UNIVERSITAT DE BARCELONA

Multidisciplinary digital tools for improving early diagnosis and treatment of respiratory disease – focus on pulmonary fibrosis

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MULTIDISCIPLINARY DIGITAL TOOLS FOR IMPROVING EARLY DIAGNOSIS AND TREATMENT OF RESPIRATORY DISEASE – FOCUS ON PULMONARY FIBROSIS

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Glossary of Acronyms

API	- application programming interface
CO	- carbon monoxide
CO_2	- carbon dioxide
COPD	- chronic obstructive pulmonary disease
EHRs	- electronic health records
FVC	- forced vital capacity (spirometry lung function)
ILD	- interstitial lung disease
IPAF	- interstitial pneumonia with autoimmune features
IPF	- idiopathic pulmonary fibrosis
NO_2	- nitrogen dioxide
NO_X	- nitrogen oxides
0_3	- ozone
PM2.5	- particulate matter 2.5
PM10	- particulate matter 10
SO_X	- sulphur oxides
UHC	- unburned hydrocarbons
VOCs	- volatile organic compounds
WHO AQG	- World Health Organization Air Quality Guidelines
YLL	- years of life lost

Thesis by Compendium

This thesis is presented in the form of a collection of published articles. The two articles included are both published in 1st quartile journals with the doctoral student as first author:

Shull JG, Pay MT, Lara Compte C, Olid M, Bermudo G, Molina-Molina M., et al. Mapping IPF helps identify geographic regions at higher risk for disease development and potential triggers. Respirology. 2021 Apr;26(4):352-359. doi: 10.1111/resp.13973.

https://pubmed.ncbi.nlm.nih.gov/33167075/

Respirology Impact Factor (JCR 2021): 6.1

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Subject Category: Pulmonary and Respiratory Medicine

Shull JG, Planas-Cerezales L, Lara Compte C, Perona R, Molina-Molina M. Harnessing PM2.5 exposure data to predict progression of fibrotic interstitial lung diseases based on telomere length. Frontiers in Medicine. May 12, 2022. Volume 9. doi: 10.3389/fmed.2022.871898

https://www.frontiersin.org/article/10.3389/fmed.2022.871898

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Quartile: 1

Subject Category: Medicine

Thesis Summary
(English)

Title:

Multidisciplinary digital tools to improve early diagnosis and treatment of respiratory diseases - focus on pulmonary fibrosis

Introduction:

In this era of powerful cloud computing and data generation, it is important to investigate the benefits we can achieve by leveraging these tools to improve health outcomes. In respiratory medicine, the ability to predict and prevent certain lung diseases can be aided by digital data science. Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal diffuse interstitial lung disease (ILD). When IPF is diagnosed in the initial stages, the prevention of inducers of fibrosis progression (exposure to smoke, infections, etc..) and the initiation of anti-fibrotic drugs that slow the progression of fibrosis can modify the natural history of the disease and improve life expectancy. This research discusses a methodology, a model, and the results of a set of digital tools harnessing an analysis of air pollution as a potential risk factor that could be applied to improve predictions and outcomes in IPF and other ILDs.

Hypothesis:

Pollution is a factor in lung disease(1–3). Pollution data has become very detailed and specific in the number of pollutants we can analyse, where they are generated, and density – all on an hourly basis. Mapping this data over a 10-year period would allow the development of predictive models and the identification of geographic areas with a higher probability of developing lung disease, in this case IPF and other fibrosing ILDs.

Objectives:

Main objective

Analyse the prevalence of IPF in the air pollution map averaging exposure over 10 years in Catalonia. Identify, through our digital health tool, the regions with a higher probability of developing the disease to help in the implementation of early detection programs and optimization of resources.

Secondary objectives

- Identify air contaminants present in greater concentration juxtaposed with those areas with a greater prevalence of ILDs.
-Study the relationship between genetic and environmental factors (air quality and known exposures).

Methods:

• Two specific databases were compiled for patients with IPF and other fibrosing ILDs.
• The patient's clinical history has been analysed in detail to determine which common aspects and additional risk factors could be relevant in the diagnosed ILD.
• A tool has been built using the R program and a Google API to trace pollution data from Catalonia for 10 years to map the average exposure to air pollutants, with a special focus on PM2.5 given its greater impact direct on the alveoli and taking into account the pathogenesis of fibrosing ILDs (alveolo-interstitial space).

Main Results:

In the first phase of the work, the results showed that in the analysis of other risk factors for the development of IPF (smoking history, occupational exposure and family aggregation), the distribution of these factors between provinces was similar, especially for smoking history. However, in areas where there was a markedly high level of PM2.5, we found that 40.3% of patients in these areas had no history of smoking and 69% of these patients had no occupational exposure. Interestingly, of the 68 patients (23.5%) without any of the three targeted risk factors, 67 lived in areas with PM2.5 above WHO AQG standards, 40 of them exposed to annual averages of 17 μg /m3 or more. Areas with a higher concentration of PM2.5 have been associated with a higher prevalence of cases with IPF, therefore, these regions deserve special attention to implement rapid detection programs for this disease.

The second phase of work included the analysis of telomere shortening (a risk factor in fibrosing ILD) and the study of its potential relationship with PM2.5 concentrations. The results did not demonstrate a direct correlation between PM2.5 exposure and telomere length. However, this analysis found that shorter telomere length was related to worse disease progression; FVC decreased by 7 for every 1-unit decrease in telomere Z-score over 3 years.

Conclusions:

We cannot establish a direct correlation or causality between PM2.5 and fibrous ILD. However, the results show that there are more cases of IPF where there are high levels of PM2.5, so they would be target regions for assistance programs for rapid detection in pulmonary fibrosis. Furthermore, although the results did not demonstrate a direct correlation between PM2.5 and

telomere shortening in this cohort, the methodology is functional and new modelling tools can be derived for this type of analysis.

Thesis Summary

Català

Títol:

Eines digitals multidisciplinàries per a millorar el diagnòstic precoç i el tractament de les malalties respiratòries - amb focus en la fibrosi pulmonar.

Introducció:

En aquesta era de poderosa computació en núvol i generació de dades, és important investigar els beneficis que podem aconseguir aprofitant aquestes eines per millorar els resultats en Salut. En medicina respiratòria, la capacitat de predir i prevenir determinades malalties pulmonars pot ser ajudada per la ciència de dades digitals. La fibrosi pulmonar idiopàtica (FPI) és una malaltia pulmonar intersticial difusa (MPID) progressiva i letal. Quan la FPI es diagnostica en fases inicials la prevenció d'inductors de progressió de fibrosi (exposició a fums, infeccions, etc..) i l'inici de fàrmacs anti-fibròtics que enlenteixen la progressió de fibrosis poden modificar la historia natural de la malaltia i millorar l'expectativa de vida. Aquesta investigació analitza una metodologia, un model i els resultats d'un conjunt d'eines digitals que es podrien aplicar per millorar les prediccions i els resultats en FPI i altres MPID.

Hipòtesi:

La contaminació és un factor de malaltia pulmonar (1–3). Les dades de contaminació han esdevingut molt detallades i específiques pel que fa al nombre de contaminants, on es generen i la densitat per hora. Mapejar aquestes dades durant un període de 10 anys permetria desenvolupar models predictius e identificar àrees geogràfiques amb major probabilitat de desenvolupar malaltia pulmonar, en aquest cas FPI i altres MPID fibrosants.

Objectius:

Objectiu principal-

Analitzar la prevalença de FPI en el mapa de contaminació-qualitat d'aire durant els darrers 10 anys a Catalunya. Identificar, a través d'eines digitals en Salud, les regions amb major probabilitat de desenvolupar la malaltia ajudaria en la implementació de programes de detecció precoç i optimització de recursos.

Objectius secundaris-

- Identificar quins elements contaminants de l'aire es presenten en més concentració en aquelles àrees amb més prevalença de FPI.
- Estudiar la relació entre els factors genètics i ambientals (qualitat d'aire i exposicions conegudes).

Mètodes:

• Es van compilar dues bases de dades específiques per a pacients amb FPI i altres MPID fibrosants.

• S'ha analitzat en detall la historia clínica del pacient per a determinar quins aspectes comuns i factors de risc addicionals podrien ser rellevants en la MPID diagnosticada.

• S'ha construït una eina utilitzant el programa R i una API de Google per traçar dades de contaminació de Catalunya durant 10 anys per a cartografiar l'exposició mitjana als contaminants aeris, realitzant un especial enfoc sobre PM2.5 donat el seu impacte més directe sobre els alvèols i tenint en compte la patogènia de les MPID fibrosants (alveolo-intersticial).

• S'han provat les capacitats ampliades de la metodologia digital afegint un paràmetre addicional (longitud dels telòmers) que s'ha demostrat que està directament relacionat amb l'exposició a la contaminació de l'aire i amb el desenvolupament de la FPI.

Resultats principals:

En la primera fase del treball, els resultats van demostrar que en l'anàlisi d'altres factors de risc per al desenvolupament de la FPI (historial de tabaquisme, exposició ocupacional i agregació familiar), la distribució d'aquests factors entre províncies era similar, especialment per als antecedents de tabaquisme. Tanmateix, a les zones on hi havia un nivell notablement elevat de PM2.5, vam trobar que el 40,3% dels pacients d'aquestes zones no tenien antecedents de tabaquisme i el 69% d'aquests pacients no tenien exposició laboral. Curiosament, dels 68 pacients (23,5%) sense cap dels tres factors de risc dirigits, 67 vivien en zones amb PM2,5 per sobre de les normes AQG de l'OMS, 40 d'ells exposats a mitjanes anuals de 17 μg/m3 o més. Les àrees amb major concentració de PM2.5 s'han associat amb major prevalença de casos amb FPI, per tant, aquestes regions mereixerien especial atenció per a implantar programes de detecció ràpida en aquesta malaltia.

La segona fase de treball va incloure l'anàlisi de l'escurçament dels telòmers (factor de risc en MPID fibrosant) i l'estudi de la seva potencial relació amb les concentracions de PM2.5. Els resultats no van demostrar una correlació directa entre l'exposició a PM2.5 i la longitud dels telòmers. Tanmateix, a través d'aquesta anàlisi es va trobar que la longitud dels telòmers més curta estava relacionada amb una pitjor progressió de la malaltia; La FVC va disminuir en 7 per cada disminució d'1 unitat de la Z-score del telòmer durant 3 anys.

Conclusions:

No podem establir una correlació directa o causalitat entre PM2,5 i MPID fibrosants. Tanmateix, els resultats mostren que hi ha més casos de FPI on hi ha nivells elevats de PM2.5, pel que serien regions diana per programes assistencials de detecció ràpida en fibrosi pulmonar. A més, tot i que els resultats no van demostrar una correlació directa entre PM2.5 i l'escurçament dels telòmers en aquesta cohort, la metodologia és funcional i es poden derivar noves eines de modelització per aquest tipus d'anàlisi.

Multidisciplinary digital tools for improving early diagnosis and treatment of respiratory disease – focus on pulmonary fibrosis

Introduction

With the proliferation of digital technology in the 21st century we, as a society, are generating terabytes of data on a regular basis. We generate data in our transportation patterns, our consumer habits, and what we read online. The World Economic Forum stated that hospitals can produce 50 petabytes of data per year (4). In the field of medicine, the image this usually conjures is one of electronic health records (EHRs), DICOM images for radiology, or perhaps databanks of genomic sequence information. In the last decade, with the advent of connected devices, we can also now include oximetry and walking gait data from smartphones, on-demand readings from continuous glucose monitors, and numerous other personal devices which are taking increasingly more accurate readings for medical purposes. This body of work examines the addition of another realm of data – air pollution - and undertakes to demonstrate methodologies for utilizing this rich and relatively untapped wealth of digital information with the aim improving outcomes in respiratory disease.

When Sir Richard Doll first utilised statistics in the 1950s to demonstrate that lung cancer was associated with smoking, it was a brand-new idea (5). It was thought at that time that perhaps inhaled residue from burning coal was a factor, or occupational exposures. By analysing the additional factor of smoking habits, it was determined, indeed proven, over several years that this greatly increased one's chances of developing lung cancer. Therefore, it is important to keep investigating new and perhaps not obvious data sources, as they can lead to new insights for what may be at the root of disease development.

New Digital Data: PM2.5

In this work, pollution data was the source for new insights into impact on respiratory disease. The Executive Summary of the 2021 WHO Global Air Quality Guidelines states, “The global burden of disease associated with air pollution exposure exacts a massive toll on human health worldwide: exposure to air pollution is estimated to cause millions of deaths and lost years of healthy life annually. The burden of disease attributable to air pollution is now estimated to be on a par with other major global health risks such as unhealthy diet and tobacco smoking, and air pollution is now recognized as the single biggest environmental threat to human health.” Perhaps most obviously, pollution and airway disease are increasingly shown to be linked(6–9), and is a recognised factor in increased risk for asthma (10–13); however, it is also associated with more than 500,000 lung cancer deaths, over 1 million COPD deaths, and could account for 19% of cardiovascular mortalities (14–18). In addition, there is a growing body of evidence that air pollution should be considered a risk factor for interstitial lung disease(19–23), much like it is for COPD and asthma(24–26).

Given the documented impact of pollution on lung disease, it was determined to investigate this potential risk factor, and to focus on one contaminant in particular: PM2.5. There is a body of research already demonstrating the negative effects of PM2.5. Increased levels of PM2.5 correlates with an increase in emergency room visits for respiratory issues (27), and one recent study showed that PM2.5 induced fibrosis in 12 weeks in mice that were exposed to PM2.5 at levels of ~64 $\mu g/m^3$(28), which is more than twice the level of exposure to PM2.5 that many citizens experience in certain areas of Barcelona and other large cities.

Therefore, this work cross-analysed traditional risk factors of fibrosing interstitial lung disease with new digital data and geolocation of PM2.5. Combined, this would create a tool to understand which parts of the patient population is most at risk. The second phase incorporated the additional risk factor of shortened telomeres, which has been shown to correlate with development of IPF (29,30).

Key to unravelling the relationship between lung disease, telomeres, and pollution, is the theory described by Martens and Nawrot(31), which proposes that air pollution - specifically particulate matter – damages DNA replication resulting in shorter telomeres, which leads to mitochondrial dysfunction and subsequently, disease.

The logic behind this theory rests on evidence from Sahin et al.(32) wherein telomeres which are no longer replicating properly activate the p53 gene, which represses peroxisome proliferator-activated receptor gamma, coactivator 1 alpha and beta (PGC-1α and PGC-1β). These two proteins are transcriptional coactivators which have been closely studied as activators and suppressors of mitochondrial function, associated with oxidative metabolism, the dysfunction of which is implicated in diabetes and cardiac disease(33,34). The theory presented by Sahin et al. further proposes that an initiator of this cascade of events, PM2.5, induces inflammation and oxidative stress on mitochondrial DNA by way of reactive oxygen species (ROS). These highly reactive molecules are not completely understood; ROS refers to an extensive variety of oxidant molecules including peroxides and superoxides, which are byproducts of the metabolism of oxygen (O_2), and the specific reactions need to be further studied(35). However, it has been suggested that oxidative stress induced by PM derives from the generation of ROS through interactions of soluble metals like iron on the PM surface, which produces reactive hydroxyl radicals(36) and thereby mitochondrial dysfunction including

PGC-1α and PGC-1β. The effect of ROS on the telomeres is proposed to be through this same oxidative stress, damaging the single strand portions of telomeres, which are already vulnerable due to the end-replication problem(37,38).

Interstitial Lung Diseases

Interstitial lung diseases (ILDs) are a group of approximately 300 diseases of known and unknown aetiology, the most common of which is IPF(39–41). Certain ILDs present with fibrosis at a certain stage, and a percentage of these cases will develop a debilitating progressive fibrosis marked by loss of lung function and premature death(42–45). Increased knowledge about the genesis of this progressive fibrosis and how to detect development before it becomes an impediment to quality of life would benefit not only thousands of patients but also healthcare systems, especially where recourses are limited.

Incidence of ILDs is increasing globally(46) and air-borne pollution has been found to have adverse impact on clinical outcomes and lung function in patients with idiopathic pulmonary fibrosis (IPF)(47). In addition, from 1990 until 2017 there is a documented increase of 86% in years of life lost (YLL) due to ILDs(48). This can be attributable in part to better diagnosis by multidisciplinary teams, however the upward trend is present, with a 39.8% increase in chronic respiratory disease globally compared with two decades earlier(48).

Prevalence and pathogenesis of fibrotic ILDs

There is not yet conclusive evidence that pollution contributes to the development of IPF or the other ILDs, and myriad factors contribute to this uncertainty. For one thing, ILDs are not easy to diagnose, the diagnosis and classification methodologies as well as inconsistencies in

electronic patient records(49) vary from country to country, as do the treatment protocols, and the expertise of multidisciplinary teams should be used(50–53). Therefore, incidence and prevalence for ILDs vary widely according to region but fall within 1.0 to 31.5 per 100,000(54–57). Incidence for IPF however has been estimated at 3.3 to 45.1 per 100,000 depending on region(55,58)

The causes and sequence of events that lead to development of an ILD such as IPF are still unclear. Detailed study over the last 20 year has generated evidence indicating that IPF is an epithelial cell disorder resulting from an interaction of genetic, environmental, aging cells, and epi-genetic reprogramming(59–63). The degree of contribution of each of these factors is not completely understood, however these epithelial cells lining the alveoli seem subject to a "perfect storm" in the combination of these factors: susceptibility caused by genetics and/or aging, results in epithelial cell injury possibly due to foreign particles being inhaled (smoke from tobacco, air pollution, occupational exposure, etc.), and over time this leads to an abnormal repair mechanism which becomes subsequently becomes fibrosis.

This would be a slow process and difficult to detect. Lung epithelial cells interact with molecules in the ambient air ceaselessly throughout life. The mucus membrane covering these cells traps inhaled particles that could be detrimental and ferries them away with ciliary movements and inducing cough(64). Excessive mucus as well as deficiencies in the system lead to infections as well as build-up of unwanted material in both the upper and lower respiratory tract(65).

The key to alterations in the way the mucus membrane operates is a nucleotide polymorphism within the MUC5B gene polymorphism, the presence of which has been shown to indicate a

7-fold increase in probability for development of IPF(66). However, no clear effect on disease progression or patient phenotype has been identified with this gene polymorphism. The variant in the MUC5B gene increases mucin production while simultaneously impeding the cilia from ferrying away toxins effectively, which could be related with disease pathogenesis (67,68).

Aging and telomeres are another two factors in the accumulative "storm." Telomeres are nucleotide sequences forming the rounded tip of each arm of a chromosome, serving to maintain the integrity of the structure(69,70). Humans have relatively short telomeres compared to other mammals such as mice, and as the cells multiply over time, the telomeres grow yet shorter; this is part of the natural process of cellular aging. However, accelerated or severe shortening of telomeres occurs in some people and an association has been established between more advanced telomere shortening and patients who have developed IPF(29). Telomere dysfunction is also associated with cell senescence and genetic instability(69), which reaffirms the possible pathogenicity of some gene mutations. Several telomerase related gene (TRG) mutations, such as DKC1, TERT, TERC, RTEL1, TIF1, and PARN, have been identified to increase susceptibility and progression in IPF and other fibrotic ILDs. In fact, TRG mutations and severe telomere shortening have been widely associated with poor prognosis, independently of the type of fibrotic ILD (30). These gene mutations may be found in up to 25% of familial pulmonary fibrotic (FPF) patients and in 12% of sporadic IPF (29). The recognition of common frequent clinical features in these patients has optimized the telomere dysfunction analyses in recent years.

Pollution and PM2.5

Air-borne pollution is not just one substance, it is made up of a variety of residues and particles, and the composition varies from region to region depending on traffic modalities. Automobiles produce brake mechanism residue and rubber particle suspension from tires which contributes to particulate matter (PM) in addition to carbon monoxide (CO) from combustion and diesel engines. Ships and airplanes produce CO, CO_2 nitrogen oxides (NO_X), sulphur oxides (SO_X), unburned hydrocarbons (UHC), as well as particulate matter (PM) of all sizes plus a group of toxins called volatile organic compounds (VOCs) such as benzene and formaldehyde(71,72); in 1993 aircraft produced approximately 159 million kg of VOCs and NO_X(73). A combination of NOX, CO, and VOCs lead to ground-layer ozone formation(72), increased level of which have been shown to impair lung function and cause inflammation of lung tissue(74,75).

Temperatures, which cause lifting or settling of particles in addition to wind, also affect pollution presence, as does and proximity to geographical features such as deserts and extensive plains. In the area of north-eastern Spain where this thesis work was performed, there are specific variations in regional pollution production where agricultural areas are dominant as opposed to where there are shipping ports. During certain times of the year, this region of Spain sees a great deal of airborne dust carried from the Sahara(76). Research from 2017 demonstrated that on days dust that intrusions from the Sahara were recorded in Spain there was an association with mortality in those areas(77), noting that this dust may carry biological materials and microorganisms.

All these contributing sources produce components of PM, measured in categories from 1-10 micrometres (μm). PM is therefore not one substance, but a combination of a variety of substances depending on region, including mineral dust, sea salt, sulphates, nitrates, black

carbon, and organic carbon, among other elements(78,79). Due to the makeup of the contributing factors to the pollution in this region, and given the data sets available, it was decided to analyse PM with an aerodynamic diameter of ≤ 2.5 µm, known more succinctly as PM2.5.

PM2.5 is smaller than PM10, and due to this miniscule size can reach the distal airways, invading the bronchioles and the alveoli (see Fig 1).

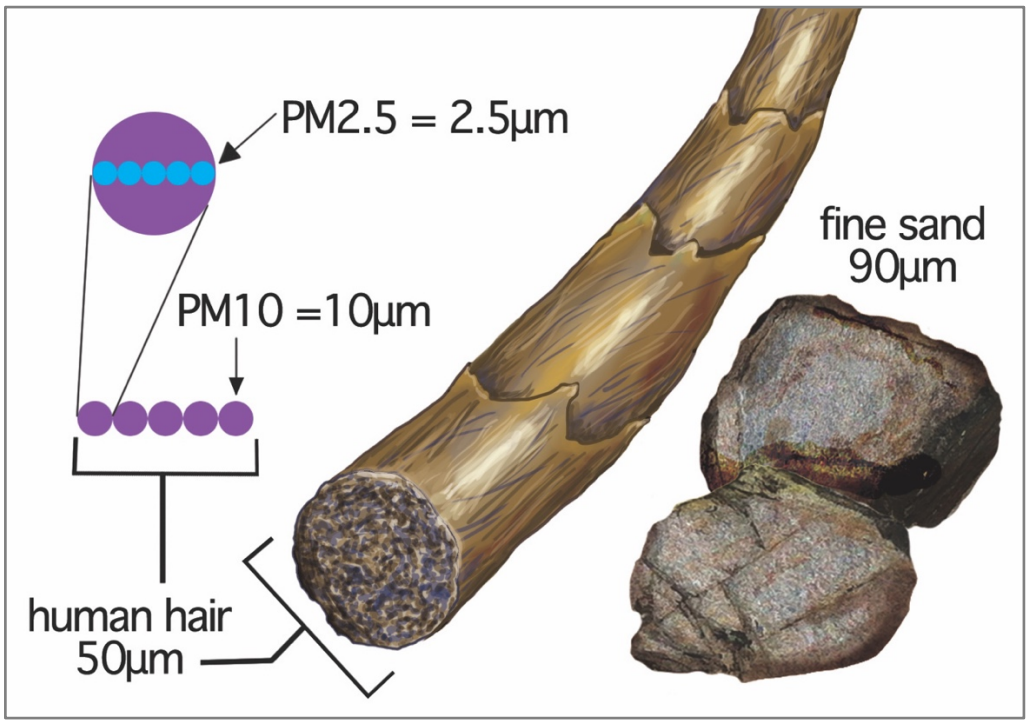

Figure 1. Illustration of relative size of PM2.5

PM2.5 has been implicated in development of respiratory disease(80–82) and efforts by governments and health agencies demonstrate awareness of the need to reduce PM generation(83)

The body of evidence illustrating the relationship between PM2.5 and ILDs is growing. PM2.5 has been shown to accelerate functional decline in patients with IPF(84), and in lower FVC(85), though correlations have not yet been established.

Hypothesis

Adding data analytics to derive insights on prevention and prognosis can improve patient outcomes. Recent examples of this are the use of artificial intelligence (AI) in breast cancer detection(86), and machine learning (ML) to predict mortality for sepsis-associated encephalopathy(87), which allows physicians to triage the most at-risk patients.

The main hypothesis for this work is that by adding pollution data analytics to the evaluation of risk factors for developing fibrotic ILD, the prediction of those areas with a higher number of patients could be possible, and therefore, it would be considered a screening tool for early diagnosis and treatment.

Objectives

Main objective:

The primary objective of this work was to build a framework of some first steps that would illustrate for ILD teams one approach toward the early detection of IPF and predicting progression of fibrosing ILDs utilising digital health tools.

The Bellvitge University Hospital ILD team has for more than a decade implemented an expert and multidisciplinary approach for screening, diagnosis, and treatment of ILDs in the region of Catalonia; this expertise can be built upon and guided toward the most effective methods for respiratory disease management to improve equity and impact of existing health resources.

Secondary objectives:

1. To identify the real prevalence of IPF, a rare disease which is often misdiagnosed and underreported. Depending on the system used to code for IPF, it has been seen in our research that codes are not always accurately assigned, or that due to information missing for the medical coder, a more general term of PF is often assigned.
2. To evaluate the relationship of incidence of ILDs, genetic factors, and potential environmental factors.

Materials, Methods, and Results: PDFs of Articles

Article 1

Mapping IPF helps identify geographic regions at higher risk for disease development and potential triggers

Objective of the study:

By mapping existing cases of IPF and analysing the pollution exposure for those cases, the objective was to establish PM2.5 as a potential risk factor for early detection of IPF.

Catalan Summary:

Antecedents i objectiu: la relació entre el desenvolupament de la FPI i els factors ambientals no s'ha dilucidat completament. L'anàlisi de regions geogràfiques de casos de FPI podria ajudar a identificar aquelles àrees amb una agregació més alta i investigar els possibles desencadenants. Presentem la hipòtesi que l'anàlisi creuada de la ubicació dels casos d'FPI i les àrees de concentració de contaminació atmosfèrica constantment elevada podria conduir al reconeixement dels factors de risc ambiental per al desenvolupament de l'FPI.

Mètodes: En aquest estudi retrospectiu s'han analitzat dades epidemiològiques i clíniques de 503 pacients registrats a l'Observatori IPF.cat des de gener de 2017 fins a juny de 2019. Es van representar gràficament els casos d'incidència i prevalença de FPI de la Comunitat Valenciana a partir de la seva adreça postal. Hem generat mapes del contaminant atmosfèric PM2,5 més rellevant dels darrers 10 anys utilitzant dades del sistema de previsió de la qualitat de l'aire CALIOPE i dades d'observació.

Resultats: La prevalença de l'FPI va variar entre les províncies; de 8,1 casos per 100.000 habitants a Barcelona a 2,0 casos per 100.000 a Girona. La ràtio de FPI va ser més alta en algunes àrees. La cartografia dels nivells de PM2,5 va il·lustrar que certes àrees amb més

indústria, trànsit i transport marítim van mantenir concentracions de PM2,5 marcadament més altes. La majoria d'aquestes ubicacions es correlacionaven amb una agregació més alta de casos de FPI. En comparació amb altres factors de risc, l'exposició a PM2,5 va ser la més freqüent.

Conclusió: en aquest estudi retrospectiu, la prevalença de FPI és més alta a les zones de concentració elevada de PM2,5. S'han de fer estudis prospectius amb mapes de contaminació dirigits a geografies específiques per compilar un perfil més ampli dels factors ambientals implicats en el desenvolupament de la fibrosi pulmonar.

Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

Mapping IPF helps identify geographic regions at higher risk for disease development and potential triggers

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ABSTRACT

Background and objective: **The relationship between IPF development and environmental factors has not been completely elucidated. Analysing geographic regions of idiopathic pulmonary fibrosis (IPF) cases could help identify those areas with higher aggregation and investigate potential triggers. We hypothesize that cross-analysing location of IPF cases and areas of consistently high air pollution concentration could lead to recognition of environmental risk factors for IPF development.**

Methods: **This retrospective study analysed epidemiological and clinical data from 503 patients registered in the Observatory IPF.cat from January 2017 to June 2019. Incident and prevalent IPF cases from the Catalan region of Spain were graphed based on their postal address. We generated maps of the most relevant air pollutant PM2.5 from the last 10 years using data from the CALIOPE air quality forecast system and observational data.**

Results: **In 2018, the prevalence of IPF differed across provinces; from 8.1 cases per 100 000 habitants in Barcelona to 2.0 cases per 100 000 in Girona. The ratio of IPF was higher in some areas. Mapping PM2.5 levels illustrated that certain areas with more industry, traffic and shipping maintained markedly higher PM2.5 concentrations. Most of these locations correlated with**

SUMMARY AT A GLANCE

This study identifies geographic regions of notable air pollution, juxtaposed over locations with higher prevalence of idiopathic pulmonary fibrosis (IPF). Certain areas with elevated air pollutants may be deserving greater analysis for screening of IPF and optimizing early identification. Prospective studies are required for evaluating air pollution as an IPF risk factor.

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higher aggregation of IPF cases. Compared with other risk factors, PM2.5 exposure was the most frequent.
Conclusion: **In this retrospective study, prevalence of IPF is higher in areas of elevated PM2.5 concentration. Prospective studies with targeted pollution mapping need to be done in specific geographies to compile a broader profile of environmental factors involved in the development of pulmonary fibrosis.**

Key words: air pollution, early diagnosis, environmental risk factor, geographic region, idiopathic pulmonary fibrosis.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is considered a rare disease, with an estimated prevalence of 13–20 patients in 100 000 habitants[1] and an increasing incidence.[2] Due to the rarity and complexity of the disease, prevalence varies notably depending on the source of data and the confidence of diagnosis. IPF patients are on average diagnosed 24 months after the presentation of symptoms due to complexity in identifying the disease and a tendency for misdiagnosis.[3] The earlier IPF is identified, the better the prognosis of the patient, so identifying potential cases of IPF before symptoms are severe is critical.[4] Even though the cause remains unknown, some IPF risk factors have been identified.[3] Therefore, a better understanding of environmental risk factors could help optimize early detection.

IPF develops after repeated injury to the lung epithelium. Due to several mechanisms under study, the repair process for injury leads to abnormal scarring of the lung tissue which increases over time.[5] Experimental studies have suggested that air pollutants induce endothelial cell damage[6] and airway inflammation.[7] Another study demonstrated that environmental contaminants are associated with an increase in IPF incidence by 7.9–8.4%.[8] Previous studies showed a correlation between air pollution and other respiratory diseases such as chronic obstructive pulmonary disease[9,10] and asthma.[11] A recent study questioned whether air pollution could be associated with the development of pulmonary fibrosis[12] and evidence suggests that ambient pollution exposure also leads to exacerbations of the disease[13] and lower lung function.[14] Among the different air pollutants, evidence indicates that fine particulate matter (PM) of 2.5 μm or less in diameter (PM2.5) is particularly harmful as these particles reach deep into the lung and corrode alveoli, exacerbating respiratory disease.[15] Combined, it indicates that long-term exposure to specific pollutants such as PM2.5 may be involved in the development of IPF.

Mapping geographic regions with IPF helps identify specific areas where the prevalence is higher and therefore, could contribute towards improving the efficiency of the early diagnosis and the identification of potential environmental risk factors.

METHODS

Project background

A primary source of data was the Observatory IPF.cat, the most comprehensive registry of IPF patients in Catalonia (population 7.6 million), the most north-eastern of the 17 regions in Spain, abutting the Mediterranean and the Pyrenees. Since 2008, the region has collaborated through a cross-disciplinary network (CRAMPID group) of interstitial lung disease (ILD) practitioners, to share expertise and insight on unique cases as part of the Catalan Society for Pulmonology (SOCAP). Twenty-two hospitals across this network contributed to document features of IPF patients in the region.

Patient data

Included IPF patients were diagnosed or reviewed by a centralized expert ILD multidisciplinary committee. All patients provided written informed consent and the study was approved by the Institutional Ethics Committee (CEIC, ref. PR307/16). Data management followed the regulatory guidelines from the EU 2016/679 statement and Declaration of Helsinki.[16] A site visit to each hospital was performed to ensure data collected were accurate and current. Patient postal codes were recorded, along with factors such as age, occupational history, exposure to industrial toxins, smoking history and familial history of lung disease. Environmental factors were already under consideration for investigation using the systems biology approach to understand IPF pathology[17] and the potential role of air pollutants on the variability of IPF incidence and prevalence.

From the 503 patients registered in the Observatory IPF.cat, 379 were mapped in this study. Of the 126 drop-out cases, there were 2 cases wherein the diagnosis was not consistent and 124 contained only partial clinical data. The project defined location of patients by postal code, the area where it is estimated the majority of outdoor activity occurred.[18] Postal code population density ranged from 20 000 people per km^2 in cities to 1000 per km^2 in rural areas. Postal codes smaller than 4 km^2 were grouped by Global Positioning System (GPS) coordinates to indicate PM2.5 exposure level for those areas.

Background on air pollution data

The World Health Organization (*WHO*) *Air Quality Guidelines* (*AQG*)[19] provide acceptable threshold measurements for concentration of air pollutants that pose a threat to the health of populations. The WHO AQG set maximum values for PM2.5 concentration of 10 and 25 $\mu g/m^3$ for the annual and 1-day means, respectively.

It is worth noting that PM is composed of different chemical components such as mineral dust, sea salt, sulphates, nitrates, black carbon and organic carbon, among other elements.[20] Using the PM2.5 label refers only to mass and size, neglecting the chemical composition.

Air pollution data

The CALIOPE modelling system[21–24] is a state-of-the-art modelling system, specially developed with spatial (4 km × 4 km) and temporal resolution (1 h) to forecast air quality across Spain taking into account both anthropogenic and natural pollution. CALIOPE's

forecast includes surface concentration of gaseous and aerosol pollutants (i.e. O_3, NO_2, CO, SO_2, PM10, PM2.5 and C_6H_6). The system consists of the HERMESv2.0 emission model,[25] the WRF-ARWv3.6 meteorological model,[26] the CMAQ v5.0.2 chemical transport model[27] and the BSC-DREAM8bv2 mineral dust model.[28] The CALIOPE system has been evaluated for epidemiological research,[22] and has provided operational air quality forecasts since 2006.

To provide the most accurate estimate map of PM2.5 concentration, a combination of the CALIOPE model results and actual observations through data assimilation was used; techniques that outperform conventional frameworks, even when demonstrating inter-urban exposure gradients.[29] In this study, we processed the CALIOPE PM2.5 predictions following calibration factors already described,[24] and then applied a Barnes-type iterative objective analyses scheme[30] to assimilate PM2.5 observations from the EIONET network across Catalonia. This provided an estimate of exposure over several previous years, a calculation shown to be as accurate as data produced for current yearly exposures. The PM2.5 concentration time series (2001–2017) plot indicates that PM2.5 concentrations have remained almost constant in this region since 2009 (Fig. 1). The data from 2015 were selected for the PM2.5 map, over which was superimposed the Observatory IPF.cat location data (Fig. 2).

Geographic map generation

The PM2.5 results of the CALIOPE system for 2015 were plotted using R (version 3.6.0) and the Google Map API (Amphitheatre Pkwy, Mountain View, CA, USA). After analysing and graphing patients by postal code, these points could be translated into latitudinal and longitudinal information to be plotted and juxtaposed over the PM2.5 data.

RESULTS

Prevalence and location of IPF population

We sought to clarify that higher prevalence of the disease in certain areas was not simply due to greater population numbers. After calculating the official

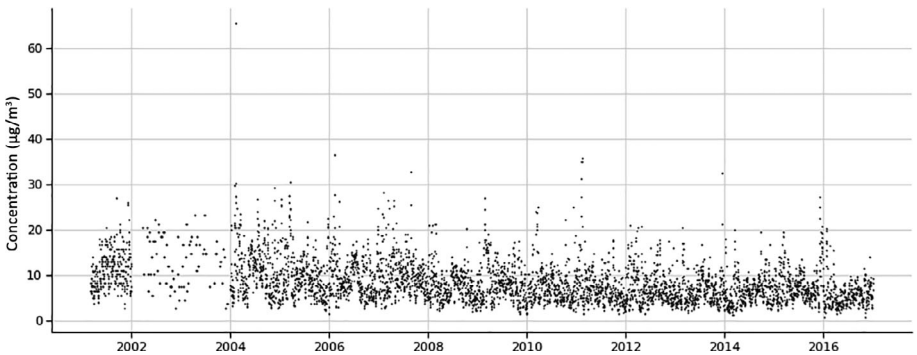

Figure 1 Time series (2001–2017) of the mean daily PM2.5 (particulate matter of 2.5 µm or less in diameter) concentrations (µg/m^3) at the stations over Catalonia: Cabo de Creus (ES0010R), Montseny (ES1778R) and Els Torms (ES0014R).

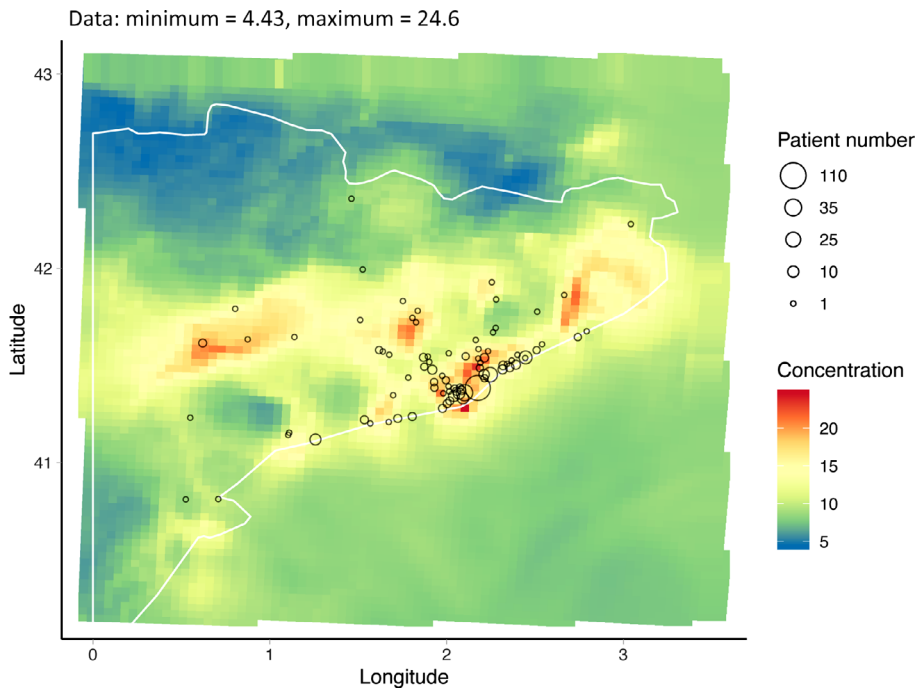

Figure 2 Region of Catalonia. Annual mean concentration of PM2.5 (particulate matter of 2.5 µm or less in diameter) in 2015 (units in µg/m^3. Data: minimum = 4.43, maximum = 24.6).

population statistics from 2018, the province of Barcelona showed a higher prevalence (8.1 in 100 000) when compared with the other three provinces (Table 1). Figures are based on real prevalence, not estimated, considering real data from participating ILD centres were used.

Examining the maps (Fig. 2), the distribution of patients varied; clear aggregation was found in Barcelona with a lower prevalence in postal codes near the hills in the eastern side of the city (Tibidabo). Two other areas with patient aggregation (Martorell and Vallès) are surrounded by industry. In the other three provinces, patient distribution followed a pattern of aggregation for rural areas, with areas where no patient was identified. In the southern province (Tarragona), most cases were located within city limits and near a big petrochemical zone. Statistics on population were derived directly from the published online data of the Catalonian Institute of Statistics: (https://www.idescat.cat/pub/?id=aec&n=246&lang=en).

Concentration of air pollutants

The map is an illustration of PM2.5 concentrations (Fig. 2). The white line delineates the border of

Table 1 Population of Catalonia, total and by province, and prevalence of IPF

Province	Population in 2018	Number of patients	Prevalence
Barcelona	5 571 822	452	8.1 in 100 000
Tarragona	797 128	23	2.9 in 100 000
Lleida	427 718	11	2.6 in 100 000
Girona	747 157	15	2.0 in 100 000
Total	7 543 825	501	5.0 in 100 000

Total number of patients registered in the Observatory IPF.cat = 503, unconfirmed diagnosis = 2.
IPF, idiopathic pulmonary fibrosis.

Table 2 Areas with highest cases of IPF; colour indicates the average exposure to PM2.5 over 1 year

Post code	City	No. of patients	Concentration	Colour	Postal code population density × km^2
08028	Barcelona	12	19 501 301		20 657
08820	El Prat de Llobregat	11	18 044 706		1940
08913	Barcelona	11	11 820 154		17 897
08940	Cornellá de Llobregat	11	18 044 706		12 325
08016	Barcelona	10	19 501 301		20 922
08830	Sant Boi De Llobregat	10	17 455 006		20 347
08902	L'Hospitalet de Llobregat	10	20 041 073		20 542
08042	Barcelona	8	19 501 301		19 187
08304	Mataró	8	14 946 873		2763
08906	L'Hospitalet de Llobregat	8	20 041 073		18 892
08030	Barcelona	6	19 501 301		20 347
08303	Mataró	6	14 946 873		9997
08011	Barcelona	5	19 501 301		19 255
08027	Barcelona	5	19 501 301		20 350
08029	Barcelona	5	19 501 301		20 781
08031	Barcelona	5	19 501 301		19 630
08320	El Masnou	5	15 010 112		4914
08340	Vilassar de Mar	5	13 532 051		4485
08760	Martorell	5	14 908 229		2058
08901	L'Hospitalet de Llobregat	5	20 041 073		20 422
08905	L'Hospitalet de Llobregat	5	20 041 073		21 432
08004	Barcelona	4	19 501 301		21 555
08019	Barcelona	4	19 501 301		21 424
08020	Barcelona	4	19 501 301		21 236
08100	Mollet de Vallès	4	1 908 028		6255
08302	Mataró	4	2 187 719		11 270
08329	Teià	4	14 102 392		942

IPF, idiopathic pulmonary fibrosis; PM2.5, particulate matter of 2.5 μm or less in diameter.

Catalonia; to the north are the Pyrenees and to the southeast the Mediterranean Sea.

The map makes clear where PM2.5 concentrations in the region of Catalonia were well above the WHO AQG. Using a roadmap, one can identify the thread of red winding its way north is the busiest highway in the region. The orange area furthest west is an agricultural region, home to a booming agriculture and pork industry where dust and chemically formed particles accumulate due to ploughing hectares of land, wind and spraying of chemicals. At every point coloured with yellow, orange or red, the PM2.5 concentrations for the year 2015 were above the annual WHO AQG of 10 μg/m^3. The zones coloured red reached more than double that concentration. The highest PM2.5 concentrations of 20–24.6 μg/m^3 are located precisely over areas of traffic congestion, industrial areas (Martorell), the airport (El Prat de Llobregat) and the ports of Barcelona (L'Hospitalet de Llobregat), not where population is highest.

We ran, in addition to these average annual concentration exposure maps, an analysis of the percentile exposures for PM2.5. Using the WHO AQG value for daily maximum of PM2.5: 25 μg/m^3, we plotted on an hourly basis where the annual percentile of 90.4 (and resulting concentration exceeded more than 35 days per year) occurs. The map is nearly identical to the annual mean (Fig. S1 in Supplementary Information).

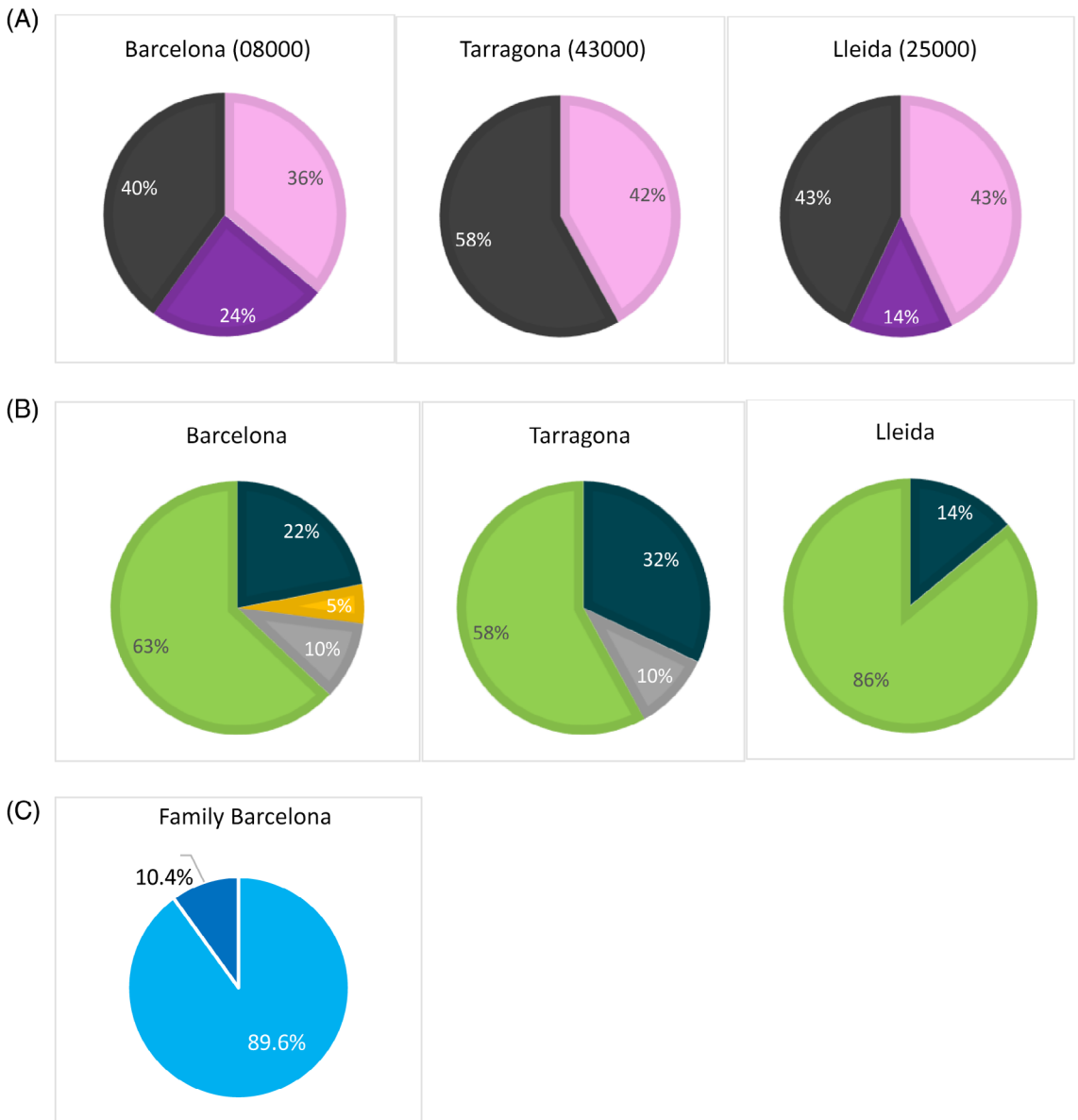

Figure 3 Patient exposure by province. (A) Non-smokers (pink), smokers of <20 pack-years (purple) and smokers of >20 pack-years (dark grey). (B) Occupational exposure: no exposure (green); inorganic dust such as iron, fibre glass and stone dust (blue); organic dust such as from paper or sausage factories (yellow); and chemical inhalation such as paint fumes and caustic cleaning supplies (grey). (C) Familial risk factor, which is present in the data for 10.4% of patients in the province of Barcelona. The region of Girona is not depicted in any chart as the database contained only three patients with the data required.

The next consideration to address was that of population density. We graphed each of the 141 postal codes according to the density of population, cross-referenced with annual PM2.5 exposure (Fig. S2 in Supplementary Information). The areas of highest population density do not coincide precisely with the highest number of patients. Table 2 shows the 27 postal codes with the highest number of IPF cases, with average PM2.5 exposure over 1 year. All 141 postcodes can be seen in Table S1 (Supplementary Information).

PM2.5 exposure: An additional IPF risk factor

As noted previously, other risk factors for IPF development (smoking history, occupational exposure and family aggregation) were analysed. Distribution for these factors across provinces was similar, especially for smoking history (Fig. 3A). Inorganic dust exposure was lower in Lleida compared with Tarragona and Barcelona (Fig. 3B). However, high-level PM2.5 areas revealed 40.3% of patients had no smoking history and 69% of patients had no occupational exposure. Family aggregation data were present in 10.4% of cases in Barcelona province (Fig. 3C). Interestingly, of the 68 patients (23.5%) with none of these three risk factors, 67 were living in areas with PM2.5 above WHO AQG norms, 40 of them exposed to annual means of 17 μg/m^3 or higher (Table S1 in Supplementary Information). From collected patient data, we tabulated exposure as binary, using the province of Barcelona for which there was a higher number of cases (Table 1). PM2.5 exposure was the most prevalent risk factor in this area (Table 3). We then modelled the risk factors of smoking, occupational exposure, familial aggregation and environmental exposure (<12 μg/m^3) in a mosaic plot (Fig. 4). These risk factors cannot be assumed to be independent from each other when the high environmental PM2.5 exposure is present (P = 0.070246) (Fig. 4).

Table 3 Barcelona province risk factors

	All	*n*
	n = 260	
Smoker		260
No	92 (35.4%)	
Yes	168 (64.6%)	
Occupational		260
No	165 (63.5%)	
Yes	95 (36.5%)	
Family		260
No	233 (89.6%)	
Yes	27 (10.4%)	
Environmental		260
No	31 (11.9%)	
Yes	229 (88.1%)	

DISCUSSION

As a hypothesis-generating study, finding coincidences between patient aggregation in geographic regions and PM2.5 concentration after superposing patient location and pollution concentration maps from the last decade suggest environmental factors may be considered for future research on disease aetiopathogenesis. This preliminary finding may also be useful to better anticipate resources and requirements to diagnosis and treatment of the disease. Additional investigation could include a control in other respiratory disease areas.

IPF incidence and prevalence are variable.[4] Due to the complexity of this rare disease, most studies are only able to estimate the numbers of patients in a region or country[1,2,4]. In our study, although there are more cases in areas with higher density of population, patient aggregation varied and did not depend on density. Previous work associated the incidence of IPF with air pollution in the north of Italy.[8] The potential bias for greater IPF identification in reference centres for

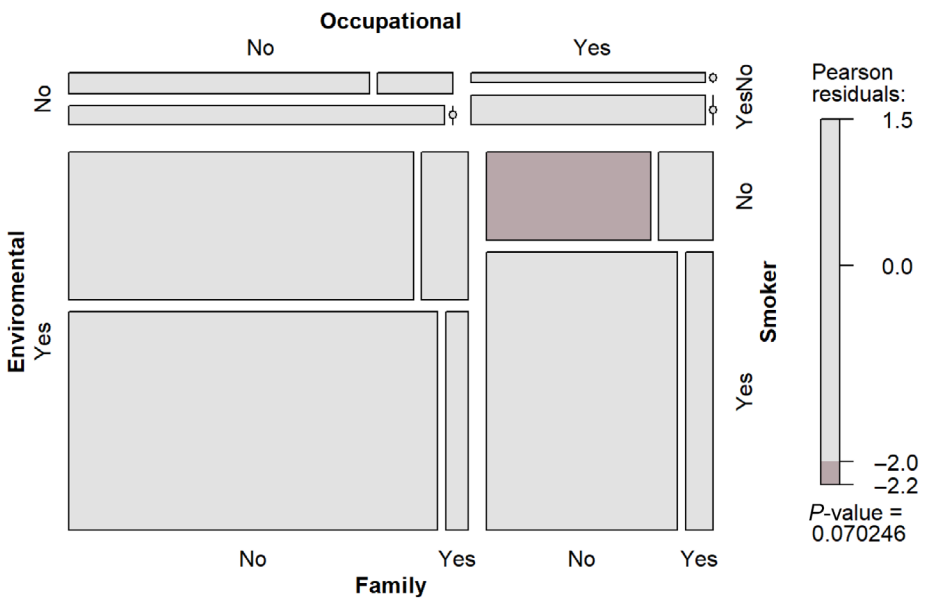

Figure 4 Mosaic plot of exposure for patients in Barcelona province. The size of the areas is proportional to the percentage of cases in that combination of variables (*n* = 260).

the disease is possible; however, bias should be reduced through ILD networks that share knowledge within the region. Naturally, ILD expert teams arise in areas with a greater number of visited cases; therefore, it is difficult to determine if the differences in ILD expert resources among regions influence IPF prevalence or if a higher demand of ILD patients influence the need for expert teams. Other risk factors could also influence IPF prevalence, including different occupational inorganic exposures, family aggregation and smoking habits.[4] A special pattern of clustering for IPF cases did not emerge. Interestingly, almost one-third of patients in our study had none of these recognized risk factors, whereas a majority were living in areas with high PM2.5 concentration.

Among the different air pollutants regulated by the 2008/50/EC Directive on Ambient Air Quality and Cleaner Air for Europe,[19] PM has been associated with adverse respiratory outcomes.[7,8,13,14,31] PM2.5 is a mixture of fine substances (metals, sand, exhaust, etc.), which may damage the respiratory system through cell injury, oxidative stress and inflammatory response.[31] Moreover, long- and short-term exposure to PM2.5 has been correlated with abnormal telomere length, so these particles could also impact abnormal tissue repair.[32] On the other hand, an increase in IPF mortality risk has been reported in those cases with long-term cumulative concentrations of PM10 and PM2.5.[33] Furthermore, PM2.5 exposure has been associated with a higher use of oxygen in the 6-min walk test (6MWT) and lower forced vital capacity (FVC) in IPF patients[14,34]. A recent histological study from the Finnish IPF Registry has found that lung samples from those regions with higher air PM levels had significant increased PM scores in lungs than those with less PM exposure.[35] Although the study did not include a normal control group to anticipate a potential role of these particles in disease development, the Finnish data clearly show that the amount of the different fine particles in IPF lungs depends on the exposure.[35]

One limitation of the study is that quantifying the precise amount of exposure to air pollution prior to diagnosis was not possible, because included patients had to have been already diagnosed. Another potential limitation would be that prevalence in rural areas and small towns could be higher than documented. However, the Catalan system uses a network for ILD; it offers knowledge, healthcare training and multidisciplinary ILD diagnosis across the entire region.

As this was a retrospective study and the raw pollution data were not generated with IPF epidemiology in mind, prospective longitudinal cohort studies and experimental studies are needed. A limitation of pollution data is its inherently non-granularity; government-designated high-sensitivity sensor distribution is limited (the sensors are the size of trucks) and calculated for large areas, no more granular than 1 km. Prospective studies would need more precise data on history of smoking and occupational exposure, as well as residential history and mapping of any previous residences. It would also be elucidative to compare two equally dense metropolitan areas, one with high pollution and one low, to equalize the population density variable. And finally, the impact of long-term pollution exposure versus spikes in pollution exposure would have to be addressed, possibly by identifying cohorts in two localities where these variables are clear.

Climate change and the impact of environmental pollutants on health are topics that deserve more research. This proof of concept is intended as a starting point for further research focused on the role of PM2.5 and other environmental risk factors in IPF development and the need for epidemiological databases in anticipating disease burden, early diagnosis and patient needs.

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Abbreviations: AQG, Air Quality Guideline; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PM, particulate matter; PM2.5, PM of 2.5 μm or less in diameter; SOCAP, Catalan Society for Pulmonology; WHO, World Health Organization

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Figure S1 Exceedances.
Figure S2 Density of postal codes.
Figure S3 One of the pollution monitoring stations in Barcelona.
Figure S4 Division of postal codes in the metropolitan centre of Barcelona.
Table S1 All postcodes analysed with PM2.5 levels.

Visual Abstract Mapping IPF helps identify geographic regions at higher risk for disease development.

Article 2

Harnessing PM2.5 Exposure Data to Predict Progression of Fibrotic Interstitial Lung Diseases Based on Telomere Length

Objective of the study:

By integrating the existing framework of PM2.5 exposure and cross-referencing telomere length data we hoped to find associations to link PM2.5 to telomere shortening to progression of ILDs.

Catalan Summary:

L'anàlisi creuada de factors de predisposició biològica (escurçament telomèrica) i de contaminació podria ajudar a calcular el risc per la malaltia pulmonar intersticial fibrosant (desenvolupament i/o progressió). La intenció d'aquest estudi és identificar factors predictors per a la detecció i el diagnòstic precoç de les malalties pulmonars, aprofitar nous conjunts de dades generats per a altres finalitats. Hem fet referència creuada a l'exposició nivells de partícules 2,5 (PM2,5) amb la longitud dels telòmers d'una cohort de 280 pacients amb ILD fibròtica per ponderar impacte i associacions. No hi havia cap correlació lineal entre PM2,5 i la longitud dels telòmers als nostres conjunts de dades, com a valor de la correlació el coeficient era de 0,08. Aquest estudi exploratori ofereix informació addicional sobre les metodologies per investigar el desenvolupament i el pronòstic de la fibrosi pulmonar. El resultat del model estimat de FVC després de 3 anys utilitzant PM2.5 com un predictor no era significatiu; tanmateix, la Z-score era indicativa de progressió.

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BRIEF RESEARCH REPORT
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Harnessing PM2.5 Exposure Data to Predict Progression of Fibrotic Interstitial Lung Diseases Based on Telomere Length

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Cross-analysis of clinical and pollution factors could help calculate the risk of fibrotic interstitial lung disease (ILD) development and progression. The intent of this study is to build a body of knowledge around early detection and diagnosis of lung disease, harnessing new data sets generated for other purposes. We cross-referenced exposure levels to particulate matter 2.5 (PM2.5) with telomere length of a cohort of 280 patients with fibrotic ILD to weigh impact and associations. There was no linear correlation between PM2.5 and telomere length in our data sets, as the value of the correlation coefficient was 0.08. This exploratory study offers additional insights into methodologies for investigating the development and prognosis of pulmonary fibrosis.

Keywords: pulmonary fibrosis, pollution, telomeres, big data, impact PM2.5

INTRODUCTION

Several characteristics have been associated with an increased risk of fibrotic interstitial lung disease (ILD) development, such as smoking, viral infections, existence of familial aggregation, and telomere dysfunction (1–4). Across all fibrotic ILDs, patients with shortened telomeres have a more accelerated disease progression. Research has also shown that air pollution has a direct effect on lung disease (5). Particulate matter with an aerodynamic diameter of $\leq 2.5\,\mu m$ (PM2.5) is the smallest particulate matter for which we have long-term exposure estimates in Catalonia, and because of its size, it is one of the pollutants that can most easily reach the deepest tissue and alveoli of the lungs. One systematic review of more than 12,000 subjects across 25 studies found associations between air pollution and telomere shortening (6), and PM2.5 has been suggested as a possible cause of COPD in studies as early as 2014 (7). In addition, it has been shown that exposure to PM2.5 resulted in shortened telomeres and altered telomerase activity in human bronchial epithelial cells (8).

Given this background, this study cross-analyzed telomere length and exposure to PM2.5 to determine associations between these known risk factors in our cohort of patients with fibrotic ILD.

METHODS

In this retrospective study, we analyzed a cohort of 280 patients with fibrotic ILD in the northeast region of Spain who were evaluated for telomere length (TL) in our center because of the indication of the potential risk of telomere shortening from 2014 to 2020. The Ethics Committee of Hospital Universitari de Bellvitge (HUB) approved the study, and all the patients provided written informed consent before inclusion. The relative telomere length was assessed at the time of diagnosis by quantitative polymerase chain reaction (qPCR), as previously described (9). Since telomere length changes with age, a Z-score value was obtained to allow for comparisons of telomere length among individuals of different ages and among cohorts (10). The Z-score compares the telomere shortening ratio value in each individual with the age-matched mean and standard deviation (SD) of the values obtained in the controls. A Z-score below the 10th percentile of a normal distribution was considered as severe telomere shortening. In the statistical analysis, a description of the baseline and clinical characteristics of the patients was made according to their distribution. A linear model was estimated using forced vital capacity (FVC) at 3 years as the dependent variable and using baseline forced vital capacity, exposure to PM2.5, industrial exposure, age, and sex as variables of interest.

Disease progression was considered when a patient presented at least two of the following criteria in the absence of any other explanation or cause: (a) worsening of respiratory symptoms,

Abbreviations: AQG, Air Quality Guidelines; COPD, chronic obstructive pulmonary disease; CTD-ILD, connective tissue disease- interstitial lung disease; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; PM 2.5, particulate matter with an aerodynamic diameter of $\leq 2.5\,\mu m$; qPCR, quantitative polymerase chain reaction; uILD, unclassifiable interstitial lung disease; WHO, World Health Organization.

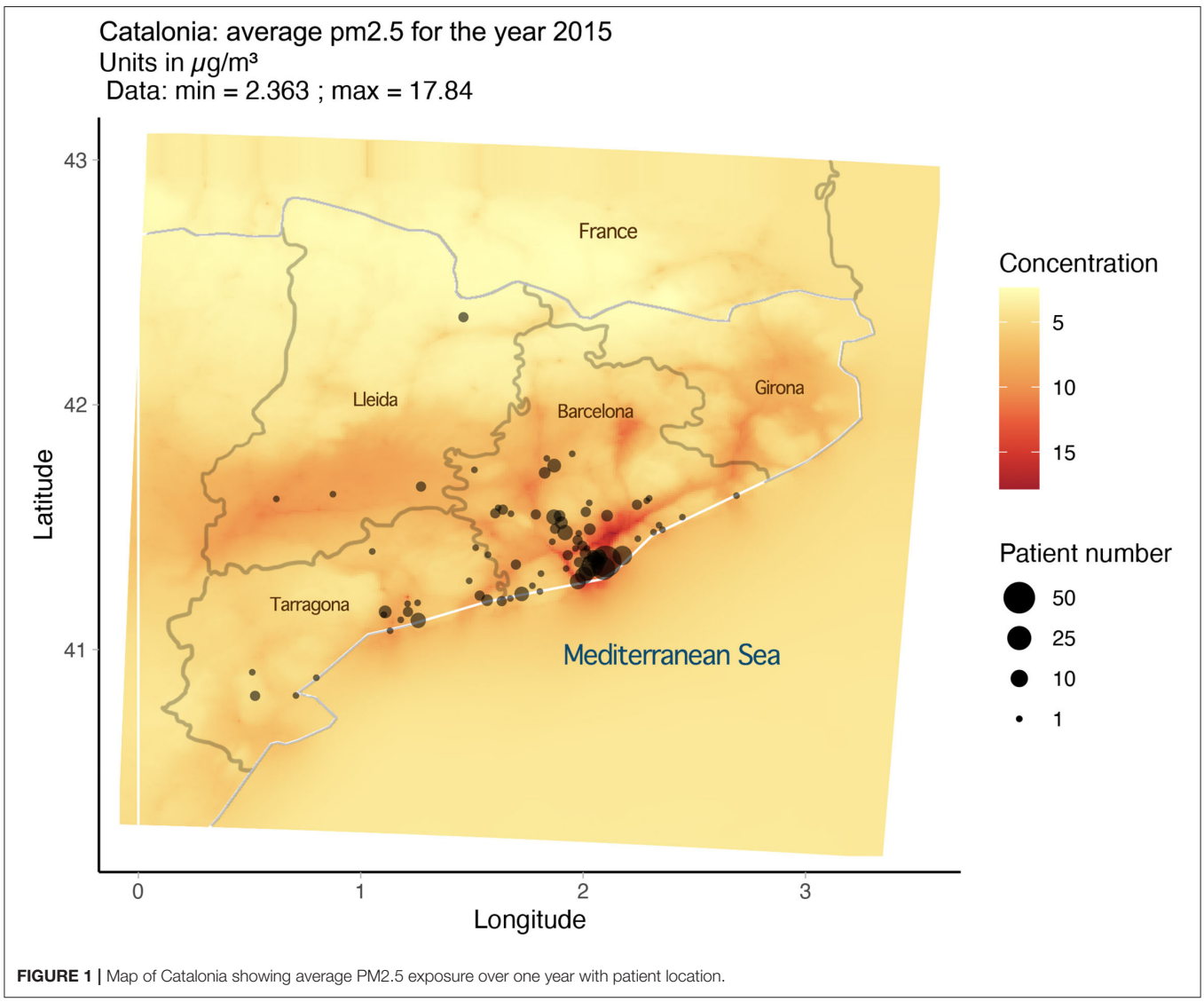

FIGURE 1 | Map of Catalonia showing average PM2.5 exposure over one year with patient location.

(b) physiological progression [absolute decline in the FVC of ≥10% or DLCO (corrected for Hb) of ≥15%], and (c) death. FVC value, over time, was used to analyze potential correlations.

The population analyzed for disease progression was generally older (average age 64.8) and of Spanish nationality. We used their current postal code as the location variable, because the tendency in this population to change residence is very low. Survey data from the province of Barcelona in 2006 show that the age at which people change residence is primarily between 25 and 40 years old; after the age of 60, the likelihood and desire to move is 2–6% (11). According to this survey, 75% of people over 60 in Catalonia believe that where they currently live is the best place to live and that number increases to 81% after the age of 75. Refer **Supplementary Data 2** for further information.

PM2.5 exposure and variables were derived from data from the CALIOPE modeling system (12–15), which has been positively evaluated for epidemiological research (12). As noted in our previous publication (16), the average exposure for PM2.5 for any year in any 1-km area remained consistent from 2001 to 2017. Based on this, the estimates of PM2.5 exposure for 2015 were utilized and extrapolated to serve as an estimate for long-term exposure (2001–2017). Approximate locations for the 280 patients were based on postal code and then plotted using R (version 3.6.0) and the Google Map API and superimposed over the exposure map (**Figure 1**). From this mapping exercise, we can assign an approximate level of long-term exposure to PM2.5 for each subject in the cohort. With the data gathered, we ran a statistical analysis on PM2.5 exposure and Z-score for the cohort.

A complete table of the average PM2.5 exposure and Z-score for each patient can be seen in **Supplementary Data 1**.

RESULTS

The diagnosis for the 280 fibrotic ILD cases was primarily IPF, with 138 cases or 49.2% of the total participants; the next largest number of cases was fibrotic forms of hypersensitivity pneumonitis (HP) with 32 cases or 11.4%. Unclassifiable ILDs (uILD) and the related interstitial pneumonia with autoimmune features (IPAF) formed the third largest group at 26 cases or 9.2% of the participants, followed by diagnoses such as CTD-ILD (24 or 8.5%), non-specific interstitial pneumonia (NSIP) (18 or 6.4 %), smoking-related interstitial fibrosis (SRIF) (11 or 3.9%), fibrosis with organizing pneumonia (6 or 2.1%), and sarcoidosis IV (4 or 1.4%). The remaining cases were other fibrotic ILDs.

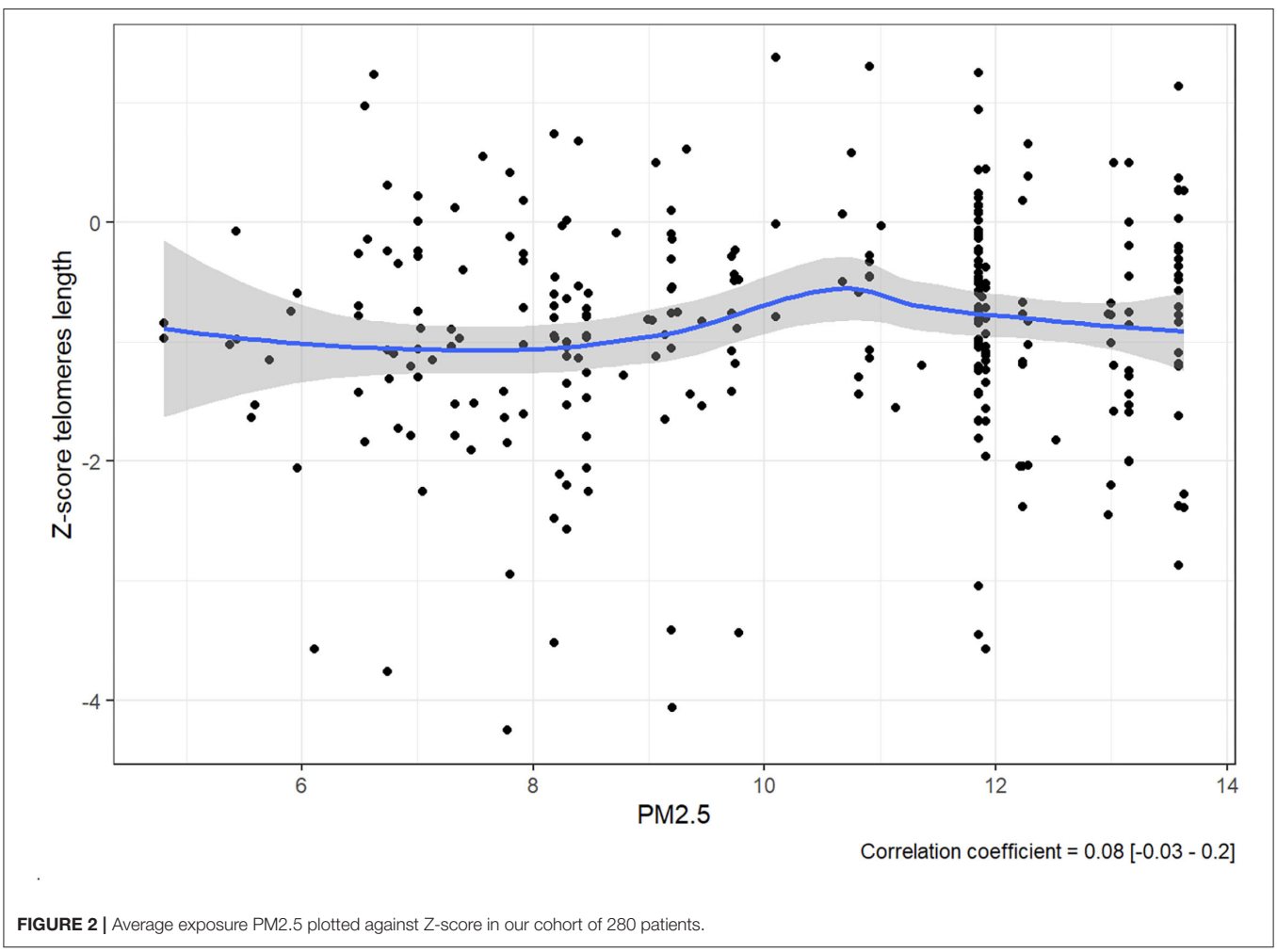

FIGURE 2 | Average exposure PM2.5 plotted against Z-score in our cohort of 280 patients.

TABLE 1 | The covariable "Z-score" is significant in the "Multivariate 1" model.

	Univariate				Multivariate 1			
Predictors	**Estimates**	**std. Error**	**CI**	***p***	**Estimates**	**std. Error**	**CI**	***P***
(Intercept)	87.11	11.13	64.83–109.38	<0.001	8.09	9.26	−10.45–26.63	0.386
Z-score	2.54	5.74	−8.95–14.02	0.660	6.92	3.21	0.49–13.34	0.035
Baseline FVC					1.02	0.09	0.84–1.20	<0.001
Observations	60			60				
R^2/R^2 adjusted	0.003/−0.014			0.698/0.688				
AIC	572.819			503.132				

For every one unit decrease in the Z-score, the forced vital capacity at 3 years (FVC-3y) decreases by about 7 points.

Twenty-nine of the 280 referred family aggregation and 84 presented severe telomere shortening (20 of them had some pathogenic telomere-related gene mutation in RTEL1, TERT, TERC, or DKC1).

The expectation was to see evidence that consistent exposure to higher levels of PM2.5 was correlated to lower Z-score. However, rather than a steady decline in Z-score as PM2.5 increases, there is no linear correlation between them since the value of the correlation coefficient was 0.08 [−0.03, 0.2] (**Figure 2**).

There is, however, an accumulation of cases at the 12 μg/m3 line, and it should be noted that all the 280 members of the cohort were exposed consistently to PM2.5 at levels between 5.565 and 13.631 μg/m3.

DISCUSSION

In 2021, the WHO published updated Air Quality Guidelines (AQG) for PM2.5 as well as other hazardous airborne pollutants. The guidelines, based on data for cause-specific mortality, lead to a recommendation of long-term exposure to PM2.5 at levels of no more than 5 μg/m3 (17). This update means that every subject in the cohort was exposed to levels of PM2.5 above the WHO recommended level.

This observational study is not intended to be conclusive, and further research should be conducted with more specific individual measurements of exposure to PM2.5 and other airborne pollutants; however, we utilized the best data available.

In a more elucidative step, we then analyzed the progression of disease in the 84 patients with severe telomere shortening. Eighty cases had the necessary data available (4 did not complete the 2nd FVC measurement) and were documented with a Z-score in the 10th and 1st percentiles. We then compared their forced vital capacity (FVC) results at baseline and after 3 years. These factors were modeled using a multivariate linear model (**Table 1**). The result of the estimated model of FVC after 3 years using PM2.5 as a predictor was non-significant; however, Z-score was indicative of progression. For every one unit decrease in Z-score, the FVC measure at 3 years after baseline decreased by approximately 7 points. Twenty-eight of the 80 analyzed were smokers, although this did not correlate to telomere shortening. We also compared the diagnosis of the 80 cases, and the numbers were similar to the larger group: of the 80 cases, 40 (50%) were IPF. In this retrospective study, it was not possible to determine at what point in each subject's life environmental pollutants might have begun to affect lung tissue.

A thorough retrospective analysis with multiple risk factors weighted for impact could provide further insight into disease progression in patients with fibrosing ILDs. The long-term objective is to gain further insights into disease development and early diagnosis of ILDs by harnessing big data and analyzing risk factors with additional innovative methodologies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The Ethics Committee of Hospital Universitari de Bellvitge (HUB) approved the study and all patients provided written informed consent before inclusion.

AUTHOR CONTRIBUTIONS

JS was the senior author. MM-M was the authority in review and has last authorship. LP-C and RP contributed equally. CL contributed the essential mapping imagery. All the authors contributed valuable contents to this manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.871898/full#supplementary-material

Supplementary Table 1 | Cohort of 280 subjects with age, gender, telomere length, and individual exposure level to PM2.5 in microns.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer PR declared a past co-authorship with the authors JS and MM-M to the handling editor.

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Discussion

Data generated by digital tools in medicine can be overwhelming. We can have digital readouts on everything – from how many steps a patient has taken per day, to constant blood-glucose monitoring, to levels of oxygenation for that person on an hourly basis. However, the data must be actionable. We have found with this research a first step in linking select key digital data which may be specifically useful for the patient and can help optimize healthcare resources and early identifying patients at risk for respiratory diseases such as pulmonary fibrosis.

After completing the two studies included in this body of work, we determined; a) those regional areas with higher prevalence of IPF, with PM2.5 as identified potential environmental risk factor for disease development among the different air pollutants, and b) the effect of interaction between patient genetic background (telomere length and telomere related gene mutations) and environmental exposure (air pollution and work exposure). Although more precise data will be needed in order to be integrated into healthcare systems, we are one step closer to a digital system for reducing risk of disease development, detecting cases before they become severe and improving tools for early identification of these patients is of great interest to modify the natural history.

Through the results of this work and current research in aging, telomeres, cell repair, and fibrotic lung disease, it is likely there is an interconnected series of weighted risk factors we could outline which could lead to predictions and preventative measures. For example, if a patient is over 65, lives in an area with an annual exposure to PM2.5 of more than 15 μg/m3, presents with telomere shortening, and reports shortness of breath, they would be required to be screened immediately for ILD (see Fig 2).

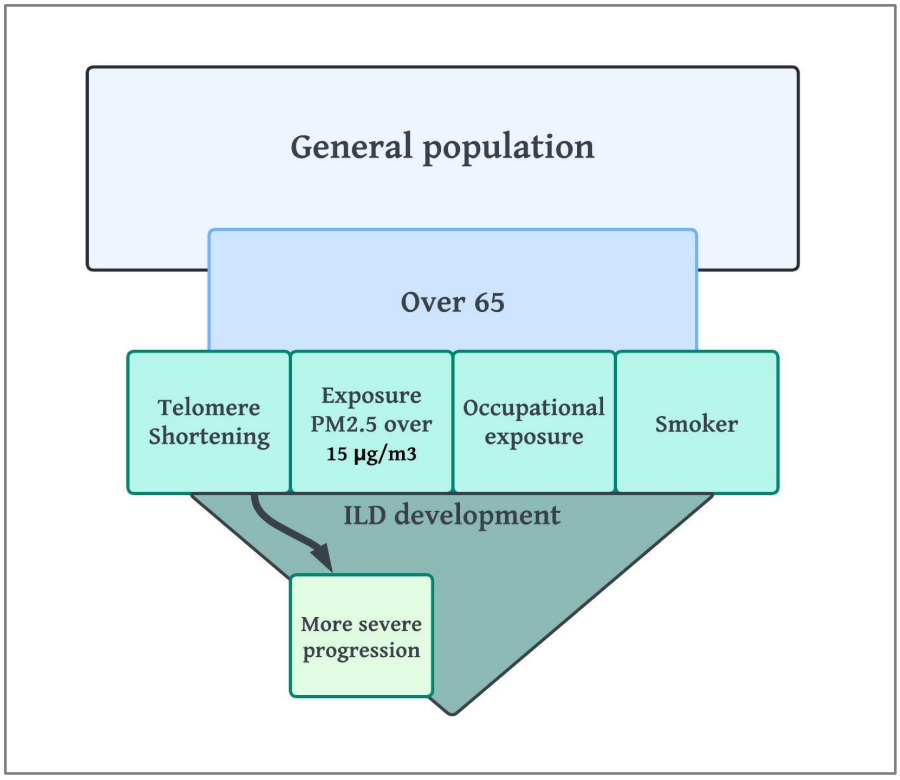

Figure 2. Example of Risk Assessment for digital tool design

The presence of PM2.5 (along with other air contaminants) will continue to be a constant in contemporary life, and we know it is damaging. However, visualizing the consistently unhealthy levels of exposure for communities in which patients live highlights the potential impact of this mostly invisible contaminant. Making this information actionable for health systems is a complex issue.

For compiling a medical history, it is possible to ask the patient and note information about smoking history and occupational exposure with relative accuracy. Although pollution exposure is associated with poorer health, reduced longevity, and exacerbation of lung disease, this is not part of the medical history. Our first publication demonstrated that when no other risk factors were present (smoking, family history, and occupational exposure), pollution was a risk factor. In order for this to be considered for the patient's medical history, more specific data would likely have to be collected. This could be achieved in a variety of ways. The patient could wear a pollution detection device for the duration of a year and have that data integrated,

along with symptom change and FVC. In a sense this is only useful for building a case for reduction of pollution exposure. Perhaps once a damaging level has been documented – this would be limited to patients in areas known to be subject to high levels of PM2.5 – those patients could be prescribed preventative measures. This could be as simple as wearing a particle-filtering face mask, something that we are all familiar with after the COVID19 epidemic.

A recent study in the US presented the use of a digital tool for screening indicators in the electronic health record for predictors of IPF(88), taking into account 3 years of medical history and comorbidities. The tool was documented as being capable of identifying 52-60 out of every 100 people who were then diagnosed with IPF, which is positive and actionable insight if the person is already a patient and has the necessary points of data. Screening for PM2.5 and other pollutant exposures could take place at any point in the patient journey and create actionable data as early as 10 years ahead of a potential future diagnosis.

In addition, we investigated the average exposure levels of other air pollution contaminants in the region of Catalonia with interesting results. Using the same methodology as the mapping of PM2.5, we were able to also map There are notable levels of PM10, NO_2, and O_3 in the region (see Figures 4-6), the impact of which merits further analysis. The WHO updates Air Quality Guidelines (Table 1) show the importance that global body has placed on lowering air pollution values. That said, these are only guidelines, and most countries in the world produce more than the recommended amounts with 90% of the world living in areas that exceed the recommended levels of PM2.5 (89,90).

Recommended 2021 AQG levels compared to 2005 air quality guidelines

Pollutant	Averaging Time	2005 AQGs	2021 AQGs
$PM_{2.5}$, $\mu g/m^3$	Annual	10	5
	24-hour[a]	25	15
PM_{10}, $\mu g/m^3$	Annual	20	15
	24-hour[a]	50	45
O_3, $\mu g/m^3$	Peak season[b]	-	60
	8-hour[a]	100	100
NO_2, $\mu g/m^3$	Annual	40	10
	24-hour[a]	-	25
SO_2, $\mu g/m^3$	24-hour[a]	20	40
CO, mg/m^3	24-hour[a]	-	4

Table 1. The WHO Air Quality Guidelines 2021, with reference to the 2005 AQGs (91)

Figure 3 highlights Catalonia in red, the area illustrated subsequently in Figures 4-6. In Figure 4 it can be seen in the map of Catalonia in north-eastern Spain that levels of PM10 maintained an average well above 20 $\mu g/m^3$ in certain areas during the month of August 2015. A portion of these areas are population-dense and heavy traffic is present. However, as is the case with PM2.5, airborne PM10 is also generated by ploughing of farmland, harvesting of grains with heavy machinery, pesticide spraying, and suspended dust that can be carried to the region from other countries and continents.

As early as 2003 studies have presented evidence that PM10 could be a cause of cellular oxidative stress and may exacerbate lung disease(92,93) and more recently PM10 has been the focus of analysis for its physical features and impact on bronchial epithelial cells(94). Other studies have shown that there is correlation between increased $\mu g/m^3$ exposure of PM10 and lower FVC and dyspnoea (95).

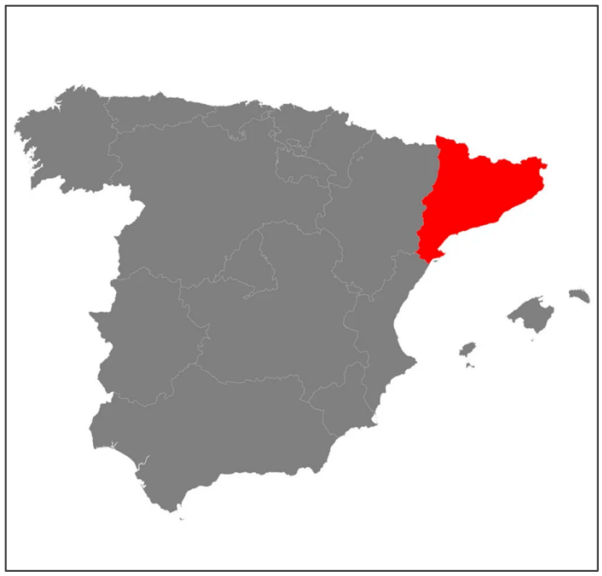

Figure 3 Map showing location of Catalonia (red), and the area depicted in Figures 4-6. Royalty free vector map.

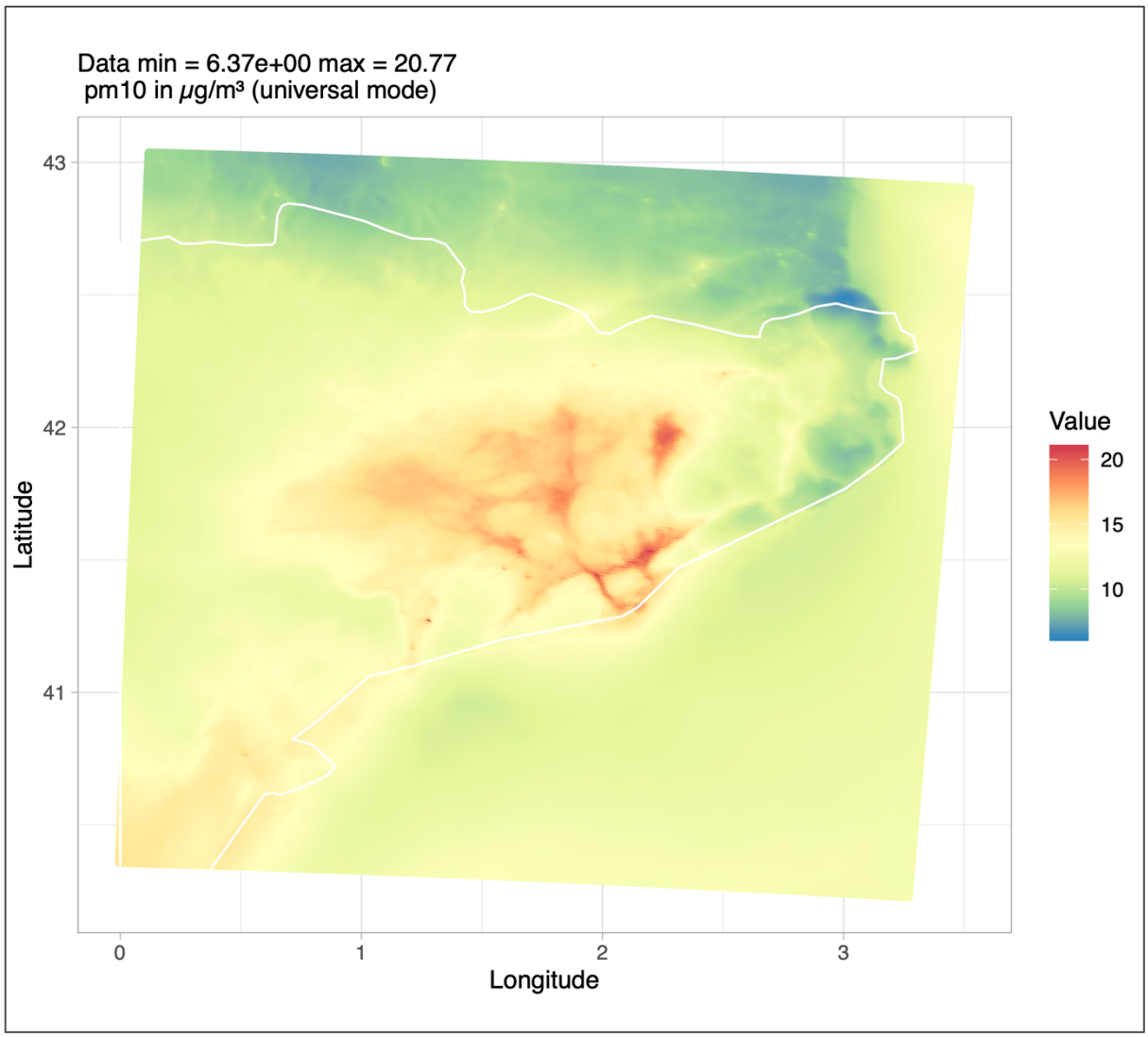

Figure 4. PM10 average in Catalonia August 2015. Colours represent levels of PM10 in µg/m³

Nitrogen dioxide (NO_2) is a volatile, pungent, reddish-brown, molecule formed primarily by road traffic combustion and exists in the atmosphere in gaseous form(96,97). NO_2 is a corrosive free radical, shown to deplete antioxidants in the human respiratory tract(98), and short-term inhalation has been shown to cause inflammation and damage to lung function(99,100)

In Figure 5 the data shows that the average levels of NO_2 were notably high in the area of high traffic density around the metropolitan area of Barcelona during the month of December 2015. We calculated average exposures for all months, and though the values vary, the contaminant is always there, which would likely have a measurable impact on the populations most exposed.

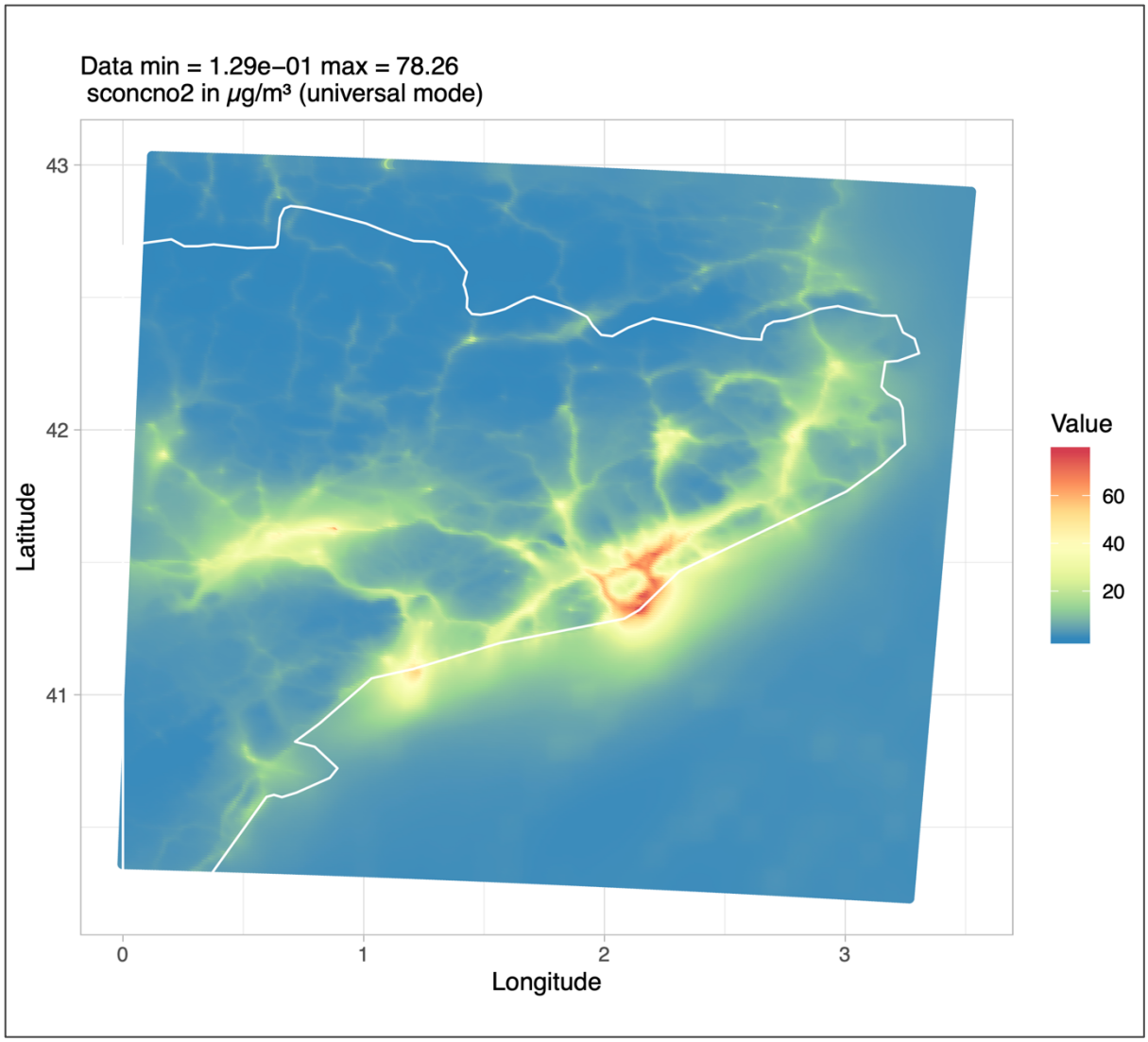

Figure 5. NO_2 average exposure in Catalonia December 2015. Colours represent levels of NO_2 in $\mu g/m^3$

We also mapped ozone. Given the evidence of the inflammatory effects of ozone (O_3) on lung tissue(101), an additional insightful study would be to investigate the impact of this molecule on development and exacerbation of ILDs.

Our mapping tool depicts the fluctuations of ground level O_3 throughout the year, illustrating quite vividly the exposure levels each month; Figure 6 shows the average levels of exposure in Catalonia in November 2015. Notable here is the fact that 0_3 is more concentrated over the sea and in the mountainous areas of the Pyrenees as O_3 is usually less concentrated in urban areas(102,103). Therefore, if ozone is a risk factor for development of ILDs, it follows logically that people in rural areas are also at-risk; prevalence of IPF, as shown in our first publication, is not dependent on population density.

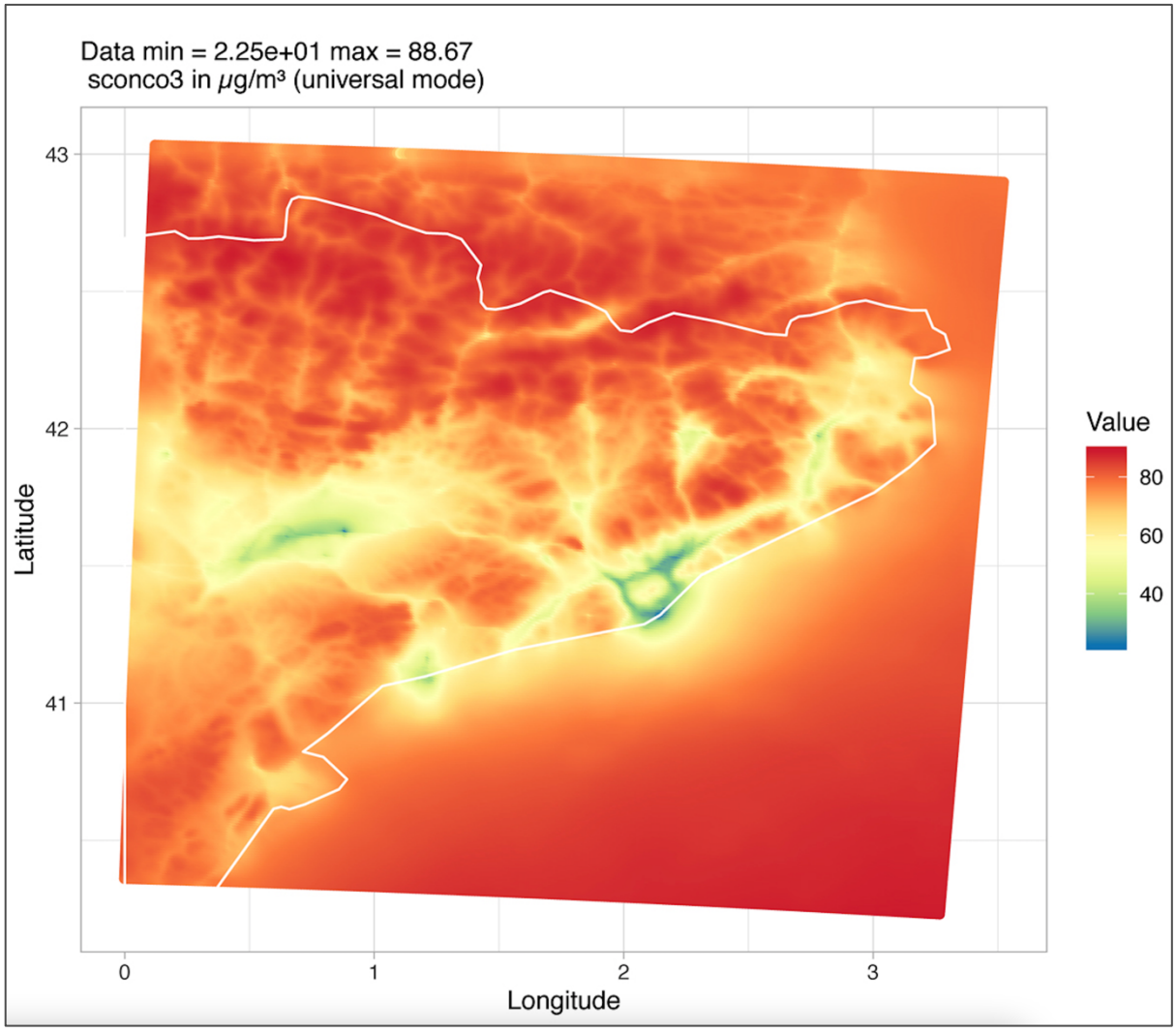

Figure 6 Average O_3 levels in Catalonia November 2015. Colours indicate values in $\mu g/m^3$

Our digital tool can map with precision any region of the world where data is available. Valuable insight could likely be derived from cross-referencing all of these contaminants, mapping most vulnerable locations, filtering again for age, and genetic disposition, to screen for possible cases where respiratory disease is likely.

As highlighted in our first publication, studies are ongoing in many parts of the world to establish correlation between PM2.5 and pulmonary fibrosis(104–106). A 2021 study from Japan demonstrates that increased mean exposure to PM2.5 is a risk factor for acute exacerbations of IPF (107), calculated from the PM2.5 and nitric oxide (NO) exposure estimates based on data derived from air monitoring stations located near the hospital where the patients were admitted for the exacerbation. Our model, though analysing a separate potential effect of PM2.5, uses a more detailed approach for estimating both the geo-location specific to the patient and the variability of exposure over time. One study in Spain (Madrid) analysing effect of multiple air contaminants including PM2.5 found that exposure to CO had the greatest impact on functional severity and mortality in IPF(108). However, in this study as well, the data on pollution exposure was generalised as it was determined by analysing output from one air surveillance system in the centre of Madrid and variability among exposure rates was estimated by calculating the distance from that monitoring station to the patient's home. In Canada, Johannson established that exposure to high levels of air pollution is associated with lower FVC% predicted(109), but not to changes in lung function. The study was a 40-week prospective study, which lends weight to the argument that analysis carried out over a longer period of time would have different results. And it has been suggested that alterations in DNA methylation due to air pollution exposure could be associated with adverse clinical outcomes

in patients with pulmonary fibrosis in that airborne contaminants may contribute to the cascade process of lung remodelling and fibrogenesis(110,111).

Regarding the integration of telomeres as a variable in this work, we have only touched the tip of the iceberg. Telomeres, genomics, and aging and how the relationship between these factors affects disease development and progression of fibrotic ILDs is an area of study with much scrutiny, the integration of which into standard of care is still unfolding(30,112–115)
Indeed, there is a need for insight into all types of ILD, as the genesis and aetiology of each is distinct, as is the interaction with airborne contaminants(116–118). For instance, ILDs deriving from connective tissue disease or interstitial pneumonia with autoimmune features (IPAF) are genetically dissimilar to IPF(119,120), yet the resulting fibrosis can develop in the same epithelial lung tissue and could be exacerbated in the same way.

The multiple variables and sheer complexity of the data needed to unravel each risk factor of ILD development simply requires the power of high through-put computing. It has already been proposed that artificial intelligence (AI) could help in assessing lung images for disease detection(121,122). This thesis provides the first steps in computer-driven *early* identification of ILDs, and perhaps even prevention.

For a next phase of study and adding to the long list of variables, due to the biomarkers of oxidative stress, it would be highly elucidative to analyse not just the telomere length of patients exposed to high levels of PM2.5, but also proliferation of p53 and suppression of PGC-1α and PGC-1β.

In summary, the study undertaken for this doctoral work brought new insights into how we could integrate digital tools to better identify those areas with higher prevalence of fibrotic ILDs, but this is only the beginning of the process. There are still questions as to what level of exposure to PM2.5 would be considered high enough to take action, which biometrics should be adopted to indicate abnormal oxidative stress and whether a Z-score measuring telomere shortening would be accepted as an indicator of risk in clinical guidelines. However, the data is there to be harnessed and by working in multidisciplinary teams, expertise can be cross-pollinated to arrive at potentially lifesaving and cost-saving system(123).

Conclusions

1. The digital health tool we developed can be used to analyse general PM2.5 exposure for ILD patients based on their postal code or more specifically to a 1km geolocation and could offer additional insight by inserting variables such as PM10, O_3, and NO_2, into the model. This tool by itself does not determine a new triage or treatment plan but serves as a first step in the evolution of combining big data and medicine in the prediction of areas at higher risk for IPF development and progression.
2. The real prevalence of IPF in Catalunya was documented within the framework of the Observatori.IPF platform. The prevalence for IPF in the province of Barcelona was higher than other provinces in Catalonia (8.1 per 100,000), whereas Tarragona, Lleida, and Girona resulted in statistics of 2.9, 2.6, and 2.0 per 100,000 respectively. The average for Catalonia as a whole was 5.0 per 100,000.
3. No clear correlation between the levels of PM2.5 and the telomere length has been observed. However, one quarter of those patients that showed severe telomere shortening were exposed to high levels of PM2.5.
4. Severe telomere shortening was associated with a poor prognosis in fibrotic ILDs.
5. As populations continue to grow and pollution has not abated, regardless of the awareness to its deleterious effects, more study is warranted in determining the precise relationship between ILDs, genetic factors, and specific environmental factors including impact of constant exposure to PM2.5. As prevalence for ILDs is increasing, and the etiopathogenesis for many ILDs including IPF is not completely understood, some basic precautionary measures could be taken in order to protect vulnerable individuals.

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