

## Population density and SARS-CoV-2: an epidemiologic urban health study

## Densità di popolazione e SARS-CoV-2: uno studio epidemiologico di urban health

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**Parole Chiave:** Salute Urbana, Densità di Popolazione, Capoluogo di Provincia, SARS-CoV-2, COVID-19

**List of abbreviations:** p.d.: population density; RT-PCR: Reverse Transcriptase-Polymerase Chain Reaction; SIR: Standardized Incidence Ratio; yrs: years.

### Abstract

Despite SARS-CoV-2 transmission being a complex phenomenon, greater population density seems to be a risk factor. The aim of this study was to analyze through an epidemiologic urban health approach the relationship between population density and SARS-CoV-2 incidence using data which are comparable with regard to testing strategies.

All 10,300 SARS-CoV-2 confirmed cases between October and December 2020 were included. We conducted separate analysis by gender standardizing and stratifying by age and month.

In the Province Capital (p.d.=765 inhabitants/km<sup>2</sup>), standardized SARS-CoV-2 incidence rate was higher than the expected, both in men (SIR=1.17, 95%CI=1.12;1.22, p<0.0001) and women (SIR=1.20, 95%CI=1.15;1.25, p<0.0001).

In municipalities with p.d. >200 inhabitants/km<sup>2</sup>, standardized SARS-CoV-2 incidence rate was similar to the expected (p>0.05).

In municipalities with p.d. <200 inhabitants/km<sup>2</sup>, standardized SARS-CoV-2 incidence rate was lower than the expected, both in men (SIR=0.85, 95%CI=0.81;0.90, p<0.0001) and women (SIR=0.84, 95%CI=0.80;0.88, p<0.0001). Stratified analysis by months with likelihood ratio test showed heterogeneity of the p.d. effect in men and women (p<0.05).

SARS-CoV-2 incidence rate seemed to be higher in most densely populated areas, both in

men and women. Our results confirmed the great importance of restrictive measures as well as the importance of limiting the epidemic wave in the initial stages and could help guide pandemic management strategies according to urban context and population density.

## Riassunto

Sebbene la trasmissione del virus SARS-CoV-2 costituisca un fenomeno complesso, un'elevata densità di popolazione sembra essere un fattore di rischio. Scopo di questo studio è analizzare, attraverso un approccio epidemiologico, la relazione tra densità di popolazione e incidenza dell'infezione da SARS-CoV-2, utilizzando dati che sono confrontabili per quanto riguarda le strategie di testing.

Sono stati inclusi tutti i 10.300 casi confermati di SARS-CoV-2 della Provincia di Taranto (Puglia, Sud Italia) testati fra ottobre e dicembre 2020. È stata condotta un'analisi separata per genere standardizzando e stratificando per età e mese.

Nel Capoluogo di Provincia (d.p.=765 abitanti/km<sup>2</sup>), il tasso di incidenza standardizzato di SARS-CoV-2 è superiore all'atteso, sia negli uomini (SIR=1.17, 95%CI=1.12;1.22,  $p<0.0001$ ) sia nelle donne (SIR=1.20, 95%CI=1.15;1.25,  $p<0.0001$ ).

Nei comuni con d.p. >200 abitanti/km<sup>2</sup>, il tasso di incidenza standardizzato di SARS-CoV-2 è simile all'atteso ( $p>0.05$ ).

Nei comuni con d.p. <200 abitanti/km<sup>2</sup>, il tasso standardizzato di incidenza di SARS-CoV-2 è inferiore all'atteso, sia negli uomini (SIR=0.85, 95%CI=0.81;0.90,  $p<0.0001$ ) sia nelle donne (SIR=0.84, 95%CI=0.80;0.88,  $p<0.0001$ ).

L'analisi stratificata per mesi con il likelihood ratio test mostra eterogeneità dell'effetto sia negli uomini che nelle donne ( $p<0.05$ ).

Il tasso di incidenza di SARS-CoV-2 sembra essere più alto nelle aree più densamente popolate, sia negli uomini che nelle donne. I nostri risultati confermano la grande importanza delle misure restrittive, nonché l'importanza di arginare l'ondata epidemica nelle fasi iniziali. Ciò potrebbe contribuire a guidare le strategie di gestione della pandemia in base al contesto urbano e alla densità di popolazione.

## Introduction

Despite SARS-CoV-2 transmission being a complex phenomenon, there are common sociological contexts that seem to contribute to transmission rates. In particular, greater population density and, consequently, more frequent human-to-human interactions, appeared to be risk factors that could facilitate the spread of the disease [1].

As a matter of fact, for scenarios that are well described by models assuming well-mixed populations, the contact rate is proportional to population density and, therefore, avoiding situations with higher population densities will be a necessary requirement to limit the spread of COVID-19 [2].

According to an English study, in fact, most densely populated areas of England showed higher incidence rates per 100 000 people compared to less densely populated areas.

Moreover, after the introduction of social distancing measures, the incidence dropped stronger in these most densely populated [3].

Similarly, in Algeria, there was a strong correlation between the population density and the number of COVID-19 infections, with the spread of cases increasing as the population density increased. [4].

In China, population density seemed to be an influential factor in the COVID-19 spread as well, with a non-linear relationship [5-6].

Likewise, in the United States, several studies have highlighted the positive correlations between COVID-19 spread and socioeconomic factors, including population density, proportions of elderly residents and presence of a large dependent youth population [7-10].

On the contrary, results from other studies in Iran, USA and Netherlands didn't find a significant association between COVID-19 and population density [11-13].

As far as Italy is concerned, with regard to socio-economic variables the country is characterized by dishomogeneous population density distribution within the territory, as the majority of people (19 million inhabitants) live in the provincial capitals of the regions. In fact, in the Italian regions, the average population density is about 183 inhabitants/km<sup>2</sup>, while the corresponding provincial capital population density is about 540 inhabitants/km<sup>2</sup> [14,15].

In the same way, in Italy areas with higher population densities showed a higher probability of contagion, being less able to guarantee social distancing, e.g. due to an increase in social activities with overcrowding [14].

## **Objectives**

The aim of this study was to analyze through an epidemiologic urban health approach the relationship between population density and SARS-CoV-2 incidence rate, using data from the Province of Taranto in Southern Italy which are comparable and homogeneous with regard to testing strategies. Specifically, the first objective is to study if there is a causal relationship between population density and incidence rate of SARS-CoV-2 infection (p.d effect). The second objective is to analyze if this effect differs depending on other factors (p.d. effect modification).

## Materials and methods

### Study design, data gathering and inclusion/exclusion criteria

This is a retrospective cohort study.

SARS-CoV-2 cases data were retrieved from the Apulian Regional Registry for COVID-19 (GIAVA COVID-19), while resident population and population density data from Italian National Institute for Statistics (ISTAT) [15,16].

We included in the study all SARS-CoV-2 confirmed cases with positive RT-PCR swab tests collected between October and December 2020 among residents of the Province of Taranto (confirmed cases notified until 5 February 2021).

Resident population and population density data referred to 1 January 2020.

We didn't include positive antigenic tests without molecular test confirmation. For each individual, we considered only the first positive molecular swab test.

We used only the Province of Taranto cases data in order to avoid whatsoever bias determined from differences in testing strategies between different provinces.

Data prior to October 2020 were excluded due to the low number of cases that would have made it impossible to stratify by month.

Data after December 2020 were excluded due to the implementation in January 2021 of a Regional Agreement with general practitioners that revolutionized the testing strategy making the data hardly comparable.

### Study area

Taranto Province in Puglia Region, Southern Italy, includes 28 municipalities and the Province Capital, Taranto City, which presents the higher values both of resident population and population density. On 1 January 2020 the resident population ranges from 1,794 to 191,050 inhabitants, with a median of 11,363 inhabitants, while the population density ranges from 68 to 765 inhabitants/km<sup>2</sup>, with a median of 226 inhabitants/km<sup>2</sup>. Total resident population is 563,995 inhabitants, 273,519 men and 290,476 women. If we exclude the Province Capital, the median population density of the municipalities is 216 inhabitants/km<sup>2</sup> [15].

## Included variables

The outcome measure was the monthly incidence rate of SARS-CoV-2 infection.

The analyzed determinant is the population density, which was categorized into three groups: 1) municipalities with p.d. <200 inhabitants/km<sup>2</sup>, 2) municipalities with p.d. >200 inhabitants/km<sup>2</sup>, 3) Province Capital (p.d.=765 inhabitants/km<sup>2</sup>). The cut-off of 200, that is close to the median population density in non-capital municipalities as well, was chosen in order to almost equally divide SARS-CoV-2 cases between the two groups. 13 municipalities fell in the first category, 15 in the second one.

In order to analyze the complex sociological context in which the hypothetical link between population density and the spread of SARS-CoV-2 infection takes place, dealing with potential confounding and effect modification, we conducted separate analysis by gender standardizing and stratifying by age and month.

Gender was included due to its known role of sociological and biological determinants of health, capable of acting as confounder and effect modifier through complex causal pathways [17].

As the goal was to analyze how age influences the incidence rate of SARS-CoV-2 infection even from a sociological perspective, age groups were chosen to be representative of working status: <20 years (students), 20-39 yrs (young workers), 40-64 (workers), ≥65 yrs (retirees).

Months inclusion in the analysis met the needs of providing some conditioning on different baseline values of SARS-CoV-2 incidence rate between months, as can be seen from the pandemic curve oscillation over time (Figure 1). Moreover, months inclusion took into account the changing national and regional regulatory framework that could affect people's behaviors.

## Data analysis

Data analysis was performed using Microsoft Excel 2016 build 16.0.4266.1001 and R version 4.0.2 (released on 2020-06-22) with package popEpi version 0.4.8 (released on 2019-09-28). Statistical significance  $\alpha$  was fixed to 0.05.

For each gender, we divided the cases in 3 cohorts based on p.d. category and stratified each of them in 12 strata derived from the combination of the 4 age groups and 3 months. The reference population data, for each gender, were the total SARS-CoV-2 cases of Taranto Province, divided and stratified in the same way.

Finally, for each of the 6 gender-specific p.d. cohorts, we computed the Standardized Incidence Ratios (SIRs), adjusting (indirect standardization) results for both age groups

and months and reporting (stratification) them for the overall cohort as well as restricted for each age group and month. SIR was a ratio of observed and expected cases and was Poisson modelled. Expected cases were derived by multiplying the strata-specific population rate (Taranto Province) with the corresponding strata-specific person-months of the cohort (p.d. cohort). Univariate confidence intervals were calculated using exact Poisson intervals.

In order to analyze effect modification, we computed a homogeneity likelihood ratio test for the different strata defined by the reporting factors.

## Results

Between October and December 2020, 10,300 SARS-CoV-2 confirmed cases were reported in Taranto Province, 4836 males and 5464 females.

Crude SARS-CoV-2 monthly incidence rate per 10,000 inhabitants, by population density and months or age were reported in figures 1 and 2.

Poisson modelled SIRs for SARS-CoV-2 infection were reported in table 1.

In the Province Capital (p.d.=765 inhabitants/km<sup>2</sup>), standardized SARS-CoV-2 incidence rate was higher than the expected, both in men (SIR=1.17, 95%CI=1.12;1.22,  $p<0.0001$ ) and women (SIR=1.20, 95%CI=1.15;1.25,  $p<0.0001$ ). When results were printed for specific variables, except for men in November ( $p=0.1866$ ), in all age groups and months standardized SARS-CoV-2 incidence rate was higher than the expected ( $p<0.05$ ).

In municipalities with p.d. >200 inhabitants/km<sup>2</sup>, standardized SARS-CoV-2 incidence rate was similar to the expected ( $p>0.05$ ). When results were printed for specific variables, except for men in October (SIR=0.85, 95%CI=0.74;0.97,  $p=0.0196$ ) and women in October (SIR=0.86, 95%CI=0.75;0.98,  $p=0.0230$ ), in all age groups and months standardized SARS-CoV-2 incidence rate was similar to the expected ( $p>0.05$ ).

In municipalities with p.d. <200 inhabitants/km<sup>2</sup>, standardized SARS-CoV-2 incidence rate was lower than the expected, both in men (SIR=0.85, 95%CI=0.81;0.90,  $p<0.0001$ ) and women (SIR=0.84, 95%CI=0.80;0.88,  $p<0.0001$ ). When results were printed for specific variables, except for men in November ( $p=0.2769$ ), in all age groups and months standardized SARS-CoV-2 incidence rate was lower than the expected ( $p<0.05$ ).

Stratified analysis by months with likelihood ratio test showed heterogeneity of the effect for Province Capital and municipalities with p.d. <200 inhabitants/km<sup>2</sup> both in men and women ( $p<0.05$ ), and for municipalities with p.d. >200 inhabitants/km<sup>2</sup> in men ( $p<0.05$ ) but not in women ( $p=0.148$ ). That is, the effect of p.d. on the SARS-CoV-2 incidence rate (SIR) is significantly different between considered months.

Stratified analysis by age groups showed homogeneity of the p.d. effect in both men and women ( $p > 0.05$ ).

## Discussion

Our results seem to indicate a higher incidence of infection in the most densely populated areas, in particular in the capital, regardless of gender, age and month. This result is in line with much of the literature that has investigated the relationship between population density and SARS-CoV-2 infection spread in different countries like Italy, England, Algeria, China and United States [1-10,14].

The only exception seems to be the lack of statistically significant population density effect (Province Capital and municipalities with p.d.  $< 200$  inhabitants/km<sup>2</sup>) in the month of November as regarding men, together with a reduction of this effect in women.

An explanation could be that, for high baseline incidence rate values, proxy of an extensive spread of the virus, the etiological role of population density is supposed to be less relevant, resulting in a reduction of the protective effect of the low population density.

In any case, this heterogeneity of the effect linked to the baseline value of incidence seems to be partly gender specific, as it has been observed predominantly in males. This could be linked to socio-cultural and behavioral factors, in a context like that of the Puglia Region where the female employment rate is significantly lower than the male one and where the gender gap could still relegate women to a prevalent domestic dimension [15].

Another explanation of this heterogeneity of the effect may derive from the change in the regulatory framework both at national and regional level between the months under review.

One of the strengths of the study is certainly the multifactorial approach which, combined with the use of an almost totally homogeneous sample for testing strategy, made it possible to minimize the risk of bias. In addition, the stratified analysis allowed us to analyze in detail also the possibility of the heterogeneity of the effect across them.

However, our study may also have potential limitations.

Firstly, although the fact that the entire Taranto Province was managed by a single Local Health Authority for COVID-19 Public Health aspects made the testing strategy effectively homogeneous at the provincial level - especially in the presence of risk factors such as suspicious symptoms or epidemiological link (high risk contact or return from high risk area) - we couldn't exclude that there were some discrepancies related to swabs performed for private purposes or by private laboratories. In any case, we expected these differences to be extremely negligible and to not significantly affect the results.

Secondly, if on one hand the homogeneity in the testing strategy made it possible to make the data comparable at the provincial level, on the other hand this could potentially have limited the generalizability/transportability of the study's conclusions from the study population to other populations. In the future it would be interesting to replicate this method by involving more Provinces with their respective Province Capitals, in order to analyze the phenomenon on a larger scale, although introducing the risk of bias linked to the inhomogeneity of testing strategies between different Local Health Authorities.

Finally, although the analysis has been adjusted for several variables, possible confounding could derive from the lack of inclusion in the models of some significant socio-cultural variables - not currently available in the regional database - such as marital status, educational level, employment status and socio-economic deprivation indexes [17]. The implementation of these informations could justify future studies that also analyze this aspect.

## Conclusions

In conclusion, SARS-CoV-2 incidence rate seemed to be higher in most densely populated areas, both in men and women. These findings could help guide pandemic management strategies according to the urban context and population density. Moreover, the reduction of the protective effect of the low population density in the presence of high baseline incidence values is a further element supporting the importance of blocking the epidemic wave in the initial stages through the Public Health measures. Our results confirmed the great importance of restrictive measures, in particular to avoid gatherings, as well as the need to raise public awareness of social distancing in private and public places.

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## Tables and Figures

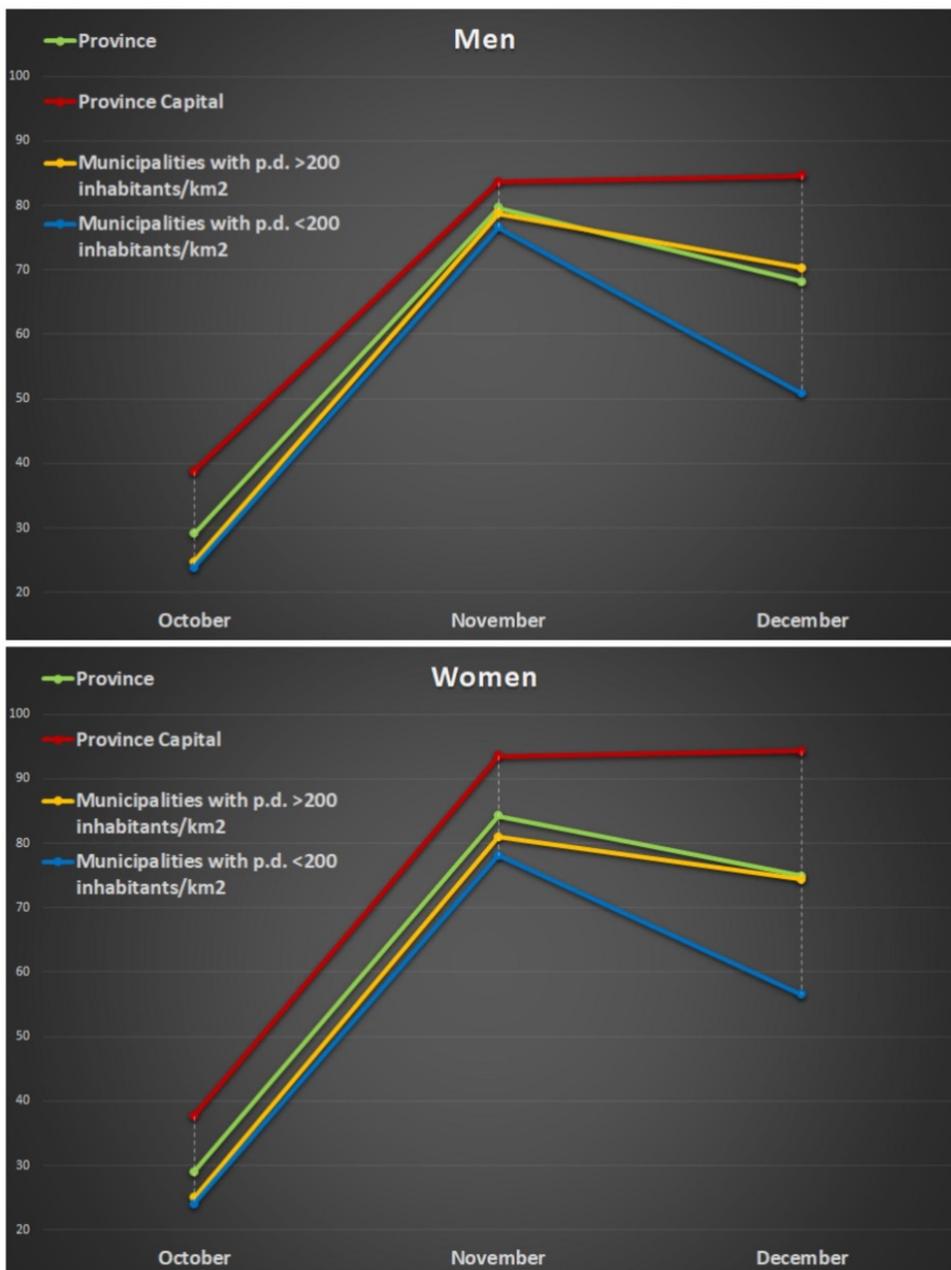


Figure 1. Crude SARS-CoV2 monthly incidence rate per 10,000 inhabitants, by population density and months (Taranto Province, Oct-Dec 2020).

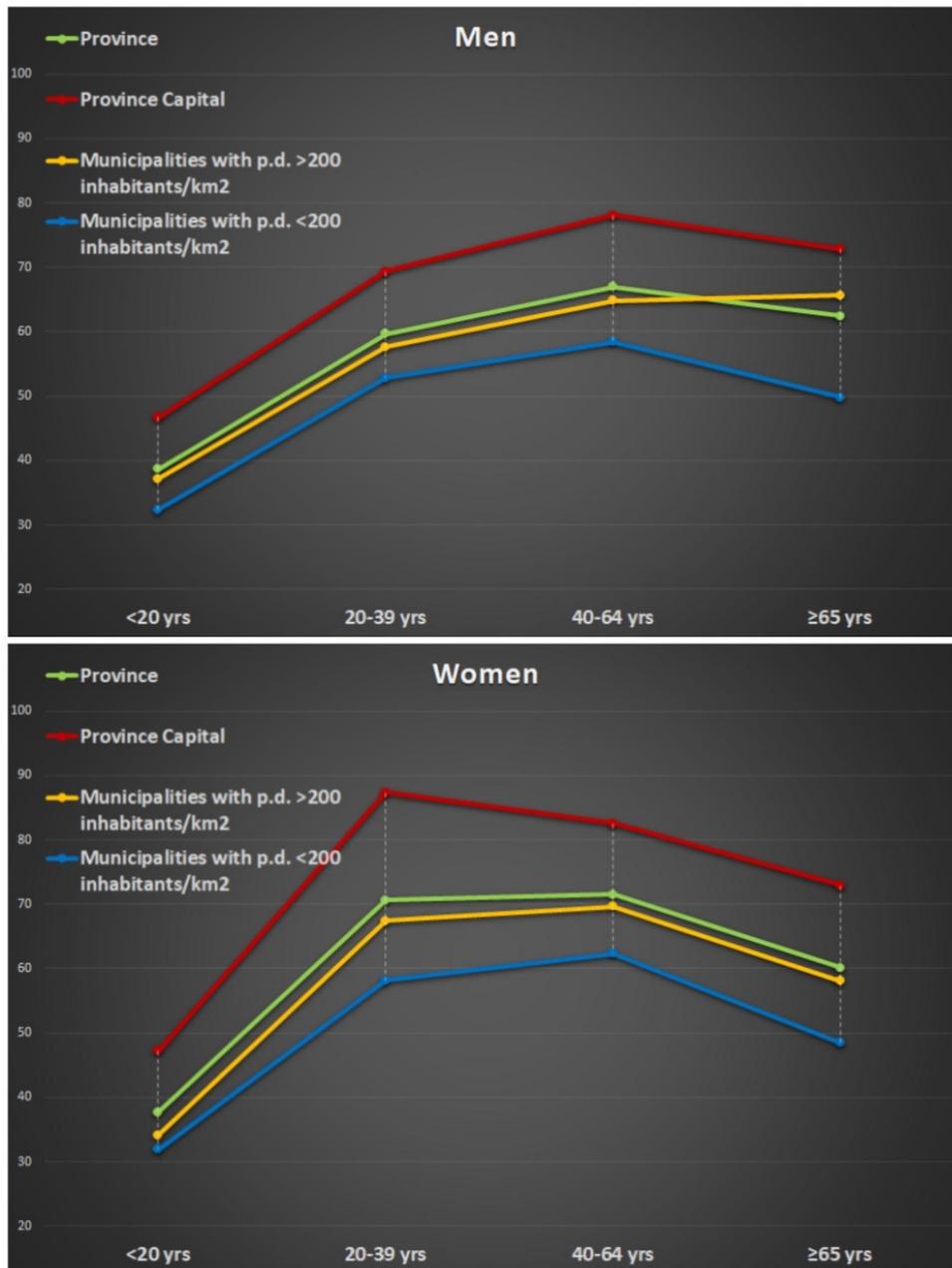


Figure 2. Crude SARS-CoV-2 monthly incidence rate per 10,000 inhabitants, by population density and age (Taranto Province, Oct-Dec 2020).

<b>2020</b>	<b>Men</b>				<b>Women</b>			
	<b>Obs.</b>	<b>Exp.</b>	<b>SIR (95% CI)</b>	<b>p</b>	<b>Obs.</b>	<b>Exp.</b>	<b>SIR (95% CI)</b>	<b>p</b>
<b><i>Province Capital</i></b>								
Overall	1889	1613.51	1.17 (1.12;1.22)	<0.0001	2250	1877.98	1.20 (1.15;1.25)	<0.0001
Age								
<20 yrs.	242	200.48	1.21 (1.06;1.37)	0.0038	234	186.87	1.25 (1.10;1.42)	0.0006
20-39 yrs.	425	365.78	1.16 (1.05;1.28)	0.0021	524	423.31	1.24 (1.13;1.35)	<0.0001
40-64 yrs.	782	670.31	1.17 (1.09;1.25)	<0.0001	909	787.43	1.15 (1.08;1.23)	<0.0001
65 yrs.	440	376.94	1.17 (1.06;1.28)	0.0013	583	480.36	1.21 (1.12;1.32)	<0.0001
Month								
October	354	265.14	1.34 (1.20;1.48)	<0.0001	376	287.68	1.31 (1.18;1.45)	<0.0001
November	763	726.89	1.05 (0.98;1.13)	0.1866	933	842.64	1.11 (1.04;1.18)	0.0020
December	772	621.48	1.24 (1.16;1.33)	<0.0001	941	747.65	1.26 (1.18;1.34)	<0.0001
<b><i>Municipalities with p.d. &gt;200</i></b>	<b>Obs.</b>	<b>Exp.</b>	<b>SIR (95% CI)</b>	<b>p</b>	<b>Obs.</b>	<b>Exp.</b>	<b>SIR (95% CI)</b>	<b>p</b>
Overall	1468	1490.86	0.98 (0.93;1.04)	0.5625	1588	1654.62	0.96 (0.91;1.01)	0.1041
Age								
<20 yrs.	183	190.10	0.96 (0.83;1.11)	0.6319	161	177.97	0.90 (0.77;1.06)	0.2169
20-39 yrs.	350	362.28	0.97 (0.87;1.07)	0.5358	402	421.13	0.95 (0.86;1.05)	0.3639
40-64 yrs.	602	622.00	0.97 (0.89;1.05)	0.4343	669	687.28	0.97 (0.90;1.05)	0.4977
65 yrs.	333	316.47	1.05 (0.94;1.17)	0.3676	356	368.24	0.97 (0.87;1.07)	0.5408
Month								
October	209	246.12	0.85 (0.74;0.97)	0.0196	220	256.93	0.86 (0.75;0.98)	0.0230
November	665	670.25	0.99 (0.92;1.07)	0.8545	713	739.27	0.96 (0.90;1.04)	0.3432
December	594	574.49	1.03 (0.95;1.12)	0.4278	655	658.42	0.99 (0.92;1.07)	0.9094
<b><i>Municipalities with p.d. &lt;200</i></b>	<b>Obs.</b>	<b>Exp.</b>	<b>SIR (95% CI)</b>	<b>p</b>	<b>Obs.</b>	<b>Exp.</b>	<b>SIR (95% CI)</b>	<b>p</b>
Overall	1479	1731.63	0.85 (0.81;0.90)	<0.0001	1626	1931.41	0.84 (0.80;0.88)	<0.0001

Age								
<20 yrs.	177	211.41	0.84 (0.72;0.97)	0.0197	165	195.16	0.85 (0.72;0.98)	0.0337
20-39 yrs.	361	407.94	0.88 (0.80;0.98)	0.0215	382	463.55	0.82 (0.74;0.91)	0.0002
40-64 yrs.	626	717.69	0.87 (0.81;0.94)	0.0007	702	805.29	0.87 (0.81;0.94)	0.0003
65 yrs.	315	394.58	0.80 (0.71;0.89)	0.0001	377	467.40	0.81 (0.73;0.89)	<0.0001
Month								
October	233	284.74	0.82 (0.72;0.93)	0.0024	246	297.39	0.83 (0.73;0.94)	0.0032
November	749	779.86	0.96 (0.89;1.03)	0.2769	801	865.09	0.93 (0.86;0.99)	0.0306
December	497	667.03	0.75 (0.68;0.81)	<0.0001	579	768.93	0.75 (0.69;0.82)	<0.0001

Table 1. Poisson modelled SIRs for SARS-CoV-2 infection (Taranto Province, Oct-Dec 2020).

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