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Supplemental Material

Long-Term Exposure to Ambient Air Pollution and Mortality among Four Million COVID-19 Cases in Italy: The EpiCovAir Study

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Additional File- Excel Document

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Table S1. Municipality-specific variables on: characteristics of the area, population, mobility, socio-economic and health status, and healthcare offer

Category	Variable	Source	Year	Description
Municipality characteristics	Code	ISTAT	2020	ISTAT code of the municipality
	Name	ISTAT	2020	Name of the municipality
	Province	ISTAT	2020	ISTAT code of the province
	Region	ISTAT	2020	ISTAT code of the region
	Area	ISTAT	2020	Size (km2)
	Elevation	ISTAT	2020	Elevation (m)
	Altimetric zone	ISTAT	2020	1 = Inland mountains; 2 = Coastal mountains; 3 = Inland hills; 4 = Coastal hills; 5 = Plane
	Coastal	ISTAT	2020	Municipality on the coast (yes/no)
	Island	ISTAT	2020	Municipality on an island (yes/no)
	Urbanization	ISTAT	2018	1 = Major city; 2 = Minor city; 3 = Sub-urban or rural area
	Longitude	ISTAT	2020	Longitude
	Latitude	ISTAT	2020	Latitude
Population	Pop 2011	ISTAT	2011	Resident population, Oct 9 2011 (Census date)
	Pop 2019	ISTAT	2019	Resident population, Dec 31 2019
	Pop class	ISTAT	2020	Population size, in classes: 1=<2.000; 2=2.000-10.000; 3=10.000-50.000, 4=>50.000
	Pop density	ISTAT	2019	Population density (pop.2019 / size of the area)
	% over 65 years	ISTAT	2020	% pop over 65 years
Mobility	attraction_index	ISTAT	2014-2015	Ratio between movements of individuals who work or study in the municipality, and total individuals in the area
	self-containment	ISTAT	2014-2015	Ratio between individuals who work or study in the municipality, and total movements in the area
	movements_2019	ASSAEROPORTI	2019	Number of flights, average 2019
	passengers_2019	ASSAEROPORTI	2019	Number of passengers, average 2019
	movements_2020	ASSAEROPORTI	2020	Number of flights at January 2020
	passengers_2020	ASSAEROPORTI	2020	Number of passengers at January 2020
	movements_out	ISTAT	2011	Number of individuals who move outboud the municipality for work or study reasons
	movements_in	ISTAT	2011	Number of individuals who move inside the municipality for work or study reasons
	movements_tot	ISTAT	2011	Number of individuals who move for work or study reasons
	SLL_index	ISTAT	2020	Code of Local Work System (Sistema Locale del Lavoro, SLL)
	train_stations	OpenStreetMap	2016	Presence of a rail station (yes/no)
	stations_number	OpenStreetMap	2016	Number of rail stations

	airport_30km	ISTAT	2015	Number of airports within 30-km buffer
Socio-economic and health status	income_14_15	ISTAT	2014-2015	Ratio between gross income and number of households components (euro)
	entrepren_14_15	ISTAT	2014-2015	Number of enterprises, per 1000 inhabitants
	SEP	ISS	2011	Socio-Economic Deprivation index, continuous
	SEP_quintiles	ISS	2011	Socio-Economic Deprivation index, in quintiles
	cvd_hosp_rate	ISS-ISTAT	2013-2018	Cardiovascular hospitalization rate (average 2013-2018, per 100)
	resp_hosp_rate	ISS-ISTAT	2013-2018	Respiratory hospitalization rate (average 2013-2018, per 100)
	all_hosp_rate	ISS-ISTAT	2013-2018	All-cause hospitalization rate (average 2013-2018, per 100)
	cvd_mort_rate	ISS-ISTAT	2013-2017	Cardiovascular mortality rate (average 2013-2017, per 100)
	resp_mort_rate	ISS-ISTAT	2013-2017	Respiratory mortality rate (average 2013-2017, per 100)
	all_mort_rate	ISS-ISTAT	2013-2017	All-cause mortality rate (average 2013-2017, per 100)
Healthcare offer	n_hosp	Min. Health	2019	Number of hospitals
	n_nursing	Min. Health	2019	Number of nursing homes
	beds_ordinary	Min. Health	2019	Number of beds in ordinary regimen wards
	beds_dh	Min. Health	2019	Number of beds in day-hospital wards
	beds_longstay	Min. Health	2019	Number of beds in long-stay wards
	beds_rehab	Min. Health	2019	Number of beds in rehabilitation wards
	beds_icu	Min. Health	2019	Number of beds in Intensive Care Units
	n_er	Min. Health	2019	Number of Emergency Rooms
	dist_hosp	Min. Health	2019	Distance (m) from closest hospital
	dist_nursing	Min. Health	2019	Distance (m) from closest nursing home
	dist_covid	Min. Health	2019	Distance (m) from closest COVID center
	dist_er	Min. Health	2019	Distance (m) from closest Emergency Room
	n_hca	ISPRA	2017	Number of healthcare residences
	workers_hca	ISPRA	2017	Average number workers in healthcare residences

Table S2. Effect of air pollutants on mortality with inclusion of healthcare professionals, main approach and sensitivity analyses: percent increase in mortality risk (%IR), and 95% Confidence Intervals (95% CI) per 1 μg/m^3 increment in air pollutants. Italy, February 20, 2020 – June 15, 2021 (n=4,126,189 COVID-19 cases, n=124,522 deaths)

Model	Description	$PM_{2.5}$			PM_{10}			NO_2		
		%IR	95% CI		%IR	95% CI		%IR	95% CI	
	Increasing adjustment levels									
M1	Crude	3.1	2.9	3.3	2.2	2.1	2.4	2.4	2.2	2.5
M2	M1 + province	1.8	1.4	2.2	1.5	1.2	1.7	2.6	2.5	2.8
M3	M2 + month	1.6	1.2	2.1	1.3	1.0	1.6	2.4	2.2	2.5
M4	M3 + age	0.9	0.6	1.2	0.7	0.5	0.9	0.5	0.4	0.6
M5	M4 + sex	1.0	0.7	1.2	0.7	0.5	0.9	0.5	0.4	0.6
M6	**Main model: M5 + GPS (matched on ventiles)**	0.7	0.5	0.9	0.3	0.2	0.5	0.6	0.5	0.7
	Sensitivity models									
M7	M5 + GPS (linear term)	1.0	0.7	1.2	0.7	0.5	0.9	0.5	0.4	0.6
M8	M5 + 4 CPs added as covariates	1.3	1.0	1.6	1.0	0.8	1.2	0.8	0.6	0.9
M9	M5 + GPS (inverse weights)	1.3	1.0	1.5	1.0	0.8	1.1	0.7	0.5	0.8
M10	M5 + GPS (matched on percentiles)	1.0	0.7	1.3	0.6	0.4	0.7	0.4	0.2	0.6
M11	M5 + GPS (matched on deciles)	0.6	0.3	0.8	0.6	0.4	0.7	0.7	0.6	0.8
M12	M5 + alternative GPS #1	1.3	1.0	1.5	0.6	0.4	0.7	0.9	0.8	1.0
M13	M5 + alternative GPS #2	1.0	0.8	1.2	0.8	0.6	0.9	0.9	0.8	1.0

Table S3. Effect of air pollutants on hospitalizations, main approach and sensitivity analyses: percent increases of risk (%IR), and 95% Confidence Intervals (95% CI), per 1 μg/m^3 increment in air pollutants. Italy, February 20, 2020 – June 15, 2021 (n=3,995,202 COVID-19 cases, n=391,329 hospitalizations)

Model	Description	$PM_{2.5}$			PM_{10}			NO_2		
		%IR	95% CI		%IR	95% CI		%IR	95% CI	
	Increasing adjustment levels									
M1	Crude	5.1	5.0	5.2	3.7	3.6	3.7	3.2	3.2	3.3
M2	M1 + province	1.7	1.5	1.9	1.4	1.3	1.5	2.3	2.2	2.4
M3	M2 + month	1.5	1.3	1.7	1.2	1.1	1.4	1.9	1.8	2.0
M4	M3 + age	0.7	0.5	0.9	0.6	0.5	0.7	0.5	0.5	0.6
M5	M4 + sex	0.8	0.6	1.0	0.6	0.5	0.8	0.6	0.5	0.7
M6	**Main model: M5 + GPS (matched on ventiles)**	**0.9**	**0.7**	**1.1**	**0.6**	**0.5**	**0.8**	**0.7**	**0.6**	**0.8**
	Sensitivity models									
M7	M5 + GPS (linear term)	0.7	0.5	0.9	0.6	0.5	0.7	0.6	0.5	0.7
M8	M5 + 4 CPs added as covariates	0.5	0.3	0.7	0.5	0.3	0.6	0.4	0.3	0.5
M9	M5 + GPS (inverse weights)	0.7	0.5	0.9	0.6	0.4	0.7	0.6	0.5	0.7
M10	M5 + GPS (matched on percentiles)	1.0	0.7	1.3	0.6	0.4	0.8	0.4	0.2	0.6
M11	M5 + GPS (matched on deciles)	0.9	0.7	1.1	0.7	0.5	0.8	0.7	0.6	0.8
M12	M5 + alternative GPS #1	1.0	0.7	1.2	0.9	0.7	1.0	0.7	0.6	0.8
M13	M5 + alternative GPS #2	1.1	0.9	1.3	0.9	0.7	1.0	0.8	0.7	0.9

Table S4. Effect of air pollutants on usage of intensive care units (ICU), main approach and sensitivity analyses: percent increases of risk (%IR), and 95% Confidence Intervals (95% CI), per 1 μg/m^3 increments in air pollutants. Italy, February 20, 2020 – June 15, 2021 (n=3,995,202 COVID-19 cases, n=54,699 accesses to intensive care units)

Model	Description	$PM_{2.5}$			PM_{10}			NO_2		
		%IR	95% CI		%IR	95% CI		%IR	95% CI	
	Increasing adjustment levels									
M1	Crude	4.5	4.2	4.7	2.1	1.9	2.3	1.9	1.8	2.1
M2	M1 + province	2.0	1.5	2.6	1.5	1.2	1.9	1.9	1.6	2.1
M3	M2 + month	2.0	1.5	2.5	1.5	1.1	1.8	1.6	1.4	1.8
M4	M3 + age	1.4	1.0	1.7	0.9	0.7	1.2	0.7	0.6	0.9
M5	M4 + sex	1.6	1.3	1.9	1.1	0.9	1.3	0.9	0.8	1.1
M6	**Main model: M5 + GPS (matched on ventiles)**	**1.6**	**1.3**	**1.9**	**1.5**	**1.3**	**1.7**	**1.0**	**0.8**	**1.1**
	Sensitivity models									
M7	M5 + GPS (linear term)	1.5	1.2	1.8	1.1	0.9	1.3	0.8	0.6	0.9
M8	M5 + 4 CPs added as covariates	1.4	1.0	1.7	0.9	0.7	1.2	0.8	0.6	1.0
M9	M5 + GPS (inverse weights)	1.9	1.6	2.2	1.3	1.0	1.5	1.2	1.1	1.4
M10	M5 + GPS (matched on percentiles)	1.9	1.6	2.2	2.1	1.9	2.3	1.1	0.9	1.4
M11	M5 + GPS (matched on deciles)	1.5	1.2	1.8	1.2	1.0	1.4	1.0	0.8	1.1
M12	M5 + alternative GPS #1	2.2	1.9	2.5	1.7	1.6	1.9	1.0	0.9	1.2
M13	M5 + alternative GPS #2	2.4	2.2	2.7	1.5	1.4	1.7	1.3	1.2	1.5

Table S5. Effect of air pollutants on mortality in the three different waves of the COVID-19 pandemic, by individual-level covariates and geographical area: percent increases of risk (%IR), and 95% Confidence Intervals (95% CI), per 1 μg/m^3 increment in air pollutants. Italy, February 20, 2020 – June 15, 2021 (first wave: n=201,210 COVID-19 cases, n=35,440 deaths; second wave: n=1,534,950 COVID-19 cases, n=41,620 deaths; third wave: n=2,259,042 COVID-19 cases, n=47,286 deaths). Results from the main model, adjusted for interaction terms between month, province, age, sex, and ventiles of the generalized propensity score

First wave: 20/02/2020 – 31/05/2020

		n	$PM_{2.5}$			PM_{10}			NO_2		
			%IR	95% CI		%IR	95% CI		%IR	95% CI	
All		201,210	1.1	0.5	1.6	0.7	0.4	1.0	0.7	0.4	1.0
Age	*0-64*	98,080	-0.6	-1.7	0.6	-0.5	-1.2	0.3	0.3	-0.3	1.0
	65-74	29,920	0.3	-1.1	1.7	0.4	-0.5	1.2	0.4	-0.3	1.2
	75-84	38,795	1.7	0.6	2.8	1.0	0.3	1.6	1.3	0.7	1.9
	85+	34,415	1.9	0.6	3.2	1.3	0.5	2.1	0.4	-0.3	1.1
Sex	*Female*	104,197	1.0	0.2	1.9	0.9	0.4	1.4	0.7	0.2	1.2
	Male	97,013	1.1	0.4	1.9	0.6	0.1	1.0	0.7	0.3	1.1
Clinical state at onset	*Symptomatic*	170,894	0.9	0.3	1.5	0.5	0.1	0.8	0.5	0.2	0.8
Geographical area	*Po Valley*	144,545	1.1	0.5	1.7	0.6	0.3	1.0	0.7	0.3	1.0

Second wave: 15/09/2020 – 15/12/2020

		n	$PM_{2.5}$			PM_{10}			NO_2		
			%IR	95% CI		%IR	95% CI		%IR	95% CI	
All		1,534,950	0.1	-0.4	0.5	0.1	-0.2	0.4	0.6	0.4	0.8
Age	*0-64*	1,225,335	0.2	-0.7	1.1	0.5	-0.1	1.1	1.8	1.4	2.2
	65-74	135,791	-0.4	-1.8	1.1	0.1	-0.8	1.1	0.1	-0.6	0.8
	75-84	106,744	-0.8	-1.9	0.3	-0.3	-1.1	0.4	0.4	-0.2	0.9
	85+	67,080	1.3	0.0	2.5	0.5	-0.4	1.3	0.8	0.1	1.4
Sex	*Female*	775,867	0.7	0.1	1.3	-0.3	-0.7	0.2	0.4	0.1	0.7
	Male	759,083	-0.4	-1.0	0.2	0.4	0.0	0.8	0.8	0.5	1.1
Clinical state at onset	*Symptomatic*	824,075	0.2	-0.3	0.8	0.5	0.2	0.9	0.5	0.3	0.8
Geographical area	*Po Valley*	759,084	-0.7	-1.2	-0.2	-0.1	-0.5	0.2	-0.1	-0.4	0.2

Third wave: 16/12/2020 – 15/06/2021

		n	$PM_{2.5}$			PM_{10}			NO_2		
			%IR	95% CI		%IR	95% CI		%IR	95% CI	
All		2,259,042	0.9	0.6	1.3	0.3	0.0	0.5	0.7	0.5	0.8
Age	*0-64*	1,849,828	-1.3	-1.9	-0.7	-1.1	-1.5	-0.7	-0.7	-1.0	-0.4
	65-74	204,196	-0.4	-1.5	0.7	-0.3	-1.0	0.5	0.5	0.0	1.0
	75-84	136,988	1.7	0.6	2.8	0.6	-0.1	1.3	1.1	0.6	1.6
	85+	68,030	2.5	1.1	3.8	1.0	0.2	1.9	1.0	0.4	1.6
Sex	*Female*	1,140,988	1.0	0.4	1.5	0.6	0.3	1.0	0.6	0.4	0.9
	Male	1,118,054	0.9	0.4	1.4	0.0	-0.3	0.3	0.7	0.4	0.9
Clinical state at onset	*Symptomatic*	1,259,975	1.3	0.9	1.8	0.4	0.1	0.7	0.8	0.5	1.0
Geographical area	*Po Valley*	984,519	0.8	0.3	1.2	0.0	-0.2	0.3	0.2	0.0	0.5

Table S6. Results of the two-pollutant models: percent increases of risk (%IR), and 95% Confidence Intervals (95% CI), per 1 μg/m^3 increment in air pollutants. Italy, February 20, 2020 – June 15, 2021 (n=3,995,202 COVID-19 cases, n=124,346 deaths). Results from the main model, adjusted for interaction terms between month, province, age, sex, and ventiles of the generalized propensity score

Exposure	Model	%IR	95% CI	
$PM_{2.5}$	Single	0.7	0.5	0.9
	+ NO_2	-0.4	-0.7	0.0
PM_{10}	Single	0.3	0.2	0.5
	+ NO_2	-0.3	-0.6	0.0
NO_2	Single	0.6	0.5	0.8
	+ $PM_{2.5}$	0.9	0.7	1.0
	+ PM_{10}	0.7	0.5	0.9

Figure S1. Flow-chart of data selection

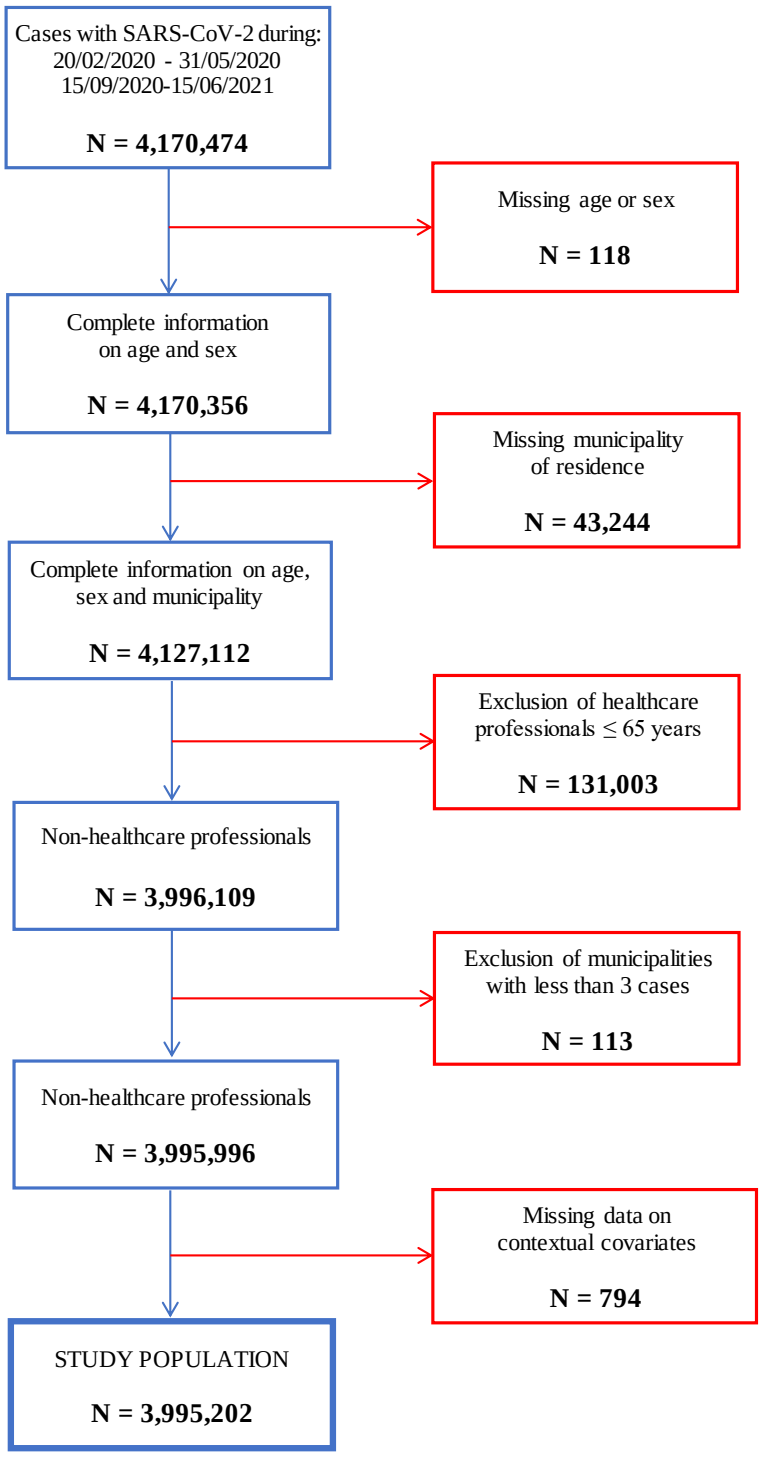
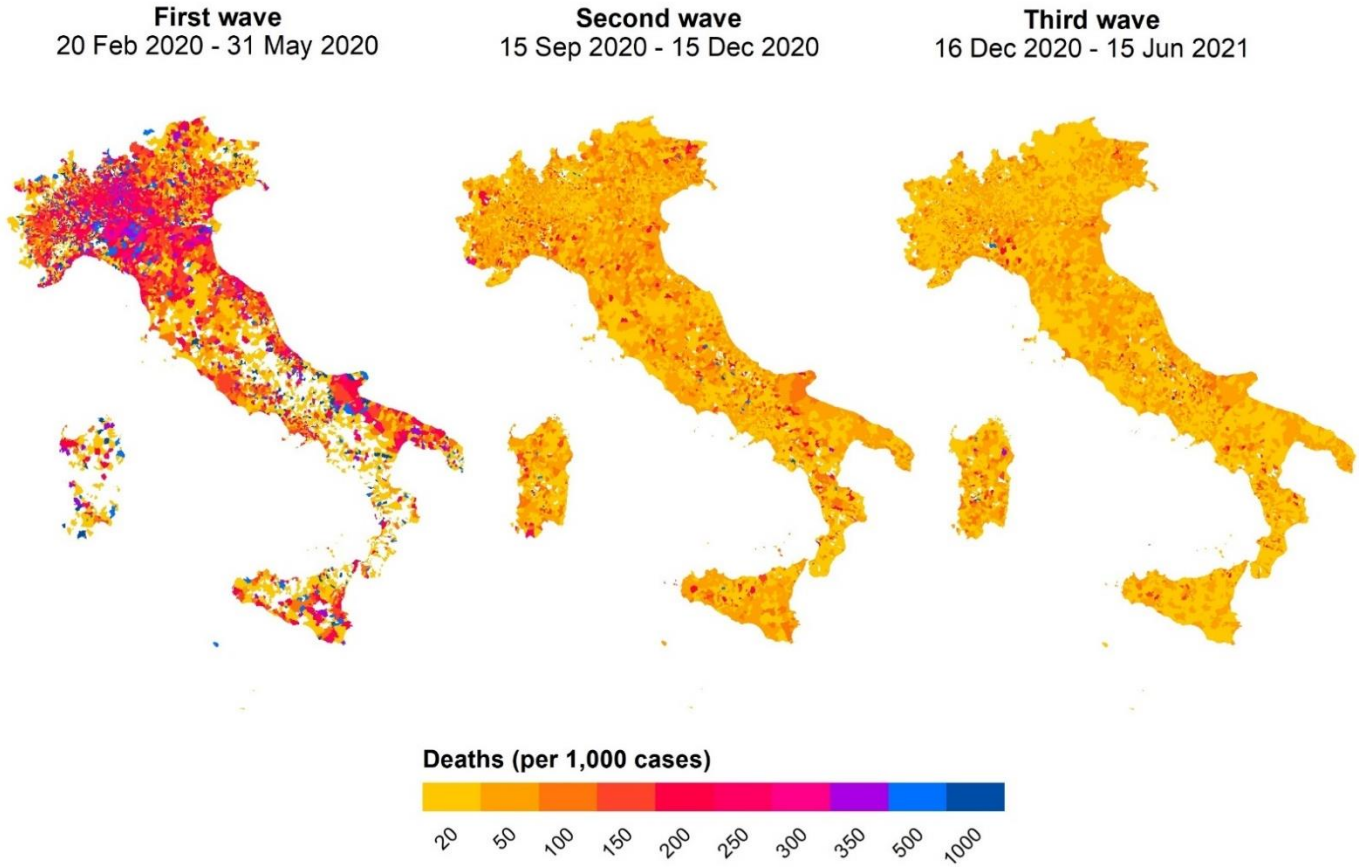
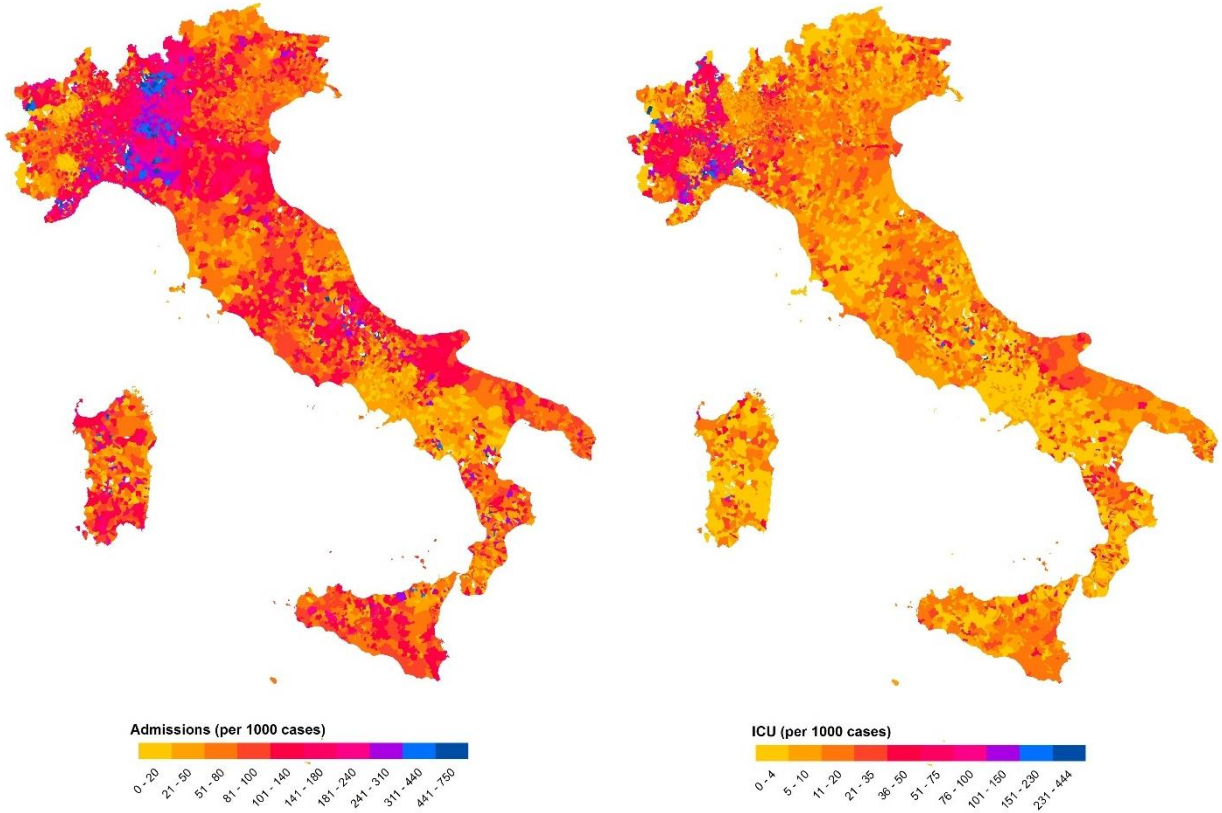


Figure S2. Map of COVID-19 case-fatality rates by municipality[a] in the three different pandemic waves: 20/02/2020 – 31/05/2020, 15/09/2020 – 15/12/2020 and 16/12/2020 – 15/06/2021



[a] Municipalities with no cases are in white

Figure S3. Map of COVID-19 hospitalization rates (left) and usage of intensive care units (ICU) rates (right) by municipality[a], Italy 20/02/2020 – 31/05/2020 and 15/09/2020 – 15/06/2021



[a] Municipalities with no cases are in white

Figure S4. Map of air pollution levels (mean 2016-2019) by municipality in Italy

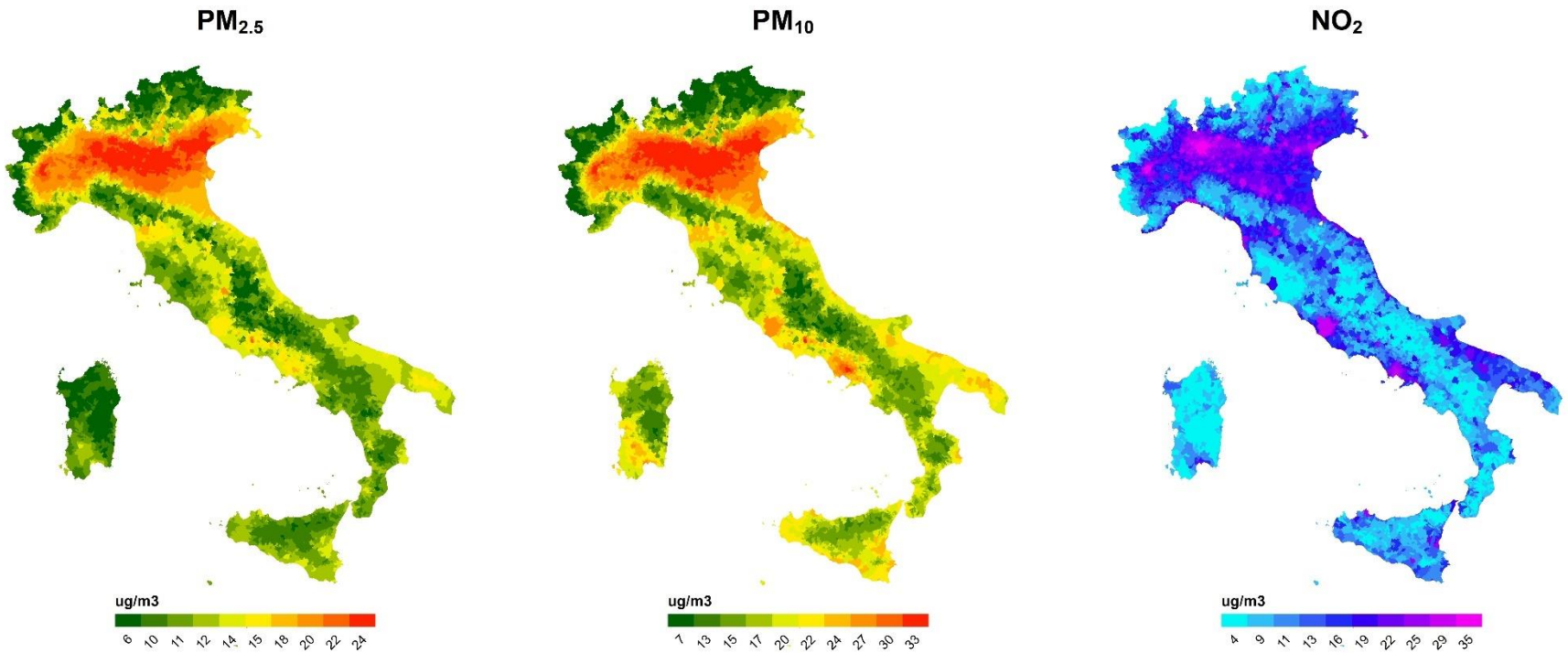
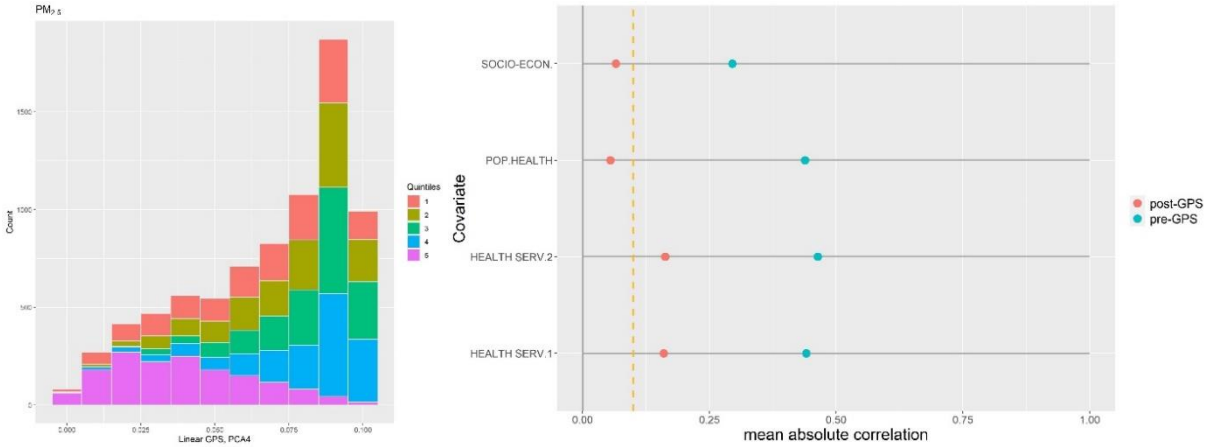
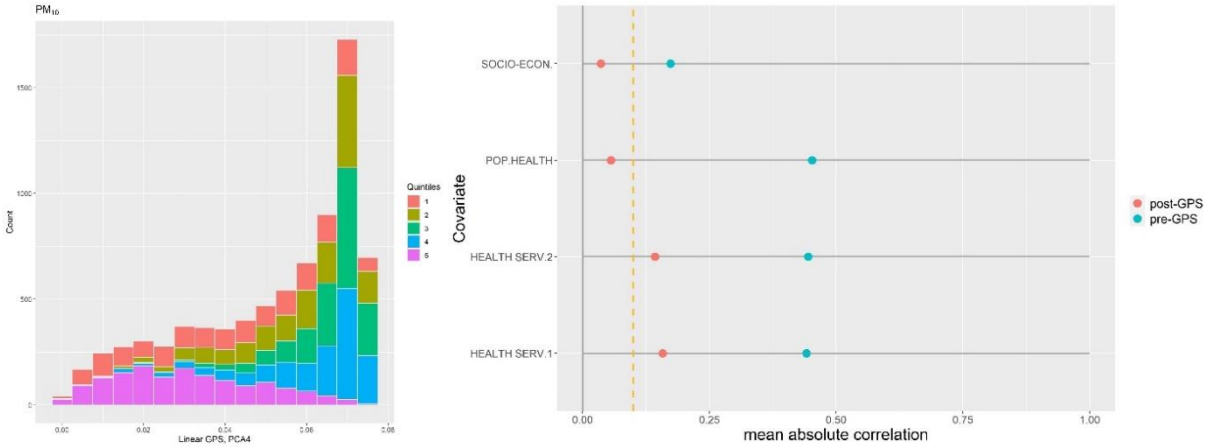


Figure S5. Generalized Propensity Score (GPS) based on 4 selected principal components (PC): distribution of GPS by quintiles of exposure (positivity assumption (left) and absolute correlation between exposure and covariates pre- and post-GPS (balancing plot, right). Relevant data on mean absolute correlations in Excel Table S3

$PM_{2.5}$



PM_{10}



NO_2

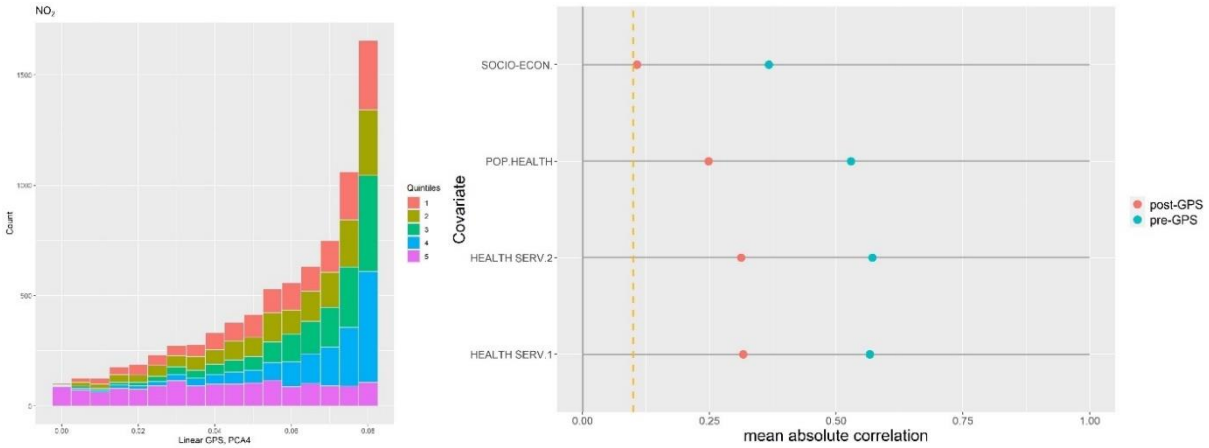
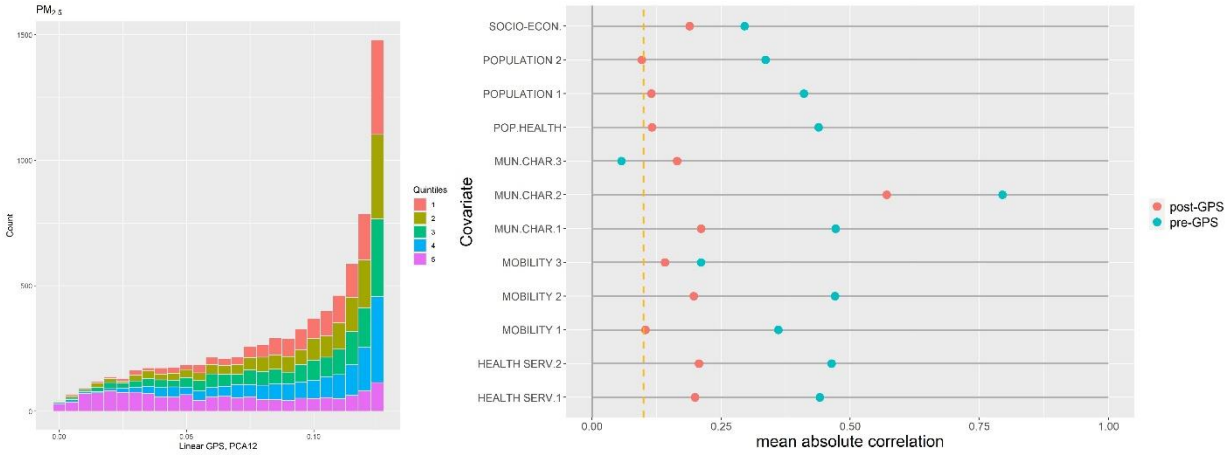
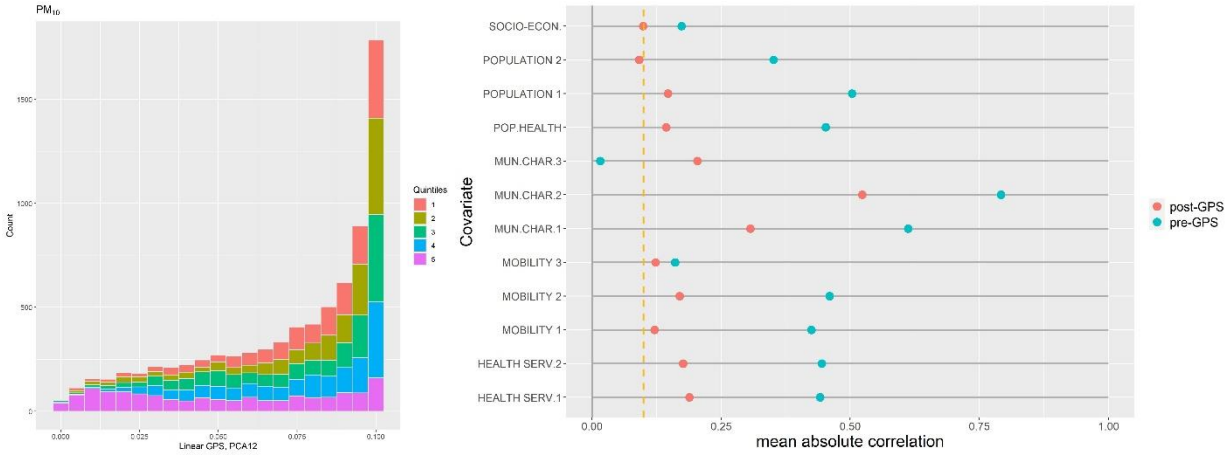


Figure S6. Generalized Propensity Score (GPS) based on all 12 principal components (PC): distribution of GPS by quintiles of exposure (positivity assumption (left) and absolute correlation between exposure and covariates pre- and post-GPS (balancing plot, right). Relevant data on mean absolute correlations in Excel Table S4

$PM_{2.5}$



PM_{10}



NO_2

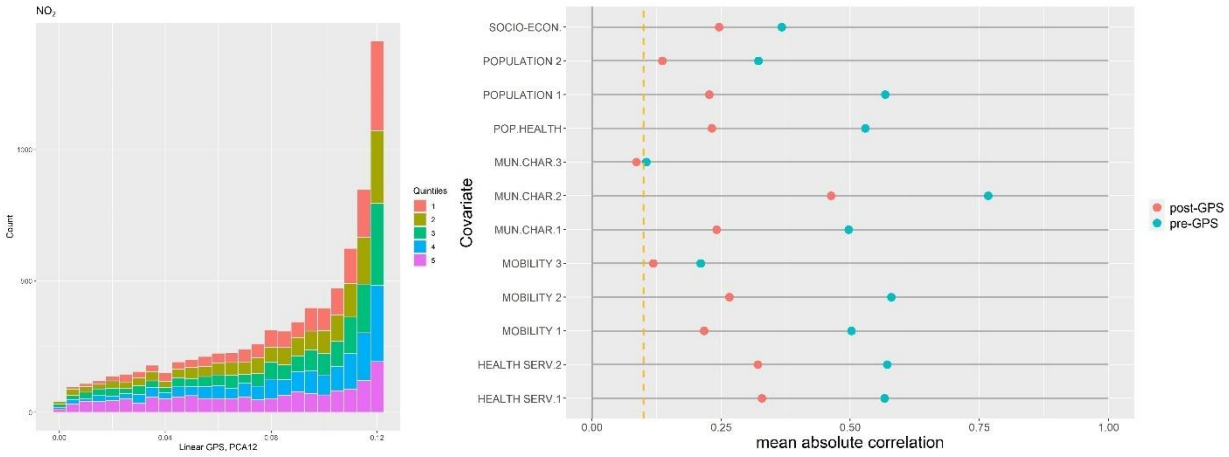
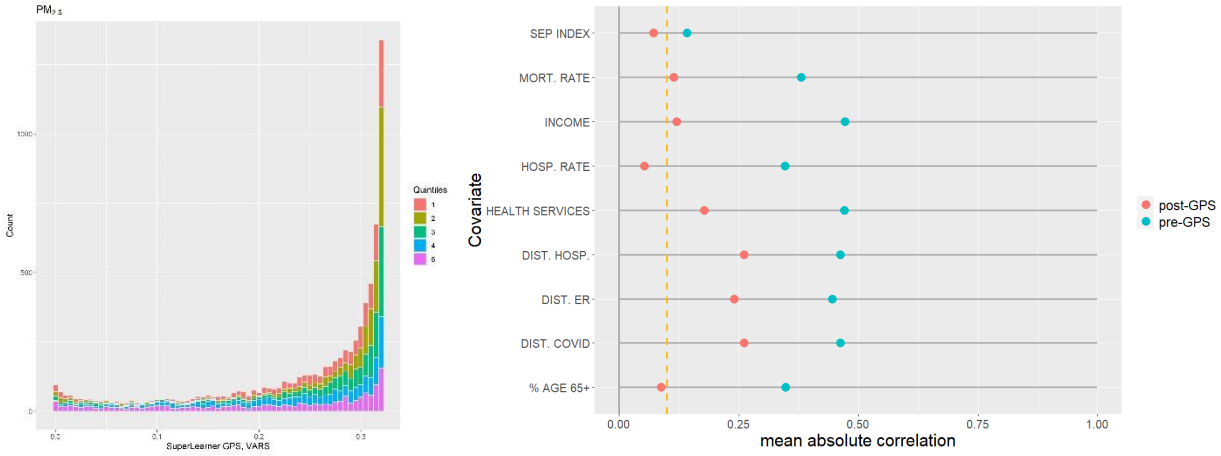
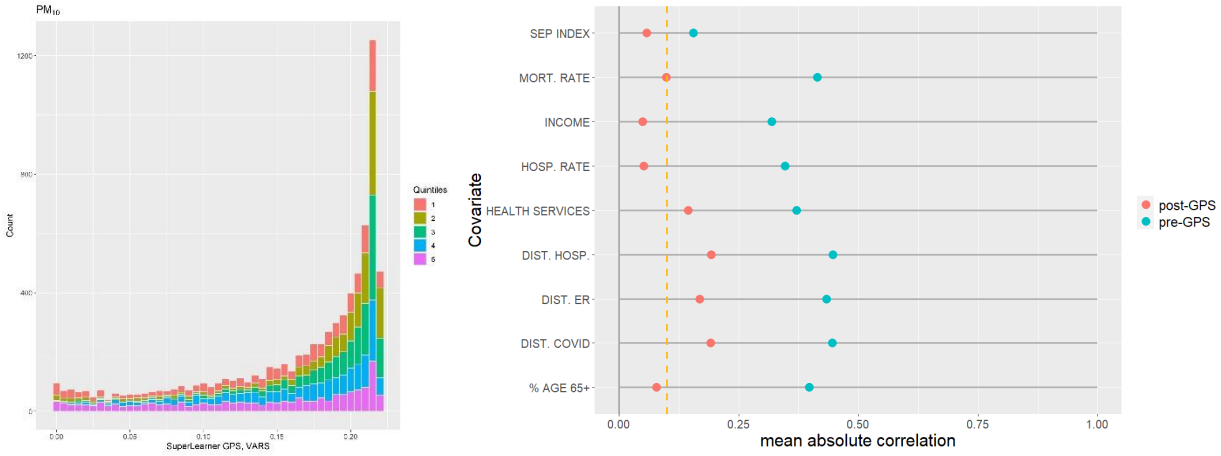


Figure S7. Generalized Propensity Score (GPS) based on selected contextual variables: distribution of GPS by quintiles of exposure (positivity assumption (left) and absolute correlation between exposure and covariates pre- and post-GPS (balancing plot, right). Relevant data on mean absolute correlations in Excel Table S5

$PM_{2.5}$



PM_{10}



NO_2