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SARS-CoV-2 in Italy: Population Density correlates with Morbidity and Mortality

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Running Head: COVID-19 in Italy: Morbidity and Mortality

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Summary

Since the beginning of the SARS-CoV-2/COVID-19 epidemic in China, elderly and multimorbid subjects showed a higher mortality rate. However, other factors could influence the mortality and the spread of contagion such as the population density. An archival research based on the Italian data stratified by region was performed in order to quantify the association between the population density, ageing index, number of positive cases, number of deaths, case-fatality rate, and medical equipment (gloves, masks, and ventilators). Results showed a significant positive linear relationship between the population density and cases, deaths, and case-fatality rate. No correlation with the ageing index was shown. Furthermore, we found a significant positive correlation between the number of medical supplies and population density, cases, and deaths. However, the medical supplies did not show any correlation with the case-fatality rate. Taken together, these findings suggest that the population density and the lack of medical equipment are key factors explaining morbidity and mortality of COVID-19 in Italy.

On 31 December 2019, a cluster of pneumonia of unknown etiology was found in the city of Wuhan, Hubei Province. Twenty-seven patients presented with fever, cough, shortness of breath, and bilateral lung infiltrates (1). On 9 January 2020, the causative agent of pneumonia was identified: a new coronavirus, provisionally named 2019-nCoV and later renamed as SARS-CoV-2 by the International Committee on Taxonomy of Viruses (1). By that moment, the infectious disease is commonly referred to as COVID-19 (COronaVIrus Disease 19). There are many hypotheses about the genesis of SARS-CoV-2/COVID-19. Although some of them are quite inventive, the zoonotic spillover appears the most reliable and comprehensive explanation. It takes into account a wide range of factors associated with the ignition and maintenance of the infection, including ecological, anthropological, and epidemiological determinants of pathogen exposure (2).

From the clinical standpoint, it was immediately clear that mortality was higher in elderly and multimorbid individuals: the first death occurred in a 61-years-old patient with abdominal tumor and chronic liver disease (3). This evidence has been further supported by the Italian epidemiological data (4). Out of a total of 73780 cases, the deaths are 6801 with a significant increase of the disease severity in patients aged over 69 years, as shown by the case-fatality rate (CFR), i.e., the proportion of deceased patients among the total number of positive cases. In particular, the highest number of deaths (5105, pairs to approximately 75%) has been recorded in patients aged between 70 and 89 years. The median age of deceased patients is 79 years, whereas it is 63 years in the whole cohort of positive cases (5). The presence of concomitant chronic pathologies has been observed in 710 patients who died, with three or more associated diseases in 50% of cases (5). Sex also appears to be a significant risk factor since the CFR is higher in men than women regardless of age (male = 11.4%, female = 6.5%) (4). However, the effect of the population density (PD) on the spread of contagion and mortality rate should not be overlooked.

In order to quantify the relationship between the impact of COVID-19 on the Italian population and the demographic/epidemiological data available for each region (4, 6–8), we carried out an explorative "archival" analysis by crossing the PD (i.e., number of inhabitants per Km^2), the ageing index (AI, i.e., the number of elders per 100 persons younger than 15 years old), the number of positive cases, the number of deaths, the CFR, and the number of the main medical supplies (MS) distributed around the country (i.e., gloves, masks, and ventilators). For this purpose, we used a non-parametric Spearman's correlation analysis (r_{rho}). The significance threshold was fixed at $\alpha < 0.05$. The descriptive statistics for each Italian region are reported in Table 1.

A significant and moderate correlation emerged between the PD and the number of cases ($r_{\text{rho}} = 0.67$, $p = .001$), deaths ($r_{\text{rho}} = 0.69$, $p = .001$), and CFR ($r_{\text{rho}} = 0.47$, $p = .03$) (Fig. 1). The housing density reasonably increases the speed with which the virus spreads since a greater number of social contacts enhances the likelihood of transmission. However, no correlation between the AI and the number of cases ($r_{\text{rho}} = -0.16$, $p = .50$), deaths ($r_{\text{rho}} = -0.04$, $p = .85$), and CFR ($r_{\text{rho}} = 0.13$, $p = .57$) was found (Fig. 2). This suggests that the areas mainly inhabited by elderly are not necessarily the most affected by the disease. For instance, the Molise and the Friuli Venezia Giulia regions have an overlapping AI, but the CFR is higher in the former. Furthermore, Lombardy is the Italian region hardest hit by the COVID-19, with the highest CFR and a weak-to-moderate AI. Liguria is the fourth region in terms of CFR, despite being the "oldest" territory as shown by the highest AI (Table 1).

What do we know about sex and multimorbidity? Based on the data released by the Italian National Institute of Statistics (ISTAT) for biennium 2018–2019 (9), 49.2% of the over-65s and 66.6% of the over-75s reported at least two serious chronic diseases. Interestingly, the percentage of multimorbidity was higher in women (over-65s = 54.5%, over-75s = 72.9%) compared to men (over-65s = 43%, over-75s = 57.6%) (9). These data would tend to suggest that elderly multimorbid women should be more affected by the infection. The Italian experience is telling us exactly the opposite, namely, women are less affected by the COVID-19 compared to men both in terms of total cases and mortality (4). A partial explanation for this evidence may be arise from the lower immune reactions observed in males compared to females in both the innate and acquired immunity responses (10).

As concerns the MS, results showed a significant moderate correlation between the PD and the number of gloves ($r_{rho} = 0.49$, $p = .03$), masks ($r_{rho} = 0.63$, $p = .003$), and ventilators ($r_{rho} = 0.56$, $p = .01$). Furthermore, a strong linear association was found i) between the number of positive cases and MS (gloves, $r_{rho} = 0.89$, $p = .0001$; masks, $r_{rho} = 0.76$, $p = .0001$; ventilators, $r_{rho} = 0.90$, $p = .0001$), and ii) between the number of deaths and MS (gloves, $r_{rho} = 0.84$, $p = .0001$; masks, $r_{rho} = 0.69$, $p = .001$; ventilators, $r_{rho} = 0.81$, $p = .0001$) (Fig 1). As previously discussed, the most densely-populated regions are also the most affected by the outbreak; consequently, they need increased resources to deal with the emergency. However, the MS showed no correlation with the CFR (gloves, $r_{rho} = 0.28$, $p = .23$; masks, $r_{rho} = 0.31$, $p = .18$; ventilators, $r_{rho} = 0.25$, $p = .29$) (Fig. 2). This finding is quite interesting, since the number of the available MS may have not been sufficiently large in terms of both primary prevention (i.e., gloves and masks) and management of patients with severe respiratory failure (i.e., ventilators).

Among other factors influencing the vulnerability to COVID-19, a recent "position" paper of the Italian Society of Environmental Medicine (SIMA) explored the role exercised by the atmospheric particulate matter (PM) (11). The PM could act as a carrier for many contaminants including viruses. Since high concentrations of PM_{10} (diameter < 10 mμ) were recorded in some provinces of Northern Italy at the beginning of the epidemic, PM may have exerted a "boost" action in these territories. Conversely, such a phenomenon was not observed in other areas of the peninsula (11). Beyond this hypothesis, inhalation of PM can certainly act as irritative stimulus for the respiratory tree; indeed, it is associated with increased respiratory morbidity (12). It should also be recalled that COVID-19, as all infectious diseases, is the result of the interaction between the virulence of the infective agent and the individual vulnerability. In this perspective, the genomic epidemiology could help to better define many aspects of the pandemic, i.e., the genetic diversity, the reliability of diagnostic methods, and the design of appropriate therapies and potential vaccines (13).

The main limitation of the present study is ascribable to its nature of ecological study; we used only regional aggregated-level data. In this vein, further studies using individual-level data are needed to confirm our hypothesis. Based on the examination of demographical and epidemiological data, we suggest that PD, in addition to age, multimorbidity, and lack of medical equipment, is one of the key factors explaining morbidity and mortality of COVID-19 in Italy. Consequently, the restrictive measures including the social distancing and quarantine remain the most effective, pending a vaccine or targeted therapies.

Conflict of interest

None to declare.

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Figure 1. Scatterplots representing the significant correlations found in this study. Gloves, masks, and ventilators are merged as Medical Supplies.

Figure 2. Scatterplots representing the non-significant correlations found in this study. Gloves, masks, and ventilators are merged as Medical Supplies.

Table 1. Descriptive statistics for each region (Data updated to 26 March 2020)

Region	PD (Inhab/Km^2)	AI (%)	Total cases	Total deaths	Cases per 1000 pop	Deaths per 1000 pop	CFR (%)	Gloves[a]	Masks[b]	Ventilators[c]
Abruzzo	121	191.8	824	12	0.62	0.01	1.45	155000	515410	5
Basilicata	56	193.2	10	0	0.01	-	-	41500	288621	2
Calabria	128	163.3	223	6	0.11	0.00	2.69	45000	288395	3
Campania	424	129.8	1151	40	0.19	0.01	3.47	140000	1368024	10
Emilia Romagna	199	182.6	10008	1068	2.24	0.23	10.67	698000	4740809	158
Friuli Venezia Giulia	153	217.2	918	66	0.75	0.05	7.18	244500	569120	3
Lazio	341	162.6	1817	88	0.30	0.01	4.84	158000	1474007	15
Liguria	286	255.8	1695	180	1.09	0.11	10.61	202000	870540	56
Lombardia	422	165.5	34907	4484	3.46	0.44	12.84	3142000	4223495	346
Marche	162	196.2	3011	97	1.97	0.06	3.22	393500	-	63
Molise	69	217.5	73	8	0.23	0.02	10.95	35500	101544	-
Piemonte	172	205.9	5111	194	1.17	0.04	3.79	821500	4005452	84
Puglia	206	168.6	1165	61	0.28	0.01	5.23	152000	622450	14
Sardegna	68	212.0	292	13	0.17	0.01	4.45	100000	307237	-
Sicilia	194	153.7	458	15	0.09	0.00	3.27	80000	927750	-

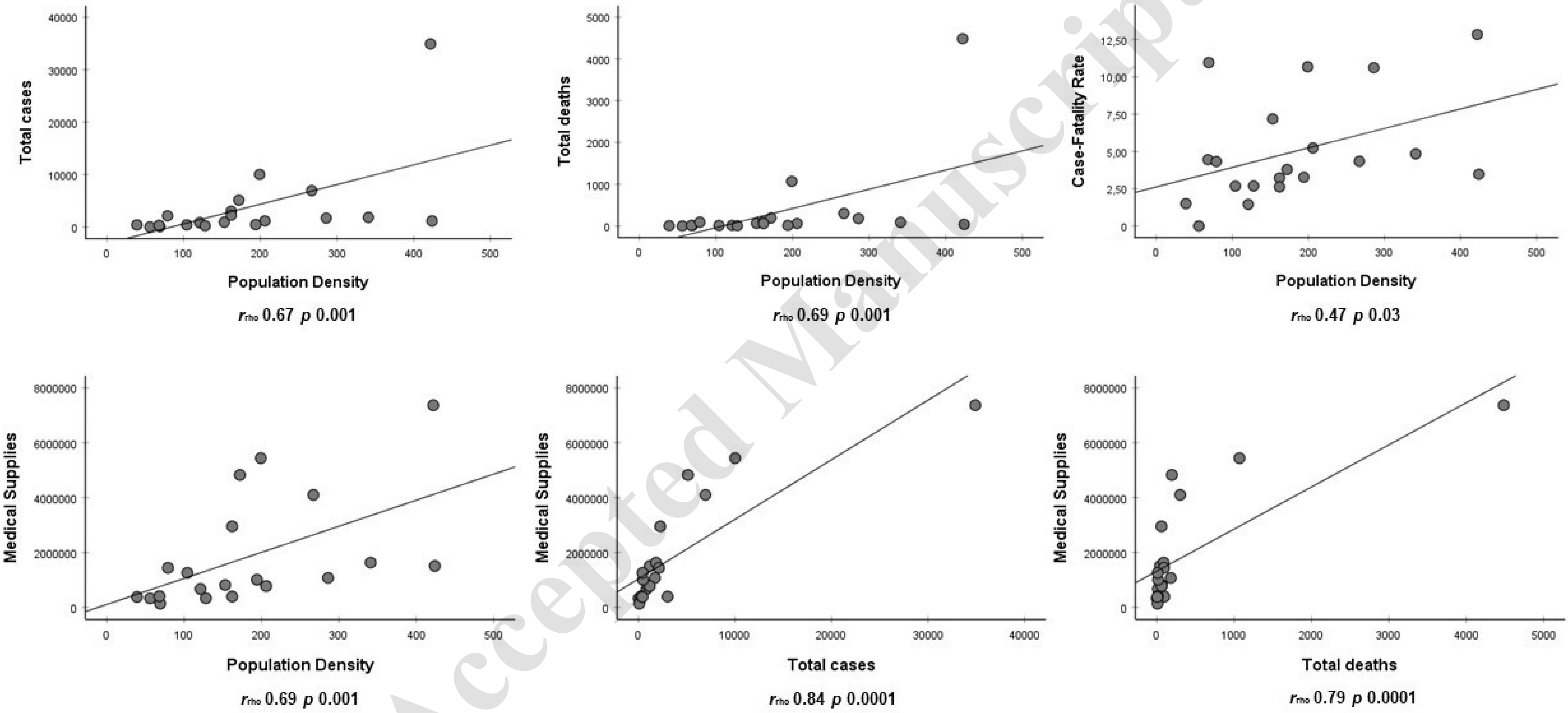
Toscana	162	204.6	2247	59	0.60	0.01	2.62	370600	2579780	28
Trentino-Alto Adige	79	138.5	2126	92	1.98	0.08	4.32	161300	1278620	17
Umbria	104	204.2	409	11	0.46	0.01	2.68	308000	950393	20
Valle d'Aosta	39	181.6	400	6	3.18	0.04	1.50	55000	324060	5
Veneto	267	172.1	6935	301	1.41	0.06	4.34	317000	3781863	177

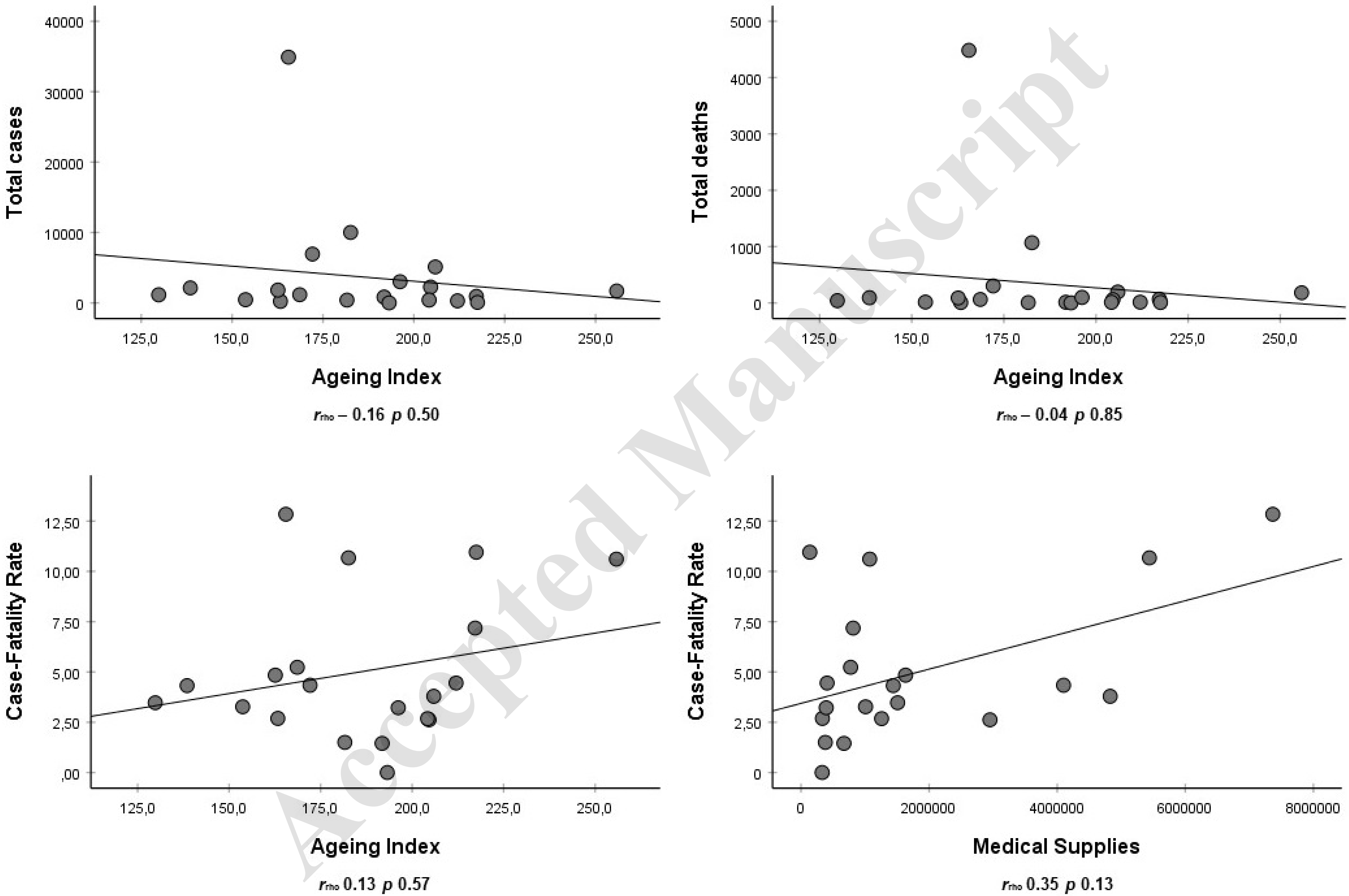
PD, Population Density; Inhab, Inhabitants; AI, Ageing Index; pop, population; CFR, Case-Fatality Rate

([a]) Latex Gloves EN420 and EN374

([b]) Surgical Face Mask, Non-Surgical Face Masks, Masks FFP2 and FFP3

([c]) Lung Ventilators for Intensive Care Unit (compressed air), Lung Ventilators for Sub-Intensive Care Unit (turbine)


Total cases
Population Density
r_{rho} 0.67 p 0.001
Total deaths
Population Density
r_{rho} 0.69 p 0.001
Case-Fatality Rate
Population Density
r_{rho} 0.47 p 0.03
Medical Supplies
Population Density
r_{rho} 0.69 p 0.001
Medical Supplies
Total cases
r_{rho} 0.84 p 0.0001
Medical Supplies
Total deaths
r_{rho} 0.79 p 0.0001


Total cases
40000
30000
20000
10000
0
125,0
150,0
175,0
200,0
225,0
250,0
Ageing Index
r rho – 0.16 p 0.50
Total deaths
5000
4000
3000
2000
1000
0
125,0
150,0
175,0
200,0
225,0
250,0
Ageing Index
r rho – 0.04 p 0.85
Case-Fatality Rate
12,50
10,00
7,50
5,00
2,50
,00
125,0
150,0
175,0
200,0
225,0
250,0
Ageing Index
r rho 0.13 p 0.57
Case-Fatality Rate
12,50
10,00
7,50
5,00
2,50
0
0
2000000
4000000
6000000
8000000
Medical Supplies
r rho 0.35 p 0.13