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The Increase of Chronic Diseases Death During Covid-19 Outbreak in Italy: The Effect of Vaccinations

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ABSTRACT

Background: In Italy Covid-19 increased the Standardized Death Rate (SDR) of some chronic diseases Objective: to assess the modification of chronic diseases SDR due to Covid-19 in 2020 and in 2021 following the first year of vaccination in the 20 Italian Regions. Methods: The SDR of 59 most common diseases was analyzed according to the data recorded by ISTAT (Istituto Italiano di Statistica) in the 20 Italian Regions. The period between 2017 and 2021 was considered. The differences among years were calculated according to the ANOVA and Tukey test calculation. Results: The SDR of only 14 diseases was modified during the Covid-19 outbreak. For 8 diseases it increased: type II diabetes, other metabolic illnesses, blood disorders, Alzheimer's, Parkinson's, other neurological diseases, genito-urinary and not definable diseases. No differences were found in 4 diseases: mental disorders, cerebrovascular, myocardial and respiratory diseases. A significant decrease was shown for infection and parasitic diseases and malignant cancers. The total of SDR in 2019 was 82.1 ± 5.66 x 10^4 while in 2020 and 2021 was respectively 92.8 ± 7.25 and 89.7 ± 6.84 x 10^4. Vaccinations in 2021 were effective only in reducing Alzheimer's, myocardial and respiratory diseases. Conclusions: Covid-19 outbreak in 2020 was increasing deaths in subjects suffering from type II diabetes, other metabolic, blood disorders, Parkinson's, Alzheimer's, other neurological, genito-urinary, and not definable diseases. The vaccinations were flattening only the Alzheimer's, myocardial and respiratory diseases.

Keywords: Standard Death Rate, Covid-19, chronic diseases, vaccination.

INTRODUCTION

Globally, for the period from January 2020 to December 2021 an estimated excess of deaths of 14.83 million (uncertainty interval 13.23-14.83 million) was reported by the WHO [1].

The excess mortality accounts for both the total number of deaths directly attributed to the Covid -19 virus and those resulting from the indirect impact mostly represented by chronic diseases.

Previous research on Covid-19 mortality rate in the world [2] reported form the Global Health Data Exchange Website indicated for Italy an estimated excess of deaths between 242,000 and 276,000 cases.

However, In Italy the estimated number of deaths due to Covid-19 are officially reported by ISTAT in terms of Standardized Death Rate x 10^4 residents (SDR). The total deaths estimated around 78,000 cases in 2019 and around 64,000 cases in 2021 [3]. These figures belong to the Italian Institute responsible for mortality data which is recognized by the WHO among the reliable Institutions.

In the joint report of ISTAT and ISS (Italian Istituto Superiore di Sanità) of July 2020 [4] was indicated that, in 71.8 % of deaths positive to the SARS-Cov-2 test, the 31.3 % of the cases was suffering from one concomitant disease, while in the case of two, three or more concomitant diseases the percentages were 26.8 % and 13.7 % respectively.

This means that more than 2/3 of deaths were determined by the combination of Covid-19 with other illnesses and chronic diseases and represents an important part of this figure.

Among the chronic diseases causing death during the 2020 pandemic, the most common (between 18% and 12% of the cases) weere hypertensive cardiac disease, diabetes (Type II), and ischemic cardiac disease, while other chronic diseases such as cerebrovascular and Azheimer's disease and obesity were present in < 10 % of the cases.

The aim of the present research was to analyze the SDR from 2017 to 2021 in the 20 Italian Regions, the impact of Covid-19 on chronic diseases deaths, and the effect of vaccination in 2021.

No data were reported for 2022 since they will become available only by December 2024.

MATERIAL AND METHODS

The SDR (Standardized Death Rate x 10^4 residents) of the 20 Italian Regions as reported by ISTAT was considered [3]. The data were relative to the deaths caused by 56 diseases and each of the 20 Italian regions was considered in the period between the years 2017 and 2021.

In order to determine the effect of Covid-19 in 2020 when vaccinations were not available the selection among the 56 illnesses was as follows:

- When the disease in the period of 2017-2019 was showing any significant modifications (ANOVA $p>0.05$) and was increasing or decreasing significantly (Tukey test) comparing 2019 Vs 2020 only.
- When the disease in the period 2017-2019 was significantly decreasing (ANOVA $p<0.05$) and the value of 2019 Vs 2020 was significantly increasing (Tukey test).

The effect of vaccinations was consistent with the modification of SDR comparing the years 2020 and 2021.

For each disease the data of the 20 Italian Regions as mean ± SD were considered. An ad hoc Excel software was used for analysis.

RESULTS

The total deaths in Italy are reported in Table 1.

Table 1: Total deaths and SDR in Italy in the years from 2017 to 2021 [3]

Year	2017	2018	2019	2020	2021
Total deaths x 10^4	659.5	640.8	644.5	746.1	709.0
SDR	122.44	116.59	114.68	130.06	122.66
Covid-19 deaths	0	0	0	78408	63651

To be noticed that deaths due to Covid-19 in Italy are around 100,000 cases lower than those reported by the Excess Mortality Collaborators [2]. The increase of total deaths during the outbreak in 2020 is evident and continues also in 2021 during the vaccination campaign. These figures are relative to total deaths including also those for chronic illnesses.

Among the 59 diseases (some as cluster diseases) considered by ISTAT as a cause of mortality, only 11 were showing some statistically significant difference compared to the years 2019 Vs 2020, while for 4 no difference was found. The data of the remaining 44 were not reported because the modifications were considered inconsistent. Among the 15 diseases only 5 were found to be modified by vaccination. The values of deaths from 2017 to 2021 due to chronic diseases are summarized in Table 1.

Table 1: Standardized Death Rate (SDR) x 10^4 residents; mean ± SD from 2017 to 2021 in the 20 Italian Regions

Disease	GHE [e]	Years				
		2017	2018	2019	2020	2021
Infectious parasitic	20-370	1.78 ± 0.357	1.73 ± 0.379	1.81 ± 0.350	1.68 ± 0.288 [a]	1.81 ± 0.317 [c]
Malignant cancers	610-790	24.38 ± 1.416	23.97 ±1.495	23.63 ±1.282	23.29 ±1.271[a]	22.83 ± 1.243 [d]
Diabetes type II	800	2.93 ± 1.070	2.76 ± 0.993	2.75 ± 1.020	3.18 ± 1.093 [b]	3.06 ± 1.240
Other Metabolic [i]	None	3.97 ± 1.249	3.70 ± 1.044	3.73 ± 1.071	4.23 ± 1.136 [b]	4.14 ± 1.349
Blood disorders [h]	810-814	0.42 ± 0.089	0.43 ± 0.073	0.42 ± 0.104	0.45 ± 0.078 [b]	0.49 ± 0.103
Mental disorders	820-890	3.28 ± 1.355	3.20 ± 1240	3.25 ± 1.084	3.23 ± 0.901	3.12 ± 0.779
Alzheimer's	950	1.62 ± 0.404	1.41 ± 0.370	1.39 ± 0.392	1.52 ± 0.428 [b]	1.39 ± 0.399 [d]
Parkinson	960	0.97 ± 0.105	0.92 ± 0.138	0.99 ± 0.137	1.03 ± 0.135 [b]	1.05 ± 0.098
Other neurological [f]	1020	1.48 ± 0.223	1.40 ± 0.286	1.45 ± 0.274	1.54 ± 0.305 [b]	1.58 ± 0.202
Cerebrovascular	1140	7.67 ± 1.539	6.99 ± 1.386	6.86 ± 1.323	6.97 ± 1.292	6.72 ± 1.343
Myocardial ischemic	1150	9.13 ± 1.534	8.19 ±1.367	7.96 ± 1.309 [L]	8.06 ± 1.355	7.55 ± 1.449 [d]
Respiratory	1170	6.86 ± 0.699	6.42 ± 0.529	6.64 ± 0.608	6.74 ± 0.989	5.52 ± 0.749 [d]
Genito-urinary [g]	1260-300	1.47 ± 0.273	1.43 ± 0.206	1.44 ± 0.268	1.68 ± 0.237 [b]	1.73 ± 0.328
Not definable		1.83 ± 0.670	1.79 ± 0.654	1.79 ± 0.682	2.92 ± 1.036 [b]	3.06 ± 1.193
Covid-19		0	0	0	8.46 ± 4.844 [b]	7.90 ± 1.837
Total SDR		86.22 ± 5.915	82.36 ± 5.249	82.13 ± 5.665	92.82 ± 7.253 [b]	89.69 ± 6.836

Key: a = decrease statistically significant (Tukey test p<0.05) Vs 2019; b = increase statistically significant (Tukey test p< 0.05 Vs 2019; c = increase statistically significant (Tukey test <0.05) Vs 2020; d = decrease statistically significant (Tuckey test) p<0.05) Vs 2020; e = GHE or Global Health Estimate [5]; f = mainly epilepsy, multiple

sclerosis; g = mainly acute glomerulonephritis, chronic kidney diseases, prostatic hyperplasia: h = mainly thalassemia, sickle cells, other haemoglobinopathies; I = mainly obesity; L = Decrease statistically significant in the period 2017-2019 (ANOVA $p<0.05$)

In 2019 the only SDR significantly reduced compared to the previous years (2017-2018) was the myocardial ischemic disease (ANOVA $p<0.05$), instead deaths from malignant cancers, Alzheimer's and cerebrovascular diseases despite lower than previous years were not significantly different (ANOVA $p>0.05$).

The deaths modification in 2020 represents the impact of Covid-19 on chronic diseases.

The mortality for infectious diseases was significantly decreased as for malignant cancers, while an increase was found for all the other illnesses apart from mental disorders, cerebrovascular, myocardial and respiratory diseases which were not modified.

The total SDR increased by 10.69×10^4 (92.82-82.13;) corresponding approximately to the sum of deaths due to Covid-19 and not definable causes.

In relation to 2021, it is possible to measure the effect of vaccination which was covering around 80 % of the population with one or two shots and 47 % with three shots [6].

The infectious parasitic diseases were similar to 2019, meaning that vaccination was not effective and at the opposite deaths were increased compared to 2020. Type II diabetes, other metabolic, blood disorders and genito-urinary, Parkinson's, other neurological, and not definable diseases were not modified.

Alzheimer's disease was returning to the values before the outbreak and, despite some reduction, Covid-19 deaths and total deaths were not significantly modified.

DISCUSSION

The present study has some limitations due to the use of SDR that sometimes is reported as cluster of illnesses (according to OMS classification) and not as single entity.

Although not detailed in this study, going back in time the values of SDR in 2003 were higher than those of 2019 for almost all diseases (ANOVA $p<0.05$) with a trend showing a significant decrease during years.

This indicates that any increase during 2019 could be considered as an effect of the Covid-19 outbreak.

In relation to vaccinations, in 2021 they were covering only around 80 % of the population with 2 shots and 47 % with 3 shots [6] which may underestimate the real effect of the vaccine.

According to these limitations, some interesting information can be drawn from this study. In 2019 the SDR of 8 diseases (or cluster diseases) showed a significant increase: type II diabetes and other metabolic diseases, blood disorders, Alzheimer's, Parkinson's and other neurological

illnesses, genito-urinary and not definable diseases. The latter was the most affected class indicating that in some cases the death cause was not easy to be determined and consistent with the mess generated by the pandemic.

In total, the death rate of chronic diseases increased of around 10.7×10^4 inhabitants. Surprisingly, the mortality due to Infectious and parasitic diseases decreased significantly before vaccinations. One may not exclude that the virus was not allowing other microorganisms to invade the cells directly or indirectly (due to the relative increase of immune defenses). However, the positivity to Covid-19 swab could suggest that the death was due to the virus instead of other type of infections.

The slight significant reduction of malignancies can be interpreted as part of the trend which has been slowly diminishing since 2003 and seems to be independent from Covid-19 outbreak. The increase of SDR following Covid-19 infection can be interpreted as due to the presence of ACE2 receptors on cellular membranes which are considered the "doors" of the viral invasion and becoming determinant for the severity of the disease [7].

The discussion regarding the ACE2 importance is out of the scope of this study and still under debate [8] as the impact of the concomitant therapies for chronic diseases.

However, ACE 2 receptor attenuates the inflammatory response and oxidative stress (OS) in experimental animals [9] and their occupation by the Covid-19 tends to deregulate these activities [10].

Diseases already characterized by OS and inflammation will be more sensible to the viral damage as it is for multiple sclerosis [11], epilepsy [12], Alzheimer's [13], and Parkinson 's disease [14], type II Diabetes [15]. The impact of Covid-19 in the genito-urinary diseases was also already described [16] raising concerns regarding long term damage of these organs because ACE2 receptors are highly expressed.

The vaccination effect was reported to save millions of lives globally [17], however the individual health status can significantly affect the immune response [18] which can be modified by chronic diseases.

According to the present study, In Italy vaccination seems to be significantly effective in case of myocardial and respiratory chronic diseases only. Surprisingly, these diseases were found almost not affected by the outbreak, and the reason most probably is due to the capability and experience of the ICU (intensive Care Units) personnel (doctors and nurses) to take care of these patients. We cannot rule out that even chronic diseases that seem refractory to vaccination could actually have caused more deaths without it. However, this latter aspect is very difficult to prove and the application of mathematical models can be the cause of an excessive approximation.

CONCLUSIONS

In Italy the Covid-19 outbreak in 2020 was increasing deaths in subject suffering from type II diabetes, other metabolic, blood disorders, Parkinson's, Alzheimer's, other neurological, genito-

urinary, and not definable diseases. The vaccinations were flattening only the Alzheimer's, myocardial and respiratory diseases.

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Authors Agreement
All the authors read and agreed the text: UC was conceiving the study and wrote the text; MR was conducting the statistical analysis; AF, BA, CP, CL, CC, CE, CV, NB, GG, GM, LF, LA, LC, ML, MA, MM, PA, PL, PM, PA, RM, SG, SGa, SM, ZN retrieved all data.

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