Convocatorias FRPA – BRN de ayudas a proyectos de investigación

Enero 2021

ANEXO 3: PUBLICACIONES PROYECTO "Observatory IPF.cat: Looking for personalizing medicine "

Ramón Pla Armengol
FUNDACIÓN PRIVADA

BARCELONA RESPIRATORY NETWORK
Collaborative research

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

Jessica Germaine SHULL,[1] Maria Teresa PAY,[2] Carla LARA COMPTE,[1] Miriam OLID,[2] Guadalupe BERMUDO,[1] Karina PORTILLO,[3] Jacobo SELLARÉS,[4] Eva BALCELLS,[5] Vanesa VICENS-ZYGMUNT,[1] Lurdes PLANAS-CEREZALES,[1] Diana BADENES-BONET,[5,6,7] Rosana BLAVIA,[8] Pilar RIVERA-ORTEGA,[1] Amalia MORENO,[9] Jordi SANS,[10] Damià PERICH,[10] Silvia BARRIL,[11] Leonardo ESTEBAN,[12] Laia GARCIA-BELLMUNT,[13] Jordi ESPLUGAS,[14] Guillermo SUAREZ-CUARTIN,[1] Jaume BORDAS-MARTINEZ,[1] Diego CASTILLO,[15] Rosa JOLIS,[16] Inma SALVADOR,[17] Saioa EIZAGUIRRE ANTON,[18] Ana VILLAR,[19] Alejandro ROBLES-PEREZ,[20] M. Josefa CARDONA,[21] Enric BARBETA,[22] Maria Guadalupe SILVEIRA,[23] Claudia GUEVARA,[24] Jordi DORCA,[1] Antoni ROSELL,[3,7,25] Patricio LUBURICH,[1] Roger LLATJÓS,[1] Oriol JORBA[2] AND Maria MOLINA-MOLINA[1,7]

[1]ILD Multidisciplinary Unit, Bellvitge University Hospital, IDIBELL, Hospitalet de Llobregat, Spain; [2]Barcelona Supercomputing Center, BSC, Barcelona, Spain; [3]ILD Multidisciplinary Unit, University Hospital Trias i Pujol, Badalona, Spain; [4]ILD Multidisciplinary Unit, Hospital Clínic of Barcelona, IDIBAPS, Barcelona, Spain; [5]Respiratory Medicine Department, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Hospital del Mar, Barcelona, Spain; [6]School of Health & Life Sciences, Pompeu Fabra University (UPF), Barcelona, Spain; [7]CIBER Enfermedades Respiratorias (CIBERES), Madrid, Spain; [8]Respiratory Department, Hospital Moises Broggi, San Joan Despi, Spain; [9]Respiratory Department, Hospital Parc Taulí, Sabadell, Spain; [10]Respiratory Department, Consorci Sanitari de Terrassa, Terrassa, Spain; [11]Respiratory Department, Hospital Arnau de Vilanova, Lleida, Spain; [12]Respiratory Department, Hospital Joan XXIII, Tarragona, Spain; [13]Respiratory Department, Hospital Sant Joan, Reus, Spain; [14]Respiratory Department, Hospital de Martorell, Barcelonès, Spain; [15]ILD Multidisciplinary Unit, Hospital Sant Pau i Santa Creu, Barcelona, Spain; [16]Respiratory Department, Hospital de Figueres, Figueres, Spain; [17]Respiratory Department, Hospital de Tortosa, Tortosa, Spain; [18]Respiratory Department, Hospital Trueta de Girona, Girona, Spain; [19]ILD Multidisciplinary Unit, Hospital Vall d'Hebron, Barcelona, Spain; [20]Respiratory Department, Hospital de Mataró, Mataró, Spain; [21]Respiratory Department, Hospital de Igualada, Igualada, Spain; [22]Respiratory Department, Hospital de Granollers, Granollers, Spain; [23]Respiratory Department, Parc Sanitari Sant Joan de Déu, Sant Boi, Spain; [24]Respiratory Department, Hospital Sant Camil, Vilanova, Spain; [25]Translational Respiratory Research Group, Institut de Recerca Germans Trias i Pujol (IGTP), Badalona, Spain

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.

Correspondence: Jessica Germaine Shull, ILD Multidisciplinary Unit, Bellvitge University Hospital, IDIBELL, Hospitalet de Llobregat, University of Barcelona, c/Jordi Girona, 29, Barcelona 08034, Spain. Email: jess.shull@gmail.com

Received 25 February 2020; invited to revise 9 May, 22 July, 27 August and 23 September 2020; revised 19 June, 10 August, 11 and 30 September 2020; accepted 20 October 2020 Associate Editor: Elisabetta Renzoni; Senior Editor: Yuben Moodley

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

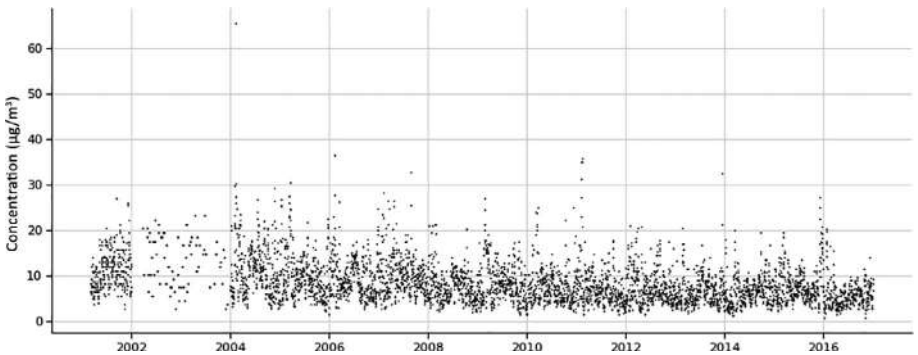

Figure 1 Time series (2001–2017) of the mean daily PM2.5 (particulate matter of 2.5 µm or less in diameter) concentrations (µg/m^3) at the stations over Catalonia: Cabo de Creus (ES0010R), Montseny (ES1778R) and Els Torms (ES0014R).

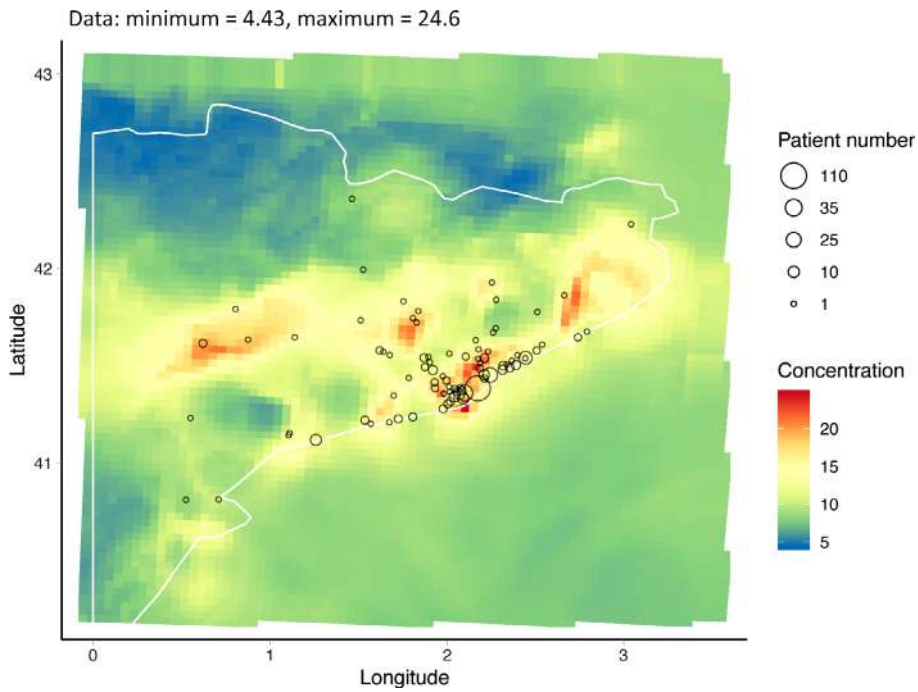

Figure 2 Region of Catalonia. Annual mean concentration of PM2.5 (particulate matter of 2.5 µm or less in diameter) in 2015 (units in µg/m^3. Data: minimum = 4.43, maximum = 24.6).

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 $\mu g/m^3$. The zones coloured red reached more than double that concentration. The highest PM2.5 concentrations of 20–24.6 $\mu g/m^3$ 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 $\mu g/m^3$, 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).

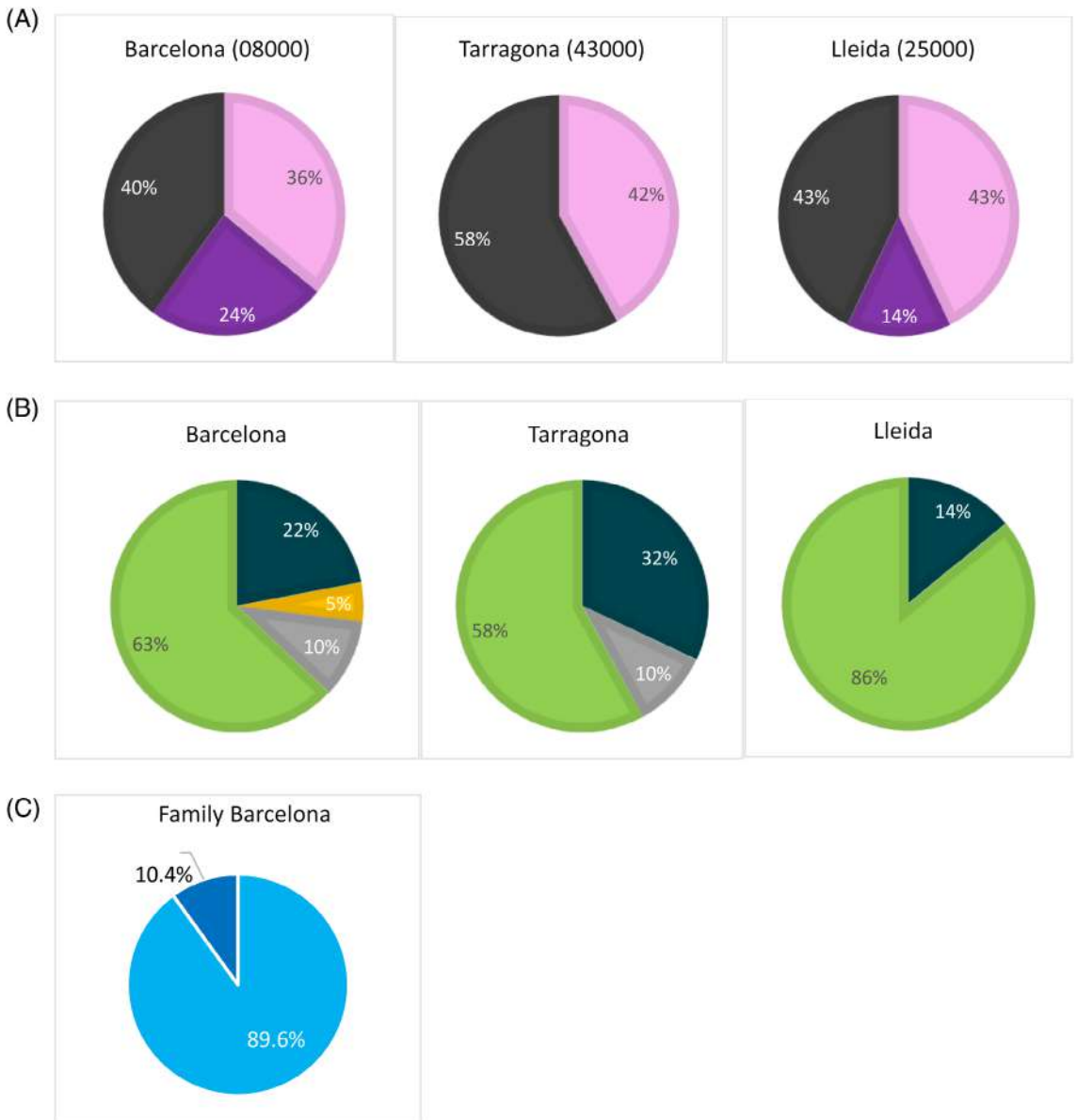

Figure 3 Patient exposure by province. (A) Non-smokers (pink), smokers of <20 pack-years (purple) and smokers of >20 pack-years (dark grey). (B) Occupational exposure: no exposure (green); inorganic dust such as iron, fibre glass and stone dust (blue); organic dust such as from paper or sausage factories (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

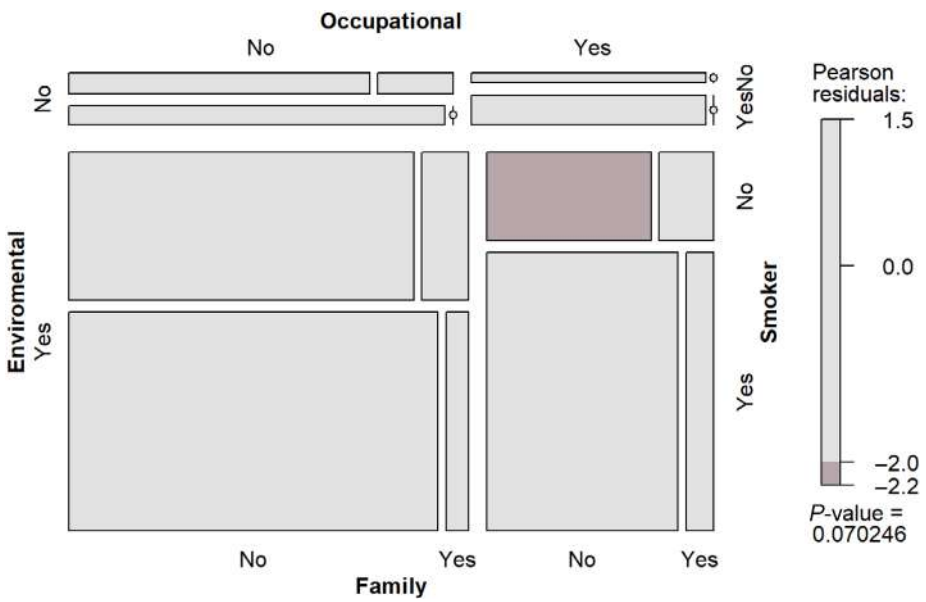

Figure 4 Mosaic plot of exposure for patients in Barcelona province. The size of the areas is proportional to the percentage of cases in that combination of variables (*n* = 260).

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.

Acknowledgements: This work was only possible with the networking of the participating hospital centres, with ILD experts across Catalonia (CRAMPID group), which was engaged through the SOCAP, and the team from the Earth Sciences Department at the Barcelona Supercomputing Centre (BSC). The BSC acknowledges the European Environment Agency for providing public access to the EIONET PM2.5 measurements. The Observatory IPF.cat has been supported by funding from the Barcelona Respiratory Network (BRN), Fundació Ramón Plà Armengol and Boehringer Ingelheim. Patient aggregation has been supported by the Health Care Ministry, ISCIII, PI18/00367 (co-funded by the European Regional Development Fund, ERDF, a way to build Europe). BSC co-authors acknowledge support by the Spanish Ministry of Economy and Competitiveness grants CGL2016-75725-R and RTI2018-099894-BI00, and the AXA Research Fund through the AXA Chair on Sand and Dust Storms established at BSC.

Disclosure statement: The Observatory IPF.cat has been supported by funding from Boehringer Ingelheim. M.M.-M. has also received grants and fees from Boehringer Ingelheim, Roche, Esteve-Teijin, Chiesi, Pfizer, Almirall, GSK and BMS.

Author contributions: Conceptualization: J.G.S., M.T.P., C.L.C., M.M.-M. Data curation: J.G.S., C.L.C., G.B., K.P., J.S., D.P., Ev.B., V.V.-Z., L.P.-C., D.B.-B., R.B., P.R.-O., A.M., J.S., S.B., L.E., L.G.-B., J.E., G.S.-C., J.B.-M., D.C., R.J., I.S., S.E.A., A.V., A.R.-P., M.J.C., En.B., M.G.S., C.G., A.R., P.L., R.L. Formal analysis: J.G.S., M.T.P. Funding acquisition: J.D. Investigation: J.G.S., M.T.P., C.L.C., M.M.-M. Methodology: J.G.S., M.T.P., M.O., O.J., M.M.-M. Project administration: J.G.S., D.C. Resources: J.G.S., R.B., J.D., O.J. Supervision: J.D., M.M.-M. Software: M.T.P., C.L.C. Visualization: J.G.S. Validation: M.O., L.P.-C., A.R., P.L., R.L., O.J., M.M.-M. Writing—original draft: J.G.S., M.T.P., C.L.C., M.O., M.M.-M. Writing—review and editing: J.G.S., M.T.P., C.L.C., M.O., G.B., K.P., J.S., D.P., Ev.B., V.V.-Z., L.P.-C., D.B.-B., R.B., P.R.-O., A.M., J.S., S.B., L.E., L.G.-B., J.E., G.S.-C., J.B.-M., D.C., R.J., I.S., S.E.A., A.V., A.R.-P., M.J.C., En.B., M.G.S., C.G., J.D., A.R., P.L., R.L., O.J., M.M.-M.

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

REFERENCES

1 Xaubet A, Ancochea J, Bollo E, Fernández-Fabrellas E, Franquet T, Molina-Molina M, Montero MA, Serrano-Mollar A. Guidelines for the diagnosis and treatment of idiopathic pulmonary fibrosis. *Arch. Bronconeumol.* 2013; **49**: 343–53.

2 Hutchinson J, Fogarty A, Hubbard R, McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *Eur. Respir. J.* 2015; **46**: 795–806.

3 Hoyer N, Prior TS, Bendstrup E, Wilcke T, Shaker SB. Risk factors for diagnostic delay in idiopathic pulmonary fibrosis. *Respir. Res.* 2019; **20**: 103.
4 Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier J-F, Flaherty KR, Lasky JA *et al*. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am. J. Respir. Crit. Care Med.* 2011; **183**: 788–824.
5 Margaritopoulos GA, Romagnoli M, Poletti V, Siafakas NM, Wells AU, Antoniou KM. Recent advances in the pathogenesis and clinical evaluation of pulmonary fibrosis. *Eur. Respir. Rev.* 2012; **21**: 48–56.
6 Cho CC, Hsieh WY, Tsai CH, Chen CY, Chang HF, Lin CS. In vitro and in vivo experimental studies of PM 2.5 on disease progression. *Int. J. Environ. Res. Public Health* 2018; **15**: 1–26.
7 Wang H, Song L, Ju W, Wang X, Dong L, Zhang Y, Ping Y, Yang C, Li F. The acute airway inflammation induced by PM2.5 exposure and the treatment of essential oils in Balb/c mice. *Sci. Rep.* 2017; **7**: 44256.
8 Conti S, Harari S, Caminati A, Zanobetti A, Schwartz JD, Bertazzi PA, Cesana G, Madotto F. The association between air pollution and the incidence of idiopathic pulmonary fibrosis in Northern Italy. *Eur. Respir. J.* 2018; **51**: 1700397.
9 Viegi G, Maio S, Pistelli F, Baldacci S, Carrozzi L. Epidemiology of chronic obstructive pulmonary disease: health effects of air pollution. *Respirology* 2006; **11**: 523–32.
10 Ko FWS, DSC H. Air pollution and chronic obstructive pulmonary disease. *Respirology* 2012; **17**: 395–401.
11 Gowers AM, Cullinan P, Ayres JG, Anderson HR, Strachan DP, Holgate ST, Mills IC, Maynard RL. Does outdoor air pollution induce new cases of asthma? Biological plausibility and evidence; a review. *Respirology* 2012; **17**: 887–98.
12 Siroux V, Crestani B. Is chronic exposure to air pollutants a risk factor for the development of idiopathic pulmonary fibrosis? *Eur. Respir. J.* 2018; **51**: 1702663.
13 Johannson KA, Vittinghoff E, Lee K, Balmes JR, Ji W, Kaplan GG, Kim DS, Collard HR. Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. *Eur. Respir. J.* 2014; **43**: 1124–31.
14 Johannson KA, Vittinghoff E, Morisset J, Wolters PJ, Noth EM, Balmes JR, Collard HR. Air pollution exposure is associated with lower lung function, but not changes in lung function, in patients with idiopathic pulmonary fibrosis. *Chest* 2018; **154**: 119–25.
15 Xing Y-F, Xu Y-H, Shi M-H, Lian Y-X. The impact of PM2.5 on the human respiratory system. *J. Thorac. Dis.* 2016; **8**: E69–74.
16 World Medical Association. 64th WMA General Assembly, Fortaleza, Brazil. World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. 2013. [Accessed 18 Feb 2020.] Available from URL: https://www.wma.net/wp-content/uploads/2016/11/DoH-Oct2013-JAMA.pdf
17 Molina-Molina M, Agusti A, Crestani B, Schwartz DA, Königshoff M, Chambers RC, Maher TM, Faner R, Mora AL, Rojas M *et al*. Towards a global initiative for fibrosis treatment (GIFT). *ERJ Open Res.* 2017; **3**: 1–7.
18 Sociales S. United Nations Second World Assembly on Ageing. Geneva: Assembly, 2002. [Accessed 22 Oct 2020.] Available from URL: http://undocs.org/A/CONF.197/9
19 World Health Organization. Air Quality Guidelines. Global update 2005. Geneva: World Health Organization, 2006. [Accessed 22 Oct 2020.] Available from URL: https://www.euro.who.int/en/health-topics/environment-and-health/Housing-and-health/publications/pre-2009/air-quality-guidelines.-global-update-2005.-particulate-matter,-ozone,-nitrogen-dioxide-and-sulfur-dioxide
20 Seinfeld JH. In: Pandis SN (ed) *Atmospheric Chemistry and Physics: From Air Pollution to Climate Change*, 3rd edn. Hoboken, NJ, Wiley, 2016.
21 Baldasano JM, Pay MT, Jorba O, Gassó S, Jiménez-Guerrero P. An annual assessment of air quality with the CALIOPE modeling system over Spain. *Sci. Total Environ.* 2011; **409**: 2163–78.
22 Aguilera I, Basagaña X, Pay MT, Agis D, Bouso L, Foraster M, Rivera M, Baldasano J, Künzli N. Evaluation of the CALIOPE air quality forecasting system for epidemiological research: the example of NO2 in the province of Girona (Spain). *Atmos. Environ.* 2013; **72**: 134–41.
23 Pay MT, Jiménez-Guerrero P, Baldasano JM. Implementation of resuspension from paved roads for the improvement of CALIOPE air quality system in Spain. *Atmos. Environ.* 2011; **45**: 802–7.
24 Pay MT, Jiménez-Guerrero P, Jorba O, Basart S, Querol X, Pandolfi M, Baldasano JM. Spatio-temporal variability of concentrations and speciation of particulate matter across Spain in the CALIOPE modeling system. *Atmos. Environ.* 2012; **46**: 376–96.
25 Guevara M, Martínez F, Arévalo G, Gassó S, Baldasano J. An improved system for modelling Spanish emissions: HERMESv2.0. *Atmos. Environ.* 2013; **81**: 209–21.
26 Skamarock WC, Klemp JB. A time-split nonhydrostatic atmospheric model for weather research and forecasting applications. *J. Comput. Phys.* 2007; **227**: 3465–85.
27 Byun D, Schere KL. Review of the governing equations, computational algorithms, and other components of the Models-3 Community Multiscale Air Quality (CMAQ) modeling system. *Appl. Mech. Rev.* 2006; **59**: 51–77.
28 Basart S, Pérez C, Nickovic S, Cuevas E, Baldasano J. Development and evaluation of the BSC-DREAM8b dust regional model over Northern Africa, the Mediterranean and the Middle East. *Tellus B Chem. Phys. Meteorol.* 2012; **64**: 18539.
29 Akita Y, Baldasano JM, Beelen R, Cirach M, De Hoogh K, Hoek G, Nieuwenhuijsen M, Serre ML, de Nazelle A. Large scale air pollution estimation method combining land use regression and chemical transport modeling in a geostatistical framework. *Environ. Sci. Technol.* 2014; **48**: 4452–9.
30 Glahn B. Objective analysis of MOS forecasts and observations. 92nd American Meteorological Society Annual Meeting, 21st Conference on Probability Statistics in the Atmospheric Sciences; 22–26 Jan 2012, New Orleans, LA. Silver Spring, MD: Meteorological Development Laboratory, National Weather Service, 2012; 1–11.
31 Johannson KA. Air pollution exposure and IPF: prevention when there is no cure. *Thorax* 2018; **73**: 103–4.
32 Miri M, Nazarzadeh M, Alahabadi A, Ehrampoush MH, Rad A, Lotfi MH, Sheikhha MH, Sakhvidi MJZ, Nawrot TS, Dadvand P. Air pollution and telomere length in adults: a systematic review and meta-analysis of observational studies. *Environ. Pollut.* 2019; **244**: 636–47.
33 Sesé L, Nunes H, Cottin V, Sanyal S, Didier M, Carton Z, Israel-Biet D, Crestani B, Cadranel J, Wallaert B *et al*. Role of atmospheric pollution on the natural history of idiopathic pulmonary fibrosis. *Thorax* 2018; **73**: 145–50.
34 Winterbottom CJ, Shah RJ, Patterson KC, Kreider ME, Panettieri RA, Rivera-Lebron B, Miller WT, Litzky LA, Penning TM, Heinlen K *et al*. Exposure to ambient particulate matter is associated with accelerated functional decline in idiopathic pulmonary fibrosis. *Chest* 2018; **153**: 1221–8.
35 Mäkelä K, Ollila H, Sutinen E, Vuorinen V, Peltola E, Kaarteenaho R, Myllärniemi M. Inorganic particulate matter in the lung tissue of idiopathic pulmonary fibrosis patients reflects population density and fine particle levels. *Ann. Diagn. Pathol.* 2019; **40**: 136–42.

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.

