALIG et al., 2016; STRICKLAND et al., 2010; TIAN et al., 2018) as well as associations between long-term ozone exposure with impaired lung function and abnormal lung development in children (GAUDERMAN et al., 2002, 2004). Both the WHO and EPA standards consider populations that are more susceptible to the effects of ozone. This includes not only people with existing respiratory conditions but also children, the elderly, and outdoor workers, underscoring the importance of protective measures for these at-risk groups (ZHANG; WEI; FANG, 2019).

In summary, the US EPA updated the ozone air quality standard to 70 ppb in 2015, based on evidence of its harmful respiratory effects, such as breathing difficulties and lung disease exacerbation. This revision, aimed at protecting public health, especially highlights children's vulnerability due to their developing lungs. Despite this effort, the WHO suggests a stricter limit of 50 ppb, pointing to additional risks like coughing and throat irritation. The EPA's review also notes ozone's link to increased hospital admissions and impaired lung function, particularly in children, underscoring the need for stringent protective measures for sensitive groups.

III.3 NITROGEN DIOXIDE (NO_2)

A substantial body of research has been dedicated to exploring the impacts of nitrogen dioxide (NO_2) in outdoor environments on human health. In the face of skepticism regarding the specificity of health effects attributed to NO_2, given the presence of other pollutants, a number of comprehensive studies have solidified the connection between exposure to NO_2 and the incidence of respiratory health problems (ATKINSON et al., 2018). These investigations affirm that the health detriments associated with NO_2 are indeed distinct and are not merely byproducts of other environmental contaminants (ATKINSON et al., 2018).

The scope of health disorders linked to outdoor NO_2 is expanding. Recent research has linked it to an increased risk of ailments such as otitis media (BRAUER et al., 2006), eczema (MORGENSTERN et al., 2008), infections of the ear, nose, and throat, as well as heightened sensitivity to food allergens in children (BRAUER et al., 2007), alongside augmented blood coagulability in adults following high exposure periods (BACCARELLI et al., 2007). Moreover, there's a burgeoning interest in examining how outdoor pollution affects reproductive health outcomes (SLAMA et al., 2008).

So, basically, studies have shown that NO_2 in the air affects human health. Researchers think that NO_2 itself can affect our respiratory health. It's also linked to ear infections, skin issues like eczema, and even makes children more likely to react to food allergens. Additionally, some findings suggest that high NO_2 levels can make blood more likely to clot. And now, scientists are also looking into how this outdoor pollutant might affect things like pregnancy outcomes.

III.4 SULFUR DIOXIDE (SO_2)

Over the past eight years, three significant reviews have been published concerning the harmful impacts of sulfur dioxide on both humans and animals. These comprehensive assessments have included epidemiological studies, the health consequences of both acute and chronic exposure to low doses in humans, as well as the effects of both low and high doses in animal subjects over short and long periods. They have also projected estimates for the thresholds of pollutant levels that lead to detrimental effects from both brief and extended exposure times and have examined the link between sulfur dioxide exposure and asthmatic episodes, including its impact on children's health. (NATIONAL RESEARCH COUNCIL (US) COMMITTEE ON TOXICOLOGY, 1984).

Case reports have shown severe health effects from accidental exposure to sulfur dioxide, including skin and cornea damage from direct liquid contact and severe respiratory conditions from brief high-concentration exposure (GRANT, 1947; WOODFORD; COUTU; GAENSLER, 1979). Controlled human exposure studies reveal that low concentrations (less than 25 ppm) lead to mucous membrane irritation and respiratory changes, with particular sensitivity noted in asthmatic individuals (KOENIG; PIERSON; FRANK, 1980; LAWTHER et al., 1975). Recovery times post-exposure vary with activity and health status (GÖKEMEIJER; DE VRIES; ORIE, 1973; KOENIG et al., 1981; SHEPPARD et al., 1980)

Epidemiological data, while challenging to assess due to associated pollutants, demonstrate increased mortality from acute sulfur dioxide pollution episodes in historical incidents in Meuse Valley, Donora, London, and New York City (NATIONAL RESEARCH COUNCIL (US) COMMITTEE ON TOXICOLOGY, 1984). Long-term studies further correlate high sulfur dioxide concentrations with increased respiratory illnesses and diminished lung function, although confounding factors like additional particles complicate interpretation. In occupational settings, significant chromosomal aberrations have been observed among workers exposed to sulfur dioxide, as noted in studies of sulfite pulp factory workers in Sweden, underscoring the broad health implications of exposure (NATIONAL RESEARCH COUNCIL (US) COMMITTEE ON TOXICOLOGY, 1984; NORDENSON et al., 1980).

Summing it all up, the past eight years have shown us clearly how bad sulfur dioxide can be for both people and animals. Studies and reports have pointed out that whether it's a short-term or long-term exposure, at low or high doses, the effects are seriously harmful. It irritates the lungs, can harm the skin and eyes directly, and is even worse for those with asthma, especially kids. There's also evidence linking it to more severe health issues over time, like lung problems and even changes in DNA for those who are around it a lot at work. All this tells us we need to be careful and make sure we're keeping the air clean to avoid these problems.

III.5 CARBON MONOXIDE (CO)

In the United States, carbon monoxide (CO) is a pervasive and potentially lethal poison, affecting an estimated 50,000 individuals annually (CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC), 2003; HAMPSON, 1998, 2016). The clinical manifestations of CO poisoning span a wide range, from mild symptoms such as headaches and dizziness to severe outcomes like coma and death, with the fatality rate fluctuating between 1 and 3% (HAMPSON et al., 2012; HAMPSON; HAUFF, 2008; PENNEY, 2007; WEAVER, 2009a). Notably, a considerable proportion of those who survive the initial poisoning experience enduring neurological and emotional disturbances (LO et al., 2007; SHPRECHER; MEHTA, 2010). These long-term impairments are not directly linked to the levels of CO found in the blood. Instead, they are more likely due to CO's diverse biological effects, which impede mitochondrial respiration within cells, disrupt normal energy use, trigger inflammation, and lead to the production of harmful free radicals, particularly affecting the brain and heart (DZIEWIERZ et al., 2013; HENRY et al., 2006; KAYA et al., 2016; LIPPI et al., 2012; PARKINSON et al., 2002; ROSE et al., 2017; SATRAN et al., 2005; WEAVER, 2009b).

CO poisoning is a big health concern in the U.S., affecting around 50,000 people every year. It can cause symptoms ranging from mild headaches to severe issues like coma or death. Survivors can have lasting brain and emotional problems, because of the CO levels in their blood causes inflammation, and damages the brain and heart. Individual exposure to air pollutants can be indirectly calculated using exposure models, which are further evaluated next.

III.6 AIR POLLUTION EXPOSURE MODELS FOR EPIDEMIOLOGIC STUDIES

The advancement of methodologies for evaluating air pollution levels in urban settings, as a means of providing data for health research, has emerged as a critical area for further investigation. This document conducts a comprehensive examination of intraurban exposure assessment models, categorized into six distinct types: (1) assessments based on proximity, (2) statistical interpolation techniques, (3) land use regression approaches, (4) line dispersion techniques, (5) models that integrate emissions and meteorological data, and (6) hybrid approaches that merge personal or household exposure monitoring with one of the aforementioned strategies. This examination is enhanced with practical instances from Hamilton, Canada, and includes a qualitative analysis of the models, focusing on criteria vital for researching health effects (JERRETT et al., 2001). Hybrid models are noted for their potential in addressing the challenge of obtaining samples that represent the population while also delineating individual-level exposure variations. The incorporation of remote sensing and activity-space analysis, along with anticipated progress in existing methodologies, suggests that the domain of exposure assessment could significantly diminish the scientific uncertainties currently hindering policy measures designed to safeguard public health (JERRETT et al., 2005).

Future research prioritizes the creation of models to assess air pollution exposures in urban environments, assigning these data to participants in health studies (BRAUER et al., 2003; BRUNEKREEF; HOLGATE, 2002). Traditional surrogate measures like proximity to roads, associated with significant health impacts (HOEK et al., 2002), may not accurately classify exposure as they don't derive directly from monitored data. Geographic and dispersion exposure methods provide potential alternatives, utilizing geographic information systems (GIS) to merge geographic data with short-term monitoring to develop models that detect small-area pollution variations. These models' results can then be mapped onto geo-referenced health data to allocate exposure to individuals at their residences or workplaces (JERRETT et al., 2005).

The focus on ambient air pollution exposure assessment at the intraurban level has intensified for various reasons. Firstly, the increasing significance of traffic pollution, alongside a consensus that transportation demand will surpass emission reduction advancements (DELUCCHI, 2000; FAIZ, 1993), suggests ongoing high exposure to traffic-related pollution, particularly near major roads and highways (GILBERT et al., 2003). For certain traffic-related pollutants, intra-city variation often surpasses inter-city differences (BRIGGS, 2005; ZHU et al., 2002), with studies highlighting substantial variability within short distances.

Secondly, although results are mixed (ENGLISH et al., 1999), enough studies indicate positive health effects from city-level exposure to warrant significant attention. For instance, a Dutch study linked proximity to major roads to a considerable increase in cardiopulmonary mortality, emphasizing the need for more sophisticated exposure measurements beyond basic models like buffers (HOEK et al., 2002).

Thirdly, the past decade has seen advancements in GIS and related statistical methods, enhancing exposure analysis capabilities (GATTRELL; LOYTONEN, 1998; MELNICK, 2002). Such technological progress has accelerated research in intraurban exposure, enabling complex characterizations of such exposures through the integration of dispersion, atmospheric, and time-activity models with GIS (JERRETT et al., 2005).

III.6.1 PROXIMITY MODELS

Evaluating subjects' proximity to pollution sources is a fundamental technique for differentiating air pollution exposure levels within urban areas. This method assumes that closeness to emission sources is indicative of exposure in human populations, typically employing road buffer models to assign binary exposure values to individuals. Studies have frequently applied this method to understand the exacerbation of asthma symptoms in children through empirical models (JERRETT et al., 2005).

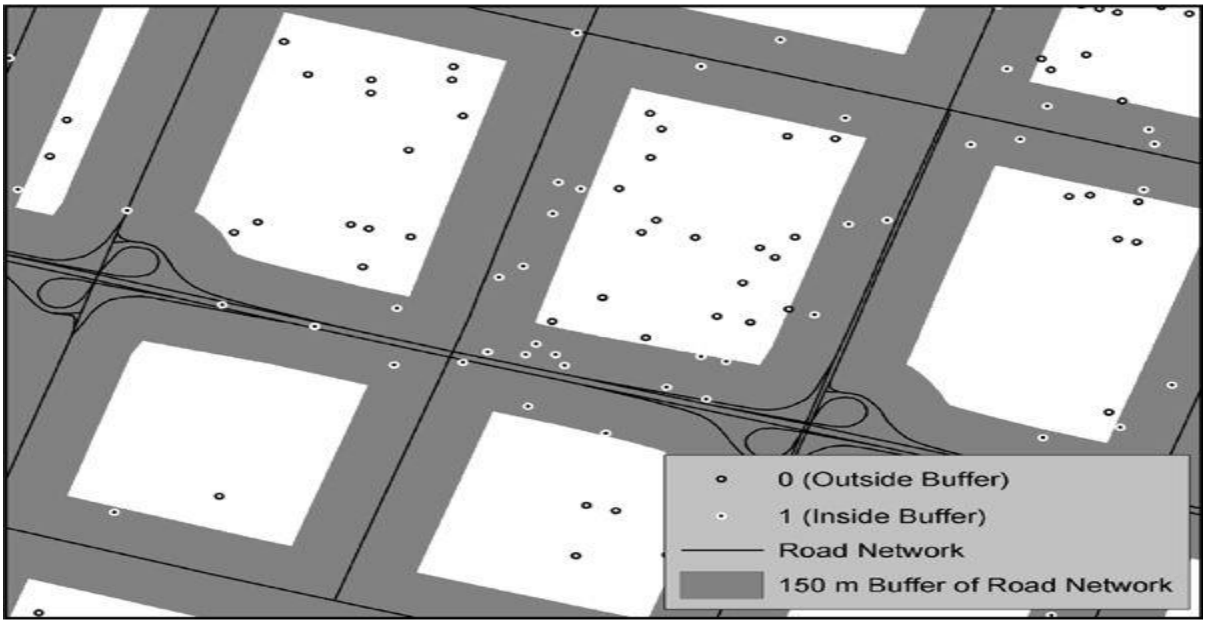

Figure 2. Example of a Binary Classification model within a buffer scheme for proximity models. Source: https://www.nature.com/articles/7500388/figures/1.

Our synthesis of 12 peer-reviewed articles (CICCONE et al., 1998; ENGLISH et al., 1999; JANSSEN et al., 2001; LANGHOLZ et al., 2002; MAHESWARAN; ELLIOTT, 2003; VAN VLIET et al., 1997; VENN et al., 2000; WILKINSON et al., 1999; WYLER et al., 2000) revealed a primary focus on the link between road proximity and respiratory diseases, lung cancer, and stroke mortality, primarily in Europe, with additional studies in North America. These investigations varied in their application of proximity measures, incorporating aspects like traffic volume, particulate matter, and the type of nearby roads to refine exposure estimates. The methodologies included direct measurements of pollutants, use of traffic activity indexes, and different approaches to buffer zone implementation.

Despite the widespread application of proximity measures, the evidence linking them to the onset of asthma or other diseases is mixed, with some studies indicating a significant health impact while others find no clear association (ENGLISH et al., 1999; RIJNDERS et al., 2001; VENN et al., 2000). Notably, these studies highlight a range of methodological considerations and limitations, including the neglect of exposure at locations other than residence or school, the influence of vehicle types, and the assumption of uniform pollutant dispersion (ENGLISH et al., 1999). Moreover, the use of self-reported data in some studies introduces the potential for recall bias (VENN et al., 2000).

In conclusion, while proximity-based methods have provided valuable insights into the health effects of air pollution, particularly in the context of asthma and respiratory diseases, their limitations underscore the need for more nuanced exposure assessments. Future research should aim to address these shortcomings, leveraging advances in technology and methodology to develop more accurate and representative measures of air pollution exposure within urban environments.

III.6.2 INTERPOLATION MODELS

Interpolation models, particularly kriging, use deterministic and stochastic techniques to estimate pollutant concentrations at unmonitored sites, utilizing measurements from distributed monitoring stations. Kriging, a common geostatistical technique, offers the best linear unbiased estimate (BLUE) of the variable's value, along with quantifying uncertainty in predictions through standard errors. This model capitalizes on spatial dependence in the data, incorporating both broad trends (first-order effects) and local variations (second-order effects) to generate continuous pollution surfaces (JERRETT et al., 2005).

Studies across North America and Europe have applied interpolation models to various pollutants and health outcomes, demonstrating associations between higher pollution levels and increased health risks. These include respiratory effects, mortality, and preterm births. The studies utilized various techniques like universal kriging and inverse distance weighting, showing the versatility and application of interpolation in environmental health research (ABBEY et al., 1999; FINKELSTEIN et al., 2003; JERRETT et al., 2001; MULHOLLAND et al., 1998; PIKHART et al., 2001; RITZ et al., 2000).

Despite their advantages, interpolation models have limitations, particularly related to the availability and density of monitoring data. They require a substantial number of sampling sites and may not accurately represent pollution patterns when data are sparse or unrepresentative. The assumptions inherent in kriging, such as spatial homogeneity, can also lead to errors, particularly at the edges of the study area or where trends in pollution levels are strong. Overcoming these challenges often necessitates primary data collection, which can be costly and logistically challenging(1996; MULHOLLAND et al., 1998; PIKHART et al., 2001).

Ultimately, while interpolation models offer a sophisticated means of estimating pollution exposure and linking it to health outcomes, their effectiveness is contingent on the quality and density of monitoring data, as well as the careful application of the model's assumptions and parameters. Proper implementation requires both specialized software and expertise in geostatistical analysis.

III.6.3 LAND USE REGRESSION MODELS

Land-use regression (LUR) methodology predicts pollution concentrations at specific sites based on surrounding land use and traffic features, using measured pollution concentrations as the response variable and various land uses as predictors. This regression mapping is a practical method for assessing exposure to traffic-related pollution, employing least-squares regression modeling to predict pollution surfaces from monitoring data and other independent variables (RYAN; LEMASTERS, 2007).

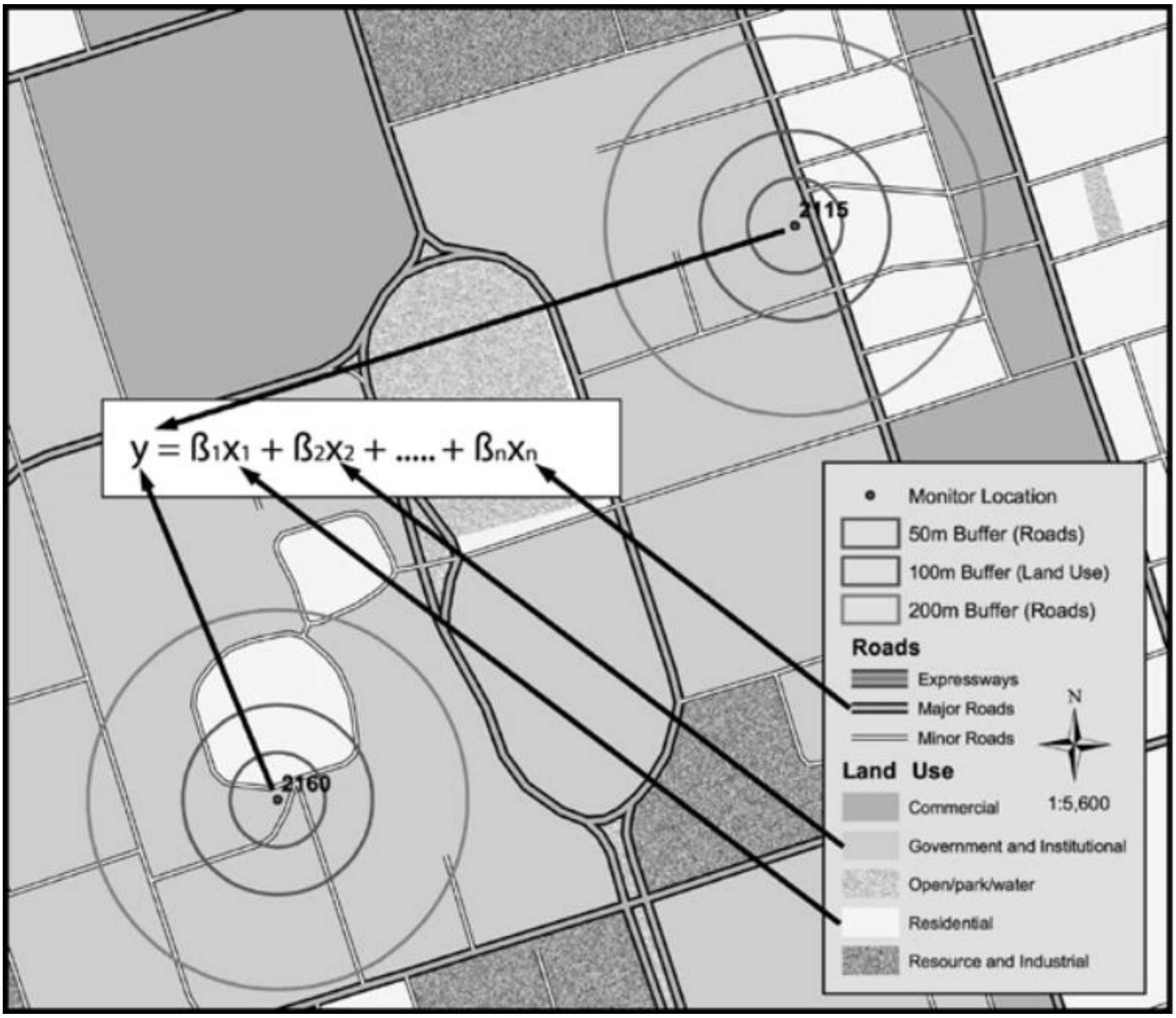

Figure 3. Example of the of a LUR model to predict a pollutant in a point in the map. Source: https://www.nature.com/articles/7500388/figures/3.

The application of LUR has primarily been in European cities at the intraurban scale, focusing on traffic-related air pollution. These studies have utilized variables such as road traffic volume, land-use type, and altitude to predict mean NO2 levels, with some reporting good predictive accuracy. Additionally, comparisons between different regression analyses have demonstrated that multiple regression techniques, incorporating both GIS-derived and additional variables, can produce statistically reliable results (BRAUER et al., 2003; BRIGGS, 2005; LEBRET et al., 2000).

The strength of LUR lies in its empirical nature and adaptability to local areas, often requiring less additional monitoring or data collection compared to other methods. It identifies areas needing more intensive monitoring and is relatively cost-effective. However, its limitations become apparent when extrapolating to areas with different land use and topography. For instance, applying a model developed for Amsterdam to Hamilton, Canada, yielded poor correlation with measured data, highlighting the method's area-specificity. While extrapolation may work within similar geographic settings, a dense network of monitoring samples, often necessitating primary data collection, is usually required to ensure accuracy.

This can introduce the typical challenges associated with data collection, including costs and logistical difficulties (BRAUER et al., 2003; BRIGGS, 2005).

To sum up, LUR is a technique used to estimate pollution levels at specific locations by analyzing surrounding land use and traffic features. It's been mainly applied in European cities to measure traffic-related air pollution, using data like road traffic volume and land-use type to predict pollutants like NO_2. LUR is valued for its practicality and cost-effectiveness, allowing for targeted monitoring without extensive data collection. However, its effectiveness is limited to the area it was developed for; models are not always transferable to different locations with varying land use and geography. While useful within similar settings, ensuring accuracy in new areas often requires collecting new, local data, which can be costly and logistically challenging.

III.6.4 DISPERSION MODELS

Dispersion models, primarily based on Gaussian plume equations, utilize deterministic processes and data on emissions, meteorology, and topography to estimate spatial exposure to air pollution concentrations. Integrating with GIS, these models enhance the analysis by incorporating empirical monitoring systems and data on population distribution, topography, and traffic observations, offering a more realistic depiction of air pollution (NICHOLLS et al., 1995). Studies have applied these models across various pollutants such as TSP, NOx, SO_2, and CO (HOLMES; MORAWSKA, 2006).

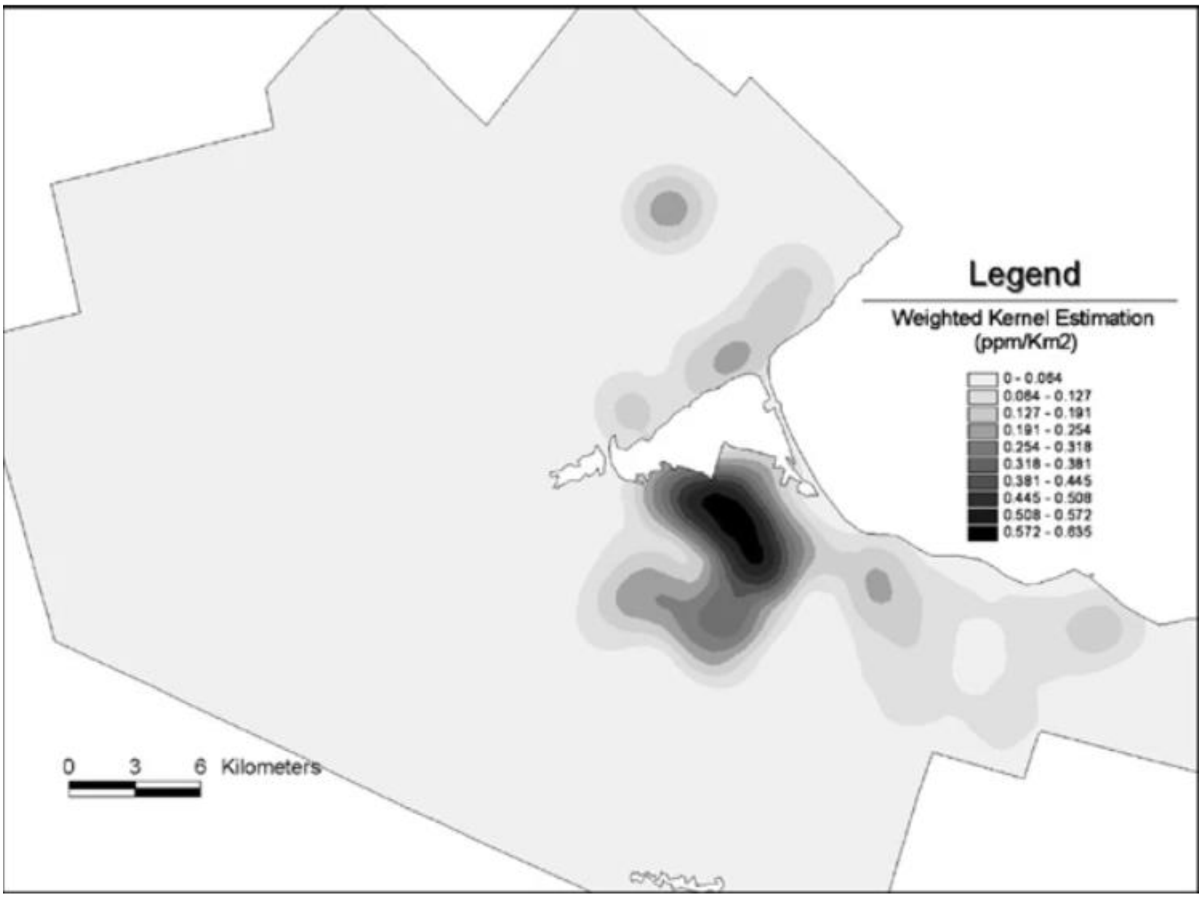

Figure 4. Example of dispersion model in using a kernel estimate of CALINE4 receptor locations for Hamilton. Source: https://www.nature.com/articles/7500388/figures/6.

To operate effectively, dispersion models require detailed pollution, meteorological, and emission data. Pollution data, often from government monitoring stations, calibrate the model, while meteorological data detail conditions like wind speed and temperature. Emission data, categorized into stationary (e.g., industries) and mobile (e.g., traffic) sources, provide information on pollutants' release. After meeting these data requirements and calibrating the model, dispersion models compute pollution levels for the desired time intervals, making further data updates as necessary (HERRING; HUQ, 2018; SNOUN; KRICHEN; CHÉRIF, 2023).

Several studies (BELLANDER et al., 2001; GUALTIERI; TARTAGLIA, 1998; HRUBÁ et al., 2001; NAFSTAD et al., 2003; NYBERG et al., 2000) have demonstrated the application of dispersion models in assessing air pollution and its health effects. These include estimating ambient particulate air pollution, assessing traffic-related pollution, and evaluating individual exposure to NO_2 and SO_2. The results have shown associations between air pollution and health outcomes like respiratory symptoms, lung cancer, and exposure classification.

Dispersion models offer the advantage of incorporating spatial and temporal variation in air pollution without requiring dense monitoring networks. They account for differences in source strength, wind velocity, atmospheric conditions, and topography and can be applied across various spatial scales (HOLMES; MORAWSKA, 2006). However, these models come with disadvantages, including costly data inputs, unrealistic assumptions about dispersion patterns, the need for extensive cross-validation with monitoring data, and potential temporal mismatches in data causing estimation errors. Implementing these models also requires considerable programming and GIS expertise, as well as substantial hardware resources. Despite these challenges, when accurately applied and validated, dispersion models can provide valuable high-resolution analyses of environmental factors and health outcomes (JERRETT et al., 2005).

III.6.5 INTEGRATED METEOROLOGICAL-EMISSION MODELS

Integrated meteorological-emission (IME) models merge meteorological and chemical modules to simulate the dynamics of atmospheric pollutants, drawing on meteorological data at every time step to inform chemistry modules (NICHOLLS et al., 1995; TILMES et al., 2002; VOGEL; FIEDLER; VOGEL, 1995, p. 199). These models are particularly useful for areas lacking comprehensive observations to define key meteorological fields needed for air quality applications. The sophistication and efficiency of IME models depend on aspects like model physics, input data, grid resolution, and land surface schemes (ABBEY et al., 1999; CHEN; DUDHIA, 2001; FROHN; CHRISTENSEN; BRANDT, 2002; PEARSON; FITZGERALD, [s.d.]; TILMES et al., 2002; VOGEL; FIEDLER; VOGEL, 1995).

Application-wise, IME models are composed of meteorological, chemistry transport, and visualization and analysis modules. The meteorological module describes atmospheric conditions and influences the transport and dispersion of pollutants, while the chemistry transport module concerns emissions and their movement in the atmosphere. Types of emission sources considered include point, line, and distributed sources. The visualization and analysis module provides capabilities for data plotting, including 3D animation and graphic user interfaces, enhancing the understanding and presentation of data (BAKLANOV; ZHANG, 2020; GAO; ZHOU, 2024; WILSON et al., 2021).

While IME models have not been extensively used to link air quality to health due to their high implementation cost and data requirements, they have significant potential, particularly in densely populated areas where small air pollution risks can significantly impact public health (WILSON et al., 2021). These models can simulate a wide range of exposure scenarios and incorporate the transport and fate of chemical pollutants, allowing for precise estimates of pollution mix and potential health associations (GAO; ZHOU, 2024).

However, IME models have their challenges, including the need for high-end computational facilities, sophisticated software, and specialized personnel, making them a costly endeavor. Creating a usable exposure data set from these models involves interpolating between receptor locations on an array, with accuracy potentially reduced if the array's resolution is low (BAKLANOV; ZHANG, 2020). Each type of meteorological module within the IME framework has its advantages and disadvantages, from the inexpensive and less demanding diagnostic models to the more complex and accurate dynamic and FDDA models (WILSON et al., 2021).

Despite their promise, IME models' barriers include intensive data input requirements, coarse grid resolution for local-scale pollutants, and the need for computing resources and expertise in meteorology and climatology. These factors have limited their widespread implementation in health-related studies. Yet, the dynamic modelling capabilities and precise representation of complex pollutant pathways they offer make them a valuable tool in understanding and predicting air quality and its health impacts (JERRETT et al., 2005).

In conclusion, IME models combine weather data with pollution chemistry to simulate how atmospheric pollutants move and change. These models are especially helpful where detailed meteorological observations are scarce, using various data to predict air quality accurately. IME models consist of modules that describe atmospheric conditions, track emissions through the air, and provide tools for data visualization, including 3D animations. Although their high cost and complex data needs have limited their use in linking air quality directly to health impacts, IME models hold significant promise for densely populated areas. However, challenges like the need for advanced computing, specialized software, and expert personnel, along with issues related to data resolution, have made widespread adoption in health studies difficult. Despite these hurdles, the detailed simulations provided by IME models are invaluable for understanding and managing air quality and health outcomes.

III.6.6 HYBRID MODELS

Hybrid models represent a combination of personal or regional monitoring with other air pollution exposure methodologies, aiming to compare or validate ambient exposure modelling results with monitored data at various scales (ABBEY et al., 1999; CLENCH-AAS et al., 1999; KRÄMER et al., 2000; MUKALA et al., 2000; ZMIROU et al., 2002, 2002). Typically conducted within European cities, these studies use personal air samplers alongside fixed outdoor stations to examine disparities in derived health outcomes. Personal monitoring involves attaching air samplers to individuals, while regional monitoring employs techniques like inverse distance weighting and regression models to estimate pollution levels (HOEK et al., 2001, 2002).

Comparing exposure significance across studies reveals that personal monitoring often yields lower concentration measurements than fixed monitoring stations but may provide more accurate exposure estimates as it considers the predominant indoor environment where individuals spend most of their time (LEECH et al., 2002; LEVY, 1998;

ZIPPRICH et al., 2002). These hybrid studies have employed multiple linear and logistic regressions to correlate exposure with health outcomes, primarily focusing on school children, with some studies extending to adults (GAUVIN et al., 2001; KRÄMER et al., 2000; LIU; DELFINO; KOUTRAKIS, 1997; MUKALA et al., 2000). Significant variations in NO2 and ozone levels were noted between personal and ambient background measures across different settings and populations.

The advantages of hybrid models include measurement validation and the capacity to incorporate different exposure assessment methodologies. However, the complexity and feasibility of implementing these models depend on the specific combination of methodologies used and the availability of ambient data. The type of pollutant under study also affects the cost and practicality of implementing hybrid models, with passive monitors like NO_2 being more cost-effective compared to real-time particle monitors. Despite these challenges, hybrid models provide a robust framework for understanding the variations and correlations between personal exposure and ambient air pollution, contributing significantly to the field of environmental health research (JERRETT et al., 2005).

Hybrid models mix personal or regional pollution monitoring with other methods to check or confirm the results of ambient exposure models. Mainly used in European cities, these models pair personal air samplers worn by individuals with data from fixed outdoor stations to explore health outcome differences. Personal monitoring captures the air quality in the indoor environments where people spend most of their time, potentially offering more accurate exposure estimates than fixed stations, which might show higher pollution levels. Hybrid models stand out for validating measurements and blending various exposure assessments, though their complexity and cost depend on the pollutants studied and available data. Despite difficulties like the expense of certain monitors, hybrid models significantly enhance our understanding of how personal exposure to air pollution compares to the broader environmental backdrop, marking a valuable advance in environmental health research.

III.6.7 ANALYZING SHORT- AND LONG-TERM MEAN POLLUTION EXPOSURES

As these models usually predict one day of a pollutant exposure for each participant, studies normally make means or medians of the predicted exposure in different time frames, such as the prediction for 30 days or 1 or 2 years. As air pollutants tend to vary in concentration in specific days, depending on situations that can occur (like wildfires), it is advocated by some that short-term exposure is more susceptible to variability (outliers), and long-term exposures are more reliable. It poses the question of whether some diseases are associated with long-term and not short-term exposures because of the accuracy of the results. Nevertheless, there is no sufficient evidence that this variability phenomenon exists, however, we do need to consider a more reliable way to measure short-term exposures.

As previously discussed, air pollution can be inhaled through the upper respiratory tract (particularly the nose and nasal cavity) and is linked to several health conditions, playing an important role in human health. Because of the possible effects in the upper respiratory tract, a review of the nose and nasal cavity anatomy and physiology is presented next.

III.7 NASAL CAVITY ANATOMY AND SMELL PHYSIOLOGY

Situated at the uppermost section of the respiratory pathway, the nasal cavity serves as a gateway to the external environment via the anterior nostril openings, or nares, and links to the nasopharynx through the posterior nostril openings, known as choanae (Figure 5). This space is divided into two separate chambers by a dividing structure called the septum, which is made rigid by bone and cartilage to maintain openness. Each of these chambers is composed of a top section, a bottom section, and walls on the inside and outside. Within these chambers, there are three key areas: the initial entry area called the vestibule, the area responsible for breathing, and the area sensitive to odors (PATEL, 2017).

Encasing the nasal chambers are air-filled sinuses lined with a mucous membrane. These are categorized as the frontal sinuses located in the upper front area, the ethmoid sinuses in the upper area, the maxillary sinuses on each side, and the sphenoid sinuses towards the rear. All these sinuses, with the exception of the sphenoid, have pathways that lead into the nasal cavity through openings on the side wall. The sphenoid sinus, however, drains into the area at the back top. Comprehending the nasal cavity's anatomy is essential for understanding its functional roles (ONEAL; BEIL JR RJ; SCHLESINGER, 1999).

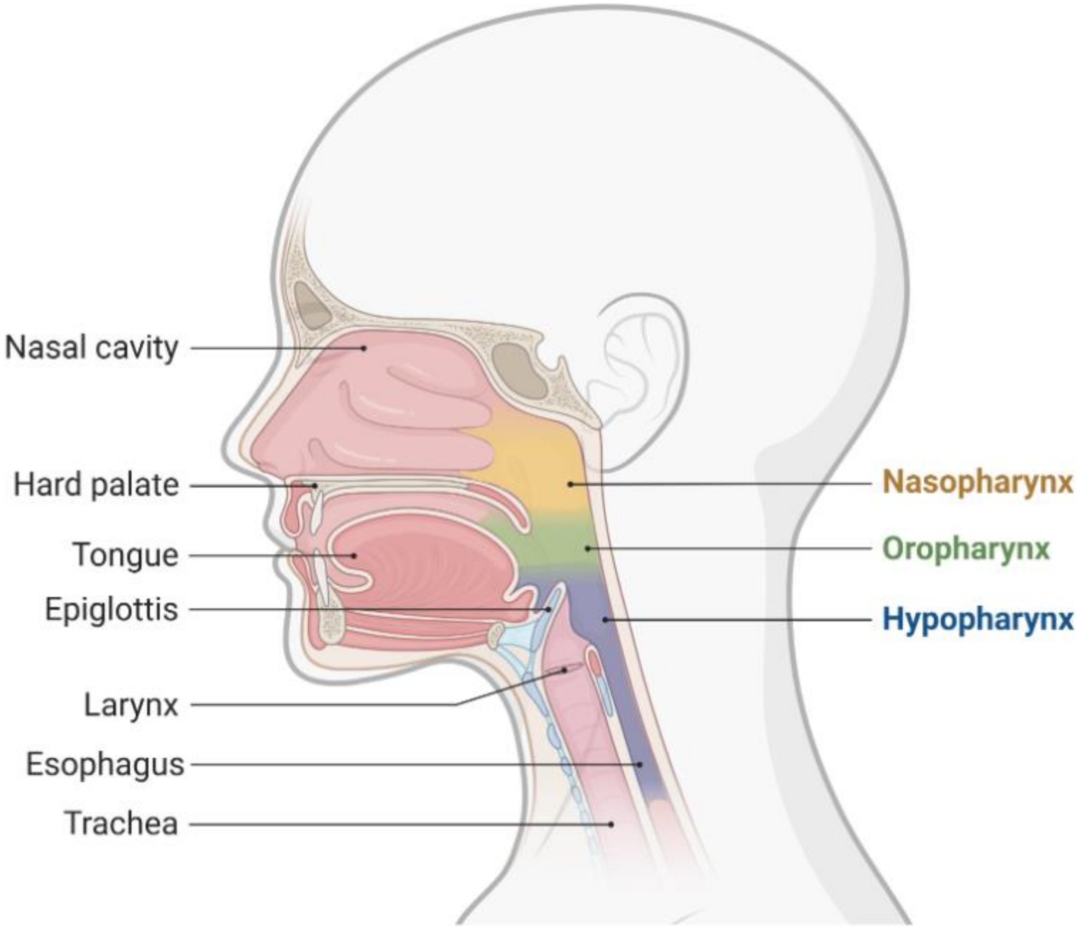

Figure 5. Upper respiratory tract anatomy. Source: biorender.

III.7.1 NASAL CAVITY – RESPIRATORY PART

The primary role of the respiratory region is to moisten, heat, filter, guard, and clear away foreign particles. This region, which is the largest within the nasal cavity, is lined with respiratory epithelium and mucous-producing cells. As air moves through this space, it is heated to body temperature and its humidity level approaches 100%. The blood supply and nerves in this area facilitate these changes, particularly by managing blood flow in the erectile tissue found in the lower turbinate and front part of the septum. Usually, this tissue receives constant stimulation from sympathetic nerves through the superior cervical ganglia, ensuring the nasal passages remain clear (LAFCI FAHRIOGLU; VANKAMPEN; ANDALORO, 2024).

Any particles that bypass the initial vestibule are caught in the nasal cavity's mucosal lining. Here, the mucociliary apparatus plays a crucial role in removing these particles by moving them at a pace of one centimeter per minute toward the nasopharynx for expulsion (LAFCI FAHRIOGLU; VANKAMPEN; ANDALORO, 2024; PATEL, 2017).

The mucus within the nasal cavity also acts as a defensive barrier against pathogens we might inhale. Its protective elements include immunoglobulin A, lysozymes, and lactoferrin, which all play a part in the body's immune response (ONEAL; BEIL JR RJ; SCHLESINGER, 1999; PATEL, 2017).

III.7.2 NASAL CAVITY – OLFACTORY PART

Smelling, or olfaction, depends on either orthonasal or retronasal airflow to carry odorant molecules to the olfactory epithelium located at the top of the nasal cavity. Once these molecules are caught in the mucus, they bind to specific proteins that aid in concentrating and dissolving the odorants. Subsequently, these molecules connect to olfactory receptors on the cilia, which then relay distinct signals through the cribriform plate to connect with the olfactory bulb's neurons. These neurons, in turn, transmit signals via the olfactory nerve (CNI) to secondary neurons for advanced processing before they reach the brain. An interesting aspect of olfactory receptors is their specificity; each receptor cell is tuned to recognize a single type of odorant molecule, and these cells do not have the ability to regenerate (LAFCI FAHRIOGLU; VANKAMPEN; ANDALORO, 2024).

Located at the nasal cavity's uppermost part, near the cribriform plate—a section of the ethmoid bone dotted with holes that separates the brain's frontal lobe from the nasal space—the olfactory system begins its process. Here, odorant molecules first contact receptors found on the primary cilia of olfactory sensory neurons (PINCHING; POWELL, 1971). Despite each neuron carrying receptors for only one protein type on its dendrites, a single odorant can interact with multiple receptor types. These neurons' dendritic ends, situated in a slim mucous layer alongside supportive epithelium, are where the initial detection occurs. The secretion of a serous fluid rich in glycoprotein by Bowman glands plays a crucial role in heating, moistening, and capturing air, thereby aiding in the dissolution of odorant particles in gas form (PINCHING; POWELL, 1971) (Figure 6).

The axonal parts of these sensory neurons then merge, forming neurovascular bundles that pass through the cribriform plate, ultimately creating the olfactory nerves. These nerves' axonal projections meet the dendrites of mitral and tufted cells within spherical units called glomeruli on the olfactory bulb's surface, essential for smell transduction. Each glomerulus gathers axons from neurons sharing the same receptor protein, ensuring a highly organized olfactory signal transmission (PERSAUD, 2013).

It's believed that humans possess between 1100 and 1200 glomeruli in each olfactory bulb (PINCHING; POWELL, 1971). The secondary neurons, or mitral cells, extend via the olfactory tracts to brain regions specialized in processing smells, such as the piriform cortex, olfactory tubercle, amygdala, and entorhinal cortex (BENIGNUS; PRAH, 1982; HATT, 2004).

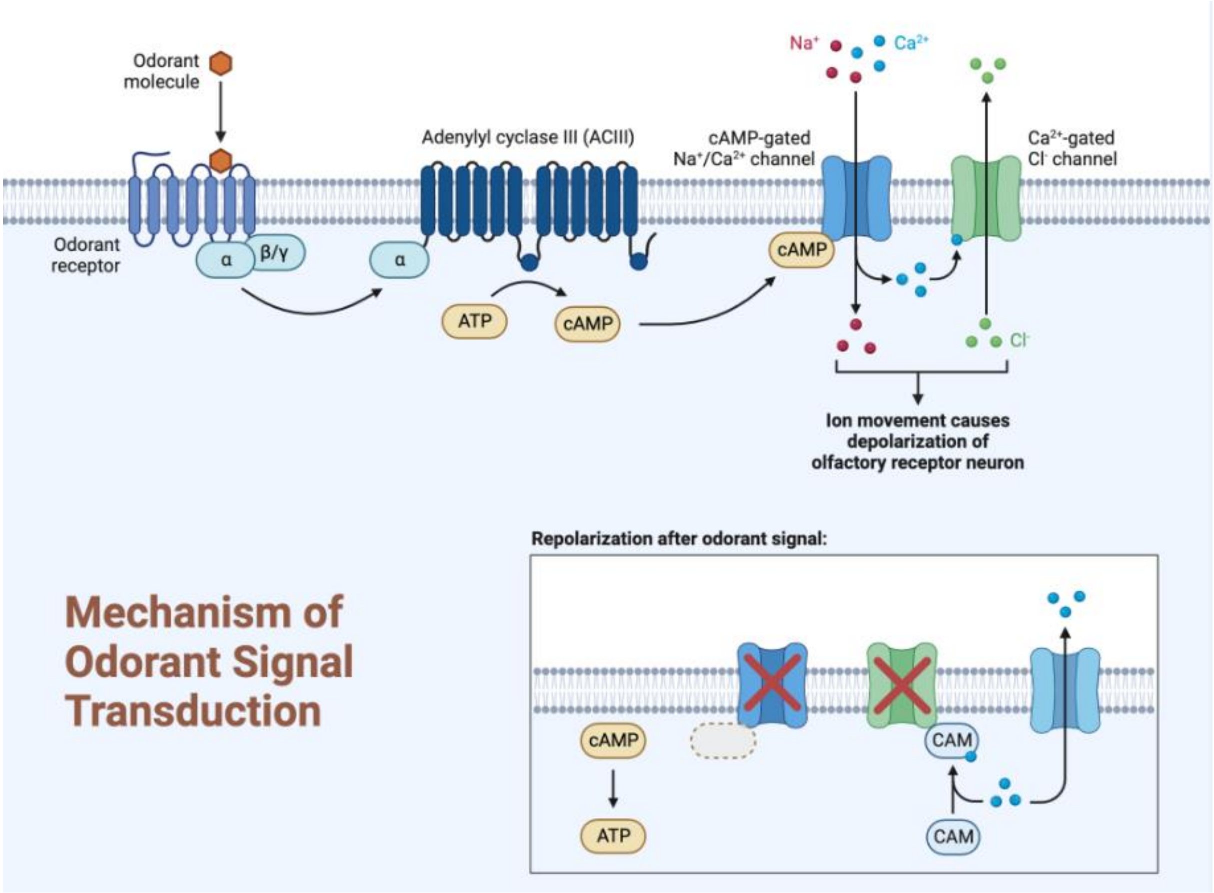

Figure 6. Mechanism of odorant signal transduction. Source: Biorender.

III.7.3 NASAL CAVITY HISTOLOGY

The structure of the nasal vestibule is closely akin to that of the skin. At the transition zone, known as the limen nasi, which marks the division between the bone and cartilage portions of the nasal cavity, there's a gradual shift in the type of cells lining the area. The change begins with keratinizing squamous epithelium and transitions first to either cuboidal or columnar epithelium before finally becoming ciliated respiratory-type epithelium. This latter type of epithelium coats the majority of the nasal cavity and all the paranasal sinuses, except for the uppermost section. Within this respiratory epithelium, numerous goblet cells are dispersed throughout. The underlying layer, or lamina propria, houses a mix of seromucous glands, lymphocytes, monocytes, and a dense network of blood vessels, particularly noted in the lower and middle turbinate areas (OGLE; WEINSTOCK; FRIEDMAN, 2012).

The horizontal portion of the nasal cavity's roof is covered by the olfactory mucosa. The olfactory epithelium within this area mainly consists of non-ciliated columnar support cells, along with a mix of bipolar sensory neurons and basal cells. Embedded in the lamina propria are the olfactory serous glands, known as Bowman's glands, contributing to the unique cellular composition of this region (LAFCI FAHRIOGLU; VANKAMPEN; ANDALORO, 2024; OGLE; WEINSTOCK; FRIEDMAN, 2012) (Figure 7).

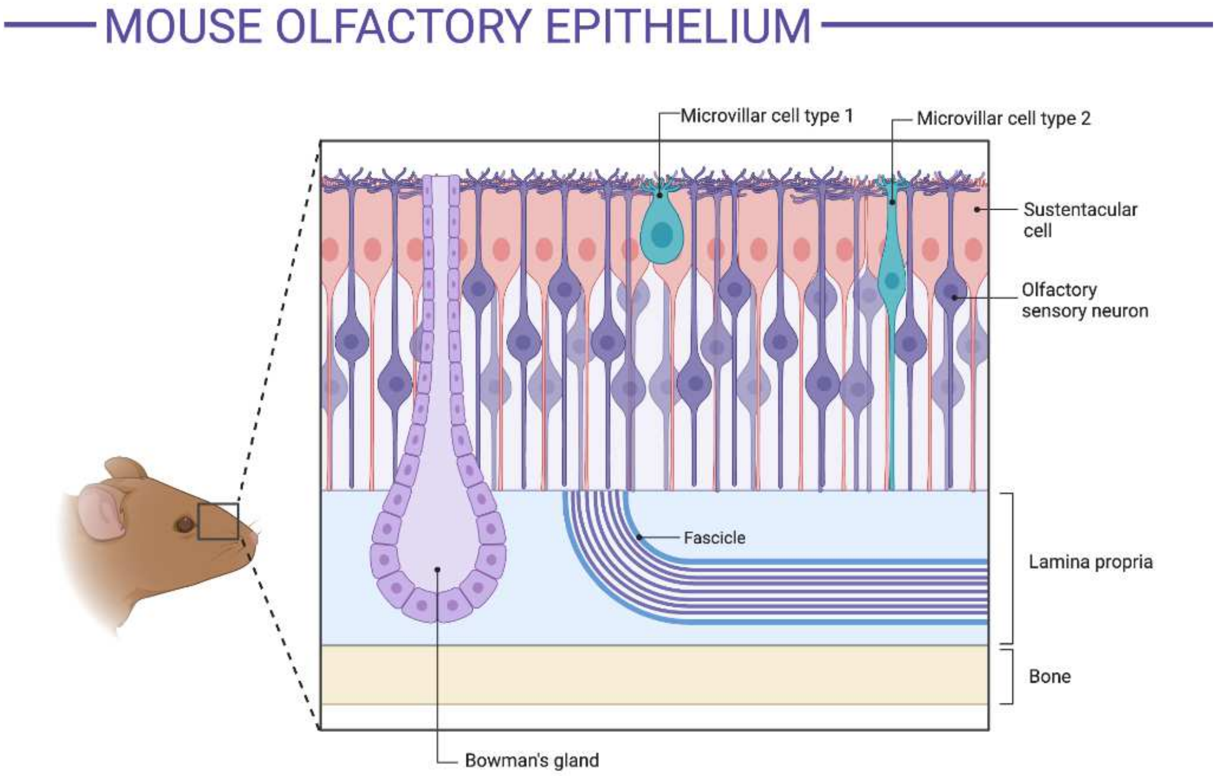

Figure 7. Animal model of the histology of the olfactory epithelium. Source: Biorender.

In summary, the nose and nasal cavity are important parts of the conductive upper airway and are responsible for the olfactory function. Besides that, some physiologic reflexes are linked to the nose and nasal cavity, such as the nasopulmonary reflex, which is analyzed next.

III.7.4 NASOPULMONARY REFLEX

The nasopulmonary reflex is the physiologic mechanism in which nasal irritants could induce changes, such as bronchoconstriction and inflammation, in the lungs. Among the nasal irritants there are nasal packing, cold and dry air, mites, dust, and air pollution. The study of the nasopulmonary reflex has been limited, with existing research offering mixed findings. Some reports indicate that traditional practices such as nasal packing might introduce risks like the naso-pulmonary reflex, discomfort, sleep disturbances, and a higher death rate (JACOBS et al., 1981; LOFTUS; BLITZER; COZINE, 1994; NAGHIBZADEH; PEYVANDI; NAGHIBZADEH, 2011). It's important to note that the connection between nasal packing, the nasopulmonary reflex, and increased mortality might not stem from hypoxic episodes. Instead, mortality could be due to a variety of complex factors affecting respiratory physiology (LOFTUS; BLITZER; COZINE, 1994). On the other hand, there's skepticism regarding the direct correlation between the use of posterior nasal packs and mortality, with some studies suggesting that the resulting hypoxemia could be attributed to other causes such as aspiration, sedation, or a decline in pulmonary function due to aging (JACOBS et al., 1981).

The literature consistently points out that different nasal stimuli might trigger reflexes in the lower respiratory tract (FONTANARI et al., 1996, 1997; SATO, 1980; WHICKER; KERN; HYATT, 1978). Research indicates a possible nasopulmonary bronchoconstrictor reflex, showing varied reactions to nasal mucosa stimulation across different clinical scenarios (FONTANARI et al., 1996, 1997). For example, patients who have undergone laryngectomy show decreased airway resistance following nasal mucosa stimulation, a response that contrasts with the increased resistance observed in individuals without such medical interventions (SATO, 1980). Experiments involving nasal stimulation in anesthetized dogs have also revealed significant changes in breathing patterns, highlighting the complex relationship between nasal stimuli and respiratory reflexes (WHICKER; KERN; HYATT, 1978).

III.8 EFFECTS OF AIR POLLUTION ON SENSE OF SMELL

III.8.1 PREVALENCE OF SMELL IMPAIRMENT RELATED TO AIR POLLUTION

Smell impairment is defined as a complete (anosmia) or partial loss (hyposmia) of the sense of smell and/or a disturbance in the perception of odorants (phantosmia and parosmia). Olfactory dysfunction is a widespread health issue, with a reported incidence of 13.9% to 31.7% among older individuals (approx. 60–90 years) in the US (MURPHY et al., 2002; PINTO et al., 2014b; RAWAL et al., 2016; SCHUBERT et al., 2012), and comparable rates in nations like Sweden (BRÄMERSON et al., 2004) and Germany (LANDIS; KONNERTH; HUMMEL, 2004; VENNEMANN; HUMMEL; BERGER, 2008). This sensory deficit is linked with reduced life quality (SMEETS et al., 2009), including a diminished ability to recognize dangers such as gas leaks or fires (SANTOS et al., 2004) and a reduction in libido (noted by Toller 1999), potentially due to elevated levels of depression and anxiety (GUDZIOL et al., 2009; SMEETS et al., 2009). Additionally, a loss of smell often precedes significant neurodegenerative diseases (DEVANAND et al., 2000; ROSS et al., 2008) and mortality among the elderly (GOPINATH et al., 2012; PINTO et al., 2014a; WILSON; YU; BENNETT, 2011). With the global population aging (LUTZ; SANDERSON; SCHERBOV, 2008), the frequency of smell dysfunction is expected to rise. While the exact causes of smell loss in the general populace are unclear, there is a possibility that exposure to environmental pollutants may accelerate this condition, considering the known adverse effects of such pollutants on health and the direct exposure of the smell receptors to the external environment (AJMANI; SUH; PINTO, 2016).

The influence of environmental factors on smell perception, particularly in industrial or work-related scenarios, has been a subject of interest (DOTY, 2006; GOBBA, 2006). However, such environmental exposures usually involve high levels of industrial toxins, which most people rarely encounter. Preliminary research indicates that even lower levels of air pollutants, more frequently encountered by the general population, might affect human olfactory function. For instance, it has been discovered that fine airborne particulate matter can penetrate the olfactory epithelium, travel to the olfactory bulb, and even reach the olfactory cortex and other brain areas (CALDERÓN-GARCIDUEÑAS et al., 2003a). Some other large-scale populational studies have related exposure to $PM_{2.5}$ and nitrogen dioxide with hyposmia (ADAMS et al., 2016; AJMANI et al., 2016).

For decades, there has been a notable connection between occupational exposure to environmental pollutants and the reduction of smell, with more general population studies emerging in the last ten years(WERNER; NIES, 2018). The earliest epidemiological research linking ambient air pollution to olfactory loss was in 2006 (HUDSON et al., 2006), focusing on Mexico City's residents, known for high levels of pollutants like PM_{10}, $PM_{2.5}$, and O_3 (CALDERÓN-GARCIDUEÑAS et al., 1997, 1998, 2001). This research was compared with data from Tlaxcala's residents, a city with comparatively lower pollution levels. The similarity in culture, language, and lifestyle between these Mexican cities made the comparison particularly relevant, as opposed to international studies. Mexico City's pollution, especially PM_{10}, $PM_{2.5}$, and O_3, often exceeds the U.S. National Ambient Air Quality Standards (NAAQS), set by the Environmental Protection Agency (EPA). In contrast, Tlaxcala's pollution levels were reportedly below these standards, although exact figures weren't provided in these studies (CALDERÓN-GARCIDUEÑAS et al., 2006; HUDSON et al., 2006). In olfactory tests using coffee and orange drink, Tlaxcala residents showed higher sensitivity and better discrimination than those from Mexico City. This difference was particularly noticeable in participants aged 20–49, suggesting early-life pollution impact, whereas older adults showed less difference, possibly due to age-related olfactory decline (HUDSON et al., 2006).

Subsequent studies in similar populations using standardized olfactory testing (CALDERÓN-GARCIDUEÑAS et al., 2010b; GUARNEROS et al., 2009) also showed Tlaxcala residents outperforming Mexico City residents in olfactory functions. Another study compared Mexico City residents with those from Polotitlán, showing similar findings with significant differences in odor identification abilities. Internationally, studies comparing industrialized and non-industrialized regions, like Germany versus the Bolivian rainforest and Poland versus the Cook Islands (SOROKOWSKA et al., 2013; SOROKOWSKA; SOROKOWSKI; FRACKOWIAK, 2015), found that residents of less industrialized areas had better olfactory function. These findings align with the Mexico studies, suggesting pollution's adverse effects on human olfaction. Additionally, a German study (RANFT et al., 2009) found a significant correlation between olfactory function and exposure to vehicle exhaust in older women.

Smell impairment affects a significant portion of older adults worldwide, with notable impacts on quality of life, such as decreased ability to detect hazards and reduced libido. This condition is also an early indicator of neurodegenerative diseases and higher mortality rates among the elderly. As the global population ages, the prevalence of smell dysfunction is expected to increase, potentially exacerbated by environmental pollutants that directly affect the olfactory system. Research has linked occupational exposure to high levels of industrial toxins with smell loss, but recent studies suggest even low levels of common air pollutants like $PM_{2.5}$ and NO_2 could impair olfactory function.

III.8.2 SPECIFIC POLLUTANTS AND THEIR EFFECTS ON THE SENSE OF SMELL

O_3, a secondary pollutant, was shown experimentally to transiently worsen olfaction in a group of eight males exposed to extremely high levels of O_3 for 4 days (PRAH; BENIGNUS, 1979). However, this effect had diminished by the third day of exposure. The rapid diminishment of the effect of O_3 may be related in part to associated increases in expression of endogenous antioxidants such as superoxide dismutase (SOD). This was found to be the case in a study of acute (4 hr) O_3 exposure ranging from 0.1 to 1 ppm and memory formation in rats, where animals exposed to low doses of ozone (0.2 ppm) had the greatest increases in SOD expression and the greatest long-term memory retention as well (RIVAS-ARANCIBIA et al., 1998). Prah and Benignus also acknowledged the need for further studies, given the very small sample size in this study and its high ozone exposures, which were higher than would be experienced by populations living in the US. Given the known adverse health effects of ozone (BELL; ZANOBETTI; DOMINICI, 2014; MEDINA-RAMÓN; ZANOBETTI; SCHWARTZ, 2006; NUVOLONE et al., 2013), future studies in humans would need to be performed with lower exposures.

Cumulative exposure to Lead (Pb), a heavy metal and also one of the CAPs (US EPA, 2014b), has also recently been found to correlate with poorer olfactory function among a cohort of older men (GRASHOW et al., 2015). Pb is primarily stored in bone (BARRY, 1975), thus bone measurements were compared to olfactory function test results performed an average of 12 years later. Patellar Pb is considered a biomarker of 8–10 years of cumulative exposure, and tibial Pb is a marker of exposure long term (decades) (WILKER et al., 2011). The authors found that increased tibial Pb was associated with poorer olfaction after controlling for age and current smoking. While no significant association was seen with patellar Pb, the exposure–olfaction association trended in the same direction as tibial Pb. Inhaled Pb is likely able to directly reach olfactory tissues and translocate to the brain, given its strong deleterious neurocognitive effects. However, this study was unable to precisely assess the timing of exposures and whether the majority of exposure is via inhalation or ingestion (AJMANI; SUH; PINTO, 2016).

There is also evidence that exposure to another heavy metal, Manganese (Mn), may adversely impact olfaction. Mn is a naturally occurring pollutant that is also released from various industrial sources and may be found in unleaded gasoline (US EPA, 2015). Indeed, in Canada, sites with high-vehicle traffic have been found to have significantly higher levels of airborne Mn—higher than the inhalation reference concentration ($0.05\ \mu g/m^3$) published by the U.S. EPA Integrated Risk Information System (IRIS)—than did low-traffic sites (BOUDIA et al., 2006). In Italy, a study of exposure to Mn and olfactory function in children showed that olfactory function was inversely associated with Mn concentrations in soil, but not airborne Mn or internal Mn (based on an analysis of participants' urine, blood, and hair) (LUCCHINI et al., 2014). The authors asserted that this was due to the fact that the last ferroalloy plants had closed several years prior to the study, and therefore soil Mn would be a better indicator of the participants' exposure level during the period when the plants were functioning; airborne exposure and biomarkers may instead be reflecting current exposure, which may not be as relevant for olfaction. Soil Mn concentrations may even be reflective of historic airborne Mn exposure, the most relevant exposure route, as airborne Mn may be driven by suspension of soil Mn into the air (BOUDISSA et al., 2006). However, the presumed effects of Mn may still be driven by inhalation exposure, as it is inhaled Mn that may directly reach olfactory tissues (ASCHNER; ERIKSON; DORMAN, 2005).

A follow-up study in Italy by Lucchini et al. (2014) examined odor discrimination ability among elderly subjects living in an area where ferroalloy plants were previously located. They found that both soil and airborne Mn were significant independent predictors of poorer olfaction, with a significant interaction between these two exposures. These two studies in Italy are limited by their narrow geographic scope and in that the age groups examined were those particularly susceptible to toxic exposures, namely children and the elderly (LUCCHINI et al., 2012, 2014). However, they do demonstrate a consistent trend of higher Mn exposure being related to poorer olfaction. Interestingly, in neither study was internal Mn significantly associated with olfaction. This is perhaps an indication that exposure to olfactory tissues is most relevant for an ultimate impact on olfaction, irrespective of absorption in the bloodstream. Alternatively, it is also possible that environmental Mn acts as a surrogate for other chemicals or pollutants, as industrial releases are likely to be a complex mixture of many potentially harmful substances (AJMANI; SUH; PINTO, 2016).

Similarly, Guarneros et al. (2013) found that people living close to a Mn mining district in Mexico performed significantly worse in olfactory testing compared to a non-exposed group of people. This also suggests that Mn exposure is associated with olfactory dysfunction, but in this study no dose–response association was observed between Mn concentrations in the hair and olfactory performance of the participants (GUARNEROS et al., 2013).

Other pollutants. A few other pollutants have been assessed for an association with olfactory function. Formaldehyde is an ambient air pollutant that is also an important indoor exposure for people living in homes insulated with formaldehyde-containing foam (SALTHAMMER, 2013). Residing in homes with this insulation was not found to be correlated with poorer olfaction, compared to residing in formaldehyde-free homes (BRODER et al., 1988a, 1988b). Although polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) have been associated with a variety of adverse health outcomes (BERGKVIST et al., 2016; LINARES; BELLÉS; DOMINGO, 2015; RUDER et al., 2014), exposure levels as measured by serum concentration have not been found to be associated with olfactory function among older adults (FITZGERALD et al., 2008, 2012).

Exposure to high levels of O_3 temporarily is associated with worse olfaction, with effects lessening after a few days, possibly due to the body's antioxidant response. Pb exposure, especially long-term, was linked to worse smell function in older men, suggesting inhaled Pb can directly affect olfactory tissues. Similarly, Mn exposure, from both soil and air, has been associated with poorer olfaction, especially in areas with high industrial activity or traffic. Other pollutants like formaldehyde and chemicals such as PCBs and PBDEs have been investigated, but no clear association with smell impairment was found. These findings highlight the potential of environmental pollutants, particularly heavy metals, to impair olfactory function, suggesting a need for further research into the mechanisms and preventive measures.

III.8.3 PATHOPHYSIOLOGY OF OLFACTORY LOSS ASSOCIATED TO AIR POLLUTION

Several investigations have delved into the underlying biological processes related to olfactory impairment caused by air pollution. A considerable amount of this research, especially those involving direct examination of olfactory tissues, has been conducted in Mexico. Here, studies have compared the olfactory tissues of Mexico City inhabitants with those from residents in less polluted urban areas, focusing on lower exposure to fine particulate matter ($PM_{2.5}$) and ozone (O_3) (CALDERÓN-GARCIDUEÑAS et al., 2003b). It's important to note that air quality in these less polluted cities isn't monitored as rigorously as in Mexico City, leading to an assumption of reduced pollution levels due to fewer industrial activities and vehicular emissions, as well as geographical differences. Investigations involving both humans and canines in these less polluted areas have shown an absence of pathology related to air pollution (CALDERÓN-GARCIDUEÑAS et al., 2003b).

The study by Calderón-Garcidueñas et al. (1998) revealed that nasal biopsies from young adults in Mexico City showed pathological alterations when compared to individuals from a cleaner air town (CALDERÓN-GARCIDUEÑAS et al., 1998). The biopsies from Mexico City residents exhibited basal cell hyperplasia, squamous metaplasia, and epithelial dysplasia, particularly in the anterior segment of the middle turbinate—an area selected to represent olfactory exposure due to its proximity to air currents reaching the olfactory mucosa (LEOPOLD et al., 2000). These individuals also reported upper respiratory symptoms like nasal dryness, crusting, congestion, and episodes of nosebleeds and rhinorrhea. In contrast, inhabitants of the less polluted town displayed neither such symptoms nor abnormal biopsy findings. This suggests that air pollutants might directly harm the olfactory epithelium, causing DNA and cellular damage. The study underscores the broad impact of environmental pollution on sinonasal health and its indirect effect on olfaction through inflammatory responses in the sinonasal mucosa. Nasal blockage and inflammation are linked to olfactory dysfunction, with treatments like corticosteroids potentially improving smell perception in affected individuals (WOLFENSBERGER; HUMMEL, 2002).

Subsequent research by Calderón-Garcidueñas et al. (CALDERÓN-GARCIDUEÑAS et al., 2004, 2008, 2010b, 2013) also identified pathological signs in brain tissues, including olfactory bulbs, in residents of Mexican cities with high pollution levels compared to those from cleaner environments. A 2004 study found cyclooxygenase-2 (COX-2) and beta-amyloid in the olfactory bulbs of subjects from more polluted areas, but not in those from cleaner cities (CALDERÓN-GARCIDUEÑAS et al., 2004). In 2008, an autopsy of 35 Mexico City residents showed particulate matter in neurons of the olfactory bulb in some cases, a finding absent in control city subjects (CALDERÓN-GARCIDUEÑAS et al., 2008). Elevated inflammatory markers and the presence of beta-amyloid and α-synuclein were also noted in the olfactory bulbs of Mexico City residents. Later studies continued to show particle accumulation and abnormal histological patterns in olfactory tissues of these residents (CALDERÓN-GARCIDUEÑAS et al., 2010b). Conversely, control city subjects exhibited normal brain structures.

A further autopsy study in 2013 revealed higher levels of COX-2 in the olfactory bulbs of Mexico City residents, though the increase in IL-1β was not significant (CALDERÓN-GARCIDUEÑAS et al., 2013). DNA repair enzyme levels were similar across both groups, possibly influenced by higher heavy metal concentrations in Mexico City residents' brains. Interestingly, certain metal levels in the frontal lobes showed correlations with gene expressions in olfactory bulb tissues.

In summary, studies comparing Mexico City residents with those from less polluted areas found that the former showed pathological changes in nasal biopsies, such as basal cell hyperplasia and squamous metaplasia, indicative of air pollution's direct damage to the olfactory epithelium. These changes were associated with common upper respiratory symptoms and a reduction in olfactory function. Further investigations have extended to examining brain tissues, revealing that inhabitants of polluted areas exhibit signs of inflammation, accumulation of PM, and markers of neurodegeneration like beta-amyloid in their olfactory bulbs, unlike their counterparts from cleaner environments. This body of evidence underscores the profound impact environmental pollutants have on olfactory health, hinting at a broader concern for overall sinonasal and neurological well-being related to air quality.

III.9 EFFECTS OF AIR POLLUTION ON CHRONIC RHINOSINUSSITIS

III.9.1 PREVALENCE OF CHRONIC RHINOSINUSITIS RELATED TO AIR POLLUTION

Chronic rhinosinusitis (CRS) is defined as all inflammatory disorders of the nose and paranasal sinuses with a minimum duration of 12 weeks and can be classified as with (CRSsNP) or without nasal polyposis (CRSwNP) (BENNINGER et al., 2003). CRS is a widely prevalent condition with substantial effects on individuals and society at large (DIETZ DE LOOS et al., 2019; FU et al., 2015; KHAN et al., 2019; PHILLIPS et al., 2017; RUDMIK, 2017; SMITH; ORLANDI; RUDMIK, 2015; TALAT et al., 2020). The underlying mechanisms of CRS are complex and not entirely understood, but include chronic inflammation of the mucosa due to issues with mucociliary clearance, defects in the epithelial barrier, or imbalances in immune responses (CAO et al., 2019; GUDIS; ZHAO; COHEN, 2012; KHALMURATOVA; PARK; SHIN, 2017; MAJIMA et al., 1986; SOYKA et al., 2012; TIEU; KERN; SCHLEIMER, 2009).

Environmental factors are increasingly recognized as important in the development and exacerbation of CRS, given that nasal mucosa acts as a primary defense against external pollutants. The Environmental Protection Agency (EPA) identifies six primary pollutants—ozone (O_3), particulate matter (PM), carbon monoxide (CO), lead (Pb), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2)—and maintains air quality standards for these in the US (US EPA, 2014a). PM is often classified into PM_{10} and $PM_{2.5}$, based on the particle size. Elevated levels of these pollutants are linked to various health issues, including heart disease, asthma, and chronic obstructive pulmonary disease (AL-KINDI et al., 2020; KELLY; FUSSELL, 2011; THURSTON et al., 2020), and are also associated with increased overall morbidity and mortality (KIM et al., 2017; LOGUE et al., 2012; MANISALIDIS et al., 2020; POPE et al., 2019).

Recent studies indicate a significant connection between air pollution and upper airway diseases like CRS. Pollutants such as PM and O_3 are known to increase reactive oxygen species, leading to DNA damage, augmented oxidative stress, and inflammation (BORM et al., 2007; GHIO; CARRAWAY; MADDEN, 2012; MUMBY; CHUNG; ADCOCK, 2019; OHYAMA et al., 2007). Support for this comes from cellular and animal studies showing that air pollution contributes to oxidative stress, influencing the development, progression, and severity of CRS. For instance, exposure of human nasal epithelial cells to PM has been shown to reduce cell viability and increase cytotoxicity (SHIN et al., 2020). Disruption in epithelial barrier function was observed in human sinonasal epithelial cell lines exposed to PM_{10} (LONDON et al., 2016). Additionally, chronic exposure to $PM_{2.5}$ in murine models has been linked to heightened inflammatory responses and tissue remodeling (RAMANATHAN et al., 2017; ZHAO et al., 2018).

While these hypotheses have been explored in observational human studies over recent decades, a systematic review conducted to assess the impact of air quality on CRS primarily focused on occupational exposures, offering limited insights into the effects of environmental air pollution (SUNDARESAN et al., 2015).

Four distinct studies explored the link between air pollution and the occurrence or prevalence of Chronic Rhinosinusitis (CRS), each finding a significant connection. These studies were conducted in different geographical areas and estimated air pollutant exposure based on the residential addresses of patients.

In Cologne, Germany, a study (WOLF, 2002) assessed the influence of modeled air pollution levels (based on SO_2, total suspended particulate, and NO_x) on the rates of CRS patients in specific city districts. The research highlighted those districts with higher-than-average pollution levels had increased patient rates ($r = 0.38$, $p < 0.05$). This trend was more pronounced in earlier years (1990–1994) compared to later years (1995–1999), which the authors attributed to a reduction in air pollution levels over time.

Another investigation, drawing data from the Korea National Health and Nutrition Examination Survey (PARK; LEE; PARK, 2019), examined the effects of various pollutants including PM_{10}, NO_2, O_3, SO_2, and CO. A notable correlation was found between PM_{10} exposure and CRS prevalence, with each 1 μg/m3 increase in PM_{10} linked to a 1.2-fold increase in CRS risk (OR: 1.22 [95% CI: 1.02–1.46], $p = 0.03$). However, there was no significant correlation between CRS incidence and any air pollutant.

A third study (LU et al., 2020) in Xinxiang, China, identified chronic sinusitis patients using ICD-9/ICD-10 codes from hospital records. The research evaluated the impact of $PM_{2.5}$, PM_{10}, NO_2, O_3, SO_2, and CO on outpatient cases of chronic sinusitis. All pollutants, except O3, were associated with an increase in cases. After adjusting for co-pollutant exposure, only the associations with $PM_{2.5}$ and NO_2 remained significant. For every 10 $\mu g/m^3$ increase in $PM_{2.5}$ or NO_2, there was a corresponding increase in hospital outpatient cases by 0.48% (95% CI: 0.22–0.74%) and 1.98% (95% CI: 1.31–2.64%), respectively. These relationships were observed in patients under 65 years but not in those aged 65 and above.

The most recent study (ZHANG et al., 2021) was large case-control research focusing on the impact of long-term $PM_{2.5}$ exposure on CRS development. The authors measured $PM_{2.5}$ exposure at 12, 24, 36, and 60 months prior to CRS diagnosis, and recorded the location of the affected sinuses. At all timepoints, a 5 $\mu g/m^3$ increase in $PM_{2.5}$ was linked to a higher likelihood of CRS diagnosis, particularly in cases involving the ethmoidal sinus (e.g., 60-month OR: 3.27 [95% CI: 2.03–5.25]) and severe sinusitis affecting multiple sinuses (e.g., 36-month OR: 7.91 [95% CI: 3.06–20.42]).

In conclusion, CRS is a common condition significantly influenced by air pollution, including particulate matter PM and O_3, which can damage nasal mucosa and contribute to the disease's development and severity. Studies have linked air pollutants to increased oxidative stress, inflammation, and DNA damage, affecting sinus health. Research across various geographic locations has found consistent associations between higher levels of air pollution and increased CRS prevalence. Further, long-term exposure to $PM_{2.5}$ has been linked to a higher likelihood of CRS, particularly affecting the ethmoidal sinus and severe cases involving multiple sinuses. These findings highlight the significant impact of environmental pollutants on CRS prevalence and severity.

III.9.2 CHRONIC RHINOSINUSITIS AND QUALITY OF LIFE

Other commonly evaluated outcomes were metrics of disease severity and quality of life. Four studies evaluated these metrics, but notably, three of the studies were performed by the same author group. Common disease severity indicators evaluated included sinonasal outcome test (SNOT-22), Lund-Mackay score (LMS), systemic steroid usage, and functional endoscopic sinus surgery (FESS) requirement (LELAND et al., 2022).

The first report studied disease severity in CRSsNP and CRSwNP patients through SNOT-22 scores, LMS, steroid usage, and FESS requirement (MADY et al., 2018a). $PM_{2.5}$ and black carbon (BC, a major component of PM) exposures were calculated. In CRSsNP patients, $PM_{2.5}$ exposure was associated with FESS requirement ($p = 0.015$), with each unit increase in $PM_{2.5}$ exposure corresponding to a 1.89-fold increased risk in proportion of CRSsNP patients requiring revision FESS surgery ($p = 0.01$). Additionally, BC exposure was associated with SNOT-22 scores in CRSsNP patients ($p = 0.01$), with each 0.1-unit increase in BC corresponding to a 7.97-unit increase in SNOT-22 scores ($p = 0.01$). There was no relationship with LMS scores or steroid usage in CRSsNP patients, and there was no relationship between air pollution and any disease severity metric in CRSwNP patients. This was not explained by differences in air pollutant exposure, as exposure was similar between CRSsNP and CRSwNP groups.

A second paper by the same author group was performed similarly but considered allergy status of patients (MADY et al., 2018b). In this report, similar to above data, in CRSsNP patients, BC exposure was associated with higher SNOT-22 scores. $PM_{2.5}$ exposure was not correlated with disease severity metrics in CRSsNP patients, and neither air pollutant was associated with outcomes in CRSwNP patients. Allergy status was not associated with severity metrics in either CRSsNP or CRSwNP patients. Interestingly, allergy-negative patients were associated with higher exposure levels to both $PM_{2.5}$ ($p = 0.03$) and BC ($p = 0.04$) than allergy-positive counterparts. This trend was carried by CRSwNP patients—in which allergy-negative patients had higher PM2.5 ($p = 0.03$) and BC ($p = 0.02$) exposure than allergy-positive patients—but not seen in CRSsNP patients.

Finally, the third paper from the group evaluated the impact of both air pollutants and occupational exposures on CRSsNP and CRSwNP disease severity (VELASQUEZ et al., 2020). This review will focus solely on the air pollutant exposure. In this study, air pollutant exposure did not vary between subgroups, and disease severity metrics were not correlated with air pollutant exposure in either CRSsNP or CRSwNP groups. Although this is presumably the same study population as the previous papers, (MADY et al., 2018b, 2018a) a subgroup analysis on aspirin-exacerbated respiratory disease was also performed by Velasquez et al. Authors hypothesized the loss of significance was due to small subgroup analyses (VELASQUEZ et al., 2020).

The last paper evaluated the quality of life in CRSsNP and CRSwNP patients based on NO_2 and NOx exposure (SOMMAR et al., 2014). Authors utilized the Swedish Global Allergy and Asthma European Network to collect data on patients with CRS and/or asthma. There was no difference in air pollutant exposure between CRSsNP and CRSwNP patients. The Euro Quality of Life questionnaire was utilized, and air pollution was not associated with the quality of life in CRS patients.

Ultimately, several studies have explored the impact of air pollution on disease severity and quality of life in patients with CRS, with mixed results. One group of studies found that exposure to $PM_{2.5}$ and BC was linked to an increased need for sinus surgery and higher symptom scores in patients with CRSsNP, but not in those with CRSwNP. Interestingly, allergy status didn't seem to influence these outcomes, although allergy-negative patients in the CRSwNP group had higher exposure to pollutants. There was no significant association between air pollution exposure and disease severity in either CRSsNP or CRSwNP patients, suggesting that the relationship between air pollution and CRS may be complex and vary based on specific pollutants and patient subgroups. Additionally, no association was found relating the exposure to NO_2 and NOx with CRS, indicating that the effects of air pollution on CRS symptoms and patient well-being require further investigation.

III.9.3 HISTOPATHOLOGICAL CHANGES IN CHRONIC RHINOSINUSITIS RELATED TO AIR POLLUTION

Two investigations were conducted to explore how exposure to air pollution affects the histopathological characteristics of CRS tissue samples. It is important to note that these samples were taken from patients undergoing functional endoscopic sinus surgery (FESS), indicating severe cases of the disease that did not respond to conservative or pharmacological treatment (LUONG; MARPLE, 2006).

The first study (PATEL et al., 2021) examined the effects of O_3 and $PM_{2.5}$ on patients with CRSsNP and CRSwNP. Across the overall CRS group, O3 exposure correlated with heightened inflammatory responses ($p = 0.03$) and the presence of Charcot–Leyden crystals ($p = 0.04$). However, no similar correlations were found for $PM_{2.5}$ exposure. A more detailed analysis showed that these trends were particularly evident in CRSwNP patients. In this subgroup, increased O_3 exposure was linked to more pronounced inflammation ($p < 0.01$), eosinophilic aggregates ($p = 0.02$), and Charcot–Leyden crystals ($p = 0.04$). There were no associations between $PM_{2.5}$ exposure and CRSwNP, nor between CRSsNP and any of the pollutants studied. Remarkably, these findings were not attributed to varying levels of exposure to O_3 and $PM_{2.5}$ between CRSsNP and CRSwNP patients.

In contrast, another research effort (PADHYE et al., 2021) focused solely on the impact of $PM_{2.5}$ in both CRS patients and control groups. CRS cases were associated with higher neighborhood $PM_{2.5}$ levels compared to controls ($p < 0.01$). $PM_{2.5}$ was also linked to eosinophilic markers in CRS patients ($p < 0.01$), but no other significant relationships were observed with the various histopathological markers examined. Furthermore, Mahdavinia et al (MAHDAVINIA et al., 2018) investigated microbial alterations in relation to air pollution. Notably, increased exposure to $PM_{2.5}$ was correlated with a relative decrease in Corynebacterium in both CRS cases and controls ($r = -0.20$, $p = 0.02$). The authors highlighted that a reduction in Corynebacterium has been previously associated with sinonasal inflammation, reinforcing the potential connection between air pollution exposure and CRS.

Overall, O_3 exposure was associated with increased inflammation and the presence of Charcot–Leyden crystals, especially in patients with CRSwNP, but no significant relationship was found for $PM_{2.5}$. Additionally, higher neighborhood levels of $PM_{2.5}$ was related with eosinophilic markers in CRS tissues, suggesting a specific inflammatory response to this pollutant. Moreover, higher $PM_{2.5}$ levels were associated with a decrease in Corynebacterium in the nasal cavity, which is connected to sinonasal inflammation. These findings suggest that air pollutants, particularly O_3 and $PM_{2.5}$, may contribute to the severity of inflammation in CRS, highlighting the intricate relationship between environmental factors and sinonasal health.

III.9.4 EFFECTS OF CHRONIC RHINOSINUSSITIS ON THE SENSE OF SMELL

Chronic Rhinosinusitis (CRS) involves both subjective and objective elements for its diagnosis, where a noticeable shift in smell perception stands out as one of its four main symptoms (FOKKENS; LUND; MULLOL, 2007; ORLANDI et al., 2021). The disturbance in smell, or olfactory dysfunction, is categorized into two types: qualitative and quantitative. The qualitative aspect includes conditions like phantosmias, dysosmias, parosmias, and agnosias. Though such qualitative dysfunctions are less common in CRS, instances have been observed (REDEN et al., 2007). For instance, Reden's study noted that 7% of 392 individuals with CRS experienced some kind of phantosmia or parosmia (REDEN et al., 2007). On the flip side, quantitative assessments of smell—spotting hyposmia and anosmia—are frequently seen in CRS patients, with 60% to 80% reporting varying degrees of smell impairment (JIANG et al., 2008; REDEN et al., 2007; SOLER; MACE; SMITH, 2008). A comprehensive analysis focusing on objective olfactory evaluations in the CRS demographic found that 67% of individuals exhibited smell dysfunction as per the 40-item smell identification test (SIT-40), and 78% as determined by the total Sniffin' Sticks score (KOHLI et al., 2017). Notably, a fraction of those with olfactory loss might not even recognize their condition, likely due to a slow and gradual decrease in their sense of smell (DOTY; FRYE, 1989).

Despite being commonly disregarded, the repercussions of olfactory dysfunction can be serious, affecting safety, nutrition, and quality of life (QOL). Research by Pinto et al. indicated that older patients with anosmia had a threefold higher risk of mortality compared to those with normal smell, even after adjusting for chronic health conditions (PINTO et al., 2014a). Moreover, olfactory function emerged as a key predictor of mortality over a five-year period (PINTO et al., 2014a). The link between loss of smell and depression has been well established (KOHLI et al., 2016), with a noteworthy correlation also existing between CRS and depression, where depression is present in about 11% to 40% of CRS sufferers (SCHLOSSER et al., 2016). Other studies have delved into the intricate relationship between smell dysfunction, CRS, and depression (MATTOS et al., 2017).

Beyond smell disturbances, taste perception is also often compromised in CRS patients, which is crucial to consider during olfactory assessments in such individuals. Recent research highlighted dysgeusia in 28% of CRS patients (OTHIENO et al., 2018a). Furthermore, the ability to identify flavors strongly correlates with QOL, satisfaction with life, depressive symptoms, and overall health evaluations in these patients (OLESZKIEWICZ et al., 2019). Not to be overlooked, orthonasal olfactory dysfunction has a direct link to diminished QOL related to eating (BOJANOWSKI; HUMMEL, 2012; ROWAN et al., 2019), and the significance of retronasal olfaction in food perception cannot be understated (GANJAEI et al., 2018; OTHIENO et al., 2018b). Hence, the impact of chemosensory dysfunction in CRS patients is profound, affecting not just the pleasure of eating but also the communal experience associated with it.

In summary, CRS often leads to smell disturbances, a key symptom impacting diagnosis. While qualitative smell disorders like phantosmia or parosmia are less frequent, quantitative impairments such as hyposmia and anosmia are common, affecting 60% to 80%

of patients. Studies show significant numbers of CRS patients exhibit measurable olfactory dysfunction, with many unaware of their condition due to its gradual onset. This loss of smell not only diminishes quality of life but also raises safety concerns, affects nutrition, and has been linked to higher mortality rates and depression. Additionally, CRS can impair taste perception, further influencing life satisfaction and health outcomes. Thus, the consequences of chemosensory dysfunction in CRS are substantial, affecting daily well-being and social interactions.

III.10 EFFECTS OF AIR POLLUTION ON ALLERGIC RHINITIS

Allergic rhinitis (AR), a prevalent allergic condition of the respiratory system linked to immunoglobulin E (IgE), manifests with symptoms such as nasal itching, congestion, and sneezing (PASSALI et al., 2018). It ranks among the most prevalent global diseases, often persisting throughout one's lifetime (BROŻEK et al., 2017). In Western societies, allergic rhinitis affects approximately 10–25% of the population, with its incidence continually rising (GENUNEIT et al., 2017). AR significantly diminishes life quality (BLAISS et al., 2018) and escalates the risk of associated conditions like bronchial asthma, rhinosinusitis, nasal polyps, otitis media, and allergic conjunctivitis (KIM et al., 2019). The socioeconomic burden of AR is substantial, with varying prevalence rates between 1% and 20% and associated healthcare costs reaching around US$17.5 billion (BLAISS et al., 2018). Consequently, AR's impact on public health is increasingly recognized.

Research indicates that both genetic (FERREIRA et al., 2020) and environmental factors (LEE et al., 2020; NORBÄCK et al., 2019) significantly influence allergic diseases. There's a noted correlation between exposure to air pollutants and heightened risks of respiratory and allergic conditions (EGUILUZ-GRACIA et al., 2020; SCHULTZ et al., 2016). Specifically, exposure to ambient particulate matter (PM_{10} and $PM_{2.5}$) and nitrogen dioxide (NO_2) has been associated with asthma (ZHENG et al., 2021), rhinitis (NORDEIDE KUIPER et al., 2021), and eczema (FUERTES et al., 2020). In Europe, cohort studies have established a significant link between air pollution and allergic sensitization (Burte et al., 2018; Melén et al., 2021). Other research has suggested a connection between air pollutant levels and increased consultations for AR (TODKILL et al., 2020; ZHANG; ZHANG, 2018), with oxidative stress being a possible underlying mechanism (NACLERIO et al., 2020).

The link between AR and air pollutants is increasingly substantiated (BURTE et al., 2020; LEE et al., 2003; MIN et al., 2020), though it's not universally acknowledged in all related studies. Some reports have indicated a correlation between rising allergy rates and air pollution, especially particulate matter (DUNLOP; MATSUI; SHARMA, 2016). Research has identified urbanization, higher NO_2 levels, and proximity to busy roads as risk factors for

AR (WANG et al., 2021). Additionally, there is evidence linking AR onset with increased ozone (O_3) exposure (BÉDARD et al., 2020; PÉNARD-MORAND et al., 2005). However, some studies challenge this association, finding little connection between AR and air pollution levels (FUERTES et al., 2013; GEHRING et al., 2015; KIM; JAHAN; KABIR, 2013; LUO et al., 2023). Notably, much of the research on AR and air pollution focuses on children, leading to potential variations in population data.

To date, two systematic review studies (LIN et al., 2021; ZOU et al., 2018) have explored the relationship between air pollution and childhood AR. This review comprehensively examines the scientific evidence on the association between six air pollutants ($PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3, and CO) and AR in individuals across all age groups, incorporating a meta-analysis of the link between air pollution exposure and the prevalence of allergic rhinitis.

In conclusion, AR is a widespread condition causing nasal symptoms like itching and congestion, affecting 10–25% of people in Western societies. Its prevalence is increasing, leading to significant health and economic burdens, including a higher risk of asthma and other respiratory issues. Research highlights the role of genetic and environmental factors, notably air pollution, in exacerbating AR. Studies link exposure to PM and NO_2 with an increased risk of respiratory allergies, and evidence points to air pollution as a contributing factor to the rising rates of AR, especially near urban and high-traffic areas. However, findings are mixed, with some research showing little association between AR and air pollution. Systematic reviews have specifically examined this relationship in children, indicating a need for further investigation across all age groups to fully understand the impact of air pollution on AR.

III.10.1 ALLERGIC RHINITIS AND SMELL IMPAIRMENT

The link between allergic rhinitis (AR) and chronic rhinosinusitis significantly affects smell disturbance (APTER et al., 1995; APTER; GENT; FRANK, 1999). Smell disorders are noted in 21% to 23% of AR patients (COWART et al., 1993; RYDZEWSKI; PRUSZEWICZ; SULKOWSKI, 2000). While the medical community has acknowledged smell disorders in seasonal allergic rhinitis (SAR) (HILBERG, 1995; HINRIKSDÓTTIR; MURPHY; BENDE, 1997; KLIMEK; EGGERS, 1997; LANE et al., 1996; MELTZER et al., 1998; MOLL et al., 1998; SIMOLA; MALMBERG, 1998), fewer studies have explored olfactory changes in perennial allergic rhinitis (PAR) (MOLL et al., 1998; SIMOLA; MALMBERG, 1998), with none focusing on persistent allergic rhinitis (PER). One investigation observed a moderate decline in smell (15%) alongside a 70% reduction in nasal passage size, as determined by acoustic rhinometry, following allergen exposure (LANE et al., 1996). Additionally, 31% of AR patients reportedly experience taste disorders (RYDZEWSKI; PRUSZEWICZ; SULKOWSKI, 2000).

Various odor-identification tests have been developed globally, reflecting diverse cultures. The University of Pennsylvania Smell Identification Test (UPSIT) (DOTY; SHAMAN; DANN, 1984) and the Connecticut Chemosensory Clinical Research Center identification test (CCCRC) (CAIN, 1977) originated in the USA, while Europe has adopted the “sniffin' sticks” test (KOBAL et al., 1996) and the Smell Diskettes Test (BRINER; SIMMEN, 1999). However, the effectiveness of these olfactory tests is often confined to their country or region of origin due to the reliance on familiar and culturally specific scents. In this study, the Barcelona Smell Test-24 (BAST-24), validated for the Spanish and Mediterranean demographics, was employed to assess smell loss in PER patients (CARDESÍN et al., 2006).

Ultimately, the relationship between AR and smell disorders is significant, with about 21% to 23% of AR patients experiencing some form of olfactory dysfunction. This issue is well-documented in SAR, but less so in PAR, and almost not at all in PER. Research has shown that allergen exposure can moderately reduce smell ability and significantly narrow nasal passages. Additionally, about 31% of AR patients also report taste disorders.

III.11 REVIEW OF STUDIES RELATED TO AIR POLLUTION IN SÃO PAULO

A review of articles examining the impact of air pollution in São Paulo was conducted. A total of 92 studies were identified using search terms in databases such as Scielo, Google Scholar, Pubmed, and online university libraries. Out of these, 14 articles met the criteria for inclusion in this review and were thus chosen for analysis.

Table 2. Key research in the state of São Paulo on the effect of air pollution on health.

Author	City	Year	Journal	Title
Cançado et al.	Espírito Santo	2006	Estudos Avançados	Sugarcane Burning: Assessment of Effects on Air Quality and Respiratory Health of Children
Jasinski et al.	Cubatão	2011	Cadernos de Saúde Pública	Atmospheric Pollution and Hospital Admissions for Respiratory Diseases in Children and Adolescents in

			Poluição	Cubatão, São Paulo, Brazil, from 1997 to 2004
Amâncio and Nascimento	São José dos Campos	2012	Revista da Associação Médica Brasileira	Asthma and Environmental Pollutants: A Time Series Study
Carneseca et al.	Ribeirão Preto	2012	Cadernos de Saúde Pública	Association Between Atmospheric Pollution by Particulate Matter and Monthly Counts of Inhalation and Nebulization Procedures in Ribeirão Preto, São Paulo, Brazil
Yanagi et al.	São Paulo	2012	Cadernos de Saúde Pública	Influence of Atmospheric Particulate Matter on Cancer Incidence and Mortality in the City of São Paulo, Brazil
Cesar et al.	Piracicaba	2013	Revista de Saúde Pública	Association Between Exposure to Particulate Matter and Hospitalizations for Respiratory Diseases in Children
Nardocci et al.	Cubatão	2013	Cadernos de Saúde	Air Pollution and Respiratory and Cardiovascular Diseases: A Time Series Study in Cubatão, São Paulo, Brazil
Negrisoli and Nascimento	Taubaté	2013	Revista Paulista de Pediatria	Atmospheric Pollutants and Hospitalizations for Pneumonia in Children
Gavinier e Nascimento	Sorocaba	2014	Ambiente & Água	Atmospheric Pollutants and Hospitalizations for Stroke
Lima et al.	José dos Campos	2014	Ambiente & Água	Association Between Maternal Exposure to Particulate Matter and Preterm Birth
Nicolussi et al.	Ribeirão Preto	2014	Revista de Saúde Pública	Air Pollution and Allergic Respiratory Diseases in School Children
Pinheiro et al.	São Paulo	2014	Revista de Saúde	Isolated and Synergistic Effects of PM_{10} and Average Temperature on

			Pública	Mortality from Cardiovascular and Respiratory Diseases
Santos et al.	São José dos Campos	2014	Revista Paulista de Pediatria	The Role of Atmospheric Pollutants on Birth Weight in a Medium-Sized City in São Paulo
Barbosa et al.	Cadernos de Saúde Pública	2015	Cadernos de Saúde Pública	Air Pollution and Children's Health: Sickle Cell Disease

In these studies, the association of respiratory, cardiovascular, hematological diseases, and obstetric complications with air pollution was reviewed. Below is a summary of the main associations described.

The study conducted by Cançado et al. show revealed a significant correlation between increases in particulate matter ($PM_{2.5}$ and PM_{10}) concentrations and higher rates of hospital admissions for respiratory issues among both children and the elderly, with respective increases of 21.4% and 31.03%. Notably, the adverse effects were more pronounced during the sugar cane burning period compared to the non-burning period. Elements identified as by-products of sugar cane combustion were most strongly linked to respiratory admissions. This evidence underscores the detrimental health impacts of sugar cane burning emissions, highlighting the urgent need for public interventions to mitigate and ultimately cease this form of air pollution (CANÇADO et al., 2006).

It was also found in Sorocaba, São Paulo, Brazil, between 2007 and 2008, the link between air pollution exposure and hospital admissions for pneumonia in children. Specifically, nitrogen dioxide showed a direct impact on the day of exposure, while particulate matter demonstrated a delayed effect four days post-exposure, indicating both immediate and lagged adverse effects of air pollutants on pneumonia admissions in children (JASINSKI; PEREIRA; BRAGA, 2011).

In São José dos Campos, SP, Brazil, it was assessed the risk of hospitalization for asthma in children under 10 years old following exposure to air pollutants. This ecological time series study also used hospitalization data and monitored levels of particulate matter, sulfur dioxide, and ozone, along with relative humidity and temperature. The study revealed significant relative risks associated with exposure to these pollutants on the same day and up to three days afterward, highlighting an 8% to 19% increased risk of asthma hospitalizations. These findings underscore the acute impact of specific air pollutants on children's respiratory health in medium-sized cities in Southeast Brazil (AMÂNCIO; NASCIMENTO, 2012).

In Ribeirão Preto, São Paulo, Brazil, between 2004 and 2010, it was explored the connection between air pollution, specifically particulate matter (PM_{10}), and the frequency of inhalation/nebulization procedures. The study found an association between PM_{10} levels and the procedures. However, the influence of these covariates indicated potential confounding effects, urging caution in interpreting the direct impact of particulate matter on respiratory health service usage (CARNESECA; ACHCAR; MARTINEZ, 2012).

Further research in São Paulo analyzed the effects of PM_{10} on cancer incidence and mortality, revealing significant correlations for various cancers, with spatial analysis indicating higher relative risks in districts further from the city center. This suggests urban air pollution's role in cancer rates, emphasizing the necessity for pollution reduction and monitoring (YANAGI; ASSUNÇÃO; BARROZO, 2012). Another study in Piracicaba evaluated $PM_{2.5}$'s association with hospitalizations for respiratory diseases in children, demonstrating a significant risk increase with higher particulate matter levels (CESAR; NASCIMENTO; DE CARVALHO, 2013). Additionally, a study in Cubatão linked air pollutants (PM_{10}, SO_2, O_3) with increased hospital admissions for respiratory and cardiovascular diseases, highlighting substantial health impacts across all ages and underscoring the urgent need for effective air quality control measures (NARDOCCI et al., 2013). These studies collectively underline the significant health risks posed by air pollution, advocating for enhanced environmental policies and public health interventions.

In Sorocaba, São Paulo, Brazil, a study conducted from 2007 to 2008 explored the connection between air pollutant exposure and pediatric hospitalizations for pneumonia. The results showed a significant correlation, particularly with nitrogen dioxide showing immediate effects and particulate matter demonstrating delayed effects on hospital admissions for pneumonia, emphasizing the acute and latent dangers of these pollutants on children's respiratory health (NEGRISOLI; NASCIMENTO, 2013).

Another study focused on the adverse effects of $PM_{2.5}$ exposure during pregnancy on preterm birth (PTB) and early-term birth (ETB) among high-risk pregnant women in Beijing. Analyzing data from 2014 to 2018, the study found that high $PM_{2.5}$ levels in the third trimester significantly increased the risks of PTB and ETB, identifying this period as a critical exposure window. These findings underscore the importance of mitigating air pollution exposure, particularly during vulnerable stages of pregnancy, to prevent adverse birth outcomes (LIMA et al., 2014). Additionally, studies on air pollution's impact on allergic respiratory diseases in schoolchildren and the synergistic effects of air pollution and temperature on mortality due to cardiovascular and respiratory diseases further highlight the broad and significant health risks associated with environmental pollutants, reinforcing the need for comprehensive air quality and public health policies (NICOLUSSI et al., 2014; PINHEIRO et al., 2014).

In São José dos Campos, São Paulo, Brazil, a study spanning from 2005 to 2009 aimed to understand how air pollution affects birth weight. This cross-sectional analysis utilized data from live births, comparing it against air quality metrics (PM_{10}, SO_2, and O_3)

sourced from local environmental monitoring. Despite examining various pollutants, only maternal exposure to sulfur dioxide (SO_2) in the final month of pregnancy showed a marginal association with low birth weight, suggesting a potential risk factor for reduced neonatal weight. However, the study concluded that there was no statistically significant link between the general levels of air pollutants and birth weight, with the slight exception noted for SO_2 exposure late in pregnancy (SANTOS et al., 2014).

Another investigation focused on the impact of air pollution on emergency room visits by children and adolescents with sickle cell disease in São Paulo, Brazil, using a case-crossover design from 1999 to 2004. This study found that increases in air pollutants (PM_{10}, NO_2, SO_2, CO, and O_3) correlated with significant upticks in sickle cell-related emergency visits, with PM_{10} exposure notably increasing visits due to pain by 40.3%. These results highlight the broader cardiovascular and health risks air pollution poses to vulnerable populations, including children with sickle cell disease, underscoring the need for targeted public health strategies to mitigate these environmental health hazards (BARBOSA et al., 2015).

Table 3. Key Diseases and Pollutants Studied in the State of São Paulo (2010-2015).

Author and year of publication	Variables		Age of the participants
	Diseases	Pollutants	
Cançado et al., 2010	Respiratory	PM_{10}, TSP and NO_2	10 a 13
Jasinski et al., 2011	Respiratory	PM_{10}, NO_2	00 a 19
Carneseca et al., 2012	Inhalation/Nebulization Procedures	PM_{10}	No age limit
Nascimento et al., 2012	Stroke	PM_{10}, SO_2, O_3	≥50
Yanagi et al., 2012	Cancer incidence and mortality	PM_{10}	No age limit

Cesar et al., 2013	Respiratory	PM_{10}	0 a 10
Nardocci et al., 2013	Respiratory and cardiovascular	PM_{10}, O_3, SO_2	39
Negrisoli and Nascimento, 2013	Pneumonia	PM_{10}, NO, NO_2 SO_2, O_3	0 a 10
Gavinier and Nascimento, 2014	Stroke	PM_{10}, O_3, NO, NO_2	≥50
Lima et al., 2014	Prematurity	PM_{10}, SO_2, O_3	Recém-nascidos
Nicolussi et al., 2014	Asthma, allergic rhinitis, and eczema	PM_{10}, SO_2, O_3	6 a 7
Pinheiro et al., 2014	Respiratory and cardiovascular	PM_{10}	0 >40 >60
Santos et al., 2014	Birth weight	PM_{10}, SO_2, O_3	Newborns
Barbosa et al., 2015	Falciforme anemia	PM_{10}, NO_2, SO_2, CO, O_3	<18

PM_{10}: Particula matter of ≤ 10μm or less
TSP: Total suspended particles
NO_2: Nitrogen dioxide
O_3: Ozone
SO_2: Sulfur dioxide
NO: Nitrogen monoxide
CO: Carbon monoxide

IV. METHODS

IV.1 STUDY POPULATION

One-thousand three-hundred and fifty-two adults aged 18 year or older living in São Paulo were recruited in 2011-12, the data collection was done in the same period. This city was chosen due to the presence of environmental monitoring stations and the higher concentration of pollutants relative to rural areas. The recruitment locations were banks, churches, and commercial centers, selected due to the large flow of people from all neighborhoods of the city. All subjects provided written, informed consent and the study was approved by our institution's human subjects review board.

The following demographic data were collected: age, sex, address, race, monthly income, education, occupation, and general comorbidity. Education was divided in two categories: high (individuals with High School degree or more) and low education (less than High School). According to the Brazilian Institute of Geography and Statistics (IBGE) the main categories of race or color in Brazil are white, black, brown, yellow, and Indian. The brown category is composed of people who declare themselves mulattoes, caboclos, cafuzos, mamelucos or mestizos (black plus another race). The yellow category consists of people of Asian descent and the Indian category is composed of the those who declare themselves as Amerindians or native Americans (PETRUCCELLI; SABOIA, 2013). For study power, we analyzed the race variable as whites and non-whites. Age and sex have a known association with the olfactory identification performance (DOTY et al., 1984; MURPHY et al., 2002; PINTO et al., 2014b), as does employment status (AJMANI; SUH; PINTO, 2016). Information on other factors that could influence olfactory identification were also collected, including history of nasal disease (SÁNCHEZ-VALLECILLO et al., 2012), smoking (VENNEMANN; HUMMEL; BERGER, 2008) and general comorbidity. People with upper respiratory tract infections on the day of the olfactory examination (DUNCAN; SEIDEN, 1995) and individuals with occupational exposure to substances known to alter the sense of smell, such as benzene, formaldehyde, paint solvents and ammonia (UPADHYAY; HOLBROOK, 2004b), were excluded. All subjects had lived for more than 1 year in São Paulo.

This study was approved by the ethics committee of the University of São Paulo (number 345.784 07/31/2013). All participants signed a written, free, and informed consent.

IV.2 VARIABLES FOR ASSESSING INDIVIDUAL EXPOSURE TO POLLUTION

Assigning exposure to PM_{10} in the participants' addresses was performed by interpolation (the kriging method), a validated technique (DIAS; TCHEPEL, 2018). Briefly, the mean monthly concentrations of PM_{10} were collected from a government monitoring stations database in the city of São Paulo. PM_{10} averages of 30, 60, 90, 180 and 364 days prior to the data collection of the present study were calculated for each station. These environmental monitoring stations check the levels of this pollutant 24 hours a day throughout the year, by means of inertial separation and filtration ("Relatorio-de-Qualidade-do-Ar-no-Estado-de-Sao-Paulo-2021.pdf", [s.d.]).The averages of PM_{10} concentrations at the environmental monitoring stations were interpolated for the geographical points of the study region, using the kriging spatial analysis method (JERRETT et al., 2001). Subsequently, the geographical points of the participants' addresses were placed on the interpolated maps of PM_{10}, and the approximate value of exposure to pollution were assigned based on the addresses of the subjects. The spatial analysis, extraction and interpolation of meteorological data were conducted using ArcGIS software.

IV.3 OLFACTORY ANALYSIS

The UPSIT® test (University of Pennsylvania Smell Identification Test, Sensonics, Inc., Haddon Hts., NJ) was used to assess olfactory identification performance. UPSIT® is a self-administered, easy, and quick assessment (takes approximately 30 minutes in our center experience) and examines the ability to identify the odorants presented. The test consists of four booklets, each containing ten pages, each with a different odorant (n=40 odorants total). The stimulus is incorporated into microcapsules of 10 to 50 µm in diameter and is placed in a small brown strip at the bottom of each page. Each smell has a corresponding multiple-choice question, with four alternatives to be chosen by the interviewee (each correct answer scores 1 point) (DOTY, 2007; FORNAZIERI et al., 2013). From the score obtained of number correct, the individual's olfactory identification performance can be assessed, with age and sex normative values available. This test has been shown to be valid in Brazil. Subjects were categorized into categories: normosmia (>34 for women and >33 for men), mild microsmia (31-34 for women and 30-33 for men), moderate microsmia (26-30 for women and 26-29 for men), severe microsmia (19-25), and anosmia (6-18) (FORNAZIERI et al., 2010, 2015).

IV.4 STATISTICAL ANALYSIS

IV.4.1 POWER

A sample size of approximately 262 individuals was estimated to be sufficient to identify an association with 95% power to detect an effect size of 0.05 in a multiple linear regression with 9 covariates.

IV.4.2 ANALYSIS STRATEGY

The 30, 60-, 90-, 180- and 364-day average concentrations of PM10 at the address of each participant were calculated and were correlated with the UPSIT® score, using an unadjusted simple linear regression for each time interval. The normality of the quantitative variables was calculated using the Shapiro-Wilk test. Subsequently, multivariate linear regressions were performed with each PM_{10} exposure time interval, controlling age, sex, race, education, monthly household income, tobacco smoking, general comorbidity, and presence of chronic nasal disease. The regressions were scaled such that the β signifies a 1 $\mu m/m^3$ increase in PM_{10} corresponds to a 1-point decrease in UPSIT® score). Significance was set at a $p<0.05$ and analyses were performed using Stata (StataCorp) and R (RStudio).

V. RESULTS AND DISCUSSION

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ORIGINAL ARTICLE

Association of air pollution with olfactory identification performance of São Paulo residents: a cross-sectional study

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Abstract

Objective Exposure to particulate matter of 10 µm or less in diameter (PM_{10}) has been implicated in pulmonary and cardiovascular diseases. However, the effect of PM_{10} on olfaction has not been well established. We estimated individual acute and chronic PM_{10} exposure levels in a large Brazilian cohort and related them to the ability to identify odors.

Methods Adults from São Paulo ($n = 1358$) were recruited from areas with different levels of air pollution. To verify individual exposure to air pollution, the averages of 30, 60, 90, 180 and 364 days of PM_{10} were interpolated to subjects' zip codes using the kriging method. Olfactory identification performance was tested using the University of Pennsylvania Smell Identification Test (UPSIT®). Multiple linear regressions were used to calculate the effect of air pollution on olfactory identification performance, controlling for demographic and other variables that affect the sense of smell.

Results Acute exposures to PM_{10} were related to worse UPSIT® scores, including 30- ($\beta = -0.94$, 95% Confidence Interval [CI] −0.98, −0.89), 60- ($\beta = -1.09$, 95% CI = −1.13, −1.04) and 90-day intervals ($\beta = -1.06$, 95% CI −1.10, −1.02) (reference for β: 1 µm/m^3 increase in PM10 exposure per point decrease in UPSIT® score). Chronic exposures were also associated with worse olfaction for both 180- ($\beta = -1.06$, 95% CI −1.10, −1.03) and 364-day ($\beta = -0.87$, 95% CI −0.90, −0.84) intervals. As in prior work, men, older, low-income, and low-schooling people demonstrated worse olfactory performance.

Conclusion Acute and chronic exposure to PM_{10} is strongly associated with olfactory identification performance in Brazilian adults. Understanding the mechanisms which underlie these relationships could help to improve chemosensory function with a large public health impact.

Keywords Smell · Smell disorders · Olfactometry · Air pollution · Olfaction · PM_{10}

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Introduction

Olfactory loss is associated with a reduction in quality of life, affecting the perception of pleasure (thereby affecting eating and sexual behavior), and the detection of dangerous situations such as fire or toxic exposure (Auinger et al. 2020; Deng et al. 2020; Schäfer et al. 2021; Liu et al. 2021). Because of its direct contact with the environment, the olfactory epithelium is susceptible to damage from substances present in the air (Poindexter and Garrett 2020).

Temporary or continuous exposure to a variety of airborne toxic agents, including metallic organic compounds and other chemical particles can cause total or partial olfactory loss (Upadhyay and Holbrook 2004) which can be transient or permanent (Upadhyay and Holbrook 2004; Guarneros et al. 2009). Thus, air pollution may influence the olfactory identification performance of inhabitants of large industrial and urban centers (Hudson et al. 2006; Calderón-Garcidueñas et al. 2010) exposed to industrial and road exhaust-based pollutants. Indeed, early population-scale data shows that exposure to nitrogen dioxide and particulate matter of 2.5 µm or less in diameter ($PM_{2.5}$) is associated with worse olfactory ability, depending on the exposure window and age of the individual (Adams et al. 2016; Ajmani et al. 2016).

Other previous studies have measured the influence of pollution on smell by comparing people in less polluted regions or cities with those living in more polluted ones; however, they did not quantify individual exposure to pollutants (Hudson et al. 2006; Guarneros et al. 2009; Calderón-Garcidueñas et al. 2010; Sorokowska et al. 2013, 2015). Other obstacles to a better understanding of this topic include small samples (Guarneros et al. 2009; Calderón-Garcidueñas et al. 2010), failure to assess olfactory identification with validated tests (Hudson et al. 2006), limited or unknown exposure windows (Guarneros et al. 2009; Calderón-Garcidueñas et al. 2010; Sorokowska et al. 2013, 2015), or restricted age ranges (Lucchini et al. 2014; Adams et al. 2016; Ajmani et al. 2016). Besides that, to our knowledge, there are no studies analyzing the relationship between PM_{10} and olfactory identification in adults (nitrogen oxides and $PM_{2.5}$ have been previously studied) (Adams et al. 2016; Ajmani et al. 2016). Therefore, the aim of this study was to determine whether there is an association between the olfactory identification performance with acute and chronic exposures to particulate matter of 10 µm or less in diameter (PM_{10}) in adults living in São Paulo, Brazil.

Methods

Study population

One-thousand three-hundred and fifty-two adults aged 18 year or older living in São Paulo were recruited in 2011–12, the data collection was done in the same period. This city was chosen due to the presence of environmental monitoring stations and the higher concentration of pollutants relative to rural areas. The recruitment locations were banks, churches, and commercial centers, selected due to the large flow of people from all neighborhoods of the city. All subjects provided written, informed consent and the study was approved by our institution's human subjects review board.

The following demographic data were collected: age, sex, address, race, monthly income, education, occupation, and general comorbidity. Education was divided into two categories: high (individuals with a High School degree or more) and low education (less than High School). According to the Brazilian Institute of Geography and Statistics (IBGE) the main categories of race or color in Brazil are white, black, brown, yellow, and Indian. The brown category is composed of people who declare themselves mulattoes, caboclos, cafuzos, mamelucos or mestizos (black plus another race). The yellow category consists of people of Asian descent and the Indian category is composed of those who declare themselves as Amerindians or native Americans (Petruccelli and Saboia 2013). For study power, we analyzed the race variable as whites and non-whites. Age and sex have a known association with olfactory identification performance (Doty et al. 1984; Murphy et al. 2002; Pinto et al. 2014), as does employment status (Ajmani et al. 2016). Information on other factors that could influence olfactory identification were also collected, including the history of the nasal disease (Sánchez-Vallecillo et al. 2012), smoking (Vennemann et al. 2008) and general comorbidity. People with upper respiratory tract infections on the day of the olfactory examination (Duncan and Seiden 1995) and individuals with occupational exposure to substances known to alter the sense of smell, such as benzene, formaldehyde, paint solvents and ammonia (Upadhyay and Holbrook 2004), were excluded. All subjects had lived for more than 1 year in São Paulo.

This study was approved by the ethics committee of the University of São Paulo (number 345.784 07/31/2013). All participants signed a written, free, and informed consent.

Variables for assessing individual exposure to pollution

Assigning exposure to PM_{10} in the participants' addresses was performed by interpolation (the kriging method), a validated technique (Dias and Tchepel 2018). Briefly, the mean monthly concentrations of PM_{10} were collected from a government monitoring stations database in the city of São Paulo (Santos et al. 2022). PM_{10} averages of 30, 60, 90, 180 and 364 days prior to the data collection of the present study were calculated for each station. These environmental monitoring stations check the levels of this pollutant 24 h a day throughout the year, by means of inertial separation and filtration (Komatsu et al. 2011).

The averages of PM_{10} concentrations at the environmental monitoring stations were interpolated for the geographical points of the study region, using the kriging spatial analysis method (Jerrett et al. 2001). Subsequently, the geographical points of the participants' addresses were placed on the interpolated maps of PM_{10}, and the approximate value of exposure to pollution was assigned based on the addresses of the subjects. The spatial analysis, extraction and interpolation of meteorological data were conducted using ArcGIS software.

Olfactory analysis

The UPSIT® test (University of Pennsylvania Smell Identification Test, Sensonics, Inc., Haddon Hts., NJ) was used to assess olfactory identification performance. UPSIT® is a self-administered, easy, and quick assessment (takes approximately 30 min in our center experience) and examines the ability to identify the odorants presented. The test consists of four booklets, each containing ten pages, each with a different odorant ($n = 40$ odorants total). The stimulus is incorporated into microcapsules of 10 to 50 μm in diameter and is placed in a small brown strip at the bottom of each page. Each smell has a corresponding multiple-choice question, with four alternatives to be chosen by the interviewee (each correct answer scores 1 point) (Doty 2007; Fornazieri et al. 2013). From the score obtained of number correct, the individual's olfactory identification performance can be assessed, with age and sex normative values available. This test has been shown to be valid in Brazil. Subjects were categorized into categories: normosmia (> 34 for women and > 33 for men), mild microsmia (31–34 for women and 30–33 for men), moderate microsmia (26–30 for women and 26–29 for men), severe microsmia (19–25), and anosmia (6–18) (Fornazieri et al. 2010, 2015).

Statistical analysis

Power

A sample size of approximately 262 individuals was estimated to be sufficient to identify an association with 95% power to detect an effect size of 0.05 in a multiple linear regression with 9 covariates.

Analysis strategy

The 30, 60-, 90-, 180- and 364-day average concentrations of PM_{10} at the address of each participant were calculated and were correlated with the UPSIT® score, using an unadjusted simple linear regression for each time interval. The normality of the quantitative variables was calculated using the Shapiro–Wilk test. Subsequently, multivariate linear regressions were performed with each PM_{10} exposure time interval, controlling age, sex, race, education, monthly household income, tobacco smoking, general comorbidity, and presence of chronic nasal disease. The regressions were scaled such that the β signifies a 1 μm/m^3 increase in PM_{10} corresponds to a 1-point decrease in UPSIT® score). Significance was set at a $p < 0.05$ and analyses were performed using Stata (StataCorp) and R (RStudio).

Results

The demographic characteristics of the 1358 individuals included are shown in Table 1. The average UPSIT® score was 32.5 (Standard Deviation (SD) 5.0). Normosmia was found in 51% of males and in 56.6% of females, hyposmia in 46.4% of males and 42.6% of females and anosmia in 2.7% of males and 0.7% of females.

Interpolations and individual exposure to PM_{10}

The following averages of exposure to atmospheric PM_{10} were calculated: 30 days 31.16 µg / m^3 (Standard Deviation [SD] 8.74), 60 days 28.48 µg/m^3 (SD 5.09), 90 days 31.26 (SD 1.85), 180 days 31.83 (SD 1.66), and 364 days exposures 37.55 (SD 2.32) (Table 2). The distribution of PM_{10} levels over 1 year is shown in Fig. 1.

Simple and multivariate linear regressions

Across all exposure windows, increased PM_{10} exposure was associated with worse UPSIT® scores by simple univariate linear regression (Table 3). After controlling for age, sex, race, schooling, income, cigarette smoking, nasal disease, and general comorbidity, increased exposure to PM_{10} was still associated with worse olfaction across all exposure

Table 1 Demographic characteristics and olfactory identification performance for the population of São Paulo. The monthly income is given in US Dollars

Characteristic	Percentage (%)	Mean ± SD
UPSIT®		32.5 ± 5.0
Age (in years)		51.3 ± 18.5
Sex (% of men)	49.6	
Race		
White	61.0	
Black	10.8	
Brown	23.6	
Yellow	3.8	
Indian	0.2	
Monthly income		
< US$ 269.00	8.2	
US$270.00–1079.00	49.9	
US$ 1080.00–2699.00	25	
> US$ 2700.00	13.5	
Schooling[a]		
High education	35.7	
Low education	64.3	
Nasal disease	14.9	
General comorbidity (any other disease, other than nasal)	35.4	
Active smokers	16.3	
Past Smokers	24.3	

[a] The high education category was composed of individuals with High School or more and the low education by participants with less than High School

windows (Table 4). The entire results of all the multivariate linear regressions can be found in the supplementary tables 1, 2, 3 and 4.

More specifically, increased in PM_{10} (one-year window) was associated with worse olfaction in adjusted analysis ($\beta = -0.87$, 95% CI -0.90, -0.84). Women ($\beta = 2.13$, 95% CI 1.63, 2.64), those with higher monthly incomes ($\beta = 1.47$, 95% CI 0.91, 2.02) and increased number of years of schooling ($\beta = 2.69$, 95% CI 2.09, 3.29) showed better UPSIT® scores, whereas those who were older ($\beta = -0.07$, 95% CI -0.09, -0.05) and active smokers ($\beta = -0.83$, 95% CI -1.54, -0.13) had worse scores. Race, nasal disease and general comorbidity did not significantly predict UPSIT® scores, when analyzed together with the other covariates. The results of the other regressions were similar to those of 1-year exposure, with the exception of race for 30 days exposure ($\beta = 0.63$, 95% CI 0.16, 1.10).

Discussion

Both acute and chronic exposures to PM_{10} were associated with worse UPSIT® scores when adjusting for demographic variables in this urban Brazilian cohort. These results are novel in that the association extends prior work across the full range of adults from age 18 to 100 and into an ethnically diverse population with a different cultural and environmental context. To date, there have been few studies identifying the effects of specific pollutants, like $PM_{2.5}$ and NO_2, on olfactory identification performance (Adams et al. 2016; Ajmani et al. 2016). Our outcome is one of the first to identify an association between PM_{10} and olfactory identification in a developing country, which have different populational and environmental characteristics compared to developed countries (Adams et al. 2016; Ajmani et al. 2016).

More than that, our findings regarding adult exposure to PM_{10} and impaired olfactory identification are consistent with previous results in children living in developing countries (Guarneros et al. 2020). This increases our understanding of how the particulate matter-olfactory identification relationship is present across various age groups and culturally diverse populations.

Although São Paulo PM_{10} concentration levels are decreasing over time (from a mean of 36 µg/m^3 in 2012 to 27 µg/m^3 in 2021), due to emission control programs, our results are still applicable nowadays as PM_{10} was related to olfactory identification in a dose-dependent linear relationship. Besides that, an annual average of 27 µg/m^3 is still considered high accordingly to the World Health Organization (WHO). Also, in our work, we did not identify a lower threshold of safety for PM_{10} (World Health Organization 2021; Santos et al. 2022).

Another advantage to our approach was the use of the kriging method for exposure estimation, which is more accurate than isolated measures of pollutants by proximity (Han

Table 2 PM_{10} exposures at 30, 60-, 90-, 180- and 364-days windows

Time interval of PM_{10} exposure	Mean concentration (µg/m^3) ± Standard Deviation	25–75 percentile intervals (µg/m^3)	Maximum (µg/m^3)	Minimum (µg/m^3)
30 days	31.19 ± 2.26	29.25, 32.64	41.40	25.43
60 days	28.41 ± 2.26	27.07, 29.41	37.07	24.65
90 days	31.26 ± 1.85	30.05, 31.94	38.45	28.24
180 days	31.83 ± 1.66	30.68, 32.43	38.31	29.42
364 days	37.55 ± 2.32	36.07, 38.35	47.45	34.31

Fig. 1 Map of interpolated pollution exposure in São Paulo of the study for 1-year PM_{10} average

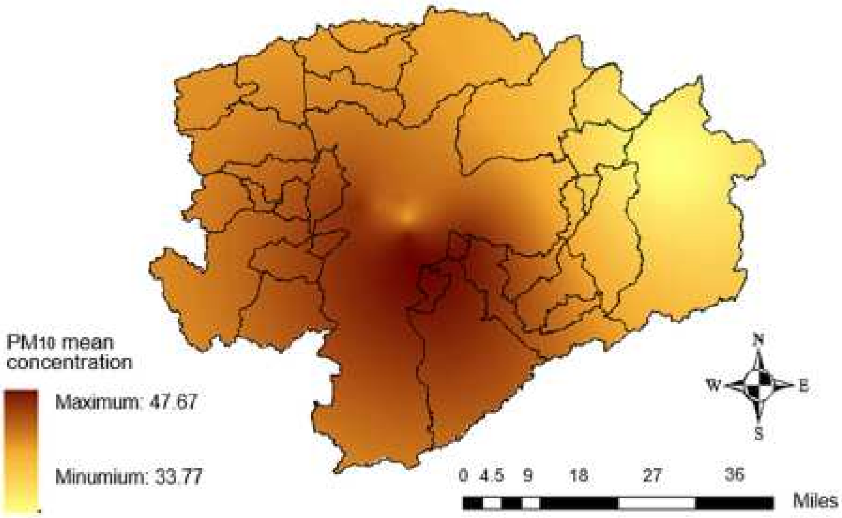

Table 3 Multivariate linear regressions of the association between PM_{10} exposures and UPSIT® score, controlling for age, sex, schooling, monthly income, tobacco smoking, nasal disease, and general comorbidity

Exposures to PM_{10}	Beta (95% CI)	*p* value	Adjusted R^2
30 days	−0.97 (−1.01, −0.93)	**<0.01**	0.97
60 days	−1.11 (−1.16, −1.07)	**<0.01**	0.97
90 days	−1.07 (−1.11, −1.04)	**<0.01**	0.98
180 days	−1.07 (−1.11, −1.04)	**<0.01**	0.98
364 days	−0.88 (−0.91, −0.85)	**<0.01**	0.98

The other regression results can be found in the complementary materials

The level of significance is 0.05 or less (in bold)

et al. 2017). In this sense, the concentration ratio of PM_{10} with the value of the UPSIT® test was evaluated, potentially providing greater reliability in measures of individual exposure to pollution (Wrobel and Leopold 2004; Jerrett et al. 2005; Ranft et al. 2009).

Our results were robust to factors that could influence olfactory identification, in addition to excluding other factors that could interfere with the test score, such as upper respiratory tract infections on the day of the olfactory examination (Duncan and Seiden 1995) and occupational exposure to substances that alter the sense of smell, such as benzene, formaldehyde, paint solvents and ammonia (Genter and Doty 2019). Finally, we used a well-validated test (UPSIT®), with 40 odorants, making our assessment of olfactory identification rigorous (Guarneros et al. 2009; Hugh et al. 2015; Otorhinolaryngol et al. 2015; Fornazieri et al. 2015).

Those with higher monthly income and increased schooling scored better on the UPSIT®, consistent with prior work by us and others (Goette et al. 2017; Fornazieri et al. 2019).

Table 4 Multivariate linear regression of UPSIT® and 1-year PM_{10} exposure, adjusting for age, sex, schooling, monthly income, tobacco smoking, nasal disease and general comorbidity. Adjusted R^2 0.98

Variable	Beta (95% CI)	*p* value[a]
PM_{10}	−0.88 (−0.91, −0.85)	**< 0.01**
Age (per year)	−0.08 (−0.09, −0.06)	**< 0.01**
Sex (women vs men)	1.87 (1.36, 2.38)	**< 0.01**
Race (non-whites vs whites)	−1.22 (−1.76, 0.67)	0.55
Monthly income[b]	1.29 (0.74, 1.84)	**< 0.01**
Schooling (high education vs low education)[c]	2.53 (1.93, 3.13)	**< 0.01**
Tobacco smoke (vs non-smokers)		
Active smokers	−0.83 (−1.54, −0.13)	**0.02**
Past smokers	0.15 (−0.66, 0.96)	0.72
Nasal disease	0.09 (−0.61, 0.81)	0.78
General comorbidity	−0.05 (−0.65, 0.54)	0.86

The level of significance is 0.05 or less (in bold)

[a] The *p* values are given in the third column as exact values unless specified as ">" or "<"

[b] In the monthly income, the comparison used was high income (more than US$ 269 per month) against low income (less than US$270)

[c] The high education category was composed of individuals with high school or more and the low education by participants with less than high school

Women also scored higher, as has been widely reported (Pinto et al. 2014; Doty 2019). As has been shown repeatedly, older adults had worse scores (Murphy et al. 2002; Vennemann et al. 2008; Xu et al. 2020).

Inflammatory changes are thought to be induced by acute pollution exposure. Increased levels of cyclooxygenase (COX) 2, interleukin (IL) 1β and CD14, which are inflammatory markers, are present in olfactory tissues of individuals that live in highly polluted areas and absent in the ones living in non-polluted sites (Calderón-Garcidueñas et al. 2013). Chronic olfactory effects of air pollution seem to be mediated by long-term inflammation in the olfactory epithelium and bulbs, as demonstrated by the deposition of β-amyloid in this area. Basal cell hyperplasia, epithelial dysplasia and squamous metaplasia are also present in the olfactory tissues of chronically exposed individuals (Calderón-Garcidueñas et al. 2008, 2010, 2013).

We note several limitations in our study. The time that each participant spent at work was not considered, which is, in most cases, a different location from home. Also, the amount of time spent indoors when not working and the level of activity of each respondent were not measured and may have influenced our results. The kriging method is based on indirect predictions of PM_{10} levels, which can generate less precise pollution exposure data than using direct measures (portable monitors can be used for that purpose). Considering that the study analyzed only the maximum of one-year exposure, it is also not possible to draw conclusions regarding exposure to air pollutants beyond this timeframe. Although we accounted for general health by comorbidity, we did not control for a specific disease such as cardiovascular disease, which may also have influenced our results (Doty 2019). We also did not measure other aspects of the olfactory function, like the detection of odorants, (olfactory threshold), which could also be affected by PM_{10} and other air pollutants, maybe even more than olfactory identification.

In conclusion, both acute and chronic exposures to outdoors PM_{10} are associated with loss of smell identification in São Paulo residents. Further studies are needed to verify how other pollutants affect olfaction and variation across populations and geography.

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Author contributions HOS: Conceptualized and designed the study, conducted the data collection, conducted the analyses, drafted the initial manuscript, and revised the manuscript. JLBS: coordinated data collection, conducted the analyses, drafted the initial manuscript, and revised the manuscript. RAMRR and AFF: Conducted the data collection, drafted the initial manuscript, and critically reviewed the manuscript. FRP, RLV and Jayant MP: Prof. Voegels, Prof. Pinna and Prof. Pinto conceptualized and designed the study, and critically reviewed the manuscript. MAF: Professor Fornazieri provided statistical guidance, coordinated the data colletion and critically revised and reviewed the manuscript. All authors approved the final manuscript as submitted.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

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Human subject protections The research was approved by the ethics committee of the University of São Paulo (number 345.784, 07/31/2013). All research participants signed a written, free, and informed consent.

Consent for publication All authors have read the manuscript, agree the work is ready for submission to the International Archives of Occupational and Environmental Health, and accept responsibility for the manuscript's contents.

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Insights on nasopulmonary reflex and its implications in clinical practice

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Introduction

The nasopulmonary reflex has been an understudied physiologic mechanism, with few studies reporting conflicting results. Notably, some studies suggest that, while nasal packing has been a routine practice, it may pose risks such as naso-pulmonary reflex, pain, sleep disorders, and even increased mortality[1–3]. It is also worth mention that there is evidence that nasal packing and the increased mortality by nasopulmonary reflex may not be related to hypoxic episodes mortality may not be associated with hypoxia, but with other complex factors that interfere with the respiratory physiology[2]. However, some data contests the established link between posterior nasal packs and mortality, attributing observed hypoxemia to alternative factors like aspiration, sedation, and age-related pulmonary function decline[3].

A common point in the literature about nasopulmonary reflex is that various types of nasal stimuli can potentially cause lower respiratory tract reflexes[4–7]. Some data suggests the existence of a nasopulmonary bronchoconstrictor reflex and demonstrate varying responses to nasal mucosal stimulation in different clinical contexts[4,5]. For instance, laryngectomized patients exhibit reduced airway resistance in response to nasal mucosal stimulation, contrasting with increased resistance in normal subjects[6]. Additionally, it's been demonstrated that nasal stimulation in anesthetized dogs induces marked breathing pattern alterations, further underlining the intricate connection between nasal stimuli and respiratory reflexes[7]. Because of the sparce literature and conflicting data on this topic, we propose to critically review the literature on nasopulmonary reflex.

Methods

Two databases were queried with two broad categories of MeSH terms: one related to the nose, including "nose", "nasal cavity", "paranasal sinuses", "nasal mucosa", and other related to the lower respiratory tract, including "respiratory tract", "lung", "bronchi". Two databases were queried with the same MeSH terms: PubMed and Google Scholar. We included papers that mentioned nasopulmonary reflex in the abstract and/or mentioned nasal physiologic connections with the lungs. We included prospective and retrospective cohorts, case controls, cross-sectional studies, animal studies, case series, case reports and reviews. We excluded papers that mentioned nasal and/or pulmonary function but did not relate one to the other. The database search and application of inclusion and exclusion criteria were done by two independent reviewers. After the first analysis, the two reviewers met and discussed to enter in a consensus about the differences in the papers` selection. This whole process was supervised by a specialist in the area, who agreed with the final selection of studies.

Results

Our primary search returned 1093 studies in PubMed and 661 papers in Google Scholar. After applying our inclusion criteria, we ended with 13 papers in PubMed and 6 papers in Google Scholar. After removing duplicates, we yielded 12 articles that were fully reviewed by two independent reviewers, with the supervision of a specialist in the area (figure 1).

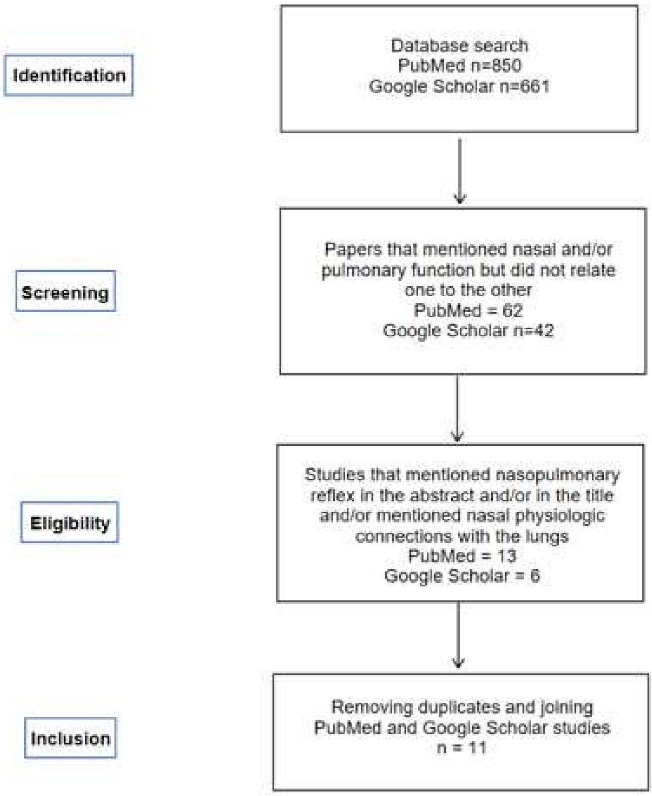

Figure 1. PRISMA flow diagram for nasopulmonary reflex.

Most of the analyzed studies focused on nasal packing as a form of irritation and/or stimulation of nasal mucosa to cause a reflexive reaction in the lungs[1–3,8]. Few papers focused on the effect of other nasal irritants, such as cold dry air inhalation, as the trigger of nasopulmonary reflex[4,5]. Other tried to induce the nasopulmonary effect on special circumstances, such as post laryngectomy[6,9] individuals and asthmatics[5]. There was one paper that tried to explain the mechanism behind this phenomenon, which involves interruption of the trigeminal and vagus nerves[7]. Additionally, one study compared inhalation of dry cold air by the nose and by mouth, reporting the nasopulmonary reflex only in inhalation by the nose[4]. Most of the clinical studies considered nasopulmonary reflex clinically relevant[1,3–6,9–12], however one study did not[2]. Additionally, one theory that lung compression by lying down sideways would be possible mechanism for nasal congestion on the same side has scarce literature and has not been proved yet[13] (figure 2).

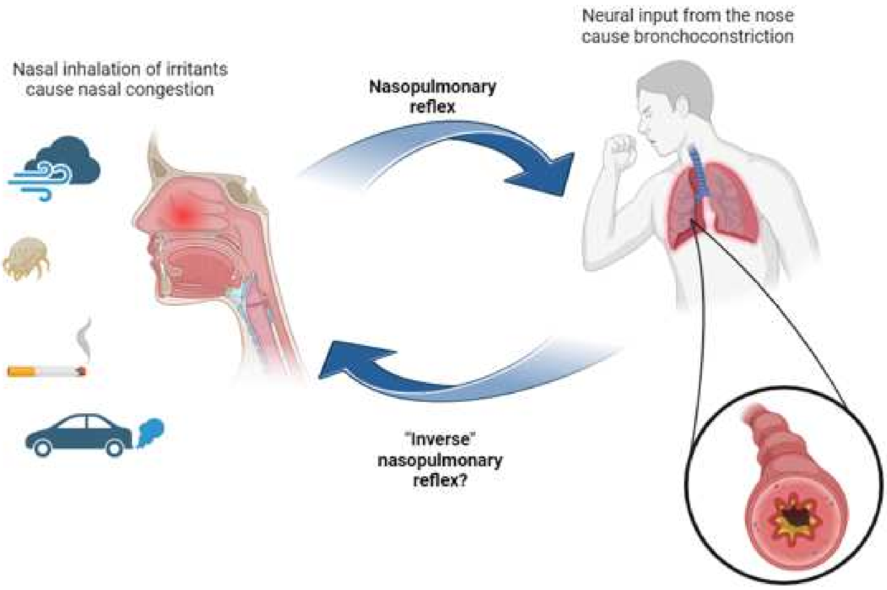

Figure 2. Summary of the mechanism of the nasopulmonary reflex with a projection for a possible "inverted" mechanism, in which lung irritation could cause nasal congestion (still needs investigation).

Discussion

We are one of the first studies to comprehensive and critically review the literature on nasopulmonary reflex. The understanding and consequences of this phenomenon are understudied and in need of further high-quality investigation. Besides the sparce literature on the subject, most studies have small samples[2,4–6,10], which prevents the generalization of the nasopulmonary reflex. Additionally, some studies lacked a control group, which could have affected the outcomes[9,14]. Nevertheless, these preliminary findings point to an interesting phenomenon.

These studies collectively offer a nuanced exploration of nasal surgery outcomes, complications, and the intricate interplay between nasal interventions and respiratory physiology. In this sense, one study challenges the conventional practice of routine nasal packing after septoplasty, suggesting its potential omission for patients without a heightened risk of bleeding[1]. This finding go against the theme in Loftus et al, which questions the existence of a "nasopulmonary reflex" in the context of posterior epistaxis management, emphasizing that complications may be more closely tied to rebleeding or underlying medical conditions than to primary oxygen status[2].

The physiological aspects of the nose, both before and after laryngectomy, reveal the enduring potential of nasal functions and reflexes even when the nose is eliminated from the primary respiratory pathway. There is evidence identifying specific bronchoconstrictor reflexes triggered by nasal stimulation after laryngectomy, affirming the continued influence of the nose on respiratory responses[6,9]. These results emphasize the complexity and adaptability of nasal physiology.

In animal models, specifically anesthetized, nonparalyzed dogs, it was revealed marked changes in breathing patterns and pulmonary airflow resistance following nasal stimulation[7]. Additionally, the potential occurrence of peristalsis in the bronchi was explored, with indirect evidence suggesting rhythmic contractions in chick embryos and reflex effects on respiration from stimuli applied to the nasal mucous membrane[14].

Most of the studies involving the nasopulmonary reflex show that it is clinically significant and could affect decisions on which patients nasal packing is indicated, with a special consideration regarding asthmatic patients. Additionally, more studies on whether an inverted nasopulmonary reflex would also exist or not are needed and would possibly explain one extra mechanism of nasal congestion caused by lung compression.

There are several limitations to this study. We just analyzed two different databases, which limited our scope of studies. We also did not consider unpublished research, which could have added more input on nasopulmonary reflex. Only two reviewers and one specialist were available to read and interpret the results of our review, limiting our analysis by the interpretation of three researchers. Additionally, as did not do a systematic review and/or a metanalysis, we could not draw any definitive conclusions about clinical relevance of the nasopulmonary reflex.

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VI. CONCLUSION

This study is one of first ones to relate air pollution exposure to olfactory loss in a developing country. Further large-scale longitudinal studies are necessary to confirm this hypothesis. If confirmed, it could help public policies to focus on reducing PM_{10} emissions and prevent smell loss impact in the Brazil`s health system. Additionally, if other similar studies prove this finding in other parts of the world, our work will have worldwide impact in peoples` health, not only in terms of olfaction, but also in mental health (as the sense of smell is directly linked to Alzheimer`s and Parkinson`s diseases).

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VIII. COMPLEMENTARY MATERIALS (FOR PAPER ONE)

Complementary Table 1 Multivariate linear regression of UPSIT and 30 days PM_{10} exposure, adjusting for age, gender, schooling, monthly income, tobacco smoking, nasal disease, and general comorbidity. Adjusted R^2 0.97

Variable	**Beta (95% CI)**	**p value**[a]
PM_{10}	-0.97 (-1.01, -0.93)	**<0.01**
Age (per year)	-0.05 (-0.06, -0.03)	**<0.01**
Gender (women vs men)	2.11 (1.55, 2.68)	**<0.01**
Race (non-whites vs whites)	-0.81 (-1.41, -0.21)	**0.01**
Monthly income[b]	1.42 (0.81, 2.03)	**<0.01**
Schooling (high education vs low education)[c]	3.41 (2.75, 4.07)	**<0.01**
Tobacco smoke (vs non-smokers)		
Past smokers	0.73 (-0.16, 1.62)	0.11
Active smokers	-1.43 (-2.21, -0.66)	**<0.01**
Nasal disease	0.34 (-0.44, 1.13)	0.87
General comorbidity	-0.40 (-1.05, 0.25)	0.23

[a] The p values are given in the third column as exact values, unless specified as “>” or “<”.

[b] In the monthly income, the comparison used was high income (more than US$ 269 per month) against low income (less than US$270).

[c] The high education category was composed by individuals with high school or more and the low education by participants with less than high school.

Complementary Table 2 Multivariate linear regression of UPSIT and 60 days PM_{10} exposure, adjusting for age, gender, schooling, monthly income, tobacco smoking, nasal disease, and general comorbidity. Adjusted R^2 0.97

Variable	**Beta (95% CI)**	**p value**[a]
PM_{10}	-1.11 (-1.16, -1.07)	**<0.01**
Age (per year)	-0.06 (-0.08, -0.05)	**<0.01**
Gender (women vs men)	2.02 (1.48, 2.56)	**<0.01**
Race (non-whites vs whites)	-0.95 (-1.52, -0.37)	**<0.01**
Monthly income[b]	1.32 (0.74, 1.91)	**<0.01**
Schooling (high education vs low education)[c]	3.01 (2.38, 3,64)	**<0.01**
Tobacco smoke (vs non-smokers)		
Active smokers	-1.12 (-1.86, -0.38)	**<0.01**
Past smokers	0.39 (-0.46, 1.25)	0.36
Nasal disease	0.36 (-0.39, 1.11)	0.35
General comorbidity	-0.27 (-0.89, 0.36)	0.41

[a] The p values are given in the third column as exact values, unless specified as “>” or “<”.

[b] In the monthly income, the comparison used was high income (more than US$ 269 per month) against low income (less than US$270).

[c] The high education category was composed by individuals with high school or more and the low education by participants with less than high school.

Complementary Table 3 Multivariate linear regression of UPSIT and 90 days PM_{10} exposure, adjusting for age, gender, schooling, monthly income, tobacco smoking, nasal disease, and general comorbidity. Adjusted R^2 0.98

Variable	**Beta (95% CI)**	**p value**[a]
PM_{10}	-1.07 (-1.11, -1.04)	**<0.01**
Age (per year)	-0.08 (-0.10, -0.07)	**<0.01**
Gender (women vs men)	1.89 (1.39, 2.41)	**<0.01**
Race (non-whites vs whites)	-1.13 (-1.67, -0.59)	**<0.01**
Monthly income[b]	1.17 (0.62, 1.72)	**<0.01**
Schooling (high education vs low education)[c]	2.45 (1.85, 3.06)	**<0.01**
Tobacco smoke (smokers vs non-smokers)		
Active smokers	-0.78 (-1.47. -0.08)	**0.03**
Past smokers	0.11 (-0.70, 0.91)	0.79
Nasal disease	0.13 (-0.57, 0.84)	0.70
General comorbidity	-0.06 (-0.65, 0.52)	0.83

[a] The p values are given in the third column as exact values, unless specified as “>” or “<”.

[b] In the monthly income, the comparison used was high income (more than US$ 269 per month) against low income (less than US$270).

[c] The high education category was composed by individuals with high school or more and the low education by participants with less than high school.

Complementary Table 4 Multivariate linear regression of UPSIT and 180 days PM_{10} exposure, adjusting for age, gender, schooling, monthly income, tobacco smoking, nasal disease, and general comorbidity. Adjusted R^2 0.98

Variable	**Beta (95% CI)**	**p value**[a]
PM_{10}	-1.07 (-1.11, -1.04)	**<0.01**
Age (per year)	-0.09 (-0.11, -0.07)	**<0.01**
Gender (women vs men)	1.85 (1.35, 2.35)	**<0.01**
Race (non-whites vs whites)	-1.17 (-0.64, 0.71)	0.32
Monthly income[b]	1.10 (0.56, 1.64)	**<0.01**
Schooling (high education vs low education)[c]	2.26 (1.67, 2.85)	**<0.01**
Tobacco smoke (vs non-smokers)		
Active smokers	-0.67 (-1.35, 0.01)	0.05
Past smokers	-0.01 (-0.79, 0.80)	0.99
Nasal disease	0.07 (-0.62, 0.76)	0.71
General comorbidity	0.01 (-0.57, 0.58)	0.98

[a] The p values are given in the third column as exact values, unless specified as “>” or “<”.

[b] In the monthly income, the comparison used was high income (more than US$ 269 per month) against low income (less than US$270).

[c] The high education category was composed by individuals with high school or more and the low education by participants with less than high school.

IX. ATTACHMENTS

INFORMED CONSENT FORM

I, Marco Aurélio Fornazieri, responsible for the research entitled "Effects of Air Pollution on Olfactory Function", am extending an invitation for you to participate as a volunteer in my study.

Throughout the research period, you have the right to ask any questions or request further clarification simply by contacting the researcher or the Ethics Committee in Research Involving Human Beings at the State University of Londrina, located at LABESC – School Laboratory, on the University Campus, phone 3371-5455, email: cep268@uel.br. This form must be filled out in two copies of the same content, one of which must be properly filled out, signed, and delivered to the gentleman/lady.

This information is provided for your voluntary participation in this study, which aims to describe whether there are olfactory changes related to pollution. This objective will be achieved through the analysis of air pollutant concentration during the year prior to the interview, the application of a questionnaire, and testing your ability to smell.

There is no discomfort or expected risk in performing the olfactory test and the questionnaire.

You are guaranteed the right to refuse to participate or to withdraw your permission at any time without any type of prejudice to the continuity of your care at the Institution.

The information from this research will be confidential and will be disclosed only at events or scientific publications, without the identification of volunteers, ensuring secrecy about your participation.

There are no personal expenses for the participant at any stage of the study. There is also no financial compensation related to your participation.

I, ____, after reading (or listening to the reading of) this document and having had the opportunity to talk with the responsible researcher to clarify all my doubts, believe to be sufficiently informed, understanding clearly that my participation is voluntary and that I can withdraw this consent at any time without penalties or loss of any benefits. I am also aware of the research objectives, the procedures to which I will be subjected, the possible harms or risks arising from them, and the guarantee of confidentiality and clarifications whenever I wish. Given the above, I express my agreement of free will to participate in this study.

Researcher Information
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