Comparing methods to predict baseline mortality for excess mortality calculations

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Contents

Abstract

Background: The World Health Organization's excess mortality estimates presented in May 2022 stirred controversy, one point of which was the high estimate for Germany, later attributed to the used spline-model. This paper aims to reproduce the problem using synthetic datasets, thus allowing the investigation of its sensitivity to parameters, both of the mortality curve and of the used method, thereby shedding light on the conditions that gave rise to this error and its possible remedies. Methods: A negative binomial model was used accounting for long-term change, seasonality and flu seasons and heat waves. Simulated mortality curves from this model were then analysed with simple methods (mean, linear trend), with the WHO's method and with the method of Acosta and Irizarry. Results: The performance of the WHO's method with its original parametrization is indeed very poor, however it can be profoundly improved by a better choice of parameters. The Acosta-Irizarry method outperformed WHO's method despite being also based on splines, but it was also dependent on its parameters. Linear extrapolation could produce very good results, but is highly dependent on the choice of the starting year, while average was the worst in almost all cases. Conclusions: Splines are not inherently unsuitable for predicting baseline mortality, but care should be taken, in particular, results suggest that the key issue is the rigidity of the splines. Model diagnostics must be performed before accepting any result, and used methods should be validated. Further research is warranted to understand how these results can be generalized to other scenarios.

Keywords

Excess mortality; Spline regression; Prediction; Robustness.

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Introduction

Excess mortality is the difference between the actual all-cause mortality (number of deaths) of a time period in a given country or (sub- or supranational) region and its "expected" mortality, defined as the mortality statistically forecasted from the region's historical data. Calculation of excess mortality can be used to characterize the impact of an event on mortality if the historical data is prior to the onset of the event, therefore the prediction pertains to a counterfactual: mortality that would have been observed without the event [1]. Thus, the difference, i.e., excess mortality indeed measures the impact of the event, assuming the prediction was correct.

Calculating excess mortality is particularly useful if the event's impact on mortality is hard to measure directly, for instance, one of the typical applications is characterizing the mortality associated with natural disasters [2–4], but is is also used for epidemics where direct mortality registration is missing, incomplete or unreliable, a prime example being the seasonal flu [5,6].

COVID-19 is no exception. While mortality is reported in developed countries, typically daily or weekly, this suffers from two drawbacks, first, the number of reported deaths is – while to much less extent than the number of reported cases – but still contingent on testing activity, which might be vastly different between countries or time periods, and second, despite efforts at standardization the criteria for the certification of deaths might be different between countries [7]. Excess mortality resolves both of these problems as it is completely immune to differences in testing intensity and cause of death certification procedure. This makes it especially suitable for between-country comparisons, which is a critical issue to better understand the pandemic, in particular, to evaluate different control measures and responses [8].

This, however, comes at a price. First, and perhaps most importantly, excess mortality is inherently a gross metric, measuring both the direct and the indirect effects, the latter of which can be both positive (e.g., COVID control measures also provided protection against flu) or negative (e.g., the treatment of other diseases became less efficient) [9]. Second, the excess mortality is the slowest indicator: the necessary data, that is, the number of deaths usually becomes available with a 4 week lag (and even that is typically revised to some extent later) even in the developed countries (in contrast to reported COVID-deaths, which is available by next week or even by next day). Finally, the whole calculation depends on how accurate the forecast was.

The last of these issues will be the focus now: given the importance of cross-country comparisons, it is crucial the results indeed reflect differences and are not too sensitive to the used prediction method.

Only those methods will be considered now that use traditional regression approach, i.e., methods using ARIMA models [10–13], Holt-Winters method [14] or those based on Gaussian process [15] won't be considered, just as ensemble methods [16,17]. Questions concerning age- or sex stratification or standardization [18], small area estimation [19,20] and inclusion of covariates, such as temperature, to improve modelling [16,17,19] will also not be considered here.

This leaves us with two questions, the handling of seasonality and the handling of long-term trend. For the latter, these are the typical solutions in the literature concerning COVID-19:

- Using the last pre-pandemic year [16,21]. This is good – even if not perfect – considering the long-term trends, as it uses data closest to the investigated period, but it has a huge variance, due to the natural year-to-year variability of mortality.
- Using the average of a few pre-pandemic years (typically 5) [22–28]. This is more reliable as averaging reduces variability, however, it is even more biased in case the mortality has a long-term trend (which it almost always has), for instance, if mortality is falling, this provides an overestimation, thus, excess mortality is underestimated.
- Using a linear trend extrapolation [29–31]. This accounts for the potential trends in mortality, removing the bias of the above methods, at least as far as linearity is acceptable, but it depends on the selection of the starting year from which the linear curve is fitted to the data. It also has higher variance than the averaging approach, but is is usually less of concern, given the huge amount of data typically used (unless a small country, and/or age or sex strata is investigated).
- Using splines [32,33]. The method of Acosta and Irizarry [34,35] is based on splines, just as many other custom implementation [16,36], which, crucially, includes the model used by the World Health

Organization (WHO) [37].

While this issue received minimal public attention, the choice of the method (and its parameters) to handle long-term trend might have a highly relevant impact on the results of the calculation, as evidenced by the case of the excess mortality estimation of the WHO. On May 5, 2022, WHO published its excess mortality estimates [38], which immediately raised questions: among others, the estimates for Germany were surprisingly high [39]. The reason why it came as a shock is that WHO's estimate, 195 000 cumulative excess death for Germany in the years 2020 and 2021, was inexplicably outlying from every previous estimate, for instance, World Mortality Dataset reported 85 123 deaths for the same period [1].

The case was so intriguing, that one paper termed it the "German puzzle" [39]. Figure 1 illustrates the "German puzzle" using actual German data, with the curves fitted on 2015-2019 data and extrapolated to 2020 and 2021 (as done by the WHO): while the dots visually indicate rather clearly a simple upward trend (as shown by the linear extrapolation), the spline prediction turns back.

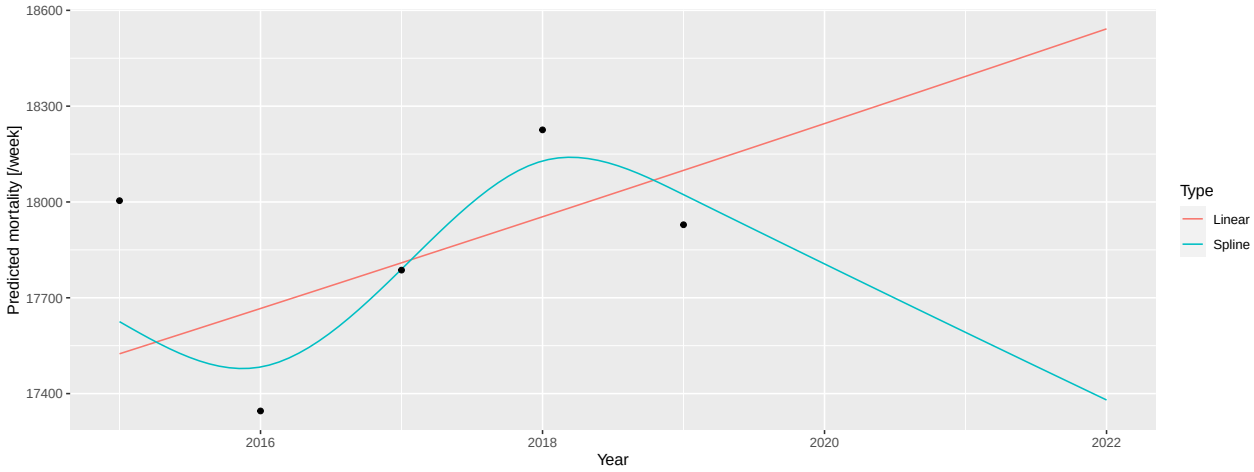

Figure 1: A linear trend and a spline fitted on German mortality data 2015-2019 and extrapolated to 2020 and 2021.

The explanation later provided by the WHO [37] stated that the problem was due to two issues, first, the WHO applied a rescaling method to the raw data to compensate for underreporting (due to late registration, for instance), but this was unnecessary in case of Germany, with excellent death registration. Figure 1 shows the unadjusted German data avoiding this problem, so that focus can be placed on the second issue that will be the subject of investigation now: the usage of splines.

As described above, WHO's method uses a spline to capture the long-term trend, and it seems that the problem is that the lower data of 2015 had a very high impact on the spline, with that single observation turning the entire spline, despite earlier points showing an upward trend. It seems to much weight is put on this – likely short-term, random, noise-like – fluctuation, i.e., the extrapolation was too sensitive to this. The culprit is quickly identified as spline-regression itself, with one commentator saying "[e]xtrapolating a spline is a known bad practice" [39].

But really splines are to be blamed? Motivated by obtaining a better understanding of the "German puzzle", this paper aims to investigate the following questions: 1) Really splines *per se* were the culprit? 2) What were the particlar characteristics, both of the scenario and of the used spline-regression, that gave rise to the problem? 3) Is there a better way to predict baseline for excess mortality calculation avoiding this problem?

To answer these questions, first a model will be devised that is able to generate mortality curves that capture the relevant features exhibited by the real-life German example. Thus, it'll be possible to calculate the accuracy of a forecast (as the ground truth is now known), and also to investigate how parameters of the simulation influence it. With averaging several simulations, the mean accuracy can be approximated, allowing the comparison of the methods, and investigating its dependence on the parameters – both of the mortality

curve and of the parameters of the method – thereby hopefully resolving the "German puzzle".

Note that age/sex-stratification will not be used, and the background population will not be taken into account: while one could very well argue for the importance of these, the WHO's study, the investigation of which is the aim of the present paper, also did not take these into account.

Methods

Data source

Weekly all-cause mortalities for Germany were obtained from the European Statistical Office (Eurostat), database `demo_r_mwk_ts` [40]. No additional preprocessing or correction was applied such as that for late registration, i.e., the part of the problem with the WHO's approach due to upscaling was avoided, so that the focus is now solely on the modeling aspect. A detailed comparison of the possible data sources can be found in Additional File 1.

Basic properties (raw weekly values, yearly trend, seasonal pattern) are shown on Figure 2.

Simulation model

Based on the patterns that can be observed on Figure 2, the following three components will be used to create synthetic datasets:

- Long-term change, modelled with quadratic trend; described by three parameters (constant, linear and quadratic term)
- Deterministic seasonality, modelled with a single harmonic (sinusoidal) term; described by two parameters (amplitude and phase)
- Random additional peaks during the winter (i.e., flu season) and during the summer (i.e., heat waves); described in each season by five parameters (probability of the peak, minimum and maximum value of the peak height, minimum and maximum value of the peak width)

These govern the expected value; the actual counts are obtained from a negative binomial distribution with constant size and log link function.

Thus, the number of deaths at time t, D_t, has been simulated according to a negative binomial model $D_t \sim \text{NegBin}\left(\mu_t, s\right)$, with mean μ_t and size parameter $s = 1000$. The mean is modelled such that $\log\left(\mu_t\right) = \beta_0 + \beta_1 \cdot t + \beta_2 \cdot t^2 + A \cdot \cos\left(2\pi \cdot w\left[t\right] + \varphi\right)$, where $w\left[t\right]$ is the week of time t, scaled from 0 to 1. The first three terms in this equation refers to the "long-term trend" (characterized by parameters $\beta_0 = 10.11$, $\beta_1 = -7.36 \cdot 10^{-5}$ and $\beta_2 = 3.04 \cdot 10^{-9}$), the latter to the seasonality (characterized by parameters $A = 0.07$ and $\varphi = -0.61$). Additionally some peaks have been randomly added to $\log\left(\mu_t\right)$, of widths between 8.41 and 35.36 and height between 0.11 and 0.33 positioned in the winter (uniformly between weeks 1 to 11) with a probability of 0.45 in each year and of widths between 0.86 and 9.24 and height between 0.10 and 0.24 positioned in the summer (uniformly between weeks 26 to 37) with a probability of 0.40 in each year. The shape of the peaks follows the probability density function of the Cauchy distribution. These parameters were chosen so that the simulated curves mimic the properties of the real-life mortality curve.

Detailed description of how the above model is built (including the estimation from the actual German data which resulted in these parameters and example of the simulated data along with real data) can be found in Additional File 2.

Baseline mortality prediction

Four methods will be used for predicting mortality, including the WHO's method, an advanced alternative method that also uses splines, developed by Acosta and Irizarry in 2020 [34], and two simple methods as a comparison. These cover the widely used, classical statistical methods used for predicting baseline mortality in excess mortality studies.

- Average: after accounting for seasonality with a single cyclic cubic regression spline, the average of the preciding years will be used as the – constant – predicted value. The response distribution is assumed

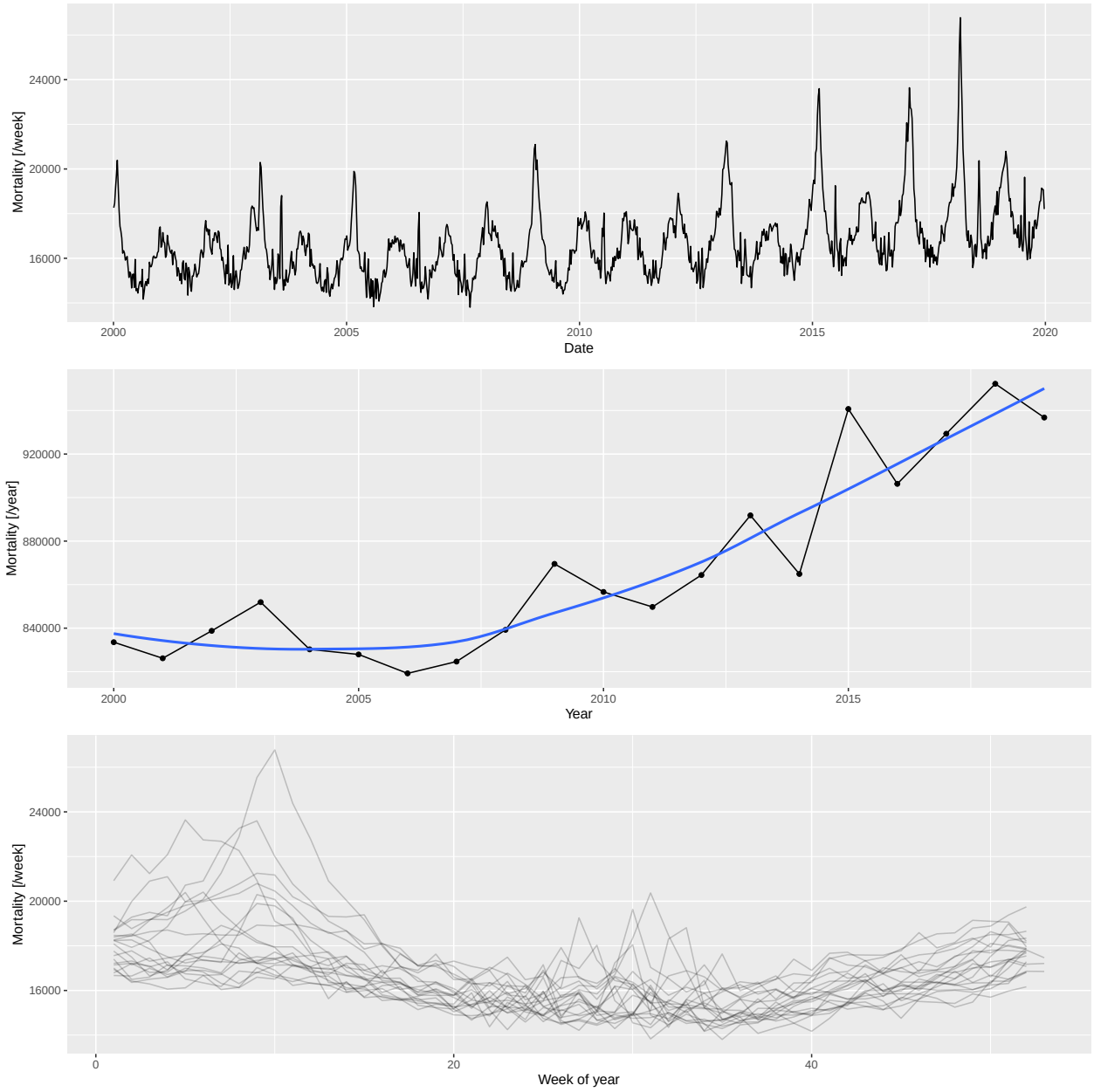

Figure 2: Weekly mortalities (upper), yearly mortalities with LOESS-smoother (middle) and seasonal pattern (bottom) of the German mortality data, 2000-2019.

to be negative binomial (with the overdispersion parameter estimated from the data), with log link function. Parameter: starting year (i.e., how many previous year is used for averaging). Some studies used the last pre-pandemic year (2019) as the predicted baseline mortality, this is just the special case of this method, with the starting year set to 2019.

- Linear: after accounting for seasonality with a single cyclic spline, the long-term trend is modelled with a linear trend, that is extrapolated. The response distribution is assumed to be negative binomial (with the overdispersion parameter estimated from the data), with log link function. Parameter: starting year (from which the model is fitted).
- WHO's method: the method is reconstructed from the description provided in [37]. In brief, seasonality is accounted with single a cyclic spline (as done in the previous cases), and the long-term trend is accounted with a thin plate regression spline. The only deviation compared to WHO's paper is that the actual time (number of days since 1970-01-01) is used as the predictor for long-term trend, not the abruptly changing year. The response distribution is assumed to be negative binomial (with the overdispersion parameter estimated from the data), with log link function, and the model is estimated with restricted maximum likelihood (REML). Second derivative penalty was used for constructing the spline, meaning that the forecasting will be a linear extrapolation. Parameters: starting year (from which the model is fitted) and k, the dimension of the basis of the spline used for capturing the long-term trend.
- Acosta-Irizarry (AI) method: the method described in [34] using their reference implementation. It offers many advantages when estimating excess mortality, however, these partly appear only in the second stage (i.e., calculating the excess after the expected is forecasted). In terms of the baseline prediction, the method is similar to that of WHO in using splines, with three differences: first, to capture seasonality, two harmonic terms are used (with pre-specified frequencies of 1/365 and 2/365 as default, and arbitrary phase estimated from the data) instead of the cyclic spline, second, the spline to capture the long-term trend is a natural cubic spline, not a thin plate regression spline, with the number of knots selectable. Note that if the number of years in the training data is less than 7, linear trend is used instead of the spline. Finally, the response distribution is quasi-Poisson (with log link function). Parameters: starting year (from which the model is fitted) and *tkpy*, the number of trend knots per year; other parameters are left on their default values (i.e., two harmonic term is used).

Table 1 provides an overview of these modelling approaches.

Table 1. Overview of the models used to create predictions.

Name	**Model**
Average	$Y_t \sim NegBin\left(\mu_t, \theta\right) \log\left(\mu_t\right) = \beta_0 + f_{cc}\left(w\left[t\right]\right)$
Linear	$Y_t \sim NegBin\left(\mu_t, \theta\right) \log\left(\mu_t\right) = \beta_0 + \beta_1 t + f_{cc}\left(w\left[t\right]\right)$
WHO	$Y_t \sim NegBin\left(\mu_t, \theta\right) \log\left(\mu_t\right) = f_{tp}\left(t\right) + f_{cc}\left(w\left[t\right]\right)$
Acosta-Irizarry	$Y_t \sim QuasiPoi\left(\mu_t\right) \log\left(\mu_t\right) =$
	$\begin{cases} \beta_0 + f_{nc}\left(t\right) + \sum_{k=1}^{2}\left[\sin\left(2\pi \cdot k \cdot w\left[t\right]\right) + \cos\left(2\pi \cdot k \cdot w\left[t\right]\right)\right] & * \\ \beta_0 + \beta_1 t + \sum_{k=1}^{2}\left[\sin\left(2\pi \cdot k \cdot w\left[t\right]\right) + \cos\left(2\pi \cdot k \cdot w\left[t\right]\right)\right] & ** \end{cases}$

Legend. cc: cyclic cubic regression spline, tp: thin plate regression spline, nc: natural cubic spline, *: >7 years training data, **: $\leq$ 7 years training data, $w\left[t\right]$: week of the year scaled to 0-1.

As already noted, population size is not included in the models, consistent with what the WHO did for country-level analysis for countries with frequent data available. Thus, changes in the population size are absorbed into the changes of death count without explicit modelling, which is clearly of potential room for improvement.

Validation through simulation

First, a synthetic dataset is randomly generated from the model described above using the investigated parameters (parameters of the scenario). This dataset simulates mortalities from the beginning of 2000 to the

end of 2023. Then, the investigated prediction method with the investigated parametrization (parameters of the method) is applied, and after fitting on the data from 2000 to 2019, a prediction is obtained for 2020 to 2023, where it can be contrasted with the actual values of the simulation, which represent the ground truth in this case. Denoting the actual number of deaths in the simulated dataset for year y with $M_y = \sum_{t:y[t]=y} D_t$ and the predicted number with $\widehat{M_y}$, the goodness of prediction is quantified with mean squared error ($MSE = \frac{1}{4}\sum_{y=2020}^{2023}\left(M_y - \widehat{M_y}\right)^2$), mean absolute percentage error ($MAPE = \frac{1}{4}\sum_{y=2020}^{2023}\left|\frac{M_y - \widehat{M_y}}{M_y}\right|$) and bias ($Bs = \frac{1}{4}\sum_{y=2020}^{2023}\left(M_y - \widehat{M_y}\right)$). This whole procedure is repeated 1000 times, and metrics are averaged over these replications. This is then repeated for all prediction method, all parameters of the method and all parameters of the scenario.

Investigated parameters of the prediction methods were the following:

- Average: starting year 2000, 2005, 2010, 2015, 2019
- Linear: starting year 2000, 2005, 2010, 2015
- WHO's method: all possible combination of starting year 2000, 2005, 2010, 2015 and k (basis dimension) 5, 10, 15, 20
- Acosta-Irizarry method: all possible combination of starting year 2000, 2005, 2010, 2015 and *tkpy* (trend knots per year) 1/4, 1/5, 1/7, 1/9, 1/12

For the scenario, simulations were run with the optimal parameters as discussed previously (base case scenario) and three further parameter sets, describing a scenarios where the long-term trend is linear ($\beta_0 = 10.11$, $\beta_1 = -7.36 \cdot 10^{-5}$ and $\beta_2 = 0$), constant ($\beta_0 = 10.11$, $\beta_1 = 0$ and $\beta_2 = 0$) and when it is non-monotone ($\beta_0 = 10$, $\beta_1 = 9.5 \cdot 10^{-5}$ and $\beta_2 = -3 \cdot 10^{-9}$). The framework allows the investigation of any further scenario, including varying parameters other than long-term trend, or varying several ones in a combinatorial fashion (although this latter has a very high computational burden).

Details of the simulation are provided in Additional File 3.

Programs used

All calculations are carried out under the R statistical program package version 43.1 [41] using packages `data.table` [42] (version 1.14.8) and `ggplot2` [43] (version 3.4.2), as well as `excessmort` (version 0.6.1), `mgcv` (version 1.8.42), `scorepeak` (version 0.1.2), `parallel` (version 4.3.1) `lubridate` (version 1.9.2), `ISOweek` (version 0.6.2) and `eurostat` (version 3.8.2).

Full source code allowing complete reproducibility is openly available at https://github.com/tamas-ferenci/MortalityPrediction.

Results

Figure 3 illustrates the predictions (for 2020-2023) for the base case scenario by showing the estimated yearly deaths for 200 randomly selected simulation together with the ground truth for all 4 method with all possible parameters.

Figure 3 already strongly suggests some tendencies, but to precisely evaluate it, error metrics have to be calculated. Figure 4. shows all three error metrics for all methods and for all possible parametrizations. As it can been seen from the Figure, the ordering of the methods according to different criteria are largely consistent.

As already suggested by Figure 3, this confirms that $k = 3$ (WHO) and $tkpy = 1/12$ or $1/7$ (Acosta-Irizarry) are the best parameters in this particular scenario. Note that the default value in the method used by the WHO is $k = 10$, but it is just $tkpy = 1/7$ for the Acosta-Irizarry method.

It worth mentioning that Figures 3 and 3 shed light on the nature of error. The linear trend and average methods are particularly clear in this respect: early starting ensures low variability, but is highly biased, a later starting reduced the bias, but increases the variance. Thus, this is a typical example of the bias-variance trade-off.

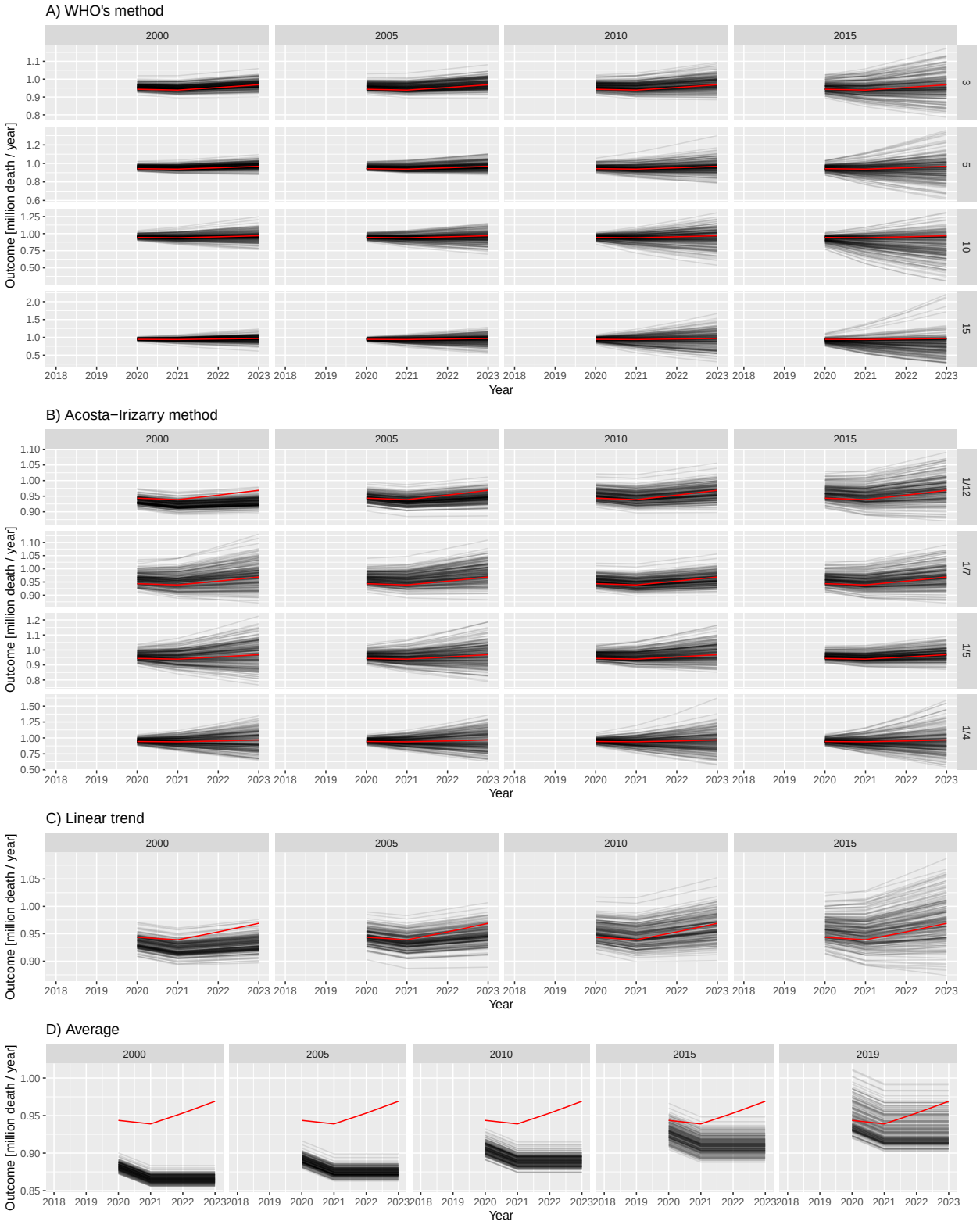

Figure 3: Estimated yearly deaths (for 2020-2023) for 200 randomly selected simulation together with the ground truth: A) WHO's method, B) Acosta-Irizarry method, C) Linear trend, D) Average; parameters of the methods are shown in column and row headers, parameters of the scenario are set to the base case values. (Note that 2020 is a long year, i.e., it consists of 53 weeks.)

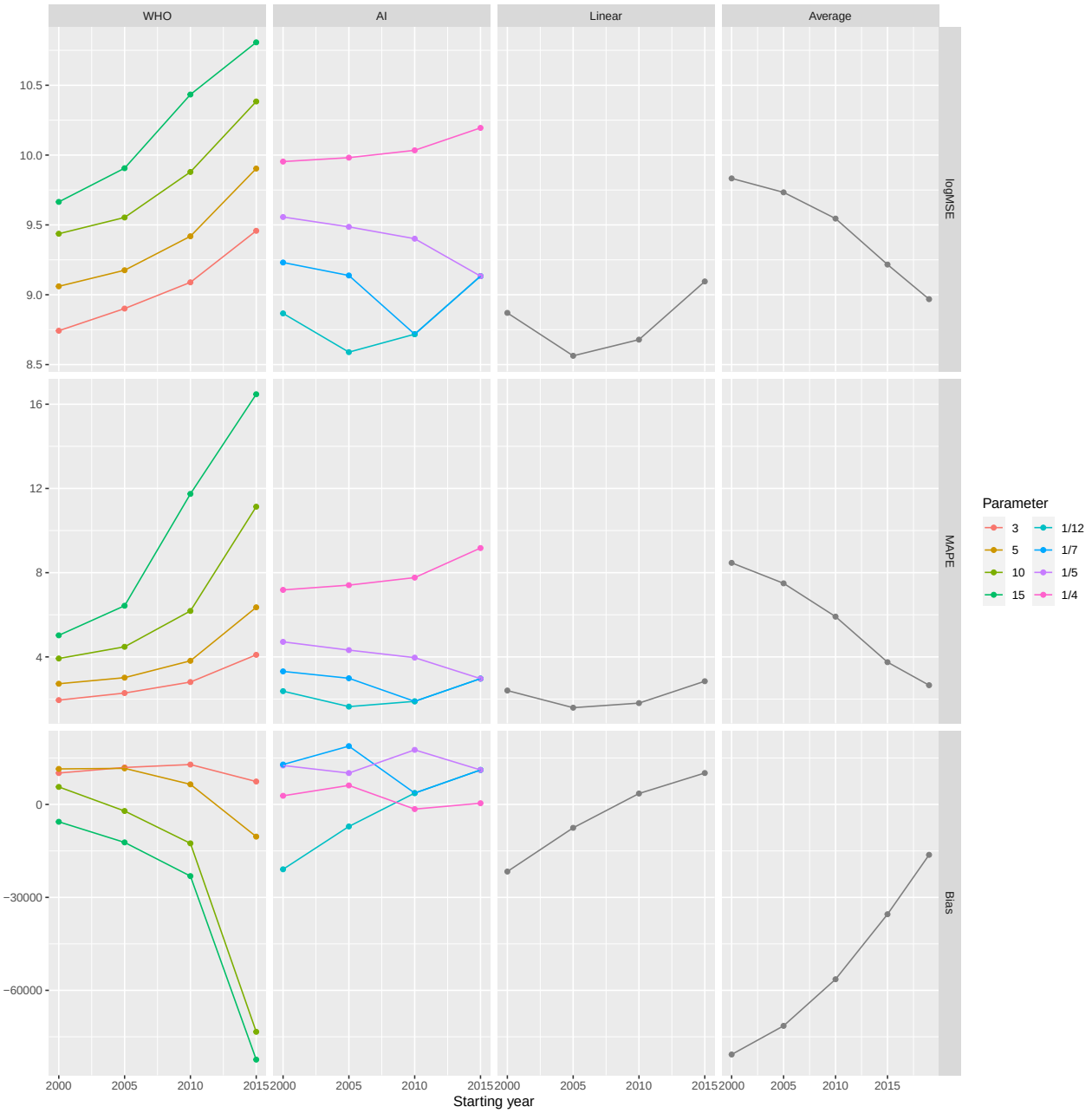

Figure 4: Different error metrics (MSE, MAPE, Bias) for all methods and for all possible parameter combinations of all methods; parameters of the scenario are set to the base case values.

All the above investigations used the base case scenario for the simulated mortality curve. Figure 5. shows the mean squared errors achievable with each method in the further investigated scenarios, depending on the starting year (with k=3 for the WHO method and tkpy = 1/7 for the AI approach).

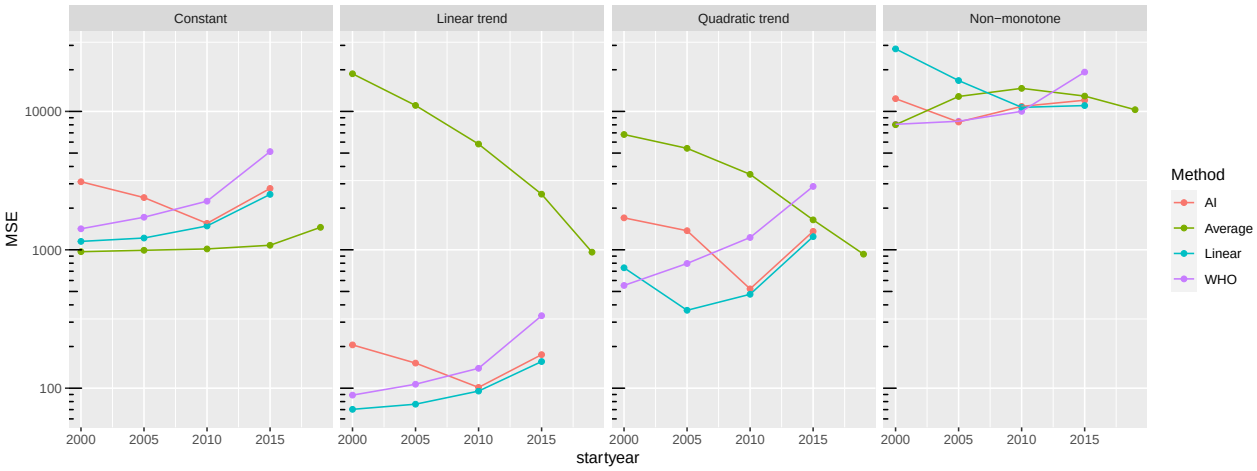

Figure 5: Mean squared errors of the investigated methods by starting year (with k=3 for the WHO method and tkpy = 1/7 for the AI approach) for the four defined scenarios.

Finally, note that as different methods were evaluated on the same simulated dataset for each simulation, it is possible to compare not only the averages, but directly compare the errors themselves. Additional File 4 explores this possibility.

Discussion

These results demonstrate that we were able to reliably reproduce the "German puzzle" using synthetic datasets. This approach allowed a deep investigation of how the results depend on the used method, its parameters and on the parameters of the scenario.

As expected, prediction with average has the highest error, except for very poor parametrizations of the spline-based methods and is highly biased. Its performance is improved by a later starting year, i.e., smaller bias offsets the larger variability. Naturally, it performs the best in the – practically very unlikely – case when even the true mortality is constant.

Linear extrapolation seems to be a very promising alternative, comparable to the much more sophisticated spline-based methods, the only problem being that it is very sensitive to the appropriate choice of the starting year: that phase should be covered where the change in historical mortality is linear. This is prone to subjectivity and might not work at all if the linear phase is too short (limiting the available information), i.e., it depends on how wiggly is the historical curve. Naturally, it works best if the true mortality is linear, but can perform very poorly with non-monotone curves when the starting year is not selected to match the last section that can be approximated with a linear curve, in line with the previous remark.

Splines in contrast can work theoretically well even in those cases as non-monotone mortality: it can use all historical data, i.e., it is not abruptly cut off as with linear extrapolation, but more weight is placed on the trends suggested by the recent observations. At first glance, this seems to be the ideal solution, delivering the benefits of the linear extrapolation, but without the need to "guess" the good starting point. However, as this investigation reveals, what is meant by "more weight" and "recent" is crucial, and certain parameter choices can results in very poor extrapolations, despite the tempting theoretical properties.

The overall picture in selecting the optimal parameters, confirmed by the results of both spline-based methods, is that splines should be quite simple in baseline mortality prediction for excess mortality calculation. This is the concordant conclusion from the experiences both with the WHO method (where increasing basis

dimension decreased performance) and the Acosta-Irizarry method (where increasing trend knots per year decreased performance).

The likely explanation is that mortality curves exhibit only slow changes, so high flexibility is not required, and – as with any regression model with too high model capacity – can be downright detrimental, as it allows the model to pick up noise, i.e., can result in overfitting.

It worth pointing out that the Acosta-Irizarry method only uses spline to model the long-term trend if it has more than 7 years of data, otherwise it switches to simple linear trend. This is completely in line with the above remarks: flexibility is useful, but can backfire with small amount of training data.

In Germany, the data for 2019 was somewhat lower, likely due to simple random fluctuation, but unfortunately the spline was flexible enough to be "able to take this bend". Note that data are presented using the ISO 8601 year defintion meaning that year can be either 52 or 53 weeks long [44]; from 2015 to 2019 every year is 52 weeks long except 2015 which is one week longer. This adds to the reasons why the value of 2015 is higher, increasing the wiggliness of the German data and thereby potentially contributing to the problem, as the increased wigliness of the data forces the thin plate regression spline used in the WHO's method to be more flexible. (This was not a problem with WHO's original analysis, as it used monthly data, but appears if the WHO's method is directly applied to weekly data.)

The WHO method is only acceptable with $k \leq 5$ (but even that requires longer observation than starting from 2015, as was done by the WHO), not higher. For the Acosta-Irizarry method, 1/4 trend knots per year was definitely too flexible, perhaps even 1/5 is too high. Note that the default value in the reference implementation of the Acosta-Irizarry method is 1/7, and authors in fact do not recommend using a value much higher. The WHO's paper unfortunately does not specify what basis dimension was used [37], but the default of the package used there is $k = 10$, so even $k = 5$ is substantially lower, not to speak of $k = 3$. This is likely a crucial component in WHO's experience, where the starting year was 2015 (and probably $k = 10$ was used).

Among the two spline-based methods, when the rigidity parameters were used that are optimal in this particular scenario, WHO's method performed better with longer fitting periods, Acosta-Irizarry performed better with shorter ones. However, the performance of the Acosta-Irizarry method was much less dependent on the starting year (i.e., its disadvantage compared to WHO's method was less for earlier starting year than that of the WHO's method for later starting years).

Perhaps one of the most important lesson learned, especially from Figures 4 and 5 is that there is no "one size fits all" optimal choice: a method that performs well for a given true mortality curve can exhibit very poor performance for another shape of mortality. More than that, even the optimal choice of parameters for one given method can substantially depend on the scenario, and a parameter that works well for one situation might be poor for another one. This suggests that there while there are "safer choices", there is no point in recommending a universally "optimal" parameter. What can be done to nevertheless select a good parameter for a particular case? Perhaps the most important is to examine the fit of the model on historical data. Figure 6 provides an example using the German data. The Figure shows the prediction for three years (2020 to 2022) from the historical data, using all methods and all parameters. A quick visual inspection immediately reveals relevant and likely meaningless predictions. The latter, unfortunately, includes that of WHO (2015 as starting year, $k = 10$), thus, this inspection would have likely revealed the problem. Time series bootstrap and time-series cross-validation are promising options to replace the – potentially subjective – visual inspection with a more objective method, still using only historical data.

We are aware of two previous works from the literature that are comparable to the present investigation. Both Nepomuceno et al [45] and Shöley [46] is similar to ours in a sense that they used – among others – several models, partly overlapping those presented here, but, importantly, neither of them considered splines for long-term trend at all. Nepomuceno et al did not try to evaluate the methods, it compared them to each other without having ground truth, i.e., the aim was to investigate concordance. In contrast, Shöley did try to give an objective evaluation, but in contrast to the synthetic dataset simulation approach used here, it applied time series cross-validation with historical data to measure accuracy. Cross-validation has the advantage that is guaranteed to be realistic – as opposed to a simulation – but there is less freedom, as

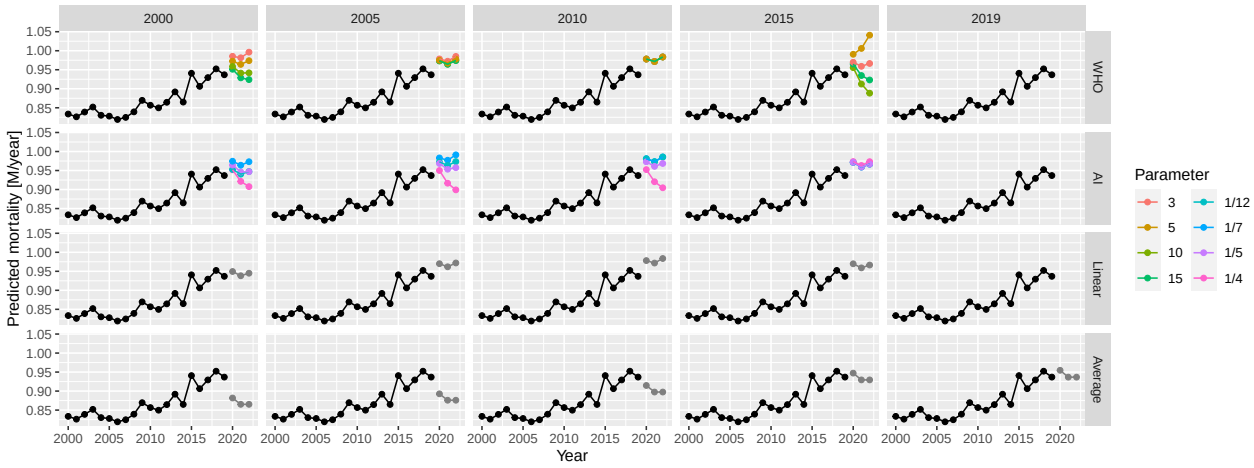

Figure 6: Predictions for 2020 to 2022 from all methods with all possible parameters, using historical German data.

investigators are bound to empirical data, with limited possibility in varying the parameters.

We did not investigate the impact of using the population and modelling death rates versus modelling death counts directly, nor did we examine the potential impact of the frequency of the data. Weekly data was used throughout this study: this might not be available for developing countries, but it is almost universally available for developed countries, in which case, the use of the most frequent data seems to be logical (with the appropriate handling of seasonality). In the same vein, adjustment for late registration and imputation of missing data, which might be needed where full data is not available, is not considered here, as the focus is on developed countries.

A further limitation of the present study is that it only analyses point estimates: the applied prediction models can provide confidence intervals, so the investigation of their validity (such as coverage properties) could be a relevant future research direction.

Finally, it is worth repeating that age and sex structure of the population is not considered here (consistent with the approach of the WHO). However, inclusion of these – together with an explicit modelling of the population size – has the potential to improve predictions by capturing and separating mechanisms that govern the change of population size and structure in the models. To explore whether and to which extent predictions could be improved by taking these into account is an important further research area.

Conclusion

The performance of the WHO's method with its original parametrization is indeed very poor as revealed by extensive simulations, i.e., the "German puzzle" was not just an unfortunate mishap, however it can be profoundly improved by a better choice of parameters. After that, its performance is similar to that of Acosta-Irizarry method, with WHO slightly dominating for longer fitting periods, Acosta-Irizarry in the shorter ones. Despite simplicity, linear extrapolation could exhibit a good performance, but it is highly dependent on the choice of the starting year; in contrast, Acosta-Irizarry method exhibits a relatively stable performance (much more stable than WHO's method) irrespectively of the starting year. Using the average method is almost always the worst except for very special circumstances.

This proves that splines are not inherently unsuitable for predicting baseline mortality, but care should be taken, in particular, these results suggest that the key issue is that the structure of the splines should be rigid. No matter what approach or parametrization is used, model diagnostics must be performed before accepting the results. In particular, it is imperative to examine the data at hand (for instance with appropriate visualizations) to check the adequacy of the fit of the used model. If possible, used methods should be validated with simulations on synthetic datasets or time series cross validation or bootstrap.

Additional File 1: Comparison of data sources

For a country like Germany, four data sources come into consideration for weekly mortality data: Eurostat [40], the Short-Term Mortality Fluctuations (STMF) dataset of the Human Mortality Database (WMD) [47], the World Mortality Database [1] and the national data provider (in this case, the Federal Statistical Office of Germany). The last is usually more complicated, limits extension to other countries and is unnecessary for developed countries, so it'll be avoided in this case. Also, for Germany, WMD simply copies the data of the STMF ("We collect the weekly STMF data for the following countries: [...] Germany, [...].") leaving us with two options.

We shall compare whether these two report identical data (Figure 7).

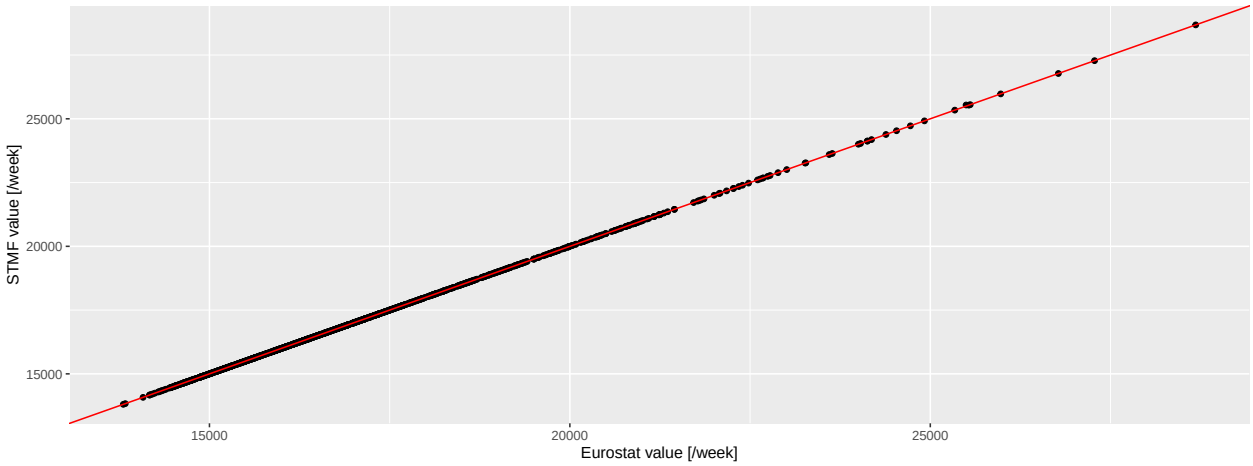

Figure 7: Weekly number of deaths according to the Eurostat (horizontal axis) and the STMF database (vertical axis) in Germany. Red line indicates the line of equality.

The two are almost identical (with a correlation of 0.9999998), with differences only occuring for the latest data and of minimal magnitude, so we can safely use the Eurostat database.

Additional File 2: Generating realistic synthetic datasets

First, Figure 2 should be inspected, as it already gives important clues on the setup of a realistic model from which synthetic datasets could be generated. Figure 8 gives further insight by plotting each year separately.

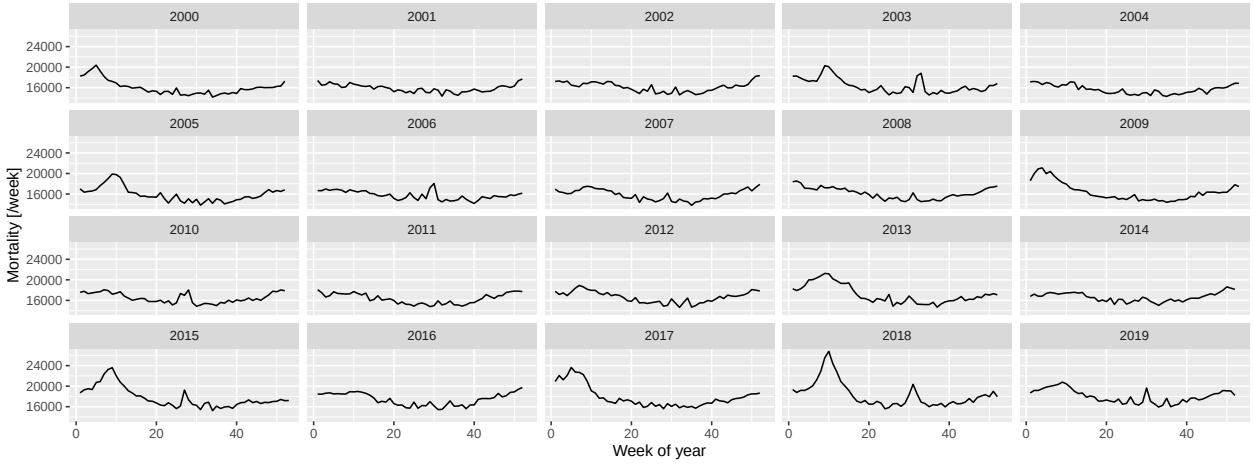

Figure 8: Weekly number of deaths in Germany, separated according to year.

The following observations can be made:

- There is a long-term trend, seemingly quadratic.
- There is a strong seasonality with winter peak and summer trough.
- There are peaks – in addition to the seasonality – in the winter and also during the summer (although the shape seems to be different, with winter peaks seeming to be broader and higher).

To investigate these, first a spline-smoothing – with thin plate regression spline [32] – is applied to obtain the long-term trend, and a single harmonic term is included as a covariate to remove seasonality. No interaction is assumed between the two, i.e., it is assumed that the seasonal pattern is the same every year. (The peaks are not accounted for at this stage which means that the curve is above the true one, but the difference is likely has minimal due to the rarity and short duration of the peaks. This will be later corrected, after the peaks were identified.) All analysis will be carried out on the log scale (meaning the effect of covariates is multiplicative) using negative binomial response distribution to allow for potential overdispersion [48].

Figure 9 shows the results, overplotted with the model where the long-term trend is a completely parametric quadratic trend. One can observe very good fit between the two, so all subsequent investigation will use the quadratic trend which is much easier to handle. This is only meaningful for short-term extrapolation, but this is what will be needed now (two years of extrapolation will be used in the present study); also it is not possible to better differentiate between functional forms at this sample size.

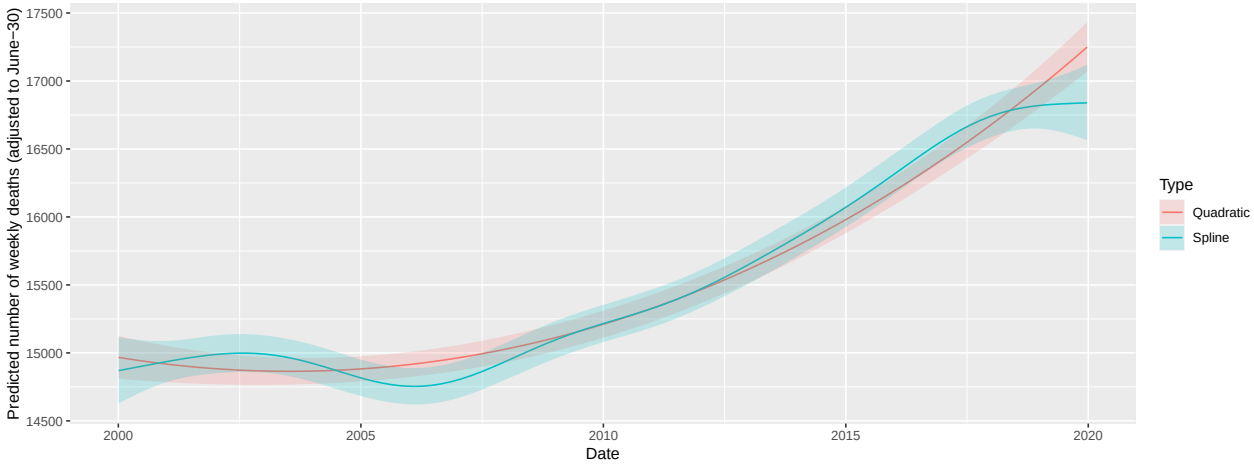

Figure 9: Fitting long-term trend as spline (black) and as quadratic trend (red); shaded area indicated 95% confidence interval. Seasonality is removed by including a single harmonic term in the regression in both cases.

The coefficients can be transformed to equivalent forms that are more meaningful. Thus, the three parameters of the quadratic trend can be expressed as a minimum point (2003-07-15), value at the minimum (15918.54) and value at the end of 2020 (18825.83). (This differs from the value seen on Figure 9, as that also includes the effect of the harmonic term.) The two parameters of the harmonic regression can be expressed as an amplitude, a multiplier (9.4%) and a phase shift (-0.7, i.e., minimum at week 32 of the year).

Figure 10 shows the predictions of the above model.

A good fit can be observed, apart from summer and winter peaks. Thus, to capture them, the predictions are subtracted; with the results shown on Figure 11.

Peaks in the residuals were identified with the peak detector of Palshikar [49] using parameters that were empirically tuned to identify to visually clear peaks. Results are shown on Figure 11 with black dots; an indeed good identification of the unequivocal peaks can be seen.

Figure 12 shows the peaks themselves with a $\pm$ 100 days neighbourhood. This reinforces the idea that summer and winter peaks are somewhat different, but more importantly, suggests that the rescaled probability density

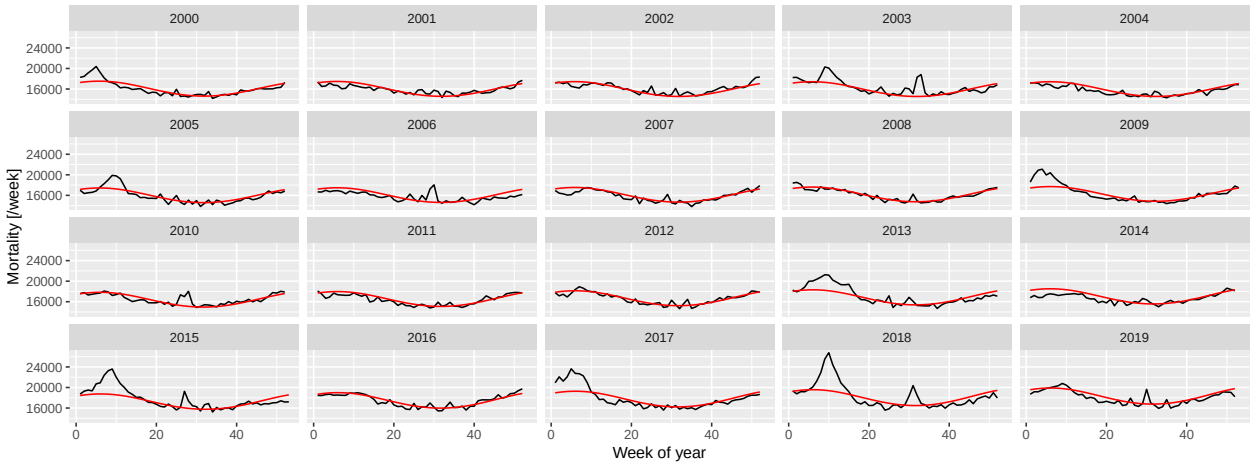

Figure 10: Weekly number of deaths in Germany, separated according to year, showing the predictions from the model with quadratic long-term trend and a single, fixed harmonic term.

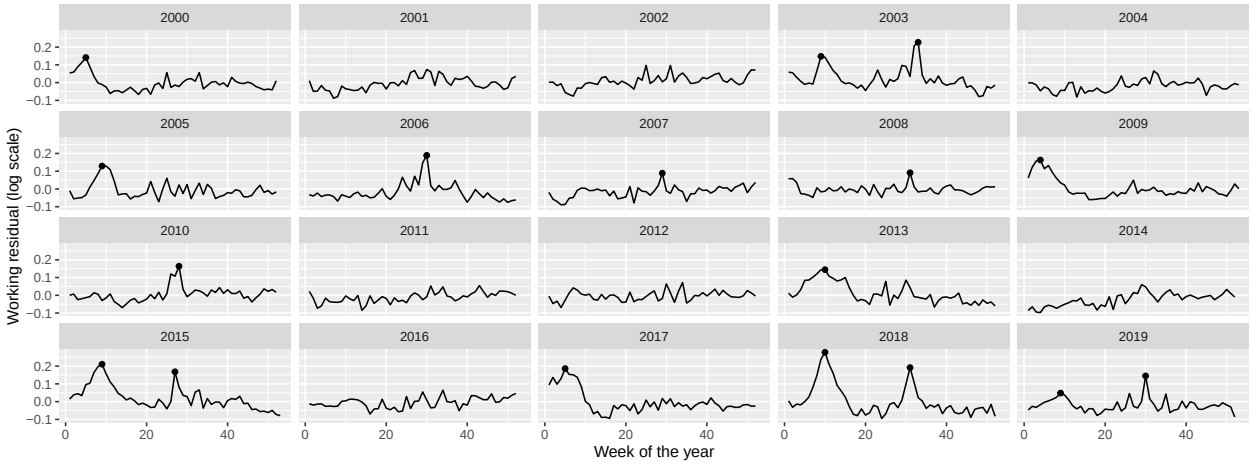

Figure 11: Residuals of the fitted model with quadratic long-term trend and a single, fixed harmonic term. Dots indicate identified peaks.

function of the Cauchy distribution, i.e., $\frac{a}{\pi s}\frac{1}{1+\left(\frac{x-x_0}{s}\right)^2}+b$ might be a good – and parsimonious – function form to capture the shape of the peaks.

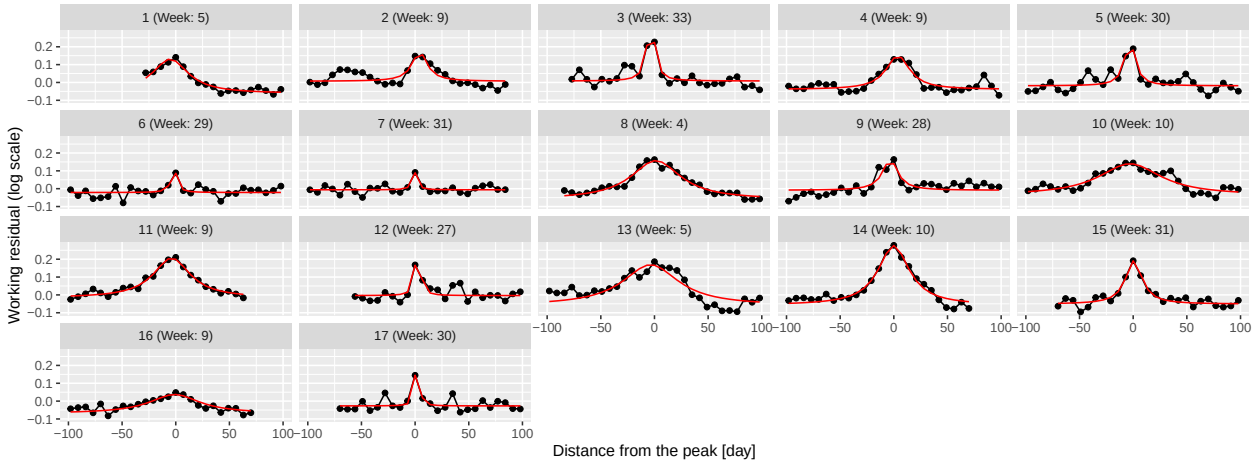

Figure 12: 100-day width neighbourhood of the identified peaks. Red line indicates the best fitting rescaled Cauchy density.

To check this theory, the best fitting function was found for each peak individually using the Nelder-Mead method [50] with mean squared error objective function. Results are shown on 12 as red lines; an almost perfect fit can be observed for all peaks confirming the initial idea of using Cauchy density.

This now puts us in a position to investigate the distribution of the parameters (i.e., a, b, s and x_0), which is shown on Figure 13 separated according to whether the peak is during the summer or not. Peak height is also calculated, defined as height at zero (which is $\frac{a}{\pi s\left(1+\frac{x_0^2}{s^2}\right)}$) not the actual maximum height (which is at x_0) to avoid extremely large heights – which were never actually observed – due to peaks with small s, i.e., very narrow peaks.

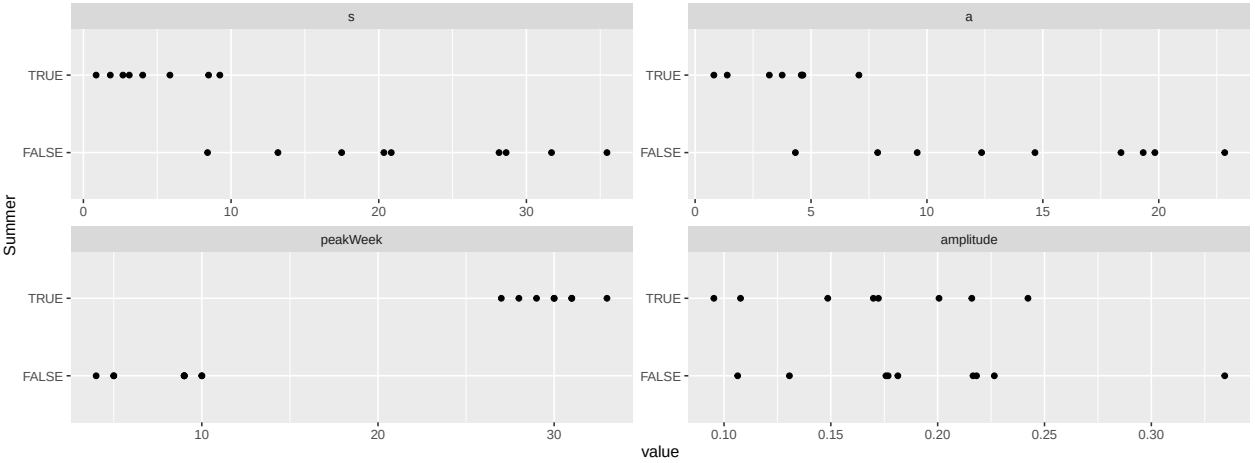

Figure 13: Distribution of the parameters of the best fitting rescaled Cauchy densities for each peak, separated according to whether the peak is during the summer.

This verifies that the width is indeed different, with the s of the summer peaks being below 10, and the winter peaks being above, i.e., summer peaks are shorter in duration, raise and fall faster. Interestingly, the peak heights are not substantially different between winter and summer. Also note that the probability of

having a peak at all is different: there are 8 summer peaks and 9 winter peaks (from 20 years). Winter peaks occur between weeks 4 and 10, summer peaks occur from weeks 25 to 35.

This allows the removal of the peaks (Figure 14), and, after these peaks are removed, it is possible to re-estimate trend and seasonality, now without the biasing effect of the peaks. This "bootstrap" procedure is adequate after this second iteration, as no further peaks can be seen after the removal of the re-estimated trend and seasonality.

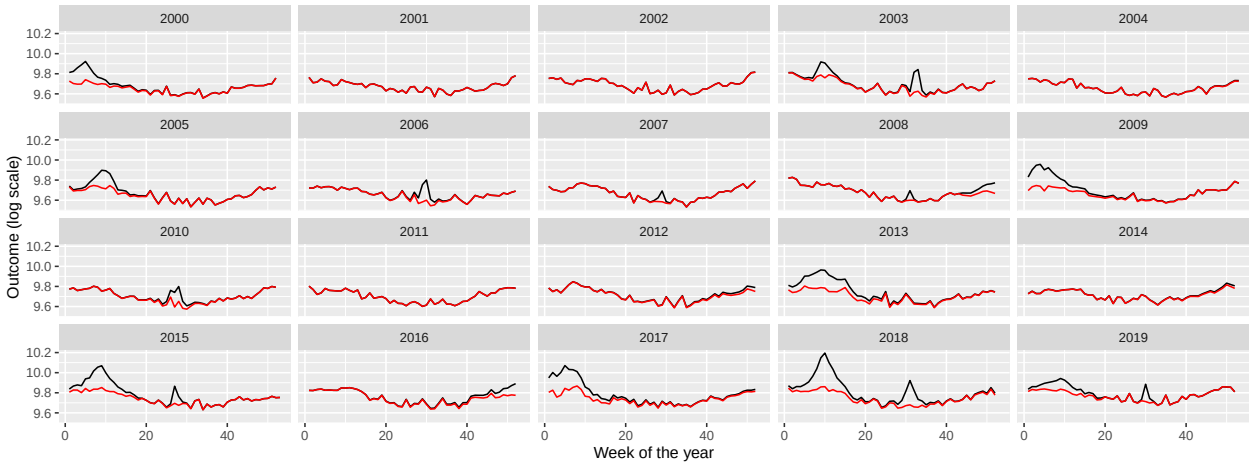

Figure 14: Weekly number of deaths in Germany, separated according to year (black) and with peaks removed (red).

Creating the appropriate model to simulate such peaks is not straightforward: there is stochasticity in the position of the peaks and in its shape, i.e., height and width. (Actually, even the presence of a peak is stochastic.) The following procedure will be used: the presence is generated as a Bernoulli random variate (with the probabilities described above, different for summer and winter), the onset date is uniformly distributed (from 0 to 0.2 in scaled weeks for the winter peak and from 0.5 to 0.7 for the summer peak), i.e., the position itself is random, but the parameters of the underyling distribution are fixed. The b parameter is set to zero (irrespectively of its estimated value, to really capture only the peak, locally – a non-zero b would mean a non-local effect), while s and a are randomly generated for each peak, again, separately for summer and winter peaks. Given the high correlation between s and a, not these, but rather s (width) and the amplitude will be generated as a random variate from – independent – uniform distributions. The parameters (minimum and maximum) of the uniform distributions both for s and the amplitude will be considered as a parameter (hyperparameter) of the simulational procedure, just as the p probability of the Bernoulli distribution, all different for summer and winter.

The following table summarizes the parameters:

Parameter	Value
Constant term of the trend	$1.01\cdot 10^{+01}$
Linear term of the trend	$-7.36\cdot 10^{-05}$
Quadratic term of the trend	$3.04\cdot 10^{-09}$
Amplitude of seasonality (log scale)	$7.34\cdot 10^{-02}$
Phase of seasonality	$-6.13\cdot 10^{-01}$
Minimum of winter peak amplitude (log scale)	$1.06\cdot 10^{-01}$
Maximum of winter peak amplitude (log scale)	$3.34\cdot 10^{-01}$
Minimum of winter peak width	$8.41\cdot 10^{+00}$
Maximum of winter peak width	$3.55\cdot 10^{+01}$
Probability of winter peak	$4.50\cdot 10^{-01}$
Minimum of summer peak amplitude (log scale)	$9.53\cdot 10^{-02}$
Maximum of summer peak amplitude (log scale)	$2.42\cdot 10^{-01}$
Minimum of summer peak width	$8.63\cdot 10^{-01}$
Maximum of summer peak width	$9.24\cdot 10^{+00}$
Probability of summer peak	$4.00\cdot 10^{-01}$
Size parameter of the negative binomial distribution	$1.00\cdot 10^{+03}$

Given the mechanism described above, the procedure to simulate synthetic datasets can easily be created. Of course, as every calculation is carried out on the log scale, the mean should be exponentiated at the last step.

Figure 15 illustrates the synthetic data set creation with a single simulation. (Of course, to assess the correctness of the simulation, several realizations have to be inspected.) In addition to the plots of 2, it also gives the autocorrelation function so that it can also be compared. (The simulated outcomes are themselves independent – meaning that effects like the increased probability of a flu season if the previous year did not have one are neglected –, but the trend, seasonality and the peaks induce a correlation structure.)

Several simulations confirm an overall good fit between the actual data set and the simulated ones. Thus, it is now possible to investigate the properties of the mortality prediction on algorithms using simulated datasets, where the actual outcome is known, and the parameters can be varied.

Additional File 3: Validation through simulation

Two sets of parameters have to be set up: parameters of the simulation (i.e., parameters of the scenario, on which the methods will be run) and parameters of the methods. They're set up as given in the main text.

One thousand simulation will be run for each parameter of the scenario, and for each of the 1000 simulated data set all 4 methods with all possible parameters of the methods will be evaluated. To increase the speed, simulations will be run in parallel. (The problem is embarrassingly parallel, as different simulations are completely independent of each other [51].)

Additional File 4: Directly comparing the errors in simulation runs

As different methods were evaluated on the same simulated dataset for each simulation, it is possible to compare not only the averages, but directly compare the errors themselves. Figure 16 shows direct comparison between the best parametrization of the WHO's method and the Acosta-Irizarry method for 200 randomly selected simulations in each scenario, with 2015 as the starting year. In the base case scenario, Acosta-Irizarry performed better in 55.4% of the cases.

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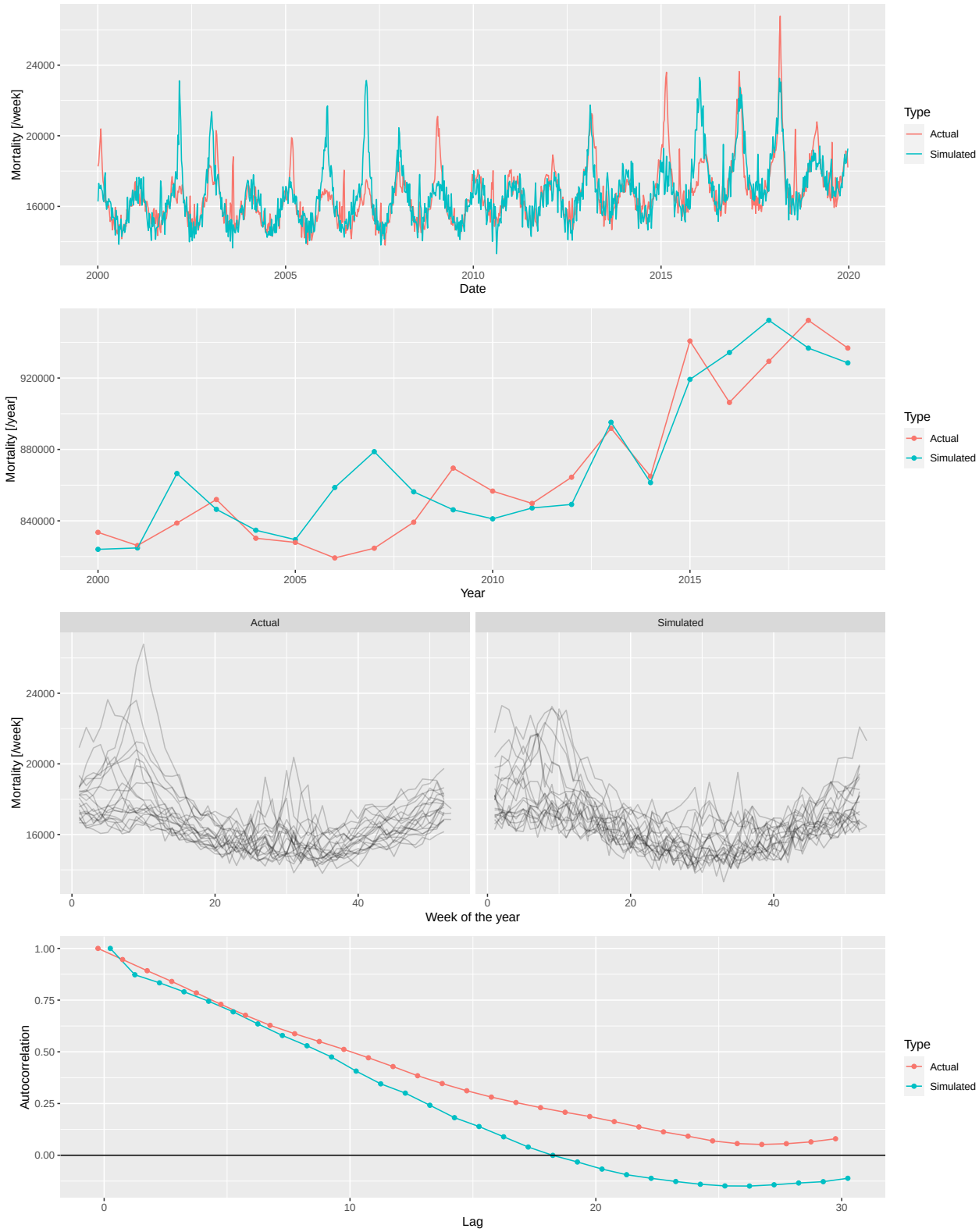

Figure 15: From top to bottom: weekly mortalities, yearly mortalities, seasonal pattern and autocorrelation function of the actual German mortality data and a single simulated dataset, 2000-2019.

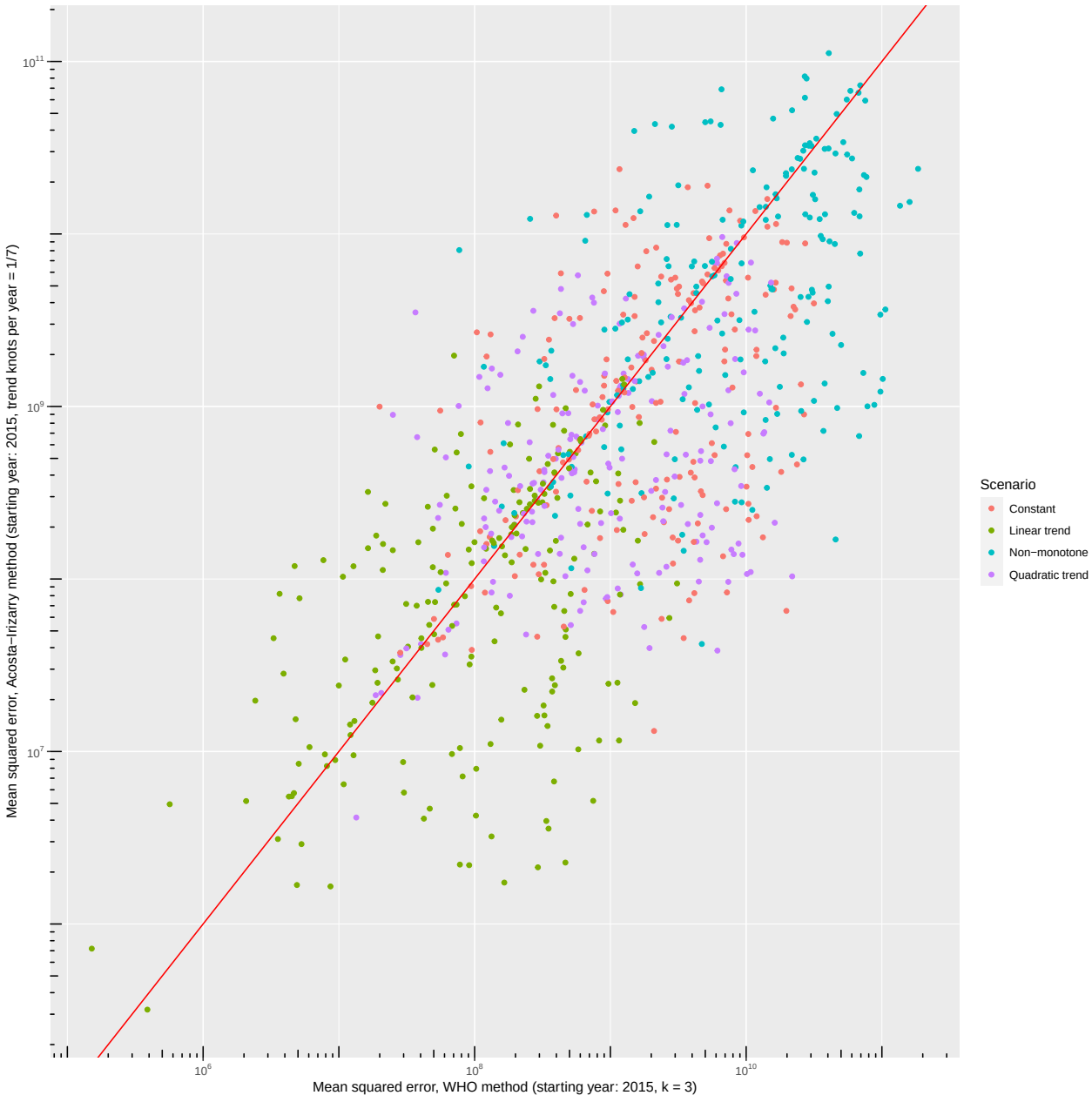

Figure 16: Errors – squared distance of the predicted outcome from its true value – of the WHO's method and the Acosta-Irizarry method (under best parametrization) on the same simulated datasets for 200 randomly selected simulations with different scenarios; black dots indicate the base case scenario, scenario #1 to #5 represent varying the parameter shown on the panel from half of its base case value to twice (with the exception of the constant term where it is varied from 90% to 110%), and probabilities are limited to be below 100%.

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