Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

areas, an upstream (Northern) zone and a downstream (Central-Southern) zone, with respect to the river Po. More recent data from the Italian Ministry of Health assessed that the 7 regions in the Northern macro area account for about 79.81% of the whole severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive population. This singular circumstance fits perfectly with the observation that the Central-Southern part, downstream the Po, is completely surrounded by Mediterranean. Fundamental insights come from past studies conducted in our Academy, where the authors assessed that the Italian population in the Central-Southern part of the peninsula has a higher risk to be affected by chronic airway allergy, that is, asthmatic disease, compared with more rainy-cold Northern regions.[2] The peninsular part of Italy is exactly the portion of the country with only about one-fifth (21.19%) of COVID-19–positive subjects and also being endowed with the largest near-coastal environment. The latter is particularly enriched in troposphere ozone (O_3), which is a well-known risk factor for asthmatic allergy disorders, particularly during sunlight exposure in warm season.[3] The role of O_3 in pulmonary physiology and airway allergy might be particularly intriguing to shed light on the progress of COVID-19, particularly in such circumstance described by the authors, that is, following a reduction in the anthropic pollutants.[1] So far, very few associations were established between SARS-CoV-2 and subjects with asthma, although it is observed that the prevalence of asthma in severe patients with COVID-19 is lower than in the general adult population.[4] Moreover, some reports have shown that, particularly in elder subjects with hypertension-derived cardiovascular disease, the expression of angiotensin-converting enzyme 2 (ACE2) is reduced, whereas, on the contrary, in people predisposed to develop asthmatic symptoms, the expression of ACE2 was much higher and exerting a protective role against the COVID-19 exacerbation, which otherwise should lead to interstitial bilateral pneumonia and lung fibrosis.[5] Finally, Central-Southern Italy is characterized by a higher frequency of ACE I/D polymorphism in the II allele compared with the Northern macro area, which has a prevalence in the DD allele, usually linked with a higher risk for cardiovascular disease.[6]

Although lockdown with its drastic reduction in engine exhausts has decreased airborne urban pollutants[1] such as particulate matter ≤10 μm (PM_{10}), NO_2, SO_2, CO, and O_3, the coexistence of O_3 high levels and PM_{10} low levels is associated with a low COVID-19 incidence odds ratio (OR). Furthermore, it is well known that in Italy urban pollutants decrease from inlands to offshore and near the coastal environment and are associated with interstitial pneumonia.[7]

On the basis of several publicly available data from government's environmental, health, and statistical institutions for the latest 3 years, we calculated that the Northern regions have an OR of 11.44 (95% CI, 10.707-12.238) for COVID-19 incidence risk in subjects living in inland areas with PM_{10} levels of greater than or equal to 40 $\mu g/m^3$ and NO_2 levels of greater than or equal to 40 $\mu g/m^3$ for at least 3 months/y, whereas the Central-Southern regions, including major islands, have an OR of 0.97 (95% CI, 0.898-1.068) with same values in the same time course; that is, there is no relevant risk association between the onset of COVID-19 following SARS-CoV-2 infections and major urban pollutants. Furthermore, we calculated from data of the Italian Government "Institute of STATistics" (ISTAT) and the National Institute of Health that the OR of COVID-19 risk incidence in subjects with asthma living permanently in Northern inland macro area was 1.44 (95% CI, 1.395-1.488), whereas in the Central-Southern macro area (including Sardinia and Sicily), the OR was 0.76 (95% CI, 0.721-0.807). This result is in agreement with the latitude dependency in asthma prevalence in Italy and assesses that asthma is not a risk factor for COVID-19.[2] According to our opinion, one possible leading factor in the paradoxical bimodal distribution of COVID-19 cases in Italy, very high in the Northern part and slightly modest in the Central-Southern part, is not only the favorable genetic endowment of ACE I/D polymorphism but also the presence of environmental O_3, because ozone, besides being a nontoxic asthma trigger, is able to modulate the pulmonary microbiome, thus assessing the correct cross-talk between airway bacteria and the immune surveillance of lung physiology, whereas PM_{10} alters this interelationship.[5-7] It is possible therefore to suggest that the increasing asthma prevalence from North to South is a sign of the different impact of the troposphere ozone in Italy.

The article by Navel et al offered us the opportunity to boost current research about COVID-19 in Italy, trying to shed light on the unusual COVID-19 distribution, which might even drive the political decision about lockdown and "Fase-2", if taking into consideration both allergy and environmental issues.

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Reply

To the Editor:

We read with considerable interest the relevant comment of Chirumbolo and Bjørklund[1] concerning our recent Editorial.[2] The authors discussed the complex link between the prevalence of coronavirus disease 2019 (COVID-19) in Italy and the geographic zones of a peninsula location, air pollution related to different climates, and allergic diseases of the respiratory

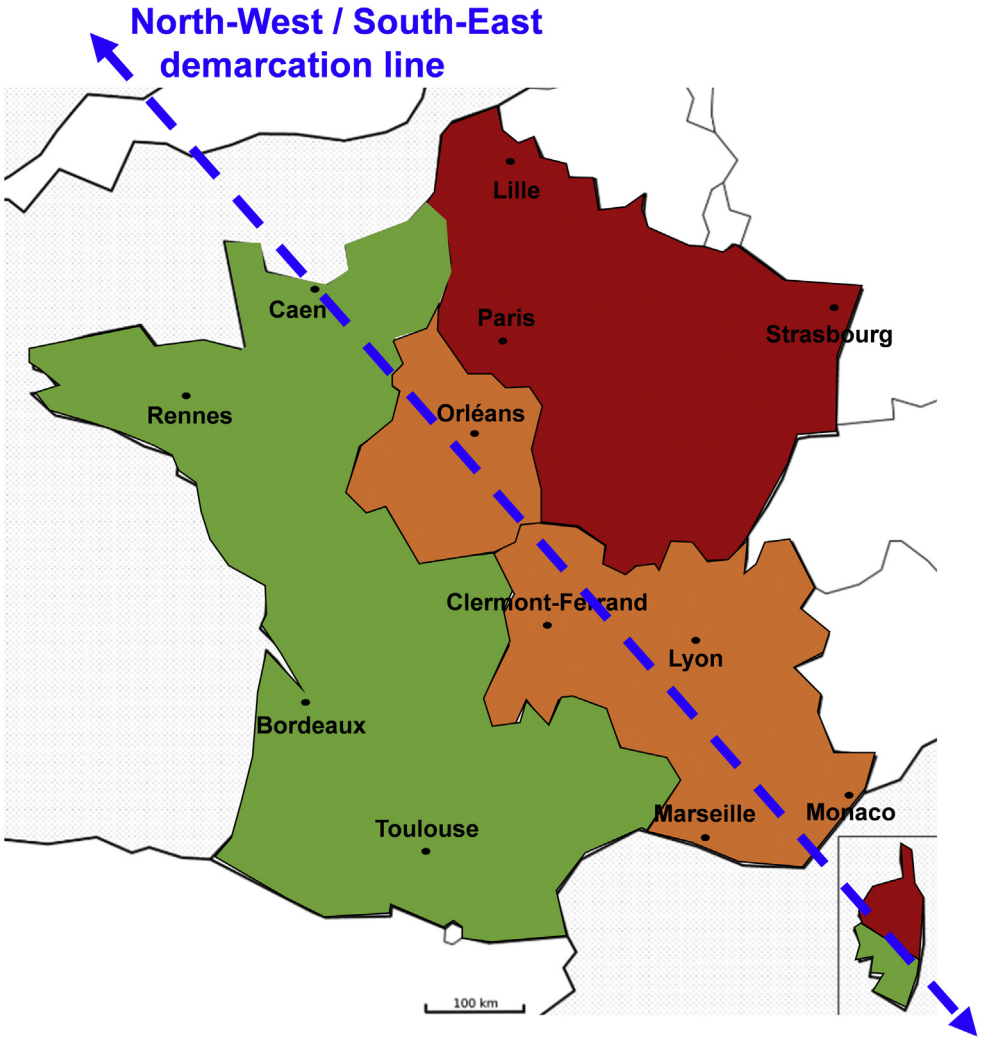

FIG 1. Repartition of SARS-CoV-2 cases in metropolitan French territory. Three levels of SARS-CoV-2 spreading, and saturation of intensive care units, that is, red for high risk, orange for moderate risk, and green for low risk. Data from Santé Publique France and Ministère des Solidarités et de la Santé—French Government.[3]

tract. As explained by the authors, it is very intriguing that the Northern zone of the Italian peninsula (ie, north of the river Po) is more affected by COVID-19 than the Central-Southern zone, but it is a common observation in most of the affected countries around the world. The provinces around Wuhan, where the first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were identified (ie, Henan, Hubei, Hunan, Jiangsu, and Anhui), are located in the Northern and Eastern parts of China with continental rainy-cold climates. These provinces are particularly industrialized with considerable pollution in cities, ensuring populations are heavily exposed to particulate matter (PM), ozone (O_3), carbon dioxide (CO_2), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) produced by diesel combustion. Similar to Italy and China, the North-eastern population of France is more affected by COVID-19 than the population of the Atlantic coast and Mediterranean regions.[3,4] Similar to the Italian peninsula, France could be isolated into 2 macro-area zones on both sides of the river Loire, highlighting a clear North-West/South-East line coinciding with the French Demarcation line during World War II (Fig 1).

The populations living next to coasts with daily exposure to oceanic or Mediterranean climates seem to be less at risk of COVID-19. However, the putative link between COVID-19 and geographic zones could be associated with genetic variations in the population and explained by the importance of human exchanges around continental frontiers areas (eg, North-eastern part of France, BENELUX countries, and urban area of Ruhr). Similar to the environmental exposures affecting the incidence and decompensation of allergic diseases, COVID-19 could be affected by internal and external exposome.[5] In crowded areas and industrialized territories exposed to hot warm season, the high levels of O_3 seem to be associated with variations in epigenetic modulation. Globally, emerging data may identify air pollution as a modulator to DNA methylation (DNAm) disturbing the inflammation process, allergic diseases development, and exacerbation risk.[6] As such, NO_2 and PM exposures during pregnancy could significantly deregulate DNAm of antioxidants or anti-inflammatory genes related to the oxidative stress pathway *in utero*.[7,8] Interestingly, lower DNAm of IL-6 and IFN-γ genes was

identified in adults exposed to PM, black carbon, and O_3, involving an increase in specific immune system.[9] The change in DNAm was often observed at specific locations within the promoter region, deregulating the expression of genetic heritage. Considering that SARS-CoV-2 infection involves a proinflammatory cytokine storm as IL-6 and IL-1β, a putative hypothesis could explain that populations exposed to chronic air pollution are associated with a different COVID-19 incidence in line with chronic epigenetic deregulation. Affecting the immune system and the inflammatory pathways, DNAm related to air pollution could explain the disparities in COVID-19 in geographic zones in which genetically predisposed populations were living in climate favoring SARS-CoV-2 distribution.

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Prevalence of comorbid asthma in COVID-19 patients

To the Editor:

The article by Li et al[1] titled "Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan" provides much-needed detail to inform risk assessment in the presence of preexisting comorbidities in such patients. Given the potentially protracted time line for complete eradication of the public health threat from coronavirus disease 2019 (COVID-19), there is an urgent need for such data to clarify the risk to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients with asthma, particularly because severe asthma represents a sizable patient group included in public health advice to shield/stay home.[2] Surprisingly, the authors report a low prevalence of asthma (0.9% [5 of 548]) in patients with COVID-19, markedly lower than in the adult population of Wuhan (6.4%) and hence speculate that there may be a T_H2-mediated reduced susceptibility to COVID-19 in patients with asthma.[1] A recent literature review including an additional 12 predominantly Chinese COVID-19 cohorts/cases (874 patients) showed that asthma was "surprisingly underreported,"[3] and entirely absent in a Chinese nationwide analysis of 1590 COVID-19 cases, where a lack of chronic airways disease awareness and lack of community spirometric testing were postulated reasons.[4]

TABLE I. Demographic and clinical characteristics of hospitalized asthma patients with COVID-19

Characteristic	All patients (n = 17)	No pneumonia* (n = 10)	Pneumonia (n = 7)
Age (y)	61 (28-86)	58 (28-82)	64 (46-86)
Sex: male/female	9/8	6/4	3/4
Length of hospital stay (d)†	7 (1-34)	4 (1-15)	11 (4-34)
Intensive care admission, no. of patients	1	0	1
Mechanical ventilation, no. of patients	0	0	0
Clinical outcomes			
Discharged from hospital	15	10	5
Remains hospitalized	1	0	1
Death	1	0	1

For age, data are expressed as mean (range).
*No pneumonia describes the absence of any consolidation on chest radiograph at any stage during admission.
†Length of stay data are censored at day 34 for 1 patient.

In contrast, a more recent case series from New York of 393 consecutive confirmed COVID-19 admissions documented a rate of asthma of 12.5%, slightly higher than the prevalence of current adult asthma of 10.1% in New York state.[5,6] As a European comparison of asthma prevalence in hospitalized patients with COVID-19, and with local institutional review board approval, we conducted a retrospective study in our 836-bed tertiary referral center in Dublin, Ireland. We assessed the medical records of 193 consecutive admissions who were SARS-CoV-2–positive over a 1-month period and found that 8.8% (17 of 193) had a physician diagnosis of asthma. Although most of these patients with comorbid asthma had a milder inpatient course and none required invasive mechanical ventilation, there was 1 death, related to COVID-19 and other life-limiting comorbidities (Table I). The herein-reported rate of comorbid asthma diagnosis is higher than that reported by Li et al, and is comparable to the estimated prevalence of current asthma of 7.0% in adults in Ireland.[7]

We theorize that the rate of comorbid asthma in our urban center in Ireland reflects the complex interaction of perhaps greater susceptibility to symptomatic COVID-19 in asthma and an increasingly forewarned and engaged patient population with asthma who may have recently improved their asthma medicine adherence and anticipated/better adhered to public health advice than others in advance of widespread community transmission in their geographic region. We suspect that the low comorbid asthma