

A municipality-level analysis of excess mortality in Italy in the period January-April 2020

L'accesso di mortalità nei comuni italiani nel periodo gennaio-aprile 2020

Annibale Biggeri,¹ Corrado Lagazio,² Dolores Catelan,¹ Fabio Barbone,³ Mario Braga⁴

¹ Department of Statistics, Computer Science, Applications "G. Parenti" University of Florence, Florence (Italy)

² Department of Economics, University of Genoa, Genoa (Italy)

³ Department of Medical Area, University of Udine, Udine, (Italy)

⁴ Tuscany Health Agency, Florence (Italy)

Corresponding author: Annibale Biggeri; annibale.biggeri@unifi.it

ABSTRACT

BACKGROUND: the first confirmed cases of COVID-19 in WHO European Region was reported at the end of January 2020 and, from that moment, the epidemic has been speeding up and rapidly spreading across Europe. The health, social, and economic consequences of the pandemic are difficult to evaluate, since there are many scientific uncertainties and unknowns.

OBJECTIVES: the main focus of this paper is on statistical methods for profiling municipalities by excess mortality, directly or indirectly caused by COVID-19.

METHODS: the use of excess mortality for all causes has been advocated as a measure of impact less vulnerable to biases. In this paper, observed mortality for all causes at municipality level in Italy in the period January-April 2020 was compared to the mortality observed in the corresponding period in the previous 5 years (2015-2019). Mortality data were made available by the Ministry of Internal Affairs Italian National Resident Population Demographic Archive and the Italian National Institute of Statistics (Istat). For each municipality, the posterior predictive distribution under a hierarchical null model was obtained. From the posterior predictive distribution, we obtained excess death counts, attributable community rates and q-values. Full Bayesian models implemented via MCMC simulations were used.

RESULTS: absolute number of excess deaths highlights the burden paid by major cities to the pandemic. The Attributable Community Rate provides a detailed picture of the spread of the pandemic among the municipalities of Lombardy, Piedmont, and Emilia-Romagna Regions. Using Q-values, it is clearly recognizable evidence of an excess of mortality from late February to April 2020 in a very geographically scattered number of municipalities. A trade-off between false discoveries and false non-discoveries shows the different values of public health actions.

CONCLUSIONS: despite the variety of approaches to calculate excess mortality, this study provides an original methodological approach to profile municipalities with excess deaths accounting for spatial and temporal uncertainty.

Keywords: excess mortality, COVID-19, Bayesian models, attributable risk, Q-values, hierarchical models

RIASSUNTO

INTRODUZIONE: il primo caso confermato di COVID-19 nella regione europea dell'OMS è stato registrato alla fine di gennaio 2020 in Italia, e da quel momento in poi la veloci-

WHAT IS ALREADY KNOWN

- Excess mortality is considered a valid measure of the impact of COVID-19.
- Among known unknowns, it is listed how to calculate excess mortality.
- The raw mortality burden paid to COVID-19 pandemic in Italy is already known.

WHAT THIS STUDY ADDS

- Profiling municipalities for excess mortality during the period January-April 2020 highlights specific geographical patterns.
- Absolute numbers of excess deaths, attributable community rates and positive false-discovery rates (Q-values) provide different information of the dynamics of the phenomenon under study.
- Whatever procedure would have been followed to calculate predicted mortality, a fixed-point null hypothesis of risk equivalence is unrealistic. A more realistic range of values of practical equivalence is obtained using a Bayesian approach and municipality-specific posterior predictive distributions.

tà di progressione dell'epidemia ha avuto una forte accelerazione e si è rapidamente diffusa in tutta Europa. L'impatto e le conseguenze sullo stato di salute della popolazione europea, sulla tenuta sociale delle sue comunità e sugli equilibri economici dei singoli paesi sono difficili da valutare dal momento che agli effetti diretti dell'epidemia si debbono sommare quelli indiretti e che ci sono ancora molti aspetti incerti ed ignoti relativi alle caratteristiche di questo virus e alla malattia che esso genera.

OBIETTIVI: proporre un approccio statistico per la descrizione dei comuni italiani in relazione all'eccesso di mortalità, direttamente o indirettamente causata dall'epidemia.

METODI: l'utilizzo della mortalità per tutte le cause, eccedente la mortalità attesa, è stato proposto come una misura di impatto globale, meno vulnerabile alle distorsioni determinate dal processo di codifica e di identificazione della causa di morte. L'articolo confronta la mortalità osservata per tutte le cause a livello comunale durante il periodo gennaio-aprile 2020 con quella rilevata nei corrispondenti mesi dei precedenti 5 anni (2015-2019). I dati di mortalità sono stati resi disponibili dal Ministero dell'interno (Archivio demografico nazionale della popolazione italiana residente) e dall'Istituto nazionale di statistica (Istat). Per ciascuno dei comuni considerati, è stata calcolata la distribuzione predittiva a posteriori sotto l'ipotesi nulla del modello gerarchico. L'eccesso di morti, il tasso attribuibile di comunità e i valori Q sono stati ricavati dalla distribuzione predittiva a posteriori. Per le analisi è stato utilizzato un modello bayesiano completo stimato attraverso un processo di simulazione MCMC.

RISULTATI: come numero assoluto di morti in eccesso il peso maggiore è stato sopportato dalle grandi città. In termini di tasso, rapportando i morti in eccesso alla popolazione, si evidenzia l'impatto della pandemia a carico di alcune zone delle Regioni Lombardia, Piemonte ed Emilia-Romagna. I valori Q mostrano come l'eccesso di mortalità si concentra nel periodo febbraio-aprile in alcuni comuni variamente dispersi nel Centro-Nord del Paese. Differenti bilanciamenti tra falsi positivi e falsi negativi si legano a differenti obiettivi delle azioni di sanità pubblica.

CONCLUSIONI: nonostante la varietà di approcci alla stima dell'eccesso di mortalità, questo lavoro fornisce un approccio metodologico originale per la descrizione dei comuni in relazione all'eccesso di mortalità, aggiustando per l'incertezza spaziale e temporale.

Parole chiave: eccesso di mortalità, COVID-19, modelli bayesiani, rischio attribuibile, valori Q, modelli gerarchici

INTRODUCTION

The first confirmed cases of COVID-19 in WHO European Region were reported at the end of January 2020 and, from that moment, the epidemic has been speeding up and rapidly spreading across Europe. The health, social and economic consequences of the pandemic are difficult to evaluate both in terms of premature death and excess morbidity. Effects are not only acute but also chronic and they may be related to the virus, directly or indirectly.¹⁻⁴ Relevant examples of these negative effects include delayed or lack of care for chronic diseases or delayed access to emergency care for acute myocardial infarction or stroke due to fear of the virus, social inequalities or other barriers due to the COVID-19 restrictions. There may be also some positive effects of the lockdown (e.g., reduced workplace injuries and car accidents).

In this context, total mortality can be seen as the result of several factors, some directly related to the epidemic (diagnosed COVID-19, COVID-19 without a direct diagnosis or a recognition on the death certificate) and some indirectly (unwillingness of seeking care or delay in receiving care in people with serious health conditions, insufficient or lack of hospital and/or intensive care, lack of specific professional skills, use of unskilled doctors and nurses in Intensive Care Units (ICU), heavy workload and stress in hospital wards, increase of mental and physical stress due to lockdown in the general population, improvement in registration efficiency and accuracy).

The main focus of this paper is on statistical methods for profiling municipalities by excess mortality, directly or indirectly caused by COVID-19.

To this purpose, the total mortality by municipality level in Italy in the period January-April 2020 was analysed and compared with the mortality observed during the same period of time in the previous 5 years.

MATERIALS AND METHODS

The total number of deaths by municipality was made available by the Ministry of Internal Affairs Italian National Resident Population Demographic Archive (*Ministero dell'interno, Anagrafe nazionale della popolazione residente,*

ANPR) and Italian National Institute of Statistics (Istat) for the first four months of 2020 (released on 03.06.2020). The data consist in all causes of death counts by age group, gender and municipality for the whole Italy in the period 1 January-30 April 2020 of the five years 2015-2019. For the period 1 January-15 April 2020 death counts are available for a subset of 7,485 over 7,905 Italian municipalities. The total death counts over the period 1 January-30 April 2020 by municipality for each single available year (2015-2019) was considered in this study.

The statistical analysis followed these steps. For each of the 7,485 Italian municipalities expected death counts were obtained by fitting a negative binomial model to the death counts of the period 1 January-30 April 2020 for the calendar years 2015-2019. From model fitting an estimate of the expected average death counts for the period 1 January-30 April 2020 was obtained. This choice was done to account for harvesting of frail subjects during winter season.⁵ A four-month average was considered sufficient to this purpose. The 2020 winter was milder than in previous years – and particularly when compared to year 2015 and 2017 – allowing a larger proportion of frail people to survive. Then, for each of municipality, the posterior predictive distribution was calculated using the estimate from the previous step. Posterior predictive distributions are negative binomial distributions with parameters based on the observed death counts in the period January-April for the five years 2015-2019. The tail probabilities over the posterior predictive distribution were calculated using the observed death counts on January-April 2020. To account for multiplicity, posterior predictive probabilities were post-processed. Q-values are calculated using the Benjamini-Hochberg approach.⁶ Excess death counts are obtained from the posterior relative risk calculated using the observed 2020 death counts and the municipality-specific expected counts – the mean of the posterior predictive distribution. Attributable Community Rate⁷ is also calculated using excess deaths over population denominators.

All the analysis was done specifying a full Bayesian model and implemented via MCMC simulations.⁸

THE BAYESIAN MODEL

A suitable Bayesian model was defined using 2015-2019 data to estimate a baseline mortality level (i.e., mortality in absence of COVID-19) for 2020. To this purpose, the predictive distribution was used (for details, see Appendix 1) and then compared the observed 2020 mortality with the baseline value.

The approach used is in line with cross-validatory techniques, where a single observed value (in this case 2020 mortality) is compared with a prediction obtained without using that observation (in this case baseline mortality based on the previous five years)

The components of the hierarchical Bayesian models are specified as follows. At the lowest level of the hierarchy there is the Poisson likelihood:

$$f(Y_{ij} | \theta_i) = \text{Poi}(\theta_i)$$

where Y_{ij} is the observed death count for the i -th municipality in the j -th year and the parameter θ_i represents the expected number of events for the i -th municipality in each of the five years of the study period 2015-2019.

It was then assumed a Gamma distribution for θ_i :

$$f(\theta_i | \alpha_i, v_i) = \text{Ga}(v_i, \alpha_i)$$

where v_i and α_i are respectively the shape and the rate parameter of the Gamma distribution.

The last stage of the hierarchy specifies the prior distribution for v_i and α_i :

$$\begin{aligned} f(\alpha_i | a, b) &= f_1(a, b) \\ f(v_i | c, d) &= f_2(c, d) \end{aligned}$$

where a , b , c and d are the hyperparameters of the two distributions.

A simpler re-parameterization of this model consists of specifying a Negative Binomial Likelihood by combining the first two levels of the hierarchy integrating out the $\{\theta_i\}$ parameters:

The integrated likelihood is then:

$$f(Y_{ij} | \alpha_i, v_i) = \text{NegBin}(Y_{ij} | \alpha_i, v_i)$$

and the priors

$$\begin{aligned} f(\alpha_i | a, b) &= f_1(a, b) \\ f(v_i | c, d) &= f_2(c, d) \end{aligned}$$

In other words, the estimation of the parameters of the Negative Binomial distribution is directly addressed. The Bayesian approach allows to borrow strength from the whole set of municipalities. A simpler Empirical Bayes procedure would have treated each i -th municipality separately, estimating by maximum likelihood the param-

eters v_i and α_i using the data of the five years 2015-2019. This approach works properly with big municipalities but is inefficient and lacks of robustness when the data come from a municipality with small population size. Embedding the model in a more complex one with priors depending on hyper-parameters not dependent on a particular i -th municipality permits to gain stability. A tuning of the hyper-parameters is necessary due to the presence of municipalities with very small population size located in the Alpine Regions of Piedmont and Lombardy Regions. But having more than 7 thousand municipalities the resulting posteriors are not very dependent on the prior choices. For computational efficiency, the negative binomial was re-parametrized in terms of k (number of failures) and p (probability of success). The hyperprior was specified for k as a Gamma density with hyperparameters (100,100), the hyperprior for p as a Beta density with hyperparameters (1,1).

As reported in Appendix 1, the negative binomial is the predictive distribution. In particular, the cross-validated (leave-2020-out) posterior predictive distribution is:

$$\begin{aligned} &\int f(Y_i^{2020} | \mathbf{Y}^{-2020}, \alpha_i, v_i) f(\alpha_i, v_i | \mathbf{Y}^{-2020}) d\alpha_i, dv_i \\ &= \int \text{NegBin}(Y_j^{2020} | \alpha_i, v_i) f(\alpha_i, v_i | \mathbf{Y}^{-2020}) d\alpha_i, dv_i \end{aligned}$$

which has no closed form because is mathematically intractable. The resulting full posteriors $f(\mathbf{Y}, \boldsymbol{\alpha}, \mathbf{v} | \mathbf{Y})$ were approximated by Monte Carlo Markov Chain algorithms. By comparison and for matter of clarity, the Empirical Bayes solution consists in evaluating Y_i^{2020} using the $\text{NegBin}(Y_i^{2020} | \hat{v}_i, \hat{\alpha}_i)$ distribution with parameters obtained by maximum likelihood fitting a negative binomial model on the $j=2015, \dots, 2019$ five year data, separately for each municipality.

A simple OpenBugs code implementing the model is given in Appendix 2. For the Negative Binomial distribution, the parametrization based on the probability of success in each Bernoulli trial and on the number of failures to be reached for the experiment to be stopped was adopted. A uniform distribution was used for the probability of success, while the number of failures was modeled using a flat Gamma.

There are connections of this proposal with the mixed predictive distributions.^{9,10} Their approach makes use of the so-called 'predictive prior' - $\int f(\theta | \alpha, v) f(\alpha, v | \mathbf{Y}) d\alpha dv$ - in a hierarchical model with second stage priors, to integrate out the θ parameters. As explained by Marshall and Spiegelhalter⁹ we will compare new data with a reference distribution. The reference distribution was built using the observed 2015-2019 data to get a posterior for the second stage parameters, in a way similar to the mixed approach. Connections with cross-validatory approach are also discussed in the literature.

POSTERIOR DISTRIBUTION OF RELATIVE RISK

In the Poisson-Gamma model, the relative risk parameter is estimated as a summary measure on the Gamma posterior distribution

$$f(\theta_i | \mathbf{Y}) = \frac{f(Y_i | \theta_i) f(\theta_i)}{\int f(Y_i | \theta_i) f(\theta_i) d\theta_i} = \frac{Poi(\theta_i, E_i) Ga(v, \alpha)}{NegBin(\mathbf{Y} | v, \alpha)} = Ga(\theta_i | \mathbf{Y})$$

for which the mean has a nice closed form as a shrinkage James-Stein estimator

$$\hat{\theta}_i = \left(\frac{Y_i + v}{E_i + \alpha} \right)$$

Since it would be inappropriate to shrink the 2020 estimate towards the overall 6-year average and inconsistent with the adopted predictive approach, the posterior predictive distribution was heuristically used to derive a posterior distribution for the relative risk parameter θ

$$f(\theta_i^{2020} | Y_i^{2020}) = \frac{f(Y_i^{2020} | \mathbf{Y}, \theta_i) f(\theta_i | \mathbf{Y})}{\int f(Y_i^{2020} | \mathbf{Y}, \theta_i) f(\theta_i | \mathbf{Y}) d\theta_i} = Ga(\theta_i^{2020} | Y_i^{2020}, \mathbf{Y})$$

and the posterior mean was used to estimate the 2020 relative risk:

$$\hat{\theta}_i^{2020} = \left(\frac{Y_i^{2020} + E(v | \mathbf{Y})}{E_i + E(\alpha | \mathbf{Y})} \right)$$

The excess deaths are obtained as:

$$ED_i = Y_i^{2020} \left(\frac{\hat{\theta}_i^{2020}}{\hat{\theta}_i^{2020} - 1} \right)$$

and the attributable community rates as $ACR_i = ED_i / P_i$ where P_i is the population denominator.

Credibility intervals for relative risk and derived indicators are obtained using the centiles of the posterior predictive distribution.

POST-PROCESSING POSTERIOR PREDICTIVE TAIL PROBABILITIES

If the objective of the analysis is profiling municipalities for excess deaths in 2020, we have to formally account for multiplicity. A sophisticated computationally intensive specification would require to formulate a tri-level Bayesian model.¹¹ To say it simply, a mixture model assigning non-zero probability to the null and to the alternative hypothesis (2020 divergence, 2020 non-divergence; one-sided) should be specified. It can be shown that posterior classification probabilities (i.e., the probabilities of the null) from a tri-level Bayesian model can be roughly approximated by a simple post-processing of posterior predictive probabilities:

$$q_{(i)} = \frac{P(Y \geq Y_{(i)}^{2020} | \mathbf{Y}, \alpha, v) \times P(H_0)}{i/m}$$

where (i) are the ordered observations, $i=1, \dots, m$ and $P(H_0)$ is the prior probability of the null. The formula is due to Storey,¹² it is simple and can be used also assuming conservatively $P(H_0)=1$.^{13,14}

Q-value is interpreted as the expected proportion of false rejections among the first i rejected hypothesis, ordered on the basis of the p-value.

This procedure is exploratory and should be interpreted as a rule of thumb when screening a so large dataset of empirical tail probabilities. Indeed, the asymptotic distribution of p-values has been derived by Robins et al.¹⁵ According to their results, our p values are anticonservative, a result which justifies caution and supports our simple post-processing via q-values.¹⁶

RESULTS

The spatial distribution of the absolute number of excess deaths by municipality (figure 1) has a clear North-South gradient with a visible peak in the Lombardy areas most affected by COVID-19 and along the Via Emilia road. This is particularly evident in March and April. A second cluster can be spotted along the coastal area of the Marche Region.

The epidemic peak in absolute terms was reached in the second half of March with a slow decrease afterwards.

Some small and dispersed spots can be observed along the country, particularly in Puglia, probably due to positive subjects migrating from the high-risk areas of the North to the Southern Regions.

In general, a larger absolute number of excess deaths can be observed for the main cities with some spots also in January.

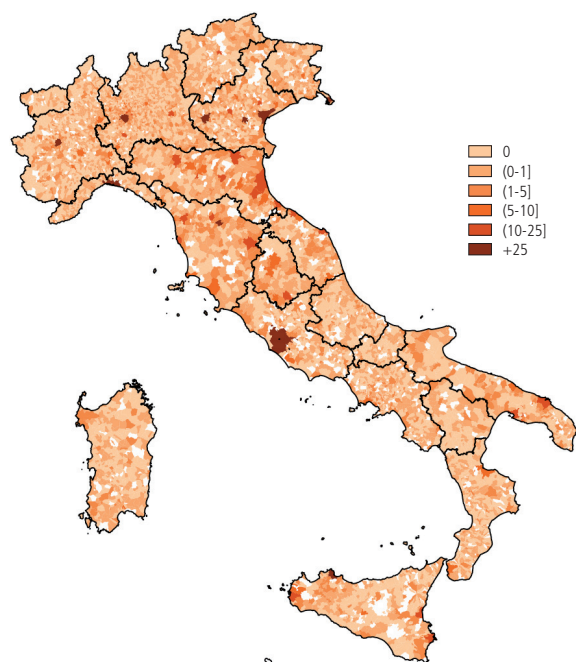
The Attributable Community rates (i.e., the number of excess deaths per 100,000 inhabitants) by municipality (figure 2) highlight the Central-Eastern part of the Lombardy Region and the neighbouring municipalities of Emilia-Romagna. Those were the areas most affected by the COVID-19 epidemic.

The trend of the epidemic, with the March peak, is also clearly visible comparing the different maps.

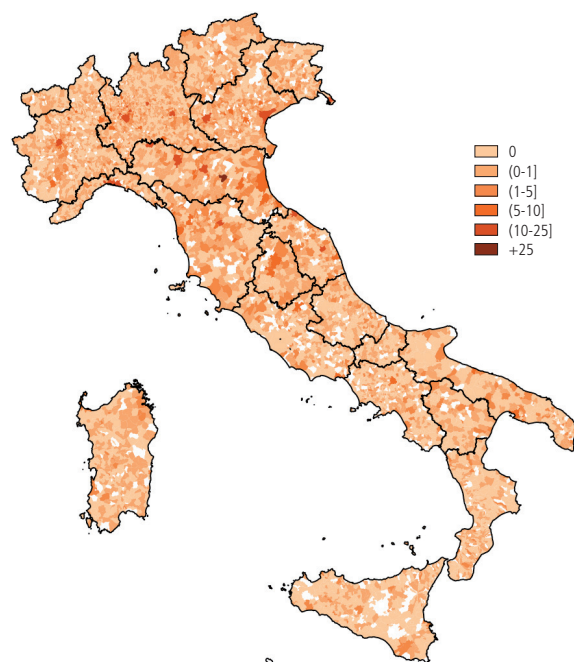
Finally, the map of q-values (figure 3) helps to identify the municipalities where the observed excess mortality can be considered anomalous and worth of further investigation. It is worth pointing to the absence of any statistically significant excess mortality during January and February, which is a clear indication that the dramatic consequences of the pandemic in Italy began in March.

Overall, 25,700 (95%CrI 15,963-51,045) excess deaths were found for the two months of March and April 2020. If a False Discovery Rate (FDR) of 1% was chosen, 18,497 excess deaths would be obtained (95%CrI 13,079-28,541). This corresponds to 882 municipalities declared positive, of which 9 falsely declared positive.

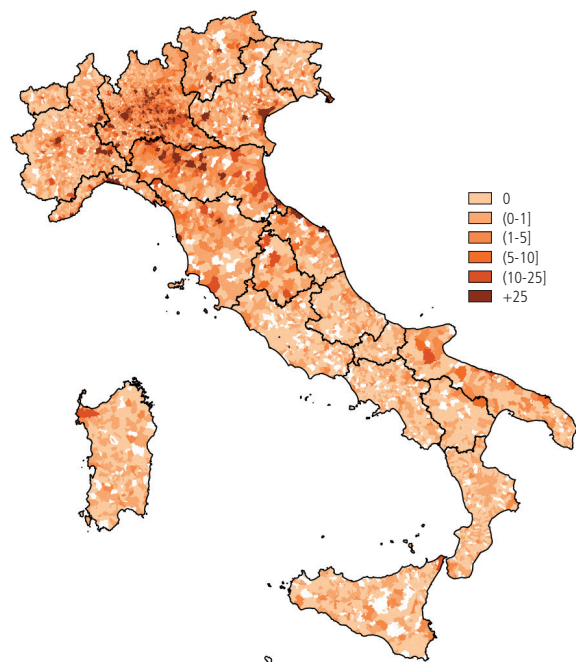
JANUARY



FEBRUARY



MARCH



APRIL

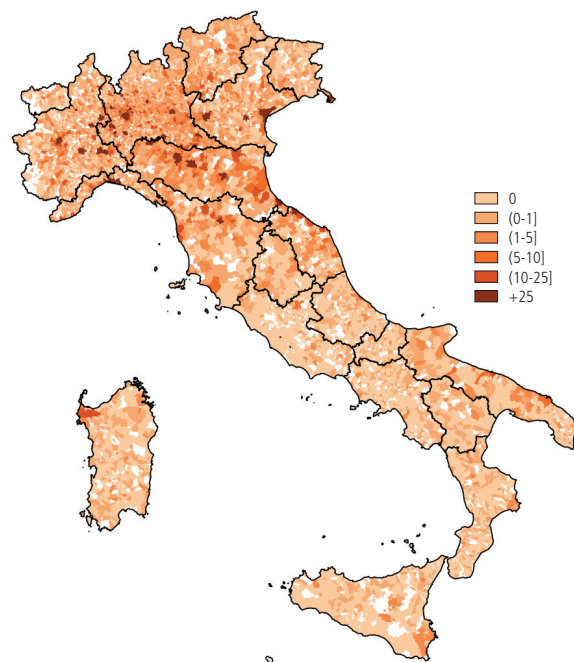
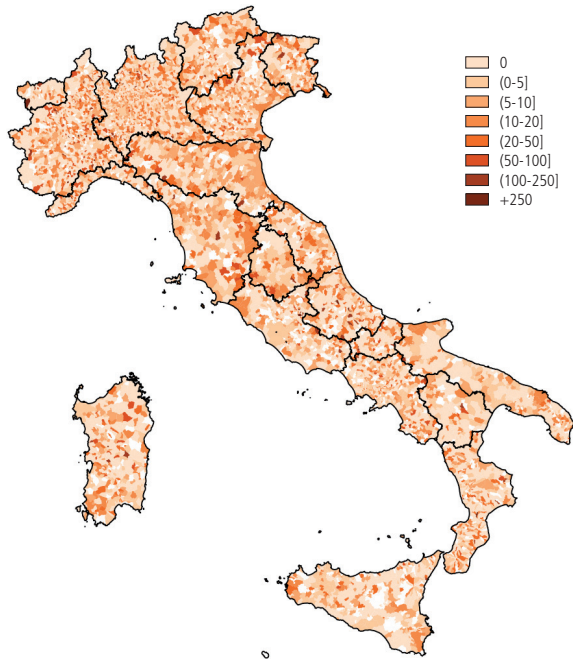


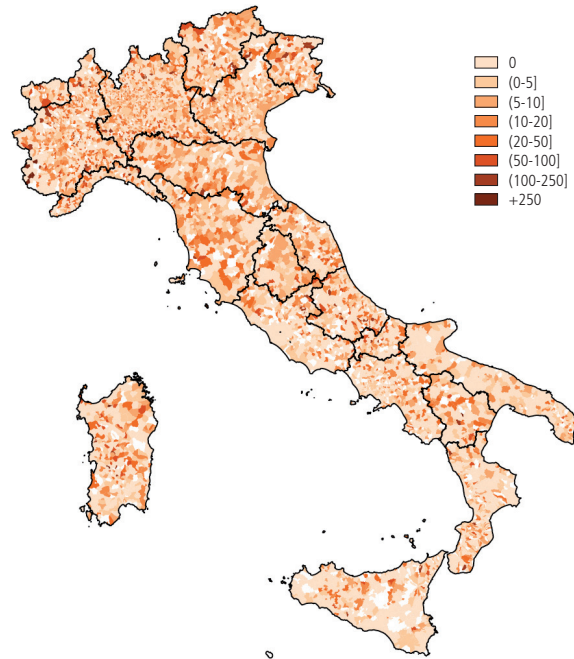
Figure 1. Excess deaths by municipality. Absolute number of excess deaths. Italy, January-April 2020. White indicates municipalities with missing data.

Figura 1. Numero assoluto di morti in eccesso per Comune. Italia, gennaio-aprile 2020. In bianco i Comuni per i quali non sono disponibili dati di mortalità.

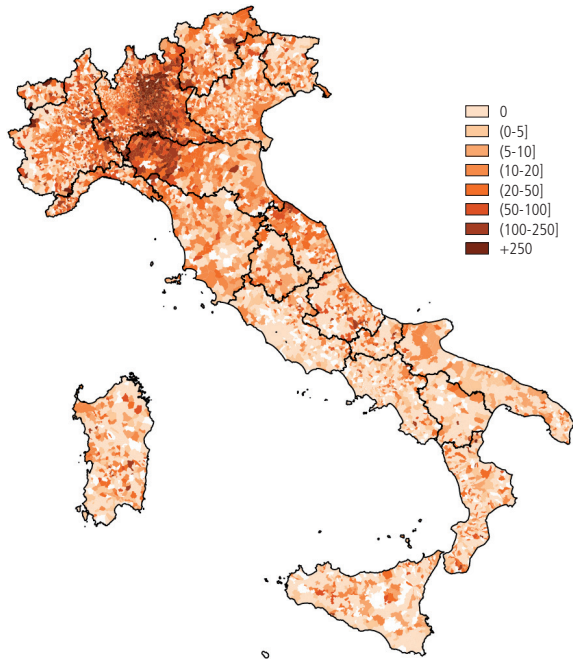
JANUARY



FEBRUARY



MARCH



APRIL

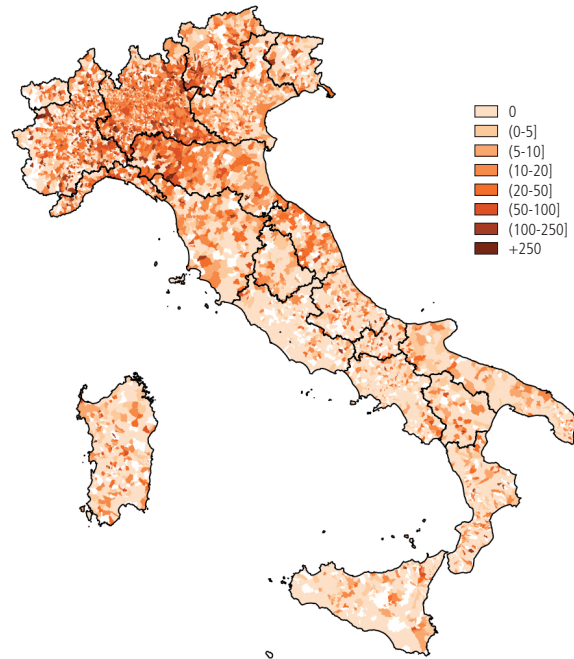


Figure 2. Attributable Community Rate by Municipality, per 100,000. Italy, January-April 2020. White indicates municipalities with missing data.

Figura 2. Mortalità attribuibile (morti in eccesso per 100.000 abitanti) per Comune. Italia, gennaio-aprile 2020, Italia. In bianco i Comuni per i quali non sono disponibili dati di mortalità.

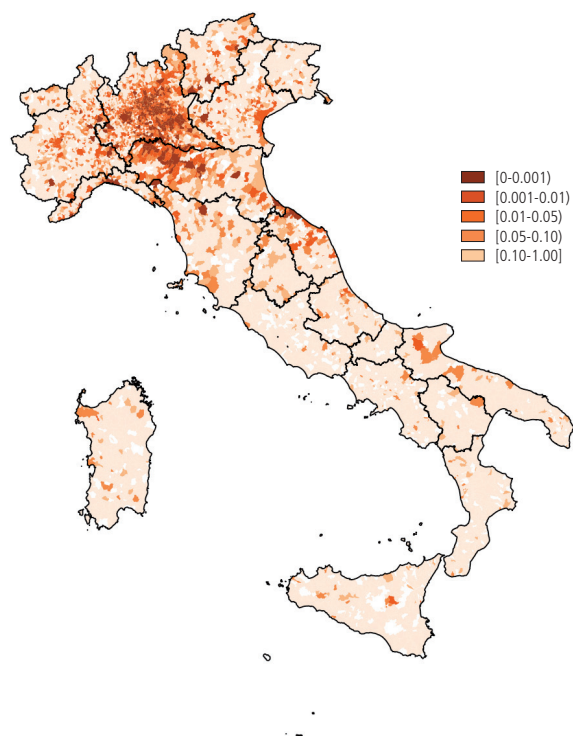
JANUARY



FEBRUARY



MARCH



APRIL

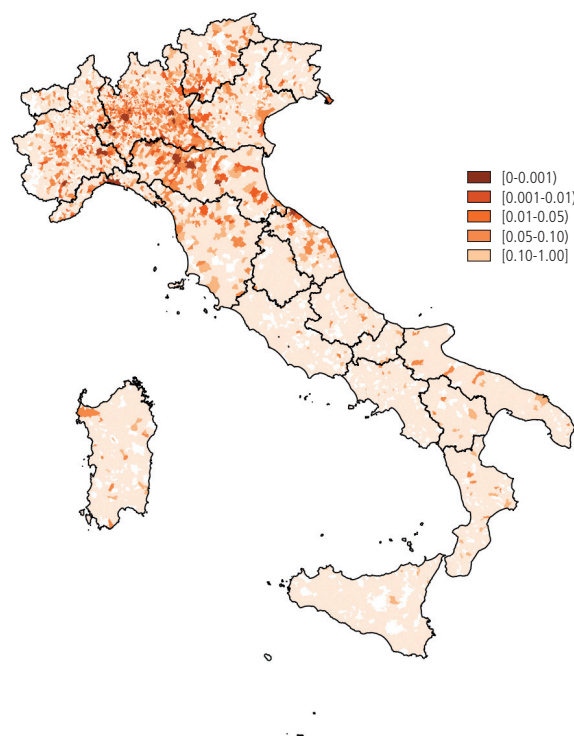


Figure 3. Q-value based on Posterior Predictive Probabilities, by Municipality. Italy, January-April 2020. White indicates municipalities with missing data.

Figura 3. Q-valori ottenuti dalle probabilità di eccesso della distribuzione predittiva a posteriori per Comune. Italia, gennaio-aprile 2020. In bianco i Comuni per i quali non sono disponibili dati di mortalità.

DISCUSSION AND CONCLUSIONS

The chosen modelling procedure can be viewed as a sort of hierarchical null procedure, similar to those proposed in profiling health providers.¹⁷ In fact, it was considered inappropriate to assume that in each municipality the death risk is constant for the entire time windows (2015-2020). Some winters may be milder, an influenza epidemic may occur and these fluctuations may not be synchronous among municipalities. The data were left to tune the parameters of the hierarchical null – the negative binomial distribution.

The European Mortality Monitoring Project (EUROMOMO <https://www.euromomo.eu/>), which is aimed at detecting and measuring the excess number of deaths related to possible public health threats across participating European Countries, reports the weekly total death counts by age group, from 2016 to 2020 for the participating Countries. The excess mortality in 2020 is already present at the age class 14-44 and tends to increase progressively as age increases.

The 2020 peak is delayed in comparison to the 2017-2018 peaks, it is steeper and higher. This finding is consistent with the general opinion of the scientific community that SARS-CoV-2 infection is not comparable with the influenza epidemics, even when compared with 2017-2018 cases, and that the general picture obtained by the mortality data results even more dramatic than that derived by considering only the cause specific mortality by COVID-19.

According to preliminary, but official, numbers, in Italy, the SARS-CoV-2 virus has infected several hundred thousand people and has caused more than 34 thousand deaths, placing our country as one of the most affected country at a global level.

Several articles have been published in the last few months using mortality data released directly by Istat,¹⁸ derived from the Italian Heat health watch warning system (HHWW Systems)¹⁹ or collected by the municipal registries at regional level.²⁰

At subnational level a recent paper analyses the weekly excess mortality in Italy.²¹ The paper gives a comprehensive picture of the evolution of all-cause mortality in Italy from 2016 onward and describes the spatio-temporal differences in excess mortality during the COVID-19 pandemic. The approach is based on posterior quantities from a Bayesian spatio-temporal model.

Following an epidemiological time series approach Scortichini et al.,²² Alicandro et al.,²³ Modi et al.,²⁴ Magnani et al.²⁵ estimated an overall excess death count of 47,490, 44,000, 51,000, 50,000 respectively. Blangiardo et al.²¹ provided a lesser estimate of 41,030.

As reported in the results section, we calculated 25,700 (95%CrI 15,963; 51,045) excess deaths for the two months

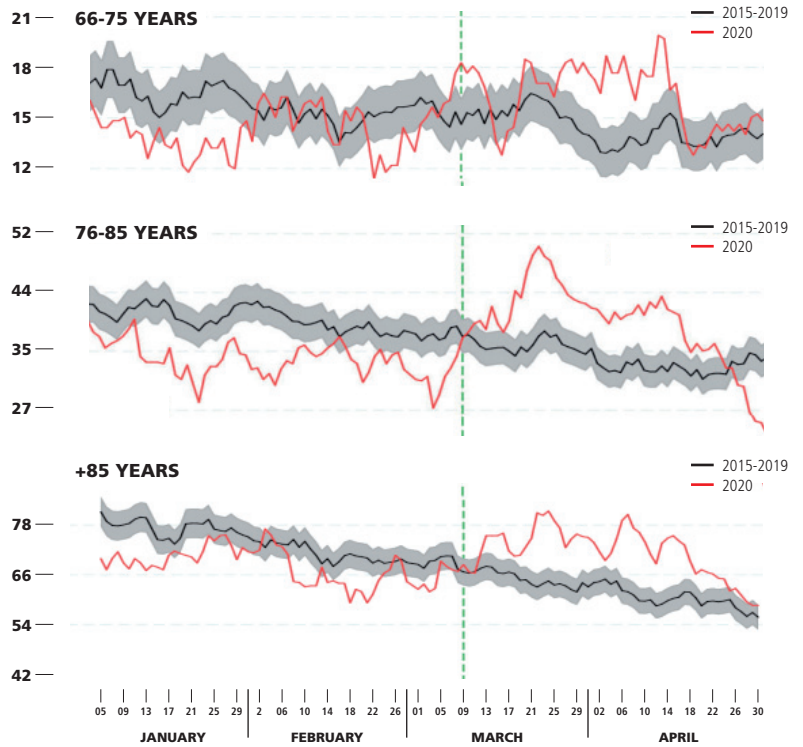


Figure 4. Observed 2020 and predicted (5-days moving average 2015-2019) number of deaths in older age classes. Tuscany Region (Central Italy).
Figura 4. Decessi osservati nel 2020 e predetti (media mobile su 5 giorni 2015-2019) per le classi di età anziane. Regione Toscana.

of March and April 2020. If a FDR of 1% was chosen 18,497 excess deaths would be obtained (95%CrI 13,079-28,541). This corresponds to 882 municipalities declared positive, of which 9 falsely declared positive. At this FDR threshold, the negative discovery rate (NDR) is estimated less than 4% for an assumed true prevalence of municipalities with excess death of 12.5%, an NDR of 10% for an excess prevalence of 13.5% and an NDR of 20% for an excess prevalence of 15%.²⁶ The posterior predictive distributions are skewed with a long right tail, and this is reflected in the upper limit of the credibility interval. Assuming a hierarchical null provides lower estimates than reported in the previous mentioned papers. Small variations around the expected value of mortality is considered natural and not be counted as excess mortality.

All the papers mentioned above have observed an excess mortality in the first four months of year 2020 compared with the expected number of deaths derived from the same period of the previous 5 years (2015-2019). In addition, this evidence has identified a peak between the end of March and beginning of April, a concentration of this phenomenon in North-West Regions (Lombardy, Emilia-Romagna, Piedmont) and among the most fragile subjects, i.e., the very old and people with chronic diseases (see the latest official report https://www.epicentro.iss.it/en/coronavirus/bollettino/Report-COVID-2019_22_october_2020.pdf from the website of the Ministry of Health <http://www.salute.gov.it/portale/nuovocoronavirus/dettaglioContenutiNuovoCoronavirus.jsp?id=5367&area=nuovoCoronavirus&menu=vuoto>). A second aspect, underlined by other authors, was the lower mortality observed in the last part

of the 2019 and the beginning of 2020, probably due to the mild weather conditions that characterized this period. This aspect is presented in figure 4 for the older age groups (66-75; 76-85; >85 years). The observed mortality (red line) is generally below the mortality that should be expected using the 2015-2019 prediction.²⁰

However, it is worth noticing that the total number of deaths observed in 2019 was 435,000 people. The death counts in the first 4 months of 2020 is above 250,000 deaths, meaning that almost 60% of the expected annual deaths are concentrated in that period, with obvious consequences on the health sector and on the social perception of this dreadful epidemic.

The scientific community has been debating how strongly this pandemic has stricken Italy or, in other terms, how many deaths were caused by the virus well above the seasonal mortality.

The media have boosted this debate reporting the results of different studies which were published in Italy, some of them with very low scientific value.

As mentioned in the introduction, the difficulty of evaluating the impact of COVID-19 is due to the uncertainties in recognizing all the deaths caused by the virus because not all the people who died were tested for the presence of the infection, and because the consequences of this pandemic exceed the casualties directly caused by the infection.

This study is not intended to give an answer to this question, but to provide a methodological approach to the analysis of epidemic data accounting for spatial and temporal uncertainty.

Conflict of interest: none declared.

Submission date: 08.10.2020

Accepted on: 16.12.2020

APPENDIX 1. RATIONALE OF THE BAYESIAN ANALYSIS

Bayesian inference is based on posterior densities. The statistical model is hierarchical, at level 1 we specify the data likelihood and at level 2 the prior density. Bayes formula is used to derive the posterior density. In our context, the death counts (Y_i) at municipality level ($i=1, 2, \dots, n$; n being the total number of municipalities) are assumed to follow a Poisson distribution, given the municipality specific relative risk or rate (θ_i) and known person-time at risk (E_i). The parameters θ_i are unknown and we specify a suitable prior density to reflect our previous belief – a conjugate useful distribution is a Gamma density. The Poisson-Gamma model is widely used, a seminal paper in geographical epidemiology is Clayton & Kaldor.²⁷

The likelihood is:

$$f(Y_i|\theta_i) = Poi(\theta_i; E_i)$$

the prior is:

$$f(\theta_i) = Ga(\alpha, \nu)$$

from the Bayes formula, the posterior for the unknown parameter is

$$f(\theta_i|\mathbf{Y}) = \frac{f(Y_i|\theta_i)f(\theta_i)}{\int f(Y_i|\theta_i)f(\theta_i)d\theta_i} = \frac{Poi(\theta_i; E_i)Ga(\alpha, \nu)}{NegBin(\mathbf{Y}|\alpha, \nu; E_i)} = Ga(\theta_i|\mathbf{Y}; E_i)$$

which is again a Gamma density thanks to the conjugacy.

The denominator in the Bayes formula is obtained by marginalization over all possible prior values of the unknown parameter

$$\int f(Y_i|\theta_i)f(\theta_i)d\theta_i = NegBin(\mathbf{Y}|\alpha, \nu; E_i)$$

Which, in the Poisson-Gamma model, has a closed form: the negative binomial distribution.

This distribution is also called the prior predictive distri-

bution.²⁸ This distribution summarizes our information on Y_i^{new} before having seen the data. For example, we may want to assess how divergent is the new data from the distribution under some a priori guess. In health service profiling, we may wish to state that a relative risk range between $0.9 \div 1.1$ is perfectly compatible with a process under control and translate this information in a suitable set of prior parameters.²⁹ In Bayesian inference, the Region of Practical Equivalence procedure consists in calculating the percentage of the High-Density Interval of a posterior distribution that falls within a predefined interval of compatible values for the null. ROPE is defined in opposition to a point null hypothesis as a range of values.³⁰⁻³³ However, the ROPE procedure refers to the posterior distribution under the alternative, while we are considering a predictive distribution under the null. Our approach is more coherent with the hierarchical null used in Ohlssen et al.¹⁷ As a metric of divergence, we can use the prior predictive tail probability $P(Y \geq Y_i^{new} | \alpha, \nu; E_i)$.³⁴

The posterior predictive distribution³⁵ is defined as

$$\int f(Y_i^{new}|\mathbf{Y}, \theta_i)f(\theta_i|\mathbf{Y})d\theta_i = NegBin(Y_i^{new}|\mathbf{Y}\alpha, \nu; E_i)$$

Differently from the prior predictive distribution, it uses the posterior density for the unknown parameter and takes advantage of independence between the new and the observed data. For example, in the Poisson-Gamma model the posterior Gamma for θ has parameter $(Y_i+\alpha, E_i+\nu)$ and the Negative Binomial posterior predictive distribution using the parameterization based on the inverse binomial sampling,³⁶ i.e., the probability distribution of n trials given k successes and p probability of success, has parameters

$$k = Y_i + \nu \quad \pi = (E_i + \alpha)/(2E_i + \alpha)$$

Posterior predictive tail probabilities $P(Y \geq Y_i^{obs} | \mathbf{Y} \alpha, \nu; E_i)$ are used in model checking and have been denoted as Bayesian p-values^{37,38} – note here the use of the observed value as statistical threshold in the predictive distribution. These checks have been criticized as optimistic since they use the observed data twice, to estimate model parameters and to assess divergence.³⁹

Gelfand et al.⁴⁰ suggested a cross-validatory (leave-one out) approach defining a conditional posterior predictive distribution

$$\int f(Y_i | \mathbf{Y}_i, \theta_i) f(\theta_i | \mathbf{Y}_i) d\theta_i = \text{NegBin}(Y_i | \mathbf{Y}_i, \alpha, \nu; E_i)$$

The actual value of

$$\int f(Y_i | \mathbf{Y}_i, \theta_i) f(\theta_i | \mathbf{Y}_i) d\theta_i \int f(Y_i | \mathbf{Y}_i, \theta_i) f(\theta_i | \mathbf{Y}_i)$$

is called conditional predictive ordinate and it is used as an outlier diagnostic in Bayesian model checking.

APPENDIX 2. OPENBUGS CODE

A simple OpenBugs code would be the following (note that $y_{20}[i]$ is a stochastic node)

```

model{
  for (i in 1:n){
    y15[i]~dnegbin(p[i],k[i])
    y16[i]~dnegbin(p[i],k[i])
    y17[i]~dnegbin(p[i],k[i])
    y18[i]~dnegbin(p[i],k[i])
    y19[i]~dnegbin(p[i],k[i])

    y20[i]~dnegbin(p[i],k[i])

    p[i]~dbeta(a,b)
    k[i]~dgamma(c,d)
  }
}

```

REFERENCES

- Figuerola JD, Brennan PM, Theodoratou E, et al. Distinguishing between direct and indirect consequences of covid-19. *BMJ* 2020;369:m2377.
- Masroor S. Collateral damage of COVID-19 pandemic: Delayed medical care. *J Card Surg* 2020;35(6):1345-47.
- Harrison G, Newport D, Robbins T, Arvanitis TN, Stein A. Mortality statistics in England and Wales: the SARS-CoV-2 paradox. *J Int Med Res* 2020;48(6):300060520931298.
- Muellbauer J, Aron J. Measuring excess mortality: the case of England during the COVID-19 Pandemic. Oxford: INET Oxford COVID-19 Research, Economics Department, Oxford University; 2020.
- Hope C. COVID-19 Death Rate is higher in European Countries with a low Flu Intensity since 2018. Working Paper No. 03/2020. Cambridge Judge Business School (UK).
- Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J R Stat Soc B* 1995;57:289-300.
- Wacholder S. The impact of a prevention effort on the community. *Epidemiology* 2005;16(4):555.
- Gilks WR, Richardson S, Spiegelhalter DJ. *Markov Chain Monte Carlo in Practice*. London: Chapman & Hall; 1996.
- Marshall EC, Spiegelhalter DJ. Identifying outliers in Bayesian hierarchical models: A simulation based approach. *Bayesian Ana* 2007;2:409-44.
- Presanis AM, Ohlssen D, Spiegelhalter DJ, De Angelis D. Conflict Diagnostics in Directed Acyclic Graphs, with Applications in Bayesian Evidence Synthesis. *Statistical Science* 2013;28(3):376-97.
- Catelan D, Lagazio C, Biggeri A. A hierarchical Bayesian approach to Multiple Testing in Disease Mapping. *Biometrical Journal* 2010;52(6):784-97.
- Storey JD. The positive false discovery rate: a Bayesian interpretation and the q-value. *Ann Stat* 2003;31(6):2013-35.
- Jones HE, Ohlssen DI, Spiegelhalter DJ. Use of the false discovery rate when comparing multiple health care providers. *J Clin Epidemiol* 2008;61(3):232-40.
- Catelan D, Biggeri A. Multiple Testing in Descriptive Epidemiology. *GeoSpatial Health* 2010;4(2):219-29.
- Robins JM, Van Der Vaart A, Ventura V. Asymptotic distribution of p values in composite null models. *J Amer Statist Assoc* 2000;95(452):1143-67.
- Gelman A. Two simple examples for understanding posterior p-values whose distributions are far from uniform. *Electron J Stat* 2013;7:2595-602.
- Ohlssen DI, Sharples LD, Spiegelhalter DJ. A hierarchical modelling framework for identifying unusual performance in health care providers. *J Roy Stat Soc A* 2007;170:865-90.
- Istat, ISS. Impact of the COVID-19 Epidemic on the Total Mortality of the Resident Population in the First Quarter of 2020. Rome: Istat-ISS; 2020.
- Michelozzi P, de' Donato F, Scortichini M, et al. Mortality impacts of the coronavirus disease (COVID-19) outbreak by sex and age: rapid mortality surveillance system, Italy, 1 February to 18 April 2020. *Euro Surveill* 2020;25(19):2000620.
- Nuvolone D, Bartolacci S, Padovano C, et al. Toscana: analisi dei dati di mortalità per il periodo 1 gennaio - 30 aprile 2020. Firenze: Agenzia Regionale di Sanità Toscana; 2020.
- Blangiardo M, Cameletti M, Pirani M, Corsetti G, Battaglini M, Baio G. Estimating weekly excess mortality at sub-national level in Italy during the COVID-19 pandemic. *PLoS ONE* 15(10):e0240286.
- Scortichini M, Schneider dos Santos R, de' Donato F, et al. Excess mortality during the COVID-19 outbreak in Italy: a two-stage interrupted time-series analysis. *Int J Epidemiol* 2020;dyaa169.
- Alicandro G, Remuzzi G, La Vecchia C. COVID-19 pandemic and total mortality in the first six months of 2020 in Italy: COVID-19 pandemic and total mortality. *Med Lav* 2020;111(5):351-53.
- Modi C, Boehm V, Ferraro S, Stein G, Seljak U. How deadly is COVID-19? A rigorous analysis of excess mortality and age-dependent fatality rates in Italy. *medRxiv* 2020. doi: <https://doi.org/10.1101/2020.04.15.20067074>
- Magnani C, Azzolina D, Gallo E, Ferrante D, Gregori D. How Large Was the Mortality Increase Directly and Indirectly Caused by the COVID-19 Epidemic? An Analysis on All-Causes Mortality Data in Italy. *Int J Environ Res Public Health* 2020;17:3452.
- Craiu RV, Sun L. Discovery Rate and Non-Discovery Rate. *Statistica Sinica* 2008;18(3):861-79.
- Clayton DG, Kaldor J. Empirical Bayes estimates of age-standardized relative risks for use in disease mapping. *Biometrics* 1987;43(3):671-81.
- Box GEP. Sampling and Bayes' inference in scientific modelling and robustness (with discussion). *J Roy Statist Soc Ser* 1980;143(4):383-430.
- Clayton D, Hills M. *Statistical models in Epidemiology*. Oxford: Oxford University Press; 2013.
- Kruschke JK. What to believe: Bayesian methods for data analysis. *Trends Cog Sci* 2010;14(7):293-300.
- Kruschke, JK, Aguinis H, Joo H. The time has come: Bayesian methods for data analysis in the organizational sciences. *Organizational Research Methods* 2012;15(4):722-52.
- Kruschke, J. *Doing bayesian data analysis: A tutorial with r, jags, and stan*. Academic Press, 2014.
- Kruschke, JK, Liddell TM. The bayesian new statistics: Hypothesis testing, estimation, meta-analysis, and power analysis from a bayesian perspective. *Psychon Bull Rev* 2018;25(1):178-206.
- Bayarri, MJ, Berger JO. P-values for composite null models. *JASA* 2000;95(452):1127-42.
- Rubin DB. Bayesianly justifiable and relevant frequency calculations for the applied statistician. *Ann Statist* 1984;12(4):1151-72.
- Johnson NL, Kemp AW, Kotz S. *Univariate Discrete Distributions*. 3rd edition. New York: Wiley; 2005.
- Gelman A, Meng XL, Stern H. Posterior predictive assessment of model fitness via realized discrepancies. *Statistica Sinica* 1996;6:733-807.
- Gelman A, Carlin JB, Stern HS, Rubin DB. *Bayesian Data Analysis*. 2nd edition. London: Chapman & Hall/CRC; 2003.
- Bayarri, MJ, Berger JO. Quantifying surprise in the data and model verification. *Bayesian Statistics* 6, 53-82. New York: Oxford University Press; 1998.
- Gelfand AE, Dey DK, Chang H. Model determination using predictive distributions with implementation via sampling-based methods. *Bayesian Statistics* 1992;4:147-67.