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Is obesity the missing link between COVID-19 severity and air pollution?
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Response to Reviewers:	Reviewer #1: The authors addressed all my requests and significantly improved the manuscript. The manuscript can be accepted in current form for publication on Environmental Pollution. Response to Reviewer #1: Dear Reviewer 1, thank you again for your positive feedback and for helping us to improve our manuscript. Reviewer #2: Thank you for the revisions! I have some comments to the new text Abstract: It was very interesting to see the epidemiological data in Table 1. However I do not agree with your statement that you have "showed that obesity may be the missing link between COVID-19 severity and high level of air pollution", rows 16-17. As you yourselves remark, Veneto has a much lower incidence that Lombardia, despite Veneto having higher PM levels and more obesity. But I think this might be due to the fact that Table 1 presents incidence. Perhaps covid mortality would have shown a clearer pattern, since it is a marker of severity. Response: Dear Reviewer 2, thank you for your constructive comments. We have modified rows 16-17 as follow: "(…)We hypothesized that obesity may be one of the links between COVID-19 severity and high level of air pollution. First, obesity is a predisposing factor for SARS-Cov-2 infection and worse COVID-19 outcomes(…)" Furthermore, we have added data relating to mortality rate for COVID-19 in Italian regions, as a marker of severity (table1). We did not find a positive correlation between

mortality rate for COVID-19 and overweight/obesity prevalence, being the first higher in the northern regions, similarly to Sars-cov2 Incidence, and the latter in the southern ones.
However, some variables should be taken into account in the interpretation of data relating COVID-19 lethality. In fact, it is acknowledged that those regions that experienced the greatest number of COVID-19 cases adopted different health policies in the management of the pandemic. In particular, as we explained in section 5, Lombardy, the most hit region by the virus, adopted a conservative approach to testing, partially forced by the scarcity of resources, limiting diagnostic swabs to severe symptomatic cases; this approach is likely to have overestimated the mortality rate for COVID-19 compared to regions that have carried out more extensive screenings such as Veneto. We focused on this aspect in section 5, as follow:

"(…)However, although the two regions adopted similar approaches in terms of social distancing and retail closures, Veneto proceeded towards a more proactive strategy for the containment of the virus, with a policy based on extensive testing of both symptomatic and asymptomatic cases, whereas Lombardy opted instead for a more conservative approach to testing, with a stronger focus only on symptomatic cases [35]. It is likely that the different regional policies may have overestimated the mortality data reported in Lombardy compared to Veneto, making data related to virus lethality uncertain and difficult to interpret(…)"

Moreover, we cannot rule out that virus lethality was really higher in Lombardy, where hospitals were significantly more overcrowded during the outbreak compared to other regions, such as Veneto. We emphasized this aspect in section 5, as follow:

(…)Furthermore, it has been reported that in Lombardia, where during the pandemic outbreak hospitals were overcrowded and contaminated, and medications, mechanical ventilators, oxygen, and personal protective equipment were not available, home care and mobile clinics have been encouraged [36]; on the other hand, it is reasonable to hypothesize that in Veneto, where the pandemic did not reach the same frightening proportions, a more patient-centered care strategy has been adopted. The different health-care strategies adopted by the two neighboring regions could explain the milder impact of the pandemic and the lower virus lethality in Veneto in comparison to Lombardia, despite the higher air pollution levels and overweight/obesity prevalence (Table 1)(…)"

There seems to be a contradiction between the abstract (row 21) and Section 3 (row 112): "obesity may partly mediate air pollution-induced lung injury" and "ponderal excess although not a mediator of air pollution-derived injury". Do you consider obesity to be a mediator or not?

Response: Thank you for your comments. We do not consider obesity a mediator, but an effect modifier of smog-induced lung-injury. We have corrected the abstract as follow:
(…)Moreover, it has been shown that obesity may intensify the detrimental effects of air pollution on the lungs, and this is not surprising if we consider that these conditions share an excessive activation of the immune system and a lung inflammatory infiltrate(…)

Section 2, row 68: I would think it is too early to say that the evidence is "unequivocal".

Response: We modified "unequivocal evidence" with "emerging evidence".

Section 5, row 164: "advanced age is one of the most important predictors for severe Covid 19". This is not confirmed by the data in Table 1, the correlation between incidence and ageing index is -0.06. But as said before, perhaps covid mortality would show a stronger correlation with age.
Response: We have added mortality rate index in table 1, which do not show a correlation with the ageing index. However, strong evidence in literature support the hypothesis that advanced age predict severe covid-19. We emphasized this aspect in section 5, as follow:
"(...)Although we do not derive a significant correlation between the ageing index and mortality rate for COVID-19 ($p=.6$), which is influenced itself by several other variables,

	it is worth recalling that advanced age was previously proved a predictive factor for severe COVID-19 (...)". Moreover, data related to virus mortality are uncertain and difficult to interpret, as explained previously. Table 1: please give the definition of Ageing index in the foot note (now it appears only in Section 5). Response: We have added this information in the foot now of table 1. Minor comments: You use the word "re-known", what does it mean? Abstract row 18, Section 3 row 81, Conclusion row 210. Response: We have deleted the word reknown from the text. Section 1, row 57: Should be "(ARDS) - one of the worst…" Response: We have corrected the sentence. Section 1, row 58: Should be "correlated to a hyper-activation" Response: We have corrected the sentence. Section 1, row 59: Should be "as reflected by the increase of pro-inflammatory cytokines" Response: We have corrected the sentence. Section 4, row 129: Perhaps delete "Intriguingly"? Response: We have deleted “intriguingly” Section 4, row 146: Should be "prospective population studies are" Response: We have corrected the sentence.

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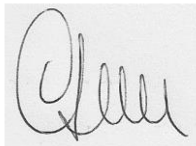
"Is obesity the missing link between COVID-19 severity and air pollution?"

Dear Editor,

Thank you for your kind consideration of our manuscript entitled "Is obesity the missing link between COVID-19 severity and air pollution?" for publication in Environmental Pollution as article type "Correspondence", in reference to the previously published article "Can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in Northern Italy?* of Conticini E et al.

We also thank the reviewers for their positive feedback and their constructive comments that helped in our efforts to improve the manuscript. We have revised the manuscript according to the minor revisions; changes requested by the reviewer 2 are highlighted in bold. We hope it will now be acceptable for publication.
The revised manuscript has been approved by all authors.

Yours sincerely,



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Is obesity the missing link between COVID-19 severity and air pollution?

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Abstract

In the previous publication "Can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in Northern Italy?" Conticini et al. hypothesized that the surplus of lethality of the novel SARS-CoV-2 in Northern Italy may be at least in part explained by the evidence of highest pollution reported in this area, as both severe COVID-19 and smog exposure are correlated to an innate immune system hyper-activation with subsequent lung inflammation and injury. Since this hypothesis alone does not fully explain why specific subgroups of patients are at major risk**, we hypothesized that obesity may be one of the links between COVID-19 severity and high level of air pollution. First, obesity is a predisposing factor for SARS-Cov-2 infection and worse COVID-19 outcomes**, and unequivocal evidence demonstrated that fat mass excess is independently associated with several pulmonary diseases and lung inflammation. Moreover, it has been shown that obesity **may intensify the detrimental effects of air pollution on the lungs**, and this is not surprising if we consider that these conditions share an excessive activation of the immune system and a lung inflammatory infiltrate. Finally, fat mass excess has also been speculated to be itself a consequence of air pollutants exposure, which has been

proved to induce metabolic disruption and weight gain in murine models. In conclusion, although many variables must be taken into account in the analysis of the pandemic, our observations suggest that obesity may act as effect modifier of smog-induced lung-injury, and the concomitant presence of these two factors could better explain the higher virulence, faster spread and greater mortality of SARS-CoV-2 in Northern Italy compared to the rest of the country.

Keywords: obesity, air pollution, covid-19 lethality, immune system

Main Text

1. Introduction

In the previous publication "Can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in Northern Italy?" Conticini et al. investigated the correlation between high lethality of the novel Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) and the atmospheric pollution in Northern Italy, one of the worst hit areas in Europe by the pandemic [1]. In fact, it has been observed that the Northern regions of Lombardy and Emilia Romagna showed death rates of about 12%, unexpectedly higher compared to the rest of the country, where it was around 4.5% [2]. In particular, the authors hypothesized that the surplus of lethality in Northern Italy may be at least in part explained by the evidence of highest pollution reported in this area. To note, Fattorini D. & Regoli, F. recently reported data on the distribution of atmospheric pollutants (Nitric Oxid, NO2; atmospheric particulate matter with a diameter ≤2.5 mm, PM2.5; and atmospheric particulate matter with a diameter ≤10.0 mm, PM10) in Italian regions during the last 4 years, the number of days exceeding regulatory limits, and the years of the last decade (from 2010 to 2019) in which the limits have been exceeded for at least 35 days. In this regard, they highlighted that Northern Italy has been constantly exposed to air pollution; moreover, air-quality data have been shown to significantly correlate with cases of Coronavirus Disease 19 (COVID-19) in up to 71 Italian provinces providing that chronic exposure to atmospheric contamination may have played a role in facilitating the spread of the virus [3], and this is not surprising if we consider that atmospheric particulate matter can act as a carrier for many chemical and biological contaminants, including viruses, as they can facilitate their transport and spread [4].

Furthermore, Conticini et al. highlighted that both acute respiratory distress syndrome (ARDS) – **one of the worst** COVID-19 clinical manifestation, strongly associated with intensive care unit (ICU) and death - and air pollution exposure **are correlated to a hyper-activation of the innate immune system,** as reflected by the increase of pro-inflammatory cytokines in either serum or lung parenchyma [1].

However, this hypothesis alone does not fully explain why particular subgroups of subjects are at major risk of severe manifestation of COVID-19. Therefore, we **hypothesized** that obesity may represent a further missing link between COVID-19 lethality and air pollution in Northern Italy.

2. Obesity as predisposing factor for worse COVID-19 outcome

The features most associated with COVID-19 infection and its respiratory complications are male gender, older age, cardiovascular disease, diabetes and higher BMI [5-7]. Although assessment of obesity is rarely reported in clinical studies**, emerging evidence** suggest that fat mass excess is associated with either COVID-19 prevalence or severity. In fact, a recent study involving 4103 patients diagnosed with COVID-19 in an academic hospital in the United States proved that a BMI >40 kg/m2, suggestive for severe obesity, was one of the strongest predictive factors for hospitalization (OR 6·2) [8]. Moreover, another retrospective study including 103 hospitalized patients with COVID-19, showed that morbid obesity was associated with admission to ICU [9], while Simonnet A. et al. reported that weight excess in 124 patients admitted to ICU for SARS-CoV-2 was an independent predictor for the need of invasive mechanical ventilation [10]. **Finally, it has been recently proved that abdominal visceral fat is significantly associated with COVID-19 radiological severity and clinical outcomes [11].** These findings reinforce the hypothesis that obesity represents an independent risk factor for COVID-19 prevalence and severity.

3. Obesity as effect modifier of air pollution-induced lung dysfunction

Several evidence support the hypothesis that a mutual relationship between obesity, air pollution and lung inflammation may exist. First, it is largely known that excessive fat mass is associated with several respiratory pathological conditions, such as asthma, obstructive sleep apnea, obstructive chronic pulmonary disease and ARDS [12]. The detrimental effects of the increased fat mass on lung could be mediated not only by the anatomical encumbrance of adipose tissue in excess, but also by the low grade systemic inflammation typically associated to obesity [13,14]; the chronic systemic inflammation on the one hand contributes to the metabolic disruption associated with adipose tissue expansion and on the other hand it can exert detrimental effects on the immune system, making it more susceptible to infections and less responsive to vaccinations, antivirals and antimicrobial drugs [15]. Intriguingly it has recently been observed that adipocytes can accumulate within the lungs of obese subjects, thus generating an abnormal ectopic fat deposition site and exerting a role in enhancing pulmonary inflammatory infiltrate [16], similarly to what happens in the lungs of subjects exposed to air pollutants, as previously highlighted by Conticini et al [1]. Moreover, if it is largely accepted that air pollution may contribute to the pathogenesis of pulmonary diseases, some studies have also highlighted that the expansion of adipose tissue, namely visceral fat, is strongly associated with air pollution-induced lung dysfunction [16-19], and this is not surprising considering that both fat excess and air pollution-derived lung injury have been linked to increased local and systemic inflammation [21-22]. In this regard, it has been observed in Asian men that obesity may exhibit a synergistic effect on the relationship between prolonged exposure to air pollutants and worse pulmonary function, suggesting that excessive fat, especially the abdominal one, may intensify the adverse effects of air pollutants on lung function [18].

Another link between air pollution, obesity and COVID-19 severity may be Vitamin D deficiency; obesity is closely associated with low vitamin D levels, as higher body mass index leads to lower vitamin concentrations [23] and, in light of its largely known and beneficial immunomodulating actions, Vitamin D deficiency may represent an independent risk factor for COVID-19 severity [24, 25]. Interestingly, air pollution itself predisposes to lower levels of vitamin D, as air pollutants skin deposition prevents local vitamin D synthesis [26].

Taken together these considerations, it appears reasonable to hypothesize that ponderal excess, although not a mediator of air pollution-derived lung injury, may represent an effect modifier of this damage, since obesity can intensify the detrimental effects of air pollutants on the lungs [27].

4. Is obesity a consequence of air pollution?

In addition to representing a contributing factor to the development of smog-induced lung damage, obesity has also been speculated to be itself a consequence of air pollution, although few evidence support this hypothesis. In fact, it is largely accepted that environmental factors, such as the presence of endocrine disrupting compounds (EDCs), play a key role in the pathogenesis of ponderal excess, and specific EDCs, including also inhaled pollutants, are identified as “obesogenic and/or diabetogenic” [20, 28, 29]. To interest, a recent metanalysis found that long-term exposure to ambient air pollution represents a predisposing factor not only for obesity but also for Type 2 Diabetes [30]. Furthermore, the exposure to Bisphenol A, an organic synthetic compound commonly employed as plasticizer, may exert detrimental effects on glycemic homeostasis [31]. To note, it is largely known that obesity is strongly associated with type 2 diabetes [32], which is itself an independent risk factor for poor prognosis in COVID-19 patients [5-7]. It has been observed that in Chinese cities, where the smog is alarmingly increasing, the amount of air pollutants and the prevalence of obesity are strongly correlated, especially among older people, suggesting that aged subjects are more sensitive to ambient air pollutants [19], which is relevant considering that both advanced age and obesity are major risk factors for COVID-19 severity [5-7]. Although it is almost impossible to define the causal relationship between obesity and air pollution from epidemiological studies, some evidence deriving from preclinical studies support that air pollutants may represent a direct contributing factor to the pathogenesis of obesity; In fact, air pollutants might act as “obesogens” by altering the methylation of peroxisome proliferator-activated receptor gamma (PPARγ) or PPARγ target molecules, known to exert a pivotal role in the regulation of adipogenesis [33], or via their binding to the α and β estrogen receptors (ER), actively involved in the regulation of energy metabolism pathways [34]; furthermore, a recent preclinical study showed that inhaled air pollutants can activate local and systemic inflammatory processes, leading to recruitment of inflammatory cells in adipose tissue with consequent weight gain and metabolic disruption [21]; these findings suggest that air pollution may predispose to obesity and its comorbidities in several ways, although prospective population **studies** are needed to confirm this hypothesis.

5. Obesity, pollution and COVID-19 cases in Italy: an epidemiological analysis

In light of the previous considerations, we would ideally expect a similar trend in obesity prevalence, air quality data and **COVID-19 severity** in Italy; however, while the incidence of COVID-19 infections, **the mortality rate for COVID-19** and mean NO2, PM2.5 and PM10 levels follow a similar trend, as they are higher in the North compared to the South of the country, the prevalence of obesity/overweight seems to behave in the opposite way, being higher in the southern regions compared to the northern ones (Table 1). However, many variables must be taken into account in the interpretation of these data. First, the disparity in obesity prevalence within the country may be explained by the different cultural buffering, socio-economic condition, and the heterogeneous availability of obesity care public services between the northern and southern Italy [35]; therefore, even if air pollution plays a role in obesity development, this could be limited by the other several factors involved in the pathogenesis of this multifactorial disease. Second, if it is true that the prevalence of ponderal excess is higher in the southern regions, it has also been reported that the population living in the northern ones is older, as expressed by the ageing index, which represent the ratio of elderly persons (aged 65 and over) to the number of young persons (from 0 to 14) (Table 1). **Although we do not derive a significant correlation between the ageing index and mortality rate for COVID-19 (p=.6), which is influenced itself by several other variables, it is worth recalling that advanced age was previously proved a predictive factor for severe COVID-19 [5-7].**

Furthermore, Italian regions adopted different health policies in the management of the pandemic, and this has certainly influenced the spread of Sars-Cov2 infection; for example, in Veneto, despite the higher NO2, PM2.5 and PM10 levels in the weeks preceeding SARS-Cov2 outbreak and the greater prevalence of overweight/obesity, there were lower cumulative incidence of Covid-19 cases and **mortality** compared to Lombardia. However, although the two regions adopted similar approaches in terms of social distancing and retail closures, Veneto proceeded towards a more proactive strategy for the containment of the virus, with a policy based on extensive testing of both symptomatic and asymptomatic cases, whereas Lombardy opted instead for a more conservative approach to testing, with a stronger focus only on symptomatic cases [36]. **It is likely that the different regional policies may have overestimated the mortality data reported in Lombardy compared to Veneto, making data related to virus lethality uncertain and difficult to interpret.**

Furthermore, it has been reported that in Lombardia, where during the pandemic outbreak hospitals were overcrowded and contaminated, and medications, mechanical ventilators, oxygen, and personal protective equipment were not available, home care and mobile clinics have been encouraged [37]; on the other hand, it is reasonable to hypothesize that in Veneto, where the pandemic did not reach the same frightening proportions, a more patient-centered care strategy has been adopted. The different health-care strategies adopted by the two neighboring regions could explain the milder impact of the pandemic **and the lower virus lethality** in Veneto in comparison to Lombardia, despite the higher air pollution levels and overweight/obesity prevalence (Table 1). Intriguingly, when we analyzed specific sub-regions of Lombardia, in which comparable health policy strategies were adopted, we noted that in Bergamo, by far the most affected by the pandemic, PM2.5 and PM10 levels registered between February 10 and March 10 were 35.4 ug/m3 and 43.8 ug/m3, higher than the mean regional ones, and overweight/obesity prevalence was 36.2% [38], which is still higher than the one reported in Lombardia (Table 1). These data suggest that other variables in association to obesity and pollution should be taken into consideration in the analysis of the pandemic trend, but they do not exclude that the two factors may act synergistically to facilitate the spread and severity of COVID-19.

Regions	**COVID-19 Cumulative Incidence per 100000 inhab.**[a]	**Mortality rate for COVID-19 standardized per 100000 inhab.**[b]	**NO2 (ug/m3)**[c]	**PM2.5 (ug/m3)**[c]	**PM10.0 (ug/m3)**[c]	**Overweight and/or Obesity Prevalence (%)**[d]	**Ageing Index**[e]
Lombardia	913.64	129.3	36.66	31.15	43.25	35.4	169.1
Piemonte	722.15	39.8	30.88	/	/	37.5	210.3
Emilia-Romagna	629.76	64.1	31.91	/	41.29	42.4	185.6
Veneto	301.8	26.4	33.52	42.88	71.74	40.6	177.6
Toscana	267.59	17.4	29	15.63	26.76	36.4	209.1
Liguria	635.42	51.3	/	/	/	34.3	260.4
Lazio	136.04	8.2	33.57	15.28	32.41	40.3	167.3

Marche	442.35	42.4	23.68	26.53	48.53	42.3	201.8
Campania	79.7	6.4	22.9	23.01	37.02	50.9	134.7
Puglia	112.09	9.3	11.4	15.73	25.65	45.8	175
Trentino	1007.77	57.2	48.18	20.35	32.15	34	142.4
Sicilia	61.54	4.2	25.28	/	/	46.6	158.6
Friuli-Venezia Giulia	273.61	17.9	15.46	/	44.9	41	223.2
Abruzzo	250.23	19.4	34.7	22.05	33.25	44.6	197.6
Alto Adige	489.29	57.2	41.54	/	/	34.7	127.2
Umbria	162.81	5.4	25.46	20.67	26.04	43	209.6
Sardegna	82.7	6.5	19.28	/	/	38.8	221.2
Calabria	59.11	4.3	17.31	10.94	21.67	48.4	168.3
Valle d'Aosta	953.32	94.1	/	/	/	37.8	187.2
Molise	143.64	4.4	15.03	/	/	48.4	224.8
Basilicata	65.02	2.6	/	/	17.1	51.3	200.3

Table 1. Covid-19 cumulative incidence per 100000 inhab., NO2, Mortality rate for COVID-19 standardized per 100000 inhab., PM2.5, PM10.0 mean levels registered from the 10th of February to the 10th of March 2020, Overweight/Obesity prevalence and Ageing Index in Italian Regions. Data have been obtained from: Ministero della Salute (www.salute.gov.it), updated to June 19, 2020 [a]; Report on impact of the Covid-19 epidemic on the total mortality, Istat, June 4, 2020 [b]; European Environment Agency (https://www.eea.europa.eu/themes/air/air-quality-and-covid19/monitoring-covid-19-impacts-on) updated to June 29, 2020 [c]; Studio Passi (2015-2018) [d]; Istat, Indicatori Demografici 2020 [e]. **COVID-19 Cumulative Incidence per 100000 inhab**.: number of new cases per 100000 inhab. From March 3 to June 19, 2020**.** **Mortality rate for COVID-19 standardized per 100000 inhab.**: adjustment of the mortality rate that allows to compare populations having different age distributions; the standardization method by age consists of summarizing the mortality rates calculated for each specific age group on a standard population (in this case the italian population at Census 2011). **Ageing Index**: the ratio of elderly persons (aged 65 and over) to the number of young persons (from 0 to 14). **Abbreviation**: COVID-19, Corona Virus Disease 2019; inhab., inhabitants; NO2, nitrix oxid; PM2.5, atmospheric particulate matter with a diameter ≤2.5 mm; PM10.0, atmospheric particulate matter with a diameter ≤10.0 mm.

Conclusion

The high degree of smog has been proposed as an explanation for the increased COVID-19 severity in Northern Italy, strengthened by the observation that ARDS and smog-induced lung damage share similar pathogenetic mechanisms involving an hyperactivation of the innate immune system. However, this hypothesis alone does not fully explain why particular subgroups of subjects, such as elderly and obese patients, are at major risk of severe manifestation of COVID-19.

In the current correspondence, we suggested that obesity may be one of the missing piece to complete this puzzle. In fact, in addition to representing a predisposing factor for COVID-19 infection and worse clinical outcomes, fat mass excess has also been associated to increased pulmonary and systemic inflammation, similarly to what happens in the lungs of subjects exposed to air pollutants and of patients diagnosed with COVID-19. In particular, obesity may be considered as an effect modifier of smog-derived lung injury, since its presence intensifies the detrimental effects of air pollutants on the lungs and it predisposes to Sars-Cov-2 infection and severity. Although several variables, such as age and health care policies, must be taken into account in the analysis of the pandemic trend, our observations suggest that ponderal excess and air pollution may act synergistically to contribute to severe COVID-19, and that the concomitant presence of obesity together and air pollution could better explain the higher virulence, faster spread and greater mortality of SARS-CoV-2 in Northern Italy compared to the rest of the country.

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Bibliography

1. Conticini E, et al. Can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in Northern Italy? Environ. Poll. 2020; 261:114465. doi: 10.1016/j.envpol.2020.114465
2. Protezione Civile Italiana. Map available at: http://opendatadpc.maps.arcgis.com

3. Fattorini, D. & Regoli, F. Role of the chronic air pollution levels in the Covid-19 outbreak risk in Italy. Environ. Poll. 2020; 264:114732. doi: 10.1016/j.envpol.2020.114732
4. Després VR, et al. Primary biological aerosol particles in the atmosphere: A review. *Tellus, Ser B Chem Phys Meteorol*. 2012;64(1). doi:10.3402/tellusb.v64i0.15598
5. Peng YD, et al. Clinical Characteristics and Outcomes of 112 Cardiovascular Disease Patients Infected by 2019-nCoV. Zhonghua Xin Xue Guan Bing Za Zhi, 2020;48(0):E004. doi:10.3760/cma.j.cn112148-20200220-00105
6. Liu M, et al. Clinical characteristics of 30 medical workers infected with new coronavirus pneumonia Zhonghua Jie He He Hu Xi Za Zhi. 2020;43(0):E016. doi:10.3760/cma.j.issn.1001-0939.2020.0016
7. Coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK – seventh update, 25 March 2020. Stockholm: ECDC; 2020.
8. Petrilli CM, et al. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City; MedRxiv 2020 April. https://doi.org/10.1101/2020.04.08.20057794
9. Kalligeros M, et al. (2020), Association of Obesity with Disease Severity among Patients with COVID-19. Obesity (Silver Spring). Accepted Author Manuscript. doi:10.1002/oby.22859.
10. Simonnet A, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation [published online ahead of print, 2020 Apr 9]. Obesity (Silver Spring). 2020;10.1002/oby.22831. doi:10.1002/oby.22831
11. Watanabe M, et al. Visceral fat shows the strongest association with the need of intensive Care in Patients with COVID-19. *Metabolism. In Press.* doi: 10.1016/j.metabol.2020.154319

12. Mancuso P. Obesity and lung inflammation. J Appl Physiol (1985). 2010;108(3):722-728. doi:10.1152/japplphysiol.00781.2009
13. Reilly SM, et al. Adapting to obesity with adipose tissue inflammation. Nat Rev Endocrinol. 2017;13(11):633-643. doi:10.1038/nrendo.2017.90
14. Watanabe M, et al. Obesity and SARS-CoV-2: a population to safeguard. *Diabetes Metab Res Rev*. 2020;(April):15-16. doi:10.1002/dmrr.3325
15. Muscogiuri G, et al. Commentary: Obesity: The "Achilles heel" for COVID-19?. *Metabolism*. 2020;108:154251. doi:10.1016/j.metabol.2020.154251
16. Elliot JG, et al. Fatty airways: implications for obstructive disease. Eur Respir J 2019; 54 (6).doi: 10.1183/13993003.00857-2019
17. Conti S, et al. The association between air pollution and the incidence of idiopathic pulmonary fibrosis in Northern Italy. Eur Respir J 2018; 51: 1700397. Doi: 10.1183/13993003.00397-2017
18. Kim H-J, et al., Abdominal adiposity intensifies the negative effects of ambient air pollution on lung function in Korean men Int J Obes (2017) 41, 1218–1223. Doi: 10.1038/ijo.2017.97
19. Yang Z, et al. Air Pollution as a Cause of Obesity: Micro-Level Evidence from Chinese Cities. Int J Environ Res Public Health. 2019;16(21):4296. Published 2019 Nov 5. doi:10.3390/ijerph16214296
20. Lubrano C, et al. Obesity and metabolic comorbidities: Environmental diseases? Oxid Med Cell Longev. 2013;2013. doi:10.1155/2013/640673Wei Y
21. Zhang JJ, et al. Chronic exposure to air pollution particles increases the risk of obesity and metabolic syndrome: findings from a natural experiment in Beijing. FASEB J. 2016;30 (6):2115–2122. Doi: 10.1096/fj.201500142

22. Bastard JP, et al. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. J Clin Endocrinol Metab. 2000;85(9):3338-3342. doi:10.1210/jcem.85.9.6839
23. Barrea L, et al. Low serum vitamin D-status, air pollution and obesity: A dangerous liaison. *Rev Endocr Metab Disord*. 2017;18(2):207-214. doi:10.1007/s11154-016-9388-6
24. Muscogiuri G, et al. Nutritional recommendations for CoVID-19 quarantine. *Eur J Clin Nutr*. 2020;74(6):850-851. doi:10.1038/s41430-020-0635-2
25. Grant WB, et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients*. 2020;12(4):988. Published 2020 Apr 2. doi:10.3390/nu12040988
26. Kurylowicz A. Impact of Air Pollution on Vitamin D Status and Related Health Consequences. *Impact Air Pollut Heal Econ Environ Agric Sources*. 2011. doi:10.5772/17838
27. Corraini P, et al. Effect modification, interaction and mediation: an overview of theoretical insights for clinical investigators [published correction appears in Clin Epidemiol. 2018 Mar 01;10 :223. doi:10.2147/CLEP.S129728
28. Nappi F, et al. Endocrine Aspects of Environmental "Obesogen" Pollutants. *Int J Environ Res Public Health*. 2016;13(8):765. Published 2016 Jul 28. doi:10.3390/ijerph13080765
29. Darbre PD. *Endocrine Disruption and Disorders of Energy Metabolism*. Elsevier Inc.; 2015. doi:10.1016/B978-0-12-801139-3.00015-6
30. Liu F, et al. Associations between long-term exposure to ambient air pollution and risk of type 2 diabetes mellitus: A systematic review and meta-analysis. *Environ Pollut*. 2019;252(Pt B):1235-1245. doi:10.1016/j.envpol.2019.06.033

31. Provvisiero DP, et al. Influence of Bisphenol A on Type 2 Diabetes Mellitus. *Int J Environ Res Public Health*. 2016;13(10):989. Published 2016 Oct 6. doi:10.3390/ijerph13100989
32. Al-Goblan AS, et al. Mechanism linking diabetes mellitus and obesity. *Diabetes Metab Syndr Obes*. 2014;7:587-591. Published 2014 Dec 4. doi:10.2147/DMSO.S67400
33. Janani C, et al. PPAR gamma gene--a review. Diabetes & Metabolic Syndrome. 2015 Jan-Mar;9(1):46-50. DOI: 10.1016/j.dsx.2014.09.015.
34. Chen JQ, et al. Regulation of energy metabolism pathways by estrogens and estrogenic chemicals and potential implications in obesity associated with increased exposure to endocrine disruptors. *Biochim Biophys Acta*. 2009;1793(7):1128-1143. doi:10.1016/j.bbamcr.2009.03.009
35. Watanabe M, et al. Obesity treatment within the Italian national healthcare system tertiary care centers- what can we learn? Eating and weight disorders. Accepted Author Manuscript. Doi: 0.1007/s40519-020-00936-1
36. Romagnani P, et al. The COVID-19 infection: lessons from the Italian experience. *J Public Health Policy*. 2020;(0123456789). doi:10.1057/s41271-020-00229-y
37. Nacoti M, et al. At the Epicenter of the Covid-19 Pandemic and Humanitarian Crises in Italy: Changing Perspectives on Preparation and Mitigation. *NEJM Catalyst Innovations in Care Delivery.* 2020;1(2):1-5. doi:10.1056/CAT.20.0080
38. Press release 61/2019 8/11/2019 ATS Bergamo Lombardy Region

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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