Low Vitamin D Status and Influenza Vaccination Rates are Positive Predictors of Early Covid-19 Related Deaths in Europe – A Modeling Approach

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Abstract

Objectives: To clarify the high variability in Covid-19 related deaths whose origin is unclear.

Study Design: Modeling of available data

Methods: We used six individual- and country-specific variables to predict the number of population standardized Covid-19 related deaths in 44 European countries using generalized linear models: Percent test-standardized number of SARS-CoV-2-cases, population size, life expectancy, severity of governmental responses, influenza-vaccination coverage and vitamin D status in the elderly.

Results: We found that flu-vaccination coverage in the elderly was the most important predictor, together with test-standardized cases and vitamin D status explaining approximately 47% of the variation in Covid-19 related deaths. Higher flu vaccination coverage and low vitamin D status were associated with more Covid-19 related deaths. Life-expectancy, population size and the severity of governments' responses to the outbreak did not emerge as significant predictors in multivariable modeling. The latter variable even appeared to be completely negligible.

Conclusion: Adequate vitamin D levels are important, while – contrary to current opinion – flu-vaccination in the elderly is a putative aggravating factor of Covid-19 related deaths.

Keywords: SARS-Cov2, Europe, general linear model, lethality, flu vaccination, vitamin D, non-pharmaceutical interventions

Introduction

Current public opinion seems to assume that a death following the infection with SARS-Corona-Virus 2 (CoV2) is largely due to this virus, because of its virulence. Untreated Covid-19 disease may lead to severe atypical pneumonia [1,2], a cytokine storm and other potentially lethal sequelae [3–5]. Other potential factors, such as host factors or population factors, are not much considered in the scientific and political discourse. We know that initially mostly elderly patients with a mean age above 70 years have been severely affected [6,7]. However, during the initial phase of the CoV2 outbreak, there was a wide variation across countries and regions. This variation is partially shrouded by the fact that most agencies and their dashboards propagate unstandardized figures of cases and deaths. A publication that estimated excess death rates in the US during the early time of the CoV2 pandemic as compared with the same months of previous years reveals a wide variation from -71,9 deaths per 100.000 inhabitants in North Dakota to 299,1 deaths per 100.000 inhabitants in New York City, with seven states actually exhibiting less excess mortality than in the previous comparison years, and 12 US states presenting with excess mortality figures below 10 per 100.000 inhabitants [8]. The same is true for Europe: Miles and colleagues listed excess deaths of 21% for Spain, 20% for the UK, 18% for Italy down to 6% for Sweden, 3% for Portugal, -1% for Germany, -3% for Denmark and -4% for Norway [9].

Thus, there is clearly a need to identify other drivers of mortality than the infection itself, or rather, to understand what might have mediated the course from infection to death during the initial phase of the outbreak. Are there population variables, public health variables, or host factors that can be identified that make this variation understandable? This was the guiding question of this modeling study.

Materials & Methods

The outcome of interest was the number of Covid-19 related deaths per 1.000.000 inhabitants up until 30th August 2020. The following variables were used as putative predictors of this dependent variable which we subsequently refer to as "y" (Supplementary Table 1): (i) the influenza vaccination rate in the elderly; (ii) the test-standardized number of cases (in %), calculated as the number of cases in a country divided by the number of tests in that country × 100; (iii) life expectancy (in years); (iv) the population size; (v) mean GRSI between 15th February and 15th August 2020; (vi) vitamin D status. The data sources are given in Supplementary Data File 1.

Because the distribution of y followed a gamma distribution well (Figure 1), we calculated generalized linear models (GLMs) on a gamma-distributed variable with a log-link function. Since a log-transformation produced an outcome variable with an approximately normal distribution (Shapiro-Wilk normality test p=0.635, Figure 1), we also calculated standard multiple linear regression models (LRMs) on log(y).

The final sample thus included 44 European countries of which 41 had known flu vaccination rates, 36 had known flu vaccination rates and GRSI values, and 31 had known flu vaccination rates, GRSI values and vitamin D status estimates. To utilize as many cases as possible for multivariable modeling [10] missing covariates were imputed with multiple imputation by chained equations using the R package 'mice' [11]. A total of 100 imputation data sets were created. Each was used to fit the regression models, and the model parameters were averaged over all 100 model fits.

Different regression models were pre-specified according to plausible scientific hypothetical explanations for Covid-19 related deaths and compared using the bias-corrected Akaike Information criterion [12]. As the simplest hypothesis, it was assumed that the number of standardized deaths could be predicted by the number of test-standardized cases:

y ~ test-standardized cases (1)

The second most-plausible simple hypothesis was that in addition to the number of cases, the severity of governmental responses would allow better predictions of the outcome:

y ~ test-standardized cases + GRSI (2)

In a third model, we related the outcome to population-specific predictors in addition to case numbers:

y ~ test-standardized cases + population size + life expectancy (3)

Alternatively, it was assumed that in addition to case numbers, the outcome mainly depends on the two individual factors flu vaccination and vitamin D status:

y ~ test-standardized cases + flu vaccination rate + vitamin D status (4)

Finally, the fifth hypothesis assumes that using all possible predictors is important to explain the outcome:

y ~ test-standardized cases + flu vaccination rate + vitamin D status + population size + life expectancy + GRSI (5)

The best model was identified as the one with the smallest AICc, and all other models were compared to the best model by computing AICc differences Δ_i, probabilities w_i of model i being the best model (in the Kullback-Leibler information sense) and evidence ratios $E_{i,j} = w_i/w_j$ [12]. Model adequacy was measured by R^2, the proportion of variance explained by the predictors; for the GLMs a Kullback-Leibler divergence-based R^2 measure was used [13].

All analyses were calculated with R version 4.0.2, and statistical significance was defined as p-values <0.01. A detailed description of the statistics is given in Supplementary Data File 1.

Results

The results of both the GLMs (assuming a Gamma distribution for the outcome variable y) and the LRMs fitted to log(y) are presented in Table 1. The GLMs and LRMs yielded qualitatively similar results for all five hypotheses considered. Test-standardized cases alone were only able to explain 9-10% of the variance in y or log(y), respectively, while the full model (model 5) was able to explain about 51-58%. As expected, test-standardized cases were positive predictors of Covid-19 related deaths in all models with significant associations in models 3-5. As also expected, sufficient vitamin D status was associated with fewer deaths. Surprisingly, however, it was found that the GRSI was the least important predictor of Covid-19 related deaths, which did not emerge in any of the models as significant. Also surprisingly, flu vaccination rates were significantly and positively related to the outcome, i.e., there were more deaths in countries with higher flu-vaccination coverage.

Results of comparing the different models are given in Table 2. The evidence clearly favored model 3 which utilized test-standardized cases, flu vaccination rates and vitamin D

status to predict the outcome over all other models, whereby only the full model 5 had a high enough probability of being a possible alternative. This shows that individual-specific factors were much more important than population-specific factors for predicting Covid-19-related deaths. Model 3 was thereby able to explain almost half of the variance in outcomes.

In order to check if our results are dependent on the imputation of missing variables, we refitted a full GLM and LRM model to the original dataset with missing variables removed (Table 3). This model resulted in qualitatively similar results as model 5 in Table 1 and confirmed that the two most important predictors of standardized COVID-19 deaths were again influenza vaccination rates and the number of test-standardized cases, which were both positively associated with the outcome. Due to more uncertainty in the regression coefficient estimate of test-standardized cases, the flu vaccination rate now was the only statistically significant predictor ($p<0.01$) in both the GLM and LRM.

Discussion

Modeling Covid-19 related death rates in 44 European countries during the initial phase of the outbreak until August 2020, unravels some interesting findings:

a) Unsurprisingly, test-standardized CoV2-cases predict the number of deaths. This variable on its own, however, explains only about 8% of the variance.
b) Surprisingly, more important is the flu-vaccination coverage in the elderly: the higher this vaccination rate is, the more Covid-19 related deaths we see in a country. This variable on its own explains about 18-19% of the variance.
c) We confirmed that population-wide vitamin D status may have acted protectively against COVID-19-related deaths during the initial phase of the outbreak.

These findings are strengthened by the fact that two different models reach the same conclusions: a GLM predicting a gamma-distributed outcome variable with log-linked predictors and a standard multiple LRM with identity link functions of predictors on a log-transformed outcome variable.

It is easy to understand that more CoV2 cases translate into more Covid-19 related deaths. What is unexpected is the fact that the importance of this predictor on its own is comparatively minor. Thus, obviously, there remains variance to be explained. Although we do not assume we have captured all important variables, we have captured at least some as only three variables were able to explain about 47% of the total variance. A reassuring finding was that country-wide vitamin D status was inversely associated with Covid-19 related deaths, consistent with clinical and epidemiological data [14–18]. Most surprising and most counterintuitive are the two findings that there are more Covid-19 related deaths in countries with higher flu vaccination coverage in the elderly, and, in addition, that the severity of governments' responses with non-pharmaceutical interventions was completely negligible and inconsistent in its effect (Table 1, models 2 and 5).

How can this negative impact of flu vaccination rates be explained? A careful randomized trial of flu vaccination in children showed that children who were vaccinated against influenza were better protected against influenza but suffered a fourfold higher risk of other respiratory virus dependent diseases [19]. This might have to do with unknown mechanisms that disturb the ecology of pathogens, known as the virus interference phenomenon. A study

conducted during the 2017/2018 influenza season revealed that flu vaccination was associated with a 36% increased odds of contracting respiratory coronavirus diseases (odds ratio 95% confidence interval 1.14-1.63, p<0.01), while affording specific protection against influenza and parainfluenza viruses [20].

Thus, the negative impact of flu vaccination might have to do with several mechanisms: First, the virus interference phenomenon as shown for non-CoV2 coronaviruses [20]; second, the fact that the immunological load on an organism that has to deal with a flu vaccine binds resources that cannot be mustered against a new and dangerous pathogen like CoV2. Third, it might also be the case that immune-enhancers in vaccines, such as aluminum derivates, which are potentially toxic, burden the organism and hamper natural immunity. For example, it was shown experimentally in chicks that aluminum can disturb vitamin D metabolism [21]. Furthermore, it has been argued that influenza vaccines are produced in eggs and other cell-systems that are not routinely tested against corona-viruses. Hence, corona-virus proteins from other corona-viruses might be present in these vaccines and induce allergic reactions against the novel CoV2 [22]. Our finding is in contrast to data from the US [23,24]. However, the correlation between influenza vaccination and COVID-19 death rate in the US is much lower than in Europe [25], probably because there is little variation in influenza vaccine coverage in the US. Our results are derived from population level data in Europe in the elderly, which might be a specifically susceptible fraction of the population.

Non-pharmaceutical interventions are widely hailed in modeling studies as having prevented higher incidence figures of cases and deaths [26–28]. While this might be true for some countries and some single interventions, some authors are skeptical [29–34]. Careful modeling studies for Germany, for instance, show that, although Germany was comparatively early to react – first measures were introduced on March 8 and shortly after this a full country lockdown was enacted – the peak of the infection and of the reproduction numbers was reached in nearly all 420 German districts on or around March 8 and thus none of the non-pharmaceutical interventions could have been causally related to the reduction of cases, and hence deaths [35,36]. The ensuing reduction of cases is a misattribution: it is not due to the lockdown, but obviously to the fact that the virus follows its own dynamic which needs to be better understood. Thus, there is independent evidence that non-pharmaceutical interventions are less effective than often thought. This would explain the negligible association with Covid-19 related deaths in our analysis.

We find it quite remarkable that only three variables help to explain roughly 47% of the variation in Covid-19 related deaths. Because vitamin D status was one of them, it might be interesting to study other variables related to health. Although vitamin D entered the best model number 3 with a strong regression weight of -0,48, it is not significant as a predictor. But it nevertheless seems to be a strong predictor, as models without it are clearly inferior. We also calculated a model without vitamin D which was slightly weaker in terms of model fit (AIC = 535.8 vs. 535.0 for model 3) and less efficient in explaining variance (KL-R^2_{adj} = 0.453 vs. KL-R^2_{adj} = 0.477). We would argue that, as a theoretically and numerically strong predictor, vitamin D improves model fit and therefore it should be part of the equation. Its lack of significance is likely due to the coarse grained nature of our data.

The limitations of our approach need to be kept in mind:

First, there might have been collinearity between the three predictors found to be significant in the best model. However, variance inflation factors (all <1.11) showed that there was no collinearity between these three variables.

Second, we were unable to find flu vaccination data, GRSI and vitamin D estimates for all countries. We tried to overcome this limitation through multiple imputation by chained equations, and the results were consistent with an analysis using only the cases for which every variable value was known.

Third, one potential problem we cannot remedy is the notorious unreliability of data or differences in the definition of cases, of deaths, and in reporting standards. This can be seen in the fact that Belgium is a clear outlier in all analyses that decreases the fit of the model. It is well known that the definition of Covid-19 related deaths in Belgium is more lenient than in other countries. Vitamin D estimates also have several uncertainties, such as having been measured in rather small cohorts, in different years and during different times of the year. Whenever possible, we preferred vitamin D values from the literature that had been measured in elderly people and during winter/spring. Also, Covid-19 reporting systems might be less reliable in some countries compared with others. These are the limits of our data and our analyses. But considering the fact that the whole world, politicians and public health officials use exactly the same data for their decisions should allow us to use them for analysis. The fact that the relationship between Covid-19 related deaths and test-standardized cases is weaker than one would expect is exactly due to this situation and to the fact that being a case, when considering the number of tests in a country, has only a weak relationship with becoming a fatality. It has been shown that the case fatality rate is much less than previously assumed and estimated to be 0.15% [37]. In Germany the case-fatality rate has been calculated from well documented cohorts to be 0.12 to 0.35% [38,39]. The still widely circulating higher case fatality rates are due to the fact that they are largely calculated using raw, absolute figures without knowledge of the real prevalence [40]. But also standardized figures might be unreliable. Often the same person is tested multiple times. Thus, we likely overestimate the number of cases by some margin. This would mean: the true link between being a case and becoming a fatality is probably even weaker.

Considering all these weaknesses our paper also has some strengths. First, care was taken to ensure that the essential requirements for linear modeling were met. Second, we pre-specified plausible hypotheses (expressed as GLMs or LRMs) and used a robust model comparison framework based on Kullback-Leibler information to compare them, in this way automatically incorporating penalties for potential overfitting. Third, restricting the analysis to Europe means that we have a comparatively homogeneous sample which nevertheless has enough variability. While all countries issued warnings the way it was implemented differed widely, from suggestions and recommendations in Sweden to very strict stay-at-home orders that were policed in Spain, from nearly no regard in Belarus to strict political measures in Italy. Thus, we likely see a representative laboratory for the world, except that we do not cover any variance in ethnicity.

In conclusion we see that Covid-19 related deaths are most importantly dependent on the flu-vaccination rate among the elderly in a country: the higher the vaccination rate, the higher the Covid-19 death toll, explaining about 18% of the total variation. The number of cases is the second, unsurprising predictor, but its relationship is weaker than one would assume. The third important predictor was country-wide vitamin D status in the elderly, for which a causal relationship appears well supported by clinical and mechanistic evidence. These three variables predict the variability in Covid-19 related deaths much better than the severity of governmental responses, population size or life expectancy. This might encourage others to look for other, perhaps even more important host factors that can explain why we see such a wide variability in cases and deaths in the initial phases of the CoV2 outbreak.

Data Availability Statement

The underlying data for this analysis are given in Supplementary Table 1.

Author Contributions

HW initiated this study, collated the data, calculated the first analyses using Statistica and wrote the first draft of the MS. RJK checked the original data, contributed data, calculated the GLM using R, calculated all additional analysis in R and contributed to writing and discussion of the results.

Conflict of Interests

None of the authors has a conflict of interest.

Role of the funding source

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Ethical Approval

This study was a secondary analysis on publicly available data and hence no ethical approval was required.

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Figure

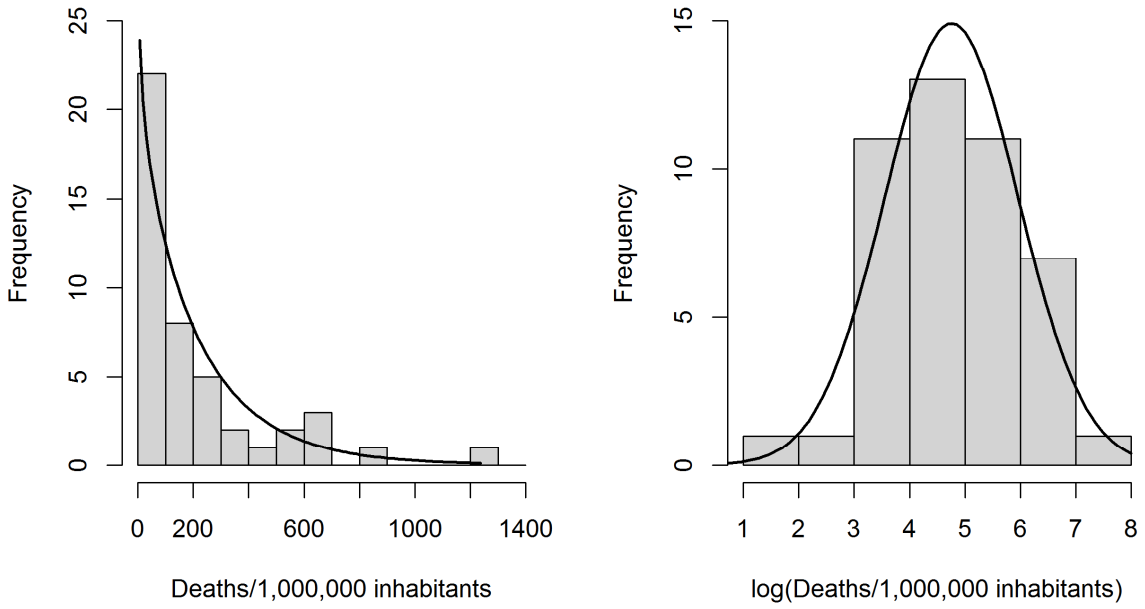

Figure 1: Left: Observed distribution of the outcome variable "Covid-19 related deaths per 1 million inhabitants" and a gamma distribution (rate = 0.004071, shape = 0.9044) fitted through maximum likelihood estimation. Right: Observed distribution of the log-transformed outcome variable, with a best-fit normal distribution.

Table 1: Parameters of the generalized linear models fitted to standardized deaths and and linear models fitted to the logarithm of standardized deaths

Model 1	**Generalized linear model**					**Linear model**				
Variable	**Regression coefficient**	**p-value**	**KL-R^2**	**KL-$R^2_{adj.}$**	**AICc**	**Regression coefficient**	**p-value**	**R^2**	**$R^2_{adj.}$**	**AICc**
Test-standardized cases [%]	0.102 (0.042)	0.019	0.090	0.068	561.3	0.091 (0.042)	0.036	0.101	0.080	140.9
Model 2	**Generalized linear model**					**Linear model**				
Variable	**Regression coefficient**	**p-value**	**KL-R^2**	**KL-$R^2_{adj.}$**	**AICc**	**Regression coefficient**	**p-value**	**R^2**	**$R^2_{adj.}$**	**AICc**
Test-standardized cases [%]	0.097 (0.042)	0.026	0.136	0.094	561.0	0.079 (0.045)	0.086	0.117	0.074	142.5
GRSI	0.029 (0.020)	0.153				0.016 (0.021)	0.441			
Model 3	**Generalized linear model**					**Linear model**				
Variable	**Regression coefficient**	**p-value**	**KL-R^2**	**KL-$R^2_{adj.}$**	**AICc**	**Regression coefficient**	**p-value**	**R^2**	**$R^2_{adj.}$**	**AICc**
Test-standardized cases [%]	0.166 (0.030)	3.1×10^{-6}	0.513	0.477	535.0	0.138 (0.037)	0.00065	0.444	0.403	124.6
Flu vaccination rate [%]	0.038 (0.006)	1.5×10^{-7}				0.035 (0.007)	4.6×10^{-5}			
Vitamin D status (sufficient vs. deficient)	-0.482 (0.303)	0.124				-0.533 (0.371)	0.162			
Model 4	**Generalized linear model**					**Linear model**				
Variable	**Regression coefficient**	**p-value**	**KL-R^2**	**KL-$R^2_{adj.}$**	**AICc**	**Regression coefficient**	**p-value**	**R^2**	**$R^2_{adj.}$**	**AICc**
Test-standardized cases [%]	0.148 (0.035)	0.00014	0.382	0.336	546.7	0.136 (0.040)	0.0016	0.311	0.259	134.2
Population [10^6]	0.012 (0.005)	0.021				0.014 (0.006)	0.014			
Life expectancy [years]	0.165 (0.039)	0.00013				0.123 (0.044)	0.0084			

Model 5	**Generalized linear model**					**Linear model**				
Variable	**Regression coefficient**	**p-value**	**KL-R^2**	**KL-$R^2_{adj.}$**	**AICc**	**Regression coefficient**	**p-value**	**R^2**	**$R^2_{adj.}$**	**AICc**
Test-standardized cases [%]	0.178 (0.033)	5.9×10^{-6}	0.576	0.507	536.9	0.160 (0.041)	0.00049	0.512	0.433	127.4
Flu vaccination rate [%]	0.029 (0.007)	0.00011				0.028 (0.008)	0.0017			
Vitamin D status (sufficient vs. deficient)	-0.527 (0.305)	0.097				-0.546 (0.402)	0.187			
Population [10^6]	0.008 (0.004)	0.077				0.011 (0.006)	0.063			
Life expectancy [years]	0.085 (0.040)	0.072				0.066 (0.051)	0.207			
GRSI	-0.007 (0.016)	0.676				-0.009 (0.021)	0.685			

Table 2: Comparison of the five different models specified in equations (1-5)

		Generalized linear model				Linear regression model				
Rank	Model	AICc	$\triangle_i$	w_i	$E_{3,i}$	Model	AICc	$\triangle_i$	w_i	$E_{3,i}$
1	3	535.0	0.0	0.722	1	3	124.6	0	0.798	1
2	5	536.9	1.93	0.276	2.62	5	127.4	2.81	0.195	4.08
3	4	546.7	11.72	0.002	350.7	4	134.2	9.60	0.007	121.5
4	2	561.0	26.08	<0.0000	459964	1	140.9	16.30	0.0001	3468.7
5	1	561.3	26.35	<0.0000	527127	2	142.5	17.93	0.0002	7821.8

Models were ranked according to increasing AICc. AICc: Bias-corrected Akaike Information Citerion; $\triangle_i$: Difference in AICc to the best model; w_i: probability of model i being the Kullback-Leibler best model; $E_{3,i}$: evidence ratio between model 3 (the best model) and model i

Table 3 – Results of the full generalized linear models fitted to the original dataset with missing variables removed (intercept not reported)

	Full Generalized linear model (N=30)		**Full linear regression model (N=30)**	
Variables	Coefficient Estimate (SE)	p-value	Coefficient Estimate (SE)	p-value
Test-standardized cases [%]	0.126 (0.046)	0.011	0.130 (0.053)	0.023
Flu vaccination rate [%]	0.027 (0.007)	0.0010	0.024 (0.008)	0.0076
Vitamin D status (sufficient vs. deficient)	-0.470 (0.293)	0.122	-0.497 (0.342)	0.159
Population [10^6]	0.007 (0.005)	0.168	0.012 (0.006)	0.057
Life expectancy [years]	0.122 (0.052)	0.030	0.138 (0.062)	0.035
GRSI	0.009 (0.018)	0.640	0.000 (0.021)	0.99

GRSI: Government Response Stringency Index; SE: Standard error